An impressionistic painting in dark, moody tones. It depicts a person, possibly a woman, wearing a vibrant red garment. The figure is positioned on the right side of the frame, looking down. The background is a blend of dark purples, blues, and browns, with visible brushstrokes and a textured, painterly quality. The overall mood is somber and artistic.

European Association of Urology Guidelines

2015 edition



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Introduction

We are honoured and privileged to introduce you to the 2015 update of the EAU Guidelines. The Guidelines are a priority for the EAU, they are a priority for every practicing urologist across Europe and beyond, and importantly, they are a priority for the continued improvement of patient care and outcomes. This means that the EAU Guidelines are by default an important priority for healthcare policy-makers and funders. The EAU Guidelines Office oversees the production of 20 International Guidelines across 20 Guideline Panels. Our Guideline panels have some of the most respected, talented and dedicated urologists from across the breadth of Europe and beyond that work on a voluntary basis for the Guidelines Office.

For this 2015 print, observant readers will notice a decrease in size of all individual guidelines topics based on structured templates (oncology- and non-oncology) developed by the EAU Guidelines Office Methods sub-Committee. All texts have been subjected to a robust double blind peer review process prior to publication.

In mapping out the future of the EAU Guidelines over the next 5 years, our readership will witness increasing standardisation of the structure of the guidelines, high quality systematic reviews underpinning key recommendations, and increasing standardisation in phrasing of actionable recommendations. In order to meet this requirement of high quality systematic reviews underpinning recommendations, the Guidelines Office has embarked on systematically introducing Cochrane review methodology across all 20 Guideline panels. This process is ongoing and the benefits and impact of this transition will be seen in this and future updates of the EAU Guidelines. The past year has seen a considerable uptake of new systematic review projects, the results of which will become more apparent to the readers in each subsequent update.

Strengthening the evidence base that underpin EAU Guidelines recommendations and improving the transparency from evidence to recommendations is a critical area the EAU Guidelines Office must continue to be vigilant about. More meaningful involvement of patients in the development of the EAU guidelines is another area that the EAU is investing in. After all, we produce guideline recommendations for urologists to use in their daily practice but the recommendations are not applied to urologists, they are applied to patients, and so we are committed to ensuring that the clinical questions the recommendations are based on, and the outcomes of interest that are considered, take important patient views into account. Difficult as such a transition may be, that is our responsibility, if we are to maintain our position at the cutting edge of quality international guideline production.

Important as it is to produce comprehensive high quality clinical practice guidelines, more effective dissemination and assessment of their value in day-to-day clinical practice is crucial and the EAU Guidelines Office is well positioned now to embark on this programme of work. Doing so, could provide further insight into what may well be more optimum ways to present our findings in the future, thereby making EAU guideline recommendations more relevant and actionable, also enhancing their influence on patient care.

The EAU Guidelines Office is embracing New Media tools (Facebook / Twitter) as a means to enhance not only the dissemination of the EAU guidelines but also to promote discussion and feedback from our users. We are counting on your active engagement in helping us with this endeavor, which is led by a dedicated Guidelines Office Dissemination sub-Committee.

The yearly publication of the EAU Guidelines would not be possible without the trust and support of each and every user of the Guidelines globally, our EAU membership, our valued Guideline panels, the young Guideline Associates, the EAU Executive Committee & Management team, our EAU National Societies, and importantly, the Guidelines Office staff (especially Karin Plass, Esther Robijn and Eva Lowther). So, on behalf of the EAU Guidelines Office Board, thank you for your support and inspiration.

We hope you enjoy using the 2015 update of the EAU Guidelines!



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The EAU Guidelines Office has set up dedicated sub-Committees responsible for critical aspects of guidelines development. The Methods sub-Committee, supported by methodologists, is charged with the development of methodological standards and quality control. The Dissemination sub-Committee oversees the development of dissemination and implementation strategies.

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Dr. S. MacLennan, Aberdeen (UK)
Dr. M.I. Omar, Aberdeen (UK)

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Methodology section

In this 2015 EAU Guidelines compilation, all standard information on levels of evidence (LE) and grading of recommendations (GR) has been taken out of the individual guidelines topics for the sake of brevity.

Recommendations and statements issued in the EAU guidelines are based on the following system, modified from the Oxford Centre for Evidence-based Medicine [1].

Table 1.1: Level of evidence [1]*

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials.
1b	Evidence obtained from at least one randomised trial.
2a	Evidence obtained from one well-designed controlled study without randomization.
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study.
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports.
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities.

Table 1.2: Grade of recommendation [1]*

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial.
B	Based on well-conducted clinical studies, but without randomised clinical trials.
C	Made despite the absence of directly applicable clinical studies of good quality.

** Modified from [1].*

The aim of assigning a LE and grading recommendations is to provide transparency between the underlying evidence and the recommendation given.

It should be noted that when recommendations are graded, the link between the level of evidence and grade of recommendation is not directly linear. Availability of randomized controlled trials may not necessarily translate into a grade A recommendation where there are methodological limitations or disparity in published results. Alternatively, absence of high level evidence does not necessarily preclude a grade A recommendation, if there is overwhelming clinical experience and consensus. In addition, there may be exceptional situations where corroborating studies cannot be performed, perhaps for ethical or other reasons and in this case unequivocal recommendations are considered helpful for the reader. The quality of the underlying scientific evidence - although a very important factor - has to be balanced against benefits and burdens, values and preferences and costs when a grade is assigned.

The EAU Guidelines Office do not perform cost assessments, nor can they address local/national preferences in a systematic fashion. But whenever this data is available, the panel will include the information.

Reference

1. Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998. Updated by Jeremy Howick March 2009.
<http://www.cebm.net/index.aspx?o=1025> [Accessed February 2015]

The Assistance and support of the European National Urological Associations has been invaluable for the European Association of Urology guidelines project over the past years. Whilst in many European countries the EAU guidelines are being used in clinical practice, or form the basis of national urological guidelines, the EAU Guidelines Office have recently started to formalise endorsement of their guidelines. Formal replies have been sent in by the following National Urological Associations:

National Societies Endorsements

- The Algerian Association of Urology
- The Argentinian Society of Urology
- The Armenian Association of Urology
- The Austrian Urological Society
- The Belarusian Association of Urology
- La Sociedad Chilena de Urología
- La Sociedad Colombiana de Urología
- The Cyprus Urological Association
- The Czech Urological Society
- The Dutch Association of Urology
- The German Urological Association
- The Hellenic Urological Association
- The Hong Kong Urological Association
- The Hungarian Urological Association
- The Indonesian Urological Association
- The Italian Association of Urology
- The Kosova Urological Association
- The Latvian Association of Urology
- The Macedonian Association of Urology
- The Malaysian Urological Association
- The Polish Urological Association
- The Portuguese Urological Association
- The Russian Society of Urology
- The Slovenian Urological Association
- The Swedish Urology Association
- The Spanish Association of Urology
- The Taiwan Urological Association
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Reviewers were identified based on their expert knowledge within the urological field and bordering specialties. The EAU Guidelines Office Board is most grateful for their time and diligence in providing complete and extensive reviews of the individual EAU Guidelines. Whenever feasible, feedback from lay reviewers and patient advocacy groups has been sought.

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Non-muscle-invasive (Ta, T1 and CIS) Bladder Cancer

Upper Urinary Tract Urothelial Cell Carcinomas

Muscle-Invasive and Metastatic Bladder Cancer

Primary Urethral Carcinoma

Prostate Cancer

Renal Cell Carcinoma

Testicular Cancer

Penile Cancer

**Management of Non-Neurogenic Male Lower Urinary Tract Symptoms (LUTS),
incl. benign prostatic obstruction (BPO)**

Male Sexual Dysfunction: Erectile dysfunction and premature ejaculation

Priapism

Penile Curvature

Male Infertility

Male Hypogonadism

Urological Infections

Urinary Incontinence

Neuro-Urology

Urolithiasis

Paediatric Urology

Urological Trauma

Chronic Pelvic Pain

Reporting complications

EAU Standardised Medical Terminology for Urologic Imaging: A Taxonomic Approach

Abbreviations

Guidelines on Non-muscle-invasive **Bladder Cancer** (Ta, T1 and CIS)

M. Babjuk (Chair), A. Böhle, M. Burger, E. Compérat,
E. Kaasinen, J. Palou, M. Rouprêt, B.W.G. van Rhijn, S. Shariat,
R. Sylvester, R. Zigeuner

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1. INTRODUCTION

1.1 Aims and scope

This overview represents the updated European Association of Urology (EAU) guidelines for Non-muscle-invasive Bladder Cancer (NMIBC) Ta, T1 and CIS. The information presented is limited to urothelial carcinoma, unless specified otherwise. The aim is to provide practical guidance on the clinical management of NMIBC with a focus on clinical presentation and recommendations.

Separate EAU guidelines documents are available addressing upper tract urothelial carcinomas (UTUCs) [1], muscle-invasive and metastatic bladder cancer (MIBC) [2], and primary urethral carcinomas [3].

1.2 Panel composition

The EAU Guidelines Panel on NMIBC consists of an international multidisciplinary group of clinicians, including a pathologist and a statistician. Members of this panel have been selected based on their expertise and to represent the professionals treating patients suspected of harbouring bladder cancer.

All experts involved in the production of this document have submitted potential conflict of interest statements.

1.3 Available publications

A quick reference document (Pocket guidelines) is available, both in print and in a number of versions for mobile devices, presenting the main findings of the NMIBC Guidelines. These are abridged versions which may require consultation together with the full text versions. Several scientific publications are available, as are a number of translations of all versions of the EAU NMIBC Guidelines. All documents can be accessed through the EAU website Uroweb: <http://www.uroweb.org/guidelines/online-guidelines/>.

1.4 Publication history and summary of changes

1.4.1 Publication history

The first EAU Guidelines on Bladder Cancer were published in 2000. This 2015 MIBC guidelines document presents a limited update of the 2014 full text document.

1.4.2 Summary of changes

Key changes for this 2015 print:

- The literature for the complete document has been assessed and updated, whenever relevant.
- A new section on resection techniques has been added, also expanding on the significance of biopsy for bladder cancer pathology.
- The sections on the role of imaging for initial diagnosis and follow-up have been updated.
- The sections on stratification of patients into risk groups and high-risk disease have been enlarged.
- A new section on Bacillus Calmette-Guérin (BCG) is included and the section on intravesical BCG and immunotherapy schedule has been expanded in this 2015 version of the NMIBC Guidelines.

Recommendations have been rephrased and added to throughout the current document, not resulting in a change in the grade of recommendation (GR). New recommendations have been included in sections:

5.14 Guidelines for TURB and/or biopsies, tumour classification and pathology report

	GR
Avoid cauterization as much as possible during TURB to avoid tissue deterioration.	C
In patients with positive cytology, but negative cystoscopy, exclude a UTUC, CIS in the bladder (random biopsies or PDD targeted biopsies) and tumour in prostatic urethra (prostatic urethra biopsy).	C
If indicated, perform a second TURB within 2-6 weeks after initial resection. It should include resection of the primary tumour site.	C
Classification and pathological report	
Do not use the term "Superficial BC".	A
In difficult cases, consider an additional review by an experienced genitourinary pathologist.	B

CIS = carcinoma in situ; PDD = photodynamic diagnosis; TURB = transurethral resection of the bladder.

6.3.1 Recommendations for stratification of NMIBC

	GR
In patients treated with BCG, use CUETO risk tables for individual prediction of the risk of tumour recurrence and progression.	B

7.5 Recommendations for adjuvant therapy in Ta, T1 tumours and for therapy of CIS

	GR
In patients with intermediate-risk tumours, one immediate instillation of chemotherapy should be followed by 1-year full-dose BCG treatment, or by further instillations of chemotherapy for a maximum of 1 year. The final choice should reflect the individual patient's risk of recurrence and progression as well as the efficacy and side effects of each treatment modality.	A
In patients with high-risk tumours, full-dose intravesical BCG for 1-3 years is indicated. The additional beneficial effect of the second and third years of maintenance should be weighed against its added costs and inconvenience.	A
Intravesical chemotherapy	
Give clear instructions to the nursing staff to control the free flow of the bladder catheter at the end of the immediate instillation.	C

8.1 Guidelines for follow-up in patients after TURB of NMIBC

	GR
Consider R-biopsies or biopsies with PDD after intravesical treatment (at 3 or 6 months) in patients with CIS.	C

2. METHODS

2.1 Data Identification

For the current update, all articles published in 2014 and 2015 on NMIBC were considered. A systematic literature search for each section of the NMIBC Guidelines was performed by the Panel members. For identification of original and review articles, Medline, Web of Science, and Embase databases were used. These literature searches focused on identification of all level 1 scientific papers (randomized controlled trials [RCTs], systematic reviews [SRs], and meta-analyses of RCTs).

In this 2015 EAU Guidelines compilation, all standard information on levels of evidence (LE) and grading of recommendations (GR) has been taken out of the individual guidelines topics for the sake of brevity. This information is included in the introductory section of this print.

2.2 Review

This document was subjected to double-blind peer review prior to publication.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Bladder cancer (BC) is the 11th most commonly diagnosed cancer in the world [4]. The worldwide age-standardised incidence rate (per 100,000 person-years) is 8.9 for men and 2.2 for women (2008 data) [4]. In the European Union (EU), the age-standardised incidence rate is 27 for men and six for women [4]. In Europe, the highest age-standardised incidence rate has been reported in Spain (41.5 in men and 4.8 in women) and the lowest in Finland (18.1 in men and 4.3 in women) [4].

Worldwide, BC is the 14th leading cause of cancer deaths, age-standardised mortality rate (per 100,000 person-years) was 3.3 for men versus 0.9 for women in 2008 [4]. In the EU, the age-standardised mortality rate was 8 for men and 3 for women, respectively [4].

BC incidence and mortality rates vary across the countries due to differences in risk factors, detection and diagnostic practices, and availability of treatments. The variations are however partly caused by the different methodology and quality of data collection [5, 6].

The incidence and mortality of BC has decreased in some registries, possibly reflecting the decreased impact of causative agents [6, 7].

Approximately 75% of patients with BC present with a disease confined to the mucosa (stage Ta, CIS) or submucosa (stage T1). They have a high prevalence due to long-term survival in many cases and lower risk of cancer specific mortality compared to T2-4 tumours [5, 8].

3.2 Aetiology

Tobacco smoking is the most important risk factor for BC, accounting for approximately 50% of cases [5, 9-11] (LE: 3). Tobacco smoke contains aromatic amines and polycyclic aromatic hydrocarbons, which are renally excreted.

Occupational exposure to aromatic amines, polycyclic aromatic hydrocarbons and chlorinated hydrocarbons is the second most important risk factor for BC, accounting for about 10% of all cases. This type of occupational exposure occurs mainly in industrial plants processing paint, dye, metal and petroleum products [5, 12-14]. In developed industrial settings, these risks have been reduced by work safety guidelines so that chemical workers no longer have a higher incidence of BC compared to the general population [15].

Genetic predisposition has an influence on the incidence of BC, especially via its impact on susceptibility to other risk factors [5, 16].

Although the significance of the amount of fluid intake is uncertain, the chlorination of drinking water and subsequent levels of trihalomethanes are potentially carcinogenic, while exposure to arsenic in drinking water increases risk [5, 8, 17] (LE: 3). The association between personal hair dye use and risk remains uncertain; an increased risk has been suggested in users of permanent hair dyes with an NAT2 slow acetylation phenotype [18, 19].

Exposure to ionizing radiation is connected with increased risk; weak association was also suggested for cyclophosphamide and pioglitazone [5, 8] (LE: 3). Schistosomiasis, a chronic endemic cystitis, based on recurrent infection with a parasitic trematode, is also a cause of BC [5] (LE: 3).

3.3 Pathology

The information presented in text is limited to urothelial carcinoma, unless specified otherwise.

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Definition of non-muscle-invasive bladder cancer

Papillary tumours confined to the mucosa and invading the lamina propria are classified as stage Ta and T1, respectively, according to the Tumour, Node, Metastasis (TNM) classification system. Flat, high-grade tumours that are confined to the mucosa are classified as CIS (Tis). These tumours can be treated by transurethral resection of the bladder (TURB) and/or intravesical instillations and are therefore grouped under the heading of NMIBC for therapeutic purposes. However, molecular biology techniques and clinical experience have demonstrated the highly malignant potential of CIS and T1 lesions. The terms “NMIBC” and older one “superficial BC” are therefore suboptimal descriptions.

4.2 Tumour, Node, Metastasis Classification (TNM)

The 2002 TNM classification approved by the Union International Contre le Cancer (UICC) was updated in 2009 (7th version), but it had no changes for bladder tumours (Table 4.1) [20].

Table 4.1: 2009 TNM classification of urinary bladder cancer

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma <i>in situ</i> : 'flat tumour'
T1	Tumour invades subepithelial connective tissue Tumour invades muscle
T2	T2a Tumour invades superficial muscle (inner half) T2b Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue T3a Microscopically T3b Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall T4a Tumour invades prostate, uterus or vagina T4b Tumour invades pelvic wall or abdominal wall
N - Lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N2	Metastasis in multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N3	Metastasis in common iliac lymph node(s)
M - Distant metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

4.3 Histological grading of non-muscle-invasive bladder urothelial carcinomas

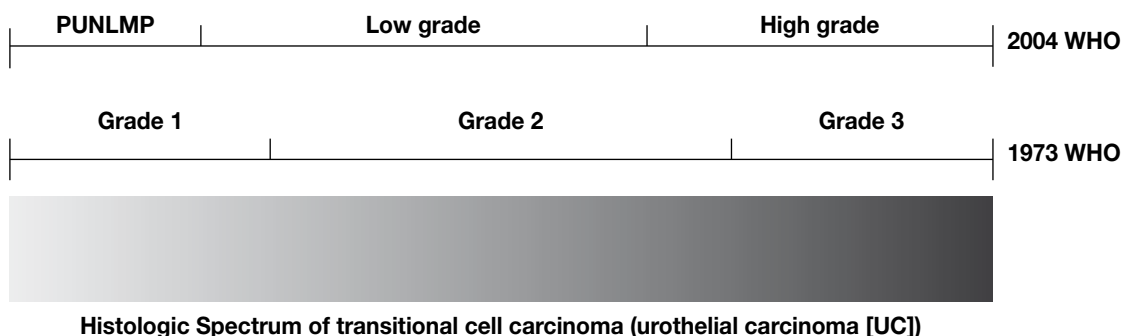
In 2004, the World Health Organization (WHO) and the International Society of Urological Pathology (ISUP) published a new histological classification of urothelial carcinomas which provides a different patient stratification between individual categories compared to the older 1973 WHO classification [21, 22] (Tables 4.2, 4.3, Fig 4.1). A website (www.pathology.jhu.edu/bladder) that illustrates examples of the various grades has been developed to further improve accuracy in using the system.

Table 4.2: WHO grading in 1973 and in 2004 [21, 22]

1973 WHO grading <i>Urothelial papilloma</i> Grade 1: well differentiated Grade 2: moderately differentiated Grade 3: poorly differentiated
2004 WHO grading system [papillary lesions] <i>Urothelial papilloma (completely benign lesion)</i> Papillary urothelial neoplasm of low malignant potential (PUNLMP) Low-grade (LG) papillary urothelial carcinoma High-grade (HG) papillary urothelial carcinoma

The prognostic value of both WHO 1973 and 2004 grading systems has been confirmed. Attempts to demonstrate better prognostic value of one of them, however, have yielded controversial results [23-28] (LE: 2a). Moreover the WHO 2004 system has not been fully incorporated into prognostic models yet. Most clinical trials published to date on Ta, T1 bladder tumours have been performed using the 1973 WHO classification, and the following guidelines are therefore based on this version.

Figure 4.1: Stratification of tumours according to grade in the WHO 1973 and 2004 classifications [23]*



**1973 WHO Grade 1 carcinomas have been reassigned to papillary urothelial neoplasm of low malignant potential (PUNLMP) and low-grade (LG) carcinomas in 2004 WHO classification, and Grade 2 carcinomas to LG and high-grade (HG) carcinomas. All 1973 WHO Grade 3 carcinomas have been reassigned to HG carcinomas (Reproduced with permission from Elsevier).*

PUNLMP = papillary urothelial neoplasm of low malignant potential; WHO = World Health Organization.

4.4 CIS and its classification

Carcinoma *in situ* (CIS) is a flat, high-grade, non-invasive urothelial carcinoma. It can be missed at cystoscopy or be considered as an inflammatory lesion if it is not biopsied. CIS is often multifocal and can occur in the bladder, but also in the upper urinary tract, prostatic ducts, and prostatic urethra [29].

Classification of CIS into clinical type [30]:

- Primary: isolated CIS with no previous or concurrent papillary tumours and no previous CIS;
- Secondary: CIS detected during follow-up of patients with a previous tumour that was not CIS;
- Concurrent: CIS in the presence of any other urothelial tumour in the bladder.

Table 4.3: WHO 2004 grading system

WHO 2004 grading system (flat lesions):
• Hyperplasia (flat lesion without atypia or papillary aspects)
• Reactive atypia (flat lesion with atypia)
• Atypia of unknown significance
• Urothelial dysplasia
• Urothelial CIS is always high-grade

4.5 Inter- and intra-observer variability in staging and grading

There is significant variability among pathologists for diagnosis of CIS, for which agreement is achieved in only 70-78% of cases [31, 32] (LE: 2a). There is also interobserver variability in the classification of stage T1 versus Ta tumours and tumour grading in both 1997 and 2004 classifications. The general conformity in staging and grading is between 50% and 60% [27, 31-36] (LE: 2a). The published comparisons have not clearly confirmed that the WHO 2004 classification has better reproducibility than the 1973 classification [24, 27].

4.6 Further promising pathology parameters

Some novel parameters based on pathological investigation of resected tissue have been considered for subclassification and prognostic purposes.

In T1 tumours, the depth and extent of invasion into the lamina propria (T1 substaging) can be evaluated. The prognostic value of this evaluation has been demonstrated by some retrospective cohort studies [37-40] (LE: 3); nevertheless, it is not recommended in the WHO classification.

According to a meta-analysis of retrospective trials, the presence of lymphovascular invasion (LVI) in TURB specimens was connected with increased risk of pathological upstaging [41] (LE: 3). Lymphovascular invasion has been reported as an unfavourable prognostic factor in T1 tumours [42] (LE: 3).

Some variants of urothelial carcinoma (micropapillary, plasmocytoid, nested, sarcomatoid, squamous and adeno variants of urothelial carcinoma etc.), have a poor prognosis [43-47] (LE: 3).

Molecular markers, particularly FGFR3 mutation status, are promising but need further evaluation [25, 40, 48-50].

4.7 Recommendations

The recommendations for BC classification can be found in section 5.14.

5. DIAGNOSIS

5.1 Patient history

A comprehensive patient history is mandatory.

5.2 Signs and symptoms

Haematuria is the most common finding in NMIBC. Ta, T1 tumours do not cause bladder pain and rarely present with lower urinary tract symptoms. CIS might be suspected in patients who do complain of these symptoms, particularly if they are refractory to symptomatic treatment.

5.3 Physical examination

Physical examination does not reveal NMIBC.

5.4 Imaging

5.4.1 Computed tomography urography and intravenous urography

Computed tomography (CT) urography is used to detect papillary tumours in the urinary tract, which can be seen as filling defects or indicated by hydronephrosis.

Intravenous urography (IVU) can be an alternative if CT is not available [51] (LE: 3), but particularly in muscle-invasive tumours of the bladder and in UTUCs, CT urography gives more information than IVU does (including status of lymph nodes and neighbouring organs).

The necessity to perform a baseline CT urography or IVU once a bladder tumour has been detected is questioned because of the low incidence of significant findings obtained [52-54] (LE: 2a). The incidence of UTUCs is low (1.8%), but increases to 7.5% in tumours located in the trigone [53] (LE: 2b). The risk of UTUC during follow-up increases in patients with multiple- and high-risk tumours [55] (LE: 3).

5.4.2 Ultrasound (US)

Transabdominal US permits characterization of renal masses, detection of hydronephrosis, and visualization of intraluminal masses in the bladder. It is as accurate as IVU for diagnosis of UTUC [52] (LE: 3). Ultrasound is therefore a useful tool for detection of obstruction in patients with haematuria. However, it cannot exclude the presence of UTUC and cannot replace CT urography.

The diagnosis of CIS cannot be made with imaging methods (CT urography, IVU or US) (LE: 4).

5.5 Urinary cytology

The examination of voided urine or bladder-washing specimens for exfoliated cancer cells has high sensitivity in G3 tumours, but low sensitivity in G1 tumours. The sensitivity in CIS detection is 28-100% [56] (LE: 2b). Cytology is useful, particularly as an adjunct to cystoscopy, when a G3 malignancy or CIS is present. Positive voided urinary cytology can indicate an urothelial tumour anywhere in the urinary tract; negative cytology, however, does not exclude the presence of a tumour.

Cytological interpretation is user-dependent [57]. Evaluation can be hampered by low cellular yield, urinary tract infections, stones, or intravesical instillations, but in experienced hands specificity exceeds 90% [58] (LE: 2b). Urine collection should respect recommendations (see Section 5.9). One cytospin slide from the sample is usually sufficient [59]. In patients with suspect cytology it is reasonable to repeat the investigation [60] (LE: 3).

5.6 Urinary molecular marker tests

Driven by the low sensitivity of urine cytology, numerous urinary tests were developed [58, 61-68]. None of these markers have been accepted for diagnosis or follow-up in routine urology or in guidelines. Some urine tests that have been evaluated in several laboratories/centres and with sufficient numbers of patients are listed in Table 5.1.

The following conclusions can be drawn regarding the existing tests.

- Sensitivity is usually higher and at the cost of lower specificity compared to urine cytology [58, 62-72] (LE: 3).
- Benign conditions and BCG influence many urinary marker tests [58, 61-68] (LE: 3).
- Sensitivity and specificity of a urinary marker test depend on the clinical context of the patient

- (screening, primary detection, follow-up [high risk, low-/intermediate-risk]) [62-65] (LE: 3).
- Patient selection explains the wide range in performance of the markers listed in Table 5.1.
- Unlike other urine tests, false-positive results of UroVysion and microsatellite analysis can be attributed to occult disease and thus identify patients likely to experience early recurrence [73-77] (LE: 3).

Table 5.1: Summary of main urinary markers

Markers (or test specifications)	Overall sensitivity (%)	Overall specificity (%)	Sensitivity for high-grade tumours (%)	Point-of-care test	LE
UroVysion (FISH)	30-86	63-95	66-70	No	2b
Microsatellite analysis	58-92	73-100	90-92	No	1b
Immunocyt/uCyt +	52-100	63-79	62-92	No	2a
Nuclear matrix Protein 22	47-100	55-98	75-92	Yes	2a
BTA stat	29-83	56-86	62-91	Yes	3
BTA TRAK	53-91	28-83	74-77	No	3
Cytokeratins	12-88	73-95	33-100	No	3

BTA = bladder tumour antigen; LE = level of evidence.

5.7 Potential application of urinary cytology and markers

The following objectives of urinary cytology or molecular tests must be considered.

5.7.1 Screening of the population at risk of BC

The application of haematuria dipstick, NMP22 or UroVysion in BC screening in high-risk populations has been reported [78, 79]. The low incidence of BC in the general population and the short lead-time impair feasibility and cost-effectiveness [65, 77-79]. Routine application of screening is not recommended.

5.7.2 Exploration of patients after haematuria or other symptoms suggestive of BC (primary detection)

It is generally accepted that none of the tests can replace cystoscopy. However, urinary cytology or markers can be used as an adjunct to cystoscopy to detect invisible tumours, particularly CIS. In this setting, sensitivity for high-grade tumours and specificity are particularly important. Urinary cytology is highly specific, but urinary markers lack this high specificity and are not recommended for primary detection.

5.7.3 Surveillance of NMIBC

Research has been carried out into the usefulness of urinary cytology versus markers in the follow-up of NMIBC [65, 67, 80, 81].

5.7.3.1 Follow-up of high-risk NMIBC

High-risk tumours should be detected early in follow-up, and the percentage of tumours missed should be as low as possible. Therefore, the best surveillance strategy for these patients will continue to include frequent cystoscopy and cytology.

5.7.3.2 Follow-up of low-/intermediate-risk NMIBC

To reduce the number of cystoscopy procedures, urinary markers should be able to detect recurrence before the tumours are large and numerous. The limitation of urinary cytology is its low sensitivity for low-grade recurrences. Several urinary markers are better, but still do not detect half of the low-grade tumours identified by cystoscopy [62, 65] (LE: 3).

According to current knowledge, no urinary marker can replace cystoscopy during follow-up or help to lower cystoscopic frequency in a routine fashion. One prospective randomized study confirmed that knowledge of positive test results (microsatellite analysis) can improve the quality of follow-up cystoscopy [82] (LE: 1b). It supports the adjunctive role of a non-invasive urine test performed before follow-up cystoscopy [82].

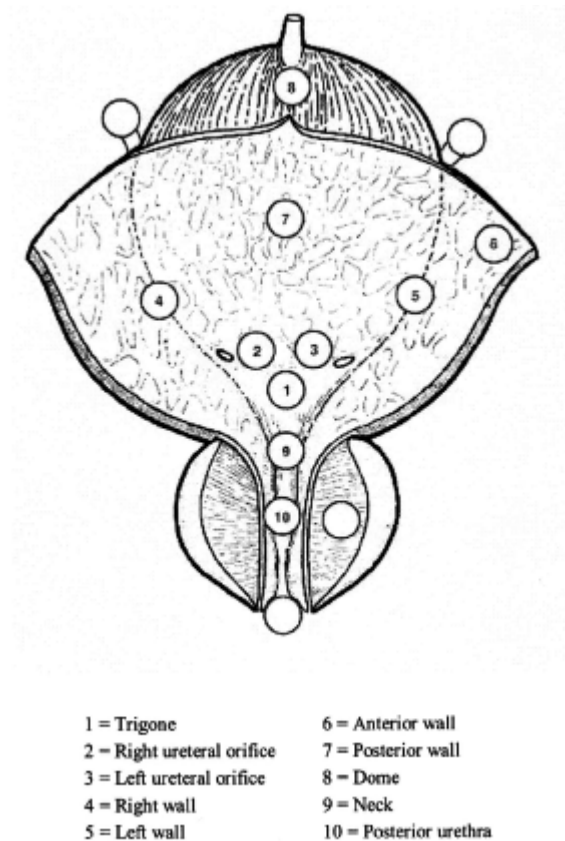
5.8 Cystoscopy

The diagnosis of papillary BC ultimately depends on cystoscopic examination of the bladder and histological evaluation of the resected tissue. CIS is diagnosed by a combination of cystoscopy, urine cytology, and

histological evaluation of multiple bladder biopsies [83].

Cystoscopy is initially performed in the office. A flexible instrument with topical intra-urethral anaesthetic lubricant instillation results in better compliance compared to a rigid instrument, especially in men [84].

Figure 5.1: Bladder diagram



5.9 Guidelines for the primary assessment of NMIBC

	GR
Patient history should be taken.	A
Renal and bladder US may be used during the initial work-up in patients with haematuria.	C
At the time of the initial diagnosis of NMIBC, CT urography (or IVU) should be performed only in selected cases (e.g., tumours located in the trigone, multiple- or high-risk tumours).	B
Cystoscopy is recommended in all patients with symptoms suggestive of BC. It cannot be replaced by cytology or by any other non-invasive test.	A
Cystoscopy should describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities. A bladder diagram is recommended (Figure 5.1).	C
Voided urine cytology is advocated to predict high-grade tumour before TURB.	C
Cytology should be performed on fresh urine with adequate fixation. Morning urine is not suitable because of the frequent presence of cytolysis.	C

BC = bladder cancer; CT = computed tomography; GR = grade of recommendation; IVU = intravenous urography; US = ultrasound; NMIBC = non-muscle invasive bladder cancer; TURB = transurethral resection of the bladder.

5.10 Transurethral resection of Ta, T1 bladder tumours

5.10.1 Strategy of the procedure

The goal of TURB in Ta,T1 BC is to make the correct diagnosis and completely remove all visible lesions. It is a crucial procedure in the diagnosis and treatment of BC. TURB should be performed systematically in individual steps (see Section 5.14). The strategy of resection depends on the size of the lesion (see Section 5.14). Separate resection of larger tumours provides good information about the vertical and horizontal extent of the tumour and helps to improve resection completeness [85, 86] (LE: 3).

Complete and correct TURB is essential to achieve a good prognosis [87]. It has been confirmed that the absence of detrusor muscle in the specimen is associated with a significantly higher risk of residual disease, early recurrence and tumour understaging [86, 88] (LE: 2b). It has been shown that surgical experience can improve TURB results, which supports the role of teaching programmes [89].

5.10.2 **Office-based fulguration**

In patients with a history of small, Ta LG/G1 tumours, fulguration of small papillary recurrences on an outpatient basis can reduce the therapeutic burden and can be a treatment option [90] (LE: 3).

5.10.3 **New resection techniques**

Compared to monopolar resection, the bipolar electrocautery system has been introduced to reduce the risk of complications (e.g., bladder perforation due to obturator nerve stimulation) and produce better specimens for the pathologist [91] (LE: 3). As yet, the results are controversial [92-94].

5.10.4 **Bladder and prostatic urethral biopsies**

Carcinoma *in situ* can present as a velvet-like, reddish area indistinguishable from inflammation, or it may not be visible at all. For this reason, the strategy of biopsies from abnormal urothelium and biopsies from normal-looking mucosa (random/mapping biopsies) was recommended (see Section 5.14). The indication of random biopsies reflects the fact, that the likelihood of detecting CIS, especially in low-risk tumours, is extremely low (< 2%) [95] (LE: 2a). The risk increases in patients with high-risk tumours and with positive cytology [96].

If equipment is available, photodynamic diagnosis (PDD) is a useful tool to target the biopsy (see Section 5.11.1).

Involvement of the prostatic urethra and ducts in men with NMIBC has been reported. Palou et al. [97] showed that in 128 men with T1G3 BC, the incidence of CIS in the prostatic urethra was 11.7% (LE: 2b). The risk of prostatic urethra- or duct involvement is higher if the tumour is located on the trigone or bladder neck, in the presence of bladder CIS and multiple tumours [98] (LE: 3). Based on this observation a biopsy from the prostatic urethra is necessary in some cases. A recommendation is included in Section 5.14 [97, 99].

5.11 **New methods of tumour visualization**

As a standard procedure, cystoscopy and TURB are performed using white light. However, the use of white light can lead to missing lesions that are present but not visible, which is why new technologies are being developed.

5.11.1 **Photodynamic diagnosis (fluorescence cystoscopy)**

Photodynamic diagnosis (PDD) is performed using violet light after intravesical instillation of 5-aminolaevulinic acid (ALA) or hexaminolaevulinic acid (HAL). It has been confirmed that fluorescence-guided biopsy and resection are more sensitive than conventional procedures for detection of malignant tumours, particularly for CIS [100, 101] (LE: 2a). In a systematic review and meta-analysis, PDD had higher sensitivity than white-light endoscopy in the pooled estimates for analyses at both the patient-level (92% versus 71%) and biopsy-level (93% versus 65%) [101].

PDD had lower specificity than white-light endoscopy (63% vs. 81%) [101]. False-positivity can be induced by inflammation or recent TURB and during the first 3 months after BCG instillation [102, 103] (LE: 3). Prospective randomized studies evaluating the impact of ALA fluorescence-guided (FC) TURB on disease recurrence rate provided controversial results [101, 104, 105].

The beneficial effect of HAL FC on recurrence rate in patients with TURB was confirmed by a multicentre, prospective, randomized trial and by raw-data based meta-analysis of controlled trials. A meta-analysis reported in HAL arms an increase in detection of tumour lesions across all risk groups and an absolute reduction of < 10% in recurrence rates within 12 months [106] (LE: 1a). The beneficial effect of HAL FC on recurrence rate in patients with TURB and early intravesical instillation of chemotherapy was not confirmed by a prospective randomized trial [107]. The value of FC for improvement of outcome in relation to progression rate, survival and clinical management remains to be demonstrated.

5.11.2 **Narrow-band imaging**

In narrow-band imaging (NBI), the contrast between normal urothelium and hyper-vascular cancer tissue is enhanced. Initial studies have demonstrated improved cancer detection by NBI-guided biopsies and resection [108, 109] (LE: 3). The suggested reduction of recurrence rate if NBI is used during TURB has not been fully confirmed yet [110].

5.12 **Second resection**

The significant risk of residual tumour after initial TURB of Ta, T1 lesions has been demonstrated [87] (LE: 2a).

Persistent disease after resection of T1 tumours has been observed in 33-55% of patients, and after resection of TaG3 tumour in 41.4% [111-115].

Moreover, the tumour is often understaged by initial resection. The likelihood that muscle-invasive disease is detected by second resection of initially T1 tumour ranges from 4-25%, and it increases to 45% if there was no muscle in the initial resection [86]. This risk has increased up to 50% in some radical cystectomy (RC) series, although these studies only enrolled selected patients [116-118] (LE: 2a). Treatment of a Ta, T1 high-grade tumour and a T2 tumour is completely different; correct staging is therefore important.

It has been demonstrated that a second TURB can increase recurrence-free survival [111, 112] (LE: 2a), improve outcomes after BCG treatment [119] (LE: 3) and provide prognostic information [116, 120] (LE: 3)

Based on these arguments, a second TURB is recommended in selected cases (see Section 5.14).

5.13 Pathology report

Pathology investigation of the specimen obtained by TURB and biopsies is an essential step in the diagnosis and treatment decision-making process for BC. Close co-operation between urologists and pathologists is recommended.

A high quality of resected and submitted tissue is essential for correct pathological assessment. The presence of sufficient muscle is necessary for the correct assignment of T category. To achieve all required information, the specimen collection, handling and evaluation should respect the recommendations provided below (section 5.14) [121].

5.14 Guidelines for TURB and/or biopsies, tumour classification and pathology report

	GR
Perform TURB systematically in individual steps: <ul style="list-style-type: none"> • bimanual palpation under anaesthesia; • insertion of the resectoscope, under visual control with inspection of the whole urethra; • inspection of the whole urothelial lining of the bladder; • biopsy from prostatic urethra (if indicated); • cold-cup bladder biopsies (if indicated); • resection of the tumour; • surgical report formulation; • precise description of the specimen for pathology evaluation. 	C
Performance of individual steps:	
Perform resection in one piece for small papillary tumours (< 1 cm), including a part from the underlying bladder wall.	B
Perform resection in fractions including the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle, and the edges of the resection area for tumours > 1 cm in diameter.	B
Avoid cauterization as much as possible during TURB to avoid tissue deterioration.	C
Take biopsies from abnormal-looking urothelium.	
Biopsies from normal-looking mucosa (trigone, bladder dome, and right, left, anterior and posterior bladder walls) are recommended when cytology is positive or when high-risk exophytic tumour is expected (non-papillary appearance).	C
Take biopsy of the prostatic urethra in cases of bladder neck tumour, when bladder CIS is present or suspected, when there is positive cytology without evidence of tumour in the bladder, or when abnormalities of the prostatic urethra are visible. If biopsy is not performed during the initial procedure, it should be completed at the time of the second resection.	C
Take the biopsy from abnormal areas in the prostatic urethra and from the precollicular area (between the 5 and 7 o'clock position) using a resection loop. In primary non-muscle-invasive tumours when stromal invasion is not suspected, the cold-cup biopsy with forceps can be used.	C
If equipment is available, use fluorescence-guided (PDD) biopsy instead of random biopsies when bladder CIS or high-grade tumour is suspected (e.g., positive cytology, recurrent tumour with previous history of a high-grade lesion).	B
Refer the specimens from different biopsies and resection fractions to the pathologist in separate containers and label them separately.	C
TURB protocol must describe tumour appearance, all steps of the procedure, as well as the extent and completeness of resection.	C
In patients with positive cytology, but negative cystoscopy, exclude a UTUC, CIS in the bladder (random biopsies or PDD targeted biopsies) and tumour in the prostatic urethra (prostatic urethra biopsy).	C

Perform a second TURB in the following situations: <ul style="list-style-type: none"> • after incomplete initial TURB; • if there is no muscle in the specimen after initial resection, with the exception of TaG1 tumours and primary CIS; • in all T1 tumours; • in all G3 tumours, except primary CIS. 	A
If indicated, perform a second TURB within 2-6 weeks after initial resection. It should include resection of the primary tumour site.	C
Classification and pathological report	
For classification of the depth of tumour invasion (staging) use the 2009 TNM system.	A
For histological classification, use both the 1973 and 2004 WHO grading.	A
Do not use the term "Superficial BC".	A
Whenever using the terminology NMIBC, in individual cases, mention the tumour stage and grade.	A
The pathological report should specify tumour location, tumour grade, depth of tumour invasion, presence of CIS, and whether the detrusor muscle is present in the specimen.	A
The pathological report should specify the presence of LVI or unusual (variant) histology.	C
In difficult cases, consider an additional review by an experienced genitourinary pathologist.	B

BC = bladder cancer; CIS = carcinoma in situ; CT = computed tomography; LVI = lymphovascular invasion; PDD = photodynamic diagnosis; TNM = Tumour, Node, Metastasis; TURB = transurethral resection of the bladder; WHO = World Health Organisation.

6. PREDICTING DISEASE RECURRENCE AND PROGRESSION

6.1 Ta, T1 tumours

In order to predict separately the short- and long-term risks of disease recurrence and progression in individual patients, the European Organization for Research and Treatment of Cancer (EORTC) Genito-Urinary Cancer Group (GUCG) has developed a scoring system and risk tables [122]. The basis for these tables are individual patient data for 2,596 patients diagnosed with Ta, T1 tumours, who were randomized into seven EORTC-GUCG trials. Patients with CIS alone were not included. Seventy-eight percent of patients received intravesical treatment, mostly chemotherapy. However, they did not undergo a second TURB or receive maintenance BCG.

The scoring system is based on the six most significant clinical and pathological factors which are shown in Table 6.1.

It also illustrates the weights applied to various factors for calculating the total scores for recurrence and progression. Table 6.2 shows the total scores stratified, as in the original article [122], into four categories that reflect various probabilities of recurrence and progression at 1 and 5 years (LE: 2a).

Table 6.1: Weighting used to calculate disease recurrence and progression scores

Factor	Recurrence	Progression
Number of tumours		
Single	0	0
2-7	3	3
≥ 8	6	3
Tumour diameter		
< 3 cm	0	0
≥ 3	3	3
Prior recurrence rate		
Primary	0	0
≤ 1 recurrence/year	2	2
> 1 recurrence/year	4	2
Category		
Ta	0	0
T1	1	4
Concurrent CIS		
No	0	0
Yes	1	6
Grade		
G1	0	0
G2	1	0
G3	2	5
Total Score	0-17	0-23

Table 6.2: Probability of recurrence and disease progression according to total score

Recurrence score	Probability of recurrence at 1 year		Probability of recurrence at 5 years	
	%	(95% CI)	%	(95% CI)
0	15	(10-19)	31	(24-37)
1-4	24	(21-26)	46	(42-49)
5-9	38	(35-41)	62	(58-65)
10-17	61	(55-67)	78	(73-84)

Progression score	Probability of progression at 1 year		Probability of progression at 5 years	
	%	(95% CI)	%	(95% CI)
0	0.2	(0-0.7)	0.8	(0-1.7)
2-6	1	(0.4-1.6)	6	(5-8)
7-13	5	(4-7)	17	(14-20)
14-23	17	(10-24)	45	(35-55)

NB: Electronic calculators for Tables 6.1 and 6.2, which have been updated for the iPhone, iPad and Android phones and tablets, are available at <http://www.eortc.be/tools/bladdercalculator/>.

A scoring model for BCG-treated patients that predicts the short- and long-term risks of recurrence and progression has been published by the Club Urológico Español de Tratamiento Oncológico (CUETO) (Spanish Urological Oncology Group). It is based on an analysis of 1,062 patients from four CUETO trials that compared different intravesical BCG treatments. Patients received 12 instillations over 5-6 months. No immediate postoperative instillation or second TURB was performed in these patients. The scoring system is based on the evaluation of seven prognostic factors:

- sex;
- age;
- prior recurrence status;
- number of tumours;
- T category;
- associated CIS;
- tumour grade.

Using these tables, the calculated risk of recurrence is lower than that obtained by the EORTC tables. For progression, probability is lower only in high-risk patients [123] (LE: 2a). The lower risks in the CUETO tables may be attributed to using BCG, which is a more effective instillation therapy. The CUETO risk calculator is available at: <http://www.aeu.es/Cueto.html>.

The prognostic value of the EORTC scoring system has been confirmed by data from the CUETO patients treated with BCG and by long-term follow-up in an independent patient population [124, 125] (LE: 2a).

Further prognostic factors have been described in selected patient populations:

- In T1G3 tumours important prognostic factors were female sex and CIS in the prostatic urethra in patients treated with an induction course of BCG, and age, tumour size and concurrent CIS in BCG treated patients (62% with induction course only) [97, 126] (LE: 2b).
- Attention must be given to patients with T1G3 tumours in bladder (pseudo) diverticulum because of an absence of muscle layer in the diverticular wall [127] (LE: 3).
- In patients with high-risk disease, the tumour stage at the time of the 2nd TURB is an unfavourable prognostic factor [116, 120] (LE: 3)
- In patients with T1G2 tumours treated with TURB, recurrence at 3 months was the most important predictor of progression [128] (LE: 2b).
- The prognostic value of pathological factors has been discussed elsewhere (see Section 4.6). More research is needed to determine the role of molecular markers in improving the predictive accuracy of currently existing risk tables [124, 129].

6.2 Carcinoma *in situ*

Without any treatment, approximately 54% of patients with CIS progress to muscle-invasive disease [130] (LE: 3). Unfortunately, there are no reliable prognostic factors that can be used to predict the course of the disease. Publications are based on retrospective analyses of small series of patients and conclusions are not homogeneous. Some studies have reported a worse prognosis in concurrent CIS and T1 tumours compared to primary CIS [131, 132], in extended CIS [133], and in CIS in the prostatic urethra [97] (LE: 3).

The response to intravesical treatment with BCG or chemotherapy is an important prognostic factor for subsequent progression and death caused by BC [123-125, 128]. Approximately 10-20% of complete responders eventually progress to muscle-invasive disease, compared with 66% of non-responders [134, 135] (LE: 2a).

6.3 Patients' stratification into risk groups

To facilitate treatment recommendations it is important to categorise patients into risk groups. Based on available prognostic factors and in particular data from the EORTC risk tables, the Guidelines Panel recommends stratification of patients into three risk groups. Table 6.3 provides a definition of these risk groups, which takes into account the EORTC risk tables' probabilities of recurrence and especially progression.

Table 6.3: Risk group stratification

Risk group stratification	Characteristics
Low-risk tumours	Primary, solitary, Ta, G1* (PUNLMP, LG), < 3 cm, no CIS
Intermediate-risk tumours	All tumours not defined in the two adjacent categories (between the category of low- and high-risk).
High-risk tumours	Any of the following: <ul style="list-style-type: none"> • T1 tumour • G3** (HG) tumour • CIS • Multiple and recurrent and large (> 3 cm) Ta G1G2 tumours (all conditions must be presented in this point)*

Substratification of high-risk tumours for clinical purposes can be seen in Table 7.2.

**low grade is a mixture of G1 and G2*

*** high grade is a mixture of some G2 and all G3 (see Figure 4.1)*

CIS = carcinoma in situ; HG = high-grade; LG = low-grade.

6.3.1 Recommendations for stratification of NMIBC

	GR
Stratify patients into three risk groups according to Table 6.2.	B
Apply the EORTC risk tables and calculator for individual prediction of the risk of tumour recurrence and progression in different intervals after TURB.	B
In patients treated with BCG, use the CUETO risk tables for individual prediction of the risk of tumour recurrence and progression.	B

BCG = *Bacillus Calmette-Guérin*; CUETO = *Club Urológico Español de Tratamiento Oncológico*; GR = grade of recommendation; EORTC = *European Organization for Research and Treatment of Cancer*; TURB = *transurethral resection of the bladder*.

7. DISEASE MANAGEMENT

7.1 Counselling of smoking cessation

It has been confirmed that smoking increases the risk of tumour recurrence and progression [136, 137] (LE: 3).

While it is still controversial whether smoking cessation in bladder cancer will favourably influence the outcome of BC treatment, patients should be counselled to stop smoking due to the general risks connected with tobacco smoking [138-140, 141] (LE: 3).

7.2 Adjuvant treatment

7.2.1 Intravesical chemotherapy

Although TURB by itself can eradicate a Ta, T1 tumour completely, these tumours commonly recur and can progress to MIBC. The high variability in the 3-month recurrence rate indicates that the TURB was incomplete or provokes recurrences in a high percentage of patients [87]. It is therefore necessary to consider adjuvant therapy in all patients.

7.2.1.1 A single, immediate, post-operative intravesical instillation of chemotherapy

Immediate single instillation (SI) has been shown to act by the destruction of circulating tumour cells resulting from TURB, and by an ablative effect (chemoresection) on residual tumour cells at the resection site and on small overlooked tumours [142-145] (LE: 3).

Three large meta-analyses comprising 1,476 to 3,103 patients have consistently shown that SI after TURB significantly reduced the recurrence rate by 11.7% to 13.0% compared to TURB alone [146-148] (LE: 1a). Although none of the three meta-analyses adequately answered the question concerning which patients benefitted the most, some underpowered data from two subgroup analyses [149, 150] suggest that SI is most effective in tumour types with the lowest tendency towards recurrence, i.e., in single primary or small tumours. Mitomycin C (MMC), epirubicin, and doxorubicin have all shown a beneficial effect; no efficacy comparisons have been made [146-148] (LE: 1a).

There is evidence from one subgroup- and one combined analysis that SI might have an impact on recurrence, even when further adjuvant instillations are given [151-153] (LE: 2a). In contrast, a sufficient number of delayed repeat chemotherapy instillations can also reduce recurrence stemming from tumour implantation [151-154]. Clearly, more studies comparing immediate and delayed-start regimens are needed.

The prevention of tumour cell implantation should be initiated within the first hours after cell seeding. Within a few hours, the cells are implanted firmly and are covered by extracellular matrix [142, 155-157] (LE: 3). In all SI studies, the instillation was administered within 24 hours. To maximize the efficacy of SI, one should devise flexible practices that allow the instillation to be given as early as possible, which is in the recovery room or even in the operating theatre.

As severe complications have been reported in patients with drug extravasation [158, 159], safety measures should be maintained (see Section 7.5).

7.2.1.2 Additional adjuvant intravesical chemotherapy instillations

The need for further adjuvant intravesical therapy depends on prognosis. In low-risk patients (Tables 6.1, 6.2 and 6.3), a SI reduces the risk of recurrence and is considered to be the standard and sufficient treatment [146] (LE: 1a). For other patients, however, a SI remains an incomplete treatment because of the considerable likelihood of recurrence and/or progression (Tables 6.1, 6.2 and 6.3). It was shown that further chemotherapy instillations can improve RFS in intermediate-risk tumours [154].

A large meta-analysis of 3,703 patients from 11 randomized trials showed a highly significant

44% reduction in the odds of recurrence at one year in favour of chemotherapy over TURB alone [160]. This corresponds to an absolute difference of 13-14% in the number of patients with recurrence. Contrary to chemotherapy, two meta-analyses have demonstrated that BCG therapy may reduce the risk of tumour progression [161, 162] (LE: 1a) (see Section 8.2.1). Moreover, BCG maintenance therapy appears to be significantly better in preventing recurrences than chemotherapy [163-165] (see Section 7.2.2) (LE: 1a). However, BCG causes significantly more side effects than does chemotherapy [165] (LE: 1a).

The length and frequency of chemotherapy instillations is still controversial. A systematic review of RCTs, comparing different schedules of intravesical chemotherapy instillations, concluded that the ideal duration and intensity of the schedule remains undefined because of conflicting data [153]. The available evidence does not support treatment longer than one year (LE: 3).

7.2.1.3 Options for improving efficacy of intravesical chemotherapy

Some promising data have been presented on enhancing the efficacy of MMC using microwave-induced hyperthermia or electromotive drug administration (EMDA) in patients with high-risk tumours. The current evidence, however, is limited [166, 167] and both treatment modalities are considered to be experimental (LE: 2b).

One RCT using MMC has demonstrated that adapting urinary pH, decreasing urinary excretion, and buffering the intravesical solution reduced the recurrence rate [168] (LE: 1b). Another trial reported that a 1-hour instillation of MMC was more effective than 30 minutes instillation, but no efficacy comparisons are available for 1- and 2-hour instillations [169] (LE: 3). Another RCT using epirubicin has documented that concentration is more important than treatment duration [170] (LE: 1b). In view of these data, instructions are provided (see Section 7.5)

7.2.2 Intravesical bacillus Calmette-Guérin (BCG) immunotherapy

7.2.2.1 Efficacy of BCG

Five meta-analyses have confirmed that BCG after TURB is superior to TURB alone or TURB + chemotherapy for preventing the recurrence of NMIBC [163, 171-174] (LE: 1a). Three recent RCTs of intermediate- and high-risk tumours have compared BCG with epirubicin + interferon [175], MMC [176], or epirubicin alone [164] and have confirmed the superiority of BCG for prevention of tumour recurrence (LE: 1a). The effect is long-lasting [164, 176] and was also observed in a separate analysis of patients with intermediate-risk tumours [164].

One meta-analysis [163] has evaluated the individual data from 2,820 patients enrolled in nine RCTs that have compared MMC versus BCG. In the trials with BCG maintenance, there was a 32% reduction in the risk of recurrence for BCG compared to MMC, but a 28% increase in the risk of recurrence for patients treated with BCG in the trials without BCG maintenance.

Two meta-analyses have demonstrated that BCG therapy prevents, or at least delays, the risk of tumour progression [161, 162] (LE: 1a). A meta-analysis carried out by the EORTC-GUCG has evaluated data from 4,863 patients enrolled in 24 RCTs. Five different BCG strains were used, and in 20 of the trials, some form of BCG maintenance was used. Based on a median follow-up of 2.5 years, in 260 out of 2,658 patients (9.8%) treated with BCG, tumours progressed compared to 304 out of 2,205 (13.8%) in the control groups (TURB alone, TURB + intravesical chemotherapy, or TURB + other immunotherapy). This shows a reduction of 27% in the odds of progression with BCG maintenance treatment. The size of the reduction was similar in patients with Ta, T1 papillary tumours and in those with CIS [162]. A recent RCT with long-term observation has demonstrated significantly fewer distant metastases and better overall- and disease-specific survival in patients treated with BCG compared to epirubicin [164] (LE: 1b). On the contrary, a meta-analysis of individual patient data was not able to confirm any statistically significant difference between MMC and BCG for progression, survival and cause of death [163].

The conflicting results in the outcomes of these studies can be explained by different patient characteristics, duration of follow-up, methodology and statistical power. However, most studies showed a reduction in the risk of progression in high- and intermediate-risk tumours if BCG was applied including a maintenance schedule.

Two other meta-analyses have suggested a possible bias in favour of BCG arising from the inclusion of patients previously treated with intravesical chemotherapy [177]. In the most recent meta-analysis, however, BCG maintenance was more effective than MMC both in patients previously treated and not previously treated with chemotherapy [163] (LE: 1a).

It was demonstrated that BCG was less effective in patients > 70 years of age, but it was still more effective than epirubicin [178] (LE: 1a).

According to a published meta-analysis of 4 RCTs, the addition of chemotherapy to maintenance BCG does not improve the efficacy [179]. One smaller RCT demonstrated promising results of the addition of electromotive administered MMC to BCG, however, this requires further confirmation [167].

7.2.2.2 BCG strain

The EORTC meta-analysis suggested no large differences in efficacy between various BCG strains [162]. Recently published smaller studies without maintenance demonstrated some differences between strains. This clearly needs further evaluation in prospective trials [180, 181] (LE: 2a).

7.2.2.3 BCG toxicity

BCG intravesical treatment is associated with more side effects compared to intravesical chemotherapy [162] (LE: 1a). However, serious side effects are encountered in < 5% of patients and can be treated effectively in almost all cases [182] (LE: 1b). It has been shown that a maintenance schedule is not associated with an increased risk of side effects compared to an induction course [182]. Side effects requiring treatment stoppage were seen more often in the first year of therapy [183].

Major complications can appear after systemic absorption of the drug. Thus, contraindications of BCG intravesical instillation should be respected (see Section 7.5).

The presence of leukocyturia, non-visible haematuria or asymptomatic bacteriuria is not a contraindication for BCG application, and antibiotic prophylaxis is not necessary in these cases [184, 185] (LE: 3).

BCG should be used with caution (relative contraindication) in immunocompromised patients (immunosuppression, human immunodeficiency virus [HIV] infection) [186], although some small studies have shown similar efficacy and no increase in complications compared to non-immunocompromised patients [187, 188] (LE: 3).

The management of side effects after BCG should reflect their type and grade according the recommendations provided by the International Bladder Cancer Group (IBCG) and by a Spanish group [189, 190] (Table 7.1).

Table 7.1: Management options for side effects associated with intravesical BCG [190-193]

Management options for local side effects (modified from the IBCG group)	
Symptoms of cystitis	Phenazopyridine, propantheline bromide, or NSAIDs.
	If symptoms improve within a few days: continue instillations.
	If symptoms persist or worsen: a. Postpone the instillation; b. Perform a urine culture; c. Start empirical antibiotic treatment.
	If symptoms persist even with antibiotic treatment: d. With positive culture: antibiotic treatment according to sensitivity e. With negative culture: quinolones and potentially analgesic anti-inflammatory instillations once daily for 5 days (repeat cycle if necessary) [191].
	If symptoms persist: anti-tuberculosis drugs + corticosteroids.
	If no response to treatment and/or contracted bladder: radical cystectomy.
Haematuria	Perform urine culture to exclude haemorrhagic cystitis, if other symptoms present.
	If haematuria persists, perform cystoscopy to evaluate presence of bladder tumour.
Symptomatic granulomatous prostatitis	Symptoms rarely present: perform urine culture.
	Quinolones.
	If quinolones are not effective: isoniazid (300 mg/day) and rifampicin (600 mg/day) for 3 months.
	Cessation of intravesical therapy.
Epididymo-orchitis [192]	Perform urine culture and administer quinolones.
	Cessation of intravesical therapy.
	Orchidectomy if abscess or no response to treatment.

Management options for systemic side effects	
General malaise, fever	Generally resolve within 48 hours, with or without antipyretics.
Arthralgia and/or arthritis	Rare complication and considered autoimmune reaction.
	Arthralgia: treatment with NSAIDs.
	Arthritis: NSAIDs.
	If no/partial response, proceed to corticosteroids, high-dose quinolones or anti-tuberculosis drugs [193].
Persistent high-grade fever (> 38.5°C for > 48 h)	Permanent discontinuation of BCG instillations.
	Immediate evaluation: urine culture, blood tests, chest X-ray.
	Prompt treatment with > two antimicrobial agents while diagnostic evaluation is conducted.
	Consultation with an infectious diseases specialist.
BCG sepsis	Prevention: initiate BCG at least 2 weeks post-TURB (if no signs and symptoms of haematuria).
	Cessation of BCG.
	For severe infection:
	<ul style="list-style-type: none"> • High-dose quinolones or isoniazid, rifampicin and ethambutol 1.2 g daily for 6 months. • Early, high-dose corticosteroids as long as symptoms persist. Consider an empirical non-specific antibiotic to cover Gram-negative bacteria and/or Enterococcus.
Allergic reactions	Antihistamines and anti-inflammatory agents.
	Consider high-dose quinolones or isoniazid and rifampicin for persistent symptoms.
	Delay therapy until reactions resolve.

BCG = *bacillus Calmette-Guérin*; IBCG = *International Bladder Cancer Group*; NSAID = *non-steroidal anti-inflammatory drug*; TURBT = *transurethral resection of bladder tumour*.

7.2.2.4 Optimal BCG schedule

Induction BCG instillations are given according to the empirical 6-weekly schedule introduced by Morales in 1976 [194]. For optimal efficacy, BCG must be given in a maintenance schedule [161-163, 174] (LE: 1a). Many different maintenance schedules have been used, ranging from a total of 10 instillations given in 18 weeks to 27 over 3 years [195]. The EORTC meta-analysis was unable to determine which BCG maintenance schedule was the most effective [162]. In their meta-analysis, Böhle et al. concluded that at least one year of maintenance BCG is required to obtain superiority of BCG over MMC for prevention of recurrence or progression [161] (LE: 1a).

The optimal number of induction instillations and optimal frequency and duration of maintenance instillations remain unknown [196]. However, in a RCT of 1,355 patients, the EORTC has shown that when BCG is given at full dose, 3 years' maintenance reduces the recurrence rate compared to one year in high- but not in intermediate-risk patients. There were no differences in progression or overall survival. In the 3-year arm, however, 36.1% of patients did not complete the 3-years schedule [197] (LE: 1b). The benefit of the two additional years of maintenance in the high-risk patients should be weighed against its added costs and inconvenience.

7.2.2.5 Optimal dose of BCG

To reduce BCG toxicity, instillation of a reduced dose was proposed. However, it has been suggested that a full dose of BCG is more effective in multifocal tumours [198, 199] (LE: 1b). The CUETO study compared one-third dose to full-dose BCG and found no overall difference in efficacy. One-third of the standard dose of BCG might be the minimum effective dose for intermediate-risk tumours. A further reduction to one-sixth dose resulted in a decrease in efficacy with no decrease in toxicity [200] (LE: 1b).

The EORTC did not find any difference in toxicity between one-third and full-dose BCG, but one-third dose BCG was associated with a higher recurrence rate, especially when it was given only for one year [183, 197] (LE: 1b). Moreover, the routine application is complicated by potential technical difficulties in preparing the reduced dose reliably.

7.2.2.6 Indications for BCG

Although BCG is a very effective treatment, there is a consensus that not all patients with NMIBC should be treated with BCG due to the risk of toxicity. Ultimately, the choice of treatment depends upon the patient's risk (Table 6.2). The recommendation for individual risk groups is provided in Section 7.5.

7.2.3 **Specific aspects of treatment of CIS**

7.2.3.1 *Treatment strategy*

The detection of concurrent CIS increases the risk of recurrence and progression of Ta,T1 tumours [122, 123], further treatment according to the criteria summarized in Sections 7.2.1, 7.2.2, 7.3 and 7.4 is mandatory.

CIS cannot be cured by an endoscopic procedure alone. Histological diagnosis of CIS must be followed by further treatment, either intravesical BCG instillations or RC (LE: 4). Tumour-specific survival rates after immediate RC for CIS are excellent, but as many as 40-50% of patients might be over-treated [130] (LE: 3).

7.2.3.2 *Cohort studies on intravesical BCG or chemotherapy*

In retrospective evaluations of patients with CIS, a complete response rate of 48% was achieved with intravesical chemotherapy and 72-93% with BCG [130-133, 201] (LE: 2a). Up to 50% of complete responders might eventually show recurrence with a risk of invasion and/or extravesical recurrence [133, 195, 201, 202] (LE: 3).

7.2.3.3 *Prospective randomized trials on intravesical BCG or chemotherapy*

Unfortunately, there have been few randomized trials in patients with CIS alone. A meta-analysis of clinical trials comparing intravesical BCG to intravesical chemotherapy in patients with CIS has shown a significantly increased response rate after BCG and a reduction of 59% in the odds of treatment failure with BCG [203] (LE: 1a).

In an EORTC-GUCG meta-analysis of tumour progression (a subgroup of 403 patients with CIS), BCG reduced the risk of progression by 35% as compared to intravesical chemotherapy or different immunotherapy [162] (LE: 1b). The combination of BCG and MMC is not superior to BCG alone [204]. In summary, compared to chemotherapy, BCG treatment of CIS increases the complete response rate, the overall percentage of patients who remain disease free, and reduces the risk of tumour progression (LE: 1a).

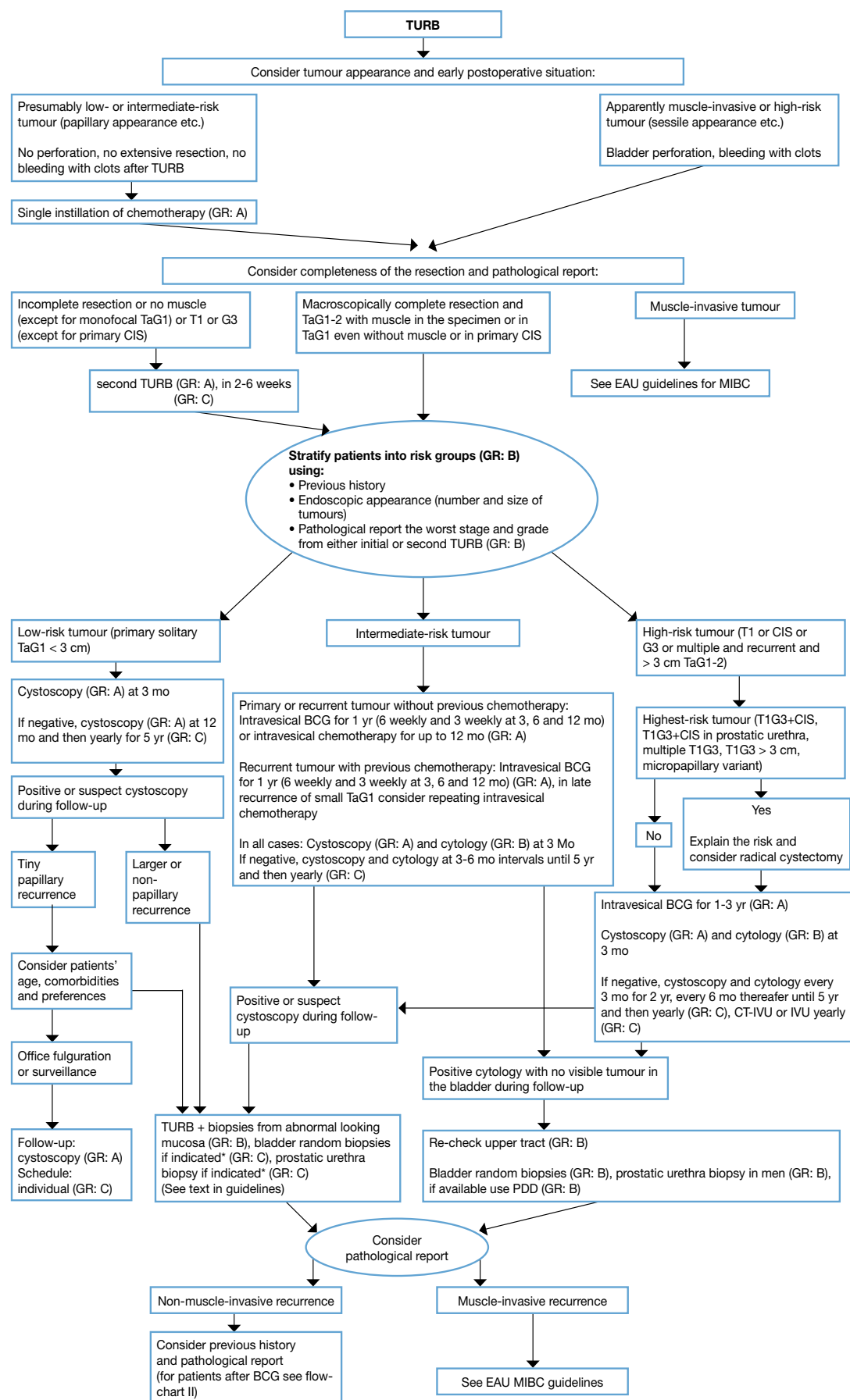
7.2.3.4 *Treatment of extravesical CIS*

Patients with CIS are at high risk of extravesical involvement in the UUT and in the prostatic urethra. Solsona et al. found that 63% of 138 patients with CIS developed extravesical involvement initially or during follow-up [205]. Patients with extravesical involvement had worse survival than those with bladder CIS alone [205] (LE: 3).

In the prostate, CIS might be present only in the epithelial lining of the prostatic urethra or in the prostatic ducts [29]. These situations should be distinguished from tumour invasion into the prostatic stroma (stage T4a in bladder tumours), and for which immediate radical cystoprostatectomy is mandatory. Patients with CIS in the epithelial lining of the prostatic urethra can be treated by intravesical instillation of BCG. TUR of the prostate can improve contact of BCG with the prostatic urethra [84, 206] (LE: 3).

In patients with prostatic duct involvement, there are promising results after BCG instillation, but only from small series, so the data are insufficient to provide clear treatment recommendations and radical surgery should be considered [206, 207] (LE: 3). Treatment of CIS that involves the UUT is discussed in the Guidelines on Urothelial Tumours of the Upper Urinary Tract (UTUCs).

Flowchart 7.1: Treatment strategy in primary or recurrent tumour(s) without previous BCG*



*For details and explanations see the text of the guidelines

BCG = bacillus Calmette-Guérin; GR = grade of recommendation; MIBC = muscle-invasive bladder cancer; PDD = photodynamic diagnosis; TURB = transurethral resection of the bladder.

7.3 Treatment of failure of intravesical therapy

7.3.1 Failure of intravesical chemotherapy

Patients with non-muscle-invasive recurrence of BC after a chemotherapy regimen can benefit from BCG instillations. Prior intravesical chemotherapy has no impact on the effect of BCG instillation [163] (LE: 1a).

7.3.2 Recurrence and failure after intravesical BCG immunotherapy

Table 7.2: Categories of unsuccessful treatment with intravesical BCG

BCG failure
Whenever a MIBC is detected during follow-up.
BCG-refractory tumour: 1. If high-grade, non-muscle-invasive papillary tumour is present at 3 months [208]. Further conservative treatment with BCG is associated with increased risk of progression [134, 209] (LE: 3). 2. If CIS (without concomitant papillary tumour) is present at both 3 and 6 months. In patients with CIS present at 3 months, an additional BCG course can achieve a complete response in > 50% of cases [29] (LE: 3). 3. If high-grade tumour appears during BCG therapy*.
High-grade recurrence after BCG. Recurrence of high-grade/grade 3 (WHO 2004/1973) tumour after completion of BCG maintenance, despite an initial response [210] (LE: 3)*.
BCG intolerance
Severe side effects that prevent further BCG instillation before completing induction [190].

* Patients with low-grade recurrence during or after BCG treatment are not considered to be a BCG failure. BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; LE = level of evidence.

7.3.3 Treatment of BCG failure and recurrences after BCG

Treatment recommendations are provided in Table 7.4. They reflect categories mentioned in Table 7.2 and tumour characteristics at the time of recurrence.

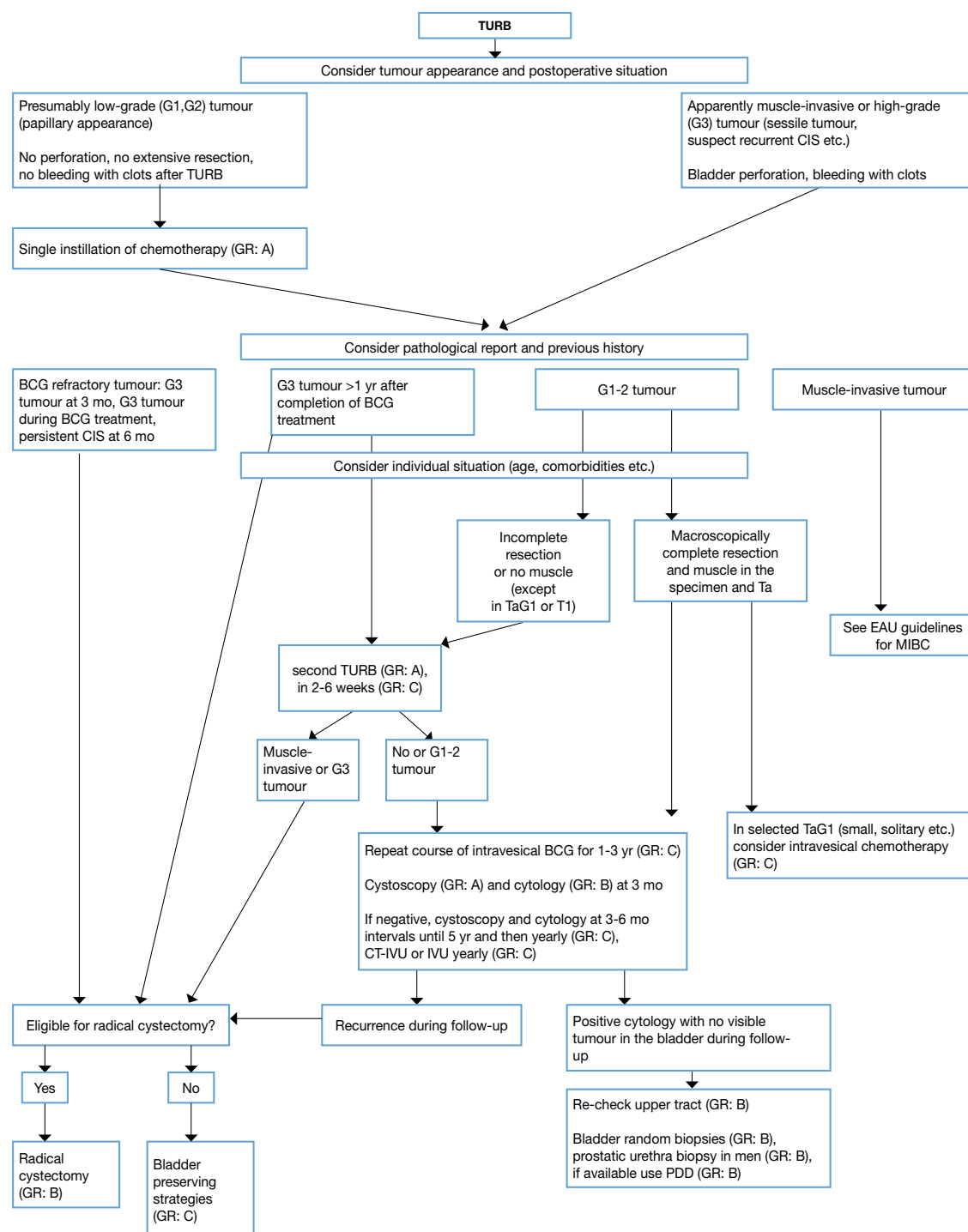
Patients with BCG failure are unlikely to respond to further BCG therapy; RC is therefore the preferred option. Various studies suggest that repeat BCG therapy is appropriate for non-high grade and even for some high-grade recurrent tumours [211, 212] (LE: 3). Additionally, there are now several bladder preservation strategies available that can be categorized as immunotherapy, chemotherapy, device-assisted therapy, and combination therapy [213]. Changing from BCG to these options can yield responses in selected cases with BCG treatment failure [211, 214-221] (LE: 3).

Treatments other than RC must be considered oncologically inferior in patients with BCG failure at the present time [134, 208, 209] (LE: 3).

Little is known about the optimal treatment in patients with high-risk tumours who could not complete BCG instillations because of intolerance.

Non-high grade recurrence after BCG is not considered as BCG failure. Treatment decision should be individual according to the tumour characteristics. It could include chemotherapy or repeat BCG instillations, but the published evidence is very low.

Flowchart 7.2: Treatment strategy in recurrence during or after intravesical BCG*



*For details and explanations, see the text of the guidelines.

BCG = bacillus Calmette-Guérin; GR = grade of recommendation; IVU = intravenous urography; PDD = photodynamic diagnosis; TURB = transurethral resection of the bladder.

7.4 Radical cystectomy for NMIBC

If RC is indicated before progression to muscle-invasive tumour, it can be performed as an immediate (immediately after NMIBC diagnosis) or early (after BCG failure) procedure.

There are several reasons to consider immediate RC for selected patients with NMIBC:

- The staging accuracy for T1 tumours by TURB is low with 27-51% of patients being upstaged to muscle-invasive tumour at RC [99, 117, 222-227] (LE: 3).
- Some patients with NMIBC experience disease progression to muscle-invasive disease (Table 6.2).

The potential benefit of RC must be weighed against the risk, morbidity, and impact on quality of life. It is reasonable to propose immediate RC in those patients with NMIBC who are at highest risk of progression (see Table 7.3) [44, 97, 122, 123] (LE: 3).

The benefits and risks of immediate and delayed RC should be discussed with patients. Individual additional prognostic factors in T1 G3 tumours mentioned in Section 6.1, as well as pathologic parameters (particularly LVI and unusual histologies) mentioned in Section 4.6, should be considered.

Early RC is strongly recommended in patients with BCG-refractory tumours, as mentioned above. A delay in RC might lead to decreased disease-specific survival [228] (LE: 3). In patients in whom RC is performed at the time of pathological NMIBC, the 5-year disease-free survival rate exceeds 80% [229-233] (LE: 3).

Table 7.3: Treatment recommendations in Ta, T1 tumours and CIS according to risk stratification

Risk category	Definition	Treatment recommendation
Low-risk tumours	Primary, solitary, Ta, LG/G1, < 3 cm, no CIS	One immediate instillation of chemotherapy.
Intermediate-risk tumours	All cases between categories of low and high risk	One immediate instillation of chemotherapy followed by further instillations, either chemotherapy for a maximum of 1 year or 1-year full-dose BCG.
High-risk tumours	Any of the following: <ul style="list-style-type: none"> • T1 tumours; • HG/G3 tumours; • CIS; • Multiple and recurrent and large (> 3 cm) Ta G1G2 tumours (all these conditions must be present). 	Intravesical full-dose BCG instillations for 1-3 years or cystectomy (in highest-risk tumours).
Subgroup of highest-risk tumours	T1G3 associated with concurrent bladder CIS, multiple and/or large T1G3 and/or recurrent T1G3, T1G3 with CIS in prostatic urethra, unusual histology of urothelial carcinoma, LVI (see Sections 4.6 and 6.2).	Radical cystectomy should be considered in those who refuse RC, intravesical full-dose BCG instillations for 1-3 years.
	BCG failures	Radical cystectomy is recommended.

BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; GR = grade of recommendation; HG = high-grade; LG = low-grade; LVI = lymphovascular invasion.

Table 7.4: Treatment recommendations for BCG failure and recurrences after BCG

Category	Treatment recommendation	GR
BCG-refractory tumour	1. Radical cystectomy 2. Bladder-preserving strategies in patients unsuitable for cystectomy	B
HG recurrence after BCG	1. Radical cystectomy 2. Repeat BCG course 3. Bladder-preserving strategies	C
Non-HG recurrence after BCG for primary intermediate-risk tumour	1. Repeat BCG or intravesical chemotherapy 2. Radical cystectomy	C

BCG = bacillus Calmette-Guérin; GR = grade of recommendation; HG = high-grade.

7.5 Recommendations for adjuvant therapy in Ta, T1 tumours and for therapy of CIS

	GR
Smokers with confirmed NMIBC should be counselled to stop smoking.	B
The type of further therapy after BCG should be based on the risk groups shown in Tables 6.3 and 7.3.	A
In patients with tumours presumed to be at low- or intermediate risk, one immediate chemotherapy instillation is recommended.	A
In patients with low-risk tumours, one immediate instillation of chemotherapy is recommended as the complete adjuvant treatment.	A
In patients with intermediate-risk tumours, one immediate instillation of chemotherapy should be followed by 1-year full-dose BCG treatment, or by further instillation of chemotherapy for a maximum of 1 year. The final choice should reflect the individual patient's risk of recurrence and progression as well as the efficacy and side effects of each treatment modality.	A
In patients with high-risk tumours, full-dose intravesical BCG for 1-3 years is indicated. The additional beneficial effect of the second and third years of maintenance should be weighed against its added costs and inconvenience.	A
In patients with CIS in the epithelial lining of the prostatic urethra, TUR of the prostate followed by intravesical instillation of BCG can be offered.	C
In patients at highest risk of tumour progression (Table 7.3), immediate radical cystectomy should be considered.	C
In patients with BCG failure, radical cystectomy is indicated.	B
Intravesical chemotherapy	
One immediate instillation of chemotherapy should be administered within 24 hours after TURB.	C
One immediate instillation of chemotherapy should be omitted in any case of overt or suspected intra- or extra-peritoneal perforation (after extensive TURB, or bleeding requiring bladder irrigation).	C
Give clear instructions to the nursing staff to control the free flow of the bladder catheter at the end of the immediate instillation.	C
The optimal schedule of further intravesical chemotherapy instillation and its duration is not defined, but it should not exceed 1 year.	C
If intravesical chemotherapy is given, it is advised to use the drug at its optimal pH and to maintain the concentration of the drug by reducing fluid intake before and during instillation.	B
The length of an individual instillation should be 1-2 hours.	C
BCG intravesical immunotherapy	
Absolute contraindications of BCG intravesical instillation are: <ul style="list-style-type: none"> • during the first 2 weeks after TURB; • in patients with visible haematuria; • after traumatic catheterisation; • in patients with symptomatic urinary tract infection. 	C
The management of side effects after BCG intravesical instillation should reflect their type and grade (Table 7.1).	C

BCG = *bacillus Calmette-Guérin*; CIS = *carcinoma in situ*; GR = grade of recommendation;

MMC = *mitomycin C*; TUR = *transurethral resection*; TURB = *transurethral resection of the bladder*.

8. FOLLOW-UP OF PATIENTS WITH NMIBC

As a result of the risk of recurrence and progression, patients with NMIBC need to be followed up. However, the frequency and duration of cystoscopy and imaging should reflect the individual patient's degree of risk. Using risk tables (see Tables 6.1 and 6.2), the short- and long-term risks of recurrence and progression in individual patients may be predicted and the follow-up schedule adapted accordingly [122, 123].

When planning the follow-up schedule and methods, the following aspects should be considered:

- The prompt detection of muscle-invasive and HG/G3 non-muscle-invasive recurrence is crucial because a delay in diagnosis and therapy can be life-threatening.
- Tumour recurrence in the low-risk group is nearly always low stage and LG/G1. Small, Ta LG/G1 papillary recurrence does not present an immediate danger to the patient and early detection is not essential for successful therapy [234-238] (LE: 2b). Fulguration of small papillary recurrences on

- an outpatient basis could be a safe option that reduces the therapeutic burden [90] (LE: 3). Some authors have even defended temporary surveillance in selected cases [237-239] (LE: 3).
- The first cystoscopy after TURB at 3 months is a very important prognostic indicator for recurrence and progression [128, 134, 240-242] (LE: 1a). Therefore, the first cystoscopy should always be performed 3 months after TURB in all patients with Ta, T1 tumours and CIS.
- In tumours at low-risk, the risk of recurrence after 5 recurrence-free years is low [241] (LE: 3). Discontinuation of cystoscopy or its replacement with less-invasive methods can be considered [242].
- In tumours originally intermediate- or high-risk, recurrences after 10 years tumour-free are not unusual [243] (LE: 3). Therefore, life-long follow-up is recommended [242].
- The follow-up strategy must reflect the risk of extravesical recurrence (prostatic urethra in men and UUT)
- The risk of UUT recurrence increases in patients with multiple- and high-risk tumours [55] (LE: 3).
- Positive urine test results have a positive impact on the quality of performed follow-up cystoscopy [82] (LE: 1b). It supports the adjunctive role of urine tests during follow-up.

No non-invasive method has been proposed that can replace endoscopy and follow-up is therefore based on regular cystoscopy (see Section 5.7). There is a lack of randomized studies that have investigated the possibility of safely reducing the frequency of follow-up cystoscopy.

As CIS is often not visible, multiple biopsies may be necessary in selected cases to confirm the efficacy of intravesical treatment in patients treated for CIS [83].

The following recommendations are based mostly on retrospective data.

8.1 Guidelines for follow-up in patients after TURB of NMIBC

	GR
The follow-up of Ta, T1 tumours and CIS is based on regular cystoscopy.	A
Patients with low-risk Ta tumours should undergo cystoscopy at 3 months. If negative, subsequent cystoscopy is advised 9 months later, and then yearly for 5 years.	C
Patients with high-risk tumours should undergo cystoscopy and urinary cytology at 3 months. If negative, subsequent cystoscopy and cytology should be repeated every 3 months for a period of 2 years, and every 6 months thereafter until 5 years, and then yearly.	C
Patients with intermediate-risk Ta tumours should have an in-between follow-up scheme using cystoscopy and cytology, which is adapted according to personal and subjective factors.	C
Regular (yearly) upper tract imaging (CT-IVU or IVU) is recommended for high-risk tumours.	C
Endoscopy under anaesthesia and bladder biopsies should be performed when office cystoscopy shows suspicious findings or if urinary cytology is positive.	B
Consider R-biopsies or biopsies with PDD after intravesical treatment (at 3 or 6 months) in patients with CIS.	C
During follow-up in patients with positive cytology and no visible tumour in the bladder, R-biopsies or biopsies with PDD (if equipment is available) and investigation of extravesical locations (CT urography, prostatic urethra biopsy) are recommended.	B

CIS = carcinoma in situ; CT-IVU = computed tomography intravenous urography; GR = grade of recommendation; IVU = intravenous urography; PDD = photodynamic diagnosis; R-biopsies = random biopsies.

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10. CONFLICT OF INTEREST

All members of the Non-Muscle-Invasive Bladder Cancer guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: <http://www.uroweb.org/guidelines/>. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

Guidelines on Urothelial Carcinomas of the Upper Urinary Tract

M. Rouprêt, M. Babjuk, A. Böhle, M. Burger, E. Compérat,
N. Cowan, E. Kaasinen, J. Palou, B.W.G. van Rhijn, S. Shariat,
R. Sylvester, R. Zigeuner

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1. INTRODUCTION

Upper tract urothelial carcinoma (UTUC) are relatively uncommon compared to bladder cancer, but 60% of UTUCs are invasive at diagnosis.

1.1 Panel composition

The European Association of Urology (EAU) Guidelines Panel on UTUC consists of an international multidisciplinary group of clinicians, including a pathologist and a statistician. Members of this panel have been selected based on their expertise and to represent the professionals treating patients suspected of harbouring urothelial carcinoma.

All experts involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU website.

1.2 Available publications

A quick reference document (Pocket guidelines) is available in print and in a number of versions for mobile devices, presenting the main findings of the UTUC Guidelines. These are abridged versions which may require consultation together with the full text versions. Several scientific publications are available as are a number of translations of all versions of the EAU UTUC Guidelines. All documents are accessible through the EAU website Uroweb: <http://www.uroweb.org/guidelines/online-guidelines/>.

1.3 Publication history & summary of changes

The first EAU guidelines on UTUC were published in 2011. The current 2015 EAU guidelines on UTUC present an update of the 2014 version, and provide evidence-based information for clinical management of UTUC.

1.3.1 Summary of changes

A detailed overview of changes for this 2015 print version is posted online.

The literature for the complete document has been assessed and updated, whenever relevant;

Key changes for this 2015 print:

- New algorithms have been included:
 - Fig. 3.1: Selection of patients with UTUC for hereditary screening from first medical interview.
 - Fig. 6.1: UTUC prognostic factors;
 - Fig. 6.2: Risk stratification of UTUC (table presentation in the 2014 print version);
 - Fig. 7.1: Proposed flowchart for the management of UTUC was amended.

Recommendations have been rephrased and added to throughout the current document.

In Table 7.1. Guidelines for kidney sparing management of low-risk UTUC, the open surgical approach options have been expanded, not resulting in a change in the grade of recommendation (GR).

Surgical open approach	
<i>Renal pelvis or calyces:</i> Partial pyelectomy or partial nephrectomy is seldom indicated.	C
<i>Ureter - Mid & proximal:</i> Ureteroureterostomy is indicated for tumours that cannot be removed completely endoscopically.	C
<i>Ureter - Distal:</i> Complete distal ureterectomy and neocystostomy are indicated for tumours in the distal ureter that cannot be removed completely endoscopically.	C

2. METHODS

2.1 Data identification

Medline was searched for urothelial malignancies and UTUC management using combinations of the following: *urinary tract cancer, urothelial carcinoma, upper urinary tract, renal pelvis, ureter, chemotherapy, nephroureterectomy, adjuvant treatment, neoadjuvant treatment, recurrence, risk factors, nomogram, and survival*, with a November 2013 cut-off. Articles were selected using the following criteria: evolution of concepts, intermediate- and long-term clinical outcomes, study quality, and relevance. To facilitate evaluation of information quality, level of evidence (LE) and grade of recommendation (GR) were inserted according to evidence-based medicine (EBM) [1].

In this 2015 EAU Guidelines compilation, all standard information on levels of evidence (LE) and grading of recommendations (GR) has been taken out of the individual guidelines topics for the sake of brevity. This information is included in the introductory section of this print.

2.2 Review

This document was subjected to double-blind peer review prior to publication.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

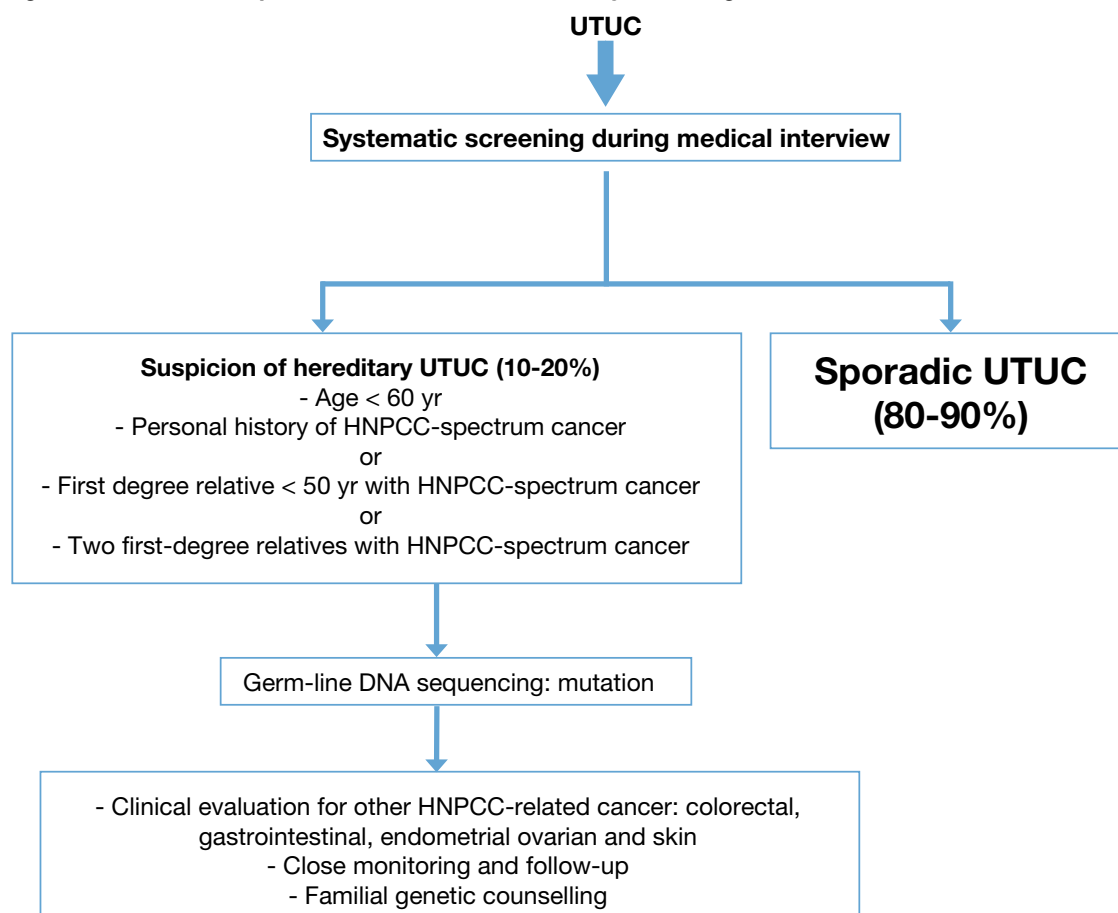
3.1 Epidemiology

Urothelial carcinomas (UCs) are the fourth most common tumours [2]. They can be located in the lower (bladder and urethra) or upper (pyelocaliceal cavities and ureter) urinary tract. Bladder tumours account for 90-95% of UCs and are the most common malignancy of the urinary tract [3]. However, UTUCs are uncommon and account for only 5-10% of UCs [2, 4], with an estimated annual incidence in Western countries of ~2 cases per 100,000 inhabitants. Pyelocaliceal tumours are about twice as common as ureteral tumours. In 17% of cases, concurrent bladder cancer is present [5]. Recurrence in the bladder occurs in 22-47% of UTUC patients [6-8], compared with 2-6% in the contralateral upper tract [9, 10].

Sixty percent of UTUCs are invasive at diagnosis compared with 15-25% of bladder tumours [11, 12]. UTUCs have a peak incidence in people aged 70-90 years and are three times more common in men [13, 14].

Familial/hereditary UTUCs are linked to hereditary non-polyposis colorectal carcinoma (HNPCC) [15], which can be screened during interview (Figure 3.1) [16]. Patients should undergo DNA sequencing to identify hereditary cancers misclassified as sporadic [15, 17].

Figure 3.1: Selection of patients with UTUC for hereditary screening from first medical interview



HNPCC = hereditary non-polyposis colorectal carcinoma.

3.2 Risk factors

Many environmental factors contribute to UTUC development [18, 19]. Tobacco exposure increases the relative risk from 2.5 to 7 [18, 19]. Historically, UTUC 'amino tumours' were related to occupational exposure to carcinogenic aromatic amines, including benzidine and β -naphthalene - both of which have been banned since the 1960s in most industrialised countries.

Upper tract urothelial carcinoma is mostly secondary to an amino tumour of the bladder. The average duration of exposure needed to develop UTUC is ~7 years, with a latency of ~20 years following termination of exposure. The odds ratio of developing UC after exposure to aromatic amines is 8.3 [19, 20]. Upper urinary tract tumours caused by phenacetin consumption almost disappeared after the product was banned in the 1970s [19].

Several studies have revealed the carcinogenic potential of aristolochic acid contained in *Aristolochia fangchi* and *Aristolochia clematis*. The aristolochic acid derivative d-aristolactam causes a specific mutation in the p53 gene at codon 139, which occurs mainly in patients with nephropathy due to Chinese herbs or Balkan endemic nephropathy, who present with UTUC [19, 21, 22].

There is a high incidence of UTUC in Taiwan, especially on the South-west coast which represents 20-25% of UCs in the region [19, 22]. There is a possible association of UTUC with blackfoot disease and arsenic exposure in drinking water in this population [19, 22, 23].

Differences in the ability to counteract carcinogens may contribute to host susceptibility to UTUC. Some genetic polymorphisms are associated with an increased risk of cancer or faster disease progression, which introduces variability in the inter-individual susceptibility to the risk factors previously mentioned. UTUC may share some risk factors or molecular disruption pathways with bladder urothelial carcinoma. Only two UTUC-specific polymorphisms have been reported [24, 25].

3.2 Histology and classification

3.2.1 Histological types

There are morphological variants of UTUC that are more often observed in urothelial kidney tumours. These variants always correspond to high-grade tumours that are associated with one of the following [26]: micropapillary, clear cell, neuroendocrine or lymphoepithelial variants [27, 28]. Collecting-duct carcinoma can have similar characteristics to UTUC because of its common embryological origin [29].

UTUC with pure non-urothelial histology is an exception [30, 31] but variants are present in ~25% of cases [26, 32]. Squamous cell carcinoma of the upper urinary tract represents < 10% of pyelocaliceal tumours and is even rarer within the ureter. Squamous cell carcinoma of the urinary tract is associated with chronic inflammatory and infectious diseases arising from urolithiasis [27, 28]. Other histological subtypes are adenocarcinoma (< 1%), small cell carcinoma, and sarcoma.

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Classification

The classification and morphology of UTUC and bladder carcinoma are similar [11]. It is possible to distinguish between non-invasive papillary tumours (papillary urothelial tumours of low malignant potential, and low-grade and high-grade papillary UC), flat lesions (carcinoma *in situ* [CIS]), and invasive carcinoma.

4.2 Tumour Node Metastasis staging

The Tumour Node Metastasis (TNM) classification is shown in Table 4.1 [33]. The regional lymph nodes that should be considered are the hilar, abdominal para-aortic, and paracaval nodes, and, for the ureter, the intrapelvic nodes. Laterality does not affect N classification.

Renal pelvic pT3 subclassification may discriminate between microscopic infiltration of the renal parenchyma (pT3a) and macroscopic infiltration or invasion of peripelvic adipose tissue. pT3a and pT3b have been suggested as a subclassification [26, 34, 35]. pT3b UTUC is more likely to have aggressive pathology and higher risk of recurrence [26, 34].

Table 4.1: TNM classification 2009 for upper tract urothelial carcinoma

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma <i>in situ</i>
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
T3	(Renal pelvis) Tumour invades beyond muscularis into peripelvic fat or renal parenchyma (Ureter) Tumour invades beyond muscularis into periureteric fat
T4	Tumour invades adjacent organs or through the kidney into perinephric fat
N - Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node 2 cm or less in the greatest dimension
N2	Metastasis in a single lymph node more than 2 cm but not more than 5 cm in the greatest dimension or multiple lymph nodes, none more than 5 cm in greatest dimension
N3	Metastasis in a lymph node more than 5 cm in greatest dimension
M - Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

4.3 Tumour grade

Until 2004, the World Health Organization (WHO) classification of 1973 was used most often, which distinguished only three grades (G1-G3) [36, 37]. The recent 2004 WHO classification considers histological data to distinguish non-invasive tumours: papillary urothelial neoplasia of low malignant potential, and low-grade and high-grade carcinomas (low grade vs. high grade). Only few tumours of low malignant potential are found in the upper urinary tract [27, 28].

5. DIAGNOSIS

5.1 Symptoms

Diagnosis of UTUC may be fortuitous or related to exploration of symptoms, which are generally limited [38]. The most common symptom is visible- or non-visible haematuria (70-80%) [39]. Flank pain occurs in 20-40% of cases, and a lumbar mass is present in 10-20% [40, 41]. Systemic symptoms (including anorexia, weight loss, malaise, fatigue, fever, night sweats, or cough) associated with UTUC should prompt more rigorous metastatic evaluation [40, 41].

5.2 Diagnosis

5.2.1 Imaging

5.2.1.1 Computed tomography urography

Computed tomography urography (CTU) has the highest diagnostic accuracy for high-risk patients [39]. The sensitivity of CTU for UTUC is 0.67-1.0 and the specificity is 0.93-0.99 [42-49].

Computed tomography urography acquires at least one image series during the excretory phase, usually 10-15 min, following administration of intravenous contrast medium [50]. Rapid acquisition of thin sections allows for high-resolution isotropic images that can be viewed in multiple planes to assist with diagnosis without loss of resolution [51, 52].

Flat lesions are not detectable unless they exert a mass effect or cause urothelial thickening [53].

The secondary sign of hydronephrosis upon imaging of UTUC is associated with advanced disease and poor oncological outcome [50, 54, 55]. The presence of enlarged lymph nodes is highly predictive of metastasis in UTUC [56].

5.2.1.2 Magnetic resonance imaging

Magnetic resonance urography (MRU) is indicated in patients who cannot undergo CTU, usually when radiation

or iodinated contrast media are contraindicated [57]. The sensitivity of MRU is 75% after contrast injection for tumours < 2 cm [57]. The use of MRU with gadolinium-based contrast media should be limited in patients with severe renal impairment (< 30 mL/min creatinine clearance), due to the risk of nephrogenic systemic fibrosis.

Computed tomography urography is generally preferred over MRU for diagnosing UTUC.

5.2.2 Cystoscopy and urinary cytology

Positive urine cytology is highly suggestive of UTUC when bladder cystoscopy is normal, provided that no CIS in the bladder or prostatic urethra CIS has been detected [11, 58]. Cytology is less sensitive for UTUC than bladder tumours and it should be performed *in situ* in the renal cavities [59]. Retrograde ureteropyelography remains an option to detect upper urinary tract tumours [43, 60]. Urinary cytology of the renal cavities and ureteral lumina is preferable before application of contrast agent for retrograde ureteropyelography, because it may cause deterioration of cytological specimens [59, 60].

The sensitivity of fluorescence *in situ* hybridisation (FISH) for molecular abnormalities characteristic of UTUCs parallels its performance in bladder cancer. However, its use may be limited by the preponderance of low-grade recurrent disease in the population undergoing surveillance and minimally invasive therapy for UTUCs [61, 62]. FISH appears to have a limited value for surveillance of UTUCs [61, 62].

5.2.3 Diagnostic ureteroscopy

Flexible ureteroscopy is used to visualise and biopsy the ureter, renal pelvis and collecting system. Such ureteroscopic biopsies can determine tumour grade in 90% of cases with a low false-negative rate, regardless of sample size [63]. Undergrading may occur from diagnostic biopsy, making intensive follow-up necessary if renal-sparing treatment is selected [64]. Ureteroscopy also facilitates selective ureteral sampling for cytology *in situ* [60, 65, 66].

Flexible ureteroscopy is especially useful for diagnostic uncertainty, when conservative treatment is considered, or in patients with a solitary kidney. Ureteroscopy and biopsy should be performed in preoperative assessment of UTUC. Combining ureteroscopic biopsy grade, imaging findings such as hydronephrosis, and urinary cytology, may help decide between radical nephroureterectomy (RNU) and endoscopic treatment [65, 67].

Technical developments in flexible ureteroscopes and the use of novel imaging techniques improve visualisation and diagnosis of flat lesions. Narrow-band imaging is the most promising technique but results are preliminary [67, 68]. Table 5.1 lists the recommendations for diagnosis.

Table 5.1: Diagnostic guidelines for upper tract urothelial carcinoma

Recommendations	GR
Urinary cytology should be performed as part of a standard diagnostic work-up.	A
A cystoscopy should be done to rule out concomitant bladder tumour.	A
CTU must be part of the diagnostic work-up.	A
Diagnostic ureteroscopy and biopsy should be performed, certainly in cases where additional information will impact treatment decisions.	C
Retrograde ureteropyelography is an optional tool for the detection of UTUC.	C

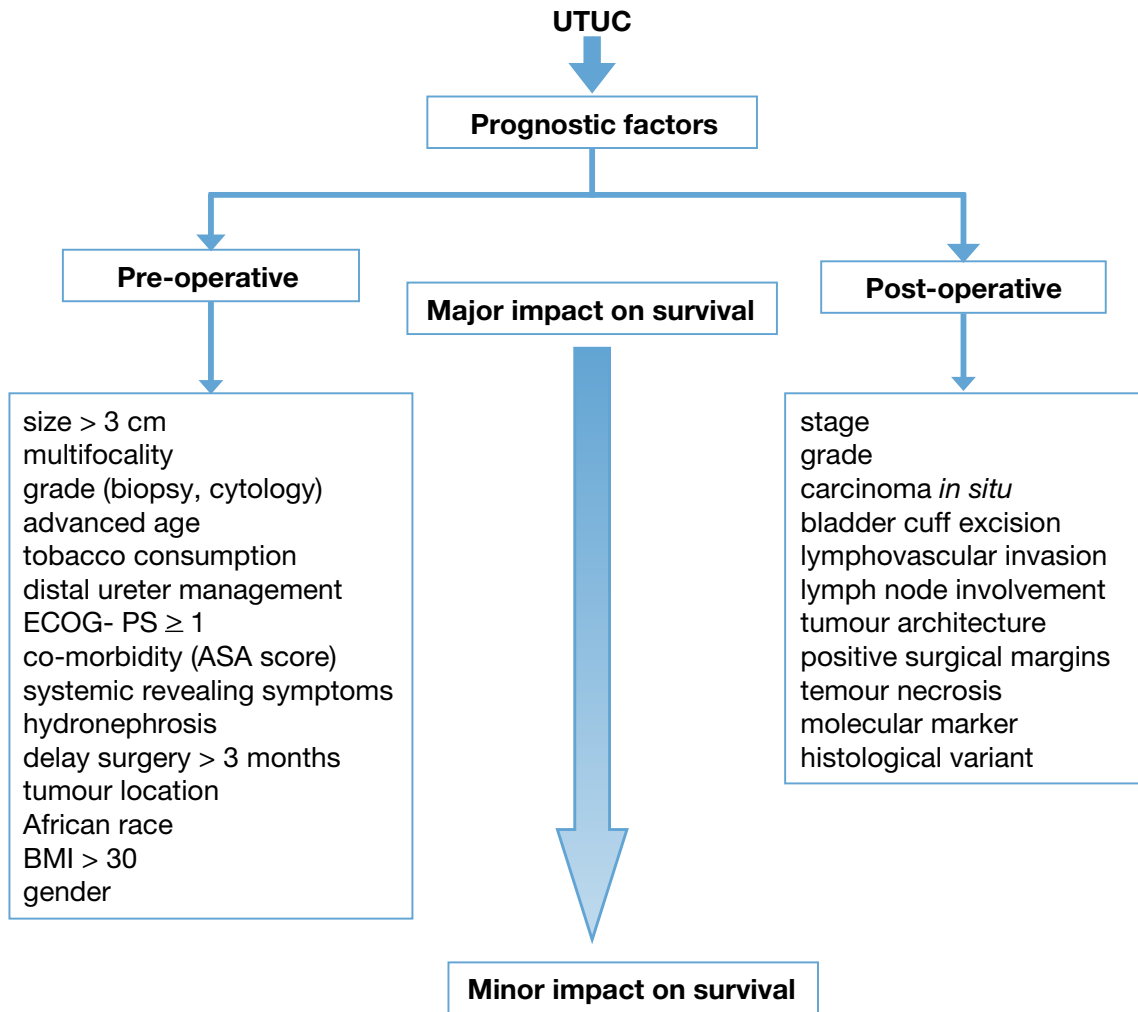
CTU = computed tomography urography; GR = grade of recommendation.

6. PROGNOSIS

6.1 Prognostic factors

Upper tract urothelial carcinomas that invade the muscle wall usually have poor prognosis. The 5-year specific survival is < 50% for pT2/pT3 and < 10% for pT4 [68-70]. The main prognostic factors are briefly listed below; Figure 6.1 presents an exhaustive list.

Figure 6.1: Upper tract urothelial carcinoma - Prognostic factors



ASA = American Society of Anesthesiologists; BMI = body mass index; ECOG = Eastern Cooperative Oncology Group.

6.1.1 Preoperative factors

6.1.1.1 Age and sex

Sex is no longer considered an independent prognostic factor that influences UTUC mortality [13, 70, 71]. Older age at the time of RNU is independently associated with decreased cancer-specific survival [70, 72] (LE: 3). Many elderly patients can be cured with RNU [72], suggesting that age alone is an inadequate indicator of outcome [72, 73]. Advanced age is linked with survival but it does not have to be considered as an absolute exclusion criterion for decision of treatment of potentially curable UTUC.

6.1.1.2 Ethnicity

One multicentre study did not show any difference between races [74] but population-based studies have indicated that African-American patients have worse outcomes compared to other racial groups [73] (LE: 3).

6.1.1.3 Tobacco consumption

Being a smoker at diagnosis increases the risk for poor oncological outcomes [75-77] and recurrence within the bladder [78] (LE: 3).

6.1.1.4 Tumour location

Initial location of the tumour within the upper urinary tract is a prognostic factor [79-81] (LE: 3). After adjustment for tumour stage, ureteral and multifocal tumours have a worse prognosis than renal pelvic tumours [70, 80-83].

6.1.1.5 Surgical waiting time

A delay between diagnosis and tumour removal may increase the risk of disease progression. The cut-off for

removal is controversial and ranges between 30 days and 3 months [84-87] (LE: 3).

6.1.1.6 *Other*

The American Society of Anesthesiologists (ASA) score also significantly correlates with cancer-specific survival after RNU [88] (LE: 3), but Eastern Cooperative Oncology Group (ECOG) performance status correlates only with overall survival [89]. Obesity and higher body mass index adversely affect cancer-specific outcomes in UTUCs [90] (LE: 3).

6.1.2 **Post-operative factors**

6.1.2.1 *Tumour stage and grade*

The primary recognised prognostic factors are tumour stage and grade [65, 70, 91, 92].

6.1.2.2 *Lymph node involvement*

Extranodal extension is a powerful predictor of clinical outcomes in UTUCs and positive lymph node metastases [93]. Lymph node dissection (LND) associated with RNU allows for optimal tumour staging [94, 95] (LE: 3). Lymph node invasion is an important prognostic factor, indicating metastatic spread to the lymph nodes.

6.1.2.3 *Lymphovascular invasion*

Lymphovascular invasion is present in ~20% of UTUCs and is an independent predictor of survival [96, 97]. Lymphovascular invasion status should be systematically included and specifically reported in the pathological reports of all RNU specimens [96, 98] (LE: 3).

6.1.2.4 *Surgical margins*

Positive surgical margin after RNU is a significant factor for developing UTUC metastases. Pathologists should look for and report positive margins at the level of ureteral transection, bladder cuff, and around the tumour if it is T > 2 [99] (LE: 3).

6.1.2.5 *Pathological factors*

Extensive tumour necrosis (> 10% of the tumour area) is an independent prognostic predictor in patients who undergo RNU [100, 101] (LE: 3). The tissue architecture of UTUC is associated with prognosis after RNU. Sessile growth pattern is associated with the worst outcome [102, 103] (LE: 3). Concomitant CIS in organ-confined UTUC, and a history of bladder CIS are associated with a higher risk of recurrence and cancer-specific mortality [104-106] (LE: 3). Similar to lower tract UC, concomitant CIS is an independent predictor of worse outcomes in organ-confined disease [107].

6.2 **Molecular markers**

Several studies have investigated the prognostic impact of markers related to cell adhesion (E-cadherin and CD24), cell differentiation (Snail and epidermal growth factor receptor), angiogenesis (hypoxia-inducible factor-1 α and metalloproteinases), cell proliferation (Ki67), epithelial-mesenchymal transition (Snail), mitosis (Aurora-A), apoptosis (Bcl-2 and survivin), vascular invasion (RON), and c-met protein (MET) [70, 108-112]. Microsatellite instability (MSI) is an independent molecular prognostic marker [113]. MSI can help detect germline mutations and hereditary cancers [15].

The rarity of UTUC means that the main limitations of the above studies were their retrospective nature and small sample size. None of the markers have fulfilled the criteria necessary to support their introduction in daily clinical decision making.

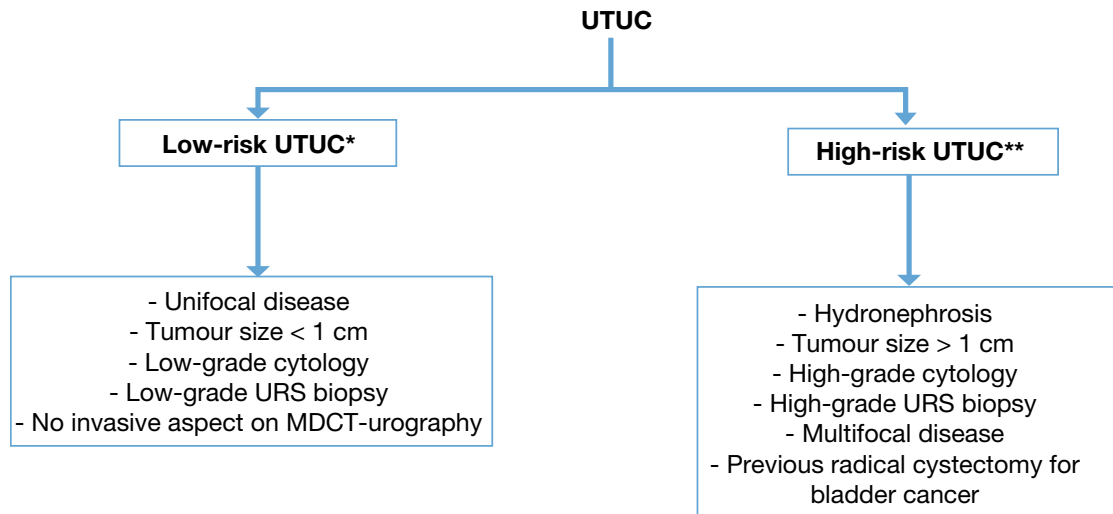
6.3 **Predictive tools**

Accurate predictive tools are rare for UTUC. There are two models in a preoperative setting: one for prediction LND of locally advanced cancer that could guide the extent of LND at the time of RNU [114]; and one for selection of non-organ-confined UTUC that is likely to benefit from nephroureterectomy [115]. Four nomograms predict survival rates postoperatively based on standard pathological features [116-119].

6.4 **Risk stratification**

As with NMIBC, it is necessary to 'risk stratify' UTUC before treatment to identify tumours that are more suitable for kidney-sparing treatment than radical extirpative surgery [120] (Figure 6.2).

Figure 6.2: Risk stratification of upper tract urothelial carcinoma



* All of these factors need to be present

** Any of these factors need to be present

MDCT = multidetector-row computed tomography; URS = ureterorenoscopy.

7. DISEASE MANAGEMENT

7.1. Localised disease

7.1.1 Kidney-sparing surgery

Conservative management of UTUC can be discussed in low-risk cases when the contralateral kidney is functional [121-123]. Kidney-sparing surgery for low-risk UTUC (Table 7.1) allows sparing the morbidity associated with open radical surgery, without compromising oncological outcomes and kidney function [124]. In addition, it can also be considered in all imperative cases (i.e.; renal insufficiency or solitary functional kidney) (LE: 3).

7.1.1.1 Ureteroscopy

Endoscopic ablation can be considered in highly selected cases and in the following situations [125, 126]:

- Laser generator [127] and pliers are available for biopsies [126, 128] (LE: 3);
- Flexible rather than rigid ureteroscope;
- The patient is informed of the need for closer, more stringent, surveillance;
- Complete tumour resection is strongly advocated.

However, there is a risk of understaging and undergrading with pure endoscopic management.

7.1.1.2 Percutaneous access

Percutaneous management can be considered for low-grade or non-invasive UTUCs in the renal cavities [126, 129, 130] (LE: 3). This may be offered for low-grade tumours in the lower caliceal system that are inaccessible or difficult to manage by flexible ureteroscopy. This approach is being used less due to the availability of enhanced materials and advances in distal-tip deflection of recent ureteroscopes [126, 129, 130].

7.1.1.3 Segmental resection

Segmental ureteral resection with wide margins provides adequate pathological specimens for staging and grading, while preserving the ipsilateral kidney.

- Ureteroureterostomy is indicated for non-invasive, low-grade tumours of the proximal- or mid-ureter that cannot be removed completely endoscopically, and for high-grade or invasive tumours when renal-sparing surgery for renal function preservation is a goal.
- High-grade tumours of the proximal- or mid-ureter should undergo RNU with bladder cuff excision. Complete distal ureterectomy +/- neocystostomy are indicated for non-invasive, low-grade tumours

in the distal ureter that cannot be removed completely endoscopically, and for high-grade, locally-invasive tumours [131-133] (LE: 3).

- Segmental resection of the iliac and lumbar ureter is associated with greater failure than for the distal pelvic ureter [131-133].
- Open resection of tumours of the renal pelvis or calices has almost disappeared.
- Resection of pyelocaliceal tumours is technically difficult and has higher recurrence than ureteral tumours.

Table 7.1: Guidelines for kidney-sparing management of low-risk upper tract urothelial carcinoma

Indications for endourological management	GR
Unifocal tumour.	B
Tumour < 1 cm.	B
Low-grade tumour.	B
No evidence of infiltrative lesion on CTU.	B
Understanding of close follow-up.	B
Techniques used according to location:	
• Laser should be used for endoscopic treatment.	C
• Flexible is preferable to rigid ureteroscopy: renal pelvis, distal-, mid- and proximal ureter.	C
• Percutaneous approach remains an option for low grade tumours not accessible by ureteroscopic approach.	C
Surgical open approach	
<i>Renal pelvis or calyces:</i> Partial pyelectomy or partial nephrectomy is seldom indicated.	C
<i>Ureter - Mid & proximal:</i> Ureteroureterostomy is indicated for tumours that cannot be removed completely endoscopically.	C
<i>Ureter - Distal:</i> Complete distal ureterectomy and neocystostomy are indicated for tumours in the distal ureter that cannot be removed completely endoscopically.	C

CTU = computed tomography urography; GR = grade of recommendation.

7.1.1.4 Adjuvant topical agents

The antegrade instillation of bacillus Calmette-Guérin (BCG) vaccine or mitomycin C in the upper urinary tract by percutaneous nephrostomy via a three-valve system open at 20 cm (after complete tumour eradication) is feasible after conservative treatment of UTUC or for treatment of CIS [134] (LE: 3). Retrograde instillation through a ureteric stent is also used but it can be dangerous due to possible ureteric obstruction and consecutive pyelovenous influx during instillation/perfusion. The reflux obtained from a double-J stent has been used [135], but is not advisable since it often does not reach the renal pelvis.

7.1.2 Radical nephroureterectomy

Open RNU with bladder cuff excision is the standard for high-risk UTUC, regardless of tumour location [12] (LE: 3). Radical nephroureterectomy must comply with oncological principles, which consist of preventing tumour seeding by avoiding entry into the urinary tract during resection [12].

Resection of the distal ureter and its orifice is performed because there is a considerable risk of tumour recurrence in this area. After removal of the proximal ureter, it is difficult to image or approach it by endoscopy. Removal of the distal ureter and bladder cuff is beneficial after RNU [121, 136, 137]. Regardless of the technique, the surgeon must be confident that the bladder is closed appropriately.

Several techniques have been considered to simplify distal ureter resection, including pluck technique, stripping, transurethral resection of the intramural ureter, and intussusception [9, 137, 138]. Except for ureteral stripping, none of these techniques is inferior to bladder cuff excision [72-74, 80] (LE: 3). Endoscopy is associated with a higher risk of subsequent bladder recurrence [139, 140].

7.1.2.1 Laparoscopic radical nephroureterectomy

Retroperitoneal metastatic dissemination and dissemination along the trocar pathway following manipulation of large tumours in a pneumoperitoneal environment have been reported in only few cases [141, 142].

Several precautions are needed with pneumoperitoneum because it may increase tumour spillage:

- Entering the urinary tract should be avoided;
- Direct contact between instruments and tumour should be avoided;

- Laparoscopic RNU must take place in a closed system. Morcellation of the tumour should be avoided and an endobag is necessary for tumour extraction;
- The kidney and ureter must be removed en bloc with the bladder cuff;
- Invasive or large (T3/T4 and/or N+/M+) tumours are contraindications for laparoscopic RNU until proven otherwise.

Safety of laparoscopic RNU has been demonstrated. There is a tendency towards equivalent oncological outcomes after laparoscopic or open RNU [142-148] (LE: 3).

Only one prospective randomised study has shown that laparoscopic RNU is not inferior to open RNU for non-invasive UTUC [149] (LE: 2). Oncological outcomes after RNU have not changed significantly over the past three decades despite staging and surgical refinements [150] (LE: 3).

7.1.2.2 Lymph node dissection

Anatomical sites of LND have not been clearly defined. The LND template is likely to have a greater impact on patient survival than the number of lymph nodes removed [127].

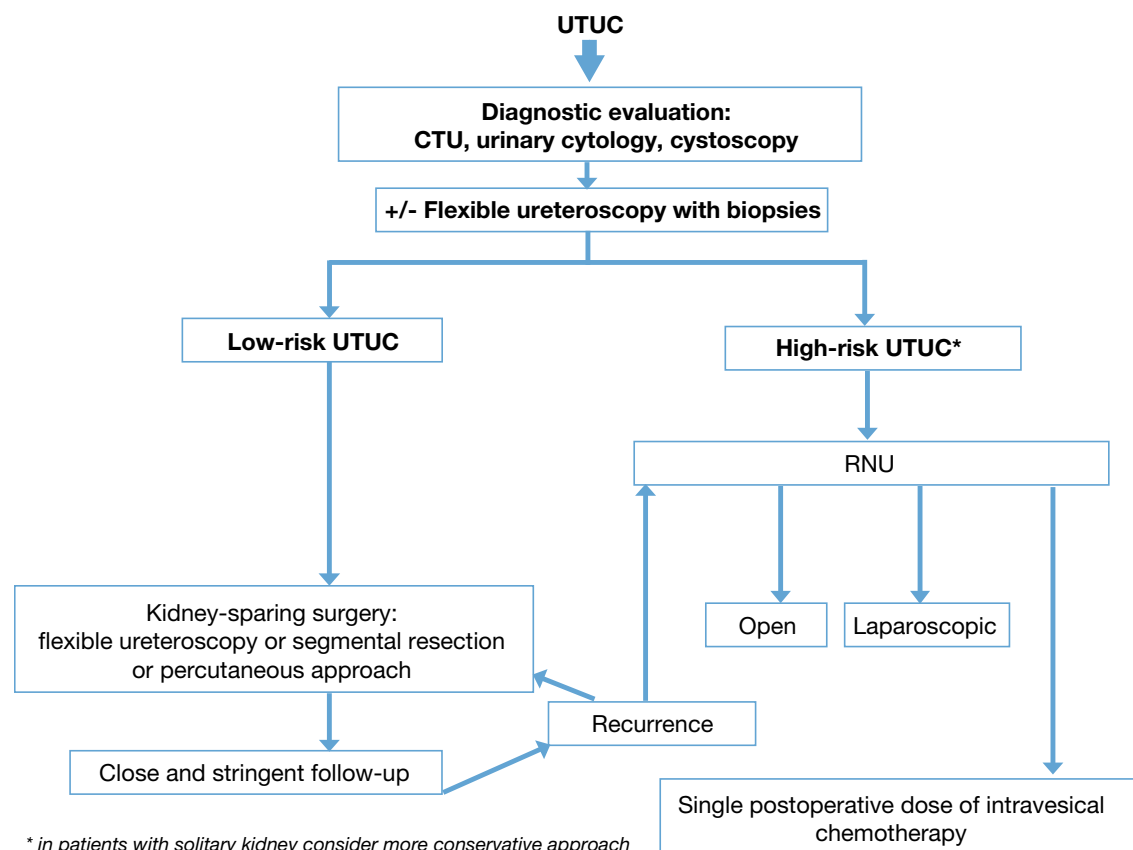
Lymph node dissection appears to be unnecessary in cases of TaT1 UTUC because lymph node retrieval is reported in only 2.2% of T1 versus 16% of pT2-4 tumours [95]. An increase in the probability of lymph-node-positive disease is related to pT classification [95]. However, it is likely that the true rate of node-positive disease has been under-reported because these data are retrospective.

It is not possible to standardise indication or extent of LND. Lymph node dissection can be achieved following lymphatic drainage as follows: LND medial to the ureter in ureteropelvic tumour, retroperitoneal LND for higher ureteral tumour and/or tumour of the renal pelvis (i.e. right side: border vena cava or right side of the aorta; and left side: border aorta) [94, 95, 127].

7.1.2.3 Chemotherapy

One prospective randomised study has demonstrated that a single postoperative dose of intravesical mitomycin on the day of catheter removal reduces the risk of bladder tumour within the first year post-RNU [151] (LE: 2). This therapeutic strategy was confirmed in another prospective trial with pirarubicin [152] and in a meta-analysis [153]. Management is outlined in Figure 7.1.

Figure 7.1: Proposed flowchart for the management of upper tract urothelial carcinoma



CTU = computed tomography urography; RNU = radical nephroureterectomy.

Table 7.2: Guidelines for radical nephroureterectomy in upper tract urothelial carcinoma

Indications for RNU	GR
Suspicion of infiltrating UTUC on imaging.	B
High-grade tumour (urinary cytology).	B
Multifocality (with two functional kidneys).	B
Non-invasive but large (> 1 cm) UTUC.	B
Techniques for RNU	
Open and laparoscopic access has equivalent efficacy in T1-T2/N0 tumours.	B
Bladder cuff removal is imperative.	A
Several techniques for bladder cuff excision are acceptable, except stripping.	C
Lymphadenectomy is recommended for invasive UTUC.	C
Postoperative instillation is recommended after RNU to avoid bladder recurrence.	B

GR = grade of recommendation; RNU = radical nephroureterectomy.

7.2 Advanced disease

7.2.1 Radical nephroureterectomy

There are no benefits of RNU in metastatic disease, although it can be considered as palliative [12, 95] (LE: 3).

7.2.2 Systemic chemotherapy

Upper tract urothelial carcinomas are urothelial tumours; therefore, platinum-based chemotherapy is expected to have similar efficacy as in bladder cancer. However, there are currently insufficient data for recommendations.

There are several platinum-based regimens [154], but the risk of impaired postoperative function means that neoadjuvant chemotherapy is only optional. Not all patients can receive chemotherapy because of comorbidity and impaired renal function after radical surgery. Chemotherapy-related toxicity, particularly nephrotoxicity from platinum derivatives, may significantly reduce survival in patients with postoperative renal dysfunction [155, 156].

There were no adverse effects of neoadjuvant chemotherapy for UTUCs in the only study published to date [157], although survival data need to mature and longer follow-up is awaited.

Adjuvant chemotherapy can achieve a recurrence-free rate of $\leq 50\%$ [158, 159]. After a recent comprehensive search of studies examining the role of chemotherapy for UTUC, there appears to be an overall survival and disease-free survival benefit for cisplatin-based adjuvant chemotherapy [160] (LE: 3). However, it is challenging to make a definitive statement until further evidence from an ongoing prospective trial is available [161].

7.2.3 Radiotherapy

Radiotherapy is no longer relevant, either alone or as an adjunct to chemotherapy [162, 163] (LE: 3).

8. FOLLOW-UP

The risk of recurrence and death evolves over the follow-up after surgery [164]. Stringent follow-up (Table 6) is mandatory to detect metachronous bladder tumours, local recurrence, and distant metastases. When RNU is performed, local recurrence is rare and the risk of distant metastases is directly related to the risk factors listed previously. The rate of bladder recurrence after treatment of primary UTUC is 22-47% [6, 8].

Surveillance regimens are based on cystoscopy and urinary cytology for ≥ 5 years [6-8]. Bladder recurrence should not be considered as distant recurrence. When conservative treatment is performed, the ipsilateral upper urinary tract requires careful follow-up due to the high risk of recurrence [122, 128, 165]. Despite endourological improvements, follow-up after conservative therapy is difficult, and frequent, repeated endoscopic procedures are necessary.

Table 8.1: Guidelines for follow-up of upper tract urothelial carcinoma patients after initial treatment

After RNU, ≥ 5 years	GR
<i>Non-invasive tumour</i>	
• Cystoscopy/urinary cytology at 3 months and then yearly.	C
• CT every year	C
<i>Invasive tumour</i>	
• Cystoscopy/urinary cytology at 3 months and then yearly.	C
• CT urography every 6 months over 2 years and then yearly.	C
After conservative management, ≥ 5 years	
• Urinary cytology and CTU at 3 and 6 months, and then yearly.	C
• Cystoscopy, ureteroscopy and cytology <i>in situ</i> at 3 and 6 months, and then every 6 months over 2 years, and then yearly.	C

CTU = computed tomography urography; GR = grade of recommendation; RNU = radical nephroureterectomy.

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10. CONFLICT OF INTEREST

All members of the Upper Urinary Tract Urothelial Carcinomas Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: <http://www.uroweb.org/guidelines/>. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organization, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

Guidelines on **Muscle-invasive and Metastatic Bladder Cancer**

J.A. Witjes (Chair), E. Compérat, N.C. Cowan, M. De Santis,
G. Gakis, N. James, T. Lebrét, A. Sherif,
A.G. van der Heijden, M.J. Ribal
Guidelines Associates: M. Bruins, V. Hernandez, E. Veskimäe

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1. INTRODUCTION

1.1 Aims and scope

The European Association of Urology (EAU) Guidelines Panel for Muscle-invasive and Metastatic Bladder Cancer (MIBC) has prepared these guidelines to help urologists assess the evidence-based management of MIBC and to incorporate guideline recommendations into their clinical practice.

Separate EAU guidelines documents are available addressing upper urinary tract tumours [1], non-muscle-invasive bladder cancer (Ta, T1 and carcinoma *in situ*) [2], and primary urethral carcinomas [3].

1.2 Panel Composition

The EAU Guidelines Panel consists of an international multidisciplinary group of experts from the fields of urology, pathology, radiology and oncology.

All experts involved in the production of this document have submitted potential conflict of interest statements.

1.3 Available publications

A quick reference document (Pocket guidelines) is available, both in print and in a number of versions for mobile devices. These are abridged versions which may require consultation together with the full text versions. Several scientific publications are available (the most recent paper dating back to 2014 [4]), as are a number of translations of all versions of the EAU MIBC Guidelines. All documents are accessible through the EAU website Uroweb: <http://www.uroweb.org/guidelines/online-guidelines/>.

1.4 Publication history and summary of changes

1.4.1 Publication history

The EAU published its first guidelines on bladder cancer in 2000. This document covered both superficial (non-muscle-invasive) bladder cancer and MIBC. Since these conditions require different treatment strategies, it was decided to give each condition its own guidelines, resulting in the first publication of the MIBC guidelines in 2004. This 2015 document presents a limited update of the 2014 version.

1.4.2 Summary of changes

The literature in the complete document has been assessed and updated, whenever relevant.

Key changes for the 2015 publication:

- Section 7.4.2 on timing and delay of cystectomy was revised.
- Section 7.4.4.2.5 on orthotopic neobladder; additional information on female patients has been included.
- A table on the management of neobladder morbidity (Table 7.1) has been added.
- Section 7.6.4 on multimodality bladder-preserving treatment was completely revised.

Recommendations have been rephrased and added to throughout the current document:

3.3.3 Recommendations for the assessment of tumour specimens

<i>Mandatory evaluations</i>
Depth of invasion (categories pT2 vs pT3a, pT3b or pT4);
Margins with special attention paid to the radial margin, prostate, ureter, urethra and peritoneal fat and uterus and vaginal top.
Histological subtype, if it has clinical implications;
Extensive lymph node representation (more than nine);
<i>Optional evaluations</i>
Bladder wall blood vessel invasion;
Pattern of muscle invasion.

7.2.4 Conclusions and recommendations for neoadjuvant chemotherapy

Conclusions	LE
Neoadjuvant chemotherapy has its limitations regarding patient selection, current development of surgical techniques, and current chemotherapy combinations.	3

Conclusions	LE
No conclusive evidence exists as to the optimal extent of LND.	2a

Conclusions	LE
External beam radiotherapy alone should only be considered as a therapeutic option when the patient is unfit for cystectomy or a multimodality bladder-preserving approach.	3
Radiotherapy can also be used to stop bleeding from the tumour when local control cannot be achieved by transurethral manipulation due to extensive local tumour growth.	3

Recommendation	GR
Radiotherapy alone is not recommended as primary therapy for localised bladder cancer.	B

2. METHODS

2.1 Data identification

The recommendations provided in the current guidelines are based on literature searches performed by the expert panel members. A systemic literature search was performed for the systematic review of the role and extent of lymphadenectomy during radical cystectomy for cN0M0 muscle-invasive bladder cancer (see Section 7.4: Radical surgery and urinary diversion [5]).

There is clearly a need for continuous re-evaluation of the information presented in the current guidelines by an expert panel. It must be emphasised that these guidelines contain information for the treatment of individual patients according to a standardised approach.

In this 2015 EAU Guidelines compilation, all standard information on levels of evidence (LE) and grading of recommendations (GR) has been taken out of the individual guidelines topics for the sake of brevity. This information is included in the introductory section of this print.

2.2 Peer review

This document was subjected to double-blind peer review prior to publication.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Bladder cancer (BC) is the ninth most commonly diagnosed cancer worldwide, with more than 380,000 new cases each year and more than 150,000 deaths per year, and an estimated male-female ratio of 3.8:1.0 [6]. At any one time, 2.7 million people have a history of urinary BC [7].

Recently, overall and stage-specific age-adjusted incidence rates of bladder cancer have been analysed in the U.S. (5-year survival and mortality rates between 1973 and 2009). Although the analysis of the Surveillance, Epidemiology and End Results (SEER) database implies some limitations, it is worrying to note that in the last 30 years the mortality rate associated with BC has not changed substantially, highlighting gaps in diagnosis, monitoring and management of these patients [8].

3.2 Aetiology

3.2.1 Tobacco smoking

Tobacco smoking is the most well-established risk factor for BC, causing 50-65% of male cases and 20-30% of female cases [9]. A causal relationship has been established between exposure to tobacco and cancer in

studies in which chance, bias and confounding can be discounted with reasonable confidence [10].

The incidence of BC is directly related to the duration of smoking and the number of cigarettes smoked per day [11]. A meta-analysis looked at 216 observational studies on cigarette smoking and cancer from 1961 to 2003, and the pooled risk estimates for BC demonstrated a significant association for both current and former smokers [12]. Recently, an increase in risk estimates for current smokers relative to never smokers has been described suggesting this could be due to changes in cigarette composition [9]. An immediate decrease in the risk of BC was observed in those who stopped smoking. The reduction was about 40% within 1-4 years of quitting smoking and 60% after 25 years of cessation [11]. Encouraging people to stop smoking would result in the incidence of BC decreasing equally in men and women.

3.2.2 **Occupational exposure to chemicals**

Occupational exposure is the second most important risk factor for BC. Work-related cases have accounted for 20-25% of all BC cases in several series. The substances involved in chemical exposure include benzene derivatives and aryl amines (2-naphthylamine, 4-ABP, 4,4'-methylenedianiline, and o-toluidine), and it is likely to occur in occupations in which dyes, rubbers, textiles, paints, leathers, and chemicals are used [13]. The risk of BC due to occupational exposure to carcinogenic aromatic amines is significantly greater after 10 years or more of exposure; the mean latency period usually exceeds 30 years [14, 15]. The chemicals involved have contributed minimally to the current incidence of BC in Western countries because of strict regulations. Importantly, in recent years, the extent and pattern of occupational exposure have changed because awareness has prompted safety measures, and population-based studies established the occupational attribution for BC in men to be 7.1%, while no such attribution was discernible for women [16, 17].

3.2.3 **Radiotherapy**

Increased rates of secondary bladder malignancies have been reported after external-beam radiotherapy (EBRT) for gynaecological malignancies, with relative risks of 2-4 [18]. In a population cohort study, the standardised incidence ratios for BC developing after radical prostatectomy (RP), EBRT, brachytherapy (BT), and EBRT-BT were 0.99, 1.42, 1.10, and 1.39, respectively, in comparison with the general U.S. population [19]. It has recently been proposed that patients who have received radiotherapy for prostate cancer with modern modalities such as intensity-modulated radiotherapy (IMRT) may have lower rates of in-field bladder- and rectal secondary malignancies [20]. Nevertheless, since longer follow-up data are not yet available, and as BC requires a long period to develop, patients treated with radiation and with a long life-expectancy are at a higher risk of developing BC [20].

3.2.4 **Dietary factors**

Several dietary factors have been considered to be related to BC; however, the links remain controversial. The EPIC study is an on-going multicentre cohort study designed to examine the association between diet, lifestyle and environmental factors and cancer. They found no links between BC and fluid intake, red meat, vegetable and fruit consumption, and only recently they have described an inverse association between dietary intake of flavonols and lignans and the risk of BC, in particular aggressive tumours [21].

3.2.5 **Bladder schistosomiasis and chronic urinary tract infection**

Bladder schistosomiasis (bilharzia) is the second most common parasitic infection after malaria, with about 600 million people exposed to infection in Africa, Asia, South America, and the Caribbean [22]. There is a well-established relationship between schistosomiasis and squamous cell carcinoma of the bladder, although a better control of the disease is decreasing the incidence of squamous carcinoma of the bladder in endemic zones such as Egypt [23, 24].

Similarly, invasive squamous cell carcinoma has been linked to the presence of chronic urinary tract infection (UTI) distinct from schistosomiasis. A direct association between BC and UTIs has been observed in several case-control studies, which have reported a two-fold increased risk of BC in patients with recurrent UTIs in some series. However, some of these results may be attributed to recall bias [25].

3.2.6 **Gender**

Although men are more likely to develop BC than women, women present with more advanced disease and have worse survival [26].

It has been suggested that women are more likely to be older than men when diagnosed, with a direct effect on their survival. In addition, delayed diagnosis is more likely in women after haematuria is observed, as the differential diagnosis in women includes diseases that are more prevalent than BC [27].

Differences in the gender prevalence of BC may be due to other factors besides tobacco and chemical

exposure. In a large prospective cohort study, postmenopausal status was associated with an increase in BC risk, even after adjustment for smoking status. This result suggests that the differences in oestrogen and androgen levels between men and women may be responsible for some of the difference in the gender prevalence of BC [28-30]. A large German retrospective multicentre study including 2,483 patients submitted to radical cystectomy showed that cancer-specific mortality was higher in female patients. This difference was more pronounced in earlier time periods. These findings could suggest different tumour biology and potentially unequal access to timely radical cystectomy in earlier periods because of reduced awareness of BC in women [31].

3.2.7 Genetic factors

There is growing evidence that genetic susceptibility factors and family associations may influence the incidence of BC. The relationship between family history of cancer and risk of BC was examined in the Spanish Bladder Cancer Study. It was found that family history of cancer in first-degree relatives was associated with an increased risk of BC; the association being stronger among younger patients. Shared environmental exposure was recognised as a potentially confounding factor [32]. These results support the hypothesis that genetic factors play a role in the aetiology of BC.

Genome-wide association studies (GWAS) of BC identified several susceptibility loci associated with BC risk [33, 34]. Polymorphisms in two carcinogen-metabolizing genes, NATS and GSTM1, have been related to BC risk, and furthermore they have demonstrated, together with UGT1A6, to confer additional risk to exposure of carcinogens such as tobacco smoking [35].

3.2.8 Conclusions and recommendations for epidemiology and risk factors

Conclusions	LE
The incidence of muscle-invasive disease has not changed for 5 years.	
Active and passive tobacco smoking continues to be the main risk factor, while the exposure-related incidence is decreasing.	2a
The increased risk of developing bladder cancer in patients undergoing external-beam radiotherapy (EBRT), brachytherapy, or a combination of EBRT and brachytherapy, must be taken into account during patient follow-up. As bladder cancer requires time to develop, patients treated with radiation at a young age are at the greatest risk and should be followed up closely.	3
The estimated male-to-female ratio for bladder cancer is 3.8:1.0. Women are more likely to be diagnosed with primary muscle-invasive disease than men.	3

Recommendations	GR
The principal preventable risk factor for muscle-invasive bladder cancer is active and passive smoking.	B
Notwithstanding stricter regulations, workers should be informed about the potential carcinogenic effects of a number of recognised substances, duration of exposure, and latency periods. Protective measures should be recommended.	A

GR = grade of recommendation; LE = level of evidence.

3.3 Pathology

3.3.1 Handling of transurethral resection and cystectomy specimens

In transurethral resection (TUR) specimens, the superficial and deep areas of the tumour should be sent to the pathology laboratory separately, in case the outcome will impact on treatment decisions. If random biopsies of the flat mucosa are taken, each biopsy specimen of the flat mucosa should also be sent separately.

In radical cystectomy, bladder fixation must be carried out as soon as possible. The pathologist must open the specimen from the urethra to the bladder dome and fix the specimen in formalin. In some circumstances this procedure can also be performed by the urologist. In a female cystectomy specimen, the length of the urethral segment removed en bloc with the specimen should be checked, preferably by the urological surgeon [36].

Specimen handling should follow the general rules as published by a collaborative group of pathologists and urologists [37, 38]. It must be stressed that it may be very difficult to confirm the presence of a neoplastic lesion using gross examination of the cystectomy specimen after TUR or chemotherapy, so the entire retracted or ulcerated area should be included.

It is compulsory to study the urethra, the ureters, the prostate in men and the radial margins [39]. In urethra-sparing cystectomy, the level of urethral dissection, completeness of the prostate specifically at the apex (in men), and the inclusion of the entire bladder neck and amount of adjacent urethra, uterus and vaginal top (in women) should be documented.

All lymph node specimens should be provided in their totality, in clearly labelled containers. In case of doubt, or adipous differentiation of the lymph node, the entire specimen is to be included.

Lymph nodes should be counted and measured on slides, capsular effraction and percentage of lymph node invasion should be reported as well as vascular embols. In the case of metastatic spread in the perivesical fat without real lymph node structures (capsule, subcapsular sinus), this localisation should nevertheless be considered as N+.

Positive margins in the peripelvic fat tissue (soft tissue margins), should be inked by the pathologist for evaluation. Positive margins have decreased cancer-specific survival (CSS) in cases of pNOM0 urothelial carcinomas [40].

In selected cases, fresh frozen sections may be helpful to determine treatment strategy. A recent study confirmed the reliability of fresh frozen sections of obturator lymph nodes, but similar studies are warranted to confirm these results [41].

3.3.2 **Pathology of muscle-invasive bladder cancer**

In muscle-invasive BC there are usually no cases of PUNLMP and low-grade carcinoma. All cases are high-grade urothelial carcinomas (grade II or grade III). For this reason, no more prognostic information can be provided by grading muscle-invasive BC [42]. However, some morphological subtypes can be important in helping with prognosis and treatment decisions. Currently the following differentiation is used:

1. urothelial carcinoma (more than 90% of all cases);
2. urothelial carcinomas with squamous and/or glandular partial differentiation [43, 44];
3. micropapillary urothelial carcinoma;
4. nested carcinoma [45];
5. some urothelial carcinomas with trophoblastic differentiation;
6. small-cell carcinomas [46];
7. spindle cell carcinomas.

3.3.3 **Recommendations for the assessment of tumour specimens**

<i>Mandatory evaluations</i>
Depth of invasion (categories pT2 vs pT3a, pT3b or pT4).
Margins with special attention paid to the radial margin, prostate, ureter, urethra and peritoneal fat and uterus and vaginal top.
Histological subtype, if it has clinical implications.
Extensive lymph node representation (more than nine).
<i>Optional evaluations</i>
Bladder wall blood vessel invasion.
Pattern of muscle invasion.

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 **Pathological staging**

For staging, TNM 2002/2009 (6th or 7th edition) is recommended (both editions are identical for BC). The pattern of muscular invasion can provide some prognostic information. Most cases show nodular or cordonal growth, but about 44% have an infiltrative pattern. According to some authors [42], the median survival time of a patient with an infiltrative pattern is lower than that for an individual with other pattern types ($p = 0.06$). Blood vessel invasion and lymph node infiltration have an independent prognostic significance [47]. It seems that the pN category is closely related to the number of lymph nodes studied by the pathologist [48]. For this reason, some authors have observed that more than nine lymph nodes have to be investigated to reflect pN0 appropriately [49].

New prognostic markers are under study [50]. Currently, insufficient evidence exists to recommend the standard use of the prognostic marker p53 in high-risk muscle-invasive disease, as it will not yield sufficient

data upon which to base treatment in an individual patient.

4.2 Tumour, node, metastasis classification

The tumour, node, metastasis (TNM) classification of malignant tumours is the method most widely used to classify the extent of cancer spread. A seventh edition was published, effective as of 2010 [51] (Table 4.1). There are no significant modifications in it for BC, compared with the previous edition (2002).

Table 4.1: TNM classification of urinary bladder cancer [51]

T - Primary Tumour	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma <i>in situ</i> : “flat tumour”
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
T2a	Tumour invades superficial muscle (inner half)
T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue:
T3a	Microscopically
T3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostate stroma, seminal vesicles, uterus, or vagina
T4b	Tumour invades pelvic wall or abdominal wall
N - Regional Lymph Nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph-node metastasis
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N2	Metastasis in multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N3	Metastasis in common iliac lymph node(s)
M - Distant Metastasis	
M0	No distant metastasis
M1	Distant metastasis

5. DIAGNOSTIC EVALUATION

5.1 Primary diagnosis

5.1.1 Symptoms

Painless haematuria is the most common presenting complaint. Others include urgency, dysuria, increased frequency, and in more advanced tumours, pelvic pain and symptoms related to urinary tract obstruction.

5.1.2 Physical examination

Physical examination should include rectal and vaginal bimanual palpation. A palpable pelvic mass can be found in patients with locally advanced tumours. In addition, bimanual examination under anaesthesia should be carried out before and after TURB, to assess whether there is a palpable mass or if the tumour is fixed to the pelvic wall [52, 53]. However, considering the discrepancy between bimanual examination and pT stage after cystectomy (11% clinical overstaging and 31% clinical understaging), some caution is suggested with the interpretation of bimanual examination [54].

5.1.3 Bladder imaging

Patients with a bladder mass identified by any diagnostic imaging technique should undergo cystoscopy, biopsy and/or resection for histopathological diagnosis and staging.

5.1.4 **Urinary cytology and urinary markers**

Examination of voided urine or bladder washings for exfoliated cancer cells has high sensitivity in high-grade tumours (LE: 3) and is a useful indicator in cases of high-grade malignancy or CIS.

Positive urinary cytology may originate from a urothelial tumour located anywhere in the urinary tract. Evaluation of cytology specimens can be hampered by low cellular yield, UTIs, stones or intravesical instillations, but for experienced readers, specificity exceeds 90% [55, 56] (LE: 2b). However, negative cytology does not exclude tumour. There is no known urinary marker specific for the diagnosis of invasive BC [57].

5.1.5 **Cystoscopy**

Ultimately, the diagnosis of BC is made by cystoscopy and histological evaluation of resected tissue. In general, cystoscopy is initially performed in the office using a flexible instrument. If a bladder tumour has been visualised unequivocally in earlier imaging studies, such as computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound (US), diagnostic cystoscopy may be omitted and the patient can proceed directly to TURB for histological diagnosis. Currently, there is no evidence for the role of photodynamic diagnosis (PDD) in the diagnosis of invasive BC.

A careful description of the cystoscopic findings is necessary. This should include documentation of the site, size, number, and appearance (papillary or solid) of the tumours, as well as a description of mucosal abnormalities. Use of a bladder diagram is recommended.

The use of photodynamic diagnosis could be considered, especially if a T1 high-grade tumour is present, to find associated CIS. The additional presence of CIS may lead to a modified treatment plan (see Section 7.1). Photodynamic diagnosis is highly sensitive for the detection of CIS, but in experienced hands, the rate of false-positive results may be similar to that with regular white-light cystoscopy [58].

5.1.6 **Transurethral resection of invasive bladder tumours**

The goal of TURB is to enable histopathological diagnosis and staging, which requires the inclusion of bladder muscle in the resection biopsies.

The strategy of resection depends on the size of the lesion. Small tumours (< 1 cm in diameter) can be resected *en bloc*, where the specimen contains the complete tumour plus a part of the underlying bladder wall including muscle. Larger tumours need to be resected separately in parts, which include the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle, and the edges of the resection area. At least the deeper part of the resection specimen must be referred to the pathologist in a separate labelled container to enable him/her to make a correct diagnosis. In cases in which radiotherapy is considered and CIS is to be excluded, photodynamic diagnosis can be used [59].

The involvement of the prostatic urethra and ducts in men with bladder tumours has been reported. The exact risk is not known, but it seems to be higher if the tumour is located on the trigone or bladder neck, in the presence of bladder CIS, and in multiple tumours [60, 61] (LE: 3). Involvement of the prostatic urethra can be determined either at the time of primary TURB or by frozen section during the cystoprostatectomy procedure. A frozen section has a higher negative predictive value and is more accurate [62-64].

5.1.7 **Second resection**

In the case of high-grade non-muscle-infiltrative tumour, residual disease is observed in 33-53% of patients [65-71]. In order to reduce the risk of understaging [66, 67], a second TURB resection is often required to determine the future treatment strategy.

Diagnosis of urethral tumour before cystectomy or positive urethral frozen section leads to urethrectomy and therefore excludes neobladder reconstruction. If indicated, in males, urethral frozen section has to be performed on the cysto-prostatectomy specimen just below the verumontanum bladder neck and on the inferior limits of the bladder neck for females.

5.1.8 **Concomitant prostate cancer**

Prostate cancer is found in 25-46% of patients undergoing cystectomy for BC [72, 73]. The impact on survival is unknown, however, the impact on surgical treatment is limited.

5.1.9 **Specific recommendations for the primary assessment of presumably invasive bladder tumours**

(For general information on the assessment of bladder tumours, see EAU Guidelines on Non-muscle-invasive Bladder cancer [2]).

Conclusion	LE
Currently, treatment decisions cannot be based on molecular markers.	3

Recommendations	GR
Cystoscopy should describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities. A bladder diagram is recommended.	C
Biopsy of the prostatic urethra is recommended for cases of bladder neck tumour, when bladder CIS is present or suspected, when there is positive cytology without evidence of tumour in the bladder, or when abnormalities of the prostatic urethra are visible.	
If biopsy is not performed during the initial procedure, it should be completed at the time of the second resection.	C
In women undergoing subsequent orthotopic neobladder construction, procedural information is required (including histological evaluation) of the bladder neck and urethral margin, either prior to or at the time of cystoscopy.	C
The pathological report should specify the grade, depth of tumour invasion, and whether the lamina propria and muscle tissue are present in the specimen.	C

CIC = carcinoma in situ; GR = grade of recommendation; LE = level of evidence.

5.2 Imaging for staging of MIBC

The treatment and prognosis of MIBC is determined by tumour stage and grade [74]. In clinical practice, CT and MRI are the imaging techniques used. The purpose of using imaging for staging MIBC is to determine prognosis and provide information to assist treatment selection. Tumour staging must be accurate to ensure that the correct choice of treatment is made. Imaging parameters required for staging MIBC are:

- extent of local tumour invasion;
- tumour spread to lymph nodes;
- tumour spread to the upper urinary tract (UUT) and other distant organs (e.g., liver, lungs, bones, peritoneum, pleura, and adrenal glands).

5.2.1 Local staging of MIBC

Both CT and MRI may be used for assessment of local invasion, but they are unable to accurately diagnose microscopic invasion of perivesical fat (T2 versus T3a) [75]. The principal aim of CT and MRI is therefore to detect T3b disease or higher.

5.2.1.1 MRI for local staging of invasive bladder cancer

Magnetic resonance imaging has superior soft tissue contrast resolution compared with CT, but poorer spatial resolution. In studies performed before the availability of multidetector CT, MRI was reported as more accurate in local assessment. The accuracy of MRI for primary tumour staging varies from 73% to 96% (mean 85%). These values were 10-33% (mean 19%) higher than those obtained with CT [76]. Dynamic contrast-enhanced (DCE) MRI may help to differentiate bladder tumour from surrounding tissues or post-biopsy reaction, because enhancement of the tumour occurs earlier than that of the normal bladder wall, due to neovascularisation [77-79].

In 2006, a link was established between the use of gadolinium-based contrast agents and nephrogenic systemic fibrosis (NSF), which may result in fatal or severely debilitating systemic fibrosis. Patients with impaired renal function are at risk of developing NSF and the non-ionic linear gadolinium-based contrast agents should be avoided (gadodiamide, gadopentetate dimeglumine and gadoversetamide). A stable macrocyclic contrast agent should be used (gadobutrol, gadoterate meglumine or gadoteridol). Contrast-enhanced CT using iodinated contrast media should be considered as an alternative [80] (LE: 4).

5.2.1.2 CT imaging for local staging of MIBC

The advantages of CT include high spatial resolution, shorter acquisition time, wider coverage in a single breath hold, and lower susceptibility to variable patient factors. Computed tomography is unable to differentiate between stages from Ta to T3a tumours, but it is useful for detecting invasion into the perivesical fat (T3b) and adjacent organs. The accuracy of CT in determining extravesical tumour extension varies from 55% to 92% [81] and increases with more advanced disease [82].

5.2.2 Imaging of lymph nodes in MIBC

Assessment of lymph node metastases based solely on size is limited by the inability of both CT and MRI to identify metastases in normal-sized or minimally enlarged nodes. The sensitivity for detection of lymph node metastases is low (48-87%). Specificity is also low because nodal enlargement may be due to benign disease. Overall, CT and MRI show similar results in the detection of lymph node metastases in a variety of primary pelvic tumours [83-88]. Pelvic nodes > 8 mm and abdominal nodes > 10 mm in maximum short-axis diameter, detected by CT or MRI, should be regarded as pathologically enlarged [89, 90].

Currently, there is no evidence supporting the routine use of positron emission tomography (PET) in the nodal staging of BC, although the method has been evaluated with varying results in small prospective trials [91-94].

5.2.3 **Upper urinary tract urothelial carcinoma**

Excretory-phase CT urography is the imaging technique with the highest diagnostic accuracy for upper urinary tract urothelial carcinoma (UTUC) and has replaced conventional intravenous urography and US as the first-line imaging test for investigating high-risk patients [95]. The sensitivity of CT urography for UTUC is reported to range from 0.67 to 1.0 and specificity from 0.93 to 0.99, depending on the technique used [96-103]. Attention to technique is therefore important for optimum results.

For UTUC detected by CT urography, a biopsy for histopathological confirmation of diagnosis is recommended to eliminate false-positive results and to provide information regarding the grade of the tumour to aid in the choice of treatment [97, 98, 104-106]. The biopsy is usually performed endoscopically.

5.2.4 **Distant metastases at sites other than lymph nodes**

Prior to any curative treatment, it is essential to evaluate the presence of distant metastases. Computed tomography and MRI are the diagnostic techniques of choice to detect lung [107] and liver metastases [108], respectively. Bone and brain metastases are rare at the time of presentation of invasive BC. A bone scan and additional brain imaging are therefore not routinely indicated unless the patient has specific symptoms or signs to suggest bone or brain metastases [109, 110]. Magnetic resonance imaging is more sensitive and specific for diagnosing bone metastases than bone scintigraphy [111, 112] (LE: 2b).

5.2.5 **Future developments**

Evidence is accruing in the literature suggesting that fluorodeoxyglucose (FDG)-PET/CT might have potential clinical use for staging metastatic BC [113, 114], but there is no consensus as yet. The results of further trials are awaited before a recommendation can be made. Recently, the first study was published showing the superior feasibility of diffusion-weighted imaging (DWI) over T2-weighted and DCE MRI for assessing the therapeutic response to induction chemotherapy against MIBC [115]. The high specificity of DWI indicates that it is useful for accurate prediction of a complete histopathological response, allowing better patient selection for bladder-sparing protocols. Results from prospective studies are awaited.

5.2.6 **Conclusion and recommendations for staging in MIBC**

Conclusion	LE
Imaging as part of staging in MIBC provides information about prognosis and assists in selection of the most appropriate treatment.	2b
There are currently insufficient data on the use of DWI and FDG-PET/CT in MIBC to allow a recommendation to be made.	

Recommendations	GR
In patients with confirmed MIBC, CT of the chest, abdomen and pelvis is the optimal form of staging, including excretory-phase CT urography for complete examination of the upper urinary tract.	B
Excretory-phase CT urography is preferred to MR urography for the diagnosis of UTUC in terms of greater diagnostic accuracy, less cost, and greater patient acceptability. MR urography is used when CT urography is contraindicated for reasons related to contrast administration or radiation dose.	C
Endoscopically-guided biopsy is recommended for histopathological confirmation of preoperative diagnosis of UTUC.	C
CT or MRI is recommended for staging locally advanced or metastatic disease in patients in whom radical treatment is being considered.	B
CT and MRI are generally equivalent for diagnosing local disease and distant metastases in the abdomen. CT is preferred for diagnosis of pulmonary metastases.	C

CT = computed tomography; DWI = diffusion-weighted imaging; FDG-PET/CT = fluorodeoxyglucose-positron emission tomography; GR = grade of recommendation; LE = level of evidence; MIBC = muscle-invasive bladder cancer; MRI = magnetic resonance imaging; UTUC = upper urinary tract urothelial carcinoma.

6. PROGNOSIS

6.1 Introduction

The treatment and prognosis for MIBC is determined by tumour stage and grade [74]. In clinical practice, CT and MRI are the imaging techniques used.

6.2 MIBC and comorbidity

Complications related to radical cystectomy may be directly related to pre-existing comorbidity as well as the surgical procedure, bowel anastomosis, or urinary diversion. A significant body of literature has evaluated the usefulness of age as a prognostic factor for radical cystectomy [116-118]. Advanced age has been identified as a risk factor for complications in the case of radical cystectomy, although chronological age is less important than biological age. Other risk factors for morbidity include prior abdominal surgery, extravesical disease, and prior radiotherapy [119], while an increased body mass index is associated with a higher rate of wound dehiscence and hernia [120].

6.2.1 Evaluation of comorbidity

Rochon et al. have shown that evaluation of comorbidity provides a better indicator of life expectancy in MIBC than patient age [121]. The evaluation helps to identify the medical conditions likely to interfere with, or have an impact on, treatment and the evolution and prognosis of MIBC [122].

The value of assessing overall health before recommending and proceeding with surgery was emphasised by Zietman et al., has demonstrated an association between comorbidity and adverse pathological and survival outcome following radical cystectomy [123]. Similar results were found for the impact of comorbidity on cancer-specific and other-cause mortality in a population-based competing risk analysis of > 11,260 patients from the SEER registries. Age carried the highest risk for other-cause mortality but not for increased cancer-specific death, while the stage of locally advanced tumour was the strongest predictor for decreased CSS [124]. Stratifying elderly patients according to their risk-benefit profile using a multidisciplinary approach will help to select patients most likely to benefit from radical surgery and to optimise treatment outcomes [125]. Unfortunately, most series evaluating radical cystectomy do not include indices of comorbidity in the patient evaluation.

6.2.2 Comorbidity scales, anaesthetic risk classification and geriatric assessment

A range of comorbidity scales has been developed [126]; six of which have been validated [127-132] (LE: 3).

The Charlson Comorbidity Index (CCI) ranges from 0 to 30 according to the importance of comorbidity described at four levels and is calculated by healthcare practitioners from the patients' medical records. The score has been widely studied in patients with BC and found to be an independent prognostic factor for perioperative mortality [133, 134], overall mortality [135], and cancer-specific mortality [136-139]. Only the age-adjusted version of the CCI was correlated with both cancer-specific and other-cause mortality [140].

The age-adjusted CCI (Table 6.1) is the most widely used comorbidity index in cancer for estimating long-term survival and is easily calculated [141].

Table 6.1: Calculation of the Charlson Comorbidity Index

Number of points	Conditions
1 point	50-60 years Myocardial infarction Heart failure Peripheral vascular insufficiency Cerebrovascular disease Dementia Chronic lung disease Connective tissue disease Ulcer disease Mild liver disease Diabetes
2 points	61-70 years Hemiplegia Moderate to severe kidney disease Diabetes with organ damage Tumours of all origins

3 points	71-80 years Moderate to severe liver disease
4 points	81-90 years
5 points	> 90 years
6 points	Metastatic solid tumours AIDS

Interpretation

1. Calculate Charlson Score or Index = i
 - a. Add comorbidity score to age score
 - b. Total denoted as 'i' in the Charlson Probability calculation (see below). i = sum of comorbidity score to age score
2. Calculate Charlson Probability (10-year mortality)
 - a. Calculate $Y = 10^{(i \times 0.9)}$
 - b. Calculate $Z = 0.983^Y$ (where Z is the 10-year survival)

Health assessment of oncology patients must be supplemented by measuring their activity level. Extermann et al. have shown that there is no correlation between morbidity and competitive activity level [142]. Eastern Cooperative Oncology Group (ECOG) PS scores and Karnofsky index have been validated to measure patient activity [143] (LE: 3). PS is correlated with patient OS after radical cystectomy [138, 144] and palliative chemotherapy [145-147].

The ASA score has been validated to assess the risk of postoperative complications prior to surgery. In the BC setting, ASA scores ≥ 3 are associated with major complications [148, 149], particularly those related to the type of urinary diversion (Table 6.2) [150]. However, the ASA score is not a comorbidity scale and should not be used as such.

Table 6.2: ASA score [151]

ASA	
1	No organic pathology, or patients in whom the pathological process is localised and does not cause any systemic disturbance or abnormality.
2	A moderate but definite systemic disturbance caused either by the condition that is to be treated or surgical intervention, or which is caused by other existing pathological processes.
3	Severe systemic disturbance from any cause or causes. It is not possible to state an absolute measure of severity, as this is a matter of clinical judgment.
4	Extreme systemic disorders that have already become an imminent threat to life, regardless of the type of treatment. Because of their duration or nature, there has already been damage to the organism that is irreversible.
5	Moribund patients not expected to survive 24 h, with or without surgery.

According to a consensus conference of the National Institutes of Health, the aim of the Standardized Geriatric Assessment (SGA) is to discover, describe and explain the many problems of elderly people, to catalogue their resources and strengths, to assess individual service needs, and to develop a coordinated plan of care. The SGA can be carried out by means of several protocols. These protocols differ in the completeness of diagnostic research. The protocol is the most complete Comprehensive Geriatric Assessment (CGA) [152]. The CGA is suited to the care of cancer patients [153]. In BC, the CGA has been used to adapt gemcitabine chemotherapy in previously untreated elderly patients with advanced bladder carcinoma [154].

6.2.3 Conclusions and recommendations for comorbidity scales

Conclusions	LE
Chronological age is of limited relevance	3
A comorbidity score developed in particular for assessment of patients diagnosed with bladder cancer would be helpful.	3

Recommendations	GR
The decision regarding bladder-sparing or radical cystectomy in elderly/geriatric patients with invasive bladder cancer should be based on tumour stage and comorbidity best quantified by a validated score, such as the Charlson Comorbidity Index.	B
The ASA score does not address comorbidity and should not be used in this setting.	B

ASA = American Society of Anesthesiologists; GR = grade of recommendation; LE = level of evidence.

7. DISEASE MANAGEMENT

7.1 Treatment failure of non-muscle-invasive bladder cancer

7.1.1 High-risk non-muscle-invasive urothelial carcinoma

The recurrence and progression rates of non-muscle-invasive BC (NMIBC) is strongly associated with several factors as described in the EORTC risk calculator [155]. According to this calculator, the risk of progression after 5 years ranges from 6 to 45% for high-risk tumours. However, in a prospective, multicentre trial, the progression rate was significantly lower than previously reported, even when the presence of concomitant CIS was considered. This was probably due to the combination of a second resection, prior to inclusion in the trial and maintenance treatment as part of the protocol [156]. Meta-analyses have demonstrated that Bacillus Calmette-Guérin (BCG) therapy prevents the risk of tumour recurrence [157, 158].

Two other meta-analyses have shown that BCG therapy decreases the risk of tumour progression [159, 160] but so far, no significant overall- or disease-specific survival advantages have been shown, as compared to no intravesical therapy [159-161].

As also reported in the EAU NMIBC guidelines, there are reasons to consider cystectomy in selected patients with NMIBC [2].

There is a risk of an understaging error in Ta, T1 tumours of 35-62% presented in large cystectomy series. This seems due to the presence of persisting or recurrent tumours due to the lack of a second TURB or re-TURB and the absence of neoadjuvant therapy [162-164]. Second TURB identifies 24-49% of T2 tumours that have been diagnosed initially as non-muscle-invasive tumours [67, 165]. Progression to MIBC significantly decreases cancer-specific survival (CSS). In a review of 19 trials including 3,088 patients, CSS after progression from NMIBC to MIBC was 35%, which is significantly worse compared to patients with MIBC without a history of NMIBC. This underlines the need to recommend early radical treatment, such as f.i. radical cystectomy, in the case of intravesical therapy failure [2, 166, 167].

According to the EAU NMIBC Guidelines, it is reasonable to propose immediate radical cystectomy to those patients with non-muscle-invasive tumour who are at highest risk of progression [166]. These are:

- T1 tumour
- G3** (high-grade) tumour
- CIS
- Multiple and recurrent and large (> 3 cm) Ta G1G2 tumours (all conditions must be presented in this point)*.

*low grade is a mixture of G1 and G2.

** high grade is a mixture of some G2 and all G3.

Although the percentage of patients with primary Ta, T1 tumours and the indication for cystectomy in Ta, T1 tumours is not specified in large cystectomy series, the 10-year recurrence-free survival rate is ~80% and similar to that with TURB and BCG maintenance therapy [2, 163, 168, 169] (LE: 3).

Radical cystectomy is also strongly recommended in patients with BCG-refractory tumours, defined in the NMIBC guideline as:

- whenever muscle-invasive tumour is detected during follow-up;
- if high-grade, non-muscle-invasive papillary tumour is present at 3 months;
- if CIS (without concomitant papillary tumour) is present at both 3 and 6 months;
- If high-grade tumour appears during BCG therapy;
- high-grade recurrence after BCG (Recurrence of high-grade/grade 3 [WHO 2004/1973] tumour after completion of BCG maintenance, despite an initial response).

Patients with disease recurrence within 2 years of initial TURB plus BCG therapy have a better outcome than patients who already have muscle-invasive disease, indicating that cystectomy should be performed at first recurrence, even in non-muscle-invasive disease [167] (LE: 3; GR: C).

There are now several bladder-preservation strategies available that can be categorised as immunotherapy, chemotherapy, device-assisted therapy, and combination therapy [170]. However, experience is limited and treatments other than radical cystectomy must be considered oncologically inferior at the present time [171-173].

7.1.2 **Recommendations for treatment failure of non-muscle-invasive bladder cancer**

Recommendations	GR
In all T1 tumours at high risk of progression (i.e., high grade, multifocality, CIS, and tumour size, as outlined in the EAU guidelines for non-muscle-invasive bladder cancer [2]), immediate radical treatment is an option.	C
In all T1 patients failing intravesical therapy, radical treatment should be offered.	B

CIS = carcinoma in situ; GR = grade of recommendation.

7.2 **Neoadjuvant chemotherapy**

7.2.1 **Introduction**

The standard treatment for patients with muscle-invasive BC is radical cystectomy. However, this gold standard only provides 5-year survival in about 50% [164, 174-177]. To improve these unsatisfactory results, neoadjuvant chemotherapy (NAC) has been used since the 1980s [178, 179].

There are many advantages and disadvantages of administering chemotherapy before planned definitive surgery to patients with operable muscle-invasive urothelial carcinoma of the bladder and cN0M0:

- Chemotherapy is delivered at the earliest time-point, when the burden of micrometastatic disease is expected to be low.
- Potential reflection of in vivo chemosensitivity.
- Tolerability of chemotherapy and patient compliance are expected to be better pre-cystectomy.
- Patients might respond to NAC and reveal a favourable pathological status, determined mainly by achieving pT0, pN0 and negative surgical margins.
- Delayed cystectomy might compromise the outcome in patients not sensitive to chemotherapy [180, 181], although published studies on the negative effect of delayed cystectomy only entail series of chemo-naïve patients. There are no trials indicating that delayed surgery, due to NAC, has a negative impact on survival.
- Neoadjuvant chemotherapy does not seem to affect the outcome of surgical morbidity. In one randomised trial the same distribution of grade 3-4 postoperative complications was seen in both trial arms [182].

In the combined Nordic trials (n = 620), NAC did not have any major adverse effect on the percentage of performable cystectomies. The cystectomy frequency was 86% in the experimental arm and 87% in the control arm, 71% received all three chemotherapy cycles [183].

- Clinical staging using bimanual palpation, CT or MRI may often result in over- and understaging and have a staging accuracy of only 70% [184, 185]. Overtreatment is a possible negative consequence.
- NAC should only be used in patients eligible for cisplatin combination chemotherapy; other combinations (or monotherapies) are inferior in metastatic BC and have not been tested adequately in the neoadjuvant setting [182, 186-198].

7.2.2 **The role of imaging and biomarkers to identify responders**

In small published series entailing imaging, attempts to identify the responders among patients undergoing NAC, suggested that response after two cycles of treatment is related to outcome. To date, no firm conclusions can be made [199, 200]. The definition of stable disease after two cycles of NAC is still undefined. To identify progression during NAC, imaging is being used in many centres, notwithstanding the lack of supporting evidence.

For responders to NAC, especially in those with a complete response (pT0 N0), treatment has a major positive impact on overall survival (OS) [201]. The overtreatment of non-responders and patients in the non-target population (i.e. patients without micrometastatic disease) are major drawbacks of NAC. Preoperative

identification of responders utilizing tumour molecular profiling in TURB specimens might guide the use of NAC [202, 203] (see Section 7.8.11 - Biomarkers). In addition, imaging methods for the early identification of responders during treatment have been explored. So far, neither PET, CT, nor conventional MRI or DCE MRI can accurately predict response [199, 200, 204, 205].

7.2.3 Summary of available data

Several randomised phase III trials have addressed the question of NAC improving survival, with conflicting results [182, 186-195, 206-211]. The main differences in trial design were the type of chemotherapy (i.e. single-agent cisplatin or combination chemotherapy) and the number of cycles planned. From the statistical point of view, the studies differed in size, patient characteristics (e.g. clinical T-stages included) and the type of definitive treatment allowed (cystectomy and/or radiotherapy). Patients had to be fit for cisplatin. As a result of the lack of clarity, even though a considerable number of randomised trials had been performed, three meta-analyses were undertaken to answer the important question of whether NAC prolongs survival or not [196-198].

In the most recent meta-analysis, published in 2005 [198], with updated patient data from 11 randomised trials (3,005 patients), a significant survival benefit was shown in favour of NAC. The results of this analysis confirmed the previously published data and showed a 5% absolute improvement in survival at 5 years. The Nordic combined trial showed an absolute benefit of 8% survival at 5 years and 11% in the clinical T3 subgroup, translating into nine patients needed to treat [183]. Only cisplatin combination chemotherapy with at least one additional chemotherapeutic agent resulted in a meaningful therapeutic benefit [196, 198]; the regimens tested were MVA(E)C, CMV, CM, cisplatin/adriamycin, cisplatin/5-fluorouracil (5-FU), and CarboMV. More modern chemotherapy regimens like gemcitabine/cisplatin have shown similar pT0/pT1 rates as MVAC in the most recent retrospective series and pooled data analysis, but have not been used in randomised controlled trials [212-215].

The updated analysis of the largest randomised phase III trial [186] with a median follow-up of 8 years confirmed previous results and provided some additional interesting findings:

- 16% reduction in mortality risk;
- Improvement in 10-year survival from 30% to 36% with neoadjuvant CMV;
- Benefit with regard to distant metastases; No benefit for locoregional control and locoregional disease-free survival, with the addition of neoadjuvant CMV independent of the definitive treatment.

The presence of micrometastases is postulated to be lower in smaller tumours (T2) compared to more extensive tumours (T3b-T4b). T4 stage tumours are prone to a higher degree of clinical understaging because macrometastatic nodal deposits are detected more often in post-cystectomy specimens of these extensive tumours [183]. Further data support the use of NAC in the T2b-T3b tumour subgroup (former classification T3), which has shown to provide a modest but substantial improvement in long-term survival and significant downstaging [201].

7.2.4 Conclusions and recommendations for neoadjuvant chemotherapy

Conclusions	LE
Neoadjuvant chemotherapy has its limitations regarding patient selection, current development of surgical techniques, and current chemotherapy combinations.	3
Neoadjuvant cisplatin-containing combination chemotherapy improves OS (5-8% at 5 years).	1a
Neoadjuvant treatment of responders, and especially patients who show complete response (pT0 N0) has a major impact on OS.	2
Currently, no tools are available to select patients who have a higher probability of benefitting from neoadjuvant chemotherapy. In the future, genetic markers, in a personalised medicine setting, might facilitate the selection of patients for neoadjuvant chemotherapy and differentiate responders from non-responders.	

Recommendations	GR
Neoadjuvant chemotherapy is recommended for T2-T4a, cN0M0 bladder cancer and should always be cisplatin-based combination therapy.	A
Neoadjuvant chemotherapy is not recommended in patients who are ineligible for cisplatin-based combination chemotherapy.	A

GR = grade of recommendation; LE = level of evidence; OS = overall survival.

7.3 Pre- and postoperative radiotherapy in muscle-invasive bladder cancer

There is very limited and only older data on adjuvant radiotherapy after radical cystectomy. However, advances in targeting, reducing damage to surrounding tissue, may yield better results in the future [216]. A recent RCT in 100 patients, comparing pre-operative versus post-operative radiotherapy and radical cystectomy, showed comparable OS, DFS and complication rates [217]. Approximately half of these patients had UC, while the other half had squamous cell carcinoma.

7.3.1 Pre-operative radiotherapy

7.3.1.1 Retrospective studies

Several old and retrospective studies reporting on pre-operative radiotherapy at doses over 40 Gy, followed after 4-6 weeks by cystectomy, showed down-staging, improved local control, especially in T3b tumours, and an improved survival, especially in complete responders to radiotherapy (references available upon request). However, these results cannot be used as a basis for modern Guideline advice due to major study limitations, including concomitant chemotherapy and differences in surgery and radiotherapy. This conclusion was supported by a 2003 systematic review [218]. A more recent retrospective study compared the long-term outcome of pre-operative versus no pre-operative radiotherapy in clinical T1-3 tumours [219]. Down-staging to T0 after cystectomy occurred in 7% (7/97) without radiotherapy versus 57% (51/90) with radiotherapy. In cT3 tumours, these results were 0% (0/16) versus 59% (19/34), respectively. Down-staging resulted in a longer PFS.

7.3.1.2 Randomised studies

Six randomised studies were published investigating pre-operative radiotherapy, although again from several decades ago. In the largest trial, pre-operative radiotherapy at a dose of 45 Gy was used in patients with muscle-invasive tumours [220]. There was a significant increase in pCR (9% to 34%) in favour of pre-operative radiotherapy, which was also a prognostic factor for better survival. The OS data was difficult to interpret because chemotherapy was used in a subset of patients and > 50% of patients (241/475) did not receive the planned treatment and were excluded for the final analyses. Two smaller studies using a dose of 20 Gy did not show a survival advantage or only a small advantage in \geq T3 tumours [221, 222]. Two other small trials confirmed down-staging after pre-operative radiotherapy [223, 224].

A meta-analysis of the above five randomised trials showed an odds ratio for the difference in 5-year survival of 0.71 (95% CI: 0.48-1.06) in favour of pre-operative radiotherapy [225]. However, the meta-analysis was potentially biased by the patients in the largest trial who were not given the planned treatment. When the largest trial was excluded, the odds ratio was 0.94 (95% CI: 0.57-1.55, which is not significant).

7.3.2 Conclusions and recommendations for pre- and postoperative radiotherapy

Conclusions	LE
No data exist to support that pre-operative radiotherapy for operable MIBC increases survival.	2a
Pre-operative radiotherapy for operable MIBC, using a dose of 45-50 Gy in fractions of 1.8-2 Gy, results in down-staging after 4-6 weeks.	2
Limited high-quality evidence supports the use of pre-operative radiotherapy to decrease local recurrence of MIBC after radical cystectomy.	3

Recommendations	GR
Pre-operative radiotherapy is not recommended to improve survival.	A
Pre-operative radiotherapy for operable MIBC can result in tumour down-staging after 4-6 weeks.	C

GR = grade of recommendation; LE = level of evidence; MIBC = muscle-invasive bladder cancer.

7.4 Radical surgery and urinary diversion

7.4.1 Removal of the tumour-bearing bladder

7.4.1.1 Introduction

Radical cystectomy is the standard treatment for localised MIBC in most Western countries [164, 226]. Recent interest in patients' quality of life (QoL) has promoted the trend toward bladder-preserving treatment modalities, such as radio- and/or chemotherapy (see Sections 7.2 and 7.6). Performance status (PS) and age influence the choice of primary therapy, as well as the type of urinary diversion, with cystectomy being reserved for younger patients without concomitant disease and with a better PS. The value of assessing overall health before recommending and proceeding with surgery was emphasised in a multivariate analysis [136]. The analysis found an association between comorbidity and adverse pathological and survival outcome following radical cystectomy [136]. Performance status and comorbidity have a different impact on treatment outcomes and must be evaluated independently [142].

Controversy remains regarding age, radical cystectomy and the type of urinary diversion. Cystectomy is associated with the greatest risk reduction in disease-related and non-disease-related death in patients aged > 80 years [136]. The largest, retrospective, single-institution study on cystectomy to date found that patients aged > 80 years had increased postoperative morbidity, but not increased mortality. Although some patients successfully underwent a neobladder procedure, most patients were treated with an ileal conduit diversion [227].

It is particularly important to evaluate the function and QoL of elderly patients using a standardised geriatric assessment, as well as carrying out a standard medical evaluation (see Section 6.2) [228].

7.4.2 Timing and delay of cystectomy

Nielsen et al. reported that a delay of radical cystectomy > 3 months in three American centres, was not associated with a worse clinical outcome [229]. Ayres et al. investigated whether a delay > 3 months would have the same effect in England [230]. Initially they found, in agreement with Nielsen et al, that cystectomy within 90 days of diagnosis had no effect on OS for MIBC (n = 955). However, analysis of T2 tumours showed a statistically significant survival benefit if patients had surgery within 90 days of diagnosis (n = 543; HR 1.40, 95% CI 1.10-1.79). A population-based study from the US SEER-database analysed patients who underwent a cystectomy between 1992 and 2001, also concluded that a delay of more than 12 weeks has a negative impact on outcome and should be avoided [231].

7.4.2.1 Indications

Traditionally, radical cystectomy was recommended for patients with MIBC T2-T4a, N0-Nx, M0 [226]. Other indications include high-risk and recurrent superficial tumours, BCG-resistant Tis, T1G3 (see Section 7.1), as well as extensive papillary disease that cannot be controlled with TURB and intravesical therapy alone. Salvage cystectomy is indicated in non-responders to conservative therapy, recurrence after bladder-sparing treatment, and non-urothelial carcinoma (these tumours respond poorly to chemo- and radiotherapy). It is also used as a purely palliative intervention, including in fistula formation, for pain or recurrent visible haematuria (macrohaematuria) (see Section 7.5.1 - Palliative cystectomy).

When there are positive lymph nodes, in the case of N1 involvement (metastasis in a single node in the true pelvis) orthotopic neobladder can still be considered, but not in N2 or N3 tumours [232].

7.4.3 Radical cystectomy: technique and extent

In men, standard radical cystectomy includes removal of the bladder, prostate, seminal vesicles, distal ureters, and regional lymph nodes. In women, standard radical cystectomy includes removal of the bladder, entire urethra and adjacent vagina, uterus, distal ureters, and regional lymph nodes [233]. Controversies in evaluating the clinical significance of lymphadenectomy are related to two main aspects of nodal dissection: therapeutic procedure and/or staging instrument.

Two important autopsy investigations for radical cystectomy have been performed so far. The first investigation showed that in 215 patients with MIBC and nodal dissemination, the frequency of metastasis was 92% in regional (perivesical or pelvic), 72% in retroperitoneal, and 35% in abdominal lymph nodes. There was also a significant correlation between nodal metastases and concomitant distant metastases ($P < 0.0001$). Approximately 47% of the patients had both nodal metastases and distant dissemination and only 12% of the patients had nodal dissemination as the sole metastatic manifestation [234]. The second autopsy investigation focussed on the nodal yield when super-extended pelvic lymph node dissection (LND) was performed. Substantial inter-individual differences were found with counts ranging from 10 to 53 nodes [235]. These findings demonstrate the limited utility of node count as a surrogate for extent of dissection.

Regional lymph nodes have been shown to consist of all pelvic lymph nodes below the bifurcation of the aorta [236-240]. Mapping studies have also found that skip lesions at locations above the bifurcation of the aorta, without more distally located lymph node metastases, are rare [240, 241].

The extent of LND has not been established to date. Standard lymphadenectomy in bladder cancer patients involves removal of nodal tissue cranially up to the common iliac bifurcation, with the ureter being the medial border, and including the internal iliac, presacral, obturator fossa and external iliac nodes [242]. Extended lymphadenectomy includes all lymph nodes in the region of the aortic bifurcation, and presacral and common iliac vessels medial to the crossing ureters. The lateral borders are the genitofemoral nerves, caudally the circumflex iliac vein, the lacunar ligament and the lymph node of Cloquet, as well as the area described for standard lymphadenectomy [242-246]. A super-extended lymphadenectomy extends cranially to the level of the inferior mesenteric artery [247, 248].

In order to assess how and if cancer outcome is influenced by the extent of lymphadenectomy in patients with clinical N0M0 MIBC, a systematic review of the literature was undertaken [5]. Out of 1,692 abstracts retrieved and assessed, 19 studies fulfilled the review criteria and were included [242-246, 248-261]. All five studies comparing LND versus no LND reported a better oncological outcome for the former group. Seven out of 12 studies comparing (super-)extended with limited or standard LND reported a beneficial outcome for (super-)extended in at least a subset of patients. No difference in outcome was reported between extended and super-extended LND in the two high-volume-centre studies identified [248, 259].

Two other reviews reported that more limited pelvic LND was associated with suboptimal staging as well as poorer outcome compared with standard or extended LND [262, 263]. However, all of these identified studies suffered from significant methodological limitations and were prone to bias, thereby compromising the quality and reliability of the evidence. Further data from on-going randomised trials on the therapeutic impact of the extent of lymphadenectomy are awaited.

It has been suggested that progression-free survival as well as OS might be correlated with the number of lymph nodes removed during surgery, although there are no data from randomised controlled trials on the minimum number of lymph nodes that should be removed. Nevertheless, survival rates increase with the number of dissected lymph nodes [264]. Removal of at least 10 lymph nodes has been postulated as sufficient for evaluation of lymph node status, as well as being beneficial for OS in retrospective studies [265-267]. In conclusion, extended LND might have a therapeutic benefit compared to less-extensive LND, but due to bias, no firm conclusions can be drawn [5].

7.4.3.1 Laparoscopic/robotic-assisted laparoscopic cystectomy

Laparoscopic cystectomy and robotic-assisted laparoscopic cystectomy (RALC) are feasible both in male and female patients [268, 269].

Laparoscopic cystectomy is a technically challenging procedure that requires a high level of skill and has a long learning curve [270]. Recently, Aboumarzouk and co-workers conducted a systematic review in line with both Cochrane and PRISMA guidelines [271, 272]. All the included studies were observational cohort studies with no randomisation, and all reported experience with laparoscopic compared with open cystectomy [273-280]. A total of 427 patients were included: 211 underwent laparoscopic cystectomy with extracorporeal reconstruction, and 216 were included in the open cystectomy group. Patients in the laparoscopy group were significantly younger than those in the open cystectomy group. The laparoscopic group had significantly longer operative times, but less blood loss, less time to oral intake, less analgesic requirement, and shorter length of hospital stay. Patients who underwent open cystectomy developed significantly more minor complications than those treated laparoscopically. There was no difference between the two groups regarding LND yields, major complications, positive margins, pathological results, local recurrence, or distant metastases. However, there were significantly more positive nodes in the open cystectomy group. The main limitation of this meta-analysis was the inclusion of non-randomised observational studies with small patient cohorts. Only five of the studies had > 20 patients and all the studies had cohorts with < 50 patients. This led to a substantial risk of bias in the results. Another limitation was the age selection bias.

Laparoscopic cystectomy and RALC data often suffer from selection bias including younger patients, lower stage of disease, and minimal comorbidity compared to most contemporary studies of open cystectomy [281-286]. To date, laparoscopic cystectomy and RALC still need to be considered experimental because of the limited number of cases reported, absence of long-term oncological and functional outcome data, and possible selection bias [281, 287].

Laparoscopic intracorporeal construction of urinary diversion (with or without robotic assistance) has been tested in small series only [282-284, 286]. It is a challenging and lengthy procedure with the currently available equipment and must therefore be regarded as experimental. Furthermore, there are no long-term results available. Laparoscopic cystectomy and pelvic lymphadenectomy (with or without robotic assistance), with extracorporeal construction of urinary diversion, is an option for surgical treatment only in experienced centres [287] (LE: 3).

7.4.4 Urinary diversion after radical cystectomy

From an anatomical standpoint, three alternatives are currently used after cystectomy:

- Abdominal diversion, such as an ureterocutaneostomy, ileal or colonic conduit, and various forms of a continent pouch.
- Urethral diversion, which includes various forms of gastrointestinal pouches attached to the urethra as a continent, orthotopic urinary diversion (neobladder, orthotopic bladder substitution).

- Rectosigmoid diversions, such as uretero- (ileo-)rectostomy.

Different types of segments of the intestinal tract have been used to reconstruct the urinary tract, including the stomach, ileum, colon and appendix [288]. Several studies have compared certain aspects of health-related QoL, such as sexual function, urinary continence and body image, in patient cohorts with different types of urinary diversion. However, further research is needed on preoperative tumour stage and functional situation, socioeconomic status, and time interval to primary surgery.

7.4.4.1 Preparations for surgery

In consultation with the patient, both an orthotopic neobladder and ilial conduit should be considered in case reconstructive surgery exposes the patient to excessive risk (as determined by comorbidity and age).

Diagnosis of urethral tumour before cystectomy or positive urethral frozen section leads to urethrectomy and therefore excludes neobladder reconstruction. If indicated, in males, urethral frozen section has to be performed on the cysto-prostatectomy specimen just under the verumontanum and on the inferior limits of the bladder neck for females.

When there are positive lymph nodes, orthotopic neobladder can nevertheless be considered in the case of N1 involvement (metastasis in a single node in the true pelvis) but not for N2 or N3 tumours [289].

Oncological results after orthotopic neobladder substitution or conduit diversion are similar in terms of local or distant metastasis recurrence, but secondary urethral tumours seem less common in patients with neobladder compared to those with conduits or continent cutaneous diversions [290].

For cystectomy, general preparations are necessary as for any other major pelvic and abdominal surgery. If the urinary diversion is constructed from gastrointestinal segments, the length or size of the respective segments and their pathophysiology when storing urine must be considered [291]. Despite the necessary interruption and re-anastomosis of bowel, a formal bowel preparation may not be necessary [292]. Furthermore, bowel recovery time has been reduced by the use of early mobilisation, early oralisation, and gastrointestinal stimulation with metoclopramide and chewing gum [293].

Patients undergoing continent urinary diversion must be motivated to learn about their diversion and to be manually skilful in manipulating their diversion. Contraindications to more complex forms of urinary diversion include :

- debilitating neurological and psychiatric illnesses;
- limited life expectancy;
- impaired liver or renal function;
- transitional cell carcinoma of the urethral margin or other surgical margins.

Relative contraindications specific for an orthotopic neobladder are high-dose preoperative radiotherapy, complex urethral stricture disease, and severe urethral sphincter-related incontinence [294-296].

7.4.4.2 Patient selection for orthotopic diversion

Radical cystectomy and urinary diversion are the two steps of one operation. However, the literature uniformly reports the complications of radical cystectomy, while ignoring the fact that most complications are diversion related [297]. Age alone is not a criterion for offering continent diversion [296, 298]. Comorbidity, cardiac and pulmonary function, and cognitive function are all important factors that should be considered, along with the patient's social support and preference.

Age > 80 years is often considered to be the threshold after which neobladder reconstruction is not recommended, however, there is no exact age for strict contraindication. In most large series from experienced centres, the rate of orthotopic bladder substitution after cystectomy for bladder tumour is up to 80% for men and 50% for women [299-302]. Nevertheless, no randomised controlled studies comparing conduit diversion with neobladder or continent cutaneous diversion have been performed.

7.4.4.2.1 Ureterocutaneostomy

Ureteral diversion to the abdominal wall is the simplest form of cutaneous diversion. It is considered a safe procedure. It is therefore preferred in older, or otherwise compromised, patients, who need a supravescical diversion [303, 304]. However, others have demonstrated that, in carefully selected elderly patients, all other forms of wet and dry urinary diversions, including orthotopic bladder substitutions, are possible [227]. Technically, either one ureter, to which the other shorter one is attached end-to-side, is connected to the skin (transureteroureterocutaneostomy) or both ureters are directly anastomosed to the skin. Due to the smaller diameter of the ureters, stoma stenosis has been observed more often than in intestinal stomas [303].

In a retrospective comparison with short or median follow-up of 16 months, the diversion-related complication rate was considerably lower for ureterocutaneostomy compared to ileal or colon conduit [305]. Despite the limited comparative data available, however, it must be taken into consideration that older data and clinical experience suggest ureter stenosis at the skin level and ascending UTI are more frequent complications in comparison to those with ileal conduit diversion. In a retrospective study comparing various forms of intestinal diversion, ileal conduits had fewer late complications than continent abdominal pouches or orthotopic neobladders [306].

7.4.4.2.2 Ileal conduit

The ileal conduit is still an established option with well-known/predictable results. However, up to 48% of patients develop early complications including UTIs, pyelonephritis, ureteroileal leakage and stenosis [306]. The main complications in long-term follow-up studies are stomal complications in up to 24% of cases and functional and/or morphological changes of the UUT in up to 30% [307-309]. An increase in complications was seen with increased follow-up in the Berne series of 131 patients followed for a minimum of 5 years (median follow-up 98 months) [307]: the rate of complications increased from 45% at 5 years to 94% in those surviving > 15 years. In the latter group, 50% of patients developed UUT changes and 38% developed urolithiasis.

7.4.4.2.3 Continent cutaneous urinary diversion

A low-pressure detubularised ileal reservoir can be used as a continent cutaneous urinary diversion for self-catheterisation; gastric, ileocecal and sigma pouches have also been described [310-312]. Different antireflux techniques can be used [233]. Most patients have a well-functioning reservoir with day-time and night-time continence approaching 93% [313]. In a retrospective study of > 800 patients, stomal stenosis was seen in 23.5% of patients with an appendix stoma and 15% of those with an efferent intussuscepted ileal nipple [313]. Stone formation in the pouch occurred in 10% of patients [313-315]. In a small series of previously irradiated female patients, incontinence and stomal stenosis was seen in eight of 44 patients (18%) [316].

7.4.4.2.4 Ureterocolonic diversion

The oldest and most common form of ureterocolonic diversion was primarily a refluxive and later an antirefluxive connection of ureters to the intact rectosigmoid colon (uretero-rectosigmoidostomy) [317, 318]. Most indications for this procedure have become obsolete due to a high incidence of upper UTIs and the long-term risk of developing colon cancer [289, 290]. Bowel frequency and urge incontinence are additional adverse effects of this type of urinary diversion. However, it may be possible to circumvent the above-mentioned problems by interposing a segment of ileum between the ureters and rectum or sigmoid in order to augment capacity and avoid direct contact between the urothelium and colonic mucosa, as well as faeces and urine [319].

7.4.4.2.5 Orthotopic neobladder

An orthotopic bladder substitution to the urethra is now commonly used both in men and women. Contemporary reports document the safety and long-term reliability of this procedure. In several large centres, this has become the diversion of choice for most patients undergoing cystectomy [174, 226, 296]. In elderly patients (> 80 years), however, it is rarely performed, even in high-volume expert centres [320, 321].

The terminal ileum is the gastrointestinal segment most often used for bladder substitution. There is less experience with the ascending colon, including the caecum, and the sigmoid [226]. Emptying of the reservoir anastomosed to the urethra requires abdominal straining, intestinal peristalsis, and sphincter relaxation. Early and late morbidity in up to 22% of the patients is reported [322, 323]. In two studies with 1,054 and 1,300 patients [296, 324], long-term complications included diurnal (8-10%) and nocturnal (20-30%) incontinence, ureterointestinal stenosis (3-18%), metabolic disorders, and vitamin B12 deficiency. In a recent study that compared cancer control and patterns of disease recurrence in patients with neobladder and ileal conduit, there was no difference in CSS between the two groups when adjusting for pathological stage [325]. Urethral recurrence in neobladder patients seems rare (1.5-7% for both male and female patients) [296, 326]. These results indicate that neobladder in male and female patients does not compromise the oncological outcome of cystectomy. It remains debatable whether neobladder is better for QoL compared to non-continent urinary diversion [327-329].

Various forms of UUT reflux protection, including a simple isoperistaltic tunnel, ileal intussusception, tapered ileal prolongation implanted subserosally, and direct (sub)mucosal or subserosal ureteral implantation, have been described [315, 323]. According to the long-term results, the UUT is protected sufficiently by either method.

In conclusion, standard radical cystectomy in male patients with bladder neoplasms includes removal of the

entire bladder, prostate, seminal vesicles, distal ureters (segment length undefined), and corresponding lymph nodes (extent undefined) (LE: 2b). In female patients, standard radical cystectomy includes removal of the entire bladder, urethra and adjacent vagina, uterus, distal ureters, and corresponding lymph nodes.

A detailed investigation of the bladder neck prior to radical cystectomy is important for women who are scheduled for an orthotopic bladder substitute [330]. In women undergoing radical cystectomy the rate of concomitant urethral malignancy has been reported to range around 12-16% [331]. Localisation of the primary tumour at the bladder neck correlated strongly with concomitant urethral malignancy. Additionally, the tumours were at higher risk of advanced stage and nodal involvement [332].

Currently, it is not possible to recommend a particular type of urinary diversion. However, most institutions prefer ileal orthotopic neobladders and ileal conduits, based on clinical experience [333, 334]. In selected patients, f.i. patients with a single kidney, ureterocutaneostomy is surgically the least burdensome type of diversion (LE: 3). Recommendations related to radical cystectomy and urinary diversions are listed in section 7.5.

7.4.5 **Morbidity and mortality**

In two long-term studies, and one population-based cohort study, the perioperative mortality was reported as 1.2-3% at 30 days and 2.3-5.7% at 90 days [174, 297, 299, 335]. In a large single-centre series, early complications (within 3 months of surgery) were seen in 58% of patients [297]. Late morbidity is usually due to the type of urinary diversion (see also above) [300, 336]. Early morbidity associated with radical cystectomy for NMIBC (at high risk for disease progression) is similar and no less than that associated with muscle-invasive tumours [337]. In general, lower morbidity and (perioperative) mortality have been observed by surgeons and in hospitals with a higher caseload and therefore more experience [338-341].

Table 7.1: Management of neobladder morbidity (30-64%) [342].

CLAVIEN System		Morbidity	Management
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs such as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.	Immediate complications:	
		Post-operative ileus	Nasogastric intubation (usually removed at J1) Chewing gum Avoid fluid excess and hypovolemia (provoke splanchnic hypoperfusion)
		Postoperative Nausea and Vomiting	Antiemetic agent (decrease opioids) Nasogastric intubation
		Urinary infection	ATB, no ureteral catheter removal Check the 3 drainages (ureters and neobladder)
		Ureteral catheter (UC) obstruction	5cc saline UC injection to avoid the obstruction Increase volume infusion to increase diuresis
		Intra abdominal urine leakage (anastomosis leakage)	Check drainages and watchful waiting
		Anaemia well tolerated	Martial treatment (give iron supplement)
		Late complications:	
		Non compressive lymphocele	Watchful waiting
		Mucus cork	Cough Indwelling catheter to remove the obstruction

		Incontinence	Urine analysis (infection), echography (post-void residual) Physiotherapy
		Retention	Drainage and self- catheterisation education
Grade II	Requiring pharmacological treatment with drugs other than those allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.	Anaemia badly tolerated or if myocardial cardiopathy history	Transfusion
		Pulmonary embolism	Heparinotherapy
		Pyelonephritis	ATB and check kidney drainage (nephrostomy if necessary)
		Confusion or neurological disorder	Neuroleptics and avoid opioids
Grade III	Requiring surgical, endoscopic or radiological intervention	UC accidentally dislodged	Indwelling leader to raise the UC
		Anastomosis stenosis (7%)	Renal drainage (ureteral catheter or nephrostomy)
		Ureteral reflux	No treatment if asymptomatic
III-a	Intervention not under general anaesthesia	Compressive lymphocele	Transcutaneous drainage or intraoperative marsupialisation (cf grade III)
III-b	Intervention under general anaesthesia	Ileal anastomosis leakage	Ileostomy ASAP
		Evisceration	Surgery in emergency
		Compressive lymphocele	Surgery (marsupialisation)
Grade IV	Life-threatening complication (including CNS complications: brain haemorrhage, ischaemic stroke, subarachnoid bleeding, but excluding transient ischaemic attacks) requiring IC/ICU management.	Rectal necrosis	Colostomy
		Neobladder rupture	Nephrostomy and indwelling catheter / surgery for repairing neobladder
		Severe sepsis	ATB and check all the urinary drainages and CT Scan in emergency
IV-a	Single organ dysfunction (including dialysis)	Non obstructive renal failure	Bicarbonate / aetiology treatment
IV-b	Multi-organ dysfunction	Obstructive pyelonephritis and septicaemia	Nephrostomy and ATB
Grade V	Death of a patient		
Suffix 'd'	<i>If the patient suffers from a complication at the time of discharge, the suffix "d" (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.</i>		

ASAP = as soon as possible; ATB = antibiotics; CNS = central nervous system; CT = computed tomography; IC = intensive care; ICU = intensive care unit; UC = urethral catheter.

7.4.6 Survival

According to a multi-institutional database of 888 consecutive patients undergoing radical cystectomy for BC, the 5-year recurrence-free survival was 58% and the CSS was 66% [343]. Recent external validation of postoperative nomograms for bladder-cancer-specific mortality showed similar results, with bladder-cancer-specific survival of 62% [344].

Recurrence-free survival and OS in a large single-centre study of 1,054 patients was 68% and 66% at 5 years and 60% and 43%, at 10 years, respectively [164]. However, the 5-year recurrence-free survival in node-positive patients who underwent cystectomy was considerably less at 34-43% [163, 164, 345]. In a surgery-only study, the 5-year recurrence-free survival was 76% in patients with pT1 tumours, 74% for pT2, 52% for pT3, and 36% for pT4 [164].

A trend analysis according to the 5-year survival and mortality rates of BC in the United States, between 1973 and 2009 with a total of 148,315 BC patients, revealed an increased stage-specific 5-year survival rate for all stages, except for metastatic disease [8].

7.4.7 Conclusions and recommendations for radical cystectomy and urinary diversion

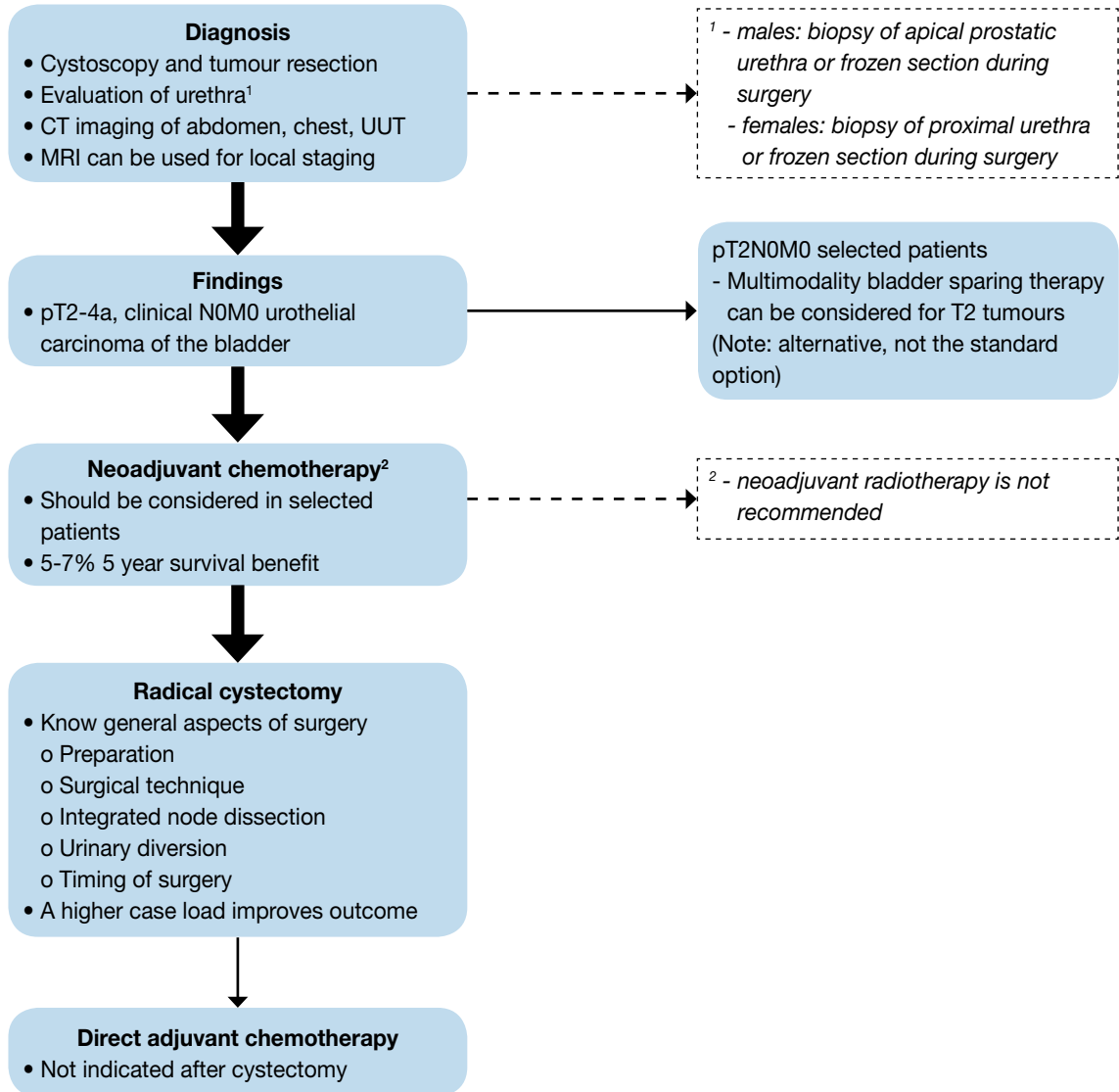
Conclusions	LE
For MIBC, radical cystectomy is the curative treatment of choice.	3
A higher case load reduces morbidity and mortality of cystectomy.	3
Radical cystectomy includes removal of regional lymph nodes.	3
There are data to support that extended LND (vs. standard or limited LND) improves survival after radical cystectomy.	3
Radical cystectomy in both sexes must not include removal of the entire urethra in all cases, which may then serve as the outlet for an orthotopic bladder substitution. The terminal ileum and colon are the intestinal segments of choice for urinary diversion.	3
The type of urinary diversion does not affect oncological outcome.	3
Laparoscopic cystectomy and robotic-assisted laparoscopic cystectomy are feasible but still investigational. Current best practice is open radical cystectomy.	3
In patients aged > 80 years with MIBC, cystectomy is an option.	3
Surgical outcome is influenced by comorbidity, age, previous treatment for bladder cancer or other pelvic diseases, surgeon and hospital volumes of cystectomy, and type of urinary diversion.	2
Surgical complications of cystectomy and urinary diversion should be reported using a uniform grading system. Currently, the best-adapted, graded system for cystectomy is the Clavien grading system.	2
No conclusive evidence exists as to the optimal extent of LND.	2a

Recommendations	GR
Do not delay cystectomy for > 3 months because it increases the risk of progression and cancer-specific mortality.	B
Before cystectomy, the patient should be fully informed about the benefits and potential risks of all possible alternatives, and the final decision should be based on a balanced discussion between patient and surgeon.	B
An orthotopic bladder substitute or ileal conduit diversion should be offered to male and female patients lacking any contraindications and who have no tumour in the urethra or at the level of urethral dissection.	B
Preoperative radiotherapy is not recommended in subsequent cystectomy with urinary diversion.	A
Pre-operative bowel preparation is not mandatory. "Fast track" measurements may reduce the time of bowel recovery.	C
Radical cystectomy is recommended in T2-T4a, N0 M0, and high-risk non-MIBC (as outlined above).	A*
Lymph node dissection must be an integral part of cystectomy.	A
The urethra can be preserved if margins are negative. If no bladder substitution is attached, the urethra should be checked regularly.	B
Laparoscopic cystectomy and robot-assisted laparoscopic cystectomy are both management options. However, current data have not sufficiently proven the advantages or disadvantages for oncological and functional outcomes.	C

*Upgraded following EAU Working Panel consensus.

GR = grade of recommendation; LE = level of evidence; LND = lymph node dissection; MIBC = muscle-invasive bladder cancer.

Figure 7.1: Flowchart for the management of T2-T4a N0M0 urothelial bladder cancer



CT = computed tomography; MRI = magnetic resonance imaging; UUT = upper urinary tract.

7.5. Unresectable tumours

7.5.1 Palliative cystectomy for muscle-invasive bladder carcinoma

Locally advanced tumours (T4b, invading the pelvic or abdominal wall) may be accompanied by several debilitating symptoms, including bleeding, pain, dysuria and urinary obstruction. These patients are candidates for palliative treatments, such as palliative radiotherapy. Palliative cystectomy with urinary diversion carries the greatest morbidity and should be considered for symptom relief only if there are no other options [346-348].

Locally advanced MIBC can be associated with ureteral obstruction due to a combination of mechanical blockage by the tumour and invasion of ureteral orifices by tumour cells. In a series of 61 patients with obstructive uraemia, radical cystectomy was not an option in 23 patients, and obstruction was relieved using permanent nephrostomy tubes [349]. Another 10 patients underwent palliative cystectomy, but local pelvic recurrence occurred in all 10 patients within the first year of follow-up. Another small (n = 20) study showed that primary cystectomy for T4 BC was technically feasible and associated with a very tolerable therapy-related morbidity and mortality [350].

7.5.1.1 Recommendations for unresectable tumours

Recommendations	GR
In patients with inoperable locally advanced tumours (T4b), primary radical cystectomy is a palliative option.	B
In patients with symptoms, palliative cystectomy may be offered.	

GR = grade of recommendation.

7.5.2 Supportive care

7.5.2.1 Obstruction of the UUT

Unilateral (best kidney) or bilateral nephrostomy tubes provide the easiest solution for UUT obstruction, but patients find the tubes inconvenient and prefer ureteral stenting. However, stenting can be difficult to achieve, stents must be regularly replaced and there is the risk of stent obstruction or displacement. Another possible solution is a urinary diversion with, or without, a palliative cystectomy.

7.5.2.2 Bleeding and pain

In the case of bleeding, the patient must first be screened for coagulation disorders or the patient's use of anticoagulant drugs must be reviewed. Transurethral (laser) coagulation may be difficult in a bladder full of tumour or with a bleeding tumour. Intravesical rinsing of the bladder with 1% silver nitrate or 1-2% alum can be effective [351]. It can usually be done without any anaesthesia. The instillation of formalin (2.5-4% during 30 minutes) is a more aggressive and more painful procedure, requiring anaesthesia. Formalin instillation has a higher risk of side-effects, e.g. bladder fibrosis, but is more likely to control the bleeding [351]. Vesicoureteral reflux should be excluded to prevent renal complications.

Radiation therapy is another common strategy for control of bleeding, and is also used to control pain. An older study reported control of haematuria in 59% of patients and pain control in 73% [352]. Irritative bladder and bowel complaints due to irradiation are possible, but are usually mild. Non-conservative options are embolisation of specific arteries in the small pelvis, with success rates as high as 90% [351]. Radical surgery is a last resort and includes cystectomy and diversion (see above Section 7.5.1).

7.6 Bladder-sparing treatments for localised disease

7.6.1 Transurethral resection of bladder tumour (TURB)

TURB alone in patients with muscle-invasive bladder tumours is only possible as a therapeutic option if tumour growth is limited to the superficial muscle layer and if re-staging biopsies are negative for residual (invasive) tumour [353]. In general about half will still have to undergo radical cystectomy for recurrent muscle-invasive cancer with a disease-specific mortality rate of up to 47% within this group [354]. A disease-free status at re-staging TURB appears to be crucial in making the decision not to perform radical cystectomy [355, 356]. A prospective study by Solsona et al., which included 133 patients with a radical TURB and re-staging negative biopsies, has recently reported a 15-year follow-up [356]. 30% had recurrent NMIBC and went on to intravesical therapy, and 30% (n = 40) progressed, of which 27 died of BC. After 5, 10 and 15 years the results showed a CSS of 81.9%, 79.5%, and 76.7%, and a progression-free survival (PFS) with an intact bladder of 75.5%, 64.9%, and 57.8%, respectively.

In conclusion, TURB alone should only be considered as a therapeutic option for muscle-invasive disease after radical TURB, when the patient is unfit for cystectomy or a multimodality bladder-preserving approach, or refuses open surgery [357].

7.6.1.2 Recommendation for transurethral resection of bladder tumour

Recommendation	LE	GR
Transurethral resection of bladder tumour alone is not a curative treatment option in most patients.	2a	B

GR = grade of recommendation; LE = level of evidence.

7.6.2 External beam radiotherapy (EBRT)

The target field usually comprises the bladder only, with a safety margin of 1.5-2 cm to allow for unavoidable organ movements [358]. Any beneficial effect with larger pelvic fields has not been demonstrated. The target dose for curative radiotherapy for BC is 60-66 Gy, with a subsequent boost using external radiotherapy or interstitial brachytherapy. The course of radiotherapy should not extend beyond 6-7 weeks to minimise the repopulation of cancer cells [359, 360]. The use of modern standard radiotherapy techniques results in major,

related, late morbidity of the urinary bladder or bowel in less than 5% of tumour-free patients [361]. As well as the response to radiotherapy, important prognostic factors for outcome include tumour size, hydronephrosis and completeness of the initial TURB. Additional prognostic factors found in a recent single institution study (n = 459, including 30% of unfit T1 patients) were age and stage [362]. Overall, 5-year survival rates in patients with MIBC range between 30% and 60%, depending on whether they show a complete response (CR) following radiotherapy. Cancer-specific survival rates are between 20% and 50% [360, 363-365]. Similar long-term results were reported by Chung et al. [366]. A total of 340 patients with MIBC were treated with EBRT alone, EBRT with concurrent chemotherapy, or neoadjuvant chemotherapy followed by EBRT. The overall CR was 55% and the 10-year DSS and OS were 35% and 19%, respectively. Complete response was 64% after EBRT alone, 79% after concurrent chemotherapy (n = 36), and 52% after neoadjuvant chemotherapy (n = 57). Younger age, lower tumour stage and absence of CIS were associated with a significant improvement in survival.

Based on available trials, a Cochrane analysis has demonstrated that radical cystectomy has an OS benefit compared to radiotherapy [367].

Similar long-term results were reported by Chung et al. [366]. A total of 340 patients with MIBC were treated with EBRT alone, EBRT with concurrent chemotherapy, or neoadjuvant chemotherapy followed by EBRT. The overall CR was 55% and the 10-year DSS and OS were 35% and 19%, respectively. Complete response was 64% after EBRT alone, 79% after concurrent chemotherapy (n = 36), and 52% after neoadjuvant chemotherapy (n = 57). Younger age, lower tumour stage and absence of CIS were associated with a significant improvement in survival.

In conclusion, EBRT can be an alternative treatment in patients unfit for radical surgery.

7.6.2.1 Conclusions and recommendation for external beam radiotherapy

Conclusions	LE
External beam radiotherapy alone should only be considered as a therapeutic option when the patient is unfit for cystectomy or a multimodality bladder-preserving approach.	3
Radiotherapy can also be used to stop bleeding from the tumour when local control cannot be achieved by transurethral manipulation due to extensive local tumour growth.	3

Recommendation	GR
Radiotherapy alone is not recommended as primary therapy for localised bladder cancer.	B

GR = grade of recommendation; LE = level of evidence.

7.6.3 Chemotherapy

Chemotherapy alone rarely produces durable CRs. In general, a clinical CR rate of up to 56%, as reported in some series, must be weighed against a staging error of > 60% [368, 369]. Response to chemotherapy is a prognostic factor for treatment outcome and eventual survival [184], though it may be confounded by patient selection.

Several groups have reported the effect of chemotherapy on resectable tumours (neoadjuvant approach), as well as unresectable primary tumours [182, 211, 370, 371]. Neoadjuvant chemotherapy with 2-3 cycles of methotrexate, vinblastine, adriamycin plus cisplatin (MVAC) or cisplatin, methotrexate plus vinblastine (CMV) has led to a down-staging of the primary tumour in different prospective series [182, 211, 370]. Pathological complete responses of primary bladder tumours were reached in 12-50% of patients after MVAC and in 12-22% of patients after gemcitabine/cisplatin (GC) in phase II and phase III trials [182, 211, 370, 372-379]. Contemporary series with GC followed by radical cystectomy reported inferior pT0 rates, which may have been related to a lack of dose density and inappropriate delay of surgery [215].

For highly selected patients, a bladder-conserving strategy with TURB and systemic cisplatin-based chemotherapy, preferably with MVAC, may allow long-term survival with intact bladder [184]. However, this approach cannot be recommended for routine use.

7.6.3.1 Conclusion and recommendation for chemotherapy for muscle-invasive bladder tumours

Conclusion	LE
With cisplatin-based chemotherapy as primary therapy for locally advanced tumours in highly selected patients, complete and partial local responses have been reported.	2b

Recommendation	GR
Chemotherapy alone is not recommended as primary therapy for localised bladder cancer.	A

GR = grade of recommendation; LE = level of evidence.

7.6.4 Multimodality bladder-preserving treatment

Multimodality treatment (MMT) or trimodality treatment combines TURB, chemotherapy and radiation. The rationale for performing TURB and radiation is to achieve local tumour control. The addition of systemic chemotherapy or other radiosensitisers (mentioned below) aims at the potentiation of radiotherapy.

Micrometastasis is targeted by platinum-based combination chemotherapy which is covered in Section 7.2 on neoadjuvant chemotherapy. The aim of multimodality therapy is to preserve the bladder and QoL, without compromising outcome. A collaborative review addressed this approach [380].

There are no completed randomised controlled trials to compare the outcome of MMT with the gold standard, radical cystectomy. Many of the reported series have differing characteristics to the large surgical series which typically have median ages in the mid-late 60s compared to mid-70s for some large radiotherapy series (reviewed in [381]). In the case of MMT, two distinct patterns of care may be distinguished: treatment aimed at patients fit for cystectomy and treatment aimed at older, less fit patients. For the former category, MMT is a selective bladder preservation option. In that case the initial step is a radical TURB, where as much tumour as possible should be resected. This implies that appropriate patient selection (T2 tumours, no CIS) is critical [382]. For patients who are not candidates for cystectomy, less stringent criteria can be applied, although extensive CIS and poor bladder function should both be regarded as strong contraindications.

Following TURBT and staging, treatment then comprises EBRT with concurrent radiosensitising drugs. Two schedules are in common use worldwide: a split dose format with interim cystoscopy is used in North America [383], whilst single phase treatment is more commonly used elsewhere (reviewed in [381]). A typical schedule for single phase radiotherapy would be either 64-66 Gy in 32-33 fractions or 55 Gy in 20 fractions, generally to the bladder plus tumour only. For radiosensitising chemotherapy cisplatin [383] or mitomycin C plus 5-fluorouracil [381] can be used, but other schedules have also been used. In particular, hypoxic cell sensitisation with nicotinamide and carbogen has been evaluated in a large phase 3 trial [384]. With MMT, 5-year CSS and OS rates of 50% to 82% and from 36% to 74% were achieved, respectively [361, 381, 383-387]. Salvage cystectomy rates are 10-30% [381, 383, 387]. There are data to show that major complication rates are similar for salvage and primary cystectomy [388]. The majority of recurrences post-MMT are non-invasive and can be managed conservatively [381].

The collaborative review came to the conclusion that there are accumulating data to suggest that bladder preservation with MMT leads to acceptable outcomes and therefore may be considered a reasonable treatment option in well-selected patients as compared to radical cystectomy. It should also be considered in all patients where surgery is contraindicated, either relatively or absolutely as the factors that determine fitness for surgery and chemoradiotherapy differ.

A bladder-preserving multimodality strategy requires very close multidisciplinary co-operation and a high level of patient compliance. Even if a patient has shown a CR to a multimodality bladder-preserving strategy, the bladder remains a potential source of recurrence, hence long-term bladder monitoring is essential and patient counselling is required.

7.6.4.1 Conclusions and recommendations for multimodality treatment in MIBC

Conclusions	LE
In a highly selected patient population, long-term survival rates of multimodality treatment are comparable to those of early cystectomy.	3
Delay in surgical therapy can compromise survival rates.	2b

Recommendations	GR
Surgical intervention or multimodality treatments are the preferred curative therapeutic approaches as they are more effective than radiotherapy alone.	B
Multimodality treatment could be offered as an alternative in selected, well-informed and compliant patients, especially for whom cystectomy is not an option.	B

GR = grade of recommendation; LE = level of evidence.

7.7 Adjuvant chemotherapy

Adjuvant chemotherapy after radical cystectomy for patients with pT3/4 and/or lymph node positive (N+) disease without clinically detectable metastases (M0) is under debate [389, 390] and still infrequently used [178].

The general benefits of adjuvant chemotherapy include:

- Chemotherapy is administered after accurate pathological staging, therefore treatment in patients at low risk for micrometastases is avoided;
- No delay in definitive surgical treatment.

The drawbacks of adjuvant chemotherapy are:

- Assessment of in vivo chemosensitivity of the tumour is not possible and overtreatment is an unavoidable problem;
- Delay or intolerability of chemotherapy, due to postoperative morbidity [391].

There is limited evidence from adequately conducted and accrued randomised phase III trials in favour of the routine use of adjuvant chemotherapy [390, 392-397]. Individual patient data from six randomised trials [398-402] of adjuvant chemotherapy were included in one meta-analysis [392] with 491 patients for survival analysis (unpublished data from Otto et al, were included in the analysis). All these trials were suboptimal with serious deficiencies, including small sample size (underpowered), early cessation of patient entry, and flaws in design and statistical analysis, including irrelevant endpoints or a lack of recommendations concerning salvage chemotherapy for relapse or metastases [390]. In these trials, three or four cycles of CMV (cisplatin, methotrexate and vinblastine), CISCA (cisplatin, cyclophosphamide, and adriamycin), MVA(E)C (methotrexate, vinblastine, adriamycin or epirubicin, and cisplatin) and CM (cisplatin and methotrexate) were used [403], and one trial used cisplatin monotherapy [401]. These data were not convincing enough to give an unequivocal recommendation for the use of adjuvant chemotherapy.

In a more recent meta-analysis [393], an additional three studies were included [394-396]. However, the patient number in this meta-analysis of nine trials was only 945, and none of the trials were fully accrued and no individual patient data were used [393]. For one trial, only an abstract was available at the time of the meta-analysis [395], and none of the included trials by themselves were significantly positive for overall survival (OS) in favour of adjuvant chemotherapy. In two of the trials, more modern chemotherapy regimens were used (gemcitabine/cisplatin and paclitaxel/gemcitabine and cisplatin) [394, 395]. The hazard ratio (HR) for OS was 0.77 and there was a trend towards an OS benefit when including all nine trials. The effect was stronger for disease-free survival (DFS) (HR: 0.66; 95% CI: 0.48-0.92) and when stratified for the ratio of nodal positivity (HR: 0.64; 95% CI: 0.45- 0.91). The background of this finding was a heterogeneity in outcomes observed between the included studies. After stratification of the studies by the ratio of node positivity, no further heterogeneity was identified. The HR for DFS associated with adjuvant cisplatin-based chemotherapy in studies with higher nodal involvement was 0.39 (95% CI: 0.28-0.54), compared with 0.89 (95% CI: 0.69-1.15) in studies with less nodal involvement.

Furthermore, a retrospective cohort analysis that included 3,974 patients after cystectomy and lymph node dissection showed an OS benefit in high-risk subgroups (extravesical extension and nodal involvement) [HR: 0.75; CI 0.62-0.90] [404]. The most recent publication of the so far largest RCT (EORTC 30994), although not fully accrued, showed a significant improvement of PFS for immediate compared with deferred treatment (HR 0.54, 95% CI 0.4-0.73, $p < 0.0001$), there was, however, no significant OS benefit [405].

From the currently available evidence, it is still unclear whether immediate adjuvant chemotherapy or chemotherapy at the time of relapse is superior, or if the two approaches are equivalent with respect to the endpoint of OS. Cisplatin-based combination chemotherapy results in long-term DFS, even in metastatic disease, mainly in patients with lymph node metastases only, and with a good performance status [376, 406, 407]. With the most recent meta-analysis, the positive role of adjuvant chemotherapy for BC has been strengthened, however, still with a poor level of evidence [393]. Patients should be informed about potential chemotherapy options before radical cystectomy, including neoadjuvant and adjuvant chemotherapy, and the limited evidence for adjuvant chemotherapy.

7.7.1 Recommendations for adjuvant chemotherapy

Recommendations	GR
Adjuvant cisplatin-based combination chemotherapy can be offered to patients with pT3/4 and/or pN+ disease if no neoadjuvant chemotherapy has been given.	C

GR = grade of recommendation.

7.8 Metastatic disease

7.8.1 Introduction

Half of the patients with muscle-invasive urothelial cancer (UC) relapse after radical cystectomy, depending on the pathological stage of the primary tumour and the nodal status. Local recurrence accounts for 30% of relapses, whereas distant metastases are more common. Ten to fifteen percent of patients are already metastatic at diagnosis [408]. Before the development of effective chemotherapy, patients with metastatic urothelial cancer rarely had a median survival that exceeded 3-6 months [409].

7.8.1.1 Prognostic factors and treatment decisions

Prognostic factors are crucial for assessing phase II study results and stratifying phase III trials [374, 410]. In a multivariate analysis, Karnofsky performance status (PS) of $\leq 80\%$ and presence of visceral metastases were independent prognostic factors of poor survival after treatment with MVAC (methotrexate, vinblastine, adriamycin and cisplatin [378]. They have also been validated for newer combination chemotherapy regimens [411-413].

For patients refractory to, or progressing shortly after, platinum-based combination chemotherapy, four prognostic groups have been established, based on three adverse factors that have been developed in patients treated with vinflunine and that have been validated in an independent data set: Hb < 10 g/dL; presence of liver metastases; and ECOG PS ≥ 1 [414]. Cisplatin, using different schedules, has also been administered in patients with a GFR down to 40 mL/min. The respective studies were mostly small sized phase I and II trials [415-418]. One phase III trial used a cut off for cisplatin eligibility of ≥ 50 mL/min [419].

7.8.1.2 Comorbidity in metastatic disease

Comorbidity is defined as “the presence of one or more disease(s) in addition to an index disease” (see Section 6.2.1). Comorbidity increases with age. However, chronological age does not necessarily correlate with functional impairment. There are several definitions by which patients can be selected as potentially fit or unfit for chemotherapy, but age is not among them [420].

7.8.1.3 Not eligible for cisplatin (unfit)

The European Organisation for Research and Treatment of Cancer (EORTC) conducted the first randomised phase II/III trial for urothelial carcinoma patients who were unfit for cisplatin chemotherapy [421]. The EORTC definitions were GFR < 60 mL/min and/or PS 2.

An international survey among BC experts [422] was the basis for a consensus statement on how to classify patients unfit for cisplatin-based chemotherapy. At least one of the following criteria has to be present: PS > 1 ; GFR ≤ 60 mL/min; grade ≥ 2 audiometric loss and peripheral neuropathy; and New York Heart Association (NYHA) class III heart failure [423].

More than 50% of patients with urothelial cancer are not eligible for cisplatin-based chemotherapy [424-427].

Renal function assessment in UC is of utmost importance for treatment selection. Calculation of creatinine clearance (CrCl) (24-h urine collection) with current formulae tend to underestimate clearance in patients aged > 65 years compared to measured CrCl [424, 428].

7.8.2 Single-agent chemotherapy

Response rates to single-agent, first-line chemotherapy vary. The most robust data have shown a response rate of about 25% for first- and second-line gemcitabine in several phase II trials [429, 430]. Responses with single agents are usually short-lived, complete responses are rare and no long-term disease-free survival has been reported. The median survival in such patients is only 6-9 months.

7.8.3 Standard first-line chemotherapy for fit patients

Cisplatin-containing combination chemotherapy has been the standard of care since the late 1980s (for a review see [431]). MVAC and gemcitabine/cisplatin (GC) prolonged survival to up to 14.8 and 13.8 months, respectively, compared to monotherapy and older combinations. Neither of the two combinations is superior to the other, but equivalence has not been tested. Response rates were 46% and 49% for MVAC and GC, respectively. The long-term survival results have confirmed the anticipated equivalence of the two regimens [406]. The major difference between the above-mentioned combinations is toxicity. The lower toxicity of GC [146] has resulted in it becoming a new standard regimen [432]. MVAC is better tolerated when combined with granulocyte colony-stimulating factor (G-CSF) [432, 433].

High-dose intensity MVAC (HD-MVAC) with G-CSF is less toxic and more efficacious than standard MVAC in terms of dose density, complete response, and 2-year survival rate. However, there is no significant difference in median survival between the two regimens [434, 435].

In general, all disease sites have been shown to respond to cisplatin-based combination chemotherapy. A response rate of 66% and 77% with MVAC and HD-MVAC, respectively, has been reported in retroperitoneal lymph nodes versus 29% and 33% at extranodal sites [434]. The disease sites also have an impact on long-term survival. In lymph-node-only disease, 20.9% of patients were alive at 5 years compared to only 6.8% of patients with visceral metastases [406].

Further intensification of treatment using the new PCG triple regimen (paclitaxel, cisplatin and gemcitabine) did not result in a significant improvement in OS in the intent-to-treat (ITT) population of a large randomised phase III trial, comparing PCG triple regimen to GC [436]. However, the overall response rate (ORR) was higher with the triple regimen (56% vs. 44%; $P = 0.0031$), and the trend for OS improvement in the ITT population (15.8 vs. 12.7 months; HR = 0.85, $P = 0.075$) became significant in the eligible population. Adding paclitaxel to GC did not induce major additional side effects. G4 neutropenia was more common (35.8% vs. 20% for GC), as was febrile neutropenia (13.2% vs. 4.3%), and the need for G-CSF was higher (17% vs. 11%). GC alone caused more grade 4 thrombocytopenia and thrombocytopenia-induced bleeding (11.4% vs. 6.8%). PCG is one additional option for first-line treatment of UC.

7.8.4 Carboplatin-containing chemotherapy for fit patients

Carboplatin-containing chemotherapy is not equivalent to cisplatin combinations, and should not be considered interchangeable or standard. Several randomised phase II trials of carboplatin versus cisplatin combination chemotherapy have produced lower CR rates and shorter OS for the carboplatin arms [437].

7.8.5 Non-platinum combination chemotherapy

Different combinations of gemcitabine and paclitaxel have been studied as first- and second-line treatments. Apart from severe pulmonary toxicity with a weekly schedule of both drugs, this combination is well tolerated and produces response rates between 38% and 60% in both lines. Non-platinum combination chemotherapy has not been compared to standard cisplatin chemotherapy in randomised trials, therefore, it is not recommended for first-line use in cisplatin eligible patients [438-445].

7.8.6 Chemotherapy in patients unfit for cisplatin

Up to 50% of patients are ineligible for cisplatin-containing chemotherapy [423]. The first randomised phase II/III trial in this setting was conducted by the EORTC and compared methotrexate/carboplatin/vinblastine (M-CAVI) and carboplatin/gemcitabine (GemCarbo) in patients unfit for cisplatin. Both regimens were active. Severe acute toxicity (SAT) was 13.6% in patients treated with GemCarbo versus 23% with M-CAVI, while the ORR was 42% for GemCarbo and 30% for M-CAVI. Further analysis showed that in patients with PS 2 and impaired renal function, combination chemotherapy provided limited benefit [421]. The ORR and SAT were both 26% for the former group, and 20% and 24%, respectively, for the latter group [421]. Recent phase III data have confirmed these results [413].

7.8.7 Second-line treatment

Second-line chemotherapy data are highly variable and prognostic factors have been established recently (see Section 7.8.1.1) [414]. A reasonable strategy may be to re-challenge former cisplatin-sensitive patients if progression occurs at least 6-12 months after first-line cisplatin-based combination chemotherapy.

Second-line response rates of paclitaxel (weekly), docetaxel, nab-paclitaxel [446] oxaliplatin, ifosfamide, topotecan, pemetrexed, lapatinib, gefitinib and bortezomib have ranged between 0% and 28% in small phase II trials [430]. Although gemcitabine has also shown excellent response rates in second-line use, most patients already receive this drug as part of their front-line treatment [429].

Paclitaxel/gemcitabine studies have shown response rates of 38-60%. No randomised phase III trial with an adequate comparator arm has been conducted to assess the true value and OS benefit of this second-line combination [409, 444, 447].

Vinflunine, a novel third-generation vinca alkaloid, provided promising results in phase II trials [448]. A randomised phase III trial compared vinflunine plus best supportive care (BSC) against BSC alone in patients progressing after first-line treatment with platinum-containing combination chemotherapy for metastatic disease [449]. The results showed a modest ORR (8.6%), a clinical benefit with a favourable safety profile and, most importantly, a survival benefit in favour of vinflunine, which was statistically significant in the eligible patient population (not in the ITT population). For second-line treatment of advanced or metastatic urothelial cancer, this trial reached the highest level of evidence ever reported. Currently, vinflunine is the only approved second-line treatment.

7.8.8 **Low-volume disease and post-chemotherapy surgery**

With cisplatin-containing combination chemotherapy, excellent response rates may be obtained in patients with lymph node but no other metastases, good PS, and adequate renal function, including a high number of CRs, with up to 20% of patients achieving long-term disease-free survival [406, 435, 450, 451]. The role of surgery after chemotherapy is still unclear. Although some studies suggest a survival benefit and QOL improvement, the level of evidence supporting this practice is very limited [452-466]. A retrospective study of post-chemotherapy surgery after a partial or complete response has indicated that surgery may contribute to long-term disease-free survival in selected patients [379, 467, 468].

7.8.9 **Treatment of bone metastases**

The prevalence of metastatic bone disease (MBD) in patients with advanced/metastatic urothelial cancer is 30-40% [469]. Skeletal complications due to MBD have a detrimental effect on pain and QoL and are also associated with increased mortality [470]. Bisphosphonates reduce and delay skeletal-related events (SREs) due to bone metastases by inhibiting bone resorption. In a small pilot study in patients with BC, SREs caused by bone metastases were delayed [471]. Denosumab is a fully human monoclonal antibody that binds to and neutralises RANKL (receptor activator of nuclear factor- κ B ligand), thereby inhibiting osteoclast function and preventing generalised bone resorption and local bone destruction. Denosumab is not inferior to zoledronic acid (ZA) in preventing or delaying SREs in patients with advanced MBD, including patients with urothelial carcinoma [472]. Denosumab has recently been approved by the European Medicines Agency (EMA) for treatment of patients with bone metastases from solid tumours. Patients with MBD, irrespective of the cancer type, should be considered for bone-targeted treatment [470].

Patients treated with ZA or denosumab should be informed about possible side effects and receive prophylactic treatment for jaw osteonecrosis and hypocalcaemia, which is more common with denosumab. Aggressive calcium and vitamin D supplementation is recommended. Dosing regimens of ZA should follow regulatory recommendations and should be adjusted according to pre-existing medical conditions [473]. For denosumab, no dose adjustments are required for variations in renal function.

7.8.10 **Conclusions and recommendations for metastatic disease**

Conclusions	LE
In a first-line setting, PS and the presence or absence of visceral metastases are independent prognostic factors for survival.	1b
In a second-line setting, negative prognostic factors are: liver metastasis, PS \geq 1 and low haemoglobin (< 10 g/dL).	1b
Cisplatin-containing combination chemotherapy can achieve median survival of up to 14 months, with long-term disease-free survival reported in ~15% of patients with nodal disease and good PS.	1b
Single-agent chemotherapy provides low response rates of usually short duration.	2a
Carboplatin combination chemotherapy is less effective than cisplatin-based chemotherapy in terms of complete response and survival.	2a
Non-platinum combination chemotherapy produces substantial responses in first- and second-line settings.	2a
Non-platinum combination chemotherapy has not been tested against standard chemotherapy in patients who are fit or unfit for cisplatin combination chemotherapy.	4
There is no defined standard chemotherapy for unfit patients with advanced or metastatic urothelial cancer.	2b
Vinflunine reaches the highest level of evidence ever reported for second-line use.	1b
Post-chemotherapy surgery after partial or complete response may contribute to long-term disease-free survival.	3
Zoledronic acid and denosumab have been approved for all cancer types including urothelial cancer, because they reduce and delay skeletal related events in metastatic bone disease.	1b

Recommendations	GR
<i>First-line treatment for fit patients:</i>	
Use cisplatin-containing combination chemotherapy with GC, PCG, MVAC, preferably with G-CSF, or HD-MVAC with G-CSF.	A
Carboplatin and non-platinum combination chemotherapy is not recommended.	B
<i>First-line treatment in patients ineligible (unfit) for cisplatin:</i>	
Use carboplatin combination chemotherapy or single agents.	C
For cisplatin-ineligible (unfit) patients, with PS2 or impaired renal function, as well as those with 0 or 1 poor Bajorin prognostic factors and impaired renal function, treatment with carboplatin-containing combination chemotherapy, preferably with gemcitabine/carboplatin is indicated.	B
<i>Second-line treatment:</i>	
In patients progressing after platinum-based combination chemotherapy for metastatic disease, vinflunine should be offered. Alternatively, treatment within a clinical trial setting may be offered.	A*
Zoledronic acid or denosumab is recommended for treatment of bone metastases.	B

* Grade A recommendation is weakened by a problem of statistical significance.

GC = gemcitabine plus cisplatin; G-CSF = granulocyte colony-stimulating factor; GR = grade of recommendation; MVAC = methotrexate, vinblastine, adriamycin plus cisplatin; HD MVAC = high-dose methotrexate, vinblastine, adriamycin plus cisplatin; LE = level of evidence; PS = performance status; PCG = paclitaxel, cisplatin, gemcitabine.

7.8.11 Biomarkers

Modest disease control rates, with sporadic marked responses, in some patients with urothelial BC have led to the investigation of biomarkers for assessment of postoperative prognosis and the potential value of perioperative chemotherapy, and as predictors of response to chemotherapy or its monitoring. Most of the biomarkers are associated with tumour angiogenesis. Small studies, usually retrospective, have investigated microvessel density, altered p53 tumour expression [474], serum vascular endothelial growth factor [475], urinary and tissue basic fibroblast growth factor [476], urinary (wild-type and mutant) and tissue fibroblast growth factor receptor-3 [477], and more recently, thrombospondin-1 [478], circulating tumour cells [479, 480], and multidrug resistance gene expression [481]. Although a few biomarkers have shown potential, as yet, there is insufficient evidence to support its routine clinical use (LE: 3).

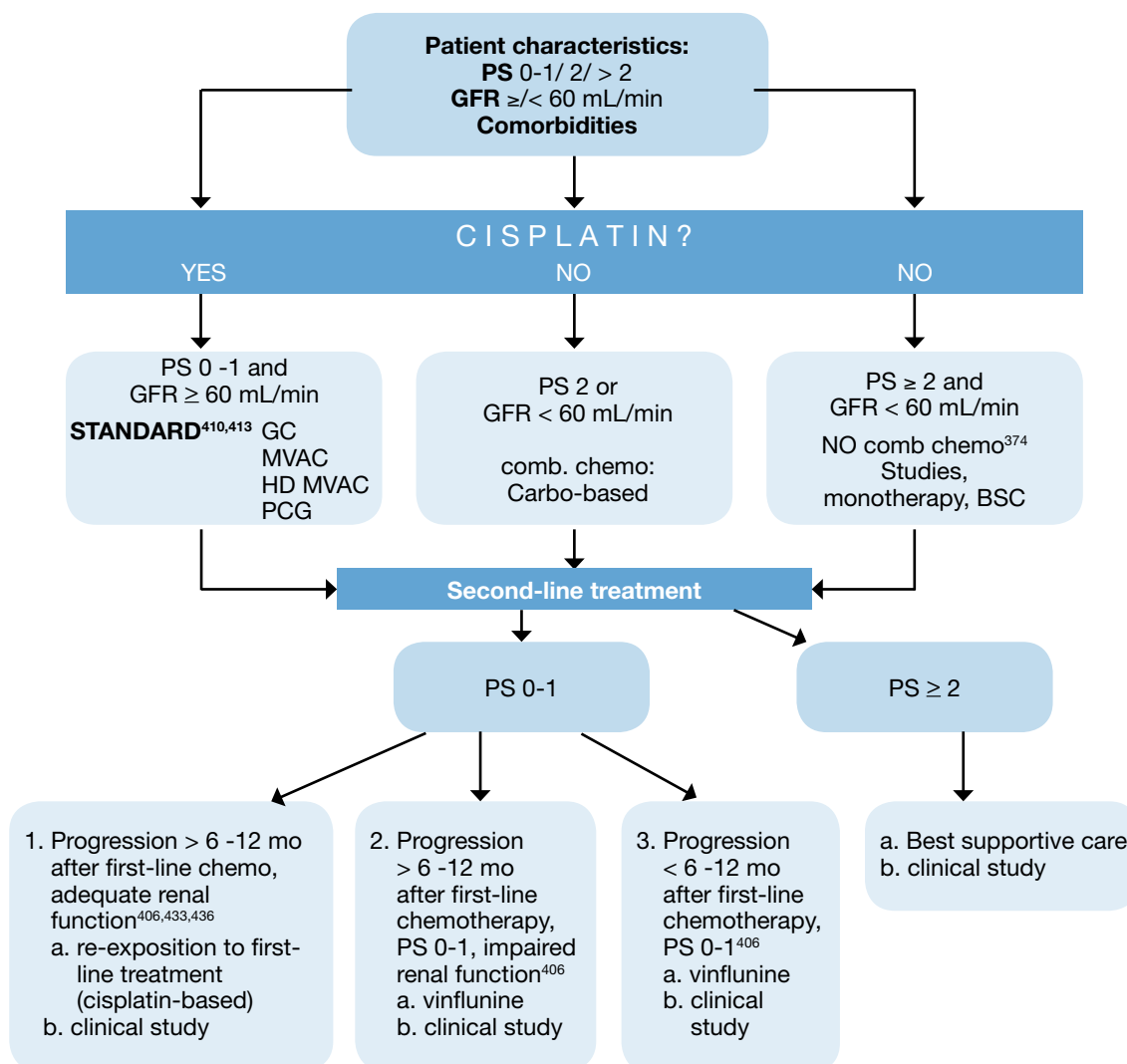
7.8.11.1 Recommendation on the use of biomarkers

	GR
Currently, no biomarkers can be recommended in daily clinical practice because they have no impact on predicting outcome, treatment decisions, or monitoring therapy in muscle-invasive bladder cancer.	A*

*Upgraded following panel consensus.

GR = grade of recommendation.

Figure 7.2: Algorithm for the management of metastatic urothelial cancer



BSC = best supportive care; GC = gemcitabine plus cisplatin; GFR = glomerular filtration rate; MVAC = methotrexate, vinblastine, adriamycin plus cisplatin; HD MVAC = high-dose methotrexate, vinblastine, adriamycin plus cisplatin; PS = performance status; PCG = paclitaxel, cisplatin, gemcitabine.

7.9 Quality of life

7.9.1 Introduction

The evaluation of health-related quality of life (HRQoL) considers physical, psychological, emotional and social functioning.

Several questionnaires have been validated for assessing HRQoL in patients with BC, including FACT (Functional Assessment of Cancer Therapy)-G [482], EORTC QLQ-C30 [483], EORTC QLQ-BLM (muscle-invasive bladder cancer module) [484], and SF (Short Form)-36 [485, 486] and recently the BCI questionnaire specifically designed and validated for BC patients [487].

A psychometric test, such as the FACT-BL, should be used for recording BC morbidity. New intensive interviewing techniques have added valuable information to our knowledge of HRQoL, which greatly depends on patients' individual preferences in life [488].

Unfortunately, most retrospective studies do not evaluate the association between HRQoL and BC-specific issues after cystectomy, such as day-time and night-time incontinence or potency. Furthermore, important co-variables, such as a patient's age, mental status, coping ability and gender, have rarely been considered [489, 490]. It remains difficult to predict the impact of post-therapeutic symptoms because of individual differences in symptom tolerance.

7.9.2 **Choice of urinary diversion**

There is controversy about which type of urinary diversion is best for a patient's HRQoL [226]. Some studies have not demonstrated any difference in HRQoL [490-492]. Nevertheless, most patients stated that, given a choice, they would still opt for an orthotopic diversion rather than an ileal conduit [493]. Another study reported that, although urinary function is better in conduit patients, the urinary bother is the same in both diversion groups, resulting in the same HRQoL evaluation [494].

Due to improved surgical techniques in orthotopic bladder substitution, some recent studies are supportive of continent bladder substitutes [334, 484, 495-497]. Patients with an orthotopic substitution had significantly better physical function and a more active lifestyle compared to patients with an ileal conduit. It is important to note that HRQoL parameters are independent prognostic factors for OS [498]. Patients with a continent bladder-substitute generally scored more favourably than those with an incontinent diversion, as judged by body image, social activity and physical function [494, 495, 499].

7.9.3 **Non-curative or metastatic bladder cancer**

In non-curative or metastatic BC, HRQoL is reduced because of associated micturition problems, bleeding, pain and therefore disturbance of social and sexual life [500]. There is limited literature describing HRQoL in BC patients receiving palliative care [501], but there are reports of bladder-related symptoms relieved by palliative surgery [350], radiotherapy [502], and/or chemotherapy [503].

Alternative definitive treatments of MIBC, e.g. trimodality bladder-sparing procedures, have shown similar survival times compared to cystectomy. However, the impact on HRQoL has been controversial [123, 361, 503-507].

7.9.4 **Conclusions and recommendations for HRQoL**

Conclusions	LE
No randomised, prospective HRQoL study has evaluated the different forms of definitive treatment for MIBC.	2b
In most patient groups studied, the overall HRQoL after cystectomy remains good, irrespective of the type of urinary diversion used. The suggestion that continent diversions are associated with a higher HRQoL has not been sufficiently substantiated.	
Important determinants of (subjective) QoL are a patient's personality, coping style and social support.	

Recommendations	GR
The use of validated questionnaires is recommended to assess HRQoL in patients with MIBC.	B
Unless a patient's comorbidities, tumour variables and coping abilities present clear contraindications, a continent urinary diversion should also be offered.	C
Pre-operative patient information, patient selection, surgical techniques, and careful post-operative follow-up are the cornerstones for achieving good long-term results.	C
Patients should be encouraged to take active part in the decision-making process. Clear and exhaustive information on all potential benefits and side-effects should be provided, allowing them to make informed decisions.	C

HRQoL = health-related quality of life; MIBC = muscle-invasive bladder cancer.

8. FOLLOW-UP

8.1 Introduction

An appropriate schedule for disease monitoring should be based on:

- natural timing of recurrence;
- probability and site of recurrence;
- functional monitoring after urinary diversion;
- possible treatment of recurrence [508].

Nomograms on cancer-specific survival following radical cystectomy have been developed and externally validated. However, their wider use cannot be recommended prior to further data [509-511].

Surveillance protocols are commonly based on patterns of recurrence observed from retrospective series. Diagnosis of asymptomatic recurrence based on routine oncological follow-up and results from retrospective studies are controversial [512, 513]. Importantly, these retrospective studies use different follow-up regimens and imaging techniques that make final analysis and conclusive recommendations difficult. Prospective trials demonstrating the effectiveness of follow-up after RC and its impact on overall survival (OS) are lacking [514].

8.2 Site of recurrence

8.2.1 Local recurrence

Local recurrence takes place in soft tissues at the original surgical site or lymph nodes in the area of LND. Lymph node involvement above the aortic bifurcation can be considered metastatic recurrence [512].

Contemporary cystectomy has a 5-15% probability of pelvic recurrence. Most recurrence manifests during the first 24 months, often within 6-18 months after surgery. However, late recurrence can occur up to 5 years after cystectomy. Pathological stage and lymph node status are predictive for pelvic recurrence, as well as positive margins, extent of LND, and perioperative chemotherapy [515].

Patients have poor prognosis after pelvic recurrence. Even with treatment, the median survival ranges from 4 to 8 months following diagnosis. Definitive therapy can prolong survival, but mostly provides significant palliation of symptoms. Treatment includes systemic chemotherapy, local surgery, or radiotherapy [514].

8.2.2 Distant recurrence

Distant recurrence is seen in up to 50% of patients treated with cystectomy. Stage and nodal involvement are risk factors [516]. Systemic recurrence is more common in locally advanced disease (pT3/4), ranging from 32 to 62%, and in patients with lymph node involvement (range 52-70%) [517].

The most likely sites for distant recurrence are lymph nodes, lungs, liver and bone [518]. Nearly 90% of distant recurrence appears within the first 3 years after RC, mainly in the first 2 years, although late recurrence has been described after > 10 years. Median survival of patients with progressive disease treated with platinum-based chemotherapy is 9-26 months [519-521].

Despite periodic monitoring, > 50% of metastases are diagnosed after symptom appearance.

The value of monitoring in the diagnosis of asymptomatic metastases and its impact on survival is questionable. Some studies have demonstrated no impact on survival despite using routine monitoring, although others have suggested that diagnosis of asymptomatic metastases, especially in the lungs, improves survival [512, 513]. We must also consider the possibility of longer survival in patients with minimal metastatic disease undergoing multimodal treatment, including metastasectomy. There are reports of survival rates of 28-33% at 5 years in patients undergoing resection of metastases after objective response to chemotherapy [461, 468].

8.2.3 Post-cystectomy urothelial tumour recurrence

The incidence of new urethral tumours after RC is 1.5-6.0% in men, with a mean recurrence-free interval of 13.5-39.0 months and median survival of 28-38 months, of which > 50% die from systemic disease.

Secondary urethral tumours are likely to occur at 1-3 years after surgery. Prophylactic urethrectomy at cystectomy is no longer justified in most patients. Independent predictors for urethral recurrence are: cystectomy for NMIBC, prostate involvement, and history of recurrent NMIBC [514].

In women, the main risk factor is bladder neck disease [522]. Many studies have demonstrated that the risk of urethral recurrence after orthotopic diversion (0.9-4.0%) [523-526] is significantly less than after non-orthotopic diversion (6.4-11.1%) [523, 525].

There are limited data and agreement about urethral follow-up, with some recommending routine surveillance with urethral wash and urine cytology [526], and others doubting the need for routine urethral surveillance [524, 527-529]. Urethral washes and urine cytology do not appear to affect survival [527, 530, 531]. However, there is a significant survival advantage in men with urethral recurrence diagnosed asymptotically versus symptomatically, so follow-up of the male urethra is indicated in patients at risk of urethral recurrence [514].

Treatment is influenced by local stage and grade of urethral occurrence:

- in urethral CIS, BCG instillations have success rates of 83% [526];
- in invasive disease, urethrectomy should be performed if the urethra is the only site of disease;
- in distant disease, systemic chemotherapy is indicated [518].

Upper urinary urothelial carcinomas (UTUC) occur in 1.8-6.0% of cases and represent the most common sites of late recurrence (3 years disease-free survival following RC). Median OS is 10-55 months, and 60-67% of patients die of metastatic disease [514].

A recent meta-analysis found that 38% of UTUC recurrence was diagnosed by follow-up investigation, whereas in the remaining 62%, diagnosis was based on symptoms. When urine cytology was used in surveillance, the rate of primary detection was 7% and 29.6% with UUT imaging [532]. This meta-analysis concluded that patients with non-invasive cancer are twice as likely to have UTUC as patients with invasive disease. Multifocality increases the risk of recurrence by threefold, while positive ureteral or urethral margins increase the risk by sevenfold. Radical nephroureterectomy can prolong survival [533].

8.2.4 Conclusions and recommendations for specific recurrence sites

Site of recurrence	Conclusion	LE	Recommendation	GR
Local recurrence	Poor prognosis. Treatment should be individualised depending on the local extent of tumour.	2b	Radiotherapy, chemotherapy and possibly surgery are options for treatment, either alone or in combination.	C
Distant recurrence	Poor prognosis.	2b	Chemotherapy is the first option, and consider individualised cases for metastasectomy in the case of a unique metastasis site.	C
Upper urinary tract recurrence	Multifocal disease (NMIBC/ CIS or positive ureteral margins.		See EAU guidelines on Upper Urinary Tract Carcinomas [1].	
Secondary urethral tumour	Staging and treatment should be done as for primary urethral tumour.	3	Local conservative treatment is possible for non-invasive tumour.	C
			In isolated invasive disease, urethrectomy should be performed.	B
			Urethral washes and cytology are not recommended.	A

Although general recommendations are not advised based on high level of evidence, closer follow-up could be considered in patients with locally advanced disease or lymph node involvement. The suggested follow-up includes 4-monthly CT scans during the first year, 6-monthly until the 3rd year, and annual imaging thereafter.

In patients with multifocal disease, NMIBC with CIS or positive ureteral margins are at higher risk of developing UTUC which can develop late (> 3 years). In those cases, monitoring of the UUT is mandatory during follow-up. Computed tomography should be used to assess the UUT [532].

8.3 Follow-up of functional outcomes and complications

Apart from oncological surveillance, patients submitted for urinary diversion deserve functional follow-up. Complications related to urinary diversion are detected in 45% of patients during the first 5 years follow-up.

This rate increases over time, and exceeds 54% after 15 years follow-up. Therefore, long-term follow-up of functional outcomes is desirable [514] (LE: 3), and may stop after 15 years.

The functional complications are diverse and include: vitamin B12 deficiency, metabolic acidosis, worsening of renal function, urinary infections, urolithiasis, stenosis of uretero-intestinal anastomosis, stoma complications in patients with ileal conduit, neobladder continence problems, and emptying dysfunction [514].

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10. CONFLICT OF INTEREST

All members of the Muscle-invasive and Metastatic Bladder Cancer Guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website: <http://www.uroweb.org/guidelines/>. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

Guidelines on Primary Urethral Carcinoma

G. Gakis, J.A. Witjes, E. Compérat, N.C. Cowan, M. De Santis,
T. Lebrecht, M.J. Ribal, A. Sherif, A.G. van der Heijden

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1. INTRODUCTION

1.1 Aims and scope

The aim of these guidelines is to deliver current evidence-based information on the diagnosis and treatment of patients with primary urethral carcinoma (UC). When the first carcinoma in the urinary tract is detected in the urethra, this is defined as primary UC, in contrast to secondary UC, which presents as recurrent carcinoma in the urethra after prior diagnosis and treatment of carcinoma elsewhere in the urinary tract. Most often, secondary UC is reported after radical cystectomy for bladder cancer [1] (see Chapter 7.4 of the EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer [2] of the full text versions).

1.2 Panel composition

The EAU Guidelines Panel on Muscle-invasive and Metastatic Bladder Cancer is responsible for this publication. This is an international multidisciplinary group of clinicians, including a pathologist, an oncologist and a radiologist. Members of this panel have been selected based on their expertise to represent the professionals treating patients suspected of harbouring urethral carcinoma.

All experts involved in the production of this document have submitted potential conflict of interest statements.

1.3 Publication history and summary of changes

The Primary Urethral Carcinoma Guidelines were first published in 2013 [3]. This is the first update of this document.

1.3.1 Summary of changes

The literature for the complete document has been assessed and updated, whenever relevant.

Key changes for the 2015 publication:

- Evaluation of recent data on prognostic factors on oncologic outcomes in primary UC;
- Evaluation of recent data on the degree of concordance between clinical and pathologic staging;
- Evaluation of recent data on distal urethrectomy in men;
- Evaluation of recent data on the prognostic effect of multimodal treatment in advanced primary UC.

Conclusions and recommendations have been rephrased and added throughout the document, not resulting in a change in the level of evidence (LE) or grade of recommendation (GR). These changes can be found in the following sections:

6.2 Predictors of survival in primary urethral carcinoma

Conclusion	LE
Risk factors for survival in primary UC are: age, race, tumour stage and grade, nodal stage, presence of distant metastasis, histological type, tumour size, tumour location, concomitant bladder cancer and type and modality of treatment.	3

7.1 Treatment of localised primary urethral carcinoma in males

Recommendation	LE	GR
In localised anterior urethral tumours, distal urethrectomy presents an alternative to achieve negative surgical margins and should be offered as an alternative to penile amputation.	3	B

7.2.2 Radiotherapy

Recommendations	LE	GR
In women, local radiotherapy is an alternative to urethral surgery for localised urethral tumours but local toxicity needs to be considered.	3	C

7.3.2 Preoperative chemoradiotherapy in locally advanced squamous cell carcinoma of the urethra

Conclusions	LE
In locally advanced UC, cisplatin-based chemotherapy with curative intent prior to surgery improves survival compared to chemotherapy alone or surgery followed by chemotherapy.	4
In locally advanced squamous cell carcinoma (SCC) of the urethra, the prognostic role and timing of surgery after completion of chemoradiotherapy is unclear.	4

Recommendations	LE	GR
Chemotherapeutic regimens with curative intent prior to surgery should be cisplatinum-based.	4	C
In locally advanced SCC of the urethra, combination of curative radiotherapy with radiosensitising chemotherapy is an option for genital preservation.	4	C

SCC = squamous cell carcinoma; UC = urethral carcinoma.

2. METHODS

2.1 Literature identification

An updated systematic literature search was performed to identify studies reporting data on urethral malignancies since the last search on 15th October 2012 until 15th August 2014. Medline was searched using the controlled vocabulary of the Medical Subject Headings (MeSH) database, along with a free-text protocol, using one or several combinations of the following terms: *adenocarcinoma, adjuvant treatment, anterior, chemotherapy, distal urethral carcinoma, lower, neoadjuvant, partial, penectomy, penile-preserving surgery, posterior, primary, proximal urethral carcinoma, radiotherapy, recurrence, risk factors, squamous cell carcinoma, survival, transitional cell carcinoma, urethra, urethrectomy, urethral cancer, urinary tract, and urothelial carcinoma*. No randomised controlled trials were identified and articles were selected based on study design, treatment modality and long-term outcomes. Older studies (> 10 years) were considered if they contained historically relevant data or in the absence of newer data.

In this 2015 EAU Guidelines compilation, all standard information on levels of evidence (LE) and grading of recommendations (GR) has been taken out of the individual guidelines topics for the sake of brevity. This information is included in the introductory section of this print.

2.2 Review

This document was subjected to double-blind peer review prior to publication.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Primary UC is considered a rare cancer, accounting for < 1% of all malignancies [4] (ICD-O3 topography code: C68.0 [5]).

In early 2008, the prevalence of UC in the 27 EU countries was 4,292 cases with an estimated annual incidence of 655 new cases [6]. The age-standardised ratio was 1.1 per million inhabitants (1.6/million in men and 0.6/million in women; with a male to female ratio of 2.9) [6]. There were differences between European regions; potentially caused by registration or classification [6]. Likewise, in an analysis of the Surveillance, Epidemiology and End Results (SEER) database, the incidence of primary UC peaked in the ≥ 75 years age group (7.6/million). The age-standardised rate was 4.3/million in men and 1.5/million in women, and was almost negligible in those aged < 55 years (0.2/million) [7].

3.2 Aetiology

For male primary UC, various predisposing factors have been reported, including urethral strictures [8, 9], chronic irritation after intermittent catheterisation/urethroplasty [10-12], external beam irradiation therapy [13], radioactive seed implantation [14], and chronic urethral inflammation/urethritis following sexually transmitted diseases (i.e. condylomata associated with human papilloma virus 16) [15, 16]. In female UC, urethral diverticula [17-19] and recurrent urinary tract infections [20] have been associated with primary urethral carcinoma. Clear cell adenocarcinoma may also have a congenital origin [21, 22].

3.3 Histopathology

Both the Surveillance of Rare Cancers in Europe (RARECARE) project and SEER database have reported that urothelial carcinoma of the urethra is the predominant histological type of primary urethral cancer (54-65%), followed by squamous cell carcinoma (SCC; 16-22%) and adenocarcinoma (AC; 10-16%) [6, 7]. A recent SEER

analysis of 2,065 men with primary urethral cancer (mean age: 73 years) found that urothelial carcinoma (78%) was most common, and SCC (12%) and AC (5%) were significantly less frequent [23]. In women, a recent report of the Dutch National Cancer Registry on primary urethral cancer reported that urothelial carcinoma occurred in 45% of cases, followed by AC in 29%, SCC in 19%, and other histological entities in 6% [24].

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Tumor, Node, Metastasis (TNM) staging system

In men and women, UC is classified according to the 7th edition of the TNM classification [5] (Table 4.1). It should be noted that there is a separate TNM staging system for prostatic UC [5]. Of note, for cancers occurring in urethral diverticulum stage, T2 is not applicable as urethral diverticula are lacking periurethral muscle [25].

Table 4.1: TNM classification (7th edition) for UC [5]. Primary tumour stage is separated into UC and UC of the prostate

T - Primary tumour (men and women)	
Tx	Primary tumour cannot be assessed
Tis	Carcinoma <i>in situ</i>
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades any of the following structures: corpus spongiosum, prostate, peri-urethral muscle
T3	Tumour invades any of the following structures: corpus cavernosum, invasion beyond prostatic capsule, anterior vaginal wall, bladder neck
T4	Tumour invades other adjacent organs
Primary tumour in prostatic urethra	
Tx	Primary tumour cannot be assessed
Tis pu	Carcinoma <i>in situ</i> in the prostatic urethra
Tis pd	Carcinoma <i>in situ</i> in the prostatic ducts
T0	No evidence of primary tumour
T1	Tumour invades subepithelial connective tissue (only in case of concomitant prostatic urethral involvement)
T2	Tumour invades any of the following structures: corpus spongiosum, prostatic stroma, periurethral muscle
T3	Tumour invades any of the following structures: corpus cavernosum, beyond prostatic capsule, bladder neck
T4	Tumour invades other adjacent organs
N - Regional lymph nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in a single lymph node ≤ 2 cm in greatest dimension
N2	Metastasis in a single lymph node > 2 cm in greatest dimension or in multiple nodes
M - Distant metastasis	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

4.2 Tumour grade

The former World Health Organization (WHO) grading system of 1973 which differentiated urothelial carcinomas into three different grades (G1-G3) has been replaced by the grading system of 2004 that differentiates urothelial UC into papillary urothelial neoplasm of low malignant potential (PUNLMP), low grade and high grade. Non-urothelial UC is graded by a trinomial system that differentiates between well-differentiated (G1), moderately differentiated (G2), and poorly differentiated tumours (G3). Table 4.2 lists the different grading systems according to the WHO 1973 and 2004 systems [26].

Table 4.2: Histopathological grading of urothelial and non-urothelial primary UC [26]

PUNLMP	Papillary urothelial neoplasm of low malignant potential
Low grade	Well differentiated
High grade	Poorly differentiated

Non-urothelial UC	
Gx	Tumour grade not assessable
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated

Recommendation	LE	GR
Pathological staging and grading of primary UC should follow the 2009 TNM classification and WHO 2004 grading system.	3	B

TNM = Tumour, Node, Metastasis; WHO = World Health Organization.

5. DIAGNOSTIC EVALUATION AND STAGING

5.1 History

When becoming clinically apparent, most patients (45-57%) with primary UC present with symptoms associated with locally advanced disease (T3/T4) [25, 27]. At initial presentation visible haematuria or bloody urethral discharge is reported in up to 62% of the cases. Further symptoms of locally advanced disease include an extraurethral mass (52%), bladder outlet obstruction (48%), pelvic pain (33%), urethrocutaneous fistula (10%), abscess formation (5%) or dyspareunia [27].

5.2 Clinical examination

In men, physical examination should comprise palpation of the external genitalia for suspicious indurations or masses and digital rectal examination [28]. In women, further pelvic examination with careful inspection and palpation of the urethra should be performed, especially in those with primary onset of irritative or obstructive voiding. In addition, bimanual examination, when necessary under general anaesthesia, should be performed for local clinical staging and to exclude the presence of colorectal or gynaecological malignancies. Bilateral inguinal palpation should be conducted to assess the presence of enlarged lymph nodes, describing location, size and mobility [29].

5.3 Urinary cytology

The role of urinary cytology in primary UC is limited, and its sensitivity ranges between 55% and 59% [30]. Detection rate depends on the underlying histological entity. In male patients, the sensitivity for urothelial carcinoma and SCC was reported to be 80% and 50%, respectively, whereas in female patients sensitivity was found to be 77% for SCC and 50% for urothelial carcinoma.

5.4 Diagnostic urethrocystoscopy and biopsy

Diagnostic urethrocystoscopy and biopsy enables primary assessment of a urethral tumour in terms of tumour extent, location and underlying histology [28]. To enable accurate pathological assessment of surgical margins, biopsy sites (proximal/distal end) should be marked and sent together with clinical information to the pathologist.

Careful cystoscopic examination is necessary to exclude the presence of concomitant bladder tumours [3, 31]. A cold-cup biopsy enables accurate tissue retrieval for histological analysis and avoids artificial tissue damage. In patients with larger lesions, transurethral resection (optionally in men under penile blood arrest using a tourniquet) can be performed for histological diagnosis. In patients with suspected urothelial carcinoma of the prostatic urethra or ducts, resectoscope loop biopsy of the prostatic urethra (at 5 and 7 o'clock positions from the bladder neck and distally around the area of the verumontanum) can contribute to an improved detection rate [32].

5.5 Radiological imaging

Radiological imaging of urethral cancer aims to assess local tumour extent and to detect lymphatic and distant metastatic spread. For local staging, there is increasing evidence that magnetic resonance imaging (MRI) is an accurate tool for monitoring tumour response to neoadjuvant chemoradiotherapy and evaluating the extent of local disease prior to exenterative surgery [33]. Imaging for regional lymph node metastases should concentrate on inguinal and pelvic lymph nodes, using either MRI or CT. Distant staging should concentrate on chest and liver, with CT of the thorax and abdomen in all patients with invasive disease (\geq cT1N0M0 [33-37]. If imaging of the remainder of the urothelium is required, then CT should include CT urography with an excretory phase [38].

5.6 Regional lymph nodes

Enlarged lymph nodes in urethral cancer often represent metastatic disease [39, 40]. In men, lymphatics from the anterior urethra drain into the superficial- and deep inguinal lymph nodes and subsequently to the pelvic (external, obturator and internal iliac) lymph nodes. Conversely, lymphatic vessels of the posterior urethra drain into the pelvic lymph nodes. In women, the lymph of the proximal third drains into the pelvic lymph node chains, whereas the distal two-thirds initially drain into the superficial- and deep inguinal nodes [41, 42].

Nodal control in urethral cancer can be achieved either by regional lymph node dissection [28], radiotherapy [43] or chemotherapy [39]. Currently, there is still no clear evidence to support prophylactic bilateral inguinal and/or pelvic lymphadenectomy in all patients with urethral cancer. However, in patients with clinically enlarged inguinal/pelvic lymph nodes or invasive tumours, regional lymphadenectomy should be considered for initial treatment because cure might still be achievable with limited disease [28].

Conclusion	LE
Patients with clinically enlarged inguinal or pelvic lymph nodes often exhibit pathological lymph node metastasis.	3

Recommendations	LE	GR
Diagnosis includes urethrocystoscopy with biopsy and urinary cytology.	3	B
CT of the thorax and abdomen should be used to assess distant metastases.	3	B
Pelvic MRI is the preferred method to assess local extent of urethral tumour.	3	B

CT = computed tomography; MRI = magnetic resonance imaging.

6. PROGNOSIS

6.1 Long-term survival after primary urethral carcinoma

According to the RARECARE project, the mean 1- and 5-year overall survival in patients with UC in Europe is 71% and 54%, respectively [6]. With longer follow-up, a SEER analysis of 1,615 cases reported median 5- and 10-year overall survival rates of 46% and 29%, respectively. Cancer-specific survival at 5 and 10 years was 68% and 60%, respectively [7].

6.2 Predictors of survival in primary urethral carcinoma

In Europe, mean 5-year overall survival does not substantially differ between the sexes [6]. Predictors of decreased survival in patients with primary UC are:

- advanced age (\geq 65 years) and black race [6, 44];
- stage, grade, nodal involvement [40] and metastasis [23];
- tumour size and proximal tumour location [23];
- extent of surgical treatment and treatment modality [23, 44];
- underlying histology [6, 24, 44];
- presence of concomitant bladder cancer [31].

Some limitations have to be taken into account in the interpretation of these results. In the Dutch study, the numbers were low ($n = 91$) [25]. In the large SEER database ($n = 2,046$), therapy is not well specified in relation to survival [24]. Finally, in contrast to the RARECARE project [6], the opposite findings were reported in the SEER database in relation to the role of histology on survival in male patients [44].

Conclusion	LE
Risk factors for survival in primary UC are: age, race, tumour stage and grade, nodal stage, presence of distant metastasis, histological type, tumour size, tumour location, concomitant bladder cancer and type and modality of treatment.	3

7. DISEASE MANAGEMENT

7.1 Treatment of localised primary urethral carcinoma in males

Previously, treatment of male anterior urethral cancer has followed the procedure for penile cancer, with aggressive surgical excision of the primary lesion with a wide safety margin [28]. Distal urethral tumours exhibit significantly improved survival rates compared with proximal tumours [45]. Therefore, optimising treatment of distal urethral cancer has become the focus of clinicians to improve functional outcome and quality of life, while preserving oncological safety. A retrospective series found no evidence of local recurrence, even with < 5 mm resection margins (median follow-up: 17-37 months), in men with pT1-3N0-2 anterior UC treated with well-defined penis-preserving surgery and additional iliac/inguinal lymphadenectomy for clinically suspected lymph node disease [46]. This suggests that prognosis is mainly determined by nodal stage. Similar results for the feasibility of penile-preserving surgery have been also reported in a recent series [47].

Recommendation	LE	GR
In localised anterior urethral tumours, distal urethrectomy presents an alternative to achieve negative surgical margins and should be offered as an alternative to penile amputation.	3	B

7.2 Treatment of localised urethral carcinoma in females

7.2.1 Urethrectomy and urethra-sparing surgery

In women with localised urethral cancer, to provide the highest chance of local cure, primary radical urethrectomy should remove all the periurethral tissue from the bulbocavernosus muscle bilaterally and distally, with a cylinder of all adjacent soft tissue up to the pubic symphysis and bladder neck. Bladder neck closure and via an appendico-vesicostomy for primary anterior urethral lesions has been shown to provide satisfactory functional results in women [28].

Recent series have reported outcomes in women with mainly anterior urethral cancer undergoing primary treatment with urethra-sparing surgery or radiotherapy, compared to primary urethrectomy, with the aim of maintaining integrity and function of the lower urinary tract [48-50]. In long-term series with a median follow-up of 153-175 months, local recurrence rates in women undergoing partial urethrectomy with intraoperative frozen section analysis were 22-60%, and distal sleeve resection of > 2 cm resulted in secondary urinary incontinence in 42% of patients who required additional reconstructive surgery [48, 49]. Ablative surgical techniques, i.e., transurethral resection (TUR) or laser, used for small distal urethral cancer, have also resulted in a considerable local failure rate of 16%, with a cancer-specific survival rate of 50%. This emphasises the critical role of local tumour control in women with distal urethral cancer to prevent local and systemic progression [48].

7.2.2 Radiotherapy

In women, radiotherapy was investigated in several older long-term series with a medium follow-up of 91-105 months [43, 46]. With a median cumulative dose of 65 Gy (range: 40-106 Gy), the 5-year local control rate was 64% and 7-year cancer-specific survival was 49% [43]. Most local failures (95%) occurred within the first two years after primary treatment [46]. The extent of urethral tumour involvement was found to be the only parameter independently associated with local tumour control but the type of radiotherapy (external beam radiotherapy vs. interstitial brachytherapy) was not [43]. In one study, the addition of brachytherapy to external beam radiotherapy reduced the risk of local recurrence by a factor of 4.2 [51]. Of note, pelvic toxicity in those achieving local control was considerable (49%), including urethral stenosis, fistula, necrosis, and cystitis and/or haemorrhage, with 30% of the reported complications graded as severe [43].

Recommendations	LE	GR
In women with anterior urethral tumours, urethra-sparing surgery is an alternative to primary urethrectomy if negative surgical margins can be achieved intraoperatively.	3	B
In women, local radiotherapy is an alternative to urethral surgery for localised urethral tumours but local toxicity needs to be considered.	3	C

7.3 Multimodal treatment in advanced urethral carcinoma in both genders

7.3.1 Preoperative platinum-based chemotherapy

Recent retrospective studies have reported that modern platinum-based polychemotherapeutic regimens are effective in advanced primary urethral cancer, providing prolonged survival even in lymph-node-positive disease. Moreover, they have emphasised the critical role of surgery after chemotherapy for achieving long-term survival in patients with locally advanced urethral cancer.

In a series of 39 patients treated with perioperative platinum-based chemotherapy for advanced primary UC, preoperative chemotherapy was found to be associated with improved progression-free and overall survival compared to surgery followed by adjuvant chemotherapy [52]. Another series reported outcomes in 44 patients with advanced primary urethral cancer treated with specific cisplatin-based polychemotherapeutic regimens according to the underlying histology. The overall response rate for the various regimens was 72% and the median overall survival 32 months. Patients who underwent surgery after chemotherapy had significantly improved overall survival compared with those who were managed with chemotherapy alone [39].

7.3.2 Preoperative chemoradiotherapy in locally advanced squamous cell carcinoma of the urethra

The clinical feasibility of preoperative local radiotherapy with concurrent radiosensitising chemotherapy as an alternative to surgery in locally advanced SCC has been reported in several recent series. This approach offers a potential for genital preservation [52-57]. The largest and recently updated series reported outcomes in 25 patients with primary locally advanced SCC of the urethra treated with two cycles of 5-fluorouracil and mitomycin C with concurrent external beam radiotherapy. A complete response to primary chemoradiotherapy was observed in ~80%. The 5-year overall- and disease-specific survival was 52% and 68%, respectively. In this updated series, salvage surgery initiated only in non-responders or in case of local failure was not reported to be associated with improved survival [53].

Conclusions	LE
In locally advanced UC, cisplatin-based chemotherapy with curative intent prior to surgery improves survival compared to chemotherapy alone or surgery followed by chemotherapy.	4
In locally advanced SCC of the urethra, the prognostic role and timing of surgery after completion of chemoradiotherapy is unclear.	4

Recommendations	LE	GR
Patients with locally advanced UC should be discussed within a multidisciplinary team of urologists, radio-oncologists and oncologists.	4	A
Chemotherapeutic regimens with curative intent prior to surgery should be cisplatin-based.	4	C
In locally advanced SCC of the urethra, combination of curative radiotherapy with radiosensitising chemotherapy is an option for genital preservation.	4	C

SCC = squamous cell carcinoma; UC = urothelial carcinoma.

7.4 Treatment of urothelial carcinoma of the prostate

Local conservative treatment with extensive TUR and subsequent Bacille-Calmette-Guérin (BCG) instillation is effective in patients with Ta or Tis prostatic UC [58, 59]. Likewise, patients undergoing TUR of the prostate prior to BCG experience improved complete response rates compared with those who do not (95% vs. 66%) [60]. Risk of understaging local extension of prostatic urethral cancer at TUR is increased, especially in patients with ductal or stromal involvement [61]. In smaller series, response rates to BCG in patients with prostatic duct involvement have been reported to vary between 57 and 75% [58, 62]. Some earlier series have reported superior oncological results for the initial use of radical cystoprostatectomy as a primary treatment option in patients with ductal involvement [63, 64]. In 24 patients with prostatic stromal invasion treated with radical cystoprostatectomy, a lymph node mapping study found that 12 patients had positive lymph nodes, with an increased proportion located above the iliac bifurcation [65].

Recommendations	LE	GR
Patients with non-invasive UC or carcinoma <i>in situ</i> of the prostatic urethra and prostatic ducts can be treated with a urethra-sparing approach with TUR and BCG.	3	C
In patients with non-invasive UC or carcinoma <i>in situ</i> , prior TUR of the prostate should be performed to improve response to BCG.	3	C
Cystoprostatectomy with extended pelvic lymphadenectomy should be reserved for patients not responding to BCG or as primary treatment option in patients with extensive ductal or stromal involvement.	3	C

BCG = *Bacille-Calmette-Guérin*; TUR = *transurethral resection*; UC = *urothelial carcinoma*.

8. FOLLOW-UP

COMMENTARY: Given the low incidence of primary urethral cancer, defined follow-up has not been investigated systematically so far. Therefore, it seems reasonable to tailor surveillance regimens according to the patients' individual risk factors (Chapter 6.2). In patients undergoing urethra-sparing surgery, it seems prudent to advocate a more extensive follow-up with urinary cytology, urethrocytscopy and cross-sectional imaging despite the lack of specific data.

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10. CONFLICT OF INTEREST

All members of the Muscle-invasive and Metastatic Bladder Cancer guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: <http://www.uroweb.org/guidelines/>. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

Guidelines on Prostate Cancer

N. Mottet (Chair), J. Bellmunt, E. Briers (Patient Representative), R.C.N. van den Bergh (Guidelines Associate), M. Bolla, N.J. van Casteren (Guidelines Associate), P. Cornford, S. Culine, S. Joniau, T. Lam, M.D. Mason, V. Matveev, H. van der Poel, T.H. van der Kwast, O. Rouvière, T. Wiegel

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1. INTRODUCTION

1.1 Aims and scope

The European Association of Urology (EAU) Prostate Cancer Guidelines Panel have prepared this guidelines document to assist medical professionals assess the evidence-based management of prostate cancer (PCa).

1.2 Panel composition

The Prostate Cancer Guidelines Panel consists of an international multidisciplinary group of urologists, radiation oncologists, medical oncologists, a radiologist, a pathologist and a patient stakeholder organisation representative.

1.2.1 Acknowledgement

The EAU Prostate Cancer Guidelines Panel are most grateful for the support and considerable expertise provided by Prof. Dr. J-P. Droz, Emeritus Professor of Medical Oncology (Lyon, France) for the topic of 'Management of prostate cancer in senior adults'. As a leading expert in this field, and prominent member of the International Society of Geriatric Oncology, his contribution has been invaluable.

1.2.2 Potential conflict of interest

All experts involved in the production of this document have submitted potential conflict of interest statements.

1.3 Available publications

A quick reference document (Pocket guidelines) is available, both in print and in a number of versions for mobile devices. These are abridged versions which may require consultation together with the full text version. Several scientific publications are available [1, 2] as are a number of translations of all versions of the Prostate Cancer guidelines. All documents can be viewed, free access, through the EAU website Uroweb: <http://www.uroweb.org/guidelines/online-guidelines/>.

1.4 Publication history and summary of changes

1.4.1 Publication history

The first EAU Guidelines on Prostate Cancer were published in 2001. This current 2015 document presents a full update of the 2014 full text document. The literature for the complete document has been assessed and updated, whenever relevant.

1.4.2 Summary of changes

Key changes for this 2015 print:

Table 4.1.2: EAU risk groups for biochemical recurrence of localised and locally advanced prostate cancer

	Low-risk	Intermediate-risk	High-risk	
Definition	PSA < 10 ng / mL and GS < 7 and cT1-2a	PSA 10-20 ng /mL or GS 7 or cT2b	PSA > 20 ng / mL or GS > 7 or cT2c	any PSA any GS cT3-4 or cN+
	Localised			Locally advanced

Conclusions and recommendations have been rephrased and added to throughout the current document. Changed or new conclusions and recommendations can be found in sections:

5.2.4.3 Guidelines for imaging

	LE	GR
When clinical suspicion of PCa persists in spite of negative biopsies, MRI-targeted biopsies are recommended.	2b	B

Table 5.2.4: Recommended terminology for reporting prostate biopsies [3]

• Benign/negative for malignancy. If appropriate, include a description.
• Active inflammation.
• Granulomatous inflammation.
• High-grade PIN.
• High-grade PIN with atypical glands, suspicious for adenocarcinoma (PINATYP).
• Focus of atypical glands/lesion suspicious for adenocarcinoma/atypical small acinar proliferation, suspicious for cancer.
• Adenocarcinoma.

5.2.7 Guidelines for the clinical diagnosis of prostate cancer

	LE	GR
Transurethral resection of the prostate should not be used as a tool for cancer detection.	2a	A

5.3.4 Guidelines for staging of prostate cancer

Any risk group staging	LE	GR
Additional imaging is required only if it changes patient management.	2a	A*
For local staging, CT and TRUS should not be used.	3	A
For up-front staging, PET-scanning should not be used.	2a	A

Low-risk localised PCa	LE	GR
No additional imaging is recommended for staging purposes.	2a	A

Intermediate-risk PCa	LE	GR
In predominantly Gleason pattern 4, bone scan and cross-sectional imaging is required.	2a	A*

High-risk localised PCa/ High-risk locally advanced PCa	LE	GR
Prostate mpMRI should be used for local staging.	2b	A
CT/MRI and bone-scan should be used in staging.	2b	A
For up-front staging, PET-scanning should not be used.	2a	A

7.1.5 Guidelines for active surveillance and watchful waiting

Recommendations - active surveillance	LE	GR
Patients who are suitable for surgery and radiotherapy must have these options discussed with them.	4	A*

7.2.11 **Guidelines for radical prostatectomy**

	LE	GR
Patients who are suitable for AS and radiotherapy must have these options discussed with them.	4	A*
In patients with low- and intermediate-risk PCa and a life expectancy > 10 years, RP should be offered.	1b	A
Nerve-sparing surgery may be attempted in pre-operatively potent patients with low risk for extracapsular disease (T1c, GS < 7 and PSA < 10 ng/mL, or refer to Partin tables/nomograms).	2b	B
Multiparametric MRI may help in deciding when to perform nerve-sparing procedures in intermediate- and high-risk disease.	2b	B
In patients with high-risk localised PCa and a life expectancy of > 10 yr, RP should be offered in a multimodality setting.	2a	A
In selected patients with locally advanced (cT3a) PCa, and a life expectancy > 10 yr, RP may be offered in a multimodality setting.	2b	B
In highly selected patients with locally advanced PCa (cT3b-T4 N0 or any T N1), RP may be offered in a multimodality setting.	3	C
NHT before RP is not recommended.	1a	A
Adjuvant HT for pN0 is not recommended.	1a	A
Adjuvant ADT is the standard of care for node-positive (pN+) patients.	1b	A

7.3.10 **Conclusion and Guidelines for definitive radiotherapy**

Statement	LE
The highest effect of adjuvant radiotherapy is seen in patients with pT3R1 PCa.	1a

Recommendations	LE	GR
Patients who are suitable for AS and surgery must have these options discussed with them.	4	A
EBRT should be offered in all risk groups of non-metastatic PCa.	2a	A
In low-risk PCa, the total dose should be 74 to 78 Gy.	1a	A
In patients with low-risk PCa, without a previous TURP and with a good IPSS and a prostate volume < 50 mL, LDR brachytherapy is a treatment option.	2a	A
In intermediate-risk PCa, a total dose should be 76-78 Gy, in combination with short-term ADT (4-6 mo).	1b	A
In patients with high-risk localised PCa, a total dose of 76-78 Gy in combination with long-term ADT (2-3 yr) is recommended.	1b	A
In patients with locally advanced cN0 PCa, radiotherapy must be given in combination with long-term ADT (2-3 yr).	1a	A
IMRT is the recommended modality for definitive treatment of PCa by EBRT.	2a	A
In patients with cN+ PCa, pelvic external irradiation can be given in combination with immediate long-term ADT.	2b	B
In patients with pT3,N0M0 PCa and an undetectable PSA following RP, adjuvant external beam irradiation should be discussed as an option because it improves at least biochemical-free survival.	1a	A
Patients with pT3,N0M0 PCa and an undetectable PSA following RP should be informed about salvage irradiation as an alternative to adjuvant irradiation when PSA increases (See Section 6.10.5.1).	2b	A

Primary treatment of prostate cancer			GR
General comments	Patients suitable for several treatment modalities (active surveillance, surgery, radiotherapy) must have these options discussed with them.		A*
	In patients who are surgical candidates for radical prostatectomy, all approaches (i.e. open, laparoscopic or robotic) are acceptable as no single approach has shown clear superiority in terms of functional or oncological results.		A
	EBRT should be offered in all risk groups of non-metastatic PCa.		A
	IMRT is the recommended modality for definitive treatment of PCa by EBRT.		A
	Treatment	Comment	
Low risk PCa	Watchful waiting	Watchful waiting may be offered to patients not eligible for local curative treatment and those with a short life expectancy.	A
		During watchful waiting, the decision to start non-curative treatment should be based on symptoms and disease progression.	B
	Active surveillance	Active surveillance is an option in patients with the lowest risk of cancer progression: > 10 years life expectancy, cT1/2, PSA ≤ 10 ng/mL, biopsy Gleason score ≤ 6, ≤ 2 positive biopsies, minimal biopsy core involvement (≤ 50% cancer per biopsy).	A
		Follow-up should be based on DRE, PSA and repeat biopsies. The optimal follow-up interval is still unclear.	A
	Radical prostatectomy	In patients with a life expectancy > 10 years, RP should be offered.	A
		Nerve-sparing surgery may be attempted in pre-operatively potent patients with low risk for extracapsular disease (T1c, GS < 7 and PSA < 10 ng/mL, or refer to Partin tables/nomograms).	B
		LND is not indicated in low-risk PCa.	A
	Radiotherapy	In low-risk PCa the total dose should be 74 to 78 Gy.	A
		In patients with low-risk PCa, without a previous TURP and with a good IPSS and a prostate volume < 50 mL, LDR brachytherapy is a treatment option.	A
	Cryotherapy, HIFU	In patients who are unfit for surgery or radiotherapy, cryotherapy or HIFU might be an alternative treatment for PCa. The lack of long-term efficacy compared to standard modality should be discussed with patients.	C
	Focal treatment	Focal therapy of PCa is still in its infancy and cannot be recommended as a therapeutic alternative outside clinical trials.	A
	Androgen suppression	Unsuitable.	A
Intermediate risk PCa	Watchful waiting	Watchful waiting may be offered to patients not eligible for local curative treatment and those with a short life expectancy.	A
	Active surveillance	Not an option.	A
	Radical prostatectomy	In patients with a life expectancy > 10 years, RP should be offered.	A
		Nerve-sparing surgery may be attempted in pre-operatively potent patients with low risk for extracapsular disease (T1c, GS < 7 and PSA < 10 ng/mL, or refer to Partin tables/nomograms).	B

		Multiparametric MRI may help in deciding when to perform nerve-sparing procedures in intermediate- and high-risk disease.	B
		eLND should be performed if the estimated risk for positive lymph nodes exceeds 5%.	B
		Limited LND should not be performed.	A
		In patients with pT3,N0M0 PCa and an undetectable PSA following RP, adjuvant external beam irradiation should be discussed as an option because it improves at least biochemical-free survival.	A
		Patients with pT3,N0M0 PCa and an undetectable PSA following RP should be informed about salvage irradiation as an alternative to adjuvant irradiation when PSA increases.	A
		Adjuvant HT for pN0 is not recommended.	
	Radiotherapy	In intermediate-risk PCa, the total dose should be 76-78 Gy, in combination with short-term ADT (4-6 mo).	A
	Androgen suppression monotherapy	No place in asymptomatic patients.	A
High risk PCa	Watchful waiting	High risk localised: Watchful waiting may be offered to patients not eligible for local curative treatment and those with a short life expectancy.	
		High risk locally advanced: In M0 patients unwilling or unable to receive any form of local treatment, a deferred treatment policy using ADT as monotherapy is feasible in asymptomatic patients with a PSA-DT > 12 months and a PSA < 50 ng/mL and non-poorly differentiated tumour.	A
	Active surveillance	Not appropriate.	A
	Radical prostatectomy	NHT before RP is not recommended.	A
		eLND should be performed in high-risk PCa.	A
		Limited LND should not be performed.	A
		High risk localised: In patients with high-risk localised PCa and a life expectancy of > 10 yr, RP should be offered in a multimodality setting.	B
		Nerve-sparing surgery may be attempted in pre-operatively potent patients with low risk for extracapsular disease (refer to Partin tables/nomograms).	B
		Multiparametric MRI may help in deciding when to perform nerve-sparing procedures in intermediate- and high-risk disease.	B
		High risk locally advanced: In highly selected patients with locally advanced PCa (cT3b-T4 N0 or any T N1), RP may be offered in a multimodality setting.	C
		In patients with pT3,N0M0 PCa and an undetectable PSA following RP, adjuvant external beam irradiation should be discussed as an option because it improves at least biochemical-free survival.	A
		Patients with pT3,N0M0 PCa and an undetectable PSA following RP should be informed about salvage irradiation as an alternative to adjuvant irradiation when PSA increases.	A

	Radiotherapy	In patients with high-risk localised PCa, the total dose is 76-78 Gy in combination with long-term ADT (2-3 yr is recommended).	A
		In patients with locally advanced cN0 PCa, radiotherapy must be given in combination with long-term ADT (2-3 yr is recommended).	A
	Androgen suppression monotherapy	Reserved for those unwilling or unable to receive any form of local treatment and either symptomatic or asymptomatic with a PSA-DT < 12 months and a PSA > 50 ng/mL and a poorly differentiated tumour.	A
N1 patients			
cN1		In patients with cN+ PCa, pelvic external irradiation can be given in combination with immediate long-term ADT.	B
pN1 after eLND		Adjuvant ADT is the standard of care for node-positive (pN+) patients.	A
		Adjuvant ADT with additional radiotherapy may have a role.	B
		Expectant management is optional when the patient has undergone eLND and ≤ 2 nodes show microscopic involvement and a PSA < 0.1 ng/mL and absence of extranodal extension.	B
Metastatic PCa	Watchful waiting	In M1 asymptomatic patients, deferred castration should be discussed with a well-informed patient.	B
	Active surveillance	Unsuitable.	A
	Radical prostatectomy	Unsuitable outside clinical trial.	A
	Radiotherapy to the prostate	Unsuitable outside clinical trial.	A
	Androgen suppression	Surgical- or medical castration (LHRH agonist or antagonist).	A
		No recommendation can be made to define the best population for combining castration with upfront Docetaxel.	A
		Castration combined with local treatment / other new hormonal treatments (abiraterone acetate or Enzalutamide) should not be used outside clinical trials.	A
		In M1 asymptomatic patients, immediate castration should be offered to defer progression to a symptomatic stage and prevent serious disease progression-related complications.	A
		In M1 symptomatic patients, immediate castration should be offered to palliate symptoms and reduce the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, extraskeletal metastasis).	A
		In M1 patients, short-term administration of anti-androgens is recommended to reduce the risk of the 'flare-up' phenomenon in patients with advanced metastatic disease who are to receive an LHRH agonist.	A
		In M1 patients short-term administration of anti-androgens should be given for some weeks only (starting treatment on the same day as an LHRH analogue is started or for up to 7 days before the first LHRH analogue injection).	A
		In M1 patients, administration of anti-androgens as monotherapy should not be considered.	A
		In asymptomatic M1 patients, intermittent treatment can be offered to highly motivated men, with a major PSA response after the induction period.	B

	Based on the schedules in use in clinical trials, treatment is stopped when the PSA is < 4 ng/mL after 6 to 7 months of treatment. Treatment is resumed when the PSA is > 10-20 ng/mL.	C
	Combined treatment with LHRH agonists and NSAA is recommended.	A
	Antagonists might be an option.	B
Castrate resistant status	Patients should not be started on second-line therapy unless their testosterone serum levels are < 50 ng/dL.	A
	There is no evidence for treatment of non-metastatic CRPC outside a clinical trial.	A
	Patients with mCRPC should be counseled, managed and treated by a multidisciplinary team.	A
	Men treated with maximal androgen blockade should stop the anti-androgen therapy once PSA progression is documented. <i>Comment: Four to six weeks after discontinuation of flutamide or bicalutamide, an eventual anti-androgen withdrawal effect will be apparent.</i>	A
	No clear-cut recommendation can be made for the most effective drug for secondary treatment (i.e. hormone therapy or chemotherapy) as no clear predictive factors exist.	A
	Salvage hormonal treatment using abiraterone acetate is a valid option.	A
	Salvage hormonal treatment using enzalutamide is a valid option.	A
	In patients with metastatic CRPC who are candidates for salvage cytotoxic therapy, docetaxel at 75 mg/m ² every 3 weeks has shown a significant survival benefit.	A
	In patients with relapse following salvage docetaxel chemotherapy cabazitaxel, abiraterone acetate and enzalutamide are regarded as first-choice options for second-line treatment in mCRPC.	A
	In men with mCRPC with symptomatic bone metastases, who are ineligible for or progressing after docetaxel, treatment with Ra 223 (alpharadin) has shown a survival benefit.	A
	Bone protective agents may be offered to patients with skeletal metastases (denosumab being superior to zoledronic acid) to prevent osseous complications. However, the benefits must be balanced against the toxicity of these agents, and jaw necrosis in particular must be avoided.	A
	Calcium and vitamin D supplementation must be systematically considered when using either denosumab or bisphosphonates.	A
	In patients with neurological symptoms, spinal surgery or decompressive radiotherapy might be indicated as emergency interventions. High-dose corticosteroids must always be initially considered.	A

A* Upgraded following panel consensus.

ADT = androgen deprivation therapy; DRE = digital rectal examination; EBRT = external beam radiation therapy; HIFU = high-intensity focused ultrasound; LHRH = luteinising-hormone-releasing hormone; (e)LND = (extended) lymph node dissection; mCRPC = metastatic castrate-resistant prostate cancer; MRI = magnetic resonance imaging; NHT = neoadjuvant hormonal therapy; NSAA = non-steroidal anti-androgen; PSA-DT = PSA doubling time; RP = radical prostatectomy; TURP = transurethral resection of the prostate.

2. METHODS

2.1 Data identification and evidence sources

For all chapters of this 2015 Guidelines document, the literature has been assessed and updated. In this 2015 EAU Guidelines compilation, all standard information on levels of evidence (LE) and grading of recommendations (GR) has been taken out of the individual guidelines topics for the sake of brevity. This information is included in the introductory section of this print.

2.2 Review

This document was subjected to double-blind peer review prior to publication.

2.3 Future plans

For their 2016 update, the Guidelines Panel aim to present the results of a number of ongoing systematic reviews.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Prostate cancer (PCa) is the most common cancer in elderly males (> 70 years of age) in Europe. It is a major health concern, especially in developed countries with their greater proportion of elderly men in the general population. The incidence is highest in Northern and Western Europe (> 200 per 100,000), while rates in Eastern and Southern Europe have showed a continuous increase [4]. There is still a survival difference between men diagnosed in Eastern Europe and those in the rest of Europe [5]. Overall, during the last decade, the 5-year relative survival percentages for PCa steadily increased from 73.4% in 1999-2001 to 83.4% in 2005-2007 [5].

With the expected increase in the life expectancy of men and in the incidence of prostate cancer, the disease's economic burden in Europe is also expected to increase substantially. It is estimated that the total economic costs of PCa in Europe exceed € 8.43 billion [6], with a high proportion of the costs of PCa care occurring in the first year after diagnosis. In European countries with available data (UK, Germany, France, Italy, Spain, the Netherlands), this amounted to € 106.7-179.0 million for all PCa patients diagnosed in 2006.

3.2 Risk factors and chemoprevention

The factors that determine the risk of developing clinical PCa are not well known, although a few have been identified. There are three well-established risk factors for PCa:

- increasing age;
- ethnic origin;
- heredity.

If one first-line relative has PCa, the risk is at least doubled. If two or more first-line relatives are affected, the risk increases by 5-11-fold [7, 8]. A small subpopulation of men with PCa (about 9%) have true hereditary PCa. This is defined as three or more affected relatives, or at least two relatives who have developed early-onset disease, i.e. before age 55 [8]. Patients with hereditary PCa usually have an onset six to seven years earlier than spontaneous cases, but do not differ in other ways [8].

The frequency of incidentally- and autopsy-detected cancers is roughly the same in different parts of the world [273]. This finding is in sharp contrast to the incidence of clinical PCa, which differs widely between different geographical areas, being high in the USA and northern Europe and low in South-East Asia. However, if Japanese men move from Japan to Hawaii, their risk of PCa increases. If they move to California their risk increases even more, approaching that of American men [9].

These findings indicate that exogenous factors affect the risk of progression from so-called latent PCa to clinical PCa. Factors such as the foods consumed, the pattern of sexual behaviour, alcohol consumption, exposure to ultraviolet radiation, chronic inflammation [10, 11] and occupational exposure have all been discussed as being aetiologically important [11]. PCa may be an ideal candidate for exogenous preventive measures, such as dietary and pharmacological prevention, due to the following specific features:

- high prevalence
- long latency
- endocrine dependency
- availability of serum markers (PSA)
- the histological precursor lesion prostatic intraepithelial neoplasia [10].

Nevertheless, there is currently no evidence to suggest that dietary interventions would reduce the risk of PCa. The outcome of the Selenium and Vitamin E Cancer Prevention Trial (SELECT) was negative, and therefore vitamin E and selenium are not recommended for the prevention of PCa [12]. Similarly, a meta-analysis of eight randomised controlled trials comparing lycopene with placebo did not identify a significant decrease in the incidence of PCa [13].

Metabolic syndrome is weakly and non-significantly associated with the risk of PCa, but associations vary with geography. Among single components of the syndrome (body mass index, dysglycaemia or dyslipidaemia, high triglycerides, low HDL cholesterol) only hypertension and waist circumference >102 cm were associated with a significantly greater risk of PCa, increasing it by 15% ($p = 0.035$) and 56% ($p = 0.007$), respectively [14]. Currently, there are no data to suggest that medical intervention would effectively reduce progression of PCa. Several 5-alpha-reductase inhibitors (5-ARIs) have been studied to assess their effect on reducing the risk of developing PCa. Although it seems that 5-ARIs have a potential benefit in preventing or delaying the development of PCa (~25%, only of Gleason 6 cancer), this must be weighed against treatment-related side-effects as well as the potential increased risk of high-grade PCa [15-17]. None of the available 5-ARIs have been approved for this indication.

In summary, hereditary factors are important in determining the risk of developing clinical PCa, while exogenous factors may have an important impact on the risk of progression. There is, as yet, insufficient evidence to recommend lifestyle changes (such as a reduced intake of animal fat and an increased intake of fruit, cereals and vegetables) in order to decrease the risk [18].

3.2.1 **Guideline for preventative measures**

At this moment in time no definitive recommendation can be provided for preventive measures due to the lack of conclusive data.

4. CLASSIFICATION AND STAGING SYSTEMS

4.1 **Classification**

The objective of a tumour classification system is to combine patients with a similar clinical outcome. This allows for the design of clinical trials on relatively homogeneous patient populations, the comparison of clinical and pathological data obtained from different hospitals across the world and to make recommendations on their treatment. Throughout this guideline we made use of the 2009 TNM classification for staging of PCa (Table 4.1.1) [19] and the EAU risk group classification essentially based on D'Amico's classification system for PCa (Table 4.1.2) [20]. The latter classification is based on the grouping of patients with a similar risk of biochemical recurrence (BCR) after surgery or external beam radiotherapy.

Table 4.1.1: Tumour Node Metastasis (TNM) classification of PCa [19]

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically inapparent tumour not palpable or visible by imaging
T1a	Tumour incidental histological finding in 5% or less of tissue resected
T1b	Tumour incidental histological finding in more than 5% of tissue resected
T1c	Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen (PSA) level)
T2	Tumour confined within the prostate ¹
T2a	Tumour involves one half of one lobe or less
T2b	Tumour involves more than half of one lobe, but not both lobes
T2c	Tumour involves both lobes
T3	Tumour extends through the prostatic capsule ²
T3a	Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement
T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall
N - Regional lymph nodes³	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis ⁴
M - Distant metastasis⁵	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s)

¹ Tumour found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T1c.

² Invasion into the prostatic apex, or into (but not beyond) the prostate capsule, is not classified as pT3, but as pT2.

³ The regional lymph nodes are the nodes of the true pelvis, which essentially are the pelvic nodes below the bifurcation of the common iliac arteries.

⁴ Laterality does not affect the N-classification

⁵ When more than one site of metastasis is present, the most advanced category should be used.

Table 4.1.2: EAU risk groups for biochemical recurrence of localised and locally advanced prostate cancer

	Low-risk	Intermediate-risk	High-risk	
Definition	PSA < 10 ng / mL and GS < 7 and cT1-2a	PSA 10-20 ng /mL or GS 7 or cT2b	PSA > 20 ng / mL or GS > 7 or cT2c	any PSA any GS cT3-4 or cN+
	Localised			Locally advanced

5. DIAGNOSTIC EVALUATION

5.1 Screening and early detection

Population or mass screening is defined as the systematic examination of asymptomatic men (at risk) and is usually initiated by health authorities. In contrast, early detection or opportunistic screening consists of individual case findings, which are initiated by the person being screened (patient) and/or his physician. The co-primary endpoints of both types of screening are:

- reduction in mortality due to PCa;
- at least, a maintained QoL as expressed by quality-of-life-adjusted gain in life years (QUALYs).

Prostate cancer mortality trends range widely from country to country in the industrialised world [21]. Mortality due to PCa has decreased in most Western countries but the magnitude of the reduction varies between countries. The reduced mortality seen recently in the USA is considered to be partly due to a widely adopted aggressive PCa screening policy [22]. However, there is still no level 1 evidence that prostate-specific antigen (PSA) screening reduces mortality due to PCa [23].

Currently, screening for PCa is one of the most controversial topics in the urological literature [24]. Three large prospective RCTs published data on screening in 2009 [25-27]. Heated discussions and debates resulted in many conflicting positions and policy papers. Some authors argue that the use of current AUA guidelines recommendations for screening may lead to missing a substantial number of men with aggressive disease [28, 29]. The potential impact of this topic would necessitate the highest level of evidence produced through a systematic literature search of all published trials or cohorts summarised in a structured meta-analysis. Subgroup analyses of cohorts that are part of large trials, or mathematical projections, cannot provide the quality of evidence needed to appropriately address this clinical question.

The main summary of findings from literature published on PCa screening is the Cochrane review published in 2013 [23]. This review was based on an up-to-date systematic literature search until November 2012 and is an update of a 2010 paper with the same methodology. Its findings are as follows:

- Screening was associated with an increased diagnosis of PCa (RR: 1.3; 95% CI: 1.02-1.65).
- Screening was associated with more localised disease (RR: 1.79; 95% CI: 1.19-2.70) and less advanced PCa (T3-4, N1, M1) (RR: 0.80; 95% CI: 0.73-0.87).
- From the results of five RCTs, representing more than 341,000 randomised men, no PCa-specific survival benefit was observed (RR: 1.00; 95% CI: 0.86-1.17). This was the main objective of all the large trials.
- From the results of four available RCTs, no overall survival followed by (OS) benefit was observed (RR: 1.00; 95% CI: 0.96-1.03).

Moreover, screening was associated with minor and major harms such as overdiagnosis and overtreatment. Surprisingly, the diagnostic tool (i.e. the biopsy) was not associated with any mortality in the selected papers, which is in contrast with other known data [16, 17].

The impact on the patient's overall QoL is still unclear. It appears to be minimal in some subgroup analyses [30], but significant in others [31]. This has led to strong advice against population-based systematic screening in all countries, including Europe.

Since 2013, the ERSPC data have been updated with a 13 years of follow up (see Table 5.1.1) [32]. The key message is that with extended follow up, the mortality reduction remains unchanged (21%, and 29% after non-compliance adjustment). However the number needed to screen and to treat is decreasing, and is now below the number needed to screen observed in breast cancer trials [33].

Table 5.1.1 Follow-up data from the ERSPC study [32]

	Number needed to screen	Number needed to treat
9 years of follow-up	1410	48
11 years of follow-up	979	35
13 years of follow-up	781	27

Thus, an individualised risk-adapted strategy for early detection might be offered to a well-informed man with a least 10-15 years of individual life expectancy. However, this approach may still be associated with a substantial risk of overdiagnosis. It is therefore important to carefully identify those patient cohorts likely to benefit most from individual early diagnosis, taking into account the potential balances and harms involved.

Men at elevated risk of having PCa are those > 50 years, or with a family history of PCa and age > 45 years, or African-Americans [34]. In addition, men with PSA > 1 ng/mL at 40 years and > 2 ng/mL at 60 years [35, 36] are also at increased risk of PCa metastasis or death several decades later. Recently, as for breast cancer, a genetic abnormality likely to be associated with an increased risk has been shown prospectively [37]. Its everyday use requires further studies and cannot yet be recommended.

Risk calculators may be useful in helping to decide (on an individual basis) the potential risk of cancer whilst reducing the number of unnecessary biopsies. Several tools exist developed from several cohorts (from the PCPT cohort: PCPTRC 2.0: <http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp>; from the ERSPC cohort: <http://www.prostatecancer-riskcalculator.com/seven-prostate-cancer-risk-calculators>, from a local Canadian cohort: <http://sunnybrook.ca/content/?page=occ-prostatecalc>, among others). Since none has clearly shown superiority it is impossible to provide a recommendation and it remains a personal decision which one to use [38].

Early baseline testing could be used to detect men at risk and in need of further follow-up. However, the long-term benefit for survival and QoL of such an approach remains to be proven at a population level.

Informed men requesting an early diagnosis should be given a PSA test and undergo a DRE [39]. The optimal intervals for PSA testing and DRE follow-up are unknown, and it has varied between several prospective trials. A risk-adapted strategy might be considered based on the initial PSA level. This could be every 2 years for those initially at risk, or postponed up to 8 years in those not at risk.

The age at which attempts to make an early diagnosis of PCa should be stopped remains controversial, but is influenced by an individual's life expectancy. Men who have less than a 15-year life expectancy are unlikely to benefit based on the PIVOT and the ERSPC trials. Furthermore, although there is no simple tool to evaluate individual life expectancy, co-morbidity is at least as important as age. A detailed review can be found in the section on senior adults and in the recently updated SIOG guidelines [40].

Based on the tools currently available, an individualised strategy will diagnose many insignificant lesions (above 50% in some trials), most of which will not require any form of active treatment (Section 7.1, Deferred treatment). It is important to realise that breaking the link between diagnosis and active treatment is the only way to decrease overtreatment, while still maintaining the potential benefit of individual early diagnosis for men requesting it.

From a public health point of view, mass screening of PCa is not indicated. However, early diagnosis on an individual basis is possible based on DRE and PSA testing. Individual patient screening requires informed consent from the patient following a full discussion with their physician on the pros and cons of the complete procedure, taking into account the patient's risk factors, age and life expectancy. The interval for follow-up screening depends on age and baseline PSA level.

5.1.1 Guidelines for screening and early detection

	LE	GR
An individualised risk-adapted strategy for early detection might be offered to a well-informed man with a good performance status and at least 10-15 years of life expectancy.	3	B
Early PSA testing should be offered to men at elevated risk for PCa. Risk groups are: <ul style="list-style-type: none"> men over 50 years of age men over 45 years of age and a family history of PCa African-Americans men with a PSA level of > 1 ng/mL at 40 years of age men with a PSA level of > 2 ng/mL at 60 years of age 	2b	A
A risk-adapted strategy might be considered (based on initial PSA level), which may be every 2 years for those initially at risk, or postponed up to 8 years in those not at risk.	3	C
The age at which early diagnosis of PCa should be stopped is influenced by life expectancy and performance status; men who have < 15-year life expectancy are unlikely to benefit based on the PIVOT and the ERSPC trials.	3	A

5.2 Clinical diagnosis

Prostate cancer is usually suspected on the basis of digital rectal examination (DRE) and/or prostate-specific antigen (PSA) levels. Definitive diagnosis depends on histopathological verification of adenocarcinoma in prostate biopsy cores or specimens from TURP or prostatectomy for benign prostatic enlargement (BPE).

5.2.1 Digital rectal examination

Most prostate cancers are located in the peripheral zone and may be detected by DRE when the volume is ≥ 0.2 mL. In ~18% of cases, PCa is detected by suspect DRE alone, irrespective of PSA level [41]. Suspect DRE in patients with PSA level ≤ 2 ng/mL has a positive predictive value of 5-30% [42]. Abnormal DRE is associated with an increased risk of higher Gleason score and is an indication for biopsy [43, 44].

5.2.2 Prostate-specific antigen

The use of PSA as a serum marker has revolutionised PCa diagnosis [45]. PSA is organ- but not cancer-specific, therefore, it may be elevated in benign prostatic hypertrophy (BPH), prostatitis and other non-malignant conditions. As an independent variable, PSA is a better predictor of cancer than DRE or transrectal ultrasound (TRUS) [46].

There are no agreed standards defined for measuring PSA [47]. PSA is a continuous parameter, with higher levels indicating greater likelihood of PCa. Many men may harbour PCa despite having low serum PSA [48]. Table 5.2.1 demonstrates the occurrence of Gleason ≥ 7 PCa at low PSA levels, precluding an optimal PSA threshold for detecting non-palpable but clinically significant PCa. The use of nomograms may help in predicting indolent PCa [49].

Table 5.2.1: Risk of PCa in relation to low PSA values

PSA level (ng/mL)	Risk of PCa (%)	Risk of Gleason ≥ 7 PCa (%)
0.0-0.5	6.6	0.8
0.6-1.0	10.1	1.0
1.1-2.0	17.0	2.0
2.1-3.0	23.9	4.6
3.1-4.0	26.9	6.7

5.2.2.1 PSA density

PSA density is the level of serum PSA divided by the TRUS-determined prostate volume. The higher the PSA density, the more likely that PCa is clinically significant (see Section 6.1.3).

5.2.2.2 PSA velocity and doubling time

There are two methods of measuring PSA kinetics:

- PSA velocity (PSAV): absolute annual increase in serum PSA (ng/mL/year) [50];
- PSA doubling time (PSA-DT): which measures the exponential increase in serum PSA over time [51].

PSAV and PSA-DT may have a prognostic role in treated PCa [52], but limited diagnostic use because of background noise (total prostate volume, and BPH), different intervals between PSA determinations, and acceleration/deceleration of PSAV and PSA-DT over time. These measurements do not provide additional information compared with PSA alone [53-56].

5.2.2.3 Free/total PSA ratio

Free/total (f/t) PSA ratio is widely used to differentiate BPH from PCa. It stratifies the risk of PCa in men with 4-10 ng/mL total PSA and negative DRE. PCa was detected by biopsy in 56% of men with f/t PSA < 0.10 , but in only 8% with f/t PSA > 0.25 [57]. f/t PSA is of no clinical use if total serum PSA is > 10 ng/mL or during follow-up of known PCa.

f/t PSA must be used cautiously because it may be adversely affected by several preanalytical and clinical factors (e.g., instability of free PSA at 4°C and room temperature, variable assay characteristics, and concomitant BPH in large prostates) [58].

5.2.2.4 Prostate Health Index (PHI) test

The Prostate Health Index (PHI) test is a recently approved diagnostic blood test, combining free and total PSA and the (-2) pro PSA isoform (p2PSA), intended to reduce the number of unnecessary prostate biopsies in PSA tested men. A few prospective multicentre studies demonstrated that the PHI test not only outperforms free and total PSA PCa detection, but has an improved prediction of clinically significant PCa, both in men with a PSA between 4-10 ng/mL and between 2-10 ng/mL. The PHI test may therefore also have a role in monitoring men under active surveillance [59]. Its clinical impact is, as yet undetermined, given the slight net benefit for clinical decision-making [60].

5.2.2.5 *PCA3 marker*

PCA3 is a prostate-specific, non-coding mRNA biomarker that is detectable in urine sediments obtained after three strokes of prostatic massage during DRE. The ProgenSA urine test for PCA3 is now commercially available. PCA3 is superior to total and percent-free PSA for detection of PCa in men with elevated PSA as it shows significant increases in the area under the receiver-operator characteristic curve for positive biopsies [61-64].

PCA3 score increases with PCa volume, but there are conflicting data about whether it independently predicts Gleason score, and its use for monitoring in active surveillance is unconfirmed [65]. Currently, the main indication for the ProgenSA test is to determine whether repeat biopsy is needed after an initially negative biopsy.

5.2.3 **Prostate biopsy**

5.2.3.1 *Baseline biopsy*

The need for prostate biopsy is based on PSA level and/or suspicious DRE. Age, potential comorbidity, and therapeutic consequences should also be considered and discussed beforehand [66]. Risk stratification is a potential tool for reducing unnecessary biopsies [66].

Limited PSA elevation alone, should not prompt immediate biopsy. PSA level should be verified after a few weeks using the same assay under standardised conditions (i.e., no ejaculation, manipulations, and urinary tract infections) in the same laboratory [67, 68]. Empiric use of antibiotics in an asymptomatic patient in order to lower the PSA should not be undertaken [69].

Ultrasound-guided biopsy is now the standard of care. A transrectal approach is used for most prostate biopsies, although some urologists prefer a perineal approach. Cancer detection rates are comparable with both approaches [70, 71].

5.2.3.2 *Repeat biopsy after previously negative biopsy*

The indications for repeat biopsy are:

- rising and/or persistently elevated PSA (see Table 5.2 for risk estimates);
- suspicious DRE, 5-30% cancer risk [41, 42];
- atypical small acinar proliferation (i.e., atypical glands suspicious for cancer), 40% risk [72];
- extensive (multiple biopsy sites, i.e., ≥ 3) high grade prostatic intraepithelial neoplasia (HGPIN), ~30% risk [72, 73];
- A few atypical glands immediately adjacent to high grade prostatic intraepithelial neoplasia (i.e., PINATYP), ~50% risk [74].

Isolated high-grade PIN in one or two biopsy sites is no longer an indication for repeat biopsy [75].

5.2.3.3 *Saturation biopsy*

The incidence of PCa detected by saturation repeat biopsy (> 20 cores) is 30-43% and depends on the number of cores sampled during earlier biopsies [76]. Saturation biopsy may be performed with the transperineal technique, which detects an additional 38% of PCa. The high rate of urinary retention (10%) is a drawback [77].

5.2.3.4 *Sampling sites and number of cores*

On baseline biopsies, the sample sites should be bilateral from apex to base as far posterior and lateral as possible in the peripheral gland. Additional cores should be obtained from suspect areas by DRE/TRUS.

Sextant biopsy is no longer considered adequate. For prostate volume 30-40 mL, ≥ 8 cores should be sampled. Ten to 12 core biopsies are recommended [78], with > 12 cores not being significantly more conclusive [79, 80].

5.2.3.5 *Diagnostic transurethral resection of the prostate*

Transurethral resection of the prostate (TURP) should not be used as a tool for cancer detection [81].

5.2.3.6 *Seminal vesicle biopsy*

Indications for seminal vesicle (staging) biopsies are poorly defined. At PSA > 15 ng/mL, the odds of tumour involvement are 20-25% [82]. Seminal vesicle staging biopsy is only useful if it has a decisive impact on treatment, such as ruling out radical tumour resection or radiotherapy. Its added value compared with multiparametric MRI (mpMRI) is questionable.

5.2.3.7 Transition zone biopsy

Transition zone sampling during baseline biopsies has a low detection rate and should be confined to repeat biopsies [83].

5.2.3.8 Antibiotics prior to biopsy

Oral or intravenous antibiotics are state-of-the-art. Quinolones are the drugs of choice, with ciprofloxacin being superior to ofloxacin [84]. Increased quinolone resistance [85] is associated with a rise in severe post-biopsy infection [86].

5.2.3.9 Local anaesthesia prior to biopsy

Ultrasound-guided periprostatic block is state-of-the-art [87]. It is not important whether the depot is apical or basal. Intrarectal instillation of local anaesthesia is inferior to periprostatic infiltration [88].

5.2.3.10 Fine-needle aspiration biopsy

Fine-needle aspiration biopsy is no longer state-of-the-art.

5.2.3.11 Complications

Biopsy complications are listed in Table 5.2.2 [89]. Severe postprocedural infections were initially reported in < 1% of cases, but have increased as a consequence of antibiotic resistance [90].

Low-dose aspirin is no longer an absolute contraindication [91].

Table 5.2.2: Percentage of complications per biopsy session, irrespective of the number of cores

Complications	Percentage of patients affected
Haemospermia	37.4
Haematuria > 1 day	14.5
Rectal bleeding < 2 days	2.2
Prostatitis	1.0
Fever > 38.5°C	0.8
Epididymitis	0.7
Rectal bleeding > 2 days +/- surgical intervention	0.7
Urinary retention	0.2
Other complications requiring hospitalisation	0.3

5.2.4 Role of imaging

5.2.4.1 TRUS

Classic hypoechogenicity in the peripheral prostate is not always seen. Grey-scale TRUS is not reliable at detecting PCa [92]. Thus, there is no evidence that targeted biopsies can replace systematic biopsies. New sonographic modalities such as sonoelastography, contrast-enhanced ultrasound or computerised ultrasound (Histoscanning™) are being investigated. There is not currently enough evidence for their routine use.

5.2.4.2 Multiparametric MRI (mpMRI)

Correlation with radical prostatectomy (RP) shows that mpMRI, associating T2-weighted imaging with diffusion-weighted imaging, dynamic contrast-enhanced imaging, or H1-spectroscopy, has excellent sensitivity for Gleason score ≥ 7 cancers (Table 5.2.3) [93-96].

Table 5.2.3: PCa detection rates (%) by mpMRI by tumour volume and Gleason score [96]

Gleason score	Tumour volume (mL)		
	< 0.5	0.5-2	> 2
GS6	21-29%	43-54%	67-75%
GS7	63%	82-88%	97%
GS > 7	80%	93%	100%

mpMRI may detect anterior tumours missed by systematic biopsy [97, 98]. In 265 patients undergoing repeat biopsy, mpMR-guided samples were positive in 41%, and 87% of the cancers were clinically significant [99].

Biopsies targeted on MR abnormalities also seem to evaluate PCa aggressiveness better than systematic biopsy [100]. Although some authors proposed mpMRI as a triage test for biopsy candidates, to increase

detection of aggressive cancers and reduce over-detection of non-significant foci [101-103], only a few controlled trials have currently been published [104-106]. A recent systematic review concluded that, whereas there was currently not enough evidence to recommend mpMRI before a first set of prostate biopsies, the use of targeted biopsy often achieved significantly higher cancer detection rate in the repeat biopsy setting [107].

Inter-reader variability remains a concern with mpMRI. The Prostate Imaging Reporting and Data System (PIRADS) scoring system has been recently proposed to standardise mpMRI interpretation [108], but two independent evaluations suggested that it did not improve inter-reader variability as compared to subjective scoring [109, 110].

5.2.4.3 Guidelines for imaging

	LE	GR
When clinical suspicion of PCa persists in spite of negative biopsies, MRI-targeted biopsies are recommended.	2b	B

GR = grade of recommendation; LE = level of evidence; MRI = magnetic resonance imaging.

5.2.5 Pathology of prostate needle biopsies

5.2.5.1 Processing

Prostate core biopsies from different sites are processed separately. Before processing, the number and length of the cores are recorded. The length of biopsy tissue significantly correlates with PCa detection rate [111]. To achieve optimal flattening and alignment, a maximum of three cores should be embedded per tissue cassette, and sponges or paper used to keep the cores stretched and flat [3, 112]. To optimise detection of small lesions, paraffin blocks should be cut at three levels [83] and intervening unstained sections are kept for immunohistochemistry.

5.2.5.2 Microscopy and reporting

Diagnosis of PCa is based on histology. The diagnostic criteria include features pathognomonic of cancer, major and minor features favouring cancer and features against cancer. Ancillary staining and additional (deeper) sections should be considered if a suspect lesion is identified [113-115]. Diagnostic uncertainty is resolved by intradepartmental or external consultation [113]. Table 5.2.4 lists the recommended terminology for reporting prostate biopsies [3].

Table 5.2.4: Recommended terminology for reporting prostate biopsies [3]

•	Benign/negative for malignancy. If appropriate, include a description
•	Active inflammation
•	Granulomatous inflammation
•	High-grade PIN
•	High-grade PIN with atypical glands, suspicious for adenocarcinoma (PINATYP)
•	Focus of atypical glands/lesion suspicious for adenocarcinoma/atypical small acinar proliferation, suspicious for cancer
•	Adenocarcinoma

Each biopsy site should be reported individually, including its location (in accordance with site of sampling) and histopathologic findings, which include the histological type and the International Society of Urological Pathology (ISUP) 2005 Gleason score (i.e., 2005 ISUP Modified Gleason System) [116]. As compared to the traditional Gleason grading, the ISUP 2005 Gleason score improved the concordance of the grading of the corresponding prostatectomy specimens [117].

The (2005 ISUP modified) Gleason score of biopsy-detected PCa comprises the Gleason grade or pattern of the most extensive (primary pattern) pattern, plus the second most common pattern (secondary pattern), if two are present. If one pattern is present, double it to yield the Gleason score. For three grades, the Gleason score comprises the most common grade plus the highest grade, irrespective of its extent. When the carcinoma is largely grade 4/5, identification of < 5% of Gleason grade 2 or 3 glands should not be incorporated in the Gleason score. A Gleason score ≤ 4 should not be given on prostate biopsies [116]. Intraductal carcinoma, lymphovascular invasion and extraprostatic extension must be reported. In addition to reporting the carcinoma features for each biopsy, an overall Gleason score based on the carcinoma-positive biopsies can be provided.

The proportion of carcinoma-positive cores as well as the extent of tumour involvement per biopsy core

correlates with the Gleason score, tumour volume, surgical margins and pathologic stage in radical prostatectomy (RP) specimens and predicts BCR, post-prostatectomy progression and radiation therapy failure. These parameters are included in nomograms created to predict pathologic stage and seminal vesicle invasion after RP and RT failure [118-120]. A pathology report should therefore provide both the proportion of carcinoma-positive cores and the extent of cancer involvement for each core. The length in mm and percentage of carcinoma in the biopsy have equal prognostic impact [121]. An extent of > 50% of adenocarcinoma in a single core is used in some active surveillance protocols as a cut off [122] triggering immediate treatment vs. active surveillance in patients with Gleason score 6.

A prostate biopsy that does not contain glandular tissue should be reported as diagnostically inadequate.

5.2.6 **Histopathology of radical prostatectomy specimens**

5.2.6.1 *Processing of radical prostatectomy specimens*

Histopathological examination of RP specimens describes the pathological stage, histopathological type, grade and surgical margins of PCa. It is recommended that RP specimens are totally embedded, to enable assessment of cancer location, multifocality and heterogeneity. For cost-effectiveness, partial embedding may also be considered, particularly for prostates > 60 g. The most accepted method includes complete embedding of the posterior prostate, and a single mid-anterior left and right section. Compared with total embedding, partial embedding detected 98% of PCa with a Gleason score ≥ 7 and accurate staging in 96% of cases [123].

Entire RP specimens are inked upon receipt in the laboratory, to demonstrate the surgical margins. Specimens are fixed by immersion in buffered formalin for at least 24 hours, preferably before slicing. Fixation can be enhanced by injecting formalin, which provides more homogeneous fixation and sectioning after 24 h [124]. After fixation, the apex and the base (bladder neck) are removed and cut into (para)sagittal or radial sections; the shave method is not recommended [116]. The remainder of the specimen is cut in transverse, 3-4-mm sections, perpendicular to the long axis of the urethra. The resultant tissue slices can be embedded and processed as whole-mounts or after quadrant sectioning. Whole-mounts provide better topographic visualisation, faster histopathological examination and better correlation with preoperative imaging, although they are more time-consuming and require specialist handling. For routine sectioning, the advantages of whole mounts do not outweigh their disadvantages.

5.2.6.1.1 Guidelines for processing prostatectomy specimens

	LE	GR
Total embedding is preferred, by conventional (quadrant) or whole-mount sectioning.	3	C
The entire surface should be inked before cutting, to evaluate the surgical margin.	3	A
The apex and base should be examined separately using the cone method with sagittal or radial sectioning.	3	A

GR = grade of recommendation; LE = level of evidence.

5.2.6.2 *RP specimen report*

The pathology report provides essential information on the prognostic characteristics relevant for clinical decision-making (Table 5.2.5). As a result of the complex information provided on each RP specimen, the use of synoptic(-like) or checklist reporting is recommended (Table 5.2.6). Synoptic reporting results in more transparent and complete pathology reporting [125].

Table 5.2.5: Information provided by the pathology report

Histopathological type: > 95% of PCa represents conventional (acinar) adenocarcinoma.
Grading according to Gleason score (or therapy-related changes).
Tumour (sub)staging and surgical margin status: location and extent of extraprostatic extension, presence of bladder neck invasion, laterality of extraprostatic extension or seminal vesicle invasion, location and extent of positive surgical margins.
Additional information may be provided on multifocality, and diameter/volume and zonal location of the dominant tumour.

Table 5.2.6: Example checklist: reporting of prostatectomy specimens

Histopathological type
<ul style="list-style-type: none"> Type of carcinoma, e.g. conventional acinar, or ductal
Histological grade
<ul style="list-style-type: none"> Primary (predominant) grade Secondary grade Tertiary grade (if applicable) Global Gleason score Approximate percentage of Gleason grade 4 or 5 (optional)
Tumour quantitation (optional)
<ul style="list-style-type: none"> Percentage of prostate involved Size/volume of dominant tumour nodule
Pathological staging (pTNM)
<i>If extraprostatic extension is present:</i> <ul style="list-style-type: none"> o indicate whether it is focal or extensive o specify sites o Indicate whether there is seminal vesicle invasion <i>If applicable, regional lymph nodes:</i> <ul style="list-style-type: none"> o location o number of nodes retrieved o number of nodes involved
Surgical margins
<i>If carcinoma is present at the margin:</i> <ul style="list-style-type: none"> o specify sites
Other
<ul style="list-style-type: none"> Presence of lymphovascular / angio-invasion Location of dominant tumour Presence of intraductal carcinoma

5.2.6.2.1 Gleason score

Grading of conventional prostatic adenocarcinoma using the (modified) Gleason system [116] is the strongest prognostic factor for clinical behaviour and treatment response. The Gleason score is incorporated in nomograms that predict disease-specific survival after prostatectomy [126].

5.2.6.2.2 Interpreting Gleason score

The Gleason score is the sum of the most and second-most dominant (in terms of volume) Gleason grade. If only one grade is present, the primary grade is doubled. If a grade comprises $\leq 5\%$ of the cancer volume it is not incorporated in the Gleason score (5% rule). The primary and secondary grades are reported in addition to the Gleason score. A global Gleason score is given for multiple tumours, but a separate tumour focus with a higher Gleason score should also be mentioned. Tertiary Gleason grade 4 or 5, particularly if $> 5\%$ of the PCa volume, is an unfavourable prognostic indicator for BCR. The tertiary grade and its approximate proportion of the cancer volume should also be reported [127] in addition to the Gleason score.

5.2.6.2.3 Definition of extraprostatic extension

Extraprostatic extension is defined as carcinoma mixed with periprostatic adipose tissue, or tissue that extends beyond the prostate gland boundaries (e.g., neurovascular bundle, anterior prostate). Microscopic bladder neck invasion is considered extraprostatic extension. It is useful to report the location and extent of extraprostatic extension because the latter is related to recurrence risk [128].

There are no internationally accepted definitions of focal or microscopic, vs. non-focal or extensive extraprostatic extension. Some describe focal as a few glands [129] or extension as < 1 high-power field (HPF) [130], whereas others measure the depth of extent in millimetres [131].

At the apex of the prostate, tumour mixed with skeletal muscle does not constitute extraprostatic extension. In the bladder neck, microscopic invasion of smooth muscle fibres is not equated to bladder wall invasion, i.e., not as pT4, because it does not carry independent prognostic significance for PSA recurrence [132, 133] and should be recorded as extraprostatic extension (pT3a). A positive margin at the bladder neck should be reported as extraprostatic extension (pT3a) with positive margin, and not as pT4.

Stage pT4 is only assigned when the tumour invades the bladder muscle wall as determined macroscopically [134].

5.2.6.3 Prostate cancer volume

The independent prognostic value of PCa volume in RP specimens has not been established [130, 135-138]. Nevertheless, a cut-off of 0.5 mL is commonly used to distinguish insignificant from clinically relevant cancer [135]. Improvement in prostatic radioimaging allows more accurate preoperative measurement of cancer volume. It is recommended that at least the diameter/volume of the dominant tumour nodule should be assessed, or a rough estimate of the percentage of cancer tissue provided [139].

5.2.6.4 Surgical margin status

Surgical margin is an independent risk factor for BCR. Margin status is positive if tumour cells are in contact with the ink on the specimen surface. Margin status is negative if tumour cells are close to the inked surface [136] or at the surface of the tissue lacking ink.

In tissues that have severe crush artefacts, it may not be possible to determine margin status [140]. Surgical margin is separate from pathological stage, and a positive margin is not evidence of extraprostatic extension [141]. There is insufficient evidence to prove a relationship between margin extent and recurrence risk [130]. However, some indication must be given of the multifocality extent of margin positivity, such as the linear extent in mm of involvement: focal, ≤ 1 mm vs. extensive, > 1 mm [142], or number of blocks with positive margin involvement.

5.2.6.5 Other factors

According to the College of American Pathologists' consensus statement [143], additional potential biomarkers have not been sufficiently studied to demonstrate their additional prognostic value and clinical usefulness outside the standard patient care setting, including perineural invasion, neuroendocrine differentiation, microvessel density, nuclear roundness, chromatin texture, other karyometric factors, proliferation markers, and PSA derivatives.

5.2.7 Guidelines for the clinical diagnosis of prostate cancer

	LE	GR
Transurethral resection of the prostate should not be used as a tool for cancer detection.	2a	A
PCa should be graded according to the ISUP 2005 modified Gleason grading system.	2a	A
Biopsy decision should be based on PSA testing and DRE.	2b	A
Transition zone biopsies are not recommended initially due to low detection rates.	2b	B
For initial diagnosis, a core biopsy of 10-12 systematic transrectal or transperineal peripheral zone biopsies should be performed under ultrasound guidance.	2a	B
Transrectal prostate needle biopsies should be taken under antibiotic protection.	1b	A
Local anaesthetic by periprostatic infiltration is recommended for prostate needle biopsies.	1a	A
Prostate core biopsies from different sites should be submitted separately for processing and pathology reporting.	3	A
Processing and reporting of prostatectomy specimens should follow the guidelines of the 2010 ISUP consensus meeting.	3	A
One set of repeat biopsies is warranted for persistent indications for PCa (abnormal DRE, elevated PSA or histopathological findings suggestive of malignancy at initial biopsy).	2a	B

DRE = digital rectal examination; GR = grade of recommendation; ISUP = International Society of Urological Pathology; LE = level of evidence; PSA = prostate-specific antigen.

5.3 Diagnosis: Clinical staging

The extent of PCa is evaluated by DRE and PSA, and may be supplemented with bone scanning and computed tomography (CT) or mpMRI.

5.3.1 T-staging

5.3.1.1 Definitions

Extraprostatic extension is defined as carcinoma mixed with periprostatic adipose tissue, or tissue that extends beyond the prostate gland (e.g., neurovascular bundle, anterior prostate, or bladder neck) and corresponds to stage T3a. It is to be distinguished from seminal vesicles (SVI) invasion that corresponds to stage T3b (see Section 5.2 for details).

5.3.1.2 DRE, PSA level and biopsy findings

The first level of assessment is local tumour stage because the distinction between organ-confined (T1/T2) and extraprostatic (T3/T4) disease affects treatment decisions. DRE is positively correlated with tumour stage

in < 50% of cases [144], although it often underestimates tumour extension. More extensive T-staging is only recommended if it directly affects treatment decisions

Serum PSA levels increase with tumour stage, although they are limited for accurate prediction of final pathological stage. PSA is produced by benign and malignant tissue, thus, there is no direct relationship between serum PSA and clinicopathological tumour stage [145]. In prostate needle biopsy, the percentage of cancerous tissue is a strong predictor of positive surgical margins, SVI, and non-organ-confined disease [146]. An increase in tumour-positive biopsies is an independent predictor of extraprostatic extension, margin involvement, and lymph node invasion [147]. Serum PSA, Gleason score, and T stage are more useful together than alone in predicting final pathological stage [126, 148]. These models may help to select candidates for nerve-sparing surgery and lymphadenectomy (Section 7.2).

SVI is predictive of local relapse and distant metastatic failure. SV biopsies can improve preoperative staging accuracy [149]. This is not recommended for first-line examination, but is reserved for patients with high risk of SVI, in whom a positive biopsy would modify treatment. Patients with T stage > 2a and serum PSA > 10 ng/mL are candidates for SV biopsy [150, 151]. Patients with positive biopsies from the base of the prostate are more likely to have positive SV biopsies [152].

Transperineal 3D prostate mapping biopsy (PMB) is an alternative to transrectal biopsies because it provides more accurate tumour localization, extent and Gleason grading [153], and has acceptable morbidity.

5.3.1.3 *Transrectal ultrasound (TRUS)*

Only 60% of tumours are visible with TRUS, and 40% are undetectable due to isoechogenicity. TRUS is no more accurate at predicting organ-confined disease than DRE [154, 155]. Combined DRE and TRUS can detect T3a PCa more accurately than either method alone [156].

3D-TRUS is claimed to have better staging accuracy than 2D techniques [157]. Greater sensitivity for cancer detection is achieved by the addition of power colour Doppler and contrast agents [158-160]. All TRUS techniques are largely operator-dependent and cannot differentiate between T2 and T3 tumours with sufficient accuracy to be recommended for routine staging.

5.3.1.4 *Multiparametric magnetic resonance imaging (MRI)*

T2-weighted imaging (WI) remains the most useful method for local staging on MRI. At 1.5T (Tesla), MRI has low sensitivity for detecting extraprostatic extension of carcinoma (22-82%) or SVI (0-71%), but higher specificity (61-100% and 62-100%, respectively) [161-176]. Global MRI accuracy for distinguishing T1/T2 stages from T3 stage is 50-85% [163-165, 171, 172, 177-180]. These disappointing results are because MRI cannot detect microscopic extra-prostatic extension. Its sensitivity increases with the radius of extension within periprostatic fat. In one study, the EEC detection rate increased from 14 to 100% when the radius of extension increased from < 1 mm to > 3 mm [163]. In another study, MRI sensitivity, specificity and accuracy for detecting pT3 stage were, 40, 95 and 76%, respectively, for focal (i.e. microscopic) extra-prostatic extension, and 62, 95 and 88% for extensive extra-prostatic extension [171].

An endorectal coil improves staging accuracy at 1.5T, and accuracy of 77-83% has been shown for combined endorectal and external coils vs. 59-68% for external coil alone [174, 181]. Dynamic contrast-enhanced imaging combined with T2-WI may also improve local staging [172, 175]. The high field strength allows high-resolution T2-WI [182] and results at 3T seem better than at 1.5T [173, 183], even if the experience of the reader remains of paramount importance, MRI accuracy at 3T varies between 67% and 93% depending on the experience of the reader [173]. Even if MRI is not perfect for local staging, it may improve prediction of the pathological stage when combined with clinical data [184, 185].

Given its low sensitivity for focal (microscopic) extra-prostatic extension, mpMRI is not recommended for local staging in low-risk patients [184, 186, 187]. However, mpMRI can still be useful for treatment planning in selected low-risk patients (e.g. candidates for brachytherapy) [188].

5.3.2 *N-staging*

5.3.2.1 *PSA level and biopsy findings*

N-staging should be performed only when it might directly influence treatment decisions. High PSA values, T2b-T3 stage, poor tumour differentiation and perineural invasion are associated with high risk of nodal metastases [126, 189, 190]. Measurement of PSA alone is unhelpful in predicting lymph node metastases.

Nomograms or Partin tables can define patients at low risk (< 10%) of nodal metastasis, although nomograms may be more accurate in establishing the extent of nodal involvement [148, 191]. The simple Roach formula can also be used [192]. Patients with low- and intermediate-risk PCa may be spared N-staging before potentially curative treatment [126].

Gleason 4 pattern in sextant biopsies can define the risk of N1 disease. Risk of nodal metastases

was 20-45% if any core had a predominant Gleason 4 pattern, or > 3 cores had any Gleason 4 pattern. For the remaining patients, the risk was 2.5%, suggesting that nodal staging is unnecessary in selected patients [193].

5.3.2.2 *Nodal staging using computed tomography (CT) and magnetic resonance imaging (MRI)*

Abdominal CT and MRI indirectly assess nodal invasion by measuring lymph node diameter. Their sensitivity is low and microscopic invasion cannot be detected. Using a 10-mm threshold, CT or MR sensitivity is < 40% [194-206]. Among 4,264 patients, 654 (15.3%) had positive lymph nodes at lymphadenectomy but only 105 (2.5%) had positive CT. Median estimated CT sensitivity, specificity, NPV and PPV were 7%, 100%, 85% and 100%, respectively [205].

Fine-needle aspiration biopsy (FNAB) may be decisive in cases with positive imaging. The lymph nodes can be difficult to reach because of their position. FNAB is not highly sensitive for staging and has a false-negative rate of 40% [207].

For CT or MRI, detection of microscopic lymph node invasion is < 1% in patients with a Gleason score < 8, PSA < 20 ng/mL, or localised disease [202, 208, 209]. CT and MRI should not be used for nodal staging in low-risk patients and reserved for high-risk cancer.

5.3.2.3 *Lymphadenectomy*

The gold standard for N-staging is open or laparoscopic lymphadenectomy. Pelvic lymph node dissection (LND) limited to the obturator fossa will miss ~50% of metastases [210, 211]. When deciding on pelvic LND, extended lymphadenectomy should be considered (Section 7.2.6).

Primary removal of sentinel lymph nodes aims to improve accuracy of detecting tumour bearing nodes while reducing morbidity associated with extended pelvic LND [212, 213]. Image guidance allows intraoperative sentinel node (SN) detection visually [214]. Difficulty in accessing the SN and the lack of large multicenter cohorts are major limitations of this technique. Therefore, for the time being, this remains experimental [215].

5.3.3 *M-staging*

5.3.3.1 *Alkaline phosphatase*

The axial skeleton is involved in 85% of PCa fatalities [216]. The presence and extent of bone metastases accurately reflect prognosis of PCa. Elevated skeletal alkaline phosphatase (ALP) indicates bone metastasis in 70% of cases [217]. Simultaneous measurement of skeletal ALP and PSA increases clinical effectiveness to ~98% [218]. The extent of bone disease is the only variable influencing serum levels of skeletal ALP and PSA, and the former is significantly correlated with extent of bone disease [219].

5.3.3.2 *Bone scan*

Bone scan (BS) has been the most widely used method for evaluating bone metastases of PCa. However, it suffers from relatively low specificity [220]. Thus, in patients with equivocal findings or a small number of hot spots, the metastatic nature of the lesions needs to be checked by other imaging modalities.

The NPV for bone scanning is 87-100% [207, 221-229]. Its diagnostic yield is significantly influenced by the PSA level, the clinical stage and the tumour Gleason score [221-234] and these three factors were the only independent predictors of BS positivity in a study of 853 patients [235]. BS positivity rate is extremely low (< 1%) in low-risk patients [234, 236-238]. In contrast, it is 6.6-38.5% in patients with PSA level of 20-50 ng/mL [221, 224-227, 229, 230, 236-238], 19-90.7% in patients with stage \geq T3 [221, 225, 227, 228, 230, 236] and 16.9-29.6% in patients with Gleason \geq 8 tumours [232, 233, 236, 238]. The proportion of positive BS in patients with PSA level of 10-20 ng/mL (1-33.3%) or Gleason 7 (2.8-22%) is quite variable from one study to another [207, 221, 222, 224-228, 230, 237-239]. In two studies, a major Gleason pattern of 4 was found to be a significant predictor of positive BS [237, 239].

Bone scanning should be performed in symptomatic patients, independent of PSA level, Gleason score or clinical stage [205].

5.3.4 *New imaging modalities*

5.3.4.1 *Nodal metastases*

^{11}C - or ^{18}F -choline positron emission tomography (PET)/CT have good specificity for lymph node metastases, but sensitivity of 10-73% [240, 241].

In a meta-analysis of 609 patients pooled sensitivity and specificity of choline PET/CT for pelvic lymph node metastases were 62% (95% CI, 51-66%) and 92% (95% CI, 89-94%), respectively [242]. In a prospective trial of 75 patients at intermediate risk of nodal involvement (10-35%), the sensitivity was only 8.2% in a region based and 18.9% at a patient-based analysis, too low to be of clinical interest [243]. PET-choline has no place for up-front staging in nodal metastasis. Currently, psmaPET-CT (prostate-specific membrane antigen-PET CT) remains experimental.

MR sensitivity is low for lymph node metastases and similar to that of ¹¹C-choline PET/CT [244, 245]. Ultra-small particles of iron oxide (USPIOs) improve detection of microscopic lymph node metastases on MRI. This approach is cost-effective [246], but is limited by a lack of availability.

5.3.4.2 Bone metastasis

¹⁸F-fluoride PET or PET/CT shows superior sensitivity to bone scanning [240, 247-250]. It remains unclear whether ¹¹C-choline PET/CT is more sensitive than conventional bone scanning, but it has higher specificity, with fewer indeterminate lesions [240, 242, 251].

Diffusion-weighted whole-body and axial MRI are more sensitive than bone scanning and targeted radiography [252-254] in detecting bone metastases in high-risk PCa. Whole-body MRI is also more sensitive and specific than combined bone scan, targeted radiography and abdominopelvic CT [255]. A recent meta-analysis found MRI to be better than choline PET/CT and bone scan for detecting bone metastases on a per-patient basis, although PET/CT had the highest specificity [256].

However, as with PET/CT, the cost-effectiveness of these new MR-based approaches remains to be assessed [257]. Bone scan is therefore preferred on the basis of availability and cost.

5.3.5 Guidelines for staging of prostate cancer

Any risk group staging	LE	GR
Additional imaging is required only if it changes patient management.	2a	A*
For local staging, CT and TRUS should not be used.	3	A
For up-front staging, PET-scanning should not be used.	2a	A

*Upgraded following panel consensus.

Low-risk localised PCa	LE	GR
No additional imaging is recommended for staging purposes.	2a	A

Intermediate-risk PCa	LE	GR
In predominantly Gleason pattern 4, bone scan and cross-sectional imaging is required.	2a	A*

High-risk localised PCa/ High-risk locally advanced PCa	LE	GR
Prostate mpMRI should be used for local staging.	2b	A
CT/MRI and bone-scan should be used in staging.	2b	A
For up-front staging, PET-scanning should not be used.	2a	A

CT = computed tomography; GR = grade of recommendation; LE = level of evidence; mpMRI = multiparametric magnetic resonance imaging; PET = positron emission tomography.

6. DISEASE MANAGEMENT

6.1 Treatment: Deferred treatment (active surveillance/watchful waiting)

6.1.1 Introduction

Many men with localised PCa will not benefit from definitive treatment [258], and ~45% of men with PSA-detected PCa are candidates for deferred management [259]. In men with comorbidity and limited life expectancy, treatment of localised PCa may be deferred to avoid loss of quality of life (QoL). There are two distinct strategies for conservative management that aim to reduce overtreatment: active surveillance and watchful waiting (Table 7.1.1).

6.1.1.1 Definition

6.1.1.1.1 Active surveillance

Active surveillance aims to achieve correct timing for curative treatment, rather than delayed application of palliative treatment [260]. Patients remain under close surveillance, and treatment is prompted by predefined thresholds indicative of potentially life-threatening disease, while considering individual life expectancy.

6.1.1.1.2 Watchful waiting

Watchful waiting (also known as deferred or symptom-guided treatment) arose in the pre-PSA screening era (before 1990). It refers to conservative management, until the development of local or systemic progression with (imminent) disease-related complaints. Patients are then treated palliatively with TURP or other procedures for urinary tract obstruction, and hormonal therapy or radiotherapy for palliation of metastatic lesions. No standardised follow-up is recommended.

Table 6.1.1: Definitions of active surveillance and watchful waiting [261-263]

	Active surveillance	Watchful waiting
Treatment intent	Curative	Palliative
Follow-up	Predefined schedule	Patient-specific
Assessment/markers used	DRE, PSA, re-biopsy, optional MRI	Not predefined
Life expectancy	> 10 years	< 10 years
Aim	Minimise treatment-related toxicity without compromising survival	Minimise treatment-related toxicity
Comments	Only for a subgroup of low-risk patients	Can apply to patients with all stages

6.1.2 **Deferred treatment of localised PCa (stage T1/T2, Nx/N0, M0)**

Clinical stage T1c currently represents 40-50% of new PCa cases [264]. The incidence of small, localised, well-differentiated PCa is increasing, mainly because of PSA screening and multicore biopsy [259]. One clinical trial [265] did not show any difference in 10-year survival between watchful waiting and RP in screen-detected PCa with PSA < 10 ng/mL.

The lead-time in PSA screening is ~10 years [261, 262]. Mortality from untreated, non-screen-detected PCa in patients with Gleason scores of 6 might be only 10% at 20 years follow-up [263].

6.1.2.1 *Active surveillance*

Active surveillance might mean no treatment for patients aged > 70 years, while in younger patients treatment may be delayed for several years. The aim is to reduce overtreatment in patients with clinically confined, very-low-risk PCa, without relinquishing curative treatment, as happens with watchful waiting [260]. Active surveillance is only proposed for highly selected low-risk patients. Current data are from ongoing prospective or retrospective cohorts, without any available randomised clinical trials and the results of active surveillance (AS) are consistent throughout the published cohorts for survival.

One of the largest cohorts with the longest follow-up in a mainly low-risk population includes 993 patients (mean age: 67.8 years) [266]. These men presented with stage T1c or T2a PCa and PSA ≤ 10 ng/mL, age ≤ 70 years and a Gleason score ≤ 6 or age > 70 years with a score of ≤ 7. Initially, six biopsies were performed, but in recent years the 12-core protocol was introduced. After a median follow-up of 6.4 years (21% followed for more than 10 years), the 10- and 15-year OS were 80% and 62%, respectively. At 10 and 15 years, disease-specific survival (DSS) were 98.1% and 94.3% respectively. Twenty-eight men (2.8%) developed metastases during follow-up (all but 2 being Gleason ≥ 7), and 15 died. 63.5% and 55% of men are still alive on active surveillance at 10 and 15 years, respectively. Twenty-seven percent of this cohort eventually underwent radical treatment, prompted by a PSA-DT < 3 years in (43.5%), a Gleason score progression on repeat biopsies (35%) and patient preference (6%).

Several studies have investigated active surveillance in organ-confined disease, the findings of which were summarized in a systematic review including more than 3,900 patients [267]. There is considerable variation between studies regarding patient selection, follow-up policies and when active treatment should be instigated.

Selection criteria discussed in this review suggest: low volume intraprostatic non-aggressive disease: Gleason 6, when specified < 2 - 3 positive cores with < 50% cancer involvement of every positive core, a clinical T1c or T2a, a PSA < 10 ng/mL and a PSA density < 0.15 ng/mL/cc.

A consensus meeting recently suggested also excluding men from AS when any of the following features were present: predominant ductal carcinoma (including pure intraductal carcinoma), sarcomatoid carcinoma, small cell carcinoma, extraprostatic extension or lymphovascular invasion in needle biopsy [269]. Some studies would include men with a PSA < 20 ng/mL, or up to T2b PCa. Even patients with Gleason score 7 (3 + 4) were considered since only 19% of men with a PSA level < 10 ng/mL, PSA-DT < 0.15 ng/mL/g, T1c, and < 2 positive cores, had unfavourable disease at RP [268]. However these criteria are not yet considered as acceptable for AS and should therefore not be used.

A comprehensive review of the currently available patient selection- and follow-up criteria has been published [270], highlighting that repeat-biopsies should be systematically included in an AS policy, even though they are associated with increased erectile dysfunction [271] and infectious complications [272]. Imaging with mpMRI is of particular interest due to its high negative-predictive value for lesion upgrading and for staging anterior prostate lesions [273]. As yet, mpMRI cannot replace follow-up biopsies and should not be used alone as an assessment tool to prompt active treatment [274]. Biological markers, include urine markers such as PCA3, the TMPRSS2: ERG fusion gene or PSA isoforms such as the Phi index appear promising as does genomics on the tissue sample itself [275]. However, further study data will be needed before such markers can be used in standard clinical practice.

Follow up in AS should be based on repeat biopsy, serial PSA measurements and clinical examination (DRE). There is no agreement on which criteria to use as the basis for the decision to proceed to active treatment [276]. Criteria include a change in the Gleason score, the modification of the biopsy results (number of positive cores, increase in the core involvement). These criteria are recognised in all the published cohorts. T- stage increase is also considered. A PSA change (in particular a PSA-DT < 3 years) is often used which is questionable considering the weak link between PSA-DT and grade progression on repeat biopsy [277].

Active treatment may also be instigated upon a patient's request. This occurs in 10-18% of patients on AS [278]. Self-administered questionnaires show that patients experience anxiety and depression during an AS policy, the extent of which, however, does not significantly differ from anxiety reported by men treated by RP [279]. Overall, the discontinuation rate of AS is between 14% to 40% and 40% to 60% at 5 and 10 years, respectively. Depending on the criteria used, CSS at 10 years is reported to be between 96-100%.

Table 6.1.2: Active surveillance in screening-detected PCa

Studies	n	Median follow-up (mo)	pT3 in RP* patients	OS	CSS
Van As et al, 2008 [280]	326	22	8/18 (44%)	98	100
Carter et al, 2007 [281]	407	41	10/49 (20%)	98	100
Adamy et al, 2011 [282]	533-1,000	48	4/24 (17%)	90	99
Soloway et al, 2010 [283]	99	45	0/2	100	100
Roemeling et al, 2007 [284]	278	41		89	100
Khatami et al, 2007 [285]	270	63		NR	100
Klotz et al, 2015 [266]	993	77	NR	85	98.1
Total	2,130-3,000	43		90	99.7

* Patients receiving active therapy following initial active surveillance.

CSS = case-specific survival; n = number of patients; OS = overall survival

6.1.2.2 Watchful waiting

The rationale behind watchful waiting is that PCa often progresses slowly, and is predominantly diagnosed in older men with a high incidence of comorbidity and other causes of mortality [286]. Watchful waiting is possible in patients with localised PCa and limited life expectancy, or older patients with less aggressive cancer.

Studies of watchful waiting have included patients with up to 25 years follow-up, with endpoints of OS and DSS. Several series showed a consistent DSS rate of 82-87% at 10 years [287-292], and 80-95% for T1/T2 and Gleason score ≤ 7 [293]. In three studies with data beyond 15 years, the DSS was 80%, 79% and 58% [289, 291, 292], and two reported a 20-year DSS of 57% and 32% [289, 291]. It must be highlighted that the used Gleason classification is not the revised version which is associated with a slight increase in the Gleason classification. Practically, many patients classified as Gleason 6 in older studies would now be classified as Gleason 7. Therefore, the current Gleason 6 population has less aggressive disease compared to the patients classified in the above mentioned cohorts.

Patients with well-, moderately- and poorly differentiated tumours had 10-year CSS of 91%, 90% and 74%,

respectively, correlating with data from the pooled analysis [293].

Observation was most effective in men aged 65-75 years with low-risk PCa [258].

In patients with stage cT1a PCa, 10-year CSS rates were 96% and 94% for grade 1 and 2 tumours, respectively [287]. MFS rate was 92% and 78% for patients with grade 1 and 2 tumours, respectively, indicating a higher risk of progression for moderately differentiated tumours. Similar results were found in other studies of stage cT1a disease [294, 295].

Gleason 6-10 tumours carry a continuously increasing mortality risk for up to 15 years follow-up after watchful waiting [296]. Others have shown that the mortality risk of PCa was high in Gleason 7-10 tumours, intermediate in Gleason 6 tumours, but low in Gleason 2-5 tumours (Table 6.1.4) [297, 298].

Table 6.1.4: 15-year mortality risk for localised PCa in relation to Gleason score in patients aged 55-74 years [297-299]

Gleason score	Cancer mortality risk* (%)	Cancer-specific mortality† (%)
2-4	4-7	8
5	6-11	14
6	18-30	44
7	42-70	76
8-10	60-87	93

* Figures differ among age groups and represent the true risk in the study population (considering actual competing mortality from other causes)

† Figures compensate for differences in competing mortality and indicate outcome if the patient lives for 15 years

Six hundred and ninety-five patients with T1/T2 PCa were randomised to watchful waiting or RP (Table 6.1.5) [299]. Although the study was begun after PSA screening was introduced, only 5% of men were diagnosed by screening. After a median follow-up of 12.8 years, there was a significant decrease in cancer-specific mortality, overall mortality, metastatic progression, and local progression in the RP group vs. watchful waiting.

Table 6.1.5: Outcome of Scandinavian Prostate Cancer Group Study Number 4 at 15 years follow-up [299]

	RP (n = 347) (%)	Watchful waiting (n = 348) (%)	Relative risk (95% CI)	P value
Disease-specific mortality	14.6	20.7	0.62	0.010
Overall mortality	46.1	57.2	0.75 (0.61-0.92)	0.007
Metastatic progression	21.7	33.4	0.59 (0.45-0.79)	< 0.001
Local progression	21.5	49.3	0.34 (0.26-0.45)	NR

CI = confidence interval.

The overall difference was not modified by PSA level (below or above 10 ng/mL) or Gleason score (below or above 7) at diagnosis. Age at randomisation had a profound impact, with a benefit in OS and MFS only in those aged < 65 years.

Another study randomised 731 men with clinically organ-confined PCa (PSA < 50 ng/mL and age < 75 years) to RP or watchful waiting [265]. Half the patients had non-palpable PCa, compared with only 12% in the other trial [299]. Despite a 10-year life expectancy being an inclusion criterion, > 33% of the men died within 10 years, suggesting that the population was less fit than expected, and reduced the ability to assess survival benefit for active treatment [265].

After a mean follow-up of 10 years, there was no significant difference between the treatments for overall mortality (47% for RP vs. 49.9% for the observation group) and PCa-specific survival (5.8% (RP group) vs. 8.4% (observation group)). There were no significant differences in OS when considering patient age, Gleason score, performance status, and Charlson comorbidity index (CCI) score. Only patients with serum PSA > 10 ng/mL or high-risk PCa had a significant OS benefit from RP, with a relative-risk reduction in mortality of 33% and 31%, respectively. There was a relative-risk and absolute-risk reduction of 31% and 10.5%, respectively, for patients with intermediate/high-risk PCa. Patients who underwent RP also had a significant reduction in bone metastases (4.7% vs. 10.6%).

Data from a 1995 study showed a tendency for a higher probability of metastases in the deferred treatment group and shorter CSS was reported after deferred therapy compared with immediate hormone therapy in presumed localised PCa after 15 years of follow-up [300]. Another study showed higher mortality in men with localised PCa treated with 150 mg/day bicalutamide compared with placebo [301].

The data on deferred and conservative management of low-risk disease contrast with the recent increase in the incidence of local treatment from 25 to 34% in the USA in men with life expectancy < 10 years [302]. Swedish data show a higher prevalence of deferred treatment in low-risk disease of 46% [303].

Many small, localised, well-differentiated tumours do not progress, and radical therapy may lead to substantial overtreatment. This was confirmed by a recent analysis at 5 and 10 years in 19,639 patients aged > 65 years who were not given curative treatment. Most men with a CCI score ≥ 2 died from competing causes at 10 years whatever their initial age. However, men without comorbidity or CCI score 1 had a low risk of death at 10 years, especially for well- or moderately differentiated lesions (Table 8.7) [304]. For CCI score ≥ 2 , tumour aggressiveness had little impact on OS, suggesting that patients could have been spared biopsy and diagnosis of cancer. Thus, evaluation of initial comorbidity and survival probability before proposing biopsy or treatment is important [305].

6.1.3 **Deferred treatment for locally advanced PCa (stage T3-T4, Nx-N0, M0)**

The final analysis of the largest RCT focusing on this specific question was published in 2013 [306]. Nine hundred and eighty-five patients with T0-4 N0-2 M0 PCa were treated with androgen-deprivation therapy (ADT) immediately or after symptomatic progression or occurrence of serious complications. After a median follow-up 12.8 years, the OS hazard ratio was 1.21 (95% CI = 1.05-1.39), favouring immediate treatment. The time from randomisation to progression of hormone-refractory disease did not differ significantly, nor did CSS. The median time to start of deferred treatment was 7 years. One hundred and twenty-six patients died without needing treatment (44% of deaths). Immediate ADT resulted in a modest but significant increase in OS, but no significant difference in PCa mortality or symptom-free survival, raising the question of its clinical value. Patients with a baseline PSA > 50 ng/mL had a > 3.5-fold higher mortality risk than those with ≤ 8 ng/mL. If baseline PSA was 8-50 ng/mL, the mortality risk was ~7.5-fold higher in patients with a PSA-DT of < 12 months compared with > 12 months. The time to PSA relapse after response to immediate ADT correlated significantly with baseline PSA.

6.1.4 **Deferred treatment for metastatic PCa (stage M1)**

The only candidates for deferred treatment are asymptomatic patients with a strong wish to avoid treatment-related side-effects. Median survival is ~2 years, therefore, the time without treatment (before symptoms) is short in most cases. The risk of developing symptoms, and even death from PCa, without receiving any benefit from hormone treatment has been highlighted [307, 308]. Patients with deferred treatment for advanced PCa must be amenable to close follow-up.

6.1.5 **Guidelines for active surveillance and watchful waiting**

Recommendations - active surveillance	LE	GR
Patients who are suitable for surgery and radiotherapy must have these options discussed with them.	4	A*
Active surveillance is an option in patients with the lowest risk of cancer progression: > 10 years life expectancy, cT1/2, PSA ≤ 10 ng/mL, biopsy Gleason score ≤ 6 , ≤ 2 positive biopsies, minimal biopsy core involvement ($\leq 50\%$ cancer per biopsy).	2a	A
Follow-up should be based on DRE, PSA and repeat biopsies.		
The optimal follow-up interval is still unclear.	2a	A
Patients should be counselled on the possibility of needing further treatment in the future.	2a	A

Recommendations - watchful waiting for localised prostate cancer	LE	GR
Watchful waiting may be offered to patients not eligible for local curative treatment and those with a short life expectancy	1b	A
During watchful waiting, the decision to start non-curative treatment should be based on symptoms and disease progression (see section 6.1.2.2).		B

Recommendations - watchful waiting for locally advanced prostate cancer	LE	GR
In locally advanced M0 patients unwilling or unable to receive any form of local treatment, a deferred treatment policy using ADT as monotherapy is feasible in asymptomatic patients with a PSA DT > 12 months and a PSA < 50 ng/mL and non-poorly differentiated tumour.	1b	A

**Upgraded following panel consensus.*

ADT = androgen-deprivation therapy; DRE = digital rectal examination; GR = grade of recommendation; LE = level of evidence; PSA = prostate-specific antigen.

6.2 Treatment: Radical prostatectomy

6.2.1 Introduction

The surgical treatment of PCa consists of radical prostatectomy (RP). This involves removal of the entire prostate gland between the urethra and bladder, and resection of both seminal vesicles, along with sufficient surrounding tissue to obtain a negative margin. Often, this procedure is accompanied by bilateral pelvic lymph node dissection. The goal of RP by any approach must be eradication of disease, while preserving continence and whenever possible potency [309]. There is no age threshold for RP and a patient should not be denied this procedure on the grounds of age alone [305]. However, patients with a life expectancy of ≥ 10 years are more likely to benefit from the procedure. Increasing comorbidity greatly increases the risk of dying from non-PCa-related causes [304]. An estimation of life expectancy is paramount in counselling a patient about surgery [310] (see also Section 6.6 - Management of prostate cancer in older men).

Currently, RP is the only treatment for localised PCa to show a benefit for OS and cancer-specific survival (CSS), compared with conservative management, as shown in one prospective randomised trial [311]. During 23.2 years of follow-up, the SPCG-4 trial showed that RP was associated with a reduction of all-cause mortality. The relative risk (RR) of death at 18 years was 0.71 (95% CI, 0.59-0.86). The number needed to treat (NNT) to prevent one death at 18 years of follow-up was 8; the NNT decreased to 4 for men younger than 65 years of age. Radical prostatectomy was also associated with a reduction in PCa-specific mortality at 18 years (RR = 0.56; 95% CI, 0.41-0.77). The benefit of surgery with respect to death from PCa was largest in men younger than 65 years (RR, 0.45) and in those with intermediate-risk PCa (RR, 0.38). However, RP was associated with a reduced risk of metastases among older men (RR, 0.68).

The benefits in OS and CSS were not reproduced in the overall study population (mean age 67 yr) of another prospective randomised trial. After a median follow-up of 10 years, the PIVOT trial showed that RP did not significantly reduce all-cause mortality (hazard ratio (HR) = 0.88; 95% CI, 0.71-1.08) or significantly reduce PCa mortality (HR = 0.63; 95% CI, 0.36-1.09) [265].

- Among men with intermediate-risk tumours, RP significantly reduced all-cause mortality (HR = 0.69; 95% CI, 0.49-0.98).
- Among men with high-risk tumours, RP non-significantly reduced all-cause mortality (HR = 0.40; 95% CI, 0.16-1.00).
- Among men with PSA > 10, RP significantly reduced all-cause mortality (HR = 0.67; 95% CI, 0.48-0.94).

Radical retropubic prostatectomy (RRP) and perineal prostatectomy are performed through open incisions. More recently, minimally invasive laparoscopic radical prostatectomy (LRP) and robot-assisted laparoscopic prostatectomy (RALP) have been developed. RALP is displacing RRP as the gold standard surgical approach for clinically localised PCa in the USA and is being increasingly used in Europe and other parts of the world. This trend has occurred despite the paucity of high-quality evidence to support the superiority of RALP over more-established treatment modalities. A recent systematic review and economic modelling of the relative clinical benefit and cost-effectiveness of laparoscopic and robotic radical prostatectomy demonstrated that robotic surgery had lower perioperative morbidity and a reduced risk of positive surgical margins compared with laparoscopic prostatectomy, although there was considerable uncertainty. There was no evidence of differences in urinary incontinence at 12 months and there was insufficient evidence to draw conclusions on differences in cancer-related, patient-driven or erectile dysfunction outcomes [312]. A recent cohort study demonstrated that RALP and RRP had comparable rates of complications and additional cancer therapies. However, although associated with lower risk of blood transfusions and a slightly shorter length of hospital stay, RALP was associated with a higher probability of experiencing 30- and 90-day genitourinary and miscellaneous medical complications [313].

Surgical expertise has decreased the complication rates of RP and improved cancer cure [314-317]. Lower rates of positive surgical margins for high-volume surgeons suggest that experience and careful attention to surgical details, adjusted for the characteristics of the cancer being treated, can decrease positive surgical margin rates and improve cancer control with RP [318, 319]. More evidence for a volume-outcome relationship was provided by a recent systematic review. There was undeniable evidence suggesting that increased surgeon

volume improves outcomes [320].

The main gap in the evidence base are the lack of direct comparative studies of robotic, laparoscopic and open radical prostatectomy with low risk of bias. Moreover, there is a lack of longer-term outcomes allowing comparison of more certain measures of cancer control, such as cancer-specific mortality and overall mortality [312, 321-325]. Even though there appears to be a clear volume-outcome relationship, suggesting that referral of patients to high-volume centres would seem reasonable, the impact of a shift in practice has yet to be fully determined [320].

6.2.2 **Low-risk prostate cancer**

Patients with low-risk PCa should be informed about the results of two randomised trials comparing retropubic RP vs. watchful waiting (WW) in localised PCa. In the SPCG-4 study, death from any cause (RR 0.57 [95% CI 0.40-0.81]) and distant metastases (RR 0.40; 95% CI, 0.21-0.73) were significantly reduced in low-risk PCa. However, death from PCa [RR 0.54; 95% CI, 0.26-1.13] was not reduced. In the PIVOT trial, a preplanned subgroup analysis of men with low-risk PCa showed that RP did not significantly reduce all-cause mortality (HR 1.15; 95% CI 0.80-1.66), or death from PCa (RR 0.54; 95% CI, 0.26-1.13).

The decision to offer RP in cases of low-risk cancer should be based upon the probabilities of clinical progression, side-effects and potential benefit to survival [326]. It might therefore be reasonable to propose active monitoring to selected patients whose tumours are most likely to be insignificant.

Apart from disease characteristics, age, comorbidities and individual patient preferences impact the choice for surgery vs. active monitoring and should be considered in shared decision making. A recent study assessed the effect of age, health status and patient preferences on outcomes of surgery vs. active surveillance for low risk PCa. As expected, older age and worse baseline health status were associated with a smaller benefit in prostate-cancer-specific mortality and life expectancy with surgery, and increased incremental years with treatment side effects [327].

Pelvic lymph node dissection (eLND) is not necessary in low-risk PCa because the risk for positive lymph nodes does not exceed 5% [328].

6.2.3 **Intermediate-risk, localised prostate cancer**

Patients with intermediate-risk PCa should be informed about the results of two randomised trials comparing RRP vs. WW in localised PCa. In the SPCG-4 study, death from any cause (RR 0.71; 95% CI 0.53-0.95), death from PCa (RR 0.38; 95% CI, 0.23-0.62) and distant metastases (RR 0.49; 95% CI, 0.32-0.74) were significantly reduced in intermediate-risk PCa. In the PIVOT trial, according to a preplanned subgroup analysis among men with intermediate-risk tumours, RP significantly reduced all-cause mortality (HR = 0.69 [95% CI, 0.49-0.98]), but not death from PCa (0.50; 95% CI, 0.21-1.21).

When the tumour is palpable or visible on imaging and clinically confined to the prostate, disease progression can be expected. When managed with non-curative intent, intermediate-risk PCa is associated with 10-year and 15-year prostate-cancer-specific mortality rates of 13 and 19.6%, respectively [329].

The risk of having positive LNs in intermediate-risk PCa is between 3.7-20.1% [328]. An eLND should be performed in intermediate-risk PCa if the estimated risk for positive lymph nodes exceeds 5% [328]. In all other cases, eLND can be omitted, which means accepting a low risk of missing positive nodes. Limited LND should no longer be performed because this misses at least half of the nodes involved [243].

6.2.3.1 *Oncological results of radical prostatectomy in low- and intermediate-risk prostate cancer*

The results achieved in 2 prospective studies involving RP are shown in Table 6.2.1.

Table 6.2.1: Oncological results of radical prostatectomy in organ-confined disease

Study	Year of RP	Median follow-up (mo)	Risk category	12-year CSS (%)	18-year CSS (%)
Bill-Axelson et al, 2014 [311]	1989-1999	160	Low-risk Intermediate-risk	89.8	84.9
Wilt et al, 2012 [265]	1994-2002	120	Low-risk Intermediate-risk	100	94.2

CSS = cancer-specific survival; n = number of patients; PSA = prostate-specific antigen; RP = radical prostatectomy.

6.2.4 **High-risk and locally advanced prostate cancer**

Patients classified with high-risk PCa are at an increased risk of PSA failure, need for secondary therapy, metastatic progression and death from PCa. Nevertheless, not all high-risk PCa patients have a uniformly poor

prognosis after RP [330].

There is no consensus regarding the optimal treatment of men with high-risk PCa. Provided that the tumour is not fixed to the pelvic wall, or that there is no invasion of the urethral sphincter, RP is a reasonable first step in selected patients with a low tumour volume. Extended LND should be performed in all high-risk PCa cases, because the estimated risk for positive lymph nodes is 15-40% [328]. Limited LND should no longer be performed, because it misses at least half the nodes involved [243].

Management decisions should be made after all treatments have been discussed by a multidisciplinary team (including urologists, radiation oncologists, medical oncologists and radiologists), and after the balance of benefits and side effects of each therapy modality has been considered by the patient.

6.2.4.1 *High-risk prostate cancer*

6.2.4.1.1 Gleason score 8-10

Although most poorly differentiated tumours extend outside the prostate, the incidence of organ-confined disease is 26-31%. Patients with high-grade tumours confined to the prostate at histopathological examination have a good prognosis after RP. One of the reasons to opt for surgery is the high rate of downgrading between the biopsy Gleason score and the Gleason score of the resected specimen [331]. These men, in particular, may benefit most from potentially curative resection.

Several retrospective case series have demonstrated good outcomes after RP in the context of a multimodal approach (adjuvant or salvage ADT and/or RT) for patients with a biopsy GS \geq 8. Biochemical PFS (BPFS) at 5- and 10-years follow-up ranged between 35-51% and 24-39%, respectively, while the CSS at 5-, 10- and 15-years follow-up was 96%, 84-88% and 66%, respectively [331-334].

6.2.4.1.2 Prostate-specific antigen > 20 ng/mL

Yossepowitch et al. have reported the results of RP as monotherapy in 275 men with PSA > 20 ng/mL in a cohort with mostly clinically organ-confined tumours and found a PSA failure rate of 44% and 53% at 5 and 10 years, respectively [330]. Thirty-three and 53% of patients with PSA > 20 ng/mL needed secondary treatment at 5 and 10 years, respectively [333]. D'Amico et al. found that men with PSA levels > 20 ng/mL had a 50% risk of PSA failure at 5 years after RP [335]. Spahn et al. published the largest multicentre surgical series to date, including 712 patients with PSA > 20 ng/mL, and reported a CSS of 90% and 85% at 10 and 15 years follow-up, respectively [336].

Reports in patients with a PSA > 20 ng/mL who underwent surgery as initial therapy within a multimodal approach demonstrated a BPFS at 5-, 10- and 15-years follow-up, ranging between 40-63%, 25-48% and 25%, respectively. The CSS at 5, 10 and 15 years ranged between 93-97%, 83-91% and 71-78%, respectively [333-338].

6.2.4.2 *Locally advanced prostate cancer:*

The surgical treatment of clinical stage T3 PCa has traditionally been discouraged [339], mainly because patients have an increased risk of positive surgical margins and lymph node metastases and/or distant relapse [340, 341].

In recent years, however, there has been renewed interest in surgery for locally advanced PCa and several retrospective case series have been published. Although still controversial, it is increasingly evident that surgery has a place in treating locally advanced disease [342-344]. In up to 50% of cases this is part of multi-modality treatment (adjuvant or salvage radiotherapy and/or ADT).

The problem remains the selection of patients before surgery. Nomograms, including PSA level, stage and Gleason score, can be useful in predicting the pathological stage of disease [345, 346]. Radical prostatectomy for clinical T3 cancer requires sufficient surgical expertise to keep the level of morbidity acceptable. It has been shown that continence can be preserved in most cases, and in some cases, potency can also be preserved [347].

Retrospective case series demonstrated 5-, 10- and 15-year biochemical BPFS ranged between 45-62%, 43-51% and 38-49%, respectively. CSS at 5-, 10- and 15-years ranged between 90-99%, 85-92% and 62-84%, respectively. Five- and 10-year OS ranged between 90-96% and 76-77%, respectively [342-344, 346-350].

Only a limited number of cohort studies provided survival data of surgery for cT3b-T4 PCa. In these studies, the CSS was 88-92% at 5 years and 87-92% at 10 years, while the OS was 73-88% at 5 years and 65-71% at 10 years [351-353].

The indication for RP in all previously described stages assumes the absence of clinically detectable nodal involvement. Clinical lymph node-positive (N+) disease will mostly be followed by systemic disease progression. No good evidence exists supporting RP of cN+ patients, therefore local treatment to N+ patients

in a multimodal approach should be discussed with the patients on an individual basis.

6.2.5 Rationale for RP in patients with cN0 but pathologically confirmed lymph node invasion (pN1) PCa

The combination of RP and early adjuvant HT in pN+ PCa has been shown to achieve a 10-year CSS rate of 80% [354, 355]. Furthermore, a retrospective observational study has shown a dramatic improvement in CSS and OS in favour of completed RP vs. abandoned RP in patients who were found to be N+ at the time of surgery. These results suggest that RP may have a survival benefit and the discontinuation of RP in pN+ cases may not be justified [356]. These findings have been corroborated in a contemporary retrospective analysis [357]. This highlights the fact that frozen section is probably useless and should no longer be considered. Radical prostatectomy resulted in superior survival of patients with pN+ PCa after controlling for lymph node tumour burden. The findings from these studies support the role of RP as an important component of multimodal strategies of pN+ PCa.

The incidence of tumour progression is lower in patients with fewer positive lymph nodes [236, 358]. In patients who prove to be pN+ after RP, early adjuvant HT has been shown to significantly improve CSS and OS in a prospective randomised trial. However, this trial included mostly patients with high-volume nodal disease and multiple adverse tumour characteristics. It is unclear whether early adjuvant HT should still be used in the present era of increased detection of microscopic involvement as a result of more frequently performed extended LND. The benefits should be judged against the side effects of long-term HT. Follow-up of PSA and delaying the initiation of HT until rising PSA level is therefore an acceptable option in selected cases with ≤ 2 microscopically involved lymph nodes in an extended nodal dissection. Interestingly, in a retrospective cohort study, maximal local control with RT of the prostatic fossa appeared to be beneficial in PCa patients with pN+ after RP, treated adjuvantly with continuous ADT [359]. The beneficial impact of adjuvant RT on survival in patients with pN1 PCa was highly influenced by tumour characteristics. Men with low-volume nodal disease (≤ 2 lymph nodes) in the presence of intermediate- to high-grade, non-specimen-confined disease and those with intermediate-volume nodal disease (3-4 lymph nodes) represent the ideal candidates for RT after surgery.

Recent studies described survival outcomes after surgery in pN1 PCa, with 5-, 10- and 15-year CSS ranging from 84-95%, 51-86% and 45%, respectively. The OS at 5, 10 and 15 years ranged from 79-85%, 36-69% and 42%, respectively [236, 354-359].

6.2.6 Indication and extent of pelvic lymph node dissection (LND)

It is generally accepted that extended pelvic lymph node dissection (eLND) provides important information for prognosis (number of nodes involved, tumour volume within the lymph node, and capsular perforation of the node), which cannot be matched by any other current procedure [244]. Sentinel node mapping studies have shown that aside from the obturator and external iliac lymph nodes, the prostate also drains to the presacral nodes and most commonly to the internal iliac nodes [243, 360]. Performing eLND results in removal of all lymph nodes in these particular anatomical regions, producing a higher yield of excised lymph nodes compared with a limited LND.

The individual risk of finding positive lymph nodes can be estimated using preoperative nomograms. Only a few of these nomograms are based on extended LND templates. One of those, the Briganti nomogram with the cutoff of 5% as proposed in the EAU Prostate Cancer guidelines, has been externally validated in both open and robot-assisted RP series and showed the highest accuracy when compared with other similar prognostic tools [328, 361, 362].

6.2.6.1 Extent of lymph node dissection

Extended LND includes removal of the nodes overlying the external iliac artery and vein, the nodes within the obturator fossa located cranially and caudally to the obturator nerve, and the nodes medial and lateral to the internal iliac artery. Some lymph node mapping studies have advocated extending the template to include the common iliac lymph nodes up to the ureteric crossing. With this template, 75% of all anatomical landing sites are cleared [360]. A recent prospective mapping study confirmed that a template including the external iliac, obturator and internal iliac areas was able to correctly stage 94% of patients. Nevertheless, in pN+ patients, this template was associated with a 24% incomplete clearance from positive nodes [243]. Adding the common iliac area and the presacral area decreased this risk to only 3%.

It is recommended for each region that the nodes should be sent in separate containers for histopathological analysis, because this will usually be associated with a higher diagnostic gain by the uropathologist.

6.2.6.2 Therapeutic role of extended lymph node dissection (eLND)

Besides being a staging procedure, pelvic eLND may be curative, or at least beneficial, in a subset of patients with limited lymph node metastases [363-366]. In some series, the number of nodes removed during lymphadenectomy has been significantly correlated with time to disease progression [211]. In one population-based study with a 10-year follow-up, patients undergoing excision of at least 10 nodes (node-negative patients) had a lower risk of PCa-specific death at 10 years than those who did not undergo lymphadenectomy [367]. In another series, it was demonstrated that a more extensive LND was associated with improvement in CSS in patients with lymph node invasion [368]. Nevertheless, results from ongoing confirmatory prospective studies are awaited.

6.2.6.3 Morbidity

Pelvic eLND remains a surgical procedure that increases morbidity in the treatment of PCa. When comparing extended vs. limited LND, three-fold higher complication rates have been reported by some authors [369]. Overall complication rates of 19.8% vs. 8.2% were noted for eLND vs. limited LND, respectively, with lymphocoeles (10.3% vs. 4.6%) being the most common. Other authors have reported more acceptable complication rates [370].

Similar rates of lymphocoeles have been observed in RALP series, however, in one subgroup analysis lymphocoeles were more common in the extraperitoneal approach (19%) vs. the transperitoneal approach (0%) [371, 372].

6.2.7 Guidelines for eLND in prostate cancer

	LE	GR
LND is not indicated in low-risk PCa.	2b	A
eLND should be performed in intermediate-risk PCa if the estimated risk for positive lymph nodes exceeds 5%.	2b	B
eLND should be performed in high-risk PCa.	2a	A
Limited LND should not be performed.	2a	A
When nodal involvement is detected after RP:		
• Adjuvant ADT is the standard of care for node-positive (pN+)	1b	A
• Adjuvant ADT with additional radiotherapy may have a role (see Section 6.3.3.3)	2b	B
• Expectant management is optional when the patient has undergone eLND and ≤ 2 nodes show microscopic involvement and a PSA < 0.1 ng/mL and absence of extranodal extension.	2b	B

ADT = androgen deprivation therapy; eLND = extended lymph node dissection; GS = Gleason score; LND = lymph node dissection; PCa = prostate cancer; RP = radical prostatectomy.

6.2.8 Neoadjuvant and adjuvant hormonal therapy and radical prostatectomy

Neoadjuvant hormonal therapy (NHT) is defined as therapy given before definitive local curative treatment. Since PCa is an androgen-dependent tumour, NHT is an appealing concept. A recent review and meta-analysis studied the role of NHT and prostatectomy [373]. NHT significantly reduced positive margin rates (RR = 0.49; $p < 0.00001$), extra-prostatic extension (RR = 1.63; $p < 0.0001$) and lymph node invasion (RR = 0.49; 0.42-0.56; $p < 0.02$). However, this was not associated with improved OS or disease-free survival (DFS).

Regarding adjuvant HT, a Cochrane review has been published [374]: the pooled data showed a non-significant 5-year OS benefit (OR: 1.50 [95% CI: 0.79-2.84]) and no 10-year OS benefit (with again a trend favouring the adjuvant approach). The pooled data for DFS gave an overall OR of 3.73 (95% CI: 2.3-6.03). The overall effect estimate was highly significant ($p < 0.00001$) in favour of the HT arm. The Early Prostate Cancer Trialists' Group (EPC) trial using bicalutamide 150 mg daily [375] could not be included in the Cochrane review due to missing information. After a median follow-up of 7.2 years, there was a significant improvement in objective PFS that was only significant in the locally advanced disease group (HR: 0.75; 95% CI: 0.61-0.91). There was an OS decrease trend in the localised disease group (HR: 1.16; 95% CI: 0.99-1.37). No OS benefit was observed in both localised and locally advanced groups.

The main limitations of the above data are the mixing of pN0 and pN1 populations. For pN+ patients, 2 RCT are available and drive the main conclusion of the Cochrane review, even if non RCT suggest that the benefit might not be so large in all patients [376]. Regarding pN0 / N0 stages, the only RCT is the EPC project [375]. Using more conventional HT, a large retrospective data base with a median follow up of 10 years [377] suggests that adjuvant HT might be linked to an increased specific, but not OS benefit.

6.2.9 Complications and functional outcomes

The intra- and peri-operative complications of retropubic RP and RALP are listed in Table 6.2.2 [378] and see also section 7.8.3 - Radical prostatectomy.

Table 6.2.2: Intra- and peri-operative complications of retropubic RP and RALP (Adapted from [312])

Predicted probability of event	RALP	Laparoscopic RP	RRP
Bladder neck contracture	0.010	0.021	0.049
Anastomotic leak	0.010	0.044	0.033
Infection	0.008	0.011	0.048
Organ injury	0.004	0.029	0.008
Ileus	0.011	0.024	0.009
Deep-vein thrombosis	0.006	0.002	0.014
Predicted rates of event	RALP (%)	Laparoscopic RP (%)	RRP (%)
Clavien I	2.1	4.1	4.2
Clavien II	3.9	7.2	17.5
Clavien IIIa	0.5	2.3	1.8
Clavien IIIb	0.9	3.6	2.5
Clavien IVa	0.6	0.8	2.1
Clavien V	< 0.1	0.2	0.2

RALP = robot-assisted laparoscopic prostatectomy; RP = radical prostatectomy; RRP = radical retropubic prostatectomy.

Post-operative incontinence and erectile dysfunction are common problems following surgery for PCa. A recent systematic review found that the mean continence rates at 12 months were 89-100% for patients treated with RALP and 80-97% for patients treated with retropubic RP [325]. A similar study reported mean potency recovery rates at 12 months of 55-81% for patients treated with RALP and 26-63% for patients treated with retropubic RP [324]. The major limitations of the included studies were the frequent retrospective study design and the use of different assessment tools preventing a proper comparison between techniques and series.

6.2.10 Indications for nerve-sparing surgery

Nerve-sparing RP can be performed safely in most men with localised PCa undergoing RP [379, 380]. In the past decade, a dramatic shift towards lower-stage tumours has become evident. More importantly, men are younger at the time of diagnosis and more interested in preserving sexual function. Nevertheless, clear contraindications are patients in whom there is a high risk of extracapsular disease, such as any cT2c or cT3 PCa, any GS > 7 on biopsy, or more than one biopsy > 6 at the ipsilateral side. Partin tables help to guide decision making [345]. Multiparametric MRI is increasingly being used in the decision-making process to select a nerve-sparing approach [381-383].

If any doubt remains regarding residual tumour, the surgeon should remove the neurovascular bundle (NVB). Alternatively, the use of intra-operative frozen-section analysis can help guide these decisions. This is especially helpful in patients with a palpable lesion close to the capsule during nerve-sparing RP. A wedge of the prostate can then be resected and inked differently. When there is carcinoma extending into the inked margin on frozen-section analysis, the NVB is resected; otherwise, the NVB remains *in situ* [384].

Before surgery the patient must be informed about the potency rates achieved. The patient must be aware that, to ensure adequate cancer control, the nerves may be sacrificed despite any pre-operative optimism suggesting their salvage might be possible.

The early use of phosphodiesterase-5 inhibitors in penile rehabilitation remains controversial. Placebo-controlled prospective studies have shown no benefit from daily early administration of vardenafil or sildenafil vs. on-demand vardenafil or sildenafil in the post-operative period [385, 386]. Conversely, another placebo-controlled prospective study has shown that sildenafil has a significant benefit on the return of normal spontaneous erections [387].

6.2.11 Guidelines for radical prostatectomy

	LE	GR
Patients who are suitable for AS and radiotherapy must have these options discussed with them.	4	A*
In patients with low- and intermediate-risk PCa and a life expectancy > 10 years, RP should be offered.	1b	A
Nerve-sparing surgery may be attempted in pre-operatively potent patients with low risk for extracapsular disease (T1c, GS < 7 and PSA < 10 ng/mL, or refer to Partin tables/nomograms).	2b	B
Multiparametric MRI may help in deciding when to perform nerve-sparing procedures in intermediate- and high-risk disease.	2b	B
In patients with high-risk localised PCa and a life expectancy of > 10 years, RP should be offered in a multimodality setting.	2a	A
In selected patients with locally advanced (cT3a) PCa, and a life expectancy > 10 years, RP may be offered in a multimodality setting.	2b	B
In highly selected patients with locally advanced PCa (cT3b-T4 N0 or any T N1), RP may be offered in a multimodality setting.	3	C
NHT before RP is not recommended.	1a	A
Adjuvant HT for pN0 is not recommended.	1a	A
Adjuvant ADT is the standard of care for node-positive (pN+) patients.	1b	A
In patients who are surgical candidates for radical prostatectomy, all approaches (i.e. open, laparoscopic or robotic) are acceptable because none has clearly shown superiority in terms of functional or oncological results.	1a	A

DFS = disease-free survival; GS = Gleason score; GR = grade of recommendation; LE = level of evidence; MRI = magnetic resonance imaging; NHT = neoadjuvant hormonal therapy; OS = overall survival; PCa = prostate cancer; RP = radical prostatectomy.

6.3 Treatment: definitive radiotherapy

6.3.1 Introduction

There are no published RCT comparing radiotherapy with watchful waiting or active surveillance. The only randomised trial in the modern era is the ProtecT study which has not yet reported its first results. Intensity-modulated radiotherapy (IMRT), with or without image-guided radiotherapy (IGRT), is the gold standard for EBRT. All centres that do not yet offer IMRT should plan to introduce it as a routine method for the definitive treatment of PCa.

Regardless of the technique used, the choice of treatment is multidisciplinary. After the extent of the tumour has been properly assessed, the following are taken into account:

- 2009 TNM classification;
- Gleason score, defined using an adequate number of core biopsies (at least 10);
- Baseline prostate-specific antigen (PSA);
- Age of the patient;
- Patient's comorbidity, life expectancy, and QoL;
- International Prostate Symptom Score (IPSS) and uroflowmetry recordings;
- and the EAU prognostic factor classification.

Additional information on the various aspects of radiotherapy in the treatment of PCa is available in an extensive overview [388].

6.3.2 Technical aspects: three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated external-beam radiotherapy (IMRT)

Anatomical data is acquired by scanning the patient in a treatment position. The data are transferred to the three-dimensional (3D) treatment planning system, which visualises the clinical target volume and then adds a surrounding safety margin. Real-time verification of the irradiation field using portal imaging allows comparison of the treated and simulated fields, and correction of deviations where displacement is more than 5 mm. Three-dimensional CRT improves local control through dose escalation, without significantly increasing the risk of morbidity.

It is possible to use IMRT with linear accelerators, equipped with the latest multileaf collimators and specific software. At the time of irradiation, a multileaf collimator automatically (and in the case of IMRT continuously) adapts to the contours of the target volume seen by each beam. This allows for a more complex distribution of the dose to be delivered within the treatment field and provides concave isodose curves, which

are particularly useful as a means of sparing the rectum. To date, no randomised trials have been published comparing dose escalation using IMRT and 3D-CRT.

With dose escalation using IMRT, organ movement becomes a critical issue, in terms of both tumour control and treatment toxicity. Evolving techniques will therefore combine IMRT with some form of IGRT, in which organ movement can be visualised and corrected for in real time, although the optimum means of achieving this is still unclear [389]. Tomotherapy is another evolving technique for the delivery of IMRT, which uses a linear accelerator mounted on a ring gantry that rotates as the patient is delivered through the centre of the ring, analogous to spiral CT scanning. Preliminary data suggest that this technique is feasible in PCa treatment [390].

Whatever the techniques and their degree of sophistication, quality assurance plays a major role in the management of radiotherapy, requiring the involvement of physicians, physicists, dosimetrists, radiographers, radiologists and computer scientists.

6.3.3 **Radiotherapy for localised PCa**

6.3.3.1 *Dose escalation*

Several randomised studies (see below) have shown that dose escalation (range 74-80 Gy) has a significant impact on 5-year survival without biochemical relapse [391-397]. These trials have generally included patients from several risk groups, and the use of neoadjuvant/adjuvant hormone therapy (see below) has varied. To date, no trials have shown that dose escalation results in an OS benefit. However, the trials have been remarkably consistent in reporting improvements in freedom from biochemical progression in patients treated with dose-escalated radiotherapy.

In everyday practice, a minimum dose of ≥ 74 Gy is recommended for EBRT + hormone therapy. Currently, it is not possible to make different recommendations according to the patient's risk group.

If IMRT and IGRT are used for dose escalation, severe late side effects \geq grade III for the rectum is about 2-3% and for the genito-urinary tract is 2-5% [393, 394, 424-437] (see also Section 6.8.4.1 Post-treatment quality of life in patients with localised PCa).

Table 6.3.1: Randomised trials on dose escalation in localised prostate cancer

Trial	n	PCa condition	Radiotherapy Dose	Follow-up	Outcome	Results
MD Anderson study 2011 [391]	301	T1-T3, N0, M0, PSA 10 ng/mL vs. PSA > 10 ng/mL	70 vs. 78 Gy	Median 9 years	Disease specific mortality (DSM) vs. other cause of death	High risk / PSA >10 16% DSM @ 70 Gy 4% DSM @ 78 Gy (p = 0.05) Higher risk 15% DSM @ 70 Gy 2% DSM @ 78 Gy (p = 0.03)
PROG 95-09 study [392]	393	T1b-T2b PSA 15 ng/mL 75% GLS < 6	70.2 vs. 79.2 Gy including proton boost 19.8 vs. 28.8 Gy	Median 8.9 years for survivors	10-year ASTRO Biochemical failure (BF)	All patients: 32% BF @ 70.2 Gy 17% BF @ 79.2 Gy (p < 0.0001) Low-risk patients: 28% BF @ 70.2 Gy 7% BF @ 79.2 Gy (p < 0.0001)
MRC RT01 study [388]	843	T1b-T3a, N0, M0 PSA < 50 ng/mL neoadjuvant HT	64 vs. 74 Gy	Median 10 years	Biochemical progression free survival (BFS); OS	43% BFS @ 64 Gy 55% BFS @ 74 Gy (p = 0.0003) 71% OS both groups (p = 0.96)
Dutch randomised phase III trial [394]	664	T1b-T4 143 pts. with (neo)adjuvant HT	68 vs. 78 Gy	Median 51 mo	Freedom from biochemical- or clinical failure (FFF @ 5 years)	54% FFF @ 68 Gy 64% FFF @ 78 Gy (p = 0.02)

French GETUG 06 randomised trial [395]	306	T1b-T3a, N0, M0 PSA < 50 ng/mL	70 vs. 80 Gy	Median 61 mo	Biochemical failure (ASTRO)	39% BF @ 70 Gy 28% BF @ 80 Gy
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HT = hormone therapy; OS = overall survival.

6.3.3.2 Hypofractionation (HFX)

In radiobiology, the linear quadratic model uses two coefficients, alpha (α) and beta (β) to describe the dose-response relationship. In clinical practice, these coefficients are used to calculate the effect of different fractionation schemes. Fractionated radiotherapy utilises differences in the DNA repair capacity of normal and tumour tissue. In fast growing tissue including many tumours, cells have little time to repair photon-induced DNA damage. The α/β ratio is then typically around 10 Gy. In contrast, tissue with a low cell renewal has a good opportunity for repair between fractions of irradiation. In such tissue, the α/β ratio is 3 Gy or lower. Slowly proliferating cells with low α/β ratios are very sensitive to an increased dose per fraction [398].

While the correct α/β ratio is still controversial, a meta-analysis of 25 studies with > 14,000 patients concludes that PCa due to its slow growth has an α/β ratio of approximately 1.5 Gy. Assuming this value, hypofractionated radiotherapy could be more effective than conventional fractions of 1.8 - 2 Gy [399]. Beyond the radiobiological aspects, hypofractionation HFX can increase the convenience for the patient and lower costs for the health care system.

Several studies report on HFX applied in various techniques and in part also including hormone treatment [400-406]. A systematic review concludes that studies on moderate HFX (2.5 - 4 Gy/fx) delivered with conventional 3D-CRT/IMRT have sufficient follow-up to support the safety of this therapy, but long-term efficacy data are still lacking [407]. Extreme HFX (5-10 Gy/fx) typically requires IGRT and stereotactic body radiotherapy SBRT. Short-term biochemical control is comparable to conventional fractionation. However, there are concerns about high-grade genitourinary and rectal toxicity, and long-term side effects may not all be known, yet [407-409].

Taking into account the published results and the uncertainties of the correct α/β ratio, moderate HFX (Table 6.3.2) plus dose escalation should be done by experienced teams, accompanied by meticulous radiotherapy QA and close attention to organ at risk dose constraints until long-term data are available.

For extreme HFX, it seems prudent to restrict this therapy to prospective clinical trials and to inform patients on the uncertainties of the long-term outcome.

Table 6.3.2: Phase 3 randomised trials of moderate hypofractionation for intact prostate cancer

Study	n	Risk, GS, or NCCN	Regimen	BED, Gy	Median FU, mo	Outcome	Toxicity
Lukka et al. [400]	466	60% GS 6	52.5 Gy/20 fx	62	68	5 yr FFBF 40% (NS)	Gr \geq 3 2% (NS)
	470	31% GS 7 9% GS 8-10	66 Gy/33 fx	66		5 yr FFBF 43%	Gr \geq 3 1%
Yeoh et al. [401]	108	n.s.	55 Gy/20 fx	66.8	90	7.5 yr FFBF 53%	Late GU; HR: 1.58 (95% CI, 1.01-2.47) favouring hypofractionation
	109		64 Gy/32 fx	64		7.5 yr FFBF 34% (p < 0.05)	
Dearnaley et al. [402]	151	n.s.	57 Gy/19 fx	73.4	51	n.s.	Gr \geq 2 GU 0% (NS)
	153		60 Gy/20 fx	77			Gr \geq 2 GI 1% (NS)
	153		74 Gy/37 fx	74			Gr \geq 2 GU 2% Gr \geq 2 GI 4% Gr \geq 2 GU 2% Gr \geq 2 GI 4%
Kuban et al. [403]	102	29% low	72 Gy/30 fx	80.2	56	5 yr FFBF 96% (NS)	5 yr Gr \geq 2 GU 19% (NS)
	102	70% intermediate 1% high	75.6 Gy/42 fx	71.4		5 yr FFBF 92%	5 yr Gr \geq 2 GI 14% (NS) 5 yr Gr \geq 2 GU 19% 5 yr Gr \geq 2 GI 6%

Arcangeli et al. [404, 405]	83 85	26% GS 7 74% GS > 7	62 Gy/20 fx 80 Gy/40 fx	81.4 80	70	5 yr FFBF 85% (p = 0.065) *p ss for GS ≥ 4 + 3 5 yr FFBF 79%	3 yr Gr ≥ 2 GU 16% (NS) 3 yr Gr ≥ 2 GI 17% (NS) 3 yr Gr ≥ 2 GU 11% 3 yr Gr ≥ 2GI 14%
Pollack et al. [406]	151 152	34% GS 6 47% GS 7 19% GS 8-10	70.2 Gy/26 fx 78 Gy/36 fx	84 78	68	5 yr BCDF 23% (NS) 5 yr BCDF 21%	5 yr Gr ≥ 2 GU 13% (p = 0.16) 5 yr Gr ≥ 2 GI 9% (NS) 5 yr Gr ≥ 2 GU 13% 5 yr Gr ≥ 2 GI 9%

BCDF = biochemical or clinical disease failure; BED = biologically equivalent dose, calculated to be equivalent in 2 Gy fractions using an α/β of 1.5 Gy; CI = confidence interval; FFBF = freedom from biochemical failure; FU = follow-up; fx = fractions; GI = gastrointestinal; Gr = grade; GS = Gleason score; GU = genitourinary; HR = hazard ratio; NCCN = National Comprehensive Cancer Network; NS = not significant; n.s. = not stated; ss = statistically significant.

6.3.3.3 Neoadjuvant or adjuvant hormone therapy plus radiotherapy

The combination of radiotherapy with LHRH ADT has definitively proven its superiority compared with radiotherapy alone followed by deferred ADT on relapse, as shown by phase III randomised trials [410-414] (Table 7.3.3). These trials included high risk PCa patients, mostly by virtue of locally advanced (T3-T4 N0-X) disease, though with a wide range of clinical risk factors, such as PSA level or Gleason grade (high risk localised, T1-2, N0-X PCa). The most powerful conclusion from these studies comes from the EORTC 22863 trial, which is the basis for the combination of radiotherapy and ADT in patients with locally advanced PCa as standard practice today.

In daily practice, ADT starts either at the onset of RT (for adjuvant ADT) or 2 or 3 months before (for neoadjuvant), but the concomitant component is crucial to potentiate RT; Long-term ADT, ranging from 2 to 3 years is recommended for locally advanced disease [397, 415] rather than short term (6-months) [414]. Dose escalation phase III randomised trials are going on to assess its impact on DFS. Cardiovascular mortality may be related to ADT, not radiotherapy, as addressed in Section 12.9.3.3.

Whether these results should be applied to patients with intermediate- or high-risk localised PCa is unclear. The Boston trial has shown an improved 8-year OS rate for patients without moderate or severe comorbidity assigned to 6 months of complete ADT (p=0.01) [413], and the RTOG 94-08 study showed an increased 10-year OS rate for intermediate risk only with 4 months of complete ADT (p=0.003) [396].

The EORTC trial 22961 with 970 patients (78% T3-4, 92% N0) combined radiotherapy (70 Gy) with either 6 months or with 3 years of LHRH analogue treatment. With a median follow-up of 6.4 years, both cancer-specific and overall mortality were lower with long-term androgen suppression [397].

In the RTOG 9910 trial, 1,579 intermediate-risk PCa patients were randomised to LHRH antagonist therapy for 8 weeks before radiotherapy (70.2 Gy in 2-D or 3-D techniques) followed by either another 8 or 28 weeks of anti-hormonal treatment. Extended androgen suppression did not significantly improve 10-year rates of distant (both arms 6%), loco-regional (6% vs. 4%) or biochemical progression (both arms 27%), or disease-specific (96% vs. 95%) or OS (66% vs. 67%). The 8+8 week scheme was confirmed as a standard procedure [417].

Table 6.3.3: Studies of use and duration of ADT in combination with RT for prostate cancer

Trial	Year	TNM stage	n	Trial	ADT	RT	Effect on OS
EORTC 22863 [410]	2010	T1-2 poorly differentiated and M0, or T3-4 N0-1 M0	415	EBRT ± ADT	LHRH agonist for 3 yrs (adjuvant)	70 Gy RT	Significant benefit at 10 years for combined treatment (HR 0.60, 95% CI 0.45-0.80, p = 0.0004).
RTOG 85-31 [411]	2005	T3 or N1 M0	977	EBRT ± ADT	Orchiectomy or LHRH agonist 15% radical prostatectomy	65-70 Gy RT	Significant benefit for combined treatment (p = 0.002) seems to be mostly caused by patients with Gleason score 7-10.
Granfors [419]	2006	T3 N0-1 M0	91	EBRT ± ADT	Orchiectomy	65 Gy RT	Significant benefit (p = 0.02 p = 0.03), mainly caused by lymph-node-positive tumours.
D'Amico [413]	2008	T2 N0 M0 (localised unfavourable risk)	206	EBRT ± ADT	LHRH agonist plus flutamide for 6 mo	70 Gy 3D-CRT	Significant benefit (HR 0.55, 95% CI 0.34-0.90, p = 0.01) that may pertain only to men with no or minimal comorbidity.
TROG 96-01 Denham 2011 [414]	2011	T2b-4 N0 M0	802	Neoadjuvant ADT duration	Goserelin plus flutamide 3 or 6 mo before, plus concomitant suppression	66 Gy 3D-CRT	No significant difference in overall survival reported; benefit in prostate-cancer-specific survival (HR 0.56, 95% CI 0.32-0.98, p = 0.04) (10 yrs: HR 0.84, 0.65-1.08; p = 0.18).
RTOG 94-13 [420]	2007	T1c-4 N0-1 M0	1292	ADT timing comparison	2 mo neoadjuvant plus concomitant vs. 4 mo adjuvant suppression	Whole pelvic RT vs. prostate only; 70.2 Gy	No significant difference between neoadjuvant plus concomitant vs. adjuvant androgen suppression therapy groups (interaction suspected).
RTOG 86-10 [412]	2008	T2-4 N0-1	456	EBRT ± ADT	Goserelin plus flutamide 2 mo before, plus concomitant therapy	65-70 Gy RT	No significant difference at 10 years.
RTOG 92-02 [415]	2008	T2c-4 N0-1 M0	1554	Short vs prolonged ADT	LHRH agonist given for 2 years as adjuvant after 4 mo as neoadjuvant	65-70 Gy RT	p = 0.73 p=0.36 overall; significant benefit (p = 0.044) (p = 0.0061) in subset with Gleason score 8-10.
EORTC 22961 [397]	2009	T1c-2ab N1 M0, T2c-4 N0-1 M0	970	Short vs prolonged ADT	LHRH agonist for 6 mo vs. 3 yrs	70 Gy 3D-CRT	Better result with 3-year treatment than with 6 months (3.8% improvement in survival at 5 years).
Pisansky [417]	2014	intermediate risk (94% T1-T2, 6% T3-4)	1579	Short vs prolonged ADT	LHRH antagonist 8+ 8 vs 8+28 weeks	70.2 Gy 2D / 3D	67 vs 68% p = 0.62, confirms 8+8 weeks LHRH as a standard.
SPCGF-7/ SFUO-3 [416]	2009	T1b-2 Grade 2-3, T3 N0 M0	880	ADT ± EBRT	LHRH agonist for 3 mo plus continuous flutamide	70 Gy 3D-CRT vs. no RT	Significantly better survival with combined treatment (HR 0.68, 95% CI 0.52-0.89, p = 0.04).

NCIC CTG PR.3/ MRC PRO7/ SWOG [421]	2015	T3-4 (88%), PSA > 20 ng/mL (64%), GLS 8-10 (36%) N0 M0	1205	ADT ± EBRT	Continuous LHRH agonist	65-70 Gy 3D-CRT vs. no RT	10-years OS = 49% vs 55% favouring combined treatment (HR = 0.7, p < 0.001).
Mottet 2012 [422]	2012	T3-4 N0 M0	273 264	ADT ± EBRT	LHRH agonist for 3 yrs	70 Gy 3D-CRT vs. no RT	Significant reduction of clinical progression; 5-years OS 71.4% vs 71.5%.

LHRH = luteinising-hormone-releasing hormone; RT = radiotherapy; HR = hazard ratio; 3D-CRT = three-dimensional conformal radiotherapy.

6.3.3.4 Neoadjuvant chemotherapy plus radiotherapy

The GETUG 12 trial investigated the impact of neoadjuvant chemotherapy with docetaxel on the PFS in a cohort of 413 high-risk patients, defined as having one or more of the following criteria: T3-4, Gleason score ≥ 8, PSA ≥ 20 ng/mL, pN+. Patients were randomly assigned to either goserelin 10.8 mg every 3 months for 3 years, + four cycles of docetaxel, 70 mg/m² every 3 weeks, + estramustine 10 mg/kg/dL on days 1-5 (arm 1) or to goserelin alone (arm 2). Local therapy was administered at 3 months and consisted of radiotherapy in 358 patients (87%). Toxicity included grade 3-4 neutropenia (27%) with neutropenic fever in 2%, but no toxicity-related death and no secondary leukaemia. A PSA response (PSA < 0.2 ng/mL after 3 months of treatment) was obtained in 34% in the ADT+DE arm and 15% in the ADT arm. With a median follow-up period of 4.6 years, the 4-year PFS was 85% in arm 1 vs. 81% in arm 2 (p = 0.26), but the data need to mature [423].

6.3.3.5 Combined dose-escalated radiotherapy (RT) and androgen-deprivation therapy (ADT)

Zelefsky et al. [438] reported a retrospective analysis comprising 571 patients with low-risk PCa (22.4%), 1074 with intermediate-risk PCa (42.1%), and 906 with high-risk PCa (35.5%). 3D-conformal radiotherapy or IMRT were administered to the prostate and seminal vesicles. The prostate dose ranged from 64.8 to 86.4 Gy; doses beyond 81 Gy were delivered during the last 10 years of the study using image-guided IMRT. Complete androgen blockade with LHRH agonist plus oral antiandrogen was administered at the discretion of the treating physician to 623 high-risk PCa (69%), 456 intermediate-risk PCa (42%) and 170 low-risk PCa (30%) patients. The duration of ADT was 3 months for low-risk patients and 6 months for intermediate-risk and high-risk patients, starting at 3 months before radiotherapy. The 10-year BDFR was significantly improved by dose escalation: 84% (> 75.6 Gy) vs. 70% for low-risk PCa (p = 0.04), 76% (> 81 Gy) vs. 57% for intermediate-risk PCa (p = 0.0001), and 55% (> 81 Gy) vs. 41% for high-risk patients (p = 0.0001). The 6-month ADT also influenced the BDFR in intermediate- and high-risk patients, with 55% for intermediate-risk vs. 36% for high-risk patients (p < 0.0001). In the multivariate analysis, a dose > 81 Gy (p = 0.027) and ADT (p = 0.052) were found to be predictive factors for distant metastasis-free survival, but none of these parameters influenced OS.

6.3.3.6 Recommended external beam radiation therapy (EBRT) treatment policy for localised PCa

6.3.3.6.1 Low-risk PCa

Intensity-modulated radiotherapy with escalated dose and without ADT is an alternative to brachytherapy (see below).

6.3.3.6.2 Intermediate-risk PCa

Patients suitable for ADT can be given combined IMRT with short-term ADT (4-6 months) [396, 439, 440]. For patients unsuitable for ADT (e.g. due to comorbidities) or unwilling to accept ADT (e.g. to preserve their sexual health), the recommended treatment is IMRT at an escalated dose (76-80 Gy) or a combination of IMRT and brachytherapy.

6.3.3.6.3 Localised High-risk PCa

The high risk of relapse outside the irradiated volume makes it mandatory to use a combined modality approach, consisting of dose-escalated IMRT, including the pelvic lymph nodes + long-term ADT. The duration of ADT has to take into account WHO performance status, comorbidities, and the number of poor prognostic factors, including cT stage (> T2c), Gleason score 8-10, and PSA > 20 ng/mL. It is important to recognise that EBRT + short-term ADT did not improve OS in high-risk localised PCa, in the Boston and 04-08 RTOG trials, and long-term ADT is currently recommended for these patients.

6.3.3.6.4 Locally advanced PCa: T3-4 N0, M0

The results of radiotherapy alone are very poor [441]. The randomised trials discussed above have clearly established that the use of ADT produces better outcomes in patients with locally advanced disease who are treated with radiotherapy. Some clinicians have considered that the better outcomes were due to the earlier use

of ADT, and questioned the benefits of radiotherapy itself in this context. However, three trials have established that, in locally advanced disease, radiotherapy is effective and that combined radiotherapy + ADT is clearly superior to ADT alone.

6.3.3.3.6.4.1 MRC PR3/PR07 study - The National Cancer Institute of Canada (NCIC)/UK Medical Research Council (MRC)/Southwest Oncology Group (SWOG) intergroup PR3/PR07 study

This study comprised 1,205 patients, consisting of T3-4 (n = 1057), or T2, PSA > 40 ng/mL (n = 119), or T2, PSA > 20 ng/mL and Gleason score > 8 (n = 25) and T-category unknown (n = 4), who were randomly assigned to lifelong ADT (bilateral orchiectomy or LHRH agonist), with or without radiotherapy (65-70 Gy to the prostate, with or without 45 Gy to the pelvic lymph nodes). After a median follow-up period of 6 years, the addition of radiotherapy to ADT reduced the risk of death from any cause by 23% (p = 0.03) and the risk of death due to PCa by 46% (p = 0.0001) [442, 443].

6.3.3.3.6.4.2 The TAP 32 trial

A total of 273 patients with locally advanced PCa T3-4 or pT3 N0 M0 were randomly assigned to 3 years of ADT using an LHRH agonist (leuporelin), with or without radiotherapy (70 Gy to the prostate plus 48 ± 2 Gy to the pelvic lymph nodes). After a median follow-up period of 67 months, there was a significant improvement in the 5-year disease free survival (p < 0.001), metastatic disease-free survival (p < 0.018), and locoregional PFS (p < 0.0002), but the effect on OS was not reported [422].

6.3.3.3.6.4.3 The SPCG-7/SFUO-3 randomised study [416]

The study compared hormonal treatment alone (i.e. 3 months of continuous androgen blockade followed by continuous flutamide treatment (n = 439) with the same treatment combined with radiotherapy (n = 436). After a median follow-up period of 7.6 years, the 10-year cumulative incidences for PCa specific mortality were 23.9% and 11.9%, respectively (95% CI: 4.9-19.1%), and the 10-year cumulative incidences for overall mortality were 39.4% in the hormonal treatment-only group and 29.6% in the hormonal treatment + radiotherapy group (95% CI: 0.8-18%).

6.3.3.7 Lymph node irradiation

6.3.3.7.1 Prophylactic lymph node irradiation in clinically N0 PCa (estimated cN0)

There is no level 1 evidence for prophylactic whole-pelvic irradiation, since randomised trials have failed to show that patients benefit from prophylactic irradiation (46-50 Gy) of the pelvic lymph nodes in high-risk cases. Such studies include the RTOG 77 06 study (n = 484 with T1b-T2) [441], the Stanford study (n = 91) [444], and the GETUG 01 trial (n = 444 with T1b-T3 N0 pNx M0) [445]. In the RTOG 94-13 study [420], there were no differences in the PFS in patients treated with whole-pelvic or prostate-only radiotherapy, but interactions between whole-pelvic radiotherapy and the duration of ADT were reported following the subgroup analysis.

Pelvic lymphadenectomy may be needed to improve the selection of patients who may be able to benefit from pelvic lymph node irradiation and to supplement the use of Briganti tables [328] and/or the Roach formula [446]. The results of pelvic lymphadenectomy, especially in young patients, allows radiation oncologists to tailor both the planning target volume and the duration of ADT, particularly ensuring that there is no pelvic irradiation for pN0 patients, while it is possible to irradiate, in combination with long-term ADT. The real impact of such an approach remains, so far, hypothetical, since no randomised trials are available. The benefits of pelvic nodal irradiation at a high dosage using IMRT merit further investigation in a phase II trial. One such trial is currently recruiting through the RTOG, and PIVOTAL, a randomised phase II in the UK, has completed accrual.

6.3.3.7.2 Clinical, or pathological node positive, M0 disease

Outcomes in this group after radiotherapy as a sole modality are poor [397], and as a minimum these patients should receive radiotherapy plus long-term ADT. The RTOG 85-31 randomised phase III trial, with a median follow-up period of 6.5 years, showed that 95 of the 173 pN1 patients who received pelvic radiotherapy with immediate hormonal therapy had better 5-year (54%) and 9-year (10%) PFS rates (PSA < 1.5 ng/mL) vs. 33% and 4%, respectively, for radiation alone (p < 0.0001). Multivariate analysis showed that this combination had a statistically significant impact on the OS, disease-specific failure, metastatic failure and biochemical control rates [447]. Evidence concerning the efficacy of pelvic radiotherapy in patients with established lymph node disease is circumstantial. Patients with pelvic lymph node involvement lower than the iliac regional nodes, < 80 years old, with a WHO performance status 0-1 and no severe comorbidity, may be candidates for EBRT + immediate long-term hormonal treatment. Recent data from the UK STAMPEDE trial suggests that pelvic radiotherapy could be beneficial for N1 disease, but this is not based on a randomised comparison [448].

6.3.4 **Proton beam therapy**

In theory, proton beams are an attractive alternative to photon-beam radiotherapy for PCa, as they deposit almost all their radiation dose at the end of the particle's path in tissue (the Bragg peak), in contrast to photons, which deposit radiation along their path. There is also a very sharp fall-off for proton beams beyond their deposition depth, meaning that critical normal tissues beyond this depth could be effectively spared. In contrast, photon beams continue to deposit energy until they leave the body, including an exit dose.

Two recent planning studies comparing conformal proton therapy with IMRT have yielded conflicting results; one study suggested that the two are equivalent in terms of rectal dose sparing, but that IMRT is actually superior in terms of bladder sparing [449]; the other study suggested a clearer advantage for protons [450].

One randomised trial on dose escalation (70.2 vs. 79.2 Gy) has incorporated protons for the boost doses of either 19.8 or 28.8 Gy. This trial shows improved outcome with the higher dose, but it cannot be used as evidence for the superiority of proton therapy per se [392]. Thus, unequivocal information that shows an advantage of protons over IMRT photon therapy is still not available.

Studies from the SEER database, and from Harvard [451, 452], describing toxicity and patient reported outcomes, respectively, do not point to an inherent superiority for protons - indeed, in terms of longer term GI toxicity, proton therapy might even be inferior to IMRT [452].

A retrospective 2:1 matched-control analysis of 27,647 US Medicare patients compared 314 men receiving proton therapy with 628 men who had IMRT. Despite the considerably higher costs for proton therapy, there was some improvement in GU-tract toxicity after 6 months, but not after 12 months, and not at the GI tract [453].

A randomised trial comparing equivalent doses of proton-beam therapy with IMRT is needed to compare the efficacy of protons vs. photons; a study of this type is under consideration by the RTOG. Meanwhile, proton therapy must be regarded as a promising, but experimental, alternative to photon-beam therapy.

6.3.5 **Low-dose rate (LDR) and high-dose rate (HDR) brachytherapy**

6.3.5.1 **LDR brachytherapy**

LDR brachytherapy is a safe and effective technique. There is a consensus on the following eligibility criteria:

- Stage cT1b-T2a N0, M0;
- A Gleason score ≤ 6 assessed on an adequate number of random biopsies;
- An initial PSA level of ≤ 10 ng/mL;
- $\leq 50\%$ of biopsy cores involved with cancer;
- A prostate volume of < 50 cm³;
- An International Prostatic Symptom Score (IPSS) ≤ 12 [454].

Patients with low-risk PCa are the most suitable candidates for LDR brachytherapy. Further guidelines on the technical aspects of brachytherapy have been published recently and are strongly recommended [455]. Outcomes data have been reported for a large population-based cohort in Canada, in which both low- and intermediate-risk patients were treated [456].

There have been no randomised trials comparing brachytherapy with other curative treatment modalities. Outcomes are based on non-randomised case series. The results of permanent implants have been reported from different institutions, with a median follow-up ranging from 36 to 120 months [457]. The recurrence-free survival after 5 and 10 years has been reported to range from 71% to 93% and from 65% to 85%, respectively [458-464]. A significant correlation has been shown between the implanted dose and recurrence rates [465]. Patients receiving a D90 (dose covering 90% of the prostate volume) of > 140 Gy had a significantly higher biochemical control rate (PSA < 1.0 ng/mL) after 4 years than patients who received less than 140 Gy (92% vs 68%). There is no benefit in adding neoadjuvant or adjuvant ADT to LDR salvage brachytherapy [457].

Some patients experience significant urinary complications following implantation, such as urinary retention (1.5-22%), post-implantation transurethral resection of the prostate (TURP), which is required in up to 8.7% of cases, and incontinence (0-19%) [466]. A small randomised trial has suggested that prophylactic tamsulosin does not reduce the rates of acute urinary retention, but may improve urinary morbidity [467]. This observation requires further study in a larger number of patients. Chronic urinary morbidity can occur in up to 20% of patients, depending on the severity of the symptoms before brachytherapy. Previous TURP for benign prostatic hyperplasia increases the risk of post-implantation incontinence and urinary morbidity.

The incidence of grade III toxicity is less than 5%. Erectile dysfunction develops in about 40% of the patients after 3-5 years. In a recent retrospective analysis of 5,621 men who had undergone LDR salvage brachytherapy [468], the urinary, bowel, and erectile morbidity rates were 33.8%, 21%, and 16.7%, respectively, with invasive procedure rates of 10.3%, 0.8%, and 4%, respectively. In patients with permanent

implants, iodine-125 in granular form is the radioactive element of reference, while palladium-103 may be used for less differentiated tumours with a high doubling time. The doses delivered to the planning target volume are 144 Gy for iodine-125 and 125 Gy for palladium-103. A Gleason score of 7 is still a 'grey area', but patients with a Gleason score of 4 + 3 showed no difference in outcome [469].

A small randomised trial has suggested that using stranded rather than loose seeds is associated with better seed retention and less seed migration, and this should be the standard choice [470]. In cases of intermediate- or high-risk localised PCa, brachytherapy + supplemental external irradiation [471] or neoadjuvant hormonal treatment [472] may be considered. The optimum dose of supplemental EBRT is unclear. A randomised trial comparing 44 Gy vs. 20 Gy of EBRT + palladium-103 brachytherapy closed early, showing no difference in the biochemical outcomes [473].

6.3.5.2 HDR brachytherapy

Non-permanent transperineal interstitial prostate brachytherapy using a high-dose-rate iridium-192 stepping source and a remote afterloading technique can be applied with a total dose of 12-20 Gy in two to four fractions, combined with fractionated external radiotherapy of 45 Gy [474]. Higher doses of supplemental EBRT than this may best be delivered with IMRT, as supported by a report from the Memorial Sloan-Kettering Cancer Center indicating that this approach is safe and feasible [475].

Data suggest an equivalent outcome in terms of the BDFS in comparison with high-dose EBRT (HD-EBRT) [476]. In a retrospective analysis of modern series [477, 478], BDFS rates of 85.8%, 80.3% and 67.8% in men with low-risk, intermediate-risk, and high-risk PCa, respectively, were reported after a mean follow-up of 9.43 years. Quality-of-life changes are similar with high-dose EBRT and high-dose-rate (HDR) brachytherapy in terms of diarrhoea and insomnia [479]. However, the frequency of erectile dysfunction was significantly increased with HDR brachytherapy (86% vs 34%). A single randomised trial of EBRT vs. EBRT + HDR brachytherapy has been reported [480]. A total of 220 patients with organ-confined PCa were randomised to EBRT alone with a dose of 55 Gy in 20 fractions, or EBRT with a dose of 35.75 Gy in 13 fractions, followed by HDR brachytherapy with a dose of 17 Gy in two fractions over 24 hours. In comparison with EBRT alone, the combination of EBRT and HDR brachytherapy showed a significant improvement in the BDFR ($p = 0.03$). There were no differences in the rates of late toxicity. Patients randomly assigned to EBRT + brachytherapy had a significantly better QoL as measured by their Functional Assessment of Cancer Therapy-Prostate (FACT-P) score at 12 weeks. However, a very high, uncommon rate of early recurrences was observed in the EBRT arm alone, even after 2 years, possibly due to the uncommon fractionation used [480]. There is still a need to compare dose-escalated EBRT + hormone therapy with the same followed by a brachytherapy boost in intermediate-risk and high-risk patients. A systematic review of non-randomised trials has suggested the possibility that outcomes with EBRT plus HDR brachytherapy are superior to brachytherapy alone, but this needs confirmation in a prospective, randomised trial [481].

For T1-2 N0 M0 disease, the 5-year BDFRs are similar for permanent seed implantation, high-dose (> 72 Gy) external radiation, combination seed/external irradiation, and radical prostatectomy, according to a study of 2991 patients diagnosed with T1-2 consecutive localised PCa treated between 1990 and 1998 at the Cleveland Clinic Foundation and Memorial Sloan-Kettering Cancer Center, with a minimum follow-up period of 1 year [476].

6.3.5.3 Side effects of percutaneous irradiation and brachytherapy

Radiotherapy affects erectile function to a lesser degree than surgery, according to retrospective surveys of patients [482]. A meta-analysis has shown that the 1-year probability rates for maintaining erectile function were 0.76 after brachytherapy, 0.60 after brachytherapy + external irradiation, 0.55 after external irradiation, 0.34 after nerve-sparing RP, and 0.25 after standard RP. When studies with more than 2 years of follow-up were selected (i.e. excluding brachytherapy), the rates became 0.60, 0.52, 0.25, and 0.25, respectively, with a greater spread between the radiation techniques and surgical approaches [483].

Studies have demonstrated a significantly increased risk of developing secondary malignancies of the rectum and bladder following EBRT [484, 485]. In a retrospective evaluation of 30,552 and 55,263 men, who had undergone either EBRT or RP, the risk of being diagnosed with rectal cancer increased by 1.7-fold in comparison with the surgery group [484]. Another analysis [485] showed that the relative risk of developing bladder cancer increased by 2.34-fold in comparison with a healthy control population. On the other hand, a re-analysis of SEER data including more than 100,000 patients, demonstrated a risk of about 0.16% (i.e. 160 cases per 100,000 patients) of radiation-induced malignant tumours [486]. The Memorial Sloan-Kettering Cancer Center group have also reported corresponding data on late toxicity from their experience in 1571 patients with T1-T3 disease treated with either 3D-CRT or IMRT at doses of between 66 Gy and 81 Gy, with a median follow-up of 10 years [487]. Both acute gastrointestinal and genitourinary toxicity appeared to be predictive for corresponding late toxicity. The overall rate of NCIC/Common Toxicity Criteria (CTC) grade 2 or more gastrointestinal toxicity was 5% with IMRT vs. 13% with 3D-CRT. The incidence of grade 2 or higher late

genitourinary toxicity was 20% in patients treated with 81 Gy vs. 12% in patients treated with lower doses. The overall incidences of grade 3 toxicity were 1% for gastrointestinal toxicity and 3% for genitourinary toxicity. These data suggest that IMRT can successfully protect against late gastrointestinal toxicity. Interestingly, with dose escalation, genitourinary toxicity may become the predominant type of morbidity [487].

6.3.6 **Immediate (adjuvant) post-operative external irradiation after RP (cN0 or pN0) (Table 6.3.5)**

Extracapsular invasion (pT3), Gleason score ≥ 7 and positive surgical margins (R1) are associated with a risk of local recurrence, which can be as high as 50% after 5 years [488]. Three prospective randomised trials have assessed the role of immediate post-operative radiotherapy (adjuvant radiotherapy, ART), as follows:

6.3.6.1 *EORTC 22911*

EORTC 22911 [489], with a target sample size of 1005 patients, compared immediate post-operative radiotherapy (60 Gy) with radiotherapy delayed until local recurrence (70 Gy) in patients classified as pT3 pN0 with risk factors R1 and pT2R1 after retropubic RP. Immediate post-operative radiotherapy was well tolerated. Grade 4 toxicity was not observed (Tables 6.8.1 and 6.8.2). The rate of grade 3 genitourinary toxicity was 5.3% vs. 2.5% in the observation group after 10 years. For patients younger than 70 years, the study concluded that immediate post-operative radiotherapy after surgery significantly improved the 10-year biological PFS to 60.6% vs. 41.1% in the observation group. A difference was observed in the clinical progression rates for the entire cohort that favoured ART after 5 years, but this trend was not sustained after 10 years. Locoregional control was better in the long-term follow-up at 10 years after immediate irradiation (hazard ratio (HR) = 0.45; $p < 0.0001$). However, ART patients with pT2-3 R1 also showed an improved clinical PFS after 10 years (HR = 0.69; $p = 0.008$). Overall survival did not differ significantly between the treatment arms. After re-evaluation using a central pathological review, the highest impact of ART was on biochemical progression (HR reduced to 0.3) seen in patients with positive margins, but there was also a positive effect of 10% after 5 years for pT3 with negative margins and other risk factors [490, 491].

6.3.6.2 *ARO trial*

The most suitable candidates for immediate radiotherapy may be those with multifocal positive surgical margins and a Gleason score > 7 . The conclusions of ARO trial 96-02 ($n = 385$) appear to support those of the EORTC study. After a median follow-up period of 112 months, the radiotherapy group demonstrated a significant improvement in BDFR of 56% vs. 35%, respectively ($p = 0.0001$). However, unlike other studies, and of major interest, the randomization of patients was carried out after they had achieved an undetectable PSA level following RP (< 0.1 ng/mL) and only pT3 tumours were included. This result indicates that ART is effective, even in the setting of an undetectable PSA after RP and additional risk factors [491].

6.3.6.3 *SWOG 8794 trial*

Conversely, the updated results, with a median follow-up of more than 12 years, of the SWOG 8794 trial, which randomly assigned 425 pT3 patients, showed that adjuvant radiation significantly improved the metastasis-free survival, with a 10-year metastasis-free survival of 71% vs. 61% (median prolongation of 1.8 years, $p = 0.016$) and a 10-year OS of 74% vs. 66% (median: 1.9 years prolongation; $p = 0.023$) [492].

6.3.6.4 *Conclusion*

Thus, for patients classified as pT3 pN0 with a high risk of local failure after RP due to positive margins (highest impact), capsule rupture, and/or invasion of the seminal vesicles, who present with a PSA level of < 0.1 ng/mL, two options can be offered in the framework of informed consent. These are:

- Immediate ART to the surgical bed [489, 491, 493] after recovery of urinary function;
or
- Clinical and biological monitoring followed by salvage radiotherapy (SRT) before the PSA exceeds 0.5 ng/mL [494, 495] (see Section 6.10.5.1).

Table 6.3.4: Overview of all three randomised trials for adjuvant radiation therapy after RP

Reference	n	Inclusion criteria	Randomization	Definition of BCR PSA (ng/mL)	Median follow-up (mo)	Biochemical Progression-free survival (bNED)	Overall survival
SWOG 8794 [493]	431	pT3 cN0 ± involved SM	60-64 Gy vs observation	> 0.4	152	10 years: 53% vs 30% (p < 0.05)	10 years: 74% vs 66% Median time: 15.2 vs 13.3 years p = 0.023
EORTC 22911 [489]	1005	pT3 ± involved SM pN0 pT2 involved SM pN0	60 Gy vs observation	> 0.2	127	10 years: 60.6% vs 41% (p < 0.001)	81% vs 77% NS
ARO 96-02 [491]	388	pT3 (± involved SM) pN0 PSA post-RP undetectable	60 Gy vs observation	> 0.05 + confirmation	112	10 years: 56% vs 35% (p = 0.0001)	10 years: 82% vs 86% n.s.

BCR = biochemical recurrence; NS = not significant; PSA = prostate-specific antigen; RP = radical prostatectomy; SM = surgical margin.

see Section 6.10.5.1 for delayed (salvage) post-radical prostatectomy external irradiation.

6.3.7 **Immediate (adjuvant) post-operative external irradiation after radical prostatectomy (RP) (pN1)**

In a retrospective matched-pair analysis with 364 pN+ patients, men who received adjuvant RT in addition to androgen deprivation therapy after radical prostatectomy had a 16% better 10-year cancer specific survival as compared to those without ADT [496]. In a recent study comparing lymph node positive prostatectomy patients who received either adjuvant ADT alone (n = 721) or ADT+ART (n = 386), the multimodal treatment reduced 8-year cancer-specific mortality (7.6% vs 13.8%, p = 0.08) [359]. Subgroup analysis in this retrospective study demonstrated a significant benefit from additional ART for patients with intermediate risk (1-2 positive nodes, GLS 7-10 and pT3b/4 or positive surgical margins; 6.9% vs 15.8%, p = 0.03) and for patients with high risk (3-4 positive nodes irrespective of further risk parameters; 3.5% vs 21.2%, p = 0.02). The results could be confirmed with the end-point OS. These data need prospective validation, but could be helpful in individual decision making.

6.3.8 **Conclusion and Guidelines for definitive radiotherapy**

Statement	LE
The highest effect of adjuvant radiotherapy is seen in patients with pT3R1 PCa.	1a

	LE	GR
Patients who are suitable for AS and surgery must have these options discussed with them.	4	A
EBRT should be offered in all risk groups of non-metastatic PCa.	2a	A
In low-risk PCa, the total dose should be 74 to 78 Gy.	1a	A
In patients with low-risk PCa, without a previous TURP and with a good IPSS and a prostate volume < 50 mL, LDR brachytherapy is a treatment option.	2a	A
In intermediate-risk PCa the total dose should be 76-78 Gy, in combination with short-term ADT (4-6 mo).	1b	A
In patients with high-risk localised PCa, a total dose of 76-78 Gy in combination with long-term ADT (2-3 yr) is recommended.	1b	A
In patients with locally advanced cN0 PCa, radiotherapy must be given in combination with long-term ADT (2-3 yr).	1a	A
IMRT is the recommended modality for definitive treatment of PCa by EBRT.	2a	A
In patients with cN+ PCa, pelvic external irradiation can be given in combination with immediate long-term ADT.	2b	B
In patients with pT3,N0M0 PCa and an undetectable PSA following RP, adjuvant external beam irradiation has to be discussed as an option because it improves at least biochemical-free survival	1a	A
Patients with pT3,N0M0 PCa and an undetectable PSA following RP should be informed about salvage irradiation as an alternative to adjuvant irradiation when PSA increases (see Section 6.10.5.1).	2b	A

ADT = androgen deprivation therapy; CRT = conformal radiotherapy; EBRT = external-beam radiation therapy; GR = grade of recommendation; IMRT = intensity-modulated radiotherapy; LE = level of evidence; PCa = prostate cancer; PSA = prostate-specific antigen; TURP = transurethral resection of prostate; WHO = World Health Organization.

6.4 Treatment: Options other than surgery and radiotherapy for the primary treatment of localised prostate cancer

6.4.1 Background

Besides radical prostatectomy (RP), external-beam radiation and brachytherapy, other modalities have emerged as therapeutic options in patients with clinically localised PCa [497-500]. In this chapter, we will consider both whole gland and focal treatment, looking particularly at high-intensity focused ultrasound (HIFU) and cryosurgery (CSAP) as sufficient data are available to form the basis of some initial judgements on these latest additions to the management of PCa.

Other options - such as photodynamic therapy, radiofrequency ablation and electroporation, among others - are considered to be in the early phases of evaluation and will therefore not be discussed in this edition of the guidelines.

Both HIFU and CSAP have been developed as minimally invasive procedures with the aim of equivalent oncological safety with reduced toxicity.

6.4.2 Cryosurgery

Cryosurgery uses freezing techniques to induce cell death by:

- dehydration resulting in protein denaturation;
- direct rupture of cellular membranes by ice crystals;
- vascular stasis and microthrombi, resulting in stagnation of the microcirculation with consecutive ischaemic apoptosis [497-500].

Freezing of the prostate is ensured by the placement of 12-15 x 17 gauge cryoneedles under transrectal ultrasound (TRUS) guidance, placement of thermosensors at the level of the external sphincter and bladder neck, and insertion of a urethral warmer. Two freeze-thaw cycles are used under TRUS guidance, resulting in a temperature of -40°C in the mid-gland and at the neurovascular bundle. Currently, the so-called third-generation cryosurgery devices are mainly used.

6.4.2.1 Indication for cryosurgery

Patients who are potential candidates for CSAP are those who have organ-confined PCa and those identified as having minimal tumour extension beyond the prostate [497-499]. The prostate should be < 40 mL in size. Prostate glands > 40 mL should be hormonally downsized to avoid any technical difficulty in placing cryoprobe under the pubic arch. Prostate-specific antigen (PSA) serum levels should be < 20 ng/mL, and the

biopsy Gleason score should be ≤ 7 . Potential candidates for CSAP are:

- patients with low-risk PCa, or intermediate-risk PCa whose condition prohibits radiotherapy or surgery;
- at the time of therapy, the size of the prostate should be < 40 mL; volume reduction may be achieved by androgen ablation.

It is important that patients with a life expectancy > 10 years should be fully informed that there are limited data on the long-term outcome for cancer control at 10 and 15 years.

6.4.2.2 *Results of modern cryosurgery for PCa*

The therapeutic results of cryotherapy have improved over time with the introduction of enhanced techniques such as gas-driven probes and transperineal probe placement, as used in third-generation cryosurgery [501-506].

An objective assessment of PSA outcome is not easily performed because some institutions use PSA values < 0.1 ng/mL as an indicator of therapeutic success, whereas others use the old American Society of Therapeutic Radiology and Oncology (ASTRO) criteria, which require three initial consecutive increases in PSA level.

With regard to second-generation CSAP, if a PSA nadir < 0.5 ng/mL is used, BDFS at five years is 60% and 36% for low-risk and high-risk patients, respectively [501, 502].

Long et al. [501] have performed a retrospective analysis of the multicentre, pooled, CSAP results of 975 patients stratified into three risk groups. Using PSA thresholds of 1.0 ng/mL and < 0.5 ng/mL at a mean follow-up of 24 months, the five-year actuarial BDFS rate was:

- 76% and 60%, respectively, for the low-risk group
- 71% and 45%, respectively, for the intermediate-risk group
- 61% and 36%, respectively, for the high-risk group.

According to a recent meta-analysis of 566 cryosurgery-related publications, there were no controlled trials, survival data or validated biochemical surrogate end-points available for analysis [507].

Cryosurgery showed progression-free survival (PFS) of 36-92% (projected one- to seven-year data), depending on risk groups and the definition of failure. Negative biopsies were seen in 72-87% of cases, but no biopsy data were available for the currently used third-generation cryotherapy machines.

With regard to third-generation cryosurgery, clinical follow-up is short, with a 12-month PSA follow-up carried out in only 110/176 (63%) patients [501-506]. Eighty of these (73%) patients still had a PSA nadir < 0.4 ng/mL, whereas 42/65 (64.6%) low-risk patients remained free from biochemical progression using the 0.4 ng/mL cut-off.

Longer follow-up has been reported by Bahn et al. [504], who have analysed the therapeutic results of 590 patients undergoing CSAP for clinically localised and locally advanced PCa. At a PSA cut-off level of < 0.5 ng/mL, the seven-year BDFS for low-, medium- and high-risk groups was 61%, 68% and 61%, respectively. PSA nadir levels in 2,427 patients registered in the Cryo On-Line Data (COLD) Registry showed that a PSA nadir of 0.6 ng/mL or above was associated with significant risks of biochemical failure (29.5%, 46% and 54% in low-, intermediate- and high-risk groups, respectively) within the first two years [508].

In a randomized comparison between whole-gland cryotherapy and external-beam radiotherapy, no difference in 36 months of disease progression was observed at 100 months follow-up [509]. Men in both arms of the study received three to six months of neoadjuvant androgen ablative therapy.

6.4.2.3 *Complications of cryosurgery for primary treatment of PCa*

Erectile dysfunction occurs in about 80% of patients and this remains a consistent complication of the CSAP procedure, independent of the generation of the system used [510]. The complication rates described in third-generation cryosurgery include tissue sloughing in about 3%, incontinence in 4.4%, pelvic pain in 1.4% and urinary retention in about 2% [501-506]. The development of fistula is usually rare, being $< 0.2\%$ in modern series. About 5% of all patients require transurethral resection of the prostate (TURP) for subvesical obstruction.

6.4.3 *High-intensity focused ultrasound of the prostate*

HIFU consists of focused ultrasound waves, emitted from a transducer, that cause tissue damage by mechanical and thermal effects as well as by cavitation [511]. The goal of HIFU is to heat malignant tissues above 65°C so that they are destroyed by coagulative necrosis.

HIFU is performed under general or spinal anaesthesia, with the patient lying in the lateral position.

The procedure is time-consuming, with about 10 g prostate tissue treated per hour. In a 2006 review, 150 papers related to HIFU were identified and evaluated with regard to various oncological and functional outcome parameters [507]. No controlled trial was available for analysis, and no survival data were presented. No validated biochemical, surrogate end-point was available for HIFU therapy. Potential candidates are patients with low to moderate risk in investigational settings. The patient should be informed about the lack of long-term outcome data at > 10 years (see 7.4.4.2).

6.4.3.1 Results of high-intensity focused ultrasound in PCa

As with CSAP, various PSA thresholds are defined for biochemical cure, and no international consensus exists on objective response criteria. The Stuttgart criteria ($> \text{PSA nadir} + 1.2 \text{ ng/mL}$) have been proposed to define BCR after HIFU treatment [512]. As a consequence of the lower PSA cut-off for recurrence than in the Phoenix criteria ($\text{PSA nadir} + 2 \text{ ng/mL}$), the outcome may be approximately 10% lower using the Stuttgart criteria than the Phoenix criteria [513]. According to the review mentioned above [507], HIFU showed PFS (based on PSA \pm biopsy data) of 63-87% (projected three- to five-year data), but median follow-up in the studies ranged from 12-24 months only.

In one of the largest single-centre studies, 227 patients with clinically organ-confined PCa were treated with HIFU, and their outcome data were analysed after a mean follow-up of 27 months (range: 12-121 months) [514] (see Table 6.4.1). The projected five-year BDFS was 66%, or only 57% if patients had exhibited a pre-therapeutic PSA value of 4-10 ng/mL. Incontinence and bladder neck stricture decreased over time from 28% and 31%, respectively, to 9% and 6%, respectively. In another study [515], a significant decrease in pre-treatment PSA serum levels from 12 ng/mL to 2.4 ng/mL was observed. However, 50% of the 14 patients demonstrated positive prostate biopsies during follow-up. In a third study [516], a complete response rate (i.e. $\text{PSA} < 4 \text{ ng/mL}$) and six negative biopsies were achieved in 56% of the patients.

From a single centre, the eight-year BDFS rates (Phoenix definition) were 76%, 63%, and 57% for low-, intermediate-, and high-risk patients, respectively ($p < 0.001$) after whole-gland treatment. At 10 years, the PCa-specific survival rate and metastasis-free survival rate (MFSR) were 97% and 94%, respectively [517].

Thüroff et al. [516] have summarised the efficacy results of a European multicentre study comprising the data of 559 patients with mainly low- and intermediate-risk PCa, and have reported a negative biopsy rate of 87.2% in 288 men with a follow-up of at least six months. A PSA nadir after six months' follow-up could be determined in 212 patients, and was 1.8 ng/mL. However, following the initial procedure, it could be demonstrated that the PSA nadir might be reached in 12-18 months.

Blana et al. have reported the results of 146 patients undergoing HIFU with a mean follow-up of 22.5 months [518]. The mean PSA level before treatment was 7.6 ng/mL; the PSA nadir achieved after three months was 0.07 ng/mL. However, after 22 months, the median PSA level was 0.15 ng/mL. Of the 137 men available for analysis, 93.4% demonstrated a negative control biopsy. The PSA nadir appeared to be strongly associated with treatment failure [519] ($p < 0.001$). Patients with a PSA nadir of 0.0-0.2 ng/mL had a treatment failure rate of only 11% compared with 46% in patients with a PSA nadir of 0.21-1.00 ng/mL, and 48% with a PSA nadir of $> 1.0 \text{ ng/mL}$. Recently, the group has updated its results, with a total of 163 men treated for clinically organ-confined PCa. Within the 4.8 ± 1.2 years of follow-up, the actuarial DFS rate at five years was 66%, with salvage treatment initiated in 12% of patients [520].

In another study, 517 men with organ-confined or locally advanced PCa were treated with HIFU [521]. Biochemical failure was defined as the $\text{PSA nadir} + 2 \text{ ng/mL}$, according to the Phoenix guidelines with regard to radiotherapy. After a median follow-up of 24 months, the BDFS was 72% for the entire cohort. The BDFS in patients with stage T1c, T2a, T2b, T2c and T3 groups at five years was 74%, 79%, 72%, 24% and 33%, respectively ($p < 0.0001$). The BDFS in patients in the low-, intermediate- and high-risk groups at five years was 84%, 64% and 45%, respectively ($p < 0.0001$). The BDFS in patients treated with or without neoadjuvant hormonal therapy at seven years was 73% and 53% ($p < 0.0001$), respectively. Post-operative erectile dysfunction was noted in 33 out of 114 (28.9%) patients who were pre-operatively potent.

In a retrospective study, 137 patients with PCa underwent HIFU [522]. After a median follow-up of 36 months, 22% of the patients relapsed according to the Phoenix criteria. The five-year DFS rate was 78% based on these criteria, and 91%, 81% and 62% in the low-, intermediate- and high-risk groups, respectively. Urge incontinence (16 cases) and dysuria (33 cases) occurred after removal of the urethral catheter in 11.8% and 24.1%, respectively.

To evaluate whether the location (apex/mid-gland/base) of PCa influences the risk of incomplete transrectal HIFU ablation, Boutier et al. [523] analysed 99 patients who underwent PCa HIFU ablation (Ablatherm; EDAP, Vaulx-en-Velin, France) with a 6 mm safety margin at the apex, and had systematic biopsies at three to six months after treatment. Residual cancer was found in 36 patients (36.4%) and 50 sextants (8.4%); 30 (60%) positive sextants were in the apex, 12 (24%) in the mid-gland, and eight (16%) in the base. Statistical analysis showed that the mean (95% CI) probability for a sextant to remain positive after HIFU ablation was 8.8% (3.5-20.3%) in the base, 12.7% (5.8-25.9%) in the mid-gland, and 41.7% (27.2-57.89%)

in the apex. When a 6 mm apical safety margin was used, treatment-associated side-effects, especially incontinence and erectile dysfunction, were fewer, but residual cancer after HIFU ablation was significantly more frequent in the apex.

Komura et al. [524] have analysed the oncological outcome in 144 patients with T1/T2 PCa and a median follow-up of 47 (2-70) months. Thirty-nine percent of patients relapsed and approximately 40% developed a clinical or subclinical urethral stricture post-operatively. Most interestingly, the five-year DFS was significantly better in those with a stricture than in those without (78.2% vs 47.8%, $p < 0.001$), indicating the need for more aggressive treatment, especially at the apex of the prostate. Crouzet et al. [517] published the results of 1,002 men treated with whole-gland HIFU with a median follow-up of 6.4 years. PCa-specific survival and metastasis-free survival at 10 years were 97% and 94%, respectively. Overall, 37.1% of men received any form of salvage treatment.

Table 6.4.1: Summary of studies addressing HIFU in PCa

Study (reference no.)	n	Median follow-up	Outcome measure
Blana et al. 2004 [518]	137	22.5 mo	87% PSA < 1 at follow-up
Poissonnier et al. 2007 [514]	227	27 mo	66% BCR-free at 5 y
Crouzet et al. 2013 [517]	1,002	6.4 y	76%, 63% and 57% BCR-free (Phoenix) for low-, intermediate- and high-risk disease, respectively DFS at 10 y: 97%; metastasis-free: 94%
Thüroff et al. 2003 [516]	559	6 mo	87% biopsy negative at 6 mo
Uchida et al. 2009 [521]	517	24 mo	72% BCR-free (Phoenix)
Inoue et al. 2011 [522]	137	36 mo	78% BCR-free (Phoenix)
Boutier et al. 2011 [523]	99	6 mo	64% biopsy tumour-free
Komura et al. 2011 [524]	144	47 mo	61% BCR-free (Phoenix)
Thüroff and Chaussy 2013 [525]	704	5.3 y	60%, BCR-free (Phoenix) at 10 y 99% DFS at 10 y; 95% metastasis-free at 10 y
Pfeiffer et al. 2012 [526]	191	53 mo	85%, 65% and 55% biochemical-free survival rate (Stuttgart) for low-, intermediate- and high-risk disease, respectively
Pinthus et al. 2012 [527]	402	24 mo	68% BCR-free (Stuttgart) at 4 y

BCR = biochemical recurrence; DFS = disease-free survival; n = number of patients; PSA = prostate-specific antigen.

6.4.4 Focal therapy of PCa

During the past two decades, there has been a trend towards earlier diagnosis of PCa as a result of greater public and professional awareness, leading to the adoption of both formal and informal screening strategies. The effect of this has been to identify men at an earlier stage with smaller tumours that occupy only 5-10% of the prostate volume, with a greater propensity for unifocal or unilateral disease [528-530].

Most focal therapies to date have been achieved with ablative technologies: cryotherapy, HIFU or photodynamic therapy, electroporation, focal radiotherapy by brachytherapy, or CyberKnife Robotic Radiosurgery System technology (Accuray Inc., Sunnyvale, CA, USA). The main purpose of focal therapy is to limit treatment toxicity in patients that could benefit from local disease control [531-533].

6.4.4.1 Pre-therapeutic assessment of patients

The high number of random and systematic errors associated with TRUS-guided random biopsy regimens means that this procedure is not sufficiently accurate for selecting candidates for focal therapy. Perineal biopsy or magnetic resonance imaging (MRI) may be useful tools. For characterizing men considering focal therapy, transperineal prostate biopsy using a template-guided approach is recommended [534-536]. When used with a 5 mm sampling frame, this approach can rule in or out PCa foci with volumes of 0.5 mL and 0.2 mL with 90% certainty [537]. Thus, the exact anatomical localization of the index lesion - defined as the biologically most aggressive - can be accurately determined.

6.4.4.2 Patient selection for focal therapy

The primary objective of treatment must be the eradication of measurable and biologically aggressive disease with minimal toxicity. However, although treatment is usually intended to be a single session, patients should know that further treatment might be necessary in the future. Standardised follow-up schedules and retreatment indications are currently non-existent. Based on published data, the following criteria identify

possible candidates for currently ongoing trials of focal treatment:

- candidates for focal therapy should ideally undergo transperineal template mapping biopsies; multiparametric MRI with or without TRUS biopsy may be an option in the hands of experts;
- focal therapy should be limited to patients with a low to moderate risk in investigational settings; retrospective data have shown the presence of grade I-III toxicity in 13% of cases [538];
- patients should be counselled with caution as no data on functional and oncological outcomes are available;
- patients must be informed that:
 1. the therapy is investigational;
 2. the long-term consequences are unknown;
 3. the optimal method for follow-up and the criteria for salvage therapy are not clear;
 4. focal therapy is not without toxicity.

Early reports suggest the feasibility of MRI-guided focal salvage cryotherapy after local radiotherapy [539] and focal electroporation [540].

6.4.5 **Conclusions and guidelines for experimental therapeutic options to treat clinically localised PCa**

Conclusions	LE
HIFU has been shown to have a therapeutic effect in low-stage PCa, but prospective randomised comparison studies are not available.	3
Cryotherapy for PCa compares unfavourably with external-beam radiation for the preservation of sexual function.	2
PSA nadir values after ablative therapies may have prognostic value.	3
Focal therapy of any sort is investigational, and the follow-up and retreatment criteria are unclear.	3
HIFU treatment for localised PCa results in mild to moderate urine incontinence in less than 20% of men.	

Recommendations	GR
In patients who are unfit for surgery or radiotherapy, CSAP can be an alternative treatment for PCa.	C
If HIFU is offered, the lack of long-term comparative outcome data (> 10 y) should be discussed with the patient.	C
Focal therapy of PCa is still in its infancy and cannot be recommended as a therapeutic alternative outside clinical trials.	A

CSAP = cryosurgery; GR = grade of recommendation; HIFU = high-intensity focused ultrasound; LE = level of evidence; PSA = prostate specific antigen.

6.5 **Treatment: Hormonal therapy - rationale and available drugs**

6.5.1 **Introduction**

6.5.1.2 *Different types of hormonal therapy*

ADT can be achieved by either suppressing the secretion of testicular androgens or inhibiting the action of circulating androgens at the level of their receptor using competing compounds known as anti-androgens. In addition, these two methods can be combined to achieve what is known as complete (or maximal or total) androgen blockade (CAB) [541].

6.5.2 **Testosterone-lowering therapy (castration)**

6.5.2.1 *Castration level*

Surgical castration is still considered the 'gold standard' for ADT, against which all other treatments are rated. It leads to a considerable decline in testosterone levels and induces a hypogonadal status, known as the 'castration level'.

The standard castrate level was < 50 ng/dL (1.7 nmol/L). It was defined more than 40 years ago, when testosterone level testing was limited. Current testing methods have found that the mean value of testosterone after surgical castration is 15 ng/dL [542]. This has led to a revisiting of the current definition of castration, with a more appropriate level defined as below 20 ng/dL (1 nmol/L). This new definition is important as better results are repeatedly observed with levels around or below 1 nmol/L compared to 1.7 nmol/L [543-545]. However, the castrate level considered by the regulatory authorities is still 50 ng/dL (1.7 nmol/L), which is

also the threshold that has been used in all clinical trials addressing castration in PCa patients.

6.5.2.2 *Bilateral orchiectomy*

Bilateral orchiectomy, either total or subcapsular pulpectomy, is a simple, cheap and virtually complication-free surgical procedure. It is easily performed under local anaesthesia [546] and is the quickest way to achieve a castration level, usually within less than 12 hours. It is irreversible and does not allow for intermittent treatment.

6.5.3 *Oestrogens*

Opposed to castration, oestrogens resultant testosterone suppression is not associated with bone loss [547].

6.5.3.1 *Diethylstilboesterol (DES)*

Early studies by the Veterans Administration (VACURG) tested oral Diethylstilboesterol (DES) at 5 mg/day. This dosage was associated with high cardiovascular morbidity and mortality, which was secondary to first-pass hepatic metabolism and the formation of thrombogenic metabolites. Lower doses of 1 mg/day and 3 mg/day were found to be as effective as bilateral orchiectomy [548], with still more side effects compared to castration.

6.5.3.2 *Strategies to counteract the cardiotoxicity of oestrogen therapy*

Two strategies have been attempted to neutralise oestrogen cardiotoxicity.

- Parenteral oestrogen (polyoestradiol phosphate) to avoid first-pass hepatic metabolism was as effective as CAB for survival, but with still more non-fatal cardiovascular events [549].
- The use of either warfarin sodium, 1 mg/day, or aspirin, 75-100 mg/day in combination with DES, 1 mg/day or 3 mg/day, did not suppress the thromboembolic complications associated with DES [550, 551].

These results precluded oestrogen as a standard first-line treatment.

6.5.4 *Luteinising-hormone-releasing hormone agonists*

Long-acting LHRH agonists are currently the main forms of ADT. These synthetic analogues of LHRH, are delivered as depot injections on a 1-, 2-, 3-, 6-monthly, or yearly basis. After the first injection, they stimulate pituitary LHRH receptors, inducing a transient rise in LH and FSH leading to the 'testosterone surge' or 'flare-up' phenomenon, which begins 2-3 days later and lasts for about 1 week. The different products have practical differences that need to be considered in everyday practice, including the storage temperature, whether a drug is ready for immediate use or requires reconstitution, and whether a drug is given by subcutaneous or intramuscular injection.

6.5.4.1 *Achievement of castration levels*

Chronic exposure to LHRH agonists results in the down-regulation of LHRH-receptors, suppressing LH and FSH secretion and therefore testosterone production. The castration level is usually obtained within 2-4 weeks [552]. However, about 10% of treated patients fail to achieve castration levels [543], which rise to 15% if the castration threshold is defined as 1 nmol/l. Although there is no formal direct comparison between the various compounds, they are considered to be equally active [548] and comparable to orchiectomy [549].

6.5.4.2 *Flare-up phenomenon*

The 'flare phenomenon' might lead to detrimental effects such as increased bone pain, acute bladder outlet obstruction, obstructive renal failure, spinal cord compression, and cardiovascular death due to hypercoagulation status.

Clinical flare needs to be distinguished from the biochemical flare and even from asymptomatic radiographic evidence of progression [553]. Patients at risk are usually those with high-volume, symptomatic, bony disease. Concomitant therapy with an anti-androgen decreases the incidence of clinical flare, but does not completely suppress the risk.

Some testosterone mini-flares have also been observed with the LHRH agonists. The clinical impact might be associated with a negative impact on OS (see Section 6.6.3.1).

6.5.5 *Luteinising-hormone-releasing hormone antagonists*

LHRH antagonists bind immediately and competitively to LHRH receptors in the pituitary gland. The effect is a rapid decrease in LH, FSH and testosterone levels without any flare. The practical shortcoming of these compounds is the lack of a long-acting depot formulation.

6.5.5.1 *Abarelix*

Abarelix was as effective as LHRH agonists in achieving and maintaining castration levels of testosterone and in reducing serum PSA [554, 555]. However, the FDA has issued a warning about allergic reactions with the

long-term use of abarelix, which has resulted in suspension of its further development. It is, however, licensed in metastatic and symptomatic PCa, for which no other treatment option is available, or as a short-term induction modality (http://www.accessdata.fda.gov/drugsatfda_docs/label/2003/21320_plenaxis_lbl.pdf).

6.5.5.2 *Degarelix*

Degarelix is an LHRH antagonist with a monthly subcutaneous formulation. The standard dosage of degarelix is 240 mg in the first month, followed by 80 mg monthly injections. More than 95% of patients have achieved a castrate level at day 3. No allergic reactions were observed. Its main specific side-effect is a somewhat painful injection (moderate or mild) reported by 40% of patients, mainly after the first injection. An extended follow-up has been published, suggesting a better progression-free survival compared to monthly leuporelin [556]. Its definitive superiority over the LHRH analogues remains to be proven. Their use is limited by a monthly formulation.

6.5.6 **Anti-androgens**

These oral compounds are classified according to their chemical structure as:

- steroidal, e.g. cyproterone acetate (CPA), megestrol acetate and medroxyprogesterone acetate;
- non-steroidal or pure, e.g. nilutamide, flutamide and bicalutamide.

Both classes compete with androgens at the receptor level. This is the sole action of non-steroidal antiandrogens that leads to an unchanged or slightly elevated testosterone level. Conversely, steroidal antiandrogens have progestational properties leading to a central inhibition by crossing the blood-brain barrier.

6.5.6.1 *Steroidal anti-androgens*

These compounds are synthetic derivatives of hydroxyprogesterone. Their main pharmacological side-effects are secondary to castration, while gynaecomastia is quite rare. The non-pharmacological side effects are cardiovascular toxicity (4-40% for CPA) and hepatotoxicity.

6.5.6.1.1 *Cyproterone acetate (CPA)*

This was the first anti-androgen to be licensed, but the least studied. Its most effective dose in monotherapy is still unknown. Although CPA has a relatively long half-life (31-41 hours), it is usually administered in two or three fractionated doses of 100 mg each. Only one randomised trial [557] compared CPA with standard medical castration, suggesting a poorer OS compared to LHRH analogues. Although there are other studies in CPA monotherapy, methodological limitations prevent firm conclusions.

An underpowered monotherapy comparison with flutamide in M1b PCa did not show any difference in specific- and overall survival at a median follow-up of 8.6 years [558].

6.5.6.1.2 *Megestrol acetate and medroxyprogesterone acetate*

Very limited information is available on these two compounds, but they are associated with a poor overall efficacy [559].

6.5.6.2 *Non-steroidal anti-androgens*

Non-steroidal anti-androgens monotherapy have been promoted on the basis of improved quality of life (QoL) and compliance compared to castration. They do not suppress testosterone secretion and it is claimed that libido, overall physical performance and bone mineral density (BMD) are preserved [560]. Non-androgen pharmacological side-effects differ, with bicalutamide showing a more favourable safety and tolerability profile than nilutamide and flutamide [561]. All three agents share a common liver toxicity (occasionally fatal) and liver enzymes must be monitored regularly.

6.5.6.2.1 *Nilutamide*

There are no comparative trials of nilutamide monotherapy with castration. Non-androgen pharmacological side-effects are visual disturbances (i.e. delayed adaptation to darkness), alcohol intolerance, nausea, and specifically exceptional interstitial pneumonitis (potentially life-threatening). Nilutamide is not licensed for monotherapy.

6.5.6.2.2 *Flutamide*

Flutamide has been studied as monotherapy for more than 20 years. No dose-finding studies against a currently accepted endpoint (e.g. PSA response) are available. Flutamide is a pro-drug, and the half-life of the active metabolite is 5-6 hours, so it must be administered three times daily. The recommended daily dosage is 750 mg. The non-androgen pharmacological side-effect of flutamide is diarrhoea.

6.5.6.2.3 Bicalutamide

The dosage licensed for use in CAB is 50 mg/day, and 150 mg for monotherapy. The androgen pharmacological side-effects are mainly gynaecomastia (70%) and breast pain (68%), which may be prevented by anti-oestrogens [562, 563], prophylactic radiotherapy [559], or surgical mastectomy. However, bicalutamide monotherapy clearly offers bone protection compared with LHRH analogues and probably LHRH antagonists [560, 564].

6.5.7 **New compounds (for the castrate resistant status only)**

During castration, the occurrence of castration-resistant status (CRPC) is systematic. It is thought that it is mediated through two main overlapping mechanisms, which are androgen-receptor (AR)-independent and AR-dependent (see Section 6.11 - Castrate-resistant Prostate Cancer). In CRPC, the intracellular androgen level is increased compared to androgen sensitive cells, and an over-expression of the AR has been observed in CRPC, suggesting an adaptative mechanism [565]. This has led to the development of two new major compounds targeting the androgen axis: abiraterone acetate and enzalutamide.

6.5.7.1 *Abiraterone acetate*

Abiraterone acetate (AA) is a CYP17 inhibitor (a combination of 17 hydrolase and a 17-20 lyase inhibition). It represents an improvement over ketoconazole, which is no longer available. By blocking CYP 17, AA significantly decreases the intracellular testosterone level by suppressing its synthesis at the adrenal level inside the cancer cells (intracrine mechanism). This compound must be used together with prednisone/prednisolone (2 x 5 mg).

6.5.7.2 *Enzalutamide*

Enzalutamide (previously known as MDV 3100) is a novel anti-androgen with a higher affinity than bicalutamide for the AR receptor. While non-steroidal anti-androgens still allow transfer of ARs to the nucleus, enzalutamide also blocks AR transfer and therefore suppresses any possible agonist-like activity.

Both drugs were developed for use in mCRPC after docetaxel. Both drugs have resulted in a significant overall improvement in survival [566, 567]. Detailed results are presented in section 6.11 - Castrate-resistant Prostate Cancer).

6.5.8 **Cost-effectiveness of hormonal therapy options**

A formal meta-analysis and literature review evaluated the cost-effectiveness of various long-term androgen suppression options in advanced PCa (e.g. bilateral orchiectomy, DES, LHRH-agonist, NSAA monotherapy, and CAB using NSAA). For men who can accept it, bilateral orchiectomy is the most cost-effective form of ADT, providing a higher quality-adjusted survival, while CAB is the least economically attractive option, yielding small health benefits for a high relative cost. Furthermore, the greatest QoL gains and least costs may be obtained by starting ADT when symptoms from distant metastases have occurred [568]. Finally, once ADT is started, if a major response is obtained, IAD might be a useful way to lower treatment costs.

6.6 **Treatment: Metastatic prostate cancer**

6.6.1 **Introduction**

A systematic review of ADT in PCa has recently been published [541].

6.6.2 **Prognostic factors**

In recent years, the median survival of patients with newly diagnosed metastases is 42 months [569]. The M1 population is heterogeneous, with the most convincing data on prognosis produced by the large SWOG 8894 trial [570] discriminating patients into three groups based on the location of metastases (axial bone only compared to appendicular or visceral), the performance status (< 1 compared to ≥ 1), the Gleason score (< 8 compared to ≥ 8) and the PSA (< 65 compared to > 65 ng/mL). Patients with axial bone metastases only or appendicular or visceral metastases, an PS < 1 and a Gleason score < 8 have a median survival of 54 months, compared to those with appendicular or visceral metastases a PS ≥ 1 and a PSA > 65 with only 21 months median survival.

After starting ADT, the PSA level after 7 months of ADT may lead to 3 groups with very different survival expectancy. The median survival is 75 months if the PSA level < 0.2 ng/mL, 44 months if the PSA < 4 ng/mL and only 13 months if the PSA is > 4 ng/mL [571]. Although these predictions are based on data from the large SWOG 9346 cohort, the prognostic use of PSA at 7 months of ADT still requires independent confirmation.

6.6.3 **First-line hormonal treatment**

Primary ADT is the standard of care [541]. There is no level 1 evidence to choose between an LHRH analogue

or antagonist, except in patients with an impending spinal cord compression. In these patients, the choice for first-line treatment is between bilateral orchidectomy and an LHRH antagonist.

6.6.3.1 *Prevention of flare-up*

Starting with an LHRH analogue results in an initial testosterone flare, which can usually be prevented by starting an anti-androgen at the same time [572]. Prevention of flare-up is important in symptomatic patients or when a clinical flare might lead to severe complications. The anti-androgen is usually continued for 4 weeks, although this duration is not based on evidence since there are no trials of the best regimen for preventing flare-up. In addition, the long-term impact of preventing flare-up is unknown [573].

6.6.4 **Combination therapies**

6.6.4.1 *Complete androgen blockade (CAB)*

There are conflicting results from the many studies comparing CAB with monotherapy [572]. The largest RCT in 1,286 M1b patients found no difference between surgical castration plus flutamide compared to surgical castration without flutamide [574]. Systematic reviews have shown that CAB using non-steroidal anti-androgen (NSAA) appears to provide a small survival advantage (< 5%) vs. monotherapy (surgical castration or LHRH agonists) [575, 576] beyond 5 years [577]. However, some of the larger trials included in these reviews were methodologically flawed and it is unlikely that this small advantage, if any, is useful in daily clinical practice. LHRH analogues and NSAA have the highest estimated quality-adjusted survival. However, the use of CAB increases side effects and the economic cost. There is an incremental cost of more than US\$1 million per quality-adjusted life-year vs. orchiectomy alone.

6.6.4.2 *Non-steroidal anti-androgen (NSAA) monotherapy*

A systematic review has been published comparing non-steroidal antiandrogen monotherapy to castration (either medical or surgical) by the Cochrane group [578]. The key message is that use of non-steroidal antiandrogen monotherapy compared with medical or surgical castration monotherapy for advanced PCa is less effective in terms of OS, clinical progression, treatment failure and treatment discontinuation due to adverse events. The evidence quality was rated as moderate.

6.6.4.3 *Intermittent versus continuous androgen deprivation therapy (IAD)*

Long-term castration stimulates prostate cell apoptosis. After an average period of 24 months, the tumour relapses, characterised by a castrate-independent state of growth. Experimental data indicate that castrate-independent progression may begin early after castration, coinciding with the cessation of androgen-induced differentiation of stem cells [579]. It has been suggested that stopping castration prior to progression would mean that any subsequent tumour growth would be solely sustained by the proliferation of androgen-dependent stem cells. The stem cells should therefore be susceptible once again to androgen withdrawal. Thus, IAD could delay the emergence of the androgen-independent clone. This rationale has been developed mainly through models (e.g. the Shionoggi breast model), which may be significantly different to tumour behaviour in men. Other possible benefits of IAD include the preservation of QoL in off-treatment periods and a reduction in treatment cost.

IAD is feasible and accepted by patients [580]. Two independent reviews [581, 582] summarised the clinical efficacy of this attitude. They were based on seven RCTs. Of the seven trials, only three trials were in patients with M1 disease. The three remaining trials were combinations of different relapse situations, mainly locally advanced and metastatic cases.

The design of the seven trials is summarised in Table 6.6.1, while the main results for survival are summarised in Table 6.6.2. The most important survival finding was the lack of a significant difference in OS between continuous and intermittent ADT. Table 6.6.3 summarises the expected treatment benefits of IAD. The most important finding was that the benefit in overall QoL was at best minimal if any. However, some treatment side effects were decreased using IAD.

Table 6.6.1: Patient population and treatment cycles in phase III trials on IAD in M1 patients

Parameter	SEUG9401 [583]	FINN VII [584]	SWOG9346 [585]	TULP [586]	TAP22 [587]	De Leval [588]
n	766	554	1535	193	173	68
Tumour stage	Locally advanced/ metastatic	Locally advanced/ metastatic	Metastatic	Metastatic	Metastatic	Locally advanced/ metastatic/BCR
PSA (ng/mL) at inclusion	4-100	Any value	> 5	Any value	> 20	Any value
Therapy	CAD	CAD	CAD	CAD	CAD	CAD
Induction period (mo)	3	6	7	6	6	6
PSA (ng/mL) level to stop on-phase	< 4	< 10	< 4	< 4	< 4	< 4
PSA (ng/mL) level to restart on-phase	> 10 for symptomatic and > 20 for asymptomatic	> 20	> 20	> 10 no metastatic and > 20 metastatic	> 10	> 10
Time off therapy	50% at least 52 weeks; 29% for 36 mo	10.9-33.5 weeks	> 40% of time	0.7-4.9 mo	1.0- 48.9 mo	3.3-8.3 mo
Follow-up (mo) median	50	65	108	31	44	31

CAD = complete androgen deprivation; mo = months; n = number of patients; PSA = prostate specific antigen.

Table 6.6.2: Oncological results in the 7 phase III trials on IAD

Parameter	SEUG9401 [583]	FINN VII [584]	SWOG9346 [585]	TULP [586]	TAP22 [587]	De Leval [588]
End points considered	Time to progression/ survival	Time to progression/ survival	Time to progression/ survival	Time to progression	Time to progression/ survival	Time to progression
Time to progression	HR 0.81 in favour continuous arm. p = 0.11	IAD 34.5 mo. Continuous 30.2 mo. HR 1.08; p = 0.43	IAD 16.6 mo. Continuous 11.5 mo. p = 0.17	IAD 18.0 mo. Continuous 24.1 mo	IAD 20.7 mo. Continuous 15.1 mo p = 0.74	IAD 28 mo. Continuous 21 mo.
PC-specific survival	IAD 23.6% dead. Continuous 20.8% dead. HR 0.88	IAD 43% dead; 45.2 mo. Continuous 47% dead; 44.3 mo. HR 1.17; p = 0.29	IAD 64% dead. Continuous 56% dead	-	-	-
Overall survival	IAD 54.1% dead. Continuous 54.2% dead. HR 0.99; p = 0.84	IAD 45.2 mo Continuous 45.7 mo HR 1.15; p = 0.17	IAD 5.1 yr. Continuous 5.8 yr. HR 1.09	-	IAD 56.9% dead; 42.2 mo. Continuous 54.2% dead; 52.0 mo p = 0.75	-

HR = hazard ratio; IAD = intermittent androgen deprivation; mo = months.

Table 6.6.3: QoL and safety in the 7 phase III trials on IAD

Parameter	SEUG9401 [583]	FINN VII [584]	SWOG9346 [585]	TULP [586]	TAP22 [587]
Hot flashes	IAD 19% Continuous 30%	IAD 47.1% Continuous 50.4%	-	IAD 50% Continuous 59%	IAD 60.4% Continuous 63.8%
Sexual dysfunction	At 15 months sexually active: IAD 28% Continuous 10%	IAD 15.7% Continuous 7.9%	-	IAD 9% Continuous 10%	-
Long-term consequences	Cardiovascular deaths: IAD 13.1% Continuous 16.7%	Cardiovascular deaths: IAD 12.8% Continuous 15.4%	-	-	-
QoL	Overall no clinically relevant differences. Favourable for IAD in sexual function domains	Favourable for IAD in activity limitation, physical capacity and sexual functioning domains	-	No clinically relevant difference	No clinically relevant difference

IAD = intermittent androgen deprivation; QoL = quality of life.

- The SWOG 9346 [585] is the largest-ever conducted trial in M1b patients. Out of 3,040 selected patients, only 1,535 were randomised based on the inclusion criteria. This highlights again that at best only 50% of M1b patients might be candidates for IAD, i.e. the best PSA responders.
- The SWOG 9346 was a non-inferiority trial. The results are inconclusive: (HR: 1.1; CI: 0.99-1.23), with the upper limit being above the pre-specified 90% upper limit of 1.2.

6.6.4.3.1 Potential other benefits of intermittent androgen deprivation

Other possible long-term benefits include bone protection [589] and/or a protective effect against the metabolic syndrome. Testosterone recovery is seen in most studies [580], leading to an intermittent castration. Finally, IAD is associated with a very significant decrease in the treatment cost.

6.6.4.3.2 Practical aspects for intermittent androgen deprivation

The optimal thresholds at which ADT must be stopped or resumed are empirical [580, 582]. Nevertheless, several points are clear.

- IAD is based on intermittent castration. Therefore, only drugs leading to castration are suitable for use in IAD.
- Most published experiences are based on CAB, which is considered as standard treatment. An LHRH antagonist might be a valid alternative [2], without any significant benefits.
- The induction cycle must last 9 months at the most, otherwise testosterone recovery is unlikely.
- The treatment is stopped only if patients have fulfilled all the following criteria:
 - well-informed and compliant patient;
 - no clinical progression;
 - clear PSA response, empirically defined as a PSA < 4 ng/mL in metastatic disease.
- Strict follow-up is mandatory, with clinical examination every 3-6 months. The more advanced the disease, the closer the follow-up. The same laboratory should be used to measure the PSA level.
- Treatment is resumed when the patient reaches either a clinical progression, or a PSA above a predetermined, empirically fixed, threshold: usually 10-20 ng/mL in metastatic cases.
- The same treatment is used for at least 3-6 months.
- Subsequent cycles of treatment are based on the same rules until the first sign is seen of a castrate-resistant status.
- The best population for IAD has still to be fully characterised. However, the most important factor seems to be the patient's response to the first cycle of IAD, e.g. the PSA level response [582].

IAD might be an option in metastatic situations after a standardised induction period, even if the benefits are fewer compared to those with less advanced situations.

6.6.4.4 *Immediate versus deferred androgen deprivation therapy*

There is no discussion regarding the introduction of IAD in symptomatic patients. However, there is still controversy concerning the best time to introduce hormonal therapy in asymptomatic metastatic patients due to the lack of properly conducted RCTs. These are underpowered trials with heterogeneous patient enrolment (i.e. locally advanced, M1a, M1b status) and variations in ADT modalities and follow-up schedules.

ADT was shown to be the most cost-effective therapy if started at the time the patient developed symptomatic metastases [568].

The Cochrane Library review extracted four good-quality RCTs: VACURG I and II trials, the MRC trial, and the ECOG 7887 study. These studies were all conducted in the pre-PSA era and included patients with advanced PCa, who had received early vs. deferred ADT, either as primary therapy or adjuvant to radical prostatectomy [590]. The Cochrane review found that the M1a/b population showed no improvement in OS, although early ADT significantly reduced disease progression and complication rates due to progression.

Based on a systematic review of the literature, the ASCO guidelines on initial hormonal treatment for androgen-sensitive, metastatic, recurrent or progressive PCa concluded it was not possible to make a recommendation on when to start hormonal therapy in advanced asymptomatic PCa [591]. The ESMO guidelines do not make any statement [592].

6.6.5 *Hormonal treatment combined with chemotherapy*

Two large RCT were conducted, one is fully published [593], the second one just presented recently [594], but representing a cohort twice as large. They both compared ADT alone as standard with AT combined with upfront Docetaxel. They came to different findings regarding survival benefit and it is not possible to make a clear recommendation at the present time.

6.6.6 *Guidelines for the first-line treatment of metastatic prostate cancer*

	Modality	Recommendation	LE	GR
Castration alone	Surgical: agonist, antagonist.	Standard of care	1b	A
	New hormonal treatment (Abiraterone acetate, Enzalutamide)	To be used in an experimental setting only.	4	A
Castration combined with chemotherapy	Docetaxel combined with castration.	No specific recommendation can be made.	1b	A
Castration combined with any other local treatment	Radiotherapy or surgery	To be used in an experimental setting only.	3	A

6.6.7 *Guidelines for hormonal treatment of metastatic prostate cancer*

Recommendations	LE	GR
In M1 symptomatic patients, immediate castration should be offered to palliate symptoms and reduce the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, extraskelatal metastasis).	1b	A
In M1 asymptomatic patients, immediate castration should be offered to defer progression to a symptomatic stage and prevent serious disease progression-related complications.	1b	A
In M1 asymptomatic patients, deferred castration should be discussed with a well-informed patient.	2b	B
Anti-androgens		
In M1 patients, short-term administration of anti-androgens is recommended to reduce the risk of the 'flare-up' phenomenon in patients with advanced metastatic disease who are to receive an LHRH agonist.	2a	A
In M1 patients, short-term administration of anti-androgens should be given for some weeks only (starting treatment on the same day as an LHRH analogue is started or for up to 7 days before the first LHRH analogue injection).	3 4	A B
In M1 patients, administration of anti-androgens as monotherapy should not be considered.	1a	A

Intermittent treatment			
Population	In asymptomatic M1 patients, intermittent treatment can be offered to highly motivated men, with a major PSA response after the induction period.	1b	B
Threshold to start and stop ADT	In M1 patients, timing of intermittent treatment should follow the schedules currently in use in clinical trials. Treatment is usually stopped when the PSA level is < 4 ng/mL after 6 to 7 months of treatment. Treatment is resumed when the PSA is > 10-20 ng/mL.	4	C
Drug	Combined treatment with LHRH agonists and NSAA is recommended.	1b	A
	Antagonists might be an option.	4	B

ADT = androgen deprivation therapy; GR = grade of recommendation; LE = level of evidence; LHRH = luteinising hormone-releasing hormone; NSAA = non-steroidal anti-androgen; PSA = prostate specific antigen; RCT = randomised controlled trial.

6.6.8 Contraindications for various therapies

Therapy	Contraindications	LE	GR
Bilateral orchiectomy	Psychological reluctance to undergo surgical castration.	3	A
Oestrogens	Known cardiovascular disease.	2b	B
LHRH agonists monotherapy	Patients with metastatic disease at high risk for clinical 'flare-up' phenomenon.	2b	A

ADT = androgen deprivation therapy; GR = grade of recommendation; LE = level of evidence; LHRH = luteinising hormone-releasing hormone.

6.7 Management of prostate cancer in older men

6.7.1 Evaluating health status in senior adults

6.7.1.1 Introduction

With a median age at diagnosis of 68 years, PCa is generally a disease of men aged > 70 years. In the USA, the increase in men aged > 65 years will result in an estimated 70% increase in annual diagnosis of PCa by 2030 [595]. A similar increase is expected in Europe [4].

The Surveillance, Epidemiology and End Results (SEER) database shows that 71% of PCa-related deaths occur in men aged ≥ 75 years [596], probably due to the higher incidence of advanced/metastatic disease [597-599].

Despite the high incidence and mortality rates in senior adults, they may be undertreated in the USA [600] and Europe [601]. In the USA, only 41% of patients aged > 75 years with intermediate- and high-risk disease receive curative treatment compared to 88% aged 65-74 [602]. Two large studies showed that PCa-specific mortality was low for localised low- and intermediate-risk PCa, irrespective of age [329, 603]. In contrast, cancer-related mortality of up to 64% was found for high-risk PCa.

6.7.1.2 Evaluation of life expectancy, comorbidity and health status

In localised disease, > 10 years life expectancy is considered mandatory for any benefit from local treatment. Life expectancy varies within each age group. This can be explained by comorbidity, which is more important than age in predicting death in localised PCa [304]. Besides comorbidities, dependence in daily activities, malnutrition and cognitive impairment are associated with worse survival.

6.7.1.2.1 Comorbidity

Comorbidity is a major predictor of non-cancer-specific death in localised PCa treated with RP [604]. This was confirmed in a patient group who did not receive any form of local treatment within 180 days after diagnosis [304]. At 10 years, most men with a Charlson Comorbidity Index (CCI) score > 2 had died from competing causes, irrespective of age or tumour aggressiveness.

Currently, the Cumulative Illness Score Rating-Geriatrics (CISR-G; Table 6.7.1) [605] is the best tool for assessing mortality risk unrelated to PCa [606]. Although CCI measures only potentially lethal comorbidity, the CISR-G also rates non-lethal conditions [607].

Table 6.7.1: Cumulative Illness Score Rating-Geriatrics (CISR-G)

Cumulative Illness Rating Scale			
Patient		Age	
Rater		Date	
Rating strategy			
0		None	
1		Mild (or past significant problem)	
2		Moderate (moderate disability or morbidity, requires first-line therapy)	
3		Severe (constant significant disability/ uncontrollable chronic problems)	
4		Extremely severe (immediate treatment required/ end organ failure / severe impairment in function)	
		Score	
Heart			
Vascular			
Respiratory			
Eyes, ears, nose, throat and larynx			
Upper GI			
Lower GI			
Hepatic			
Renal			
Genitourinary			
Musculoskeletal/integument			
Neurological			
Endocrine/metabolic			
Psychiatric illness			
Total score			

Patients are considered fit if they have no Grade 3 score

Vulnerable: one or two Grade 3 scores

Frail: > 2 Grade 3, or any Grade 4 scores

Too sick: multiple Grade 4 scores

6.7.1.2.2 Independent daily activities

The level of dependence in daily activities influences survival in senior adults [608-610]. The Activities of Daily Living (ADL) scale rates accomplishment of basic activities of daily living, while the Instrumental Activities of Daily Living (IADL) scale rates activities requiring higher cognition and judgement.

6.7.1.2.3 Malnutrition

Malnutrition is associated with increased mortality in senior patients [611]. Nutritional status can be estimated from body weight during the previous 3 months:

- Good nutritional status < 5% weight loss;
- Risk of malnutrition: 5-10% weight loss;
- Severe malnutrition: > 10% weight loss.

6.7.1.2.4 Cognitive impairment

Cognitive impairment is associated with increased mortality risk in senior adults [612]. In patients undergoing major elective surgery, there is an association between baseline cognitive impairment and long-term postoperative complications and mortality [613]. Intervention is unlikely to reverse cognitive impairment, except in depression [40].

6.7.1.2.5 Baseline screening using the G8 screening tool

The International Society of Geriatric Oncology (SIOG) Prostate Cancer Working Group (PCWG) recommends that treatment for senior adults should be based on systematic evaluation of health status [40]. The G8 (Geriatric 8) health status screening tool is described in Table 6.7.2, the Karnofsky and ECOG Scores in Table 6.7.3 [614].

Table 6.7.2: G8 screening tool (Adapted from [615])

	Items	Possible responses (score)
A	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing, or swallowing difficulties?	0 = severe decrease in food intake
		1 = moderate decrease in food intake
		2 = no decrease in food intake
B	Weight loss during the last 3 months?	0 = weight loss > 3 kg
		1 = does not know
		2 = weight loss between 1 and 3 kg
		3 = no weight loss
C	Mobility?	0 = bed or chair bound
		1 = able to get out of bed/chair but does not go out
		2 = goes out
E	Neuropsychological problems?	0 = severe dementia or depression
		1 = mild dementia
		2 = no psychological problems
F	BMI? (weight in kg)/(height in m ²)	0 = BMI < 19
		1 = BMI 19 to < 21
		2 = BMI 21 to < 23
		3 = BMI ≥ 23
H	Takes more than three prescription drugs per day?	0 = yes
		1 = no
P	In comparison with other people of the same age, how does the patient consider his/her health status?	0.0 = not as good
		0.5 = does not know
		1.0 = as good
		2.0 = better
	Age	0: > 85
		1: 80-85
		2: < 80
	Total score	0-17

G8 score > 14 shows that patients should receive the same treatment as younger patients. Patients with $G8 \leq 14$ should undergo full geriatric evaluation, assessing comorbidity, nutritional status, and cognitive and physical functions, to determine if the impairment is reversible [615]. Patients with reversible impairment (vulnerable patients) should be treated according to EAU Guidelines. Patients with irreversible impairment (frail patients) should receive adapted treatment [40].

Table 6.7.3: Performance Scales - Karnofsky & ECOG Scores [614]

Karnofsky Status	Karnofsky Grade	ECOG Grade	ECOG Status
Normal, no complaints.	100	0	Fully active, able to carry on all pre-disease performance without restriction.
Able to carry on normal activities. Minor signs or symptoms of disease.	90	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
Normal activity with effort.	80	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
Care for self. Unable to carry on normal activity or to do active work.	70	2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
Requires occasional assistance, but able to care for most of his needs.	60	2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
Requires considerable assistance and frequent medical care.	50	3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
Disabled. Requires special care and assistance.	40	3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
Severely disabled. Hospitalisation indicated though death nonimminent.	30	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
Very sick. Hospitalisation necessary. Active supportive treatment necessary.	20	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
Moribund	10	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.

6.7.1.2.6 Conclusions

Systematic assessment, using the G8 tool, is recommended by The SIOG PCWG [40]. Patients with G8 score < 14 should undergo complete geriatric assessment to evaluate reversibility of any impairments [40].

Senior adults can be classified into one of four groups regarding health status based on G8 score > 14 (patient considered fit), or score < 14 (patient considered vulnerable or frail). The treatment policy is then:

- fit or healthy older men should receive standard treatment;
- vulnerable patients may receive standard treatment after resolution of any geriatric problems;
- frail patients should receive adapted treatment;
- patients who are too sick with terminal illness should receive only palliative treatment [40].

After resolution of reversible impairments, a similar urological approach should be carried out in fit or vulnerable patients [1, 2]. Older men with PCa should be managed according to their individual health status, which is directed by the presence of any associated comorbidity and not age.

6.7.1.3 Guidelines for the evaluation of health status in elderly men

	LE	GR
Senior adults with localised PCa should systematically undergo health status screening	1b	A
Health status screening should be performed using the G8 screening tool	2a	A
Patients with G8 score ≤ 14 should undergo full specialist geriatric evaluation	2a	A
Senior adults can be classified as follows:	3	B
1. Fit or healthy older men, should receive standard treatment;		
2. Vulnerable patients (reversible impairment) may be given standard treatment after resolution of geriatric problems;		
3. Frail patients (irreversible impairment) should receive adapted treatment;		
4. Patients who are too sick with terminal illness should receive only symptomatic palliative treatment.		

6.7.2 Specific aspects of PCa treatment in older men

6.7.2.1 Localised PCa

6.7.2.1.1 Deferred treatment (active surveillance, watchful waiting)

This has been described in Chapter 8 and 9. Active treatment mostly benefits patients with intermediate- or high-risk disease and longest expected survival. A recent study assessed the effect of age, health status and patient preferences on outcomes of surgery vs active surveillance for low risk PCa. As expected, older age and worse baseline health status were associated with a smaller benefit in prostate-cancer-specific mortality and life expectancy with surgery, and increased incremental years with treatment side effects. Older men and men in poor health were likely to have better quality adjusted life expectancy with active surveillance [327].

6.7.2.1.2 Radical prostatectomy

Senior adults (aged ≥ 75 years) are more likely to present with very advanced disease and have a greater risk of death from PCa, despite higher death rates from competing causes [597]. In the most recent update of the SPCG-4 study, randomising patients with localised PCa to RP vs watchful waiting, the benefit of surgery with respect to death from PCa was largest in the men younger than 65 years of age (relative risk, 0.45). However, radical prostatectomy was associated with a reduced risk of metastases and use of androgen deprivation therapy among older men (relative risk, 0.68 and 0.60, respectively) [311]. Risk of short-term complications after RP is related more to comorbidity severity than age. Conversely, risk of long-term incontinence is influenced more by increasing age [616, 617].

6.7.2.1.3 External beam radiotherapy

External beam radiotherapy (EBRT) and RP have similar cancer control and treatment-related comorbidity, regardless of age, assuming a dose of > 72 Gy when using intensity-modulated or image-guided radiotherapy [618].

The drawback of associating ADT with EBRT in senior adults is discussed in Chapter 12. Cardiac status should be assessed because ADT in patients with pre-existing heart conditions is associated with increased morbidity and mortality. Patients with moderate to severe comorbidities might not have a significant survival-benefit when associating ADT with EBRT [413].

6.7.2.1.4 Minimally invasive therapies

Minimally invasive energy-ablative therapies are being developed rapidly, but there is still a lack of evidence to support their use.

6.7.2.1.5 Androgen deprivation therapy

In patients with non-metastatic localised PCa not suitable for curative treatment, immediate ADT should be used only in patients requiring symptom palliation. In locally advanced T3-T4 disease, immediate ADT may benefit patients with PSA > 50 ng/mL and PSA-DT < 12 months [619, 620].

6.7.2.2 Advanced PCa

6.7.2.2.1 Hormone-naïve metastatic PCa

ADT is the first-line treatment in hormone-sensitive metastatic PCa. The SIOG PCWG recommends evaluation of baseline bone mineral density and prevention of osteoporosis by calcium and vitamin D supplements [40].

Routine bisphosphonates or denosumab to prevent skeletal complications in ADT is not recommended, unless

there is a risk of fracture, or castration-resistant PCa (CRPC) with skeletal metastasis [621].

6.7.2.2.2 Metastatic CRPC

In metastatic CRPC, docetaxel is standard in fit and vulnerable older men [622], with comparable response and tolerance to younger patients [623]. Tolerability has not been specifically studied in frail older men. In elderly and frail patients, granulocyte colony-stimulating factor prophylaxis should be considered.

Cabazitaxel, abiraterone acetate, enzalutamide, and sipuleucel-T increase survival in chemotherapy-treated and chemotherapy-naïve senior adults [566, 567, 624-628].

Palliative treatment includes surgery, radiopharmaceuticals, EBRT, and medical treatment for pain and symptoms.

6.7.2.3 Guidelines for the treatment of prostate cancer in older men

Treatment	LE	GR
<i>Localised disease</i>		
Fit and vulnerable senior adults with life expectancy > 10 years and high-risk disease should be offered standard treatment.	2b	A
In frail or 'too-sick' patients, immediate ADT should only be used for symptom palliation.	1b	A
Minimally invasive energy-ablative therapies should not be routine in senior adults. These only have a role in selected fit and vulnerable senior adults with intermediate-risk disease.	3	B
<i>Advanced disease</i>		
Evaluation of bone mineral status and prevention of osteoporotic fracture are recommended in patients at high-risk of fractures.	2b	A
New chemotherapeutic and hormonal agents can be used in fit and vulnerable adults.	1b	B

ADT = androgen deprivation therapy; GR = grade of recommendation; LE = level of evidence.

6.8 Treatment: Post-treatment quality of life in patients with localised prostate cancer

6.8.1 Introduction

Increased life expectancy in PCa makes post-treatment QoL a key issue. Health-related QoL (HRQoL) refers to the impact of disease and treatment on well-being and physical, emotional and social functioning, including daily functioning [629]. HRQoL is rated by patients, and is important because physicians often underestimate the impact of disease and treatment on patients [630].

PCa-specific HRQoL refers to the disease-specific outcome of PCa, including urinary, bowel and sexual functioning. General HRQoL refers to well-being, vitality, fatigue, pain, general health status, global QoL, and life satisfaction [631].

HRQoL is measured using standardised questionnaires, which provide an objective assessment of general and disease-specific domains [632, 633].

Comparison of the most common contemporary therapies for localised PCa is necessary to inform patients about treatment options and address patient preferences for the various possible outcomes. There is still limited objective data about HRQoL in PCa treatment.

6.8.2 Active surveillance and watchful waiting

Although active surveillance (AS) and watchful waiting (WW) avoids treatment-related side effects, they carry an increased risk of psychological distress, which significantly affects HRQoL [634]. Risk factors for not doing well on AS include: patient perception that the physician is making most of the decisions, poor physical health, high anxiety, high PSA, lack of a partner, mental impairment, recent diagnosis of PCa, and lower number of core samples taken at diagnostic biopsy. These factors are significantly associated with low HRQoL [635, 636]. Anxiety and distress remained low during the first 9 months of AS [636].

In contrast to AS, men managed with WW in SPCG-4 were not followed closely to induce curative treatment if needed, which could explain the less favourable anxiety and depression scores compared to the PRIAS results [637].

A long-term comparison of WW and RP [637] found that depression, well-being and psychological status did not differ significantly among treatment groups over 8 years. However, men in the RP group reported more physical symptoms related to leakage, erection and libido.

Apart from psychological distress, untreated men may have a higher level of irritative/obstructive urinary symptoms compared to patients treated with RP or radiotherapy after 1-3 years [638].

6.8.3 **Radical prostatectomy**

RP has a significant negative effect on multiple QoL domains, including sexual and urinary function, and physical HRQoL [639-641]. In the Prostate Cancer Outcomes Study (PCOS), at 2 years 8.7% of men had a lack of urinary control and 41.9% reported sexual dysfunction [642]. Recovery from sexual dysfunction and urinary incontinence occurs over 2-3 years [617, 643], with the latter being at its worst by 2 months after surgery [639].

Although some advances have reduced these side effects, such as nerve-sparing RP or robot-assisted radical prostatectomy (RALP), their impact on HRQoL remains controversial. Preserving neurovascular bundles aims to reduce erectile dysfunction [639, 644] and improves urinary function [645]. RALP and open RP have comparable functional outcomes and similar HRQoL scores [646]. There is no reliable data to compare HRQoL following RALP and laparoscopic RP. General HRQoL domains such as pain and energy worsen immediately post-RP, but usually improve by 12 months [643, 647].

New methods for reporting outcomes after RP combine major outcomes, including continence, potency and cancer control [309] and perioperative complications and positive surgical margins [648]. Pentafecta rates reflect postoperative expectations and satisfaction more accurately and are used in counselling patients with clinically localised PCa. The use of trifecta and pentafecta outcomes in postoperative HRQoL assessment needs further validation.

6.8.4 **External-beam radiotherapy and low-dose rate brachytherapy**

EBRT and I-125 low-dose rate (LDR) brachytherapy may cause urinary, sexual- and bowel dysfunction. Both methods can result in irritative voiding symptoms, such as urgency, frequency, and urge incontinence, that negatively affect overall urinary function and HRQoL [639]. In the radiotherapy group, urinary incontinence was reported to be at its worst by 2 months after surgery, but the effects of EBRT on urinary symptoms had resolved at 12 months and improved over baseline at 24 months [639]. Patients in the LDR brachytherapy group reported significant detriments in urinary irritation or obstruction and incontinence. At 1-2 years after LDR brachytherapy, incontinence was reported by 4-6% of patients. Eighteen percent of the LDR brachytherapy group and 11% of the EBRT group reported distress from overall urinary symptoms at 1 year [639].

EBRT and LDR brachytherapy significantly affected the bowel and rectal HRQoL domains [639], which were almost as important as urinary problems [649, 650]. Symptom onset occurred during or early after treatment, and sometimes persisted into follow-up. Rectal urgency, frequency, pain, faecal incontinence, or haematochezia-caused distress related to bowel function was reported in 9% of patients at 1 year after EBRT or LDR brachytherapy [639]. At 2 years after dose-escalated EBRT, $\leq 11\%$ of patients had problems with bowel HRQoL. Bowel HRQoL was related to baseline function, $\leq 25\%$ volume of rectum treated with 70 Gy, and aspirin [651]. Bowel and rectal symptoms were less severe after LDR brachytherapy than EBRT [632].

Significant deterioration in HRQoL was reported at 6 years after I-125 LDR brachytherapy, including urinary and bowel symptoms, pain, physical functioning, and sexual activity [652]. HRQoL scores returned close to baseline at 1 year and remained stable up to 6 years after treatment. The only clinically relevant changes occurred in emotional functioning and sexual activity. Dietary intervention did not significantly affect gastrointestinal side effects or other aspects of HRQoL in patients undergoing RT [653].

Adjuvant androgen suppression may exacerbate the adverse effects of EBRT or LDR on sexuality, vitality [639] and long-term bowel function [654].

Fatigue is commonly reported following EBRT, with the highest level seen at the end of treatment. 4% of patients reported severe fatigue 5-years post-treatment, adversely affecting QoL [655]. Men treated with interstitial LDR brachytherapy had only slight declines in general HRQoL. Physical and functional status declines have been reported in the first few months after implantation, but pretreatment function was regained by most men after 1 year [652].

6.8.4.1 **Radiotherapy toxicity**

Patients must be informed about acute and late genitourinary or gastrointestinal toxicity and the impact of irradiation on erectile function. In contemporary practice, the NCIC toxicity grading system is increasingly used, but most studies have used the RTOG scales, which are described in Tables 6.8.1 and 6.8.2. Risk factors for acute or late gastrointestinal toxicities after RT include advanced age, preexisting diabetes mellitus, haemorrhoids, inflammatory bowel disease, a history of prior abdominal surgery, larger rectal volume and the concomitant use of androgen deprivation [466].

Pre-treatment genitourinary complaints, prior transurethral resection of the prostate and the presence of acute genitourinary toxicity are suggested as contributing to long-term urinary morbidity.

Table 6.8.1: Acute gastrointestinal and genitourinary complications according to the Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer morbidity scale (adaptations with regard to the original RTOG scale in italics) according to Huang et al. [656]*

	Grade 1	Grade 2	Grade 3	Grade 4
GI	Increased frequency or change in quality of bowel habits not requiring medication. Rectal discomfort not requiring analgesics.	Diarrhoea requiring parasympatholytic drugs. Mucous discharge not necessitating sanitary pads. Rectal or abdominal pain requiring analgesics.	Diarrhoea requiring parenteral support. Severe mucous or blood discharge necessitating sanitary pads. Abdominal distension (flat plate radiograph demonstrates distended bowel loops).	Obstruction, fistula, or perforation GI bleeding requiring transfusion; Abdominal pain or tenesmus requiring tube decompression or bowel diversion.
GU	Frequency of urination or nocturia twice pretreatment habit. Dysuria or urgency not requiring medication.	Frequency of urination is less frequent than every hour (<i>day: 12-16 times; nocturia 5-8 times</i>). Dysuria, urgency, bladder spasm requiring local anaesthetic.	Frequency of urination is more frequent than every hour (<i>day: > 16 times; nocturia: > 8 times</i>). Dysuria, bladder spasm, urgency requiring frequent regular narcotic. Gross haematuria <i>complaints requiring permanent or suprapubic catheter.</i>	Haematuria requiring transfusion. Obstruction not resulting from clots. Ulceration Necrosis

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GI = gastrointestinal; GU = genitourinary.

Table 6.8.2: Late gastrointestinal and genitourinary complications according to the Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer (EORTC) morbidity scale (adaptations with regard to the original RTOG/EORTC scale in *italics*) according to Huang et al. [656]*

	Grade 1	Grade 2	Grade 3	Grade 4
GI*	Mild diarrhoea Mild cramping Bowel movements 2-5 per day Slight rectal discharge or bleeding	Moderate diarrhoea Intermittent, severe cramping. Bowel movements (5 per day). <i>Moderate excessive, rectal discharge. Intermittent, frequent bleeding (3 single laser treatments or transfusion).</i>	<i>Watery diarrhoea</i> Obstruction requiring surgery. Bleeding requiring surgery or 2 <i>laser treatments or transfusions.</i>	Necrosis Perforation Fistula <i>Abdominal pain or tenesmus requiring tube decompression or bowel diversion.</i>
GU	<i>Frequency during day 0.5-1 h</i> <i>Nocturia 2-3/night</i> <i>Slight dysuria or microscopic haematuria requiring no medication</i> <i>Slight epithelial atrophy, minor telangiectasia</i> <i>Bladder capacity > 300 mL</i>	<i>Frequency during day: 1-2 h</i> <i>Nocturia 4-6/night</i> <i>Moderate dysuria or intermittent (mild, moderate) haematuria requiring medication†</i> <i>Moderate telangiectasia</i> <i>Bladder capacity: 150-300 mL</i>	<i>Frequency during day: 2 h</i> <i>Nocturia 6/night</i> Severe dysuria Frequent (severe) haematuria Severe telangiectasia Bladder capacity: 100-150 mL <i>Benign urethral strictures requiring TURP, dilation, or suprapubic or permanent catheter</i>	Necrosis Severe haemorrhagic cystitis Bladder capacity > 100 mL

* The difference between grade 1 and grade 2 GI pain, mucosal loss, or bleeding is most easily made when grade 2 is defined as morbidity requiring specific medication: grade 1 = stool softener, diet modification, occasional (< 2/wk) non-narcotic drug, occasional antidiarrhoeal agent (2/wk), occasional use of incontinence pads (1-2 d/wk); grade 2 = regular (> 2/wk) use of (non)narcotic drugs for pain, regular (2/wk) antidiarrhoeals, steroid suppositories, one laser.

† With the exception of antibiotics.

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GI = gastrointestinal; GU = genitourinary; TURP = transurethral resection of the prostate.

6.8.5 Complications of high-intensity focused ultrasound

Urinary retention appears to be one of the most common side-effects of HIFU, developing in almost all patients, with the mean interval of catheterization via a suprapubic tube varying between 12 and 35 days [511, 514, 515]. Grade I and II urinary stress incontinence occurs in about 12% of patients. Subsequent TURP or bladder neck incision to treat subvesical obstruction is common, and is sometimes even performed at the time of HIFU. Post-operative impotence occurs in 55-70% of patients.

Elterman et al. [657] have treated 95 patients with clinically organ-confined PCa using the Sonablate 500 device (SonaCare Medical, Charlotte, NC, USA) and have evaluated the type and frequency of treatment-associated complications. With a minimum follow-up of six months, 17% (7/41) of the men had significant incontinence, and 2% developed significant erectile dysfunction. Early and late subvesical obstruction necessitating surgical treatment occurred in 17 (17.9%) and 20 (21.1%) patients, respectively.

Moderate to severe stress urinary incontinence was rare, occurring in fewer than 6.4% of men, and decreased in more recent treatment to 3.1% [517]. Acute urinary retention was seen in 7.6% of men. Even in more recent treatment, the rate of urethral-rectal fistula was 0.7%.

6.8.6 Cryotherapy

Quality of life and sexuality following CSAP were investigated in a clinical phase II trial that recruited 75 men [658]. Quality-of-life analysis by the prostate-specific FACT-P questionnaire showed that most subscales return to pre-treatment levels by 12 months after CSAP. Furthermore, no significant changes were seen when

comparing data at 36 months with those at 12 months. With regard to sexuality, 37% of men were able to have intercourse three years after CSAP.

In a prospective, randomised clinical trial, 244 men with newly diagnosed organ-confined PCa were randomised to receive either external-beam radiation therapy (EBRT) or to undergo CSAP [659]. After a follow-up of three years, sexual function was significantly less impaired in the EBRT group.

6.8.7 Hormonal therapy

There is a lack of data on the effects of hormonal treatment on QoL, with only a single, large, prospective, RCT comparing orchiectomy + flutamide or placebo in M1 patients. Combined therapy resulted in a lower QoL in the first 6 months, with more frequent diarrhoea and worse emotional functioning, compared with castration alone [660]. A small RCT evaluated the health-related quality of life (HRQoL) at 1-year follow-up in patients with non-localised PCa, between various ADT, or no treatment. Both sexual and cognitive function significantly declined with ADT, while emotional distress significantly increased if no treatment [661]. A prospective observational study of non-metastatic PCa, found that immediate ADT was associated with a lower overall QoL compared to deferred treatment [662]. Another retrospective, non-randomised study suggested that men receiving LHRH agonists reported more worry and physical discomfort and poorer overall health, and were less likely to believe themselves free of cancer than did orchiectomised patients. The stage at diagnosis had no effect on health outcome [663].

Using a specific non-validated questionnaire, bicalutamide monotherapy showed a significant advantage over castration in the domains of physical capacity and sexual interest (not sexual function) at 12 months [664]. A post-hoc analysis, including only patients with sexual interest suggested that bicalutamide was associated with better sexual preservation, including maintained sexual interest, feeling sexually attractive [665], preserved libido and erectile function [666].

Intermittent androgen deprivation has been discussed elsewhere (see Section 6.6 - Metastatic Prostate Cancer - Hormonal therapy).

6.8.7.1 Side-effects, quality of life and cost of hormonal therapy

The many deleterious side-effects of long-term ADT have been well known for years. As the use of ADT increases, it is increasingly important to consider these side-effects. A systematic review of the side-effects of long-term ADT has been recently published [667].

6.8.7.1.1 Sexual function

Loss of libido and erectile dysfunction are usual. The management of acquired erectile dysfunction is mostly non-specific [668].

6.8.7.1.2 Hot flushes

They are the most common side-effect of ADT. They appear 3 months after starting ADT, usually persist long-term and have may a significant impact on QoL.

Oestrogen-receptor modulators or low-dose oestrogen therapies, e.g. DES, 0.5-1 mg/day, reduce the frequency and severity of hot flushes. Both treatments carry a risk of cardiovascular complications. Soya phytoestrogens have shown an efficacy in breast cancer patients, but have not been evaluated in men. Progesterone-based treatments have demonstrated efficacy with 80% of patients showing an improvement [669].

Serotonin reuptake inhibitors (e.g. venlafaxine or sertraline) appear to be effective in men, but less than hormonal treatments based on a prospective randomised trial comparing venlafaxine, 75 mg daily, with medroxyprogesterone, 20 mg daily, or CPA, 100 mg daily [670]. After 6 months of LHRH (n = 919), 311 men had significant hot flushes and were randomised to one of the treatments. Venlafaxine was clearly inferior compared to the hormonal agents, which showed similar efficacy to each other.

With a placebo effect influencing up to 30% of patients [671], the efficacy of clonidine, veralipride, gabapentine [672] and acupuncture [673] must be compared in prospective, randomised, controlled trials.

6.8.7.1.3 Other systemic side-effects of androgen-deprivation therapy

They are frequent and may lead to significantly increased morbidity or even mortality.

6.8.7.1.3.1 Non-metastatic bone fractures

Due to increased bone turnover and decreased BMD in a time-dependent manner, ADT use is linked to an increased risk of fracture (up to 45% relative risk with long-term ADT [674]). Hip fractures in men are associated with a significant risk of death [675]. A precise evaluation of BMD should be performed by dual emission X-ray absorptiometry (DEXA) before starting long-term ADT. An initial low BMD (T-score < -2.5 or < -1, with other risk

factors) indicates a high risk of subsequent non-metastatic fracture. The WHO FRAX tool (<http://www.shef.ac.uk/FRAX>) should be used to evaluate individual risk. Obesity (increase in body fat mass by up to 10%) and sarcopenia (decrease in lean tissue mass by up to 3%) are common and occur during the first year of ADT [676]. Both changes increase the fracture risk.

- Lifestyle changes before starting long-term androgen-deprivation therapy

Patients should be encouraged to adopt lifestyle changes, e.g. increased physical activity, cessation of smoking, decreased alcohol consumption, and to normalise their body mass index. Calcium and vitamin D supplements should be considered if low values are detected. (Normal values: calcium: 2.2-2.6 nmol/L, vitamin D: 100-160 nmol/L). A daily intake of at least 1200 mg/day of calcium and 1000 UI of vitamin D is useful.

- Hormonal treatment modalities

Bicalutamide monotherapy could be a bone-protective treatment [677, 678], but is limited by its suboptimal efficacy (see Section 6.6 - Metastatic Prostate Cancer - Hormonal Therapy).

The intermittent modality might be associated with less bone impact [589].

- Bisphosphonates

Bisphosphonates increase BMD in the hip and spine by up to 7% in 1 year. The optimal regimen for zoledronic acid remains unclear: quarterly [679] or yearly [680] injections. The question is relevant as the risk of jaw necrosis is both dose- and time-related [681]. A quarterly regimen could be considered for a BMD ≤ 2.5 as a yearly injection is unlikely to provide sufficient protection [682].

In contrast to breast cancer, a significant benefit in OS has only been demonstrated in PCa in a post-hoc analysis for the oral first-generation clodronate with an absolute 8% OS increase after 8 years of follow-up [683]. This benefit has never been observed with more recent bisphosphonates.

- Denosumab (a fully human monoclonal antibody against RANKL)

In M0 patients, Denosumab has been shown to increase the lumbar BMD by 5.6% compared to a 1% decrease in the placebo arm after 2 years, using a 60 mg subcutaneous regimen every 6 months [684]. This was associated with a significant decrease in vertebral fracture risk (1.5% vs 3.9%, $p = 0.006$). The benefits were similar whatever the age ($<$ or $>$ 70 years), the duration or type of ADT, the initial BMD, the patient's weight or the initial BMI. This benefit was not associated with any significant toxicity, e.g. jaw osteonecrosis or delayed healing in vertebral fractures. In M0 patients, with the use of a higher dosage (120 mg every 4 weeks), a delay in bone metastases of 4.2 months has been shown [685] without any impact on OS, and with increased side effects. Therefore, this regimen cannot be recommended.

6.8.7.1.3.2 Metabolic effects

Lipid alterations are common and may occur as early as the first 3 months of treatment [676]. ADT also decreases insulin sensitivity and increases fasting plasma insulin levels, which is a marker of insulin resistance. Once again, exercise is strongly recommended for its protective effect. In diabetic patients, metformin appears to be an attractive option for protection against metabolic effects [686], but there is insufficient data to recommend its use in non-diabetic patients.

Metabolic syndrome is an association of independent cardiovascular disease risk factors, often associated with insulin resistance. The definition requires at least three of the following criteria [687]:

- waist circumference > 102 cm;
- serum triglyceride > 1.7 mmol/L;
- blood pressure $> 130/80$ mmHg or use of medication for hypertension;
- HDL cholesterol < 1 mmol/L;
- glycaemia > 5.6 mmol/L or the use of medication for hyperglycaemia.

The prevalence of a metabolic-like syndrome is higher during ADT compared with men not receiving ADT [688].

6.8.7.1.3.3 Cardiovascular morbidity

Cardiovascular mortality is now the most common cause of death in PCa patients, even exceeding PCa mortality [689]. Several studies showed that ADT, even after only 6 months, was associated with an increased risk of diabetes mellitus, cardiovascular disease, and myocardial infarction [690]. The RTOG 92-02 [691] and 94-08 [396] confirmed an increased cardiovascular risk, unrelated to the duration of ADT and not accompanied by an overall increased cardiovascular mortality. No increase in cardiovascular mortality has been reported in a systematic meta-analysis of trials RTOG 8531, 8610, 9202, EORTC 30891 or EORTC 22863 [692]. However, an increase in cardiovascular mortality has been reported in patients suffering from previous congestive

heart failure or myocardial infarction in a retrospective database analysis [693] or presenting with a metabolic syndrome [694].

It has been suggested that LHRH antagonists might be associated with less cardiovascular morbidity compared to agonists [695]. However, the used methodology does not provide convincing evidence to show a clear superiority of these compounds.

These data resulted in an FDA warning and consensus paper from the American Heart, Cancer Society and Urological Associations [696]. Preventive advice includes non-specific measures: loss of weight, increased exercise, improved nutrition and smoking cessation.

6.8.7.1.3.4 Fatigue

Fatigue often develops as a side-effect of ADT. Regular exercise appears to be the best protective measure [697, 698], with prolonged efficacy [699] and improved specific survival [700].

Anaemia may be a cause of fatigue. Anaemia requires an etiological diagnosis (medullar invasion, mainly inflammatory, renal insufficiency, iron deficiency, chronic bleeding) and individualised treatment. Iron supplementation (using injectable formulations only) must be systematic if deficiency is observed. Regular blood transfusion is required if severe anaemia is present. Erythropoiesis-stimulating agents might be considered in dedicated cases, taking into account the possible increased risk of thrombovascular events [667].

6.8.8 **Comparison of health-related quality of life between treatment modalities**

So far, any comparisons between treatment-related QoL were assessed in non-randomised observational cohorts, with limited follow-up. Only a few trials have directly compared treatment modalities but longer follow-up is needed. When comparing general HRQoL for treatments of clinically localised PCa [631, 701] the differences were limited. Data from longitudinal studies show that surgery and radiotherapy have a greater impact on role functioning and vitality/energy with surgery being associated with increased dysfunction [647]. Most men recovered function by 1 year after treatment.

QoL outcomes have been reported for RP or EBRT [642]. At 5 years after diagnosis, sexual function declined similarly in both groups. Erectile dysfunction was more prevalent in the RP group (79.3% vs 63.5%). Incontinence was reported in 14-16% of RP and 4% of EBRT patients at 5 years. Bowel urgency and painful haemorrhoids were more common in the EBRT group. At 15 years, there were no significant differences between RP and EBRT [34]. RP incurred a significantly higher incidence of urinary incontinence (39-49%) and erectile dysfunction (80-91%) compared with radiotherapy (6-7% and 41-55%, respectively) [649]. Bowel problems (urgency) affected 30-35% of the EBRT group vs. 6-7% of the RP group [649].

Patients treated with LDR brachytherapy had significantly higher urinary function scores at 0-6 months after treatment (84.5%) than patients treated with RP (63.3%) [702]. Urinary bother did not differ significantly (67.7% vs. 67.4%, respectively). Decreased sexual function did not return to pretreatment levels in either group.

Urinary incontinence increased at 2 years after RP, whereas bowel problems and urinary irritation-obstruction occurred after EBRT and LDR brachytherapy [632]. Sexual function deteriorated immediately after surgery and then improved, whereas sexual function continued to slowly decline after EBRT and brachytherapy. There was no change in urinary function and little change in bowel function after 1 year. Patients with bowel dysfunction at 1 year after EBRT may expect modest improvement. Although diarrhoea continues to subside, there is little change in tenesmus and rectal urgency, while rectal bleeding becomes more prevalent.

Three years follow-up confirmed long-term changes in adverse effects, e.g., increased urinary symptoms after EBRT or increased sexual dysfunction after LDR brachytherapy, which tended to reduce any differences between treatments over time [703]. RP caused greater deterioration in urinary incontinence and sexual function, but improved urinary irritative-obstructive symptoms compared with LDR brachytherapy. Treatment differences persisted for up to 3 years [703].

A comparative trial of RP and LDR brachytherapy was closed after 2 years due to poor accrual [704]. For LDR brachytherapy vs. RP, there were no differences in bowel or hormonal domains. The LDR brachytherapy patients scored better for the urinary QoL and sexual domains, and patient satisfaction.

A study in Norway investigated the relationship between urinary, bowel or sexual dysfunction and global QoL in PCa survivors, including untreated patients [638]. The RP group reported more urinary incontinence than other groups, but had the lowest level of urinary irritative-obstructive symptoms. Untreated patients had the highest level of these symptoms. The radiotherapy group reported more intestinal irritation and faecal leakage than the RP and untreated groups. In all groups, poor sexual drive and erectile function were common, with

the RP group reporting the highest prevalence of erectile dysfunction. Irritative-obstructive urinary symptoms and poor sexual drive were independently associated with low global QoL, whereas erectile function and use of medication for erectile dysfunction were not [638].

All typical adverse events (moderate/severe IPSS, urinary incontinence, irritative intestinal symptoms, faecal leakage, poor sexual drive and poor erectile function) were significantly associated with low global QoL in univariate analyses. Low educational level, comorbidity and moderate or high neuroticism were all significantly associated with low global QoL in univariate analyses. No significant associations with global QoL were observed for age, a paired relationship or D'Amico risk group.

LDR brachytherapy and prostate cryoablation were associated with better urinary function and bother scores compared to open RP and laparoscopic and robotic radical prostatectomy in a non-randomised cohort of patients [705]. LDR brachytherapy was associated with higher sexual function and bother scores compared to other treatments. The study used the UCLA-PCI questionnaire, which does not evaluate irritative urinary symptoms, which are often observed after LDR brachytherapy [702]. This may have significantly compromised the results of the HRQoL assessment.

Many men treated for clinically localised PCa experience post-treatment problems that may affect their daily lives. Each patient must decide which side-effect profile is most acceptable when making treatment decisions.

6.8.9 Guidelines on quality of life in prostate cancer management

	LE	GR
Patients with low-risk PCa should be informed that functional outcome of active surveillance is better than for local active treatment.	2	B
Patients should be informed that functional outcome after RALP and open prostatectomy are similar.	2	B
Patients should be informed that long-term (15 years) QoL outcomes of EBRT and RP are similar.	2	B

EBRT = external beam radiation therapy; GR = grade of recommendation; LE = level of evidence; RALP; RP = radical prostatectomy; QoL = quality of life.

6.9 Summary of guidelines for the primary treatment of prostate cancer

EAU risk groups for biochemical recurrence of localised and locally advanced prostate cancer

	Low-risk	Intermediate-risk	High-risk
Definition	PSA < 10 ng/mL and GS < 7 and cT1-2a	PSA 10-20 ng/mL or GS 7 or cT2b	PSA > 20 ng/mL or GS > 7 or cT2c
	Localised		Locally advanced

Primary treatment of prostate cancer			Gr
General comments	Patients suitable for several treatment modalities (active surveillance, surgery, radiotherapy) must have these options discussed with them.		A*
	In patients who are surgical candidates for radical prostatectomy, all approaches (i.e. open, laparoscopic or robotic) are acceptable as no single approach has shown clear superiority in terms of functional or oncological results.		A
	EBRT should be offered in all risk groups of non-metastatic PCa.		A
	IMRT is the recommended modality for definitive treatment of PCa by EBRT.		A
	Treatment	Comment	
Low risk PCa	Watchful waiting	Watchful waiting may be offered to patients not eligible for local curative treatment and those with a short life expectancy.	A
		During watchful waiting, the decision to start non-curative treatment should be based on symptoms and disease progression.	B
	Active surveillance	Active surveillance is an option in patients with the lowest risk of cancer progression: > 10 years life expectancy, cT1/2, PSA ≤ 10 ng/mL, biopsy Gleason score ≤ 6, ≤ 2 positive biopsies, minimal biopsy core involvement (≤ 50% cancer per biopsy).	A

		Follow-up should be based on DRE, PSA and repeat biopsies. The optimal follow-up interval is still unclear.	A
	Radical prostatectomy	In patients with a life expectancy > 10 years, RP should be offered.	A
		Nerve-sparing surgery may be attempted in pre-operatively potent patients with low risk for extracapsular disease (T1c, GS < 7 and PSA < 10 ng/mL, or refer to Partin tables/nomograms).	B
		LND is not indicated in low-risk PCa	A
	Radiotherapy	In low-risk PCa the total dose should be 74 to 78 Gy.	A
		In patients with low-risk PCa, without a previous TURP and with a good IPSS and a prostate volume < 50 mL, LDR brachytherapy is a treatment option.	A
	Cryotherapy, HIFU	In patients who are unfit for surgery or radiotherapy, cryotherapy or HIFU might be an alternative treatment for PCa. The lack of long-term efficacy compared to standard modality has to be discussed with patients.	C
	Focal treatment	Focal therapy of PCa is still in its infancy and cannot be recommended as a therapeutic alternative outside clinical trials.	A
Intermediate risk PCa	Androgen suppression	Unsuitable.	A
	Watchful waiting	Watchful waiting may be offered to patients not eligible for local curative treatment and those with a short life expectancy.	A
	Active surveillance	Not an option.	A
	Radical prostatectomy	In patients with a life expectancy > 10 years, RP should be offered.	A
		Nerve-sparing surgery may be attempted in pre-operatively potent patients with low risk for extracapsular disease (T1c, GS < 7 and PSA < 10 ng/mL, or refer to Partin tables/nomograms).	B
		Multiparametric MRI may help in deciding when to perform nerve-sparing procedures in intermediate- and high-risk disease.	B
		eLND should be performed if the estimated risk for positive lymph nodes exceeds 5%.	B
		Limited LND should not be performed.	A
		In patients with pT3,N0M0 PCa and an undetectable PSA following RP, adjuvant external beam irradiation should be discussed as an option because it improves at least biochemical-free survival.	A
		Patients with pT3,N0M0 PCa and an undetectable PSA following RP should be informed about salvage irradiation as an alternative to adjuvant irradiation when PSA increases.	A
		Adjuvant HT for pN0 is not recommended.	
	Radiotherapy	In intermediate-risk PCa the total dose should be 76-78 Gy, in combination with short-term ADT (4-6 mo).	A
	Androgen suppression monotherapy	No place in asymptomatic patients.	A
High risk PCa	Watchful waiting	High risk localised: Watchful waiting may be offered to patients not eligible for local curative treatment and those with a short life expectancy.	
		High risk locally advanced: In M0 patients unwilling or unable to receive any form of local treatment, a deferred treatment policy using ADT as monotherapy is feasible in asymptomatic patients with a PSA-DT > 12 months and a PSA < 50 ng/mL and non-poorly differentiated tumour.	A
	Active surveillance	Not appropriate.	A
	Radical prostatectomy	NHT before RP is not recommended.	A

		eLND should be performed in high-risk PCa.	A
		Limited LND should not be performed.	A
		High risk localised: In patients with high-risk localised PCa and a life expectancy of > 10 yr, RP should be offered in a multimodality setting.	B
		Nerve-sparing surgery may be attempted in pre-operatively potent patients with low risk for extracapsular disease (refer to Partin tables/nomograms).	B
		Multiparametric MRI may help in deciding when to perform nerve-sparing procedures in intermediate- and high-risk disease.	B
		High risk locally advanced: In highly selected patients with locally advanced PCa (cT3b-T4 N0 or any T N1), RP may be offered in a multimodality setting.	C
		In patients with pT3,N0M0 PCa and an undetectable PSA following RP, adjuvant external beam irradiation should be discussed as an option because it improves at least biochemical-free survival.	A
		Patients with pT3,N0M0 PCa and an undetectable PSA following RP should be informed about salvage irradiation as an alternative to adjuvant irradiation when PSA increases.	A
	Radiotherapy	In patients with high-risk localised PCa, the total dose is 76-78 Gy in combination with long-term ADT (2-3 yr is recommended).	A
		In patients with locally advanced cN0 PCa, radiotherapy must be given in combination with long-term ADT (2-3 yr is recommended).	A
	Androgen suppression monotherapy	Reserved for those unwilling or unable to receive any form of local treatment and either symptomatic or asymptomatic with a PSA-DT < 12 months and a PSA > 50 ng/mL and a poorly differentiated tumour.	A
N1 patients			
cN1	In patients with cN+ PCa, pelvic external irradiation can be given in combination with immediate long-term ADT.		B
pN1 after eLND	Adjuvant ADT is the standard of care for node-positive (pN+) patients.		A
	Adjuvant ADT with additional radiotherapy may have a role.		B
	Expectant management is optional when the patient has undergone eLND and ≤ 2 nodes show microscopic involvement and a PSA < 0.1 ng/mL and absence of extranodal extension.		B
Metastatic PCa	Watchful waiting	In M1 asymptomatic patients, deferred castration should be discussed with a well-informed patient.	B
	Active surveillance	Unsuitable.	A
	Radical prostatectomy	Unsuitable outside clinical trial.	A
	Radiotherapy to the prostate	Unsuitable outside clinical trial.	A
	Androgen suppression	Surgical- or medical castration (LHRH agonist or antagonist).	A
		No recommendation can be made to define the best population for combining castration with upfront Docetaxel.	A
		Castration combined with local treatment / other new hormonal treatments (abiraterone acetate or Enzalutamide) should not be used outside clinical trials.	A
		In M1 asymptomatic patients, immediate castration should be offered to defer progression to a symptomatic stage and prevent serious disease progression-related complications.	A
		In M1 symptomatic patients, immediate castration should be offered to palliate symptoms and reduce the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, extraskeletal metastasis).	A

	In M1 patients, short-term administration of anti-androgens is recommended to reduce the risk of the 'flare-up' phenomenon in patients with advanced metastatic disease who are to receive an LHRH agonist.	A
	In M1 patients short-term administration of anti-androgens should be given for some weeks only (starting treatment on the same day as an LHRH analogue is started or for up to 7 days before the first LHRH analogue injection).	A
	In M1 patients, administration of anti-androgens as monotherapy should not be considered.	A
	In asymptomatic M1 patients, intermittent treatment can be offered to highly motivated men, with a major PSA response after the induction period.	B
	Based on the schedules in use in clinical trials, treatment is stopped when the PSA is < 4 ng/mL after 6 to 7 months of treatment. Treatment is resumed when the PSA is > 10-20 ng/mL.	C
	Combined treatment with LHRH agonists and NSAA is recommended.	A
	Antagonists might be an option.	B
Castrate resistant status	Patients should not be started on second-line therapy unless their testosterone serum levels are < 50 ng/dL.	A
	There is no evidence for treatment of non-metastatic CRPC outside a clinical trial.	A
	Patients with mCRPC should be counseled, managed and treated by a multidisciplinary team.	A
	Men treated with maximal androgen blockade should stop the anti-androgen therapy once PSA progression is documented. <i>Comment: Four to six weeks after discontinuation of flutamide or bicalutamide, an eventual anti-androgen withdrawal effect will be apparent.</i>	A
	No clear-cut recommendation can be made for the most effective drug for secondary treatment (i.e. hormone therapy or chemotherapy) as no clear predictive factors exist.	A
	Salvage hormonal treatment using abiraterone acetate is a valid option.	A
	Salvage hormonal treatment using enzalutamide is a valid option.	A
	In patients with metastatic CRPC who are candidates for salvage cytotoxic therapy, docetaxel at 75 mg/m ² every 3 weeks has shown a significant survival benefit.	A
	In patients with relapse following salvage docetaxel chemotherapy, cabazitaxel, abiraterone acetate and enzalutamide are regarded as first-choice options for second-line treatment in mCRPC.	A
	In men with mCRPC and with symptomatic bone metastases, who are ineligible for or progressing after docetaxel, treatment with Ra 223 (alpharadin) has shown a survival benefit.	A
	Bone protective agents may be offered to patients with skeletal metastases (denosumab being superior to zoledronic acid) to prevent osseous complications. However, the benefits must be balanced against the toxicity of these agents, and jaw necrosis in particular must be avoided.	A
	Calcium and vitamin D supplementation must be systematically considered when using either denosumab or bisphosphonates.	A
	In patients with neurological symptoms, spinal surgery or decompressive radiotherapy might be indicated as emergency interventions. High-dose corticosteroids must always be initially considered.	A

A* Upgraded following panel consensus.

ADT = androgen deprivation therapy; DRE = digital rectal examination; EBRT = external beam radiation therapy; HIFU = high-intensity focused ultrasound; LHRH = luteinising-hormone-releasing hormone; LND = (extended) lymph node dissection; mCRPC = metastatic castrate-resistant prostate cancer; MRI = magnetic resonance imaging; NHT = neoadjuvant hormonal therapy; NSAA = non-steroidal anti-androgen; PSA-DT = PSA doubling time; RP = radical prostatectomy; TURP = transurethral resection of the prostate.

Guidelines for the treatment of senior adults (> 70 years of age)

	GR
Senior adults with localised PCa should systematically undergo health status screening	A
Health status screening should be performed using the G8 screening tool	A
Patients with G8 score ≤ 14 should undergo full specialist geriatric evaluation	A
Senior adults can be classified as follows: 1. Fit or healthy older men, should receive standard treatment; 2. Vulnerable patients (reversible impairment) may be given standard treatment after resolution of geriatric problems; 3. Frail patients (irreversible impairment) should receive adapted treatment; 4. Patients who are too sick with terminal illness should receive only symptomatic palliative treatment.	B

Treatment	LE	GR
<i>Localised disease</i>		
Fit and vulnerable senior adults (after status optimisation) with life expectancy > 10 years and high-risk disease should be offered standard treatment.	2b	A
In frail or 'too-sick' patients, immediate ADT should only be used for symptom palliation.	1b	A
Minimally invasive energy-ablative therapies should not be routine in senior adults. These only have a role in selected fit and vulnerable senior adults with intermediate-risk disease.	3	B
<i>Advanced disease (locally advanced / metastatic disease)</i>		
Evaluation of bone mineral status and prevention of osteoporotic fracture are recommended in patients at high-risk of fractures.	2b	A
New chemotherapeutic and hormonal agents can be used in fit and vulnerable adults.	1b	B

DT = doubling time; NHT = neoadjuvant hormonal treatment; GR = grade of recommendation;

IPSS = International Prostatic Symptom Score; LE = level of evidence; PSA = prostate specific antigen; TRUS = transrectal ultrasound; TURP = transurethral resection of the prostate.

6.10 Treatment of PSA-only recurrence after treatment with curative intent

6.10.1 Background

Primary curative procedures such as RP, and RT are well-established therapeutic options in the management of localised PCa. Despite technical improvements, there is still a significant risk of cancer recurrence after therapy. Between 27% and 53% of all patients undergoing RP or RT develop PSA-recurrence (see Sections 6.2 and 6.3). While a rising PSA level universally antedates metastatic progression and prostate-cancer-specific mortality (PCSM), physicians must inform the patient that the natural history of PSA-only recurrence may be prolonged and that a PSA rise is not a surrogate for these survival endpoints. Physicians treating patients with PSA-only recurrence face a difficult set of decisions in attempting to delay the onset of metastatic disease and death while avoiding over-treating patients whose disease may never affect their OS or QoL. It has to be emphasised that the treatment recommendations for these patients should be given after discussion with a multidisciplinary team.

6.10.2 Definitions

6.10.2.1 Definition of biochemical failure

The PSA level that defines treatment failure differs between men who have undergone RP and those who have received RT. However, following RP, there is international consensus that recurrent cancer may be defined by two consecutive PSA values of > 0.2 ng/mL and rising [706]. Although a retrospective analysis including 2,782 men who had undergone RP for clinically localised PCa [707] was used to determine the best PSA cut-off point for defining BCR. Once PSA recurrence was detected, there was a subsequent increase in PSA in 49%, 62%, and 72% of patients with PSA levels of 0.2, 0.3, and 0.4 ng/mL, respectively [707].

After primary RT, with or without short-term hormonal manipulation, the RTOG-ASTRO Phoenix Consensus Conference definition of PSA failure (with an accuracy of > 80%) is any PSA increase ≥ 2 ng/mL higher than the PSA nadir value, regardless of the serum concentration of the nadir [708].

Importantly, patients with PSA-recurrence after RP or primary RT have different risks of subsequent PCSM. Therefore, physicians should carefully interpret BCR endpoints when comparing treatments.

6.10.3 **Natural history of biochemical failure**

Once a PSA relapse has been diagnosed, it is important to determine whether the recurrence has developed at local or distant sites. The risk of subsequent metastases and PCSM may be predicted by the initial clinical factors (e.g. T-category, PSA, biopsy Gleason score). If the patient has undergone RP, the pathological outcomes of the surgery (e.g. pathologic T-category and prostatectomy Gleason score, nodal and margin status) may provide further information. Beyond pre- and posttreatment clinico-pathological factors, PSA kinetics (PSA doubling-time (PSA-DT) and interval to PSA failure) may be used to estimate the risk of metastases and subsequent PCSM.

6.10.3.1 *Post-radical prostatectomy biochemical recurrence*

According to Pound et al. [363], not all patients with BCF after RP develop clinical recurrence. The authors evaluated the follow-up data for 1,997 patients after RP, and only 34% of those with BCF subsequently had a clinical recurrence. These data were confirmed by Boorjian et al. in a study including approximately 2,400 patients; only a minority of those with BCF after RP developed a clinically evident recurrence (22.9%) and only a few died of PCa (5.8%) [709]. Overall, these studies demonstrated a general trend among men with PSA-only recurrence after RP (i.e. 7-40% of relapsing men): for every 100 men treated with RP, approximately 15-30 will develop BCR and 2-6 of those will die of PCa.

Several studies have attempted to identify risk factors for metastases and PCSM in patients experiencing PSA-only recurrence following RP. Compiling the results of several studies, a subgroup with a high risk of metastases and PCSM was characterised by a PSA-DT < 3 months, seminal vesicle invasion (pT3b), specimen Gleason score 8-10, or time to PSA-recurrence < 3 years. Furthermore, a low-risk subgroup was defined as patients with a PSA-recurrence > 3 years following surgery, specimen Gleason score ≤ 7, pathologically organ confined disease or limited extracapsular extension (pT3a), and PSA-DT > 12 months [710-713]. Patients in the high-risk subgroup universally have an exponentially higher risk of developing metastases and dying of PCa. In other words, many patients in the high-risk subgroup likely have micro-metastatic disease or significant local recurrence at the time of PSA-rise, while those in the low-risk subgroup likely have a slow-growing local recurrence only. Indeed, patients in the low-risk subgroup typically respond very well to salvage RT with a high probability of PSA being undetectable [714]. However, it must be stressed that most patients within the low-risk subgroup have an excellent outcome even without any salvage treatment. Therefore, the decision to treat these patients should be made after careful consideration of the pro and cons, taking into account the life expectancy of the patient and his expectations. Patients within the high-risk subgroup need early and aggressive salvage treatment [715]. Trock et al. demonstrated that salvage RT was associated with a significant 3-fold increase in prostate-cancer-specific survival relative to those who received no salvage treatment. The increase in prostate-cancer-specific survival associated with salvage RT was limited to men with a PSA-DT of < 6 months and remained after adjustment for pathological stage and other established prognostic factors. Salvage RT initiated > 2 years after recurrence provided no significant increase in prostate-cancer-specific survival [715].

6.10.3.2 *Post-radiotherapy biochemical recurrence*

Similar to patients experiencing PSA-recurrence after RP, patients with a PSA-rise following RT can be subdivided into prognostic categories. A high-risk subgroup with elevated risk of metastases and PCSM are those patients with a PSA-DT < 3 months, time to biochemical progression < 3 years, biopsy Gleason score 8-10 and clinical stage cT3b-T4. Conversely, patients at low risk of metastases and PCSM are those with a PSA-DT > 15 months, biopsy Gleason score ≤ 7, clinical stage ≤ cT3a and time to biochemical progression > 3 years [712, 716, 717].

Zumsteg et al. have designed a risk score to further subdivide patients who develop PSA recurrence following RT. Those with either 0, 1 or ≥ 2 high-risk factors (PSA-DT < 3 months, time to biochemical progression < 3 years, biopsy Gleason score 8-10 and clinical stage cT3b-T4) have an increased risk of developing metastases and PCSM [717].

Again, the choice of local salvage treatment (salvage RP, salvage cryo, salvage HIFU, salvage brachytherapy) should be guided by the life expectancy and oncological risk profile of each patient, together with the patient's expectations.

6.10.4 **Assessment of metastases**

6.10.4.1 *Bone scan and abdominopelvic computed tomography*

The standard workup to detect PCa metastases usually includes bone scan and abdominopelvic CT. However, because biochemical failure after RP or radiation therapy precedes clinical metastases by 7-8 years on average, the diagnostic yield of usual imaging techniques is poor in asymptomatic patients [718]. In men with

PSA-only relapse after RP, the probability of a positive bone scan is < 5%, when the PSA level is < 7 ng/mL [719, 720]. A PSA doubling time (PSA-DT) < 6 months or a PSA velocity > 0.5 ng/mL/month are predictors of positive bone scan [719, 721].

CT sensitivity for detecting local recurrences or lymph node metastases is low. Only 11-14% of patients with biochemical failure after RP have positive CT [719]. In a series of 132 men with biochemical failure after RP, the mean PSA level and PSA velocity associated with positive CT was 27.4 ng/mL and 1.8 ng/mL/month, respectively [721]. Therefore, bone scan and abdominopelvic CT should only be considered in patients with biochemical failure after RP who have a high baseline PSA (> 10 ng/mL) or high PSA kinetics (PSA-DT < 6 months or PSA velocity > 0.5 ng/mL/month) or in patients with symptoms of bone disease [719].

However, more sensitive methods are needed to detect metastatic patients among candidates for local salvage treatment.

6.10.4.2 Choline and Acetate positron emission tomography (PET)/computed tomography (CT)

¹⁸F-fluorodeoxyglucose (FDG) is of limited value due to low uptake by PCa. In contrast, ¹¹C- or ¹⁸F-Choline and ¹¹C-Acetate have shown promising results in the early detection of local and distant recurrences [240]. However, their accuracy remains difficult to assess because most published studies are retrospective, evaluate heterogeneous populations (often mixing recurrences after various types of primary treatments), use non-standardised definitions of biochemical failure and are limited by the lack of a reliable histological gold standard. Furthermore, results may be reported on a per-patient or a per-lesion basis and may combine the detection of local recurrences and distant metastases [240].

Recent studies report overall sensitivities and specificities of 55-96% and 57-100%, respectively [240, 722-724]. ¹¹C-Choline PET/CT may detect multiple bone metastases in patients showing a single metastasis on bone scan [725] and may be positive for bone metastases in up to 15% of patients with biochemical failure after RP and negative bone scan [726]. The specificity of ¹¹C-Choline PET/CT is also higher than bone scan with less false positive and indeterminate findings [248, 727].

Several studies evaluated ¹¹C-Choline PET/CT in lymph node staging in patients with biochemical failure after primary treatment, using lymph node dissection as the gold standard. They reported conflicting results. One study found a sensitivity of 64%, a specificity of 90%, a positive predictive value of 86% and a negative predictive value of 72% [728]. The main explanation for the low sensitivity was the lack of detection of micrometastases in lymph nodes. In contrast, others found poor specificity with a 30-47% false-positive rate [729-731]. In a meta-analysis of 609 patients with primary or recurrent PCa, the pooled sensitivity and specificity of Choline PET/CT for pelvic lymph node metastases were 62% (95% CI, 51%-66%) and 92% (95% CI, 89%-94%), respectively [242].

Despite these limitations, Choline- or Acetate-PET/CT changed medical management in 28-48% of patients with biochemical failure after primary treatment [732-735].

However, a large body of literature suggests that Choline or Acetate PET/CT sensitivity is strongly dependent on the PSA level and kinetics [240, 722, 724, 736]. In patients with biochemical failure after RP, PET/CT detection rates are only 5-24% when the PSA level is < 1 ng/mL, but rises to 67-100% when the PSA level is > 5 ng/mL. Similarly, PET/CT sensitivity seems much higher when the PSA velocity is high or the PSA-DT is short. In a recent meta-analysis, Choline PET/CT detection rates were 65% (95% CI, 58%-71%) when the PSA-DT was ≤ 6 months, and were 71% (95% CI, 66%-76%) and 77% (95% CI, 71%-82%) when the PSA velocity was > 1 and > 2 ng/mL/year, respectively [722].

Due to its high cost, PET/CT cannot be recommended in all patients with PSA relapse. After RP, the optimal PSA cutoff level seems to be between 1 and 2 ng/mL [724, 736]. It is unclear whether PSA velocity or PSA-DT thresholds can be used to further select groups of patients in whom PET/CT could be recommended.

After RT, the PSA cutoff level is unclear due to the lack of sufficient data and because the PSA level is more difficult to interpret due to the “physiological” amount of measurable PSA produced by the non-tumoural prostate [724]. In a study of 46 patients with PSA relapse after RT or brachytherapy, the ¹⁸F-Choline PET/CT detection rate was 54.5%, 81%, 89% and 100% when the PSA level was 1-2 ng/mL, 2-4 ng/mL, 4-6 ng/mL and > 6 ng/mL, respectively [737]. In another study of 140 patients the ¹¹C-Choline PET/CT detection rate was not influenced by the PSA level, but only by PSA kinetics [738].

6.10.4.3 Other radionuclide techniques

A ¹¹¹In-capromab pendetide scan (ProstaScint™) yielded disappointing results in patients with biochemical failure after RP or radiation therapy [718, 719]. Its use is therefore not recommended.

¹⁸F-Fluoride PET and PET/CT have a higher sensitivity than bone scan in detecting bone metastases [727]. However, ¹⁸F-Fluoride is limited by a relative lack of specificity and by the fact that it does not assess soft-tissue metastases [248].

6.10.4.4 Whole-body and axial magnetic resonance imaging (MRI)

Diffusion-weighted whole-body MRI and the so-called axial MRI (evaluation of the spine and the pelvi-femoral area only) are more sensitive than bone scan and targeted radiographs [252-254] and seem equally effective as ¹¹C-Choline PET/CT [739] in detecting bone metastases in patients with high-risk PCa. Their sensitivity for lymph node metastases remains low, even if it is slightly higher than that of ¹¹C-Choline PET/CT in high-risk patients [244].

However, little is known regarding the accuracy of whole-body or axial MRI in patients with biochemical failure after RP or radiation therapy [740]. Therefore, the role of these techniques in detecting occult bone or lymph node metastases in the case of biochemical failure remains to be assessed.

6.10.4.5 Assessment of local recurrences

6.10.4.5.1 Local recurrence after radical prostatectomy

The precise localisation of the local recurrence by imaging techniques is needed only if histological proof of the recurrence is mandatory before salvage treatment and/or if this localisation could change treatment planning. Transrectal ultrasound is neither sensitive nor specific in detecting local recurrences after RP. Even with TRUS guidance, the sensitivity of anastomotic biopsies remains low: 40-71% for PSA levels > 1 ng/mL and 14-45% for PSA levels < 1 ng/mL [718]. As a consequence, salvage radiation therapy is usually decided on the basis of the BCR, without histological proof of the local recurrence. The dose delivered to the prostatic bed also tends to be uniform as it has not been demonstrated that a focal dose escalation at the site of recurrence improves the outcome. Thus, most patients undergo salvage radiation therapy without local imaging.

Nonetheless, several studies have reported promising results in the detection of local recurrences using MRI, particularly dynamic contrast-enhanced MRI which showed sensitivities and specificities of 84-88% and 89-100%, respectively [741-743]. However, the mean PSA level in these studies was 0.8-1.9 ng/mL, which is higher than the 0.5 ng/mL threshold usually used for salvage therapy. Recently, two studies evaluated mpMRI in patients with PSA level < 0.5 ng/mL. One found a sensitivity of only 13% in men with PSA level < 0.3 ng/mL [744], while the other reported a sensitivity of 86% in patients with PSA level < 0.4 ng/mL [745]. Thus, it remains to be defined whether MRI is able to correctly detect local recurrences in patients with PSA level < 0.5 ng/mL in order to allow a stereotaxic boost to the recurrence site during salvage radiation therapy. Choline or Acetate PET/CT can also detect local recurrences, but are less sensitive than MRI [723, 746].

6.10.4.5.2 Local recurrence after radiation therapy

In patients with biochemical failure after radiation therapy, the biopsy status is a major predictor of outcome, provided the biopsies are obtained 18-24 months after treatment. Given the morbidity of local salvage options, it is thus necessary to obtain histological proof of the local recurrence before treating the patient [718].

TRUS is not reliable in depicting local recurrences after radiation therapy. In contrast, mpMRI has yielded excellent results [718, 747-749] and can be used for biopsy targeting and guiding local salvage treatment. Detection of recurrent cancer is also feasible with Choline and Acetate PET/CT, but PET/CT has poorer spatial resolution than MRI [732, 733, 738, 750].

6.10.4.6 Guidelines for imaging and second-line therapy after treatment with curative intent

Biochemical recurrence (BCR) after RP	LE	GR
In the case of BCR, bone scan and abdominopelvic CT should be performed only in patients with a PSA level > 10 ng/mL, or with high PSA kinetics (PSA-DT < 6 mo or a PSA velocity > 0.5 ng/mL/mo) or in patients with symptoms of bone disease.	3	A
A Choline PET/CT is not recommended in patients with BCR and a PSA-level < 1 ng/mL	3	A
Biochemical recurrence after RT		
In patients with BCR who are candidates for local salvage therapy, prostate mpMRI may be used to localise abnormal areas and guide biopsy.	3	C

BCR = biochemical recurrence; CT = computed tomography; GR = grade of recommendation; LE = level of evidence; mpMRI = multiparametric magnetic resonance imaging; PET = positron emission tomography; PSA-DT = prostate specific antigen doubling time; RP = radical prostatectomy; RT = radiotherapy.

6.10.5 Treatment of PSA-only recurrences

The timing and mode of treatment for PSA-only recurrences after RP or RT are still controversial.

After RP, the therapeutic options are:

- Radiotherapy at least to the prostatic bed;

- (Complete) androgen deprivation (CAD, AD);
- Intermittent androgen deprivation (IAD);
- Observation.

Following RT, the same therapeutic options - except repeat percutaneous RT - may apply in relation to PSA recurrences. In addition, salvage RP, cryotherapy or brachytherapy may be indicated in carefully selected patients.

6.10.5.1 Radiotherapy (Salvage radiotherapy [SRT] - with or without androgen-deprivation therapy for PSA-only recurrence after radical prostatectomy)

Early SRT provides a possibility of cure for patients with an increasing or persistent PSA after RP. More than 60% of patients who are treated before the PSA level rises to > 0.5 ng/mL will achieve an undetectable PSA level again [494, 751-753], providing patients with an ~ 80% chance of being progression-free 5 years later [495]. A retrospective analysis based on 635 patients who underwent RP in 1982-2004, followed up through December 2007, who experienced BCR and/or local recurrence and received no salvage treatment (n = 397) or salvage RT alone (n = 160) within 2 years of BCR, showed that SRT was associated with a threefold increase in the PCa-specific survival relative to those who received no salvage treatment (P < 0.001). Salvage radiotherapy has also been effective in patients with a short PSA-DT [715]. Despite the indication of salvage RT a “wait and see” strategy is an option in patients with a long PSA-DT of more than 12 months [709]. For an overview see Table 6.10.1.

Table 6.10.1: Selected studies on post-prostatectomy salvage radiotherapy (SRT), sorted by pre-salvage radiotherapy (SRT) PSA level.

Hormone suppression treatment (HT) can influence the outcome ‘biochemically no evidence of disease (bNED)’ or ‘progression-free survival’ (PFS). Therefore, data sets without HT are highlighted. To facilitate comparisons, 5-year bNED/PFS read-outs from Kaplan-Meier plots are included.

Reference	Yr	n	HT %	pre-SRT PSA (ng/mL) median	Median dose (Gy)	bNED / PFS yr	5-yr results
Siegmann, et al. [754]	2011	301	0	0.28	66.6 / 70.2	74% (2)	55% vs. 88% @ 66.6 vs. 70.2 Gy
Wiegel, et al. [495]	2009	162	0	0.33	66.6	54% (3.5)	60% vs. 33% @ PSA ≤ 0.5 vs. > 0.5
Goenka, et al. [755]	2011	285	31	0.4	> 70 (72%)	37% (7)	39%
Cremers, et al. [756]	2010	197	0	0.59	63 / 2.25 frct. (88%)	59% (5)	
Bernard, et al. [757]	2010	364	0	0.6	64.8	50% (5)	
Buskirk, et al. [758]	2006	368	15	0.7	64.8	46% (5)	63% vs. 51% @ PSA < 0.5 vs. 0.5-1.0
Pazona, et al. [759]	2005	223	4.5	0.8	63	40/25% (5/10)	42% vs. 30% @ < 1.3 vs. ≥ 1.3
Pisansky, et al. [760]	2000	166	4	0.9	64	46% (5)	61% vs. 36% @ PSA ≤ 1 vs. > 1
Soto, et al. [761]	2012	441	24	< 1 (58%)	68	63/55% (3) HT / no HT	44/40% HT / no HT
Stephenson, et al. [494]	2007	1540	14	1.1	64.8	32% (6)	37%

bNED/PFS = biochemically no evidence of disease/progression-free survival; HT = hormone suppression treatment; n = number of patients; SRT = salvage radiotherapy.

The addition of HT to SRT (n = 78) was not associated with an additional increase in the CSS compared with SRT alone [715]. So far, adding ADT to SRT has only shown benefit in terms of biochemical PFS after 5 years in retrospective series [755, 762] and in PFS for “high-risk” tumours [761], however data from prospective randomised trials are missing. Results are awaited from recently completed randomised controlled phase III studies: the Radiation Therapy Oncology Group (RTOG-9061) comparing RT + placebo vs. a combination of RT + bicalutamide (150 mg daily) in the postoperative setting and the French GETUG 16 trial, comparing salvage

EBRT with- or without 6 months of ADT. To date there is no recommendation for patients with primary pN0-stage at RP for a combination of SRT plus additional ADT.

6.10.5.1.1 Dose, target volume, toxicity

To date, the optimal salvage RT dose has not been well defined. It should be at least 66 Gy to the prostatic fossa (plus/minus the bed of the seminal vesicles according to the pathological stage after RP) [751]. Similarly, a US guideline panel regarded 64-65 Gy as the minimum dose that should be delivered post RP [763]. However, more recent data suggest that higher total doses can achieve higher rates of biochemical control at 3-5 years [757]. In a systematic review, the pre-SRT PSA level and SRT dose were correlated with BCR, showing that the relapse-free survival decreased by 2.6% per 0.1 ng/mL PSA and improved by 2% per Gy, suggesting that a treatment dose above 70 Gy should be administered at the lowest possible PSA [751, 764, 765].

There have been various attempts to define common outlines for “clinical target volumes” of PCa [766-768] and for organs at risk of normal tissue complications [769]. However, depending on the applied techniques and accepted constraints, a satisfactory consensus has not yet been achieved. The RTOG consensus was achieved considering two PCa cases, one T2c with positive margins at both sides of the apex and one T3b with extracapsular extension at the right base and right seminal vesicle, but with negative margins [766].

In one report on SRT with 66.6-70.2 Gy in 1.8 Gy fractions, only 2.7% of the patients had moderate proctitis or cystitis grade II. Four patients (1.3%) had grade III cystitis. Six out of 301 patients (2%) developed urethral stricture which was not solely attributable to SRT but also resulted from RP alone [752]. In a retrospective cohort of 285 men receiving 3D-CRT (38%) or IMRT (62%) with 66 Gy in 95% of cases, the high-dose subgroup did not show a significant increase in toxicity [755]. In an analysis involving 30 participating centres, a quality assurance programme assessing target volumes, RT techniques (3D-CRT, IMRT, VMAT) and RT doses (64 vs. 70 Gy) it was found that 3D-CRT was applied in nearly half of the centres and was not associated with significantly worse rectum and bladder DVH parameters, for salvage RT using 70 Gy, when compared with IMRT [770].

However, with dose escalation (72 Gy) or up to a median of 76 Gy, the rate of severe side effects especially for the GU-system clearly increases, even with newer planning and treatment techniques [771, 772]. Of note, compared with 3D-CRT, IMRT was associated with a reduction in grade 2 GI toxicity from 10.2 to 1.9% ($P = 0.02$), while RT technique had no differential effect on the relatively high level of GU toxicity (5-yr: 3D-CRT 15.8% vs. IMRT 16.8%) [771]. After a median salvage IMRT dose of 76 Gy, the 5-year risk of grade 2-3 toxicity rose to 22% for GU and 8% for GI symptoms, respectively [772].

6.10.5.1.2 Comparison of adjuvant radiotherapy (ART) and salvage radiotherapy (SRT)

In a case-control analysis, 361 ART patients were compared with 722 non-ART patients, who were selected to match the cases by treatment period, age, pre-RP PSA, tumour stage, Gleason score and surgical margin status. While the 10-year bNED after ART was significantly improved compared with non-ART (63 vs. 45%), there was no difference in OS. In the same study, an SRT cohort of 856 patients who were treated after biochemical relapse (median PSA 0.8 ng/mL) was followed up over a median of 5.9 years. Sixty-three percent of the SRT patients achieved an undetectable PSA after salvage RT and the hazard ratio for local recurrence after salvage RT was 0.13. However, similar to that after ART, no improved OS was seen after salvage RT [773].

The largest retrospective case-matching study to evaluate ART versus early SRT included pT3N0 R0/R1 patients only (HT was excluded), 390 out of 500 observation-plus-early-SRT patients (median pre-SRT PSA was 0.2 ng/mL) were propensity matched with 390 ART patients. Two and five years after surgery, bNED rates were 91% and 78% for ART vs. 93% and 82% after salvage RT, respectively. Subgroup analyses did not yield significant differences for the two approaches. It was concluded that early SRT does not impair PCa control, but clearly helps to reduce overtreatment which is a major issue in ART [774].

Both approaches (ART and SRT) together with the efficacy of neoadjuvant hormone therapy are currently being compared in three prospectively randomised clinical trials: the Medical Research Council (MRC) Radiotherapy and Androgen Deprivation In Combination After Local Surgery (RADICALS) in the United Kingdom, the Trans-Tasman Oncology Group (TROG) Radiotherapy Adjuvant Versus Early Salvage (RAVES), and Groupe d'Etude des Tumeurs Uro-Génitales (GETUG 17).

Decision-making on whether to proceed with adjuvant RT for high risk PCa - pT3-4 pN0 M0 with undetectable PSA after RP, or to postpone RT as an early salvage procedure in the case of biochemical relapse, remains difficult. In everyday practice, the urologist should explain to the patient before RP that adjuvant RT may be administered if the patient has negative prognostic risk factors. Ultimately, the decision on whether to treat requires a multidisciplinary approach that takes into account the optimal timing of RT when it is used and

provide justification when it is not, and this will help the discussion between the physician and the patient.

6.10.5.2 *Hormonal therapy*

Currently there is no available RCT comparing the effect of salvage ADT, although retrospective comparative studies are available. Still, salvage ADT is often used and represents one major practice of ADT use [775].

A retrospective study including 1,352 patients with post-RP PSA recurrence showed that early ADT was associated with a delay to clinical metastases only in patients with a Gleason score > 7 and/or a PSA-DT < 12 months. After a median follow-up after relapse of 3.7 yr, ADT had no impact on the PCa-specific mortality [776].

A multivariate analysis performed by Choueiri et al. [777] showed that whereas salvage ADT in univariate analysis was harmful in the whole patient population, it showed a survival benefit in multivariate analysis correcting for risk factors (logPSA, age, pGS, pT, surgical margins, PSA failure and salvage RT). In a subanalysis of patients where PSA-DT was known, if corrected for the same risk factors plus PSA-DT (< 6 months vs ≥ 6 months), the survival benefit of salvage ADT increased even more with a HR for death of 0.55 (95% CI 0.36-0.82).

In patients initially treated with radiotherapy, Klayton et al [778] showed there was a clinical benefit of ADT versus observation in patients with a PSA-DT < 6 months. At 7 years follow-up, these patients had a significantly better metastases-free survival and disease-specific survival, whilst this was not the case for patients with a PSA-DT ≥ 6 months.

Regarding the timing of salvage ADT, two large comparative studies show no benefit of early vs. late ADT in patients with BCR [377, 779]. After a median of 10-yr follow-up, Siddiqui et al documented that there was no progression-free or disease-specific survival benefit for early ADT. In patients with a PSA ≥ 2 ng/mL, early ADT even showed worse CSS. A recent study based on the CAPSURE database of relapsing patients did not show any 5- and 10-year specific or overall survival difference when comparing immediate and deferred ADT [779]. In the deferred ADT group, patients with a PSA-DT < 12 months were included; again suggesting PSA-DT might be an important risk factor.

If salvage ADT is considered, an intermittent strategy may be appealing as it decreased by almost 60% the amount of drug used. In a large non-inferiority RCT of 1,386 patients primarily treated with radiotherapy [780], intermittent treatment was non-inferior compared to continuous treatment (median OS: 8.8 years (intermittent), and 9.1 years (continuous (HR: 1.02 (0.86 - 1.21)). In the intermittent ADT group, testosterone recovery to the trial-entry threshold occurred in 79% of patients. Intermittent androgen deprivation provided potential benefits with respect to physical function, fatigue, urinary problems, hot flushes, libido, and erectile function. In metastatic patients (see Section 6.8.7), this modality is reserved for responding patients (achieving a PSA at least below 4 ng/mL after 6 to 8 mo of ADT), and treatment is resumed when the PSA is above 10 ng/mL.

In conclusion, not all patients with relapse after primary curative treatment benefit from salvage ADT. A favourable effect is observed in a high-risk group, which may be defined by short PSA-DT and/or tumour characteristics. Intermittent ADT seems non-inferior to continuous hormones.

6.10.5.3 *Observation*

Observation until the development of clinically evident metastatic disease may represent a viable option for patient with low-risk features (PSA-DT > 12 months, time to BCR > 3 years, GS ≤ 7 and stage ≤ T3a) or unfit patients with a life expectancy < 10 years and/or are unwilling to undergo salvage treatment. In these patients, the median actuarial time to the development of metastasis will be 8 years and the median time from metastasis to death will be a further 5 years [363].

6.10.6 **Management of PSA failures after radiation therapy**

Therapeutic options in these patients are ADT or local procedures such as SRP, cryotherapy, interstitial brachytherapy and high-intensity focused US [781-790]. As a general rule, strong recommendations regarding the choice of any of these techniques cannot be made as the available evidence for these treatment options is of (very) low quality. The following is an overview of the most important findings regarding each of these techniques with a proposal for their indications.

6.10.6.1 *Salvage radical prostatectomy (SRP)*

Salvage radical prostatectomy after RT has the longest history and best likelihood of local control relative to other salvage treatments. However, this must be weighed against the possible adverse events, which are increased compared to primary surgery because of the risk of fibrosis and poor wound healing due to radiation.

6.10.6.1.1 Oncological outcomes

In a recent systematic review of the literature, Chade et al. showed that SRP gave 5- and 10-year biochemical recurrence-free survival (BCR-FS) estimates ranging from 47-82% and from 28-53%, respectively. The 10-yr cancer-specific and OS rates ranged from 70-83% and from 54-89%, respectively. The pre-SRP PSA value and prostate biopsy Gleason score were the strongest predictors of the presence of organ-confined disease, progression, and CSS [791].

In most contemporary series, organ-confined disease, negative SMs, and the absence of seminal vesicle and/or lymph node metastases were favorable prognostic indicators associated with a better disease-free survival of approximately 70-80%, in comparison with 40-60% in patients with locally advanced PCa [790].

Table 6.10.2: Oncological results of selected SRP case series, including at least 30 patients

Reference	Yr	n	Median FU (mo)	Pathologic organ confined, %	PSM, %	Lymph node involvement, %	BCR-free probability, %	CSS, %	Time probability, yr
Sanderson, et al. [792]	2006	51	-	25	36	28	47	-	5
Leonardo, et al. [793]	2009	32	35	53	34	0	75	-	3
Heidenreich, et al. [789]	2010	55	23 (2-56)	73	11	20	87	-	2
Chade, et al. [794]	2011	404	55	55	25	16	37	83	10

BCR = biochemical recurrence; FU = follow-up; mo = months; n = number of patients; PSM = positive surgical margin; CSS = cancer-specific survival.

6.10.6.1.2 Morbidity

Compared to primary open RP, SRP is associated with a higher risk of later anastomotic stricture (47% vs 5.8%), urinary retention (25.3% vs 3.5%), urinary fistula (4.1% vs 0.06%), abscess (3.2% vs 0.7%) and rectal injury (9.2% vs 0.6%) [795]. In more recent series, these complications appear to be less common [788, 791]. Functional outcomes are also worse compared to primary surgery, with urinary incontinence (UI) ranging from 21% to 90% and erectile dysfunction in nearly all patients [791].

Table 6.10.3: Perioperative morbidity in selected SRP case series, including at least 30 patients

Reference	Yr	n	Rectal injury (%)	Anastomotic stricture (%)	Clavien 3-5, %	Blood loss, mL, mean, range
Stephenson, et al. [788]	2004	100	15 vs 2*	30	33 vs 13*	-
Ward, et al. [796]	2005	138	5	22	-	-
Sanderson, et al. [792]	2006	51	2	41	6	-
Gotto, et al. [795]	2010	98	9	41	25	-
Heidenreich, et al. [789]	2010	55	2	11	3.6	360 (150-1450)

* SRP performed before vs after 1993.

n = number of patients; SRP = salvage radical prostatectomy.

6.10.6.2 Summary of salvage radical prostatectomy

In general, SRP should be considered only for patients with low comorbidity, a life expectancy of at least 10 years, a pre-SRT PSA < 10 ng/mL and biopsy Gleason score ≤ 7, no lymph node involvement pre-SRT, and whose initial clinical staging was T1 or T2 [791].

6.10.7 Salvage cryoablation of the prostate

6.10.7.1 Oncological outcomes

In cases in which RT fails, salvage cryoablation of the prostate (SCAP) has been proposed as an alternative to SRP, as it has a potentially lower risk of morbidity and equal efficacy. However, the very few studies available have shown disappointing results. In a review of the use of SCAP for recurrent cancer after RT, the 5-year BDFS estimates ranged from 50-70%. A durable response can be achieved in ~50% of patients with a pre-SCAP PSA < 10 ng/mL [797]. In a multicentre study reporting the current outcome of SCAP in 279 patients, the 5-year biochemical recurrence-free survival (BCR-FS) estimate according to the Phoenix criteria was 54.5 ± 4.9%. Positive biopsies were observed in 15/46 patients (32.6%) who underwent prostate biopsy after SCAP [798].

A case-matched control study comparing SRP and SCAP was performed in men with recurrent PCa after RT. The authors compared the oncological outcomes of the two salvage treatment options after mean follow-up periods of 7.8 (SRP group) and 5.5 years (SCAP group). The 5-year BCR-FS was 61% following SRP, significantly better than the 21% detected after SCAP. The 5-year OS was also significantly higher in the SRP group (95% vs. 85%) [799].

Table 6.10.4: Oncological results of selected SCAP case series, including at least 50 patients

Reference	Yr	n	Median FU (mo)	BCR-free probability, %	Time probability, yr	Definition of failure
Pisters, et al. [800]	1997	150	17	44	-	Nadir + 0.2
Bahn, et al. [801]	2003	59	82	59	7	PSA > 0.5
Ismail, et al. [797]	2007	100	33	73 (low risk)	5	ASTRO
Pisters, et al. [798]	2008	279	22	58	5	ASTRO and Phoenix
Williams, et al. [802]	2011	187	7.46 yr	39	10	Nadir +2
Spiess, et al. [803]	2010	450	40.8	34	-	PSA > 0.5

BCR = biochemical recurrence; FU = follow-up; mo = months; n = number of patients.

6.10.7.2 Morbidity

According to Cespedes et al. [804], the risks of urinary incontinence and erectile dysfunction at least 12 months after SCAP were as high as 28% and 90%, respectively. In addition, 8-40% of patients reported persistent rectal pain, and an additional 4% of patients underwent surgical procedures for the management of treatment-associated complications. In a recent study by Pisters et al, the UI rate was 4.4%. The rectal fistulae rate was 1.2%, and 3.2% of patients required transurethral resection of the prostate (TURP) for removal of sloughed tissue [798]. With the use of third-generation technology, complications such as UI and obstruction/retention have significantly decreased during the last decade (see Table 6.10.5) [805].

Table 6.10.5: Perioperative morbidity, erectile function and urinary incontinence in selected SCAP case series, including at least 50 patients

Reference	Yr	n	Incontinence, %	Obstruction/Retention, %	Rectourethral fistula, %	ED, %
Pisters [800]	1997	150	73	67	1	72
Bahn [801]	2003	59	8	-	3.4	-
Ismail [797]	2007	100	13	4	1	-
Pisters [798]	2008	279	4.4	3.2	1.2	-
Ahmad [806]	2013	283	12	7	1.8	83

ED = erectile dysfunction; n = number of patients.

6.10.7.3 Summary of salvage cryoablation of the prostate

In general, SCAP should be considered only for patients with low comorbidity, a life expectancy of at least 10 years, an initial organ-confined PCa cT1c to cT2, initial Gleason score ≤ 7, a pre-salvage PSA-DT ≥ 16 months and a pre-salvage PSA < 10 ng/mL.

6.10.8 Salvage brachytherapy for radiotherapy failure

Following local recurrence after previous definitive RT there is no indication for external beam salvage RT as

the total dose is limited and therefore the chance of cure is low. For carefully selected patients with primary localised PCa and histologically proven local recurrence, high- or low-dose rate (H/LDR) brachytherapy remain effective treatment options with an acceptable toxicity profile [807-809]. However, the published series are relatively small, therefore this treatment should be offered in experienced centres only. Fifty-two patients were treated at the Scripps Clinic with HDR-brachytherapy over a period of nine years [807]. With a median follow-up of 60 months the 5-year biochemical control was 51% and only 2% grade 3 GU toxicities were reported. Comparable with these data, 42 patients were treated in a phase-II-trial at MSCCC in New York [810]. Of note, the median pre-treatment dose was 81 Gy given with IMRT and the prescription HDR-dose of 32 Gy was delivered in four fractions over 30 hours. The biochemical relapse-free survival after 5 years was 69% (median follow-up 36 months). Grade 2 late side effects were seen in 15% and one patient developed Grade 3 incontinence. However, older data with higher rates of side effects have been reported [811].

Using LDR-brachytherapy with 103Pd (palladium), long-term outcome was reported in 37 patients with a median follow-up of 86 months [114]. The biochemical control rate after 10 years was 54%. However, the crude rate of \geq grade 2 toxicity was 46% and \geq grade 3 toxicity was 11%. These side effects were comparable with a series of 31 patients treated with salvage 125I brachytherapy in the Netherlands. Therefore, in these small series, late side effects seem to be lower with HDR-brachytherapy [812].

In conclusion, freedom from BCR after salvage HDR- and LDR-brachytherapy is promising and the rate of severe side effects in experienced centres seem to be acceptable. Therefore salvage brachytherapy remains a treatment option for selected patients with histologically proven local recurrence after RT.

6.10.9 **Salvage High-intensity focused ultrasound (HIFU)**

6.10.9.1 *Oncological outcomes*

Salvage HIFU has more recently emerged as an alternative thermal ablation option for radiation-recurrent PCa. Most of the data were generated by one high-volume centre. Median follow-up was very short, and outcome measures were non-standardised.

Table 6.10.6: Oncological results of selected salvage HIFU case series, including at least 20 patients

Reference	Yr	n	Median FU (mo)	BCR-free probability, %	Negative biopsy rate
Colombel, et al. [813]	2006	224	15-18	-	80
Gelet, et al. [814]	2000				
Gelet, et al. [815][121]	2004				
Uchida, et al. [816]	2011	22	24	59 (Phoenix) (24 mo)	92 (only 12 biopsied)
Berge, et al. [817]	2011	46	9	60.9 (9 mo)	

FU = follow-up; mo = months; n = number of patients.

6.10.9.2 *Morbidity*

Again, most of the data were generated by one high-volume HIFU centre. Important complication rates were mentioned and are at least comparable to other salvage treatment options.

6.10.9.3 *Summary of salvage high-intensity focused ultrasound (HIFU)*

There is a paucity of data which prohibits any recommendation regarding the indications for salvage HIFU.

6.10.10 **Observation**

Patients who have signs of only local recurrence (i.e., low-risk patients with late recurrence and a slow PSA rise) who do not wish to undergo second-line curative options are best managed by observation alone. A retrospective cohort analysis of HT vs. watchful waiting in 248 men with PSA failure after RT showed no advantage for HT in the subgroup of men with a PSA-DT of > 12 months after RT. The 5-year metastasis-free survival rate was 88% with hormone therapy versus 92% with watchful waiting ($p = 0.74$) [818].

6.10.11 Guidelines for imaging and second-line therapy after treatment with curative intent

Local salvage treatment	LE	GR
Biochemical recurrence (BCR) after RP		
For patients with a PSA rise from the undetectable range and favourable prognostic factors (\leq pT3a, time to BCR > 3 yr, PSA-DT > 12 mo, Gleason score \leq 7) surveillance and possibly delayed salvage RT (SRT) may be offered.	3	B
Patients with a PSA rise from the undetectable range should be treated with SRT. The total dose of SRT should be at least 66 Gy and should be given early (PSA < 0.5 ng/mL).	2	A
Biochemical recurrence (BCR) after RT		
Selected patients with localised PCa at primary treatment and histologically proven local recurrence should be treated with salvage RP (SRP).	3	B
Due to the increased rate of side effects, SRP should be performed in experienced centres.	3	A
High intensity focused ultrasound (HIFU), cryosurgical ablation and salvage brachytherapy are treatment options for patients without evidence of metastasis and with histologically proven local recurrence. Patients must be informed about the experimental nature of these approaches.	3	B
Systemic salvage treatment		
In asymptomatic men with BCR, ADT should not be given routinely.	3	A
Patients with a PSA-DT > 12 mo, should not receive ADT.	3	B
If salvage ADT (post-primary RT) is started, intermittent therapy should be considered in responding patients.	1b	A

ADT = androgen-deprivation therapy; BCR = biochemical recurrence; GR = grade of recommendation; LE = level of evidence; PSA-DT = prostate-specific antigen doubling time; RT = radiotherapy; SRP = salvage radical prostatectomy.

6.11 Treatment: Castration-resistant prostate cancer (CRPC)

6.11.1 Background

Our knowledge of the mechanisms involved in the development of castration-resistant prostate cancer (CRPC), remains incomplete [819, 820]. An alteration in normal androgen signaling is thought to be central to the pathogenesis of CRPC [821]. It is mediated through two main, overlapping, mechanisms. These are androgen-receptor (AR)-independent and AR-dependent.

6.11.2 Definition of progressing prostate cancer after castration

Table 6.11.1: Definition of CRPC

Castrate serum testosterone < 50 ng/dL or 1.7 nmol/L plus either;
Biochemical progression: Three consecutive rises in PSA 1 week apart resulting in two 50% increases over the nadir, with PSA > 2 ng/mL or
Radiological progression: The appearance of two or more new bone lesions on bone scan or enlargement of a soft tissue lesion using RECIST (Response Evaluation Criteria in Solid Tumours) [822].
Symptomatic progression alone must be questioned and is not sufficient to diagnose CRPC.

Frequent post-treatment PSA surveillance has resulted in earlier detection of progression [823]. In such patients occult micro-metastasis might exist, but are usually undetectable using conventional methods [824]. Although 33% will develop bone metastases within 2 years [825], there are no available studies suggesting a benefit for treatment.

In men with CRPC and no detectable clinical metastases, baseline PSA level, PSA velocity and PSA doubling time have been associated with time to first bone metastasis, bone metastasis-free and overall survival [825, 826]. These factors may be used when deciding which patients should be evaluated for metastatic disease. A consensus statement by the Prostate Cancer Radiographic Assessments for Detection of Advanced Recurrence (RADAR) group [827] suggested a bone scan when the PSA reached 2 ng/mL and if this was negative it should be repeated when the PSA reached 5 ng/mL and again after every doubling of the PSA based on PSA testing every 3 months.

The rest of this chapter focuses on management of men with proven metastatic CRPC (mCRPC)

6.11.3 Assessing treatment outcome in castration-resistant PCa (CRPC)

Precise quantification of the effect of treatments on metastatic bone disease is difficult to quantify and rarely used in clinical practice. Improvements in QoL, progression-free survival and prostate-cancer-specific survival are all used, but the gold standard remains OS [828].

6.11.3.1 PSA level as marker of response

Many contemporary studies use PSA as a marker of response, even though there is no consensus about the magnitude and duration of a decline in PSA level. Although PSA is used as a rapid screening tool to test the activity of new agents, there is conflicting evidence about the role of PSA as a surrogate marker. Trials of the vaccines sipuleucel-T (Provenge) [829] and TRICOM (PROSTVAC) [830] have demonstrated a significant OS benefit without any PSA change, raising questions about the value of PSA response for non-hormonal non-cytotoxic drugs [831]. In addition, wide fluctuations have been seen in PSA values due to a transient effect of drugs on PSA production. The effect of drugs on PSA expression should be considered when interpreting PSA response data, which should be viewed together with other clinical data [832-835]. Nevertheless, it has been shown reproducibly that > 30% PSA decline following therapy carries a significant survival advantage [836, 837]. An improved PSA response was also associated with prolonged survival in the TAX 327 study, with a median survival of 33 months when the PSA was normalised (< 4 ng/mL) vs. 15.8 months for an abnormal PSA.

6.11.4 Androgen deprivation in castration-resistant PCa

Eventually men with PCa show evidence of disease progression despite castration. In this situation continued testicular androgen suppression in CRPC is debatable [838].

These data have been challenged by two trials that showed only a marginal survival benefit for patients remaining on LHRH analogues during second- and third-line therapies [839, 840]. However, in the absence of prospective data, the modest potential benefits of a continuing castration outweigh the minimal risk of treatment. In addition, all subsequent treatments have been studied in men with ongoing androgen suppression and therefore it should be continued indefinitely in these patients.

Table 6.11.2: Randomised phase III controlled trials - first-line treatment of mCRPC*

Author	Year	Intervention (N)	Comparison (N)	Selection criteria	Main outcomes
DOCETAXEL					
SWOG 99-19 [841]	2004	Docetaxel/EMP, every 3 weeks, 60 mg/m ² , EMP 3 x 280 mg/day	Mitoxantrone, every 3 weeks, 12 mg/m ² prednisone 5 mg BID		OS: 17.52 vs. 15.6 mo. PFS: 6.3 vs. 3.2 mo.
TAX 327 [842]	2004	Docetaxel, every 3 weeks, 75 mg/m ² prednisone 5 mg BID or Docetaxel, weekly, 30 mg/m ² prednisone 5 mg BID	Mitoxantrone, every 3 weeks, 12 mg/m ² , Prednisone 5 mg BID		OS: 18.91 for 3 weekly vs. 17.4 mo for weekly and 16.5 in the control group.
ABIRATERONE					
COU-AA-302 Ryan [843, 844]	2013	Abiraterone + Prednisone (546)	Placebo + Prednisone (542)	No previous docetaxel. ECOG 0-1. PSA or radiographic progression. No or mild symptoms. No visceral metastases.	OS: 34.7 vs. 30.3 mo (p= 0.0027). FU: 49.2 mo. PFS: 16.5 vs. 8.3 mo. P < 0.0001) (p = Main side effects outcomes: 48% vs. 42% grade 3-4.

ENZALUTAMIDE					
PREVAIL Beer [845]	2014	Enzalutamide (872)	Placebo (845)	No previous docetaxel. ECOG 0-1. PSA or radiographic progression. No or mild symptoms 10% had visceral metastases	<u>OS</u> : 32.4 vs 30.2 mo (p < 0.001). FU: 22 mo. <u>PFS</u> : median not reached vs 3.9 mo (p < 0.001) <u>Main side effects outcomes</u> : Hypertension, fatigue and hot flush
SIPULEUCEL-T					
Kantoff [830]	2010	Sipuleucel-T (341)	Placebo (171)	Some with previous docetaxel. ECOG 0-1. Asymptomatic or minimally symptomatic.	<u>OS</u> : 25.8 vs. 21.7 mo (p.0.03). FU: 34.1 mo. <u>PFS</u> : 3.7 vs 3.6 mo. <u>Main side effects outcomes</u> : 31.7% vs. 35.1%.
Small [829]	2006	Sipuleucel-T (82)	Placebo (45)	ECOG 0-1. No visceral metastases. No bone or cancer pain. No corticosteroids.	<u>OS</u> : 25.9 vs. 21.4 mo (p. 0.01). FU: 36 mo. <u>PFS</u> : 11.7 vs. 10.0 weeks. <u>Main side effects outcomes</u> : 31.1% vs. 29.3% grade 3, 24.45% both groups grade 4.

ECOG = Eastern Cooperative Oncology Group; EMP = estramustine; FU = follow-up; PFS = progression-free survival; OS = overall survival.

6.11.5 Hormonal drugs targeting the endocrine pathways in the pre-docetaxel space

6.11.5.1 Abiraterone

The use of abiraterone in the pre-docetaxel setting was evaluated in the large phase III trial COU-AA-302, in which 1,088 chemo-naïve mCRPC patients were randomised to abiraterone acetate and placebo, both combined with prednisone [843]. Patients were mCRPC, Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 and were asymptomatic or mildly symptomatic. The study had two joint primary end-points: OS and radiographic PFS. The results reported are from the second preplanned interim analysis. After a median follow-up of 49.2 months, there was significant radiological PFS (median 16.5 vs. 8.2 months, HR: 0.52, p < 0.001) and the trial was unblinded. At that point there was a trend to improved OS, which with further follow-up has become significant [846]. With a median follow-up of 49.4 months OS was 34.7 vs 30.3 months (HR = 0.80, (CI 0.69-0.93) p = 0.0027). All the subgroup analyses and secondary end-points consistently favoured the abiraterone arm. Side effects related to mineralocorticoids and liver function were more frequent with abiraterone, but mostly grade 1/2.

6.11.5.2 Enzalutamide

The Enzalutamide, phase III trial (PREVAIL) has also been unblinded early [845]. In a similar chemo-naïve population of 1717 men this also showed a significant improvement in time to radiological progression (HR 0.186 (CI 0.15-0.23) p < 0.0001) and a marked delay in the initiation of chemotherapy (HR 0.35) with 78% of men seeing at least a 50% decrease in PSA. This also showed statistical improvement in OS (HR 0.706 (CI 0.6-0.84) p < 0.001). The most common clinically relevant adverse events were fatigue and hypertension.

6.11.6 Non-hormonal therapy

6.11.6.1 Docetaxel regimen

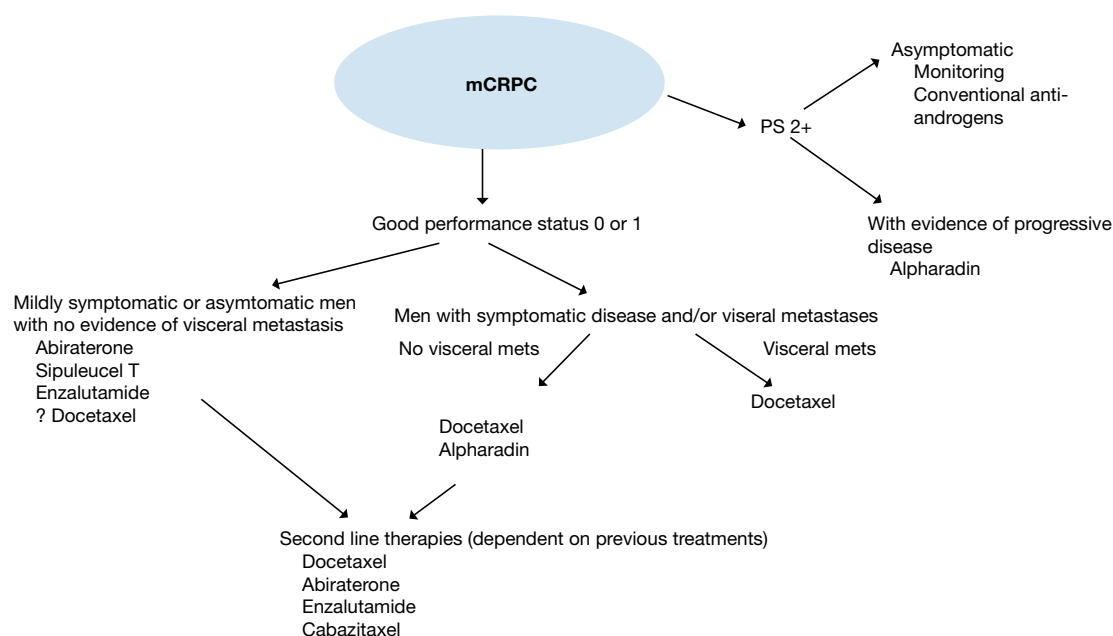
A significant improvement in median survival of 2-2.5 months occurred with docetaxel-based chemotherapy compared to mitoxantrone + prednisone therapy [841, 842]. The standard for first-line cytotoxic chemotherapy is docetaxel using the same regimen as in the TAX 327 trial, that is, 75 mg/m² 3 weekly combined with prednisone 5 mg BID, up to 10 cycles, and palliation is the main target.

The patients considered for docetaxel represent a heterogeneous population. Several poor prognostic factors have been described, such as a PSA level > 114 ng/mL, PSA-DT < 55 days, or the presence of visceral metastases [847]. A better risk group definition has recently been presented, based on the TAX 327 study cohort. The predictive factors were visceral metastases, pain, anaemia (Hb < 13 g/dL), bone scan progression, and prior estramustine before docetaxel. Patients were categorised into three risk groups: low risk (0 or 1 factor), intermediate (2 factors) and high risk (3 or 4 factors), leading to three different lengths of median OS: 25.7, 18.7 and 12.8 months, respectively [848]. In addition, two independent studies have suggested that improved survival can be predicted by C-reactive protein (CRP) levels < 8 mg/L (HR, 2.96) [849, 850]. Age by itself is not a contraindication to docetaxel [851].

6.11.6.2 Vaccine

In 2010, a phase III trial of Sipuleucel T showed a survival benefit in 512 CRPC patients [626]. This was the first time that a PCa vaccine had shown a benefit and led to FDA and EMA approval. Sipuleucel T is an active cellular immunotherapy agent consisting of autologous peripheral blood mononuclear cells, activated in vitro by a recombinant fusion protein comprising prostatic acid phosphatase fused to granulocyte-macrophage colony-stimulating factor, which is an immune-cell activator. In the above trial, patients with metastatic CRPC, with PSA > 5 ng/mL, castrate testosterone level, and no visceral metastases, were randomised to three infusions 2 weeks apart with Sipuleucel T or placebo. The main objective was OS. After a median follow-up of 34 months, the median survival was 25.8 months in the Sipuleucel T group compared to 21.7 months in the placebo group, leading to a significant HR of 0.78 (P = 0.03). Surprisingly, no PSA decline was observed and PFS was equivalent in both arms (14 weeks). The overall tolerance was acceptable, with more cytokine-related adverse events in the Sipuleucel T group, but the same grade 3-4 in both arms. Uptake of Sipuleucel T has been affected by access, cost and questions of timing.

Figure 6.11.1: Flowchart of the potential therapeutic options after PSA progression following initial hormonal therapy



The timing of second-line treatment remains unclear in metastatic CRPC although it is clearly advisable to start immediately in men with symptomatic metastatic disease. As the number of effective treatments available increases and without head to head trials or data assessing the effectiveness of different sequencing options it is not clear how to choose the first “second-line” treatment. In the absence of other data, the inclusion criteria from licensing trials have been used to prioritise treatment sequencing.

Eastern Cooperative Oncology group performance status was used to stratify patients. Generally

men with a performance status of 0-1 are likely to tolerate treatments and those with performance status of 2 or more are less likely to benefit. However, it is important that treatment decisions are individualised and in particular where symptoms related to disease progression are determining performance status it may be appropriate to trial novel treatments in order to see if response is accompanied by improvement in PS.

6.11.7 **Salvage treatment after first-line docetaxel**

All patients who receive docetaxel-based chemotherapy for CRPC will progress, thus, there have been many clinical trials investigating the role of salvage chemotherapy. Several groups have used second-line intermittent docetaxel re-treatment in patients who had clearly responded to first-line docetaxel. In general, a PSA response can be achieved in about 60% of patients with a median time to progression of about 6 months, while treatment-associated toxicity is minimal and similar to that of first-line docetaxel [852, 853].

Available treatments and the setting tested are presented in Table 6.11.3.

Table 6.11.3: Randomised phase III controlled trials - second-line treatment of mCRPC*

Author	Year	Intervention (N)	Comparison (N)	Selection criteria	Main outcomes
ABIRATERONE					
Fizazi [625]	2012	Abiraterone + Prednisone (797)	Placebo + Prednisone (398)	Previous docetaxel. ECOG 0-2. PSA or radiographic progression.	Overall survival: 15.8 vs. 11.2 mo (p < 0.0001). FU: 20.2 mo. Progression-free survival: 5.6 vs. 3.6 mo. Main side effects outcomes: Similar.
de Bono [566]	2011				Overall survival: 14.8 vs. 10.9 mo (p < 0.001). FU: 12.8 mo. Progression-free survival: 5.6 vs. 3.6 mo. Main side effects outcomes: More mineralocorticoid adverse events with abiraterone.
ALPHARADIN					
Parker [854]	2013	Alpharadin (614)	Placebo (307)	Previous or no previous docetaxel. ECOG 0-2. Two or more bone metastases. No visceral metastases.	Overall survival: 14.9 vs. 11.3 mo (p 0.002). FU: Interim analysis. Progression-free survival: 3.6 vs. 3.4 mo (PSA-progression). Main side effects outcomes: 56% vs. 62% grade 3-4.
CABAZITAXEL					
Bahl [628]	2013	Cabazitaxel + Prednisone (378)	Mitoxantrone + Prednisone (377)	Previous docetaxel. ECOG 0-2.	Overall survival: 318/378 vs. 346/377 events (odds ratio 2.11; 95% CI 1.33-3.33). FU: 2 years. Progression-free survival: - Main side effects outcomes: Similar.
deBono [624]	2010 check				Overall survival: 15.1 vs. 12.7 mo (p < 0.0001). FU: 12.8 mo. Progression-free survival: 2.8 vs. 1.4 mos. Main side effects outcomes: 82% vs. 58% neutropenia.

ENZALUTAMIDE					
Scher [567]	2012	Enzalutamide (800)	Placebo (399)	Previous docetaxel. ECOG 0-2.	<p><u>Overall survival:</u> 18.4 vs. 13.6 mo (p < 0.001). FU: 14.4 mo.</p> <p><u>Progression-free survival:</u> 8.3 vs 2.9 mo.</p> <p><u>Main side effects outcomes:</u> 45.3% vs. 53.1% grade 3-4.</p>

**Only studies reporting survival outcomes have been included.*

6.11.7.1 Cabazitaxel

Cabazitaxel is a taxane derivative with some significant differences compared to docetaxel. Positive results have been published from a large prospective, randomised, phase III trial (TROPIC trial) comparing cabazitaxel + prednisone vs. mitoxantrone + prednisone in 755 patients with CRPC, who had progressed after or during docetaxel-based chemotherapy [624]. Patients received a maximum of 10 cycles of cabazitaxel (25 mg/m²) or mitoxantrone (12 mg/m²) plus prednisone (10 mg/day), respectively. Overall survival was the primary end-point and PFS, treatment response and safety were secondary end-points. An OS benefit (15.1 vs. 12.7 months p < 0.0001) was observed in the cabazitaxel arm. There was also a significant improvement in PFS (2.8 vs. 1.4 months, p < 0.0001), objective response rate according to RECIST criteria (14.4% vs. 4.4%, p < 0.005), and PSA response rate (39.2% vs. 17.8%, p < 0.0002). Treatment-associated WHO grade 3/4 side effects developed significantly more often in the cabazitaxel arm, particularly haematological (68.2% vs. 47.3%, p < 0.0002) and non-haematological (57.4% vs. 39.8%, p < 0.0002) toxicity [628]. This drug should be administered by physicians with expertise in handling neutropenia and sepsis, with granulocyte colony-stimulating factor administered prophylactically in the high-risk patient population.

6.11.7.2 Abiraterone acetate

Positive preliminary results of the large phase III COU-AA-301 trial were reported after a median follow-up of 12.8 months [566] and the final results have been reported more recently [625]. A total of 1,195 patients with metastatic CRPC were randomised in a 1/1 fashion to abiraterone acetate or placebo. All patients had progressive disease based on the PCWG2 criteria after docetaxel therapy (with a maximum of two previous chemotherapeutic regimens). The primary end-point was OS, with a planned HR of 0.8 in favour of abiraterone. After a median follow-up of 20.2 months, the median survival in the abiraterone group was 15.8 months compared to 11.2 months in the placebo arm (HR: 0.74, p < 0.001). The benefit was observed irrespective of age, baseline pain intensity, and type of progression. All the secondary objectives were in favour of abiraterone (PSA, radiologic tissue response, time to PSA or objective progression). The incidence of the most common grade 3/4 side effects did not differ significantly between both arms, but mineralocorticoid-related side effects were more frequent in the abiraterone group, mainly grade 1/2 (fluid retention, oedema or hypokalaemia). The longer follow-up did not lead to an unexpected increased in toxicity compared to the preliminary analysis.

6.11.7.3 Enzalutamide

The planned preliminary analysis of the AFFIRM study was published in 2012 [567]. This trial randomised 1,199 patients with metastatic CRPC in a 2/1 fashion to enzalutamide or placebo. The patients had progressed after docetaxel treatment, according to the PCWG2 criteria. Corticosteroids were not mandatory, but could be prescribed, and were therefore received by 30% of the population. The primary end-point was OS, with an expected HR benefit of 0.76 in favour of enzalutamide. After a median follow-up of 14.4 months, the median survival in the enzalutamide group was 18.4 months compared to 13.6 months in the placebo arm (HR: 0.63, p < 0.001). This led to the recommendation that the study be halted and unblinded. The benefit was observed irrespective of age, baseline pain intensity, and type of progression. All the secondary objectives were in favour of enzalutamide (PSA, soft tissue response, QoL, time to PSA or objective progression). No difference in terms of side effects were observed in the 2 groups, with a lower incidence of grade 3-4 side effects in the enzalutamide arm. There was a 0.6% incidence of seizures in the enzalutamide group compared to none in the placebo arm mainly seen in patients with predisposing conditions.

As of today, the choice between third-line hormonal treatment (using enzalutamide or abiraterone) or second-line chemotherapy (cabazitaxel) remains unclear with no clear decision-making findings published. Clinical/biological factors guiding treatment decision are urgently awaited. The optimal sequencing of drugs is not currently known. The cost of each drug will be a major challenge to public health.

6.11.8 Bone targeted therapies in metastatic castration-resistant PCa

CRPC is usually a debilitating disease, often affecting the elderly male. A multidisciplinary approach is often

required with input from medical oncologists, radiation oncologists, urologists, nurses, psychologists and social workers [855]. Critical issues of palliation must be addressed when considering additional systemic treatment, including management of pain, constipation, anorexia, nausea, fatigue and depression, which often occur.

6.11.8.1 Common complications due to bone metastases

Common complications due to bone metastases include bone pain, vertebral collapse or deformity, pathological fractures and spinal cord compression. Cementation is an effective treatment for painful spinal fracture, whatever its origin, clearly improving both pain and QoL [856]. However, it is still important to offer standard palliative surgery, which can be effective for managing osteoblastic metastases [857, 858]. Impending spinal cord compression is an emergency. It must be recognised early and patients should be educated to recognise the warning signs. Once suspected, high-dose corticosteroids must be given and MRI performed as soon as possible. A systematic neurosurgery consultation should be planned to discuss a possible decompression, followed by external beam irradiation [859]. Otherwise, external beam radiotherapy, with or without systemic therapy, is the treatment of choice.

6.11.8.2 Painful bone metastases

Most patients with CRPC have painful bone metastases. External beam radiotherapy is highly effective [860], even as a single fraction [861].

6.11.8.2.1 Radium 223

The only bone-specific drug that is associated with a survival benefit is alfaradin, a radium 223 α -emitter. In a large phase III trial (ALSYMPCA), 921 patients with symptomatic CRPC, who failed or were unfit for docetaxel therapy, were randomised to six injections of 50 kBq/kg alfaradin or placebo. The primary end-point was OS. Alfaradin significantly improved OS by 3.6 months (HR = 0.70; $p < 0.001$) [854]. It was also associated with prolonged time to first skeletal event, improvement in pain scores and improvement in QoL. The associated toxicity was minimal, especially haematologic toxicity, and did not differ significantly from that in the placebo arm [854].

6.11.8.2.2 Bisphosphonates

Bisphosphonates have been used to inhibit osteoclast-mediated bone resorption in CRPC and have proven to be highly effective in reducing bone pain. 643 patients who had CRPC [862] with bone metastases were randomised to receive zoledronic acid, 4 or 8 mg every 3 weeks for 15 consecutive months, or placebo. At 15 and 24 months of follow-up, patients treated with 4 mg zoledronic acid had fewer skeletal-related events (SREs) compared to the placebo group (44% vs. 33%, $P = 0.021$) and fewer pathological fractures (13.1% vs. 22.1%, $P = 0.015$). Furthermore, the time to first SRE was longer in the zoledronic acid group, thus improving QoL.

Patients were initially randomised to 4 or 8 mg of zoledronic acid, but the 8 mg dosage was later modified to 4 mg due to toxicity. The toxicity (e.g., jaw necrosis) of these drugs, especially aminobisphosphonate, must always be kept in mind [859, 860]. Patients should have a dental examination before starting bisphosphonate therapy. The risk of jaw necrosis is increased by a history of trauma, dental surgery or dental infection, as well as long-term intravenous bisphosphonate administration [863].

No survival benefit has been seen in any prospective trial with bisphosphonates.

6.11.8.2.3 RANK ligand inhibitors

Denosumab is a fully human monoclonal antibody directed against RANKL (receptor activator of nuclear factor κ B ligand), a key mediator of osteoclast formation, function, and survival. In M0 CRPC, denosumab has been associated with increased bone-metastasis-free survival compared to placebo (median benefit: 4.2 months, HR: 0.85, $P = 0.028$) [685]. However, this benefit did not translate into a survival difference (43.9 compared to 44.8 months, respectively). The practical impact of this finding remains under discussion. The efficacy and safety of denosumab ($n = 950$) compared with zoledronic acid ($n = 951$) in patients with metastatic CRPC was assessed in a phase III trial. Denosumab was superior to zoledronic acid in delaying or preventing SREs, as shown by time to first on-study SRE (pathological fracture, radiation or surgery to bone, or spinal cord compression) of 20.7 vs. 17.1 months, respectively (HR 0.82; $P = 0.008$). Both urinary NTX and BAP were significantly suppressed in the denosumab arm compared with the zoledronic acid arm ($p < 0.0001$ for both). However, these positive findings were not associated with any survival benefit.

6.11.9 **Conclusion and guidelines for treatment after hormonal therapy (first, second-line modality) in metastatic CRPC**

Conclusion	LE	GR
No definitive strategy regarding treatment choice (which drug/drug family first) can be devised.	4	
Recommendations	LE	GR
In patients with a PSA rise only, two consecutive increases of PSA serum levels above a previous reference level should be documented.	2b	B
Patients should not be started on second-line therapy unless their testosterone serum levels are < 50 ng/dL.	4	A
Patients should not be started on second-line therapy unless their PSA serum levels are > 2 ng/mL to ensure correct interpretation of therapeutic efficacy.	4	B
There is no evidence for treatment of non-metastatic CRPC outside of a clinical trial.	3	A
Men treated with maximal androgen blockade should stop the anti-androgen therapy once PSA progression is documented. <i>Comment: Four to six weeks after discontinuation of flutamide or bicalutamide, an eventual anti-androgen withdrawal effect will be apparent.</i>	2a	A
No clear-cut recommendation can be made for the most effective drug for secondary treatment (i.e. hormone therapy or chemotherapy) as no clear predictive factors exist.	3	A
Salvage hormonal treatment using abiraterone acetate is a valid option.	1b	A
Salvage hormonal treatment using enzalutamide is a valid option.	1b	A

CRPC = castration-resistant prostate cancer; GR = grade of recommendation; LE = level of evidence; PSA = prostate-specific antigen; MAB = maximal androgen blockade.

6.11.10 **Guidelines for cytotoxic treatment and pre/post-docetaxel therapy in mCRPC**

Recommendations	LE	GR
Patients with mCRPC should be counseled, managed and treated by a multidisciplinary team.	3	A
In non-metastatic CRPC, cytotoxic therapy should only be used in a clinical trial setting.	3	B
Prior to treatment, the potential benefits of second-line therapy and expected side effects should be discussed with the patient.		C
In patients with metastatic CRPC who are candidates for salvage cytotoxic therapy, docetaxel at 75 mg/m ² every 3 weeks has shown a significant survival benefit.	1a	A
Docetaxel chemotherapy improves QoL and provides pain relief for men with symptomatic bone metastases due to mCRPC.	1a	A
In patients with relapse following salvage docetaxel chemotherapy, cabazitaxel, abiraterone and enzalutamide are regarded as first-choice options for second-line treatment in mCRPC.	1a	A
In men with mCRPC with symptomatic bone metastases, who are ineligible for or progressing after docetaxel, treatment with Ra 223 (alpharadin) has shown a survival benefit.	1b	A

GR = grade of recommendation; LE = level of evidence; mCRPC = metastatic castration-resistant prostate cancer; PSA = prostate-specific antigen.

6.11.11 **Guidelines for “non-specific” management of mCRPC**

Recommendations	LE	GR
Management of patients with extended symptomatic bone metastases has to be directed at improvement of QoL and mainly pain reduction.	1a	A
Effective medical management with the highest efficacy and a low frequency of side-effects is the major goal of therapy.	1a	A
Bone protective agents may be offered to patients with skeletal metastases (denosumab being superior to zoledronic acid) to prevent osseous complications. However, the benefits must be balanced against the toxicity of these agents, and jaw necrosis in particular must be avoided.	1a	A
Calcium and vitamin D supplementation must be systematically considered when using either denosumab or bisphosphonates.	1b	A
In the management of painful bone metastases, early use of palliative treatments such as radionuclides, external beam radiotherapy and adequate use of analgesics is recommended.	1a	B

In patients with neurological symptoms, spinal surgery or decompressive radiotherapy might be indicated as emergency interventions. High-dose corticosteroids must always be initially considered.	1b	A
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GR = grade of recommendation; LE = level of evidence; mCRPC = metastatic castration-resistant prostate cancer.

7. FOLLOW-UP

7.1 Follow-up: After local treatment

7.1.1 Definition

Local treatment is defined as radical prostatectomy (RP) or radiotherapy, either by external beam radiotherapy or low- or high-dose brachytherapy, or any combination of these. Unestablished alternative treatments, such as HIFU and cryosurgery do not have a well-defined, validated PSA cut-off to define biochemical failure, but do follow the outlines below.

7.1.2 Why follow-up?

Recurrence occurs after primary therapy in many patients who have previously received treatment with intent to cure. Reasons for follow-up vary depending on treatment, patient age, comorbidity and the patient's own wishes. Patients who receive curative therapy are followed up to:

- assess immediate- and long-term oncological results, side effects or complications of therapy, functional outcome and to provide psychological support to PCa survivors;
- discuss the possibility of second-line treatment with curative intent; early hormonal therapy or watchful waiting with the patient.

7.1.3 How to follow-up?

The procedures indicated at follow-up visits vary according to clinical situation. The examinations discussed below are routinely used to detect PCa progression or residual disease. PSA level and DRE are the only tests that should be performed routinely. Disease-specific history is mandatory at every follow-up visit and includes psychological aspects, signs of disease progression, and treatment-related complications. Evaluation of treatment-related complications must be individualised and is beyond the scope of these guidelines. The examinations used most often for cancer-related follow-up after curative surgery or radiotherapy are discussed below.

7.1.3.1 Prostate-specific antigen monitoring

Measurement of PSA is a cornerstone in follow-up after local treatment. Expectations differ after RP and radiotherapy, but PSA recurrence often precedes clinical recurrence [864, 865]. A single, elevated, serum PSA level should be confirmed before starting second-line therapy based solely on PSA elevation.

7.1.3.2 Definition of prostate-specific antigen progression

The PSA level for definition of treatment failure differs between RP and radiotherapy. International consensus defines recurrent cancer after RP by two consecutive PSA values ≥ 0.2 ng/mL [866]. However, others have argued for a higher cut-off of 0.4 ng/mL for patients with a high-risk of clinical progression [865].

Ultrasensitive PSA (US PSA) assay remains controversial for routine follow-up after RP. Men with a US PSA nadir < 0.01 ng/mL have a 4% likelihood of early biochemical relapse [867]. Detectable postoperative US PSA does not predict BCR in all cases, although it adds prognostic value. In men with US PSA > 0.05 ng/mL, 66.8% remained free of biochemical disease at 5 years [868]. If survival is improved by early adjuvant treatment after RP (before PSA reaches > 0.2 ng/mL), higher US PSA nadir levels may help to identify suitable candidates.

At the 2006 RTOG-ASTRO Consensus conference, a new definition of radiation failure was proposed to establish better correlation between definition and clinical outcome, namely, an increase of 2 ng/mL above the post-treatment PSA nadir [708]. It applies to patients with or without hormonal therapy.

After HIFU or cryotherapy, there are various definitions for PSA relapse [507]. Most of these are based on a cut-off PSA level of ~ 1 ng/mL, combined with negative post-treatment biopsy. No end-points have been validated against clinical progression or survival; therefore, it is not possible to give a firm recommendation of biochemical failure.

7.1.3.3 Prostate-specific antigen monitoring after radical prostatectomy

Prostate-specific antigen is expected to be undetectable within 6 weeks after successful RP [869]. Persistently elevated PSA in patients treated with RP is thought to be due to residual cancer, either micrometastases or residual pelvic disease.

Rapidly increasing PSA level indicates distant metastases, whereas later, slowly increasing level most likely indicates local recurrence. Time to PSA recurrence and tumour differentiation are important predictive factors distinguishing local and systemic recurrence [870]. Local treatment failure and distant metastases occur with undetectable PSA levels. This is rare and occurs mostly in patients with undifferentiated tumours [871].

Thus, in patients with favourable pathology (< pT3, pN0, Gleason score < 8), PSA measurement and disease-specific history could be a single test in follow-up after RP.

7.1.3.4 PSA monitoring after radiotherapy

PSA level falls slowly after radiotherapy compared with RP. A nadir < 0.5 ng/mL is associated with a favourable outcome after radiotherapy [872], although the optimal value is controversial. The interval before reaching the nadir can be up to 3 years or more. Biochemical failure after radiotherapy is currently defined as PSA > 2 ng/mL above the nadir [708]. After radiotherapy, PSA-DT is correlated with site of recurrence: patients with local recurrence have a DT of 13 months compared to 3 months for those with distant failure [873].

7.1.3.5 Digital rectal examination

Local recurrence after curative treatment is possible without a concomitant rise in PSA level [871]. However, this has only been proven in patients with unfavourable pathology, namely, undifferentiated tumours. PSA measurement and DRE comprise the most useful combination for first-line examination in follow-up after radiotherapy or RP, but PSA measurement may be the only test in cases with favourable pathology (< pT3, pN0, Gleason < 8) [874].

7.1.3.6 Transrectal ultrasonography (TRUS), bone scintigraphy, computed tomography (CT), magnetic resonance imaging (MRI), and ¹¹C-choline positron emission tomography computed tomography (PET/CT)

Imaging techniques have no place in routine follow-up of localised PCa. They are only justified in patients with biochemical failure or in patients with symptoms for whom the findings affect treatment decisions. (See Section 6.19.4 for a more detailed discussion).

7.1.3.6.1 Transrectal ultrasonography/magnetic resonance imaging biopsy

Biopsy of the prostate bed and urethrovesical anastomosis are only indicated if local recurrence affects treatment decisions.

7.1.4 When to follow-up?

Most patients who fail treatment for PCa do so early, even if failure only becomes clinically obvious after years. Patients should be followed-up more closely during the initial post-treatment period when risk of failure is highest. PSA measurement, disease-specific history and DRE are recommended at 3, 6 and 12 months postoperatively, every 6 months thereafter until 3 years, and then annually.

The first clinic visit is mainly to detect treatment-related complications and assist patients in coping with their new situation. Tumour or patient characteristics may allow alterations to this schedule. Patients with poorly differentiated and locally advanced tumours or with positive margins may be followed-up more closely than those with a well-differentiated, intracapsular or specimen-confined tumour. Advanced age or associated comorbidity may make further follow-up in asymptomatic patients superfluous.

7.1.5 Conclusions and guidelines for follow-up after treatment with curative intent

Conclusions	LE
After RP, serum PSA level > 0.2 ng/mL is associated with residual or recurrent disease.	
After radiotherapy, an increase in PSA > 2 ng/mL above the nadir, rather than a specific threshold value, is the most reliable sign of recurrence.	B
Palpable nodules and increasing serum PSA are signs of local recurrence.	B

Recommendations	GR
In asymptomatic patients, disease-specific history and serum PSA measurement supplemented by DRE are recommended for routine follow-up. These should be performed at 3, 6 and 12 months after treatment, then every 6 months until 3 years, and then annually.	B
Imaging to detect local recurrence is only recommended if it affects treatment planning. Biopsy is usually not necessary before second-line therapy, except after EBRT when local salvage treatment is considered.	B
Routine bone scans and other imaging are not recommended in asymptomatic patients if there are no signs of biochemical relapse. In patients with bone pain or other symptoms of progression, re-staging should be considered irrespective of serum PSA level.	B

DRE = digital rectal examination; GR = grade of recommendation; LE = level of evidence; PSA = prostate-specific antigen; RP = radical prostatectomy.

7.2 Follow-up: During hormonal treatment

7.2.1 Introduction

A large proportion of patients treated with hormonal therapy have either metastatic or locally advanced tumours at diagnosis. This will affect the follow-up schedule as biochemical failure is often associated with rapid symptomatic progression.

7.2.2 Purpose of follow-up

The main objectives of follow-up in these patients are to:

- monitor the response to treatment;
- ensure compliance with treatment;
- detect potential complications of endocrine therapy;
- guide the modalities of palliative symptomatic treatment at the time of CRPC.

It is important to be clear about which complementary investigations are helpful at different stages of the disease to avoid unnecessary patient examinations and excessive costs. Based on current knowledge, it is not possible to formulate level 1 evidence guidelines for follow-up procedures following hormonal therapy.

7.2.3 Methods of follow-up

7.2.3.1 Clinical follow-up

Clinical follow-up is mandatory. Neither biology nor imaging modalities can replace face to face clinic visits. Patients should be seen on a regular basis to check for possible troublesome symptoms. Of upmost importance in patients in the M1b stage is to highlight and check for possible early signals of spinal cord compression, urinary tract complications (ureteral obstruction, bladder outlet obstruction, etc) or bone lesions at an increased fracture risk.

7.2.3.1.1 Prostate-specific antigen monitoring

Prostate-specific antigen (PSA) is a good marker for following the course of PCa.

Treatment response may be assessed using the change in serum PSA level as a surrogate endpoint for survival in patients with newly diagnosed metastatic PCa. Patients with a PSA nadir < 0.2 ng/mL after 7 months of treatment have been shown to have the best survival (median 75 months) compared to patients with a value of 0.2-4.0 ng/mL (median 44 months) or > 4.0 ng/mL (median 13 months) [571]. Similar results have been found in locally advanced and metastatic PCa [875, 876], as in salvage ADT for elevated PSA following treatments with curative intent [877].

Patients should be regularly monitored to detect and treat any complications of endocrine treatment as well as disease progression, usually after a median of 12-18 months in patients with stage M1 disease. A rise in PSA level usually precedes the onset of clinical symptoms by several months. However, it must be stressed that the PSA level is insufficient as clinical progression (usually bone pain) with normal PSA levels has been reported.

7.2.3.1.2 Creatinine, haemoglobin and liver function monitoring

Creatinine monitoring is good clinical practice as an increase may be linked to silent bilateral ureteral obstruction or bladder retention. Liver function tests may suggest disease progression and/or toxicity of hormonal treatment (especially non-steroidal antiandrogens), which can lead to interruption of hormonal treatment. A decline in haemoglobin after 3 months of ADT is independently associated with a shorter progression-free and OS [878] and might explain significant fatigue.

Alkaline phosphatase may increase secondary to bone metastases and androgen-induced osteoporosis [879]. Therefore, it may be helpful to determine its bone-specific isoenzymes as none are directly influenced by hormonal therapy.

7.2.3.1.3 Bone scan, ultrasound and chest X-ray

Asymptomatic patients with a stable PSA level should not undergo imaging at regular intervals [207].

In the case of bone symptoms or PSA progression under castration, a bone scan might be helpful, if a treatment modification is considered. The Prostate Cancer Clinical Trials Working Group 2 has clarified the definition of bone scan progression as the appearance of at least two new lesions [880], later confirmed.

Suspicion of disease progression indicates the need for additional imaging modalities, guided by symptoms or subsequent possible treatment decisions. In CRPC, follow-up examinations should be individualised with the aim of maintaining the patient's QoL.

7.2.3.1.4 Testosterone monitoring

Most PCa patients receiving LHRH analogues will achieve serum testosterone values at or below the castration level (< 1 nmol/L). However, approximately 13-38% of patients fail to achieve this therapeutic goal. In addition, up to 24% of men treated with LHRH analogues may experience testosterone surges (testosterone > 50 ng/dL) during long-term treatment, which is described as the 'acute on-chronic effect' or 'breakthrough response'.

The measurement of serum testosterone levels should be considered part of clinical practice for men on LHRH therapy. The timing of testosterone measurements is not clearly defined. A 3 to 6-month testosterone level assessment may be performed to ensure the castration level is being maintained. If it is not being maintained, switching to another LHRH agonist or antagonist or to surgical orchiectomy should be considered. In patients with rising PSA and/or clinical signs of progression, serum testosterone must be evaluated in all cases to confirm a castrate-resistant state.

7.2.3.1.5 Monitoring of metabolic complications

Androgen deprivation therapy is beneficial in patients with PCa, but has a greater range of complications than might be expected. The most severe complications are bone problems, the metabolic syndrome and cardiovascular morbidity (see section 7.5). The patient's GP or family physician should probably be more involved.

All patients should be screened for diabetes by checking fasting glucose and HbA1c (at baseline and then every 3 months), as for blood lipid levels. In selected cases, glucose tolerance testing may be required. Men with impaired glucose tolerance and/or diabetes should be referred for an endocrine consultation. A cardiology consultation should be considered in men with a history of cardiovascular disease and men older than 65 years prior to starting ADT. Monitoring serum levels of vitamin D and calcium is important. If necessary, supplements should be given to ensure a daily intake of at least 1200 mg/day of calcium and 1000 IU of vitamin D. Preventive therapy with bisphosphonates or denosumab using specific doses (which differ from those used in the CRPC stage) could be considered in patients who have an initial T-score of less than -2.5 on DEXA. It is suggested that bone monitoring should be performed every 2 years after castration, provided there are no other risk factors [881], or yearly if there are risk factors [882, 883]. However, prospective trials are needed.

Patients on ADT should be given advice on modifying their lifestyle (e.g. diet, exercise, smoking cessation, etc) and should be treated for any existing conditions, such as diabetes, hyperlipidaemia, and/or hypertension [884, 885]. Furthermore, the risk-to-benefit ratio of ADT must be considered in patients with a higher risk of cardiovascular complications, especially if it is possible to delay starting ADT [676].

7.2.4 **When to follow-up**

After the initiation of hormonal treatment, it is recommended that patients are followed up at 3 and 6 months. These guidelines must be individualised and each patient should be advised to contact his physician in the event of troublesome symptoms.

7.2.4.1 *Stage M0 - M1 patients*

If there is a good treatment response, i.e. PSA response (less than 4 ng/mL), symptomatic improvement, good psychological coping, good treatment compliance, and a serum PSA level of less than 4 ng/mL, follow-up visits are scheduled every 6 months (a 3-month schedule can be considered in M1 patients).

7.2.4.2 *Castration-refractory PCa*

Patients whose disease progresses, or who do not respond according to the criteria mentioned above, warrant an individualised follow-up scheme.

7.2.5 Guidelines for follow-up after hormonal treatment

Recommendations	GR
Patients should be evaluated at 3 and 6 months after the initiation of treatment.	A
As a minimum, tests should include serum PSA measurement, DRE, serum testosterone, and careful evaluation of symptoms in order to assess the treatment response and side effects.	A
In patients undergoing intermittent androgen deprivation, PSA and testosterone should be monitored at fixed intervals during the treatment pause (one or three months).	A
Follow-up should be tailored for the individual patient, according to symptoms, prognostic factors and the treatment given.	A
In patients with stage M0 disease with a good treatment response, follow-up is scheduled every 6 months, and as a minimum should include a disease-specific history, DRE and serum PSA determination.	A
In patients with stage M1 disease with a good treatment response, follow-up is scheduled for every 3 to 6 months. As a minimum, this should include a disease-specific history, DRE and serum PSA determination, and is frequently supplemented with haemoglobin, serum creatinine and alkaline phosphatase measurements. The testosterone level should be checked, especially during the first year.	A
Patients (especially with M1b status) should be advised about the clinical signs that could suggest spinal cord compression.	A
When disease progression occurs, or if the patient does not respond to treatment, follow-up should be individualised.	A
In patients with suspected progression, the testosterone level must be checked. By definition, CRPC is based on the assumption that the patient has a testosterone level of at least < 50 ng/mL (< 1 mL/L).	B
Routine imaging of stable patients is not recommended.	B

CRPC = castrate-resistant prostate cancer; DRE = digital rectal examination; GR = grade of recommendation; PSA = prostate-specific antigen.

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9. CONFLICT OF INTEREST

All members of the Prostate Cancer Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: <http://www.uroweb.org/guidelines/>. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

Guidelines on **Renal Cell Carcinoma**

B. Ljungberg (Chair), K. Bensalah, A. Bex (Vice-chair), S. Canfield,
S. Dabestani (Guidelines Associate), R.H. Giles (Patient Advocate),
F. Hofmann (Guidelines Associate), M. Hora, M.A. Kuczyk, T. Lam,
L. Marconi (Guidelines Associate), A.S. Merseburger,
T. Powles, M. Staehler, A. Volpe

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1. INTRODUCTION

1.1 Aims and scope

The European Association of Urology (EAU) Renal Cell Cancer (RCC) Guidelines Panel has compiled these clinical guidelines to provide urologists with evidence-based information and recommendations for the management of RCC.

1.2 Panel composition

The RCC panel is an international group of clinicians consisting of urological surgeons, an oncologist, methodologists, a pathologist and a radiologist, with particular expertise in the field of urological care. For the 2015 guideline update, the panel incorporated a patient advocate to provide a consumer perspective for its guidelines.

All experts involved in the production of this document have submitted potential conflict of interest statements.

The panel is most grateful for the methodological and scientific support provided by the following individuals in specific parts of the guideline document:

- Prof. Dr. O. Hes, pathologist, Plzen (CZ) (Other renal tumours);
- Dr. T. Adewuyi, Aberdeen, UK: (systematic review - Systemic therapy for metastatic disease and providing general assistance for various aspects of the systematic review);
- Dr. H. Bekema, Groningen (NL): (systematic review - Lymph node dissection in localised and locally advanced RCC);
- Dr. F. Stewart, Aberdeen (UK): (systematic review - Tumour thrombus)
- Prof. Dr. A. Graser, radiologist, Munich (DE): (development of a systematic review for the diagnosis and follow-up chapters [in progress]).

1.3 Available publications

A quick reference document (Pocket guidelines) is available, both in print and in a number of versions for mobile devices. These are abridged versions which may require consultation together with the full text versions. Several scientific publications are available as are a number of translations of all versions of the EAU RCC Guidelines [1-3]. All documents are available free access through the EAU website Uroweb: <http://www.uroweb.org/guidelines/online-guidelines/>.

1.4 Publication history and summary of changes

1.4.1 Publication history

The EAU RCC Guidelines were first published in 2000. This 2015 RCC Guidelines document presents a limited update of the 2014 publication.

1.4.2 Summary of changes

All chapters of the 2015 RCC Guidelines have been updated, based on the 2014 update. The consistency of the data work-up will differ between sections. An overview is presented in Table 1.1.

Table 1.1: Description of update and summary of review methodology for the 2015 update

Chapter	Brief description of review methodology
1. Introduction	Not applicable
2. Methods	Not applicable
3. Epidemiology, Aetiology and Pathology	Updated using a structured data assessment. Of particular note is the inclusion of the new Vancouver Classification in the Histology section [4, 5].
4. Staging and grading classification systems	Updated using a traditional narrative review.
5. Diagnostic evaluation	Updated using a systematic review on tumour biopsy. Updated using a structured data assessment [6].
6. Prognosis	Updated using a traditional narrative review, based on a structured literature search.
7. Treatment (Disease management)	Updated using a systematic review mostly based on a literature search from 2000. A new section, 'Management of RCC with venous thrombus' has been added which is based on a systematic review [7]. A new section on recurrent RCC was added.
8. Surveillance following radical or partial nephrectomy or ablative therapies	Updated using a traditional narrative review, based on a structured data search.

Changed recommendations

Recommendations have been rephrased and added to throughout the current document, not resulting in a change in the grade of recommendation (GR). New recommendations have been included in Sections:

3.4 Recommendations for other renal tumours

Recommendations	GR
<p>AMLs, active surveillance is the most appropriate option for most AMLs. Treatment with selective arterial embolisation (SAE) or NSS can be considered in:</p> <ul style="list-style-type: none"> • large tumours (recommended threshold of intervention does not exist, the formerly recommended size of > 4 cm wide is disputed); • females of childbearing age; • patients in whom follow-up or access to emergency care may be inadequate. 	C

7.1.2.2.4 Conclusions and recommendations

Recommendation	GR
PN should be favoured over RN in patients with T1b tumour, whenever feasible.	B

7.2.4.3 Conclusions and recommendations

Conclusions	LE
In patients with locally advanced disease due to clinically enlarged LNs the survival benefit of LND is unclear. In these cases LND can be performed for staging purposes.	3

7.3.3.8 Conclusions and recommendations for systemic therapy in mRCC

Recommendation	LE	GR
Sunitinib can be recommended as first-line therapy for non-clear-cell mRCC.		B

2. METHODS

2.1 Introduction

For sections of the guidelines that have been updated using a systematic review, the review methodology is outlined in detail elsewhere [8]. Briefly, a systematic review of the literature was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9]. Important topics and questions were prioritised for the present update. Elements for inclusion and exclusion, including patient population, intervention, comparison, outcomes, study design, and search terms and restrictions were developed using an iterative process involving all members of the panel, to achieve consensus. Individual literature searches were conducted separately for each update question, and in most instances the search was conducted up to the end of November 2013. Two independent reviewers screened abstracts and full texts, carried out data abstraction and assessed risk of bias. The results were presented in tables showing baseline characteristics and summaries of findings. Meta-analyses were performed only for randomised controlled trials (RCTs) which demonstrated consistency and homogeneity of data. When this was not possible, a narrative synthesis of the evidence was provided.

The remaining sections of the guidelines were updated using a traditional narrative review strategy. Structured literature searches using an expert information specialist were designed. Searches of the Cochrane Database of Systematic Reviews, the Cochrane Library of Controlled Clinical Trials, and Medline and Embase on the Dialog-Datastar platform were performed. The controlled terminology of the respective databases was used, and both MesH and Emtree were analysed for relevant entry terms. The search strategies covered the last 3 years (from 2011). An update was carried out before the publication of this document. Other data sources were also consulted, including the Database of Abstracts of Reviews of Effectiveness (DARE), and relevant reference lists from other guidelines producers such as the National Institute for Clinical Excellence (NICE) and the American Urological Association (AUA).

The majority of studies in this guideline update are retrospective analyses that include some larger multicentre studies and well-designed controlled studies. As only a few RCTs are available, most of the data are not based on high levels of evidence. Conversely, in the systemic treatment of metastatic RCC, a number of randomised studies have been performed, resulting in more reliable recommendations based on higher levels of evidence.

In this 2015 EAU Guidelines compilation, all standard information on levels of evidence (LE) and grading of recommendations (GR) has been taken out of the individual guidelines topics for the sake of brevity. This information is included in the introductory section of this print.

2.2 Future goals

In addition to further systematic data work-up, the RCC panel intend to focus on patient-reported outcomes.

The use of clinical quality indicators is an area of interest. A number of key quality indicators for this patient group have been selected:

1. Thorax CT for staging of pulmonary metastasis.
2. Proportion of patients with T1aN0M0 tumours undergoing nephron sparing surgery as first treatment.
3. The proportion of patients treated within 6 weeks after diagnosis.
4. The proportion of patients with metastatic RCC offered treatment with targeting agents.
5. Proportion of patients who undergo minimally invasive or operative treatment as first treatment who die within 30 days.

2.3 Peer review

This document was subjected to double-blind peer review prior to publication.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Renal cell carcinoma (RCC) represents 2-3% of all cancers [10], with the highest incidence in Western countries. Over the last two decades until recently, the incidence of RCC increased by about 2% both worldwide and in Europe, although a continuing decrease has been observed in Denmark and Sweden [11]. In 2012, there were approximately 84,400 new cases of RCC and 34,700 kidney cancer-related deaths in the European Union [12]. In Europe, overall mortality rates for RCC increased up to the early 1990s, and stabilised or declined thereafter [13]. Mortality has decreased since the 1980s in Scandinavian countries and since the early 1990s in France, Germany, Austria, the Netherlands, and Italy. However, in some European countries (Croatia, Estonia, Greece, Ireland, Slovakia), mortality rates still show an upward trend [13].

Different RCC types have specific histopathological and genetic characteristics [14]. There is a 1.5:1 male predominance, with peak incidence between 60 and 70 years. Aetiological factors include smoking, obesity, and hypertension [15-18]. Having a first-degree relative with kidney cancer also increases the risk of RCC [19]. A number of other factors associated with higher or lower RCC risk include specific dietary habits and occupational exposure to specific carcinogens, however, literature results are inconclusive [20, 21]. Moderate alcohol consumption appears to have a protective effect for unknown reasons [22, 23]. Effective prophylaxis includes avoidance of cigarette smoking and obesity.

Due to increased detection of tumours by ultrasound (US) and computed tomography (CT), the number of incidentally diagnosed RCCs has increased. These tumours are usually smaller and of lower stage [24-26].

3.1.1 Conclusion and recommendation

Conclusion	LE
Several verified risk factors have been identified including smoking, obesity and hypertension. These are considered definite risk factors for RCC.	2a

Recommendation	GR
The most important primary prevention for RCC is elimination of cigarette smoking and obesity reduction.	B

3.2 Histological diagnosis

Renal cell carcinomas comprise a broad spectrum of histopathological entities described in 2004 WHO classification [4] and modified by ISUP Vancouver Classification [5]. There are three main RCC types: clear cell (ccRCC), papillary (pRCC - type I and II) and chromophobe (chRCC). RCC type classification has been confirmed by cytogenetic and genetic analyses [27-29] (LE: 2b). Collecting duct carcinoma and other infrequent renal tumours are discussed in Section 3.3.

Histological diagnosis includes, besides RCC type, evaluation of nuclear grade, sarcomatoid features, vascular invasion, tumour necrosis, and invasion of the collecting system and perirenal fat. Fuhrman nuclear grade has been the most widely accepted grading system [30]. At the ISUP conference, a simplified, nuclear grading system, based only on size and shape of nucleoli, has been proposed which will replace the Fuhrman grading system [5].

3.2.1 Clear cell (ccRCC)

Grossly, ccRCC is well circumscribed, capsule is usually absent. The cut surface is golden-yellow, often with haemorrhage and necrosis. The Fuhrman nuclear grading system is generally used [30]. Loss of chromosome 3p and mutation of the VHL (von Hippel-Lindau) gene at chromosome 3p25 are frequently found. ccRCC has a worse prognosis compared with pRCC and chRCC [31, 32] even after stratification for stage and grade [33]. The 5-year CSS rate was 91%, 74%, 67% and 32% for TNM stages I, II, III and IV (patients treated 1987-98) [34]. The indolent variant of ccRCC is multilocular cystic and accounts for approximately 4% of all ccRCC [5].

3.2.2 Papillary (pRCC)

Macroscopically, pRCC is well circumscribed with pseudocapsule, yellow or brown in colour, and a soft structure. Genetically, pRCC shows trisomies of chromosomes 7 and 17 and the loss of chromosome Y. Papillary RCCs are heterogeneous, with three different subtypes; two basic (1 and 2) and a third type,

oncocytic. Compared with ccRCC, pRCC has a significantly higher rate of organ confined tumour (pT1-2N0M0) and higher 5-year CSF [35]. Prognosis of pRCC type 2 is worse than for type 1 [36-38]. Exophytic growth, pseudonecrotic changes and pseudocapsule are typical signs of pRCC type 1. Pseudocapsules and extensive necrotic changes cause a spherical tumour in the extrarenal section. Tumours with massive necroses are fragile and vulnerable to spontaneous rupture or rupture resulting from minimal trauma followed by retroperitoneal bleeding. A well-developed pseudocapsule in pRCCs type 1 probably prevents these tumours from rupturing despite necroses. Necroses cohere with a hypodense central area of tumour on postcontrast CT. This area is surrounded by a vital tumour tissue, seen as a serpiginous contrast-enhancing margin on CT [39]. Some authors consider type 3; oncocytic pRCC, to have no pseudocapsule or massive necrosis, rare extrarenal growth and low malignant potential [38], although this type is not generally accepted [5].

3.2.3 **Chromophobe (chRCC)**

Grossly, chRCC is a pale tan, relatively homogenous and tough, well-demarcated mass without a capsule. Instead of the Fuhrman grading system, a special histopathological grading system by Paner et al. was proposed in 2010 [40, 41]. Loss of chromosomes 2, 10, 13, 17 and 21 are typical genetic changes [42]. The prognosis is relatively good, with high 5-year recurrence-free survival, CSS and 10-year CSS [43].

3.3 **Other renal tumours**

Other renal tumours constitute the remaining 10-15 % of renal cortical tumours. These include a variety of uncommon, sporadic, and familial carcinomas, some only recently described, and a group of unclassified carcinomas. A summary of these tumours are given in Table 3.1, but some clinically relevant tumours and extremely rare entities are mentioned below.

3.3.1 **Carcinoma associated with end-stage renal disease; acquired cystic disease-associated RCC**

Cystic degenerative changes (acquired cystic kidney disease [ACKD]) and a higher incidence of RCC are typical features of ESKD (end-stage kidney disease). RCCs of native end-stage kidneys are found in about 4% of patients. The lifetime risk of developing RCCs is at least 10 times higher than in the general population. Compared with sporadic RCCs, ACKDs generally are multicentric and bilateral, found in younger patients (mostly male), and are less aggressive [44, 45]. The relatively indolent outcome of tumours in ESKD is due to the mode of diagnosis and a specific ACKD related molecular pathway still to be determined [45]. Although the histological spectrum of ACKD tumours is similar to that in sporadic RCC, the predominant form is pRCC. The remaining tumours are mostly ccRCC [44-46]. A specific subtype of RCC occurring in end-stage kidneys only was described as Acquired Cystic Disease-associated RCC (ACD-RCC) [5].

3.3.2 **Papillary adenoma**

These tumours have papillary or tubular architecture of low nuclear grade and are 5 mm in diameter or smaller [4]. They are found incidentally in nephrectomy specimens.

3.3.3 **Hereditary kidney tumours**

Hereditary kidney tumours are found in the following entities: Von Hippel-Lindau syndrome, hereditary pRCC, Birt-Hogg-Dubé syndrome (see Hybrid oncocytoma-chromophobe carcinoma), hereditary leiomyomatosis and renal cell cancer (HLRCC), tuberous sclerosis complex, germline succinate dehydrogenase (SDH) mutation, nonpolyposis colorectal cancer syndrome, hyperparathyroidism-jaw tumour syndrome, PTEN hamartoma syndrome, constitutional chromosome 3 translocation, and familial nonsyndromic ccRCC. RMC can be included because of its association with hereditary haemoglobinopathies [4, 5, 36, 47].

3.3.4 **Angiomyolipoma (AML)**

Angiomyolipoma is a benign mesenchymal tumour, can occur sporadically, and is four times more likely in women. It also occurs in tuberous sclerosis (TS). It accounts for approximately 1% of surgically removed tumours. Ultrasound, CT, and MRI often lead to diagnosis due to the presence of adipose tissue. Biopsy is rarely useful. Pre-operatively, it may be difficult to differentiate between smooth muscle cell tumours and epithelial tumours. AML can be found in TS in LNs, but is not metastases, and has a multicentric genesis. AML can be due to angiotropic-type growth in the renal vein or the IVC. AML with LN involvement and tumorous thrombus is benign. Only epithelioid AML is potentially malignant [4, 48]. AML has a slow and consistent growth rate, and minimal morbidity [49]. The main complications of renal AML are retroperitoneal bleeding or bleeding into the urinary collection system, which can be life-threatening [50]. The bleeding tendency is related to the angiogenic component of the tumour that includes irregular and aneurysmatic blood vessels [50]. The major risk factors for bleeding are tumour size, grade of the angiogenic component, and the presence of TS [50, 51]. Indications for intervention are pain, bleeding, or suspected malignancy.

3.3.4.1 Treatment

Active surveillance (AS) is the most appropriate option for most AMLs [49, 52] (LE: 3). Risk factors for delayed intervention include tumour size ≥ 4 cm and symptoms at diagnosis [52]. Selective arterial embolisation (SAE) seems to be the first-line option used for active treatment after AS was discontinued [52] (LE: 3). SAE is an efficient treatment for AML devascularisation but only volume reduction [53]. And although SAE controls haemorrhage in the acute setting, it has limited value in the longer-term [49, 50]. If surgery is selected, most cases of AML can be managed by conservative NSS, although some patients may require complete nephrectomy [51] (LE: 3). Radiofrequency ablation (RFA) can be option as well [49, 50, 54]. The volume of AML can be reduced by the m-Tor inhibitor everolimus [55] and sirolimus can be combined with deferred surgery [56].

Table 3.1: Other renal cortical tumours, and recommendations for treatment (GR: C)

Entity [4, 5]	Clinical relevant notes	Malignant potential	Treatment of localised tumour/metastatic tumour
Sarcomatoid variants of RCC	Sign of high-grade transformation without being a distinct histological entity	High	Surgery/sunitinib, option of gemcitabine plus doxorubicin [57].
Multilocular ccRCC		Low, no metastasis	Surgery, NSS*
Carcinoma of the collecting ducts of Bellini	Rare, often presenting at an advanced stage (N+ 44% and M1 33% at diagnosis). The hazard ratio in CSS in comparison with ccRCC is 4.49 [32].	High, very aggressive. Median survival 30 months [58].	Surgery/Response to targeted therapies was poor [59].
Renal medullary carcinoma	Very rare. Mainly young black men with sickle cell trait	High, very aggressive, median survival is 5 months [58].	Surgery/different chemotherapy regimes, radiosensitive.
Translocation RCC (TRCC) Xp11.2	Rare, mainly younger patients under 40, more common in females. It constitute with TRCC 6p21 MiT translocation renal cell carcinomas [60].	High	Surgery/VEGF-targeted therapy.
Translocation RCC t(6;11)		Low/intermediate	Surgery, NSS/VEGF-targeted therapy.
Mucinous tubular and spindle cell carcinoma	Tumour is associated with the loop of Henle	Intermediate	Surgery, NSS
Acquired cystic disease-associated RCC		Low	Surgery
Clear cell (tubulo) papillary RCC	It has been reported under the term renal angiomyomatous tumour (RAT) as well.	Low	Surgery, NSS
Tubulocystic RCC	Mainly men, imaging can be Bosniak III or IV.	Low (90% indolent)	Surgery, NSS
Hybrid oncocytic chromophobe tumour	Mixture of cells of chRCC and renal oncocytoma. Three clinicopathological situations: sporadic, in association with renal oncocytosis/oncocytomatosis or in patients with Birt-Hogg-Dubé syndrome.	Low or benign	Surgery, NSS
Metanephric tumours	Divided into metanephric adenoma, adenofibroma, and metanephric stromal tumours.	Benign	Surgery, NSS

Cystic nephroma/ Mixed Epithelial and Stromal Tumour	Term renal epithelial and stromal tumours (REST) is used as well. Imaging – Bosniak type III or II/IV.	Low/benign	Surgery, NSS
Oncocytoma	3-7% of all renal tumours. Imaging characteristics alone are unreliable when differentiating between oncocytoma and RCC. Histopathological diagnosis remains the reference standard [61, 62].	Benign	Observation (when histologically confirmed) [63, 64]/NSS.
Hereditary kidney tumours	Details see above	High	Surgery, NSS
Angiomyolipoma	Details see above	Benign	Consider treatment only in very well selected patients.
Carcinoma associated with neuroblastoma	Long-term survivors of childhood neuroblastoma have a 329-fold increased risk of renal carcinoma.	Variable	Surgery, NSS
Thyroid-like follicular carcinoma of the kidney (TLFC)	Succinate Dehydrogenase B Mutation-associated RCC, ALK Translocation RCC (ALK - anaplastic lymphoma kinase).	Low	Surgery, NSS
Unclassified RCC	RCC that cannot be assigned to any other category of RCC- type carcinoma [4].	Variable	Surgery, NSS

*NSS = *nephron-sparing surgery*; CSS = *cancer specific survival*.

3.3.4.2 Summary

A variety of renal tumours exist, and about 15% are benign. All kidney lesions require examination for malignant behaviour.

3.4 Conclusions and recommendations

Conclusions	LE
Except for AML, most other renal tumours cannot be differentiated from RCC by radiology and should be treated in the same way as RCC.	3
In biopsy-proven oncocytomas, watchful waiting is an option.	3
In advanced uncommon renal tumours, a standardised oncological treatment approach does not exist.	3

Recommendations	GR
Bosniak cysts \geq type III should be regarded as RCC and treated accordingly.	C
AMLs, active surveillance is the most appropriate option for most AMLs. Treatment with selective arterial embolisation (SAE) or NSS can be considered in: <ul style="list-style-type: none"> large tumours (recommended threshold of intervention does not exist, the formerly recommended size of > 4 cm is disputed); females of childbearing age; patients in whom follow-up or access to emergency care may be inadequate. 	C

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Staging

The TNM classification system is recommended for clinical and scientific use [65], but requires continuous improvements [66]. The latest version was published in 2009 with supplement 2012 (Table 4.1), and its prognostic value was confirmed in single and multi-institution studies [67, 68]. Tumour size, venous invasion, renal capsular invasion, adrenal involvement, and lymph node (LN) and distant metastasis are included in the TNM classification system (Table 4.1). However, some uncertainties remain:

- The sub-classification of T1 tumours using a cut-off of 4 cm might not be optimal in NSS for localised cancer.
- The value of size stratification of T2 tumours has been questioned [69].
- Since the 2002 version, tumours with renal sinus fat invasion have been classified as pT3a. However, renal sinus fat invasion might carry a worse prognosis than perinephric fat invasion but is included in the same pT3a stage group [70-72] (LE: 3).
- Sub T-stages (pT2b, pT3a, pT3c and pT4) may overlap [68].
- For adequate M staging, accurate preoperative imaging (chest and abdominal CT) should be performed [73, 74] (LE: 4).

Table 4.1: 2009 TNM classification system [65] and TNM supplement 2012 [75]

T - Primary tumour			
TX	Primary tumour cannot be assessed		
T0	No evidence of primary tumour		
T1	Tumour ≤ 7 cm in greatest dimension, limited to the kidney		
	T1a	Tumour ≤ 4 cm in greatest dimension, limited to the kidney	
	T1b	Tumour > 4 cm but ≤ 7 cm in greatest dimension	
T2	Tumour > 7 cm in greatest dimension, limited to the kidney		
	T2a	Tumour > 7 cm but ≤ 10 cm in greatest dimension	
	T2b	Tumours > 10 cm limited to the kidney	
T3	Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland or beyond Gerota's fascia		
	T3a	Tumour grossly extends into the renal vein or its segmental (muscle-containing) branches, or invades perirenal and/or renal sinus fat (peripelvic), but not beyond Gerota's fascia	
	T3b	Tumour grossly extends into the vena cava (VC) below the diaphragm	
	T3c	Tumour grossly extends into vena cava above the diaphragm or invades the wall of the VC	
T4	Tumour invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)		
N - Regional LNs			
NX	Regional LNs cannot be assessed		
N0	No regional LN metastasis		
N1	Regional LN metastasis		
M - Distant metastasis			
M0	No distant metastasis		
M1	Distant metastasis		
TNM stage grouping			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1, T2, T3	N1	M0
Stage IV	T4	Any N	M0
	Any T	Any N	M1

A help desk for specific questions about TNM classification is available at <http://www.uicc.org/tnm>.

4.2 Anatomic classification systems

Objective anatomic classification systems, such as the Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) classification system, the R.E.N.A.L. nephrometry score and the C-index have been

proposed, to standardise the description of renal tumours [76-78]. These systems include assessment of tumour size, exophytic/endophytic properties, nearness to the collecting system and renal sinus, and anterior/posterior location.

The use of such a system is helpful as it allows objective prediction of potential morbidity of NSS and tumour ablation techniques. These tools provide information for treatment planning, patient counselling, and comparison of PN and tumour ablation series. However, when selecting the best treatment option, anatomic scores must always be considered together with patient features and surgeon experience.

5. DIAGNOSTIC EVALUATION

5.1 Symptoms

Many renal masses remain asymptomatic until the late disease stages. More than 50% of RCCs are detected incidentally by non-invasive imaging used to investigate various nonspecific symptoms and other abdominal diseases [68, 79] (LE: 3). The classic triad of flank pain, gross haematuria, and palpable abdominal mass is rare (6-10%) and correlates with aggressive histology and advanced disease [80, 81] (LE: 3).

Paraneoplastic syndromes are found in approximately 30% of patients with symptomatic RCCs (LE: 4). Some symptomatic patients present with symptoms caused by metastatic disease, such as bone pain or persistent cough [82] (LE: 3).

5.1.1 Physical examination

Physical examination has a limited role in RCC diagnosis. However, the following findings should prompt radiological examinations:

- Palpable abdominal mass;
- Palpable cervical lymphadenopathy;
- Non-reducing varicocele and bilateral lower extremity oedema, which suggests venous involvement.

5.1.2 Laboratory findings

Commonly assessed laboratory parameters are serum creatinine, glomerular filtration rate (GFR), complete cell blood count, erythrocyte sedimentation rate, liver function study, alkaline phosphatase, lactate dehydrogenase (LDH), serum corrected calcium [83, 84], coagulation study, and urinalysis (LE: 4).

For central renal masses abutting or invading the collecting system, urinary cytology and possibly endoscopic assessment should be considered in order to exclude urothelial cancer (LE: 4).

Split renal function should be estimated using renal scintigraphy in the following situations [85, 86] (LE: 2b):

- when renal function is compromised, as indicated by increased serum creatinine or significantly decreased GFR;
- when renal function is clinically important - e.g., in patients with a solitary kidney or multiple or bilateral tumours.

Renal scintigraphy is an additional diagnostic option in patients at risk of future renal impairment due to comorbid disorders.

5.2 Imaging investigations

Most renal tumours are diagnosed by abdominal US or CT performed for other medical reasons [79] (LE: 3). Renal masses are classified as solid or cystic based on imaging findings.

5.2.1 Presence of enhancement

With solid renal masses, the most important criterion for differentiating malignant lesions is the presence of enhancement [87] (LE: 3). Traditionally, US, CT, or magnetic resonance imaging (MRI) are used for detecting and characterising renal masses. Most renal masses are diagnosed accurately by imaging alone. Contrast-enhanced US can be helpful in specific cases [88-90] (LE: 3).

5.2.2 CT or MRI

CT or MRI are used to characterise renal masses. Imaging must be performed before and after administration of intravenous contrast material to demonstrate enhancement. In CT imaging, enhancement in renal masses is determined by comparing Hounsfield units (HUs) before and after contrast administration. A change of 15 or more HUs demonstrates enhancement [91] (LE: 3). To maximise differential diagnosis and detection, the

evaluation should include images from the nephrographic phase for best depiction of renal masses, which do not enhance to the same degree as the renal parenchyma.

CT or MRI allow accurate diagnosis of RCC, but cannot reliably distinguish oncocytoma and fat-free angiomyolipoma from malignant renal neoplasms [61, 92-94] (LE: 3). Abdominal CT provides information on:

- Function and morphology of the contralateral kidney [95] (LE: 3);
- Primary tumour extension;
- Venous involvement;
- Enlargement of locoregional lymph nodes;
- Condition of the adrenal glands and other solid organs (LE: 3).

Abdominal contrast-enhanced biphasic CT angiography is useful in selected cases for detailed information on renal vascular supply [96, 97].

If the results of CT are indeterminate, MRI may provide additional information on:

- enhancement in renal masses [98];
- locally advanced malignancy [99-101];
- venous involvement if the extent of an inferior vena cava (IVC) tumour thrombus is poorly defined on CT [99-102] (LE: 3). Doppler US is less accurate for identifying the extent of a venous tumour thrombus [101] (LE: 3).

MRI is indicated in patients who are allergic to intravenous CT contrast medium and in pregnancy without renal failure [100, 103] (LE: 3). Advanced MRI techniques such as diffusion-weighted and perfusion-weighted imaging are being explored for renal mass assessment [104].

In patients with hereditary RCC who are worried about the radiation exposure of frequent CT scans, MRI may be offered as alternative.

5.2.3 **Other investigations**

Renal arteriography and inferior venacavography have a limited role in the work-up of selected RCC patients (LE: 3). In patients with any sign of impaired renal function, an isotope renogram and total renal function evaluation should be considered to optimise treatment decision-making [85, 86] (LE: 2a).

The value of positron-emission tomography (PET) in the diagnosis and follow-up of RCC remains to be determined, and PET is not currently recommended [105] (LE: 3).

5.2.4 **Radiographic investigations for metastatic RCC**

Chest CT is accurate for chest staging [73, 74, 106-108] (LE: 3). However, routine chest radiography must be performed for metastases, but is less accurate than chest CT (LE: 3). There is a consensus that most bone and brain metastases are symptomatic at diagnosis, thus routine bone or brain imaging is not generally indicated [106, 109, 110] (LE: 3). However, bone scan, brain CT, or MRI may be used in the presence of specific clinical or laboratory signs and symptoms [110-112] (LE: 3).

5.2.5 **Bosniak classification of renal cystic masses**

This classification system classifies renal cysts into five categories, based on CT imaging appearance, to predict malignancy risk [113, 114] (LE: 3). This system also advocates treatment for each category (Table 5.1).

Table 5.1: Bosniak classification of renal cysts [113]

Bosniak category	Features	Work-up
I	Simple benign cyst with a hairline-thin wall without septa, calcification, or solid components. Same density as water and does not enhance with contrast medium.	Benign
II	Benign cyst that may contain a few hairline-thin septa. Fine calcification may be present in the wall or septa. Uniformly high-attenuation lesions < 3 cm in size, with sharp margins without enhancement.	Benign
IIF	These may contain more hairline-thin septa. Minimal enhancement of a hairline-thin septum or wall. Minimal thickening of the septa or wall. The cyst may contain calcification, which may be nodular and thick, with no contrast enhancement. No enhancing soft-tissue elements. This category also includes totally intrarenal, non-enhancing, high attenuation renal lesions ≥ 3 cm. Generally well-margined.	Follow-up. Some are malignant.

III	These are indeterminate cystic masses with thickened irregular walls or septa with enhancement.	Surgery or active surveillance – see Chapter 7. Over 50% are malignant
IV	Clearly malignant containing enhancing soft-tissue components.	Surgery. Most are malignant.

5.3 Renal tumour biopsy

Percutaneous renal tumour biopsy can reveal histology of radiologically indeterminate renal masses and should be considered to select patients with small masses for active surveillance, to obtain histology before ablative treatments and to select the most suitable form of medical and surgical treatment strategy in the setting of metastatic disease [115-124] (LE: 3). Due to the high diagnostic accuracy of abdominal imaging, renal tumour biopsy is not necessary in patients with a contrast-enhancing renal mass for whom surgery is planned (LE: 4).

Percutaneous sampling can be performed under local anaesthesia with needle core biopsy and/ or fine needle aspiration (FNA). Biopsies can be performed with US or CT guidance, with a similar diagnostic yield [120, 123] (LE: 2b). Eighteen-gauge needles are ideal for core biopsies, as they result in low morbidity and provide sufficient tissue for diagnosis [115-123, 125] (LE: 2b). A coaxial technique allowing multiple biopsies through a coaxial cannula should always be used to avoid potential tumour seeding [115, 116-123] (LE: 3).

Core biopsies should be preferred for the characterization of solid renal masses (LE: 2b). A systematic review and meta-analysis of the diagnostic performance and complications of RTB was recently performed by the panel. Fifty-seven articles including a total of 5228 patients were included in the analysis. Needle core biopsies were found to have better accuracy for the diagnosis of malignancy compared with FNA [6]. Other studies showed that solid pattern and larger tumour size are predictors of a diagnostic core biopsy [120, 123] (LE: 2b).

In experienced centres, core biopsies have a high diagnostic yield, specificity, and sensitivity for the diagnosis of malignancy [6] (LE: 2b). However, 0-22.6% of core biopsies are non-diagnostic [115-123, 126-142] (LE: 2b). If a biopsy is non-diagnostic, and radiologic findings are suspicious for malignancy, a further biopsy or surgical exploration should be considered (LE: 4). Assessment of tumour grade on core biopsies is challenging. The accuracy of nuclear grading of biopsies is poor (62.5% on average), but can be improved (87% on average) using a simplified two-tier system (high-grade vs. low grade) [6] (LE: 2b).

The ideal number and location of core biopsies are undefined. However, at least two good quality cores should be obtained, and necrotic areas should be avoided to maximise diagnostic yield [115, 117, 120, 121, 123] (LE: 4). Peripheral biopsies are preferable for larger tumours, to avoid areas of central necrosis [143] (LE: 2b).

Core biopsies have a low diagnostic yield for cystic masses and are not recommended alone, unless areas with a solid pattern are present (Bosniak IV cysts) [120, 123] (LE: 2b). Combined FNA and core biopsies can provide complementary results, especially for complex cystic lesions [122, 127-129, 140, 144, 145] (LE: 3).

Overall, percutaneous biopsies have low morbidity [6]. Spontaneously resolving subcapsular/ perinephric haematoma are frequent complications, while clinically significant bleeding is unusual (0.0-1.4%) and generally self-limiting.

6. PROGNOSTIC FACTORS

Prognostic factors can be classified into: anatomical, histological, clinical, and molecular.

6.1 Anatomical factors

Tumour size, venous invasion, renal capsular invasion, adrenal involvement, and lymph node (LN) and distant metastasis are included in the TNM classification system [65] (Table 4.1).

6.2 Histological factors

Histological factors include Fuhrman grade, RCC subtype, sarcomatoid features, microvascular invasion, tumour necrosis, and invasion of the collecting system. Fuhrman nuclear grade is the most widely accepted grading system [30]. Although affected by intra- and inter-observer discrepancies, it is an independent prognostic factor [146]. A simplified two- or three-strata system may be as accurate for prognostication as the classical four-tiered grading scheme [147, 148] (LE: 3). In univariate analysis, patients with chRCC vs. pRCC vs. ccRCC had a better prognosis [149, 150]. However, prognostic information provided by the RCC type is lost

when stratified to tumour stage [31, 150] (LE: 3).

Differences in tumour stage, grade and cancer specific survival (CSS) between the RCC types are illustrated in Table 6.1.

Table 6.1: Basic characteristics of three main types of RCC [31, 32, 151]

Type	Percentage of RCC (~)	Advanced disease at diagnosis (T3-4, N+, M+)	Fuhrman Grade 3 or 4 [30]	CSS (HR)
ccRCC	80-90%	28%	28.5%	referent
pRCC	6-15%	17.6%	28.8%	0.64 - 0.85
chRCC	2-5%	16.9%	32.7%*	0.24 - 0.56

CSS = cancer-specific survival; HR = hazard ratio.

*The Fuhrman grading system is validated for ccRCC, but is unreliable for chRCC. Data based on the Paner et al. grading system are not available yet [30, 40, 41].

In all RCC types, prognosis worsens with stage and histopathological grade (Tables 6.2 and 6.3).

The 5-year overall survival (OS) for all types of RCC is 49%, which has improved since 2006 probably due to an increase in incidentally detected RCCs and the introduction of TKI inhibitors [152]. Sarcomatoid changes can be found in all RCC types and are equivalent of high grade and very aggressive tumours.

Table 6.2: CSS by stage and histopathological grade in RCCs - hazard ratio (95% CI) (Keegan et al, 2012 [32]).

T1N0M0	Referent
T2N0M0	2.71 (2.17-3.39)
T3N0M0	5.20 (4.36-6.21)
T4N0M0	16.88 (12.40-22.98)
N+M0	16.33 (12.89-20.73)
M+	33.23 (28.18-39.18)
Grade 1	Referent
Grade 2	1.16 (0.94-1.42)
Grade 3	1.97 (1.60-2.43)
Grade 4	2.82 (2.08-3.31)

CI = confidential interval.

Long-term survival in RCC patients treated by radical (RN) or partial nephrectomy (PN) between 1970 and 2003; for unilateral, sporadic ccRCC, pRCC or chRCC in a cohort study [151] (Table 6.3).

Table 6.3: CSS of surgically treated patients by RCC type (estimated survival rate in percentage [95% CI])

Survival time	5 years (%)	10 years (%)	15 years (%)	20 years (%)
ccRCC	71 (69-73)	62 (60-64)	56 (53-58)	52 (49-55)
pRCC	91 (88-94)	86 (82-89)	85 (81-89)	83 (78-88)
chRCC	88 (83-94)	86 (80-92)	84 (77-91)	81 (72-90)

Two subgroups of pRCC with different outcomes have been identified [153]: Type 1 are low-grade tumours with a chromophilic cytoplasm and a favourable prognosis. Type 2 are mostly high-grade tumours with an eosinophilic cytoplasm and a propensity for metastases (LE: 3).

RCC with Xp 11.2 translocation has a poor prognosis [154]. Its incidence is low, but should be systematically addressed in young patients.

RCC type classification has been confirmed by cytogenetic and genetic analyses [27-29] (LE: 2b).

6.3 Clinical factors

These include performance status, localised symptoms, cachexia, anaemia, and platelet count [82, 155-157] (LE: 3).

6.4 Molecular factors

Numerous molecular markers such as carbonic anhydrase IX (CAIX), vascular endothelial growth factor (VEGF), hypoxia-inducible factor (HIF), Ki67 (proliferation), p53, PTEN (phosphatase and tensin homolog) (cell cycle), E-cadherin, C-reactive protein (CRP), osteopontin [158] and CD44 (cell adhesion) [159, 160] have been investigated (LE: 3). None of these markers have improved the predictive accuracy of current prognostic systems and their use is not recommended in routine practice. Although gene expression profiling seems promising, it has not identified new relevant prognostic factors [161].

6.5 Prognostic systems and nomograms

Postoperative prognostic systems and nomograms combining independent prognostic factors have been developed and externally validated [162-168]. These may be more accurate than TNM stage or Fuhrman grade alone for predicting survival (LE: 3). An advantage of nomograms is their ability to measure predictive accuracy (PA), allowing all new predictive parameters to be objectively evaluated. Before being adopted, new prognostic variables or systems should demonstrate that its PA is superior to conventional postoperative histo-prognostic schemes [169]. Recently, new preoperative nomograms with excellent PAs have been designed [170, 171].

Table 6.4 summarises the current most relevant prognostic systems.

6.6 Conclusion and recommendations

Conclusion	LE
In RCC patients, TNM stage, Fuhrman nuclear grade, and RCC subtype (WHO, 2004; [21]), provide important prognostic information.	2

Recommendations	GR
Use of the current TNM classification system.	B
Grading systems and classification of RCC subtype.	B
Prognostic systems in the metastatic setting.	B
In localised disease, the use of integrated prognostic systems or nomograms is not routinely recommended, although they can provide a rationale for enrolling patients into clinical trials.	C
Molecular prognostic markers are not recommended for routine clinical use.	C

Table 6.4: Anatomical, histological, and clinical variables in the commonly used prognostic models for localised and metastatic RCC

Prognostic Models		Variables													
		TNM Stage	ECOG PS	Karnofsky PS	RCC related symptoms	Fuhrman grade	Tumour necrosis	Tumour size	Delay between diagnosis and treatment	LDH	Corrected calcium	Hemoglobin	Neutrophil count	Platelet count	
Localised RCC	UISS	X	X			X									
	SSIGN	X				X	X								
	Post operative Karakiewicz's nomogram	X			X	X	X								
Metastatic RCC	MSKCC prognostic system			X					X	X	X				
	Heng's model			X					X		X	X	X	X	

ECOG PS = Eastern Cooperative Oncology Group performance status; LDH = lactate dehydrogenase; MSKCC = Memorial Sloan Kettering Cancer Center;

PS = performance status; SSIGN = Stage Size Grade Necrosis; UISS = University of California Los Angeles integrated staging system.

7. DISEASE MANAGEMENT

7.1 Treatment of localised RCC

7.1.1 Introduction

A systematic review underpins the findings of Sections 7.1.2 through 7.2.4.2. This review included all relevant published literature comparing surgical management of localised RCC (T1-2N0M0) [172, 173]. Randomised or quasi-randomised controlled trials (RCTs) were included. However, due to the very limited number of RCTs, nonrandomised studies (NRS), prospective observational studies with controls, retrospective matched-pair studies, and comparative studies from the databases of well-defined registries were also included. For this Guidelines version, an updated search was performed up to May 31st, 2013 [174].

7.1.2 Surgical treatment

7.1.2.1 Nephron-sparing surgery versus radical nephrectomy

Based on current available oncological and QoL outcomes, localised renal cancers are better managed by NSS (partial nephrectomy, PN) rather than radical nephrectomy (RN), irrespective of the surgical approach.

The estimated CSS rates at 5 years were comparable using these surgical techniques [175-179]. This was recently confirmed in a study of solitary T1-2 N0M0 renal tumours ≤ 5 cm with normal contralateral kidney function and WHO PS 0-2. At 9.3 years survival follow-up, 198 patients were alive after RN and 173 after PN. The CSS was 98.5 vs 97%, respectively. Local recurrence occurred in one and 6 patients in the RN and PN group, respectively [180].

A number of studies compared PN vs. RN (open or laparoscopic) for renal carcinoma (≤ 4 cm) [180-184]. RN was associated with increased mortality from any cause after adjusting for patient characteristics. In a prematurely closed randomised study of RCC ≤ 5 cm, comparing PN and RN, there was no difference in OS in the targeted population [179]. In studies analysing RCCs of 4-7 cm, no differences in CSS was observed between PN and RN [183, 185-192]. When laparoscopic PN was compared with laparoscopic RN in RCCs > 4 cm, there was no difference in OS, CSS and recurrence-free survival (RFS) rates [193]. Furthermore, a retrospective matched-pair analysis in elderly patients [194] reported a CSS of 98% for PN vs. 95% for RN.

Other studies have compared various aspects of QoL and safety in open PN and RN [175-178, 190, 192, 195-197].

There was no difference in the length of hospital stay [176, 177, 196], blood transfusions [176, 196, 197], or mean blood loss [176, 196]. Complication rates were inconsistently reported and one intervention was not favoured over another [198]. One study found that mean operative time was longer for open PN [198], but other research found no difference [199]. Three studies consistently reported worse renal function after RN compared to PN [175, 178]. More patients had impaired post-operative renal function after RN after adjustment for diabetes, hypertension and age [178].

One database review compared open PN with laparoscopic RN in RCCs 4-7 cm. A significantly lower mean increase in post-operative creatinine levels was found [186]. Another study comparing laparoscopic PN vs. laparoscopic RN found that estimated GFR (eGFR) decreased less in the PN group, while the RN group had significantly more patients with a two-stage increase in CKD [193]. Another database review [200] compared safety and efficacy of laparoscopic PN in RCCs > 2 cm (2-4 cm versus > 4 cm). The laparoscopic PN group had a greater post-operative decrease in eGFR compared to the patients with smaller RCCs.

Two studies reported QoL post-surgery for RCC. Patients who underwent PN reported better scores, in many aspects of QoL [195]. Those who underwent RN reported more fear associated with living with only one kidney. Regardless of the intervention, patients with RCCs < 4 cm and a normal contralateral kidney showed the highest QoL scores after treatment, which matched their pre-diagnosis scores. Those with more complications had lower QoL scores [176].

No prospective comparative studies reporting oncological outcomes for minimally invasive ablative procedures compared with RN were identified. One trial reported on RFA vs. RN or PN for T1a RCC, resulting in CSS of 100% for all three treatments [201].

Patient and tumour characteristics permitting, the current oncological outcomes evidence base suggests that localised RCCs are best managed by PN than RN, irrespective of the surgical approach. Where open surgery is necessary, the oncological outcomes following open PN are at least as good as open RN and should be the preferred option when feasible.

PN is unsuitable in some patients with localised RCC due to:

- locally advanced tumour growth;
- partial resection is not feasible due to unfavourable tumour location;
- significant deterioration in patient health.

In these situations, the curative therapy is RN, including removal of the tumour-bearing kidney. Complete resection of the primary tumour by open or laparoscopic surgery offers a reasonable chance of cure.

7.1.2.2 Associated procedures

7.1.2.2.1 Adrenalectomy

One prospective NRS compared the outcomes of RN or PN with, or without, ipsilateral adrenalectomy [202]. Multivariate analysis showed that upper pole location was not predictive of adrenal involvement, but tumour size was. No difference in OS at 5 or 10 years was seen, with, or without, adrenalectomy. Adrenalectomy was justified using criteria based on radiographic and intra-operative findings. Only 48 of 2,065 patients underwent concurrent ipsilateral adrenalectomy of which 42 were for benign lesions.

7.1.2.2.2 Lymph node dissection for clinically negative lymph nodes (cN0)

Lymph node dissection (LND) in RCC is controversial [203]. Clinical assessment of LNs status is based on enlargement of LNs on CT/MRI and intraoperative assessment by direct palpation. Less than 20% of clinically positive (cN+) LNs are confirmed to be metastatic at pathology (pN+) [204]. CT/MRI do not allow detection of small metastases in normal sized LNs [205] and extended LND (e-LND) with histopathological examination is the only way to assess LNs status. For clinically positive LNs (cN+) see Section 7.2. on locally advanced RCC. In patients with clinically negative LNs (cN0) six clinical trials have been reported [203], one RCT [204] and five comparative studies [206-210].

Retrospective series support the hypothesis that LND may be beneficial in high-risk patients [205, 211]. However, in the EORTC study only 4% of cN0 patients had positive LNs at final pathology, suggesting that LND represents overtreatment in the majority [204].

Clinical trials of lower quality suggest that e-LND should involve the LNs surrounding the ipsilateral great vessel and the interaortocaval region from the crus of the diaphragm to the common iliac artery. Involvement of interaortocaval LNs without regional hilar involvement is reported in up to 35-45% of cases [205, 206, 212]. At least 15 LNs should be removed [213, 214]. Sentinel LND is an investigational technique [215, 216]. Better survival outcomes are seen in patients with a low number of positive LNs (< 4) and no extranodal extension [217, 218]. A preoperative nomogram to predict pN+ LNs status has been proposed [219].

7.1.2.2.3 Embolisation

Before routine nephrectomy, tumour embolisation has no benefit [220, 221]. In patients unfit for surgery, or with non-resectable disease, embolisation can control symptoms, including gross haematuria or flank pain [222-224]. These indications will be repeated in Sections 7.2 and 7.3 with cross reference to the conclusions and recommendations below.

7.1.2.2.4 Conclusions and recommendations

Conclusions	LE
PN achieves similar oncological outcomes to RN for clinically localised tumours (cT1).	1b
Ipsilateral adrenalectomy during RN or PN has no survival advantage.	3
In patients with localised disease without evidence of LN metastases, there is no survival advantage of LND in conjunction with RN.	1b
In patients unfit for surgery with massive haematuria or flank pain, embolisation can be a beneficial palliative approach.	3

Recommendations	GR
Surgery is recommended to achieve cure in localised RCC.	B
PN is recommended in patients with T1a tumours.	A
PN should be favoured over RN in patients with T1b tumour, whenever feasible.	B
Ipsilateral adrenalectomy is not recommended when there is no clinical evidence of invasion of the adrenal gland.	B
LND is not recommended in localised tumour without clinical evidence of LN invasion.	A

7.1.3 Radical and partial nephrectomy techniques

7.1.3.1 Radical nephrectomy techniques

No RCTs have assessed oncological outcomes of laparoscopic vs. open RN. A cohort study [225] and retrospective database reviews are available, mostly of low methodological quality [176, 226, 227]. Similar

oncological outcomes for laparoscopic vs. open RN were found. Data from one RCT [228] and two NRSs [176, 225] showed a significantly shorter hospital stay and lower analgesic requirement for the laparoscopic RN group compared with the open group. Convalescence time was also significantly shorter [225]. No difference in the number of patients receiving blood transfusions was observed, but peri-operative blood loss was significantly less in the laparoscopic arm in all three studies [176, 225, 228]. Surgical complications were marked by low event rates and very wide confidence intervals. There was no difference in complications, but operation time was significantly shorter in the open nephrectomy arm. Post-operative QoL scores were similar [176].

The best approach for RN was the retroperitoneal or transperitoneal with similar oncological outcomes in the two RTCs [229, 230] and one quasi-randomised study [231]. QoL variables were similar in the two approaches.

Hand-assisted vs. standard laparoscopic RN was compared in one RCT [231] and one database review [198]. Estimated 5-year OS, CSS, and RFS rates were comparable. Duration of surgery was significantly shorter in the hand-assisted approach, while length of hospital stay and time to non-strenuous activities were shorter for the standard laparoscopic RN [198, 231]. However, the sample size was small.

Robot-assisted laparoscopic RN vs. laparoscopic RN was compared in one small study [232]. There were no local recurrences, port-site or distant metastases, but the sample size was small and follow-up was short. Similar results were seen in observational cohort studies comparing 'portless' and 3-port laparoscopic RN [233, 234]. Peri-operative outcomes were similar.

7.1.3.2 *Partial nephrectomy techniques*

Studies comparing laparoscopic PN and open PN found no difference in PFS [235-238] and OS [237, 238] in centres with laparoscopic expertise. The mean estimated blood loss is lower with the laparoscopic approach [235, 237, 239], while post-operative mortality, DVT, and pulmonary embolism events are similar [235, 237]. Operative time is generally longer with the laparoscopic approach [236-238] and warm ischaemia time is shorter with the open approach [235, 237, 239, 240]. In a matched-pair comparison, GFR decline was greater in the laparoscopic PN group in the immediate post-operative period [238], but not after a follow-up of 3.6 years. In another comparative study, the surgical approach was not an independent predictor for post-operative CKD [240]. Retroperitoneal and transperitoneal laparoscopic PN have similar peri-operative outcomes [241]. Simple tumour enucleation has similar PFS and CSS rates compared to standard PN and RN in a large study [242, 243].

The feasibility of off-clamp laparoscopic PN and laparoendoscopic single-site PN has been shown in selected patients, but larger studies are needed to confirm their safety and clinical role [244, 245].

No studies have compared the oncological outcomes of robot-assisted vs. laparoscopic PN. A comparison of surgical outcomes after robotic or pure laparoscopic PN in moderate-to-complex renal tumours showed a significantly lower estimated blood loss and a shorter warm ischaemia time in the robotic group [246]. Two recent meta-analyses of relatively small series showed comparable peri-operative outcomes and a shorter warm ischaemia time for robot-assisted PN [247, 248].

7.1.3.3 *Conclusions and recommendations*

Conclusions	LE
Laparoscopic RN has lower morbidity than open surgery.	1b
Oncological outcomes for T1-T2a tumours are equivalent between laparoscopic and open RN.	2a
PN can be performed, either with an open, pure laparoscopic or robot-assisted approach, based on surgeon's expertise and skills.	2b

Recommendations	GR
Laparoscopic RN is recommended for patients with T2 tumours and localised masses not treatable by PN.	B
RN should not be performed in patients with T1 tumours for whom PN is indicated.	B

7.1.4 *Therapeutic approaches as alternatives to surgery*

7.1.4.1 *Surgical versus non-surgical treatment*

Population-based studies compared the oncological outcomes of surgery (RN or PN) and non-surgical management for tumours < 4 cm. The analyses showed a significantly lower cancer-specific mortality for patients treated with surgery [249, 250]. However, the patients assigned to the surveillance arm were older and

likely to be more frail and less suitable candidates for surgery to be addressed. Other cause mortality rates in the non-surgical group significantly exceeded that of the surgical group [249]. Analyses of older patients (> 75 years) failed to show the same benefit in cancer-specific mortality for surgical treatment [251-253].

7.1.4.2 Surveillance

Elderly and comorbid patients with incidental small renal masses have a low RCC-specific mortality and significant competing-cause mortality [254, 255]. Active surveillance is defined as the initial monitoring of tumour size by serial abdominal imaging (US, CT, or MRI) with delayed intervention reserved for tumours showing clinical progression during follow-up [256].

In the largest reported series of active surveillance, the growth of renal tumours was low and progression to metastatic disease was reported in a limited number of patients [257, 258].

A single-institutional comparative study evaluating patients aged ≥ 75 years showed decreased OS for those who underwent surveillance and nephrectomy relative to NSS for clinically T1 renal tumours; however, patients selected for surveillance were older with greater comorbidity. At multivariable analysis, management type was not associated with OS after adjusting for age, comorbidity, and other variables [254]. No statistically significant difference in OS and CSS were observed in another study of RN vs. PN vs. active surveillance for T1a renal masses with a follow-up of 34 months [259]. Overall, both short- and intermediate-term oncological outcomes indicate that in selected patients with advanced age and/or comorbidities, active surveillance is appropriate to initially monitor small renal masses, followed if required, by treatment for progression [256-258, 260-263].

A multicentre study assessed patient QoL undergoing immediate intervention vs. active surveillance. Patients undergoing immediate intervention had higher QoL scores at baseline, specifically for physical health. The perceived benefit in physical health persisted for at least 1 year following intervention. Mental health, which includes domains of depression and anxiety, was not adversely affected while on active surveillance [264].

7.1.4.3 Ablative therapies

7.1.4.3.1 Cryoablation

Cryoablation is performed using either a percutaneous or a laparoscopic-assisted approach. In comparative studies, there was no significant difference in the overall complication rates between laparoscopic and percutaneous cryoablation [265-267]. One comparative study reported similar OS, CSS, and RFS in 172 laparoscopic patients with a longer follow-up compared with 123 percutaneous patients with a shorter follow-up [266]. A shorter average length of hospital stay was found with the percutaneous technique [266, 267]. No studies compared surveillance strategies to cryoablation.

7.1.4.3.2 Cryoablation versus PN

Studies compared open, laparoscopic or robotic PN with percutaneous or laparoscopic cryoablation. Oncological outcomes were mixed, with some studies showing no difference in OS, CSS, RFS, DFS, local recurrence or progression to metastatic disease [268, 269], and some showing significant benefit for the PN techniques for some or all of these outcomes [270-273]. Not all studies reported all outcomes listed, and some were small and included benign tumours. No study showed oncological benefit for the cryoablation technique over PN.

Perioperative outcomes, complication rates and other quality of life measures were also mixed. Some studies found the length of hospital stay was shorter and surgical blood loss was less with cryoablation [268-270], while also finding no differences in other peri-operative outcomes, recovery times, complication rates or post-operative serum creatinine levels. Two studies [272, 273] reported specific Clavien rates, with mostly non-significant differences, which were mixed for intra-operative vs. post-operative complications. Estimated GFRs were not significantly different in two studies, but in favour of cryoablation in a third [271-273]. Estimates of new CKD were also mixed, with one study in favour of cryoablation [271], another strongly in favour of PN [272], and the third showing no difference [273]. One study compared PN with ablation therapy, either cryoablation or RFA [274], and showed significantly improved DSS at both 5 and 10 years for PN.

7.1.4.3.3 Radiofrequency ablation

RFA is performed laparoscopically or percutaneously. Three studies compared patients with T1a tumours treated by laparoscopic or percutaneous RFA [275-277]. Complications occurred in up to 29% of patients but were mostly minor. Complication rates were similar in patients treated laparoscopically or percutaneously. One study with a limited number of patients [277] found a higher rate of incomplete ablation in patients treated by percutaneous RFA. However, no differences in recurrence or CSS were found in the three comparative studies.

7.1.4.3.4 RFA versus PN

Most publications about RFA are retrospective cohort studies with a low number of patients and limited follow-up. Three studies retrospectively compared RFA to surgery in patients with T1a tumours [201, 278, 279].

One study [278] compared T1a patients who underwent either RFA (percutaneous or laparoscopic) or partial nephrectomy and found no difference in OS and CSS. Another study retrospectively reviewed 105 T1a patients treated by percutaneous RFA or radical nephrectomy. CSS was 100% in both groups. OS was lower in the RFA group but patients treated with surgery were younger [201].

In a monocentric study that compared 34 RFA patients to 16 open partial nephrectomy patients, there was a higher rate of complications and transfusions in the PN group. Although the tumours were larger in PN patients, progression rates were similar (0%) [279].

7.1.4.3.5 Cryoablation versus RFA

Two studies compared RFA and cryoablation [280, 281]. No significant differences were reported for OS, CSS, or RFS in either study. For local RFS at 5 years, one study [280] reported improvement with RFA, while the other [281] reported a benefit with cryoablation. One study [280] reported no differences in Clavien complication rates between the techniques.

7.1.4.3.6 Other ablative techniques

Some studies have shown the feasibility of other ablative techniques, such as microwave ablation, laser ablation, and high-intensity focused US ablation. However, these techniques are considered experimental.

7.1.4.3.7 Conclusions and recommendations

Conclusions	LE
Population-based analyses show a significantly lower cancer-specific mortality for patients treated with surgery compared to non-surgical management. However, the same benefit in cancer-specific mortality is not confirmed in analyses focusing on older patients (> 75 years).	3
In active surveillance cohorts, the growth of small renal masses is low in most cases and progression to metastatic disease is rare (1-2%).	3
Quality of the available data does not allow definitive conclusions regarding morbidity and oncological outcomes of cryoablation and RFA.	3
Low quality studies suggest a higher local recurrence rate for minimally invasive therapies compared to PN.	3

Recommendations	GR
Due to the low quality of available data no recommendation can be made on RFA and cryoablation.	C
In the elderly and/or comorbid patients with small renal masses and limited life expectancy, active surveillance, RFA and cryoablation can be offered.	C

7.2 Treatment of locally advanced RCC

7.2.1 Introduction

In addition to the conclusions and recommendations outlined in Section 7.1 for localised RCC certain therapeutic strategies arise in specific situations of locally advanced disease.

7.2.2 Management of clinically positive lymph nodes (cN+)

In the presence of clinically positive LNs (cN+), LND is always justified [34]. However, the extent of LND is controversial [205].

7.2.3 Management of locally advanced unresectable RCC

In patients with non-resectable disease, embolisation can control symptoms, including gross haematuria or flank pain [222-224]. The use of neoadjuvant targeted therapy to downsize tumours is experimental and cannot be recommended outside controlled clinical trials.

7.2.4 Management of RCC with venous thrombus

Tumour thrombus formation in the IVC in RCC patients is a significant adverse prognostic factor. Traditionally, patients with venous tumour thrombus (VTT) undergo surgery to remove the kidney and tumour thrombus (TT). Aggressive surgical resection is widely accepted as the default management option for patients with VTT [282-290]. However, uncertainties remain over the best approach for surgical treatment of these patients.

7.2.4.1 The evidence base for surgery in patients with VTT

The data on whether patients with VTT should undergo surgery is derived from case series. In one of the largest published studies [287] a higher level of thrombus was not associated with increased tumour dissemination to LNs, perinephric fat or distant metastasis. Thus, all patients with non-metastatic disease and VTT, and an acceptable performance status (PS), should be considered for surgical intervention, irrespective of the extent of TT at presentation (LE: 3). The surgical technique and approach for each case should be selected based on the extent of TT (LE: 3).

7.2.4.2 The evidence base for different surgical strategies

A systematic review was undertaken which included comparison-only studies on the management of VTT in non-metastatic RCC [174]. Only 5 studies were eligible for final inclusion. There were high risks of bias across all studies.

Minimal access techniques resulted in significantly shorter operating time compared with traditional median sternotomy [291, 292]. Pre-operative embolisation [293] was associated with increased operating time, blood loss, hospital stay and peri-operative mortality in patients with T3 RCC.

No significant differences in oncological and process outcomes were observed between cardiopulmonary bypass with deep hypothermic circulatory arrest or partial bypass under normothermia or single caval clamp without circulatory support [294].

No surgical method was shown to be superior for the excision of VTT. The surgical method was dependent on the level of TT, and the grade of occlusion of the IVC [291, 292, 294]. The relative benefits and harms of other strategies and approaches regarding access to the IVC and the role of IVC filters and bypass procedures remain uncertain.

7.2.4.3 Conclusions and recommendations

Conclusions	LE
In patients with locally advanced disease due to clinically enlarged LNs the survival benefit of LND is unclear. In these cases LND can be performed for staging purposes.	3
Low quality data suggest that tumour thrombus in non-metastatic disease should be excised.	3
Tumour embolisation or IVC filter do not appear to offer any benefits.	3

Recommendations	GR
In patients with clinically enlarged LNs, LND can be performed for staging purposes or local control.	C
Excision of the kidney tumour and caval thrombus is recommended in patients with non-metastatic RCC.	C

7.2.5 Adjuvant therapy

Confirmation is needed regarding the impact on OS of adjuvant tumour vaccination in selected patients undergoing nephrectomy for T3 renal carcinomas [295-299] (LE: 1b). Several RCTs of adjuvant sunitinib, sorafenib, pazopanib, axitinib and everlimus are ongoing. At present, there is no evidence for the use of adjuvant VEGF-R or mTOR inhibitors.

7.2.5.1 Conclusion and recommendation

Conclusions	LE
Adjuvant cytokines do not improve survival after nephrectomy.	1b

Recommendations	GR
Outside controlled clinical trials, there is no indication for adjuvant therapy following surgery.	A

7.3 Advanced/metastatic RCC

7.3.1 Local therapy of advanced/metastatic RCC

7.3.1.1 Cytoreductive nephrectomy

Tumour nephrectomy is curative only if all tumour deposits are excised. This includes patients with the primary tumour in place and single- or oligo-metastatic resectable disease. For most patients with metastatic disease, cytoreductive nephrectomy (CN) is palliative and systemic treatments are necessary. In a meta-analysis comparing CN + immunotherapy versus immunotherapy only, increased long-term survival was found in patients treated with CN [300]. Only retrospective non-comparative data for CN combined with targeting

agents, such as sunitinib, sorafenib and others are available. CN is currently recommended in mRCC patients with good PS, large primary tumours and low metastatic volume. In patients with poor PS or IMDC risk, those with small primaries and high metastatic volume and/or a sarcomatoid tumour CN is not recommended.

7.3.1.1.1 Embolisation of the primary tumour

In patients unfit for surgery, or with non-resectable disease, embolisation can control symptoms, including gross haematuria or flank pain [222-224] (see recommendation Section 7.1.2.2.4).

7.3.1.1.2 Conclusions and recommendation

Conclusions	LE
Cytoreductive nephrectomy combined with interferon-alpha improves survival in patients with mRCC and good performance status.	1a
Cytoreductive nephrectomy for patients with simultaneous complete resection of a single metastasis or oligometastases may improve survival and delay systemic therapy.	3

Recommendations	GR
Cytoreductive nephrectomy is recommended in appropriately selected patients with metastatic RCC.	C

7.3.2 Local therapy of metastases in mRCC

A systematic review of the local treatment of metastases from RCC in any organ was undertaken [301]. Interventions included metastasectomy, various radiotherapy modalities, and no local treatment. The outcomes were OS, CSS and PFS, local symptom control and adverse events. A risk-of-bias assessment was conducted [302]. Of 2,235 studies identified only 16 non-randomised comparative studies were included.

Eight studies reported on local therapies of RCC-metastases in various organs [303-310]. This included metastases to any single organ or multiple organs. Three studies reported on local therapies of RCC-metastases in bone, including the spine [311-313], two in the brain [314, 315] and one each in the liver [316] lung [317] and pancreas [318]. Three studies [307, 309, 317] were abstracts. Data were too heterogenous for a meta-analysis. There was considerable variation in the type and distribution of systemic therapies (cytokines and VEGF-inhibitors) and in reporting the results.

7.3.2.1 Complete versus no/incomplete metastasectomy

All eight studies [303-310] on RCC metastases in various organs compared complete versus no and/or incomplete metastasectomy. However, in one study [306], complete resections were achieved in only 45% of the metastasectomy cohort, which was compared with no metastasectomy. Non-surgical modalities were not applied. Six studies [303, 305-307, 309, 310] reported a significantly longer median OS or CSS following complete metastasectomy (the median value for median OS or CSS was 40.75 months, range 23-122 months) compared with incomplete and/or no metastasectomy (the median value for median OS or CSS was 14.8 months, range 8.4-55.5 months). Of the two remaining studies, one [304] showed no significant difference in CSS between complete and no metastasectomy, and one [308] reported a longer median OS for metastasectomy albeit no p-value was provided.

Three studies reported on treatment of RCC metastases to the lung [317], liver [316], and pancreas [318], respectively. The lung study reported a significantly higher median OS for metastasectomy versus medical therapy only for both target therapy and immunotherapy. Similarly, the liver and pancreas study reported a significantly higher median OS and 5-year OS for metastasectomy versus no metastasectomy.

7.3.2.2 Local therapies for RCC bone metastases

Of three studies identified, one [313] compared single-dose image-guided radiotherapy (IGRT) with hypofractionated IGRT in patients with RCC bone metastases. Single-dose IGRT (≥ 24 Gray) had a significantly better 3-year actuarial local PFS rate, also shown by Cox regression analysis. Another study [311] compared metastasectomy/curettage and local stabilization with no surgery of solitary RCC bone metastases in various locations. A significantly higher 5-year CSS rate was observed in the intervention group.

After adjusting for prior nephrectomy, gender and age, multivariate analysis still favoured metastasectomy/curettage and stabilization. A third study [312] compared the efficacy and durability of pain relief between single-dose stereotactic body radiotherapy (SBRT) and conventional radiotherapy (CRT) in patients with RCC bone metastases to the spine. Pain ORR, time-to-pain relief and duration of pain relief were similar.

7.3.2.3 Local therapies for RCC brain metastases

Two studies on RCC brain metastases were included. A three-armed study [314] compared stereotactic radiosurgery (SRS) versus whole brain radiotherapy (WBRT) versus SRS + WBRT. Each group was further subdivided into recursive partitioning analysis (RPA) classes I to III (I favourable, II moderate and III poor patient status). Two-year OS and intracerebral control were equivalent in patients treated with SRS alone and SRS + WBRT. Both treatments were superior to WBRT alone in the general study population and in the RPA subgroup analyses. A comparison of SRS versus SRS + WBRT in a subgroup analysis of RPA class I showed significantly better 2-year OS and intracerebral control for SRS + WBRT based on only three participants. The other study [315] compared fractionated stereotactic radiotherapy (FSRT) with metastasectomy + CRT or CRT alone. Several patients in all groups underwent alternative surgical and non-surgical treatments after initial treatment. 1-, 2- and 3-year survival rates were higher but not significantly so for FSRT than for metastasectomy + CRT or CRT alone. FSRT did not result in a significantly better 2-year local control rate compared with MTS + CRT.

7.3.2.4 Embolisation of metastases

Embolisation prior to resection of hypervascular bone or spinal metastases can reduce intra-operative blood loss [319]. In selected patients with painful bone or paravertebral metastases, embolisation can relieve symptoms [320] (see recommendation Section 7.1.2.2.4)

7.3.2.5 Conclusions and recommendations

Conclusions	LE
All included studies were retrospective non-randomised comparative studies, resulting in a high risk of bias associated with non-randomization, attrition, and selective reporting.	3
With the exception of brain and possibly bone metastases, metastasectomy remains by default the most appropriate local treatment for most sites.	3
Retrospective comparative studies consistently point towards a benefit of complete metastasectomy in mRCC patients in terms of overall survival, cancer-specific survival and delay of systemic therapy.	3
Radiotherapy to bone and brain metastases from RCC can induce significant relief from local symptoms (e.g. pain).	3

Recommendations	GR
No general recommendations can be made. The decision to resect metastases has to be taken for each site, and on a case-by-case basis; performance status, risk profiles, patient preference and alternative techniques to achieve local control, must be considered.	C
In individual cases, stereotactic radiotherapy for bone metastases, and stereotactic radiosurgery for brain metastases can be offered for symptom relief.	C

7.4 Systemic therapy for advanced/metastatic RCC

7.4.1 Chemotherapy

Chemotherapy is moderately effective only if 5-fluorouracil (5-FU) is combined with immunotherapeutic agents [321]. However, in one study, interferon-alpha (IFN- α) showed equivalent efficacy to IFN- α + interleukin-2 (IL-2) + 5-FU [322].

7.4.1.1 Conclusion and recommendation

Conclusion	LE
In mRCC 5-FU combined with immunotherapy has equivalent efficacy to IFN- α .	1b

Recommendation	GR
In patients with clear-cell mRCC, chemotherapy is not considered effective.	B

7.4.2 Immunotherapy

7.4.2.1 IFN- α monotherapy and combined with bevacizumab

Conflicting results exist for IFN- α in clear-cell (cc) mRCC. Several studies showed that IFN- α in mRCC has a survival advantage similar to that of hormonal therapy [323]. IFN- α resulted in a response rate of 6-15%, a 25% decrease in tumour progression risk and a modest survival benefit compared to placebo [83, 324]. However, patients with intermediate-risk disease, failed to confirm this benefit [325].

IFN- α may only be effective in some patient subgroups, including patients with ccRCC, favourable-risk criteria, as defined by the Memorial Sloan-Kettering Cancer Center (MSKCC) and lung metastases only [324]. The moderate efficacy of immunotherapy was confirmed in a Cochrane meta-analysis [324]. Bevacizumab + IFN- α increased response rates and PFS in first-line therapy compared with IFN- α monotherapy [326]. All studies comparing targeted drugs to IFN- α monotherapy therapy showed superiority for sunitinib, bevacizumab + IFN- α , and temsirolimus [326-329]. IFN- α has been superseded by targeted therapy in cc-mRCC.

Table 7.1: MSKCC (Motzer) criteria [83]

Risk factors*	Cut-off point used
Karnofsky PS	< 80
Time from diagnosis to treatment	< 12 months
Haemoglobin	< Lower limit of laboratory reference range
LDH	> 1.5 times the upper limit of laboratory range
Corrected serum calcium	> 10.0 mg/dL (2.4 mmol/L)

* Favourable (low) risk, no risk factors; intermediate risk, one or two risk factors; poor (high) risk, three or more risk factors.

7.4.2.2 Interleukin-2

IL-2 has been used to treat mRCC since 1985, with response rates ranging from 7% to 27% [329-331]. Complete responses have been achieved with high-dose bolus IL-2 [332]. The toxicity of IL-2 is substantially greater than that of IFN- α , ranging from 7% to 27% [324].

7.4.2.3 Vaccines and targeted immunotherapy

A vaccine trial with tumour antigen 5T4 + first-line standard therapy (i.e. sunitinib, IL-2 or IFN- α) showed no survival benefit compared with placebo and first-line standard therapy [333]. Several vaccination studies are ongoing. Monoclonal antibodies against programmed death-1 (PD-1) or its ligand (PD-1L), which have efficacy and acceptable toxicity in patients with RCC [334], are currently investigated in phase III trials, as first- and second line.

7.4.2.4 Conclusions and recommendations

Conclusions	LE
IFN- α monotherapy is inferior to targeted therapy in MRCC.	1b
IL-2 monotherapy may have a role in selected cases (good PS, ccRCC, lung metastases only).	2
IL-2 has more side-effects than IFN- α .	2-3
High dose IL-2 is associated with durable complete responses in a limited number of patients. However, no clinical factors or biomarkers exist to accurately predict a durable response in patients treated with HD-IL2.	1b
Bevacizumab plus IFN- α is more effective than IFN- α in treatment-naïve, low-risk and intermediate-risk tumours.	1b
Vaccination therapy with tumour antigen 5T4 showed no survival benefit over first-line standard therapy.	1b
Cytokine combinations, with or without additional chemotherapy, do not improve OS compared with monotherapy.	1b

Recommendation	GR
Monotherapy with IFN- α or HD bolus IL-2 is not routinely recommended as first-line therapy in mRCC.	A

7.4.3 Targeted therapies

In sporadic ccRCC, hypoxia-inducible factor (HIF) accumulation due to von Hippel-Lindau (VHL) inactivation results in overexpression of vascular endothelial growth factor (VEGF and platelet-derived growth factor (PDGF), which promote neoangiogenesis [335-337]. This process substantially contributes to the development and progression of RCC. There are several targeting drugs approved for treating mRCC in both the USA and Europe:

- sorafenib (Nexavar®);

- sunitinib (Sutent®);
- bevacizumab (Avastin®) combined with IFN- α ;
- pazopanib (Votrient®);
- temsirolimus (Torisel®);
- everolimus (Afinitor®);
- axitinib (Inlyta®).

Most published trials have selected for clear-cell carcinoma subtypes, thus no robust evidence-based recommendations can be given for non-ccRCC subtypes.

In major trials leading to registration of the approved targeted agents, patients were stratified according to the MSKCC risk model [323] (Table 7.1). Since the MSKCC (Motzer) criteria were developed during the cytokine era, the International Metastatic Renal Cancer Database Consortium (IMDC) risk model has been established and validated to yield an accurate prognosis for patients treated in the era of targeted therapy. Neutrophilia and thrombocytosis have been added to the list of MSKCC risk factors, while LDH has been removed [338].

The IMDC published data on conditional survival which may be used in patient counselling [339]. The IMDC risk model has been validated and compared with the Cleveland Clinic Foundation (CCF) model, the French model, MSKCC model, and the International Kidney Cancer Working Group (IKCWG) model. The IMDC model did not differ from the other models, indicating that a ceiling has been reached in predicting prognosis based solely on clinical factors [340].

Table 7.2: Median OS and patients surviving 2 years treated in the era of targeted therapy per IMDC risk group (based on references [338, 340])

IMDC Model ***	Patients**	Median OS* (months)	2-y OS (95% CI) **	
	n	%		
Favourable	157	18	43.2	75% (65-82%)
Intermediate	440	52	22.5	53% (46-59%)
Poor	252	30	7.8	7% (2-16%)

* Based on [340]; ** based on [338]; CI = confidence interval; OS = overall survival.

7.4.3.1 Tyrosine kinase inhibitors

7.4.3.1.1 Sorafenib

Sorafenib is an oral multikinase inhibitor. A trial compared sorafenib and placebo after failure of prior systemic immunotherapy or in patients unfit for immunotherapy. Sorafenib improved PFS [341] (HR: 0.44; 95% CI: 0.35-0.55; $p < 0.01$). OS improved in patients who crossed over from placebo to sorafenib [342]. In patients with previously untreated mRCC sorafenib was not superior to IFN- α . A number of studies have used sorafenib as the control arm in sunitinib-refractory disease versus axitinib, dovitinib and temsirolimus. None showed superior survival compared to sorafenib.

7.4.3.1.2 Sunitinib

Sunitinib is an oral tyrosine kinase (TK) inhibitor and has antitumour and anti-angiogenic activity. Sunitinib as second-line monotherapy in patients with mRCC demonstrated a partial response in 34-40% and stable disease > 3 months in 27-29% of patients [343]. First-line monotherapy with sunitinib demonstrated longer PFS compared with IFN- α . OS was greater in patients treated for 26.4 and 21.8 months with sunitinib despite crossover [344].

In the EFFECT trial, sunitinib 50 mg/day (4 weeks on/2 weeks off) was compared with continuous uninterrupted sunitinib 37.5 mg/day in patients with clear-cell mRCC [345]. Median time to progression (TTP) with sunitinib 50 mg was numerically longer than the 37.5 mg arm (9.9 months versus 7.1 months). No significant differences in OS were seen (23.1 vs. 23.5 months; $p = 0.615$). Toxicity was comparable in both arms. Because of the non-significant, but numerically longer TTP with the standard 50 mg dosage, the authors recommended using this regimen. Alternate scheduling of sunitinib (2 weeks on/1 week off) is being used to manage toxicity.

7.4.3.1.3 Pazopanib

Pazopanib is an oral angiogenesis inhibitor. In a trial of pazopanib versus placebo in treatment-naïve mRCC patients and cytokine-treated patients, a significant improvement in PFS and tumour response was observed

[346]. Median PFS with pazopanib compared with placebo was:

- 9.2 vs. 4.2 months in the overall study population;
- 11.1 vs. 2.8 months for the treatment-naïve subpopulation;
- 7.4 vs. 4.2 months for the cytokine-pretreated subpopulation.

A trial comparing pazopanib with sunitinib (COMPARZ) established pazopanib as another first-line option. It showed that pazopanib was not associated with significantly worse PFS or OS compared to sunitinib. The two drugs had different toxicity profiles [347], and QoL was better with pazopanib. In another patient-preference study (PISCES), patients preferred pazopanib to sunitinib due to symptomatic toxicity [348]. Both studies were limited in that intermittent therapy (sunitinib) was compared with continuous therapy (pazopanib).

7.4.3.1.4 Axitinib

Axitinib is an oral selective second-generation inhibitor of VEGFR-1, -2, and -3. Axitinib was first evaluated as second-line treatment. In the AXIS trial (axitinib versus sorafenib in patients with previously failed cytokine treatment or targeted agents), the sample size calculation was based on a 40% improvement in median PFS from 5-7 months in patients receiving axitinib [349].

The overall median PFS was greater for axitinib than sorafenib. The difference in PFS was greatest in patients in whom cytokine treatment had failed. For those in whom sunitinib had failed, axitinib was associated with a greater PFS than sorafenib (4.8 vs. 3.4 months). Axitinib showed > grade 3 diarrhoea in 11%, hypertension in 16%, and fatigue in 11%. Across all grades, nausea was recorded in 32%, vomiting in 24%, and asthenia in 21%. OS was a secondary end-point of the trial in which crossover was not permitted. Final analysis of OS showed no significant differences between the groups in second-line treatment [350, 351].

Axitinib was investigated in two first-line studies [352, 353]. One investigated the efficacy and safety of axitinib dose titration in previously untreated patients with mRCC. Although the objective RR was higher in patients treated to toxicity, median PFS was 14.5 months in the axitinib titration group, 15.7 months in the placebo titration group, and 16.6 months in nonrandomised patients [352]. This supports the hypothesis that dose escalation is associated with higher RRs.

In a trial of axitinib vs. sorafenib in first-line treatment-naïve cc-mRCC, a significant difference in median PFS between the treatment groups was not demonstrated [353]. As a result of this study, axitinib is not approved for first-line therapy.

7.4.4 **Monoclonal antibody against circulating VEGF**

7.4.4.1 *Bevacizumab monotherapy and bevacizumab + IFN- α*

Bevacizumab is a humanised monoclonal antibody. The AVOREN study compared bevacizumab + IFN- α with IFN- α monotherapy in mRCC [326]. Median OR was higher in the bevacizumab + IFN- α group. Median PFS increased from 5.4 months with IFN- α to 10.2 months with bevacizumab + IFN- α . No benefit was seen in MSKCC poor-risk patients. Median OS in this trial, which allowed crossover after progression, was not greater in the bevacizumab-IFN- α group (23.3 vs. 21.3) [354].

A similarly designed trial (CALGB 90206) [355, 356], of bevacizumab + IFN- α vs. IFN- α showed a higher median PFS for the combination group. ORR was also higher in the combination group. Overall toxicity was greater for bevacizumab + IFN- α , with significantly more grade 3 hypertension, anorexia, fatigue, and proteinuria.

7.4.5 **mTOR inhibitors**

7.4.5.1 *Temsirolimus*

Temsirolimus is a specific inhibitor of mTOR [357]. Patients with modified high-risk mRCC in the NCT00065468 trial received first-line temsirolimus or IFN- α monotherapy, or a combination of both [328]. Median OS was higher in the temsirolimus group. However, OS in the temsirolimus + IFN- α group was not significantly superior to IFN- α alone [328]. IFN- α toxicity was marked, partly due to the high doses used. The INTORSECT trial investigated temsirolimus vs. sorafenib in patients who had previously failed sunitinib. Although no benefit in PFS was observed, a significant OS benefit for sorafenib was noted [358]. Based on these results, temsirolimus is not recommended in patients with VEGF TKI refractory disease.

7.4.5.2 *Everolimus*

Everolimus is an oral mTOR inhibitor, which is established in the treatment of VEGF-refractory disease. The RECORD-1 study compared everolimus + best supportive care (BSC) vs. placebo + BSC in patients with previously failed anti-VEGFR treatment (or previously intolerant of VEGF targeted therapy) [359]. The initial data showed a median PFS of 4.0 months v.s. 1.9 months for everolimus and placebo, respectively [359]. This

was extended to 4.9 months in the final analysis HR=0.33 [360]. Subset analysis of PFS for patients receiving only 1 previous VEGF TKI was 5.4 months [361]. This included some patients who were intolerant rather than progressed on therapy (PFS also 5.4 months) [362]. RECORD-1 included patients who failed multiple lines of VEGF-targeted therapy, and received everolimus in third- and fourth-line setting [359].

The RECORD-3 study of sunitinib vs. everolimus in treatment-naïve mRCC followed by either sunitinib or everolimus upon progression reported a higher median PFS for first-line treatment in the sunitinib group [363]. A large number of the crossover patients did not receive the planned subsequent therapy making further analysis complex and underpowered. Survival in the sunitinib-followed-by-everolimus-arm was high, mature analysis is awaited.

7.4.6 Therapeutic strategies and recommendations

7.4.6.1 Therapy for treatment-naïve patients with clear-cell mRCC

Pivotal trials have established sunitinib and bevacizumab plus IFN- α as first-line treatment options in treatment-naïve patients with cc-mRCC and a favourable-to-intermediate risk score. The COMPARZ study demonstrated that pazopanib and sunitinib have similar efficacy and different toxicity profiles. This study firmly establishes pazopanib as another first-line option [347].

7.4.6.1.1 Sequencing targeted therapy

7.4.6.1.1.1 Following progression of disease with VEGF-targeted therapy

Several trials investigated therapeutic options for patients who progressed on first-line VEGF-targeted therapy. RECORD-1 established VEGF TKI until disease progression followed by everolimus as one of the treatment options for patients with mRCC [359]. AXIS was the only trial to compare two TKIs after failure of a prior TKI. The results and interpretation are described under 7.3.1.4 above [349-351]. Comparison of RECORD-1 data with AXIS data is not advised due to differences in patient populations [349-351, 359].

INTORSECT was the only trial to directly compare an mTOR inhibitor and TKI (temsirolimus vs. sorafenib) after disease progression on sunitinib [358]. Median PFS was higher, but not significant, in the temsirolimus group. However, there was a significant difference in OS in favour of sorafenib. These data are not necessarily relevant to other mTOR inhibitors such as everolimus.

No firm recommendations can currently be made as to the best sequence of targeted therapy. However, VEGF-targeted therapy should be used for patients with favourable- and intermediate-risk disease in the first-line setting.

7.4.6.1.1.2 Treatment after progression of disease with mTOR inhibition

There are limited data addressing this issue. In view of the efficacy of VEGF-targeted therapy in renal cancer, a switch to VEGF-targeted therapy is advised (expert opinion and [364].

7.4.6.1.1.3 Treatment after progression of disease with cytokines

Trials have established sorafenib, axitinib and pazopanib as therapeutic options in this setting with a median PFS of 5.5, 12.1 and 7.4 months, respectively. Based on trial data, axitinib is superior to sorafenib in patients previously treated with cytokine therapy [349-351].

7.4.6.1.1.4 Treatment after second-line targeted therapy

The RECORD-1 study demonstrated the activity of everolimus in patients who had received more than one line of targeted therapy. 26% of patients were treated with two or more lines of VEGF-targeted therapy and significant benefits were seen. Although the GOLD trial failed to demonstrate superior efficacy of dovitinib over sorafenib in patients with mRCC who experienced disease progression after receiving prior VEGF- and mTOR-targeted therapies, the results suggest efficacy and safety of sorafenib in the third-line setting [364].

7.4.6.1.1.5 Combination of targeted agents

There have been a number of trials with VEGF targeted therapy and mTOR inhibitors [365-369]. The results have all been negative. No combinations of targeted agents are currently recommended.

7.4.6.2 Non-clear-cell renal cancer

No phase III trials of patients with non-clear-cell RCC have been reported. Expanded access programmes and subset analysis from RCC studies suggest the outcome of these patients with targeted therapy is poorer than for ccRCC. Targeted treatment in non-clear-cell RCC has focused on temsirolimus, everolimus, sorafenib and sunitinib [328, 370-372].

The most common non-clear-cell subtypes are papillary type 1 and 2 RCCs. There are small single-arm data for sunitinib and everolimus [372-375]. A trial of both types of papillary RCC treated with everolimus (RAPTOR) [375], showed median PFS of 3.7 months per central review in the intention-to-treat population with a median OS of 21.0 months.

Another trial investigated foretinib (a dual MET/VEGFR2 inhibitor) in patients with papillary RCC. Toxicity was acceptable with a high RR in patients with germline MET mutations [376]. However, a randomised phase II trial of everolimus vs. sunitinib with crossover design in non-clear-cell mRCC included 73 patients (27 with papillary RCC) and was stopped after a futility analysis for PFS and OS. Median OS for everolimus was 10.5 months but not reached for sunitinib [377]. The final results presented at the 2014 annual meeting of the American Society of Clinical Oncology showed a nonsignificant trend favouring sunitinib. Both sunitinib and everolimus remain options in this population, with a preference for sunitinib. Patients with ncc-mRCC should be referred to a clinical trial where appropriate.

Collecting-duct cancers are resistant to systemic therapy. There is a lack of data to support specific therapy in these patients. There is limited data supporting the use of targeted therapy in other histological subtypes such as chromophobe tumours [328, 370].

Table 7.3: EAU 2015 evidence-based recommendations for systemic therapy in patients with mRCC

RCC type	MSKCC risk group [323]	First-line	LE [^]	Second-line*	LE [^]	Third-line*	LE [^]	Later lines	LE
Clear cell*	Favourable, Intermediate and poor	sunitinib pazopanib bevacizumab + IFN Favourable-intermediate only)	1b 1b 1b	after VEGFR: axitinib sorafenib# everolimus after cytokines: sorafenib# axitinib pazopanib	 2a 2a 2a 1b 2a 2a	after VEGFR: everolimus after mTOR: sorafenib	 2a 1b	any targeted agent	4
Clear cell*	poor [¶]	Temsirolimus	1b	any targeted agent	4				
Non-clear-cell §	any	sunitinib everolimus temsirolimus	2a 2b 2b	any targeted agent	4				
<p><i>IFN-α = interferon alpha; LE = level of evidence; MSKCC = Memorial Sloan-Kettering Cancer Center; mTOR = mammalian target of rapamycin inhibitor; RCC = renal cell carcinoma; TKI= tyrosine kinase inhibitor.</i></p> <p>* Doses: IFN-α - 9 MU three times per week subcutaneously, bevacizumab 10 mg/kg biweekly intravenously; sunitinib 50 mg daily orally for 4 weeks, followed by 2 weeks of rest (37.5 mg continuous dosing did not show significant differences); temsirolimus 25 mg weekly intravenously; pazopanib 800 mg daily orally. Axitinib 5 mg twice daily, to be increased to 7 mg twice daily, unless greater than grade 2 toxicity, blood pressure higher than 150/90 mmHg, or the patient is receiving antihypertensive medication. Everolimus, 10 mg daily orally.</p> <p>§ No standard treatment available. Patients should be treated in the framework of clinical trials or a decision can be made in consultation with the patient to perform treatment in line with ccRCC.</p> <p>¶ Poor risk criteria in the NCT00065468 trial consisted of MSKCC [323] risk plus metastases in multiple organs.</p> <p># Sorafenib was inferior to axitinib in a RCT in terms of PFS but not OS [351].</p> <p>^ Level of evidence was downgraded in instances when data were obtained from subgroup analysis within an RCT.</p>									

7.4.6.3 Conclusions and recommendations for systemic therapy in mRCC

Conclusions	LE
TKIs increase PFS and/or OS as both first-line and second-line treatments for clear-cell mRCC.	1b
Axitinib has proven efficacy and superiority in PFS as a second-line treatment after failure of cytokines and VEGF-targeted therapy in comparison with sorafenib.	1b
Sunitinib is more effective than IFN- α in treatment-naïve patients.	1b
Bevacizumab plus IFN- α is more effective than IFN- α in treatment-naïve low-risk and intermediate-risk patients.	1b
Pazopanib is superior to placebo in both naïve mRCC patients and post-cytokine patients.	1b
Pazopanib is not inferior to sunitinib in clear-cell mRCC patients.	1b
Temsirolimus monotherapy prolongs OS compared to IFN- α in poor-risk mRCC.	1b
Everolimus prolongs PFS in patients who have previously failed or are intolerant of VEGF-targeted therapy.	1b
Sorafenib has broad activity in a spectrum of settings in clear-cell patients previously treated with cytokine or targeted therapies.	4
Both mTOR inhibitors (everolimus and temsirolimus) and VEGF-targeted therapies (sunitinib or sorafenib) can be used in non-clear-cell RCC.	3
No combination has proven to be better than single-agent therapy.	1a

Recommendations	GR
Systemic therapy for mRCC should be based on targeted agents.	A
Sunitinib and pazopanib are recommended as first-line therapy for advanced/metastatic clear-cell RCC.	A
Bevacizumab + IFN- α recommended as first-line therapy for advanced/metastatic RCC in favourable-risk and intermediate-risk ccRCC.	A
Temsirolimus is recommended as first-line treatment in poor-risk RCC patients.	A
Axitinib is recommended as second-line treatment for mRCC.	A
Everolimus is recommended for ccRCC patients who have failed VEGF-targeted therapy.	A
Pazopanib and sorafenib are alternatives to axitinib and are recommended as second-line therapy after failure of prior cytokines.	B
Sequencing of targeted agents is recommended.	A
Sunitinib can be recommended as first-line therapy for non-clear-cell mRCC.	B

7.5 Recurrent RCC

7.5.1 Introduction

Locally recurrent disease can occur either after partial nephrectomy, nephrectomy and thermal ablation. After nephron sparing treatment approaches the recurrence may be intrarenal or in addition regional, e.g. venous tumour thrombi or retroperitoneal lymph node metastases. Both are often summarised as locoregional recurrences. Recurrence rates for pT1 tumours after partial nephrectomy are observed in 2.2% and are generally managed surgically depending on the extent of the locoregional recurrence [378]. After thermal ablation locoregional recurrences (intrarenal and regional) have been described in up to 12% [379]. Repeated ablation has often been recommended for intrarenal recurrences following thermal ablation. For locoregional recurrences surgical resection is mandatory as has been described for isolated local recurrences following nephrectomy.

After nephrectomy locally recurrent disease is defined as recurrent disease in the former kidney rest. However, metastasis in the not removed ipsilateral adrenal or non-resected lymph nodes makes interpretation of the true incidence of isolated recurrence in the renal fossa difficult. Treatment of adrenal metastases or lymph node metastases are often described in series of metastasectomy (Section 7.3). Isolated local recurrence however is rare.

The largest series on the treatment of isolated recurrence was published in 2009 [380]. Of 2,945 patients who underwent nephrectomy the authors identified 54 isolated local recurrences in the renal fossa. These however included those to the ipsilateral adrenal and lymph nodes. Exclusively retrospective non-comparative data exist which suggest that aggressive local resection offers durable local tumour control and improves survival. Adverse prognostic factors were a positive surgical margin after resection, the size of the recurrence and sarcomatoid histologic features [380]. In cases where complete surgical removal is not feasible due to advanced tumour growth and pain, palliative treatments including radiation treatment can be considered.

Conclusions	LE
Isolated recurrence in the local renal fossa is rare.	3
Patients with resectable local recurrences and absent sarcomatoid features may benefit from resection.	3

Recommendation	GR
Surgical resection of local recurrent disease may result in durable local control and improved survival	C

8. FOLLOW-UP AFTER RADICAL NEPHRECTOMY OR PARTIAL NEPHRECTOMY OR ABLATIVE THERAPIES FOR RCC

8.1 Introduction

Surveillance after treatment for RCC allows the urologist to monitor or identify:

- Postoperative complications
- Renal function
- Local recurrence after PN or ablative treatment
- Recurrence in the contralateral or ipsilateral (after PN) kidney
- Development of metastases

The method and timing of examinations have been the subject of many publications. There is no consensus on surveillance after RCC treatment, and there is no evidence that early vs. later diagnosis of recurrences improves survival. However, follow-up is important to increase the available information on RCC, and should be performed by the urologist, who should record the time to recurrence or the development of metastases. Postoperative complications and renal function are readily assessed by the patient's history, physical examination, and measurement of serum creatinine and eGFR. Repeated long-term monitoring of eGFR is indicated if there is impaired renal function before surgery, or postoperative deterioration. Renal function [381, 382] and non-cancer survival [180-182] can be optimised by performing NSS whenever possible for T1 and T2 tumours [383] (LE: 3). Tumour-bed recurrence is rare, but early diagnosis is useful, as the most effective treatment is cytoreductive surgery [384, 385]. Recurrence in the contralateral kidney is also rare and is related to positive margins, multifocality, and grade [386] (LE: 3). Surveillance can identify local recurrences or metastases at an early stage. This is particularly important with ablative therapies such as cryotherapy and RFA. Although the local recurrence rate is higher than after conventional surgery, the patient may still be cured using repeat ablative therapy or RN [387] (LE: 3). In metastatic disease, extended tumour growth can limit the opportunity for surgical resection, considered the standard therapy in cases of resectable and preferably solitary lesions. In addition, early diagnosis of tumour recurrence may enhance the efficacy of systemic treatment if the tumour burden is low.

8.2 Which investigations for which patients, and when?

Intensive radiological surveillance for all patients is unnecessary. The outcome after surgery for T1a low-grade tumours is almost always excellent. It is therefore reasonable to stratify the follow-up, taking into account the risk of developing recurrence or metastases. Although there is no randomised evidence, large studies have examined prognostic factors with long follow-up periods, from which conclusions can be drawn [31, 388, 389] (LE: 4):

- The sensitivity of chest radiography for small metastases is poor and US has limitations. Surveillance should not be based on these imaging modalities [390]. With low-risk tumours, surveillance intervals should be adapted relative to radiation exposure and benefit. To reduce radiation exposure, MRI can be used.
- When the risk of relapse is intermediate or high, CT of the chest and abdomen should be performed, although significant morbidity associated with the radiation exposure involved in repeated CT scans should be taken into account [391]. CT can clearly reveal metastatic lesions from RCC [392].
- Surveillance should also include clinical evaluation of renal function and cardiovascular risk factors.

- Positron-emission tomography (PET) and PET-CT as well as bone scintigraphy are not the standard of care in RCC surveillance, due to limited specificity and sensitivity.
- Depending on the availability of effective new treatments, more strict follow-up schedules may be required, particularly as there is a higher local recurrence rate after cryotherapy and RFA.

There is controversy over the optimal duration of follow-up. Some argue that follow-up with imaging is not cost-effective after 5 years; however, late metastases are more likely to be solitary and justify more aggressive therapy with curative intent. In addition, patients with tumours that develop in the contralateral kidney can be treated with NSS if the tumours are detected when small. For tumours < 4 cm, there is no difference between PN and RN with regard to recurrences during follow-up [189] (LE: 3).

Several authors [165, 167, 393, 394], have designed scoring systems and nomograms to quantify the likelihood of patients developing tumour recurrences, metastases, and subsequent death. These systems have been compared and validated [395] (LE: 2). Using prognostic variables, several stage-based surveillance regimens have been proposed [396, 397], but do not include ablative therapies. A postoperative nomogram is available for estimating the likelihood of freedom from recurrence at 5 years [162]. Recently, a preoperative prognostic model based on age, symptoms, and TNM staging has been published and validated [171] (LE: 3). A surveillance algorithm for monitoring patients after treatment for RCC is needed, recognising not only the patient risk profile, but also efficacy of the treatment given (Table 8.1).

Table 8.1: Proposed surveillance schedule following treatment for RCC, taking into account patient risk profile and treatment efficacy

Risk profile	Treatment	Surveillance						
		6 mo	1 y	2 y	3 y	4 y	5 y	> 5 y
Low	RN/PN only	US	CT	US	CT	US	CT	Discharge
Intermediate	RN/PN/cryo/ RFA	CT	CT	CT	US	CT	CT	CT once every 2 years
High	RN/PN/cryo/ RFA	CT	CT	CT	CT	CT	CT	CT once every 2 years

Cryo = cryotherapy; CT = computed tomography of chest and abdomen, or MRI = magnetic resonance imaging; PN = partial nephrectomy; RFA = radiofrequency ablation; RN = radical nephrectomy; US = ultrasound of abdomen, kidneys and renal bed.

8.3 Conclusions and recommendations for surveillance following RN or PN or ablative therapies in RCC

Conclusions	LE
Surveillance can detect local recurrence or metastatic disease while the patient is still surgically curable. Renal function should be assessed.	4
Risk stratification should be based on preexisting classification systems such as the UISS integrated risk assessment score (http://urology.ucla.edu/body.cfm?id=443 [163]).	4

Recommendations	GR
Follow-up after treatment for RCC should be based on a patient's risk factors and type of treatment.	C
For low-risk disease, CT/MRI can be used infrequently.	C
In intermediate-risk patients, intensified follow-up should be performed, including CT/MRI scans at regular intervals in accordance with a risk-stratified nomogram.	C
In high-risk patients, the follow-up examinations should include routine CT/MRI scans.	C
There is an increased risk of intrarenal recurrences in larger (> 7 cm) tumours treated with NSS, or when there is a positive margin. Follow-up should be intensified in these patients.	C

8.4 Research priorities

There is a clear need for future research to determine whether follow-up can optimise patient survival. Further information should be sought at what time point restaging has the highest chance to detect recurrence. Prognostic markers at surgery should be investigated to determine the risk of relapse over time.

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10. CONFLICT OF INTEREST

All members of the Renal Cell Cancer working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: <http://www.uroweb.org/guidelines/>. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

Guidelines on **Testicular Cancer**

P. Albers (Chair), W. Albrecht, F. Algaba,
C. Bokemeyer, G. Cohn-Cedermark, K. Fizazi,
A. Horwich, M.P. Laguna, N. Nicolai, J. Oldenburg

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1. INTRODUCTION

1.1 Aims and scope

The aim of these guidelines is to present the current evidence for the diagnosis and treatment of patients with cancer of the testis. Testicular cancer represents 5% of urological tumours affecting mostly younger males. This document addresses germ-cell tumours and sex cord/gonadal stromal tumours.

1.2 Panel composition

The EAU Guidelines Panel on Testicular Cancer consists of a multidisciplinary group of clinicians, including urologists, a pathologist, oncologists and radiotherapists. Members of this panel have been selected based on their expertise to represent the professionals treating patients suspected of harbouring testis cancer.

1.2.1 Potential conflict of interest

All experts involved in the production of this document have submitted potential conflict of interest statements.

1.3 Available publications

A quick reference document (Pocket guidelines) is available, both in print and in a number of versions for mobile devices. These are abridged versions which may require consultation together with the full text versions. Several scientific publications are available as are a number of translations of all versions of the EAU Testicular Cancer Guidelines. All documents can be viewed, free access, through the EAU website Uroweb: <http://www.uroweb.org/guidelines/online-guidelines/>.

1.4 Publication history and summary of changes

1.4.1 Publication history

The European Association of Urology (EAU) published the first guidelines on Testicular Cancer in 2001. Since 2008, the Testicular Guidelines contain a separate chapter on testicular stromal tumours. This document presents a limited update of the 2014 publication. Review papers have been published in the society scientific journal European Urology, the latest version dating to 2011 [1].

1.4.2 Summary of changes

The literature in the entire document has been assessed and updated, whenever relevant.

Key changes for this 2015 print:

- A new flowchart (Figure 2) on Treatment options in patient with seminoma clinical state IIA and IIB has been included.
- A new section on Quality of life and long-term toxicities after cure for testicular cancer was added (Section 8.6).

Conclusions and recommendations have been rephrased and added to throughout the current document.

Changed or new conclusions and recommendations can be found in sections:

5.9 Guidelines for the Diagnosis and staging of testicular cancer

Biopsy of the contralateral testis should be offered (and its consequences discussed) to patients at high risk for contralateral TIN.	A
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TIN = testicular intraepithelial neoplasia.

7.3.6 Guidelines for the treatment of NSGCT stage I

CS1B (pT2-pT4): high risk	LE	GR
Primary chemotherapy with one course of BEP is recommended	2a	A*
Patients should be informed about the advantages and disadvantages of two courses of BEP.		

BEP = cisplatin, etoposide, and bleomycin.

Table 8.1: Recommended minimum follow-up schedule in a surveillance policy: stage I non-seminoma

Procedure	Year			
	1	2	3	4-5
Physical examination	4 times	4 times	4 times	Once/year
Tumour markers	4 times	4 times	4 times	Once/year
Plain radiography chest	Twice		Twice	
Abdominopelvic CT	Twice (at 3 and 12 months)		Once in year 2 (at 24 months), Once in year 3 (at 36 months)	

CT = computed tomography.

Table 8.2: Recommended minimum follow-up schedule after retroperitoneal lymphadenectomy or adjuvant chemotherapy: stage I non-seminoma

Procedure	Year				
	1	2	3	4-5	6-10
Physical examination	4 times	4 times	4 times	Once/year	Once/year
Tumour markers	4 times	4 times	4 times	Once/year	Once/year
Plain radiography chest	Twice	Twice	Twice		
Abdominopelvic CT	Once	Once	Once	Once/year	

CT = computed tomography.

Table 8.3: Recommended minimum follow-up schedule for post-orchietomy surveillance, radiotherapy or chemotherapy: stage I seminoma

Procedure	Year		
	1	2	3-5
Physical examination	3 times	3 times	Once/year
Tumour markers	3 times	3 times	Once/year
Plain radiography chest	Twice	Twice	
Abdominopelvic CT	Twice	Twice	at 36 and 60 months

CT = computed tomography.

Table 8.4: Recommended minimum follow-up schedule in metastatic NSGCT and seminoma

Procedure	Year			
	1	2	3-5	Thereafter
Physical examination	4 times	4 times	Twice/year	Once/year
Tumour markers	4 times	4 times	Twice/year	Once/year
Plain radiography chest	4 times	4 times	Twice/year	Once/year
Abdominopelvic CT [†]	Twice	Twice	Once/year	As indicated
Chest CT [‡]	Once/year	Once/year	Once/year	As indicated
Brain CT [§]	Once/year	Once/year	Once/year	As indicated

CT = computed tomography.

* An abdominal CT must be performed at least annually if teratoma is found in the retroperitoneum.

[†] If the post-chemotherapy evaluation in a seminoma patient shows any mass > 3 cm, the appropriate CT should be repeated 2 and 4 months later to ensure that the mass is continuing to regress. If available, FDG-PET/CT can be performed.

[‡] A chest CT is indicated if abnormality is detected on a plain radiography chest and after pulmonary resection.

[§] In patients with headaches, focal neurological findings, or any central nervous system symptoms.

2. METHODS

For the Germ-cell tumour Section, the literature has been assessed and updated throughout the document.

For the Testicular Stromal tumours a scoping search as of Jan 1st, 2009 until October 13th, 2014 has been carried out. No restrictions on data level were applied. The search identified 758 unique records, of which 18 references were included in the manuscript.

2.1 Review

This document was subjected to double-blind peer review prior to publication.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Testicular cancer represents 1% of male neoplasms and 5% of urological tumours, with 3-10 new cases occurring per 100,000 males/per year in Western society [2-5]. Its incidence has been increasing during the last decades especially in the industrialised countries [6-8]. Data from the Surveillance Epidemiology and End Results (SEER) program (1973 to 1998) show a continuing increased risk among Caucasian men in the USA only for seminoma [9].

At diagnosis, 1-2% of cases are bilateral and the predominant histology is germ cell tumour (90-95% of cases) [2]. Peak incidence is in the third decade of life for non-seminoma, and in the fourth decade for pure seminoma.

Testicular cancers (TC) show excellent cure rates based on their chemosensitivity especially to cisplatin-based chemotherapy [10], careful staging at diagnosis, adequate early treatment based on multidisciplinary approach and strict follow-up and salvage therapies. A decrease in the mean time of delay to diagnosis and treatment has been observed. Although early stages can be successfully treated in a non-reference centre, the relapse rate is higher [11]. In poor prognosis non-seminomatous germ cell tumours, overall survival (OS) within a clinical trial depends on the number of patients treated at the participating centre (worse if < 5 patients enrolled) [12]. In the same context, the frequency of post-chemotherapy residual tumour resection is associated with perioperative mortality and OS [13, 14].

Genetic changes have been described in patients with testicular cancer. A specific genetic marker (an isochromosome of the short arm of chromosome 12 - i(12p) - has been described in all histological types of germ cell tumours [15] and in testicular intraepithelial neoplasia (TIN). Alterations in the p53 locus have been identified in 66% of cases of testicular TIN [16]. A deregulation in the pluripotent program of foetal germ cells (identified by specific markers, M2A, C-KIT and OCT4/NANOG) is likely responsible for the development of TIN and germ cell neoplasia. There is overlap in the development to seminoma and embryonal carcinoma as shown by genome-wide expression analysis and detection of alpha-fetoprotein (AFP) mRNA in some atypical seminoma [17, 18].

Epidemiological risk factors for the development of testicular tumours are components of the testicular dysgenesis syndrome (i.e. cryptorchidism, hypospadias, decreased spermatogenesis evidenced by sub- or infertility) [19, 20], familial history of testicular tumours among first-grade relatives and the presence of a contralateral tumour or TIN [15, 19, 21-29]. Very tall men seem to have a higher risk of GCT (OR 3.35), while short stature is protective [30, 31], although further confirmation is needed.

3.2 Pathological classification

The recommended pathological classification (modified from the 2004 version of the World Health Organization [WHO] guidance) is shown below [32].

1. Germ cell tumours

- Intratubular germ cell neoplasia, unclassified type (IGCNU)
- Seminoma (including cases with syncytiotrophoblastic cells)
- Spermatocytic seminoma (mention if there is a sarcomatous component)
- Embryonal carcinoma

- Yolk sac tumour
- Choriocarcinoma
- Teratoma (mature, immature, with malignant component)
- Tumours with more than one histological type (specify percentage of individual components).

2. **Sex cord/gonadal stromal tumours**

- Leydig cell tumour
- Malignant Leydig cell tumour
- Sertoli cell tumour
 - lipid-rich variant
 - sclerosing
 - large cell calcifying
- Malignant Sertoli cell tumour
- Granulosa cell tumour
 - adult type
 - juvenile type
- Thecoma/fibroma group of tumours
- Other sex cord/gonadal stromal tumours
 - incompletely differentiated
 - mixed
- Tumours containing germ cell and sex cord/gonadal stromal (gonadoblastoma).

3. **Miscellaneous non-specific stromal tumours**

- Ovarian epithelial tumours
- Tumours of the collecting ducts and rete testis
- Tumours (benign and malignant) of non-specific stroma.

4. **STAGING AND CLASSIFICATION SYSTEMS**

4.1 **Diagnostic tools**

To determine the presence of macroscopic or occult metastatic disease, the half-life kinetics of serum tumour markers as well as the presence of nodal or visceral metastases need to be assessed.

Consequently, it is mandatory to assess:

- the post-orchietomy half-life kinetics of serum tumour markers;
- the status of retroperitoneal and supraclavicular lymph nodes, bone and liver;
- the presence or absence of mediastinal nodal involvement and lung metastases;
- the status of brain and bone in cases of suspicious symptoms or high-risk disease, e.g. poor IGCCCG risk group, high hCG and/or multiple pulmonary metastases.

The minimum mandatory tests are:

- serial blood sampling;
- abdominopelvic and chest computed tomography (CT).

4.2 **Serum tumour markers: post-orchietomy half-life kinetics**

The mean serum half-life of AFP and hCG is 5-7 days and 2-3 days, respectively [33]. Tumour markers need to be re-evaluated after orchietomy to determine half-life kinetics. Marker decline in patients with clinical stage I disease should be assessed until normalisation has occurred. Markers before the start of chemotherapy are important to classify the patient according to the International Germ Cell Cancer Collaborative Group (IGCCCG) risk classification [34]. The persistence of elevated serum tumour markers after orchietomy might indicate the presence of metastatic disease (macro- or microscopically), while the normalisation of marker levels after orchietomy does not rule out the presence of tumour metastases. During chemotherapy, the markers should decline; persistence has an adverse prognostic value [35, 36]. Slow marker decline in patients with “poor prognosis” during the first cycle of standard BEP chemotherapy can be used as an indication for early chemotherapy dose intensification [37].

4.3 **Retroperitoneal, mediastinal and supraclavicular lymph nodes and viscera**

Retroperitoneal and mediastinal lymph nodes are best assessed by CT. The supraclavicular nodes are best assessed by physical examination.

Abdominopelvic CT offers a sensitivity of 70-80% in determining the state of the retroperitoneal nodes. Its accuracy depends on the size and shape of the nodes; sensitivity and the negative predictive value increase using a 3 mm threshold to define metastatic nodes in the landing zones [38]. Those figures decrease slightly in stages I and II [39, 40], with a rate of understaging of 25-30% [41]. New generations of CT devices do not seem to improve the sensitivity.

Magnetic resonance imaging (MRI) produces similar results to CT in the detection of retroperitoneal nodal enlargement [42, 43]. Again, the main objections to its routine use are its high cost and limited availability. Nevertheless, MRI can be helpful when abdominopelvic CT or US are inconclusive [42], when CT is contraindicated because of allergy to contrast media, or when the physician or the patient are concerned about radiation dose. MRI is an optional test, and there are currently no indications for its systematic use in the staging of testicular cancer.

A chest CT is the most sensitive way to evaluate the thorax and mediastinal nodes. This exploration has to be recommended in all patients with testicular cancer as up to 10% of cases can present with small subpleural nodes that are not visible radiologically [44]. A CT has high sensitivity, but low specificity [42].

There is no evidence to support the use of fluorodeoxyglucose-PET (FDG-PET) in the staging of testis cancer [45-48]. It is recommended in the follow-up of patients with seminoma with any residual mass at least 6 weeks after the end of the last cycle of chemotherapy in order to decide on watchful waiting or active treatment [47-51].

Fluorodeoxyglucose-PET, however, is not recommended in the re-staging of patients with non-seminomatous tumours after chemotherapy [52, 53].

Other examinations, such as brain or spinal CT, bone scan or liver ultrasound, should be performed if there is suspicion of metastases to these organs. A CT or MRI of the skull is advisable in patients with NSGCT and multiple lung metastases and poor prognosis IGCCG risk group (e.g. high beta-hCG values). Table 4.1 shows the recommended tests at staging.

Table 4.1: Recommended tests for staging at diagnosis

Test	Recommendation	GR
Serum tumour markers	Alpha-fetoprotein hCG LDH	A
Abdominopelvic CT	All patients	A
Chest CT	All patients	A
Testis ultrasound (bilateral)	All patients	A
Bone scan or MRI columna	In case of symptoms	
Brain scan (CT/MRI)	In case of symptoms and patients with metastatic disease with multiple lung metastases and/or high beta-hCG values.	
Further investigations		
Fertility investigations: Total testosterone LH FSH Semen analysis		B
Sperm banking	Should be offered	A

hCG = human chorionic gonadotrophin; LDH = lactate dehydrogenase; CT = computed tomography; LH = luteinising hormone; FSH = follicle-stimulating hormone.

4.4 Staging and prognostic classifications

The staging system recommended in these guidelines is the 2009 TNM of the International Union Against Cancer (UICC) (Table 4.2) [54]. This includes:

- determination of the anatomical extent of disease;
- assessment of serum tumour markers, including nadir values of hCG, AFP and LDH after orchiectomy (S category);
- definition of regional nodes;
- N-category modifications related to node size.

Table 4.2: TNM classification for testicular cancer (UICC, 2009, 7th edn. [54])

pT		Primary tumour ¹		
	pTX	Primary tumour cannot be assessed (see note 1)		
	pT0	No evidence of primary tumour (e.g. histological scar in testis)		
	pTis	Intratubular germ cell neoplasia (testicular intraepithelial neoplasia)		
	pT1	Tumour limited to testis and epididymis without vascular/lymphatic invasion: tumour may invade tunica albuginea but not tunica vaginalis		
	pT2	Tumour limited to testis and epididymis with vascular/lymphatic invasion, or tumour extending through tunica albuginea with involvement of tunica vaginalis		
	pT3	Tumour invades spermatic cord with or without vascular/lymphatic invasion		
	pT4	Tumour invades scrotum with or without vascular/lymphatic invasion		
N		Regional lymph nodes clinical		
	NX	Regional lymph nodes cannot be assessed		
	N0	No regional lymph node metastasis		
	N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension or multiple lymph nodes, none more than 2 cm in greatest dimension		
	N2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, any one mass more than 2 cm but not more than 5 cm in greatest dimension		
	N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension		
pN		Pathological		
	pNX	Regional lymph nodes cannot be assessed		
	pN0	No regional lymph node metastasis		
	pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and 5 or fewer positive nodes, none more than 2 cm in greatest dimension		
	pN2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumour		
	pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension		
M		Distant metastasis		
	MX	Distant metastasis cannot be assessed		
	M0	No distant metastasis		
	M1	Distant metastasis		
		M1a Non-regional lymph node(s) or lung		
		M1b Other sites		
S		Serum tumour markers		
	SX	Serum marker studies not available or not performed		
	S0	Serum marker study levels within normal limits		
		LDH (U/l)	hCG (mIU/mL)	AFP (ng/mL)
	S1	< 1.5 x N and	< 5,000 and	< 1,000
	S2	1.5-10 x N or	5,000-50,000 or	1,000-10,000
	S3	> 10 x N or	> 50,000 or	> 10,000

N indicates the upper limit of normal for the LDH assay.

LDH = lactate dehydrogenase; hCG = human chorionic gonadotrophin; AFP = alpha-fetoprotein.

¹Except for pTis and pT4, where radical orchidectomy is not always necessary for classification purposes, the extent of the primary tumour is classified after radical orchidectomy; see pT. In other circumstances, TX is used if no radical orchidectomy has been performed.

According to the 2009 TNM classification, stage I testicular cancer includes the following substages:

Stage grouping

Stage 0	pTis	N0	M0	S0,SX
Stage I	pT1-T4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2 - pT4	N0	M0	S0
Stage IS	Any patient/TX	N0	M0	S1-3
Stage II	Any patient/TX	N1-N3	M0	SX
Stage IIA	Any patient/TX	N1	M0	S0
	Any patient/TX	N1	M0	S1
Stage IIB	Any patient/TX	N2	M0	S0
	Any patient/TX	N2	M0	S1
Stage IIC	Any patient/TX	N3	M0	S0
	Any patient/TX	N3	M0	S1
Stage III	Any patient/TX	Any N	M1a	SX
Stage IIIA	Any patient/TX	Any N	M1a	S0
	Any patient/TX	Any N	M1a	S1
Stage IIIB	Any patient/TX	N1-N3	M0	S2
	Any patient/TX	Any N	M1a	S2
Stage IIIC	Any patient/TX	N1-N3	M0	S3
	Any patient/TX	Any N	M1a	S3
	Any patient/TX	Any N	M1b	Any S

- Stage IA patients have primary tumours limited to the testis and epididymis, with no evidence of microscopic vascular or lymphatic invasion by tumour cells on microscopy, no sign of metastases on clinical examination or imaging, and post-orchietomy serum tumour marker levels within normal limits. Marker decline in patients with clinical stage I disease should be assessed until normalisation.
- Stage IB patients have a more locally invasive primary tumour, but no sign of metastatic disease.
- Stage IS patients have persistently elevated (and usually increasing) serum tumour marker levels after orchietomy, indicating subclinical metastatic disease (or possibly a second germ cell tumour in the remaining testis).

In large population-based patient series, 75-80% of seminoma patients, and about 55% of patients with NSGCT cancer have stage I disease at diagnosis [55-57]. True stage IS (persistently elevated or increasing serum marker levels after orchietomy) is found in about 5% of non-seminoma patients.

In 1997, the IGCCCG defined a prognostic factor-based staging system for metastatic testis tumour based on identification of some clinical independent adverse factors. This staging system has been incorporated into the TNM Classification and uses histology, location of the primary tumour, location of metastases and prechemotherapy marker levels in serum as prognostic factors to categorise patients into 'good', 'intermediate' or 'poor' prognosis (Table 4.3) [34].

Table 4.3: Prognostic-based staging system for metastatic germ cell cancer (International Germ Cell Cancer Collaborative Group)*

Good-prognosis group	
Non-seminoma (56% of cases) 5-year PFS 89% 5-year survival 92%	<i>All of the following criteria:</i> <ul style="list-style-type: none"> • Testis/retroperitoneal primary • No non-pulmonary visceral metastases • AFP < 1,000 ng/mL • hCG < 5,000 IU/L (1,000 ng/mL) • LDH < 1.5 x ULN
Seminoma (90% of cases) 5-year PFS 82% 5-year survival 86%	<i>All of the following criteria:</i> <ul style="list-style-type: none"> • Any primary site • No non-pulmonary visceral metastases • Normal AFP • Any hCG • Any LDH
Intermediate prognosis group	
Non-seminoma (28% of cases) 5-year PFS 75% 5-year survival 80%	<ul style="list-style-type: none"> • Testis/retroperitoneal primary • No non-pulmonary visceral metastases • AFP 1,000 - 10,000 ng/mL or • hCG 5,000 - 50,000 IU/L or • LDH 1.5 - 10 x ULN
Seminoma (10% of cases) 5-year PFS 67% 5-year survival 72%	<i>All of the following criteria:</i> <ul style="list-style-type: none"> • Any primary site • Non-pulmonary visceral metastases • Normal AFP • Any hCG • Any LDH
Poor prognosis group	
Non-seminoma (16% of cases) 5-year PFS 41% 5-year survival 48%	<i>Any of the following criteria:</i> <ul style="list-style-type: none"> • Mediastinal primary • Non-pulmonary visceral metastases • AFP > 10,000 ng/mL or • hCG > 50,000 IU/L (10,000 ng/mL) or • LDH > 10 x ULN
Seminoma	No patients classified as poor prognosis

*Pre-chemotherapy serum tumour markers should be assessed immediately prior to the administration of chemotherapy (same day).

PFS = progression-free survival; AFP = alpha-fetoprotein; hCG = human chorionic gonadotrophin; LDH = lactate dehydrogenase.

5. DIAGNOSTIC EVALUATION

5.1 Clinical examination

TC presents as a painless, unilateral testicular scrotal mass, as a casual US finding or revealed by a scrotal trauma [58]. Scrotal pain may be the first symptom in 20% of cases and it is present in up to 27% of patients with testicular cancer [58, 59]. Gynaecomastia appears in 7% of cases (more common in non-seminomatous tumours). Back and flank pain due to metastasis is present in about 11% of cases [59].

Diagnosis is delayed in around 10% of cases of testicular tumour that mimic orchioepididymitis [59], physical examination reveals the features of the mass and must always be carried out together with a general examination to find possible (supraclavicular) distant metastases, a palpable abdominal mass or gynaecomastia. Ultrasound (US) must be performed in any doubtful case. A correct diagnosis must be established in all patients with an intrascrotal mass [60].

5.2 Imaging of the testis

Currently, US serves to confirm the presence of a testicular mass and to explore the contralateral testis. Its sensitivity is almost 100%, and it has an important role in determining whether a mass is intra- or extratesticular [61]. Ultrasound is an inexpensive test and should be performed even in the presence of clinically evident testicular tumour [62].

US of the testis should be performed in young men with retroperitoneal or visceral masses and/or elevated serum human chorionic gonadotrophin (hCG) or alpha-fetoprotein (AFP) and/or consulting for fertility problems and without a palpable testicular mass [63-65].

Magnetic resonance imaging (MRI) of scrotum offers higher sensitivity and specificity than US in the diagnosis of TC, but its high cost does not justify its routine use for diagnosis [61, 66].

5.3 Serum tumour markers at diagnosis

Serum tumour markers are prognostic factors and contribute to diagnosis and staging [67]. The following markers should be determined before, and 5-7 days after, orchiectomy:

- AFP (produced by yolk sac cells);
- hCG (expression of trophoblasts);
- LDH (lactate dehydrogenase).

Tumour markers are of value for diagnosis (before orchiectomy) as well as for prognosis (after orchiectomy). They are increased in approximately every second patient with testicular cancer [5, 58]. AFP and hCG are increased in 50-70% and in 40-60% of patients with non-seminomatous germ cell tumour (NSGCT), respectively. About 90% of NSGCT present with a rise in one or two of the markers. Up to 30% of seminomas can present or develop an elevated hCG level during the course of the disease [33, 68].

LDH is a less specific marker, its concentration being proportional to tumour volume. Its level may be elevated in 80% of patients with advanced testicular cancer [33]. Of note, negative marker levels do not exclude the diagnosis of a germ cell tumour. Placental alkaline phosphatase (PLAP), is an optional marker in monitoring patients with pure seminoma, but not recommended in smokers [69].

Cytogenetic and molecular markers are available in specific centres, but at present only contribute to research.

5.4 Inguinal exploration and orchiectomy

Every patient with a suspected testicular mass must undergo inguinal exploration with exteriorisation of the testis within its tunics. Orchiectomy with division of the spermatic cord at the internal inguinal ring must be performed if a malignant tumour is found. If the diagnosis is not clear, a testicular biopsy (and enucleation of the intraparenchymal tumour) is taken for frozen (fresh tissue) section histological examination.

In cases of life threatening disseminated disease, lifesaving chemotherapy should be given up-front, especially when the clinical picture is very likely testicular cancer and/or tumour markers are increased. Orchiectomy may be delayed until clinical stabilisation occurs or in combination with resection of residual lesions.

5.5 Organ-sparing surgery

Although organ-sparing surgery is not indicated in the presence of non-tumoural contralateral testis, it can be attempted in special cases with all the necessary precautions.

In synchronous bilateral testicular tumours, metachronous contralateral tumours, or in a tumour in a solitary testis with normal pre-operative testosterone levels, organ preserving surgery can be performed when tumour volume is less than 30% of the testicular volume and surgical rules are respected. In those cases, the rate of associated TIN is high (at least up to 82%) (see Section 5.7.)

5.6 Pathological examination of the testis

Mandatory pathological requirements:

- Macroscopic features: side, testis size, maximum tumour size, and macroscopic features of the epididymis, spermatic cord, and tunica vaginalis.
- Sampling: a 1 cm² section for every centimetre of maximum tumour diameter, including normal macroscopic parenchyma (if present), albuginea and epididymis, with selection of suspected areas. At least one proximal and one distal section of spermatic cord plus any suspected area.
- Microscopic features and diagnosis: histological type (specify individual components and estimate amount as percentage) according to WHO 2004 [32]:
 - presence or absence of peri-tumoural venous and/or lymphatic invasion;
 - presence or absence of albuginea, tunica vaginalis, rete testis, epididymis or spermatic cord invasion;

- presence or absence of (TIN/ITGCN [intratubular germ cell neoplasia]) in non-tumour parenchyma
Intratubular germ cell neoplasia.
- pT category according to Tumour Node Metastasis (TNM) 2009 [54].
- Immunohistochemical studies: in seminoma and mixed germ cell tumour, AFP and hCG.

Advisable immunohistochemical markers, in cases of doubt, are:

- in seminoma: cytokeratins (CAM 5.2), PLAP, c-kit;
- in intratubular germ cell neoplasia: PLAP, c-kit;
- other advisable markers: chromogranin A (Cg A), Ki-67 (MIB-1).

5.7 Diagnosis and treatment of testicular intraepithelial neoplasia (TIN)

Contralateral biopsy has been advocated to rule out the presence of TIN [70]. Although routine policy in some countries, the low incidence of TIN and contralateral metachronous testicular tumours (up to 9% and approximately 2.5%, respectively) [71, 72], the morbidity of TIN treatment, and the fact that most of metachronous tumours are at a low stage at presentation make it controversial to recommend a systematic contralateral biopsy in all patients [73-75].

It is still difficult to reach a consensus on whether the existence of contralateral TIN must be identified in all cases. However, biopsy of the contralateral testis should be offered to patients at high risk for contralateral TIN, i.e. testicular volume < 12 mL, a history of cryptorchidism or poor spermatogenesis (Johnson Score 1-3). A contralateral biopsy is not necessary in patients older than 40 years without risk factors [38, 57, 76-79]. A double biopsy increases sensitivity [77]. Patients should be informed that a testicular tumour may arise in spite of a negative biopsy [80].

Once TIN is diagnosed, local radiotherapy (16-20 Gy in fractions of 2 Gy) is the treatment of choice in the case of a solitary testis. Testicular radiotherapy in a solitary testis will result in infertility and increased long-term risk of Leydig cell insufficiency [39, 73, 81, 82]. Fertile patients who wish to father children may delay radiation therapy and be followed by regular testicular US [77].

If TIN is diagnosed and the contralateral testis is healthy, the options for management are orchiectomy or close observation (with a 5-year risk of developing TC of 50%) [83].

5.8 Screening

There are no surveys proving the advantages of screening programmes, but it has been demonstrated that stage and prognosis are directly related to early diagnosis. In the presence of clinical risk factors, self-physical examination by the affected individual is advisable.

5.9 Guidelines for the diagnosis and staging of testicular cancer

	GR
Testicular US is a mandatory assessment.	A
Biopsy of the contralateral testis should be offered (and its consequences discussed) to patients at high risk for contralateral TIN.	A
Orchiectomy and pathological examination of the testis are necessary to confirm the diagnosis and to define the local extension (pT category). In a life-threatening situation due to extensive metastasis, chemotherapy must be started before orchiectomy.	A
Serum determination of tumour markers (AFP, hCG, and LDH) must be performed both before and 5-7 days after orchiectomy for staging and prognostic reasons.	A
The state of the retroperitoneal, mediastinal and supraclavicular nodes and viscera must be assessed in testicular cancer.	A

AFP = alpha-fetoprotein; hCG = human chorionic gonadotrophin; LDH = lactate dehydrogenase; TIN = testicular intraepithelial neoplasia.

6. PROGNOSIS

6.1 Risk factors for metastatic relapse in stage I GCT

Retrospectively, for seminoma stage I, tumour size (> 4 cm) and invasion of the rete testis have been identified as predictors for relapse in a pooled analysis [84]. However, these risk factors have not been validated in a prospective setting except that the absence of both factors indicated a low recurrence rate (6%) [85].

For non-seminoma stage I, vascular invasion of the primary tumour in blood or lymphatic vessels is the most important predictor of occult metastatic disease. The proliferation rate, as well as the percentage of embryonal carcinoma, are additional predictors that improve upon the positive and negative predictive value of vascular invasion [86, 87]. Whether the absence of teratoma (as qualitative data, as opposed to the more subjective assessment of percentage of embryonal carcinoma) can independently complement vascular invasion as a predictive factor of relapse requires validation [88].

The significant prognostic pathological risk factors for stage I testicular cancer are listed in Table 6.1.

Table 6.1: Risk factors for occult metastatic disease in stage I testicular cancer

	For seminoma	For non-seminoma
Pathological (for stage I)		
Histopathological type	<ul style="list-style-type: none">• Tumour size (> 4 cm)• Invasion of the rete testis	<ul style="list-style-type: none">• Vascular/lymphatic in or peri-tumoural invasion• Proliferation rate > 70%• Percentage of embryonal carcinoma > 50%

7. DISEASE MANAGEMENT

7.1 Impact on fertility and fertility-associated issues

Sperm abnormalities are frequently found in patients with testis tumours. Furthermore, chemotherapy and radiation treatment can also impair fertility. In patients in the reproductive age group, pre-treatment fertility assessment (testosterone, luteinising hormone [LH] and follicle stimulating hormone [FSH] levels) should be performed, and semen analysis and cryopreservation should be offered. If cryopreservation is desired, it should preferably be performed before orchiectomy, but in any case prior to chemotherapy treatment [81, 89-95]. In cases of bilateral orchiectomy or low testosterone levels after treatment of TIN, life-long testosterone supplementation is necessary [96]. Patients with unilateral or bilateral orchiectomy should be offered a testicular prosthesis [97]. For more detailed information, the reader is referred to the EAU Male Infertility Guidelines [98].

7.2 Stage I Germ cell tumours

7.2.1 Stage I seminoma

After modern staging procedures, about 15-20% of stage I seminoma patients have subclinical metastatic disease, usually in the retroperitoneum, and will relapse after orchiectomy alone.

The decision regarding adjuvant treatment should always be based on a thorough discussion with the patient, taking into account the described advantages and disadvantages, as well as the individual situation of the patient.

7.2.1.1 Surveillance

Several prospective non-randomised surveillance studies have been conducted during the past decade, the largest study from Canada with > 1,500 patients [99]. Previous analyses from four studies showed an actuarial 5-year relapse-free rate of 82.3%. The Princess Margaret Hospital series (n = 1559) showed an overall relapse rate in unselected patients of 16.8%. The actuarial relapse rate is in the order of 15-20% at 5 years, and most of the relapses are first detected in infra-diaphragmatic lymph nodes [100].

In patients with low risk (tumour size ≤ 4 cm and no rete testis invasion), the recurrence under surveillance is as low as 6% [101]. Chemotherapy, according to the IGCCCG classification, is a possible treatment for seminoma relapse under surveillance. However, 70% of patients with relapse are suitable for treatment with radiotherapy alone because of small volume disease at the time of recurrence. Patients who relapse after salvage radiotherapy can be effectively treated with chemotherapy [102]. The combination of

carboplatin chemotherapy and modern radiotherapy for treatment of low stage seminoma relapse (IIA/IIB) is under investigation.

The overall cancer-specific survival rate reported under surveillance performed by experienced centres is 97-100% for seminoma stage I [100, 102]. The main drawback of surveillance is the need for more intensive follow-up, especially with repeated imaging examinations of the retroperitoneal lymph nodes.

7.2.1.2 Adjuvant chemotherapy

A joint trial by the Medical Research Council (MRC) and the European Organisation for Research and Treatment of Cancer (EORTC) (MRC TE 19 trial), which compared one cycle of carboplatin (area under curve [AUC] 7) with adjuvant radiotherapy, did not show a significant difference with regard to recurrence rate, time to recurrence and survival after a median follow-up of 4 years [103-105]. Therefore, adjuvant carboplatin therapy using a dosage of one course of AUC 7 is an alternative to radiotherapy or surveillance in stage I seminoma [100, 103-105]. Two courses of adjuvant carboplatin seem to further reduce the relapse rate to the order of 1-3% [85, 106], but additional experience and long-term observation are needed.

7.2.1.3 Adjuvant radiotherapy and risk-adapted treatment

Seminoma cells are extremely radiosensitive. Adjuvant radiotherapy to a para-aortic (PA) field or to a paraaortic and ipsilateral field (para-aortic and ipsilateral iliac nodes), with moderate doses (total 20-24 Gy), will reduce the relapse rate to 1-3% [107-110]. Adjuvant irradiation of supradiaphragmatic lymph nodes is not indicated in seminoma stage I.

With regard to the irradiation dose, a large MRC randomised trial of 20 Gy versus 30 Gy PA radiation in stage I seminoma showed equivalence for both doses in terms of recurrence rates [108]. The rate of severe radiation-induced long-term toxicity is less than 2%. Moderate chronic gastrointestinal (GI) side-effects are seen in about 5% of patients, and moderate acute GI toxicity in about 60% [107]. The main concern surrounding adjuvant radiotherapy is the increased risk of radiation-induced second non-germ cell malignancies [111-116]. Therefore, in young patients (< 40 yrs) adjuvant radiotherapy should no longer be used.

A scrotal shield should be considered during adjuvant radiotherapy in order to prevent scattered radiation toxicity in the contralateral testis [114].

7.2.1.4 Risk-adapted treatment

Using tumour size > 4 cm and rete testis invasion, patients with seminoma stage I may be subdivided into a low-and high-risk group of occult metastatic disease. Patients with and without both risk factors have a risk of occult disease of 32% and 12%, respectively. These risk factors were introduced by an analysis of retrospective trials [84]. A prospective trial based on these risk factors (no risk factors: surveillance; both risk factors: two courses of carboplatin AUC 7) showed the feasibility of a risk-adapted approach. Early data with limited follow-up indicate that patients without either risk factor have a very low risk of 6.0% - 14.8% of relapse at 5 years. Patients in the high-risk group treated with carboplatin experienced a 1.4% - 3.2% relapse rate at mean follow up of 34 months [101, 117].

7.2.1.5 Retroperitoneal lymph node dissection (RPLND)

In a prospective, non-randomised study comparing radiotherapy and RPLND in stage I seminoma, there was a trend towards a higher incidence of retroperitoneal relapses (9.5%) after RPLND as primary treatment. Therefore, this policy should not be recommended in stage I seminoma [115].

7.2.2 Guidelines for the treatment of seminoma stage I

	GR
Surveillance is a recommended management option (if facilities available and patient compliant).	A*
Carboplatin-based chemotherapy (one course at AUC 7) is recommended.	B
Adjuvant treatment is not recommended for patients at very low risk.	A
Radiotherapy is not recommended as adjuvant treatment.	A

*Upgraded following panel consensus.

7.3 NSGCT clinical stage I

Up to 30% of NSGCT patients with clinical stage I (CS1) disease have subclinical metastases and will relapse if surveillance alone is applied after orchiectomy. The decision regarding adjuvant treatment should always be based on a thorough discussion with the patient, taking into account the described advantages and

disadvantages, as well as the individual situation of the patient.

7.3.1 **Surveillance**

Improvements in clinical staging and follow-up methods, and the availability of effective salvage treatment with cisplatin-based chemotherapy and post-chemotherapy surgery, have led to studies of only close surveillance after orchiectomy in CS1 NSGCT patients. The largest reports of the surveillance strategy indicate a cumulative relapse rate of about 30%, with 80% of relapses occurring during the first 12 months of follow-up, 12% during the second year and 6% during the third year, decreasing to 1% during the fourth and fifth years, and occasionally even later [118-122]. About 35% of relapsing patients have normal levels of serum tumour markers at relapse. About 60% of relapses are in the retroperitoneum. Despite very close follow-up, 11% of relapsing patients presented with large-volume recurrent disease.

The somewhat lower relapse rates reported from surveillance studies compared with some series of patients staged by RPLND [123] can be explained by the fact that some patients (presumably at higher risk) are excluded once surveillance is advised. Based on the overall cancer-specific survival data, surveillance within an experienced surveillance programme can safely be offered to patients with non-risk stratified clinical stage I non-seminoma as long as they are compliant and informed about the expected recurrence rate as well as the salvage treatment [124-126].

7.3.2 **Adjuvant chemotherapy**

Patients with CS1 NSGCT have a 14-48% risk of recurrence within 2 years after orchiectomy. Adjuvant chemotherapy with two courses of cisplatin, etoposide, and bleomycin (BEP) was introduced in 1996 by a prospective MRC trial [127]. Subsequently, adjuvant chemotherapy was mainly given in patients with high risk (vascular invasion present) [127-132]. In these series, involving more than 200 patients, some with a median follow-up of nearly 7.9 years [127], a relapse rate of only 2.7% was reported, with very little long-term toxicity. Two cycles of cisplatin-based adjuvant chemotherapy do not seem to adversely affect fertility or sexual activity [133]. However, the very-long term (> 20 years) side effects of adjuvant chemotherapy in this setting are currently unknown, especially the long-term cardio-vascular effects of chemotherapy [134]. This should be taken in consideration for decision-making.

In 2008, the German Testicular Study Group reported a randomised trial of nerve-sparing RPLND or one course of BEP as adjuvant treatment in CS 1 NSGCT without risk-adaption. Adjuvant chemotherapy significantly increased the 2-year recurrence-free survival to 99.41% (confidence interval (CI): 95.87%, 99.92%) as opposed to surgery, which had a 2-year recurrence-free survival of 92.37% (CI: 87.21%, 95.50%). The difference was 7.04%, CI: 2.52%, 11.56% and, therefore, the main endpoint of the trial was reached. The hazard ratio to experience a tumour recurrence with surgery as opposed to chemotherapy was 7.937, CI: 1.808, 34.48. Of 174 patients having received one course of BEP, 43% had high risk features (> pT1) [135].

In a community-based prospective study, SWENOTECA recommended one course of BEP in LVI+ patients, while patients with LVI- chose between surveillance and BEP x 1 [136]. The relapse-rate of the 490 patients who received BEP x 1 at 5 years was 3.2% for patients with LVI and 1.6% for patients without LVI. After a median follow-up of 8.1 years the relapse rate was 2.3%, 3.4% and 1.3% for all, LVI+, and LVI-, respectively [137]. These numbers imply that > 90% of relapses were prevented by adjuvant chemotherapy and, importantly, no relapses were observed later than 3.3 years. Reduction from two to one cycle of BEP improves the risk-benefit ratio of adjuvant chemotherapy considerably.

In addition, it is important to be aware of slow-growing retroperitoneal teratomas after primary chemotherapy [138]. Until now, only a limited number of patients with long-term follow-up and toxicity data are reported so far [139].

The results of cost analyses comparing surveillance, RPLND and primary chemotherapy show different results among the reported studies, possibly because of differences in intensity and costs related to follow-up procedures [140]. With a low frequency of follow-up CTs (a surveillance strategy which has been proven to be effective in non-seminoma CS1), the costs of follow-up can be considerably reduced [141].

7.3.3 **Risk-adapted treatment**

Risk-adapted treatment is an alternative to the strategy of surveillance for all patients with CS 1 NSGCT. Risk-adapted treatment is based on the risk factor, vascular invasion. Stratifying patients with CS1 NSGCT according to their presumed risk of relapse is a rational option, as several studies have reported similar survival rates and a final cure rate close to 100% with all available treatment options using the risk-stratifying approach [127-132, 136, 137, 142-145].

If the risk-adapted policy is applied, patients with vascular invasion are recommended to undergo adjuvant chemotherapy and patients with absent vascular invasion are recommended a surveillance strategy. In the past, two cycles of BEP have been recommended for adjuvant treatment. In view of the low rates of recurrence (2-3%) and equivalent cancer-specific survival rates including salvage strategies in large prospective trials with sufficient follow-up, one cycle of BEP is recommended as adjuvant chemotherapy in patients with vascular invasion.

In cases of relapse after BEP x 1, three courses of BEP are recommended. However, there is not a large body of evidence to support one specific salvage regimen.

7.3.4 **Retroperitoneal lymph node dissection**

In view of the high cancer-specific survival rates of surveillance with salvage treatment in cases of relapse and the low relapse rates if adjuvant chemotherapy is chosen, the role of primary diagnostic retroperitoneal lymph node dissection has diminished. The randomised phase III trial of the German Testicular Cancer Study group compared RPLND to BEP x 1 as adjuvant treatment to show a more than expected difference of 7% in favour of chemotherapy. One course of BEP showed a significantly lower recurrence rate as compared to surgery [135].

If RPLND is performed in a multicentre setting, a higher rate of “in-field” recurrences and a higher rate of complications was reported [135, 146]. Thus, nerve-sparing RPLND - if indicated - should be performed by an experienced surgeon in specialised centres.

About 18-30% of patients are found to have retroperitoneal lymph node metastases on RPLND, corresponding to pathological stage II (PS2) disease [146-149]. If no retroperitoneal metastases are found at RPLND (PS1), approximately 10% of the PS1 patients relapse at distant sites [87, 124, 149, 150]. If metastases are present and not treated with adjuvant chemotherapy, recurrence will be found in 31% in patients [149].

The presence of vascular invasion, predominant embryonal carcinoma, pT category as well as a high number of and extranodal extension in metastatic nodes may be associated with an increased risk of recurrence in PS2 cases without adjuvant chemotherapy. Nonetheless, the clinical significance of these further parameters remains poor and not advisable in clinical practice [149, 151].

The follow-up after RPLND is simpler and less costly than that carried out during post-orchietomy surveillance because of the reduced need for abdominal CT scans [152]. If there is an indication to perform a staging RPLND, a laparoscopic or robot-assisted RPLND is feasible in expert hands. This minimal-invasive approach cannot be recommended as the standard approach outside of a specialised laparoscopic centre [153, 154].

7.3.5 **Guidelines for the treatment of NSGCT stage I**

	LE	GR
Patients with CS 1 NSGCT should be informed about all adjuvant treatment options after orchiectomy (surveillance, adjuvant chemotherapy, and RPLND) including treatment-specific recurrence rates as well as acute and long-term side effects.	2a	A*
Surveillance or risk-adapted treatment based on vascular invasion (see below) are recommended treatment options.	2a	A*
If patients are not willing to undergo the surveillance strategy, one course of BEP as adjuvant treatment has proven to be superior to RPLND in terms of recurrence rate in a community based study.	1b	A*
Salvage treatment of patients with recurrence during surveillance consists of three or four courses of BEP chemotherapy according to IGCCCG classification followed by post-chemotherapy retroperitoneal lymph node dissection if necessary.	2a	A

7.3.6 Risk-adapted treatment for CS1 based on vascular invasion

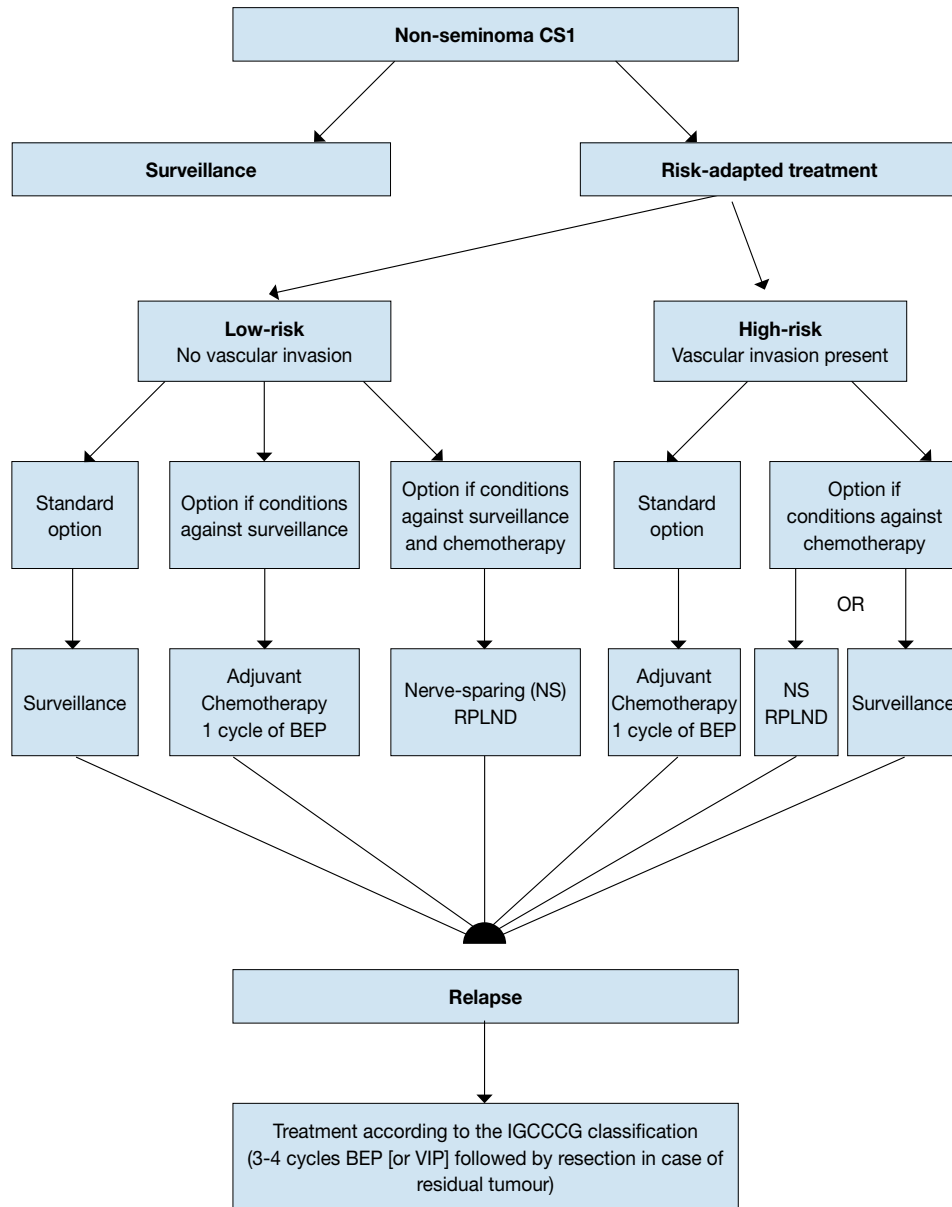
CS1A (pT1, no vascular invasion): low risk	LE	GR
Surveillance is recommended if the patient is willing and able to comply.	2a	A
In low-risk patients not willing (or suitable) to undergo surveillance, adjuvant chemotherapy with one course of BEP is recommended.	2a	A*
CS1B (pT2-pT4): high risk		
Primary chemotherapy with one course of BEP is recommended.	2a	A*
Patients should be informed about the advantages and disadvantages of two courses of BEP.		
Surveillance or nerve-sparing RPLND in high-risk patients remain options for those not willing to undergo adjuvant chemotherapy. If pathological stage II is revealed at RPLND, further chemotherapy as well as observation should be discussed with each patient.		A*

*Upgraded following panel consensus.

BEP = cisplatin, etoposide, bleomycin; RPLND = retroperitoneal lymph node dissection.

Figure 1 provides a treatment algorithm for patients with NSGCT stage I.

Figure 1: Risk-adapted treatment in patients with clinical stage 1 non-seminoma NSGCT CS1*



*All treatment options will need discussing with individual patients, to allow for them to make an informed decision as to their further care.

BEP = cisplatin, etoposide, bleomycin; CS = clinical stage; IGCCCG = International Germ Cell Cancer Collaborative Group; RLND = retroperitoneal lymph node dissection; VIP = etoposide, cisplatin, ifosfamide.

7.4 Metastatic germ cell tumours

The first-line treatment of metastatic germ cell tumours depends on:

- the histology of the primary tumour;
- prognostic groups as defined by the IGCCCG based on 5,202 non-seminoma and 660 seminoma cases (Table 4.3) [34].

In relapsed patients a new prognostic score has been developed including response to first-line therapy which can be used to estimate patient outcome following salvage chemotherapy.

7.4.1. **CS1S with (persistently) elevated serum tumour markers**

Serum tumour markers should be followed closely until levels fall into the reference values according to the expected half-life values for AFP and hCG. If the marker level increases after orchiectomy, the patient has residual disease. If RPLND is performed, up to 87% of these patients have pathologically documented nodes in the retroperitoneum [156]. An ultrasound examination of the contralateral testicle must be performed, if this was not done initially.

The treatment of true CS1S patients is still controversial. They may be treated with three courses of BEP chemotherapy and with follow-up as for CS1B patients (high risk, see below) after primary chemotherapy [157], or by RPLND [141].

7.4.2 **Metastatic disease (stage IIA/B)**

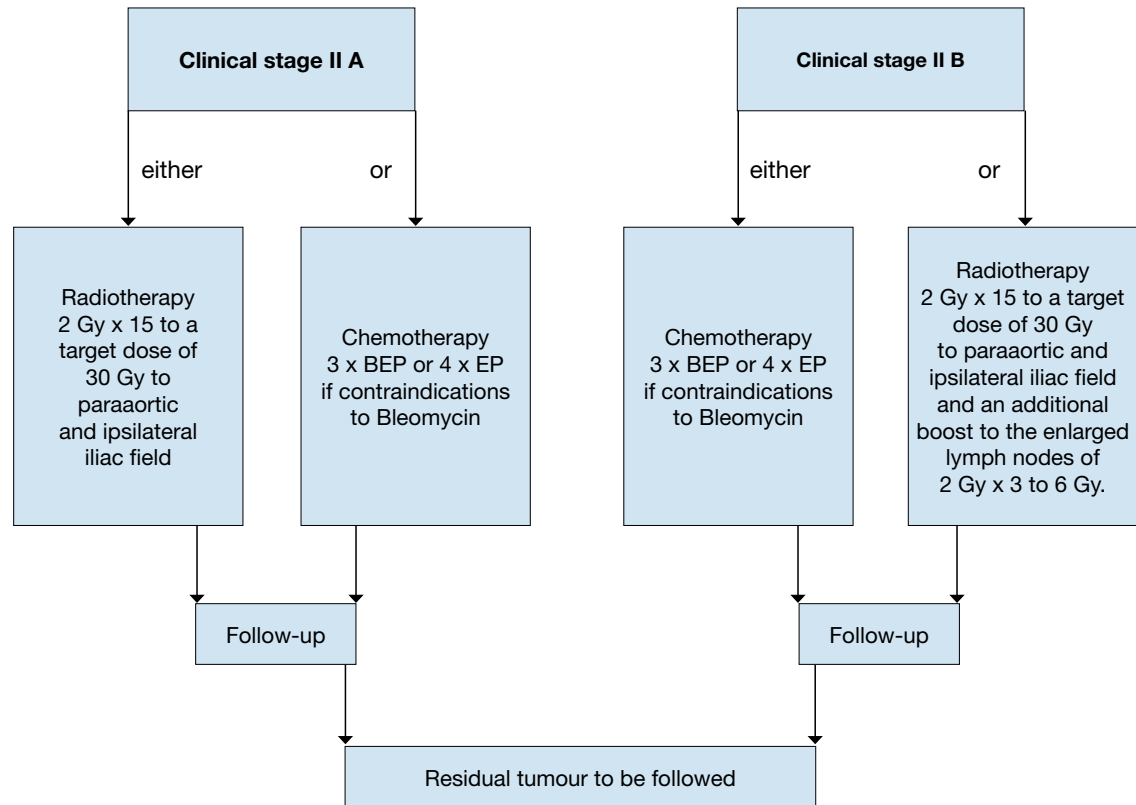
7.4.2.1 *Stage IIA/B seminoma*

Slightly enlarged retroperitoneal lymph nodes < 2 cm in patients without elevated tumour markers offer a diagnostic problem. These lymph nodes may be benign or, on the other hand, represent metastases. An observation period of 8 weeks with a second staging is recommended unless a biopsy verifies metastatic disease. Treatment should not be initiated unless metastatic disease is unequivocal, (e.g. growth or positive biopsy).

So far, the standard treatment for stage IIA/B seminoma has been radiotherapy with reported relapse rates of 9-24% [158-160]. Accumulating data on long-term morbidity, such as increased risk of cardiovascular events and increased risk of second malignancies following radiotherapy has led to concern. Most reports refer to patients irradiated with larger target volumes and higher doses but there are also more recent studies reporting on patients treated with more modern radiotherapy [56, 161]. The radiation dose delivered in stage IIA and IIB is approximately 30 Gy and 36 Gy, respectively. The standard radiation field compared with stage I will be extended from the PA region to the ipsilateral iliac field. In stage IIB, the lateral borders should include the metastatic lymph nodes with a safety margin of 1.0-1.5 cm. This technique yields a relapse-free survival in stage IIA and IIB of 92% and 90%, respectively. Overall survival is almost 100% [158, 159]. Conversely, dose reduction to 27 Gy has been associated with 11% of relapses [102, 161].

In stage IIA/B, chemotherapy; with 3 courses of BEP or 4 courses of etoposide and cisplatin (EP) in cases with contraindications to bleomycin is an alternative to radiotherapy. There are no randomised studies comparing radiotherapy versus chemotherapy. Although more toxic in the short term, 3 courses of BEP or 4 courses of EP achieve a similar level of disease control [162]. One population-based study with 67 stage IIB patients reported a relapse free-survival of 100% after a median of 5.5 years of follow-up [102]. Single-agent carboplatin is not an alternative to standard EP or BEP chemotherapy for metastatic disease [163].

Figure 2: Treatment options in patients with seminoma clinical stage II A and B



BEP = cisplatin, etoposide, bleomycin; EP = etoposide, cisplatin.

7.4.2.2 Stage IIA/B non-seminoma

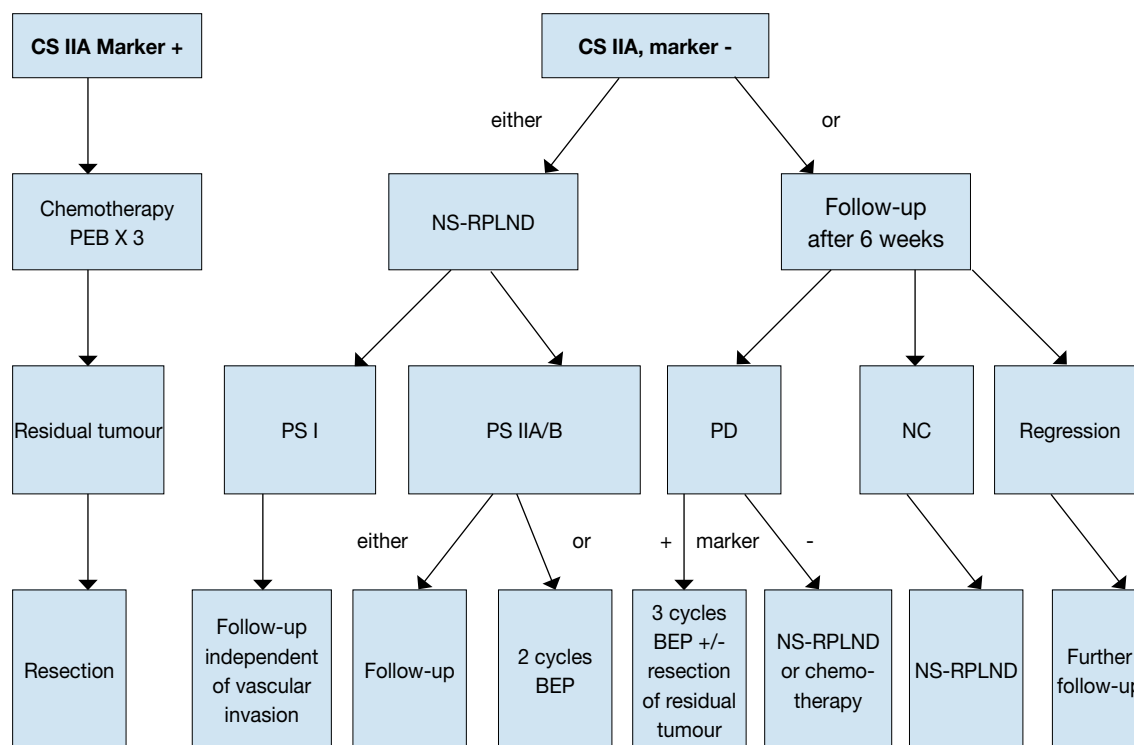
There is a general consensus that treatment should start with initial chemotherapy in all advanced cases of NSGCT except for stage II NSGCT disease without elevated tumour markers, which alternatively can be managed by primary RPLND or surveillance to clarify stage [140, 164, 165].

If surveillance is chosen, one follow-up evaluation after 6 weeks is indicated to document whether the lesion is growing, remaining stable or shrinking. A shrinking lesion is probably non-malignant in origin and should be observed further. A stable or growing lesion indicates either teratoma or an undifferentiated malignant tumour. If the lesion is growing without a corresponding increase in the tumour markers AFP or beta-hCG, RPLND represents the first option to be performed by an experienced surgeon because of suspected viable disease or teratoma [164]. Patients with a growing lesion and a concomitant increase in the tumour markers AFP or beta-hCG require primary chemotherapy with BEP according to the treatment algorithm for patients with metastatic disease and IGCCCG recommendations [166-168] (Figure 2). An alternative to the surveillance strategy in marker-negative II A/B non-seminoma with suspicion of an undifferentiated malignant tumour is a (CT-guided) biopsy, if technically possible. There is insufficient published data on PET scans in this situation.

When primary chemotherapy is refused by the patient or when it has some contraindications, primary nerve-sparing RPLND represents a viable option.

Primary chemotherapy and primary RPLND are comparable options in terms of outcome, but side-effects and toxicity are different, allowing for involvement of the patient in selecting the treatment of choice [169]. The cure rate with either approach will be close to 98% [170-176].

Figure 3: Treatment options in patients with non-seminoma clinical stage IIA



BEP = cisplatin, etoposide, bleomycin; NS = nerve-sparing; RPLND = retroperitoneal lymph node dissection; PS = pathological stage; PD = progressive disease; NC = no change.

7.4.3 Metastatic disease (stage IIC and III)

7.4.3.1 Primary chemotherapy

7.4.3.1.1 Good prognosis risk group - SGCT

For metastatic seminoma, only very limited data are available from randomised trials and they indicate that a cisplatin-based regimen should be preferred to carboplatin chemotherapy [177]. Recent data indicate that EP x 4 result in cure in almost all cases of good-prognosis seminomatous germ cell cancers [178]. Standard treatment in good-prognosis seminoma should therefore be 3 x BEP or 4 x EP. In the case of contraindications to Bleomycin, EP x 4 should be given [179]. Post-chemotherapy masses should be managed as described in Section 7.4.4.1.

7.4.3.1.2 Intermediate prognosis risk group - SGCT

For patients with intermediate-risk seminoma, 4 cycles of BEP or etoposide, cisplatin, ifosfamide (VIP) (in the case of contraindications to bleomycin) are recommended options, although no randomized trial has focused specifically on this group of rare patients [180].

7.4.3.1.3 Good prognosis risk group - NSGCT

For non-seminoma, the primary treatment of choice for metastatic disease in patients with good risk disease according to the IGCCCG risk classification is three cycles of BEP combination chemotherapy (Table 7.1). This regimen has proven superior to cisplatin, vinblastine and bleomycin (PVB) in patients with advanced disease [181-183]. While data support a 3-day regimen of administering combination chemotherapy to be equally effective as a 5-day regimen, this is associated with increased toxicity when four cycles are used [184], thus the 5-day BEP regimen is recommended.

Table 7.1: BEP regimen (interval 21 days)

Drug	Dosage	Duration of cycles
Cisplatin	20 mg/m ²	Days 1-5*
Etoposide	100 mg/m ²	Days 1-5
Bleomycin	30 mg	Days 1, 8, 15

*Plus hydration.

BEP = cisplatin, etoposide, bleomycin.

In selected cases where bleomycin is contraindicated, four cycles of EP can be given [34, 183, 185-187]. A randomised trial from the French Groupe d'Etude des Tumeurs Genito-Urinaires (GETUG) suggested that when the BEP is used in this setting the mortality was half that of EP, although the difference did not reach statistical significance [187, 188].

Therapy should be given without reduction of the doses at 21-day intervals; delaying the following chemotherapy cycle is justified only in cases of fever with granulocytopenia < 1000/mm³ or thrombocytopenia < 100,000/IU. There is no indication for prophylactic application of haematopoietic growth factors such as, for example, granulocyte colony-stimulating factor (G-CSF). However, if infectious complications have occurred during chemotherapy or the treatment interval was delayed due to myelotoxicity, prophylactic administration of G-CSF is recommended for the following cycles [185, 189].

7.4.3.1.4 Intermediate prognosis risk group - NSGCT

The 'intermediate prognosis' group in the IGCCCG has been defined as patients with a 5-year survival rate of about 80%. The available data support four cycles of BEP as standard treatment [34, 190]. A randomised trial has compared 4 cycles of BEP to 4 x BEP with the addition of paclitaxel (T-BEP) and did not show a significant improvement in OS [191]. The overall toxicity with T-BEP was higher than with BEP and thus it cannot be recommended as a standard approach.

7.4.3.1.5 Poor prognosis risk group - NSGCT

For patients with a 'poor prognosis' non-seminoma as defined by the IGCCCG and favourable marker decline, standard treatment consists of four cycles of BEP. Four cycles of cisplatin, etoposide and ifosfamide (PEI) have the same effect, but are more myelotoxic [192, 193]. The 5-year progression-free survival is between 45% and 50%. Three randomised trials have shown no advantage in OS for high-dose chemotherapy for the overall group of 'poor prognosis' patients [194-196].

However, patients with a slow tumour marker decline after the first or second cycle represent a prognostically inferior subgroup [36, 194].

An online calculator is available for free at www.igr.fr/calculation-tumor/NSGCT.xls. Recently, an international randomised phase III trial (GETUG 13) conducted in 263 patients with IGCCCG poor-risk NSGCT demonstrated that intensifying treatment with dose-dense chemotherapy improves PFS, but not OS in patients with an early unfavourable tumour marker decline [37]. Based on the results from this trial, patients with an unfavourable tumour marker decline after one cycle of BEP should be switched to a more intensive chemotherapy regimen [197]. Further prospective trials /registries are planned to validate this approach further.

Since a matched-pair analysis comparing high-dose to conventional treatment resulted in a better survival rate [36, 198, 199], poor prognosis patients should still be treated in ongoing prospective trials or registries, whenever available.

Patients meeting 'poor-prognosis' criteria should be transferred to a reference centre as a better outcome was reported for intermediate and poor prognosis patients who had been treated within a clinical trial in a high volume centre [12, 200]. There are no general recommendations for treatment modifications for patients with a poor general condition (Karnofsky < 50%) or extended liver infiltration (> 50%), but two small reports indicate that a first cycle of dose reduced therapy may reduce acute mortality without compromising long-term outcome, however, the number of subsequent cycles of full dose therapy should not be reduced after a first low dose induction cycle [201, 202].

Patients with extended pulmonary infiltration are at risk for acute respiratory distress syndrome: adapting the doses of the BEP regimen in the first cycle of chemotherapy (only 3 days of EP without bleomycin) was suggested to reduce the risk of early death in this setting [201].

7.5 Restaging and further treatment

7.5.1 Restaging

Restaging is performed by imaging investigations and re-evaluation of tumour markers. At marker decline and stable or regressive tumour manifestation, chemotherapy will be completed (three or four cycles, depending on

the initial stage) [34, 203, 204]. In the case of marker decline, but growing metastases, resection of the tumour is obligatory after termination of induction therapy, other than in an emergency, according to local tumour growth [205].

Only with documented marker increase after two courses of chemotherapy is an early crossover of therapy to a completely new regimen indicated. These patients are usually candidates for new drug trials [198, 206]. Patients with a low-level hCG marker plateau post-treatment should be observed to see whether complete normalisation occurs. In patients with a low plateau serum AFP level after chemotherapy, surgery of residual masses should be performed, with post-surgery AFP monitoring. Salvage chemotherapy is indicated for documented marker rise only [207, 208].

7.5.2 **Residual tumour resection**

7.5.2.1 *Seminoma*

A residual mass of seminoma should not be primarily resected, irrespective of the size, but controlled by imaging investigations and tumour markers [209-215].

FDG-PET has a high negative predictive value in patients with residual masses after treatment of seminoma. False positive results are less frequent when scans are scheduled >2 months after chemotherapy. In patients with residuals of > 3 cm, FDG-PET should be performed in order to gain more information on the viability of these residuals. In patients with residuals of < 3 cm, the use of FDG-PET is optional [49].

In the case of a post-chemotherapy mass that is still positive at reclassification FDG-PET with no volume increase, a second FDG-PET should be performed 6 weeks later. Alternatively, a biopsy should be taken to ascertain persistent disease. In these cases as well as in those with progressive disease (i.e. a growing mass which up-takes contrast medium at CT scans or radionuclide tracer at FDG-PET), salvage therapy is indicated (usually chemotherapy or radiotherapy) [216-220]. Patients with persistent and progressing hCG elevation after 1st line chemotherapy should immediately proceed with salvage chemotherapy. Progressing patients without hCG progression should undergo histological verification (e. g. by biopsy or mini-invasive or open surgery) before salvage chemotherapy is given.

When RPLND is indicated, this should be performed in referral centres, as residuals from seminoma may be difficult to remove due to intense fibrosis [219]. Ejaculation may be preserved in these cases [221].

7.5.2.2 *Non-seminoma*

Following first-line BEP chemotherapy, only 6-10% of residual masses contain viable cancer, 50% contain mature teratoma, and 40% contain necrotic-fibrotic tissue [222].

FDG-PET is not indicated to re-stage patients after chemotherapy [52]. In cases of complete remission after 1st line chemotherapy (no visible tumour), tumour resection is not indicated [223-227].

Residual tumour resection is mandatory in all patients with a residual mass > 1 cm in the short axis at cross-sectional CT imaging [224, 225, 228-237].

The role of surgery is debated in patients with retroperitoneal residual lesions < 1 cm. There is still a risk of residual cancer or teratoma although the vast majority of patients (> 70%) harbour fibro-necrotic tissue [238, 239]. Proponents of PC-RPLND for all patients refer to the fact that both teratoma and vital malignant germ cell tumours are still found after radiologic complete remission in lesions < 10 mm [240]. The alternative is to put patients with residual disease < 1 cm on an observation protocol based on recurrence data of 6-9% depending on the time of follow-up [226, 227]. In the series with the longer observation of 15.5 years, 12 of 141 patients (9%) relapsed after having achieved a complete response after primary treatment [227], but eight of the 12 relapsing patients were cured. Therefore, patients treated with 1st line chemotherapy should be informed about this life-long risk of recurrence in the order of 10% before consenting to observe residual lesions < 1 cm. Patients after salvage chemotherapy or high-dose chemotherapy in 1st or subsequent salvage situations harbour vital tumour at a much higher rate [241]. Therefore, there is an indication to perform surgery in salvage patients even with residual disease < 1 cm [226, 227].

If residual surgery is indicated, all areas of primary metastatic sites must be completely resected within 2-6 weeks of completion of chemotherapy. If technically feasible, a bilateral nerve-sparing procedure should be performed. There is growing evidence that "template" resections with unilateral preservation of nerves in selected patients yield equivalent long-term results compared to bilateral systematic resections in all patients. The mere resection of the residual tumour (so called "lumpectomy") should not be performed. [223, 227-229, 238, 239, 242-250].

In persistent larger volume retroperitoneal disease, all areas of primary metastatic sites must be completely resected within 2-6 weeks of completion of chemotherapy. If technically feasible, a nerve-sparing procedure should be performed [223, 227-229, 238, 239, 242-246].

Laparoscopic RPLND may yield similar outcomes to the open procedure in very selected cases of very low residual disease and in very experienced hands, but it is not recommended outside a specialised laparoscopic centre [251-253].

7.5.3 Timing of surgery in the case of multiple sites

In general, residual surgery should start at the location with the highest volume of residual disease. The histology may diverge in different organ sites [231]. In cases of retroperitoneal and lung residual masses, the presence of fibro-necrotic tissue in the retroperitoneum is associated with a probability as high as 90% that lung masses contain the same histology [254].

Resection of contralateral pulmonary lesions is not mandatory in case pathologic examination of the lesions from the first lung shows complete necrosis. However, discordant histologies between both lungs may occur in up to 20% [255, 256].

7.5.3.1 Quality and intensity of surgery

Post-chemotherapy surgery is always demanding. Most of the time, post-chemo RPLND does not require further interventions on abdominal or retroperitoneal organs. About a third of patients may require a planned intervention where removal of organs affected by the disease (for example kidney, psoas muscle or gross vessels) are provided and followed by ad hoc reconstructive surgery (e.g. vascular interventions such as vena cava or aortic prostheses) [257, 258]. In patients with intermediate or poor risk and residual disease > 5 cm the probability of vascular procedures is as high as 20% [259]. This intense ("maximal") surgery must therefore be referred to specialised centres capable of interdisciplinary surgery (hepatic resections, vessel replacement, spinal neurosurgery, thoracic surgery). Patients treated within such centres benefit from a significant reduction in perioperative mortality from 6% to 0.8% [13]. In addition, specialised urologic surgeons are capable of reducing the local recurrence rate from 16% to 3% with a higher rate of complete resections [14].

7.5.3.2 Salvage and desperation surgery.

Surgery of resectable disease after salvage treatment remains a potentially curative option in all patients with any residual mass following salvage chemotherapy. Survival after surgery and first salvage chemotherapy was improved (70% at 10 years) following taxane-containing regimens [260]. Also, in the case of extensive salvage chemotherapy, surgery remains a fundamental tool to achieve durable complete remissions in up to 20% of patients [261, 262].

Desperation surgery refers to resection of non-responsive or progressive (e.g. rising markers) disease following salvage chemotherapy. When the disease is resectable, a significant proportion of these patients can be rendered disease-free in the long term [263].

7.5.3.3 Consolidation chemotherapy after secondary surgery

After resection of necrosis or mature/immature teratoma, no further treatment is required. In cases of incomplete resection of viable cancer, two adjuvant cycles of conventionally dosed cisplatin-based chemotherapy may be given in certain subgroups (e.g. 'poor prognosis' patients) [247] (caution: cumulative doses of bleomycin). After complete resection of 'vital' tumour < 10% of the total volume, especially in patients in an initially good prognosis group according to IGCCCG, the relapse rate is very low and adjuvant chemotherapy is not beneficial for preventing further relapse [264]. The prognosis will definitely deteriorate if vital malignant neoplasm is found in resection specimens after second- and third-line chemotherapy. In this latter situation, post-operative chemotherapy is not indicated and is unable to improve the prognosis [239, 265].

7.5.4 Systemic salvage treatment for relapse or refractory disease

Cisplatin-based combination salvage chemotherapy will result in long-term remissions in about 50% of the patients who relapse after first-line chemotherapy, but the results are highly dependent on several prognostic factors [266]. The regimens of choice are four cycles of a triplet regimen including cisplatin and ifosfamide plus a third agent: etoposide (PEI/VIP), paclitaxel (TIP), or potentially gemcitabine (GIP) (Table 7.2) [267]. No randomised trial has ever compared these regimens. Due to their potentially lethal risk of haematological toxicity, these regimens should be used with G-CSF support and by well-trained oncologists.

The only available randomised trial comparing standard-dose versus high-dose chemotherapy plus transplant in the salvage setting showed no benefit in OS in patients treated with 3 cycles of vinblastine, ifosfamide, and cisplatin (VeIP) plus 1 cycle of consolidation high-dose chemotherapy, compared with 4 cycles of VeIP [268]. At present, it is impossible to determine whether conventionally dosed cisplatin-based combination chemotherapy is sufficient as first-salvage treatment or whether early intensification of first-salvage treatment with high-dose chemotherapy should be used. However, there is evidence from large retrospective analyses that there are different prognostic groups in the case of relapse after first-line

chemotherapy [269-271], and the Lorch-Beyer score has resulted in 5 prognostic subgroups (Table 7.3). A second large analysis in this cohort of 1600 patients showed an improvement of about 10-15% in OS in patients from all prognostic subgroups when treated with high-dose salvage therapy compared to standard dose therapy. To prospectively confirm this finding, an international randomised trial of high-dose versus conventional dose chemotherapy in patients with first-line relapse is planned (Tiger trial). If high-dose chemotherapy is used as a salvage treatment, sequential treatment cycles of high-dose carboplatin and etoposide HD-CE should be preferred to a single high-dose regimen because the former is associated with less toxicity-related deaths [272].

It is clearly of the utmost importance that these rare patients with relapse are treated within clinical trials and at experienced centres.

Table 7.2: Standard PEI/VIP, TIP and GIP chemotherapy (interval 21 days)

Chemotherapy agents	Dosage	Duration of cycles
PEI/VIP		
Cisplatin*	20 mg/m ²	Days 1-5
Etoposide	75-100 mg/m ²	Days 1-5
Ifosfamide†	1.2 g/m ²	Days 1-5
TIP		
Paclitaxel	250 mg/m ² ^{xx}	24 hour continuous infusion day 1
Ifosfamide†	1.5 g/m ²	Days 2-5
Cisplatin*	25 mg/m ²	Days 2-5
GIP		
Gemcitabine	1000 mg/m ²	Day 1 + 5
Ifosfamide	1200 mg/m ²	Days 1-5
Cisplatin	20 mg/m ²	Days 1-5

PEI/VIP = cisplatin, etoposide, ifosfamide; TIP = paclitaxel, ifosfamide, cisplatin; GIP = gemcitabine, ifosfamide, cisplatin

* Plus hydration.

† Plus mesna protection.

^{xx} An MRC schedule uses paclitaxel at 175 mg/m² in a 3 hour infusion [273].

The International Prognostic Factors Study Group score comprised of 7 important factors is listed in Table 7.3 (seminoma vs. non-seminoma histology, primary tumour site, response to initial chemotherapy, duration of progression-free interval, AFP marker level at salvage, hCG marker level at salvage, and the presence of liver, bone, or brain metastases at salvage). Using these factors, 5 risk groups (very low risk = -1 points; low risk = 0 points; intermediate-risk = 1-2 points, high risk = 3-4 points; and very high risk ≥ 5 points) were identified with significant differences in PFS and OS. Table 4.3 illustrates the 5 risk groups and the corresponding 2-year PFS and 3-year OS rates [274].

Table 7.3: The International Prognostic Factors Study Group Score Construction [270]

Points	-1	0	1	2	3
Variable					
Histology	Seminoma	Non-seminoma			
Primary site		Gonadal	Retroperitoneal		Mediastinal
Response		CR/PRm-	PRm+/SD	PD	
PFI		> 3 months	≤ 3 months		
AFP salvage		Normal	< 1000	1000	
hCG salvage		< 1000	1000		
LBB		No	Yes		

AFP = alpha-fetoprotein; hCG = human chorionic gonadotrophin; LBB = liver, bone, brain metastases;

PFI = progression-free interval.

Table 7.4: PFS and OS estimates for all patients according to IGCCCG-2 prognostic score [270]

	n	%	HR	2-year PFS	3-year OS
Score (n=1435)					
Very Low	76	5.30	1	75.1	77.0
Low	257	17.9	2.07	52.6	69.0
Intermediate	646	45.0	2.88	42.8	57.3
High	351	24.5	4.81	26.4	31.7
Very High	105	7.3	8.95	11.5	14.7
Missing	159				

IGCCCG = International Germ Cell Cancer Collaborative Group; OS = overall survival; PSF = progression-free survival.

7.5.5 Second relapse

There are no randomised trials for patients with second relapse; however, conventional therapy does not appear to be very effective. For patients having received two series of conventionally dosed therapy (first-line and first salvage), HD chemotherapy with autologous stem cell support should be used [270]. Even with HD-therapy the curative chance is only 20-25%.

Refractory disease: Patients relapsing within 4-8 weeks after platinum-based therapy or who are progressing despite platinum-based therapy as well as those relapsing shortly after HD-CTX are considered cis-platinum refractory. For those patients, combinations of gemcitabine and oxaliplatin or the triple combination of gemcitabine, oxaliplatin and paclitaxel have resulted in response rates of 25-45%. Cisplatin re-challenge in association with gemcitabine and paclitaxel, could be considered in patients with good renal function [275]. Those patients with a good response undergoing subsequent resection of residual tumour lesions may still have a 15-20% chance of long-term cure [261].

7.5.5.1 Late relapse (≥ 2 years after end of first-line treatment)

Late relapse is defined as recurrence more than 2 years following cure after chemotherapy for metastatic TC, with, or without, residual tumour surgery and occurs, according to a pooled analysis, in 1.4% and 3.2% in seminoma and non-seminoma patients, respectively [276, 277]. If feasible, all lesions of late relapsing non-seminoma patients should be removed by radical surgery.

Patients with rapidly rising hCG may benefit from induction salvage chemotherapy before complete resection, but in most patients surgery should be performed irrespective of the level of their tumour markers in order to completely resect all undifferentiated germ-cell tumour, mature teratoma with or without somatic transformation [138, 278, 279].

Survival strongly depends on the histology of the removed lesions rather than on the initial germ cell cancer. Interestingly, in a population-based study all late-relapsing seminoma patients had viable germ cell tumour, whereas teratoma or necrosis was found in half of the patients with initial non-seminoma [280].

If the lesions are not completely resectable, biopsies should be obtained for histological assessment, and salvage chemotherapy should be initiated according to the histological results. In these cases, consultation of an experienced pathologist is required to avoid misinterpretation of the therapeutic morphological changes in the germ cell neoplasms [281]. If the patient responds to salvage chemotherapy, secondary surgery should be conducted whenever possible. In the case of unresectable, but localised, refractory disease, stereotactic or conventional radiotherapy may be considered. To avoid excess mortality, late relapses should be treated only at centres experienced in managing such patients [282].

7.5.5.2 Treatment of brain metastases

Brain metastases occur in the frame of a systemic relapse and rarely as an isolated relapse. The long-term survival of patients presenting with brain metastases at initial diagnosis is poor (30-50%), but it is even poorer when brain metastasis develops as recurrent disease (the 5-year survival-rate is 2-5%) [283, 284]. Chemotherapy is the initial treatment in this case, and some data support the use of consolidation radiotherapy, even in the case of a total response after chemotherapy [285]. Surgery can be considered in the case of a persistent solitary metastasis, depending on the systemic state, the histology of the primary tumour and the location of the metastasis.

	LE	GR
Low volume NSGCT stage IIA/B with elevated markers should be treated like 'good or intermediate prognosis' advanced NSGCT, with three or four cycles of BEP.	2	A
In stage IIA/B without marker elevation, histology can be gained by RPLND or biopsy. A repeat staging can be performed after six weeks of surveillance before final decision on further treatment.	3	B
In metastatic NSGCT (\geq stage IIC) with a good prognosis, three courses of BEP is the primary treatment of choice.	1	A
In metastatic NSGCT with an intermediate prognosis, the primary treatment of choice is four courses of standard BEP.	1	A
In metastatic NSGCT with a poor prognosis, the primary treatment of choice is one cycle of BEP, followed by tumour marker assessment after 3 weeks: in the case of an unfavourable decline, chemotherapy intensification should be initiated; in the case of a favourable decline, BEP should be continued up to a total of four cycles.	1	A
Surgical resection of residual masses after chemotherapy in NSGCT is indicated in the case of visible residual masses and when serum levels of tumour markers are normal or normalising.	2	A
Seminoma CSII A/B can initially be treated with radiotherapy. When necessary, chemotherapy can be used as a salvage treatment with the same schedule as for the corresponding prognostic groups of NSGCT.	2	B
In seminoma stage CS IIA/B, chemotherapy (3 x BEP or 4 x EP, in good prognosis) is an alternative to radiotherapy. It appears that 3 x BEP or 4 x EP achieve a similar level of disease control.	3	B
Seminoma stage IIC and higher should be treated with primary chemotherapy according to the same principles used for NSGCT.	1	A

EP = epirubicin, cisplatin; GR = grade of recommendation; NSGCT = non-seminomatous germ cell tumour; BEP = cisplatin, epirubicin, bleomycin; RPLND = retroperitoneal lymph node dissection.

8. FOLLOW-UP AFTER CURATIVE THERAPY

8.1 Follow-up care for cancer patients

There is no consensus on a standardised follow-up of patients treated for germ-cell cancer.

8.2 General considerations

The following considerations apply in a general manner for the selection of an appropriate schedule and testing in the follow-up of all stages of testis tumour.

- Most recurrences after curative therapy will occur in the first 2 years; surveillance should therefore be most frequent and intensive during this time.
- Late relapses can occur beyond 5 years, and therefore yearly follow-up for life may be advocated.
- After RPLND, relapse in the retroperitoneum is rare, the most likely site of recurrence being the chest.
- The value of a plain radiography chest has been recently questioned in the follow-up of patients with disseminated disease after complete remission [286, 287].
- CT of the chest has a higher predictive value than plain radiography chest [287].
- The results of therapy are dependent on the bulk of disease; thus an intensive strategy to detect asymptomatic disease may be justifiable.
- After chemotherapy or radiotherapy, there is a long-term risk of the development of secondary malignancies.
- Exposure to diagnostic X-rays causes second malignancies [288]. Thus, the frequency of CT scans should generally be reduced and any exposure to X-rays should be well justified in a patient cohort with a very long life-expectancy after successful treatment.
- CT can be substituted by MRI. However, MRI is a protocol-dependent method and, thus, should be performed in the same institution with a standardised protocol.
- With special expertise, US may be used as a method to screen the retroperitoneum during follow-up.

However, the method is very much dependent on the investigator and cannot be recommended as the standard method during follow-up.

- Longer follow-up in patients after radiotherapy and chemotherapy is justified to detect late toxicities (e.g. cardio-vascular, endocrine).

A number of interdisciplinary organisations have presented recommendations for follow-up of testicular cancer patients [289-291]. The follow-up tables below (Tables 8.1 through 8.4) present the minimum recommendations of the expert opinions of the guideline authors.

8.3 Follow-up: stage I non-seminoma

Approximately 5% of patients with CS1 NSGCT present with elevated levels of tumour markers after orchiectomy, and up to 25-30% relapse during the first 2 years [7, 128, 130, 131, 171, 292-295]. The follow-up schedule will differ depending on which of the three possible treatment strategies was chosen:

- surveillance;
- nerve-sparing RPLND;
- adjuvant chemotherapy.

8.3.1 Follow-up investigations during surveillance

The results of a surveillance policy depend upon a careful pre-operative staging procedure and follow-up management. In a 'wait and see' policy, relapses will occur in 30% of cases. Of these relapses, 80% will occur in the first 12 months after orchiectomy, and approximately 12% during the second year. The median time to relapse is 6 months (range 1-62 months), but relapses after 3-5 years, and even later, can still occur, with an annual rate of 4% [108, 109]. Relapse occurs mainly in the retroperitoneum: approximately 70% of patients have evident metastases in the retroperitoneum, and 10% in the mediastinum and lungs [296]. Sometimes the only indication is an elevated level of tumour markers.

A randomised trial of two versus five CTs has been published by the MRC recommending the reduction of imaging during surveillance in this stage to one CT scan at 3 months after orchiectomy, and another at 12 months. The trial, with a cohort of 414 patients, was powered to exclude a 3% probability of detecting a patient during surveillance only, with a relapse presenting already-metastatic disease with 'intermediate' or 'poor' prognosis features. Relapses were detected in 15% with two CTs, and 20% with five CTs; 1.6% of these patients had 'intermediate' or 'poor' prognostic features. Only 10% of patients had high-risk features (vascular invasion). In summary, this first randomised trial yielded level 1 evidence for a minimum follow-up in patients with CS1 non-seminoma [142]. The recommended follow-up schedule (Table 8.1) includes the minimum requirements for imaging, and adds recommendations for other surveillance tests [296].

Table 8.1: Recommended minimum follow-up schedule in a surveillance policy: stage I non-seminoma [296]

Procedure	Year			
	1	2	3	4-5
Physical examination	4 times	4 times	4 times	Once/year
Tumour markers	4 times	4 times	4 times	Once/year
Plain radiography chest	Twice		Twice	
Abdominopelvic CT	Twice (at 3 and 12 months)		Once in year 2 (at 24 months) Once in year 3 (at 36 months)	

CT= computed tomography.

8.3.2 Follow-up after nerve-sparing RPLND

Retroperitoneal relapse after a properly performed nerve-sparing RPLND is rare. RPLND should eliminate the retroperitoneal nodes as a site of relapse and thus the need for repeated abdominal CTs. The US Testicular Cancer Intergroup study data show retroperitoneal relapse in 7/264 patients with pathological stage I disease (and 20 pulmonary relapses); four of these seven had no marker elevation [297]. In the Indiana series, only one relapse in 559 cases was reported [298]. If a relapse occurs, it is generally in the chest, neck or at the margins of the surgical field.

Pulmonary relapses occur in 10-12% of patients, and more than 90% of those relapses occur within 2 years of RPLND [55, 299]. However, the low rate of retroperitoneal relapse after RPLND can only be achieved by surgery in specialised centres, as shown by the high in-field relapse rate (7/13 relapses) in the German randomised trial

of RPLND versus one course of BEP [135]. The recommended minimum follow-up schedule is shown in Table 8.2.

Table 8.2: Recommended minimum follow-up schedule after retroperitoneal lymphadenectomy or adjuvant chemotherapy: stage I non-seminoma

Procedure	Year				
	1	2	3	4-5	6-10
Physical examination	4 times	4 times	4 times	Once/year	Once/year
Tumour markers	4 times	4 times	4 times	Once/year	Once/year
Plain radiography chest	Twice	Twice	Twice		
Abdominopelvic CT	Once	Once	Once	Once/year	

CT = computed tomography.

8.3.3 Follow-up after adjuvant chemotherapy

Prospective reports with long-term follow-up after adjuvant chemotherapy have shown a low relapse rate of about 3% [128-131]. In a randomised trial with one course of BEP versus RPLND, the relapse rate with adjuvant chemotherapy was 1% (2/174 patients, one with marker relapse, one with mature teratoma in the retroperitoneum) [135]. The need for repeated and long-term assessment of the retroperitoneum is still not clear. Owing to the risk of developing a late, slow-growing teratoma in the retroperitoneum after adjuvant chemotherapy, an abdominal CT should still be performed (see Table 8.2).

8.4 Follow-up: stage I seminoma

The majority of patients with seminoma (70-80%) present with clinical stage I disease at diagnosis. In 15-20% of cases, there is nodal radiological involvement at the level of the retroperitoneum, and only 5% of patients present with distant metastasis.

The relapse rate varies between 1% and 20%, depending on the post-orchietomy therapy chosen. Only up to 30% of seminomas present with elevation of hCG at diagnosis or in the course of the disease. Consequently, in most cases, measurement of blood markers will not be a reliable test for follow-up [300]. The treatment options post-orchietomy in stage I seminoma are surveillance or adjuvant carboplatin chemotherapy.

8.4.1 Follow-up after radiotherapy

Low doses of radiotherapy (20-24 Gy) limited to the retroperitoneal or the paraaortic and ipsilateral field achieve an OS rate of approximately 99% at 5-10 years [108-110, 301, 302]. The rate of relapse is 1-2% and the most common time of presentation is within 18 months of treatment [108, 111, 302-304], although late relapses have also been described [278]. The site of relapse is mainly at the supradiaphragmatic lymph nodes, mediastinum, lungs or bones. In a small proportion of cases, the tumour will relapse in the inguinal or external iliac nodes. After para-aortic field RT there is also a pelvic node relapse pattern.

The side-effects of radiotherapy include temporary impaired spermatogenesis, GI symptoms (peptic ulceration), and induction of second malignancies [303, 305, 306]. Up to 50% of patients can develop moderate toxicity grade I-II [300]. The follow-up schedule is described in Table 8.3.

Table 8.3: Recommended minimum follow-up schedule for post-orchietomy surveillance, radiotherapy or chemotherapy: stage I seminoma [295]

Procedure	Year		
	1	2	3-5
Physical examination	3 times	3 times	Once/year
Tumour markers	3 times	3 times	Once/year
Plain radiography chest	Twice	Twice	
Abdominopelvic CT	Twice	Twice	at 36 and 60 months

CT = computed tomography.

8.4.2 Follow-up during surveillance

The actuarial risk of relapse at 5 years ranges between 6% (low risk) and 20% [114, 307-311]. There is no increased risk of death. The median time to relapse ranges from 12-18 months, but up to 29% of relapses can develop later than this [99, 312]. The sites of relapse are the PA lymph nodes in up to 82% of cases; the pelvic

lymph nodes, inguinal nodes and lungs can also be affected [99, 134, 313-316]. Due to the high and often late rate of relapse, close and active follow-up is mandatory for at least 5 years [307] (see Table 8.3).

8.4.3 Follow-up after adjuvant chemotherapy

One or two courses of carboplatin-based chemotherapy is an effective alternative treatment in stage I seminoma. The relapse rate is 1.9-4.5%. In general, this treatment is well tolerated, with only mild, acute and intermediate-term toxicity [307, 308]. Long-term data on late relapses and survival are missing (see Table 8.3).

8.5 Follow-up: (metastatic) disease

The more advanced the nodal stage of the disease, the higher the likelihood of recurrence [170]. In general, the primary tumour bulk governs the outcome for patients with NSGCT [312]. In stage II NSGCT, regardless of the treatment policy adopted, excellent survival rates of 97% are reached provided that relapse is identified as soon as possible [140, 165, 172].

In advanced metastatic germ-cell tumours, the extent of the disease correlates with the response to therapy and with survival. The combination of cisplatin-based chemotherapy and surgery (aggressive multimodality) achieves cure rates of between 65% and 85%, depending on the initial extent of disease [310, 311]. Complete response rates to chemotherapy are in the order of 50-60% [310]; another 20-30% of patients could be disease-free with post-chemotherapy surgery [317].

The main reasons for failure of therapy in advanced NSGCT are [34, 309, 318]:

- the presence of bulky disease not responding completely to chemotherapy;
- unresectable residual teratoma after chemotherapy;
- the presence or development of chemoresistant non-germ elements, which account for 8.2% of cases.

Table 8.4 presents the recommended minimum follow-up schedule in advanced NSGCT and seminoma.

Table 8.4: Recommended minimum follow-up schedule in metastatic NSGCT and seminoma

Procedure	Year			
	1	2	3-5	Thereafter
Physical examination	4 times	4 times	Twice/year	Once/year
Tumour markers	4 times	4 times	Twice/year	Once/year
Plain radiography chest	4 times	4 times	Twice/year	Once/year
Abdominopelvic CT [†]	Twice	Twice	Once/year	As indicated
Chest CT [‡]	Once/year	Once/year	Once/year	As indicated
Brain CT [§]	Once/year	Once/year	Once/year	As indicated

CT = computed tomography.

* An abdominal CT must be performed at least annually if teratoma is found in the retroperitoneum.

† If the post-chemotherapy evaluation in a seminoma patient shows any mass > 3 cm, the appropriate CT should be repeated 2 and 4 months later to ensure that the mass is continuing to regress. If available, FDG-PET/CT can be performed.

‡ A chest CT is indicated if abnormality is detected on a plain radiography chest and after pulmonary resection.

§ In patients with headaches, focal neurological findings, or any central nervous system symptoms.

8.6 Quality of life and long-term toxicities after cure for testicular cancer

The vast majority of patients will be cured and 5-year relative survival rates approximate 95% in Western Europe. Furthermore, TC patients are usually between 18 and 40 years at diagnosis such that life expectancy after cure extends over several decades [319]. Patients should be informed before treatment of common long-term toxicities, which are probably best avoided by adherence to international guidelines. Treatment of stage I TC is controversial with some experts advocating surveillance for all, thereby avoiding unnecessary adjuvant chemotherapy [126], whereas others highlight the importance of patient autonomy and consider the prospect of avoiding salvage treatment with its known long-term toxicities as quite appealing [320]. Unfortunately, we do not know which treatment spares most patients long-term toxicities, which so far seem to be absent or mild after adjuvant chemotherapy [131, 139, 321].

During follow-up, patients should be screened and treated for known risk factors such as high blood pressure, hyperlipidaemia and testosterone deficiency. When follow-up by the TC expert is discontinued, a written cancer survivorship plan addressing late toxic effects, lifestyle recommendations, recurrence risk, and cancer-specific follow-up might be helpful [277, 322]. The following overview is not complete and interested readers are referred to review articles on this topic [319, 322, 323].

8.6.1 **Second malignant neoplasms (SMN)**

Treatment-induced SMN usually occur after the first 10 years [322]. The risk for solid SMN increases with younger age at radio- or chemotherapy and remains significantly elevated for at least 35 years [111, 115, 324-326]. RT-related SMN are primarily localised within or close to the RT field (colon, stomach, pancreas, bladder and the urinary tract) [111, 112, 115, 116, 325-328]. Fung et al. demonstrated that modern cisplatin-based chemotherapy was associated with a 40% increased risk of a solid SMN [329].

8.6.2 **Leukaemia**

In a series of 40,576 TC survivors, the observed/expected ratio for developing a leukaemia, mostly acute myeloid (AML) and lymphoblastic leukaemias was 2.6 (95% CI, 2.1 to 3.2) [330]. The risk of AML seems to be both related to the dose of cisplatin and etoposide. Doses of etoposide exceeding 2 g/m² have been shown to increase the subsequent risk of AML considerably [331]. It is important to keep in mind that the majority of TC patients do receive much lower doses of etoposide such that the absolute risk of AML after three to four courses of BEP is very low, and in patients requiring high-dose chemotherapy with cumulative etoposide doses exceeding this threshold, less than 1.5% have been reported to suffer from AML. There is a cumulative dose-disease relationship regarding cisplatin and AML. Chemotherapy-induced leukaemia is usually diagnosed within the first 10 years after treatment for TC and has a very poor prognosis [332].

8.6.3 **Infections**

Chemotherapy-treated testicular cancer survivors (TCSs) have a higher risk of dying from infections than the normal population, SMR 2.48, 95% CI: 1.70 to 3.50 [333]. This is possibly due to long-term depression of the bone-marrow, but also complications of subsequent salvage treatment (which was not reliably registered) or extensive or subsequent surgical treatment might lie behind these numbers. Furthermore, asymptomatic pulmonary fibrosis by mediastinal radiotherapy and/or bleomycin may render TCSs vulnerable to potentially deadly pneumonias many years after treatment.

8.6.4 **Pulmonary complications**

Chemotherapy exposed TCSs have a nearly 3-fold increased risk of dying of pulmonary diseases than the normal population [333]. Bleomycin-induced lung toxicity may affect 7% to 21% of patients in the long-term, resulting in death in 1%-3% [334]. TCSs treated with high cumulative cisplatin doses and/or pulmonary surgery, have a poorer pulmonary function than those cured by surgery only [335]. Intriguingly, pulmonary complications were associated with the cumulative cisplatin dose and not to the dose of bleomycin.

8.6.5 **Cardiovascular toxicity**

Mortality from cardiovascular disease (CVD) is higher in TCSs than in the general population [333, 336]. Furthermore, CVD is more common in chemotherapy-treated TCSs than in those who underwent surgery only [134, 315]. The metabolic syndrome is a strong predictor for CVD and its components, i.e. hypertension, obesity and hypercholesterolemia, increase with treatment intensity [316, 337]. Circulating residual serum platinum might exert endothelial stress [338].

8.6.6 **Raynaud-like phenomena**

Chemotherapy-related Raynaud-like phenomena were reported before the introduction of cisplatin and are usually ascribed to the application of bleomycin [339, 340]. Cisplatin is believed to contribute to cold-induced vasospasms, as Vogelzang et al. reported that the incidence of Raynaud's phenomenon was higher after treatment with CVB than after vinblastine and bleomycin only (41% vs. 21%, respectively) [341].

8.6.7 **Neurotoxicity**

Cisplatin induces a symmetric dose-dependent sensory, distal, length-dependent "glove and stocking" paraesthesias, affecting 29% of TCSs who received cisplatin-based chemotherapy as opposed to 10% after orchiectomy alone [342]. Application of five or more cycles increases the frequency of this symptom to 46%. Paclitaxel-induced acute neuropathy consists of an acute pain syndrome, which usually develops within three days of paclitaxel administration, or within a week. Platinum is measurable in the serum of TCSs many years after its application and the intensity of paraesthesias is more strongly associated with platinum serum level than with the cumulative dose of applied cisplatin [338].

8.6.8 **Ototoxicity**

Cisplatin-induced ototoxicity comprises tinnitus and hearing impairment, particularly of high frequencies of 4000 Hz and higher, and is caused by damage to the outer hair cells in the inner ear [343-345]. Both hearing impairment and tinnitus are considerably increased after application of 50 mg/m² cisplatin over two days as compared to 20 mg/m² over five days (odds ratio 5.1 and 7.3, respectively), indicating a higher impact of serum

peak concentrations than cumulative doses [342]. A significant association between GST genotypes and the risk of cisplatin-induced ototoxicity has been demonstrated [346, 347]. Hopefully, increasing insight into the pathogenesis of and vulnerability for this complication will lead to more individualised treatment in the future.

8.6.9 Nephrotoxicity

Cisplatin-based chemotherapy may lead to long-term renal function impairment in 20-30% of TCSs [342-345]. In testicular cancer patients, reduced renal elimination of cisplatin and bleomycin might increase the risk of other toxicities, e.g. bleomycin-related pneumonitis [348, 349].

8.6.10 Hypogonadism

Testicular endocrine dysfunction comprises insufficient testosterone (T) production and/or compensatory increased Luteinizing Hormone (LH) levels. Subnormal testosterone levels have been reported in TCs treated with chemotherapy compared with surgery only or the general population [322, 350].

8.6.11 Fatigue

Chronic fatigue (CF) is described as a subjective feeling of emotional, physical and/or cognitive tiredness that is not relieved by rest, persisting for more than 6 months. Significantly higher levels of C-reactive protein and interleukin-1 receptor antagonist are measured in TCSs with CF [351]. Also, a significantly higher frequency of CF (16%) was reported in a cross-sectional Norwegian study of long-term TCSs a median of 12 years after treatment for TC when compared with the age-matched Norwegian population (10%) [352]. Of note; the prevalence of CF increased from 15% to 27% during 10 years in long-term TCSs [353].

8.6.12 Quality of life

Quality of life (QoL) is transiently reduced by chemotherapy, during which patients experience a loss of appetite, increased fatigue, increased dyspnoea, reduced social-, physical- and role-functions [354]. When comparing three or four cycles of BEP in good risk patients, all outcomes favour treatment with three courses [184]. After 1 and 2 years, one third of patients reported an improvement in global QoL after chemotherapy, while one fifth of patients reported deterioration, with no difference between treatment groups. In adjuvant treatment of non-seminoma stage I patients, there was no difference in short-term or long-term (5 year) QoL between RPLND or one course of BEP [355].

9. TESTICULAR STROMAL TUMOURS

9.1 Classification

Non-germ-cell tumours of the testicle include sex cord/gonadal stromal tumours and miscellaneous non-specific stromal tumours. The different histological subtypes of testicular tumours are defined according to the WHO classification 2004 (adapted) [32].

9.2 Leydig cell tumours

9.2.1 Epidemiology

Leydig cell tumours constitute about 1-3% of adult testicular tumours [356, 357] and 3% of testicular tumours in infants and children [357]. These tumours are most common in the third to sixth decade in adults, with a similar incidence observed in each decade. Another peak incidence is seen in children aged between 3 and 9 years. Only 3% of Leydig cell tumours are bilateral [356]. These tumours occur in about 8% of patients with Klinefelter's syndrome [358].

9.2.2 Pathology of Leydig cell tumours

Leydig cell tumours are the most common type of sex cord/gonadal stromal tumours. Histopathologically, they are well delineated and usually up to 5 cm in diameter. They are solid, yellow to tan in colour, with haemorrhage and/or necrosis in 30% of cases. Microscopically, the cells are polygonal, with eosinophilic cytoplasm and occasional Reinke crystals, regular nucleus, solid arrangement and capillary stroma. The cells express vimentin, inhibin, protein S-100, steroid hormones, calretinin and cytokeratin (focally) [32].

Approximately 10% of Leydig cell tumours are malignant and present with the following parameters [359, 360]:

- large size (> 5 cm);
- older age;
- increased mitotic activity (> 3 per 10 high-power field [HPF];

- vascular invasion;
- cytological atypia;
- increased MIB-1 expression;
- necrosis;
- infiltrative margins;
- extension beyond the testicular parenchyma;
- DNA aneuploidy.

9.2.3 **Diagnosis**

Patients either present with a painless enlarged testis or the tumour is found incidentally on US. In up to 80% of cases, hormonal disorders with high oestrogen and oestradiol levels, low testosterone, and increased levels of LH and FSH are reported [361, 362], while negative results are always obtained for the testicular germ cell tumour-markers AFP, hCG, LDH and PLAP. Up to 10% of adult patients present with gynaecomastia [362, 363]. Only 3% of tumours are bilateral [356].

Diagnostic work-up must include markers, hormones (at least testosterone, LH and FSH; if not conclusive, also oestrogen, oestradiol, progesterone and cortisol), US of both testes, and CT of chest and abdomen. On US, it may be possible to observe well-defined, small, hypoechoic lesions with hypervascularisation, however, the appearance is variable and is indistinguishable from germ-cell tumours [364]. The proportion of metastatic tumours in all published case reports is less than 10%. In three old series with long follow-up, 18 metastatic tumours were found in a total of 83 cases (21.7%) [356, 359, 365], while 5 recently published studies with long follow-up reported only 2 metastatic tumours in 156 patients (1.3%) [362, 363, 366-368].

9.3 **Sertoli cell tumours**

9.3.1 **Epidemiology**

Sertoli cell tumours account for fewer than 1% of testicular tumours, and the mean age at diagnosis is around 45 years, with rare cases under 20 years of age [369, 370]. On rare occasions, these tumours may develop in patients with androgen insensitivity syndrome and Peutz-Jeghers syndrome.

9.3.2 **Pathology of Sertoli cell tumours**

These tumours are well circumscribed, yellow, tan or white in colour, with an average diameter of 3.5 cm [369]. Microscopically, the cells are eosinophilic to pale with vacuolated cytoplasm. The nuclei are regular with grooves and inclusions may be present. The arrangement of the cells is tubular or solid; a cord-like or retiform pattern is possible. The stroma is fine with capillaries, but in some cases a sclerosing aspect predominates. The cells express vimentin, cytokeratins, inhibin (40%) and protein S-100 (30%) [369].

The rate of malignancy ranges between 10% and 22%. Signs of a malignant Sertoli tumour are as follows [371, 372]:

- large size (> 5 cm);
- increased mitotic activity (> 5 per 10 HPF);
- pleomorphic nuclei with nucleoli;
- necrosis;
- vascular invasion.

9.3.2.1 **Classification**

Three subtypes have been described [370]:

- Classic Sertoli cell tumour [369];
- Large cell calcifying form with characteristic calcifications [373, 374];
- Sclerosing form [375, 376].

9.3.3 **Diagnosis**

Patients present either with an enlarged testis or the tumour is found incidentally on US. Most classic Sertoli cell tumours are unilateral and unifocal. Hormonal disorders are infrequent, although gynaecomastia is sometimes seen [369]. The testicular tumour-markers AFP, hCG, LDH and PLAP are always negative.

Diagnostic work-up must include tumour markers, hormones (at least testosterone, LH and FSH; if not conclusive, also oestrogen, oestradiol, progesterone and cortisol), US of both testes and CT of chest and abdomen. Sertoli cell tumours are generally hypoechoic on US, but they can be of variant appearance and thus cannot be safely distinguished from germ-cell tumours [370]. Only the large cell calcifying form has a characteristic image with bright echogenic foci due to calcification [377].

Metastatic disease of 12% in classic Sertoli cell tumour has been reported. In general, affected patients are older, tumours are nearly always palpable, and show more than one sign of malignancy [369].

The **large cell calcifying** form is diagnosed in younger men and is associated with genetic dysplastic syndromes (Carney's complex [378] and Peutz-Jeghers syndrome [379] or, in about 40% of cases, endocrine disorders. 44% of cases are bilateral, either synchronous or metachronous, and 28% show multifocality with good prognosis [374].

Up to 20% of the large cell calcifying forms are malignant. It has been suggested that discrimination between an early and late onset type may define a different risk for metastatic disease (5.5% compared to 23%) [370].

The sclerosing subtype is very rare, unilateral, with a mean age around 40 years and metastases are infrequent [376].

9.4 Treatment of Leydig- and Sertoli cell tumours

Asymptomatic, small volume testicular tumours are often misinterpreted as germ-cell tumours, and inguinal orchidectomy is performed. An organ-sparing procedure in every small ultrasound-detected, nonpalpable intraparenchymal lesion is highly recommended in order to obtain a histological diagnosis. The incidence of benign definitive histology is high at approximately 80% [380]. In patients with symptoms of gynaecomastia or hormonal disorders, a non-germ-cell tumour should be considered and immediate orchidectomy avoided. In cases with germ-cell tumour in either frozen section or paraffin histology, orchidectomy is recommended as long as a contralateral normal testicle is present.

When diagnosed and treated early, long-term favourable outcomes are seen at follow-up in Leydig cell tumours, even with its potential metastatic behaviour. In stromal tumours with histological signs of malignancy, especially in older patients, orchidectomy and early retroperitoneal lymphadenectomy may be an option to prevent metastases [381] or to achieve long-term cure in stage IIa cases [382]. Prophylactic retroperitoneal lymph node dissection is unjustified for patients with clinical stage I disease without high-risk features [383].

Tumours that have metastasised to lymph nodes, lung, liver or bone respond poorly to chemotherapy or radiation and survival is poor [381]. No recommendations are available for the treatment of these patients.

9.5 Follow-up of Leydig- and Sertoli cell tumours

Without clinical signs of malignancy, an individualised surveillance strategy after orchidectomy is recommended in patients with one, or more, pathological features of malignancy. Follow-up is recommended in all high-risk patients; every 3 to 6 months with physical examination, hormone assays, scrotal and abdominal ultrasonography, chest radiography, and CT [362].

9.6 Granulosa cell tumour

This is a rare tumour with two variants: juvenile and adult. Less than 100 cases are reported with a predominance of the juvenile type.

- The juvenile type is benign. It is the most frequent congenital testicular tumour and represents about 1-5% of all prepubertal testicular neoplasms. The cystic appearance is characteristic of this tumour type [384, 385].
- The average age of the adult type at presentation is 45 years. The typical morphology is a homogeneous, yellow-grey tumour, with elongated cells with grooves in microfollicular and Call-Exner body arrangements [386].

Malignant tumours represent around 20% of cases. Lymphovascular invasion, necrosis, infiltrative borders and size > 4 cm may help in identifying cases with aggressive behaviour. Mitotic counts vary and do not appear to be of prognostic significance [387].

9.7 Thecoma/fibroma group of tumours

These tumours are rare with variable histology such as minimal invasion into surrounding testis, high cellularity, and increased mitotic rate. Their immunoprofile is variable and typically not diagnostic. They seem to be uniformly benign [388].

9.8 Other sex cord/gonadal stromal tumours

Sex cord/gonadal stromal tumours may be incompletely differentiated or in mixed forms.

There is limited experience with incompletely differentiated sex cord/gonadal stromal tumours and no reported

cases of metastasis [32]. In mixed tumour forms, all the histological components should be reported. However, the clinical behaviour most likely reflects the predominant pattern or the most aggressive component of the tumour [389].

9.9 Tumours containing germ cell and sex cord/gonadal stroma (gonadoblastoma)

Some patients with disorders of sex development (DSDs) have abnormal gonadal development with ambiguous genitalia and an increased risk of germ-cell tumours. If the arrangement of the germ cells is in a nested pattern and the rest of the tumour is composed of sex cord/gonadal stroma, the term gonadoblastoma is used. Bilateral tumours are present in 40% of cases. The prognosis correlates with the invasive growth of the germinal component [390, 391].

In the case of a diffuse arrangement of the different components, there are some doubts about the neoplastic nature of the germinal cells and some authors consider them to be entrapped rather than neoplastic [392].

9.10 Miscellaneous tumours of the testis

9.10.1 Tumours of ovarian epithelial types

These tumours resemble epithelial tumours of the ovary. A cystic appearance with occasional mucinous material can be observed. Microscopically, the aspect is identical to their ovarian counterparts, and their evolution is similar to that of the different epithelial ovarian subtypes. Some Brenner types are malignant [32].

9.10.2 Tumours of the collecting ducts and rete testis

These tumours are very rare. Benign (adenoma) and malignant (adenocarcinoma) have been reported, with malignant tumours showing local growth with a mortality rate of 40% within one year [393].

9.10.3 Tumours (benign and malignant) of non-specific stroma

These are very uncommon and have similar criteria, prognosis and treatment to soft tissue sarcomas.

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11. CONFLICT OF INTEREST

All members of the Testicular Cancer Guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: <http://www.uroweb.org/guidelines/online-guidelines/>. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

Guidelines on Penile Cancer

O.W. Hakenberg (Chair), E. Compérat, S. Minhas,
A. Necchi, C. Protzel, N. Watkin

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1. INTRODUCTION

The European Association of Urology (EAU) Guidelines on Penile Cancer provide up-to-date information on the diagnosis and management of penile squamous cell carcinoma (SCC). However, these Guidelines do not provide a standardised approach and the guidance and recommendations are provided without legal implications.

1.1 Panel composition

The EAU Penile Cancer Guidelines Panel consists of an international multidisciplinary group of clinicians, including a pathologist and an oncologist. Members of this panel have been selected based on their expertise and to represent the professionals treating patients suspected of harbouring penile cancer.

All experts involved in the production of this document have submitted potential conflict of interest statements.

1.2 Available publications

A quick reference document (Pocket guidelines) is available, both in print and in a number of versions for mobile devices. These are abridged versions which may require consultation together with the full text versions. Several scientific publications are available (the most recent paper dating back to 2014 [1] as are a number of translations of all versions of the Penile Cancer Guidelines. All documents are available free access through the EAU website Uroweb: <http://www.uroweb.org/guidelines/online-guidelines/>.

1.3 Publication history

The Penile Cancer Guidelines were first published in 2000 with the most recent full update achieved in 2014.

2. METHODS

2.1 Data identification

A systematic literature search on penile cancer was performed between August 2008 and November 2013. All articles relating to penile cancer ($n = 1602$) in the relevant literature databases were reviewed and 352 papers were considered suitable for adding to the research base of the Guidelines. A fully revised Guidelines was produced using the updated research base, together with several national and international guidelines on penile cancer (National Comprehensive Cancer Network [2], French Association of Urology [3] and the European Society of Medical Oncology [4]).

In this 2015 EAU Guidelines compilation, all standard information on levels of evidence (LE) and grading of recommendations (GR) has been taken out of the individual guidelines topics for the sake of brevity. This information is included in the introductory section of this print.

2.2 Review

This document was subjected to double-blind peer review prior to publication.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Definition of penile cancer

Penile carcinoma is usually a squamous cell carcinoma (SCC), although there are other types of penile cancer (see Table 3.3). Penile SCC usually arises from the epithelium of the inner prepuce or the glans. Penile SCC exists in several histological subtypes. Its pathology is similar to SCC of the oropharynx, female genitalia (cervix, vagina and vulva) and anus and shares some of the natural history.

3.2 Epidemiology

In the Western World, primary penile cancer is uncommon, with an overall incidence of $< 1.00/100,000$ males in Europe and the USA [5, 6], although there are several geographical areas in Europe with an incidence over

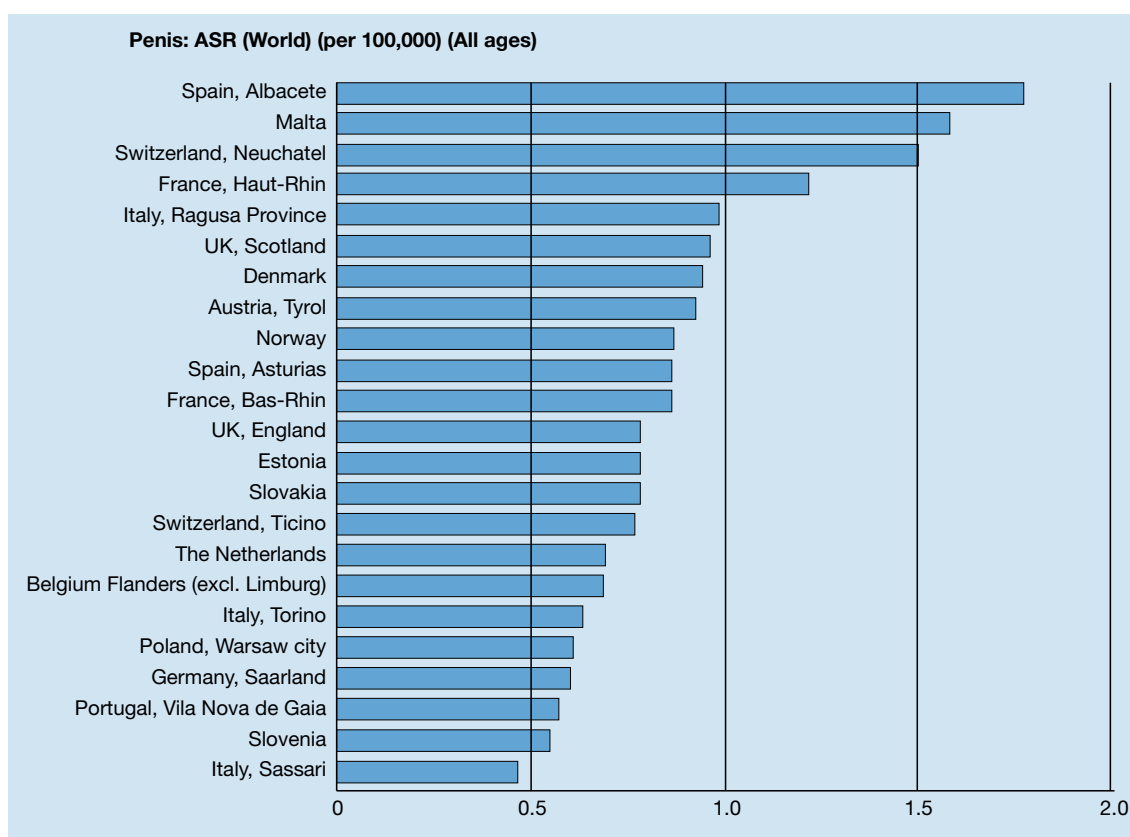
1.00/100,000 (Figure 3.1) [7]. In North America [5], the incidence of penile cancer is also affected by race and ethnicity, with the incidence highest in white Hispanics (1.01/100,000) compared to Alaskan, Native American Indians (0.77 /100,000), blacks (0.62/100,000) and white non-Hispanics (0.51/100,000), respectively. In contrast, other parts of the world, such as South America, South East Asia and parts of Africa, have a much higher incidence, representing up to 1-2% [7] of malignant diseases in men in some countries.

Penile cancer is common in regions with a high prevalence of human papilloma virus (HPV) [5]. The annual age-adjusted incidence is 0.7-3.0/100,000 men in India, 8.3/100,000 men in Brazil and even higher in Uganda, where it is the most commonly diagnosed male cancer [7, 8]. Much knowledge about penile cancer comes from countries with a high incidence.

The incidence of penile cancer is related to the prevalence of HPV in the population, which may account for the variation in incidence as the worldwide HPV prevalence varies considerably. There is also a less noticeable variation in incidence between European regions (Figure 3.1). At least one third of cases can be attributed to HPV-related carcinogenesis. There are no data linking penile cancer to HIV or AIDS.

In the USA, the overall age-adjusted incidence rate decreased from 1973 to 2002 from 0.84/100,000 in 1973-1982 to 0.69/100,000 in 1983-1992, and to 0.58/100,000 in 1993-2002 [5]. In Europe, the overall incidence has been stable from the 1980s until today [6], with an increased incidence reported in Denmark [9] and the UK. A UK longitudinal study confirmed a 21% increase in incidence during 1979-2009 [10]. The incidence of penile cancer increases with age [6]. The peak age is during the sixth decade of life, though the disease does occur in younger men [11].

Figure 3.1: Annual incidence rate (world standardised) by European region/country*



*Adapted from [7].

3.3 Risk factors and prevention

Review of the published literature from 1966-2000 identified several risk factors for penile cancer [12] (Table 3.1) (LE: 2a).

Table 3.1: Recognised aetiological and epidemiological risk factors for penile cancer

Risk factors	Relevance	Ref
Phimosis	OR 11-16 vs. no phimosis	[13, 14]
Chronic penile inflammation (balanoposthitis related to phimosis) Balanitis xerotica obliterans (lichen sclerosus)	Risk	[15]
Sporalene and UVA phototherapy for various dermatological conditions such as psoriasis	Incidence rate ratio 9.51 with > 250 treatments	[16]
Smoking	5-fold increased risk (95% CI: 2.0-10.1) vs. non-smokers	[13, 14, 17]
HPV infection condylomata acuminata	22.4% in verrucous SCC 36-66.3% in basaloid-warty	[5, 18]
Rural areas, low socioeconomic status, unmarried		[19-22]
Multiple sexual partners, early age of first intercourse	3-5-fold increased risk of penile cancer	[12, 14, 23]

HPV = human papilloma virus; OR = odds ratio; SCC = squamous cell carcinoma; UVA = ultraviolet A.

Human papilloma virus infection (HPV) is an important risk factor; HPV DNA was found in 70-100% of intraepithelial neoplasia and in 30-40% of invasive penile cancer tissue samples (LE: 2a). It is thought to be a cofactor in the carcinogenesis of some variants of penile SCC [18] through interaction with oncogenes and tumour suppressor genes (P53, Rb genes) [24]. The commonest HPV subtypes in penile cancer are types 16 and 18 [25] and the risk of penile cancer is increased in patients with condyloma acuminata [26] (LE: 2b). The incidence of penile cancer is higher in regions with high HPV prevalence.

It remains unclear whether HPV-associated penile cancer has a different prognosis to non-HPV-associated penile cancer. A significantly better 5-year disease-specific survival was reported for HPV-positive versus HPV-negative cases (93% vs. 78%) [27], while others reported no difference in lymph node metastases and a 10-year survival rate [28].

There is no direct association between the incidence of penile cancer and cervical cancer. However, both cancers are independently linked with the prevalence of HPV infections [29, 30]. Female sexual partners of patients with penile cancer do not have an increased incidence of cervical cancer. There is no current recommendation for HPV vaccination in boys because of a different HPV-associated risk pattern in penile and anal cancer. The epidemiological effects of HPV vaccination in girls are also awaited [31, 32].

Phimosis is strongly associated with invasive penile cancer [14, 19, 33, 34], probably due to associated chronic infection since smegma is not a carcinogen [33]. A further risk factor suggested by epidemiological studies is cigarette smoking (4.5-fold increased risk (95% CI: 2.0-10.1) [34]. The incidence of lichen sclerosus (balanitis xerotica obliterans) in patients with penile cancer is relatively high but is not associated with increased rates of adverse histopathological features, including carcinoma *in situ* (CIS). Other epidemiological risk factors are a low levels of socioeconomic status and education [19].

Countries and cultures practising routine neonatal circumcision have a lower incidence of penile cancer. Israeli Jews have the lowest incidence at 0.3 per 100,000/year. However, neonatal circumcision removes about half the tissue that can develop into penile cancer. A US study of 100 matched case-control pairs found that the protective effect of neonatal circumcision against invasive penile cancer (OR 0.41) became much weaker when the comparative analysis was only against men without a history of phimosis (OR 0.79, 95% CI: 0.29-2 [14]). Neonatal circumcision does not reduce the risk of CIS [14].

3.4 Pathology

Squamous cell carcinoma accounts for > 95% of cases of penile malignancies (Tables 3.2 and 3.3). It is not known how often SCC is preceded by premalignant lesions (Table 3.2) [35-38]. Some variants of primary penile cancer have not yet been included in the WHO classification, including pseudohyperplastic carcinoma, carcinoma cuniculatum, pseudoglandular carcinoma, and warty-basaloid carcinoma.

There are many mixed forms of SCC, including the warty-basaloid form (50-60% of mixed penile SCC), usual- verrucous (hybrid), usual-warty, usual-basaloid or usual-papillary and other rarer combinations.

Other penile malignant lesions include melanocytic lesions, mesenchymal tumours, lymphomas and metastases. These are unrelated to penile cancer and rarer. Aggressive penile sarcoma has been reported. Penile metastases from other neoplasias often have a prostatic or colorectal origin.

Table 3.2: Premalignant penile lesions (precursor lesions)

Lesions sporadically associated with SCC of the penis
• Cutaneous horn of the penis
• Bowenoid papulosis of the penis
• Lichen sclerosus (balanitis xerotica obliterans)
Premalignant lesions (up to one-third transform to invasive SCC)
• Intraepithelial neoplasia grade III
• Giant condylomata (Buschke-Löwenstein)
• Erythroplasia of Queyrat
• Bowen's disease
• Paget's disease (intradermal ADK)

Table 3.3: Histological subtypes of penile carcinomas, their frequency and outcome

Subtype	Frequency (% of cases)	Prognosis
Common SCC	48-65	Depends on location, stage and grade
Basaloid carcinoma	4-10	Poor prognosis, frequently early inguinal nodal metastasis [39]
Warty carcinoma	7-10	Good prognosis, metastasis rare
Verrucous carcinoma	3-8	Good prognosis, no metastasis
Papillary carcinoma	5-15	Good prognosis, metastasis rare
Sarcomatoid carcinoma	1-3	Very poor prognosis, early vascular metastasis
Mixed carcinoma	9-10	Heterogeneous group
*Pseudohyperplastic carcinoma	< 1	Foreskin, related to lichen sclerosus, good prognosis, metastasis not reported
Carcinoma cuniculatum	< 1	Variant of verrucous carcinoma, good prognosis, metastasis not reported
Pseudoglandular carcinoma	< 1	High-grade carcinoma, early metastasis, poor prognosis
Warty-basaloid carcinoma	9-14	Poor prognosis, high metastatic potential [40] (higher than in warty, lower than in basaloid SCC)
Adenosquamous carcinoma	< 1	Central and peri-meatal glans, high-grade carcinoma, high metastatic potential but low mortality
Mucoepidermoid carcinoma	< 1	Highly aggressive, poor prognosis
Clear cell variant of penile carcinoma	1-2	Exceedingly rare, associated with HPV, aggressive, early metastasis, poor prognosis, outcome is lesion-dependent, frequent lymphatic metastasis [41]

3.4.1 Gross handling

Tissue sections must completely include small lesions and at least 3-4 blocks of bigger lesions. Lymph nodes must be totally included to ensure the detection of micrometastases. Surgical margins must be completely included.

3.4.2 Pathology report

The pathology report must include the anatomical site of the primary tumour, the histological type/subtypes, grade, perineural invasion, depth of invasion, vascular invasion (venous/lymphatic), irregular growth and front of invasion, urethral invasion, invasion of corpus spongiosum/cavernosum and surgical margins.

3.4.3 Grading

The TNM classification for penile cancer includes tumour grade because of its prognostic relevance (Table 4.1). Both Broder's classification and the WHO grading system for grading penile cancer are highly dependent on the observer and are no longer used [42].

3.4.4 Pathological prognostic factors

Carcinomas limited to the foreskin have a better prognosis and lower risk of regional metastasis [43]. Perineural invasion and histological grade are very strong predictors of a poor prognosis and cancer-specific mortality [44]. Although tumour grade is a predictor of metastatic spread, it can be difficult to grade heterogeneous

tumours. Lymphatic invasion is an independent predictor of metastasis. Venous embolism is often seen in advanced stages.

Types of penile SCC with an excellent prognosis include: verrucous, papillary, warty, pseudohyperplastic and carcinoma cuniculatum. These SCCs are locally destructive, rarely metastasize and have a very low cancer-related mortality.

High-risk SCC variants are the basaloid, sarcomatoid, adenosquamous and poorly differentiated types. They metastasize early and mortality is high. An intermediate-risk SCC group comprises the usual SCC, mixed forms and the pleomorphic form of warty carcinomas.

Stage pT3 tumours that invade the distal (glandular) urethra (25% of cases) do not have a worse outcome [45]. However, invasion of the more proximal urethra, also classified as stage pT3, is due to a highly aggressive SCC with a poor prognosis (see Table 3.3).

The inclusion in the same pT2 group of invasion of the corpus spongiosum and of the corpora cavernosa is confusing clinically because these conditions have very different prognoses. After a mean follow-up of 3 years, higher rates of local recurrence (35% vs. 17%) and mortality (30% vs. 21%) were reported in pT2 tumours (n = 72) with tunica or cavernosal involvement versus glans-only invasion, respectively [46] (LE: 2b). The authors proposed defining T2a with spongiosum-only invasion and T2b with tunica and/or corpus cavernosum invasion. A similar prognostic difference was observed in a retrospective analysis of 513 patients treated between 1956 and 2006 [47].

Long-term survival is similar in patients with T2 and T3 tumours and in patients with N1 and N2 disease, using the 1987-2002 TNM classification [47] (LE: 2a).

Two nomograms, based only on small numbers, were developed to estimate prognosis in penile cancer. One study suggested that pT1G1 tumours are low-risk tumours, with 0% developing lymph node metastases, in contrast to high-risk pT2/3 G2/3 tumours, with 83% developing lymph node metastases [48].

Remaining tumours were intermediate-risk tumours with 33% developing metastases. Another study reported similar findings and recommended prophylactic lymphadenectomy for high-risk patients [49]. There is also a 'prognostic index', which ranks several pathological parameters (grade, deepest anatomical level, perineural invasion) to predict the likelihood of inguinal lymph node metastases and 5-year survival [50]. The lower the score, the higher is the probability of 95% survival at 5 years.

3.4.5 **Penile cancer and HPV**

A high prevalence of HPV infection is found in basaloid (76%), mixed warty-basaloid (82%) and warty penile SCCs (39%). The commonest HPV-types in penile SCC are HPV 16 (72%), HPV 6 (9%) and HPV 18 (6%). Verrucous and papillary penile SCCs are HPV-negative. Overall, only one-third of penile SCCs show HPV infection, but those that do are usually infected by several HPV strains.

3.4.6 **Molecular biology**

Little is known about the role of chromosomal abnormalities in penile SCC in biological behaviour and patient outcome [24]. Lower DNA copy and alteration numbers are linked to poorer survival. Alterations in the locus 8q24 may play a major role and are implicated in other neoplasms such as prostate cancer [51, 52]. Telomerase activity has been shown in invasive penile carcinoma [53], and some authors have shown that aneuploidy changed according to tumour grade [54].

Epigenetic alterations evaluating the methylation pattern of CpG islands in CDKN2A have been described. CDKN2A encodes for two tumour suppressor proteins (p16INK4A and p14ARF) which control cell growth through Rb and p53 pathways. Poetsch et al. showed that 62% of invasive SCC of the penis displayed allelic loss of p16 and 42% promoter hypermethylation. Tumours immunohistochemically negative for p16 showed hypermethylation of and/or LOH near the p16INK4A locus. In that study, p16 negativity was linked to lymph node metastasis, in another study to prognosis [55]. Allelic loss of the p53 gene is a frequent event in penile SCC (42%) [56] and p53 expression has been linked to poor prognosis [57]. Another element influencing lymph node metastasis is the metastasis suppressor protein KAI1/CD82; decreased expression of this protein favours lymph node metastasis [58].

3.4.7 **Penile biopsy**

The diagnosis of penile cancer must be confirmed by biopsy. Although penile cancer is usually obvious, very occasionally it may be confused with non-SCC penile carcinoma or inflammatory lesions.

Histological confirmation is necessary to guide management:

- when there is doubt about the exact nature of the lesion (e.g. CIS, metastasis or melanoma) and/or;
- treatment is planned with topical agents, radiotherapy or laser surgery;
- lymph node treatment is based on pre-operative histological information (risk-adapted strategy).

Biopsy size is important. In biopsies with an average size of 0.1 cm, it was difficult to evaluate the depth of invasion in 91% of biopsies. There was also discordance between the grade at biopsy and in the final

specimen in 30% of cases and failure to detect cancer in 3.5% of cases [35]. Also, vascular and lymphatic tumour emboli were detected in only 9-11% of cases. Although a punch biopsy may be sufficient for superficial lesions, an excisional biopsy is preferred because it should be deep enough to assess properly the degree of invasion and stage.

3.4.8 *Intra-operative frozen sections and surgical margins*

The aim of surgical treatment is complete removal of the penile carcinoma and negative surgical margins. The width of negative surgical margins should follow a risk-adapted strategy based on tumour grade. Negative surgical margins may be confirmed intra-operatively by frozen section [59]. If surgical margins are studied following these criteria (including urethral and periurethral tissue), only 5 mm of tumour-free tissue is sufficient to consider the surgical margins to be negative [60].

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 TNM classification

The 2009 TNM classification [61] stratifies the T1 category into two prognostically different risk groups, depending on the presence or absence of lymphovascular invasion and grading (Table 4.1). The rationale for a potential further subdivision of the T2 category is discussed under Section 3.4.4 [46, 47].

The 2009 TNM classification recognizes the adverse effect of extracapsular spread on prognosis and therefore classifies any inguinal lymph node metastasis with extracapsular extension as pN3 [61]. Retroperitoneal lymph node metastases are extraregional nodal and therefore distant metastases.

Table 4.1: 2009 TNM clinical and pathological classification of penile cancer [61]

Clinical classification	
T - Primary Tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma <i>in situ</i>
Ta	Non-invasive carcinoma
T1	Tumour invades subepithelial connective tissue
T1a	Tumour invades subepithelial connective tissue without lymphovascular invasion and is not poorly differentiated or undifferentiated (T1G1-2)
T1b	Tumour invades subepithelial connective tissue with lymphovascular invasion or is poorly differentiated or undifferentiated (T1G3-4)
T2	Tumour invades corpus spongiosum and/or corpora cavernosa
T3	Tumour invades urethra
T4	Tumour invades other adjacent structures
N - Regional Lymph Nodes	
NX	Regional lymph nodes cannot be assessed
N0	No palpable or visibly enlarged inguinal lymph node
N1	Palpable mobile unilateral inguinal lymph node
N2	Palpable mobile multiple unilateral or bilateral inguinal lymph nodes
N3	Fixed inguinal nodal mass or pelvic lymphadenopathy, unilateral or bilateral
M - Distant Metastasis	
M0	No distant metastasis
M1	Distant metastasis
Pathological classification	
The pT categories correspond to the clinical T categories. The pN categories are based upon biopsy or surgical excision	
pN - Regional Lymph Nodes	
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Intranodal metastasis in a single inguinal lymph node
pN2	Metastasis in multiple or bilateral inguinal lymph nodes
pN3	Metastasis in pelvic lymph node(s), unilateral or bilateral or extranodal extension of any regional lymph node metastasis
pM - Distant Metastasis	
pM0	No distant metastasis
pM1	Distant metastasis
G - Histopathological Grading	
GX	Grade of differentiation cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3-4	Poorly differentiated/undifferentiated

5. DIAGNOSTIC EVALUATION AND STAGING

Penile cancer can be cured in over 80% of cases if diagnosed early. Local treatment, although potentially life-saving, can be mutilating and devastating for the patient's psychological well-being.

5.1 Primary lesion

Penile carcinoma is usually a clinically obvious lesion. However, it may be hidden under a phimosis. Physical examination should include palpation of the penis to assess the extent of local invasion. Ultrasound (US) can give information about infiltration of the corpora [62, 63]. Magnetic resonance imaging (MRI) with an artificially induced erection can help to exclude tumour invasion of the corpora cavernosa if preservation of the penis is planned [64, 65].

5.2 Regional lymph nodes

Careful palpation of both groins for enlarged inguinal lymph nodes must be part of the initial physical examination of patients with penile cancer.

5.2.1 Non-palpable inguinal nodes

If there are no palpable lymph nodes, the likelihood of micrometastatic disease is about 25%. Imaging studies are not helpful in staging clinically normal inguinal regions, though imaging may be helpful in obese patients in whom palpation is unreliable or impossible:

- Inguinal US (7.5 MHz) can reveal abnormal nodes with some enlargement. The longitudinal/transverse diameter ratio and absence of the lymph node hilum are findings with relatively high specificity [66];
- Conventional CT or MRI scans cannot detect micrometastases reliably [67];
- Imaging with ¹⁸FDG-positron emission tomography (PET)/CT does not detect lymph node metastases < 10 mm [68, 69].

The further diagnostic management of patients with normal inguinal nodes should be guided by pathological risk factors. Lymphovascular invasion, local stage and grade are risk factors for the likelihood of lymphatic metastasis [70, 71]. Nomograms are not accurate enough. Invasive lymph node staging is required in patients at intermediate- or high-risk of lymphatic spread (see Section 6.2).

5.2.2 Palpable inguinal nodes

Palpable lymph nodes are highly suspicious for lymph node metastases. Physical examination should note the number of palpable nodes on each side and whether these are fixed or mobile. Additional inguinal imaging does not alter management (see Section 6) and is usually not required.

A pelvic CT scan can be used to assess the pelvic lymph nodes. Imaging with ¹⁸FDG-PET/CT has reported a high sensitivity of 88-100%, with a specificity of 98-100%, for confirming metastatic nodes in patients with palpable inguinal lymph nodes [69, 72].

5.3 Distant metastases

An assessment of distant metastases should be performed in patients with positive inguinal nodes [73-75] (LE: 2b). Computed tomography of the abdomen and pelvis and a chest X-ray are recommended. Thoracic CT is more sensitive than chest X-ray. PET/CT is an option for identifying pelvic nodal and distant metastases in patients with positive inguinal nodes [76].

There is no established tumour marker for penile cancer. The SCC antigen (SCC Ag) is increased in < 25% of penile cancer patients. One study found that SCC Ag did not predict occult metastatic disease, but was an indicator of disease-free survival in lymph-node-positive patients [77].

5.4 Guidelines for the diagnosis and staging of penile cancer

	GR
Primary tumour	
Physical examination, recording morphology, extent and invasion of penile structures.	C
MRI with artificial erection in selected cases with intended organ-preserving surgery.	
Inguinal lymph nodes	
Physical examination of both groins, recording number, laterality and characteristics of inguinal nodes: <ul style="list-style-type: none">• If nodes are not palpable, invasive lymph node staging in high-risk patients (see Section 6).• If nodes are palpable, a pelvic CT may be indicated, PET/CT is an option.	C
Distant metastases	
In N+ patients, an abdominopelvic CT scan and chest X-ray are required for systemic staging.	C
PET/CT scan is an option.	
In patients with systemic disease or with relevant symptoms, a bone scan may be indicated.	

CT = computed tomography; PET = positron emission tomography.

6. DISEASE MANAGEMENT

6.1 Treatment of the primary tumour

Treatment of the primary penile cancer lesion aims to remove the tumour completely, while preserving as much of the penis as possible without compromising radicality. Local recurrence has little effect on long-term survival so that organ preservation strategies can be used [78].

The overall quality of available research evidence is low. There are no randomised controlled trials or observational studies for surgical management of localised penile cancer nor studies comparing surgical and non-surgical modalities. The available studies are often biased.

However, penile preservation appears to be superior in functional and cosmetic outcomes. It is the primary treatment method for men with localised penile cancer. However, there are no randomised studies comparing organ-preserving and ablative treatment strategies, only retrospective studies with a level of evidence of 3 or less.

Histological diagnosis with local staging must be obtained in all cases, especially if considering non-surgical treatment modalities (GR: C).

Treatment of the primary tumour and of the regional nodes can be staged. It is mandatory to remove all malignant tissue with negative surgical margins. Patients must be counselled about all relevant treatment modalities.

Local treatment modalities for small and localised penile cancer include excisional surgery, external beam radiotherapy, brachytherapy and laser ablation.

6.1.1 Treatment of superficial non-invasive disease (CIS)

For penile CIS, topical chemotherapy with imiquimod or 5-fluorouracil (5-FU) can be an effective first-line treatment. They have relatively low toxicity and adverse events, but efficacy is limited. Complete responses have been reported in up to 57% of CIS cases [79]. For the reason of a high-rate of persistence and/or recurrence, close and long-term surveillance of such patients is required. If topical treatment fails, it should not be repeated.

Laser treatment can be used for CIS. Photodynamic control may be used in conjunction with CO₂ laser treatment [80].

Alternatively, total or partial glans resurfacing can be offered as a primary treatment modality for CIS and as a secondary treatment in case of treatment failure with topical chemotherapy or laser therapy. Glans resurfacing is a surgical technique which consists of complete abrasion of the glandular epithelium with covering by a split skin graft. With glans resurfacing for presumed non-invasive disease, up to 20% of patients are found to have superficial invasive disease [81].

6.1.2 Treatment of invasive disease confined to the glans (category Ta/T1a)

A penis-preserving strategy is recommended (GR: C) for small and localised invasive lesions (Ta/T1a).

It is mandatory to do a biopsy to confirm diagnosis prior to using conservative treatments (GR: C). All patients must be circumcised before considering conservative non-surgical treatments. For tumours confined to the prepuce, radical circumcision alone may be curative provided that negative surgical margins are confirmed by definitive histology.

For all surgical treatment options, the intraoperative assessment of surgical margins by frozen section is recommended (GR: C) because tumour-positive margins lead to local recurrence [82]. Total removal of the glans (glansectomy) and prepuce has the lowest recurrence rate of the treatments for small penile lesions (2%) [82]. Negative surgical margins are imperative when using penile-conserving treatments (GR: C) and a margin of 5 mm is considered oncologically safe [82, 83].

Treatment choice should depend on tumour size, histology, including stage and grade, localisation (especially relative to the meatus) and patient preference as there are no documented differences in long-term local recurrence rates between surgery, laser and radiation therapy.

6.1.3 Results of different surgical organ-preserving treatments

There are only retrospective case series for these treatments. The results have been reported heterogeneously so that the database for assessment is of limited quality. There have been no randomised trials.

6.1.3.1 Laser therapy

Laser ablation is carried out with a Nd:YAG laser or a CO₂ laser [84-89]. Visualization may be improved by photodynamic diagnosis.

The results of CO₂ laser treatment have been reported by three studies all from the same institution [84-86]. Laser treatment was given in combination with radiotherapy or chemotherapy and patients included had CIS or T1 penile cancers. Follow-up was 5 years (median) in all three studies. There is some overlap

between the cohorts reported, with a total of 195 patients included in these retrospective series.

No cancer-specific deaths were reported. One study reported an estimated cumulative risk of local recurrence at 5 years of 10% with CIS (n = 106) and 16% with T1 tumour (n = 78) [84]. In all three series taken together, local recurrence ranged from 14% for CIS and T1 tumours [86] to 23% for T1 tumours [85]. The reported rate of inguinal nodal recurrence after local CO₂ laser treatment was 0% (0/11) [86] and 4% (2/56) [85]. Secondary partial penectomy at 10 years was 3% and 10%, depending on the tumour (CIS vs. T1) and whether combination treatment had been given or not [84].

The four studies on the results of Nd:YAG laser treatment [87-90] together report a total of 150 patients with a follow-up of at least 4 years. Local recurrence rates at last follow-up ranged across the four studies from 10% (3/29) [87] to 48% (21/44) [88]. In one study [89], recurrence-free survival rates were reported as 100%, 95% and 89% at 1, 2 and 5 years. Inguinal nodal recurrence were reported in 21% (9/44) [87]. Cancer-related deaths were reported in 2% (1/54) [90] and 9% of patients (4/44) [88], respectively. Three studies from the same institution, probably including overlapping patient cohorts reported overall survival by censored or uncensored data which ranged from 100% at 4 years [87] and 95% [89] to 85% [91] at 7 years. The rate of secondary partial penectomy after initial Nd:YAG laser treatment was reported as 4% (1/23) [89] and 45% (20/44) [88], respectively. Complications, urinary- and sexual function outcomes were reported by only one study with 29 patients [87], which reported no complications and no change in urinary and sexual function after successful Nd:YAG laser treatment.

Other studies have reported data on a variety of laser treatments with either CO₂ laser, Nd:YAG laser, a combination of both, or a KTP laser [92-95], with a mean follow-up of 32-60 months and stages CIS up to T3 included. The four studies reported on a total of 138 patients.

The cancer-specific survival probability at 5 years was 95% in one study using the Kaplan-Meier method [93]. This was consistent with the finding from another study in which the cancer-specific mortality rate was relatively low at 2% (1/44) at a mean follow-up of around 5 years [94]. Local recurrence rates were 11% (5/44) [94], 19% (13/67) [93] and 26% (5/19) [95]. In one study recurrence-free survival at 5 years was estimated to be 88% [93].

6.1.3.2 *Moh's micrographic surgery*

Moh's micrographic surgery is a technique by which histological margins are taken in a geometrical fashion around a cone of excision. This technique has not been widely used. Only two studies reported a total of 66 patients [96, 97]. The original description [96] consisted of 33 consecutive patients treated between 1936 and 1986 and reported on 29 patients with at least 5 years' follow-up. In each study there was one secondary penile amputation and one death from penile cancer. In Mohs series, 79% (23/29) were cured at 5 years [96]. In the other series, 68% (17/25) were recurrence-free after a median of 37 months and 8% (2/25) had inguinal nodal recurrence and died of the disease [97]. One cancer-specific death was reported in each series, with the local recurrence rate was 32% (8/25) in one series [97].

6.1.3.3 *Glans resurfacing*

Three studies have reported results with glans resurfacing [81, 98, 99] in a total of 71 patients with CIS or T1. The range of the median duration of follow-up in the three studies was 21-30 months. No cancer-specific deaths were reported, the rates of local recurrence were 0% (0/10) [98] and 6% (2/33) [99], without reports of nodal recurrence. There were no reported complications.

6.1.3.4 *Glansectomy*

Results of another fairly new technique, glansectomy, were reported by three studies [82, 100, 101], while another study also reported on glans-preserving surgery [101]. A total of 68 patients with a follow-up of 114 months [100] and 63 months [101] were included. One patient (8%) had a local recurrence [100] and six patients (9%) had inguinal nodal metastases. No cancer-specific deaths were reported. Another group reported 87 patients with six local (6.9%), 11 regional (12.6%) and two systemic recurrences (2.3%), during a mean follow-up of 42 months [82].

6.1.3.5 *Partial penectomy*

Results of partial penectomy were reported in eight rather heterogeneous studies [86, 101-107] amounting to 184 included patients, with T1-T3 tumours, and follow-up from 40-194 months. 0-27% of patients died of penile cancer, with local recurrence rates ranging from 4-50% of patients. The 5-year overall survival rate was reported by three studies and ranged from 59-89% [104, 105, 107].

6.1.3.6 *Summary of results of surgical techniques*

There is not sufficient evidence to suggest a difference regarding the outcomes of different penis-sparing strategies, which generally appear to show good oncological outcomes. Although conservative surgery may

improve quality of life, local recurrence is more likely than after radical surgery, e.g. partial penectomy (5-12% vs. 5%). In a large cohort of patients undergoing conservative surgery, isolated local recurrence was 8.9%, with a 5-year disease-specific survival rate of 91.7%. Tumour grade, stage and lymphovascular invasion appear to be predictors of local recurrence.

6.1.4 Results of radiotherapy for T1 and T2 disease

Radiation treatment of the primary tumour is an alternative organ-preserving approach with good results in selected patients with T1-2 lesions < 4 cm in diameter [108-113] (LE: 2b). External radiotherapy is given with a minimum dose of 60 Gy combined with a brachytherapy boost or brachytherapy on its own [109, 111]. Radiotherapy results are best with penile brachytherapy with local control rates ranging from 70-90% [109, 111]. The American Brachytherapy Society and the Groupe Européen de Curiethérapie-European Society of Therapeutic Radiation Oncology (ABS-GEC-ESTRO) consensus statement for penile brachytherapy reported good tumour control rates, acceptable morbidity and functional organ preservation for penile brachytherapy for T1 and T2 penile cancers [114]. The rates of local recurrence after radiotherapy are higher than after partial penectomy. With local failure after radiotherapy, salvage surgery can achieve local control [115]. Patients with lesions > 4 cm are not candidates for brachytherapy.

Common complications with radiotherapy include urethral stenosis (20-35%), glans necrosis (10-20%) and late fibrosis of the corpora cavernosa [116] (LE: 3). With brachytherapy, meatal stenosis occurs in > 40% of cases.

Table 6.1: Summary of reported complications and oncological outcomes of local treatments*

Treatment	Complications	Local recurrence	Nodal recurrence	Cancer-specific deaths	References
Nd:YAG laser	None reported	10-48%	21%	2-9%	[87-90]
CO ₂ -laser	Bleeding, meatal stenosis (both < 1%)	14-23%	2-4%	None reported	[84-86]
Lasers (unspecified)	Bleeding (8%), local infection 2%	11-26%	2%	2-3%	[92-95]
Moh's micrographic surgery	Local infection 3%, Meatal stenosis 6%	32%	8%	3-4%	[96, 97]
Glans resurfacing	None reported	4-6%	Not reported	Not reported	[81, 98, 99]
Glansectomy	None reported	8%	9%	None reported	[100, 101]
Partial penectomy	Not reported	4-13%	14-19%	11-27%	[86, 104, 105, 107]
Brachytherapy	Meatal stenosis > 40%	10-30%	Not reported	Not reported	[108, 109, 111]
Radiotherapy	Urethral stenosis 20-35%, Glans necrosis 10-20%	Not reported	Not reported	Not reported	[110, 113-116]

*The ranges are the lowest and highest number of occurrences reported in different series.

6.1.5 Summary of treatment recommendations for non-invasive and localised superficially invasive penile cancer

6.1.5.1 Treatment of invasive disease confined to the corpus spongiosum/glans (Category T2)

Total glansectomy, with or without resurfacing of the corporeal heads, is recommended [102] (LE: 3; GR: C). Radiotherapy is an option (see Section 6.1.6). Partial amputation should be considered in patients unfit for reconstructive surgery [115] (GR: C).

6.1.5.2 Treatment of disease invading the corpora cavernosa and/or urethra (category T2/T3)

Partial amputation with a tumour-free margin with reconstruction is standard [112] (GR: C). A surgical margin of 5 mm is considered safe [82, 83]. Patients should remain under close follow-up. Radiotherapy is an option.

6.1.5.3 Treatment of locally advanced disease invading adjacent structures (category T3/T4)

These are relatively rare (Europe 5%, Brazil 13%) [83]. Total penectomy with perineal urethrostomy is standard surgical treatment for T3 tumours [83] (GR: C).

In more advanced disease (T4), neoadjuvant chemotherapy may be advisable, followed by surgery in responders, as in the treatment of patients with fixed enlarged inguinal nodes (see Section 6.2.4) (GR: C). Otherwise, adjuvant chemotherapy or palliative radiotherapy are options (GR: C; see Sections 6.2.4 and 6.1.6).

6.1.5.4 Local recurrence after organ-conserving surgery

A second organ-conserving procedure can be performed if there is no corpus cavernosum invasion [60, 80, 83, 112] (GR: C). For large or high-stage recurrence, partial or total amputation is required [116] (GR: C). A total phallic reconstruction may be offered to patients undergoing total/subtotal amputation [117, 118].

6.1.6 Guidelines for stage-dependent local treatment of penile carcinoma

Primary tumour	Organ-preserving treatment whenever possible	LE	GR
Tis	Topical treatment with 5-fluorouracil or imiquimod for superficial lesions with or without photodynamic control.	3	C
	Laser ablation with CO ₂ or Nd:YAG laser.		
	Glans resurfacing.		
Ta, T1a (G1, G2)	Wide local excision with circumcision CO ₂ or Nd:YAG laser surgery with circumcision.	3	C
	Laser ablation with CO ₂ or Nd:YAG laser.		
	Glans resurfacing.		
	Glansectomy with reconstructive surgery, with or without skin grafting.		
	Radiotherapy by external beam or as brachytherapy for lesions < 4 cm.		
T1b (G3) and T2 confined to the glans	Wide local excision plus reconstructive surgery, with or without skin grafting.	3	C
	Laser ablation with circumcision.		
	Glansectomy with circumcision, with reconstruction.		
	Radiotherapy by external beam or brachytherapy for lesions < 4 cm in diameter.		
T2 with invasion of the corpora cavernosa	Partial amputation and reconstruction.	3	C
	Radiotherapy by external beam or brachytherapy for lesions < 4 cm in diameter.		
T3 with invasion of the urethra	Partial penectomy or total penectomy with perineal urethrostomy.	3	C
T4 with invasion of other adjacent structures	Neoadjuvant chemotherapy followed by surgery in responders. Alternative: palliative external beam radiation.	3	C
Local recurrence after conservative treatment	Salvage surgery with penis-sparing treatment in small recurrences or partial amputation.	3	C
	Large or high-stage recurrence: partial or total amputation.	3	C

CO₂ = carbon dioxide; Nd:YAG = neodymium:yttrium-aluminium-garnet.

6.2 Management of regional lymph nodes

The development of lymphatic metastases in penile cancer follows the route of anatomical drainage. Inguinal and pelvic lymph nodes provide the regional drainage system for the penis, and the superficial and deep inguinal lymph nodes are the first regional nodal group to manifest lymphatic metastatic spread, which can be unilateral or bilateral [78].

All inguinal sentinel nodes appear to be located in the superior and central inguinal zones, with most in the medial superior zone [79]. No lymphatic drainage was observed from the penis to the two inferior regions of the groin and no direct drainage to the pelvic nodes was visualised. These findings confirm earlier studies [80, 81].

The second regional lymph node groups are the ipsilateral pelvic lymph nodes. Pelvic nodal disease does not seem to occur without ipsilateral inguinal lymph node metastasis and there are no reports of crossover metastatic spread from one inguinal side to the other pelvic side. Further metastatic lymph node spread from the pelvic nodes to para-aortic and paracaval nodes is outside the regional lymph node drainage system of the penis and is classified as systemic metastatic disease.

The management of regional lymph nodes is decisive for long-term patient survival. Cure can be achieved in metastatic disease confined to the regional lymph nodes. Lymphadenectomy is the treatment of choice for inguinal lymph node metastases (GR: B). Multimodal treatment combining surgery and polychemotherapy is often indicated.

Management of regional lymph nodes is stage-dependent. In clinically node-negative patients (cN0), micrometastatic disease occurs in about 25% of cases and is related to the local tumour stage and grade. In clinically positive lymph nodes (cN1/cN2), metastatic disease is highly likely and no time should be wasted on antibiotic treatment. Enlarged fixed inguinal lymph nodes (cN3) require multimodal treatment by chemotherapy and surgery. Even if present in only one node, capsular penetration and extranodal extension in lymph node metastasis carries a high-risk of progression and is classified as pN3, which also requires multimodal treatment.

6.2.1 Management of patients with clinically normal inguinal lymph nodes (cN0)

Risk stratification for the management of patients with clinically normal lymph nodes depends on stage, grade and the presence or absence of lymphovascular invasion in the primary tumour [82]. Tumours with low-risk of metastatic disease are those with superficial penile cancer (pTa, pTis) and low grade. pT1 tumours are a heterogeneous risk group: low risk if they are well differentiated (pT1G1), intermediate-risk group (pT1G2) [83] or high risk (pT1G3 and all higher stages).

Early inguinal lymphadenectomy in clinically node-negative patients is far superior for long-term patient survival compared to therapeutic lymphadenectomy when regional nodal recurrence occurs [84, 85]. One prospective study comparing bilateral lymphadenectomy, radiotherapy and surveillance in clinically node-negative patients reported that 5-year overall survival was significantly better with inguinal lymphadenectomy versus immediate inguinal radiotherapy or that observed with a surveillance strategy (74% vs. 66% and 63%, respectively) [86].

6.2.1.1 Surveillance

The surveillance of regional lymph nodes carries the risk of regional recurrence arising later from existing micrometastatic disease. Patient survival is over 90% with early lymphadenectomy and below 40% with lymphadenectomy for later regional recurrence [87, 88]. This risk must be taken into account when considering surveillance and the patient informed. Surveillance can only be recommended in patients with pTis and pTa penile cancer and with the appropriate caveats in pT1G1 tumours [87-89]. A prerequisite for surveillance is good patient information and compliance.

6.2.1.2 Invasive nodal staging

Staging of the inguinal lymph nodes in cN0 penile cancer requires an invasive procedure since all imaging techniques (US, CT, MRI) are unreliable in excluding small and micrometastatic lymph node involvement. Although CT criteria other than size have been defined for retrospective detection of lymph node metastases, these have not been validated prospectively [90]. Nomograms are unreliable in predicting node involvement [87, 91, 92] (LE: 2b). Fine-needle aspiration cytology does not reliably exclude micrometastatic disease and is not recommended. Instead, pathological risk factors are used to stratify node-negative patients [85, 93] (LE: 2b).

There are two invasive diagnostic procedures, whose efficacy is evidence-based: modified inguinal lymphadenectomy (mILND) and dynamic sentinel-node biopsy (DSNB). Both are standard approaches for invasive diagnosis of inguinal lymph nodes in clinically node-negative patients.

mILND is the standard surgical approach. Both the superficial inguinal lymph nodes from at least the central and both superior Daseler's zones are removed bilaterally [78, 94] (LE: 3), leaving behind the greater saphenous vein.

Dynamic sentinel node biopsy (DSNB) is based on the assumption that primary lymphatic drainage from a penile cancer initially goes to one or only a few inguinal sentinel nodes on each side before further dissemination to more inguinal nodes. Technetium-99m (Tc99m) nanocolloid is injected around the penile cancer site on the day before surgery; patent blue can be injected as well before surgery. A gamma-ray detection probe is used intra-operatively to detect the sentinel node in 97% of cases. The protocol has been standardised for routine use and has a short learning curve [95] (GR: B). DSNB has a reported high sensitivity (90-94%) [95, 96] (LE: 2b). In a pooled meta-analysis of 18 studies, pooled sensitivity was 88%, which improved to 90% with the addition of patent blue [97].

Both methods of invasive regional lymph node staging in cN0 patients may miss micrometastatic disease leading to regional recurrence and greatly reduced long-term survival [84]. The false-negative rate may be as high as 12-15% for DSNB, even in experienced centres [88, 89]. The false-negative rate of mILND is unknown. The patient must be informed of the risk of a false-negative result and the method being used. If lymph node metastasis is found with either method, an ipsilateral radical inguinal lymphadenectomy is indicated.

6.2.2 **Management of patients with palpable inguinal nodes (cN1/cN2)**

With uni- or bilateral palpable inguinal lymph nodes (cN1/cN2), metastatic lymph node disease is very likely and the traditional clinical advice to prescribe antibiotic treatment to exclude lymph node enlargement due to infection is no longer correct. Instead, appropriate oncological diagnosis and treatment should be undertaken without delay before further metastatic spread occurs. In clinically doubtful cases, US-guided fine needle aspiration cytology can be an option [119].

With palpably enlarged inguinal lymph nodes, additional staging using imaging is not useful, except in very obese patients. However, CT or MRI can provide information about the pelvic nodal status. ¹⁸F-FDG-PET/CT can identify additional metastases in lymph-node positive patients [120]. DSNB is not reliable in patients with palpably enlarged and suspicious inguinal lymph nodes and should not be used [121] (LE: 3).

6.2.2.1 **Radical inguinal lymphadenectomy**

In clinically lymph-node positive patients, surgical staging by inguinal lymphadenectomy is indicated. Intra-operative frozen sections may be used to confirm lymph node metastasis, for which an ipsilateral radical inguinal lymphadenectomy is necessary [78, 83].

Radical inguinal lymphadenectomy carries a significant morbidity due to impaired lymph drainage from the legs and often problematic wound healing. Morbidity can be as high as 50% [122] in the presence of significant risk factors such as increased body mass index. However, recent series have reported lower morbidities of about 25% [123, 124] (LE: 2b). Therapeutic radical inguinal lymphadenectomy can be life-saving and should not be underused for fear of associated morbidity [125]. Lymph-node density is a prognostic factor [126].

Tissue handling must be meticulous and take into account the absence of smooth muscle in lymphatic vessel walls. Lymphatic vessels therefore cannot be electrocoagulated and must be closed by ligation or possibly liberal use of clips [127, 128]. Post-operative morbidity is reduced by additional measures to improve drainage, such as stockings, bandaging, inguinal pressure dressings or vacuum suction [129] and prophylactic antibiotics. Advanced cases may require reconstructive surgery for primary wound closure.

The most commonly reported complications in recent series were wound infections (1.2-1.4%), skin necrosis (0.6-4.7%), lymphoedema (5-13.9%) and lymphocele formation (2.1-4%) [123, 124].

Laparoscopic and robot-assisted inguinal lymphadenectomy is feasible, but may not provide any advantage [130-133].

6.2.2.2 **Pelvic lymphadenectomy**

Patients with positive pelvic nodes have a worse prognosis compared to patients with only inguinal nodal metastasis (5-year CSS 71.0% vs. 33.2%) [134]. In the same study with 142 node-positive patients, significant risk factors for pelvic nodal metastasis were the number of positive inguinal nodes (cut-off 3), the diameter of inguinal metastatic nodes (cut-off 30 mm) and extranodal extension. The percentage of pelvic nodal metastases was 0% without any of these risk factors and 57.1% with all three risk factors [134].

If two or more positive lymph nodes, or one node with extracapsular extension (pN3), are found unilaterally, an ipsilateral pelvic lymphadenectomy is indicated. There is no direct lymphatic drainage from penile tumours to the pelvic lymph nodes [135] and lymphadenectomy is therefore not indicated if there is no involvement of inguinal nodes on that side. This recommendation is based on a study in which the rate of positive pelvic nodes was found to be 23% in cases with more than two positive inguinal nodes and 56% in those with more than three positive inguinal nodes, or if there was extracapsular involvement in at least one inguinal node [83, 136] (LE: 2b).

Pelvic lymphadenectomy may be performed simultaneously or as a secondary procedure following definitive histology. If bilateral pelvic dissection is indicated, it can be performed through a midline suprapubic extraperitoneal incision. It is important to avoid unnecessary delay if these procedures are indicated [137].

6.2.2.3 **Adjuvant treatment**

In patients with pN2/pN3 disease, adjuvant chemotherapy is recommended [138] (GR: C) (see Section 6.3.1). This is because a retrospective study reported long-term disease-free survival of 84% in node-positive patients with adjuvant chemotherapy after radical lymph node surgery versus 39% in historical controls without chemotherapy after lymphadenectomy [138].

Although adjuvant radiotherapy has been used after inguinal lymphadenectomy, the data is very limited and it is not generally recommended (see Section 6.2.5). There are no data for neoadjuvant inguinal radiotherapy.

6.2.3 **Management of patients with fixed inguinal nodes (cN3)**

Metastatic disease is always present in these cases. Staging by thoracic, abdominal and pelvic CT scan is necessary to assess the presence of further pelvic nodal disease and systemic metastatic disease. In clinically

unequivocal cases, histological verification by biopsy is not required. Rare cases with reasonable doubt require an excisional or core needle biopsy.

These patients have a poor prognosis and are unlikely to be cured by surgery alone. Upfront surgery is not generally recommended (GR: B) as it is non-curative and usually destructive. Multimodal treatment with neoadjuvant chemotherapy followed by radical lymphadenectomy in clinically responsive cases is recommended [139-141]. Responders to neoadjuvant chemotherapy with post-chemotherapy surgery have been reported to achieve long-term survival in 37% of cases [139]. There may be individual patients with reasons for upfront surgery followed by adjuvant treatment.

6.2.4 **Management of lymph node recurrence**

Patients with regional recurrence after surveillance should be treated similarly to patients with primary cN1/cN2 disease (see Section 6.2.2). Patients with regional recurrence following negative invasive staging by DSNB or modified inguinal lymphadenectomy already have disordered inguinal lymphatic drainage and are at a high-risk of irregular metastatic progression. Patients with inguinal nodal recurrence after therapeutic radical inguinal lymphadenectomy have a 5-year cancer-specific survival of 16% [142].

There is no evidence for the best management in such cases. Multimodal treatment with neoadjuvant and/or adjuvant chemotherapy after radical lymph node surgery is advised.

6.2.5 **The role of radiotherapy for the treatment of lymph node disease**

The use of radiotherapy for nodal disease follows tradition and single-institution policies and is not evidence-based. Despite the lack of data, radiotherapy is widely used in some European countries to manage regional lymph node metastasis in penile cancer.

It has not been reported that neoadjuvant or adjuvant radiotherapy improves oncological outcome in node-positive penile cancer [143]. One prospective trial found that inguinal node dissection was superior to inguinal radiotherapy [144]. Another study reported poor long-term survival in patients with adjuvant inguinal and pelvic radiotherapy [145]. Adjuvant chemotherapy has been reported to be far superior to adjuvant radiotherapy after radical inguinal lymphadenectomy in node-positive patients in one retrospective series [138]. Using the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) Program database, treatment results of 2,458 penile cancer patients treated with either surgery alone or surgery plus EBRT showed that the addition of adjuvant radiotherapy 'had neither a harmful nor a beneficial effect on CSS' [146].

Due to the lack of evidence, radiotherapy in the treatment of lymph node disease in penile cancer is not generally recommended. Prophylactic radiotherapy for cN0 disease is not indicated. Adjuvant inguinal radiotherapy may be considered as an option in selected patients with extracapsular nodal extension (cN3) or as a palliative treatment for surgically irresectable disease.

6.2.6 **Guidelines for treatment strategies for nodal metastases**

Regional lymph nodes	Management of regional lymph nodes is fundamental in the treatment of penile cancer	LE	GR
No palpable inguinal nodes (cN0)	Tis, Ta G1, T1G1: surveillance.	2a	B
	> T1G2: invasive lymph node staging by bilateral modified inguinal lymphadenectomy or DSNB.	2a	B
Palpable inguinal nodes (cN1/cN2)	Radical inguinal lymphadenectomy.		
Fixed inguinal lymph nodes (cN3)	Neoadjuvant chemotherapy followed by radical inguinal lymphadenectomy in responders.		
Pelvic lymphadenectomy	Ipsilateral pelvic lymphadenectomy is indicated if two or more inguinal nodes are involved on one side (pN2) and in extracapsular nodal metastasis (pN3).	2a	B
Adjuvant chemotherapy	Indicated in pN2/pN3 patients after radical lymphadenectomy.	2b	B
Radiotherapy	Radiotherapy is not indicated for the treatment of nodal disease in penile cancer.		

DSNB = dynamic sentinel node biopsy.

6.3 **Chemotherapy**

6.3.1 **Adjuvant chemotherapy in node-positive patients after radical inguinal lymphadenectomy**

Multimodal treatment can improve patient outcome in many tumour entities. Adjuvant chemotherapy after resection of nodal metastases in penile carcinoma has been reported in a few small and heterogeneous series [139, 147-150]. Comparing different small-scale clinical studies is fraught with difficulties.

The value of adjuvant chemotherapy after radical inguinal lymphadenectomy in node-positive penile cancer was demonstrated by an Italian group who reported long-term disease-free survival (DFS) of 84% in 25 consecutive patients treated with 12 adjuvant weekly courses of vincristine, bleomycin, and methotrexate (VBM) during the period 1979-1990 and compared this to a historical control group of 38 consecutive node-positive patients with radical lymphadenectomy (with- or without adjuvant inguinal radiotherapy) who had achieved a DFS rate of only 39% [139].

This group has also published results of a chemotherapy regimen adjuvant to radical lymphadenectomy in stage pN2-3 patients receiving three courses of cisplatin and 5-FU which they had been using since 1991 with lower toxicity and even better results compared to VBM [149] (LE: 2b). The same group has been using an adjuvant taxane-based regimen since 2004 (cisplatin, 5-FU plus paclitaxel or docetaxel [TPF]) in 19 node-positive patients receiving 3-4 cycles of TPF after resection of pN2-3 disease [150]. Of those patients, 52.6% were disease-free after a median follow up of 42 months and tolerability was good. Results of adjuvant treatment with paclitaxel and cisplatin also improved outcome [151].

The use of adjuvant chemotherapy is recommended, in particular when the administration of the triple combination chemotherapy is feasible, and curative treatment is aimed for (LE: 2b).

No data for the adjuvant chemotherapeutic treatment of penile carcinoma in stage pN1 are available. The administration of an adjuvant treatment in pN1 disease is therefore recommended only in clinical trials.

6.3.2 Neoadjuvant chemotherapy in patients with fixed or relapsed inguinal nodes

Bulky inguinal lymph node enlargement (cN3) indicates extensive lymphatic metastatic disease. Primary lymph node surgery is not generally recommended (GR: B). Complete surgical resection is unlikely and only a few patients will benefit from surgery alone.

Very limited data is available on neoadjuvant chemotherapy before inguinal lymph node surgery. This approach enables early treatment of likely systemic disease and downstaging of inguinal lymph node disease. Complete surgical treatment is possible with a good clinical response.

Results were modest in retrospective studies of 5-20 patients treated with bleomycin-vincristine-methotrexate (BVM) and bleomycin-methotrexate-cisplatin (BMP) treatments [140, 141, 152] and in the confirmatory BMP trial of the Southwest Oncology Group [153]. However, treatment-related toxicity was unacceptable due to bleomycin-related mortality.

Cisplatin/5-FU (PF) chemotherapy achieved a response rate of 25-50% and more acceptable tolerability [154, 155]. Over a period of 30 years, five different neoadjuvant chemotherapy regimens were used in 20 patients [78], with long-term survival in 37% of chemotherapy responders who underwent surgery. In EORTC study 30992, 26 patients with locally advanced or metastatic disease received irinotecan and cisplatin chemotherapy. Although the study did not meet its primary endpoint (response rate), there were three cases of pathologically complete remissions (pCR) [156].

A phase II trial evaluated treatment with four cycles of neoadjuvant paclitaxel, cisplatin, and ifosfamide (TIP). An objective response was reported in half of 30 patients, including three pCRs, which was a marginally significant predictor of survival. The estimated median time to progression (TTP) was 8.1 months and the median overall survival was 17.1 months [157] (LE: 2a).

Similarities between penile SCC and head and neck SCC led to the evaluation in penile cancer of chemotherapy regimens with an efficacy in head and neck SCC, including taxanes. The combination of cisplatin and 5-FU plus a taxane has been used in an neoadjuvant and adjuvant setting [150]. An overall objective response rate of 44% was reported in 28 patients treated neoadjuvantly, including 14% pCR (LE: 2b).

Similarly, a Cancer Research UK phase 2 trial with TPF (using only docetaxel) reported an objective response of 38.5% in 29 locally advanced or metastatic patients, although not meeting the primary endpoint. However, there was significant toxicity [158] (LE: 2a).

Overall, these results support the use of neoadjuvant chemotherapy for patients with fixed, unresectable nodal disease, particularly with a triple combination, including cisplatin and a taxane, whenever feasible (LE: 2a; GR: B).

There are hardly any data concerning radiochemotherapy with lymph-node surgery in penile cancer (very old, very few patients). Radiochemotherapy is only for clinical trials [159].

6.3.3 Palliative chemotherapy in advanced and relapsed disease

A recent retrospective study of individual patient data of 140 men with advanced penile SCC reported that visceral metastases and an ECOG-performance status > 1 were independent prognostic factors, and that cisplatin-based regimens had better outcomes than non-cisplatin-based regimens after adjusting for prognostic factors [160] (LE: 3).

In clinical practice, however, first-line chemotherapy regimens are variable. Before taxanes were introduced, the data were limited by small numbers, patient heterogeneity and its retrospective nature (except

for the EORTC trial [156]). Initial response rates ranged from 25% to 100%, but very few sustained responses and very few long-term survivors. The introduction of taxanes into penile cancer chemotherapy has enhanced the activity and efficacy of the regimens used [78, 140, 141, 151-158, 161].

There is virtually no data on second-line chemotherapy in penile cancer. One report using second-line paclitaxel monotherapy reported an initial response rate under 30% which therefore may be a reasonable option. However, no patient survived [162] (LE: 2a; GR: B). Anecdotally, a benefit has been observed by combining cisplatin with gemcitabine [163] (LE: 4).

6.3.4 ***Intra-arterial chemotherapy***

Intra-arterial chemotherapy has been trialled in locally advanced cases, especially cisplatin and gemcitabine in small case series [164-167]. Apart from a limited clinical response, outcome was not significantly improved.

6.3.5 ***Targeted therapy***

Targeted drugs have been used as second-line treatment and they could be considered as single-agent treatment in refractory cases. Anti-epidermal growth factor receptor (EGFR) targeted monotherapy has been trialled because EGFR is expressed in penile SCC [164, 165] and assumed similarities with head and neck SCC [165, 166]. There have been other studies, particularly with the anti-EGFR monoclonal antibodies, panitumumab and cetuximab. Some activity of tyrosine kinase inhibitors has been reported as well [167]. Further clinical investigations are needed (LE: 4).

6.3.6 ***Guidelines for chemotherapy in penile cancer patients***

Recommendations	LE	GR
Adjuvant chemotherapy (3-4 cycles of TPF) is an option for patients with pN2-3 tumours [150].	2b	C
Neoadjuvant chemotherapy (four cycles of a cisplatin and taxane-based regimen) followed by radical surgery is recommended in patients with non-resectable or recurrent lymph node metastases [150, 156].	2a	B
Chemotherapy for systemic disease is an option in patients with limited metastatic load.	3	C

TPF = cisplatin.

7. FOLLOW-UP

7.1 ***Rationale for follow-up***

The early detection of recurrence during follow-up increases the likelihood of curative treatment. Local recurrence does not significantly reduce long-term survival if successfully treated. In contrast, disease that has spread to the inguinal lymph nodes greatly reduces the rate of long-term disease-specific survival. Follow-up is also important in the detection and management of treatment-related complications.

Local or regional nodal recurrences usually occur within 2 years of primary treatment [78]. After 5 years, all recurrences were either local recurrences or new primary lesions [78]. These results support an intensive follow-up regimen during the first 2 years, with a less intensive follow-up after this for a total of at least 5 years. Follow-up after 5 years may be omitted in motivated patients reliably able to continue to carry out regular self-examination [78].

7.1.1 ***When and how to follow-up***

In patients with negative inguinal nodes after local treatment, follow-up should include physical examination of the penis and the groins for local and/or regional recurrence. Additional imaging has no proven benefit.

Follow-up also depends on the primary treatment modality. Histology from the glans should be obtained to confirm disease-free status following laser ablation or topical chemotherapy.

After potentially curative treatment for inguinal nodal metastases, CT or MRI imaging for the detection of systemic disease should be performed at 3-monthly intervals for the first 2 years so patients can benefit from adjuvant chemotherapy.

Although rarely late local recurrences may still occur, life-threatening metastases become very unusual after 5 years. This means regular follow-up can be stopped after 5 years, provided the patient understands the need to report any local changes immediately [168]. In patients unlikely to self-examine, long-term follow-up may be necessary.

7.1.2 Recurrence of the primary tumour

Local recurrence is more likely with all types of local organ-preserving treatment, i.e. after local excision, laser treatment, brachytherapy and associated therapies. However, it is very unlikely to increase the risk of dying from the disease in contrast to regional recurrence [78, 169]. Local recurrence occurred during the first 2 years in up to 27% of patients treated with penis-preserving modalities [170]. After partial penectomy, the risk of local recurrence is about 4-5% [78, 169, 170].

Local recurrence is easily detected by physical examination by the patient himself or the physician. Patient education is an essential part of follow-up and the patient is urged to visit a specialist if any changes are seen.

7.1.3 Regional recurrence

Most regional recurrences occur within during the first 2 years of diagnosis and treatment, irrespective of whether a surveillance strategy has been used or a sentinel-node based management or modified inguinal lymphadenectomy.

Although very unlikely, regional recurrence can occur unexpectedly after 2 years. It is therefore wise to continue close follow-up in these patients, for whom self-examination is very important [171]. The highest rate of regional recurrence (9%) occurs in patients managed using a surveillance strategy, while the lowest is in patients who have undergone invasive nodal staging by modified inguinal lymphadenectomy or DSNB and whose lymph nodes were negative (2.3%).

The use of US and fine needle aspiration cytology (FNAC) in suspicious cases has improved the early detection rate of regional recurrence [66, 171, 172]. There are no data to support the routine use of CT or MRI for the follow-up of regional nodes.

Patients who have had surgical treatment for lymph node metastases without adjuvant treatment have an increased risk of regional recurrence of 19% [78]. Regional recurrence requires timely treatment by radical inguinal lymphadenectomy and adjuvant therapy (see Section 6).

7.1.4 Guidelines for follow-up in penile cancer

	Interval of follow-up		Examinations and investigations	Minimum duration of follow-up	GR
	Years 1-2	Years 3-5			
Recommendations for follow-up of the primary tumour					
Penile-preserving treatment	3 months	6 months	Regular physician or self-examination. Repeat biopsy after topical or laser treatment for CIS.	5 years	C
Amputation	3 months	1 year	Regular physician or self-examination.	5 years	C
Recommendations for follow-up of the inguinal lymph nodes					
Surveillance	3 months	6 months	Regular physician or self-examination.	5 years	C
pN0 at initial treatment	3 months	1 year	Regular physician or self-examination. Ultrasound with FNAB optional.	5 years	C
pN+ at initial treatment	3 months	6 months	Regular physician or self-examination. Ultrasound with FNAC optional, CT/MRI optional.	5 years	C

CIS = carcinoma in situ; CT = computed tomography; FNAB = fine-needle aspiration biopsy; FNAC = fine-needle aspiration cytology; MRI = magnetic resonance imaging.

7.2 Quality of life

7.2.1 Consequences after penile cancer treatment

In patients with long-term survival after penile cancer treatment, sexual dysfunction, voiding problems and cosmetic penile appearance may adversely affect the patient's quality of life (QoL) [173]. There is very little data on sexual function and QoL after treatment for penile cancer.

7.2.2 Sexual activity and quality of life after laser treatment

A retrospective interview-based Swedish study after laser treatment for penile CIS [92] in 58/67 surviving patients with a mean age of 63 years, of whom 46 participated, reported a marked decrease in some sexual practices, such as manual stimulation, caressing and fellatio, but a general satisfaction with life overall and in other domains of life, including their sex life, similar to that of the general Swedish population.

A large study on CO₂ laser treatment of penile cancer in 224 patients reported no problems with erectile capability or sexual function following treatment [84]. In another study [95], no sexual dysfunction occurred in 19 patients treated.

7.2.3 Sexual activity after glans resurfacing

In one study with 10 patients [98], 7/10 completed questionnaires (International Index of Erectile Function [IIEF-5] and a non-validated 9-item questionnaire) at their 6-month follow-up visit. There was no erectile dysfunction according to the median IIEF-5 score of 24. All patients who were sexually active before treatment were active again within 3-5 months. According to the (non-validated) questionnaire, 7/7 patients stated that the sensation at the tip of their penis was either no different or better after surgery and that they had erections within 2-3 weeks of surgery. Six out of seven patients had had sexual intercourse within 3 months of surgery and 5/7 patients felt that their sex life had improved. Overall patient satisfaction with glans resurfacing was high.

7.2.4 Sexual activity after glansectomy

Two studies reported sexual function after glansectomy [100, 101]. In one study (n = 68) with unclear methodology [100], 79% did not report any decline in spontaneous erection, rigidity and penetrative capacity after surgery, while 75% reported recovery of orgasm. In another study [101], all 12 patients had returned to 'normal' sexual activity at 1 month after surgery.

7.2.5 Sexual function after partial penectomy

Sexual function after partial penectomy was reported by three studies [174-176]. The IIEF questionnaire was used in 18 patients with a mean age of 52 years [174]. Post-operative scores were statistically worse for all domains of sexual function after partial penectomy. After surgery, 55.6% of patients had erectile function that allowed sexual intercourse. In patients who did not resume sexual intercourse after partial penectomy, 50% were ashamed of their small penis and missing glans, while another third blamed surgical complications. Of those who had resumed sexual intercourse, 66.7% reported the same frequency and level of sexual activity as before surgery, while 72.2% continued to have ejaculation and orgasm every time they had sexual activity. Overall, only 33.3% maintained their pre-operative frequency of sexual intercourse and were satisfied with their overall sex life.

An 'Overall Sexual Functioning Questionnaire' was used in 14/18 patients with a median time since surgery of 11.5 months (range 6-72) [175]. Prior to surgery, all patients had normal erectile function and at least one intercourse per month. In 9/14 patients, overall sexual functioning was 'normal' or 'slightly decreased', while 3/14 patients had no sexual intercourse after surgery. Alei et al. showed an improvement in erectile function with time [176].

7.2.6 Quality of life after partial penectomy

Several qualitative and quantitative instruments were used to assess 'psychological behaviour and adjustment' and 'social activity' as QoL indicators [175]. Patients reported fears of mutilation and of loss of sexual pleasure, as well as fear of dying and what this would mean for their families. Patients said family and partners were important in overcoming difficulties following surgery. The study reported no significant levels of anxiety and depression on the GHQ-12 (General Health Questionnaire) and HAD scale (Hospital Anxiety and Depression Scale), 'Social activity' remained the same after surgery in terms of living conditions, family life and social interactions.

7.3 Total phallic reconstruction

There is very limited data about total phallic reconstruction [117, 177, 178] following full- or near-total penile amputation. It is not possible to restore function. Cosmetically acceptable results are obtainable.

7.4 Specialised care

It is possible to cure almost 80% of penile cancer patients at all stages. Whenever possible, organ-preserving treatment should be offered [47] because it permits better QoL and sexual function than with partial penectomy. Patients should be referred to experienced centre. Psychological support is very important for penile cancer patients.

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9. CONFLICT OF INTEREST

All members of the Penile Cancer Guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website: <http://www.uroweb.org/guidelines/>. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

Guidelines on the Management of Non-Neurogenic Male Lower Urinary Tract Symptoms (LUTS), incl. Benign Prostatic Obstruction (BPO)

S. Gravas (Chair), T. Bach, A. Bachmann,
M. Drake, M. Gacci, C. Gratzke, S. Madersbacher,
C. Mamoulakis, K.A.O. Tikkinen

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1. INTRODUCTION

1.1 Aim

Lower urinary tract symptoms (LUTS) are a common complaint in adult men with a major impact on quality of life (QoL), and substantial personal and societal expenditures. The present Guidelines offer practical evidence-based guidance on the assessment and treatment of men aged 40 years or older with various non-neurogenic benign forms of LUTS. The understanding of the LUT as a functional unit, and the multifactorial aetiology of associated symptoms, means that LUTS now constitute the main focus, rather than the former emphasis on Benign Prostatic Hyperplasia (BPH).

1.2 Publication history

Standard procedure for EAU Guidelines includes an annual assessment of newly published literature in the field to guide future updates. A shorter reference document, the Pocket Guidelines, is also available, both in print and as a mobile application, presenting the main findings of the Non-neurogenic Male LUTS Guidelines. These versions are abridged and therefore may require consultation with the full text version. All are available through the EAU website: <http://www.uroweb.org/guidelines/>.

For the 2015 Guidelines, the text has been significantly reduced so that only key information is included and re-formatted according to the EAU non-oncology template so that all Guidelines follow a similar format. This document was peer-reviewed prior to publication.

1.3 Panel composition

The Non-neurogenic Male LUTS Guidelines Panel consists of experts with a urological and epidemiological background. Although the Guidelines are written primarily for urologists, they can also be used by general practitioners, patients or other stakeholders.

2. METHODS

A systematic literature search was carried out by the Panel for articles in English language published in the PubMed, Medline, Web of Science, and Cochrane databases between 1966 and 31st December 2013 [1-4]. The search terms included 'lower urinary tract symptoms', 'benign prostatic hyperplasia', 'detrusor overactivity', 'overactive bladder', 'nocturia', and 'nocturnal polyuria', in combination with the pre-specified diagnostic tests, the various treatment modalities and the search limits, 'humans', 'adult men', 'review', 'randomised clinical trials', 'clinical trials', and 'meta-analysis'. References used in this text are graded according to their Level of Evidence (LE) and Guidelines are given a Grade of Recommendation (GR). In this 2015 EAU Guidelines compilation, all standard information on LE and GR has been taken out of the individual Guidelines topics for the sake of brevity. The methodology section (see the introduction chapter of the complete book) and supplementary online material Tables S.1 and S.2 outlines the LE and GR criteria which are used throughout the Guidelines, according to a classification system modified from the Oxford Centre for Evidence-based Medicine Levels of Evidence (modified March 2009) [1].

For Chapter 3B (Diagnostic evaluation), the Panel used the Delphi technique consensus approach. The Delphi method infers that decisions captured systematically from a structured group of individuals (the Panel) are more valid than those from unstructured groups. When published information is scarce, experts can make inferences using other data from comparable contexts. Using bespoke software (www.acord.it), propositions were put to experts who voted their preference. The results for the group were then sent back so participants could review their responses in the context of group-wide results. This was done anonymously, so review was free of peer group pressure. The web-based system offered the option to comment and justify decisions anonymously, and a second round of anonymous voting took place. Three iterations of the process were used, so that opinions of the Panel members converged towards the consensus 'correct' answer. The Panel pre-determined the threshold for consensus at 77% (7 out of 9) in regards to agreeing recommendations. The Panel classified diagnostic tests into three categories: 'must', 'should', and 'may'. 'Must' presents the highest level of obligation. 'Should' presents an intermediate level, and 'may' expresses the lowest level of obligation.

Subsections for the various types of conservative treatments, drugs, and operations are presented in a homogeneous structure listing 'mechanism of action', 'efficacy' with a table of high LE trials, 'safety' and 'practical considerations'. 'Grades of Recommendation' (GR) are derived from the relevant articles according to the modified classification system from the Oxford Centre for Evidence-based Medicine [1] (see supplementary online material Table S.2).

Where possible, recommendations are based on the strongest clinically relevant data. When recommendations are graded, there is no automatic relationship between the LE and GR. The availability of randomised controlled trials (RCTs) may not necessarily translate into a Grade A recommendation if there are methodological limitations or a disparity in published results, uncertainty about the balance of desirable and undesirable effects, uncertainty or variability in patients' values and preferences, or uncertainty about whether the intervention represents a wise use of resources. Alternatively, lack of high-level evidence does not preclude a Grade A recommendation where there is considerable clinical experience and consensus, or situations where corroborating studies cannot be performed, perhaps for ethical, financial or other reasons. Such a situation is indicated in the text with an asterisk to denote 'upgraded based on Panel consensus'. The quality of the scientific evidence is a major factor, but it has to be balanced against benefits, burdens, personal values and preferences when a Grade of Recommendation is assigned.

The Working Panel intends to update the content and recommendations regularly, according to the given structure and classification systems.

2.1 Patients to whom the guidelines apply

Recommendations apply to men aged 40 years or older who seek professional help for LUTS in various non-neurogenic and non-malignant conditions, such as LUTS/Benign Prostatic Obstruction (BPO), detrusor overactivity/overactive bladder (OAB), or nocturnal polyuria. Men with other contexts of LUT disease (e.g. concomitant neurological diseases, young age, prior LUT disease or surgery) usually require a more extensive work-up, which is not covered in these Guidelines, but may include several tests mentioned in the following section. EAU Guidelines on Neuro-Urology, Urinary Incontinence, Urological Infections, Urolithiasis, or malignant diseases of the LUT have been developed by other EAU Guidelines Panels (www.uroweb.org).

3. THE GUIDELINE

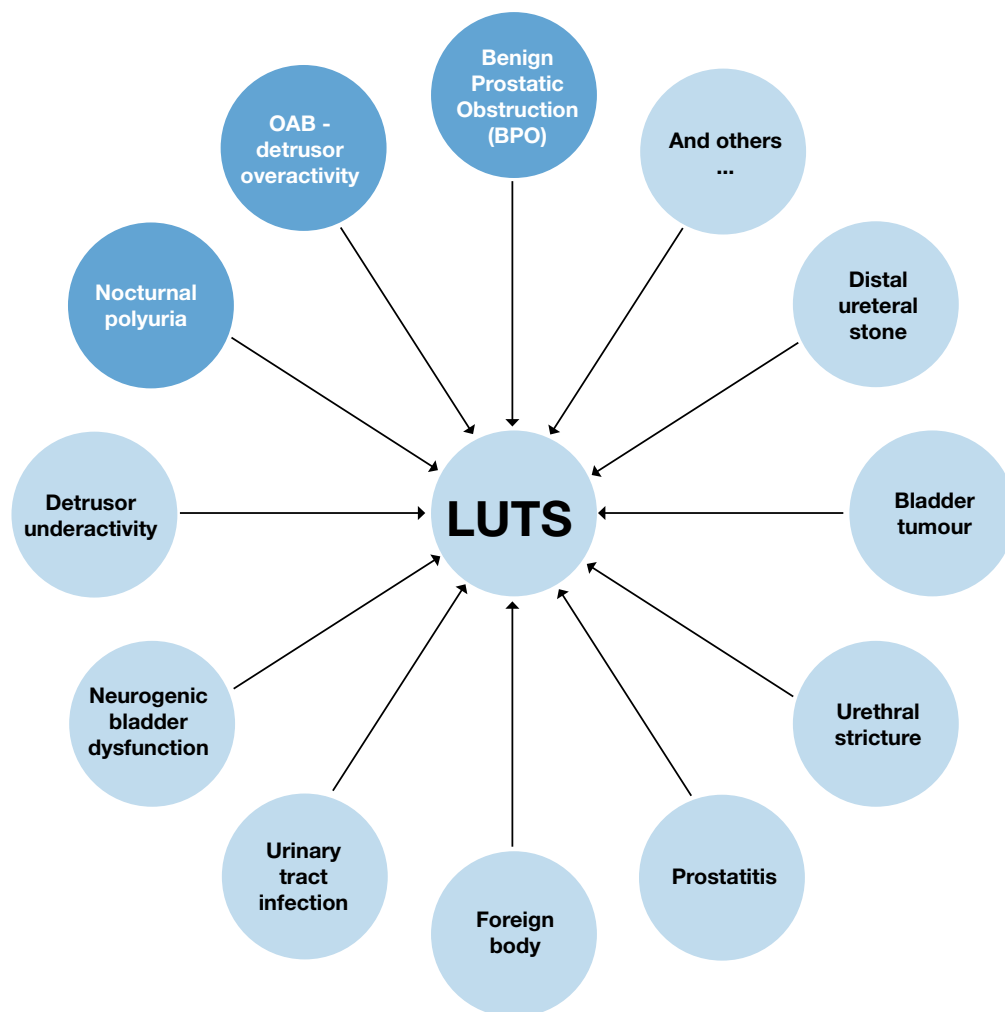
3A EPIDEMIOLOGY, AETIOLOGY AND PATHOPHYSIOLOGY

LUTS can be divided into storage, voiding and post-micturition symptoms [2]. LUTS are prevalent, cause bother and impair QoL [5-8]. They are strongly associated with ageing [5, 6], so associated costs and burden are likely to continue to increase overall in the future [6, 9].

Most elderly men report having at least one LUTS [6]. However, clinically meaningful prevalences are lower as symptoms may be mild or not very bothersome [8]. LUTS progress dynamically: for some individuals LUTS persist and progress over long time periods, and for others they remit [6].

LUTS have traditionally been related to bladder outlet obstruction (BOO), which is often caused by benign prostatic enlargement (BPE) resulting from the histologic condition of benign prostatic hyperplasia (BPH) [2, 7]. Recent studies have shown, however, that LUTS are often unrelated to prostate [3, 6]. Bladder dysfunction may also cause LUTS, including detrusor overactivity/OAB, detrusor underactivity/underactive bladder, as well as other structural or functional abnormalities of the urinary tract [3]. In addition, many non-urological conditions also contribute to LUTS, especially nocturia [6]. Figure 1 illustrates the potential causes of LUTS. In any single person complaining of LUTS, it is common for more than one of these factors to be present.

Figure 1: Causes of male lower urinary tract symptoms (LUTS)



3B DIAGNOSTIC EVALUATION

Tests are useful for diagnosis, monitoring, assessing the prognosis of disease progression, treatment planning, and the prediction of treatment outcome. The clinical assessment of patients with LUTS has two main objectives:

- To consider the differential diagnoses, since the origin of male LUTS are multifactorial. The relevant EAU Guidelines on the management of applicable conditions should be followed in these cases.
- To define the clinical profile of men with LUTS in order to provide appropriate care. The assessment should ascertain treatment options and identify men at risk of disease progression.

3B.1 Medical History

The importance of assessing the patient's history is well-recognised [4, 10, 11].

A medical history aims to identify the potential causes and relevant comorbidities, including medical and neurological diseases. In addition, it is recommended that current medication, lifestyle habits, emotional and psychological factors are reviewed. The Panel recognises the need to discuss LUTS and the therapeutic pathway from the patient's perspective. This includes reassuring the patient that there is no definite relation between LUTS and prostate cancer (PCa) [12, 13].

As part of the urological/surgical history, a self-completed validated symptom questionnaire (see section 3B.2) should be assessed to objectify and quantify LUTS. Voiding diaries are particularly beneficial when assessing patients with nocturia and/or other storage LUTS (see section 3B.3 'frequency volume chart'). When relevant, sexual function should be investigated, preferably with validated symptom questionnaires such as the International Index for Erectile Function (IIEF).

Recommendation	LE	GR
A medical history must always be taken from men with LUTS.	4	A*

**Upgraded based on Panel consensus. LUTS = lower urinary tract symptoms.*

3B.2 Symptom score questionnaires

All published guidelines for male LUTS/BPH recommend using validated symptom score questionnaires [4, 10, 11]. Several questionnaires have been developed which are sensitive to symptom changes and can be used to monitor treatment [14-20]. Symptom scores are helpful in quantifying the patient's LUTS and in identifying which type of symptoms are predominant, yet they are not disease-, age- or gender-specific.

3B.2.1 The International Prostate Symptom Score (IPSS)

The IPSS is an 8-item questionnaire, consisting of seven symptom questions and one QoL question [15]. The IPSS score is categorised as 'asymptomatic' (0 points), 'mildly symptomatic' (1-7 points), 'moderately symptomatic' (8-19 points), and 'severely symptomatic' (20-35 points). Limitations include lack of assessment of incontinence, post-micturition symptoms, and bother caused by each separate symptom.

3B.2.2 The International Consultation on Incontinence Questionnaire (ICIQ-MLUTS)

The ICIQ-MLUTS was created from the ICS Male questionnaire. It is a widely used and validated patient-completed questionnaire [16]. It contains 13 items, with subscales for nocturia and OAB, and is available in 17 languages.

3B.2.3 Danish Prostate Symptom Score (DAN-PSS)

The DAN-PSS [18] is a symptom score used mainly in Denmark and Finland. The IPSS includes only one overall QoL question. The ICIQ-MLUTS and DAN-PSS measure the bother of each individual LUTS.

Recommendation	LE	GR
A validated symptom score questionnaire with QoL question(s) should be used for the routine assessment of male LUTS in all patients and should be applied for re-evaluation of LUTS during treatment.	3	B

LUTS = lower urinary tract symptoms; QoL = quality of life.

3B.3 Frequency volume charts and bladder diaries

The recording of volume and time of each void by the patient is referred to as a frequency volume chart (FVC). Inclusion of additional information such as fluid intake, use of pads, activities during recording, or symptom scores is termed a bladder diary [2]. Parameters that can be derived from the FVC bladder diary include: day-time and night-time voiding frequency, total voided volume, the fraction of urine production during the night (nocturnal polyuria index [NPI]), and volume of individual voids.

The mean 24-hour urine production is subject to considerable variation. Likewise, circumstantial influence and intra-individual variation cause FVC parameters to fluctuate, though there is comparatively little data [21, 22]. The FVC diary is particularly relevant in nocturia, where it underpins the categorisation of underlying mechanism(s) [23-25]. The use of FVCs may cause a 'bladder training effect', and influence the frequency of nocturnal voids [26].

The duration of observation during FVC needs to be long enough to avoid sampling errors, but short enough to avoid non-compliance [27]. A systematic review of the available literature recommended FVC should continue for 3 or more days [28].

Recommendations	LE	GR
Micturition frequency volume charts or bladder diaries should be used to assess male LUTS with a prominent storage component or nocturia.	3	B
Frequency volume charts should be performed for the duration of at least 3 days.	2b	B

LUTS = lower urinary tract symptoms.

3B.4 Physical examination and digital-rectal examination

Physical examination to seek potential influences on LUTS, particularly focussing on the suprapubic area, the external genitalia, the perineum and lower limbs. Urethral discharge, meatal stenosis, phimosis and penile cancer must be identified if present.

3B.4.1 Digital-rectal examination and prostate size evaluation

Digital-rectal examination (DRE) is the simplest way to assess prostate volume, but correct estimation is not easy to achieve. Quality-control procedures for DRE have been described [29]. Transrectal ultrasound (TRUS)

is more accurate in determining prostate volume than DRE. Underestimation of prostate volume by DRE increases with increasing TRUS volume, particularly where the volume is > 30 mL [30]. A model of visual aids has been developed to help urologists estimate prostate volume more accurately [31]. One study concluded that DRE was sufficient to discriminate between prostate volumes > or < than 50 mL [32].

Recommendation	LE	GR
Physical examination including DRE should be a routine part of the assessment of male LUTS.	3	B

DRE = digital-rectal examination; LUTS = lower urinary tract symptoms.

3B.5 Urinalysis

Urinalysis (dipstick or sediment) must be included in the primary evaluation of any patient presenting with LUTS to determine conditions, such as UTI, microhaematuria and diabetes mellitus. If abnormal findings are detected further tests are recommended according to other EAU Guidelines, including Guidelines on urinary tract cancers and urological infections [33-36].

Urinalysis is recommended in most Guidelines in the primary management of patients with LUTS [37, 38]. There is limited evidence, yet there is general expert consensus that the benefits outweigh the costs [39]. The value of urinary dipstick/microscopy for diagnosing UTI in LUTS without acute frequency and dysuria has recently been questioned [40].

Recommendation	LE	GR
Urinalysis (by dipstick or urinary sediment) must be used in the assessment of male LUTS.	3	A*

**Upgraded based on Panel consensus. LUTS = lower urinary tract symptoms.*

3B.6 Prostate-specific antigen (PSA)

3B.6.1 PSA and the prediction of prostatic volume

Several reports have demonstrated the reliability of measuring the PSA concentration for predicting prostate volume. The pooled analysis of placebo-controlled BPH trials show that PSA has a good predictive value for assessing prostate volume, with areas under the curve of 0.76 - 0.78 for various prostate volume thresholds (30 mL, 40 mL, and 50 mL). To achieve a specificity of 70%, whilst maintaining a sensitivity between 65-70%, approximate age-specific criteria for detecting men with prostate glands exceeding 40 mL are PSA > 1.6 ng/mL, > 2.0 ng/mL, and > 2.3 ng/mL, for men with BPH in their 50s, 60s, and 70s, respectively [41].

A strong association between PSA and prostate volume was found in a large community-based study in the Netherlands [42]. A PSA threshold value of 1.5 ng/mL could best predict a prostate volume of > 30 mL, with a positive predictive value (PPV) of 78%. The prediction of prostate volume can also be based on total and free PSA. Both PSA forms predict the TRUS prostate volume (\pm 20%) in > 90% of the cases [43, 44].

3B.6.2 PSA and the probability of PCa

The role of PSA in the diagnosis of PCa is presented by the EAU Guidelines on Prostate Cancer [45]. The potential benefits and harms of using serum PSA testing to diagnose PCa in men with LUTS should be discussed.

3B.6.3 PSA and the prediction of BPO-related outcomes

Serum PSA is a stronger predictor of prostate growth than prostate volume [46]. In addition, the PLESS study showed that PSA also predicted the changes in symptoms, QoL/bother, and maximum flow rate (Q_{max}) [47]. In a longitudinal study of men managed conservatively, PSA was a highly significant predictor of clinical progression [48].

In the placebo arms of large double-blind studies, baseline serum PSA predicted the risk of acute urinary retention (AUR) and BPE-related surgery [49, 50]. An equivalent link was also confirmed by the Olmsted County Study. The risk for treatment was higher in men with a baseline PSA of >1.4 ng/mL [51]. Patients with BPO seem to have a higher PSA level and larger prostate volumes. The positive predictive values of PSA for the detection of BPO was recently shown to be 68% [52]. In an epidemiological study, elevated free PSA levels could predict clinical BPH, independent of total PSA levels [53].

Recommendation	LE	GR
PSA measurement should be performed only if a diagnosis of PCa will change the management or if PSA can assist in decision-making in patients at risk of progression of BPE.	1b	A

BPE = benign prostate enlargement; PCa = prostate cancer; PSA = prostate-specific antigen.

3B.7 Renal function measurement

Renal function may be assessed by serum creatinine or estimated glomerular filtration rate (eGFR).

Hydronephrosis, renal insufficiency or urinary retention are more prevalent in patients with signs or symptoms of BPO [54]. Even though BPO may be responsible for these complications, there is no conclusive evidence on the mechanism [55].

One study reported 11% of men with LUTS had renal insufficiency [54]. Neither symptom score nor QoL was associated with the serum creatinine concentration, and diabetes mellitus or hypertension were the most likely causes of the elevated creatinine concentration. Comiter et al. [56] reported that non-neurogenic voiding dysfunction is not a risk factor for elevated creatinine levels. Koch et al. [57] concluded that only those with an elevated creatinine level require investigational ultrasound of the kidney.

In the Olmsted County community-dwelling men, there was a cross-sectional association between signs and symptoms of BPO (though not prostate volume) and chronic kidney disease (CKD) [58]. In 2,741 consecutive patients who presented with LUTS, decreased Q_{max} , a history of hypertension and/or diabetes were associated with CKD [59]. Another study demonstrated a correlation between Q_{max} and eGFR in middle-aged men with moderate-to-severe LUTS [60]. Patients with renal insufficiency are at an increased risk of developing post-operative complications [61].

Recommendation	LE	GR
Renal function assessment must be performed if renal impairment is suspected, based on history and clinical examination or in the presence of hydronephrosis or when considering surgical treatment for male LUTS.	3	A*

**Upgraded based on Panel consensus. LUTS = lower urinary tract symptoms.*

3B.8 Post-void residual urine

Post-void residual (PVR) urine can be assessed by transabdominal US, bladder scan or catheterisation. PVR is not necessarily associated with BOO, since high PVR volumes can be a consequence of obstruction and/or poor detrusor function (detrusor underactivity) [62, 63].

At PVR of 50 mL, the diagnostic accuracy of PVR measurement has a positive predictive value (PPV) of 63% and a negative predictive value (NPV) of 52% to predict BOO [64]. A large PVR measurement is not a contraindication to watchful waiting (WW) or medical therapy, although large PVR may indicate a poor response to treatment and especially to WW. In both the MTOPS and ALTESS studies, a high baseline PVR was associated with an increased risk of symptom deterioration [49, 50].

Monitoring of changes in PVR over time may allow for identification of patients at risk of AUR [50]. This is of particular importance for the treatment of patients using antimuscarinic medication. In contrast, baseline PVR has little prognostic value for the risk of BPE-related invasive therapy in patients on α_1 -blocker or WW [65]. However, due to large test-retest variability and lack of outcome studies, no PVR threshold for treatment decision has yet been established and this is a research priority.

Recommendation	LE	GR
Measurement of post-void residual in male LUTS should be a routine part of the assessment.	3	B

LUTS = lower urinary tract symptoms.

3B.9 Uroflowmetry

Urinary flow rate assessment is a widely used non-invasive urodynamic test that evaluates the functioning of the LUT. Key parameters are Q_{max} and flow pattern. Uroflowmetry parameters should preferably be evaluated with voided volume > 150 mL. Q_{max} is prone to within-subject variation [66, 67]; it is therefore useful to repeat uroflowmetry measurements, especially if the voided volume is < 150 mL, or Q_{max} or flow pattern is abnormal.

The diagnostic accuracy of uroflowmetry for detecting BOO varies considerably, and is substantially influenced by threshold values. A threshold value of Q_{max} of 10 mL/s has a specificity of 70%, a PPV of 70% and a sensitivity of 47% for BOO. The specificity using a threshold Q_{max} of 15 mL/s was 38%, the PPV 67% and the sensitivity 82% [68]. If Q_{max} is ≥ 15 mL/s, physiological compensatory processes mean that BOO cannot be excluded. Low Q_{max} can arise as a consequence of BOO [69], detrusor underactivity or an underfilled bladder [70]. Thus, it is limited as a diagnostic test because it is unable to discriminate between the underlying mechanisms. Specificity can be improved by repeated flow rate testing. Uroflowmetry can be used for monitoring treatment outcomes [71] and correlating symptoms with objective findings.

Recommendation	LE	GR
Uroflowmetry in the initial assessment of male LUTS may be performed and should be performed prior to any treatment.	2b	B

LUTS = lower urinary tract symptoms.

3B.10 Imaging

3B.10.1 Upper urinary tract

Routine imaging of the upper urinary tract in men with LUTS is not recommended, as they are not at increased risk for upper tract malignancy or other abnormalities when compared to the overall population [57, 72-74].

Several arguments support the use of renal US in preference to intravenous urography (IVU).

US allows for a better characterisation of renal masses, the possibility of investigating the liver and retroperitoneum, and simultaneous evaluation of the bladder, PVR and prostate, together with a lower cost, lower radiation dose and less side-effects [72].

Recommendation	LE	GR
Imaging of the upper urinary tract (with US) in men with LUTS should be performed in patients with a large PVR, haematuria or a history of urolithiasis.	3	B

LUTS = lower urinary tract symptoms; PVR = post-void residual; US= ultrasound.

3B.10.2 Prostate

Imaging of the prostate can be performed by transabdominal US, TRUS, computed tomography, and magnetic resonance imaging (MRI). However, in daily practice, prostate imaging is performed by TRUS or transabdominal US [72].

3B.10.2.1 Prostate size and shape

Assessment of prostate size is important for the selection of interventional treatment, i.e. open prostatectomy, enucleation techniques, transurethral resection, TUIP, or minimally invasive therapies. It is also important prior to treatment with 5-ARIs. Prostate volume predicts the development of progressive symptoms and complications [74].

TRUS is superior to suprapubic (transabdominal) volume measurement [75, 76]. The presence of a median lobe may guide treatment choice in patients scheduled for a minimally invasive approach.

Recommendations	LE	GR
When considering medical treatment for male LUTS, imaging of the prostate (either by TRUS or transabdominal US) should be performed if it assists the choice of the appropriate drug.	3	B
When considering surgical treatment, imaging of the prostate (either by TRUS or transabdominal US) should be performed.	3	B

LUTS = lower urinary tract symptoms; TRUS = transrectal ultrasound.

3B.10.3 Prostatic configuration/intravesical prostatic protrusion (IPP)

Prostatic configuration has been evaluated with TRUS, using the concept of the presumed circle area ratio (PCAR) [77]. PCAR evaluates how closely the transverse US image of the prostate approaches a circular shape. The ratio tends toward 1 as the prostate becomes more circular. PCAR sensitivity was 77% for diagnosing BPO when PCAR was > 0.8, with 75% specificity [77].

Ultrasound measurement of intravesical prostatic protrusion (IPP) assesses the distance between the tip of the prostate median lobe and bladder neck in the midsagittal plane, using a suprapubically positioned US scanner, with the bladder volume at 150-250 mL; grade I protrusion is 0-4.9 mm, grade II is 5-10 mm and grade III is >10 mm.

IPP correlates well with BPO (presence and severity) on urodynamic testing, with a PPV of 94% and a NPV of 79% [78]. IPP may correlate with prostate volume, detrusor overactivity, bladder compliance, detrusor pressure at maximum urinary flow, BOO index and PVR, and negatively correlates with Q_{max} [79]. IPP also seems to predict successful outcome of trial without catheter (TWOC) after acute urinary retention [80, 81]. No information with regard to intra- or inter-observer variability and learning curve is yet available. IPP may be a feasible option to infer BPO in men with LUTS. The role of IPP as a non-invasive alternative to pressure flow studies (PFS) in the assessment of male LUTS is under evaluation.

3B.10.4 Bladder/detrusor wall thickness and ultrasound-estimated bladder weight

For bladder wall thickness (BWT) assessment, the distance between the hyperechogenic mucosa and the hyperechogenic adventitia is measured. For detrusor wall thickness (DWT) assessment, the only measurement needed is the hypoechogenic detrusor sandwiched between the hyperechogenic mucosa and adventitia [82].

A significant correlation between BWT and pressure flow studies (PFS) parameters has been reported. A threshold value of 5 mm at the anterior bladder wall with a bladder filling of 150 mL was best at differentiating between patients with or without BOO [83]. DWT at the anterior bladder wall with a bladder filling ≥ 250 mL (threshold value for BOO ≥ 2 mm) has a PPV of 94% and a specificity of 95%, achieving 89%

agreement with PFS [64]. Threshold values of 2.0, 2.5, or 2.9 mm for DWT in patients with LUTS is able to identify 81%, 89%, and 100% of patients with BOO, respectively [84].

All studies found that BWT or DWT measurements have a higher diagnostic accuracy for detecting BOO than Q_{\max} or Q_{ave} of free uroflowmetry, measurements of PVR, prostate volume, or symptom severity. One study could not demonstrate any difference in BWT between patients with normal urodynamics, BOO or detrusor overactivity; however, the study did not use a specific bladder filling volume for measuring BWT [85]. Disadvantages of the method include the lack of standardisation, and lack of evidence to indicate which measurement (BWT/DWT) is preferable [86]. Measurement of BWT/DWT is therefore not recommended for the diagnostic work-up of men with LUTS.

Ultrasound-estimated bladder weight (UEBW) may identify BOO with a diagnostic accuracy of 86% at a cut-off value of 35 g [87, 88]. Severe LUTS and a high UEBW (≥ 35 g) are risk factors for prostate/BPH surgery in men on α -blockers [89]. The role of BWT, DWT and UEBW as a non-invasive alternative to PFS in the assessment of male LUTS or BOO is under evaluation.

3B.10.5 Voiding cysto-urethrogram

Voiding cysto-urethrogram (VCUG) is not recommended in the routine diagnostic work-up of men with LUTS, but it may be useful for the detection of vesico-ureteral reflux, bladder diverticula, or urethral pathologies in selected patients. Retrograde urethrography may additionally be useful for the evaluation of urethral strictures where suspected.

3B.11 Urethrocystoscopy

Patients with a history of microscopic or gross haematuria, urethral stricture, associated risk factors, or bladder cancer, who present with LUTS, should undergo urethrocystoscopy during diagnostic evaluation.

Shoukry et al. evaluated 122 patients with LUTS using uroflowmetry and urethrocystoscopy [90]. The pre-operative Q_{\max} was normal in 25% of 60 patients who had no bladder trabeculation, 21% of 73 patients with mild trabeculation and 12% of 40 patients with marked trabeculation on cystoscopy. All 21 patients who presented with diverticula had an 'obstructive' Q_{\max} .

Anikwe showed that there was no significant correlation between the degree of bladder trabeculation (graded from I to IV), and the pre-operative Q_{\max} value in 39 symptomatic men aged 53-83 years [91]. The largest study published on this issue examined the relation of urethroscopic findings to urodynamic studies in 492 elderly men with LUTS [92]. The authors noted a correlation between cystoscopic appearance (grade of bladder trabeculation and urethral occlusion) and urodynamic indices, detrusor overactivity and low compliance. It should be noted, however, that BOO was present in 15% of patients with normal cystoscopic findings, while 8% of patients had no obstruction, even in the presence of severe trabeculation [92].

Recommendation	LE	GR
Urethrocystoscopy should be performed in men with LUTS to exclude suspected bladder or urethral pathology and/or prior to minimally invasive/surgical therapies if the findings may change treatment.	3	B

LUTS = lower urinary tract symptoms.

3B.12 Urodynamics

In male LUTS, the most widespread invasive urodynamic techniques employed are filling cystometry and PFS. The major goal of urodynamics is to explore the functional mechanisms of LUTS and to identify risk factors for adverse outcomes (for informed/shared decision-making). Most terms and conditions (e.g. detrusor overactivity, low compliance, BOO/BPO, detrusor underactivity) are defined by urodynamic investigation.

3B.12.1 Diagnosing bladder outlet obstruction

PFS are the basis for the definition of BOO, which is characterised by increased detrusor pressure and decreased urinary flow rate during voiding. BOO/BPO has to be differentiated from detrusor underactivity (DUA), which signifies decreased detrusor pressure during voiding in combination with decreased urinary flow rate [2].

Urodynamic testing may also identify detrusor overactivity, which is a urodynamic observation characterised by involuntary detrusor contractions during the filling phase which may be spontaneous or provoked. Overactive bladder is diagnosed from the patient's symptoms, not urodynamic testing, based on the presence of urgency, usually with increased daytime frequency and nocturia [2]. Studies have described an association between BOO and DO [93, 94]. In men with LUTS attributed to BPE, DO was present in 61% and independently associated with BOO grade and ageing [93].

The prevalence of DUA in men with LUTS is 11-40% [95, 96]. Detrusor contractility does not appear to decline in long-term BOO and surgical relief of BOO does not improve contractility [97, 98].

There are no published RCTs in men with LUTS and possible BPO that compare the standard practice investigation (uroflowmetry and PVR measurement) with PFS, but one such study is ongoing in the UK.

Due to the invasive nature of the test, a urodynamic investigation is generally only offered if conservative treatment has failed. The Guidelines Panel attempted to identify specific indications for PFS based on age, findings from the other diagnostic tests, and previous treatments. The Panel allocated a different degree of obligation for PFS in men > 80 years and men < 50 years, which may reflect the lack of evidence. In addition, there was no consensus whether PFS should or may be performed when considering surgery in men with bothersome predominantly voiding LUTS and $Q_{\max} > 10\text{ mL/s}$, although the Panel recognised that with $Q_{\max} < 10\text{ mL/s}$, BOO is likely and PFS are not necessarily needed.

Patients with neurological disease, including those with previous radical pelvic surgery should be assessed according to the EAU Guidelines on Neuro-Urology [99].

3B.12.2 Videourodynamics

Videourodynamics provides additional anatomical information and is primarily recommended if there is uncertainty regarding mechanisms of LUTS.

3B.12.3 Non-invasive pressure-flow testing

The penile cuff method, in which flow is interrupted to estimate isovolumetric bladder pressure), shows promising data, with good test/retest repeatability [100] and interobserver agreement [101], and a nomogram has been derived [102]. A method in which flow is not interrupted is also under investigation [103].

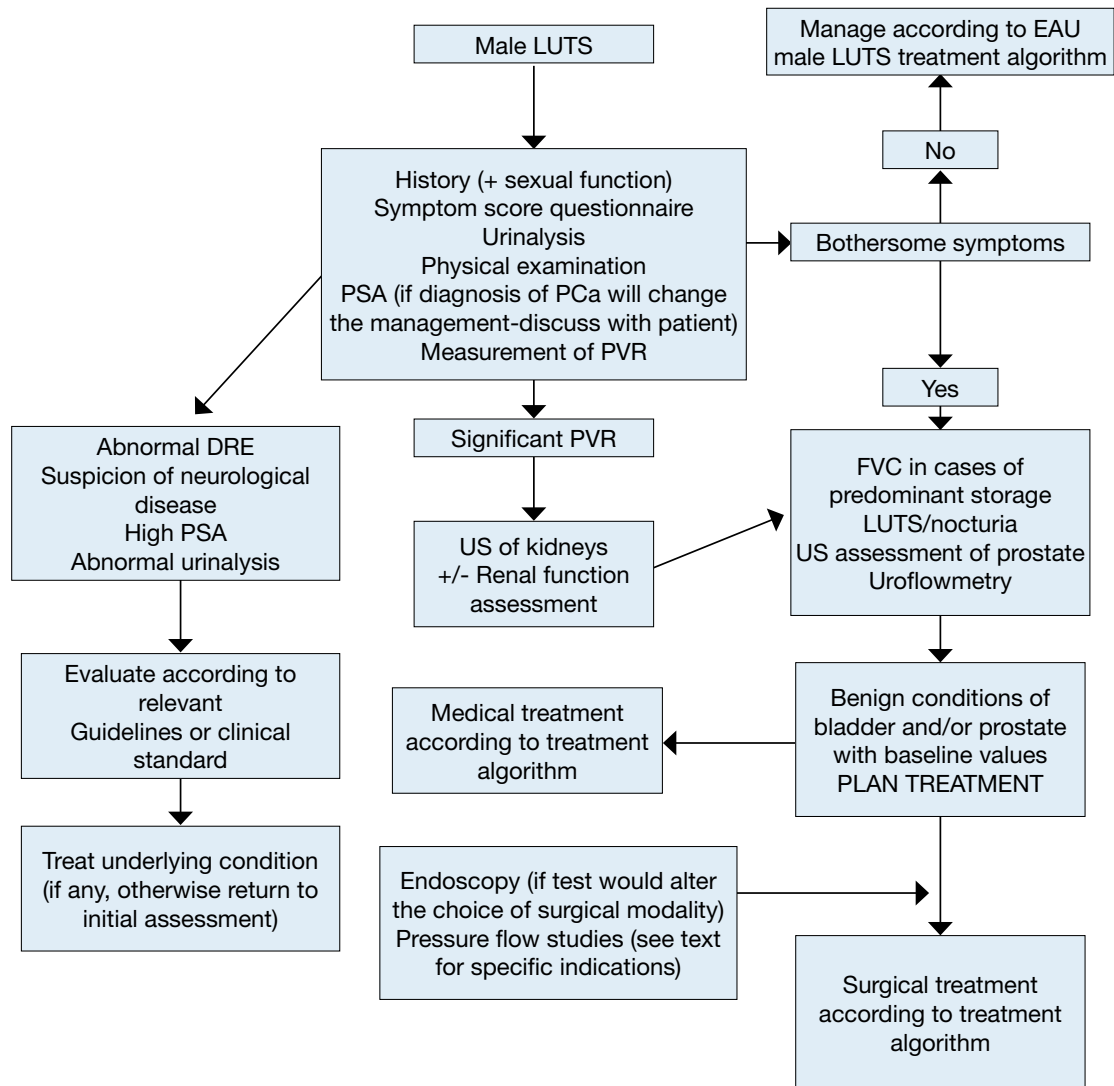
The data generated with the external condom method [104] correlates with invasive PFS in a high proportion [105]. Resistive index [106] and prostatic urethral angle [107] have also been proposed, but are still experimental.

Recommendations	LE	GR
PFS should be performed only in individual patients for specific indications prior to surgery or when evaluation of the underlying pathophysiology of LUTS is warranted.	3	B
PFS should be performed in men who have had previous unsuccessful (invasive) treatment for LUTS.	3	B
When considering surgery, PFS may be used for patients who cannot void > 150 mL.	3	C
When considering surgery in men with bothersome, predominantly voiding LUTS, PFS may be performed in men with a PVR > 300 mL.	3	C
When considering surgery in men with bothersome, predominantly voiding LUTS, PFS may be performed in men aged > 80 years.	3	C
When considering surgery in men with bothersome, predominantly voiding LUTS, PFS should be performed in men aged < 50 years.	3	B

LUTS = lower urinary tract symptoms; PFS = pressure-flow studies, PVR = post-void residual.

Figure 2: Assessment algorithm of LUTS in men aged 40 years or older

Readers are strongly recommended to read the full text that highlights the current position of each test in detail.



DRE = digital-rectal examination; FVC = frequency volume chart; LUTS = lower urinary tract symptoms; PCa = prostate cancer; PSA = prostate specific antigen; PVR = post-void residual; US = ultrasound.

3C DISEASE MANAGEMENT

3C.1 Conservative treatment

3C.1.1 Watchful waiting

Many men with LUTS are not troubled enough by their symptoms to need drug treatment or surgical intervention. All men with LUTS should be formally assessed prior to any allocation of treatment in order to establish symptom severity and to differentiate between men with uncomplicated (the majority) and complicated LUTS. Watchful waiting (WW) is a viable option for many men with non-bothersome LUTS as few will progress to acute urinary retention and complications (e.g. renal insufficiency or stones) [108, 109], and others can remain stable for years [110]. In one study, approximately 85% of men with mild LUTS were stable on WW at one year [111].

A large study comparing WW and transurethral resection of the prostate (TURP) in men with moderate LUTS showed the surgical group had improved bladder function (flow rates and PVR volumes), especially in those with high levels of bother; 36% of WW patients crossed over to surgery within five years, leaving 64% doing well in the WW group [112, 113]. Increasing symptom bother and PVR volumes are the strongest predictors of clinical failure. Men with mild-to-moderate uncomplicated LUTS who are not too troubled by their symptoms are suitable for WW.

3C.1.2 Behavioural and dietary modifications

It is customary for this type of management to include the following components:

- education (about the patient's condition);
- reassurance (that cancer is not a cause of the urinary symptoms);
- periodic monitoring;
- lifestyle advice [110, 111, 114, 115] such as:
 - reduction of fluid intake at specific times aimed at reducing urinary frequency when most inconvenient (e.g. at night or when going out in public);
 - avoidance/moderation of intake of caffeine or alcohol, which may have a diuretic and irritant effect, thereby increasing fluid output and enhancing frequency, urgency and nocturia;
 - use of relaxed and double-voiding techniques;
 - urethral milking to prevent post-micturition dribble;
 - distraction techniques such as penile squeeze, breathing exercises, perineal pressure, and mental tricks to take the mind off the bladder and toilet, to help control storage symptoms;
 - bladder retraining that encourages men to hold on when they have sensory urgency to increase their bladder capacity and the time between voids;
 - reviewing the medication and optimising the time of administration or substituting drugs for others that have fewer urinary effects (these recommendations apply especially to diuretics);
 - providing necessary assistance when there is impairment of dexterity, mobility, or mental state;
 - treatment of constipation.

There now exists evidence (LE: 1b) that self-management as part of WW reduces both symptoms and progression [114, 115] (Table 1). Men randomised to three self-management sessions in addition to standard care had better symptom improvement and QoL than men treated with standard care only for up to a year [115].

Table 1: Self-management as part of watchful waiting reduces symptoms and progression [115]

Trial	Duration (weeks)	Treatment	Patients	IPSS	Q _{max} (mL/s)	PVR (mL)	LE
Brown et al. (2007) [115]	52	Standard care	67	-1.3	-	-	1b
		Standard care plus self-management	73	-5.7 * †	-	-	

IPSS = International Prostate Symptom Score; PVR = post-void residual urine; Q_{max} = maximum urinary flow rate during free uroflowmetry. *significant compared with standard care ($p < 0.05$); †significant compared with baseline ($p < 0.05$).

3C.1.3 Practical considerations

The components of self-management have not been individually studied. The above components of lifestyle advice have been derived from formal consensus methodology [116]. Further research in this area is required.

Recommendations	LE	GR
Men with mild symptoms are appropriate for watchful waiting.	1b	A
Men with LUTS should always be offered lifestyle advice prior to or concurrent with treatment.	1b	A

LUTS = lower urinary tract symptoms.

3C.2 Pharmacological management

3C.2.1 α_1 -Adrenoceptor antagonists (α_1 -blockers)

Mechanism of action: α_1 -blockers aim to inhibit the effect of endogenously released noradrenaline on smooth muscle cells in the prostate and thereby reduce prostate tone and BOO [117]. However, α_1 -blockers have little effect on urodynamically determined bladder outlet resistance [118], and treatment-associated improvement of LUTS is correlated only poorly with obstruction [119]. Thus, other mechanisms of action may be relevant.

α_1 -adrenoceptors located outside the prostate (e.g. urinary bladder and/or spinal cord) and α_1 -adrenoceptor subtypes (α_{1B} - or α_{1D} -adrenoceptors) may play a role as mediators of effects. α_1 -adrenoceptors in blood vessels, other non-prostatic smooth muscle cells, and the central nervous system may mediate adverse events.

α_1 -blockers currently available include: alfuzosin hydrochloride (alfuzosin); doxazosin mesylate (doxazosin); silodosin; tamsulosin hydrochloride (tamsulosin); terazosin hydrochloride (terazosin). α_1 -blockers exist in different formulations (see supplementary online material Table S.3). Although different formulations

result in different pharmacokinetic and tolerability profiles, the overall clinical impact of the different formulations is modest.

Efficacy: Indirect comparisons between α_1 -blockers and limited direct comparisons demonstrate that all α_1 -blockers have a similar efficacy in appropriate doses [120]. Effects take a few weeks to develop fully, but significant efficacy over placebo can occur within hours to days [121].

Controlled studies show that α_1 -blockers typically reduce IPSS by approximately 30-40% and increase Q_{\max} by approximately 20-25% (Table 2). However, considerable improvements also occurred in the corresponding placebo arms [48, 121]. In open-label studies, an IPSS improvement of up to 50% and Q_{\max} increase of up to 40% were documented [48, 121].

α_1 -blockers are able to reduce both storage and voiding LUTS. Prostate size does not affect α_1 -blocker efficacy in studies with follow-up periods of < 1 year, but α_1 -blockers do seem to be more efficacious in patients with smaller prostates (< 40 mL) in longer-term studies [122-125]. α_1 -blocker efficacy is similar across age groups [121]. α_1 -blockers neither reduce prostate size nor prevent acute urinary retention in long-term studies [49, 123-125]; some patients must therefore be treated surgically. Nevertheless, IPSS reduction and Q_{\max} improvement during α_1 -blocker treatment appears to be maintained over at least four years.

Tolerability and safety: Tissue distribution, subtype selectivity, and pharmacokinetic profiles of certain formulations may contribute to the tolerability profile of specific drugs. The most frequent adverse events of α_1 -blockers are asthenia, dizziness and (orthostatic) hypotension. Vasodilating effects are most pronounced with doxazosin and terazosin, and are less common for alfuzosin and tamsulosin [141]. Patients with cardiovascular comorbidity and/or vaso-active co-medication may be susceptible to α_1 -blocker-induced vasodilatation [142]. In contrast, the frequency of hypotension with the α_{1A} -selective blocker silodosin is comparable with placebo [132].

An adverse ocular event termed intra-operative floppy iris syndrome (IFIS) was reported in 2005, affecting cataract surgery [143]. A meta-analysis on IFIS after alfuzosin, doxazosin, tamsulosin or terazosin exposure showed an increased risk for all the α_1 -blockers [144]. However, the odds-ratio for IFIS was much higher for tamsulosin. It appears prudent not to initiate α_1 -blocker treatment prior to scheduled cataract surgery, and the ophthalmologist should be informed about α_1 -blocker use.

A systematic review concluded that α_1 -blockers do not adversely affect libido, have a small beneficial effect on erectile function, but sometimes cause abnormal ejaculation [145]. Originally, abnormal ejaculation was thought to be retrograde, but more recent data demonstrate that it is due to a decrease or absence of seminal fluid during ejaculation, with young age being an apparent risk factor. Abnormal ejaculation has been observed more frequently with tamsulosin and silodosin than with other α_1 -blockers [10, 146]. Silodosin has the highest incidence of abnormal ejaculation; however, efficacy seems to be increased in patients experiencing abnormal ejaculation [146, 147].

Practical considerations: Alpha1-blockers are often considered the first-line drug treatment of male LUTS because of their rapid onset of action, good efficacy, and low rate and severity of adverse events. Ophthalmologists should be informed about α_1 -blocker use prior to cataract surgery.

Recommendation	LE	GR
Alpha1-blockers can be offered to men with moderate-to-severe LUTS.	1a	A

Table 2: Randomised, placebo-controlled trials with α_1 -blockers in men with LUTS

Trials	Duration (weeks)	Treatment (daily dose)	Patients (n)	Change in symptoms (%)	Change in Q_{max} (mL/s)	PVR change (%)	LE
Jardin et al. (1991) [126]	24	Placebo Alfuzosin 3 x 2.5 mg	267 251	-32 ^a -42 ^{a,b}	+1.3 ^a +1.4 ^a	-9 -39 ^{a,b}	1b
Buzelin et al. (1997) [127]	12	Placebo Alfuzosin 2 x 5 mg	196 194	-18 -31 ^{a,b}	+1.1 +2.4 ^{a,b}	0 -17 ^{a,b}	1b
van Kerrebroeck et al. (2000) [128]	12	Placebo Alfuzosin 3 x 2.5 mg Alfuzosin 1 x 10 mg	154 150 143	-27.7 -38.1 ^{a,b} -39.9 ^{a,b}	+1.4 +3.2 ^{a,b} +2.3 ^{a,b}	- - -	1b
MacDonald and Wilt (2005) [129]	4-26	Placebo Alfuzosin: all formulations	1039 1928	-0.9 ^b (Boyarski) [†] -1.8 ^b (IPSS) [†]	+1.2 ^b	-	1a
Kirby et al. (2001) [130]	13	Placebo Doxazosin 1 x 1-8 mg IR Doxazosin 1 x 4-8 mg GITS	155 640 651	-34 ^a -45 ^{a,b} -45 ^{a,b}	+1.1 ^a +2.6 ^{a,b} +2.8 ^{a,b}	- - -	1b
McConnell et al. (2003) [49]	234	Placebo Doxazosin 1 x 4-8 mg	737 756	-29 -39 ^b	+1.4 +2.5 ^{a,b}	- -	1b
Marks et al. (2009) [131]	12	Placebo Silodosin 1 x 8 mg	457 466	-16.0 -30.0 ^b	+1.5 +2.6 ^b	- -	1b
Chapple et al. (2011) [132]	12	Placebo Tamsulosin 1 x 0.4 mg Silodosin 1 x 8 mg	185 376 371	-25.0 -35.0 ^b -37.0 ^b	+2.9 +3.5 +3.7	- - -	1b
Cui et al. (2012) [133]	12	Placebo Tamsulosin 1 x 0.4 mg or 1 x 0.2 mg Silodosin 1 x 8mg or 2 x 4 mg	2543	sign. only vs placebo	sign. only vs placebo	- -	1a
Chapple et al. (1996) [134]	12	Placebo Tamsulosin MR 1 x 0.4 mg	185 364	-25.5 -35.1 ^{a,b}	+0.6 +1.6 ^{a,b}	-13.4 -22.4 ^a	1b
Lepor (1998) [135]	13	Placebo Tamsulosin MR 1 x 0.4 mg Tamsulosin MR 1 x 0.8 mg	253 254 247	-28.1 -41.9 ^{a,b} -48.2 ^{a,b}	+0.5 +1.8 ^{a,b} +1.8 ^{a,b}	- - -	1b
Chapple et al. (2005) [136]	12	Placebo Tamsulosin MR 1 x 0.4 mg Tamsulosin OCAS 1 x 0.4 mg Tamsulosin OCAS 1 x 0.8mg	350 700 354 707	-32 -43.2 ^b -41.7 ^b -42.4 ^b	- - - -	- - - -	1b
Wilt et al. (2002) [137]	4-26	Placebo Tamsulosin 1 x 0.4-0.8 mg	4122	-12 ^b (-1.1 Boyarski [†]) -11 ^b (-2.1 IPSS [†])	+1.1 ^b	-	1a
Brawer et al. (1993) [138]	24	Placebo Terazosin 1 x 1-10 mg	72 69	-11 -42 ^{a,b}	+1.2 +2.6 ^{a,b}	- -	1b
Roehrborn et al. (1996) [139]	52	Placebo Terazosin 1 x 1-10 mg	973 976	-18.4 -37.8 ^{a,b}	+0.8 ^a +2.2 ^{a,b}	- -	1b
Wilt et al. (2002) [140]	4-52	Placebo Terazosin (different doses)	5151	-37 ^b (-2.9 Boyarski [†]) -38 ^b (IPSS [†])	+1.7 ^b	-	1a

GITS = gastrointestinal therapeutic system; IPSS = International Prostate Symptom Score; IR = immediate release; MR = modified-release; OCAS = oral-controlled absorption system; PVR = post-void residual urine; Q_{max} = maximum urinary flow rate (free uroflowmetry). ^asignificant compared with baseline (indexed wherever evaluated); ^bsignificant compared with placebo; [†]absolute value.

3C.2.2 5 α -Reductase inhibitors

Mechanism of action: Androgen effects on the prostate are mediated by dihydrotestosterone (DHT), which is converted from testosterone by the enzyme 5 α -reductase, a nuclear-bound steroid enzyme [148]. Two isoforms of this enzyme exist:

- 5 α -reductase type 1, with minor expression and activity in the prostate but predominant activity in extraprostatic tissues, such as skin and liver.
- 5 α -reductase type 2, with predominant expression and activity in the prostate.

Two 5 α -reductase inhibitors (5-ARIs) are available for clinical use: dutasteride and finasteride (see supplementary online material Table S.4). Finasteride inhibits only 5 α -reductase type 2, whereas dutasteride inhibits 5 α -reductase types 1 and 2 with similar potency (dual 5-ARI). However, the clinical role of dual inhibition remains unclear. 5-ARIs act by inducing apoptosis of prostate epithelial cells [149] leading to prostate size reduction of about 18-28% and circulating PSA levels of about 50% after 6-12 months of treatment [150]. Mean prostate volume reduction and PSA decrease may be even more pronounced after long-term treatment. Continuous treatment reduces the serum DHT concentration by approximately 70% with finasteride and 95% with dutasteride. However, prostate DHT concentration is reduced to a similar level (85-90%) by both 5-ARIs.

Efficacy: Clinical effects relative to placebo are seen after a minimum treatment duration of at least 6-12 months. After two to four years of treatment, 5-ARIs improve IPSS by approximately 15-30%, decrease prostate volume by approximately 18-28%, and increase Q_{\max} by approximately 1.5-2.0 mL/s in patients with LUTS due to prostate enlargement (Table 3) [49, 124, 125, 151-157]. Indirect comparison between individual studies and one direct comparative trial indicate that dutasteride and finasteride are equally effective in the treatment of LUTS [150, 158]. Symptom reduction depends on initial prostate size.

Finasteride may not be more efficacious than placebo in patients with prostates < 40 mL [159]. However, dutasteride seems to reduce IPSS, prostate volume, and the risk of acute urinary retention, and to increase Q_{\max} even in patients with prostate volumes of between 30 and 40 mL at baseline [160, 161]. Comparative studies with α_1 -blockers and a recent meta-analysis have demonstrated that 5-ARIs reduce LUTS slower and that finasteride is less effective than either doxazosin or terazosin, but equally effective compared with tamsulosin [49, 151, 152, 162, 163]. A long-term trial with dutasteride in symptomatic men with prostate volumes >30 mL and increased risk for disease progression showed that dutasteride reduced LUTS at least as much as, or even more effectively than, the α_1 -blocker tamsulosin [124, 157, 164]. The greater the baseline prostate volume (or serum PSA concentration), the faster and more pronounced the symptomatic benefit of dutasteride.

5 α -reductase inhibitors, but not α_1 -blockers, reduce the long-term (>1 year) risk of acute urinary retention (AUR) or need for surgery [49, 155, 165]. In the Proscar Long-Term Efficacy and Safety Study, finasteride treatment reduced the relative risk of AUR by 57%, and surgery by 55% at four years, compared with placebo [155]. In the Medical Therapy of Prostatic Symptoms (MTOPS) study, a significant reduction in the risk of AUR and surgery in the finasteride arm compared with placebo was reported (68% and 64%, respectively) [49].

A pooled analysis of randomised trials with two-year follow-up data, reported that treatment with finasteride significantly decreased the occurrence of AUR by 57%, and surgical intervention by 34%, in moderately symptomatic LUTS [166]. Dutasteride has also demonstrated efficacy in reducing the risks for AUR and BPH-related surgery. Open-label trials have demonstrated relevant changes in urodynamic parameters [167, 168].

Table 3: Randomised trials with 5 α -reductase inhibitors in men with LUTS and benign prostatic enlargement due to BPH

Trials	Duration (weeks)	Treatment (daily dose)	Patients (n)	Change in symptoms (% IPSS)	Change in Q_{max} (mL/s)	Change in prostate volume (%)	LE
Lepor et al. (1996) [151]	52	Placebo	305	-16.5 ^a	+1.4	+1.3	1b
		Finasteride 1 x 5 mg	310	-19.8 ^a	+1.6	-16.9 ^b	
Kirby et al. (2003) [152]	52	Placebo	253	-33.1	+1.4	-	1b
		Finasteride 1 x 5 mg	239	-38.6	+1.8	-	
Andersen et al. (1995) [153]	104	Placebo	346	+1.5	-0.3	+11.5 ^a	1b
		Finasteride 1 x 5 mg	348	-14.9 ^{a,b}	+1.5 ^{a,b}	-19.2 ^{a,b}	
Nickel et al. (1996) [156]	104	Placebo	226	-4.2	+0.3	+8.4 ^a	1b
		Finasteride 1 x 5 mg	246	-13.3 ^{a,b}	+1.4 ^{a,b}	-21.0	
McConnell et al. (1998) [155]	208	Placebo	1503	-8.7	+0.2	+14.0 ^a	1b
		Finasteride 1 x 5 mg	1513	-22.0 ^{a,b}	+1.9 ^{a,b}	-18.0 ^{a,b}	
Marberger et al. (1998) [154]	104	Placebo	1452	-9.8 [†]	0.8	+9.0	1b
		Finasteride 1 x 5 mg	1450	-21.4 ^{†b}	+1.4 ^b	-15.0 ^b	
McConnell et al. (2003) [49]	234	Placebo	737	-23.8	+1.4 ^a	+24.0 ^a	1b
		Finasteride 1 x 5 mg	768	-28.4 ^{a,b}	+2.2 ^{a,b}	-19.0 ^{a,b}	
Roehrborn et al. (2002) [157]	104	Placebo	2158	-13.5 ^a	+0.6	+1.5 ^a	1b
		Dutasteride 1 x 0.5 mg	2167	-26.5 ^{a,b}	+2.2 ^{a,b}	-25.7 ^{a,b}	
Roehrborn et al. (2008) [124]	104	Tamsulosin 1 x 0.4 mg	1611	-27.4 ^a	+0.9	0	1b
		Dutasteride 1 x 0.5 mg	1623	-30.5 ^a	+1.9	-28.0 ^b	
Roehrborn et al. (2010) [125]	208	Tamsulosin 1 x 0.4 mg	1611	-23.2 ^a	+0.7	+4.6	1b
		Dutasteride 1 x 0.5 mg	1623	-32.3 ^a	+2.0	-28.0 ^b	

IPSS = International Prostate Symptom Score; Q_{max} = maximum urinary flow rate (free uroflowmetry)

[†]Boyarski score; ^asignificant compared with baseline (indexed wherever evaluated); ^bsignificant compared with placebo/active control.

Tolerability and safety: The most relevant adverse effects of 5-ARIs are related to sexual function, and include reduced libido, erectile dysfunction and, less frequently, ejaculation disorders such as retrograde ejaculation, ejaculation failure, or decreased semen volume [49, 125, 150]. The incidence of sexual dysfunction and other adverse events is low and even decreased with trial duration. Gynaecomastia (with breast or nipple tenderness) develops in 1-2% of patients.

Data from two trials on prostate cancer chemoprevention (the Prostate Cancer Prevention Trial and the Reduction by Dutasteride of Prostate Cancer Events trial) found a higher incidence of high-grade cancers in the 5-ARIs arms [169, 170]. Although no causal relationship with high-grade prostate cancer has been proven, men taking a 5-ARI should be followed-up regularly using serial PSA testing and any confirmed PSA increase should be evaluated accordingly.

Practical considerations: Treatment with 5-ARIs should be considered in men with moderate-to-severe LUTS and an enlarged prostate (> 40 mL) and/or elevated PSA concentration (> 1.4-1.6 ng/mL). Due to the slow onset of action, they are suitable only for long-term treatment (years). Their effect on the serum PSA concentration needs to be considered for prostate cancer screening. 5 α -reductase inhibitors (finasteride) might reduce blood loss during transurethral prostate surgery, probably due to their effects on prostatic vascularisation [171].

Recommendations	LE	GR
5 α -Reductase inhibitors can be offered to men who have moderate-to-severe LUTS and an enlarged prostate (>40 mL).	1b	A
5 α -Reductase inhibitors can prevent disease progression with regard to acute urinary retention and the need for surgery.	1b	A

LUTS = lower urinary tract symptoms.

3C.2.3 Muscarinic receptor antagonists

Mechanism of action: The detrusor is innervated by parasympathetic nerves whose main neurotransmitter is acetylcholine, which stimulates muscarinic receptors (M-cholinoreceptors) on the smooth muscle cells.

Muscarinic receptors are also present on other cell types, such as bladder urothelial cells, epithelial cells of the salivary glands, or the peripheral or central nervous system. Five muscarinic receptor subtypes (M1-M5) have been described, of which M2 and M3 are predominant in the detrusor. M2 are more numerous, but the M3 subtype is functionally more important in bladder contractions in healthy humans [172, 173]. Antimuscarinic effects might also be induced or modulated through other cell types, such as the bladder urothelium or by central nervous system [174, 175].

The following muscarinic receptor antagonists are licensed for treating overactive bladder/storage symptoms (see supplementary online material Table S.5): darifenacin hydrobromide (darifenacin); fesoterodine fumarate (fesoterodine); oxybutynin hydrochloride (oxybutynin); propiverine hydrochloride (propiverine); solifenacin succinate (solifenacin); tolterodine tartrate (tolterodine); trospium chloride.

Efficacy: Antimuscarinics were mainly tested in females in the past, because it was believed that LUTS in men are caused by the prostate, so should be treated with prostate-specific drugs. However, there is no scientific data for that assumption [176]. A sub-analysis of an open-label trial of OAB patients showed that age but not gender has an impact on urgency, frequency, or urgency incontinence [177].

Efficacy of tolterodine or fesoterodine were tested as single agents in men with OAB in the absence of BOO (Table 4) [178-184]. Most trials lasted only 12 weeks. Four post hoc analyses of large RCTs on the treatment of OAB in women and men without presumed BOO were performed focusing only on the men [179, 181, 184, 185]. Tolterodine can significantly reduce urgency incontinence, daytime or 24-hour frequency, urgency-related voiding, and improve patient perception of treatment benefit. Solifenacin significantly improved mean patient perception of bladder condition scores, mean OAB questionnaire scores, and overall perception of bladder problems. Fesoterodine improved micturition frequency, urgency episodes, and urgency urinary incontinence (UUI) episodes. In open-label trials with tolterodine, daytime frequency, nocturia, UUI, and IPSS were significantly reduced compared with baseline values after 12-25 weeks [180, 183].

In the Tolterodine and Tamsulosin in Men with LUTS including OAB: Evaluation of Efficacy and Safety study, men who received tolterodine monotherapy saw improvement only in urgency incontinence, but not urgency, IPSS (total or storage subscore), or the overall percentage of patients reporting treatment benefit compared with placebo [182].

A further analysis showed that men with PSA levels of <1.3 ng/mL (smaller prostates) might profit more from antimuscarinic drugs [186]. Two other studies found a positive effect of antimuscarinics in patients with OAB and concomitant BPO [183, 187]. In a small RCT without placebo, propiverine improved frequency and urgency episodes [187]. In an open-label study, tolterodine decreased 24-hour micturition, nocturia and American Urological Association Symptom Index scores [183].

Table 4: Trials with antimuscarinic drugs only in elderly men with LUTS, predominantly with OAB symptoms

Trials	Duration (weeks)	Treatment	n	Voiding frequency (%)	Nocturia (%)	Urgency incontinence (%)	IPSS (%)	LE
Kaplan et al. (2005) [183]	25	Tolterodine 1 x 4 mg/d (after α -blocker failure)	43	-35.7 ^a	-29.3 ^a	-	-35.3 ^a	2b
Roehrborn et al. (2006) [184]	12	Placebo	86	-4	-	-40	-	1b
		Tolterodine 1 x 4 mg/d	77	-12	-	-71 ^b	-	
Kaplan et al. (2006) [181]	12	Placebo	374	-7.9	-17.6	-	-	1b
		Tolterodine 1 x 4 mg/d	371	-10.8 ^b	-18.8	-	-	
Kaplan et al. (2006) [182]	12	Placebo	215	-13.5	-23.9	-13	-44.9	1b
		Tolterodine 1 x 4 mg/d	210	-16.5	-20.1	-85 ^b	-54	
Dmochowski et al. (2007) [178]	12	Placebo	374	-5.6	-17.6	-	-	1b
		Tolterodine 1 x 4 mg/d	371	-8.7 ^b	-18.8	-	-	
Höfner et al. (2007) [180]	12	Tolterodine 1 x 4 mg/d	741	-20 ^a	-42.9 ^a	-100 ^a	-37.9 ^a	2b
Herschorn et al. (2010) [179]	12	Placebo	124	-10.2	-	-59.3	-	1b
		Fesoterodine 1 x 4 mg/d	111	-13.2 ^b	-	-84.5 ^b	-	
		Fesoterodine 1 x 8 mg/d	109	-15.6 ^b	-	-100 ^{b,c}	-	

IPSS = International Prostate Symptom Score.

^asignificant compared with baseline ($p < 0.01$; indexed wherever evaluated); ^bsignificant compared with placebo ($p < 0.05$); ^csignificant compared with fesoterodine 4 mg ($p < 0.05$).

Tolerability and safety: Antimuscarinic drug trials generally show approximately 3-10% withdrawals, which is similar to placebo. Drug-related adverse events include dry mouth (up to 16%), constipation (up to 4%), micturition difficulties (up to 2%), nasopharyngitis (up to 3%), and dizziness (up to 5%).

Increased PVR in men without BOO is minimal and similar to placebo. Nevertheless, fesoterodine 8 mg showed higher PVRs (+20.2 mL) than placebo (-0.6 mL) or fesoterodine 4 mg (+9.6 mL) [179]. Incidence of urinary retention in men without BOO was similar to placebo for tolterodine (0-1.3% vs. 0-1.4%). With fesoterodine 8 mg, 5.3% had symptoms, which was higher than placebo or fesoterodine 4 mg (both 0.8%). These symptoms appeared during the first two weeks of treatment and mainly affected men aged 66 years or older.

Antimuscarinics theoretically might decrease bladder strength, and hence might be associated with PVR urine or urinary retention. A 12-week safety study on men with mild to moderate BOO showed that tolterodine increased the PVR (49 mL vs. 16 mL) but not acute urinary retention (3% in both arms) [188]. The urodynamic effects included larger bladder volumes at first detrusor contraction, higher maximum cystometric capacity, and decreased bladder contractility index. Q_{max} was unchanged. This trial indicated that short-term treatment with antimuscarinics in men with BOO is safe [188].

Practical considerations: Not all antimuscarinics have been tested in elderly men, and long-term studies on the efficacy of muscarinic receptor antagonists in men of any age with LUTS are not yet available. In addition, only patients with low PVR volumes at baseline were included in the studies. These drugs should therefore be prescribed with caution, and regular re-evaluation of IPSS and PVR urine is advised.

Recommendations	LE	GR
Muscarinic receptor antagonists may be used in men with moderate-to-severe LUTS who mainly have bladder storage symptoms.	1b	B
Caution is advised in men with BOO.	4	C

BOO = bladder outlet obstruction; LUTS = lower urinary tract symptoms.

3C.2.4 Phosphodiesterase 5 inhibitors

Mechanism of action: PDE type 5 inhibitors (PDE5Is) increase intracellular cyclic guanosine monophosphate, thus reducing smooth muscle tone of the detrusor, prostate and urethra. Nitric oxide and PDEs might also alter reflex pathways in the spinal cord and neurotransmission in the urethra, prostate, or bladder [189]. Moreover, chronic treatment with PDE5I seems to increase blood perfusion and oxygenation in the LUT [190]. Finally, PDE5Is could reduce chronic inflammation in the prostate and bladder [191].

Available drugs: Although clinical trials of several selective oral PDE5Is have been conducted in men with LUTS, only tadalafil (5 mg once daily) has been licensed for the treatment of male LUTS.

Efficacy: Several RCTs have demonstrated that PDE5Is reduce IPSS, storage and voiding LUTS, and QoL (Table 5). Q_{max} increases in a dose-dependent fashion, but is not significantly different from placebo in most trials. In a meta-analysis, PDE5Is were found to improve IPSS and International Index of Erectile Function (IIEF) score, but not Q_{max} [192].

Tadalafil 5 mg reduces IPSS by 22-37% (Table 5), and improvement may be seen within a week of initiation of treatment [193]; the maximum trial (open label) duration was 52 weeks [194]. A subgroup analysis of pooled data demonstrated a significant reduction in LUTS, regardless of baseline severity, age, previous use of α -blockers or PDE5Is, total testosterone level or predicted prostate volume [195]. In a study on sexually active men ≥ 45 years with comorbid LUTS/BPH and ED, tadalafil improved both conditions [196]. Another analysis showed a small but significant increase in Q_{max} , and no significant effect on PVR [197].

The combination of PDE5Is and α -blockers has also been evaluated. A meta-analysis of 5 RCTs (two studies with tadalafil 20 mg, two with sildenafil 25 mg, and one with vardenafil 20 mg), showed that combination therapy significantly improved IPSS score (-1.8), IIEF score (+3.6) and Q_{max} (+1.5 mL/s) compared with α -blockers alone [192]. However, only tadalafil 5 mg has been licensed in the context of LUTS management, so data on combinations of PDE5Is and other LUTS medications are considered insufficient.

Tolerability and safety: Reported adverse effects (AEs) in RCTs comparing the effect of all PDE5Is vs. placebo in men with LUTS include: flushing, gastroesophageal reflux, headache, dyspepsia, back pain and nasal congestion [192]. Discontinuation rate due to AEs for tadalafil is 2.0% [198] and do not differ by age, LUTS severity, testosterone levels, and prostate volume in the pooled data analyses [195].

PDE5Is are contraindicated in patients using nitrates, the potassium channel opener, nicorandil, or α_1 -blockers doxazosin or terazosin. They are also contraindicated in patients who have unstable angina pectoris, have had a recent myocardial infarction (<3 mo) or stroke (<6 mo), myocardial insufficiency (New York Heart Association stage >2), hypotension, poorly controlled blood pressure, significant hepatic or renal insufficiency, or if anterior ischaemic optic neuropathy with sudden loss of vision is known or was reported after previous use of PDE5Is.

Practical considerations: To date, only tadalafil 5 mg once daily has been officially licensed for the treatment of male LUTS with or without erectile dysfunction. The meta-analysis of PDE5Is suggested that younger men with low body mass index and more severe LUTS profit the most from treatment with PDE5Is [192].

Long-term experience with tadalafil in men with LUTS is limited to one trial [194], and therefore conclusions about its efficacy or tolerability >1 year are not possible. There is limited information about reduction of prostate size and none about disease progression.

Recommendations	LE	GR
PDE5Is reduce moderate-to-severe (storage and voiding) LUTS in men with or without erectile dysfunction.	1a	A
Only tadalafil (5 mg once daily) has been licensed for the treatment of male LUTS in Europe.		

LUTS = lower urinary tract symptoms; PDE5I = phosphodiesterase type 5 inhibitors.

Table 5: Efficacy of PDE5Is in adult men with LUTS who participated in high level clinical trials

Trials	Duration (weeks)	Treatment	Patients	IPSS	Q _{max} (mL/s)	PVR (mL)	LE
PDE5Is in monotherapy							
McVary et al. (2007) [199] [‡]	12	Placebo	180	-1.93	+0,16	-	1b
		Sildenafil 1 x 50-100 mg/day or 1 x 50-100 mg before sexual intercourse	189	-6.32*	+0.31	-	
McVary et al. (2007) [200]	12	Placebo	143	-1.7 (-9.3%)	+0.9	-2.6	1b
		Tadalafil 1 x 5-20 mg/day	138	-3.8 (-21.7%)*	+0.5	+1.4	
Roehrborn et al. (2008) [201]	12	Placebo	211	-2.3 (-13.3%)	+1.2	+4.81	1b
		Tadalafil 1 x 2.5 mg/day	208	-3.9 (-22.2%)*	+1.4	+12.1	
		Tadalafil 1 x 5 mg/day	212	-4.9 (-28.2%)*	+1.6	+6.6	
		Tadalafil 1 x 10 mg/day	216	-5.2 (-29.1%)*	+1.6	+10.6	
		Tadalafil 1 x 20 mg/day	209	-5.2 (-30.5%)*	+2.0	-4	
Stief et al. (2008) [202]	8	Placebo	113	-3.6 (-20.0%)	+1.0	+1.92	1b
		Vardenafil 2 x 10 mg/day	109	-5.8 (-34.5%)*	+1.6	-1.0	
Porst et al. (2009) [203] [‡]	12	Placebo	115	-2.1	+1.9	-6.8	1b
		Tadalafil 1 x 2.5 mg/day	113	-3.6*	+1.4	+8.6*	
		Tadalafil 1 x 5 mg/day	117	-4.2*	+1.7	-1.8	
		Tadalafil 1 x 10 mg/day	120	-4.7*	+1.3	+3.8	
		Tadalafil 1 x 20 mg/day	116	-4.7*	+2.0	-14.0	
Egerdie et al. (2012) [204] [‡]	12	Placebo	200	-3.8 (-20.9%)	+1.2	-3.0	1b
		Tadalafil 1 x 2.5 mg/day	198	-4.6 (-25.3%)	+1.7*	-8.4	
		Tadalafil 1 x 5 mg/day	208	-6.1* (-33,0%)	+1.6	-2.0	
Oelke et al. (2012) [193] [‡]	12	Placebo	172	-4.2 (-24.1%)	+1.2	-1.2	1b
		Tamsulosin 1 x 0.4 mg/day	168	-5.7* (-33.9%)	+2.2*	-10.2	
		Tadalafil 1 x 5 mg/day	171	-6.3* (-36.6%)	+2.4*	-4.6	
Yokoyama et al. (2012) [205] [‡]	12	Placebo	154	-3.0 (-17.9%)	+2.2	-1.2	1b
		Tadalafil 1 x 2.5 mg/day	151	-4.8* (-28.9%)	+1.6	-0.1	
		Tadalafil 1 x 5 mg/day	155	-4.7* (-27.3 %)	+1.3	-2.9	
Meta-analysis on PDE5Is							
Gacci et al. (2012) [192]	6-12	Placebo	964				1a
		PDE5I (any)	2250	Δ -2.8*	0.0	-	
		α ₁ -blocker	107				
		α ₁ -blocker + PDE5I	109	Δ -1.8*	Δ +1.5*		

IPSS = International Prostate Symptom Score; Q_{max} = maximum urinary flow rate during free uroflowmetry; PVR = post-void residual urine; [‡]trial included patients with both erectile dysfunction and LUTS; *significant compared with placebo (p ≤ 0.05); [†]significant compared with baseline (p ≤ 0.05 [indexed wherever evaluated]); [°]significant compared with PDE5I alone; *significant compared with α₁-blocker alone.

3C.2.5 **Plant extracts - phytotherapy**

Mechanism of action: Herbal drug preparations are made of roots, seeds, pollen, bark, or fruits of a single plant (mono-preparations); others combine the extracts of two or more plants to one pill (combination preparations). The most widely used plants are: *Cucurbita pepo* (pumpkin seeds), *Hypoxis rooperi* (South African star grass), *Pygeum africanum* (bark of the African plum tree), *Secale cereale* (rye pollen), *Serenoa repens* (syn. *Sabal serrulata*; berries of the American dwarf palm, saw palmetto) and *Urtica dioica* (roots of the stinging nettle).

Possible relevant compounds include phytosterols, β -sitosterol, fatty acids, and lectins [206]. In vitro, plant extracts can have anti-inflammatory, anti-androgenic and oestrogenic effects; decrease sexual hormone binding globulin; inhibit aromatase, lipoxygenase, growth factor-stimulated proliferation of prostatic cells, α -adrenoceptors, 5 α -reductase, muscarinic cholinceptors, dihydropyridine receptors and vanilloid receptors; and neutralise free radicals [206-208]. These effects have not been confirmed in vivo, and the precise mechanisms of action of plant extracts remain unclear.

Efficacy: The extracts of the same plant produced by different companies do not necessarily have the same biological or clinical effects and so the effects of one brand cannot be extrapolated to others [209]. Batches from the same producer might contain different concentrations of active ingredients [210]. Thus the pharmacokinetic properties can vary significantly.

Table 6 presents the trials with the highest LE for each plant extract. In general, no phytotherapeutic agent has been shown to reduce prostate size, and no trial has proven a reduction of BOO or a decrease in disease progression. Analysis of each drug class can be found in the supplementary online material (see www.uroweb.org/guidelines).

Cochrane meta-analyses suggest that a) men treated with *Pygeum africanum* were twice as likely to report symptom improvement, b) men treated with *Secale cereale* were twice as likely to benefit from therapy compared to placebo and c) *Serenoa repens* was not superior to placebo, finasteride, or tamsulosin for IPSS (similar levels of IPSS improvements in trials with finasteride or tamsulosin might be interpreted as treatment equivalence) [211-213].

Table 6: Trials with plant extracts in patients with BPH-LUTS (selection)

Trials	Duration (weeks)	Treatment	Patients (n)	Change symptoms (IPSS)[†]	Change Q_{max} (mL/s)	PVR (mL)	LE
Bach (2000) [214]	52	Placebo	243	-5.5	NS	NS	1b
		<i>Cucurbita pepo</i> (Prosta Fink TM forte)	233	-6.7 ^a	NS	NS	
Berges et al. (1995) [215]	24	Placebo	100	-2.3	+1.1	-16.8	1b
		<i>Hypoxis rooperi</i> (Harzol TM)	100	-7.4 ^a	+5.2 ^a	-35.4 ^a	
Klippel et al. (1997) [216]	26	Placebo	89	-2.8	+4.3	-4.1	1b
		<i>Hypoxis rooperi</i> (Azuprost TM)	88	-8.2 ^a	+8.8 ^a	-37.5 ^a	
Wilt et al. (2000) [217]	4-26	Placebo	475	-4.9 ^b	+3.9 ^b	-28.6 ^b	1a
		<i>Hypoxis rooperi</i>					
Wilt et al. (2002) [212]	4-18	Placebo	1562	RR 2.07 ^b	+2.5 ^b	-13.2 ^b	1a
		<i>Pygeum africanum</i> (β-sitosterol)					
Wilt et al. (2000) [213]	12-24	Placebo	444	RR 2.4 ^b	-1.6	-14.4	1a
		<i>Secale cereale</i> (Cernilton TM)					
Tacklind et al. (2012) [211]	6-18	Placebo	661	-0.16 ^b NS	+0.40 ^b NS	NA	1a
		<i>Serenoa repens</i>					
Tacklind et al. (2012) [211]	6-18	Tamuslosin	582	-0.52 ^b NS	+0.14 ^b NS	NA	1a
		<i>Serenoa repens</i>					
Carraro et al. (1996) [218]	26	Finasteride	545	-6.2	+3.2 ^a	-	1b
		<i>Serenoa repens</i> (Permixon TM)	553	-5.8	+2.7	-	
Safarinejad (2005) [219]	26	Placebo	316	-1.5	+3.4	0	1b
		<i>Urtica dioica</i>	305	-8.0 ^a	+8.2 ^a	-37	
Lopatkin et al. (2005) [220]	24	Placebo	126	-4.0	+1.9	-	1b
		<i>Sabal serrulata</i> + <i>Urtica dioica</i> (Prostatgutt TM forte)	127	-6.0 ^b	+1.8	-	
Sökeland and Albrecht (1997) [221]	48	Finasteride	244	-5.6	+2.8	-17.1	1b
		<i>Sabal serrulata</i> + <i>Urtica dioica</i> (Prostatgutt TM forte)	245	-4.8	+2.0	-10.2	

IPSS = International Prostate Symptom Score; n = number of patients; NA = not available; NS = not significant; PVR = post-void residual urine; Q_{max} = maximal urinary flow rate (free uroflowmetry); RR = relative risk.

[†]absolute values; ^asignificant reduction compared with placebo/comparison treatment arm (p < 0.05);

^bin favour of plant extract.

Tolerability and safety: Side-effects during phytotherapy are generally mild and comparable to placebo. Serious adverse events were not related to study medication. Gastrointestinal complaints were the most commonly reported. In formulations with *Hypoxis rooperi*, erectile dysfunction appeared in 0.5% of patients.

Practical considerations: Phytotherapeutic agents are a heterogeneous group and may contain differing concentrations of the active ingredient(s). Hence, meta-analyses do not seem to be justified and results of any analyses have to be interpreted with caution.

Recommendations: The Guidelines Panel have not made any specific recommendations on phytotherapy for the treatment of male LUTS because of product heterogeneity, limited regulatory framework, and methodological limitations of the published trials and meta-analyses.

3C.2.6 Vasopressin analogue - desmopressin

Mechanism of action: The antidiuretic hormone arginine vasopressin (AVP) regulates water homeostasis. It controls urine production through the V2 receptor in the renal collecting ducts. AVP increases water re-absorption and urinary osmolality, while decreasing water excretion and total urine volume. AVP also has V1 receptor mediated vasoconstrictive/hypertensive effects and a very short serum half-life, so is unsuitable as a treatment for nocturnal polyuria.

Desmopressin is a synthetic analogue of AVP with high V2 receptor affinity and antidiuretic properties, but has no relevant V1 receptor affinity or hypertensive effects. Desmopressin may be used by intravenous infusion, nasal spray, tablet or 'melt' formulation. Nasally or orally administered desmopressin is rapidly absorbed, and excreted 55% unchanged by the kidneys [222]. Desmopressin has been used for more than 30 years for diabetes insipidus or primary nocturnal enuresis, and it is approved in most European countries for the treatment of nocturia secondary to nocturnal polyuria in adults (see supplementary online material Table S.6).

Efficacy: Desmopressin significantly reduced nocturnal diuresis by approximately 0.6-0.8 mL/min (-40%), decreased the number of nocturnal voids by approximately 0.8-1.3 (-40%), and extended the time until the first nocturnal void by 1.6-2.1 hours (Table 7). Furthermore, desmopressin significantly reduced night-time urine volume, and the percentage of urine volume excreted at night [223-225].

A meta-analysis found that desmopressin significantly reduced the overall number of nocturnal voids and increased hours of undisturbed sleep. However, the RCTs were conducted in heterogeneous populations, using varied dosages [23].

The clinical effects of desmopressin were more pronounced in patients with more severe nocturnal polyuria and normal bladder capacity at baseline. The 24-hour diuresis remained unchanged during desmopressin treatment [226]. The clinical effects were stable over a follow-up period of 10-12 months and returned to baseline values after cessation of the trial [223].

Tolerability and safety: The most frequent adverse events in short-term (up to three weeks) and long-term studies (12 months) were headache, nausea, diarrhoea, abdominal pain, dizziness, dry mouth and hyponatraemia (serum sodium concentration of <130 mmol/L). Peripheral oedema (2%) and hypertension (5%) were reported in the long-term treatment trial [223].

Hyponatraemia, not necessarily associated with symptoms, occurs in 5.0-7.6% of patients soon after treatment initiation [235, 236]. The risk of developing hyponatraemia significantly increases with age (odds ratio 1.16 per year of age), lower serum sodium concentration at baseline (odds ratio 0.76), and higher basal 24-hour urine volume per bodyweight (odds ratio 1.09) [235]. The risk of hyponatraemia in patients < 65 years is < 1%; for older patients with normal sodium concentration it is 8%, but it is up to 75% in old patients with low sodium concentration at baseline [235]. A recent subanalysis suggests that oral doses of 50-100µg desmopressin (melt) are safe in men [237].

At the time of treatment initiation or dose change, older men with normal values of serum sodium should be monitored by Na⁺ measurement at day three and day seven of treatment, and one month later. If serum sodium concentration has remained normal and no dose adjustment is intended, Na⁺ should be monitored every three to six months thereafter [238]. Patients should be informed about the symptoms of hyponatraemia, (headache, nausea or insomnia).

Practical considerations

Desmopressin is taken once daily before sleeping. Because the optimal dose differs between patients, desmopressin treatment should be initiated at a low dose (0.1 mg/day) and may be gradually increased up to a dosage of 0.4 mg/day every week until maximum efficacy is reached. Patients should avoid drinking fluids at least one hour before and for eight hours after dosing. In men aged 65 years or older, desmopressin should not be used if the serum sodium concentration is below normal.

Recommendation	LE	GR
Vasopressin analogue can be used for the treatment of nocturia due to nocturnal polyuria.	1b	A

Table 7: Clinical trials with desmopressin in adult men with nocturnal polyuria

Trials	Duration (weeks)	Treatment (oral daily dose before bedtime, unless otherwise indicated)	Patients (n)	Change nocturnal urine volume (mL/min)	Change nocturnal voids (n)	Time to first void (hours)	LE
Asplund et al. (1998) [227]	3	1 x 0.1 mg	23*	-0.5 (-31%)	-	-	2b
		1 x 0.2 mg	23*	-0.7 (-44%)	-	-	
		2 x 0.2 mg	23*	-0.6 (-38%)	-	-	
Cannon et al. (1999) [228]	6	Placebo	20	-	+0.1 (+3%)	-	1b
		1 x 20 µg intranasal	20	-	-0.3 (-10%)	-	
		1 x 40 µg intranasal	20	-	-0.7 (-23%) ^a	-	
Asplund et al. (1999) [226]	2	Placebo	17*	-0.2 (-11%)	-0.2 (-11%)	+0.2	1b
		1 x 0.1-0.4 mg	17*	-0.8 (-44%) ^a	-0.8 (-42%) ^a	+1.6	
Chancellor et al. (1999) [229]	12	1 x 20-40 µg intranasal	12	-	-1.8 (-50%)	-	2b
Mattiasson et al. (2002) [224]	3	Placebo	65	-0.2 (-6%)	-0.5 (-12%)	+0.4	1b
		1 x 0.1-0.4 mg	86	-0.6 (-36%) ^a	-1.3 (-43%) ^a	+1.8 ^a	
Kuo 2002 [230]	4	1 x 0.1 mg	30*	-	-2.72 (-48.5)	-	2b
Rembratt et al. (2003) [231]	0.5	1 x 0.2 mg	72*	-0.5	-1.0	+1.9	2b
van Kerrebroeck et al. (2007) [225]	3	Placebo	66	-	-0.4 (-15%)	+0.55	1b
		1 x 0.1-0.4 mg	61	-	-1.25 (-39%) ^a	+1.66 ^a	
Lose et al. (2004) [223] [‡]	52	1 x 0.1-0.4 mg	132	-	-2.0	+2.3	2b
Wang et al. (2011) [232]	52	Placebo	58		-	-	1b
		1 x 0.1 mg	57	Δ141 mL	-	+0.5 ^a	
Weiss et al. (2012) [233] [‡]	4	Placebo	90	-125 mL	-0.84	40 min	1b
		1 x 10 µg	82	-125 mL	-0.54	48 min	
		1 x 25 µg	87	-163 mL	-0.83	61 min	
		1 x 50 µg	77	-286 mL ^a	-1.13	72 min	
		1 x 100 µg	80	-306 mL ^a	-1.38 ^a	100 min ^a	
Weiss et al (2013) [234]	12	Placebo	142	-130.9 mL	-0.88	72.9	1b
		1 x 50 µg	119	-208.7 mL ^a	-1.25 ^a	111.8 ^a	
		1 x 75 µg	124	-217.1 mL ^a	-1.29 ^a	115.6 ^a	

*The majority of study participants were male; ‡male data only; ^asignificant compared with placebo.

3C.2.7 Emerging therapies

3C.2.7.1 Beta-3 agonists

Mechanism of action: Beta-3 adrenoceptors are the predominant beta receptors expressed in the smooth muscle cells of the detrusor and their stimulation is thought to induce detrusor relaxation.

Efficacy: Mirabegron 50 mg is the first clinically available beta-3 agonist and has received approval for use in adults with OAB. Mirabegron has undergone extensive evaluation in three 12-week, RCTs conducted in Europe, Australia, and North America and a further 12-month randomised, double-blind, active treatment-controlled, study in OAB patients [239-242]. Mirabegron at daily doses of 25, 50, and 100 mg demonstrated significant efficacy in treating the symptoms of OAB, including micturition frequency, urgency incontinence, and urgency and also patient perception of treatment benefit.

Tolerability and safety: The most common treatment-related adverse events in the mirabegron groups were hypertension, urinary tract infection, headache and nasopharyngitis [239-242]. The proportion of patients with

dry mouth and constipation in the mirabegron groups was notably lower than reported in RCTs of other OAB agents or of the active control tolterodine [239]. Evaluation of urodynamic parameters in men with combined BOO and OAB concluded that mirabegron did not adversely affect voiding urodynamic parameters compared to placebo in terms of Q_{\max} , detrusor pressure at maximum flow and bladder contractility index [243].

Practical considerations: Long-term studies on the efficacy and safety of mirabegron in men of any age with LUTS are not yet available. Studies on the use of mirabegron in combination with other pharmacotherapeutic agents for male LUTS are still pending.

Recommendation	LE	GR
Beta-3 agonists may be used in men with moderate-to-severe LUTS who have predominantly bladder storage symptoms.	1b	B

LUTS = lower urinary tract symptoms.

3C.2.8 Combination therapies

3C.2.8.1 α_1 -blockers + 5 α -reductase inhibitors

Mechanism of action: Combination therapy consists of an α_1 -blocker (Section 3C.2.1) together with a 5-ARI (Section 3C.2.2). The α_1 -blocker exhibits clinical effects within hours or days, whereas the 5-ARI needs several months to develop significant clinical efficacy. Finasteride has been tested in clinical trials with alfuzosin, doxazosin or terazosin, and dutasteride with tamsulosin.

Efficacy: Several studies have investigated the efficacy of combination therapy against an α_1 -blocker, 5-ARI or placebo alone (Table 8). Initial studies with follow-up periods of 6-12 months demonstrated that the α_1 -blocker was superior to finasteride in symptom reduction, whereas combination was not superior to α_1 -blocker alone [151, 152, 162]. In studies with a placebo arm, the α_1 -blocker was consistently more effective than placebo, but finasteride was not. Data at one year in the MTOPS study (published but not specifically analysed for this timepoint), showed similar results [49].

Long-term data (4 years) from MTOPS, and Combination of Avodart and Tamsulosin (CombAT) trials showed that combination treatment is superior to monotherapy for symptoms and Q_{\max} , and superior to α -blocker in reducing the risk of acute urinary retention or need for surgery [49, 124, 125].

The CombAT study demonstrated that combination treatment is superior to either monotherapy for symptoms and flow rate starting from month nine, and superior to α_1 -blocker for acute urinary retention and the need for surgery after month eight [125]. The different results between the CombAT and MTOPS trials may reflect different inclusion and exclusion criteria, rather than the specific drugs used.

Discontinuation of the α_1 -blocker after six to nine months of combination therapy was investigated by an RCT and an open-label multicentre trial [244, 245]. The first trial evaluated the combination of tamsulosin with dutasteride and the impact of tamsulosin discontinuation after six months [244], with almost three-quarters of patients reporting no worsening of symptoms. However, patients with severe symptoms (IPSS > 20) at baseline may benefit from longer combination therapy.

A more recently published trial evaluated the symptomatic outcome of finasteride monotherapy at three and nine months after discontinuation of nine-month combination therapy [245]. LUTS improvement after combination therapy was sustained at three months (IPSS difference 1.24) and nine months (IPSS difference 0.44). However, the main limitations of the studies include the short duration and the short follow-up period after discontinuation.

In both the MTOPS and CombAT trials, combination therapy was superior to monotherapy in preventing clinical progression as defined by an IPSS increase of at least four points, acute urinary retention, urinary tract infection, incontinence, or an increase in creatinine >50%. The MTOPS study found that the risk of long-term clinical progression (primarily due to increasing IPSS) was reduced by 66% with combined therapy (vs placebo) and to a greater extent than with either finasteride or doxazosin monotherapy (34% and 39%, respectively) [49]. In addition, finasteride (alone or in combination), but not doxazosin, significantly reduced both the risks of AUR and the need for BPH-related surgery over the four-year study. In the CombAT study, combination therapy reduced the relative risks of AUR by 68%, BPH-related surgery by 71%, and symptom deterioration by 41% compared with tamsulosin, after four years [246].

Table 8: Randomised trials using α_1 -blocker, 5 α -reductase inhibitor, and the combination of both drugs in men with LUTS and benign prostatic enlargement due to BPH

Trials	Duration (weeks)	Treatment (daily dose)	Patients (n)	Symptom change (% IPSS)	Change in Q_{max} (mL/s)	Change in prostate volume (%)	LE
Lepor et al. (1996) [151]	52	Placebo	305	-16.5 ^a	+1.4	+1.3	1b
		Terazosin 1 x 10 mg	305	-37.7 ^{a,b,d}	+2.7 ^{b,d}	+1.3	
		Finasteride 1 x 5 mg	310	-19.8 ^a	+1.6	-16.9 ^{b,c}	
		Terazosin 1 x 10 mg + finasteride 1 x 5 mg	309	-39.0 ^{a,b,d}	+3.2 ^{b,d}	-18.8 ^{b,c}	
Debruyne et al. (1998) [162]	26	Alfuzosin 2 x 5 mg	358	-41.2 ^d	+1.8	-0.5	1b
		Finasteride 1 x 5 mg	344	-33.5	+1.8	-10.5 ^c	
		Alfuzosin 2 x 5 mg + finasteride 1 x 5 mg	349	-39.1 ^d	+2.3	-11.9 ^c	
Kirby et al. 2003 [152]	52	Placebo	253	-33.1	+1.4	-	1b
		Doxazosin 1 x 1-8 mg	250	-49.1 ^{b,d}	+3.6 ^{b,d}	-	
		Finasteride 1 x 5 mg	239	-38.6	+1.8	-	
		Doxazosin 1 x 1-8 mg + finasteride 1 x 5 mg	265	-49.7 ^{b,d}	+3.8 ^d	-	
McConnell et al. (2003) [49]	234	Placebo	737	-23.8 ^a	+1.4 ^a	+24.0 ^a	1b
		Doxazosin 1 x 1-8 mg	756	-35.3 ^{a,b,d}	+2.5 ^{a,b}	+24.0 ^a	
		Finasteride 1 x 5 mg	768	-28.4 ^{a,b}	+2.2 ^{a,b}	-19.0 ^{a,b,c}	
		Doxazosin 1 x 1-8 mg + finasteride 1 x 5 mg	786	-41.7 ^{a,b,c,d}	+3.7 ^{a,b,c,d}	-19.0 ^{a,b,c}	
Roehrborn et al. (2008) [124]	104	Tamsulosin 1 x 0.4 mg	1611	-27.4	+0.9	0.0	1b
		Dutasteride 1 x 0.5 mg	1623	-30.5	+1.9	-28.0 ^c	
		Tamsulosin 1 x 0.4 mg + dutasteride 1 x 0.5 mg	1610	-39.2 ^{c,d}	+2.4 ^{c,d}	-26.9 ^c	
Roehrborn et al. (2010) [125]	208	Tamsulosin 1 x 0.4 mg	1611	-23.2	+0.7	+4.6	1b
		Dutasteride 1 x 0.5 mg	1623	-32.3	+2.0	-28.0 ^c	
		Tamsulosin 1 x 0.4 mg + dutasteride 1 x 0.5 mg	1610	-38.0 ^{c,d}	+2.4 ^c	-27.3 ^c	

Note: [124] and [125] reflect different timepoints in the same study

IPSS = International Prostate Symptom Score; Q_{max} = maximum urinary flow rate (free uroflowmetry).

^asignificant compared with baseline (indexed wherever evaluated); ^bsignificant compared with placebo;

^csignificant compared with α -blocker monotherapy; ^dsignificant compared with 5 α -reductase inhibitor monotherapy.

Tolerability and safety: Adverse events for both drug classes have been reported with combination treatment [49, 124, 125]. The adverse events observed during combination treatment were typical of α_1 -blockers and 5-ARIs. The frequency of adverse events was significantly higher for combination therapy.

Practical considerations: Compared with α_1 -blockers or 5-ARI monotherapy, combination therapy results in a greater improvement in LUTS and increase in Q_{max} , and is superior in prevention of disease progression. However, combination therapy is also associated with more adverse events. Combination therapy should therefore be prescribed primarily in men who have moderate-to-severe LUTS and are at risk of disease progression (higher prostate volume, higher PSA concentration, advanced age, etc.). Combination therapy should only be used when long-term treatment (more than 12 months) is intended; this issue should be discussed with the patient before treatment. Discontinuation of the α_1 -blocker after six months might be considered in men with moderate LUTS.

Recommendation	LE	GR
Combination treatment with an α_1 -blocker together with a 5 α -reductase inhibitor can be offered to men with troublesome moderate-to-severe LUTS, enlarged prostate and reduced Q_{max} (men likely to develop disease progression).	1b	A

Q_{max} = maximum urinary flow rate.

3C.2.8.2 α_1 -blockers + muscarinic receptor antagonists

Mechanism of action: Combination treatment consists of an α_1 -blocker together with an antimuscarinic aiming to antagonise both α_1 -adrenoceptors and muscarinic receptors. The possible combinations have not all been tested in clinical trials yet.

Efficacy: Several RCTs and prospective studies investigated combination therapy, lasting 4-12 weeks, either as an initial treatment in men with OAB and presumed BPO or as a sequential treatment for storage symptoms persisting while on an α_1 -blocker [182, 183, 246-253] (Table 9). One trial used the α_1 -blocker naftopidil (not registered in most European countries) with and without antimuscarinics [254].

Combination treatment is more efficacious in reducing urgency, UII, voiding frequency, nocturia, or IPSS compared with α_1 -blockers or placebo alone, and improves QoL [182]. Symptom improvement is higher regardless of PSA concentration, whereas tolterodine alone improved symptoms mainly in men with a serum PSA of < 1.3 ng/mL [186].

Persistent LUTS during α_1 -blocker treatment can be reduced by the additional use of an antimuscarinic, especially when detrusor overactivity is demonstrated [183, 246, 250, 253]. Two systematic reviews of the efficacy and safety of antimuscarinics in men suggested that combination treatment provides significant benefit [255, 256].

Table 9: Efficacy of muscarinic receptor antagonists together with α_1 -blockers

Trials	Duration (weeks)	Treatment	Patients (n)	Voiding frequency (%)	Nocturia (%)	IPSS (%)	LE
Saito et al. (1999) [247]	4	Tamsulosin 1 x 0.2 mg/d	59	-29.6	-22.5	-	1b
		Tamsulosin 1 x 0.2 mg/d + propiverine 1 x 20.0 mg/d	75	-44.7	-44.4 ^a	-	
Lee et al. (2005) [249]	8	Doxazosin 1 x 4.0 mg/d	67	-11.8	-37.5	-54.9	1b
		Doxazosin 1 x 4.0 mg/d + propiverine 1 x 20.0 mg/d	131	-27.5 ^a	-46.7	-50.7	
Kaplan et al. (2006) [182]	12	Placebo	215	-13.5	-23.9	-44.9	1b
		Tolterodine 1 x 4.0 mg/d	210	-16.5	-20.1	-54.0	
		Tamsulosin 1 x 0.4 mg/d	209	-16.9	-40.3	-64.9 ^b	
		Tolterodine 1 x 4.0 mg/d + tamsulosin 1 x 0.4 mg/d	217	-27.1 ^b	-39.9 ^b	-66.4 ^b	
MacDiarmid et al. (2008) [252]	12	Tamsulosin 1 x 0.4 mg/d + placebo	209	-	-	-34.9	1b
		Tamsulosin 1 x 0.4 mg/d + oxybutynin 1 x 10.0 mg/d	209	-	-	-51.9 ^b	
Kaplan et al. (2005) [183] [‡]	25	Tolterodine 1 x 4.0 mg/d	43	-35.7 ^a	-29.3 ^a	-35.3	2b
Yang et al. (2007) [253] [‡]	6	Tolterodine 2 x 2.0 mg/d	33	-	-	-35.7 ^a	2b
Chapple et al. (2009) [250] [‡]	12	Tolterodine ER 4.0 mg/d + α -blocker	283	-15.8 ^b	-29.4	-25.1	1b
		Placebo + α -blocker	292	-10.5	-23.5	-23.5	
Kaplan et al. (2009) [251] [‡]	12	Tamsulosin 1 x 0.4 mg/d + placebo	195	-6.2 ^a	-	-29.0	1b
		Tamsulosin 1 x 0.4 mg/d + solifenacin 5.0 mg/d	202	-9.1 ^a	-	-31.8	
Kaplan et al. (2013) [257]	12	Tamsulosin 0.4 mg + solifenacin 6 mg	74	-17.8	-	-45.7	1b
		Tamsulosin 0.4 mg + solifenacin 9 mg	74	-17.8	-	-39.0	
		Placebo	74	-9.5	-	-36.0	

ER = extended-release; IPSS = International Prostate Symptom Score.

^asignificant compared with baseline ($p \leq 0.05$, indexed wherever evaluated); ^bsignificant reduction compared with placebo ($p < 0.05$); [‡]persisting LUTS during α_1 -blocker treatment (add-on approach).

Tolerability and safety: Adverse events of both drug classes are seen with combined treatment using

α_1 -blockers and antimuscarinics. The commonest side-effect is xerostomia. Some side-effects (e.g. xerostomia or ejaculation failure) may show increased incidence which cannot simply be explained by summing the incidence with the drugs used separately. Increased PVR may be seen, but is usually not clinically significant, and risk of AUR is low [255, 256].

A recent RCT investigated safety in terms of maximum detrusor pressure and Q_{\max} for solifenacin (6 mg or 9 mg) with tamsulosin in men with LUTS and BOO compared with placebo [257]. The combination therapy was not inferior to placebo for the primary urodynamic variables; Q_{\max} was increased versus placebo [257].

Practical considerations: Class effects are likely to underlie efficacy and QoL using an α_1 -blocker and antimuscarinic. Trials used mainly storage symptom endpoints, were of short duration, and included only men with low PVR volumes at baseline. Therefore, measuring PVR is recommended during combination treatment.

Recommendations	LE	GR
Combination treatment with an α_1 -blocker together with a muscarinic receptor antagonist may be used in patients with troublesome moderate-to-severe LUTS if relief of storage symptoms has been insufficient with monotherapy with either drug.	1b	B
Combination treatment should be prescribed with caution in men who may have BOO.	2b	B

BOO = bladder outlet obstruction; LUTS = lower urinary tract symptoms.

3C.3 Surgical treatment

3C.3.1 Transurethral resection of the prostate and transurethral incision of the prostate

Mechanism of action: Transurethral resection of the prostate (TURP) removes tissue from the transition zone of the gland. Transurethral incision of the prostate (TUIP) involves incising the bladder outlet without tissue removal. This technique may replace TURP in selected cases, especially in prostate sizes ≤ 30 mL without a middle lobe.

Efficacy: In a recent analysis of 20 contemporary RCTs with a maximum follow-up of 5 years, TURP resulted in a substantial mean Q_{\max} improvement (+162%), a significant reduction in IPSS (-70%), QoL score (-69%), and PVR (-77%) [258]. TURP delivers durable outcomes as shown by studies with a follow-up of 8-22 years. There are no similar data on durability for any other surgical treatment for BPO [259]. One study with a mean follow-up of 13 years reported a significant and sustained decrease in most symptoms and improvement in urodynamic parameters. Failures were associated with detrusor underactivity rather than re-development of BPO [98].

Table 10 presents RCTs comparing TUIP with TURP [260-267]. A meta-analysis of short- and long-term data from 10 RCTs found similar LUTS improvements and lower but insignificant improvements in Q_{\max} for TUIP [262]. In this meta-analysis, an upper limit of prostate size was reported as an entry criterion for eight studies with five < 30 ml and three < 60 ml.

A second prostatic operation, usually re-TURP, has been reported at a constant annual rate of approximately 1-2%. A review analysing 29 RCTs found a re-treatment rate of 2.6% after a mean follow-up of 16 months [268]. In a large-scale study of 20,671 men, the overall re-treatment rates (re-TURP, urethrotomy and bladder neck incision) were 5.8%, 12.3%, and 14.7%, at 1, 5, and 8 years of follow-up, respectively, and the respective incidence of re-TURP was 2.9%, 5.8% and 7.4% [269]. A meta-analysis of six trials showed that re-operation was more common after TUIP (18.4%) than after TURP (7.2%) [262].

Tolerability and safety: Peri-operative mortality and morbidity have decreased over time, but the latter remains considerable (0.1% and 11.1%, respectively) [270]. The possibility of increased long-term mortality compared to open surgery [271] has not been verified [272-274]. Data from 20,671 TURPs and 2,452 open prostatectomies (OP) showed that short- and long-term procedural mortality was similar (0.7% vs. 0.9% at 90 days, 2.8% vs. 2.7% at 1 year, 12.7% vs. 11.8% at 5 years, 20% vs. 20.9% at 8 years) and that the 8-year myocardial infarction rates were identical (4.8 vs. 4.9%) [269].

The risk of TUR-syndrome decreased to $< 1.1\%$ [268, 275]. No case has been recorded after TUIP. Data from 10,654 TURPs reported bleeding requiring transfusion in 2.9% [270]. The risk after TUIP is negligible [268]. Similar results for TURP complications were reported by an analysis of contemporary RCTs using TURP as a comparator: bleeding requiring transfusion 2% (0-9%), TUR-syndrome 0.8% (0-5%), AUR 4.5% (0-13.3%), clot retention 4.9% (0-39%), and urinary tract infection (UTI) 4.1% (0-22%) [258]. Long-term complications comprise urinary incontinence (1.8% after TUIP vs. 2.2% after TURP), urinary retention and UTIs, bladder neck contracture (BNC) (4.7% after TURP), urethral stricture (3.8% after TURP vs. 4.1% after TUIP), retrograde ejaculation (65.4% after TURP vs. 18.2% after TUIP), and erectile dysfunction (6.5% after TURP) [268].

Practical considerations: TURP and TUIP are effective treatments for moderate-to-severe LUTS secondary to BPO. The choice should be based primarily on prostate volume (< 30 mL and 30-80 mL suitable for TUIP and TURP, respectively). No studies on the optimal cut-off value exist but the complication rates increase with prostate size [270]. The upper limit for TURP is mostly suggested as 80 mL (based on Panel expert opinion, under the assumption that this limit depends on the surgeon's experience, resection speed, and choice of resectoscope size).

3C.3.1.1 Modifications of TURP: bipolar TURP

Mechanism of action: Bipolar TURP (B-TURP) addresses a major limitation of monopolar TURP (M-TURP) by allowing performance in normal saline. Contrary to M-TURP, in B-TURP systems, the energy does not travel through the body to reach a skin pad. Bipolar circuitry is completed locally; energy is confined between an active (resection loop) and a passive pole situated on the resectoscope tip ("true" bipolar systems) or the sheath ("quasi-" bipolar systems). Prostatic tissue removal is identical to M-TURP. However, B-TURP requires less energy/voltage because there is a smaller amount of interpolated tissue. Energy from the loop is transmitted to the saline solution, resulting in excitation of sodium ions to form a plasma; molecules are then easily cleaved under relatively low voltage enabling resection. During coagulation, heat dissipates within vessel walls, creating a sealing coagulum and collagen shrinkage. The various bipolar devices available differ in the way in which current flow is delivered [276, 277].

Efficacy: B-TURP is the most widely and thoroughly investigated alternative to M-TURP. Results from > 40 RCTs [278] have been reported, of which around half have been pooled in three RCT-based meta-analyses [258, 279, 280]. Early pooled results concluded that no clinically relevant differences exist in short-term (up to 12 months) efficacy (IPSS, QoL score and Q_{max}) [280]. Subsequent meta-analyses supported these conclusions [258, 279], though trial quality was generally poor. Data from RCTs with a follow-up of 12-60 months show no differences in efficacy parameters (Table 11) [281-287].

Tolerability and safety: Early pooled results concluded that no differences exist in short-term (up to 12 months) US/BNC rates, but B-TURP is preferable due to a more favourable perioperative safety profile (elimination of TUR-syndrome; lower clot retention/blood transfusion rates; shorter irrigation, catheterisation, and possibly hospitalisation times) [280]. Subsequent meta-analyses supported these conclusions [258, 279]. However, trial quality is relatively poor and limited follow-up may cause under-reporting of late complications, such as urethral stricture/BNC [280]. Data from individual RCTs with a follow-up of 12-60 months showed no differences in urethral stricture/BNC rates (Table 11) [281-288].

A focused RCT using the erectile function domain of the IIEF (IIEF-ED) showed that M-TURP and B-TURP have a similar effect [289]. A comparative evaluation of the effects on the overall sexual function, quantified with IIEF-15 showed no differences between B-TURP and M-TURP at 12 months of follow-up (erection, orgasmic function, sexual desire, intercourse satisfaction, overall satisfaction) [290].

Practical considerations: B-TURP offers an attractive alternative to M-TURP in patients with moderate-to-severe LUTS secondary to BPO, with similar efficacy but lower peri-operative morbidity [280]. The duration of improvements with B-TURP was documented in a number of RCTs with a follow-up of >12 months. Mid-term results (up to 5 years) of B-TURP showed that safety and efficacy are comparable to M-TURP. The choice of B-TURP should be based on equipment availability, surgeon's experience, and patient's preference.

Recommendations	LE	GR
M-TURP is the current surgical standard procedure for men with prostate sizes of 30-80 mL and bothersome moderate-to-severe LUTS secondary of BPO. M-TURP provides subjective and objective improvement rates superior to medical or minimally invasive treatments.	1a	A
The morbidity of M-TURP is higher than for drugs or other minimally invasive procedures.	1a	A
B-TURP achieves short- and mid-term results comparable with M-TURP.	1a	A
B-TURP has a more favourable peri-operative safety profile compared with M-TURP.	1a	A
TUIP is the surgical therapy of choice for men with prostate sizes <30 mL, without a middle lobe, and bothersome moderate-to-severe LUTS secondary to BPO.	1a	A

BPO = benign prostatic obstruction; B-TURP = bipolar TURP; LUTS = lower urinary tract symptoms; M-TURP = monopolar TURP; TUIP = transurethral incision of the prostate; TURP = transurethral resection of the prostate.

Table 10: Efficacy and safety of transurethral resection of the prostate or transurethral incision of the prostate in level 1 trials at 12 or 24 months. Absolute and relative changes compared to baseline with regard to symptoms (Madson-Iverson or IPSS) and maximum urinary flow rate

Trials	Inter- vention	Patients (n)	Decrease in symptoms at 12 months		Q _{max} (mL/s) at 12 months		Blood trans- fusion (%)	Re- operation rate at 12 months (%)	LE
			Absolute	(%)	Absolute	(%)			
Dorflinger et al. 1992 [260]	TURP	31	-11.6 ^a	-88 ^a	+22.9 ^{a,b}	+294 ^{a,b}	13	3.2 ^b	1b
	TUIP	29	-12.6 ^a	-85 ^a	+16.3 ^a	+223 ^a	0 ^c	20.7	
Jahnsen et al. 1998 [261]	TURP	43	-13 ^a	-82 ^a	+19.5 ^{a,b}	+229 ^{a,b}	2.4	7.1 ^b	1b
	TUIP	42	-11.8 ^a	-77 ^a	+13.8 ^a	+148 ^a	0	23.2	
Riehmman et al. 1995 [263]	TURP	61	-9.5 ^a	-67 ^a	No significant difference between groups		16		1b
	TUIP	56	-10 ^a	-63 ^a			23		
Saporta et al. 1996 [264]	TURP	20	-9.4 ^a	-63 ^a	+17.3 ^a	+266 ^a		0 ^b	1b
	TUIP	20	-9.3 ^a	-64 ^a	+14.6 ^a	+197 ^a		15	
Soonawalla et al. 1992 [265]	TURP	110			+20.1 ^a	+251 ^a	34.5		1b
	TUIP	110			+19.5 ^a	+246 ^a	0 ^c		
Tkocz et al. 2002 [266]	TURP	50	-12 ^{*a}	-70 [*]	6.9 ^{*a}	+255 ^a			1b
	TUIP	50	-13 ^{*a}	-77 [*]	7.6 ^{*a}	+222 ^a			
Lourenco et al. 2009 [262]	TURP	345	no significant difference between groups	no significant difference between groups			28.3	7.2 ^b	1a
	TUIP	346					1.1 ^c	18	
Yang et al. 2001 [267]	TURP	403	-11.2 to -13	-63 to -82	+17.3 to +22.9 ^b	+266 to +352 ^b	25.1	5.5	1a
	TUIP	392	-10 to -13.5	-63 to -83	+13.8 to +16.3	+189 to +223	0.87 ^c	9.3	

IPSS = International Prostate Symptom Score; Q_{max} = maximum urinary flow rate; TUIP = transurethral incision of the prostate; TURP = transurethral resection of the prostate.

* = 24 months post operatively; ^a = significantly different compared to baseline; ^b = significantly different in favour of TURP; ^c = significantly different in favour of TUIP.

Table 11: Mid-term (follow-up longer than 12 months) results from randomised controlled trials comparing monopolar and bipolar transurethral resection of the prostate

Trials	Inter- vention	Patients (n)	Follow-up (months)	IPSS Decrease		Q _{max} (mL/s)		US/ BNC (%)	LE
				Absolute	(%)	Absolute	(%)		
Autorino et al. 2009 [281]	M-TURP	31	48	-17.9 ^a	-74 ^a	+15.0 ^a	+242 ^a	6.5/3.2	1b
	B-TURP (Gyrus)	32		-17.3 ^a	-72 ^a	+12.7 ^a	+179 ^a	3.1/3.2	
Chen et al. 2010 [282]	M-TURP	50	24	-18.0 ^a	-83 ^a	+16.9 ^{a,b}	+214 ^a	6.0/4.0	1b
	B-TURP (TURIS)	50		-19.1 ^a	-84 ^a	+18.4 ^a	+259 ^a	4.0/2.0	
Geavlette et al. 2011 [284]	M-TURP	170	18	-15.9 ^a	-66 ^a	+14.2	+222	5.1/4.1	1b
	B-TURP (TURIS)	170		-16.1 ^a	-67 ^a	+14.5 ^a	+238 ^a	6.3/3.4	

Xie et al. 2012 [287]	M-TURP	79	60	-16.2 ^a	-71 ^a	+15.2 ^a	+157 ^a	5.1/10.1	1b
	B-TURP (Gyrus)	78		-16.6 ^a	-70 ^a	+16.5 ^a	+167 ^a	5.1/5.1	
Mamoulakis et al. 2012 [286]	M-TURP	108	36	-16.0 ^a	-69 ^a	+10.8 ^a	+126 ^a	9.3/1.9	1b
	B-TURP (Autocon)	122		-15.4 ^a	-66 ^a	+10.7 ^a	+122 ^a	8.2/6.6	
Giulianelli et al. 2013 [285]	M-TURP	80	36	-19.4 ^a	-83 ^a	+13.5 ^a	+208 ^a	NA/13.3	1b
	B-TURP (Gyrus)	80		-20.3 ^a	-91 ^a	+14.1 ^a	+158 ^a	NA/2.5	

BNC = bladder neck contracture; B-TURP = bipolar TURP; IPSS = International Prostate Symptom Score; M-TURP = monopolar TURP; Q_{max} = maximum urinary flow rate; TURP = transurethral resection of the prostate; US = urethral stricture.

^a = significantly different compared to baseline; NA = not available.

3C.3.2 Open prostatectomy

Mechanism of action: OP is the oldest surgical treatment for moderate-to-severe LUTS secondary to BPO. Obstructive adenomas are enucleated using the index finger, approaching from within the bladder (Freyer procedure) or through the anterior prostatic capsule (Millin procedure).

Efficacy: OP is the treatment of choice for large glands (> 80-100 mL). Three RCTs showed that Holmium laser enucleation of the prostate (HoLEP) and photoselective vaporisation of the prostate (PVP) lead to similar outcomes compared to OP in men with large glands (> 70 mL) at a significantly lower complication rate [291-293]. The results of OP studies are summarised in Table 12. OP reduces LUTS by 63-86% (12.5-23.3 IPSS points), improves QoL score by 60-87%, increases mean Q_{max} by 375% (+16.5-20.2 mL/s), and reduces PVR by 86-98% [291-295]. Efficacy is maintained for > 5 years [291, 293, 295] (Table 12).

Tolerability and safety: Mortality has decreased significantly during the past two decades (< 0.25%) [294]. The estimated transfusion rate is about 7-14% [291, 294, 295]. Long-term complications include urinary incontinence (up to 10%), BNC and US (about 6%) [291-293, 296].

Practical considerations: OP is the most invasive but also the most effective and durable procedure for the treatment of LUTS/BPO. In the absence of an endourological armamentarium and a holmium laser, OP is the surgical treatment of choice for men with prostates > 80 mL.

Recommendations	LE	GR
OP or holmium laser enucleation are the first choice of surgical treatment in men with prostate sizes > 80 mL and bothersome moderate-to-severe LUTS secondary to BPO needing surgical treatment.	1b	A
OP is the most invasive surgical method with significant morbidity.	1b	A

BPO = benign prostatic obstruction; LUTS = lower urinary tract symptoms; OP = open prostatectomy.

Table 12: Results of OP studies for treating BPH-LUTS or BPO

Studies	Duration (weeks)	Patients (n)	Change in symptoms (IPSS)		Change in Q_{max}		Change in PVR		Change in prostate volume		LE
			Absolute	%	mL/s	%	mL	%	mL	%	
Kuntz et al. 2008 [291]	260	32	-18.2	86	21.4	677	-287	98			1b
Skolarikos et al. 2008 [293]	78	60	-12.5	63	7	86	-77	86	-86	88	1b
Naspro et al. 2006 [292]	104	39	-13.2	62	15.9	291					1b
Varkarakis et al. 2004 [295]	151	232	-23.3	84	16.5	329	-104	90			3
Gratzke et al. 2007 [294]		868			13	218	-128	88	85	88	2b

BPH = benign prostatic hyperlasia; BPO = benign prostatic obstruction; IPSS = International Prostate Symptom Score; LE = level of evidence; LUTS = lower urinary tract symptoms; n = number of patients; OP = open prostatectomy; PVR = post-void residual urine; Q_{max} = maximum urinary flow rate (free uroflowmetry).

3C.3.3 Transurethral microwave therapy

Mechanism of action: Microwave thermotherapy works by emitting microwave radiation through an intra-urethral antenna to deliver heat into the prostate. Tissue is destroyed by being heated at temperatures above cytotoxic thresholds (> 45°C) (coagulation necrosis). The heat may also cause apoptosis and denervation of α -receptors, thereby decreasing the smooth muscle tone of the prostatic urethra.

Conceptually, transurethral microwave therapy (TUMT) devices are all similar in delivering microwave energy with some type of feedback system, differing mainly in the design of the urethral applicator. This can have a significant effect on the heating profile [297]. There is also variation in the catheter construction, cooling systems, treatment time, and monitoring of TUMT effects [298].

Efficacy: A systematic review assessed therapeutic efficacy in different devices/software, including Prostatron (Prostatsoft 2.0 and 2.5) and ProstaLund Feedback (Table 13) [299]. It was concluded that TUMT was less effective than TURP in reducing LUTS. Symptom score after TUMT decreased by 65% in 12 months, compared to 77% after TURP. TURP achieved a greater Q_{max} improvement (119% vs. 70%) [299].

A pooled analysis of three studies (two RCTs and one open label) of ProstaLund Feedback TUMT (PLFT) with 12-month follow-up showed the responder rate was 85.3% and 85.9% after PLFT and TURP, respectively [300]. IPSS showed a subjective, non-inferior improvement with PLFT [300]. However, one-sided 95% CI analysis showed that PLFT non-inferiority did not reach the predetermined level, even though both improved Q_{max} significantly.

One RCT compared TUMT with terazosin [301]. After 18 months' follow-up, treatment failure in terazosin-treated patients (41%) was significantly greater compared to TUMT (5.9%), with TUMT achieving a greater improvement in IPSS and Q_{max} [302].

Previously, urinary retention was considered a contraindication for TUMT. Nowadays, LE:2b studies have reported an 80-93% success rate for TUMT, defined as the percentage of patients who regained their ability to void spontaneously [303-305]. However, these studies had a short follow-up (≤ 12 months), which makes it difficult to estimate the durability of TUMT outcome in patients with retention. In a study with a longer follow-up, treatment failure was 38% in the retention group, with a cumulative risk of 59% at 5 years [306].

An RCT-based systematic review estimated re-treatment rates [299] (though the trials had different follow-up periods) of 0.075 vs. 0.010 re-treatments per person per year for TUMT and TURP, respectively.

A multicentre RCT with follow-up of 5 years compared TUMT (PLFT; the Core-Therm device) and TURP. No significant differences were found in Q_{max} and IPSS. After TUMT, 10% needed additional treatment, vs. 4.3% after TURP. These data suggest clinical results obtained with PLFT-TUMT were comparable to TURP at five years. Most durability studies have a high attrition rate; in this study, less than half of the patients were analysed at 4-5 years. In addition, patients who remained in the study were likely to represent the best data (responders).

Tolerability and safety: Treatment is well tolerated, although most patients experience perineal discomfort and urinary urgency, and require pain medication for therapy. Pooled morbidity data comparing TUMT and TURP have been published [299, 300, 307]. In the Cochrane RCT-based systematic review, catheterisation time, dysuria/urgency and urinary retention rates were significantly less with TURP. Hospitalisation time, haematuria, clot retention, transfusion, TUR syndrome, and urethral stricture rates were significantly less for TUMT [299]. Sexual dysfunction and re-treatment rates for urethral stricture/BNC were higher after TURP.

Practical considerations: Endoscopy prior to TUMT is essential to identify the presence of a prostate middle lobe or an insufficient length of the prostatic urethra. Due to the low peri- and post-operative morbidity and lack of need for anaesthesia, TUMT is a true outpatient procedure, and an option for older patients, and those with comorbidities or anaesthesia risk [308]. Independent baseline parameters that predict an unfavourable outcome include small prostates, mild-to-moderate BPO, and a low amount of energy delivered during treatment [309]. However, predictive factors for particular devices cannot necessarily be applied to other systems

Recommendations	LE	GR
TUMT achieves symptom improvement comparable with TURP, but TUMT is associated with decreased morbidity and lower flow improvements.	1a	A
Durability is in favour of TURP, which has lower re-treatment rates compared to TUMT.	1a	A

TUMT = transurethral microwave therapy; TURP = transurethral resection of the prostate.

Table 13: Efficacy of TUMT. Absolute and relative changes compared to baseline are listed for IPSS, Q_{max}, PVR and PVol

Trials	Duration (weeks)	Patients (n)	Change in IPSS (absolute [%])	Change in Q _{max} (mL/s, [%])	Change in QoL (absolute [%])	Change in PVR (absolute [%])	Change in PVol (absolute [%])	LE
Hoffman et al. 2007[299]	52	322	-12.7 ^a (-65.0)	5.6 ^a (70.0)	-2.4 ^a (58.5)	NA	NA	1a
Gravas et al. 2005 [300]	52	183	-14.5 ^a (-69.0)	8.4 ^a (109.0)	-2.97 ^a (70.9)	NA	-17.0 ^a (-33.0)	1b
Mattiasson et al. 2007[310]	260	100	-13.6 ^a (-61.5)	3.8 ^a (50.0)	-3.2 ^a (-74.4)	-36.0 (-34.0)	-4.0 (-8.1)	1b
Floratos et al. 2001[311]	156	78	-8.0 ^a (-40.0)	2.7 ^a (29.3)	-2.0 ^a (-50.0)	NS	NA	1b
Thalmann et al. 2002[312]	104	200	-20.0 ^a (-87.0)	7.0 ^a (116.6)	-4.0 ^a (-80.0)	-143 ^a (-84.1)	-17.7 ^a (-30.7)	2b
Miller et al. 2003 [313]	260	150	-10.6 ^a (-47.0)	2.4 ^a (37.0)	-2.3 ^a (-54.7)	NA	NA	2b
Trock et al. 2004 [314]	208	541	-8.9 ^a (-42.7)	2.8 ^a (35.0)	-2.1 ^a (-50.1)	NA	NA	2b

IPSS = International Prostate Symptom Score; LE = level of evidence; PVol = prostate volume; PVR = post-void residual urine; Q_{max} = maximum urinary flow rate (free uroflowmetry); QoL = quality of life; TUMT = transurethral microwave therapy; ^a = significant compared to baseline (indexed whenever evaluated); n = number of patients; NS = not significant; NA = not available.

3C.3.4 Transurethral needle ablation of the prostate

Mechanism of action: The transurethral needle ablation (TUNA™) device delivers low-level radiofrequency energy to the prostate via needles inserted transurethrally into the parenchyma under direct vision using an attachment to the standard cystoscope. The energy induces coagulation necroses in the transition zone resulting in prostate volume reduction and BPO reduction.

Efficacy: A meta-analysis of two RCTs, two non-randomised protocols and 10 single-arm studies showed that TUNA™ achieved a 50% decrease in IPSS and a 70% improvement in Q_{max} at 1 year [315], supported by a more recent meta-analysis of 35 studies (9 comparative, 26 non-comparative) [316]. TUNA™ significantly improved IPSS and Q_{max}, but compared to TURP these improvements were significantly lower at 12 months. TURP vs. TUNA™ differences in means were - 4.72 and 5.9 mL/sec for IPSS and Q_{max} respectively [316].

Clinical studies on the impact of TUNA™ on BPO [317, 318] showed a significant decrease in maximum detrusor pressure or detrusor pressure at Q_{max}, but a number of patients were still obstructed.

Most studies were short-to-midterm in duration, and there were concerns about the durability of effects. A study with 5 years' follow-up demonstrated symptomatic improvement in 58% and improved flow in 41%. However, 21% required additional treatment [319]. TUNA™ has a significantly higher re-treatment rate compared with TURP. The overall re-treatment rate after TUNA™ was 19% based on an analysis of 17 non-comparative studies [316].

Tolerability and safety: Post-operative urinary retention with a mean duration of 1-3 days is seen in 13-42% of patients; within 1 week, 90-95% of patients are catheter-free [320]. Storage LUTS are common for the first 4-6 weeks after intervention [321]. TUNA™ is associated with fewer adverse events compared to TURP, including mild haematuria, urinary infections, strictures, incontinence, ED, and ejaculation disorders [316].

Practical considerations: TUNA™ can be performed as a day-case procedure under local anaesthesia or sedation [320]. TUNA™ is unsuitable for prostates > 75 mL or isolated bladder neck obstruction. TUNA™ cannot effectively treat prostatic middle lobes. There is anecdotal evidence for TUNA™ in men receiving aspirin and anti-coagulants. TUNA™ can be performed as a day-case procedure and is associated with fewer side-effects than TURP (e.g. bleeding, ED, urinary incontinence). However, there are concerns about the durability of the effects achieved by TUNA™.

Recommendations	LE	GR
TUNA™ achieves symptom improvement comparable with TURP, but TUNA™ is associated with decreased morbidity and lower flow improvements.	1a	A
Durability is in favour of TURP with lower re-treatment rates compared to TUNA™.	1a	A

TUNA™ = transurethral needle ablation; TURP = transurethral resection of the prostate.

Table 14: Summary of comparative LE:1 data for TUNA™ versus TURP [316]

	TUNA™	TURP	TUNA™ vs. TURP (95% CI)	LE
Symptoms (IPSS): mean (% improvement)				
3 months (8,10)	-12 (56%)	-14 (62%)	-2 (-0.9 to 3.1)	1b
1 year (9-11)	-12 (55%)	-15.5 (70%)	3.4 (2.1 to 5.2) ^a	1b
3 years (9,11)	-10 (45%)	-15 (67%)	4.8 (4.2 to 5.4) ^a	1b
Quality of life scores: mean (% improvement)				
3 months (8,10)	-4.5 (54%)	-3.7 (48%)	-0.8 (-1.3 to 0.5)	1b
1 year (9-11)	-4 (50%)	-4.3 (56%)	0.63 (0.1 to 1.2) ^a	1b
3 years (9,11)	-4.2 (50%)	5.2 (67%)	1 (0.2 to 1.9) ^a	1b
Q_{max} (mL/s): mean (% improvement)				
3 months (8,10)	4.7 (54%)	11.5 (150%)	-5.8 (-6.3 to -5.4) ^a	1b
1 year (9-11)	6.5 (76%)	12.2 (160%)	-5.9 (-7.7 to -4.1) ^a	1b
3 years (9,11)	5.6 (66%)	10.8 (141%)	-5.3 (-6.8 to -3.9) ^a	1b
PVR (mL): mean (% improvement)				
1 year (10,11)	-20 (22%)	-42 (41%)	22 (-18 to 27) ^a	1b

IPSS = International Prostate Symptom Score; LE = level of evidence; Q_{max} = maximum urinary flow rate;

PVR = post-void residual urine; TUNA™ = transurethral needle ablation; TURP = transurethral resection of the prostate.

^a = TURP significantly better compared with TUNA™.

3C.3.5 Laser treatments of the prostate

3C.3.5.1 Holmium laser enucleation and holmium laser resection of the prostate

Mechanism of action: The holmium:yttrium-aluminium garnet (Ho:YAG) laser (wavelength 2140 nm) is a pulsed solid-state laser that is absorbed by water and water-containing tissues. Tissue coagulation and necrosis are limited to 3-4 mm, which is enough to obtain adequate haemostasis [322]. Holmium laser resection of the prostate (HoLRP) or holmium laser enucleation of the prostate (HoLEP) result in BPO relief and, secondarily, in LUTS reduction.

Efficacy: In a meta-analysis of studies comparing HoLRP with TURP, no difference in symptom improvement could be detected at 6 or 12 months post operatively (Table 15) [323]. One RCT comparing TURP with HoLRP with a minimum follow-up of 4 years showed no difference in urodynamics after 48 months [324]. Three meta-analyses covering trials on HoLEP versus TURP found that symptom improvement was comparable or superior with HoLEP (Table 15) [325-327]. One RCT comparing photoselective vaporisation of the prostate (PVP)

and HoLEP in patients with prostates > 60 mL showed comparable symptom improvement but significantly higher flow rates and lower PVR volume after HoLEP [328]. Another RCT on HoLAP and 80-W PVP showed comparable functional improvement within a median follow-up of 71 months [329].

RCTs indicate that HoLEP is as effective as open prostatectomy for improving micturition in large prostates [291, 292], with similar re-operation rates after 5 years (5% vs. 6.7%, respectively) [291]. One RCT comparing HoLEP with TURP in a small number of patients who completed the 7-year follow-up found that the functional long-term results of HoLEP were comparable with TURP [330]. A retrospective study of HoLEP with the longest follow-up (up to 10 years, mean 62 months) reported durable functional results with low re-operation rates [331].

Tolerability and safety: Dysuria is the most common post-operative complication [322, 325]. Compared to TURP, HoLRP has shorter catheterisation and hospitalisation times [323, 332]. Potency, continence, and major morbidity at 48 months were identical between HoLRP and TURP [324]. Three meta-analyses found that HoLEP has a shorter catheterisation time and hospital stay, reduced blood loss, and fewer blood transfusions, but a longer operation time compared with TURP [325-327]. In a meta-analysis, no significant differences were noted between HoLEP and TURP for urethral stricture (2.6% vs. 4.4%), stress urinary incontinence (1.5% vs. 1.5%), and re-intervention (4.3% vs. 8.8%) [326]. HoLEP is superior to open prostatectomy for blood loss, catheterisation and hospitalisation time [291, 292].

HoLEP has been safely performed in patients using anticoagulant medications [333, 334]. In a study of 83 patients, blood transfusion was required in seven patients (8%) [335]. A retrospective study compared the safety results of HoLEP between 39 patients who were on anticoagulant therapy at the time of their surgery, and 37 controls [334]. No transfusions were required and bleeding complication rates were not significantly different [334]. Short-term studies showed that patients with urinary retention can be treated with HoLEP [336, 337].

The impact on ED and retrograde ejaculation is comparable between HoLEP and TURP/OP [292, 338]. Erectile function did not decrease from baseline in either group; three quarters of sexually active patients had retrograde ejaculation after HoLEP.

Practical considerations: Holmium laser operations are surgical procedures that require experience and relevant endoscopic skills. The experience of the surgeon was the most important factor affecting the overall occurrence of complications [333, 339].

3C.3.5.2 532 nm ("Greenlight") laser vaporisation of prostate

Mechanism of action: The kalium-titanyl-phosphate (KTP) and the lithium triborate (LBO) lasers work at a wavelength of 532 nm. Laser energy is absorbed by haemoglobin, but not by water. Vaporisation leads to immediate removal of prostatic tissue, relief of BPO, and reduction of LUTS. In 2014, three different Greenlight lasers were in use: the 80-W (KTP), 120-W HPS (LBO), and the 180-W XPS (LBO) laser systems. They differ in maximum power output, fibre design, and maximum energy application.

Efficacy: A meta-analysis of the nine available RCTs comparing PVP using the 80-W and 120-W lasers with TURP was performed in 2012 (Table 15) [340]. No differences were found in Q_{\max} and IPSS between PVP and TURP, but only three RCTs provided sufficient 12-month data to be included in the meta-analysis [341-343].

The longest RCT using the 80-W KTP laser has a follow-up of only 12 months [341]. A case series showed durable functional outcomes after the 80-W KTP laser, with an overall re-treatment rate of 8.9% at 5 years [344]. Another case series of 500 patients treated with the 80-W system with a mean follow-up of 30.6 months reported a re-treatment rate of 14.8% [345].

Significant improvements in voiding parameters at a follow-up of 12 months were demonstrated urodynamically [346]. The longest RCT comparing the 120-W HPS laser with TURP had a follow-up of 36 months and showed a comparable improvement in IPSS, Q_{\max} , and PVR [347]. Re-operation rate was higher after PVP (11% vs. 1.8%; $p = 0.04$) [347]. Similar improvement of IPSS, QoL, Q_{\max} , or urodynamic parameters was reported from two RCTs with a maximum follow-up of 24 months [342, 348].

A multicentre case series of the 180-W laser demonstrated comparable safety and symptom improvement compared with the former Greenlight laser systems [349].

Tolerability and safety: A meta-analysis of the RCTs comparing the 80-W and 120-W lasers with TURP showed a significantly longer operating time but shorter catheterisation time and length of hospital stay after PVP [340]. Blood transfusions and clot retention were less with PVP. No difference was noted in post-operative urinary retention, infection, meatal stenosis, urethral stricture, or bladder neck stenosis [340].

The Greenlight laser appears to be safe in high-risk patients under anticoagulation treatment [350-354]. In one study, anticoagulated patients had significantly higher rate of bladder irrigation (17.2%) compared

with Greenlight laser without taking anticoagulants (5.4%) [353]. Safety in patients with urinary retention, or prostates > 80 mL was shown in various prospective non-randomised trials [354-356].

The impact of Greenlight laser on sexual function seems to be similar to that of TURP. One RCT comparing TURP and Greenlight PVP reported no significant difference in the rate of retrograde ejaculation [357]. In addition, no difference was reported between OP/TURP and Greenlight PVP for erectile function [358, 359]. IIEF-5 scores are maintained after treatment. However, in patients with preoperative IIEF-5 >19, the post-operative IIEF-5 scores were significantly decreased at 6, 12, and 24 months [360].

Practical considerations: The evolution of the Greenlight laser from 80-W to 120-W and then to 180-W resulted in a wide variation in the degree of maturity of each laser therapy. Long-term results on 120-W and RCTs on 180-W are still pending.

3C.3.5.3 Diode laser vaporisation of the prostate

Mechanism of action: For prostate surgery, diode lasers with a wavelength of 940, 980, 1318, and 1470 nm (depending on the used semiconductor) are marketed for vaporisation and enucleation. Only a few have been evaluated in clinical trials [361].

Efficacy: Case series, and two comparative studies of a 980-nm diode laser and the 120 W HPS laser, are available [362-368]. IPSS, QoL, Q_{max} , and PVR improved significantly in all studies compared to baseline and were similar compared to 120-W HPS laser, at 6 and 12 months [362, 363]. However, RCTs and long-term follow up is lacking.

One RCT with a 12 month follow-up compared 980 nm diode laser with plasmakinetic enucleation and found equal clinical outcome (Table 15). Adverse events and catheter time favoured the diode laser group [369]. One small RCT with a 6 months' follow-up comparing laser enucleation using a 1318-nm diode laser with B-TURP reported similar efficacy and safety results (Table 15) [370]. Blood loss and hospitalisation time were in favour of laser enucleation.

Tolerability and safety: Two studies (980 nm) indicate high intraoperative safety, since no bleeding was reported, although anticoagulants or platelet aggregation inhibitors were taken in 24% and 52% [362, 363]. Post-operatively, a higher rate of dysuria occurs than with 120-W HPS laser [362, 363]. Fibre modifications led to a significant reduction [365]. In summary, high re-operation rates (20-33%) and persisting stress urinary incontinence (9.1%) were reported [362-364].

Practical considerations: Diode lasers lead to immediate improvements of LUTS due to BPO and provide good haemostatic properties. Based on the lack of RCTs and controversial data on the re-treatment rate, diode lasers cannot be recommended as a standard treatment option for BPO.

3C.3.5.4 Thulium:yttrium-aluminium-garnet laser (Tm:YAG)

Mechanism of action: In the Tm:YAG laser, a wavelength of 2013 nm is emitted in continuous-wave mode. The laser is primarily used in front-fire applications [361]. Different applications, ranging from vaporisation (ThuVaP), vaporessection (ThuVaRP), and enucleation (ThuVEP/ThuLEP: similar enucleating techniques) are published.

Efficacy: A major drawback is the limited number of RCTs. Maximum follow-up of 4 years (case control study) with cumulative re-operation rates of 6% reported [371]. One RCT and one non-RCT compared ThuVaRP with M-TURP [372, 373], while two RCTs comparing ThuVaRP and B-TURP were published recently [374, 375]. In summary, studies show comparable improvement of symptoms and voiding parameters. There are only a few case studies on ThuVEP showing a significant improvement in IPSS, Q_{max} , and PVR after treatment [376-379]. ThuLEP and HoLEP were compared in one RCT with 18-months of follow-up with comparable outcome in both arms (Table 15) [380].

Tolerability and safety: Thulium laser prostatectomy shows high intra-operative safety in RCTs [372, 374, 380], as well as in case series in patients with large prostates [376], anticoagulation or bleeding disorders [377]. Catheterisation time, hospital stay, and blood loss were shorter compared to TURP [372-374]. The rate of post-operative urethral strictures after ThuVaRP was 1.9%, the rate of bladder neck contracture was 1.8%, and re-operation rate was 0-7.1% during follow-up [372, 373, 381]. Urethral stricture after ThuVEP occurred in 1.6%, and the overall re-treatment rate was 3.4% (mean follow-up 16.5 months) [382]. No urethral and bladder neck strictures after ThuLEP were reported during the 18-month follow-up [380]. Recently a large series of complications after vapoenucleation reported adverse events in 31% of cases, with 6.6% complications > Clavien grade 2 [383].

Practical considerations: The limited number of RCTs and limited follow-up (up to 18 months) do not permit final conclusions regarding the long-term efficacy of thulium laser prostatectomy.

Recommendations	LE	GR
HoLEP and 532-nm laser vaporisation of the prostate are alternatives to TURP in men with moderate-to-severe LUTS due to BPO leading to immediate, objective, and subjective improvements comparable with TURP.	1a	A
The intermediate-term functional results of 532-nm laser vaporisation of the prostate are comparable with TURP.	1b	A
The long-term functional results of HoLEP are comparable with TURP/open prostatectomy.	1b	A
Diode laser operations lead to short-term objective and subjective improvement.	1b	B
ThuVaRP is an alternative to TURP for small- and medium-size prostates.	1b	A
ThuVEP leads to short-term objective and subjective improvement.	3	C
With regard to intra-operative safety and haemostatic properties, diode and thulium lasers appear to be safe.	3	C
With regard to intra-operative safety, 532-nm laser vaporisation is superior to TURP.	1b	A
532-nm laser vaporisation should be considered in patients receiving anticoagulant medication or with a high cardiovascular risk.	3	B

BPO = benign prostatic obstruction; HoLEP = holmium laser enucleation; LUTS = lower urinary tract symptoms; TURP = transurethral resection of the prostate; ThuVaRP = Tm:YAG vaporessection; ThuVEP = Tm:YAG vapoenucleation.

Table 15: Efficacy of different lasers for the treatment based on the highest-quality study for each of the treatment options. Absolute and relative changes compared to baseline, with regard to symptoms (AUA-SI/IPSS) and maximum urinary flow rate (Q_{\max})

Trials	Duration (months)	Patients (n)	Surgery	Change symptoms (IPSS)			Change Q_{\max} (mL/s)			LE
				Absolute	(%)	WMD	Absolute	(%)	WMD	
Tooher et al. 2004 [323]	12	231	HoLRP	NA	NA	-0.4	NA	NA	+4.2	1a
			TURP	NA	NA		NA	NA		
Tan et al. 2007 [326]	12	232	HoLEP	-17.5 to -21.7	-81 to -83	NA	+13.4 to +23.0	+160 to +470	+0.59	1a
		228	TURP	-17.7 to -18.0	-76 to -82		+10.1 to +21.8	+122 to +370		
Lourenco et al. 2008 [325]	12	277	HoLEP	-17.7 to -21.7	-82 to -92	-0.82	+13.4 to +23.0	+160 to +470	+1.48	1a
		270	TURP	-17.5 to -18.7	-81 to -82		+10.1 to +21.8	+122 to +370		
Thangasamy et al. 2012 [340]	12	176	KTP (80 W and 120 W)	-15.9 to -16.1	-64 to -66	-0.7	+9.8 to +14.5	+111 to +181	+1.1	1a
		164	TURP	-14.1 to -14.4	-56 to -63		+10.5 to +13.7	+118 to +154		
Lusuardi et al. 2011 [370]	6	30	Diode laser enucleation	-22.7	-84		+14.8	+218		1b
		30	B-TURP	-21	-83		+15.2	+237		
Xu et al. 2013 [369]	12	40	Diode laser enucleation	-18.6	-79		+15.5	+196		1b
		40	PKERP	-18.5	-77		+15.6	+200		
Xia et al. 2008 [372]	12	52	ThuVaRP	-18.4	-84		+15.7	+196		1b
		48	TURP	-16.9	-81		+15.8	+190		
Peng et al. 2013 [374]	3	50	ThuVaRP	-13.2	-65		+16.2	+205		1b
		50	B-TURP	-12.1	-63		+16.2	+198		
Zhang et al. 2012 [380]	18	71	ThuLEP	-19.4	-79		+16.6	+244		1b
		62	HoLEP	-16.6	-73		+16.9	+232		

Yang et al. 2013 [375]	18	79	ThuLEP	-17	-75		+14.2	+163		1b
		79	B-TURP	-18.2	-78		+14.1	+154		

AUA-SI = American Urological Association Symptom Index; B-TURP = bipolar transurethral resection of the prostate; HoLEP = holmium laser enucleation; HoLRP = holmium laser resection of the prostate; IPSS = International Prostate Symptom Score; KTP = greenlight laser vaporisation; NA = not available; Q_{max} = maximum urinary flow rate; TURP = transurethral resection of the prostate; ThuVaP = Tm:YAG vaporisation of the prostate; ThuVaRP = Tm:YAG vaporessection; ThuLEP = Tm:YAG laser enucleation of the prostate; ThuVEP = Tm:YAG vapoenucleation; WMD = weighted mean difference.

3C.3.6 Prostatic stents

Mechanism of action: The use of an endoprosthesis to preserve luminal patency is a well-established concept. Prostatic stents were primarily designed as an alternative to an indwelling catheter but have also been assessed as a primary treatment option in patients without significant comorbidities [384, 385].

A prostatic stent requires a functioning detrusor [386]. Permanent stents are biocompatible, which allows epithelialisation. Temporary stents do not epithelialise and may be either biostable or biodegradable. Temporary stents can provide short-term relief from BPO in patients temporarily unfit for surgery, or after minimally invasive treatment [386].

Efficacy: Several small case studies on a range of stents of different designs and materials have provided low level of evidence for their use. Table 16 describes the most important studies [384, 385, 387-390].

All studies observed a significant attrition rate. There is only one RCT that has compared two versions of a blind-placement prostatic stent (BPS) for BPO [391], and there have been no studies comparing stents with sham or other treatment modalities. The BPS system is temporary, with the difference between BPS-1 and BPS-2 being an additional 2 cm bulbar segment. This bulbar segment results in a significantly lower migration rate with BPS-2 (5%) compared with BPS-1 (85%) [391]. BPS-2 also resulted in superior symptom scores and voiding function, but only Q_{max} reached statistical significance [391].

The main representative of the permanent stents is the UroLume prosthesis. A systematic review identified 20 case series, with differing follow ups [392]. These trials reported relevant symptom improvement and Q_{max} increase [392].

The pooled data from studies with patients who were catheter dependent showed that 84% of patients (148/176) regained the ability to void spontaneously after UroLume treatment [392, 393].

The best data on non-epithelialising prostatic stents are provided by a systematic review of the efficacy of Memokath, a self-expanding metallic prostatic stent [394], which reduced IPSS by 11-19 points and increased Q_{max} by 3-11 mL/s [394].

Tolerability and safety: In general, stents are subject to misplacement, migration, and poor tolerability because of exacerbation of LUTS and encrustation [386]. The main immediate adverse events include perineal pain or bladder storage symptoms.

A systematic review of the UroLume reported a 16% failure rate within 12 months, mainly due to stent misplacement or migration (37%) or recurrent obstructive or irritative LUTS (14%). The overall failure rate at 5 years was 27% (50/188 stents) [392].

Practical considerations: Due to side effects and a high migration rate, prostatic stents have a limited role in the treatment of moderate-to-severe LUTS. Prostatic stents are an alternative to catheterisation for men who have (recurrent) urinary retention and are at high risk for surgery. Temporary stents can provide short-term relief from LUTS secondary to BPO in patients temporarily unfit for surgery or after minimally invasive treatment [386].

Recommendation	LE	GR
Prostatic stents are an alternative to catheterisation for men unfit for surgery.	3	C

Table 16: Efficacy of stents: key studies

Stent	n	Symptoms		Q _{max} (mL/s)		Failure rate (follow-up in months)	LE
		Pre-operative	Post-operative	Pre-operative	Post-operative		
Urolume (P) [384]	91	14.1	4.7	9.3	17.1	Overall	3
	44	R	4.6	R	13.7	15.5% (18)	
Memotherm (P) [387]	123	24.0	6.1*	7.4	16.1*	4% (48)	3
TITAN (P) [388]	85	15.9 ^a	9.33 ¹	8.59*	11.43 ¹	Overall	3
	59	18.0	5.21	R	11.34	19% (24)	
Spanner (T) [385]	30	22.3	7.1	8.2	11.6	0% (2)	3
Memokath (T-P) [389]	211	20.3	8.2 ²	NA	NA	23% (84)	3
Horizon Bell-shaped (T) [390]	108	22.0	15.0	9.1	9.6	46% (3)	3

Q_{max} = maximum urinary flow rate (free uroflowmetry); (P) = permanent stent; R = retention; (T) = temporary stent; NA = not available. * = immediately after insertion; ^a = Madsen score; ¹ = at 2 years; ² = at 3 months.

3C.3.7 Emerging operations

3C.3.7.1 Intraprostatic ethanol injections

Mechanism of action: Liquid dehydrated ethanol (95-98%) or ethanol gel is injected into the prostatic parenchyma either transurethrally [395-405], transperineally [400, 406, 407], or transrectally [400]. There is no consensus on the number or volume of injections, which depends on prostate volume, urethral length and/or presence of a median lobe, ranging from 2 to 25 mL in different studies. Most patients need an indwelling catheter after the procedure.

Efficacy: Several open trials without randomisation [395-407] have been published. Mean follow-up varied from 3 - 54 months, showing significant reduction in IPSS (-41% to -71%), PVR (-6% to -99%) and Q_{max} (+35% to +155%) and QoL (-47% to -60%). After an initial strong reduction in prostate volume (-4% to -45%), prostate size increased again by 1-2 years, although LUTS and Q_{max} remained improved [397]. No predictive efficacy parameter or dose-response relationship has been found [399, 404]. Little is known about the durability of clinical effects later than 1 year; one trial with a mean follow-up of 3 years showed a re-treatment rate of 41% [397]. A table with the key studies is available in the supplementary online material, Table S.7.

Tolerability and safety: Adverse events included: perineal or abdominal discomfort/pain, storage LUTS (≤ 40%), haematuria (≤ 40%), UTI or epididymitis, and retention. Less frequently reported (< 5%) were: decreased libido, retrograde ejaculation, urgency urinary incontinence, urethral stenosis, and ED. Two cases of bladder necrosis required cystectomy and urinary diversion were reported [399].

Practical considerations: The mechanism of action, patient selection, and application of ethanol have not been well investigated. In addition, severe adverse events occurred and long-term results are sparse. Intraprostatic ethanol injections are therefore regarded as experimental procedures for use only in trials.

Recommendation	LE	GR
Intraprostatic ethanol injections for men with moderate-to-severe LUTS secondary to BPO are still experimental and should be performed only in clinical trials.	3	C

BPO = benign prostatic obstruction; LUTS = lower urinary tract symptoms.

3C.3.7.2 Intra-prostatic botulinum toxin injections

Mechanism of action: Experience with intra-prostatic injections for the treatment of LUTS/BPO exists only for subtype BTX-A, which reduces LUTS by induction of apoptosis of prostatic (epithelial) cells leading to tissue atrophy and size reduction, and neuronal inhibition [408-412]. Down-regulation of α₁-adrenergic receptors may contribute to smooth muscle cell relaxation [408].

BTX-A can be injected into the prostatic parenchyma transperineally, transurethrally or transrectally. Different doses (100-300 U Botox™ or 300-600 U Dysport™) and dilutions (25-50 U Botox™/mL or 75 U Dysport™/mL) were used.

Efficacy: A review of 20 studies of varying evidence levels showed significant IPSS reduction in 13 studies [413], and significant Q_{max} improvement in 14. The reduction in prostate volume varied and was statistically significant in 18 studies. Durability of the effects ranged from 3 to 30 months [413].

The results from the largest placebo-controlled study of BTX-A (100 U, 200 U, and 300 U) however,

showed no significant difference in terms of IPSS, QoL, and Q_{\max} at week 12 [414]. Re-treatment rates with BTX-A were as high as 29% [415].

Tolerability and safety: BoNTA injections were well tolerated in all studies. The main reported complications after treatment included dysuria, haematuria, epididymitis, prostatitis, and grade 2-3 events (unspecified) among 35% of patients in the series [413]. In addition, patients may receive a transurethral catheter or perform clean intermittent catheterisation during the early post-operative period (1 week to 1 month) [416-418]. Intraprostatic injection of BoNTA in patients with BPE seem to have no impact on sexual function [413, 419].

Practical considerations: Initial studies indicated that BoNTA injections into the prostatic parenchyma seem to be a promising and rapid, minimally invasive treatment modality with low morbidity for patients who are refractory to medical treatment or in urinary retention. However, BTX-A has been injected into only a few patients, and all trials have a limited follow-up. Recent studies found no significant difference in the efficacy between BoNTA and placebo arm. Trials with a larger number of patients, randomisation against saline injections, drugs, TURP, or other minimally invasive treatments, systematic evaluation of doses and dilutions, and long-term follow-up are necessary to judge adequately the value of intraprostatic BoNTA injections in the context of other available medical or surgical treatments of LUTS/BPO.

Recommendation	LE	GR
Intraprostatic BTX injections for men with bothersome moderate-to-severe LUTS secondary to BPO or men in urinary retention are still experimental and should be performed only in clinical trials.	3	C

BPO = benign prostatic obstruction; BTX = botulinum toxin ; LUTS = lower urinary tract symptoms.

3C.3.7.3 Minimal invasive simple prostatectomy

Mechanism of action: The term minimal invasive simple prostatectomy (MISP) includes the laparoscopic simple prostatectomy (LSP) and robot-assisted simple prostatectomy (RASP). The technique for LSP was first described in 2002 [420], while the first RASP was reported in 2008 [421]. Both LSP and RASP are performed using different personalised techniques, developed based on the transcapsular (Millin) or transvesical (Freyer) techniques of open simple prostatectomy. An extraperitoneal approach is mostly used for LSP, while a transperitoneal is mostly used for RASP.

Efficacy: In 14 studies (11 case series and 3 comparative retrospective non-randomised case-control studies) with a total of 626 patients with large adenomas treated with LSP were analysed [422] (see supplementary online material Table S.8). Follow-up ranged from one to six months. IPSS, and Q_{\max} improved significantly in all studies compared to baseline and improvements were similar compared to OP in the comparative studies [422]. In one retrospective study with a mean follow-up of 30 months, improvement in IPSS and Q_{\max} remained durable [423].

Seven non-comparative case series on RASP ranging in size from 3-35 patients (in total 95 cases) are available [421, 424-429]. In all these series with a mean follow-up ranging from 1-13 months, a substantial postoperative improvement in urinary symptoms and Q_{\max} was observed. The studies with >10 patients are presented in the supplementary online material Table S.8.

Tolerability and safety: The systematic review on LSP demonstrated that the most frequent complications were bleeding requiring transfusion (5.6%), secondary haematuria/urinary retention requiring re-catheterisation (3%), urogenital tract infection (1.7%), reoperation (1.3%), urosepsis (0.9%), incontinence (0.9%), clot retention (0.9%) and urinary fistula (0.8%). In the three comparative studies, LSP was associated with less blood loss and a reduced irrigation requirement, a shorter catheterisation and hospitalisation time, at the expense of a longer operative time (see online Table S.8). In one study (not included in the systematic review) of 34 cases of single-port transvesical enucleation of the prostate (STEP), there were three complications during STEP (one death, one bowel injury and one haemorrhage) and five afterwards (four bleeding, one epididymo-orchitis) [430].

The studies on RASP mainly focused on the feasibility of the method and reported only major complications. There were two cases of conversion to OP (2.1%). Transfusion was required only in two patients in the earliest series [421, 429]. In addition two cases of urinary leak, one case of postoperative umbilical hernia and a case of a bladder neck stricture were reported [424, 426, 428]. Interestingly, one study reported no significant change in the preservation of sexual activity (mean Sexual Health Inventory: 12.7 pre-operatively vs. 12.5 at 6 months post-operatively) even if a persistent, severe urinary incontinence was recorded in 1 out of 9 patients [426].

Practical considerations: It should be underlined that the available evidence comes from case series and retrospective comparative studies from selected centers. High quality studies are needed to compare the efficacy, safety, and hospitalisation between MISP and both OP and endoscopic methods. Long-term outcomes, learning curve and cost of MISP should also be evaluated

Recommendation	LE	GR
MISP seems to be feasible in men with prostate sizes > 80 mL needing surgical treatment. Since more data are required, MISP remains under evaluation.	3	C

MISP = minimal invasive simple prostatectomy.

3C.3.7.4 Prostatic urethral lift

Mechanism of action: The prostatic urethral lift (PUL) represents a novel minimally invasive approach under local or general anaesthesia. Encroaching lateral lobes are compressed by small permanent suture-based implants delivered under cystoscopic guidance (Urolift®) resulting in an opening of the prostatic urethra that leaves a continuous anterior channel through the prostatic fossa ranging from bladder neck to the verumontanum.

Efficacy: The available studies on PUL are presented in the supplementary online material Table S.9 [431-435]. In general, PUL achieves a significant improvement in IPSS (-39% to -52%), Q_{max} (+32% to +59%) and QoL (-48% to -53%). There is only one RCT comparing PUL with sham [433]. The primary endpoint was met at 3 months with a 50% reduction in AUA-SI from 22.1 to 11.0 points and remained stable up to 12 months. Change for AUA-SI was 88% greater for the treatment group than sham control. Also Q_{max} increased significantly from 8.1 to 12.4 mL/s relative to baseline at 3 months and this result could still be confirmed at 12 months. The difference in clinical response for Q_{max} between both groups was of statistical significance. A relevant benefit with regard to PVR was not demonstrated compared to baseline nor relative to sham control.

A multicenter, prospective, non-randomised study on 64 patients evaluated effectiveness of PUL over 2 years [434]. At 2 weeks, IPSS improved by 42% and was maintained for 24 months. A similar therapeutic effect was also observed for Q_{max} which increased significantly by 45% from 8.3 to 12.0 mL/s after 2 weeks. This benefit was stable up to 2 years. However, at the 2 year follow-up, 20% of patients required additional treatment due to initial PUL failure [434].

Tolerability and safety: The most common complications reported post-operatively included haematuria (16-63%), dysuria (25-58%), pelvic pain (5-17.9%), urgency (7.1-10%), transient incontinence (3.6-16%), and urinary tract infection (2.9-11%). Most symptoms were mild to moderate in severity and resolved within two to four weeks after the procedure.

PUL seems to have no significant impact on sexual function. Evaluation of sexual function as measured by IIEF-5, Male Sexual Health Questionnaire-Ejaculatory Dysfunction, and Male Sexual Health Questionnaire-Bother in patients undergoing PUL showed that erectile and ejaculatory function were preserved (supplementary online material Table S.9) [431-435].

Practical considerations: Prostates up to 100 cm³ with lateral lobe obstruction are appropriate for this technique while an obstructed or protruding medial lobe cannot be effectively treated. Of note, resection or ablation of prostatic tissue is still possible without any limitation after initial treatment with the prostatic urethral lift. High quality studies are needed to compare the efficacy, safety and durability between PUL and established invasive treatments.

Recommendation	LE	GR
Prostatic urethral lift (Urolift™) leads to short-term objective and subjective improvement. RCTs with longer follow-up are needed to confirm these initial promising results	1b	B

RCT = randomised controlled trial.

3C.4 Patient selection

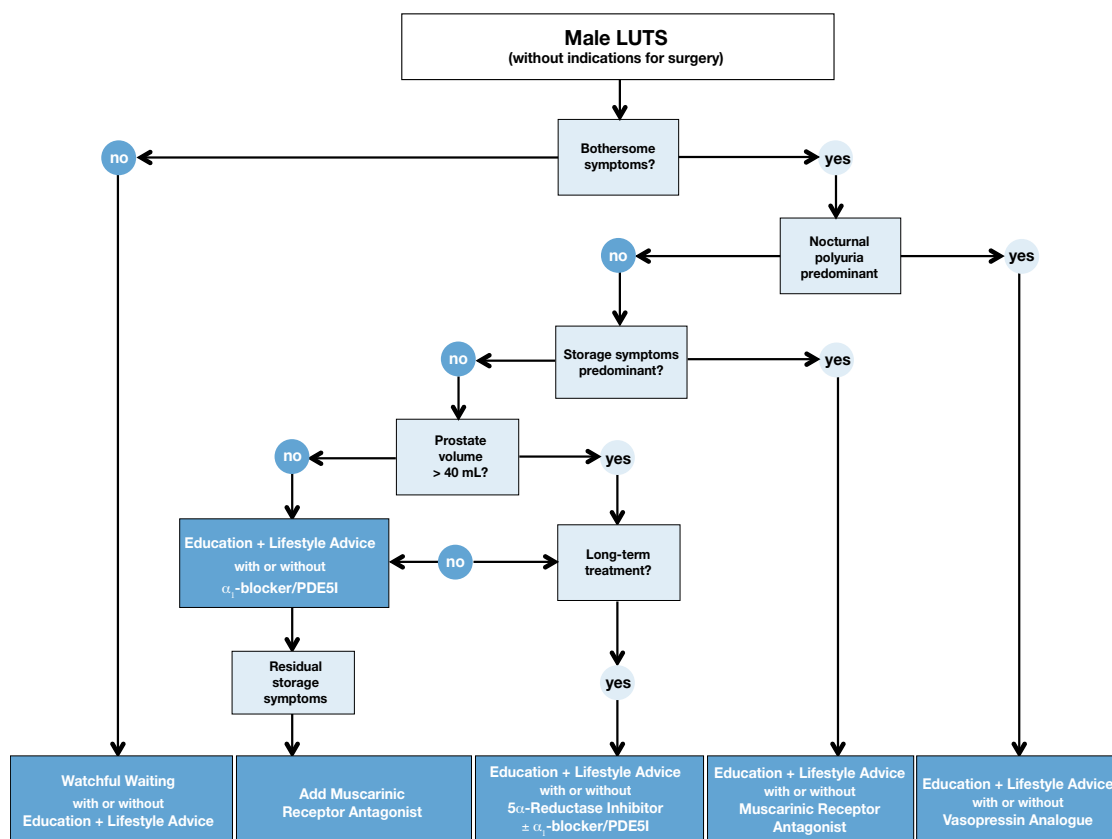
The choice of treatment depends on the assessed findings of patient evaluation, ability of the treatment to change the findings, treatment preferences of the individual patient, and the expectations to be met in terms of speed of onset, efficacy, side effects, QoL, and disease progression. A table which provides differential information about speed of onset and influence on basic parameters with conservative, medical or surgical treatment options is described in the supplementary online material, Table S.10.

Behavioural modifications, with or without medical treatments, are usually the first choice of therapy. Figure 3 provides a flow chart illustrating treatment choice according to evidence-based medicine and patient profiles.

Surgical treatment is usually required when patients have experienced recurrent or refractory urinary retention, overflow incontinence, recurrent UTIs, bladder stones or diverticula, treatment-resistant macroscopic haematuria due to BPH/BPE, or dilatation of the upper urinary tract due to BPO, with or without renal insufficiency (absolute operation indications, need for surgery).

Additionally, surgery is usually needed when patients have not obtained adequate relief from LUTS or PVR using conservative or medical treatments (relative operation indications). The choice of surgical technique depends on prostate size, comorbidities of the patient, ability to have anaesthesia, patients' preferences, willingness to accept surgery-associated specific side-effects, availability of the surgical armamentarium, and experience of the surgeon with these surgical techniques. An algorithm for surgical approaches according to evidence-based medicine and patient profile is provided in Figure 4.

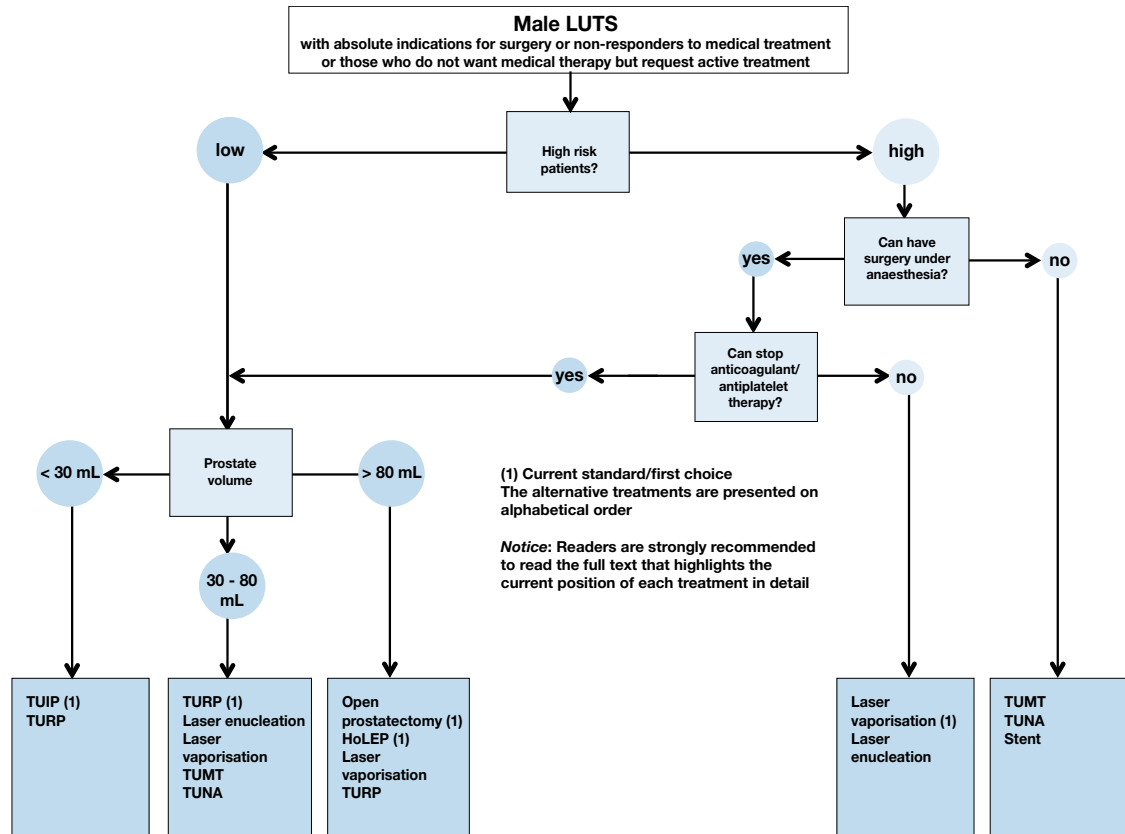
Figure 3: Treatment algorithm of male LUTS using medical and/or conservative treatment options.
Treatment decisions depend on results assessed during initial evaluation. Note that patients'



preferences may result in different treatment decisions.

LUTS = lower urinary tract symptoms; PDE5I = phosphodiesterase type 5 inhibitors.

Figure 4: Treatment algorithm of bothersome LUTS refractory to conservative/medical treatment or in cases of absolute operation indications. The flowchart was stratified by the patient's ability to have anaesthesia, cardiovascular risk, and prostate size.



Laser vaporisation includes GreenLight, thulium, and diode lasers vaporisation;
Laser enucleation includes holmium and thulium laser enucleation.

HoLEP = holmium laser enucleation; TUIP = transurethral incision of the prostate; TUMT = transurethral microwave therapy; TUNA = transurethral needle ablation; TURP = transurethral resection of the prostate.

3D FOLLOW-UP

3D.1 Watchful waiting (behavioural)

Patients who elect to pursue a WW policy should be reviewed at 6 months and then annually, provided there is no deterioration of symptoms or development of absolute indications for surgical treatment. The following are recommended at follow-up visits: IPSS, uroflowmetry, and PVR volume.

3D.2 Medical treatment

Patients receiving α_1 -blockers, muscarinic receptor antagonists, PDE5Is or the combination of α_1 -blockers + 5-ARIs or muscarinic receptor antagonists should be reviewed 4-6 weeks after drug initiation to determine the treatment response. If patients gain symptomatic relief in the absence of troublesome adverse events, drug therapy may be continued. Patients should be reviewed at 6 months and then annually, provided there is no deterioration of symptoms or development of absolute indications for surgical treatment. The following tests are recommended at follow-up visits: IPSS, uroflowmetry, and PVR volume. FVC or bladder diaries should be used to assess response to treatment for predominant storage symptoms or nocturnal polyuria.

Patients receiving 5-ARIs should be reviewed after 12 weeks and 6 months to determine their response and adverse events. The following are recommended at follow-up visits: IPSS, uroflowmetry and PVR volume.

Men taking 5-ARIs should be followed up regularly using serial PSA testing if life expectancy is > 10 years and if a diagnosis of prostate cancer could alter management. A new baseline PSA should be determined

at 6 months, and any confirmed increase in PSA while on 5-ARIs should be evaluated.

In patients receiving desmopressin, serum sodium concentration should be measured at day 3 and 7 as well as after 1 month, and if serum sodium concentration has remained normal, every 3 months subsequently. The following tests are recommended at follow-up visits: serum-sodium concentration and frequency volume chart. The follow-up sequence should be restarted after dose escalation.

3D.3 Surgical treatment

Patients after prostate surgery should be reviewed 4-6 weeks after catheter removal to evaluate treatment response and adverse events. If patients have symptomatic relief and are without adverse events, no further re-assessment is necessary.

The following tests are recommended at follow-up visit after 4 to 6 weeks: IPSS, uroflowmetry and PVR volume.

Recommendation	LE	GR
Follow-up for all conservative, medical, or operative treatment modalities is based on empirical data or theoretical considerations, but not on evidence-based studies.	3-4	C

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5. CONFLICT OF INTEREST

All members of the EAU Non-neurogenic Male LUTS Guidelines Panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the EAU website. These Guidelines were developed with the financial support of the EAU. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

Guidelines on Male Sexual Dysfunction:

Erectile dysfunction and premature ejaculation

K. Hatzimouratidis (Chair), I. Eardley, F. Giuliano,
I. Moncada, A. Salonia

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1. INTRODUCTION

1.1 Aim

The aim of these guidelines is to present the current evidence for the diagnosis and treatment of patients suffering from erectile dysfunction (ED) and premature ejaculation (PE). ED and PE are the two main complaints in male sexual medicine [1, 2]. Pharmacological therapies have completely changed the diagnostic and therapeutic approach to ED and the Guidelines Office of the European Association of Urology (EAU) has appointed an Expert Panel to update previously published EAU guidelines for ED or impotence.

1.2 Publication history

The first EAU Guidelines on Erectile Dysfunction were published in 2000 with subsequent updates in 2001, 2002, 2004, 2005, 2009, 2013 and 2014. In particular, the 2009 document presented a significant update of the previous publication with the inclusion of the topic "Premature Ejaculation" and the text was renamed to "EAU Guidelines on Male Sexual Dysfunction" [3]. In 2011 the Panel decided to develop separate guidelines addressing Penile Curvature, which resulted in a separate publication in 2012 [4]. In 2014 a guideline on Priapism was completed [5].

For this 2015 version a literature search was performed to identify the efficacy and safety of avanafil (a new phosphodiesterase type 5 inhibitors) in men with ED, and a section on the topic was included. Additionally, the text has been updated and significantly reduced so that only key information is included and re-formatted according to the EAU template for non-oncology Guidelines, so that all Guidelines follow a similar format.

Alongside several scientific summaries published in the EAU scientific journal, European Urology [6-10], a quick reference document (Pocket Guidelines) is available, both in print and in a number of versions for mobile devices, presenting the main findings of the Male Sexual Dysfunction guidelines. These are abridged versions which may require consultation together with the full text versions. All available material can be viewed and downloaded for personal use at the EAU website, which also includes a selection of translations produced by national urological associations: <http://www.uroweb.org/guidelines/online-guidelines/>.

This document was peer reviewed prior to publication.

1.3 Panel composition

The EAU Guidelines Panel on Male Sexual Dysfunction consists of urologists. Members of this Panel have been selected based on their expertise to represent the professionals treating patients suffering from ED.

2. METHODS

References used in this text are graded according to their Level of Evidence (LE) and Guidelines are given a Grade of Recommendation (GR). In this 2015 EAU Guidelines compilation, all standard information on LE and GR has been taken out of the individual Guidelines topics for the sake of brevity. The methodology section (see the introduction chapter of the complete book) outlines the LE and GR criteria which are used throughout the Guidelines, according to a classification system modified from the Oxford Centre for Evidence-based Medicine Levels of Evidence.

For both conditions (ED and PE) a systemic literature search was performed by the panel members. The MedLine database was searched using the major Medical Subject Headings (MeSH) terms "erectile dysfunction", "sexual dysfunction" "ejaculation". All articles published between January 2009 (previous update) and October 2014 were considered for review. For Premature Ejaculation the MedLine search was supplemented by the term "premature ejaculation" in all search fields, for the 2015 print, covering a time frame up to October 2014. The Panel also identified critical problems and knowledge gaps, setting priorities for future clinical research.

3. THE GUIDELINE

3A ERECTILE DYSFUNCTION

3A.1 Epidemiology/aetiology/pathophysiology

Erection is a complex phenomenon which implies a delicate and coordinated equilibrium among the neurological, vascular and the tissue compartments. It includes arterial dilation, trabecular smooth muscle relaxation, and activation of the corporeal veno-occlusive mechanism [11]. ED is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance [12]. ED may affect physical and psychosocial health and may have a significant impact on the quality of life (QoL) of sufferers and their partners [13-15]. There is increasing evidence that ED can be an early manifestation of coronary artery and peripheral vascular disease. ED should not be regarded only as a QoL issue, but also as a potential warning sign of cardiovascular disease (CVD) [16-18].

3A.1.1 Epidemiology

Epidemiological data have shown a high prevalence and incidence of ED worldwide. Among others, the Massachusetts Male Aging Study (MMAS) [13] reported an overall prevalence of 52% ED in non-institutionalised men aged 40-70 years in the Boston area; specific prevalence for minimal, moderate, and complete ED was 17.2%, 25.2%, and 9.6%, respectively. In the Cologne study of men aged 30-80 years, the prevalence of ED was 19.2%, with a steep age-related increase from 2.3% to 53.4% [19]. The incidence rate of ED (new cases per 1,000 men annually) was 26 in the long-term data from the MMAS study [20] and 19.2 (mean follow-up of 4.2 years) in a Dutch study [21]. In a cross-sectional real-life study among men seeking first medical help for new-onset ED, one in four patients was younger than 40 years, with almost 50% of the young men complaining of severe ED [22]. Differences between these studies can be explained by differences in methodology, in the ages, and socioeconomic and cultural status of the populations studied.

3A.1.2 Risk factors

ED shares both unmodifiable and modifiable common risk factors with CVD (e.g., obesity, diabetes mellitus, dyslipidemia, metabolic syndrome, lack of exercise, and smoking) [15, 23, 24]. In this context, men with mild ED have similar risk factors to those of a general ED clinical trial population [25]. Thus, mild ED emerged as an important indicator of risk for associated underlying disease (CVDs) [25]. A number of studies have shown some evidence that lifestyle modification [18, 26] and pharmacotherapy [26, 27] for cardiovascular risk factors may be of help in improving sexual function in men with ED. However, it should be emphasised that more controlled prospective studies are necessary to determine the effects of exercise or other lifestyle changes in prevention or treatment of ED [17].

Epidemiological studies have demonstrated consistent evidences for an association between lower urinary tract symptoms (LUTS)/benign prostatic hyperplasia (BPH) and sexual dysfunction regardless of age, and other comorbidities, and various lifestyle factors [28]. The Multinational Survey on the Aging Male (MSAM-7) study – performed in the US, France, Germany, Italy, Netherlands, Spain, and UK - systematically investigated the relationship between LUTS and sexual dysfunction in > 12,000 men aged 50-80 years. Of 83% men self-reported to be sexually-active, the overall prevalence of LUTS was 90%, with an overall prevalence of ED of 49%, and a reported complete absence of erection in 10% of patients. Moreover, the overall prevalence of ejaculation disorders was 46% [29].

3A.1.3 Pathophysiology

The pathophysiology of ED may be vasculogenic, neurogenic, anatomical, hormonal, drug-induced and/or psychogenic (Table 1) [11].

Table 1: Pathophysiology of ED

Vasculogenic	
-	Cardiovascular disease (hypertension, coronary artery disease, peripheral vasculopathy, etc.)
-	Diabetes mellitus
-	Hyperlipidaemia
-	Smoking
-	Major pelvic surgery (RP) or radiotherapy (pelvis or retroperitoneum)
Neurogenic	
<i>Central causes</i>	
-	Degenerative disorders (multiple sclerosis, Parkinson's disease, multiple atrophy, etc.)
-	Spinal cord trauma or diseases
-	Stroke
-	Central nervous system tumours
<i>Peripheral causes</i>	
-	Type 1 and 2 diabetes mellitus
-	Chronic renal failure
-	Polyneuropathy
-	Surgery (major surgery of pelvis/retroperitoneum, RP, colorectal surgery, etc.)
-	Surgery of the urethra (urethral stricture urethroplasty, etc)
Anatomical or structural	
-	Hypospadias, epispadias
-	Micropenis
-	Peyronie's disease
Hormonal	
-	Hypogonadism
-	Hyperprolactinemia
-	Hyper- and hypothyroidism
-	Hyper- and hypocortisolism (Cushing's disease, etc.)
-	Panhypopituitarism and multiple endocrine disorders
Drug-induced	
-	Antihypertensives (thiazide diuretics, etc.)
-	Antidepressants (selective serotonin reuptake inhibitors, tricyclics)
-	Antipsychotics (neuroleptics, etc.)
-	Antiandrogens (GnRH analogues and antagonists)
-	Recreational drugs (alcohol, heroin, cocaine, marijuana, methadone, synthetic drugs, anabolic steroids, etc.)
Psychogenic	
-	Generalised type (e.g., lack of arousability and disorders of sexual intimacy)
-	Situational type (e.g., partner-related, performance-related issues or due to distress)
Trauma	
-	Penile fracture
-	Pelvic fractures

3A.1.4 Post-radical prostatectomy ED, post-radiotherapy ED & post-brachytherapy ED

Radical prostatectomy (RP) in any form (open, laparoscopic, or robotic) is a widely performed procedure for patients with clinically localised prostate cancer (PCa) and a life expectancy of at least 10 years. This procedure may lead to treatment-specific sequelae affecting health-related QoL. This outcome has become increasingly important with the more frequent diagnosis of PCa in younger patients [30, 31]. Research has shown that 25-75% of men experience post-operative ED [32]. Given the growing clinical importance of robot-assisted RP (RARP), this type of surgery is becoming the paradigm for post-operative functional results. A systematic review has shown a significant advantage in favour of RARP in comparison with retropubic RP in terms of 12-month potency rates [33], without significant difference between laparoscopic RP and RARP. However, more controlled prospective studies are necessary to determine the actual superiority of RARP in terms of post-operative ED rates [34]. Overall, patient age and surgical volume, with the consequent ability to preserve neurovascular bundles, seem to be the main factors in promoting the highest rates of post-operative potency [30, 31].

Pre-operative potency is a major factor associated with the recovery of erectile function (EF) after surgery. Patients being considered for nerve-sparing RP (NSRP) should ideally be potent pre-operatively [30, 31]. Overall, the temporal aspects are of major clinical importance in terms of post-operative recovery of EF. Available data confirm that post-operative EF recovery can also occur years following RP (and up to 48 months). Likewise, it is shared opinion that the timing of post-operative therapy (any type) should be as close as possible to the surgical procedure [31,32].

ED is also a common sequela after external beam radiotherapy and brachytherapy for PCa [35, 36]. The mechanisms contributing to ED after prostate irradiation involve injury to the neurovascular bundles, penile vasculature, and cavernosal structural tissue [35, 36]. Alternative treatments for PCa including cryotherapy and high-intensity focused ultrasound (US) are associated with equivalent or worsened rates of ED compared to surgery or radiation therapy [37, 38].

3A.1.5 **Conclusions on the epidemiology/aetiology/pathophysiology of ED**

	LE
ED is common worldwide.	2b
ED shares risk factors with cardiovascular disease.	2b
Lifestyle modification (regular exercise and decrease in body mass index) can improve erectile function.	1b
ED is a symptom, not a disease. Some patients may not be properly evaluated or receive treatment for an underlying disease or condition that may be causing ED.	4
ED is common after RP, irrespective of the surgical technique used.	2b
ED is common after external radiotherapy and brachytherapy.	2b
ED is common after cryotherapy and high-intensity focused US.	2b

3A.2 **Classification**

ED is commonly classified into three categories based on its aetiology. These include organic, psychogenic and mixed ED. However, this classification should be used with caution since most cases are actually of mixed aetiology. It is therefore suggested to use the term primary organic or primary psychogenic.

3A.3 **Diagnostic evaluation**

3A.3.1 **Basic work-up**

The first step in evaluating ED is always a detailed medical and sexual history of patients, and partners when available [39, 40]. In this context, taking a comprehensive medical history may reveal one of the many common disorders associated with ED [39, 40]. It is important to establish a relaxed atmosphere during history-taking. This will make it easier to i) ask questions about EF and other aspects of the sexual history; and, ii) to explain the diagnosis and therapeutic approach to the patient and his partner. Figure 1 gives the minimal diagnostic evaluation (basic work-up) in patients with ED.

3A.3.2 **Sexual history**

The sexual history must include (when available) information about sexual orientation, previous and current sexual relationships, current emotional status, onset and duration of the erectile problem, and previous consultations and treatments. The sexual health status of the partner(s) (when available) can also be useful. A detailed description should be made of the rigidity and duration of both sexually-stimulated and morning erections and of problems with sexual desire, arousal, ejaculation, and orgasm [39, 41]. Validated psychometric questionnaires, such as the International Index for Erectile Function (IIEF) [42] or its short version Sexual Health Inventory for Men (SHIM), help to assess the different sexual function domains (i.e. sexual desire, EF, orgasmic function, intercourse, and overall satisfaction), as well as the impact of a specific treatment modality. Psychometric analysis also supports the use of the erectile hardness score for the assessment of penile rigidity in practice and in clinical trials research [43]. In cases of clinical depression, the use of a 2-question scale for depression is recommended in the everyday clinical practice: "During the past month have you often been bothered by feeling down, depressed or hopeless? During the past month have you often been bothered by little interest or pleasure, doing things?"[44]. Patients should always be screened for symptoms of possible hypogonadism (= testosterone deficiency), including decreased energy, libido, fatigue, and cognitive impairment, as well as for LUTS. For this specific purpose, screening questionnaires, such as the International Prostate Symptom Score may be utilised [45].

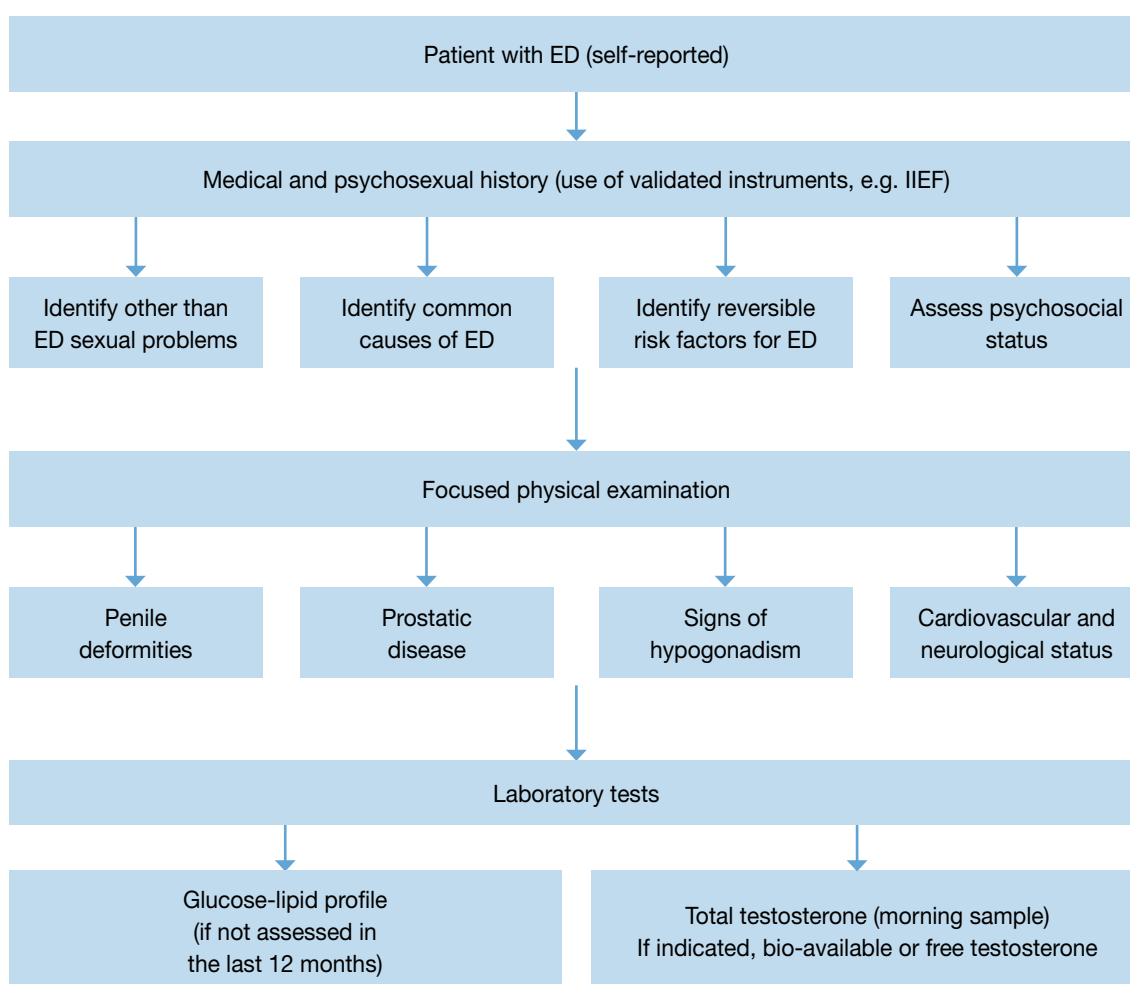
3A.3.3 **Physical examination**

Every patient must be given a physical examination focused on the genitourinary, endocrine, vascular, and neurological systems [46, 47]. A physical examination may reveal unsuspected diagnoses, such as Peyronie's disease, pre-malignant or malignant genital lesions, prostatic enlargement or irregularity/nodularity, or signs and symptoms suggesting hypogonadism (small testes, alterations in secondary sexual characteristics etc). Blood pressure and heart rate should be measured if they have not been assessed in the previous 3-6 months.

3A.3.4 **Laboratory testing**

Laboratory testing must be tailored to the patient's complaints and risk factors. Patients may need a fasting blood glucose or HbA1c and lipid profile if not recently assessed. Hormonal tests include an early morning total testosterone. If indicated, bioavailable or calculated-free testosterone may be needed to corroborate total testosterone measurements. However, the threshold of testosterone to maintain ED is low and ED is usually a symptom of more severe cases of hypogonadism [23, 48-50]. For levels > 8 nmol/l the relationship between circulating testosterone and sexual functioning is very low [23, 48-50]. Additional laboratory tests may be considered in selected patients (eg, prostate-specific antigen (PSA) [51]; prolactin, and luteinising hormone [52]). Although physical examination and laboratory evaluation of most men with ED may not reveal the exact diagnosis, these opportunities to identify critical comorbid conditions should not be missed [47].

Figure 1: Minimal diagnostic evaluation (basic work-up) in patients with ED



ED = erectile dysfunction; IIEF = International Index of Erectile Function.

3A.3.5 **Cardiovascular system and sexual activity: the patient at risk**

Patients who seek treatment for sexual dysfunction have a high prevalence of CVDs. Epidemiological surveys have emphasised the association between cardiovascular and metabolic risk factors and sexual dysfunction in both men [53] and women [54]. Overall, ED can improve the sensitivity of screening for asymptomatic CVD in men with diabetes [55, 56]. ED significantly increases the risk of CVD, coronary heart disease, stroke, and all-cause mortality, and the increase is probably independent of conventional cardiovascular risk factors [16, 18, 57].

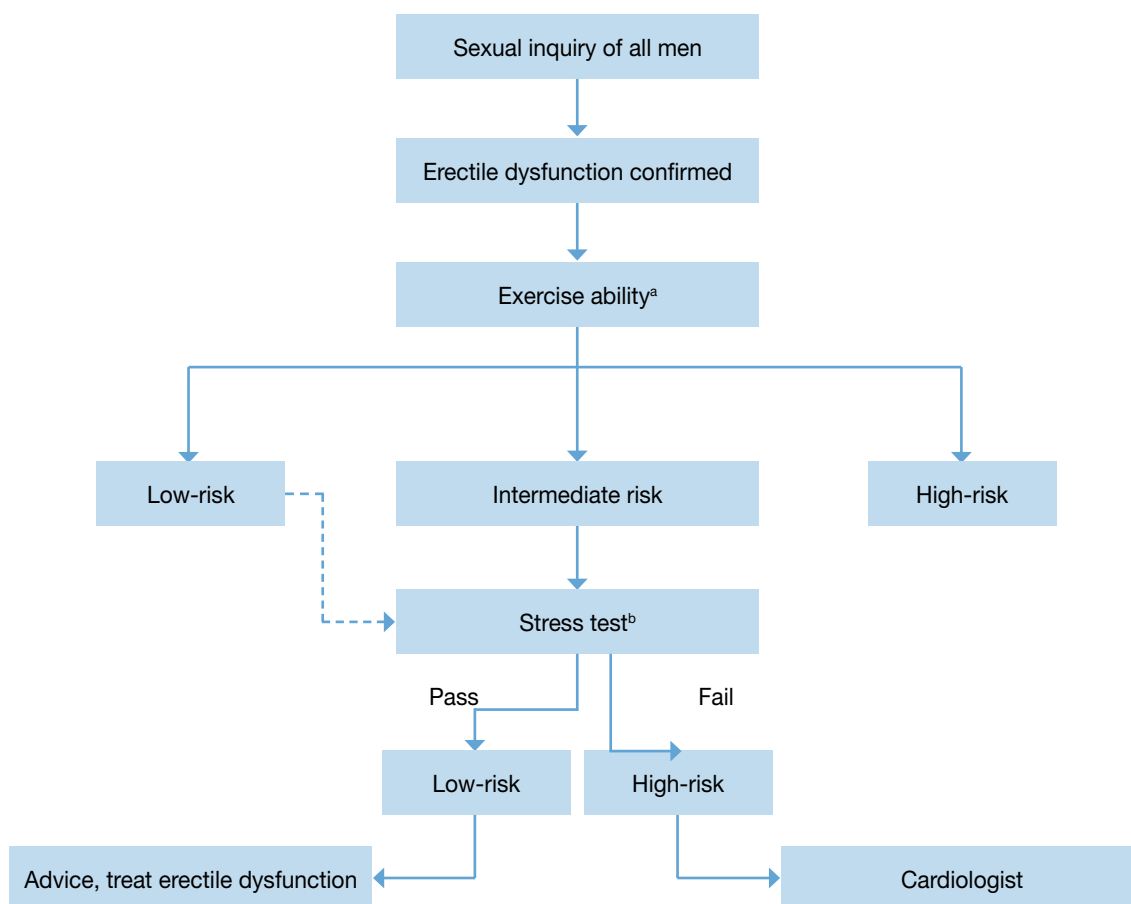
The EAU Guidelines for diagnosing and treating men with ED have been adapted from previously published recommendations from the Princeton Consensus conferences on sexual dysfunction and cardiac risk [16]. The Princeton Consensus (Expert Panel) Conference is dedicated to optimising sexual function and preserving cardiovascular health [58-60]. Accordingly, patients with ED can be stratified into three cardiovascular risk categories (Table 2), which can be used as the basis for a treatment algorithm for initiating or resuming sexual activity (Figure 2). It is also possible for the clinician to estimate the risk of sexual activity in most patients from their level of exercise tolerance, which can be determined when taking the patient's history [27].

Table 2: Cardiac risk stratification (based on 2nd Princeton Consensus [59])

Low-risk category	Intermediate-risk category	High-risk category
Asymptomatic, < 3 risk factors for CAD (excluding sex)	≥ 3 risk factors for CAD (excluding sex)	High-risk arrhythmias
Mild, stable angina (evaluated and/or being treated)	Moderate, stable angina	Unstable or refractory angina
Uncomplicated previous MI	Recent MI (> 2, < 6 weeks)	Recent MI (< 2 weeks)
LVD/CHF (NYHA class I)	LVD/CHF (NYHA class II)	LVD/CHF (NYHA class III/IV)
Post-successful coronary Revascularisation	Non-cardiac sequelae of atherosclerotic disease (e.g., stroke, peripheral vascular disease)	Hypertrophic obstructive and other cardiomyopathies
Controlled hypertension		Uncontrolled hypertension
Mild valvular disease		Moderate-to-severe valvular disease

CAD = coronary artery disease; CHF = congestive heart failure; LVD = left ventricular dysfunction; MI = myocardial infarction; NYHA = New York Heart Association.

Figure 2: Treatment algorithm for determining level of sexual activity according to cardiac risk in ED (based on 3rd Princeton Consensus) [60]



^a Sexual activity is equivalent to walking 1 mile on the flat in 20 min or briskly climbing two flights of stairs in 10 s.

^b Sexual activity is equivalent to 4 min of the Bruce treadmill protocol.

3A.3.5.1 *Low-risk category*

The low-risk category includes patients who do not have any significant cardiac risk associated with sexual activity. Low-risk is typically implied by the ability to perform exercise of modest intensity, which is defined as ≥ 6 "metabolic equivalents of energy expenditure in the resting state" without symptoms. According to current knowledge of the exercise demand or emotional stress associated with sexual activity, low-risk patients do not need cardiac testing or evaluation before the initiation or resumption of sexual activity or therapy for sexual dysfunction.

3A.3.5.2 *Intermediate- or indeterminate-risk category*

The intermediate- or indeterminate-risk category consists of patients with an uncertain cardiac condition or patients whose risk profile requires testing or evaluation before the resumption of sexual activity. Based upon the results of testing, these patients may be moved to either the high- or low-risk group. A cardiology consultation may be needed in some patients to help the primary physician determine the safety of sexual activity.

3A.3.5.3 *High-risk category*

High-risk patients have a cardiac condition that is sufficiently severe and/or unstable for sexual activity to carry a significant risk. Most high-risk patients have moderate-to-severe symptomatic heart disease. High-risk individuals should be referred for cardiac assessment and treatment. Sexual activity should be stopped until the patient's cardiac condition has been stabilised by treatment, or a decision made by the cardiologist and/or internist that it is safe to resume sexual activity.

3A.3.6 ***Specialised diagnostic tests***

Most patients with ED can be managed within the sexual care setting; conversely, some patients may need specific diagnostic tests (Tables 3 and 4).

3A.3.6.1 *Nocturnal penile tumescence and rigidity test*

The nocturnal penile tumescence and rigidity assessment should be done on at least two nights. A functional erectile mechanism is indicated by an erectile event of at least 60% rigidity recorded on the tip of the penis that lasts for ≥ 10 min [61].

3A.3.6.2 *Intracavernous injection test*

The intracavernous injection test gives limited information about vascular status. A positive test is a rigid erectile response (unable to bend the penis) that appears within 10 min after the intracavernous injection and lasts for 30 min [62]. Overall, the test is inconclusive as a diagnostic procedure and a duplex Doppler study of the penis should be requested, if clinically warranted.

3A.3.6.3 *Duplex ultrasound of the penis*

A peak systolic blood flow > 30 cm/s, an end-diastolic velocity of < 3 cm/s and a resistance index > 0.8 are generally considered normal [63]. Further vascular investigation is unnecessary when a Duplex examination is normal.

3A.3.6.4 *Arteriography and dynamic infusion cavernosometry or cavernosography*

Arteriography and dynamic infusion cavernosometry or cavernosography should be performed only in patients who are being considered for vascular reconstructive surgery [64].

3A.3.6.5 *Psychiatric assessment*

Whenever clinically indicated, patients with psychiatric disorders should be referred to a psychiatrist who is particularly interested in sexual health. In younger patients (< 40 years) with long-term primary ED [22], psychiatric assessment may be helpful before any organic assessment is carried out.

3A.3.6.6 *Penile abnormalities*

Surgical correction may be needed for patients with ED due to penile abnormalities (e.g. hypospadias, congenital curvature, or Peyronie's disease with preserved rigidity).

3A.3.7 ***Patient education - consultation and referrals***

Consultation with the patient should include a discussion of the expectations and needs of both the patient and his stable sexual partner, if available. It should also review both the patient's and partner's understanding of ED and the results of diagnostic tests, and provide a rational selection of treatment options [65]. Patient and partner education is an essential part of ED management [65, 66].

Table 3: Indications for specific diagnostic tests

Primary ED (not caused by organic disease or psychogenic disorder).
Young patients with a history of pelvic or perineal trauma, who could benefit from potentially curative vascular surgery.
Patients with penile deformities which might require surgical correction (e.g., Peyronie's disease, congenital curvature).
Patients with complex psychiatric or psychosexual disorders.
Patients with complex endocrine disorders.
Specific tests may be indicated at the request of the patient or his partner.
Medico-legal reasons (e.g., implantation of penile prosthesis, sexual abuse).

Table 4: Specific diagnostic tests

NTPR using Rigiscan
Vascular studies
- Intracavernous vasoactive drug injection
- Penile Dynamic Duplex Doppler study
- Penile Dynamic Infusion Cavernosometry and Cavernosography
- Internal pudendal arteriography
Neurological studies (e.g., bulbocavernosus reflex latency, nerve conduction studies)
Endocrinological studies
Specialised psychodiagnostic evaluation

3A.3.8 Recommendations for the diagnostic evaluation of ED

	LE	GR
A comprehensive medical and sexual history is needed.	3	B
Clinical use of validated questionnaire related to ED may help to assess all sexual function domains and the effect of a specific treatment modality.	3	B
Physical examination is needed in the initial assessment of men with ED to identify underlying medical conditions that may be associated with ED.	4	B
Routine laboratory tests, including glucose-lipid profile and total testosterone, are required to identify and treat any reversible risk factors and lifestyle factors that can be modified.	4	B
Specific diagnostic tests are indicated by only a few conditions.	4	B

ED = erectile dysfunction.

3A.4. Disease management**3A.4.1 Treatment options**

ED may be associated with modifiable or reversible risk factors, including lifestyle or drug-related factors. These factors may be modified either before, or at the same time as, specific therapies are used. Likewise, ED may be associated with concomitant and underlying conditions (such as, for instance, endocrine disorders and metabolic disorders - e.g. diabetes - some cardiovascular problems - e.g. hypertension) which should always be well-controlled as the first step of ED treatment. As a rule, ED can be treated successfully with current treatment options, but cannot be cured. The only exceptions are psychogenic ED, post-traumatic arteriogenic ED in young patients, and hormonal causes (e.g. hypogonadism and hyperprolactinaemia [49, 52]), which potentially can be cured with specific treatment. Most men with ED will be treated with therapeutic options that are not cause specific. This results in a structured treatment strategy that depends on efficacy, safety, invasiveness and cost, as well as patient preference [65]. In this context, physician-patient (partner) dialogue is essential throughout the management of ED. The assessment of treatment options must be tailored according to patient and partner satisfaction, QoL factors as well as treatment-related safety and efficacy. A treatment algorithm for ED is shown in Figure 3.

3A.4.2 Lifestyle management in ED with concomitant risk factors

The basic work-up of the patient must identify reversible risk factors for ED. Lifestyle changes and risk factor modification must precede or accompany any pharmacological treatment. Major clinical potential benefits of lifestyle changes may be obtained in men with specific comorbid cardiovascular or metabolic disorders, such as diabetes or hypertension [17, 67].

3A.4.3 **Erectile dysfunction after radical prostatectomy**

Use of pro-erectile drugs following RP is important in achieving post-operative EF. Several trials have shown higher rates of EF recovery after RP in patients receiving any drug (therapeutic or prophylactic) for ED. Early compared with delayed EF treatment seems to impact on the natural healing time of potency [31]. Currently available therapeutic armamentarium follows the treatment algorithm for ED which is shown in Figure 3.

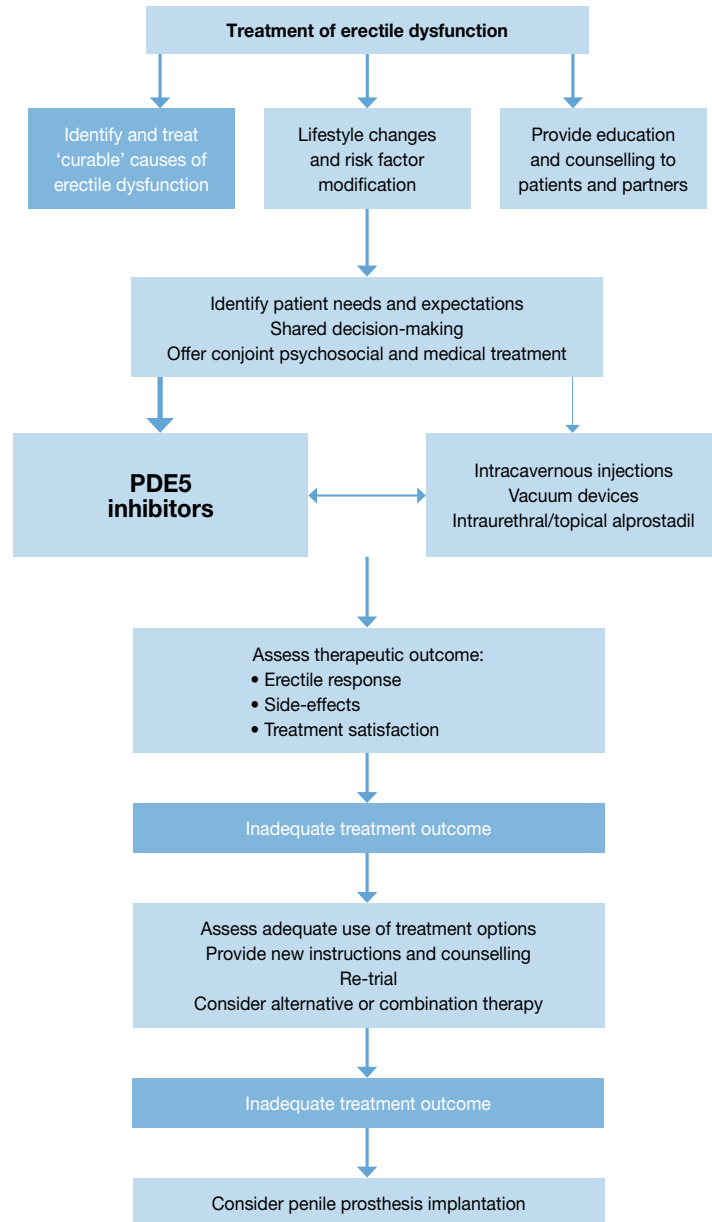
The management of post-RP ED has been revolutionised by the advent of phosphodiesterase 5 inhibitors (PDE5Is), with their demonstrated efficacy, ease of use, good tolerability, excellent safety, and positive impact on QoL. It must be emphasised that post-RP ED patients are poor responders to PDE5Is. However, PDE5Is are the first-line therapy in patients who have undergone nerve-sparing (NS) surgery regardless of the surgical technique used [30, 31]. A number of clinical parameters have been identified as potential predictors of PDE5Is in men undergoing RP. Patient age and quality of NS technique are a key factors in preserving post-operative EF [30, 31, 33]. The response rate to sildenafil treatment for ED after RP in different trials has ranged from 35% to 75% among those who underwent NSRP and from 0% to 15% among those who underwent non-NSRP [31, 68]. Early use of high-dose sildenafil after RP has been suggested to be associated with preservation of smooth muscle within the corpora cavernosa [69]. Daily sildenafil also results in a greater return of spontaneous normal EF after RP compared to placebo following bilateral NSRP in patients who were fully potent before surgery [70].

Effectiveness of tadalafil and vardenafil as on-demand treatment has been evaluated in post-RP ED. A large multicentre trial in Europe and the USA has studied tadalafil in patients with ED following bilateral NS surgery. Erectile function was improved in 71% of patients treated with 20 mg tadalafil vs. 24% of those treated with placebo, while the rate of successful intercourse attempts was 52% with 20 mg tadalafil vs. 26% with placebo [31, 71]. Similarly, vardenafil has been tested in patients with ED following NSRP in a randomised, multicentre, prospective, placebo-controlled study in North America [31, 72]. Following bilateral NSRP, EF improved by 71% and 60% with 10 and 20 mg vardenafil, respectively. An extended analysis of the same cohort of patients showed the benefit of vardenafil compared to placebo in terms of intercourse satisfaction, hardness of erection, orgasmic function, and overall satisfaction with sexual experience [31, 73]. Moreover, a randomised, double-blind, double-dummy trial in men \leq 68 yr of age and normal pre-operative EF who underwent NSRP at 50 centres from nine European countries and Canada, compared tadalafil once daily with placebo [74]. Tadalafil was most effective on drug-assisted EF in men with ED following NSRP, and data suggested a potential role for tadalafil once daily - provided early after surgery - in contributing to the recovery of post-operative EF and possibly protecting from penile structural changes [74]. Unassisted EF was not improved after cessation of active therapy for 9 months [74]. Moreover, data suggested that the use of tadalafil once daily can significantly shorten the time to EF-recovery post-NSRP compared to placebo [75].

A randomised, double-blind, double-dummy, multicentre, parallel-group study in 87 centres across Europe, Canada, South Africa and the USA, compared on-demand and nightly dosing of vardenafil in men with ED following bilateral NSRP. In patients whose pre-operative IIEF EF domain score was \geq 26, vardenafil was efficacious when used on demand, supporting a paradigm shift towards on-demand dosing with PDE5Is in post-RP ED [76]. A double-blind, placebo-controlled, parallel-group, study in 298 patients with ED after bilateral NSRP randomised to 100 or 200 mg avanafil or placebo (taken 30 minutes before sexual activity) for 12 weeks showed significantly greater increases in SEP2 (sexual encounter profile) and SEP3 and change in mean IIEF-EF domain score with 100 and 200 mg avanafil vs. placebo ($p < 0.01$) [77]. Following dosing with avanafil 36.4% (28 of 77) of sexual attempts (SEP3) at 15 minutes or less were successful vs. 4.5% (2 of 44) for placebo ($p < 0.01$) [77].

Historically, the treatment options for post-operative ED have included intracavernous injections [31, 78], urethral microsuppository [31, 79], vacuum device therapy [31, 80], and penile implants [31, 81, 82]. Intracavernous injections and penile implants are still suggested as second- and third-line treatments, respectively, when oral PDE5Is are not adequately effective or contraindicated for post-operative patients (Sections 3A.4.6 and 3A.4.7).

Figure 3: Treatment algorithm for erectile dysfunction



3A.4.4 **Causes of ED that can be potentially treated with a curative intent**

3A.4.4.1 *Hormonal causes*

The advice of an endocrinologist may be beneficial for managing patients with hormonal abnormalities [52]. Testosterone deficiency is either a result of primary testicular failure or secondary to pituitary/hypothalamic causes (e.g. a functional pituitary tumour resulting in hyperprolactinaemia) [52, 83]. When clinically indicated [25], testosterone supplementation (TS) (intramuscular, oral, or transdermal) is effective, but should only be used after other endocrinological causes for testicular failure have been excluded [23, 49, 84]. Before initiating TS, digital rectal examination, serum PSA test, haematocrit, liver function tests and lipid profile should be performed [23, 49]. Patients who are given TS should be monitored for clinical response, elevation of the haematocrit and development of hepatic or prostatic disorders [23, 49]. TS is controversial in men with a history of PCa (LE: 4) [85]. Since there is limited evidence suggesting that TS may not pose an undue risk of PCa recurrence or progression, TS is contraindicated in patients with untreated PCa (LE: 4).

TS is contraindicated in patients with unstable cardiac disease. Conversely, the role of testosterone in the cardiovascular health of men is controversial. Clinical trials examining TS have been insufficiently powered to provide definitive and unequivocal evidence of adverse events in terms of cardiovascular outcomes [86-91]. As a matter of fact, current guidelines from the Endocrine Society make no recommendations on whether patients with heart disease should be screened for hypogonadism and do not recommend supplementing patients

with heart disease to improve survival [48]. However, a recent comprehensive systematic review and meta-analysis of all placebo-controlled randomised clinical trials (RCTs) on the effect of TS on cardiovascular-related problems did not support a causal role between TS and adverse cardiovascular events [92].

3A.4.4.2 *Post-traumatic arteriogenic ED in young patients*

In young patients with pelvic or perineal trauma, surgical penile revascularisation has a 60-70% long-term success rate [93]. The lesion must be confirmed by penile pharmaco-arteriography. Corporeal veno-occlusive dysfunction is a contraindication to revascularisation and must be excluded by dynamic infusion cavernosometry or cavernosography. Vascular surgery for veno-occlusive dysfunction is no longer recommended because of poor long-term results [93].

3A.4.4.3 *Psychosexual counselling and therapy*

For patients with a significant psychological problem, psychosexual therapy may be given either alone or with another therapeutic approach. Psychosexual therapy requires ongoing follow-up and has had variable results [94].

3A.4.5 **First-line therapy**

3A.4.5.1 *Oral pharmacotherapy*

PDE5 hydrolyses cGMP in the cavernosal tissue. Inhibition of PDE5 results in smooth muscle relaxation with increased arterial blood flow, leading to compression of the subtunical venous plexus and penile erection [95]. Four potent selective PDE5Is have been approved by the European Medicines Agency (EMA) for the treatment of ED [96]. They are not initiators of erection and require sexual stimulation to facilitate an erection. Efficacy is defined as an erection with rigidity sufficient for vaginal penetration.

3A.4.5.1.1 Sildenafil

Sildenafil was launched in 1998 and was the first PDE5I available on the market [97]. It is administered in doses of 25, 50 and 100 mg. The recommended starting dose is 50 mg and should be adapted according to the patient's response and side-effects. Sildenafil is effective from 30-60 min after administration. Its efficacy is reduced after a heavy, fatty meal due to prolonged absorption. Efficacy may be maintained for up to 12 h [98]. The pharmacokinetic data of sildenafil are presented in Table 5. Adverse events (Table 6) are generally mild in nature and self-limited by continuous use [99, 100]. After 24 weeks in a dose-response study, improved erections were reported by 56%, 77% and 84% of a general ED population taking 25, 50 and 100 mg sildenafil, respectively, compared to 25% of men taking placebo [97]. Sildenafil significantly improved patient scores for IIEF, SEP2, SEP3, and General Assessment Questionnaire (GAQ) and treatment satisfaction. The efficacy of sildenafil in almost every subgroup of patients with ED has been successfully established. The overall level of evidence and grade of recommendation is Level 1 Grade A. Recently, an orally disintegrating tablet (ODT) of sildenafil citrate at the dosage of 50 mg has been developed mainly for the benefit of patients who have difficulty swallowing solid dosage forms.

3A.4.5.1.2 Tadalafil

Tadalafil was licenced for treatment of ED in February 2003 and is effective from 30 min after administration, with peak efficacy after about 2 h. Efficacy is maintained for up to 36 h [101] and is not affected by food. It is administered in on-demand doses of 10 and 20mg and also an alternative daily dose of 5mg. The recommended on-demand starting dose is 10 mg and should be adapted according to the patient's response and side-effects. Pharmacokinetic data of tadalafil are presented in Table 5. Adverse events (Table 6) are generally mild in nature and self-limited by continuous use. In premarketing studies, after 12 weeks of treatment and in a dose-response study, improved erections were reported by 67% and 81% of a general ED population taking 10 and 20 mg tadalafil, respectively, compared to 35% of men in the control placebo group [101]. Tadalafil significantly improved patient scores for IIEF, SEP2, SEP3, and GAQ and treatment satisfaction. Efficacy has been confirmed in post-marketing studies. The efficacy of tadalafil in almost every subgroup of patients with ED, thus including difficult-to-treat subgroups (e.g. diabetes mellitus), has been successfully established. The overall level of evidence and grade of recommendation is Level 1 Grade A [102].

3A.4.5.1.3 Vardenafil

Vardenafil became commercially available in March 2003 and is effective from 30 min after administration [102]. Its effect is reduced by a heavy, fatty meal (> 57% fat). Five, 10 and 20 mg doses have been approved for on-demand treatment of ED. The recommended starting dose is 10 mg and should be adapted according to the patient's response and side-effects [103]. Pharmacokinetic data of vardenafil are presented in Table 5. Adverse events (Table 6) are generally mild in nature and self-limited by continuous use [103]. After 12 weeks in a dose-response study, improved erections were reported by 66%, 76% and 80% of a

general ED population taking 5, 10 and 20 mg vardenafil, respectively, compared with 30% of men taking placebo [103, 104]. Vardenafil significantly improved patient scores for IIEF, SEP2, SEP3, and GAQ and treatment satisfaction. Efficacy has been confirmed in post-marketing studies [103, 104]. The efficacy of vardenafil in almost every subgroup of patients with ED, thus including difficult-to-treat subgroups (e.g. diabetes mellitus), has been successfully established. The overall level of evidence and grade of recommendation is Level 1 Grade A. More recently, an ODT of vardenafil has been released [104]. Orodispersable tablet formulations offer improved convenience over film-coated formulations and may be preferred by patients. Absorption is unrelated to food intake and they exhibit better bioavailability compared to film-coated tablets [105]. The efficacy of vardenafil ODT has been demonstrated in several randomised controlled trials and did not seem to differ from the regular formulation [105, 106].

3A.4.5.1.4 Avanafil

Avanafil is a highly-selective PDE5I that recently became commercially available (EMA authorisation June 2013) [107]. Avanafil has a high ratio of inhibiting PDE5 as compared with other PDE subtypes allowing for the drug to be used for ED while minimising adverse effects [108]. Fifty, 100, and 200 mg doses have been approved for on-demand treatment of ED [107]. The recommended starting dose is 100 mg taken orally as needed approximately 30 min before sexual activity and should be adapted according to efficacy and tolerability [107, 109]. In the general population with ED, the mean percentage of attempts resulting in successful intercourse was approximately 47%, 58%, and 59% for the 50 mg, 100 mg, and 200 mg avanafil groups, respectively, as compared with approximately 28% for placebo [107, 109]. Data from sexual attempts made within 15 minutes of dosing showed successful attempts in 64%, 67%, and 71% cases, with avanafil 50, 100, and 200 mg, respectively. The maximum recommended dosing frequency is once per day. Dosage adjustments are not warranted based on renal function, hepatic function, age or gender [109]. Pharmacokinetic data of avanafil are presented in Table 5 [107, 109]. Adverse events (Table 6) are generally mild in nature [107, 109]. Pairwise meta-analytic data from available studies suggested that avanafil significantly improved patient scores for IIEF, SEP2, SEP3, and GAQ, with an evident dose-response relationship [106, 107]. Administration with food may delay the onset of effect compared with administration in the fasted state but avanafil can be taken with or without food. The efficacy of avanafil in many subgroup of patients with ED, including difficult-to-treat subgroups (e.g diabetes mellitus), has been successfully established. The overall level of evidence and grade of recommendation is Level 1 Grade A.

3A.4.5.1.5 Choice or preference between the different PDE5 inhibitors

To date, no data are available from double- or triple-blind multicentre studies comparing the efficacy and/or patient preference for sildenafil, tadalafil, vardenafil, and avanafil. Choice of drug will depend on the frequency of intercourse (occasional use or regular therapy, 3-4 times weekly) and the patient's personal experience. Patients need to know whether a drug is short- or long-acting, its possible disadvantages, and how to use it.

3A.4.5.1.6 Continuous use of PDE5 inhibitors

Animal studies have shown that chronic use of PDE5Is improves or prevents significantly the intracavernous structure alterations due to age, diabetes, or surgical damage [110-114]. No data exist for a human population. In humans, it has been clinically demonstrated that tadalafil 5 mg once daily in men complaining of ED of various severities was well tolerated and effective [115]. In 2007, tadalafil 2.5 and 5 mg have been approved by the EMA for daily treatment of ED. According to EMA, a once daily regimen with tadalafil 2.5 mg or 5 mg might be considered suitable, based on patient choice and the physician's judgement. In these patients, the recommended dose is 5 mg taken once a day at approximately the same time of day. Overall, tadalafil, 5 mg once daily, provides an alternative to on-demand dosing of tadalafil for couples who prefer spontaneous rather than scheduled sexual activities or who anticipate frequent sexual activity, with the advantage that dosing and sexual activity no longer need to be temporally linked. The appropriateness of the continuous use of a daily regimen should be reassessed periodically [115, 116]. Continuous dosing may also be used in the comorbid patient with LUTS and ED.

Table 5: Summary of the key pharmacokinetic data for the four PDE5 inhibitors currently EMA-approved to treat ED*

Parameter	Sildenafil, 100 mg	Tadalafil, 20 mg	Vardenafil, 20 mg	Avanafil 200mg
C_{max}	560 µg/L	378 µg/L	18.7 µg/L	5.2 µg/L
T_{max} (median)	0.8-1 h	2 h	0.9 h	0.5-0.75 h
$T_{1/2}$	2.6-3.7 h	17.5 h	3.9 h	6 – 17 h
AUC	1685 µg.h/L	8066 µg.h/L	56.8 µg.h/L	11.6 µg.h/L
Protein binding	96%	94%	94%	99%
Bioavailability	41%	NA	15%	8-10%

C_{max} : maximal concentration, T_{max} : time-to-maximum plasma concentration; $T_{1/2}$: plasma elimination half-time; AUC: area under curve or serum concentration time curve.

* Fasted state, higher recommended dose. Data adapted from EMA statements on product characteristics.

Table 6: Common adverse events of the four PDE5 inhibitors currently EMA-approved to treat ED*

Adverse event	Sildenafil	Tadalafil	Vardenafil	Avanafil 200mg
Headache	12.8%	14.5%	16%	9.3%
Flushing	10.4%	4.1%	12%	3.7%
Dyspepsia	4.6%	12.3%	4%	uncommon
Nasal congestion	1.1%	4.3%	10%	1.9%
Dizziness	1.2%	2.3%	2%	0.6%
Abnormal vision	1.9%		< 2%	none
Back pain		6.5%		< 2%
Myalgia		5.7%		< 2%

* Adapted from EMA statements on product characteristics.

3A.4.5.1.7 Safety issues for PDE5 inhibitors

3A.4.5.1.7.1 Cardiovascular safety

Clinical trial results of the four PDE5Is and post-marketing data of sildenafil, tadalafil, and vardenafil have demonstrated no increase in myocardial infarction rates in patients receiving PDE5Is, as part of either RCTs or open-label studies, or compared to expected rates in age-matched male populations. None of the PDE5Is had an adverse effect on total exercise time or time-to-ischæmia during exercise testing in men with stable angina. Chronic or on-demand use is well tolerated with a similar safety profile. All PDE5Is are contraindicated in: i) patients who have suffered from a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months; ii) patients with resting hypotension (blood pressure < 90/50 mmHg) or hypertension (blood pressure > 170/100 mmHg); iii) patients with unstable angina, angina with sexual intercourse, or congestive heart failure categorised as New York Heart Association Class 2 or greater.

3A.4.5.1.7.2 Nitrates are contraindicated with PDE5 inhibitors

Absolute contraindication to PDE5Is is represented by patients who are using any form of organic nitrate (e.g. nitroglycerine, isosorbide mononitrate, and isosorbide dinitrate) or nitric oxide (NO) donors (e.g. other nitrate preparations used to treat angina, as well as amyl nitrite or amyl nitrate ("poppers" used for recreation). They result in cGMP accumulation and unpredictable falls in blood pressure and symptoms of hypotension. The duration of interaction between organic nitrates and PDE5Is depends upon the PDE5I and nitrate used. If a PDE5I is taken and the patient develops chest pain, nitroglycerine must be withheld for at least 24 h if sildenafil (and probably also vardenafil) is used (half-life, 4 h), or at least 48 h if tadalafil is used (half-life, 17.5 h), and for no less than 12 h if avanafil is used (half-life, 6-17 h) [117].

3A.4.5.1.7.3 Antihypertensive drugs

Co-administration of PDE5Is with antihypertensive agents (angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium blockers, β -blockers, and diuretics) may result in small additive decreases in blood pressure, which are usually minor. In general, the adverse event profile of a PDE5I is not made worse by a background of antihypertensive medication, even when the patient is taking several antihypertensive agents.

3A.4.5.1.7.4 α -Blocker interactions

All PDE5Is show some interaction with α -blockers, which under some conditions may result in orthostatic hypotension.

- Sildenafil labelling advises that 50 or 100 mg sildenafil should be used with caution in patients taking an α -blocker (especially doxazosin). Hypotension is more likely to occur within 4 h following treatment with an α -blocker. A starting dose of 25 mg is recommended [99].
- Concomitant treatment with vardenafil should only be initiated if the patient has been stabilised on his α -blocker therapy. Co-administration of vardenafil with tamsulosin is not associated with clinically significant hypotension [102-104].
- Tadalafil is not recommended in patients taking doxazosin, but this is not the case for tamsulosin [101, 118].
- Avanafil labelling currently reports that patients should be stable on α -blocker therapy prior to initiating avanafil. In these patients, avanafil should be initiated at the lowest dose of 50 mg. Conversely, in those patients already taking an optimised dose of avanafil, α -blocker therapy should be initiated at the lowest dose.

3A.4.5.1.7.5 Dosage adjustment

Drugs that inhibit the CYP3A4 pathway will inhibit the metabolic breakdown of PDE5Is, thus increasing PDE5Is blood levels (among them, ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir and telithromycin). Therefore, lower doses of PDE5Is are necessary. However, other agents, such as rifampin, phenobarbital, phenytoin and carbamazepine, may induce CYP3A4 and enhance the breakdown of PDE5Is, so that higher doses of PDE5Is are required. Severe kidney or hepatic dysfunction may require dose adjustments or warnings.

3A.4.5.1.8 Management of non-responders to PDE5 inhibitors

The two main reasons why patients fail to respond to a PDE5I are either incorrect drug use or lack of efficacy of the drug. Data suggest that an adequate trial involves at least six attempts with a particular drug [119]. The management of non-responders depends upon identifying the underlying cause.

3A.4.5.1.8.1 Check that the patient has been using a licensed medication

There is a large black market in PDE5Is. The amount of active drug in these medications varies enormously and it is important to check how and from which source the patient has obtained his medication.

3A.4.5.1.8.2 Check that the medication has been properly prescribed and correctly used

The main reason why patients fail to use their medication correctly is inadequate counselling from their physician. The main ways in which a drug may be incorrectly used are: i) failure to use adequate sexual stimulation; ii) failure to use an adequate dose; and, iii) failure to wait an adequate amount of time between taking the medication and attempting sexual intercourse.

Lack of adequate sexual stimulation: PDE5I action is dependent on the release of NO by the parasympathetic nerve endings in the erectile tissue of the penis. The usual stimulus for NO release is sexual stimulation, and without adequate sexual stimulation (and NO release), the drugs cannot work. Oral PDE5Is take different times to reach maximal plasma concentrations [98, 100, 105, 106, 120-122]. Although pharmacological activity is achieved at plasma levels well below the maximal plasma concentration, there will be a period of time following oral ingestion of the medication during which the drug is ineffective. Even though all four drugs have an onset of action in some patients within 15-30 min of oral ingestion [100, 105, 106, 120-122], most patients require a longer delay between taking the medication [103, 106, 123, 124]. Absorption of sildenafil can be delayed by a meal, and absorption of vardenafil can be delayed by a fatty meal [125]. Absorption of tadalafil is less affected provided there is enough delay between oral ingestion and an attempt at sexual intercourse [120]. When avanafil is taken with a high fat meal, the rate of absorption is reduced with a mean delay in T_{max} of 1.25 h and a mean reduction in C_{max} of 39% (200 mg). There is no effect on the extent of exposure (AUC). The small changes in avanafil C_{max} are considered to be of minimal clinical significance [106-108].

It is possible to wait too long after taking medication before attempting sexual intercourse. The half-life of sildenafil and vardenafil is about 4 h, suggesting that the normal window of efficacy is 6-8 h following drug ingestion, although responses following this time period are well recognised. The half-life of avanafil is 6-17 h. Tadalafil has a longer half-life of ~17.5 h, so the window of efficacy is much longer at ~36 h. Data from uncontrolled studies suggest patient education can help salvage an apparent non-responder to a PDE5I. After emphasising the importance of dose, timing, and sexual stimulation to the patient, EF can be effectively restored following re-administration of the relevant PDE5I [126-128].

3A.4.5.1.8.3 Possible manoeuvres in patients correctly using a PDE5 inhibitor

There is controversial and not-univocal evidence suggesting that, in patients with testosterone deficiency, TS

might improve response to a PDE5I [49, 129-131]. Modification of other risk factors may also be beneficial as discussed in section 3A.4.2. Few data suggest that some patients might respond better to one PDE5I than to another [132]. Although these differences might be explained by variation in drug pharmacokinetics, they do raise the possibility that, despite an identical mode of action, switching to a different PDE5I might be helpful. Moreover, mainly in patients with severe ED, it has been suggested to combine tadalafil daily dosing with short acting PDEI (such as sildenafil), without any significant increase in terms of side-effects [133]. If drug treatment fails, then patients should be offered an alternative therapy such as intracavernosal injection therapy or use of a vacuum erection device (VED).

3A.4.5.2 *Vacuum erection devices*

VEDs provide passive engorgement of the corpora cavernosa, together with a constrictor ring placed at the base of the penis to retain blood within the corpora. Published data report that efficacy, in terms of erections satisfactory for intercourse, is as high as 90%, regardless of the cause of ED and satisfaction rates range between 27% and 94% [134, 135]. Most men who discontinue use of VEDs do so within 3 months. Long-term use of VEDs decreases to 50-64% after 2 years [136]. The commonest adverse events include pain, inability to ejaculate, petechiae, bruising, and numbness, which occur in < 30% of patients [135]. Serious adverse events (skin necrosis) can be avoided if patients remove the constriction ring within 30 min. VEDs are contraindicated in patients with bleeding disorders or on anticoagulant therapy. VEDs may be the treatment of choice in well-informed older patients with infrequent sexual intercourse and comorbidity requiring non-invasive, drug-free management of ED [134, 135].

3A.4.5.3 *Shockwave therapy*

Recently, the use of low-intensity extracorporeal shock wave therapy (LI-SWT) was proposed as a novel treatment for ED [137]. In the first randomised, double-blind, sham-controlled study, it was demonstrated that LI-SWT had a positive short-term clinical and physiological effect on the EF of men who respond to PDE5Is [138]. Moreover, there are preliminary data showing improvement in penile haemodynamics and endothelial function, as well as IIEF-EF domain score in severe ED patients who are poor responders to PDE5Is [139, 140]. Current data are still limited and clear recommendations cannot be given.

3A.4.6 **Second-line therapy**

Patients not responding to oral drugs may be offered intracavernous injections. Success rate is high (85%) [141, 142]. Intracavernous administration of vasoactive drugs was the first medical treatment for ED more than 20 years ago [143, 144].

3A.4.6.1 *Intracavernous injections*

3A.4.6.1.1 *Alprostadil*

Alprostadil (CaverjectTM, Edex/ViridalTM) was the first and only drug approved for intracavernous treatment of ED [143, 144]. Intracavernous alprostadil is most efficacious as monotherapy at a dose of 5-40 µg (of note, 40 µg dose is not registered in every European country). The erection appears after 5-15 min and lasts according to the dose injected. An office-training programme is required for the patient to learn the correct injection process. In cases of limited manual dexterity, the technique may be taught to their partners. The use of an automatic special pen that avoids a view of the needle can resolve fear of penile puncture and simplifies the technique. Efficacy rates for intracavernous alprostadil of >70% have been found in general ED populations, as well as in patient subgroups (e.g. diabetes or CVD), with reported sexual activity after 94% of the injections and satisfaction rates of 87-93.5% in patients and 86-90.3% in partners [143, 144]. Complications of intracavernous alprostadil include penile pain (50% of patients reported pain but pain reported only after 11% of total injections), prolonged erections (5%), priapism (1%), and fibrosis (2%) [143-145]. Pain is usually self-limited after prolonged use. It can be alleviated with the addition of sodium bicarbonate or local anaesthesia [143, 144, 146]. Cavernosal fibrosis (from a small hematoma) usually clears within a few months after temporary discontinuation of the injection program. However, tunical fibrosis suggests early onset of Peyronie's disease and may indicate stopping intracavernosal injections indefinitely. Systemic side-effects are uncommon. The most common is mild hypotension, especially when using higher doses. Contraindications include men with a history of hypersensitivity to alprostadil, men at risk of priapism, and men with bleeding disorders. Despite these favourable data, drop-out rates of 41-68% have been described for intracavernous pharmacotherapy [143, 144, 147, 148], with most drop-outs occurring within the first 2-3 months. In a comparative study, alprostadil monotherapy had the lowest discontinuation rate (27.5%) compared to overall drug combinations (37.6%), with an attrition rate after the first few months of therapy of 10% per year. Reasons for discontinuation included desire for a permanent modality of therapy (29%), lack of a suitable partner (26%), poor response (23%) (especially among early drop-out patients), fear of needles (23%), fear of complications (22%), and lack of spontaneity (21%). Careful counselling of patients during the office-training phase as well as close follow-up

is important in addressing patient withdrawal from an intracavernous injection programme [149].

3A.4.6.1.2 Combination therapy

Combination therapy enables a patient to take advantage of the different modes of action of the drugs being used, as well as alleviating side-effects by using lower doses of each drug.

- Papaverine (20-80 mg) was the first oral drug used for intracavernous injections. It is most commonly used in combination therapy due to its high incidence of side-effects as monotherapy. Currently unlicensed.
- Phentolamine has been used in combination therapy to increase efficacy. As monotherapy, it produces a poor erectile response.
- Sparse data in the literature support the use of other drugs, such as vasoactive intestinal peptide (VIP), NO donors (linsidomine), forskolin, potassium channel openers, moxislyte or calcitonin gene-related peptide, usually combined with the main drugs [150, 151]. Most combinations are not standardised and some drugs have limited availability worldwide.
- Papaverine (7.5-45 mg) plus phentolamine (0.25-1.5 mg), and papaverine (8-16 mg) plus phentolamine (0.2-0.4 mg) plus alprostadil (10-20 µg), have been widely used with improved efficacy rates, although they have never been licensed for ED [152, 153]. The triple combination regimen of papaverine, phentolamine and alprostadil has the highest efficacy rates, reaching 92%; this combination has similar side-effects as alprostadil monotherapy, but a lower incidence of penile pain due to lower doses of alprostadil. However, fibrosis is more common (5-10%) when papaverine is used (depending on total dose).
- VIP (25 µg) + phentolamine mesylate (1-2 mg) (Invicorp™, currently licensed in Scandinavia), is a combination of two active components with complementary modes of action. Clinical studies showed that the combination is an effective treatment for intracavernous injections in ≥ 80% of men with ED, including those who have failed to respond to other therapies and, unlike existing intracavernosal therapies, is associated with a very low incidence of penile pain and virtually negligible risk of priapism [154].

Despite high efficacy rates, 5-10% of patients do not respond to combination intracavernous injections. The combination of sildenafil with intracavernous injection of the triple combination regimen may salvage as many as 31% of patients who do not respond to the triple combination alone [155]. However, combination therapy is associated with an incidence of adverse effects in 33% of patients, including dizziness in 20% of patients. This strategy can be considered in carefully selected patients before proceeding to a penile implant [Level 4].

3A.4.6.1.3 Intraurethral/topical alprostadil

A specific formulation of alprostadil (125-1000 µg) in a medicated pellet (MUSE™) has been approved as a treatment for ED [156]. Erections sufficient for intercourse are achieved in 30-65.9% of patients. In clinical practice, only the higher doses (500 and 1000 µg) have been used with low consistency response rates [156-158]. The application of a constriction ring at the root of the penis (ACTIS™) may improve efficacy [157, 158]. The most common adverse events are local pain (29-41%) and dizziness with possible hypotension (1.9-14%). Penile fibrosis and priapism are very rare (< 1%). Urethral bleeding (5%) and urinary tract infections (0.2%) are adverse events related to the mode of administration. Efficacy rates are significantly lower than intracavernous pharmacotherapy [142]. Intraurethral pharmacotherapy is a second-line therapy and provides an alternative to intracavernous injections in patients who prefer a less-invasive, although less-efficacious treatment. Topical alprostadil is another way of giving alprostadil. It is actually a cream that includes a permeation enhancer in order to facilitate absorption of alprostadil (200 and 300µg) through the urethral meatus [159]. Clinical data are limited. Significant improvement compared to placebo was recorded for IIEF, SEP2 and SEP3 in a broad range of patients with mild to severe ED [160]. Side-effects include penile erythema, penile burning and pain. Systemic side-effects are very rare. Topical alprostadil is approved and it is available in some European countries.

3A.4.7 **Third-line therapy (penile prostheses)**

The surgical implantation of a penile prosthesis may be considered in patients who do not respond to pharmacotherapy or who prefer a permanent solution to their problem. The two currently available classes of penile implants include inflatable (2- and 3-piece) and malleable devices [31, 81, 161, 162]. Most patients prefer the 3-piece inflatable devices due to the more “natural” erections obtained. Likewise, 3-piece inflatable devices provide the best rigidity and the best flaccidity because they will fill every part of the corporal bodies. However, the 2-piece inflatable prosthesis can be a viable option among patients who are deemed high-risk of complications with reservoir placements. Malleable prostheses result in a firm penis, which may be manually placed in an erect or flaccid state [31, 81, 161, 162].

There are two main surgical approaches for penile prosthesis implantation: penoscrotal and infrapubic [161-164]. The penoscrotal approach provides an excellent exposure, it affords proximal crural exposure if necessary, avoids dorsal nerve injury and permits direct visualisation of pump placement. However, with this approach the reservoir is blindly placed into the retropubic space, which can be a problem in patients with a history of major pelvic surgery (mainly radical cystectomy). The infrapubic approach has the advantage of reservoir placement under direct vision, but the implantation of the pump may be more challenging, and patients are at a slightly increased risk of dorsal nerve injury. Revision surgery is associated with decreased outcomes and may be more challenging. Regardless of the indication, prosthesis implantation has one of the highest satisfaction rates (92-100% in patients and 91-95% in partners) among the treatment options for ED based on appropriate consultation [31, 81, 161, 165-171]. In patients with favourable oncologic prognosis after RP for PCa, combination surgery for treatment of ED, with the implant of a penile prosthesis, and stress urinary incontinence (male sling or artificial urinary sphincter) is effective and durable and has an established, definitive role to address this problem [31, 81, 172-174].

3A.4.7.1 Complications

The two main complications of penile prosthesis implantation are mechanical failure and infection. Several technical modifications of the most commonly used 3-piece prosthesis (AMS 700CX/CXRTM and Coloplast Alpha ITM) resulted in mechanical failure rates of < 5% after 5 years of follow-up [81, 175, 176]. Careful surgical techniques with proper antibiotic prophylaxis against Gram-positive and Gram-negative bacteria reduces infection rates to 2-3% with primary implantation in low-risk patients. The infection rate may be further reduced to 1-2% by implanting an antibiotic-impregnated prosthesis (AMS Inhibizone™) or hydrophilic-coated prosthesis (Coloplast Titan™) [81, 177-180]. Higher risk populations include patients undergoing revision surgery, those with impaired host defenses (immunosuppression, diabetes mellitus, spinal cord injury) or those with penile corporal fibrosis [9, 81, 161, 181-183]. Infection requires removal of the prosthesis and antibiotic administration. Alternatively, removal of the infected device with immediate replacement with a new prosthesis has been described using a washout protocol with successful salvages achieved in > 80% of cases [181, 183, 184]. The majority of revisions are secondary to mechanical failure and combined erosion or infection. Ninety three percent of cases are successfully revised, providing functioning penile prosthesis.

3A.4.7.2 Conclusions third-line therapy

Penile implants are an attractive solution for patients who do not respond to more conservative therapies. There is sufficient evidence to recommend this approach in patients not responding to less-invasive treatments due to its high efficacy, safety and satisfaction rates.

3A.4.8 Recommendations for the treatment of ED

	LE	GR
Lifestyle changes and risk factor modification must precede or accompany ED treatment.	1a	A
Pro-erectile treatments have to be given at the earliest opportunity after RP.	1b	A
When a curable cause of ED is found, it must be treated first.	1b	B
PDE5Is are first-line therapy.	1a	A
Inadequate/incorrect prescription and poor patient education are the main causes of a lack of response to PDE5Is.	3	B
A VED can be used in patients with a stable relationship.	4	C
Intracavernous injection is second-line therapy.	1b	B
Penile implant is third-line therapy.	4	C

ED = erectile dysfunction; RP = radical prostatectomy; VED = vacuum erection devices; PDE5I = phosphodiesterase type 5 [inhibitors].

3A.5 Follow-up

Follow-up is important in order to assess efficacy and safety of the treatment provided. It is also essential to assess patient satisfaction since a successful treatment for ED goes beyond efficacy and safety. Physicians must be aware that there is no single treatment that fits all patients or all situations as described in detail in the previous section.

3B PREMATURE EJACULATION

3B.1 Epidemiology/aetiology/pathophysiology

Although premature ejaculation (PE) is a common male sexual dysfunction, it is poorly understood. Patients are often unwilling to discuss their symptoms and many physicians do not know about effective treatments. As a result, patients may be misdiagnosed or mistreated [2].

3B.1.1 Epidemiology

The major problem in assessing the prevalence of PE is the lack of an accurate (validated) definition at the time the surveys were conducted [185]. The highest prevalence rate of 31% (men aged 18-59 years) was found by the National Health and Social Life Survey (NHSL) study in USA [186]. Prevalence rates were 30% (18-29 years), 32% (30-39 years), 28% (40-49 years) and 55% (50-59 years). It is, however, unlikely that the PE prevalence is as high as 20–30% based on the relatively low number of men who present for treatment of PE. These high prevalence rates may be a result of the dichotomous scale (yes/no) in a single question asking if ejaculation occurred too early, as the prevalence rates in European studies have been significantly lower [187]. According to the four PE subtypes proposed by Waldinger et al [188], the prevalence rates were 2.3% (lifelong PE), 3.9% (acquired PE), 8.5% (natural variable PE) and 5.1% (premature-like ejaculatory dysfunction) [189]. An approximately 5% prevalence of acquired PE and lifelong PE in general populations is consistent with epidemiological data indicating that around 5% of the population have an ejaculation latency less than 2 minutes [190].

3B.1.2 Pathophysiology and risk factors

The aetiology of PE is unknown, with little data to support suggested biological and psychological hypotheses, including anxiety, penile hypersensitivity, and 5-HT receptor dysfunction [191]. In addition, the pathophysiology of PE is largely unknown. All the physiological events leading up to the forceful expulsion of sperm at the urethral meatus are not impaired in PE patients. A significant proportion of men with ED also experience PE [192]. High levels of performance anxiety related to ED may worsen PE, with a risk of misdiagnosing PE instead of the underlying ED. According to the NHLS, the prevalence of PE is not affected by age [186, 187], unlike ED, which increases with age. PE is not affected by marital or income status [186]. However, PE is more common in black men, Hispanic men and men from Islamic backgrounds [193, 194] and may be higher in men with a lower educational level [186, 192]. Other risk factors may include a genetic predisposition [195], poor overall health status and obesity [186], prostate inflammation [196, 197], thyroid hormone disorders [37], emotional problems and stress [186, 198], and traumatic sexual experiences [186, 192]. In the only published study on risk modification/prevention strategies [199], successful eradication of causative organisms in patients with chronic prostatitis and PE produced marked improvements in IELT and ejaculatory control compared to untreated patients [200].

3B.1.3 Impact of PE on QoL

Men with PE are more likely to report low satisfaction with their sexual relationship, low satisfaction with sexual intercourse, difficulty relaxing during intercourse, and less frequent intercourse [201, 202]. However, the negative impact of PE extends beyond sexual dysfunction. PE can have a detrimental effect on self-confidence and the relationship with the partner, and may sometimes cause mental distress, anxiety, embarrassment and depression [201, 203]. Sex drive and overall interest in sex does not appear to be affected by PE [204]. However, the partner's satisfaction with the sexual relationship decreases with increasing severity of the man's condition [205]. Despite the possible serious psychological and QoL consequences of PE, few men seek treatment. In the GSSAB survey, 78% of men who self-reported a sexual dysfunction sought no professional help or advice for their sexual problems [192], with men more likely to seek treatment for ED than for PE [192]. In the PEPA survey, only 9% of men with self-reported PE consulted a doctor [187]. The main reasons for not discussing PE with their physician are patient embarrassment and a belief that there is no treatment. Physicians are often uncomfortable discussing sexuality with their patients usually because of embarrassment and a lack of training or expertise in treating PE [206, 207]. Physicians need to encourage their patients to talk about PE.

3B.2 Classification

There have previously been two official definitions of PE, neither of which have been universally accepted:

- In the Diagnostic and Statistical Manual of Mental Disorders IV-Text Revision (DSM-IV-TR), PE is defined as a '*persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it. The clinician must take into account factors that affect duration of the excitement phase, such as age, novelty of the sexual partner or situation, and recent frequency of sexual activity*' [208]. This DSM definition has been recently updated in the DSM V edition [209].

- In the World Health Organization's International Classification of Diseases-10 (ICD-10), PE is defined as *'the inability to delay ejaculation sufficiently to enjoy lovemaking, which is manifested by either an occurrence of ejaculation before or very soon after the beginning of intercourse (if a time limit is required: before or within 15 seconds of the beginning of intercourse) or ejaculation occurs in the absence of sufficient erection to make intercourse possible. The problem is not the result of prolonged absence from sexual activity'* [210].

The Second International Consultation on Sexual and Erectile Dysfunction defined PE as:

'ejaculation with minimal stimulation and earlier than desired, before or soon after penetration, which causes bother or distress, and over which the sufferer has little or no voluntary control' [191].

The International Society for Sexual Medicine (ISSM) has adopted a completely new definition of PE which is the first evidence-based definition [211]:

PE (lifelong and acquired) is a male sexual dysfunction characterised by the following:

1. Ejaculation that always or nearly always occurs prior to or within about 1 minute of vaginal penetration (lifelong PE) or a clinically significant and bothersome reduction in latency time, often to about 3 minutes or less (acquired PE).
2. The inability to delay ejaculation on all or nearly all vaginal penetrations.
3. Negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy.

All four definitions have taken into account the time to ejaculation, the inability to control or delay ejaculation, and negative consequences (bother/distress) from PE. However, the major point of debate is quantifying the time to ejaculation, which is usually described by intravaginal ejaculatory latency time (IELT) [209].

Recently, two more PE syndromes have been proposed [212]:

- 'Variable PE' is characterised by inconsistent and irregular early ejaculations, representing a normal variation in sexual performance.
- 'Subjective PE' is characterised by subjective perception of consistent or inconsistent rapid ejaculation during intercourse, while ejaculation latency time is in the normal range or can even last longer. It should not be regarded as a symptom or manifestation of true medical pathology.

The addition of these new types may aid patient stratification, diagnosis and treatment, but their exact role remains to be defined [213].

3B.3 Diagnostic evaluation

Diagnosis of PE is based on the patient's medical and sexual history [214, 215]. History should classify PE as lifelong or acquired and determine whether PE is situational (under specific circumstances or with a specific partner) or consistent. Special attention should be given to the duration time of ejaculation, degree of sexual stimulus, impact on sexual activity and QoL, and drug use or abuse. It is also important to distinguish PE from ED. Many patients with ED develop secondary PE caused by the anxiety associated with difficulty in attaining and maintaining an erection [216]. Furthermore, some patients are not aware that loss of erection after ejaculation is normal and may erroneously complain of ED, while the actual problem is PE [217]. There are several overlapping definitions of PE, with four shared factors (Table 7), resulting in a multidimensional diagnosis [218].

Table 7: Common factors in different definitions of ED

•	Time to ejaculation assessed by IELT
•	Perceived control
•	Distress
•	Interpersonal difficulty related to the ejaculatory dysfunction

3B.3.1 Intravaginal ejaculatory latency time

The use of IELT alone is not sufficient to define PE, as there is significant overlap between men with and without PE [219, 220]. IELT has a significant direct effect on perceived control over ejaculation, but not a significant direct effect on ejaculation-related personal distress or satisfaction with sexual intercourse [221]. In addition, perceived control over ejaculation has a significant direct effect on both ejaculation-related personal distress and satisfaction with sexual intercourse (each showing direct effects on interpersonal difficulty related to ejaculation). In everyday clinical practice, self-estimated IELT is sufficient [222]. Self-estimated and

stopwatch-measured IELT are interchangeable and correctly assign PE status with 80% sensitivity and 80% specificity [223]. Specificity can be improved further to 96% by combining IELT with a single-item patient-reported outcome (PRO) on control over ejaculation and satisfaction with sexual intercourse (scale ranging from 0 = very poor to 4 = very good) and on personal distress and interpersonal difficulty (0 = not at all to 4 = extremely). However, stopwatch-measured IELT is necessary in clinical trials. While IELT is an objective tool for PE assessment, a recent study reported that sexual satisfaction and distress correlated more strongly with the feeling of control than with the self-reported latency time [224].

3B.3.2 PE assessment questionnaires

The need to assess PE objectively has led to the development of several questionnaires based on the use of PROs [218]. Only two questionnaires can discriminate between patients who have PE and those who do not:

- Premature Ejaculation Diagnostic Tool (PEDT): five-item questionnaire based on focus groups and interviews from the USA, Germany and Spain. Assesses control, frequency, minimal stimulation, distress and interpersonal difficulty [225, 226]. A total score ≥ 11 suggests a diagnosis of PE, a score of 9 or 10 suggests a probable diagnosis of PE while a score of ≤ 8 indicates a low likelihood of PE.
- Arabic Index of Premature Ejaculation (AIPE): seven-item questionnaire developed in Saudi Arabia assesses sexual desire, hard erections for sufficient intercourse, time to ejaculation, control, satisfaction for the patient and partner, anxiety or depression [227]. A cut-off score of 30 (range of scores 7-35) discriminated best PE diagnosis. Severity of PE was classified as severe (score: 7-13), moderate (score: 14-19), mild to moderate (score: 20-25) and mild (score: 26-30).

The most widely used tool is the PEDT. However, there is a low correlation between a diagnosis provided by PEDT and a self-reported diagnosis. A recent study reported that only 40% of men with PEDT-diagnosed PE and 19% of men with probable PE self-reported the condition [228]. Questionnaires are a significant step in simplifying the methodology of PE drug studies, although further cross-cultural validation is needed [229]. Other questionnaires used to characterise PE and determine treatment effects include the PEP [220], Index of Premature Ejaculation (IPE) (61) and Male Sexual Health Questionnaire Ejaculatory Dysfunction (MSHQ-EjD) [230]. Currently, their role is optional in everyday clinical practice.

3B.3.3 Physical examination and investigations

Physical examination may be part of the initial assessment of men with PE. It may include a brief examination of the endocrine and neurological systems to identify underlying medical conditions associated with PE or other sexual dysfunctions, such as endocrinopathy, Peyronie's disease, urethritis or prostatitis. Laboratory or physiological testing should be directed by specific findings from history or physical examination and is not routinely recommended [214].

3B.3.4 Recommendations for the diagnostic evaluation of PE

Recommendations	LE	GR
Diagnosis and classification of PE is based on medical and sexual history. It should be multidimensional and assess IELT, perceived control, distress and interpersonal difficulty due to the ejaculatory dysfunction.	1a	A
Clinical use of self-estimated IELT is adequate. Stopwatch-measured IELT is necessary in clinical trials.	2a	B
Patient-reported outcomes (PROs) have the potential to identify men with PE. Further research is needed before PROs can be recommended for clinical use.	3	C
Physical examination may be necessary in initial assessment of PE to identify anatomical abnormalities that may be associated with PE or other sexual dysfunctions, particularly ED.	3	C
Routine laboratory or neurophysiological tests are not recommended. They should only be directed by specific findings from history or physical examination.	3	C

PE = premature ejaculation; IELT = intravaginal ejaculatory latency time; ED = erectile dysfunction.

3B.4 Disease management

In men for whom PE causes few, if any problems, treatment is limited to psychosexual counselling and education. Before beginning treatment, it is essential to discuss the patient's expectations thoroughly. Furthermore, it is important to treat first, if present, ED especially and possibly prostatitis.

Various behavioural techniques have been beneficial in treating PE and are indicated for patients uncomfortable

with pharmacological therapy. In lifelong PE, behavioural techniques are not recommended for first-line treatment. They are time-intensive, require the support of a partner and can be difficult to perform. In addition, long-term outcomes of behavioural techniques for PE are unknown.

Pharmacotherapy is the basis of treatment in lifelong PE. Dapoxetine is the only on-demand pharmacological treatment approved for PE in many countries except for the USA. All other medications used in PE are off-label indications. Chronic antidepressants including selective serotonin reuptake inhibitors (SSRIs) and clomipramine, a tricyclic antidepressant and on-demand topical anaesthetic agents have consistently shown efficacy in PE. Long-term outcomes for pharmacological treatments are unknown.

An evidence-based analysis of all current treatment modalities was performed. Levels of evidence and grades of recommendation are provided and a treatment algorithm is presented (Figure 4).

3B.4.1 **Psychological/behavioural strategies**

Behavioural strategies mainly include the 'stop-start' programme developed by Semans [231] and its modification, the 'squeeze' technique, proposed by Masters and Johnson:

- In the 'stop-start' programme, the partner stimulates the penis until the patient feels the urge to ejaculate. At this point, he instructs his partner to stop, waits for the sensation to pass and then stimulation is resumed.
- The 'squeeze' technique is similar but the partner applies manual pressure to the glans just before ejaculation until the patient loses his urge.

Both these procedures are typically applied in a cycle of three pauses before proceeding to orgasm.

Behavioural strategies are based on the hypothesis that PE occurs because the man fails to appreciate the sensations of heightened arousal and to recognise the feelings of ejaculatory inevitability. Re-training may attenuate stimulus-response connections by gradually exposing the patient to progressively more intense and more prolonged stimulation, while maintaining the intensity and duration of the stimulus just below the threshold for triggering the response. There are several modifications of these techniques making comparison difficult.

Masturbation before anticipation of sexual intercourse is a technique used by younger men. Following masturbation, the penis is desensitised resulting in greater ejaculatory delay after the refractory period is over. In a different approach, the man learns to recognise the signs of increased sexual arousal and how to keep his level of sexual excitement below the intensity that elicits the ejaculatory reflex. Efficacy is similar to the 'Stop-start' programme [232].

Psychological factors may be associated with PE and should be addressed in treatment. These factors, if any, mainly relate to anxiety, but could also include relationship factors. The limited studies available suggest that behavioural therapy, as well as functional sexological treatment, lead to improvement in the duration of intercourse and sexual satisfaction.

Overall, short-term success rates of 50-60% have been reported [233, 234]. However, there is no controlled research to support the efficacy of behavioural techniques, while a double-blind, randomised, crossover study showed that pharmacological treatment (clomipramine, sertraline, paroxetine and sildenafil) resulted in greater IELT prolongation than behavioural therapy [235]. Furthermore, clinical experience suggests that improvements achieved with these techniques are generally not maintained long-term [236, 237]. Behavioural therapy may be most effective when used to 'add value' to medical interventions, although this suggestion requires proof from further randomised clinical trials. Validated assessment instruments need to be used as end-points. Longer follow-up periods are necessary to confirm these findings.

3B.4.2 **Dapoxetine**

Dapoxetine hydrochloride is a short-acting SSRI, with a pharmacokinetic profile suitable for on-demand treatment for PE. It has a rapid T_{max} (1.3 hours) and a short half-life (95% clearance rate after 24 hours) [238]. Dapoxetine has been investigated in 6081 subjects to date [239]. It is approved for on-demand treatment of PE in European countries and elsewhere, but not in the USA.

Both available doses of dapoxetine (30 mg and 60 mg) have shown 2.5- and 3.0-fold increases, respectively, in IELT overall, rising to 3.4- and 4.3-fold in patients with baseline average IELT < 0.5 minutes [240, 241]. In RCTs, dapoxetine, 30 mg or 60 mg 1-2 hours before intercourse, was effective from the first dose on IELT and increased ejaculatory control, decreased distress, and increased satisfaction. Dapoxetine has shown a similar efficacy profile in men with lifelong and acquired PE [241]. Treatment-related side-effects were dose-

dependent and included nausea, diarrhoea, headache and dizziness. Side-effects were responsible for study discontinuation in 4% (30 mg) and 10% (60 mg) of subjects [222]. There was no indication of an increased risk of suicidal ideation or suicide attempts and little indication of withdrawal symptoms with abrupt dapoxetine cessation [242].

Regarding a combination of PDE5 inhibitors with dapoxetine, the addition of dapoxetine to a given regimen of PDE5 inhibitor may increase the risk of possible prodromal symptoms that may progress to syncope compared to both PDE5 inhibitors and SSRIs administered alone. Generally, when dapoxetine is co-administered with a PDE5 inhibitor, it is well tolerated, with a safety profile consistent with previous phase 3 studies of dapoxetine alone [243]. A low rate of vasovagal syncope was reported in phase 3 studies. According to the summary of product characteristics, orthostatic vital signs (blood pressure and heart rate) must be measured prior to starting dapoxetine. No cases of syncope were observed in a post-marketing observational study, which had identified patients at risk for orthostatic reaction using the patient's medical history and orthostatic testing [244].

The mechanism of action of short-acting SSRIs in PE is still speculative. Dapoxetine resembles the antidepressant SSRIs in the following ways: the drug binds specifically to the 5-HT reuptake transporter at subnanomolar levels, has only a limited affinity for 5-HT receptors and is a weak antagonist of the 1A-adrenoceptors, dopamine D1 and 5-HT_{2B} receptors. The rapid absorption of dapoxetine might lead to an abrupt increase in extracellular 5HT following administration that might be sufficient to overwhelm the compensating autoregulation processes. Does the mechanism of action of short-acting SSRIs differ from that of the conventional chronic SSRI mechanism of action? Either such agents do not cause the autoreceptor activation and compensation reported using chronic SSRIs, or these effects occur, but they simply cannot prevent the action of short-acting SSRIs [245].

3B.4.3 Off-label use of antidepressants: SSRIs and clomipramine

Ejaculation is commanded by a spinal ejaculation generator [246, 247] under excitatory or inhibitory influences from the brain and the periphery [248]. 5-hydroxytryptamine (5-HT or serotonin) is involved in ejaculatory control, with its ejaculation-retarding effects likely to be attributable to activation of 5-HT_{1B} and 5-HT_{2C} receptors, both spinally and supraspinally. By contrast, stimulation of 5-HT_{1A} receptors precipitates ejaculation [245].

Selective serotonin reuptake inhibitors (SSRIs) are used to treat mood disorders, but can delay ejaculation and are therefore widely used 'off-label' for PE. As for depression, SSRIs must be given for 1 to 2 weeks to be effective in PE [245]. Administration of chronic SSRIs causes prolonged increases in synaptic cleft serotonin, which desensitises the 5-HT_{1A} and 5-HT_{1B} receptors [249]. Clomipramine, the most serotonergic tricyclic antidepressant, was first reported in 1973 as an effective PE treatment [250]. SSRIs have revolutionised treatment of PE, but they have also changed our understanding of PE since the first publication on paroxetine in 1970 [251]. Before dapoxetine, daily treatment with SSRIs was the first choice of treatment in PE. Commonly used SSRIs include citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline, all of which have a similar pharmacological mechanism of action.

A systematic review and meta-analysis of all drug treatment studies reported that, despite methodological problems in most studies, there still remained several, well-designed, double-blind, placebo-controlled trials supporting the therapeutic effect of daily SSRIs on PE [252]. Nevertheless, despite significant increase in IELT, there are no data available concerning the PROs in PE patients treated with daily SSRIs.

Based on this meta-analysis, SSRIs were expected to increase the geometric mean IELT by 2.6-fold to 13.2-fold. Paroxetine was found to be superior to fluoxetine, clomipramine and sertraline. Sertraline was superior to fluoxetine, whereas the efficacy of clomipramine was not significantly different from fluoxetine and sertraline. Paroxetine was evaluated in doses of 20-40 mg, sertraline 25-200 mg, fluoxetine 10-60 mg and clomipramine 25-50 mg; there was no significant relationship between dose and response among the various drugs. There is limited evidence that citalopram may be less efficacious compared to other SSRIs, while fluvoxamine may not be effective [253, 254].

Ejaculation delay may start a few days after drug intake, but it is more evident after 1 to 2 weeks since receptor desensitisation requires time to occur. Although efficacy may be maintained for several years, tachyphylaxis (decreasing response to a drug following chronic administration) may occur after 6 to 12 months [250]. Common side-effects of SSRIs include fatigue, drowsiness, yawning, nausea, vomiting, dry mouth, diarrhoea and perspiration; they are usually mild and gradually improve after 2 to 3 weeks [213, 240]. Decreased libido,

anorgasmia, anejaculation and ED have also been reported.

Because of a theoretical risk of suicidal ideation or suicide attempts, caution is suggested in prescribing SSRIs to young adolescents with PE aged 18 years or less, and to men with PE and a comorbid depressive disorder, particularly when associated with suicidal ideation. Patients should be advised to avoid sudden cessation or rapid dose reduction of daily dosed SSRIs which may be associated with a SSRI withdrawal syndrome [222].

In one controlled trial, on-demand use of clomipramine (but not paroxetine), 3 to 5 hours before intercourse, was reported to be efficacious, though IELT improvement was inferior compared to daily treatment with the same drug [255]. However, on-demand treatment may be combined with an initial trial of daily treatment or concomitant low-dose daily treatment reducing adverse effects [256, 257].

Individual countries' regulatory authorities strongly advise against prescribing medication for indications if the medication in question is not licensed/approved and prescription of off-label medication may present difficulties for physicians.

3B.4.4 Topical anaesthetic agents

The use of local anaesthetics to delay ejaculation is the oldest form of pharmacological therapy for PE [258]. Several trials [259, 260] support the hypothesis that topical desensitising agents reduce the sensitivity of the glans penis so delaying ejaculatory latency, but without adversely affecting the sensation of ejaculation.

3B.4.4.1 Lidocaine-prilocaine cream

In a randomised, double-blind, placebo-controlled trial, lidocaine-prilocaine cream increased the IELT from 1 minute in the placebo group to 6.7 minutes in the treatment group [261]. In another randomised, double-blind, placebo-controlled trial, lidocaine-prilocaine cream significantly increased the stopwatch-measured IELT from 1.49 to 8.45 minutes while no difference was recorded in the placebo group (1.67 to 1.95 minutes) [262].

Lidocaine-prilocaine cream (5%) is applied for 20-30 minutes prior to intercourse. Prolonged application of topical anaesthetic (30-45 minutes) may result in loss of erection due to numbness of the penis in a significant percentage of men [261]. A condom will prevent diffusion of the topical anaesthetic agent into the vaginal wall causing numbness in the partner.

Alternatively, the condom may be removed prior to sexual intercourse and the penis washed clean of any residual active compound. Although no significant side-effects have been reported, topical anaesthetics are contraindicated in patients or partners with an allergy to any part of the product.

An experimental aerosol formulation of lidocaine, 7.5 mg, plus prilocaine, 2.5 mg (Topical Eutectic Mixture for Premature Ejaculation [TEMPE]), was applied 5 minutes before sexual intercourse in 539 males. There was an increase in the geometric mean IELT from a baseline of 0.58 minutes to 3.17 minutes during 3 months of double-blind treatment; a 3.3-fold delay in ejaculation compared with placebo ($p < 0.001$) [263].

3B.4.5 Tramadol

Tramadol is a centrally acting analgesic agent that combines opioid receptor activation and re-uptake inhibition of serotonin and noradrenaline. Tramadol is readily absorbed after oral administration and has an elimination half-life of 5-7 hours. For analgesic purposes, tramadol can be administered between 3 and 4 times daily in tablets of 50-100 mg. Side-effects were reported at doses used for analgesic purposes (up to 400 mg daily) and include constipation, sedation and dry mouth. Tramadol is a mild-opioid receptor agonist, but it also displays antagonistic properties on transporters of noradrenaline and 5-HT [264]. This mechanism of action distinguishes tramadol from other opioids, including morphine. However, in May 2009, the US Food and Drug Administration released a warning letter about tramadol's potential to cause addiction and difficulty in breathing [265].

A large, randomised, double-blind, placebo-controlled, multicentre 12-week study was carried out to evaluate the efficacy and safety of two doses of tramadol (62 and 89 mg) by orally disintegrating tablet (ODT) in the treatment of PE [266]. Previously, a bioequivalence study had previously been performed that demonstrated equivalence between tramadol ODT and tramadol HCl. In patients with a history of lifelong PE and an IELT < 2 minutes, increases in the median IELT of 0.6 minutes (1.6-fold), 1.2 minutes (2.4-fold) and 1.5 minutes (2.5-fold) were reported for placebo, 62 mg of tramadol ODT, and 89 mg of tramadol ODT, respectively. It should be noted that there was no dose-response effect with tramadol. The tolerability during the 12-week study period was acceptable.

Overall, tramadol has shown a moderate beneficial effect with a similar efficacy as dapoxetine. From what is known about the neuropharmacology of ejaculation and the mechanism of action of tramadol, the delaying effect on ejaculation could be explained by combined CNS μ -opioid receptor stimulation and increased brain 5-HT availability. However, efficacy and tolerability of tramadol would have to be confirmed in more patients and longer-term.

3B.4.6 **Other drugs**

3B.4.6.1 *Phosphodiesterase type 5 inhibitors*

There is only one well-designed, randomised, double-blind, placebo-controlled study comparing sildenafil to placebo [267]. Although IELT was not significantly improved, sildenafil increased confidence, the perception of ejaculatory control and overall sexual satisfaction, reduced anxiety and decreased the refractory time to achieve a second erection after ejaculation.

Several open-label studies showed that sildenafil combined with an SSRI is superior to SSRI monotherapy:

- Sildenafil combined with paroxetine improved IELT significantly and satisfaction vs. paroxetine alone [268].
- Sildenafil combined with sertraline improved IELT and satisfaction significantly vs. sertraline alone [269].
- Sildenafil combined with paroxetine and psychological and behavioural counselling significantly improved IELT and satisfaction in patients in whom other treatments failed [270].
- Finally, sildenafil combined with behavioural therapy significantly improved IELT and satisfaction vs. behavioural therapy alone [271].

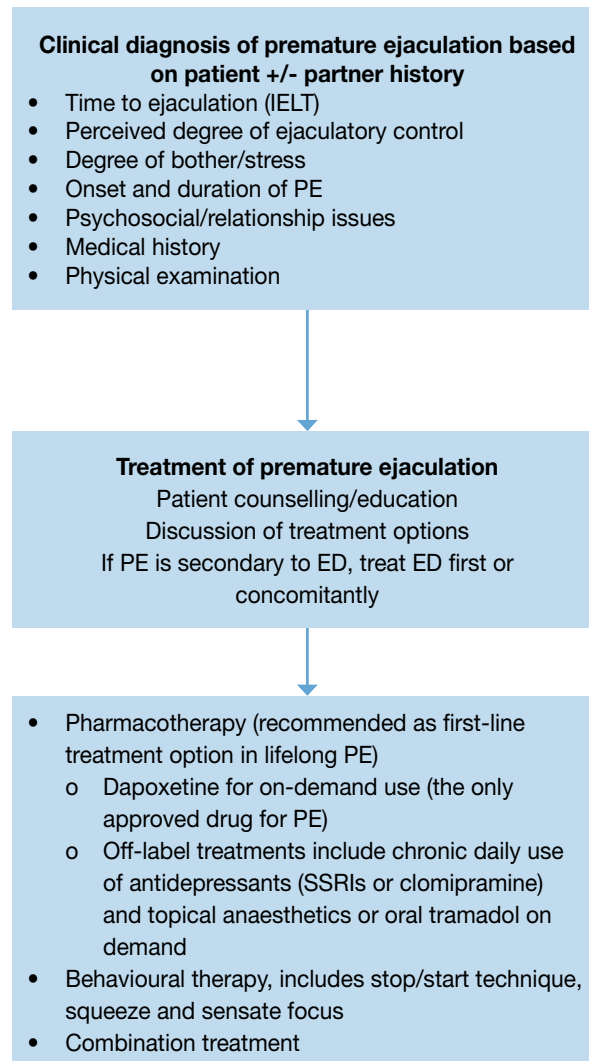
There are very limited data on the efficacy of other PDE5Is (tadalafil and vardenafil) [272, 273]. The role of PDE5Is in PE patients without ED is not established, with only minimal double-blind placebo controlled data available.

3B 4.7 **Recommendations for the treatment of PE**

Recommendations	LE	GR
Erectile dysfunction, other sexual dysfunction or genitourinary infection (e.g. prostatitis) should be treated first.	2a	B
Pharmacotherapy should be given as first-line treatment of lifelong premature ejaculation.	1a	A
Pharmacotherapy includes either dapoxetine on demand (a short-acting SSRI that is the only approved pharmacological treatment for premature ejaculation) or other off-label antidepressants, i.e. daily SSRIs and clomipramine, that are not amenable to on-demand dosing. With all antidepressant treatment for premature ejaculation, recurrence is likely after treatment cessation.	1a	A
Off-label topical anaesthetic agents can be offered as a viable alternative to oral treatment with SSRIs.	1b	A
Behavioural and sexological therapies have a role in the management of acquired premature ejaculation. They are most likely to be best used in combination with pharmacological treatment.	3	C
Psychological/behavioural therapies.	3	C
On-demand treatment of premature ejaculation		
PDE5 inhibitor.	3	C
Dapoxetine on demand.	1a	A
Tramadol on demand.	2a	B
Chronic treatment of premature ejaculation		
Off-label chronic treatment i.e. daily with selective serotonin receptor inhibitors (SSRIs) and clomipramine antidepressants.	1a	A
On-demand topical therapy for premature ejaculation		
Lidocaine-prilocaine cream.	1b	A

SSRI = selective serotonin reuptake inhibitor.

Figure 4: Management of PE*



* Adapted from Lue et al. 2004 [274].

ED = erectile dysfunction; PE = premature ejaculation; IELT = intravaginal ejaculatory latency time;

SSRI = selective serotonin receptor inhibitor.

4. FOLLOW-UP

Follow-up is important in order to assess efficacy and safety of the provided treatment as well as the satisfaction of the patient and his partner as discussed in detail in the previous section.

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6. CONFLICT OF INTEREST

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Guidelines on **Priapism**

A. Salonia, I. Eardley, F. Giuliano, I. Moncada, K. Hatzimouratidis

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1. INTRODUCTION

1.1 Aim

Priapism is a pathological condition representing a true disorder of penile erection that persists for more than 4 hours and is beyond, or is unrelated to, sexual interest or stimulation [1] (LE: 4). Overall, erections lasting up to 4 hours are by consensus defined as 'prolonged' (LE: 4).

Priapism may occur at all ages. The incidence rate of priapism in the general population is low (0.5-0.9 cases per 100,000 person-years) [2, 3]. In patients with sickle cell disease, the prevalence of priapism is up to 3.6% in patients < 18 years of age [4] increasing up to 42% in patients ≥ 18 years of age [5-8].

The aim of these guidelines is to present the current evidence for the diagnosis and treatment of patients suffering from priapism.

1.2 Publication history

The EAU Guidelines on Priapism were first published in 2014 by the EAU Male Sexual Dysfunction Guidelines Panel.

This 2015 version has been updated and re-formatted according to the EAU template for non-oncology Guidelines, so that all Guidelines follow a similar format.

Alongside a scientific publication [9], a quick reference document (Pocket Guidelines) is available, both in print and in a number of versions for mobile devices, presenting the main findings of the Priapism Guidelines. These are abridged versions which may require consultation together with the full text versions. All available material can be viewed and downloaded for personal use at the EAU website. The EAU website also includes a selection of EAU Guidelines articles as well as translations produced by national urological associations: <http://www.uroweb.org/guidelines/online-guidelines/>.

This document was peer-reviewed prior to publication.

1.3 Panel composition

The EAU Male Sexual Dysfunction Guidelines Panel consists of urologists. Members of this Panel have been selected based on their expertise to represent the professionals treating patients suffering from priapism.

2. METHODS

References used in this text are graded according to their Level of Evidence (LE) and Guidelines are given a Grade of Recommendation (GR). In this 2015 EAU Guidelines compilation, all standard information on LE and GR has been taken out of the individual Guidelines topics for the sake of brevity. The methodology section (see the introduction chapter of the complete book) outlines the LE and GR criteria which are used throughout the Guidelines, according to a classification system modified from the Oxford Centre for Evidence-based Medicine Levels of Evidence.

The EAU Guidelines on Priapism are based on a systematic literature search performed by the Panel members. The MedLine database was searched using the major Medical Subject Headings term 'priapism' with search cut-off date of October 2014. This search yielded 1,688 articles (192 review articles, 485 original articles and 911 case reports). The Panel also identified critical problems and knowledge gaps, enabling priorities to be established for future clinical research.

3. THE GUIDELINE

3A ISCHAEMIC (LOW-FLOW OR VENO-OCCLUSIVE) PRIAPISM

3A.1 Epidemiology/aetiology/pathophysiology

Ischaemic priapism is the most common form of priapism, accounting for more than 95% of all priapism episodes [10, 11]. It is usually painful, with a rigid erection characterised clinically by absent or reduced intracavernous arterial inflow. In ischaemic priapism, there are time-dependent modifications in the corporal metabolic environment, progressively leading to hypoxia, hypercapnia, and acidosis.

Ischaemic priapism beyond 4 hours is considered a compartment syndrome, characterised by supraphysiological pressure within the closed space of the corpora cavernosa, which severely compromises cavernous circulation. Emergency medical intervention is required to minimise potential irreversible consequences, such as corporal fibrosis and permanent erectile dysfunction (ED) [12, 13]. The duration of priapism represents the most significant predictor of the development of ED. In this context, interventions beyond 48-72 hours since onset may help to relieve erection and pain, but have little benefit in preventing ED.

Histologically, by 12 hours, corporal specimens show interstitial oedema, progressing to destruction of sinusoidal endothelium, exposure of the basement membrane and thrombocyte adherence at 24 hours. At 48 hours, thrombi can be found in the sinusoidal spaces and smooth muscle necrosis with fibroblast-like cell transformation is evident [13]. In terms of pathophysiology (Table 1), no specific cause can be identified in the majority of cases [11, 14]. However, ischaemic priapism can be associated with sickle cell disease, haematological dyscrasias, neoplastic syndromes, and with the use of several different medications. Ischaemic priapism may occur (0.4-35%) after intracavernous injections of erectogenic agents [11, 12, 15-17]. The risk is highest with papaverine-based combinations, while the risk of priapism is < 1% following prostaglandin E1 injection [17].

Since their introduction on the market, a few cases of priapism have been described in men who have taken phosphodiesterase type 5 inhibitors (PDE5Is) [11]. Most of these men however, had other risk factors for priapism, and it is unclear whether PDE5Is alone can cause ischaemic priapism [11]. Since most men who experienced priapism following PDE5I use had additional risk factors for ischaemic priapism, PDE5I use is usually not regarded a risk factor in itself.

Sickle cell disease is the most common cause in childhood, accounting for 63% of the cases. It is the primary aetiology in 23% of adult cases [18], with a lifetime probability of developing ischaemic priapism of 29-42% in men with sickle cell disease [11, 18-20] (LE: 4). Mechanisms of sickle cell disease associated priapism may involve dysfunctional nitric oxide synthase and ROCK signaling, and increased oxidative stress associated with NADPH oxidase mediated signaling [21].

Priapism resulting from metastatic or regional infiltration is rare and usually reflects an infiltrative process [22]. As such, the recommendations for pharmacological treatment are unlikely to work and certainly all of these men should have a magnetic resonance imaging (MRI) scan and be offered supportive care for their primary cancer.

Priapism in children is extremely rare and is most commonly related to malignancy, haematological or otherwise. The investigative focus should be on identifying any underlying causes.

Partial priapism, or idiopathic partial thrombosis of the penis, is a very rare condition. It is a subtype of priapism limited to the crura. Its aetiology is unknown, but bicycle riding, trauma, drug usage, sexual intercourse, haematological diseases and α -blockers have been associated with partial priapism [23].

Table 1: Potential causative factors for ischaemic priapism

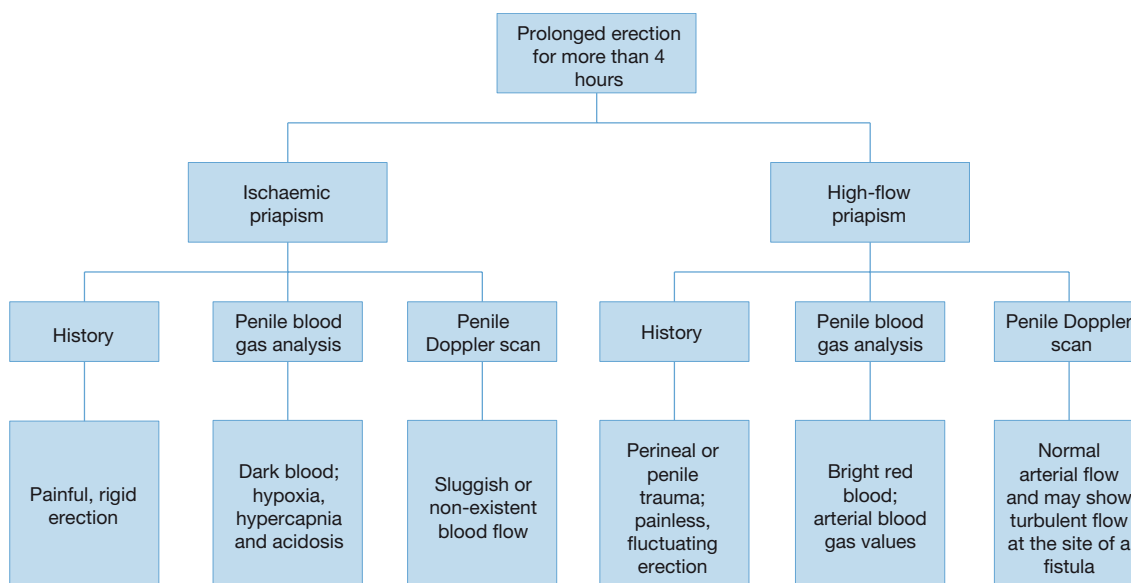
• Idiopathic
• Haematological dyscrasias (sickle cell disease, thalassemia, leukaemia; multiple myeloma, Hb Olmsted variant, fat emboli during hyperalimentation, haemodialysis, glucose-6-phosphate dehydrogenase deficiency, Factor V Leiden mutation)
• Infections (toxin-mediated) (i.e. scorpion sting, spider bite, rabies, malaria)
• Metabolic disorders (i.e. amyloidosis, Fabry's disease, gout)
• Neurogenic disorders (i.e. syphilis, spinal cord injury, cauda equina syndrome, autonomic neuropathy, lumbar disc herniation, spinal stenosis, cerebrovascular accident, brain tumour, spinal anaesthesia)
• Neoplasms (metastatic or regional infiltration) (i.e. prostate, urethra, testis, bladder, rectal, lung, kidney)
• Medications
o Vasoactive erectile agents (i.e. papaverine, phentolamine, prostaglandin E1/alprostadil, combination of intracavernous therapies)
o Alpha-adrenergic receptor antagonists (i.e. prazosin, terazosin, doxazosin, tamsulosin)
o Antianxiety agents (hydroxyzine)
o Anticoagulants (heparin, warfarin)
o Antidepressants and antipsychotics (i.e. trazodone, bupropion, fluoxetine, sertraline, lithium, clozapine, risperidone, olanzapine, chlorpromazine, thiorizadine, phenothiazines)
o Antihypertensives (i.e. hydralazine, guanethidine, propranolol)
o Hormones (i.e. gonadotropin-releasing hormone, testosterone)
o Recreational drugs (i.e. alcohol, marijuana, cocaine [intranasal and topical], crack, cocaine)

3A.1.1 Conclusions on the epidemiology, aetiology and pathophysiology of ischaemic priapism

Conclusions	LE
Ischaemic priapism is most common, accounting for more than 95% of all cases.	1b
Ischaemic priapism is identified as idiopathic in the vast majority of patients, while sickle cell anaemia is the most common cause in childhood.	1b
Ischaemic priapism occurs relatively often (up to 35%) after intracavernous injections of papaverine-based combinations, while it is rare (< 1%) after prostaglandin E1 monotherapy.	2a
Priapism is rare in men who have taken PDE5Is with only sporadic cases reported.	1a

3A.1.2 Classification

Ischaemic priapism is a persistent erection marked by rigidity of the corpora cavernosa and by little or no cavernous arterial inflow [11]. The patient typically complains of penile pain and examination reveals a rigid erection. Resolution of ischaemic priapism is characterised by return to a flaccid non-painful state. However, in many cases, persistent penile oedema, ecchymosis and partial erections can occur and may mimic unresolved priapism. The partial erections may reflect reactive hyperaemia and are sometimes misdiagnosed as persistent priapism. When left untreated, resolution may take days and ED invariably results.

Figure 1: Differential diagnosis of priapism**3A.1.3.1 History**

A comprehensive history taking is the mainstay in priapism diagnosis [11, 24]. The medical history must include a history of sickle cell disease or any other haematological abnormality [8, 25] and a history of pelvic, genital or perineal trauma. The sexual history must include complete details of the duration of erection, the presence and degree of pain, prior medical drug use, any previous history of priapism and erectile function prior to the last priapism episode (Table 2). The history can help to determine the underlying type of priapism (Table 3). Ischaemic priapism is associated with progressive penile pain and the erection is rigid.

Table 2: Key points in taking the history of priapism (adapted from Broderick et al [11])

Duration of erection
Presence and degree of pain
Previous episodes of priapism and method of treatment
Current erectile function, especially the use of any erectogenic therapies prescription or nutritional supplements
Medications and recreational drugs
Sickle cell disease, haemoglobinopathies, hypercoagulable states
Trauma to the pelvis, perineum, or penis

3A.1.3.2 Physical examination

In ischaemic priapism, the corpora are fully rigid and tender, but the glans penis is soft. The patient complains of pain. Pelvic examination may reveal cases of malignancy.

3A.1.3.3 Laboratory testing

Laboratory testing should include a complete blood count, white blood count with blood cell differential, platelet count and coagulation profile to assess anaemia and detect haematological abnormalities [11, 24].

Blood aspiration from the corpora cavernosa shows dark ischaemic blood (Table 3) (LE: 2b). Blood gas analysis is essential to differentiate between ischaemic and arterial priapism (Table 4).

Further laboratory testing should be directed by history, clinical and laboratory findings. These may include specific tests for the diagnosis of sickle cell anaemia or other haemoglobinopathies (e.g. haemoglobin electrophoresis) or urine and plasma toxicological studies when there is suspected use of recreational psychoactive drugs.

3A.1.3.4 Penile imaging

Colour Doppler ultrasound (US) of the penis and perineum is recommended and can differentiate ischaemic from arterial priapism as an alternative or adjunct to blood gas analysis [26-28] (LE: 2b). Scanning of the penis should be performed before aspiration in ischaemic priapism.

Examination of the penile shaft and perineum is recommended. In ischaemic priapism there will be an absence of blood flow in the cavernous arteries. The return of the cavernous artery waveform will result in successful detumescence [11, 28, 29]. After aspiration, a reactive hyperaemia may develop with a high arterial flow that may mislead the diagnosis as arterial priapism.

The role of MRI in the diagnostic evaluation of priapism is controversial. It may be helpful in cases of ischaemic priapism to assess the viability of the corpora cavernosa and the presence of penile fibrosis. In a prospective study in 38 patients with ischaemic priapism, the sensitivity of MRI in predicting non-viable smooth muscle was 100%, as confirmed by corporal biopsy [30]. In this study, all patients with viable smooth muscle on MRI maintained erectile function on clinical follow-up (LE: 3).

Table 3: Key findings in priapism (adapted from Broderick et al [11])

	Ischaemic priapism	Arterial priapism
Corpora cavernosa fully rigid	Usually	Seldom
Penile pain	Usually	Seldom
Abnormal penile blood gas	Usually	Seldom
Haematological abnormalities	Usually	Seldom
Recent intracorporeal injection	Sometimes	Sometimes
Perineal trauma	Seldom	Usually

Table 4: Typical blood gas values (adapted from Broderick et al [11])

Source	pO ₂ (mmHg)	pCO ₂ (mmHg)	pH
Normal arterial blood (room air) [similar values are found in arterial priapism]	> 90	< 40	7.40
Normal mixed venous blood (room air)	40	50	7.35
Ischaemic priapism (first corporal aspirate)	< 30	> 60	< 7.25

3A.1.3.5 Recommendations for the diagnosis of ischaemic priapism

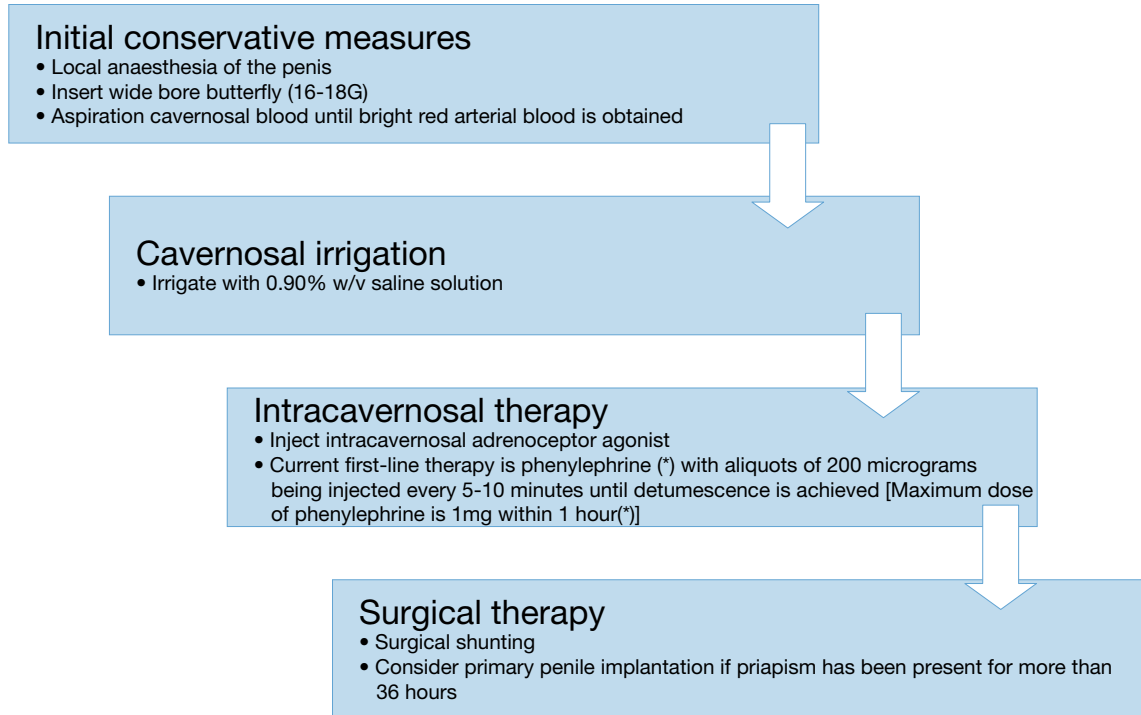
Recommendations	GR
A comprehensive history is key for diagnosis and can help to determine the underlying type of priapism.	B
Physical examination of the genitalia, the perineum and the abdomen must be included in the diagnostic evaluation and may help to determine the underlying type of priapism.	B
Laboratory testing should include complete blood count, white blood count with blood cell differential, platelet count and coagulation profile. Further laboratory testing should be directed by the history and clinical and laboratory findings. Priapism in children requires a complete evaluation of all possible causes.	B
Blood gas analysis of blood aspirated from the penis is recommended for the differentiation between ischaemic and arterial priapism.	B
Colour duplex ultrasound of the penis and perineum is recommended for the differentiation between ischaemic and arterial priapism as an alternative or adjunct to blood gas analysis. It can also be helpful in localisation of the site and extend of fistula in arterial priapism as well as in the determination of successful resolution of ischaemic priapism.	B
Magnetic resonance imaging of the penis can predict smooth muscle viability and erectile function restoration.	B
Selected pudendal arteriogram should be reserved for the management of arterial priapism when embolisation is undertaken.	B

3A.1.4 Disease management

Acute ischaemic priapism is an emergency condition. Rapid intervention is compulsory (LE: 4), and should follow a stepwise approach. The aim of any treatment is to restore penile flaccidity, without pain, in order to prevent damage to the corpora cavernosa.

Figure 2: Treatment of ischaemic priapism

The treatment is sequential and the physician should move on to the next stage if the treatment fails.



(*) The dose of phenylephrine should be reduced in children. It can result in significant hypertension and should be used with caution in men with cardiovascular disease and monitoring of pulse, blood pressure and electrocardiogram (ECG) is advisable in all patients during administration and for 60 minutes afterwards. Its use is contraindicated in men with a history of cerebro-vascular disease and significant hypertension.

3A.1.4.1 First-line treatments

First-line treatments in ischaemic priapism of > 4 hours duration are strongly recommended before any surgical treatment (LE: 4). Conversely, first-line treatments initiated beyond 72 hours while relieving the priapism have little documented benefit in terms of potency preservation (LE: 4).

Historically, several first-line treatments have been described including exercise, ejaculation, ice packs, cold baths, and cold water enemas [11]. However, there is lack of evidence of benefit for such measures.

Partial priapism usually resolves spontaneously with analgesic treatment while surgical intervention is rarely needed [31].

3A.1.4.1.1 Penile anaesthesia/systemic analgesia

It is possible to perform blood aspiration and intracavernosal injection of a sympathomimetic agent without any anaesthesia. However, anaesthesia may be necessary when there is severe penile pain. While it is recognised that the anaesthesia may not alleviate the ischaemic pain, cutaneous anaesthesia will facilitate subsequent therapies. The treatment options for penile anaesthesia/systemic analgesia include:

- dorsal nerve block;
- circumferential penile block;
- subcutaneous local penile shaft block;
- oral conscious sedation (for paediatric patients).

3A.1.4.1.2 Aspiration ± irrigation with 0.90% w/v saline solution

The first intervention for an episode of priapism lasting > 4 hours consists of corporal aspiration (LE: 4) to

drain stagnant blood from the corporal bodies, making it possible to relieve the compartment syndrome-like condition of the penis. Blood aspiration may be performed with intracorporeal access either through the glans or via percutaneous needle access on the lateral aspect of the proximal penile shaft, using a 16G or 18G angiocatheter or butterfly needle. The needle must penetrate the skin, the subcutaneous tissue and the tunica albuginea to drain the corpus cavernosum (LE: 4).

Some clinicians use two angiocatheters or butterfly needles at the same time to accelerate drainage, as well as aspirating and irrigating simultaneously with a saline solution [19] (LE: 4). Aspiration should be continued until fresh red, oxygenated, blood is aspirated (LE: 4).

This approach has up to a 30% chance of terminating the priapism. There are insufficient data to determine whether aspiration followed by saline intracorporeal irrigation is more effective than aspiration alone (LE: 4).

3A.1.4.1.3 Aspiration ± irrigation with 0.90% w/v saline solution in combination with intracavernosal injection of pharmacological agents

This combination is currently considered the standard of care in the treatment of ischaemic priapism [1, 11, 32] (LE: 4). Pharmacological agents include sympathomimetic drugs or alpha-adrenergic agonists. Options for intracavernosal sympathomimetic agents include phenylephrine, etilephrine, ephedrine, epinephrine, norepinephrine and metaraminol with a resolution rate of up to 80%. [11, 32-40] (LE: 2b). The use of intracavernosal adrenalin injection alone has also been sporadically reported [41].

3A.1.4.1.3.1 Phenylephrine

Phenylephrine is currently the drug of choice due to its high selectivity for the alpha-1-adrenergic receptor, without concomitant beta-mediated inotropic and chronotropic cardiac effects [33, 37, 38] (LE: 4).

Phenylephrine is diluted in normal saline to a concentration of 100-500 µg/mL. Usually 200 µg are given every 3-5 minutes directly into the corpus cavernosum. Maximum dosage is 1 mg within 1 hour (LE: 4). A lower concentration or volume is applicable for children and patients with severe cardiovascular disease (LE: 4).

Phenylephrine use has potential cardiovascular side-effects [11, 32-34, 37, 38] and it is recommended that blood pressure and pulse are monitored every 15 minutes for an hour after the injection. This is particularly important in older men with existing cardiovascular diseases. After injection, the puncture site should be compressed and the corpora cavernosa massaged to facilitate drug distribution.

The potential treatment-related side-effects of intracavernous phenylephrine (and other sympathomimetic agents) include headache, dizziness, hypertension, reflex bradycardia, tachycardia and palpitations, irregular cardiac rhythms and sporadic subarachnoid haemorrhage [34]. Monitoring of blood pressure and pulse with ECG should be performed during intracavernous administration of sympathomimetic agents.

Overall, the administration of intracavernosal sympathomimetic agents is contraindicated in patients suffering from malignant or poorly controlled hypertension and in those who are concurrently taking monoamine oxidase inhibitors (LE: 4).

3A.1.4.1.3.2 Etilephrine

Etilefrine is the second most widely used sympathomimetic agent, administered by intracavernosal injection at a concentration of 2.5 mg in 1-2 ml normal saline [34] (LE: 3).

3A.1.4.1.3.3 Methylene blue

Methylene blue is a guanylate cyclase inhibitor, which may be a potential inhibitor of endothelial-mediated cavernous relaxation. It has therefore been suggested for treating short-term pharmacologically induced priapism [42, 43] (LE: 3). Methylene blue, 50-100 mg [42], should be injected intracavernously and left for 5 minutes. It is then aspirated and the penis compressed for an additional 5 minutes [43]. Treatment-related side-effects include a transient burning sensation and blue discolouration of the penis.

3A.1.4.1.3.4 Adrenaline

Intracavernosal adrenaline (dosage of 2 mL of 1/100,000 adrenaline solution up to five times over a 20-minute period [41]), has been used in patients with ischaemic priapism due to an intracavernosal injection of vasoactive agents. Success rate of over 50% after a single injection, with an overall success rate of 95% with repeated injections is achieved (LE: 3).

3A.1.4.1.3.5 Oral terbutaline

Oral terbutaline is a beta-2-agonist with minor beta-1 effects and some alpha-agonist activity. A dose of 5 mg has been suggested to treat prolonged erections lasting more than 2.5 hours, after intracavernosal injection of vasoactive agents, although the mechanism of action is not yet fully understood [44-46] (LE: 1b). Its main use is in the prevention of recurrent episodes of prolonged erection. Terbutaline should be given cautiously in patients with coronary artery disease, increased intravascular fluid volume, oedema and hypokalaemia [46].

Table 5: Medical treatment of ischaemic priapism

Drug	Dosage/Instructions for use
Phenylephrine	<ul style="list-style-type: none">- Intracavernous injection of 200 µg every 3-5 minutes.- Maximum dosage is 1 mg within 1 hour.- The lower doses are recommended in children and patients with severe cardiovascular disease.
Etilephrine	<ul style="list-style-type: none">- Intracavernosal injection at a concentration of 2.5 mg in 1-2 ml normal saline.
Methylene blue	<ul style="list-style-type: none">- Intracavernous injection of 50-100 mg, left for 5 minutes. It is then aspirated and the penis compressed for an additional 5 minutes.
Adrenaline	<ul style="list-style-type: none">- Intracavernous injection of 2 mL of 1/100,000 adrenaline solution up to five times over a 20-minute period.
Terbutaline	<ul style="list-style-type: none">- Oral administration of 5 mg for prolonged erections lasting more than 2.5 hours, after intracavernosal injection of vasoactive agents.

3A.1.4.1.4 Management of sickle cell disease related priapism

Rapid intervention is essential (LE: 4) and the general approach is similar to that described in other cases of ischaemic priapism [47-49] (LE: 4).

However, as with other haematological disorders, other therapeutic practices may also need to be implemented [47, 49, 50]. Specific measures for sickle cell disease related priapism include intravenous hydration and parental narcotic analgesia while preparing the patient for aspiration and irrigation. In addition, supplemental oxygen administration and alkalinisation with bicarbonate can be helpful [20, 48].

Exchange blood transfusion has also been proposed, with the aim of increasing the tissue delivery of oxygen. The transfused blood should be HbS negative, Rh and Kell antigen matched [51]. However, the evidence is inconclusive as to whether exchange transfusion itself helps to resolve the priapism in these men. It should also be noted that several reports suggest that this treatment may result in serious neurological sequelae [52]. Because of these considerations, the routine use of this therapy is not recommended (LE: 4).

3A.1.4.2 Second-line treatments

Second-line intervention typically refers to surgical intervention in the form of penile shunt surgery and should only be considered when conservative management options fail (LE: 4). There is no evidence detailing the amount of time allowed for first-line treatment before moving on to surgery. Consensus recommendations suggest a period of at least 1 hour of first-line therapy prior to moving to surgery (LE: 4). A number of clinical indicators suggest failure of first-line treatment including continuing corporal rigidity, cavernosal acidosis and anoxia, absence of cavernosal artery inflow by penile colour duplex US, and elevated intracorporal pressures by pressure monitoring (LE: 4).

3A.1.4.2.1 Penile shunt surgery

Penile shunt surgery aims to produce an exit for ischaemic blood from the corpora cavernosa thereby allowing the restoration of normal circulation within these structures. Accordingly, any shunt creates an opening in the tunica albuginea, which may communicate with either the glans, the corpus spongiosum or a vein for blood drainage [11, 32, 53].

In general, the type of shunt procedure chosen is according to the surgeon's preference and procedure familiarity (LE: 4). It is conventional for distal shunt procedures to be tried before proximal shunting is considered (LE: 4). Cavernous biopsy has been used to identify muscle necrosis (which, if present, would suggest that shunting is likely to fail) although this has mainly a medico-legal role.

It is important to assess the success of surgery by either direct observation or by investigation (e.g. cavernous blood gas testing, penile colour duplex US) (LE: 4) [11, 32].

The recovery rates of erectile function in men undergoing shunt surgery for prolonged erections are low and directly relate to the duration of the priapism [54, 55]. Priapism for more than 36 hours appears to irreversibly impair erectile tissue both structurally and functionally [54]. In general, shunt procedure undertaken after this time period may only serve to limit pain without any benefit for erectile function (LE: 4).

Four categories of shunt procedures have been reported [1, 11, 53]. The limited available data preclude any recommendation for one procedure over another based on outcome (LE: 4).

Percutaneous distal (corpora-glanular) shunts

Winter's procedure: this procedure uses a Trucut biopsy needle to create a fistula between the glans penis and each corpora cavernosa body [1, 11, 18, 56, 57] (LE: 3). Postoperative sequelae are uncommon [58]. Winter's shunt is easy to perform, but has been reported as the least successful operation to create a distal shunt [55].

Ebbehoj's technique: this technique involves the execution of multiple tunical incision windows between the glans and each tip of the corpus cavernosum by means of a size 11 blade scalpel passed several times percutaneously [1, 11, 56, 59, 60] (LE: 3).

T-Shunt: this technique involves performing a bilateral procedure using a size 10 blade scalpel placed vertically through the glans until fully within the corpus cavernosum. The blade is then rotated 90 degrees away from the urethra and pulled out [1, 11, 56, 61] (LE: 3). The whole tunneling procedure could be performed using ultrasound for guidance, mainly in order to avoid urethral injury [61].

Open distal (corpora-glanular) shunts

Al-Ghorab's procedure: this procedure consists of an open bilateral excision of circular cone segments of the distal tunica albuginea via the glans penis, along with a subsequent glans closure by means of a running suture with absorbable material [1, 11, 56, 62, 63] (LE: 3).

Burnett's technique: a modification of the Al-Ghorab corpora-glanular shunt surgery involves the retrograde insertion of a 7/8 Hegar dilator into the distal end of each corpus cavernosum through the original Al-Ghorab glanular excision. After removal of the dilator from the corpus cavernosum, blood evacuation is facilitated by manual compression of the penis sequentially from a proximal to distal direction. After detumescence, the glans penis skin is closed as in the Al-Ghorab procedure [1, 11, 56, 64, 65] (LE: 3). Reported complications included wound infection, penile skin necrosis and a urethrocutaneous fistula [65].

Open proximal (corporospongiosal) shunts

Quackles's technique: through a trans-scrotal or perineal approach, a proximal open shunt technique creates a communication between the corpus cavernosum and the corpus spongiosum. The most frequent complications include an unwanted urethra-cavernous fistula and urethral stricture or the development of cavernositis [1, 11, 53, 66]. The risk of urethral injury is less with a perineal approach to the bulb of the corpus spongiosum (LE: 3).

Vein anastomoses/shunts

Grayhack's procedure: this mobilises the saphenous vein below the junction of the femoral vein and anastomoses the vein end-to-side onto the corpus cavernosum. Venous shunts may be complicated by saphenofemoral thrombus formation and by pulmonary embolism [1, 11, 67-69] (LE: 3).

Immediate surgical prosthesis implantation

Intractable, therapy-resistant, acute ischaemic priapism or episodes lasting more than 48-72 hours usually result in complete ED, possibly along with major penile deformity. In these cases, immediate penile prosthesis surgery has been suggested [70-73] (LE: 3).

The immediate insertion of a penile prosthesis has been recommended to avoid the difficulty and complications of delayed surgery in the presence of corporal fibrosis. Potential complications that could compromise immediate penile prosthesis implantation include distal erosion and cavernositis [70, 72], along with a mild rate of revision surgery [70]. Early surgery also offers the opportunity to maintain penile size, which is inevitably compromised by delay.

Currently, there are no clear indications for immediately implanting a penile prosthesis in a man with acute ischaemic priapism [32]. Relative indications include [11] (LE: 4):

- ischaemia that has been presented for more than 36 hours [73];
- failure of aspiration and sympathomimetic intracavernous injections;

- failure of distal and proximal shunting (although in delayed cases, implantation might be considered ahead of shunt surgery).
- MRI or corporal biopsy evidence of corporal smooth muscle necrosis [11, 70] (LE: 4).

3A.1.4.3 *Surgery for non-acute sequelae after ischaemic priapism*

Structural changes may occur after ischaemic priapism including cavernosal tissue necrosis and fibrosis with consequent penile scarring, megalophallic deformities, penile shortening, and occasional penile loss, [53, 70, 74, 75]. Erectile dysfunction is also often observed [11, 76]. Unfortunately, these outcomes can still occur despite apparently successful first-line or second-line treatment.

Prosthesis implantation is occasionally indicated in sickle cell patients with severe ED since other therapeutic options such as PDE5Is and intracavernosal injections are avoided as they may provoke a further priapism event [11, 32]. In severe corporal fibrosis, semi-rigid prosthetic devices are preferable to inflatable implants [70, 77] (LE: 3). Following severe priapism that has resulted in penile destruction with complicated deformities or even loss of penile tissue, penile reconstruction and concomitant prosthesis implant may be considered [78] (LE: 3).

3A.1.5 *Recommendations for the treatment of ischaemic priapism*

Recommendations	GR
Ischaemic priapism is an emergency condition and rapid intervention is compulsory.	B
The specific aim is to restore painless penile flaccidity, in order to prevent chronic damage to the corpora cavernosa.	C
Management of ischaemic priapism should start as early as possible (within 4-6 hours) and should follow a stepwise approach. Erectile function preservation is directly related to the duration of priapism.	B
Initial management is decompression of the corpora cavernosa by penile aspiration until fresh red blood is obtained.	C
In priapism secondary to intracavernous injections of vasoactive agents blood aspiration can be replaced by intracavernous injection of a sympathomimetic drug as the first step.	C
In priapism that persists despite aspiration, the next step is intracavernous injection of a sympathomimetic drug. Phenylephrine is the recommended drug due to its favourable safety profile on the cardiovascular system compared to other drugs. Phenylephrine is usually diluted in normal saline with a concentration of 100-500 µg/mL and given in 200 µg doses every 3-5 minutes directly into the corpus cavernosum. Maximum dosage is 1 mg within 1 hour. Patients at high cardiovascular risk should be given lower doses. Patient monitoring is highly recommended.	B
In cases that persist despite aspiration and intracavernous injection of a sympathomimetic drug, these steps should be repeated several times before considering surgical intervention.	C
Ischaemic priapism due to sickle cell anaemia is treated in the same fashion as idiopathic ischaemic priapism. Other supportive measures are recommended (intravenous hydration, oxygen administration with alkalinisation with bicarbonates, blood exchange transfusions), but these should not delay initial treatment to the penis.	B
Surgical treatment is recommended only when blood aspiration and intracavernous injection of sympathomimetic drugs have failed or for priapism events lasting ≤ 72 hours.	C
Distal shunt surgical procedures should be performed first followed by proximal procedures in case of failure. The efficacy of these procedures is questionable and cavernous biopsy may be considered to diagnose muscle necrosis. No clear recommendation on one type of shunt over another can be given.	C
In cases of priapism presenting > 36 hours after onset, or in cases for which all interventions have failed, erectile dysfunction is inevitable and the immediate implantation of a penile prosthesis should be discussed with the patient. Implantation of penile prosthesis at a later stage can be difficult due to severe corporal fibrosis.	B

3A.1.6 *Follow-up*

Follow-up of ischaemic priapism after successful treatment should include modification of risk factors (if any) in order to avoid a new event and assessment of erectile function since it may be severely compromised especially after surgical treatment with a shunt. Penile fibrosis is usually easily identified with clinical examination of the penis.

3B ARTERIAL (HIGH-FLOW OR NON-ISCHAEMIC) PRIAPISM

3B.1 Epidemiology/aetiology/pathophysiology

Epidemiological data on arterial priapism are almost exclusively derived from small case series [11, 28, 29, 79, 80]. The most frequent cause of high-flow priapism is blunt perineal or penile trauma [81]. The injury results in a laceration in the cavernosal artery leading to a high-flow fistula between the artery and the lacunar spaces of the sinusoidal tissue [80]. This unregulated flow results in a persistent erection, and has been proposed to occur via a mechanism that involves stimulation of endothelial nitric oxide synthase by the turbulent blood flow [82]. Partial erections are enhanced after sexual stimulation, as the trabecular smooth muscle fully relaxes, activating the corporal veno-occlusive mechanism [80, 83].

There is often a delay between the injury and the development of the priapism that may be up to 2-3 weeks [83]. This has been suggested to reflect either spasm or ischaemic necrosis of the injured artery, with the fistula only developing as the spasm resolves or when the ischaemic segment blows out.

Occasional cases are associated with metastatic malignancy to the penis [84, 85], with acute spinal cord injury [86] and occasionally following intracavernosal injections or aspiration due to a lacerated cavernous artery or branch [87, 88]. Under these circumstances, it may complicate low-flow priapism. It has also been reported to occur following internal urethrotomy [89] and a Nesbit procedure [90]. Although sickle cell disease is usually associated with low-flow priapism, occasional cases of high-flow priapism have been reported [91].

3B.1.1 Conclusion on the epidemiology, aetiology and pathophysiology of arterial priapism

Conclusion	LE
Arterial priapism usually occurs after blunt perineal or penile trauma.	2

3B.1.2 Classification

Arterial priapism is a persistent erection caused by unregulated cavernous arterial inflow [11]. The patient typically reports an erection that is not fully rigid and is not associated with pain although fully rigid erections may occur with sexual stimulation.

3B.1.3 Diagnostic evaluation

3B.1.3.1 History

A comprehensive history is also mandatory in arterial priapism diagnosis and follows the same principles as described in Table 2. Arterial priapism is suspected when there is no pain and erections are not fully rigid (Table 3). It can be associated with full erections under sexual stimulation and when there is a history of coital trauma or blunt trauma to the penis. The onset of post-traumatic high-flow priapism in adults and children may be delayed by hours to days following the initial injury. Sexual intercourse is usually not compromised.

3B.1.3.2 Physical examination

In arterial priapism, the corpora are tumescent but not fully rigid (Table 3). Abdominal, penile and perineal examination may reveal evidence of trauma.

3B.1.3.3 Laboratory testing

Blood aspiration from the corpora cavernosa shows bright red arterial blood in arterial priapism, while blood is dark in ischaemic priapism (Table 3) (LE: 2b). Blood gas analysis is essential to differentiate between arterial and ischaemic priapism (Table 4).

3B.1.3.4 Penile imaging

Colour duplex US of the penis and perineum is recommended and can differentiate arterial from ischaemic priapism as an alternative or adjunct to blood gas analysis [26-28] (LE: 2b). Examination of the penile shaft and perineum is recommended. In arterial priapism US will show turbulent flow at the fistula, which helps to localise the site of trauma since patients with arterial priapism have normal to high blood velocities in the cavernous arteries.

A selective pudendal arteriogram can reveal a characteristic blush at the site of the injury to the cavernosal artery in arterial priapism [92, 93]. However, due to its invasiveness it should be reserved for the management of arterial priapism, when embolisation is being considered [11, 24] (LE: 3).

The role of MRI in the diagnostic evaluation of priapism is controversial. In arterial priapism, its role is limited since the small penile vessels and arteriovenous fistulae cannot be easily demonstrated [94].

3B.1.3.5 Recommendations for the diagnosis of arterial priapism

The same recommendations as in section 3A.1.3.5 apply.

3B.1.4 Disease management

The management of high-flow priapism is not an emergency because the penis is not ischaemic. Definitive management can therefore be considered and should be discussed with the patient so that they understand the risks and complications of treatment [11, 24] (LE: 3).

3B.1.4.1 Conservative management

This may include applying ice to the perineum or site-specific perineal compression [28, 79, 95, 96]. It is an option in all cases, particularly children [97] (LE: 3). The fistula occasionally closes spontaneously. Even in those cases when it does not, the response to a sexual stimulus does allow for intercourse. Androgen deprivation therapy (leuprolide injections, bicalutamide and ketoconazole) has been reported in case series to enable closure of the fistula reducing spontaneous and sleep-related erections [98]. However, sexual dysfunction due to these treatments must be considered.

Blood aspiration is not helpful for the treatment of arterial priapism and the use of alpha-adrenergic antagonists is not recommended due to potential severe adverse effects, e.g. transfer of the drug into the systemic circulation.

3B.1.4.2 Selective arterial embolisation

Selective arterial embolisation can be performed using either an autologous clot [99-101], gel foam or sponge [100, 102], or more permanent substances, such as coils [100, 102-104] or acrylic glue [105] (LE: 3). Success rates of up to 89% have been reported [106] in relatively small, non-randomised studies. There are no robust data to demonstrate the relative merits of the different substances. At least theoretically, the use of an autologous clot has some attractions. It temporarily seals the fistula, but when the clot is lysed, the arterial damage has usually resolved and the blood flow of the penis can return to normal. The use of a permanent device, such as a coil, would permanently block an artery and may lead to adverse effects upon spontaneous sexual function. Other potential complications include penile gangrene, gluteal ischaemia, cavernositis and perineal abscess [11, 107].

Following percutaneous embolisation, a follow-up is appropriate within 1-2 weeks. Assessment by clinical examination and by colour duplex US can determine whether the embolisation has been successful [27]. If there is doubt, a repeat arteriogram is required. Recurrence rates of 7-27% after a single treatment of embolisation have been reported [100, 101, 108] (LE: 3). In a few cases, repeat embolisation is necessary. Sexual function following embolisation can be adversely affected although there is full restoration of potency in around 80% of men [108, 109] (LE: 3).

Embolisation in children, although reportedly successful, is technically challenging and requires treatment within a specialist paediatric vascular radiology department [36, 110].

3B.1.4.3 Surgical management

Selective ligation of the fistula through a transcorporeal approach under the guidance of colour duplex US is possible [1, 25, 111]. Surgery is technically challenging and may pose significant risks, mainly ED due to accidental ligation of the cavernous artery instead of the fistula. It is rarely performed and should only be considered when there are contraindications for selective embolisation, no availability of the technique or embolisation failure (LE: 4).

3B.1.4.4 Recommendations for the treatment of arterial priapism

Recommendations	GR
The management of high-flow priapism is not an emergency and definitive management can therefore be considered.	B
Conservative management includes the use of ice applied to the perineum or site-specific perineal compression. It may be successful particularly in children. Androgen deprivation therapy may enable closure of the fistula reducing spontaneous and sleep-related erections.	C
Selective artery embolisation, using temporary or permanent substances, is the suggested treatment modality and has high success rates. No definitive statement can be made on the best substance for embolisation in terms of sexual function preservation.	B
The recurrence of arterial priapism following selective artery embolisation requires the procedure to be repeated.	B
The preservation rate of sexual function is about 80%.	C
Selective surgical ligation of the fistula should be reserved as a last treatment option when embolisation has failed.	C

3B.1.5 Follow-up

Follow-up after successful treatment of arterial priapism should include assessment of erectile function and clinical examination to identify signs of recurrence especially after embolisation.

3C STUTTERING (RECURRENT OR INTERMITTENT) PRIAPISM

3C.1 Epidemiology/aetiology/pathophysiology

Robust epidemiological studies of stuttering priapism are lacking [5, 112]. However, recurrent priapism episodes are common in men with sickle cell disease (42–64%) [113, 114] while in adolescents and young men the incidence of priapism is 35%, of whom 72% have a history of stuttering priapism [5].

The aetiology of stuttering priapism is similar to that of ischaemic priapism. While sickle cell disease is the most common cause, idiopathic cases and cases due to a neurological disorder have been reported. Moreover, men who have suffered from an acute ischaemic priapic event, especially one which has been prolonged (more than 4 hours) are at risk for developing stuttering priapism [76].

Recently, several studies have proposed alternative mechanisms including inflammation, cellular adhesion, nitric oxide metabolism, vascular reactivity and coagulation [11, 21, 48, 115, 116].

3C.1.1 Conclusion on the epidemiology, aetiology and pathophysiology of stuttering priapism

Conclusion	LE
Stuttering priapism is similar to ischaemic priapism in that it is low flow, ischaemic and if left untreated would result in significant penile damage, with sickle cell disease being the most common cause. But the cause can also be idiopathic and in rare cases may be due to a neurological disorder.	3

3C.1.2 Classification

Stuttering priapism, also termed intermittent or recurrent priapism, is a distinct condition that is characterised by repetitive and painful episodes of prolonged erections. Erections are self-limited with intervening periods of detumescence [48, 115]. These are analogous to repeated episodes of low flow (or ischaemic) priapism. The duration of the erectile episodes is generally shorter than in ischaemic priapism [1]. The frequency and/or duration of these episodes is variable and a single episode can sometimes progress into a major ischaemic priapic episode.

3C.1.3 Diagnostic evaluation

3C.1.3.1 History

A comprehensive history is mandatory and follows the same principles as described in Table 2. There is a

history of recurrent episodes of prolonged erections. The onset of the priapic episodes usually occurs during sleep and detumescence does not occur upon waking. Many of these priapic episodes are painful and may be the reason that the patient seeks medical help.

3C.1.3.2 Physical examination

Erections are painful and the penis is rigid as in ischaemic priapism, but the duration of events is usually shorter. Between erections the penis is usually normal, but in some cases signs of fibrosis can be found. Rarely, the penis may become enlarged, a condition known as megalophallus.

3C.1.3.3 Laboratory testing

Laboratory testing follows the same principles as in the two other types of priapism. It is recommended to identify possible causes and should be directed by history, clinical and laboratory findings.

3C.1.3.4 Penile imaging

There are no specific findings for stuttering priapism. Colour duplex ultrasound of the penis and perineum and MRI are recommended and can differentiate arterial from ischaemic type of priapism.

3C.1.3.5 Recommendations for the diagnosis of stuttering priapism

The same recommendations as described in section 3A.1.3.5 apply. Stuttering priapism is actually a recurrent or intermittent type of ischaemic priapism.

3C.1.4 Disease management

The primary goal in the management of patients with stuttering priapism is the prevention of future episodes, which can usually be achieved pharmacologically. The management of each acute episode is similar to that for ischaemic priapism; aspiration/irrigation in combination with intracavernous injections of alpha-adrenergic agonists. Unfortunately, the efficacy and safety of the various treatment modalities reported in the medical literature are poorly characterised. Specifically, most reports are from small case series and the Expert Panel is not aware of any published, well-designed, controlled studies on the efficacy and safety of these treatments [20, 48, 115].

3C.1.4.1 Alpha-adrenergic agonists

Studies of oral alpha-adrenergic agonists have suggested some benefit for daily dosing of these agents as effective prevention [117]. Side-effects include tachycardia and palpitations. Pseudoephedrine, widely used as an oral decongestant, can also be used as a first-line treatment [45]. However, its effect on corporal smooth muscle is not fully understood. Etilefrine has been used successfully to prevent stuttering priapism due to sickle cell anaemia. It is taken orally at doses of 50-100 mg daily, with response rates of up to 72% [7, 118, 119]. In one randomized, placebo-controlled, clinical study looking at medical prophylaxis with etilefrine and ephedrine, there was no difference in efficacy between the two drugs.

3C.1.4.2 Hormonal manipulations of circulating testosterone

The aim of hormonal manipulation is to down-regulate circulating testosterone levels to suppress the action of androgens on penile erection [20, 48, 120]. This can be done through the use of gonadotropin-releasing hormone (GnRH) agonists or antagonists, antiandrogens or oestrogens [121] (LE: 4). Potential side-effects may include hot flushes, gynaecomastia, impaired erectile function, loss of libido and asthenia. All approaches have a similar efficacy profile (LE: 4) while the potential cardiovascular toxicity of oestrogens limits their clinical use. Alternative endocrine approaches that have been used with some success include 5-alpha-reductase inhibitors [122] (LE: 3) and Ketoconazole, an antifungal agent that reduces adrenal and testicular androgen production [120, 123] (LE: 4).

Of the hormonal agents suggested for preventing priapism, GnRH agonists and anti-androgens appear to be the most efficacious and safe. They are recommended as primary treatments for the management of stuttering priapism in adult men (LE: 4).

The duration of hormonal treatment for effective suppression of recurrent priapic events is problematic. It is not possible to make any conclusions on the efficacy, dose and the duration of treatment. Moreover, hormonal agents have a contraceptive effect and interfere with normal sexual maturation. Caution is therefore strongly advised when prescribing hormonal treatments to prepubertal boys, adolescents or men who are trying for their female partner to conceive. Castrate levels of testosterone, which have a contraceptive effect, interfere with growth, and significantly affect sexual function.

3C.1.4.3 Digoxin

Digoxin (a cardiac glycoside and a positive inotrope) is used to treat patients with congestive heart failure. Digoxin regulates smooth muscle tone through a number of different pathways leading to penile detumescence [20, 48, 124]. The use of maintenance digoxin doses (0.25-0.5 mg daily) in idiopathic stuttering priapism has been proven to reduce the number of hospital visits and to improve QoL [48]. A small, clinical, double-blind, placebo-controlled study, using digoxin, produced a decrease in sexual desire and excitement with a concomitant reduction in penile rigidity, regardless of any significant change in plasma levels of testosterone, oestrogens and luteinising hormone [124] (LE: 2b). Side-effects may include a decreased libido, anorexia, nausea, vomiting, confusion, blurred vision, headache, gynaecomastia, rash and arrhythmia.

3C.1.4.4 Terbutaline

Terbutaline is a beta-agonist that causes vasodilation, resulting in smooth muscle relaxation of the vasculature [20, 48] and has been used to prevent stuttering priapism with detumescence rates of 36% in patients with alprostadil-induced priapism [45] (LE: 3). The only randomised, placebo-controlled study (n = 68) in patients with pharmacologically-induced priapism, showed detumescence in 42% of the terbutaline-treated group compared to only 15% in the placebo-treated group [46] (LE: 1b). Side-effects include nervousness, shakiness, drowsiness, heart palpitations, headache, dizziness, hot flashes, nausea and weakness.

3C.1.4.5 Gabapentin

Gabapentin has anticonvulsant, antinociceptive and anxiolytic properties and is widely used as an analgesic and antiepileptic agent. Its proposed mechanism of action is to inhibit voltage-gated calcium channels, which attenuates synaptic transmission [120], and reduces testosterone- and follicle-stimulating hormone levels [125]. It is given at a dose of 400 mg, four times a day, up to 2400 mg daily, until complete penile detumescence occurs, with subsequent maintenance administration of gabapentin, 300 mg daily [126] (LE: 4). Side-effects include anorgasmia and impaired erectile function.

3C.1.4.6 Baclofen

Baclofen is a gamma-aminobutyric acid (GABA) derivative that acts as a muscle relaxant and anti-muscle spasm agent. It can inhibit penile erection and ejaculation through GABA activity and prevents recurrent reflexogenic erections or prolonged erections from neurological diseases [20]. Oral baclofen has little efficacy and it is not usually used in stuttering priapism but intrathecal baclofen dosing is more effective [48, 127-129] (LE: 4). Side-effects include drowsiness, confusion, dizziness, weakness, fatigue, headache, hypotension and nausea.

3C.1.4.7 Hydroxyurea

Hydroxyurea blocks the synthesis of DNA by inhibiting ribonucleotide reductase, which has the effect of arresting cells in the S-phase [120, 130]. It is an established treatment for ameliorating sickle cell disease and improving their life expectancy [47, 131]. For such patients with recurrent priapism there is limited evidence to suggest a medical prophylactic role (LE: 3) [120, 130, 132]. Side-effects include oligozoospermia and leg ulcers.

3C.1.4.8 Phosphodiesterase type 5 inhibitors (PDE5Is)

Low doses of PDE5Is have a paradoxical effect in alleviating and preventing stuttering priapism, mainly in patients with idiopathic and sickle cell disease-associated priapism [20, 48, 133-137] (LE: 3). It is important to remember that therapy should be started when the penis is in its flaccid state and not during an acute episode. There is a delay of one week before treatment is effective. There are no reported impairments in male sexual function (LE: 3). PDE5Is probably act in priapism by increasing the concentration of cGMP in the smooth muscle in a nitric oxide dysfunctional state. This can occur in priapism and may result in a change in the nitric oxide pathway, with down-regulation of cavernosal PDE5 thereby preventing the complete degradation of cGMP in the corpora cavernosa [20, 48, 133, 136].

3C.1.4.9 Intracavernosal injections

Some patients with stuttering priapism, who have been started on systemic treatments to prevent recurrence of unwanted erections, may not see therapeutic benefits immediately and may temporarily require intracavernous self-injections at home with sympathomimetic agents [20, 48]. The most commonly used drugs are phenylephrine and etilephrine (as described in the treatment of ischaemic priapism) [1, 11, 112, 119] (LE: 3). Side-effects include hypertension, coronary ischaemia and cardiac arrhythmias.

Tissue plasminogen activator (TPA) is a secreted serine protease that converts the proenzyme plasminogen to plasmin, which acts as a fibrinolytic enzyme. Limited clinical data have suggested that a single intracavernosal injection of TPA can successfully treat patients with recalcitrant priapism [120, 138] (LE: 3). Mild bleeding is the

most commonly observed side-effect.

3C.1.5 **Recommendations for the treatment of stuttering priapism**

Recommendations	GR
The primary goal in the management of patients with stuttering priapism is the prevention of future episodes, which can generally be achieved pharmacologically.	B
The management of each acute episode is similar to that for ischaemic priapism.	B
Hormonal therapies (mainly gonadotropin-receptor hormone agonists or antagonists) and/or antiandrogens may be used for the prevention of future episodes. They should not be used before sexual maturation is reached.	C
Phosphodiesterase type 5 inhibitors (PDE5Is) have a paradoxical effect in alleviating and preventing stuttering priapism, mainly in patients with idiopathic and sickle cell disease associated priapism. Treatment should be initiated only when the penis is in its flaccid state.	C
Other systemic drugs (digoxin, alpha-adrenergic agonists, baclofen, gabapentin, terbutaline) can be considered, but data are even more limited.	C
Intracavernosal self-injections at home of sympathomimetic drugs can be considered for the treatment of acute episodes on an interim basis until ischaemic priapism has been alleviated.	C

3C.1.6 **Follow-up**

Follow-up for stuttering priapism include history and clinical examination to assess the efficacy of treatments in preventing or alleviating erectile events as well as assessing erectile function and penile fibrosis.

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5. CONFLICT OF INTEREST

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Guidelines on Penile Curvature

K. Hatzimouratidis (Chair), I. Eardley, F. Giuliano,
I. Moncada, A. Salonia

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1. INTRODUCTION

1.1 Aim

The aim of this guideline is to provide the practising urologist with the most recent evidence on the diagnosis and management of penile curvature in order to assist in his/her decision-making process.

Penile curvature is a common urological disorder which can be congenital or acquired. Congenital curvature is briefly discussed in these guidelines as a distinct pathology in the adult population without any other concomitant abnormality present (such as urethral abnormalities). For paediatric congenital penile curvature, please refer to the EAU Guidelines on Paediatric Urology, Chapter on Congenital Penile Curvature.

Acquired curvature is mainly secondary due to La Peyronie's disease (referred to as Peyronie's disease in this text), but can also be due to the healing process of a penile fracture.

1.2 Publication history

The first version of the EAU Guidelines on Penile Curvature was published in 2012. In this 2015 version, the text has been significantly reduced so that only key information is included and re-formatted according to the EAU template for non-oncology Guidelines, so that all Guidelines follow a similar format.

A quick reference document (pocket guidelines) is available, both in print and in a number of versions for mobile devices, presenting the main findings of the penile curvature guidelines. These are abridged versions which may require consultation together with the full text versions. All available material can be viewed and downloaded for personal use at the EAU website. The EAU website also includes a selection of EAU Guidelines articles as well as translations produced by national urological associations:

<http://www.uroweb.org/guidelines/online-guidelines/>.

This document was peer-reviewed prior to publication.

1.3 Panel composition

The EAU Guidelines on Penile Curvature were written by the EAU Male Sexual Dysfunction Panel. Members of this Panel have been selected based on their expertise to represent the professional treating patients suffering from penile curvature.

2. METHODS

References used in this text are graded according to their Level of Evidence (LE) and Guidelines are given a Grade of Recommendation (GR). In this 2015 EAU Guidelines compilation, all standard information on LE and GR has been taken out of the individual Guidelines topics for the sake of brevity. The methodology section (see the introduction chapter of the complete book) outlines the LE and GR criteria which are used throughout the Guidelines, according to a classification system modified from the Oxford Centre for Evidence-based Medicine Levels of Evidence.

A systematic literature search of the Medline database was performed. The controlled vocabulary of the Medical Subject Headings (MeSH) database uses the specific term 'penile induration' for Peyronie's disease. There is no specific MeSH term for congenital penile curvature. In order to identify relevant articles, the search included the MeSH terms 'congenital abnormalities', 'penis abnormalities' and 'male' as well as the free text term 'congenital penile curvature'. The search included all relevant articles published up to July 2014. A total of 199 articles were identified for congenital penile curvature while this number was 1806 for Peyronie's disease. The panel reviewed and selected the articles with the highest evidence available. However, in several subtopics only articles with low levels of evidence were available and discussed accordingly.

3. THE GUIDELINE

3A CONGENITAL PENILE CURVATURE

3A.1 Epidemiology/aetiology/pathophysiology

Congenital curvature is rare: one well-performed study reports an incidence of less than 1% [1] while there are reports from studies with poor quality which claim that it is more common with prevalence rates of 4-10% in the absence of hypospadias [2].

Congenital penile curvature results from disproportionate development of the tunica albuginea of the corporal bodies and is not associated with urethral malformation. In the majority of cases the curvature is ventral but can be lateral and rarely dorsal.

3A.2 Diagnostic evaluation

Taking medical and sexual history are usually sufficient to establish the diagnosis of congenital penile curvature. Patients usually present after reaching puberty as the curvature becomes more apparent with erections, and severe curvature can make intercourse difficult or impossible. Physical examination during erection (autophotograph or after intracavernosal injection of vasoactive drugs) is useful to document curvature and exclude other pathologies [3].

3A.3 Disease management

The treatment of this disorder is surgical correction deferred until after puberty. Surgical treatments for congenital penile curvature generally share the same principles as in Peyronie's disease (presented in detail in the next section). Nesbit procedure with excision of an ellipse of the tunica albuginea is the gold standard of treatment but many other techniques have been described and employed. Plication techniques are widely used including techniques producing a de-rotation of the corporal bodies [4]. Most of the time, dissection of the dorsal neurovascular bundle is needed in order to avoid loss of sensation and ischaemic lesions in the glans [5-7].

Conclusions for treatment	LE
Medical and sexual history are usually sufficient to establish the diagnosis of congenital penile curvature. Physical examination during erection is useful for documentation of the curvature and exclusion of other pathologies.	3
Surgery is the only treatment option which is deferred until after puberty and can be performed at any time in adult life. Nesbit and plication techniques are the standard treatment in congenital penile curvature with high correction rates.	3

3B PEYRONIE'S DISEASE

3B.1 Epidemiology/aetiology/pathophysiology

3B.1.1 Epidemiology

Epidemiological data on Peyronie's (PD) disease are limited. Prevalence rates of 0.4-9% have been published, with a higher prevalence in patients with erectile dysfunction (ED) and diabetes [8-15]. The typical age of a patient with PD is 55-60 years.

3B.1.2 Aetiology

The aetiology of Peyronie's disease is unknown. However, an insult (repetitive microvascular injury or trauma) to the tunica albuginea is the most widely accepted hypothesis on the aetiology of the disease [16]. A prolonged inflammatory response will result in the remodelling of connective tissue into a fibrotic plaque [16-18]. Penile plaque formation can result in curvature which, if severe, may prevent vaginal intromission.

3B.1.3 Risk factors

The most commonly associated comorbidities and risk factors are diabetes, hypertension, lipid abnormalities, ischaemic cardiopathy, ED, smoking, and excessive consumption of alcohol [10, 14, 19, 20]. Dupuytren's contracture is more common in patients with Peyronie's disease affecting 9-39% of patients [11, 21-23] while 4% of patients with Dupuytren's contracture reported Peyronie's disease [22].

3B.1.4 Pathophysiology

Two phases of the disease can be distinguished [24]. The first is the acute inflammatory phase, which may be associated with pain in the flaccid state or painful erections and a palpable nodule or plaque in the tunica of the penis; typically a penile curvature begins to develop. The second is the fibrotic phase with the formation of hard palpable plaques that can be calcified, which also results in disease stabilisation. With time, penile curvature is expected to worsen in 30-50% of patients or stabilise in 47-67% of patients, while spontaneous improvement has been reported by only 3-13% of patients [19, 25, 26]. Pain is present in 35-45% of patients during the early stages of the disease [27]. Pain tends to resolve with time in 90% of men, usually during the first 12 months after the onset of the disease [25, 26].

In addition to physiological and functional alteration of the penis, affected men also suffer significant distress. Validated mental health questionnaires have shown that 48% of men with Peyronie's disease have mild or moderate depression, sufficient to warrant medical evaluation [28].

Conclusions	LE
Peyronie's disease is a connective tissue disorder, characterised by the formation of a fibrotic lesion or plaque in the tunica albuginea, which leads to penile deformity.	2b
The contribution of associated comorbidities or risk factors (e.g. diabetes, hypertension, lipid abnormalities and Dupuytren's contracture) to the pathophysiology of Peyronie's disease is still unclear.	3
Two phases of the disease can be distinguished. The first phase is the acute inflammatory phase (painful erections, 'soft' nodule/plaque), and the second phase is the fibrotic/calcifying phase with formation of hard palpable plaques (disease stabilisation).	2b
Spontaneous resolution is uncommon (3-13%) and most patients experience disease progression (30-50%) or stabilisation (47-67%). Pain is usually present during the early stages of the disease but tends to resolve with time in 90% of men.	2a

3B.2 Diagnostic evaluation

The aim of the initial evaluation is to provide information on the presenting symptoms and their duration (erectile pain, palpable nodules, curvature, length, rigidity, and girth) and erectile function status. It is mandatory to obtain information on the distress provoked by the symptoms and the potential risk factors for ED and Peyronie's disease. A disease-specific questionnaire (PDQ) has been designed to collect data, and it has been validated for use in clinical practice [29]

Major attention should be given to whether the disease is still active, as this will influence medical treatment or the timing of surgery. Patients who are still likely to have an active disease are those with short symptom duration, pain during erection, or a recent change in penile curvature. Resolution of pain and stability of the curvature for at least 3 months are well-accepted criteria of disease stabilisation and patients' referral for surgical intervention when indicated [25].

The examination should start with a routine genitourinary assessment, which is then extended to the hands and feet for detecting possible Dupuytren's contracture or Ledderhose scarring of the plantar fascia [26]. Penile examination consists generally of a palpable node or plaque. There is no correlation between plaque size and the degree of curvature [30]. Measurement of length during erection is important because it may have impact on treatment decisions [31].

An objective assessment of penile curvature with an erection is mandatory. This can be obtained by a home (self) photograph of a natural erection (preferably) or using a vacuum-assisted erection test or an intracavernosal injection using vasoactive agents [32]. Erectile function can be assessed using validated instruments such as the International Index of Erectile Function (IIEF) although this has not been validated in Peyronie's disease patients [33]. Erectile dysfunction is common in patients with Peyronie's disease (> 50%) but it is important to define whether it pre- or post-dates the onset of Peyronie's disease. It is mainly due to penile vascular disease [19, 30]. The presence of ED and psychological factors may impact on the treatment strategy [34].

Ultrasound (US) measurement of the plaque's size is inaccurate and it is not recommended in everyday clinical practice [35]. Doppler US may be required for the assessment of vascular parameters [34].

3B.2.1 Recommendations for the evaluation of Peyronie's disease

	LE	GR
Medical and sexual history in patients with Peyronie's disease must include duration of the disease, penile pain, change of penile deformity, difficulty in vaginal intromission due to deformity, and erectile dysfunction.	2b	B
Physical examination must include assessment of palpable nodules, penile length, extent of curvature (self-photograph, vacuum-assisted erection test or pharmacological-induced erection) and any other possibly related diseases (Dupuytren's contracture, Ledderhose disease).	2a	B
PDQ may be useful for establishing individual baseline scores and determining symptom changes with time and the effect of treatment	2a	B
US measurement of the plaque's size is inaccurate and operator dependent. It is not recommended in everyday clinical practice.	3	C
Doppler US is required to ascertain vascular parameters associated with erectile dysfunction.	2a	B

PDQ = Peyronie's disease-specific questionnaire; US = ultrasound.

3B.3 Disease management

3B.3.1 Non-operative treatment

Conservative treatment of Peyronie's disease is primarily focused on patients in the early stage of the disease [26, 36]. Several options have been suggested, including oral pharmacotherapy, intralesional injection therapy and other topical treatments (Table 1). Shockwave treatment of calcified plaques and clostridial collagenase injection in patients with densely fibrotic or calcified plaques have been also suggested [24, 37]. Clostridium collagenase is the only drug approved for the treatment of Peyronie's disease by the FDA. No single drug has been approved by the European Medicines Agency (EMA) for the treatment of Peyronie's disease at this time. The results of the studies on conservative treatment for Peyronie's disease are often contradictory making it difficult to provide recommendations in the everyday, real-life setting. This is due to several methodological problems including uncontrolled studies, limited number of patients treated, short-term follow-up and different outcome measures [37]. Moreover, the efficacy of conservative treatment in distinct patient populations in terms of early (inflammatory) or late (fibrotic) phases of the disease is not yet available.

Table 1: Non-operative treatments for Peyronie's disease

Oral treatments
Vitamin E
Potassium para-aminobenzoate (Potaba)
Tamoxifen
Colchicine
Acetyl esters of carnitine
Pentoxifylline
Phosphodiesterase type 5 inhibitors (PDE5i)
Intralesional treatments
Steroids
Verapamil
Clostridium collagenase
Interferon
Topical treatments
Verapamil
Iontophoresis
Extracorporeal shock wave treatment (ESWT)
Traction devices
Vacuum devices

3B.3.2 Oral treatment

3B.3.2.1 Vitamin E

Vitamin E (tocopherol, a fat-soluble compound that acts as a natural antioxidant to reduce the number of oxygen-free radicals produced in energy metabolism) is commonly prescribed by the majority of urologists at

once or twice daily doses of 400 IU because of its wide availability, low cost and safety [38]. A double-blind, placebo-controlled crossover study failed to show a significant effect on penile deformity or plaque size [39]. Moreover, there is conflicting evidence as to long-term cardiovascular effects of vitamin E usage at large doses, which urologists use for penile deformity treatment [40].

3B.3.2.2 Potassium para-aminobenzoate (Potaba)

Potassium para-aminobenzoate is thought to exert an antifibrotic effect through an increase in oxygen uptake by the tissues, a rise in the secretion of glycosaminoglycans, and an enhancement of the activity of monoamine oxidases [41]. Preliminary studies reported an improvement in penile curvature, penile plaque size, and penile pain during erection [42]. In a prospective double-blinded controlled study in 41 patients with Peyronie's disease, Potaba (12 g/day for 12 months) improved penile pain significantly, but not penile curvature or penile plaque size [43]. In another similar study in 103 patients with Peyronie's disease, Potaba decreased penile plaque size significantly, but had no effect on penile curvature or penile pain [44]. However, the pre-existing curvature under Potaba remained stable, suggesting a protective effect on the deterioration of penile curvature. Treatment-emergent adverse events are nausea, anorexia, pruritus, anxiety, chills, cold sweats, confusion and difficulty concentrating, but no serious adverse events were reported [45].

3B.3.2.3 Tamoxifen

Tamoxifen is a non-steroidal oestrogen receptor antagonist modulating transforming growth factor β 1 (TGF β 1) secretion by fibroblasts. Preliminary studies reported that tamoxifen (20 mg twice daily for 3 months) improved penile pain, penile curvature, and reduced the size of penile plaque [46]. However, a placebo-controlled, randomised study (in only 25 patients, at a late stage of the disease with a mean duration of 20 months) using the same treatment protocol, failed to show any significant improvement in pain, curvature, or plaque size in patients with Peyronie's disease [47].

3B.3.2.4 Colchicine

Colchicine has been introduced into the treatment of Peyronie's disease on the basis of its anti-inflammatory effect [48]. Clinical data should be interpreted with caution since they come from only uncontrolled studies. Preliminary results showed that half of the men given colchicine (0.6-1.2 mg daily for 3-5 months) found that painful erections and penile curvature improved, while penile plaque decreased or disappeared in 50% out of 24 men [49]. In another study in 60 men (colchicine 0.5-1 mg daily for 3-5 months with escalation to 2 mg twice daily), penile pain resolved in 95% and penile curvature improved in 30% [48]. Similar results have been reported in another uncontrolled retrospective study in 118 patients [50]. Reported treatment-emergent adverse events with colchicine are gastrointestinal effects (nausea, vomiting, diarrhoea) that can be improved with dose escalation [48].

The combination of vitamin E and colchicine (600 mg/day and 1 mg every 12 hours, respectively) for 6 months in patients with early-stage Peyronie's disease resulted in significant improvement in plaque size and curvature, but not in pain compared to ibuprofen 400 mg/day for 6 months [51].

3B.3.2.5 Acetyl esters of carnitine

Acetyl-L-carnitine and propionyl-L-carnitine are proposed to inhibit acetyl coenzyme-A and produce an antiproliferative effect on human endothelial cells. This may eventually suppress fibroblast proliferation and collagen production, thus reducing penile fibrosis. In a randomised, double-blind study in 48 patients with early-stage Peyronie's disease, patients were randomised to acetyl-L-carnitine (1 g twice daily) compared to tamoxifen (20 mg twice daily). After 3 months, acetyl-L-carnitine was significantly more effective than tamoxifen in pain and curvature reduction and inhibition of disease progression, but not in penile plaque size reduction (both drugs significantly reduced plaque size) [52]. Tamoxifen induced significantly more side-effects.

Finally, the combination of intralesional verapamil (10 mg weekly for 10 weeks) with propionyl-L-carnitine (2 g/day for 3 months) significantly reduced penile curvature, plaque size, and disease progression compared to intralesional verapamil combined with tamoxifen (40 mg/day) for 3 months [53].

3B.3.2.6 Pentoxifylline

Pentoxifylline is a non-specific phosphodiesterase inhibitor which down-regulates TGF β 1 and increases fibrinolytic activity [54]. Moreover, an increase of nitric oxide levels may be effective in preventing progression of Peyronie's disease or reversing fibrosis [55]. Preliminary data from a case report showed that pentoxifylline (400 mg three times daily for 6 months) improved penile curvature and the findings on US of the plaque [55]. In another study in 62 patients with Peyronie's disease, pentoxifylline treatment for 6 months appeared to stabilise or reduce calcium content in penile plaques [56].

3B.3.2.7 Phosphodiesterase type 5 inhibitors

The rationale for the use of phosphodiesterase type 5 inhibitors (PDE5I) in Peyronie's disease comes from animal studies showing that they can reduce the collagen/smooth muscle and collagen III/I ratios and increase the apoptotic index in the Peyronie's disease-like plaque [57]. In a retrospective controlled study, daily tadalafil (2.5 mg for 6 months) resulted in statistically significant ($p < 0.05$) resolution of septal scar in 69% of patients compared to 10% in the control group (no treatment). However, this study included patients with isolated septal scars without evidence of penile deformity [58]. Therefore, no recommendation can be given for PDE5I in patients with Peyronie's disease.

3B.3.3 Intralesional treatment

Injection of pharmacologically active agents directly into penile plaques represents another treatment option. It allows a localised delivery of a particular agent that provides higher concentrations of the drug inside the plaque. However, delivery of the compound to the target area is difficult to ensure particularly when a dense or calcified plaque is present.

3B.3.3.1 Steroids

Intralesional steroids are thought to act by opposing the inflammatory milieu responsible for Peyronie's plaque progression via inhibition of phospholipase A2, suppression of the immune response and by decreasing collagen synthesis [59]. In small, non-randomised studies, a decrease in penile plaque size and pain resolution was reported [60, 61]. In the only single-blind, placebo-controlled study with intralesional administration of betamethasone, no statistically significant changes in penile deformity, penile plaque size, and penile pain during erection were reported [62]. Adverse effects include tissue atrophy, thinning of the skin and immunosuppression [60].

3B.3.3.2 Verapamil

The rationale for intralesional use of verapamil (a calcium channel antagonist) in patients with Peyronie's disease is based on in-vitro research [63, 64]. A number of studies have reported that intralesional verapamil injection may induce a significant reduction in penile curvature and plaque volume [65-69]. These findings suggested that intralesional verapamil injections could be advocated for the treatment of non-calcified acute phase or chronic plaques to stabilise disease progression or possibly reduce penile deformity, although large scale, placebo-controlled trials have not yet been conducted [68]. Side-effects are uncommon (4%). Minor side-effects include nausea, light-headedness, penile pain, and ecchymosis [68]. However, in the only randomised, placebo-controlled study, no statistically significant differences on plaque size, penile curvature, penile pain during erection or plaque 'softening' were reported [70]. Younger age and larger baseline penile curvature were found to be predictive of favourable curvature outcomes in a case-series study [71].

3B.3.3.3 Clostridium collagenase

Clostridium collagenase (CCH) is a chromatographically purified bacterial enzyme that selectively attacks collagen, which is known to be the primary component of the Peyronie's disease plaque [72-74]. Clostridium collagenase is now approved by the Food and Drug Administration (FDA) for PD in adult men with a palpable plaque and a curvature deformity of at least 30° at the start of therapy. Findings from two independent, double-blind, placebo controlled studies, reveal the efficacy and tolerability of CCH for improving the co-primary outcomes of physical penile curvature and the psychological subject reported PD symptom bother domain of the PDQ in adults with PD. Participants were given up to four treatment cycles of CCH or placebo and were then followed for 52 weeks. Overall, of 551 treated men with CCH 60.8% were global responders compared with 29.5% of 281 who received placebo. The most commonly reported side-effects were penile pain, penile swelling, and ecchymosis at the site of injection [75]. Of note, CCH is available in the US only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) because of the risks of serious adverse reactions, including penile and other serious penile injury. CCH should be administered by a healthcare professional who is experienced in the treatment of male urological diseases. The REMS requires participating healthcare professionals to be certified within the program by enrolling and completing training in the administration of CCH treatment for Peyronie's disease. The REMS also requires healthcare facilities to be certified within the program and ensure that CCH is dispensed only for use by certified healthcare professionals [76].

3B.3.3.4 Interferon

Interferon α -2b has been shown to decrease fibroblast proliferation, extracellular matrix production and collagen production from fibroblasts and improved the wound healing process from Peyronie's disease plaques in-vitro [77]. Intralesional injections (5 x 10⁶ units of interferon α -2b in 10 mL saline, two times per week for 12 weeks) significantly improved penile curvature, plaque size and density, and pain compared to placebo [78, 79].

Side-effects include myalgias, arthralgia, sinusitis, fever and flu-like symptoms. They can be effectively treated with non-steroidal anti-inflammatory drugs before interferon injection.

3B.3.4 Topical treatments

3B.3.4.1 Topical verapamil

There is no evidence that topical treatments applied to the penile shaft result in adequate levels of the active compound within the tunica albuginea. Verapamil gel has been used in this context [80]. Iontophoresis - now known as transdermal electromotive drug administration (EMDA) - has been introduced to try and overcome limitations on the local uptake of the drugs themselves. Small studies using Iontophoresis with verapamil 5 mg and dexamethasone 8 mg resulted in inconsistent results [81, 82].

3B.3.4.2 Extracorporeal shock wave treatment

The mechanism of action involved in shock wave treatment (ESWT) for Peyronie's disease is still unclear, but there are two hypotheses. In the first hypothesis, shock wave therapy works by directly damaging and remodelling the penile plaque. In the second hypothesis, SWL increases the vascularity of the area by generating heat resulting in an inflammatory reaction, with increased macrophage activity causing plaque lysis and eventually leading to plaque resorption [83]. Most uncontrolled studies failed to show significant improvements in patients with Peyronie's disease [84-86]. In a prospective, randomised, double-blind, placebo-controlled study, four weekly treatment sessions of ESWT, with each session consisting of 2000 focused shock waves, resulted in significant improvement only for penile pain [87].

3B.3.4.3 Traction devices

The application of continuous traction in Dupuytren's contracture increases the activity of degradative enzymes [88]. This initially leads to a loss of tensile strength and ultimately to solubilisation. It is followed by an increase in newly synthesised collagen [88]. This concept has been applied in an uncontrolled study, including 10 patients with Peyronie's disease. The FastSize Penile Extender was applied as the only treatment for 2-8 hours/day for 6 months [89]. Reduced penile curvature of 10-40° was found in all men with an average reduction of 33% (range: 51-34°). The stretched penile length increased 0.5-2.0 cm and the erect girth increased 0.5-1.0 cm, with a correction of hinge effect in four out of four men. Treatment can be uncomfortable and inconvenient due to use of the device 2-8 h daily for an extended period, but has been shown to be tolerated by highly motivated patients [22]. There were no serious adverse events, including skin changes, ulcerations, hypoesthesia or diminished rigidity.

In another prospective study, there was a significant reduction in penile curvature (mean 20 degrees reduction). Erectile function and erection hardness also improved significantly. The percentage of patients who were not able to achieve penetration decreased from 62% to 20% ($P < 0.03$). Importantly, the need for surgery was reduced in 40% of patients who would otherwise have been candidates for surgery and simplified the complexity of the surgical procedure (from grafting to plication) in 1 in 3 patients [90].

3B.3.4.4 Vacuum devices

The application of vacuum devices follows the same principles as traction devices with the drawback of being non-continuous precluding remodelling of the plaque. Their efficacy has been assessed in an uncontrolled study (31 patients completed the study) [91]. Half of the patients were satisfied with the outcome and the remaining had their curvature corrected surgically.

3B.3.4.5 Recommendations for non-operative treatment of Peyronie's disease

	LE	GR
Conservative treatment for Peyronie's disease is primarily aimed at treating patients in the early stage of the disease. It is an option in patients not fit for surgery or when surgery is not acceptable to the patient.	3	C
Oral treatment with potassium para-aminobenzoate may result in a significant reduction in penile plaque size and penile pain as well as penile curvature stabilisation.	1b	C
Intralesional treatment with verapamil may induce a significant reduction in penile curvature and plaque volume.	1b	C
Intralesional treatment with clostridium collagenase showed significant decreases in the deviation angle, plaque width and plaque length.	1b	B
Intralesional treatment with interferon may improve penile curvature, plaque size and density, and pain.	1b	C
Topical verapamil gel 15% may improve penile curvature and plaque size.	1b	C
Iontophoresis with verapamil 5 mg and dexamethasone 8 mg may improve penile curvature and plaque size.	1b	C
Extracorporeal shock-wave treatment fails to improve penile curvature and plaque size, and should not be used with this intent, but may be beneficial for penile pain.	1b	C
Penile traction devices and vacuum devices may reduce penile deformity and increase penile length.	2b	C
Intralesional treatment with steroids is not associated with significant reduction in penile curvature, plaque size or penile pain. Therefore, intralesional treatment with steroids cannot be recommended.	1b	B
Oral treatment with vitamin E and tamoxifen are not associated with significant reduction in penile curvature or plaque size and should not be used with this intent.	2b	B
Other oral treatments (acetyl esters of carnitine, pentoxifylline, colchicine) are not recommended.	3	C

3B.3.5 Surgical treatment

Although conservative treatment for Peyronie's disease should resolve painful erections in most men, only a small percentage will experience any significant straightening of the penis. The aim of surgery is to correct curvature and allow satisfactory intercourse. Surgery is indicated in patients with penile curvature that does not allow satisfactory intercourse and it is associated with sexual bother [92]. Patients must have a stable disease for at least 3 months, although a 6-12 month period has also been suggested [93].

The potential aims and risks of surgery should be discussed with the patient so that he can make an informed decision. Specific issues that should be mentioned during this discussion are the risks of penile shortening, ED, penile numbness, the risk of recurrent curvature, the potential for palpation of knots and stitches underneath the skin, and the potential need for circumcision at the time of surgery [24]. Two major types of repair may be considered for both congenital penile curvature and Peyronie's disease: penile shortening and penile lengthening procedures [94].

Penile shortening procedures include the Nesbit wedge resection and the plication techniques performed on the convex side of the penis. Penile lengthening procedures are performed on the concave side of the penis and require the use of a graft. They aim to minimise penile shortening caused by Nesbit or plication of the tunica albuginea or correct complex deformities. Penile degloving with associated circumcision (as a means of preventing post-operative phimosis) is considered the standard approach for all types of procedures [94]. However, recent data suggest that circumcision is not always necessary e.g. in cases where the foreskin is normal pre-operatively [95]. Finally, in patients with Peyronie's disease and ED not responding to medical treatments, the surgical correction of the curvature with concomitant penile prosthesis implantation should be considered [96].

Choosing the most appropriate surgical intervention is based on penile length assessment, curvature severity and erectile function status, including response to pharmacotherapy in cases of ED [24]. Patient expectations from surgery must also be included in the pre-operative assessment. There are no standardised questionnaires for the evaluation of surgical outcomes [92]. Data from well-designed prospective studies are scarce, with a low level of evidence. Most data are mainly based on retrospective studies, typically noncomparative and non-randomised, or on expert opinion [24, 97].

3B.3.5.1 Penile shortening procedures

In 1965, Nesbit was the first to describe the removal of tunical ellipses opposite a non-elastic corporal segment to treat congenital penile curvature [98]. Fourteen years later, this technique became a successful treatment option, also for Peyronie's disease [99]. This operation is based on a 5-10 mm transverse elliptical excision of the tunica albuginea or approximately 1 mm for each 10° of curvature [94]. The overall short- and long-term results of the Nesbit operation are excellent. Complete penile straightening is achieved in more than 80% of patients [100]. Recurrence of the curvature and penile hypoesthesia are uncommon (about 10%) and the risk of postoperative ED is minimal [94, 101]. Penile shortening is the most commonly reported outcome of the Nesbit procedure [101]. However, shortening of only 1-1.5 cm has been reported for about 85% of patients, which is rarely the cause for post-operative sexual dysfunction [99, 102]. Patients often perceive the loss of length as greater than it actually is [100, 101]. It is therefore advisable to measure and document the penile length peri-operatively, both before and after the straightening procedure, whatever the technique used. Only one modification of the Nesbit procedure has been described (partial thickness shaving instead of conventional excision of a wedge of tunica albuginea) [103].

Plication procedures actually share the same principle as the Nesbit operation but are simpler to perform. Many of them have been described as Nesbit modifications in the older literature. They are based on single or multiple longitudinal incisions on the convex side of the penis closed in a horizontal way, applying the Heineke-Miculicz principle, or plication is performed without making an incision [104-109]. Another modification has been described as the '16 dot' technique with minimal tension under local anaesthesia [110]. The use of non-absorbable sutures reduced recurrence of the curvature. Results and satisfaction rates are similar to the Nesbit procedure [94]. However, a lot of different modifications have been described and the level of evidence is not sufficient to recommend one method over the other.

3B.3.5.2 Penile lengthening procedures

Tunical lengthening procedures entail an incision in the short (concave) side of the tunica to increase the length of this side, creating a tunical defect, which is covered by a graft. However, plaque removal may be associated with high rates of postoperative ED due to venous leak [111].

Devine and Horton introduced dermal grafting in 1974 [112]. Since then, a variety of grafting materials and techniques have been reported (Table 2) [113-127]. Unfortunately, the ideal material for grafting has yet to be identified. In addition, grafting procedures are associated with ED rates as high as 25%. Despite excellent initial surgical results, graft contracture and long-term failures resulted in a 17% re-operation rate [128].

Vein grafts have the theoretical advantage of endothelial-to-endothelial contact when grafted to underlying cavernosal tissue. Saphenous vein is the most common vein graft used, followed by dorsal penile vein [94]. In the first case, a secondary incision for graft harvesting is avoided. Postoperative curvature (20%), penile shortening (17%) and graft herniation (5%) have been reported after vein graft surgery [118, 123, 126]. Tunica vaginalis is relatively avascular, easy to harvest and has little tendency to contract due to its low metabolic requirements [116].

Dermal grafts are commonly associated with contracture resulting in recurrent penile curvature (35%), progressive shortening (40%), and a 17% re-operation rate at 10 years [129]. Cadaveric pericardium (Tutoplast®) offers good results by coupling excellent tensile strength and multi-directional elasticity/expansion by 30% [127]. In a retrospective telephone interview, 44% of patients with pericardium grafting reported recurrent curvature, although most of them continued to have successful intercourse and were pleased with their outcomes [127, 129].

Small intestinal submucosa (SIS, a collagen-based xenogenic graft derived from the submucosal layer of the porcine small intestine) has been shown to promote tissue-specific regeneration, and supports the growth of endothelial cells. Small intestinal submucosa acts as a scaffold to promote angiogenesis, host cell migration and differentiation, resulting in tissue structurally and functionally similar to the original. It has been used successfully to repair severe chordee and Peyronie's disease, without significant contraction or histological alterations, but data are limited [124].

More recently the use of buccal mucosa grafts (BMG) has been advocated. BMG provided excellent short-term results, suggested by the fast return of spontaneous erections and prevented shrinkage, which is the main cause of graft failure. It also proved to be safe and reproducible, thus representing a valuable treatment option for PD [115].

Tunical incision, preferably with grafting, offers an excellent surgical option for men with curvatures over 60° as well as patients with an hourglass deformity and good erectile function that are willing to risk a higher rate of postoperative ED [130]. The presence of pre-operative ED, the use of larger grafts, age more than 60 years, and ventral curvature are considered poor prognostic factors for functional outcome after grafting surgery [96]. Although the risk for penile shortening is significantly less compared to the Nesbit or plication procedures, it is still an issue and patients must be informed accordingly [94]. The use of geometric principles introduced by Egydio helps to determine the exact site of the incision, and the shape and size of the defect to be grafted [117].

The use of a penile extender device on an 8- to 12-hour daily regimen has been advocated as an effective and safe treatment for loss of penile length in patients operated on for Peyronie's disease [131].

Table 2: Types of grafts used in Peyronie's disease surgery

Autologous grafts
Dermis
Vein grafts
Tunica albuginea
Tunica vaginalis
Temporalis fascia
Buccal mucosa
Allografts
Cadaveric pericardium
Cadaveric fascia lata
Cadaveric dura matter
Cadaveric dermis
Xenografts
Porcine small intestinal submucosa
Bovine pericardium
Porcine dermis
Synthetic grafts
Gore-Tex
Dacron

3B.3.5.3 Penile prosthesis

Penile prosthesis implantation is typically reserved for the treatment of Peyronie's disease in patients with ED, especially when they are not responders to phosphodiesterase type 5 inhibitor (PDE5I) [94]. Although all types of penile prosthesis can be used, the implantation of inflatable penile prosthesis seems to be most effective in these patients [132].

Most patients with mild-to-moderate curvature can expect an excellent outcome simply by cylinder insertion. In cases of severe deformity, intra-operative 'modelling' of the penis over the inflated cylinders (manually bent on the opposite side of the curvature for 90 seconds, often accompanied by an audible crack) has been introduced as an effective treatment [133, 134]. If there is a residual curvature of less than 30°, no further treatment is recommended, as the prosthesis will act as a tissue expander and will result in complete correction of curvature in a few months [133]. While this technique is effective in most patients, a Nesbit/plication procedure or plaque excision/incision and grafting may be required in order to achieve adequate straightening [135-137].

The risk of complications (infection, malformation, etc) is not increased compared to the general population. However, a small risk of urethral perforation (3%) has been reported in patients with 'modelling' over the inflated prosthesis [134].

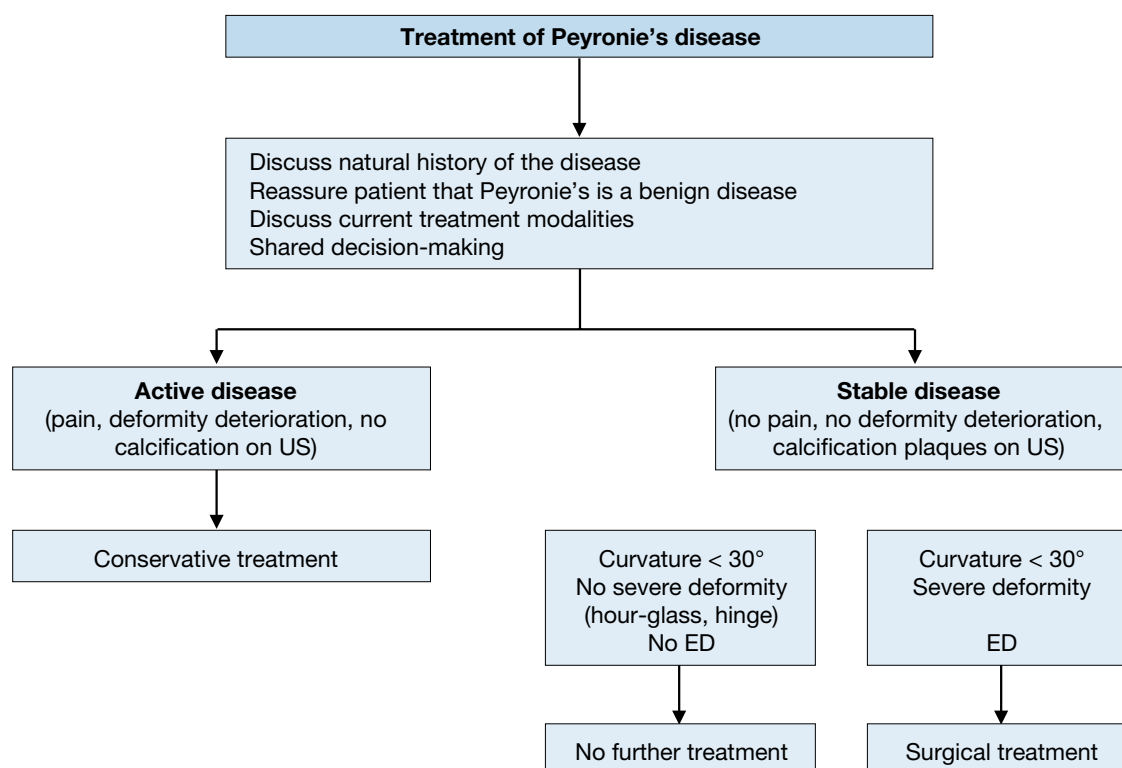
Table 3: Results of surgical treatments for Peyronie's disease (data from different, non-comparable studies) [99, 101-127, 129, 130]

	Tunical shortening procedures	Tunical lengthening procedures	
	Nesbit	Plication	Grafts
Penile shortening	4.7-30.8%	41-90%	0-40%
Penile straightening	79-100%	58-100%	74-100%
Persistent or recurrent curvature	4-26.9%	7.7-10.6%	0-16.7%
Post-operative erectile dysfunction	0-13%	0-22.9%	0-15%
Penile hypoesthesia	2-21%	0-21.4%	0-16.7%
Technical modifications	1	At least 3	Many types of grafts and techniques used

3B.3.5.4 Treatment algorithm

The decision on the most appropriate surgical procedure to correct penile curvature is based on pre-operative assessment of penile length, the degree of the curvature and erectile function status. If the degree of curvature is less than 60°, penile shortening is acceptable and the Nesbit or plication procedures are usually the method of choice. This is typically the case for congenital penile curvature. If the degree of curvature is over 60° or is a complex curvature, or if the penis is significantly shortened in patients with a good erectile function (with or without pharmacological treatment), then a grafting procedure is feasible. If there is ED, which is not responding to pharmacological treatment, the best option is the implantation of an inflatable penile prosthesis, with or without an associated procedure over the penis (modelling, plication or even grafting plus the prosthesis). The treatment algorithm is presented in Figure 1.

Figure 1: Treatment algorithm for Peyronie's disease



US = Ultrasound; ED = erectile dysfunction.

The results of the different surgical approaches are presented in Table 3. It must be emphasised that there are no randomised controlled trials available addressing surgery in Peyronie's disease. The risk of erectile dysfunction seems to be greater for penile lengthening procedures [24, 94]. Recurrent curvature implies

either failure to wait until the disease has stabilised, a reactivation of the condition following the development of stable disease, or the use of re-absorbable sutures that lose their strength before fibrosis has resulted in acceptable strength of the repair [94]. Accordingly, it is recommended that only non-absorbable sutures or slowly reabsorbed absorbable sutures be used. Although with non-absorbable sutures, the knot should be buried to avoid troublesome irritation of the penile skin, this issue seems to be alleviated by the use of slowly re-absorbed absorbable sutures [101]. Penile numbness is a potential risk of any surgical procedure involving mobilisation of the dorsal neurovascular bundle. This will usually be a neuropraxia, due to bruising of the dorsal sensory nerves. Given that the usual deformity is a dorsal deformity, the procedure most likely to induce this complication is a lengthening (grafting) procedure for a dorsal deformity [94].

3B.3.5.5 Recommendations for the surgical treatment of penile curvature

	LE	GR
Surgery is indicated when Peyronie's disease is stable for at least 3 months (without pain or deformity deterioration), which is usually the case after 12 months from the onset of symptoms, and intercourse is compromised due to deformity.	3	C
Penile length, curvature severity, erectile function (including response to pharmacotherapy in case of erectile dysfunction) and patient expectations must be assessed prior to surgery.	3	C
Tunical shortening procedures, especially plication techniques are the first treatment options for congenital penile curvature and for Peyronie's disease with adequate penile length, curvature < 60° and absence of special deformities (hour-glass, hinge).	2b	B
Grafting techniques are the preferred treatment option for patients with Peyronie's disease and normal erectile function, with no adequate penile length, curvature > 60° and presence of special deformities (hour-glass, hinge).	2b	B
Penile prosthesis implantation, with or without any additional procedure (modelling, plication or grafting), is recommended in Peyronie's disease patients with erectile dysfunction not responding to pharmacotherapy.	2b	B

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5. CONFLICT OF INTEREST

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Guidelines on **Male Infertility**

A.Jungwirth (Chair), T. Diemer, G.R Dohle, A. Giwercman,
Z. Kopa, C.Krausz, H. Tournaye

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1. INTRODUCTION

1.1 Aim

The European Association of Urology (EAU) Guidelines Panel on Male Infertility has prepared these Guidelines to assist urologists and healthcare professionals from related specialties in the treatment of male infertility. Urologists are usually the specialists who are initially responsible for assessing the male when male infertility is suspected. However, infertility can be a multifactorial condition requiring multidisciplinary involvement.

1.2 Publication history

The EAU Male Infertility Guidelines were first published in 2001, followed by full-text updates in 2004, 2007, 2010, 2013 and 2014.

In this 2015 version the text has been significantly reduced so that only key information is included and re-formatted according to the EAU template for non-oncology Guidelines, so that all Guidelines follow a similar format.

A quick reference document (Pocket Guidelines) is available, both in print and in a number of versions for mobile devices, presenting the main findings of the Male Infertility Guidelines. These are abridged versions which may require consultation together with the full text versions. The Male Infertility Panel published a number of scientific publications in the EAU journal European Urology [1-3]. A separate scientific paper on Vasectomy was published in 2012 [3]. All texts can be viewed and downloaded for personal use at the society website: <http://www.uroweb.org/guidelines/online-guidelines/>.

This document was peer-reviewed prior to publication.

1.3 Panel composition

The Male Infertility Guidelines Panel consists of urologists, endocrinologists and gynaecologists with special training in andrology and experience in the diagnosis and treatment of male infertility.

2. METHODS

References used in this text are graded according to their Level of Evidence (LE) and Guidelines are given a Grade of Recommendation (GR). In this 2015 EAU Guidelines compilation, all standard information on LE and GR has been taken out of the individual Guidelines topics for the sake of brevity. The methodology section (see the introduction chapter of the complete book) outlines the LE and GR criteria which are used throughout the Guidelines, according to a classification system modified from the Oxford Centre for Evidence-based Medicine Levels of Evidence.

The recommendations provided in these guidelines are based on a systematic literature search performed by the panel members. The controlled vocabulary of the MeSH database was used alongside a free text protocol, combining “male infertility” with the terms “diagnosis”, “epidemiology”, “investigations”, “treatment”, “spermatogenic failure”, “genetic abnormalities”, “obstruction”, “hypogonadism”, “varicocele”, “cryptorchidism”, “testicular cancer”, “male accessory gland infection”, “idiopathic”, “contraception”, “ejaculatory dysfunction”, and “cryopreservation”.

For the 2014 print a scoping search was done covering 2012 and 2013, with a cut-off date of September 2013. Embase, Medline and the Cochrane Central Register of Controlled Trials were searched, with a limitation to reviews, meta-analysis or meta-analysis of RCTs. After de-duplication 447 unique records were identified, of which five publications were selected for inclusion.

3. THE GUIDELINE

3A MALE INFERTILITY

Definition

"Infertility is the inability of a sexually active, non-contracepting couple to achieve spontaneous pregnancy in one year", World Health Organization (WHO) [4].

3A.1 Epidemiology and aetiology

About 15% of couples do not achieve pregnancy within one year and seek medical treatment for infertility. One in eight couples encounter problems when attempting to conceive a first child and one in six when attempting to conceive a subsequent child. Three percent of women remain involuntarily childless, while 6% of parous women are not able to have as many children as they would wish [5]. Infertility affects both men and women. In 50% of involuntarily childless couples, a male-infertility-associated factor is found together with abnormal semen parameters. A fertile partner may compensate for the fertility problem of the man and thus infertility usually manifests if both partners have reduced fertility [4]. Male fertility can be reduced as a result of [4]:

- congenital or acquired urogenital abnormalities;
- malignancies;
- urogenital tract infections;
- increased scrotal temperature (e.g. as a consequence of varicocele);
- endocrine disturbances;
- genetic abnormalities;
- immunological factors.

In 30-40% of cases, no male-infertility-associated factor is found (idiopathic male infertility). These men present with no previous history of diseases affecting fertility and have normal findings on physical examination and endocrine, genetic and biochemical laboratory testing. However, semen analysis might reveal pathological findings in the spermogram (see 3A.2.1). Table 1 summarises the main male-infertility-associated factors. Idiopathic male infertility is assumed to be caused by several factors, including endocrine disruption as a result of environmental pollution, reactive oxygen species, or genetic and epigenetic abnormalities.

Table 1: Male infertility causes and associated factors and percentage of distribution in 10,469 patients [6]

Diagnosis	Unselected patients (n = 12,945)	Azoospermic patients (n = 1,446)
<i>All</i>	100%	11.2%
<i>Infertility of known (possible) cause</i>	42.6%	42.6%
Mal descended testes	8.4	17.2
Varicocele	14.8	10.9
Sperm autoantibodies	3.9	-
Testicular tumour	1.2	2.8
Others	5.0	1.2
<i>Idiopathic infertility</i>	30.0	13.3
<i>Hypogonadism</i>	10.1	16.4
Klinefelter's syndrome (47, XXY)	2.6	13.7
XX male	0.1	0.6
Primary hypogonadism of unknown cause	2.3	0.8
Secondary (hypogonadotropic) hypogonadism	1.6	1.9
Kallmann syndrome	0.3	0.5
Idiopathic hypogonadotrophic hypogonadism	0.4	0.4
Residual after pituitary surgery	<0.1	0.3
Others	0.8	0.8
Late-onset hypogonadism	2.2	-
Constitutional delay of puberty	1.4	-
<i>General/systemic disease</i>	2.2	0.5
<i>Cryopreservation due to malignant disease</i>	7.8	12.5
Testicular tumour	5.0	4.3
Lymphoma	1.5	4.6

Leukaemia	0.7	2.2
Sarcoma	0.6	0.9
<i>Disturbance of erection/ejaculation</i>	2.4	-
<i>Obstruction</i>	2.2	10.3
Vasectomy	0.9	5.3
Cystic fibrosis (CBAVD)	0.5	3.1
Others	0.8	1.9

3A.1.1 **Prognostic factors**

Prognostic factors for male infertility are:

- duration of infertility
- primary or secondary infertility
- results of semen analysis and
- age and fertility status of female partner.

The cumulative pregnancy rate is 27% in infertile couples with 2 years of follow-up and oligozoospermia as the primary cause of infertility [7]. Female age is the most important single variable influencing outcome in assisted reproduction [8]. Compared to a woman aged 25 years, the fertility potential of a woman aged 35 years is reduced to 50%, to 25% at 38 years, and less than 5% at over 40 years. In many Western countries, women postpone their first pregnancy until after their education and starting a career.

3A.1.2 **Recommendations on epidemiology and aetiology**

Recommendations	GR
To categorise infertility, both partners should be investigated simultaneously.	C
In the diagnosis and management of male subfertility, the fertility status of the female partner must also be considered, because this might determine the final outcome [5].	B
The urologist/andrologist should examine any man with fertility problems for urogenital abnormalities. This applies to all men diagnosed with abnormal semen parameters. A diagnosis (even if idiopathic) is mandatory to start appropriate therapy (drugs, surgery, or assisted reproduction).	C

3A.2 **Diagnostic evaluation**

3A.2.1 **Semen analysis**

A medical history and physical examination are standard assessments in all men, including semen analysis. A comprehensive andrological examination is indicated if semen analysis shows abnormalities compared with reference values (Table 2). Important treatment decisions are based on the results of semen analysis, therefore, it is essential that the complete laboratory work-up is standardised. Ejaculate analysis has been standardised by the WHO and disseminated by publication of the WHO Laboratory Manual for the Examination and Processing of Human Semen (5th edn.) [9]. It is the consensus that modern spermatology must follow these guidelines.

Table 2: Lower reference limits (5th centiles and their 95% CIs) for semen characteristics

Parameter	Lower reference limit (range)
Semen volume (mL)	1.5 (1.4-1.7)
Total sperm number (10 ⁶ /ejaculate)	39 (33-46)
Sperm concentration (10 ⁶ /mL)	15 (12-16)
Total motility (PR + NP)	40 (38-42)
Progressive motility (PR, %)	32 (31-34)
Vitality (live spermatozoa, %)	58 (55-63)
Sperm morphology (normal forms, %)	4 (3.0-4.0)
Other consensus threshold values	
pH	> 7.2
Peroxidase-positive leukocytes (10 ⁶ /mL)	< 1.0
Optional investigations	
MAR test (motile spermatozoa with bound particles, %)	< 50
Immunobead test (motile spermatozoa with bound beads, %)	< 50
Seminal zinc (μmol/ejaculate)	≥ 2.4
Seminal fructose (μmol/ejaculate)	≥ 13
Seminal neutral glucosidase (mU/ejaculate)	≤ 20

CIs = confidence intervals; MAR = mixed antiglobulin reaction NP = non-progressive; PR = progressive.

3A.2.1.1 Frequency of semen analysis

If the results of semen analysis are normal according to WHO criteria, one test is sufficient. If the results are abnormal in at least two tests, further andrological investigation is indicated. It is important to differentiate between the following:

- oligozoospermia: spermatozoa < 15 million/mL;
- asthenozoospermia: < 32% progressive motile spermatozoa;
- teratozoospermia: < 4% normal forms.

Often, all three anomalies occur simultaneously, which is defined as oligo-asteno-teratozoospermia (OAT) syndrome. As in azoospermia, in extreme cases of oligozoospermia (spermatozoa < 1 million/mL), there is an increased incidence of obstruction of the male genital tract and genetic abnormalities.

3A.2.2 Recommendations for the diagnostic evaluation of male infertility

Recommendations	GR
According to WHO criteria, andrological investigations are indicated if semen analysis is abnormal in at least two tests to define a diagnosis.	A*
Diagnosis and evaluation of male subfertility according to the WHO Manual for the standardised investigation, diagnosis and management of the infertile male is recommended [10].	C
Semen analysis must follow the guidelines of the WHO Laboratory Manual for the Examination and Processing of Human Semen (5th edn.) [9].	A*
The WHO laboratory manual proposes reference values based on fertility, hence, these reference values do not allow to classify a man as being infertile.	A

*Upgraded following panel consensus.

3B PRIMARY SPERMATOGENIC FAILURE

Testicular deficiency as a consequence of primary spermatogenic failure is caused by conditions other than hypothalamic-pituitary disease and obstruction of the male genital tract. It is the commonest form of reduced male fertility. Testicular deficiency may have different aetiologies and present clinically as severe OAT or non-obstructive azoospermia (NOA) [10].

3B.1 Aetiology

The causes of testicular deficiency are summarised in Table 3.

Table 3: Causes of testicular deficiency

Factors	Causes
Congenital	Anorchia
	Testicular dysgenesis/cryptorchidism
	Genetic abnormalities (karyotype, Y-chromosome deletions)
Acquired	Trauma
	Testicular torsion
	Post-inflammatory forms, particularly mumps orchitis
	Exogenous factors (medications, cytotoxic or anabolic drugs, irradiation, heat)
	Systemic diseases (liver cirrhosis, renal failure)
	Testicular tumour
	Varicocele
Idiopathic	Surgery that may compromise vascularisation of the testes and lead to testicular atrophy
	Unknown aetiology
	Unknown pathogenesis

3B.2 Diagnostic evaluation

Routine investigations include semen analysis and hormonal determinations. Other investigations may be required depending on the individual situation.

Typical findings from the history and physical examination of a patient with testicular deficiency are:

- cryptorchidism (uni- or bilateral)
- testicular torsion
- genitourinary infection
- testicular trauma
- exposure to environmental toxins
- gonadotoxic medication including anabolic drugs
- exposure to radiation or cytotoxic agents
- testicular cancer
- absence of testes
- abnormal secondary sexual characteristics
- gynaecomastia
- abnormal testicular volume and/or consistency
- varicocele.

3B.2.1 Semen analysis

In NOA, semen analysis shows normal ejaculate volume and azoospermia after centrifugation. A recommended method is semen centrifugation at 3000 g for 15 min and a thorough microscopic examination by phase contrast optics at $\times 200$ magnification of the pellet. All samples can be stained and re-examined microscopically [9].

3B.2.2 Hormonal determinations

In men with testicular deficiency, hypergonadotrophic hypogonadism is usually present, with high levels of follicle-stimulating hormone (FSH) and luteinising hormone (LH), and sometimes low levels of testosterone. Generally, the levels of FSH correlate with the number of spermatogonia: when spermatogonia are absent or markedly diminished, FSH values are usually elevated; when the number of spermatogonia is normal, but maturation arrest exists at the spermatocyte or spermatid level, FSH values are within the normal range. However, for an individual patient, FSH levels do not accurately predict the spermatogenesis status because men with maturation arrest histology could have normal FSH and normal testis volume and still be azoospermic [11, 12].

3B.2.3 Testicular biopsy

Testicular biopsy can be part of intracytoplasmic sperm injection (ICSI) treatment in patients with clinical evidence of NOA. Testicular sperm extraction (TESE) is the technique of choice. Spermatogenesis may be focal, which means that in about 50% of men with NOA, spermatozoa can be found and used for ICSI. Most authors therefore recommend taking several testicular samples. There is a good correlation between the histology found upon diagnostic biopsy and the likelihood of finding mature sperm cells during testicular sperm retrieval and ICSI [13-15]. However, no threshold value has been found for FSH, inhibin B, or testicular volume

and successful sperm harvesting. When there are complete AZFa and AZFb microdeletions, the likelihood of sperm retrieval is virtually zero and therefore TESE procedures are contraindicated. Microsurgical TESE increases retrieval rates vs. conventional TESE, and should be preferred in severe cases of non-obstructive azoospermia [16-19]. Positive retrievals are reported even in conditions such as Sertoli cell only syndrome type II [10].

The results of ICSI are worse when using sperm retrieved from men with NOA compared to sperm from ejaculated semen and from men with obstructive azoospermia (OA) [20-24]. Birth rates are lower in NOA vs. OA (19% vs 28%) [25].

- ICSI results in significantly lower fertilisation and implantation rates.
- Neonatal health in terms of birth parameters, major anomalies and chromosomal aberrations in a large cohort of children born after use of non-ejaculated sperm, are comparable to the outcome of children born after use of ejaculated sperm [26].

3B.3 Conclusions and recommendations for testicular deficiency

Conclusions	LE
Impaired spermatogenesis is often associated with elevated FSH concentration.	3
Spermatozoa are found in about 50% of patients with NOA.	2a
Pregnancies and live births are eventually obtained in 30-50% of couples with NOA, when spermatozoa have been found in the testicular biopsy.	3

Recommendations	GR
Men who are candidates for sperm retrieval must receive appropriate genetic counselling.	A
Testicular biopsy is the best procedure to define the histological diagnosis and retrieve sperm in the same procedure. Spermatozoa have to be cryopreserved for use in ICSI.	A
For patients with NOA who have spermatozoa in their testicular biopsy, ICSI with fresh or cryopreserved spermatozoa is the only therapeutic option.	A
Men with NOA can be offered TESE with cryopreservation of the spermatozoa to be used for ICSI [27].	A
To increase the chances of positive sperm retrieval in men with NOA, TESE (microsurgical or multiple) should be used.	A

ICSI = intracytoplasmic sperm injection; TESE = testicular sperm extraction; NOA = non-obstructive azoospermia.

3C GENETIC DISORDERS IN INFERTILITY

All urologists working in andrology must have an understanding of genetic abnormalities associated with infertility, so that they can provide correct advice to couples seeking fertility treatment. Men with very low sperm counts can be offered a reasonable chance of paternity, using in vitro fertilisation (IVF), ICSI, and sperm harvesting from the testes in case of azoospermia. However, the spermatozoa of infertile men show an increased rate of aneuploidy, structural chromosomal abnormalities, and DNA damage, carrying the risk of passing genetic abnormalities to the next generation. Current routine clinical practice is based on the screening of genomic DNA from peripheral blood samples, however, screening of chromosomal anomalies in spermatozoa is also feasible and can be performed in selected cases [28].

3C.1 Chromosomal abnormalities

Chromosome abnormalities can be numerical (e.g. trisomy) or structural (e.g. inversions or translocations). In a survey of pooled data from 11 publications, including 9,766 infertile men, the incidence of chromosomal abnormalities was 5.8% [29]. Of these, sex chromosome abnormalities accounted for 4.2% and autosomal abnormalities for 1.5%. In comparison, the incidence of abnormalities was 0.38% in pooled data from three series, with a total of 94,465 newborn male infants, of which 131 (0.14%) were sex chromosome abnormalities and 232 (0.25%) autosomal abnormalities [29]. The frequency of chromosomal abnormalities increases as testicular deficiency becomes more severe. Patients with a spermatozoa count < 5 million/mL already show a 10-fold higher incidence (4%) of mainly autosomal structural abnormalities compared with the general population [30, 31]. Men with NOA are at highest risk, especially for sex chromosomal anomalies.

Based on the frequencies of chromosomal aberrations in patients with different sperm concentration, karyotype analysis is indicated in men with azoospermia or oligozoospermia (spermatozoa < 10 million/mL) [31]. A recent study proposes to restrict karyotype to NOA men with the purpose to prevent adverse pregnancy outcomes [32]. If there is a family history of recurrent spontaneous abortions, malformations or mental retardation, karyotype analysis should be requested, regardless of the sperm concentration.

3C.1.1 Sex chromosome abnormalities (Klinefelter's syndrome and variants [47,XXY; 46,XY/47,XXY mosaicism])

Klinefelter's syndrome is the most common sex chromosome abnormality [29, 33]. Adult men with Klinefelter's syndrome have small firm testicles, devoid of germ cells. The phenotype varies from a normally virilised man to one with the stigmata of androgen deficiency, including female hair distribution, scant body hair, and long arms and legs due to late epiphyseal closure. Leydig cell function is commonly impaired in men with Klinefelter's syndrome [34]. Testosterone levels may be normal or low, oestradiol levels normal or elevated, and FSH levels increased. Libido is often normal despite low testosterone levels, but androgen replacement may be needed as the patient ages.

Germ cell presence and sperm production are variable in men with Klinefelter's mosaicism, 46,XY/47,XXY. Based on sperm fluorescence in situ hybridisation (FISH) studies showing an increased frequency of sex chromosomal abnormalities and increased incidence of autosomal aneuploidy (disomy for chromosomes 13, 18 and 21), concerns have been raised about the chromosomal normality of the embryos generated through ICSI [35].

The production of 24,XY sperm has been reported in 0.9% and 7.0% of men with Klinefelter's mosaicism [36, 37] and in 1.36-25% of men with somatic karyotype 47,XXY [38-41]. In patients with azoospermia, TESE or (micro-TESE) can be proposed as a therapeutic option since spermatozoa can be recovered in about 30% of cases. Numerous healthy children have been born using ICSI without pre-implantation genetic diagnosis (PGD) and the conception of one 47,XXY foetus has been reported [33]. However, a study of ICSI combined with PGD in 113 embryos reported a significant fall in the rate of normal embryos for couples with Klinefelter's syndrome with respect to controls (54% vs. 77.2%) [41]. Due to the significant increase of sex chromosomal and autosomal abnormalities in the embryos of Klinefelter's patients, PGD or amniocentesis analysis should be considered.

Follow-up (possibly every year) of men with Klinefelter's syndrome is required and androgen replacement therapy should be started after fertility issues have been addressed and when testosterone level is in the range of hypoandrogenism.

3C.1.2 Autosomal abnormalities

Genetic counselling should be offered to all couples seeking fertility treatment (including IVF/ICSI) when the male partner has an autosomal karyotype abnormality. The most common autosomal karyotype abnormalities are Robertsonian translocations, reciprocal translocations, paracentric inversions, and marker chromosomes. It is important to look for these structural chromosomal anomalies because there is an increased associated risk of aneuploidy or unbalanced chromosomal complements in the foetus. As with Klinefelter's syndrome, sperm FISH analysis provides a more accurate risk estimation of affected offspring, however, the diffusion of this genetic test is largely limited by the availability of laboratories able to perform this analysis.

When IVF/ICSI is carried out for men with translocations, PGD or amniocentesis should be performed.

3C.1.3 Sperm chromosomal abnormalities

Sperm can be examined for their chromosomal constitution using multicolour FISH both in men with normal karyotype and with anomalies. Aneuploidy in sperm, particularly sex chromosome aneuploidy, is associated with severe damage to spermatogenesis [29, 42-44] and with translocations [45].

Florescence in situ hybridisation analysis of spermatozoa is only indicated for specific andrology conditions e.g. macrocephalia [44].

3C.2 Genetic defects

3C.2.1 X-linked genetic disorders and male fertility

Each man has only one X-chromosome. An X-linked recessive disorder manifests in males. The defect will be transmitted to daughters, but not to sons.

3C.2.2 **Kallmann syndrome**

Patients with Kallmann syndrome have hypogonadotrophic hypogonadism and anosmia, but may also have other clinical features, including facial asymmetry, cleft palate, colour blindness, deafness, maldescended testes, and unilateral renal aplasia. This syndrome can be due to mutation in the Kalig-1 gene [on the X-chromosome] or in several other autosomal genes and should be tested [44,45] .

Spermatogenesis can be relatively easily induced by hormonal treatment [46], therefore, genetic screening prior to therapy is advisable although it is limited by the rarity of specialised genetic laboratories that can offer this genetic test. Treatment with gonadotropins allows natural conception in most cases, even for men with a relatively low sperm count. Thus, identification of the involved gene (X-linked, autosomal dominant or recessive) can help to provide more accurate genetic counselling, that is, risk estimation for transmission to the offspring.

3C.2.3 **Mild androgen insensitivity syndrome**

The AR gene is located on the long arm of the X-chromosome. Mutations in the AR gene may result in mild to complete androgen insensitivity. The phenotypic features of complete androgen insensitivity syndrome are female external genitalia and absence of pubic hair (Morris syndrome). In partial androgen insensitivity syndrome, phenotypes range from predominantly female phenotype through ambiguous genitalia, to predominantly male phenotype with micropenis, perineal hypospadias, and cryptorchidism. The latter phenotype is also termed Reifenstein syndrome. In the forementioned severe forms of androgen resistance, there is no risk of transmission because affected men cannot generate their own biological children using the current technologies. Patients with mild androgen insensitivity syndrome have male infertility as their primary or even sole symptom. Disorders of the androgen receptor causing infertility in the absence of any genital abnormality are rare, and only a few mutations have been reported in infertile [47-50] or fertile [51] men.

3C.2.4 **Other X-disorders**

An unexpectedly high number of genes with a testis-specific or enriched expression pattern have been identified on the X-chromosome, and in particular, premeiotic genes are over-represented on the X-chromosome compared with autosomal chromosomes [52]. Nevertheless, to date only a few genes have been screened in relatively small populations and none of them appear relevant for male infertility [53, 54]. On the other hand, two recent independent studies showed a significantly higher deletion load on the X-chromosome in men with spermatogenic failure with respect to normozoospermic controls [55, 56].

3C.3 **Y-chromosome and male infertility**

Microdeletions on the Y-chromosome are termed AZFa, AZFb and AZFc [57]. Clinically relevant deletions remove partially, or in most cases completely, one or more of the AZF regions, and are the most frequent molecular genetic cause of severe oligozoospermia and azoospermia [58]. In each AZF region, there are several spermatogenesis candidate genes [59]. Deletions occur en bloc (i.e. removing more than one gene), thus, it is not possible to determine the role of a single AZF gene from the AZF deletion phenotype and it is unclear if they all participate in spermatogenesis. Gene-specific deletions, which remove a single gene, have been reported only in the AZFa region and concern the USP9Y gene. These studies have suggested that USP9Y is most likely to be a “fine tuner” of sperm production, and its specific screening is not advised [60].

3C.3.1 **Clinical implications of Y microdeletions**

The clinical significance of Yq microdeletions can be summarised as follows:

- They are not found in normozoospermic men, proving there is a clear cut cause-and-effect relationship between Y-deletions and spermatogenic failure [61].
- The highest frequency of Y-deletions is found in azoospermic men (8-12%), followed by oligozoospermic (3-7%) men.
- Deletions are extremely rare with a sperm concentration > 5 million/mL (~0.7%).
- AZFc deletions are most common (65-70%), followed by Y-deletions of the AZFb and AZFb+c or AZFa+b+c regions (25-30%). AZFa region deletions are rare (5%).
- Complete removal of the AZFa region is associated with severe testicular phenotype (Sertoli cell only syndrome), while complete removal of the AZFb region is associated with spermatogenic rest. Complete removal of the AZFc region causes a variable phenotype ranging from azoospermia to oligozoospermia.
- Classical (complete) AZF deletions do not confer a risk for cryptorchidism or testicular cancer [58].

The specificity and genotype/phenotype correlation reported above means that Y-deletion analysis has both a diagnostic and prognostic value for testicular sperm retrieval [58].

3C.3.1.1 Testing for Y microdeletions

Indications for AZF deletion screening are based on sperm count and include azoospermia and severe oligozoospermia (spermatozoa count < 5 million/mL). Thanks to the European Academy of Andrology (EAA) guidelines [62] and the EAA/EMQN (European Molecular Genetics Quality Network) external quality control programme (<http://www.emqn.org/emqn/>), Yq testing has become more reliable in different routine genetic laboratories. The EAA guidelines provide a set of primers capable of detecting > 95% of clinically relevant deletions [62].

3C.3.1.2 Genetic counselling for AZF deletions

After conception, any Y-deletions are transmitted obligatorily to the male offspring, and genetic counselling is therefore mandatory. In most cases, father and son have the same microdeletion [62], but occasionally the son has a larger one [63]. The extent of spermatogenic failure (still in the range of azoo-/oligozoospermia) cannot be predicted entirely in the son, due to the different genetic background and the presence or absence of environmental factors with potential toxicity for reproductive function. A significant proportion of spermatozoa from men with complete AZFc deletion are nullisomic for sex chromosomes [64, 65], indicating a potential risk for any offspring to develop 45,X0 Turner's syndrome and other phenotypic anomalies associated with sex chromosome mosaicism, including ambiguous genitalia [66]. Despite this theoretical risk, babies born from fathers affected by Yq microdeletions are phenotypically normal [58, 67]. This could be due to the reduced implantation rate and a likely higher risk of spontaneous abortion of embryos bearing a 45,X0 karyotype. When ICSI is used in the presence of a Y microdeletion, long-term follow-up of any male children is needed with respect to their fertility status, and cryopreservation of spermatozoa at a young age can be considered.

3C.3.1.3 Y-chromosome: 'gr/gr' deletion

A new type of Yq deletion, known as the gr/gr deletion, has been described in the AZFc region [68]. This deletion removes half of the gene content of the AZFc region, affecting the dosage of multicopy genes mapping inside this region. This type of deletion confers a 2.5-8 fold increased risk for oligozoospermia [62, 69-71]. The frequency of gr/gr deletion in oligozoospermic patients is ~4%.

According to four meta-analyses, gr/gr deletion is a significant risk factor for impaired sperm production [70, 71]. It is worth noting that both the frequency of gr/gr deletion and its phenotypic expression vary between different ethnic groups, depending on the Y-chromosome background. For example, in some Y haplogroups, the deletion is fixed and appears to have no negative effect on spermatogenesis. Consequently, the routine screening for gr/gr deletion is still a debated issue, especially in those laboratories serving diverse ethnic and geographic populations. A large multicentre study has shown that gr/gr deletion is a potential risk factor for testicular germ cell tumours [72]. However, these data need further confirmation in an ethnically and geographically matched case-control study setting. For genetic counselling it is worth noticing that partial AZFc deletions (gr/gr and b2/b3) may predispose to complete AZFc deletion in the next generation [73].

3C.3.1.4 Autosomal defects with severe phenotypic abnormalities and infertility

Several inherited disorders are associated with severe or considerable generalised abnormalities and infertility. Among them, Prader-Willy Syndrome, Bardet-Biedl Syndrome, Noonan's Syndrome, Myotonic dystrophy, dominant polycystic kidney disease, 5 α -reductase deficiency, etc. Patients with these defects will be well known to doctors, often from childhood. A fertility problem must be managed in the context of the care of the man as a whole and considering the couple's ability to care for a child.

3C.4 Cystic fibrosis mutations and male infertility

Cystic fibrosis (CF) is a fatal autosomal-recessive disorder. It is the most common genetic disease of Caucasians; 4% are carriers of gene mutations involving the CF transmembrane conductance regulator (CFTR) gene located on chromosome 7p. It encodes a membrane protein that functions as an ion channel and influences the formation of the ejaculatory duct, seminal vesicle, vas deferens and distal two-thirds of the epididymis.

Congenital bilateral absence of the vas deferens (CBAVD) is associated with CFTR gene mutations and was found in ~2% of men with OA attending a clinic in Edinburgh, UK [74]. The incidence in men with OA varies between different countries. The clinical diagnosis of absent vasa is easy to miss and all men with azoospermia should be very carefully examined to exclude CBAVD, particularly those with a semen volume < 1.5 mL and pH < 7.0. Approximately 1,500 mutations are listed on the CFTR database (<http://www.geneticsickkids.on.ca/cftr/>). The most frequently found mutations are the F508, R117H and W1282X, but their frequency and the presence of other mutations largely depend on the ethnicity of the patient [75, 76]. Given the functional relevance of a DNA variant (the 5T allele) in a non-coding region of CFTR [75], it is now considered a mild CFTR mutation

rather than a polymorphism and it should be analysed in each CAVD patient. As more mutations are defined and tested for, almost all men with CBAVD will probably be found to have mutations. It is not practical to test for all known mutations, because many have a very low prevalence in a particular population. Routine testing is usually restricted to the most common mutations in a particular community through the analysis of a mutation panel. Given that this is a recessive disease if a second mutation is not found with the routine panel, a second step analysis is advised which comprises the direct sequencing of the entire gene. Men with CBAVD often have mild clinical stigmata of CF (e.g., history of chest infections). When a man has CBAVD, it is important to test also his partner for CF mutations. If the female partner is found to be a carrier of CFTR mutations, the couple must consider very carefully whether to proceed with ICSI using the male's sperm, as the risk of having a child with CF or CBAVD will be 50%, depending on the type of mutations carried by the parents. If the female partner is negative for known mutations, the risk of being a carrier of unknown mutations is ~0.4%.

3C.4.1 Unilateral or bilateral absence/abnormality of the vas and renal anomalies

Unilateral absence of the vas deferens is usually associated with ipsilateral absence of the kidney and probably has a different genetic causation [77]. Consequently, in these subjects CFTR mutation screening is not indicated. Men with unilateral absence of the vas deferens are usually fertile, and the condition is most commonly encountered as an incidental finding in the vasectomy clinic. CFTR gene mutation screening is indicated in men with unilateral absence of the vas deferens with normal kidneys.

An abdominal ultrasound should be undertaken both in unilateral and bilateral absence of vas deferens. Findings may range from unilateral absence of the vas with ipsilateral absence of the kidney, to bilateral vessel abnormalities and renal abnormalities, such as pelvic kidney [78].

3C.4.2 Unknown genetic disorders

Considering the high predicted number of genes involved in male gametogenesis, it is likely that most idiopathic forms of spermatogenic disturbances are caused by mutations or polymorphisms in spermatogenesis candidate genes [53]. However, despite an intensive search for new genetic factors, no clinically relevant gene mutations or polymorphisms (except those related to the Y-chromosome) have so far been identified [53, 79, 80], and references therein. The introduction of new analytical approaches provided evidence for the importance of CNVs [55, 56] and further advances are expected with Next Generation Sequencing. Intracytoplasmic sperm injection is used to enable men with severely damaged spermatogenesis to father children in situations formerly considered hopeless and where very few spermatozoa can be obtained. This has led to concern that children may be born with a foetal abnormality, because ICSI may enable defective sperm to bypass the selective processes of the female genital tract and egg covering.

Intracytoplasmic sperm injection babies have a higher risk of de novo sex chromosomal aberrations (about a threefold increase compared with natural conceptions) and paternally inherited structural abnormalities. Treatment with assisted reproductive technology was associated with increased risk of cardiovascular, musculoskeletal, urogenital, and gastrointestinal defects and cerebral palsy [81-83].

3C.4.3 DNA fragmentation in spermatozoa

There is increased DNA damage in spermatozoa from men with oligozoospermia. This increase is associated with reduced chances of natural conception and an increased chance of early pregnancy loss [84].

3C.4.4 Genetic counselling and ICSI

Initially, the couple should be given full information about the risks to the child in order to help them decide whether to proceed with ICSI. Where there is conflict between the wishes of the couple and the interests of the future child, it may be ethically correct to withhold therapy. When both partners are known to carry defects (e.g., CFTR mutations), there is up to a 50% chance of the child developing a clinical condition. Many clinicians and infertility clinic personnel may consider it unethical to proceed because their duty of care to the future child and the interests of society outweigh the wishes of the individual couple. If there is a conflict that cannot be resolved by agreement, the interests of a future child probably take precedence over the interests of a couple. The couple also need to give consideration to preimplantation diagnosis.

3C.5 Conclusions and recommendations for genetic disorders in male infertility

Conclusions	LE
New insights into the genetic basis of infertility and the advent of ICSI require a good understanding of genetics by clinicians and the general public.	3
Diagnostic advances will allow us to identify the genetic basis of more disorders and diagnose known disorders at a lower cost. For some of these disorders, gene therapy might be practical in the future.	2a
In men with spermatogenic damage there is a higher prevalence of chromosome abnormalities reaching the highest frequency in NOA men.	1b
AZF deletions are clear-cut causes of spermatogenic impairments with diagnostic and prognostic value for TESE.	1a
AZF deletion will be obligatorily transmitted to the son.	1a
gr/gr deletion has been confirmed as a significant risk factor for impaired sperm production, whereas further evidence of the prognostic significance of gr/gr and development of a testicular germ cell tumour is needed.	2b

Recommendations	GR
From a diagnostic view point, standard karyotype analysis should be offered to all men with damaged spermatogenesis (spermatozoa < 10 million/mL) who are seeking fertility treatment by IVF.	B
Genetic counselling is mandatory in couples with a genetic abnormality found in clinical or genetic investigation and in patients who carry a (potential) inheritable disease.	A
All men with Klinefelter's syndrome need long-term endocrine follow-up and usually require androgen replacement therapy.	A
Testing for microdeletions is not necessary in men with OA (with normal FSH) when ICSI is used because spermatogenesis should be normal.	A
Men with severely damaged spermatogenesis (spermatozoa < 5 million/mL) should be advised to undergo Yq microdeletion testing for both diagnostic and prognostic purposes. Yq microdeletion also has important implications for genetic counselling.	A
If complete AZFa or AZFb microdeletions are detected, micro-TESE should not be performed because it is extremely unlikely that any sperm will be found.	A
If a man with Yq microdeletion and his partner wish to proceed with ICSI, they should be advised that microdeletions will be passed to sons, but not to daughters.	A
When a man has structural abnormalities of the vas deferens (unilateral or bilateral absence), he and his partner should be tested for CF gene mutations.	A

IVF = *in vitro* fertilisation; OA = obstructive azoospermia; FSH = follicle-stimulating hormone; ICSI = intracytoplasmic sperm injection; TESE = testicular sperm extraction; CF = cystic fibrosis.

3D OBSTRUCTIVE AZOOSPERMIA

Obstructive azoospermia (OA) is the absence of spermatozoa and spermatogenic cells in semen and post-ejaculate urine due to obstruction. OA is less common than NOA and occurs in 15-20% of men with azoospermia. Men with OA present with normal FSH, normal size testes, and epididymal enlargement. Sometimes, the vas deferens is absent. Obstruction in primary infertile men is often present at the epididymal level.

3D.1 Classification

3D.1.1 Intratesticular obstruction

Intratesticular obstruction occurs in 15% of men with OA [85]. Congenital forms are less common than acquired forms (post-inflammatory or post-traumatic).

3D.1.2 Epididymal obstruction

Epididymal obstruction is the most common cause of OA, affecting 30-67% of azoospermic men [85-88]. Congenital epididymal obstruction usually manifests as CBAVD, which is associated with at least one mutation of the CF gene in 82% of cases [89]. Congenital forms of epididymal obstruction include chronic

sinopulmonary infections (Young's syndrome) [90]. Acquired forms secondary to acute (e.g., gonococcal) and subclinical (e.g., chlamydial) epididymitis are most common [91, 92]. Other causes may be trauma or surgical intervention [93, 94].

3D.1.3 Vas deferens obstruction

Vas deferens obstruction is the most common cause of acquired obstruction following vasectomy [95]. Approximately 2-6% of these men request vasectomy reversal (see Chapter 3G). Vasal obstruction may also occur after hernia repair [96, 97]. The most common congenital vasal obstruction is CBAVD, often accompanied by CF. Unilateral agenesis or a partial defect is associated with contralateral seminal duct anomalies or renal agenesis in 80% and 26% of cases, respectively [98] (see Chapter 3C).

3D.1.4 Ejaculatory duct obstruction

Ejaculatory duct obstruction is found in 1-3% of cases of OA [85] and is classified as either cystic or post-inflammatory. Cystic obstructions are usually congenital (i.e., Mullerian duct cyst or urogenital sinus/ejaculatory duct cysts) and are typically midline. In urogenital sinus abnormalities, one or both ejaculatory ducts empty into the cyst [99], while in Mullerian duct anomalies, the ejaculatory ducts are laterally displaced and compressed by the cyst [100]. Paramedian or lateral intraprostatic cysts are rare [101]. Post-inflammatory obstructions of the ejaculatory duct are usually secondary to urethroprostatitis [102]. Congenital or acquired complete obstructions of the ejaculatory ducts are commonly associated with low semen volume, decreased or absent seminal fructose, and acid pH. The seminal vesicles are usually dilated (anterior-posterior diameter > 15 mm) [102, 103].

3D.1.5 Functional obstruction of the distal seminal ducts

Functional obstruction of the distal seminal ducts might be attributed to local neuropathy [104]. This abnormality is often associated with urodynamic dysfunction. Impaired sperm transport may be idiopathic or associated with SSRI medication as well.

3D.2 Diagnostic evaluation

3D.2.1 Clinical history

Clinical history taking should follow the suggestions for the diagnostic evaluation of infertile men (3A.2).

3D.2.2 Clinical examination

Clinical examination should follow suggestions for the diagnostic evaluation of infertile men. The following findings indicate OA:

- At least one testis with a volume > 15 mL, although a smaller volume may be found in some patients with OA and concomitant partial testicular failure.
- Enlarged and hardened epididymis.
- Nodules in the epididymis or vas deferens.
- Absence or partial atresia of the vas.

3D.2.3 Semen analysis

At least two examinations must be carried out at an interval of 2-3 months, according to the WHO (see Chapter 3A.2). Azoospermia means the inability to detect spermatozoa after centrifugation at $\times 400$ magnification. When semen volume is low, a search must be made for spermatozoa in urine after ejaculation. Absence of spermatozoa and immature germ cells in semen smears suggest complete seminal duct obstruction.

3D.2.4 Hormone levels

Serum FSH levels may be normal, but do not exclude a testicular cause of azoospermia. FSH level is normal in 40% of men with primary spermatogenic failure. Inhibin B seems to have a higher predictive value for normal spermatogenesis [88].

3D.2.5 Ultrasonography

In addition to physical examination, a scrotal ultrasound may be helpful in finding signs of obstruction (e.g., dilatation of rete testis, enlarged epididymis with cystic lesions, or absent vas deferens) and may demonstrate signs of testicular dysgenesis (e.g., non-homogeneous testicular architecture and microcalcifications) and associated ITGCN. For patients with a low seminal volume and in whom distal obstruction is suspected, transrectal ultrasound (TRUS) is essential. Invasive diagnosis, including testicular biopsy, scrotal exploration, and distal seminal duct evaluation, are indicated in patients with OA in whom an acquired obstruction of the seminal ducts is suspected. Explorative and recanalisation surgery should be carried out simultaneously.

3D.2.6 **Testicular biopsy**

In selected cases, testicular biopsy may be indicated to exclude spermatogenic failure. Testicular biopsy should be combined with extraction of testicular spermatozoa (i.e., TESE) for cryopreservation.

3D.3 **Disease management**

3D.3.1 **Intratesticular obstruction**

Only TESE allows sperm retrieval in these patients and is therefore recommended.

3D.3.2 **Epididymal obstruction**

Microsurgical epididymal sperm aspiration (MESA) [105] is indicated in men with CBAVD. TESE and PESA are also viable options [106]. Usually, one MESA procedure provides sufficient material for several ICSI cycles [107] and it produces high pregnancy and fertilisation rates [108]. In patients with azoospermia due to acquired epididymal obstruction, microsurgical reconstruction is recommended, with the preferred technique being microsurgical intussusception tubulovasectomy [109]. Reconstruction may be carried out unilaterally or bilaterally; patency and pregnancy rates are usually higher with bilateral reconstruction. Anatomical recanalisation following surgery may require 3-18 months. Before microsurgery (and in all cases where recanalisation is impossible), epididymal spermatozoa should be aspirated and cryopreserved for use in ICSI [107]. Patency rates range between 60% and 87% [94, 110] and cumulative pregnancy rates between 10% and 43%. Recanalisation success rates may be adversely affected by preoperative and intraoperative findings.

3D.3.3 **Proximal vas obstruction**

Proximal vas obstruction after vasectomy requires microsurgical vasectomy reversal (see Chapter 3G). Vasovasostomy is also required in rare cases of proximal vasal obstructions. The absence of spermatozoa in the intraoperative vas deferens fluid suggests the presence of a secondary epididymal obstruction; especially if the seminal fluid of the proximal vas has a thick “toothpaste” appearance. Microsurgical tubulovasostomy is then indicated.

3D.3.4 **Distal vas deferens obstruction**

It is usually impossible to correct large bilateral vas deferens defects, resulting from involuntary excision of the vasa deferentia during hernia surgery in early childhood or previous orchidopexy [111]. In these cases TESE/ MESA or proximal vas deferens sperm aspiration [112] can be used for cryopreservation for future ICSI.

3D.3.5 **Ejaculatory duct obstruction**

The treatment of ejaculatory duct obstruction depends on its aetiology. Transurethral resection of the ejaculatory ducts (TURED) [102] can be used in large postinflammatory obstruction and when one or both ejaculatory ducts empty into an intraprostatic midline cyst. Resection may remove part of the verumontanum. In cases of obstruction due to a midline intraprostatic cyst, incision or unroofing of the cyst is required [102]. Intraoperative TRUS makes this procedure safer. If distal seminal tract evaluation is carried out at the time of the procedure, installation of methylene blue dye into the vas deferens can help to document opening of the ducts. The limited success rate of surgical treatment of ejaculatory duct obstruction in terms of spontaneous pregnancies should be weighed against sperm aspiration and ICSI. Complications following TURED include retrograde ejaculation due to bladder neck injury and urine reflux into the ejaculatory ducts, seminal vesicles, and vasa. The alternatives to TURED are MESA, TESE, proximal vas deferens sperm aspiration, seminal vesicle ultrasonically guided aspiration, and direct cyst aspiration. Spermatozoa can then be retrieved by antegrade seminal tract washout [113].

3D.4 **Conclusions and recommendation for obstructive azoospermia**

Conclusions	LE
Obstructive lesions of the seminal tract should be suspected in azoospermic or severely oligozoospermic patients with normal-sized testes and normal endocrine parameters.	3

Recommendations	GR
In azoospermia caused by epididymal obstruction, standard procedures include vasovasostomy and tubulovastomy.	B
Sperm retrieval techniques, such as MESA, TESE, and PESA, can be used additionally. These methods should be used only when cryostorage of the material obtained is available.	B
In azoospermia caused by epididymal obstruction, scrotal exploration with microsurgical epididymal sperm aspiration and cryopreservation of spermatozoa should be performed. Microsurgical reconstruction should be performed, if applicable. Results of reconstructive microsurgery depend on the cause and location of the obstruction, and the surgeon's expertise.	B

3E VARICOCELE

Varicocele is a common abnormality which may be associated with the following andrological conditions:

- Failure of ipsilateral testicular growth and development.
- Symptoms of pain and discomfort.
- Male subfertility.
- Hypogonadism.

3E.1 Classification

The following classification of varicocele [114] is useful in clinical practice:

- Subclinical: not palpable or visible at rest or during Valsava manoeuvre, but can be shown by special tests (Doppler ultrasound studies).
- Grade 1: palpable during Valsava manoeuvre, but not otherwise.
- Grade 2: palpable at rest, but not visible.
- Grade 3: visible and palpable at rest.

3E.2 Diagnostic evaluation

The diagnosis of varicocele is made by clinical examination and should be confirmed by colour Duplex analysis [10]. In centres where treatment is carried out by antegrade or retrograde sclerotherapy or embolisation, diagnosis is additionally confirmed by X-ray.

3E.3 Basic considerations

3E.3.1 *Varicocele and fertility*

Varicocele is a physical abnormality present in 11.7% of adult men and in 25.4% of men with abnormal semen analysis [115]. The exact association between reduced male fertility and varicocele is unknown, but a recent meta-analysis showed that semen improvement is usually observed after surgical correction [116]. Varicocelectomy can reverse sperm DNA damage [117].

3E.3.2 *Varicocelectomy*

Varicocele repair has been a subject of debate for several decades. The 2009 Cochrane review concluded that there is no evidence that treatment of varicocele improves a couples' chance of conception [118]. In a recent meta-analysis of four RCTs of varicocelectomy in men with a clinical varicocele, oligozoospermia and otherwise unexplained infertility, there was a trend in favour of surgical correction [119]. Although treatment of varicocele in infertile men may be effective, in adolescents there is a significant risk of overtreatment: most adolescents with a varicocele will have no problem achieving pregnancy later in life [120].

3E.4 Disease management

Several treatments are available for varicocele (Table 4). Current evidence indicates that microsurgical varicocelectomy is the most effective and least morbid method among the varicocelectomy techniques [120].

Table 4: Recurrence and complication rates associated with treatments for varicocele

Treatment	Ref.	Recurrence/ persistence %	Complication rates
Antegrade sclerotherapy	[121]	9	Complication rate 0.3-2.2%: testicular atrophy, scrotal haematoma, epididymitis, left-flank erythema
Retrograde sclerotherapy	[122]	9.8	Adverse reaction to contrast medium, flank pain, persistent thrombophlebitis, vascular perforation
Retrograde embolisation	[123, 124]	3.8-10	Pain due to thrombophlebitis, bleeding haematoma, infection, venous perforation, hydrocele, radiological complication (e.g., reaction to contrast media), misplacement or migration of coils, retroperitoneal haemorrhage, fibrosis, ureteric obstruction
<i>Open operation</i>			
Scrotal operation		-	Testicular atrophy, arterial damage with risk of devascularisation and testicular gangrene, scrotal haematoma, postoperative hydrocele
Inguinal approach	[125]	13.3	Possibility of missing out a branch of testicular vein
High ligation	[126]	29	5-10% incidence of hydrocele (< 1%)
Microsurgical inguinal or subinguinal	[127, 128]	0.8-4	Postoperative hydrocele arterial injury, scrotal haematoma
Laparoscopy	[129, 130]	3-7	Injury to testicular artery and lymph vessels; intestinal, vascular and nerve damage; pulmonary embolism; peritonitis; bleeding; postoperative pain in right shoulder (due to diaphragmatic stretching during pneumoperitoneum); pneumoscrotum; wound infection

3E.5 Conclusions and recommendations for varicocele

Conclusions	LE
Current information supports the hypothesis that the presence of varicocele in some men is associated with progressive testicular damage from adolescence onwards and a consequent reduction in fertility.	2a
Although the treatment of varicocele in adolescents may be effective, there is a significant risk of overtreatment.	3
Varicocele repair may be effective in men with subnormal semen analysis, a clinical varicocele and otherwise unexplained infertility.	1a

Recommendations	GR
Varicocele treatment is recommended for adolescents with progressive failure of testicular development documented by serial clinical examination.	B
No evidence indicates benefit from varicocele treatment in infertile men who have normal semen analysis or in men with subclinical varicocele. In this situation, varicocele treatment cannot be recommended.	A
Varicocele repair should be considered in case of a clinical varicocele, oligospermia, infertility duration of ≥ 2 years and otherwise unexplained infertility in the couple.	A

3F HYPOGONADISM

Hypogonadism is characterised by impaired testicular function, which may affect spermatogenesis and/or testosterone synthesis. The symptoms of hypogonadism depend on the degree of androgen deficiency and if the condition develops before or after pubertal development of the secondary sex characteristics.

3F.1 Epidemiology and aetiology

The aetiological and pathogenetic mechanisms of male hypogonadism can be divided into three main categories:

1. Primary (hypergonadotrophic) hypogonadism due to testicular failure.
2. Secondary (hypogonadotrophic) hypogonadism caused by insufficient gonadotropin-releasing hormone (GnRH) and/or gonadotropin (FSH, LH) secretion.
3. Androgen insensitivity (end-organ resistance).

The most common conditions within these three categories are given in Table 5 (see also Chapter 3C).

Table 5: Disorders associated with male hypogonadism*

Primary (hypergonadotrophic) hypogonadism (testicular failure)*
Anorchia
Maldescended testes
Klinefelter's syndrome
Y-chromosome microdeletions
Numerical and structural chromosomal anomalies
Trauma, testicular torsion, orchitis
Iatrogenic (surgery, medications, irradiation, or cytostatic drugs)
Exogenous factors (toxins, heat, or occupational hazards)
Systemic diseases (liver cirrhosis, or renal failure)
Testicular tumour
Varicocele
Idiopathic (e.g., late-onset hypogonadism)
Secondary (hypogonadotrophic) hypogonadism (secondary testicular failure)
Congenital
Idiopathic hypogonadotrophic hypogonadism
Normosmic
Hiposmic/anosmic (Kallmann syndrome)
Acquired (tumours in the following regions)
Diencephalon (craniopharyngioma or meningioma)
Hypothalamus or pituitary
Empty sella syndrome
Granulomatous illnesses
Fractures of the skull base
Ischaemic or haemorrhagic lesions in hypothalamic area
Hyperprolactinaemia
Drugs/anabolic steroids, radiotherapy
Target organ resistance to androgens
Testicular feminisation
Reifenstein syndrome

*Modified from Nieschlag et al. [6].

3F.2 Idiopathic hypogonadotrophic hypogonadism: aetiology, diagnosis and therapeutic management

Idiopathic hypogonadotrophic hypogonadism is characterised by low levels of gonadotropins and sex steroid in the absence of anatomical or functional abnormalities of the hypothalamic-pituitary-gonadal axis [131]. Idiopathic hypogonadotrophic hypogonadism may be an isolated condition or may be associated with anosmia/hyposmia (Kallmann syndrome). Genetic factors causing a deficit of gonadotropins may act at the hypothalamic or pituitary level. Mutations in candidate genes (X-linked or autosomal) can be found in ~30% of congenital cases [131] and should be screened prior to assisted reproduction [132]. Acquired

hypogonadotrophic hypogonadism can be caused by some drugs, hormones, anabolic steroids, or tumours. A suspected tumour requires imaging [computed tomography (CT) or magnetic resonance imaging (MRI)] of the sella region and a complete endocrine work-up. Normal androgen levels and subsequent development of secondary sex characteristics (in cases of onset of hypogonadism before puberty) and a eugonadal state can be achieved by androgen replacement alone. However, stimulation of sperm production requires treatment with human chorionic gonadotropin (hCG) combined with recombinant FSH or urinary FSH or human menopausal gonadotropins (HMGs). If hypogonadotrophic hypogonadism is hypothalamic in origin, an alternative to hCG treatment is pulsatile GnRH [133]. In patients who have developed hypogonadism before puberty and have not been treated with gonadotropins or GnRH, 1-2 years of therapy may be needed to achieve sperm production.

3F.3 Hypergonadotrophic hypogonadism: aetiology, diagnosis and therapeutic management

Many conditions in men are associated with hypergonadotrophic hypogonadism (Table 6, see also Chapter 3C). Most conditions listed in Table 6 only affect the reproductive function of the testes so that only FSH level is elevated. However, it has been reported that men with infertility are at higher risk for developing impaired Leydig cell function [134], while men with Klinefelter's syndrome often show high LH values and develop hypoandrogenism with ageing [135]. A decrease in testosterone blood concentrations after extensive testicular biopsy in the context of TESE/ICSI has been observed, raising questions about the need for long-term endocrine follow-up of these patients [136]. Laboratory diagnosis of hypergonadotrophic hypogonadism is based on a high level of FSH, decreased serum testosterone, and increased LH levels [132]. Testosterone levels should be evaluated in view of the serum concentration of sex hormone binding globulin (SHBG). Based on levels of total testosterone, albumin and SHBG, free and bioavailable testosterone can be calculated. Due to diurnal variation, blood samples for testosterone assessment should be taken before 10.00 am. Generally, androgen replacement should not be given to men who are considering parenthood or in case of male infertility. Testosterone suppresses pituitary production of LH and FSH, therefore, replacement therapy should not be given for infertility. In obese men, low levels of testosterone may exist due to the conversion of testosterone in oestradiol by the enzyme aromatase [137]. Anti-oestrogens and aromatase inhibitors may help in these patients elevating FSH and LH and potentially increase sperm quality, next to weight reduction. Injectable, oral and transdermal testosterone preparations are available for clinical use [132]. See also EAU Guidelines on Male Hypogonadism [138].

3F.4 Conclusion and recommendations for hypogonadism

Conclusion	LE
Symptomatic patients with primary and secondary hypogonadism who are not considering parenthood are candidates for testosterone substitution therapy.	1b

Recommendations	GR
Effective drug therapy is available to achieve fertility in men with hypogonadotrophic hypogonadism [114].	A*
Testosterone replacement is strictly contraindicated for the treatment of male infertility (low levels of FSH and LH) [139].	A*

**Upgraded following panel consensus.*

FSH = follicle-stimulating hormone; LH = luteinising hormone.

3G CRYPTORCHIDISM

Cryptorchidism is the most common congenital abnormality of the male genitalia and is found in 2-5% of newborn boys, depending on gestational age (cryptorchidism occurs more often in premature boys) and age after birth. At the age of 3 months, the incidence of cryptorchidism falls spontaneously to 1-2%. Approximately 20% of undescended testes are non-palpable and may be located within the abdominal cavity.

3G.1 Aetiology and pathophysiology

The aetiology of cryptorchidism is multifactorial, involving disrupted endocrine regulation and several gene defects. It has been postulated that cryptorchidism may be a part of the so-called testicular dysgenesis syndrome (TDS), which is a developmental disorder of the gonads caused by environmental and/or genetic

influences early in pregnancy. Besides cryptorchidism, TDS includes hypospadias, reduced fertility, increased risk of malignancy, and Leydig cell dysfunction [140].

3G.1.1 Incidence of cryptorchidism

The Caucasian population has a threefold higher incidence of cryptorchidism compared to African-Americans. Premature babies have a much higher incidence of cryptorchidism than full-term babies. In a British study, the incidence of cryptorchidism was 2.7% in > 3,000 boys weighing > 2.5 Kg and 21% in premature boys weighing < 2.5 Kg. At the age of 3 months, spontaneous descent occurred in most boys, and the incidence of cryptorchidism fell to 0.9% and 1.7%, in the > 2.5 Kg and < 2.5 Kg group, respectively [141].

3G.1.2 Pathophysiological effects in maldescended testes

3G.1.2.1 Degeneration of germ cells

The degeneration of germ cells in maldescended testes is apparent after the first year of life. Degenerative changes vary, depending on the position of the testis [142]. During the second year, the number of germ cells declines. In 10-45% of affected patients, a complete loss of germ cells can be detected. Early treatment is therefore recommended to conserve spermatogenesis, especially in bilateral cases. Surgical treatment is the most effective and reliable method of bringing testes into the scrotum. Hormone treatment with hCG has been used widely in the past, but it has now been abolished because of increased germ cell apoptosis after treatment [143].

3G.1.2.2 Relationship with fertility

Semen parameters are often impaired in men with a history of cryptorchidism [144]. Surgical treatment during the first or second year of life may have a positive effect on subsequent fertility [145]. However, there is no definitive proof of the protective effect of early orchidopexy. In men with a history of unilateral cryptorchidism, paternity is almost equal (89.7%) to that in men without cryptorchidism (93.7%). In men with unilateral cryptorchidism, paternity is independent of age at orchidopexy and preoperative testicular location and size [146]. However, a history of unilateral cryptorchidism may result in reduced fertility potential and therefore a longer time to achieve pregnancy. In men with bilateral cryptorchidism, oligozoospermia can be found in 31% and azoospermia in 42%. In cases of bilateral cryptorchidism, the rate of paternity is only 35-53%. In cases of bilateral cryptorchidism and azoospermia, orchidopexy performed even in adult life might lead to the appearance of spermatozoa in the ejaculate [147].

3G.1.2.3 Germ cell tumours

Cryptorchidism is a risk factor for testicular cancer and is associated with testicular microcalcification and intratubular germ cell neoplasia of unclassified type (ITGCNU); formerly carcinoma *in situ* (CIS) of the testes. In 5-10% of testicular cancers, there is a history of cryptorchidism [148]. The risk of a germ cell tumour (GCT) is 3.6-7.4 times higher than in the general population and 2-6% of men with a history of cryptorchidism will develop a testicular tumour [148]. Orchidopexy performed before the age of puberty has been reported to decrease the risk of testicular cancer [149]. However, this and other similar reports are based on retrospective data and do not exclude the possibility that boys undergoing early and late orchidopexy represent different pathogenetic groups of testicular maldescent.

3G.2 Disease management

3G.2.1 Hormonal treatment

Human chorionic gonadotropin or GnRH has been used widely in the past to treat cryptorchidism in childhood. Although 15-20% of retained testes descend during hormonal treatment, one-fifth of these reascend later, which is why hormonal treatment is no longer recommended.

3G.2.2 Surgical treatment

The success rate of surgical treatment for undescended testes is 70-90% [150]. If the spermatic cords or the spermatic vessels are too short to allow proper mobilisation of the testis into the scrotum, a staged orchidopexy (Fowler-Stephenson procedure) can be performed, using open surgery, laparoscopy, or microsurgery. The optimal age for performing orchidopexy is still debated. Some retrospective studies have indicated that early treatment (during the first 2 years of life) has a beneficial effect on preserving future fertility [151], whereas a recent randomised study showed that surgery at 9 months resulted in a partial catch-up of testicular growth until at least age 4 years vs. surgery at 3 years [152]. The results clearly indicate that early surgery has a beneficial effect on testicular growth. Testicular volume is an approximate indirect measure of spermatogenic activity, therefore, it is possible that orchidopexy at an early age might improve future spermatogenesis.

In adulthood, undescended testis should not be removed because it still produces testosterone. Furthermore, as indicated above, correction of bilateral cryptorchidism, even in adulthood, can lead to sperm production in previously azoospermic men [147]. Vascular damage is the most severe complication of orchidopexy and can cause testicular atrophy in 1-2% of cases. In men with non-palpable testes, the postoperative atrophy rate was 12% in those cases with long vascular pedicles that enabled scrotal positioning. Postoperative atrophy in staged orchidopexy has been reported in up to 40% of patients [150].

3G.3 Conclusions and recommendations for cryptorchidism

Conclusions	LE
Cryptorchidism is multifactorial in origin and can be caused by genetic factors and endocrine disruption early in pregnancy.	3
Cryptorchidism is often associated with testicular dysgenesis and is a risk factor for infertility and GCT.	2b
Whether early surgical intervention can prevent germ cell loss is still debatable, but in a randomised study it improved testicular growth in boys treated at the age of 9 months compared to those aged years at the time of orchidopexy.	3
Paternity in men with unilateral cryptorchidism is almost equal to that in men without cryptorchidism.	3
Bilateral cryptorchidism significantly reduces the likelihood of paternity.	3

GCT = germ cell tumour.

Recommendations	GR
Hormonal treatment of cryptorchidism in adults is not recommended.	A
Early orchidopexy (6-12 months of age) might be beneficial for testicular development in adulthood.	B
If undescended testes are corrected in adulthood, testicular biopsy for detection of ITGCNU (formerly CIS) is recommended at the time of orchidopexy.	B

ITGCNU = intratubular germ cell neoplasia of unclassified type.

3H IDIOPATHIC MALE INFERTILITY

No demonstrable cause of infertility is found in at least 44% of infertile men [153].

3H.1 Disease management

3H.1.1 Empirical treatments

A wide variety of empirical drug treatments of idiopathic male infertility have been used. However, there is little scientific evidence for an empirical approach [154]. Clomiphen citrate and tamoxifen have been widely used in idiopathic OAT but there is no proven evidence for their benefit. A recent meta-analysis reported some improvement in sperm quality and spontaneous pregnancy rate [155]. Androgens, hCG/HMG, bromocriptine, alpha-blockers, systemic corticosteroids and magnesium supplementation are not effective in the treatment of OAT syndrome. Follicle-stimulating hormone might be beneficial in a selection of patients [155]. A Cochrane analysis showed that men taking oral antioxidants had an associated significant increase in live birth rate in IVF patients [156] when compared with men taking the control treatment. Concerning natural conception the role of antioxidants needs further investigations [157].

3H.2 Recommendation for idiopathic male infertility

Recommendation	GR
Medical treatment of male infertility is recommended only for cases of hypogonadotrophic hypogonadism.	A

3I MALE CONTRACEPTION

Development of male contraceptive methods is important because up to 40% of women have an unmet need for family planning, with approximately 80 million women every year having unintended or unwanted pregnancies [158]. Three of the four methods of male contraception have been in use for hundreds of years (i.e., condoms, periodic abstinence, and withdrawal). The typical first-year failure rates of traditional male methods are high (withdrawal 19%, periodic abstinence 20%, and condoms 3-14%) compared to the failure rates of 0.1-3% for modern reversible female methods [159]. For men, male contraceptive methods must be acceptable, cheap, reversible, and effective. The method nearest to being generally available clinically is hormonal male contraception, which is based on the suppression of gonadotropins and testosterone substitution to maintain male sexual function and bone mineralisation, and to prevent muscle wasting [160]. Various contraceptive regimens have been developed and tested, including testosterone monotherapy, androgen/progestin combinations, testosterone with GnRH analogues, and selective androgen- and progestin-receptor modulators. There are racial differences in the response to androgens alone. However, a combination of testosterone with progestin results in complete suppression of spermatogenesis in all races, and provides contraceptive efficacy equivalent to female hormonal methods [161].

3I.1 Vasectomy

Vasectomy is an effective method of permanent male surgical sterilisation [162]. Extensive guidelines on vasectomy were published by the EAU in 2012 [2]. Before vasectomy, the couple should be fully informed about the benefits and risks, especially as an Australian telephone survey found that 9.2% of respondents regretted having a vasectomy [163].

3I.1.1 Surgical techniques

Various techniques are available for vasectomy. The least invasive approach is no-scalpel vasectomy [164], which is also associated with a low rate of complications [165]. The most effective occlusion technique is cauterisation of the lumen of the vas deferens and fascial interposition [166-168]. Most techniques can be carried out safely under local anaesthesia in an outpatient clinic.

3I.1.2 Complications

Vasectomy does not significantly alter spermatogenesis and Leydig cell function. The volume of ejaculate remains unchanged. Potential systemic effects of vasectomy, including atherosclerosis, have not been proven, and there is no evidence of a significant increase in any systemic disease after vasectomy. An increased rate of prostate cancer in men who underwent vasectomy has not been detected [162, 169]. Acute local complications associated with vasectomy include haematoma, wound infection, and epididymitis in up to 5% of cases [162]. The potential long-term complications (e.g., chronic testicular pain) [170] must be discussed with the patient before the procedure.

3I.1.3 Vasectomy failure

If an effective occlusion technique is used, the risk of recanalisation after vasectomy should be < 1% [165]. However, patients should be informed preoperatively that, although rare, long-term recanalisation might occur [171]. No motile spermatozoa should be detected 3 months after vasectomy. Persistent motility is a sign of vasectomy failure, and the procedure will need to be repeated. A "special clearance" given by the urologist with non-motile spermatozoa < 100,000/mL is still under discussion [172].

3I.1.4 Counselling

Counselling with regard to vasectomy must address the following aspects:

- Vasectomy should be considered irreversible.
- Vasectomy is associated with a low complication rate; however, because it is an elective operation, even small risks must be explained, because men (and their partners) might wish to consider these before giving consent.
- Vasectomy can fail, although the failure rate is low.
- Couples should be advised to continue with other effective contraception until clearance is confirmed.
- All available data indicate that vasectomy is not associated with any serious, long-term, side-effects [167].
- Vasectomy involving cauterisation and fascial interposition appears to be the most effective technique [165, 166, 168].

3I.2 Vasectomy reversal

A wide range of surgical success rates have been published for vasectomy reversal (up to 90%), depending on the time between vasectomy and re-fertilisation, type of vasectomy (e.g., open-ended or sealed), type

of reversal (vasovasostomy or vasoepididymostomy), and whether reversal was unilateral or bilateral. Microsurgical techniques should be used [173].

31.2.1 **Length of time since vasectomy**

Vasovasostomy results have shown patency rates up to 90%. The longer the interval is from vasectomy to reversal, the lower is the pregnancy rate. In a study of 1,469 men who had undergone microsurgical vasectomy reversal, patency and pregnancy rates were 97% and 76%, respectively, for an interval up to 3 years after vasectomy; 88% and 53% for 3-8 years, 79% and 44% for 9-14 years, and 71% and 30% for > 15 years [174].

31.2.2 **Tubulovasostomy**

The chance of secondary epididymal obstruction after vasectomy increases with time. After an interval of 10 years, 25% of men appear to have epididymal blockage. If secondary epididymal obstruction occurs, tubulovasostomy is needed to reverse the vasectomy (see Chapter 3D) [109].

31.2.3 **Microsurgical vasectomy reversal vs. epididymal or testicular sperm retrieval and ICSI**

According to the calculations of cost per delivery for vasectomy reversal vs. sperm retrieval/ICSI, under a wide variety of initial assumptions, it is clear that vasectomy reversal is associated with a considerably lower cost per delivery and higher delivery rates [106, 175-177]. Sperm retrieval and ICSI must yield an 81% pregnancy rate per cycle to achieve equal costs to vasectomy reversal.

31.3 **Conclusions and recommendations for male contraception**

Conclusions	LE
Vasectomy is considered the gold standard for the male contribution to contraception.	1
All available data indicate that vasectomy is not associated with any serious, long-term side-effects.	1b
Pregnancy is still achievable after successful vasectomy reversal.	2a
Methods of male contraception other than vasectomy are associated with high failure rates or are still experimental (e.g., hormonal approach).	3

Recommendations	GR
Vasectomy meets best the criteria for the male contribution to contraception, with regard to efficacy, safety and side effects. Cauterisation and fascial interposition are the most effective techniques.	A
Patients seeking consultation about vasectomy must be informed about the surgical method, risk of failure, irreversibility, the need for post-procedure contraception until clearance, and the risk of complications.	A*
Microsurgical vasectomy reversal is a low-risk and (cost-) effective method of restoring fertility.	B
MESA/PESA/TESE and ICSI should be reserved for failed vasectomy reversal surgery.	A
For couples wanting to achieve pregnancy, sperm aspiration together with ICSI is a second-line option for selected cases and those with failed vasovasostomy.	B

*Upgraded following panel consensus

MESA = microsurgical epididymal sperm aspiration; PESA = percutaneous epididymal sperm aspiration; TESE = testicular sperm extraction; ICSI = intracytoplasmic sperm injection.

3J **MALE ACCESSORY GLAND INFECTIONS AND INFERTILITY**

Infections of the male urogenital tract are potentially curable causes of male infertility [10, 178, 179]. The WHO considers urethritis, prostatitis, orchitis and epididymitis to be male accessory gland infections (MAGIs) [10]. However, specific data are not available to confirm that these diseases have a negative influence on sperm quality and male fertility in general.

3J.2 Diagnostic evaluation

3J.2.1 Ejaculate analysis

Ejaculate analysis (see Chapter 3A.2) clarifies whether the prostate is involved as part of a generalised MAGI and provides information about sperm quality. In addition, leukocyte analysis allows differentiation between inflammatory and non-inflammatory chronic pelvic pain syndrome (CPPS) (NIH IIa vs. NIH 3B).

3J.2.1.1 Microbiological findings

After exclusion of urethritis and bladder infection, >106 peroxidase-positive white blood cells (WBCs) per millilitre of ejaculate indicate an inflammatory process. In this case, a culture should be performed for common urinary tract pathogens. A concentration of >103 cfu/mL urinary tract pathogens in the ejaculate is indicative of significant bacteriospermia. The sampling time can influence the positive rate of microorganisms in semen and the frequency of isolation of different strains [180]. The ideal diagnostic test for *Chlamydia trachomatis* in semen has not yet been established [181]. In contrast to serological findings in women, antibody tests for *C. trachomatis* in seminal plasma are not indicative if no type-specific methods are used [181].

Ureaplasma urealyticum is pathogenic only in high concentrations (>103 cfu/mL ejaculate). No more than 10% of samples analysed for ureaplasma exceed this concentration [182]. Normal colonisation of the urethra hampers the clarification of mycoplasma-associated urogenital infections, using samples such as the ejaculate [183].

3J.2.1.2 White blood cells

The clinical significance of an increased concentration of leukocytes in the ejaculate is controversial [184]. Infection is indicated only by an increased level of leukocytes. Although leukocytospermia is a sign of inflammation, it is not necessarily associated with bacterial or viral infections [185]. According to WHO classification, leukocytospermia is defined as >106 WBCs/mL. Only two studies have analysed alterations of WBCs in the ejaculate of patients with proven prostatitis [186, 187]. Both studies found more leukocytes in men with prostatitis compared to those without inflammation (CPPS, type NIH 3B).

3J.2.1.3 Sperm quality

The deleterious effects of chronic prostatitis on sperm density, motility and morphology are under debate [179]. All investigations have given contradictory results, and have not confirmed that chronic prostatitis has a decisive role in altering conventional semen parameters [188-190].

3J.2.1.4 Seminal plasma alterations

Seminal plasma elastase is a biochemical indicator of polymorphonuclear lymphocyte activity in the ejaculate [179, 191, 192], with a suggested cut-off level of approximately 600 ng/mL [179]. Various cytokines are involved in inflammation and can influence sperm function. Several studies have investigated the association between interleukin (IL) concentration, leukocytes, and sperm function [193-195], but no correlations have been found. The prostate is the main site of origin of IL-6 and IL-8 in the seminal plasma. Cytokines, especially IL-6, play an important role in the male accessory gland inflammatory process [196]. However, elevated cytokine levels do not depend on the number of leukocytes in expressed prostatic secretion (EPS) [197].

3J.2.1.5 Glandular secretory dysfunction

Infections of the sex glands can impair their excretory function. Decreased quantities of citric acid, phosphatase, fructose, zinc, and α -glutamyl-transferase activity are indicators of disturbed prostatic secretory parameters [179]. Reduced fructose concentration indicates impaired vesicular function [182, 198].

3J.2.1.6 Reactive oxygen species

Reactive oxygen species might be increased in chronic urogenital infections associated with increased leukocyte numbers [199]. However, their biological significance in prostatitis remains unclear [179].

3J.2.2 Disease management

Treatment of chronic prostatitis is usually targeted at relieving symptoms [200, 201]. The aims of therapy for altered semen composition in male adnexitis are:

- reduction or eradication of microorganisms in prostatic secretions and semen;
- normalisation of inflammatory (e.g., leukocytes) and secretory parameters;
- improvement of sperm parameters to counteract fertility impairment [202].

Only antibiotic therapy of chronic bacterial prostatitis (NIH II) has provided symptomatic relief, eradication of microorganisms, and a decrease in cellular and humoral inflammatory parameters in urogenital secretions.

Although antibiotics might improve sperm quality [202], there is no evidence that treatment of chronic prostatitis increases the probability of conception [179, 203].

3J.3 Epididymitis

Inflammation of the epididymis causes unilateral pain and swelling, usually with acute onset. Among sexually active men < 35 years of age, epididymitis is most often caused by *C. trachomatis* or *Neisseria gonorrhoea* [204, 205]. Sexually transmitted epididymitis is usually accompanied by urethritis. Non-sexually transmitted epididymitis is associated with urinary tract infection and occurs more often in men aged > 35 years [206].

3J.3.1 Diagnostic evaluation

3J.3.3.1 Ejaculate analysis

Ejaculate analysis according to WHO criteria, might indicate persistent inflammatory activity. Transiently decreased sperm counts and forward motility are observed [204, 207, 208]. Semen culture might help to identify pathogenic microorganisms. Development of stenosis in the epididymal duct, reduction of sperm count, and azoospermia are more important in the follow-up of bilateral epididymitis (see Chapter 3D).

3J.3.2 Disease management

Antibiotic therapy is indicated before culture results are available.

Treatment of epididymitis results in:

- microbiological cure of infection;
- improvement of clinical signs and symptoms;
- prevention of potential testicular damage;
- prevention of transmission;
- decrease of potential complications (e.g., infertility or chronic pain).

Patients with epididymitis known or suspected to be caused by *N. gonorrhoeae* or *C. trachomatis* must be told to refer their sexual partners for evaluation and treatment [209].

3J.4 Conclusions and recommendations for male accessory gland infections

Conclusions	LE
Urethritis and prostatitis are not clearly associated with male infertility.	3
Antibiotic treatment often only eradicates microorganisms; it has no positive effect on inflammatory alterations, and cannot reverse functional deficits and anatomical dysfunction.	2a
Although antibiotic treatment for MAGI might provide improvement in sperm quality, it does not necessarily enhance the probability of conception.	2a

Recommendation	GR
Patients with epididymitis that is known or suspected to be caused by <i>N. gonorrhoeae</i> or <i>C. trachomatis</i> must be instructed to refer their sexual partners for evaluation and treatment.	B

3K GERM CELL MALIGNANCY AND TESTICULAR MICROCALCIFICATION

3K.1 Germ cell malignancy and male infertility

Testicular germ cell tumour (TGCT) is the most common malignancy in Caucasian men aged 15-40 years, and affects approximately 1% of subfertile men. The lifetime risk of TGCT varies between ethnic groups and countries. The highest annual incidence of TGCT occurs in Caucasians, and varies from 10/100,000 (e.g., in Denmark and Norway) to 2/100,000 (e.g., in Finland and the Baltic countries). Generally, seminomas and non-seminomas are preceded by CIS, and untreated ITGCNU will eventually progress to invasive cancer [210, 211]. The most convincing evidence for a general decline in male reproductive health is the increase in testicular cancer seen in western countries [212]. In almost all countries with reliable cancer registers, the incidence of testicular cancer has increased [213]. Cryptorchidism and hypospadias are associated with an increased risk

of testicular cancer; men with cryptorchidism and/or hypospadias are over-represented among patients with testicular cancer. Men with dysgenetic testes have an increased risk of developing testicular cancer in adulthood. These cancers arise from premalignant gonocytes or CIS cells [214]. Testicular microlithiasis (TM), seen on ultrasound, can be associated with GCT and CIS of the testes.

3K.2 Testicular germ cell cancer and reproductive function

Men with TGCT have decreased semen quality, even before cancer is diagnosed [215]. Orchidectomy implies a risk of azoospermia in these men, with sperm found in the ejaculate before the tumour-bearing testis has been removed. Semen cryopreservation before orchidectomy should therefore be considered (see Chapter 3M). Treatment of TGCT can result in additional impairment of semen quality [216]. In addition to spermatogenic failure, patients with TGCT have Leydig cell dysfunction, even in the contralateral testis [217].

The risk of hypogonadism may therefore be increased in men treated for TGCT. The measurement of pre-treatment levels of testosterone, SHBG, LH and oestradiol might help to anticipate post-treatment hypogonadism. Men who have had TGCT and have low normal androgen levels should receive long-term follow-up because they are at risk of developing hypogonadism as a result of an age-related decrease in testosterone production [218]. The risk of hypogonadism is most pronounced in TGCT patients treated with ≥ 3 cycles of chemotherapy or irradiation of retroperitoneal lymph nodes. However, this risk is greatest at 6-12 months post-treatment. This suggests there may be some improvement in Leydig cell function, and why it is reasonable to expect initiation of androgen replacement, until the patient shows continuous signs of testosterone deficiency, even at 2 years follow-up [219]. The risk of low libido and erectile dysfunction is also increased in TGCT patients [220]. In case of azoospermia, testicular sperm may be recovered to safeguard patient's fertility (Onco-TESE) [221].

3K.3 Testicular microlithiasis

Microcalcification inside the testicular parenchyma can be found in 0.6-9% of men referred for testicular ultrasound [222-225]. Although the true incidence of microcalcification in the general population is unknown, it is probably rare. However, ultrasound findings of TM are common in men with TGCT, cryptorchidism, testicular dysgenesis, infertility, testicular torsion and atrophy, Klinefelter's syndrome, hypogonadism, male pseudohermaphroditism, varicocele, epididymal cysts, pulmonary microlithiasis, and non-Hodgkin's lymphoma. The incidence reported seems to be higher with high-frequency ultrasound machines [226]. The relationship between TM and infertility is unclear, but probably relates to dysgenesis of the testes, with degenerate cells being sloughed inside an obstructed seminiferous tubule and failure of the Sertoli cells to phagocytose the debris. Subsequently, calcification occurs. Testicular microlithiasis is found in testes at risk of malignant development. The reported incidence of TM in men with TGCT is 6-46% [227-229]. TM should therefore be considered premalignant. Testicular biopsies from men with TM have found a higher prevalence of CIS, especially in those with bilateral microlithiasis [230]. However, TM is found most often in men with a benign testicular condition and the microcalcification itself is not malignant. Further investigation of the association between TM and CIS will require testicular biopsies in large series of men without signs of TGCT. However, available data indicate that men in whom TM is found by ultrasound, and who have an increased risk of TGCT, should be offered testicular biopsy for detection of CIS. The list of high-risk patients includes men with infertility and bilateral TM, atrophic testes, undescended testes, a history of TGCT, and contralateral TM [231].

3K.4 Recommendations for germ cell malignancy and testicular microcalcification

Recommendations	GR
As for all men, patients with TM and without special risk factors (see below) should be encouraged to perform self-examination because this might result in early detection of TGCT.	B
Testicular biopsy should be offered to men with TM, who belong to one of the following high-risk groups: infertility and bilateral TM, atrophic testes, undescended testes, a history of TGCT, or contralateral TM.	B
If there are suspicious findings on physical examination or ultrasound in patients with TM and associated lesions, surgical exploration with testicular biopsy or orchidectomy should be considered.	B
Testicular biopsy, follow-up scrotal ultrasound, routine use of biochemical tumour markers, or abdominal or pelvic CT, are not justified in men with isolated TM without associated risk factors (e.g. infertility, cryptorchidism, testicular cancer, and atrophic testis).	B
Men with TGCT are at increased risk of developing hypogonadism and sexual dysfunction and should therefore be followed up.	B

TM = testicular microlithiasis; TGCT = testicular germ cell tumour; CT = computed tomography.

3L DISORDERS OF EJACULATION

Disorders of ejaculation are uncommon, but important causes of male infertility.

3L.1 Classification and aetiology

3L.1.1 *Anejaculation*

Anejaculation involves complete absence of antegrade or retrograde ejaculation. It is caused by failure of semen emission from the seminal vesicles, prostate and ejaculatory ducts into the urethra [232]. True anejaculation is usually associated with a normal orgasmic sensation. True anejaculation is always associated with central or peripheral nervous system dysfunction or with drugs [233] (Table 6).

3L.1.2 *Anorgasmia*

Anorgasmia is the inability to reach orgasm and can give rise to anejaculation. Anorgasmia is often a primary condition and its cause is usually psychological.

3L.1.3 *Delayed ejaculation*

In delayed ejaculation, abnormal stimulation of the erect penis is needed to achieve orgasm with ejaculation [232]. Delayed ejaculation can be considered a mild form of anorgasmia. The causes of delayed ejaculation can be psychological, organic (e.g. incomplete spinal cord lesion [234] or iatrogenic penile nerve damage [235]), or pharmacological (e.g. selective serotonin re-uptake inhibitors (SSRIs), antihypertensives, or antipsychotics) [236].

3L.1.4 *Retrograde ejaculation*

Retrograde ejaculation is the total, or sometimes partial, absence of antegrade ejaculation as a result of semen passing backwards through the bladder neck into the bladder. Patients experience a normal or decreased orgasmic sensation. The causes of retrograde ejaculation can be divided into neurogenic, pharmacological, urethral, or bladder neck incompetence (Table 6).

Table 6: Aetiology of anejaculation and retrograde ejaculation

Neurogenic	Pharmacological
Spinal cord injury	Antihypertensives
Cauda equina lesions	α 1-adrenoceptor antagonists
Multiple sclerosis	Antipsychotics and antidepressants
Autonomic neuropathy (diabetes mellitus)	Alcohol
Retroperitoneal lymphadenectomy	
Sympathectomy or aortoiliac surgery	
Colorectal and anal surgery	
Parkinson's disease	
Urethral	Bladder neck incompetence
Ectopic ureterocele	Congenital defects/dysfunction of hemitrigone
Urethral stricture	Bladder extrophy
Urethral valves or verumontanum hyperplasia	Bladder neck resection (transurethral resection of the prostate)
Congenital dopamine β -hydroxylase deficiency	Prostatectomy

3L.1.5 *Asthenic ejaculation*

Asthenic ejaculation is characterised by an altered propulsive phase, with a normal emission phase [236]. The orgasmic sensation is reduced and the typically rhythmical contractions associated with ejaculation are missing. Asthenic ejaculation does not usually affect semen quality.

3L.1.6 *Premature ejaculation*

The International Society for Sexual Medicine (ISSM) has adopted the first evidence-based definition of lifelong premature ejaculation (PE): "Premature ejaculation is a male sexual dysfunction characterised by ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration; and inability to delay ejaculation on all or nearly all vaginal penetrations; and negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy". Premature ejaculation may be strictly organic (e.g., prostatitis-related) or psychogenic, partner-related or non-selective, and can be associated with

erectile dysfunction. It does not impair fertility, provided intravaginal ejaculation occurs.

3L.2 Diagnostic evaluation

Diagnostic management includes the following recommended procedures.

3L.2.1 Clinical history

The patient must be carefully checked for diabetes, neuropathy, trauma, urogenital infection, previous surgery, and medication. Particular attention must be paid to the characteristics of micturition and ejaculation (presence of nocturnal emission, ejaculatory ability in given circumstances, and primary or acquired disorder), as well as to psychosexual aspects.

3L.2.2 Physical examination

Genital and rectal examinations are conducted, including evaluation of the prostate, bulbocavernosus reflex and anal sphincter tone.

3L.2.3 Post-ejaculatory urinalysis

Post-ejaculatory urinalysis of centrifuged urine can be used to determine if there is total or partial retrograde ejaculation.

3L.2.4 Microbiological examination

Initial, mid-stream urine, EPS, and/or urine after prostatic massage are cultured for evidence of prostatic infection. In cases of increased leukocytes in semen, semen culture or biochemical infection marker tests are also suggested [237].

3L.2.5 Optional diagnostic work-up

This diagnostic work-up can include:

- neurophysiological tests (bulbocavernosus evoked response and dorsal nerve somatosensory evoked potentials);
- tests for autonomic neuropathy;
- psychosexual evaluation;
- videocystometry;
- cystoscopy;
- transrectal ultrasonography;
- uroflowmetry;
- vibratory stimulation of the penis.

3L.3 Disease management

Infertility caused by disorders of ejaculation is seldom treated on the basis of aetiology. Treatment usually involves retrieval of spermatozoa for use in assisted reproduction techniques (ARTs). The following aspects must be considered when selecting treatment:

- Age of patient and his partner.
- Psychological problems of the patient and his partner.
- Couple's willingness and acceptance of different fertility procedures.
- Associated pathology.
- Psychosexual counselling.

3L.3.1 Aetiological treatment

If possible, any pharmacological treatment that is interfering with ejaculation should be stopped. In painful ejaculation, tamsulosin can be administered during antidepressant treatment [238]. Treatment should be given for urogenital infections (i.e., in case of painful ejaculation) [237]. Dapoxetine is an SSRI that has been introduced for the therapy of PE [239], because it appears that PE is related to serotonin levels. Psychotherapy is usually not very effective.

3L.3.2 Symptomatic treatment

3L.3.2.1 Premature ejaculation

Premature ejaculation can be treated with the SSRI dapoxetine or topical anaesthetic agents to increase intravaginal ejaculation latency time, behavioural therapy, and/or psychotherapy.

3L.3.2.2 Retrograde ejaculation

In the absence of spinal cord injury, anatomical anomalies of the urethra, or pharmacological agents, drug treatment must be used to induce antegrade ejaculation (Table 7). Alternatively, the patient can be encouraged to ejaculate when his bladder is full to increase bladder neck closure [240].

Table 7: Drug therapy for retrograde ejaculation

Drug	Dosage regimen	Ref.
Ephedrine sulphate	10-15 mg four times daily	[241]
Midodrine	5 mg three times daily	[242]
Brompheniramine maleate	8 mg twice daily	[243]
Imipramine	25-75 mg three times daily	[244]
Desipramine	50 mg every second day	[245]

Sperm collection from post-orgasmic urine for use in ART is recommended if:

- drug treatment is ineffective or intolerable as a result of side-effects;
- the patient has a spinal cord injury;
- drug therapy inducing retrograde ejaculation cannot be interrupted.

If the biological sperm preparation is not of sufficient quality for intrauterine insemination, the couple must undergo in vitro reproductive procedures (e.g. ICSI). In the case of insufficient drug therapy, testicular (TESE or PESA) or epididymal (MESA) sperm retrieval techniques can be used for assisted reproduction.

3L.3.2.3 Anejaculation

Drug treatment for anejaculation caused by lymphadenectomy and neuropathy, or psychosexual therapy for anorgasmia is not very effective. In all these cases, and in men who have a spinal cord injury, vibrostimulation (i.e., application of a vibrator to the penis) is first-line therapy. In anejaculation, vibrostimulation evokes the ejaculation reflex [246], which requires an intact lumbosacral spinal cord segment. If the quality of semen is poor, or ejaculation is retrograde, the couple may enter an IVF programme. If vibrostimulation has failed, electro-ejaculation can be the therapy of choice [247]. When electro-ejaculation fails or cannot be carried out, sperm can be retrieved from the seminal ducts by aspiration from the vas deferens [248] (see Chapter 3D) or seminal tract washout [249]. TESE can then be used [237, 250]. Anejaculation following either surgery for testicular cancer or total mesorectal excision can be prevented using monolateral lymphadenectomy or autonomic nerve preservation [250], respectively.

3L.4 Conclusion and recommendations for disorders of ejaculation

Conclusion	LE
Ejaculation disorders can be treated using a wide range of drugs and physical stimulation, with a high level of efficacy.	3

Recommendations	GR
Aetiological treatments for ejaculatory disorders should be offered before sperm collection and ART are performed.	B
Premature ejaculation can be treated successfully with either topical anaesthetic creams or SSRIs.	A
In men with spinal cord injury, vibrostimulation and electro-ejaculation are effective methods of sperm retrieval.	B

ART = assisted reproduction technique; SSRIs = selective serotonin reuptake inhibitors.

3M SEMEN CRYOPRESERVATION

Cryopreservation is the storage of biological material at subzero temperatures [e.g., -80 or -196°C (the boiling point of liquid nitrogen)], at which biochemical processes of cell metabolism are slowed or interrupted. At -196°C, the biochemical reactions that lead to cell death are stopped.

3M.1 Indications for storage

Storage of sperm is available in many clinics for the following indications:

- Before potentially sterilising chemotherapy or radiotherapy for cancer [251] or for non-malignant diseases.
- Before surgery that might interfere with fertility (e.g. bladder neck surgery in a younger man or removal of a testicle in a man with testicular malignancy, or before vasectomy or transgender surgery).
- For men with progressive decrease in semen quality as a result of diseases that have an associated risk of subsequent azoospermia (i.e., pituitary macroadenoma, craniopharyngioma, empty sella syndrome, chronic nephropathy, uncontrolled diabetes mellitus, and multiple sclerosis).
- For men with paraplegia when sperm have been obtained by electro-ejaculation or obtained by penile vibratory stimulation.
- For men with psychogenic anejaculation, after sperm have been obtained either by electro-ejaculation or a sperm retrieval procedure.
- After gonadotropin treatment has induced spermatogenesis in men with hypogonadotrophic hypogonadism.
- For men with NOA, the chance of finding sperm using micro-TESE is ~50%.

Cryopreservation can be used for sperm collected through TESE, avoiding repeated sperm retrieval procedures and unnecessary hyperstimulation of the female partner.

- In any situation in which sperm have been obtained by a sperm retrieval procedure (e.g., after failed vasectomy reversal, or in some cases of epididymal obstruction not amenable to surgery).
- For storage of donor sperm, because cryopreservation reduces the risk of transmission of infection from sperm donors. According to the European directives 2004/23 EC and 2006/17 EC fresh sperm are no longer to be used for non-partner donations.

3M.2 Precautions and techniques

3M.2.1 *Freezing and thawing process*

The cryopreservation techniques currently used are not yet optimal because damage occurs to cells during cryopreservation and prolonged storage. Most damage occurs during freezing and thawing. Major causes of damage during freezing are ice crystal formation and cell dehydration, which disrupt the cell wall and intracellular organelles. Sperm morphology, motility and vitality decrease significantly after thawing, and cryopreservation increases the damage done to sperm DNA [252-255]. Further damage can be caused by contamination of samples with microorganisms and high levels of superoxide radicals [256, 257]. To reduce ice crystal formation, a cryopreservation solution is added before freezing. Various cryopreservation solutions are available commercially, most of which contain varying proportions of glycerol and albumin. After freezing, the samples are immersed in liquid nitrogen.

Several techniques have been developed to try to reduce damage caused by freezing and thawing, including:

- One-step freezing method [258, 259]: sample is held in the vapour phase for 10 min before being plunged into liquid nitrogen.
- Slow or multi-step method [260]: sample is gradually cooled in the vapour phase for approximately 40 min. A programmable automatic freezing machine, which is preset to cool at a rate of 1-10°C/min is used.

The method available depends on the resources of the laboratory. Whichever freezing technique is used, it should be tested using donor sperm and post-thaw examination, and should regularly undergo a quality-control programme. The likelihood of sperm survival decreases with repeated freezing and thawing. The maximum viable storage time for human sperm is not known.

3M.2.2 *Cryopreservation of small numbers of sperm*

Standard cryopreservation in straws is an efficient way of storing large numbers of sperm (e.g., for a donor insemination programme). However, in micro-TESE, few sperm might be obtained, and the choice is either to freeze testicular tissue and find sperm after thawing the tissue, or to freeze small numbers of sperm. If sperm are frozen in straws, it can be difficult to find any sperm after thawing. Instead, the sperm should be frozen in a pellet [261] or in a container [262].

3M.2.3 *Testing for infections and preventing cross-contamination*

Sperm storage in straws is used extensively. Large numbers of straws are stored in canisters, with the straws being bathed in a pool of liquid nitrogen. Microbial contamination of the pool of liquid nitrogen results in

contamination of the outside of all the straws [263]. The most widely used safeguard is to use so-called high security closed straws. According to the European directives 2004/23 and 2006/17, samples should be tested for hepatitis B and C and human immunodeficiency virus (HIV). In case of non-partner donation, samples are also tested for C. Trachomatis (by Nucleic Acid Testing [NAT]) and syphilis, as well as genetics, that is, karyotype and most prevalent genetic disorders in the population to which the non-partner donor belongs. Until the test results are known, samples must be stored in an individual quarantine vessel (separate storage). If open straws are used (e.g., for vitrification purposes) some laboratories use the additional safeguard of double-wrapping the straws before freezing, although this is more costly. Some centres carry out cytomegalovirus testing and store negative and positive samples separately. Considerable ethical issues surround the storage of samples before cancer chemotherapy in men who are hepatitis-virus- or HIV-positive. Few clinics have separate storage facilities for HIV-positive samples. However, the success of antiretroviral treatment is increasing the number of HIV-positive men who may wish to store sperm. There is also concern about HIV transmission to children conceived using HIV-positive sperm, because sperm-washing techniques fail in ~5% of cases.

3M.2.4 **Fail-safe precautions to prevent loss of stored materials**

Any laboratory that undertakes long-term storage of human biological materials should have procedures that guard against accidental loss of material caused by storage vessel failure. This is particularly important for sperm stored before potentially sterilising cancer chemotherapy, because these patients may not be able to obtain further sperm.

3M.2.5 **Orphan samples**

In malignancy and some other situations, several years might pass before stored samples are required. Inevitably, during this time, the owners of some samples might disappear or die, leaving behind orphan samples for which the owner is no longer contactable. The duty of the laboratory and the legal ownership of these samples can create considerable problems.

3M.3 **Biological aspects**

Cryopreservation induces deterioration of semen quality. After the sample has been thawed, motility [264] and morphology [265, 266] are worsened, including mitochondrial acrosomal and sperm tail damage [255]. Sperm freezing decreases motility by 31% and mitochondrial activity by 36%, and causes morphological disruption in 37% of sperm [258]. Motility is correlated best with IVF capacity of the thawed sample. Further improvement can be achieved by selecting the subpopulation of sperm with the best motility and DNA integrity and freezing these sperm in seminal plasma [261].

3M.4 **Conclusions and recommendations for semen cryopreservation**

Conclusions	LE
The purpose of sperm cryopreservation is to enable future assisted reproduction techniques procedures.	1b
Cryopreservation techniques are not optimal, and future efforts are needed to improve the outcome of sperm banking.	3

Recommendations	GR
Cryopreservation of semen should be offered to all men who are candidates for chemotherapy, radiation or surgical interventions that might interfere with spermatogenesis or cause ejaculatory disorders.	A
If testicular biopsies are indicated, sperm cryopreservation is strongly advised.	A
If cryopreservation is not available locally, patients should be advised about the possibility of visiting, or transferring to, the nearest cryopreservation unit before therapy starts.	C
Consent for cryopreservation should include a record of the man's wishes for his samples if he dies or is otherwise untraceable.	C
Precautions should be taken to prevent transmission of viral, sexually transmitted or any other infection by cryostored materials from donor to recipient, and to prevent contamination of stored samples. These precautions include testing of the patient and the use of rapid testing and quarantine of samples until test results are known. Samples from men who are positive for hepatitis virus or HIV should not be stored in the same container as samples from men who have been tested and are free from infection.	C

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5. CONFLICT OF INTEREST

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Guidelines on **Male Hypogonadism**

G.R. Dohle (Chair), S. Arver, C. Bettocchi,
T.H. Jones, S. Kliesch, M. Punab

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1. INTRODUCTION

1.1 Aim

Androgens play a crucial role in the development and maintenance of male reproductive and sexual functions, body composition, bone health, and behaviour. Low levels of circulating androgens in utero can cause disturbances in male sexual development, resulting in congenital abnormalities of the male reproductive tract. Later in life, this may cause reduced fertility, sexual dysfunction, decreased muscle formation and bone mineralisation, disturbances of fat metabolism, and cognitive dysfunction. Testosterone levels decrease slightly as a process of ageing: signs and symptoms caused by this decline can be considered a normal part of ageing. However, low testosterone levels are also associated with obesity and several chronic diseases, and some symptomatic patients may benefit from testosterone treatment. This document presents the European Association of Urology (EAU) Guidelines on the diagnosis and treatment of male hypogonadism, with the aim to provide practical recommendations on how to deal with primary hypogonadism and ageing-related decline in testosterone in male patients, as well as the treatment of testosterone deficiencies.

1.2 Publication history

The present Male Hypogonadism Guidelines are a revision of the first edition of the EAU Guidelines on Male Hypogonadism published in 2012.

This 2015 version has been updated and re-formatted according to the EAU template for non-oncology Guidelines, so that all Guidelines follow a similar format.

A quick reference document (pocket guidelines) is available, both in print and in a number of versions for mobile devices, presenting the main findings of the Male Hypogonadism Guidelines. These are abridged versions which may require consultation together with the full text versions. All available material can be viewed and downloaded for personal use at the EAU website. The EAU website also includes a selection of EAU guidelines articles as well as translations produced by national urological associations:
<http://www.uroweb.org/guidelines/online-guidelines/>.

This document was peer-reviewed prior to publication.

1.3 Panel composition

The EAU Male Hypogonadism Panel consists of a multidisciplinary group of experts, including urologists specialising in the treatment of infertility, endocrinologists and andrologists.

2. METHODS

References used in this text are graded according to their Level of Evidence (LE) and Guidelines are given a Grade of Recommendation (GR). In this 2015 EAU Guidelines compilation, all standard information on LE and GR has been taken out of the individual Guidelines topics for the sake of brevity. The methodology section (see the introduction chapter of the complete book) outlines the LE and GR criteria which are used throughout the Guidelines, according to a classification system modified from the Oxford Centre for Evidence-based Medicine Levels of Evidence.

The recommendations provided in the current guidelines are based on a systematic literature search and review performed by the panel members. MedLine, Embase and Cochrane databases were searched to identify original articles and review articles. The controlled vocabulary of the Medical Subject Headings (MeSH) database was used alongside a 'free-text' protocol, combining 'male hypogonadism' with the terms 'diagnosis', 'epidemiology', 'investigations', 'treatment', 'testosterone', 'androgens' and 'hypogonadism'. All articles published before November 2014 were considered for review. The expert panel reviewed these records and selected articles with the highest level of evidence in accordance with a rating schedule adapted from the Oxford Centre for Evidence-Based Medicine levels of evidence.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Definition: male hypogonadism is a clinical syndrome caused by androgen deficiency which may adversely affect multiple organ functions and quality of life (QoL) [1].

Androgen deficiency increases slightly with age also in healthy men [2, 3]. In middle-aged men, the incidence of biochemical hypogonadism varies from 2.1-12.8% [4]. The incidence of low testosterone and symptoms of hypogonadism in men aged 40-79 varies from 2.1-5.7% [3, 4]. Hypogonadism is more prevalent in older men, in men with obesity, those with co-morbidities, and in men with a poor health status.

3.1.1 *Role of testosterone for male reproductive health*

Androgens, which are produced by the testis and by the adrenal glands, play a pivotal role in male reproductive and sexual function. Androgens are crucial for the development of male reproductive organs, such as the epididymis, vas deferens, seminal vesicle, prostate and penis. In addition, androgens are needed for puberty, male fertility, male sexual function, muscle formation, body composition, bone mineralisation, fat metabolism, and cognitive functions [5].

3.2 Physiology

Male sexual development starts between the 7th and 12th week of gestation. The undifferentiated gonads develop into a foetal testis through expression of multiple genes located on the short arm of the Y chromosome, including the sex-determining region of the Y chromosome (SRY gene complex) and the SOX genes on chromosome 17 [6]. The foetal testis produces three hormones: testosterone, insulin-like peptide 3 (INSL3) and anti-Müllerian hormone (AMH). Testosterone is needed for the stabilisation of the Wolffian ducts, resulting in formation of the epididymis, vas deferens and seminal vesicle. AMH activity results in regression of the Müllerian ducts (Figure 1). INSL3 and AMH regulate testicular descent.

Under the influence of intratesticular testosterone, the number of gonocytes per tubule increases threefold during the foetal period [7]. In addition, testosterone is needed for development of the prostate, penis and scrotum. However, in these organs testosterone is converted into the more potent metabolite 5 α -dihydrotestosterone (DHT) by the enzyme 5 α -reductase. Testosterone and DHT are required for penile growth, both activating the androgen receptor [8].

Intratesticular testosterone is needed to maintain the spermatogenic process and to inhibit germ cell apoptosis [9]. The seminiferous tubules of the testes are exposed to concentrations of testosterone 25-100 times greater than circulating levels. Suppression of gonadotrophins (e.g. through excessive testosterone abuse) results in a reduced number of spermatozoa in the ejaculate and hypospermatogenesis [10]. Complete inhibition of intratesticular testosterone results in full cessation of meiosis up to the level of round spermatids [11, 12]. Testosterone does not appear to act directly on the germ cells, but functions through the Sertoli cells by expression of the androgen receptor (AR) and influencing the seminiferous tubular microenvironment [11]. Testosterone can also be metabolised into oestradiol by aromatase, present in fat tissue, the prostate, the testes and bone. Oestradiol is essential for bone mineralisation, also in men [13]. The production of testosterone is controlled in the foetus by placental choriongonadotropin (hCG) and after birth by luteinising hormone (LH) from the pituitary gland. Immediately after birth, serum testosterone levels reach adult concentrations over several months (minipuberty). Thereafter and until puberty, testosterone levels are low, thus preventing male virilisation. Puberty starts with the production of gonadotrophins, initiated by gonadotrophin-releasing hormone (GnRH) secretion from the hypothalamus and resulting in testosterone production, male sexual characteristics and spermatogenesis [14]. Figure 1 shows the development of the male reproductive system.

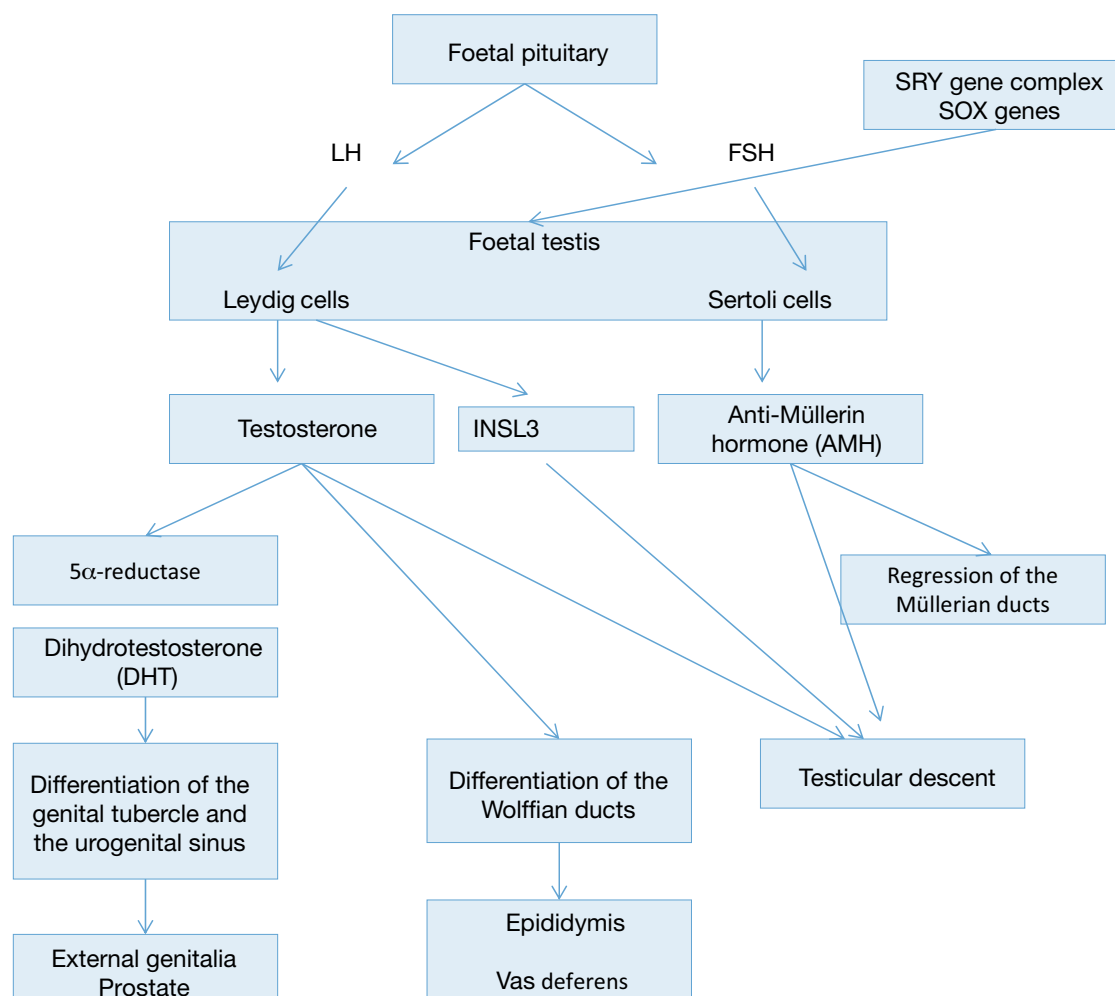
3.2.1 *The androgen receptor*

Testosterone exerts its action through the AR, located in the cytoplasm and nucleus of target cells. During the foetal period, testosterone increases the number of ARs by increasing the number of cells with the AR, but also by increasing the number of ARs in each individual cell [8, 13]. The AR gene is located on the X chromosome (Xq 11-12): defects and mutations in the AR gene can result in male sexual maldevelopment, which may cause testicular feminisation or low virilisation (i.e. disorder of sexual development [DSD]). Less severe mutations in the AR gene may cause mild forms of androgen resistance and male infertility [15]. In exon 1 of the gene, the transactivation domain consists of a trinucleotide tract (cytosine-adenine-guanine [CAG-repeats]) of variable length. Androgen sensitivity may be influenced by the length of the CAG repeats in exon 1 of the AR gene

[15]. The AR CAG repeat length is inversely correlated with serum total and bioavailable testosterone and oestradiol in men. Shorter repeats have been associated with an increased risk for prostate disease, and longer repeats with reduced androgen action in several tissues [16]. CAG repeat number may influence androgenic phenotypical effects, even in case of normal testosterone levels [17].

Conclusion
Testosterone is essential for normal male development.

Figure 1: Development of the male reproductive system



FSH = follicle-stimulating hormone; LH = luteinising hormone; SRY = sex determining region of the Y chromosome; INSL3= insulin-like peptide 3.

3.3 Aetiology

Hypogonadism results from testicular failure, or is due to the disruption of one or several levels of the hypothalamic-pituitary-gonadal axis (Figure 2).

Male hypogonadism can be classified in accordance with disturbances at the level of:

- the testes (primary hypogonadism);
- the hypothalamus and pituitary (secondary hypogonadism);
- the hypothalamus/pituitary and gonads (hypogonadism in adult men);
- androgen target organs (androgen insensitivity/resistance).

3.4 Classification

3.4.1 Male hypogonadism of testicular origin (primary hypogonadism)

Primary testicular failure is the most frequent cause of hypogonadism and results in low testosterone levels, impairment of spermatogenesis and elevated gonadotrophins. The most important clinical forms of primary hypogonadism are Klinefelter syndrome and testicular tumours.

- Klinefelter syndrome affects 0.2% of the male population. It is the most frequent form of male

hypogonadism and the most common numerical chromosomal aberration, with 47,XXY in 90% of cases [18]. It arises due to non-disjunction during paternal or maternal meiotic division of germ cells [19].

- Testicular tumours are the most frequent type of cancer in young males after puberty. Risk factors are contralateral germ cell cancer, maldescended testes, gonadal dysgenesis, infertility, testicular atrophy and familial germ cell cancer. Twenty-five per cent of men with testicular tumours develop testosterone deficiency after treatment [20-22].

The main reasons for primary testicular failure are summarised in Table 1.

3.4.2 **Male hypogonadism of hypothalamic-hypopituitary origin (secondary hypogonadism)**

Central defects of the hypothalamus or pituitary cause secondary testicular failure. Identifying secondary hypogonadism is of clinical importance, as it can be a consequence of pituitary pathology (including prolactinomas) and can cause infertility, which can be restored by hormonal stimulation in most patients with secondary hypogonadism.

The most relevant forms of secondary hypogonadism are:

- *Hyperprolactinemia* (HP), caused by prolactin-secreting pituitary adenomas (prolactinomas) (microprolactinomas < 10 mm in diameter vs. macroprolactinomas) or drug-induced (by dopamine-antagonistic effects of substances such as phenothiazine, imipramine, risperidone and metoclopramide); additional causes may be chronic renal failure or hypothyroidism.
- *Isolated* (formerly termed idiopathic) *hypogonadotrophic hypogonadism* (IHH).
- *Kallmann syndrome* (hypogonadotrophic hypogonadism with anosmia, genetically determined, prevalence one in 10,000 males).

These disorders are characterised by disturbed hypothalamic secretion or action of GnRH, as a pathophysiology common to the diseases, resulting in impairment of pituitary LH and FSH secretion. An additional inborn error of migration and homing of GnRH-secreting neurons results in Kallmann syndrome [23, 24]. The most important symptom is the constitutional delay of puberty: it is the most common cause of delayed puberty (pubertas tarda) [25]. Other rare forms of secondary hypogonadism are listed in Table 2.

3.4.3 **Male hypogonadism due to mixed dysfunction of hypothalamus/pituitary and gonads**

Combined primary and secondary testicular failure results in low testosterone levels and variable gonadotrophin levels. Gonadotrophin levels depend on the predominant primary or secondary failure. This form is also known as late-onset hypogonadism and age-related hypogonadism [26, 27].

3.4.4 **Male hypogonadism due to defects of androgen target organs**

These forms are primarily rare defects and will not be further discussed in detail in these guidelines. There are AR defects with complete, partial and minimal androgen insensitivity syndrome; Reifenstein syndrome; bulbospinal muscular atrophy (Kennedy disease); as well as 5 α -reductase deficiency (for a review, see Nieschlag et al. 2010) [28].

The classification of hypogonadism has therapeutic implications. In patients with secondary hypogonadism, hormonal stimulation with hCG and FSH or alternatively pulsatile GnRH treatment can restore fertility in most cases [29, 30]. Detailed evaluation may for example detect pituitary tumours, systemic disease, or testicular tumours. Combined forms of primary and secondary hypogonadism can be observed in ageing men, mostly obese, with a concomitant age-related decline in testosterone levels resulting from defects in testicular as well as hypothalamic-pituitary function.

Table 1: Most common forms of primary hypogonadism

Disease	Pathophysiology
Maldescended or ectopic testes	Failure of testicular descent, maldevelopment of the testis
Testicular cancer	Testicular maldevelopment
Orchitis	Viral or unspecific orchitis
Acquired anorchia	Trauma, tumour, torsion, inflammation, iatrogenic, surgical removal
Secondary testicular dysfunction	Medication, drugs, toxins, systemic diseases
(Idiopathic) testicular atrophy	Male infertility (idiopathic or specific causes)
Congenital anorchia (bilateral in 1 in 20,000 males, unilateral 4 times as often)	Intrauterine torsion is the most probable cause
Klinefelter syndrome 47,XXY	Sex-chromosomal non-disjunction in germ cells
46,XY disorders of sexual development (DSD) (formerly male pseudohermaphroditism)	Disturbed testosterone synthesis due to enzymatic defects of steroid biosynthesis (17,20- lyase defect, 17-hydroxysteroid dehydrogenase defect)
Gonadal dysgenesis (synonym 'streak gonads')	XY gonadal dysgenesis can be caused by mutations in different genes
46,XX male syndrome (prevalence of 1 in 10,000-20,000)	Males with presence of genetic information from the Y chromosome after translocation of a DNA segment of the Y to the X chromosome during paternal meiosis
Noonan syndrome (prevalence of 1 in 1,000 to 1 in 5,000)	Short stature, congenital heart diseases, cryptorchidism
Inactivating LH receptor mutations, Leydig cell hypoplasia (prevalence of 1 in 1,000,000 to 1 in 20,000)	Leydig cells are unable to develop due to the mutation [31]

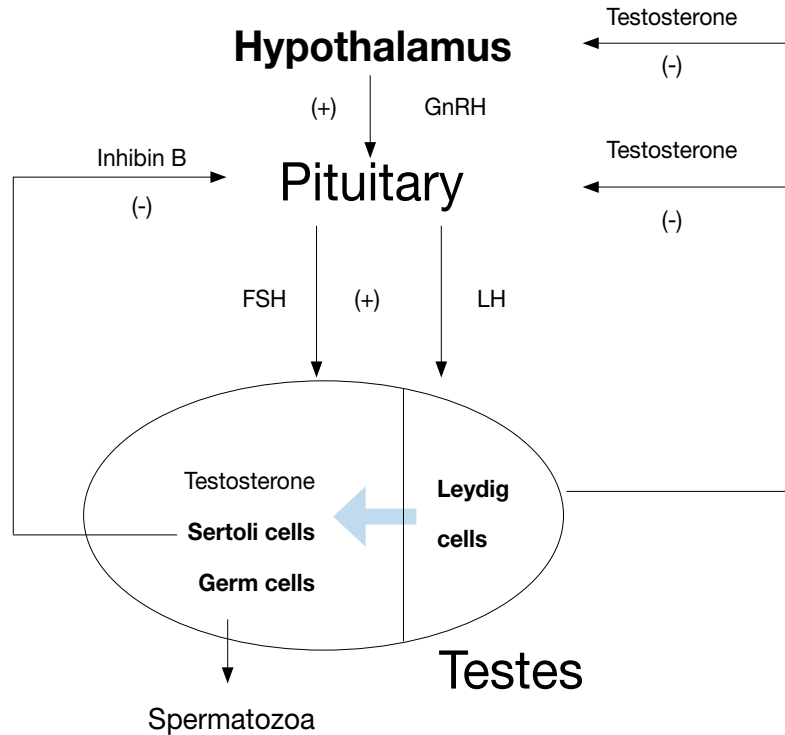
Table 2: Most common forms of secondary hypogonadism

Disease	Pathophysiology
Hyperprolactinemia	Prolactin-secreting pituitary adenomas (prolactinomas) or drug-induced
Isolated hypogonadotrophic hypogonadism (IHH) (formerly termed idiopathic hypogonadotrophic hypogonadism)	SGnRH deficiency specific (or unknown) mutations affecting GnRH synthesis or action
Kallmann syndrome (hypogonadotrophic hypogonadism with anosmia) (prevalence 1 in 10,000)	GnRH deficiency and anosmia, genetically determined
Secondary GnRH deficiency	Medication, drugs, toxins, systemic diseases
Hypopituitarism	Radiotherapy, trauma, infections, haemochromatosis and vascular insufficiency or congenital
Pituitary adenomas	Hormone-secreting adenomas; hormone-inactive pituitary adenomas; metastases to the pituitary or pituitary stalk
Prader-Willi syndrome (PWS) (formerly Prader-Labhart-Willi syndrome) (prevalence 1 in 10,000 individuals)	Congenital disturbance of GnRH secretion
Congenital adrenal hypoplasia with hypogonadotrophic hypogonadism (prevalence 1 in 12,500 individuals)	X-chromosomal recessive disease, in the majority of patients caused by mutations in the DAX1 gene
Pasqualini syndrome	Isolated LH deficiency

Recommendation	LE	GR
The two forms of hypogonadism (primary and secondary) have to be differentiated (LH levels), as this has implications for patient evaluation and treatment and makes it possible to identify patients with associated health problems and infertility.	1b	B

LH = luteinising hormone.

Figure 2: The hypothalamic-pituitary-testes axis



FSH = follicle-stimulating hormone; GnRH = Gonadotrophin-releasing hormone; LH = luteinising hormone.

4. DIAGNOSTIC EVALUATION

Hypogonadism is diagnosed on the basis of persistent signs and symptoms related to androgen deficiency and assessment of consistently low testosterone levels (at least on two occasions) with a reliable method [4, 32-35].

4.1 Clinical symptoms

Low levels of circulating androgens may be associated with signs and symptoms (Table 3) [4, 36, 37]

Table 3: Clinical symptoms and signs suggestive for androgen deficiency

Delayed puberty
Small testes
Male-factor infertility
Decreased body hair
Gynaecomastia
Decrease in lean body mass and muscle strength
Visceral obesity
Decrease in bone mineral density (osteoporosis) with low trauma fractures
Reduced sexual desire and sexual activity
Erectile dysfunction
Fewer and diminished nocturnal erections
Hot flushes
Changes in mood, fatigue and anger
Sleep disturbances
Metabolic syndrome
Insulin resistance and type 2 diabetes mellitus
Diminished cognitive function

The most prevalent symptoms of male hypogonadism in ageing men are reduced sexual desire and sexual activity, erectile dysfunction, and hot flushes [4, 37]. Other factors found associated with low testosterone were waist circumference and health status [4]. Signs and symptoms of androgen deficiency vary depending on age of onset, duration and the severity of the deficiency. Reference ranges for the lower normal level of testosterone (2.5%) have recently been compiled from three large community-based samples, suggesting a cut-off of 12.1 nmol/L for total serum testosterone and for free testosterone 243 pmol/L, to distinguish between normal levels and levels possibly associated with deficiency [36]. Symptoms suggesting the presence of hypogonadism [4, 37] are summarised in Table 3. It should however be noted that these symptoms are also found in men with normal testosterone levels and may have other causes than androgen deficiency.

In men aged 40-79 years, the threshold for total testosterone was 8 nmol/L for decreased frequency of sexual thoughts, 8.5 nmol/L for erectile dysfunction, 11 nmol/L for decreased frequency of morning erections and 13 nmol/L for diminished vigour [38]. The strongest predictor for hypogonadism in this age group was three sexual symptoms (decreased sexual thoughts, weakened morning erections, erectile dysfunction) and either a total testosterone level of < 8 nmol/L or serum testosterone in the range of 8-11 nmol/L and free testosterone < 220 pmol/L. These data are based on serum samples taken in the morning, when mean levels are highest and most reproducible in younger men [39]. Both immunoassay and mass spectrometry based assays can produce valid results, as long as they are well-validated. Evaluation should be based on reference ranges for normal men provided by the laboratory measuring the samples.

Hypogonadism may be more subtle and not always evident by low testosterone levels. For example, men with primary testicular damage often have normal testosterone levels but high LH. This could be considered a subclinical or compensated form of hypogonadism. The clinical consequences of an isolated elevation of LH is not clear yet, but potentially, these men may become hypogonadal in the future.

To differentiate between primary and secondary forms of hypogonadism and to clarify hypogonadism in adult men, determination of LH serum levels is required. Both LH and testosterone serum levels should be analysed twice.

4.2 History-taking and questionnaires

Symptoms of hypogonadism are listed in Table 3 and should be addressed during history-taking. Early onset of hypogonadism causes a lack of or minimal pubertal development, lack of development of secondary sex characteristics, possibly eunuchoid body proportions and a high-pitched voice. These signs and symptoms strongly suggest primary hypogonadism. Adult-onset hypogonadism is characterised by sexual dysfunction, obesity and loss of vigour. Published questionnaires are unreliable and have low specificity, and they are not effective for case-finding [40-43]. It is important to assess and exclude systemic illnesses, signs of malnutrition and malabsorption, as well as ongoing acute disease. Pharmacological treatments with corticosteroids, abuse of drugs such as marihuana, opiates and alcohol and previous treatment or use of testosterone or abuse of anabolic steroids should also be included in history-taking.

4.3 Physical examination

Assessment of body mass index (BMI), the waist-hip ratio (or sagittal abdominal diameter), body hair, male-pattern hair loss, presence of gynecomastia and testicular size (measured with an orchidometer or ultrasound [US]) and a structural examination of the penis as well as a digital rectal examination (DRE) of the prostate should be included.

4.4 Conclusion and recommendations for the diagnostic evaluation

Conclusion
The diagnosis of male hypogonadism is based on signs and symptoms of androgen deficiency, together with consistently low serum testosterone levels.

Recommendations	LE	GR
The diagnosis of testosterone deficiency should be restricted to men with persistent symptoms suggesting hypogonadism (Table 3) [4, 32-35, 37, 44].	3	C
Testosterone should be measured in the morning before 11.00 hours in the fasting state.	2	A
Total testosterone assessment should be repeated at least on two occasions with a reliable method. In addition, in men with: <ul style="list-style-type: none"> - Total testosterone levels close to the lower normal range (8-12 nmol/L), the free testosterone level should be measured to strengthen the laboratory assessment. - Suspected or known abnormal sex hormone-binding globulin (SHBG) levels, free testosterone should also be included [38, 44]. 	1	A
Testosterone assessment is recommended in men with a disease or treatment in which testosterone deficiency is common and in whom treatment may be indicated. This includes men with: <ul style="list-style-type: none"> - Obesity. - Metabolic syndrome (obesity, hypertension, hypercholesterolaemia). - Pituitary mass, following radiation involving the sellar region and other diseases in the hypothalamic and sellar region. - End-stage renal disease receiving haemodialysis. - Treatment with medications that cause suppression of testosterone levels - e.g. corticosteroids and opiates. - Moderate to severe chronic obstructive lung disease. - Infertility. - Osteoporosis or low-trauma fractures. - HIV infection with sarcopenia. - Type 2 diabetes mellitus. 	2	B
LH serum levels should be analysed to differentiate between primary and secondary forms of hypogonadism.	2	A

4.5 Clinical consequences of hypogonadism

The clinical consequences of hypogonadism are determined by the age of onset and the severity of hypogonadism.

4.5.1 Prenatal androgen deficiency

During the first 14 weeks of gestation, the presence of testosterone is crucial for normal virilisation of the external male genitalia. Androgen deficiency or androgen resistance due to deficient AR or LH receptor function during this stage of life may result in abnormal genital development, ranging from hypospadias to female external genitalia with intra-abdominal testis. Frequently, patients with disorders of sexual development are diagnosed at an early age because of clearly abnormal external genitalia. However, patients at both ends of the phenotypic spectrum may go unnoticed in childhood and are diagnosed during puberty because of delayed pubertal development in phenotypic men or primary amenorrhoea in XY women.

4.5.2 Prepubertal onset of androgen deficiency

At the start of puberty, rising gonadotrophin levels result in increasing testicular volume and the activation of spermatogenesis and testosterone secretion. During puberty, rising testosterone levels result in the development of male secondary sex characteristics, comprising deepening of the voice, development of terminal body hair, stimulation of hair growth in sex-specific regions, facial hair, increasing penile size, increase in muscle mass and bone size and mass, growth spurt induction and eventually closing of the epiphyses. In addition, testosterone has explicit psychosexual effects, including increased libido. Delayed puberty is defined as an absence of testicular enlargement at the age of 14 [45]. As this is a 'statistical' definition, based on reference ranges for the onset of puberty in the normal population, delayed puberty does not necessarily indicate the presence of a disease. In cases of severe androgen deficiency, the clinical picture of prepubertal-onset hypogonadism is evident (Table 4) and diagnosis and treatment are fairly straightforward. The major challenge in younger individuals with presumed idiopathic hypogonadotrophic hypogonadism is to differentiate the condition from a constitutional delay in puberty and to determine when to start androgen treatment. In milder cases of androgen deficiency, as seen in patients with Klinefelter syndrome, pubertal development can be incomplete or delayed, resulting in a more subtle phenotypic picture. In these patients, several clues may lead to a diagnosis of hypogonadism. These include: small testes, (a history of) cryptorchidism, gynaecomastia, sparse body hair, eunuchoid habitus, low bone mass and subfertility [46].

Table 4: Signs and symptoms suggesting prepubertal-onset hypogonadism

Small testes
Cryptorchidism
Gynaecomastia
High-pitched voice
Unclosed epiphyses
Linear growth into adulthood
Eunuchoid habitus
Sparse body hair/facial hair
Infertility
Low bone mass
Sarcopenia
Reduced sexual desire/activity

4.5.3 **Adult-onset hypogonadism**

Definition: adult-onset hypogonadism is defined as testosterone deficiency, usually associated with clinical symptoms or signs in a person who has had normal pubertal development and as a result developed normal male secondary sex characteristics.

Depending on the underlying cause of hypogonadism, the decline in gonadal function may be gradual and partial. The resulting clinical picture may be variable, and the signs and symptoms may be obscured by the physiological phenotypic variation. Symptoms that have been associated with adult-onset hypogonadism include: loss of libido, erectile dysfunction, sarcopenia, low bone mass, depressive thoughts, fatigue, loss of vigour, loss of body hair, hot flushes and reduced fertility (Table 3). Most of these symptoms have a multifactorial aetiology, are reminiscent of normal ageing and can also be found in men with completely normal testosterone levels [2]. As a result, signs and symptoms of adult-onset hypogonadism may be non-specific, and confirmation of a clinical suspicion by hormonal testing is mandatory. For many of the symptoms mentioned above, the probability of their presence increases with lower plasma testosterone levels. Most studies indicate a threshold level below which the prevalence of symptoms starts to increase [37, 47]. This threshold level is near the lower level of the normal range for plasma testosterone levels in young men, but there appears to be a wide variation between individuals, and even within one individual the threshold level may be different for different target organs.

4.5.3.1 *Recommendations for screening men with adult-onset hypogonadism*

Recommendations	LE	GR
Screening of testosterone deficiency is only recommended in adult men with consistent and multiple signs and symptoms listed in Table 3.	3	C
Adult men with established hypogonadism should be screened for concomitant osteoporosis.	2	B

5. DISEASE MANAGEMENT

5.1 Indications and contraindications for treatment

Testosterone treatment aims to restore testosterone levels to the physiological range in men with consistently low levels of serum testosterone and associated symptoms of androgen deficiency. The aim is to improve QoL, sense of well-being, sexual function, muscle strength and bone mineral density. Table 5 highlights the main indications for testosterone treatment. Table 6 lists the main contraindications against testosterone therapy.

Table 5: Indications for testosterone treatment

Delayed puberty (idiopathic, Kallmann syndrome)
Klinefelter syndrome with hypogonadism
Sexual dysfunction and low testosterone
Low bone mass in hypogonadism
Adult men with low testosterone and consistent and preferably multiple signs and symptoms of hypogonadism following unsuccessful treatment of obesity and comorbidities (listed in Table 5)
Hypopituitarism
Testicular dysgenesis and hypogonadism
Type 2 diabetes mellitus with hypogonadism

Table 6: Contraindications against testosterone treatment

Prostate cancer
Male breast cancer
Severe sleep apnoea
Male infertility-active desire to have children
Haematocrit > 0,54%
Severe lower urinary tract symptoms due to benign prostatic hyperplasia
Severe chronic cardiac failure/New York Heart Association Class IV

5.2 Benefits of treatment

In congenital hypogonadotrophic hypogonadism treatment is usually indicated. In these patients hormonal stimulation with hCG and FSH or alternatively pulsatile GnRH treatment can induce puberty, restore fertility in most cases and normalise bone mineralisation [29, 30].

In adult-onset hypogonadism Testosterone Replacement Therapy (TRT) may improve symptoms, but many hypogonadal men are sick and/or obese, and weight reduction, lifestyle modification and good treatment of comorbidities are more important than just TRT.

TRT may present several benefits regarding body composition, metabolic control, psychological and sexual parameters. Randomised trials show a correlation between restored physiological testosterone levels, muscle mass and strength measured as leg press strength and quadriceps muscle volume [36, 48-50]. Similar positive results are shown in meta-analysis addressed to value the role of exogenous testosterone in bone mineral density: it is evident how testosterone therapy improves mineral density at the lumbar spine producing a reduction in bone resorption markers. Available trials failed to demonstrate a similar effect at the femoral neck [49, 51, 52]. Body composition is influenced by testosterone therapy in hypogonadal men, with a consequent decrease of fat mass and an increase in lean body mass [49]. Several studies based on the experience with testosterone undecanoate, demonstrate a significant reduction in trunk and waist fat with an evident decrease in waist size [53, 54]. Testosterone undecanoate administration showed in the same trials an improvement in body weight, body mass index and lipid profile after 3 months of therapy [53]. TRT presents positive effects in glycemic and lipid control, insulin resistance and visceral adiposity in hypogonadal men with impaired glucose tolerance and lipid profile with a consequent decrease of mortality [55, 56]. A strong correlation between decreased testosterone levels and increased cardiovascular mortality has been reported in meta-analyses and retrospective studies showing that total-testosterone and free-testosterone in the normal range are related moreover to reduced all-cause mortality [57-61].

Benefits on libido, erection and ejaculation have been reported in hypogonadal men in several retrospective studies and case reports: Small improvements in satisfaction with erectile function and moderate improvements in libido have been showed by a meta-analysis of 17 placebo-control trials [49, 62-64]. In a

recent multicenter prospective study a significant increase in the IIEF (International Index of Erectile Function) regarding sexual desire, intercourse satisfaction and overall satisfaction was reported, starting 6 weeks from the start of treatment [63]. TRT showed encouraging results in several studies, where satisfactory sexual intercourses were reported after at least three months from therapy induction in hypogonadal men suffering from erectile dysfunction [49, 64]. Improvement of sexual symptoms will largely depend on the aetiology of the dysfunction: TRT in men with normal testosterone levels seems not very effective, but TRT may help improve response to PDE5 inhibitors in hypogonadal men [65].

Significant improvement on depressive symptoms in men treated with testosterone undecanoate were reported in a recent randomised trial [66], just as benefits in the cognitive spectrum [67]. Meta-analysis of data from randomised placebo-controlled trials has shown a significant positive impact of testosterone on mood [68]. Benefits in relation to the cognitive spectrum have been reported in studies with lower impact.

Conclusions	LE
Testosterone replacement therapy (TRT) may improve symptoms, but many hypogonadal men have a chronic illness and are obese: weight reduction, lifestyle modification and good treatment of comorbidities is more important than just TRT.	2
Testosterone replacement treatment can improve body composition, bone mineralisation, signs of the metabolic syndrome and male sexual problems.	3
A reduction in BMI and waist size, improved glycaemic control and lipid profile are observed in hypogonadal men receiving TRT.	2a

5.3 Choice of treatment

The aim of TRT is to restore physiological testosterone levels in hypogonadal men [69]. Several preparations are available, which differ in the route of administration and pharmacokinetics and adverse events, and the selection should be a joint decision by both the patient and the physician [70]. Short-acting preparations are preferred to long-acting depot administration in the initial treatment phase, so that any adverse events that may develop can be observed early and treatment can be discontinued if needed [71]. The available agents are oral preparations, intramuscular injections and transdermal gel and patches.

5.3.1 Preparations

5.3.1.1 Testosterone undecanoate

Testosterone undecanoate is the most widely used and safest oral delivery system. It rarely causes a rise in testosterone levels above the mid-range and it is therefore infrequently associated with side-effects [69]. In oral administration, resorption depends on simultaneous intake of fatty food. Testosterone undecanoate is also available as a long-acting intramuscular injection (with intervals of up to 3 months). This long period of action ensures a normal testosterone serum concentration for the entire period, but the relatively long wash-out period may cause problems if complications appear [72].

5.3.1.2 Testosterone cypionate and enanthate

Testosterone cypionate and enanthate are available as short-acting intramuscular delivery systems (with intervals of 2-3 weeks) and represent safe and valid preparations. However, these preparations may cause fluctuations in serum testosterone from high levels to subnormal levels, and they are consequently associated with periods of well-being alternating with periods of unsatisfactory clinical response [73, 74]. They are also associated with increased rates of erythrocytosis.

5.3.1.3 Transdermal testosterone

Transdermal testosterone preparations are available as skin patches or gel. They provide a uniform and normal serum testosterone level for 24 hours (daily interval). Common side-effects consist of skin irritation at the site of application (patches) and risk of interpersonal transfer if appropriate precautions are not taken (gel) [75, 76]. The topical application of Testosterone 2% to the axillae is recently gaining more popularity: it has been demonstrated to have a safe and effective profile in a multinational open-label clinical study and has been approved in the United States and Europe [77-79].

5.3.1.4 Sublingual and buccal testosterone

Sublingual and buccal testosterone tablets are effective and well-tolerated delivery systems that can provide a rapid and uniform achievement of a physiological testosterone level with daily administration [80, 81].

5.3.1.5 Subdermal depots

Subdermal depots need to be implanted every 5-7 months and offer a long period of action without significant serum fluctuation of the testosterone level. The risk with this kind of delivery system lies in infections and

extrusions, which may occur in up to 10% of cases [69, 82, 83].

5.4 Hypogonadism and fertility issues

Exogenous testosterone reduces endogenous testosterone production by negative feedback on the hypothalamic-pituitary-gonadal axis. If secondary hypogonadism coincides with fertility issues, hCG treatment should be considered, especially in men with low gonadotrophins. Human chorionic gonadotrophin (hCG) stimulates testosterone production of Leydig cells. Its administration should be restricted to patients with secondary hypogonadism, if fertility issues are important. Normal physiological serum levels can be achieved with a standard dosage of 1500-5000 IU administered intramuscularly or subcutaneously twice weekly. In patients with secondary hypogonadism, hCG treatment is combined with FSH treatment (usually 150 IU three times weekly i.m. or s.c.) to induce spermatogenesis in patients with secondary hypogonadism and fertility issues. Human chorionic gonadotrophin treatment has higher costs than testosterone treatment. There is insufficient information about the therapeutic and adverse effects of long-term hCG treatment. This type of treatment can therefore not be recommended for male hypogonadism, except in patients in whom fertility treatment is an issue.

Table 7: Testosterone preparations for replacement therapy

Formulation	Administration	Advantages	Disadvantages
Testosterone undecanoate	Oral; 2-6 cps every 6 h	Absorbed through the lymphatic system, with consequent reduction of liver involvement.	Variable levels of testosterone above and below the mid-range [69]. Need for several doses per day with intake of fatty food.
Testosterone cypionate	Intramuscular; one injection every 2-3 weeks	Short-acting preparation that allows drug withdrawal in case of onset of side-effects.	Possible fluctuation of testosterone levels [72, 73].
Testosterone enanthate	Intramuscular; one injection every 2-3 weeks	Short-acting preparation that allows drug withdrawal in case of onset of side-effects.	Fluctuation of testosterone levels [72, 73].
Testosterone undecanoate	Intramuscular; one injection every 10-14 weeks	Steady-state testosterone levels without fluctuation.	Long-acting preparation that cannot allow drug withdrawal in case of onset of side-effects [74].
Transdermal testosterone	Gel or skin patches; daily application	Steady-state testosterone level without fluctuation.	Skin irritation at the site of application and risk of interpersonal transfer [75, 76].
Sublingual testosterone	Sublingual; daily doses	Rapid absorption and achievement of physiological serum level of testosterone.	Local irritation [80, 81].
Buccal testosterone	Buccal tablet; two doses per day	Rapid absorption and achievement of physiological serum level of testosterone.	Irritation and pain at the site of application [80, 81].
Subdermal depots	Subdermal implant every 5-7 months	Long duration and constant serum testosterone level.	Risk of infection and extrusion of the implants [69, 82, 83].

5.5 Recommendations for testosterone replacement therapy

Recommendations	LE	GR
The patient should be fully informed about expected benefits and side-effects of the treatment option. The selection of the preparation should be a joint decision by an informed patient and the physician.	3	A
Short-acting preparations are preferred to long-acting depot administration when starting the initial treatment, so that therapy can be adjusted or stopped in case of adverse side-effects.	3	B
Testosterone therapy is contraindicated in patients with male infertility and a desire for children since it may suppress spermatogenesis	1b	A
HCG treatment can only be recommended for hypogonadotrophic hypogonadal patients with simultaneous fertility treatment.	1b	B
In patients with adult-onset hypogonadism, testosterone treatment should only be attempted in men with major symptoms and if weight loss, lifestyle modification and good treatment balance of comorbidities have proven unsuccessful.	2	A

5.6 Risk factors in testosterone treatment

Physicians are often reluctant to offer TRT especially in elderly men due to the potential risk of this therapy. The most common doubts are represented by the possible consequences on the prostate, cardiovascular risks and sleep apnoea.

5.6.1 Male breast cancer

Male breast cancer is a rare disease with an incidence of less than 1% of all male cancers [84]. The incidence is higher in men with Klinefelter syndrome. Testosterone treatment is contraindicated in men with a history of breast cancer [27]. Association between TRT and development of breast cancer is not supported by strong evidence although there are some reports based on small numbers of patients [85].

5.6.2 Risk for prostate cancer

Prostate cancer growth may be influenced by testosterone: studies report that hypogonadism is associated with a lower incidence of prostate cancer, but if prostate cancer occurs in hypogonadal men it usually has an advanced stage and a higher Gleason score [86, 87]. Short-term randomised controlled trials support the hypothesis that TRT does not result in changes in prostatic histology nor in a significant increase in intraprostatic testosterone and DHT [88, 89]. Most recent studies indicate that testosterone therapy does not increase the risk of prostate cancer [88-91], but long-term follow-up data are not yet available. A recent meta-analysis showed a higher (but not statistically significant) percentage of prostate events in middle-aged and older men on TRT, but they were more likely to have a prostatic biopsy due to some increase in PSA, which is common in men on TRT[70].

Testosterone therapy is clearly contra-indicated in men with advanced prostate cancer. A topic under debate is the use of TRT in hypogonadal men with history of prostate cancer and no evidence of active disease. So far only studies with a limited number of patients and a relatively short period of follow-up are available and indicate no increased risk for prostate cancer recurrence [89]. According to a recent retrospective study on hypogonadal men with previous history of prostate cancer receiving TRT following cancer diagnosis, treatment was not associated with increased overall or cancer-specific mortality, but TRT was more likely to be prescribed in patients undergoing radical prostatectomy for well-differentiated tumours [92]. No randomised placebo-controlled trials are available yet to document its long-term safety in these patients [69]. Symptomatic hypogonadal men who have been surgically treated for localised prostate cancer and who are currently without evidence of active disease (i.e. measurable PSA, abnormal rectal examination, evidence of bone/visceral metastasis) can be cautiously considered for a TRT [93-95]. In these men treatment should be restricted to those patients with a low risk for recurrent prostate cancer (i.e. Gleason score <8; pathological stage pT1-2; preoperative PSA < 10 ng/ml). Therapy should not start before one year of follow-up after surgery and patients should be without PSA recurrence [93, 94, 96].

Patients who underwent brachytherapy or external beam radiation (EBRT) for low risk prostate cancer can also be cautiously considered for TRT in case of symptomatic hypogonadism with a close monitoring of prostate cancer recurrence [92, 93, 96, 97], although no long-term safety data are available in these patients.

5.6.3 Cardiovascular diseases

There is good evidence that testosterone deficiency, as well as erectile dysfunction, are both independent

biomarkers, but not necessarily the cause, for cardiovascular disease and also for all-cause and cardiovascular mortality [98]. Endogenous testosterone levels within the mid-normal range are associated with the lowest risk of mortality [61]. Two studies have reported that men with testosterone levels in the upper quartile of the normal range have a reduced number of cardiovascular events when compared to the combined data from the lower three quartiles [99, 100]. The knowledge that hypogonadism and erectile dysfunction are biomarkers of cardiovascular disease demonstrates that patients should be assessed for cardiovascular risk factors and where appropriate referred to cardiology. Individual cardiovascular risk factors (e.g. lifestyle, diet, exercise, smoking, hypertension, diabetes, dyslipidaemia) should be treated in men with pre-existing cardiovascular disease. Their secondary prevention should be optimised as best possible.

TRT has also in some studies demonstrated beneficial effects on certain cardiovascular risk factors [101]. In men with angiographically proven coronary disease those with low testosterone are at greater risk of mortality [102, 103]. Over many years since TRT has been available up until recently there have been no clinical studies in the medical literature, which have shown concern in regard to an increased risk of major cardiovascular events (MACE) apart from heart failure [104]. MACE is defined as the composite of cardiovascular death, non-fatal acute myocardial infarction, acute coronary syndromes, stroke and cardiac failure. However, three recent studies (one placebo-controlled trial [105] and two observational studies [106, 107]) have suggested that TRT may be associated an increased risk of cardiovascular events. These studies have recently been reviewed by the FDA who concluded that, 'each of the studies had major limitations, precluding the ability to draw definitive conclusions' [108]. These findings are supported by letters in response to the paper by Vigen et al [109]. The European Medicines Agency (EMA) has stated 'The CMDh, a regulatory body representing EU Member States, has agreed by consensus that there is no consistent evidence of an increased risk of heart problems with testosterone medicines in men who lack the hormone (a condition known as hypogonadism). However, the product information is to be updated in line with the most current available evidence on safety, and with warnings that the lack of testosterone should be confirmed by signs and symptoms and laboratory tests before treating men with these medicines.'

The TOM trial (Basaria et al) used a testosterone dose twice that recommended for initiation of treatment, so does not reflect normal clinical practise, in addition the study being underpowered to detect an increased risk of cardiovascular events. A recent comprehensive and detailed meta-analysis of available evaluable randomised placebo-controlled trials concluded that the data did not support a causal role between TRT and adverse cardiovascular events [58]. There are however no long-term studies or RCT's that provide a definitive answer. Observational studies have reported that TRT improves survival when compared to men who were not treated [56, 110]. These findings are supported by a large retrospective analysis of 6355 men treated with TRT compared to 19065 non-users which did not demonstrate any increased risk of myocardial infarction with TRT [111].

Caution should however be used in men with pre-existing cardiovascular disease. Firstly, hypogonadism must be carefully diagnosed beyond reasonable doubt. Secondly, if TRT is prescribed then testosterone levels should not exceed the mid-normal range and the haematocrit should not exceed 0.54. Testosterone dose adjustment may be required and/or venesection (500ml) should be considered and repeated if necessary if the haematocrit is greater than 0.54. The value of >0.54 is based on the increased risk of cardiovascular mortality from the Framingham Heart Study [112] which was recently confirmed in another study [113]. This value is also supported by the known increased risk of thrombosis in the congenital condition of idiopathic erythropoiesis [114]. The majority of patients with cardiovascular disease will be receiving anti-platelet therapy. An electrocardiogram prior to TRT in the assessment of hypogonadism could be considered.

Venous thromboembolism in one study of men on TRT reported 42 cases 40 of which had evidence of underlying thrombophilia (which include Factor V Leiden deficiency, prothrombin mutations, homocysteinuria) of which 39 had their condition diagnosed after an event. High endogenous levels of testosterone and/or estradiol are not associated with an increased risk of venous thromboembolism [115]. TRT is contraindicated in men with severe chronic cardiac failure as fluid retention may lead to an exacerbation of the condition. Some studies including one of 12 months duration have shown that men with moderate chronic cardiac failure (NYHA class III) may benefit from low doses of testosterone, which achieve mid-normal range testosterone levels [48, 116, 117]. If a decision is made to treat hypogonadism in men with chronic cardiac failure it is essential that the patient is followed carefully with clinical assessment and testosterone and hematocrit measurements, on a regular basis.

5.6.4 **Obstructive sleep apnoea**

There is no consistent evidence correlating TRT with obstructive sleep apnoea (OSA). There is also no evidence that TRT can result in the onset or worsening of the condition [118].

5.7 Conclusions and recommendations on risk factors in testosterone treatment

Conclusions	LE
Case reports and small cohort studies point to a possible correlation between TRT and the onset of breast cancer, but there is as yet a lack of strong evidence for this relationship.	3
Randomised controlled trials support the hypothesis that TRT does not result in changes in prostatic histology.	1b
Recent studies indicate that testosterone therapy does not increase the risk of prostate cancer, but long-term follow-up data are not yet available.	3
There is no evidence for a relationship between TRT and obstructive sleep apnoea.	3
There is no substantive evidence that TRT, when replaced to the normal physiological range, is related to the development of major adverse cardiovascular events.	1a
TRT improves several important modifiable cardiovascular risk factors.	1b
TRT, if indicated, should be used with caution in men with pre-existing cardiovascular disease, previous venous thromboembolism (especially associated with a thrombophilia) or chronic cardiac failure.	4

Recommendations	LE	GR
Haematological, cardiovascular, breast and prostatic assessment should be performed before the start of treatment.	1a	A
Haematocrit and haemoglobin monitoring and PSA are recommended assessments at the start and during TRT therapy.	3	A
Symptomatic hypogonadal men who have been surgically treated for localised prostate cancer and who are currently without evidence of active disease (i.e. measurable PSA, abnormal rectal examination, evidence of bone/visceral metastasis) can be cautiously considered for a TRT: treatment should be restricted to those patients with a low risk for recurrent prostate cancer (i.e. Gleason score < 8; pathological stage pT1-2; preoperative PSA < 10 ng/ml) and should not start before 1 year of follow-up.	3	B
Assessment for cardiovascular risk factors should be performed before commencing TRT and optimisation of secondary prevention in men with pre-existing cardiovascular disease should be performed.	1a	A
Men with hypogonadism and either pre-existing cardiovascular disease, venous thromboembolism or chronic cardiac failure who require TRT should be treated with caution, monitored carefully with clinical assessment, haematocrit (not exceeding 0.54) and testosterone levels maintained as best possible for age within the mid-normal healthy range.	1b	A

PSA = prostate-specific antigen; TRT = testosterone replacement therapy.

6. FOLLOW-UP

6.1 Monitoring of patients receiving testosterone replacement therapy

Regular follow-up is needed in patients receiving testosterone therapy, as potentially androgen-dependent symptoms and conditions may occur as a result of TRT. The side-effects of TRT are limited, but their incidence and clinical relevance is as yet unclear. The primary aim of TRT is to alleviate the clinical symptoms of testosterone deficiency. Careful monitoring of changes in the clinical manifestations of testosterone deficiency should therefore be an essential part of every follow-up visit. Effects of TRT on sexual interest may already appear after 3 weeks of treatment, and reach a plateau at 6 weeks [49]. Changes in erectile function and ejaculation may require up to 6 months [49]. Effects on QoL, and also on depressive mood, may become detectable within 1 month, but the maximum effect may take longer [49].

6.2 Testosterone level

There are as yet insufficient data to define optimal serum levels of testosterone during TRT. Expert opinion suggests that TRT should restore the serum testosterone level to the mid-normal range of specific age groups of men, which is usually sufficient to alleviate various manifestations of hormone deficiency. An optimal monitoring schedule for serum testosterone level is also dependent on the formulation of TRT used.

6.3 Bone density

Bone mineral density (BMD) should be monitored only in men whose BMD was abnormal before initiation of TRT. An increase in lumbar spine BMD may already be detectable after 6 months of TRT and may continue for 3 more years [49].

6.4 Haematocrit

It is important to use only minimal or no venous occlusion when taking a blood sample for haematocrit measurements [114]. Elevated haematocrit is the most frequent side-effect of TRT. The clinical significance of a high haematocrit level is unclear, but it may be associated with hyperviscosity and thrombosis [115]. The effect of erythropoiesis may become evident at 3 months and peaks at 12 months [49].

6.5 Prostate safety

TRT results in a marginal increase in PSA and prostate volume, plateauing at 12 months [49]. Previous fears that TRT might increase the risk of prostate cancer have been contradicted by a number of meta-analyses [70, 88, 89, 91]. However, there are insufficient long-term data available to conclude that there is safety from prostate cancer with TRT. Prostate monitoring therefore remains indicated. Subjects with substantial or continuous increase of PSA level need to be investigated to exclude prostate cancer.

6.6 Cardiovascular monitoring

Caution should be used in men with pre-existing cardiovascular disease. In men with chronic heart failure TRT can result in fluid retention and an exacerbation of the condition [116, 117]. If a decision is made to treat hypogonadism in men with chronic cardiac diseases it is essential that the patient is followed carefully with clinical assessment and testosterone and hematocrit measurements, on a regular basis.

6.7 Recommendations for follow-up

Recommendations	LE	GR
The response to treatment should be assessed 3, 6 and 12 months after the onset of treatment, and thereafter annually.	4	C
Haematocrit should be monitored at 3, 6 and 12 months and thereafter annually. The testosterone dosage should be decreased, or therapy discontinued if the haematocrit increases above 0,54.	4	C
Prostate health should be assessed by digital rectal examination and PSA before the start of TRT. Follow-up by PSA at 3, 6 and 12 months and thereafter annually.	4	C
Men with cardiovascular diseases should be assessed for cardiovascular symptoms before TRT is initiated. There should be close clinical assessment during TRT.	1B	A

BMD = bone mineral density; PSA = prostate-specific antigen; TRT = testosterone replacement therapy.

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8. CONFLICT OF INTEREST

All members of the EAU Male Hypogonadism Guidelines Panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

Guidelines on Urological Infections

M. Grabe (Chair), R. Bartoletti, T.E. Bjerklund Johansen,
T. Cai (Guidelines Associate), M. Çek,
B. Köves (Guidelines Associate), K.G. Naber,
R.S. Pickard, P. Tenke, F. Wagenlehner, B. Wullt

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1. INTRODUCTION

1.1 Aim

The current Guidelines aim to provide both urologists and physicians from other medical specialities with evidence-based guidance regarding the treatment and prophylaxis of urinary tract infections (UTIs). These Guidelines cover male and female UTIs, male genital infections and special fields such as UTIs in paediatric urology and risk factors, e.g. immunosuppression, renal insufficiency and diabetes mellitus. Much attention is given to peri-operative antibacterial prophylaxis (ABP), aiming to reduce the overuse of antimicrobial agents in conjunction with surgery. High quality clinical research using strict internationally recognised definitions and classifications, as presented in these Guidelines, are encouraged.

1.2 Publication history

The first version of the EAU Guidelines on Urological Infections were published in 2001 and in European Urology [1]. A second updated version followed in 2006. The EAU/ICUD textbook on Urogenital Infections [2], gathering world experts in the field, was published in 2010 and has become the book of reference for the present Guidelines. Several chapters were subsequently re-written and updated during 2011-2013 (e.g. classification of UTI, uncomplicated UTI, sepsis, bacterial prostatitis and antibiotic prophylaxis). Guidelines on specific conditions of the urogenital tracts have also been published elsewhere and used as references [3-5].

A modified classification of UTI was introduced successively and for the present 2015 Guidelines, the anatomical level and gradual degree of severity of infection presented in a synoptic view in Figure 1 is used as the basis for the structure of this chapter. A new chapter on asymptomatic bacteriuria (ABU) has been introduced (Chapter 3B), to underline the importance of avoiding antibacterial over-treatment of commensal colonisation. The medical risk factors for UTI have also been integrated within Chapter 3C on cystitis and pyelonephritis. The text has been significantly reduced so that only key information is included and re-formatted according to the EAU template for non-oncology Guidelines so that all Guidelines follow a similar format. This document was peer-reviewed prior to publication.

Standard procedure for EAU Guidelines includes an annual assessment of newly published literature in the field to guide future updates. A shorter reference document, the Pocket Guidelines, is also available, both in print and as a mobile device application, presenting the main findings of the Urological Infections Guidelines. These versions are abridged and therefore may require consultation with the full text version. All are available through the EAU website: <http://www.uroweb.org/guidelines/online-guidelines/>.

1.3 Panel composition

The Urological Infections Guidelines Panel consists of a group of urologists, specialised in the treatment of UTIs and male genital infections.

1.4 Background

Urinary tract infections are among the most prevailing infectious diseases with a substantial financial burden on society. In the US, UTIs are responsible for > 7 million physician visits annually [6]. Approximately 15% of all community-prescribed antibiotics in the US are dispensed for UTI [7] and data from some European countries suggest a similar rate [8]. In the US, UTIs account for > 100,000 hospital admissions annually, most often for pyelonephritis [6]. These data do not account for complicated UTI associated with urological patients, the prevalence of which is not well known. At least 40% of all hospital acquired infections are UTIs and the majority of cases are catheter associated [9]. Bacteriuria develops in up to 25% of patients who require a urinary catheter for one week or more with a daily risk of 5-7% [10, 11]. The recent Global Prevalence Infection in Urology (GPIU) studies have shown that 10-12% of patients hospitalised in urological wards have a healthcare-associated infection (HAI). The strains retrieved from these patients are even more resistant [12].

1.4.1 Bacterial resistance development

The present state of microbial resistance development is alarming [13]. The use of antibiotics in different European countries mirrors the global increase in resistant strains [14]. The presence of extended-spectrum β -lactamase (ESBL) producing bacteria showing resistance to most antibiotics, except for the carbapenem group, is steadily increasing in the population [15]. Even more alarming are the recent reports from all continents about the emergence and increased prevalence of different carbapenemase producing organisms making them resistant even to the carbapenem group of antibiotics.

Particularly troublesome is the increasing resistance to broad-spectrum antibiotics, in particular to fluoroquinolones and cephalosporins, due to an overconsumption of these two groups and the parallel development of co-resistance to other antibiotics (collateral damage) [16]. This development is a threat to patients undergoing urological surgery in general and men subjected to prostate biopsy in particular.

An urgent and strong grip on this threatening development is thus required. With only a few new

antibiotics expected in the coming 5 to 10 years, prudent use of available antibiotics is the only option to delay the development of resistance [14] and the urological community has a responsibility to participate in this combat. It is essential to consider the local microbial environment and resistance pattern as well as risk factors for harbouring resistant microbes in individual patients.

Bacterial resistance development is a threat:
<ul style="list-style-type: none"> • To treatment of UTI. • To prophylaxis in urological surgery.
There is a direct correlation between the use of antibiotics and resistance development.
There is an urgent need for combating resistance development by a prudent use of available antibiotics.

1.4.2 Pathogenesis of UTIs

Microorganisms can reach the urinary tract by haematogenous or lymphatic spread, but there is abundant clinical and experimental evidence showing that the ascent of microorganisms from the urethra is the most common pathway that leads to a UTI, especially organisms of enteric origin (e.g. *E. coli* and other Enterobacteriaceae). This provides a logical explanation for the greater frequency of UTIs in women than in men, and for the increased risk of infection following bladder catheterisation or instrumentation. A single insertion of a catheter into the urinary bladder in ambulatory patients results in urinary infection in 1-2% of cases. Indwelling catheters with open-drainage systems result in bacteriuria in almost 100% of cases within 3-4 days. The use of a closed-drainage system, including a valve to prevent retrograde flow, delays the onset of infection, but ultimately does not prevent it. It is thought that bacteria migrate within the mucopurulent space between the urethra and catheter, and that this leads to the development of bacteriuria in almost all patients within ~ 4 weeks.

Haematogenous infection of the urinary tract is restricted to a few relatively uncommon micro-organisms, such as *Staphylococcus aureus*, *Candida sp.*, *Salmonella sp.* and *Mycobacterium tuberculosis*, which cause primary infections elsewhere in the body. *Candida albicans* readily causes a clinical UTI via the haematogenous route, but this is also an infrequent cause of an ascending infection if an indwelling catheter is present, or following antibiotic therapy.

The concept of bacterial virulence or pathogenicity in the urinary tract infers that not all bacterial species are equally capable of inducing infection. The more compromised the natural defence mechanisms (e.g. obstruction, or bladder catheterisation), the fewer the virulence requirements of any bacterial strain to induce infection. This is supported by the well-documented in vitro observation that bacteria isolated from patients with a complicated UTI frequently fail to express virulence factors. The virulence concept also suggests that certain bacterial strains within a species are uniquely equipped with specialised virulence factors, e.g. different types of pili, which facilitate the ascent of bacteria from the faecal flora, introitus vaginae or periurethral area up the urethra into the bladder, or less frequently, allow the organisms to reach the kidneys to induce systemic inflammation.

1.4.3 Microbiological and other laboratory findings

The number of bacteria is considered relevant for the diagnosis of a UTI. In 1960, Kass developed the concept of significant bacteriuria ($\geq 10^5$ cfu/mL) in the context of pyelonephritis in pregnancy [17]. Although this concept introduced quantitative microbiology into the diagnosis of infectious diseases, and is therefore still of general importance, it has recently become clear that there is no fixed bacterial count that is indicative of significant bacteriuria, which can be applied to all kinds of UTIs and in all circumstances [18]. As described in Appendix 4.1, the following bacterial counts are clinically relevant:

- $\geq 10^3$ cfu/mL of uropathogens in a mid-stream sample of urine (MSU) in acute uncomplicated cystitis in women.
- $\geq 10^4$ cfu/mL of uropathogens in an MSU in acute uncomplicated pyelonephritis in women.
- $\geq 10^5$ cfu/mL of uropathogens in an MSU in women, or $\geq 10^4$ cfu/mL uropathogens in an MSU in men, or in straight catheter urine in women, in a complicated UTI.

In a suprapubic bladder puncture specimen, any count of bacteria is relevant. The problem of counting low numbers, however, has to be considered. If an inoculum of 0.1 mL of urine is used and 10 identical colonies are necessary for statistical reasons of confidence, then in this setting, the lowest number that can be counted is 100 cfu/mL of uropathogens. Asymptomatic bacteriuria is diagnosed if two cultures of the same bacterial strain (in most cases the species only is available), taken ≥ 24 h apart, show bacteriuria of $\geq 10^5$ cfu/mL of uropathogens.

It is obvious that methods of urine collection and culture, as well as the quality of laboratory investigations, may vary. Two levels of standard must therefore be used for the management of patients. A basic standard level is necessary for routine assessment, whereas a higher standard level is

required for scientific assessment and in special clinical circumstances, e.g. fever of unknown origin in immunocompromised patients. In research, the need for a precise definition of sampling methods, such as the time that urine is kept in the bladder, must be recognised, and these parameters carefully recorded.

In clinical routine assessment, a number of basic criteria must be looked at before a diagnosis can be established, including:

- clinical symptoms;
- results of selected laboratory tests (blood, urine or expressed prostatic secretion [EPS]);
- evidence of the presence of microorganisms by culturing or other specific tests;

most of these investigations can today be performed in any laboratory.

It has to be considered, however, that microbiological methods and definitions applied must follow accepted standards with regard to specimen transport, pathogen identification, and antimicrobial susceptibility testing. These methods and microbiological definitions may vary between countries and institutions. One example is the breakpoints for classification of pathogen susceptibility. It is important to report not only the results, but also which methods and standards were applied, such as the European Committee for Antimicrobial Susceptibility Testing (EUCAST) [19, 20], or the National Committee for Clinical Laboratory Standards (NCCLS) [21]. Mixing results obtained by different methods, e.g. rates of bacterial resistance, can be problematic and requires careful interpretation. Histological investigation sometimes shows the presence of non-specific inflammation. Only in some cases, such findings (e.g. prostatitis in patients who have elevated levels of prostate-specific antigen [PSA]) might help determine the appropriate treatment, whereas in more specific inflammation, such as tuberculosis and actinomycosis, histology can be diagnostic. In general, however, histological findings usually contribute very little to the treatment decisions.

2. METHODS

The EAU/ICUD textbook on Urological Infections [2] mentioned in Chapter 1.2 was based as far as possible and appropriate on a structured literature search. One expert chaired each chapter, gathering several co-authors. Available systematic reviews, meta-analyses, and high quality review articles and controlled studies were preferably used in each chapter as references and the recommendations underwent vigorous consensus. The criteria for evidence and recommendations align with those used in the EAU Guidelines and included during subsequent updates in 2011-2013 of these Guidelines. Thereafter, the recommendations have been adjusted whenever necessary based on an annual assessment of newly published literature in the field.

The new ABU guideline (Chapter 3B) is based on a structured search for scientific articles using the term “asymptomatic bacteriuria”. The panel selected reviews, meta-analysis and randomised controlled trials (RCTs), assigned according to the different patients groups covered.

It must be emphasised that clinical guidelines present the best evidence available to the experts at the time of writing. Compliance to the guidelines is expected to result in a favourable outcome. However, guidelines can never replace clinical expertise when treatment decisions for individual patients are being taken. Guidelines help to focus decisions. Clinical decisions must also take into account patients’ personal values and preferences and their individual circumstances.

References used in this text are graded according to their level of evidence (LE) and Guidelines are given a grade of recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [22]. The aim of grading recommendations is to provide transparency between the underlying evidence and the recommendation given. In this 2015 EAU Guidelines compilation, all standard information on LE and GR has been taken out of the individual Guidelines topics for the sake of brevity. The methodology section (see the introduction chapter of the complete book) outlines the LE and GR criteria which are used throughout the Guidelines.

3. THE GUIDELINE

3A CLASSIFICATION OF UTIs

3A.1 Introduction

The following Guidelines cover UTIs and male accessory gland infections (MAGI); both infections are closely associated in males. Chapters 3A-H cover UTIs and Chapters 3I-K cover MAGI. Traditionally, UTIs are classified based on clinical symptoms, laboratory data, and microbiological findings. Practically, UTIs have been divided into uncomplicated and complicated UTIs, and sepsis. The following classification model is a working instrument useful for daily assessment and for clinical research.

A critical review of present classifications was undertaken for the EAU/ICUD Urogenital Infections initiative [23] see Appendix 4.1. The overall aim is to provide the clinician and researcher with a standardised tool and nomenclature for UTI. The present guidelines give a short summary of a tentative improved system of classification of UTI based on:

- anatomical level of infection;
- grade of severity of infection;
- underlying risk factors;
- microbiological findings.

The symptoms, signs and laboratory finding focus on the anatomical level and the degree of severity of the infection. The risk factor analysis contributes to define any additional therapeutic measure required (i.e. drainage).

3A.1.1 *Anatomical level of infection*

The symptoms (see Appendix 4.1) focus on the anatomical level of infection, defined as:

- urethra: urethritis (UR);
- urinary bladder: cystitis (CY);
- kidney: pyelonephritis (PN);
- bloodstream: sepsis (US).

Figure 1 illustrates the basic diagnostic and treatment strategy for UTI. Urethritis, being poorly understood besides sexually transmitted conditions, is for the time being not included. Also MAGI, orchitis, epididymitis and prostatitis are not included.

Asymptomatic bacteriuria needs to be considered a special entity because it can have its source in both the lower and upper urinary tracts, and requires no treatment unless the patient is subjected to urological surgery or is pregnant.

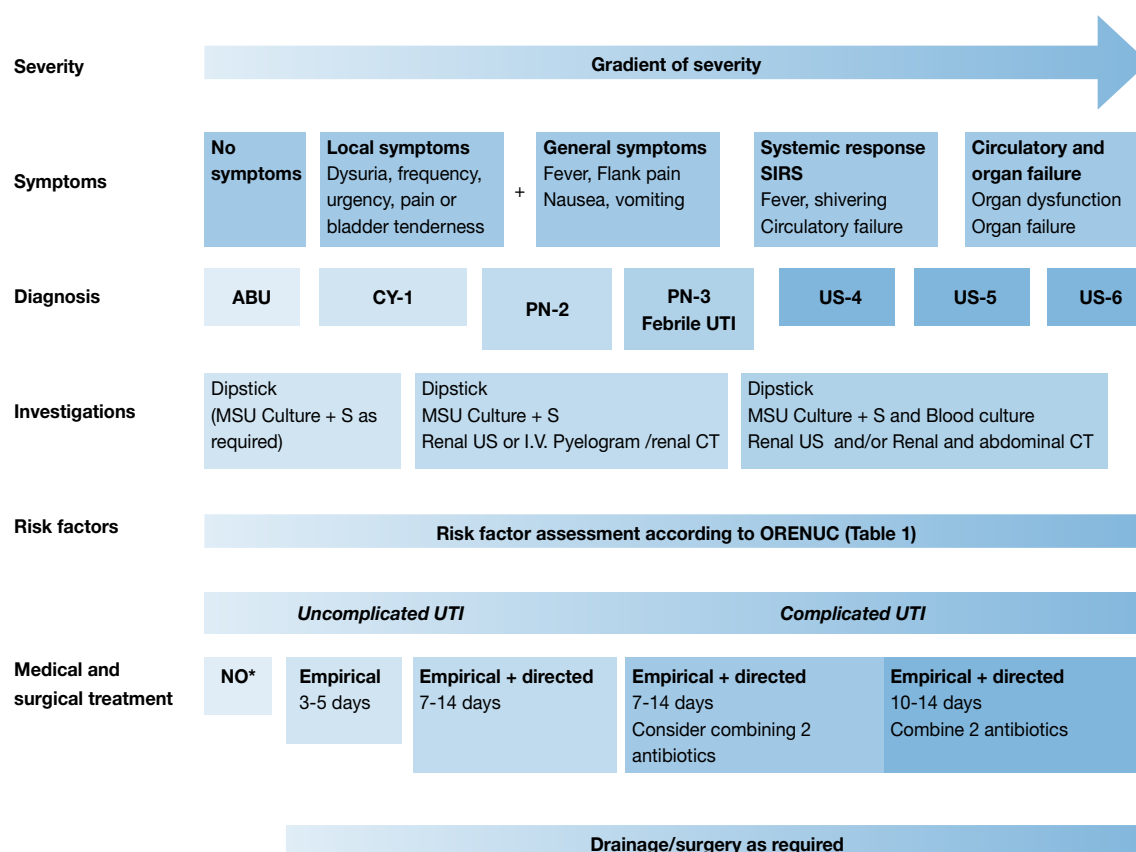
3A.1.2 *Grade of severity*

The grade of severity is set on a scale of 1-6 that is related to the risk of fatal outcome (Figure 1).

3A.2 Pathogens

Urine culture will usually identify the causative pathogen ($\geq 10^4$ cfu/mL) and its susceptibility pattern. Both characteristics can be introduced in the final classification of the clinical stage of infection. The degree of susceptibility is defined as grade a (susceptible) to c (resistant). The list of most frequent pathogens is given in Appendix 4.2.

Figure 1: Synoptic view of the classification of UTI as proposed by the EAU Section of Infection in Urology (ESIU) [23] and including the basic principles of diagnosis and treatment



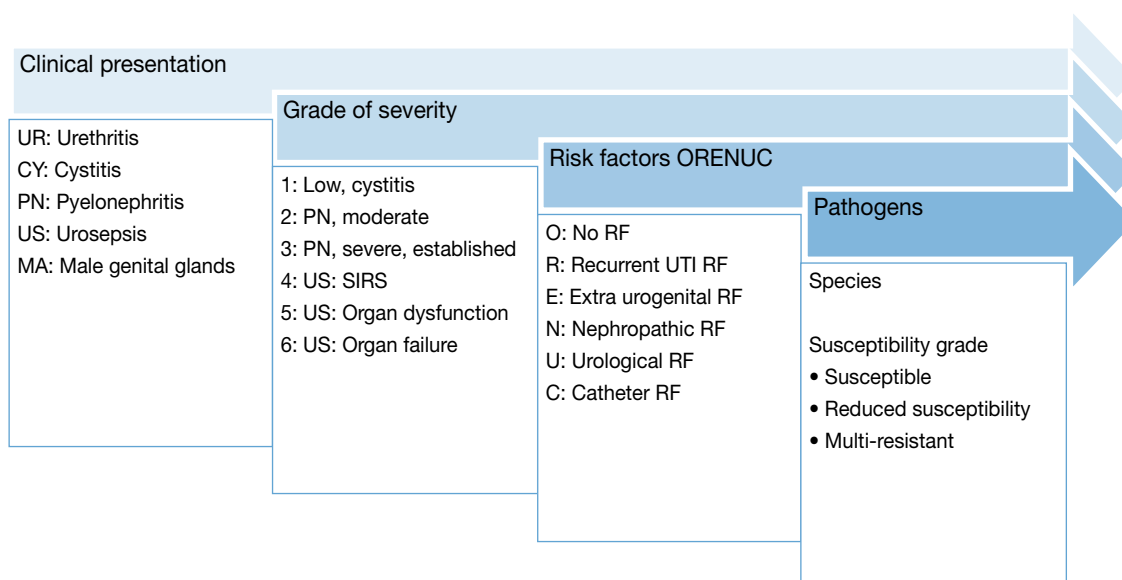
* Two presently accepted exceptions: during pregnancy and prior to urological surgery.

Table 1: Host risk factors in UTI

Type	Category of risk factor	Examples of risk factors
O	NO known/associated RF	- Healthy premenopausal women
R	Recurrent UTI RF, but no risk of severe outcome	- Sexual behaviour and contraceptive devices - Hormonal deficiency in post menopause - Secretory type of certain blood groups - Controlled diabetes mellitus
E	Extra-urogenital RF, with risk of more severe outcome	- Pregnancy - Male gender - Badly controlled diabetes mellitus - Relevant immunosuppression* - Connective tissue diseases* - Prematurity, new-born
N	Nephropathic disease, with risk of more severe outcome	- Relevant renal insufficiency* - Polycystic nephropathy
U	Urological RF, with risk of more severe outcome, which can be resolved during therapy	- Ureteral obstruction (i.e. stone, stricture) - Transient short-term urinary tract catheter - Asymptomatic Bacteriuria** - Controlled neurogenic bladder dysfunction - Urological surgery
C	Permanent urinary Catheter and non-resolvable urological RF, with risk of more severe outcome	- Long-term urinary tract catheter treatment - Non-resolvable urinary obstruction - Badly controlled neurogenic bladder

RF = risk factor; * = not well defined; ** = usually in combination with other RF (i.e. pregnancy, urological intervention).

Figure 2: Additive parameters of UTI classification and severity assessment



3A.3 Classification systems

Figure 2 shows a summary of the additive parameters that make up an individual class of UTI.

By cumulating the different parameters, a UTI can be classified as follows (examples) [23]:

- CY-1R: *E. coli* (a): simple cystitis but recurrent with susceptibility to standard antibiotics.
- PN-3U: *K pneumonia* (b): severe pyelonephritis (with high fever and vomiting), with underlying urological disease (e.g. stones or obstruction) due to *Klebsiella sp.*, with a moderate antibiotic resistance profile.
- US-5C: *Enterococcus sp.* (a): severe urosepsis with an antibiotic-sensitive *Enterococcus sp.* in a patient with an indwelling catheter.

3B ASYMPTOMATIC BACTERIURIA IN ADULTS

3B.1 Introduction

Urinary growth of bacteriae in an asymptomatic individual (ABU) is common, and corresponds to a commensal colonisation [24]. Clinical studies have shown that ABU may protect against superinfecting symptomatic UTI, thus treatment of ABU should be performed only in cases of proven benefit for the patient to avoid the risk of selecting antimicrobial resistance and eradicating a potentially protective ABU strain [25, 26]. The aim of these Guidelines is to support the clinician in deciding whether ABU should be treated or not.

3B.2 Methods

The Guidelines on ABU are based on a structured search for scientific articles using the term: “asymptomatic bacteriuria”. The panel selected reviews, meta-analyses and RCTs, assigned according to the different patient groups covered in the Guidelines.

3B.3 Epidemiology, aetiology and pathophysiology

ABU occurs in an estimated 1-5% of healthy premenopausal women. ABU increases to: 4-19% in otherwise healthy elderly women and men, 0.7-27% in diabetes patients, 2-10% in pregnant women, 15-50% in institutionalised elderly populations, and 23-89% in spinal cord injury patients [27]. ABU in younger men is uncommon, but when detected, a chronic bacterial prostatitis must be considered. The spectrum of bacteria in ABU is similar to species found in uncomplicated or complicated UTIs, depending on the presence or not of a risk factor (see Chapters 3A, C and D).

3B.4 Diagnostic evaluation

ABU is defined by a mid-stream sample of urine (MSU) showing bacterial growth $\geq 10^5$ cfu/ml in two consecutive samples in women [28] and in one single sample in men [29], in an individual without symptoms

from the urinary tract. In a single catheterised sample, bacterial growth may be as low as 10^2 cfu/ml to be considered representing true bacteriuria in both men and women [27, 30]. Diagnostic work-up should include measurement of residual urine while cystoscopy and/or imaging of the upper urinary tract is not mandatory if the medical history is otherwise without remarks (LE: 4; GR: A). If persistent growth of urease producing bacteria, i.e. *Proteus mirabilis*, is detected, stone formation in the urinary tract must be excluded [31]. In men, a DRE of the prostate has to be performed to rule out prostate diseases, including chronic bacterial prostatitis (Chapter 3I).

3B.5 Disease management

3B.5.1 Patients without identified risk factors

ABU does not cause renal disease or damage [32]. RCTs in paediatric populations and women, demonstrate that ABU treatment increases the risk for a subsequent symptomatic UTI episode, as compared to non-treated controls [25, 26]. Consequently, screening and treatment of ABU is not recommended in patients (females and young males) without risk factors (LE: 1b; GR: A).

3B.5.2 Patients with ABU and recurrent UTI, otherwise healthy

In women with recurrent symptomatic UTI and without identified risk factors, the protective effect of spontaneously developed ABU has been demonstrated [26]. Therefore, treatment of ABU in women with recurrent symptomatic UTI is not recommended (LE: 1b; GR: A). However, occasionally the eradication of a strain considered the causative agent of recurrent episodes of UTI, may be justified (LE: 4; GR: C). In men with recurrent symptomatic UTI and with ABU, chronic bacterial prostatitis must be considered and, if diagnosed, treated (Chapter 3I).

3B.5.3 Pregnant women

ABU is common during pregnancy (2-10%) and correlates to an increased risk for symptomatic UTI and pyelonephritis [27]. Evidence for the association between ABU and preterm delivery/low birth weight is however weak [33]. Screening and treatment of ABU in pregnant women is recommended by many guidelines, but the evidence for an improved outcome is low and not supported [34]. Therefore no general recommendation can be made and in case of doubt, consultation of national recommendations for pregnant women is advised.

3B.5.4 Patients with identified risk-factors

3B.5.4.1 ABU in postmenopausal women

Elderly women have an increased incidence of ABU, which should be managed as for pre-menopausal women (see 3B.5.2) [35].

3B.5.4.2 Diabetes mellitus

Diabetes mellitus, also well regulated, correlates with a higher frequency of ABU in women [36, 37]. Eradicating ABU has not been shown to reduce the risk of symptomatic UTI and infectious complications in diabetes patients, and untreated ABU does not correlate with diabetic nephropathy [38]. Screening and treatment of ABU in well-regulated diabetes mellitus is therefore not recommended (LE: 1b; GR: A). However, poorly regulated diabetes may be a risk factor for symptomatic UTI and infectious complications.

3B.5.4.3 Elderly institutionalised patients

The rate of ABU is high (15-50%) in elderly institutionalised patients [39]. Differential diagnosis to symptomatic UTI is difficult in multi-diseased and mentally deteriorated patients, and is probably a cause of unnecessary antibiotic treatment [40, 41]. It has been shown that treatment of ABU in this patient group is of no benefit [42]. Furthermore, before treatment is given the possible protective effect of spontaneously developed ABU (see 3.5.4.4.) should be taken into account. Therefore screening and treatment of ABU is not recommended in this patient group (LE: 1b; GR: A).

3B.5.4.4 Patients with dysfunctional and/or reconstructed lower urinary tracts

Patients with lower urinary tract dysfunction (LUTD), e.g. neurogenic bladder patients secondary to multiple sclerosis and spinal cord injury patients, and patients with incomplete bladder emptying, patients with neo-bladder, and ileo-cystoplasty, patients using clean intermittent catheterisation (CIC), and patients with ileal conduits, orthotopic bladder replacement and continent reservoirs, frequently become colonised [43, 44]. Studies have shown no benefit in ABU treatment in these patient groups [43, 44]. Furthermore, in LUTD patients who do not spontaneously develop ABU, deliberate colonisation with an ABU strain (*E. coli* 83972) has shown a protective effect against symptomatic recurrences [45, 46]. Screening and treatment of ABU in these patient groups is therefore not recommended (LE: 2b; GR: B). In case these patient groups develop recurrent symptomatic UTI (Chapter 3B.5.2), the potential protective effect of a spontaneously developed ABU against

lower UTI should be considered before any treatment (LE: 4; GR: B).

3B.5.4.5 Patients with catheters in the urinary tract

Patients with indwelling or supra-pubic catheters, and with nephrostomy tubes, invariably become carriers of ABU, with antibiotic treatment showing no benefit, which is also applicable for patients with ABU and internal ureteric stents [47] where treatment is not recommended see section 3F (LE: 4; GR: C).

3B.5.4.6 Patients with ABU subjected to catheter placements/exchanges

In patients subjected to uncomplicated placement/exchanges of indwelling catheters ABU is not considered a risk factor per se, and should not be screened or treated (LE: 4; GR: C). In patients subjected to placement/exchanges of nephrostomy tubes and internal stents, ABU is considered as a risk factor for infectious complications (contaminated procedure), and screening and treatment prior to the procedure is recommended (LE: 4; GR: C).

3B.5.4.7 Patients with renal transplants

Based on the result of a retrospective observational study, there are no short- or long-term benefits of antibiotic treatment of ABU in patients with renal transplants and with an uncomplicated medical history otherwise [48], therefore they should not be treated (LE: 3; GR: B). However, prospective randomised comparative studies are needed to confirm this [49].

3B.5.4.8 Immuno-compromised and severely diseased patients, patients with candiduria

These patient groups have to be considered individually and the benefit of screening and treatment of ABU should be assessed in each case (LE: 4; GR: C). Patients with asymptomatic candiduria may, but not necessarily, have an underlying disorder or defect. Treatment of asymptomatic candiduria is not recommended in patients with an otherwise uncomplicated medical history [50] (LE: 1b; GR: A).

3B.5.5 Prior to surgery

In diagnostic and therapeutic procedures not entering the urinary tract (clean procedures), ABU is generally not considered as a risk factor, and screening and treatment are not considered necessary (LE: 4; GR: C). On the other hand, in procedures entering the urinary tract and breaching the mucosa, particularly in endoscopic urological surgery, bacteriuria is a definite risk factor. In case of absence of bacteriuria, the procedure in the present guidelines is usually classified as clean-contaminated, while the presence of bacteriuria, obstruction and drainage catheters, define the procedure as contaminated. A urine culture must therefore be taken prior to such interventions and in case of ABU, pre-operative treatment should be given (LE: 3; GR: B). The recommendations for antibiotic prophylaxis in different urological procedures are given in Chapter 3N.

3B.5.6 Pharmacological management

If the decision is taken to eradicate ABU the same choice of antibiotics and treatment duration as in symptomatic uncomplicated (Table 3 and 4) or complicated (Table 7) UTI could be given, depending on gender, medical background and if complicating factors are present. Treatment should be tailored and not empirical. If ABU patients complain of odour and mild dysuria, methenamine hippurate 1g two to three times daily, and/or increased water intake, could be an option worth consideration (LE: 4; GR: C).

3B.6 Follow-up

If ABU is treated, a follow-up with subsequent urine culture should secure the treatment effect.

3C CYSTITIS AND PYELONEPHRITIS IN ADULTS

3C.1 Introduction

This chapter is based also on the EAU/ICUD publication on urogenital infections, Chapter 3 on uncomplicated UTI (uUTI), Chapter 4 on prevention of recurrent UTI in adults, and partially Chapter 7 on patients with nephropathies and immunodeficiency [2].

Acute, uncomplicated UTIs in adults include sporadic or recurrent, community-acquired episodes of acute cystitis and acute pyelonephritis in otherwise healthy individuals, comprising the host risk factors O and R, and partially E according to the ORENUC classification (see Table 1). These UTIs are seen mostly in otherwise healthy women without relevant structural and functional abnormalities within the urinary tract, kidney diseases, or comorbidity that could lead to more serious outcomes and therefore require additional

attention [51, 52]. Only a small number of men will suffer from uUTI.

3C.2 Epidemiology, aetiology and pathophysiology

Almost half of all women will experience at least one episode of UTI during their lifetime. Nearly 1 in 3 women will have had at least one episode of UTI by the age of 24 years [53].

Table 2: The most important age related known and possible risk factors for UTI in women [39, 54, 55]

Young and premenopausal women	Postmenopausal and elderly women
Sexual intercourse	History of UTI before menopause
Use of spermicide	Urinary incontinence
A new sexual partner	Atrophic vaginitis due to oestrogen deficiency
A mother with a history of UTI	Cystocoele
History of UTI during childhood	Increased post-void urine volume
	Blood group antigen secretory status
	Urine catheterisation and functional status
	deterioration in elderly institutionalised women

Only a small number of 15-50 year-old men suffer from acute uncomplicated cystitis [56]. As reviewed by Fünfstück et al. [57], UTI (cystitis and pyelonephritis) occurs more frequently in patients with diabetes mellitus, which may represent an independent risk factor. It is, however, difficult to determine the impact of renal insufficiency on the epidemiology of UTI because of the wide variety of underlying diseases [58].

The place of immunosuppression per se in the development of UTI remains also unresolved [59]. In male patients with HIV and AIDS a close relationship between CD4 counts and the risk of bacteriuria was found, particularly in patients whose counts are < 200 cells/mL [60]. About 40% of those with bacteriuria, however, were asymptomatic and there is no evidence that treatment of ABU in this group leads to improved outcome [61].

The spectrum of aetiological agents is similar in uncomplicated upper and lower UTIs, with *E. coli* the causative pathogen in 70-95% of cases and *Staphylococcus saprophyticus* in 5-10%. Occasionally, other Enterobacteriaceae, such as *Proteus mirabilis* and *Klebsiella sp.*, are isolated [62] (LE: 2a).

3C.3 Acute episode of uncomplicated cystitis (lower UTI) in adults

3C.3.1 Diagnostic evaluation

3C.3.1.1 Clinical diagnosis

The diagnosis of acute uncomplicated cystitis can be made with a high probability based on a focused history of lower urinary tract symptoms (dysuria, frequency and urgency) and the absence of vaginal discharge or irritation, in those women who have no other risk factors for complicated UTIs [52, 63] (LE: 2a, GR: B). In elderly women genitourinary symptoms are not necessarily related to UTI [55].

In otherwise healthy diabetic patients with stable glycaemic metabolism, a sporadic or even recurrent cystitis can also be considered uncomplicated. However, in the long-term patients with diabetes may develop a neuropathic bladder with voiding disturbances which may be present as a relevant complicating factor [57].

In otherwise healthy patients with mild and moderate renal insufficiency without other relevant structural and functional abnormalities within the urinary tract and the kidneys, a sporadic or recurrent cystitis can also be considered uncomplicated because no more serious outcome needs to be considered.

3C.3.1.2 Differential diagnosis

Symptomatic UTI should be differentiated from asymptomatic bacteriuria, which is considered not an infection but rather a commensal colonisation, which usually should not be treated and therefore not screened for, except if it is considered a risk factor in special situations see Section 3B.

3C.3.1.3 Laboratory diagnosis

Urine dipstick testing, as opposed to urinary microscopy, is a reasonable alternative to culture for diagnosis of acute uncomplicated cystitis [64, 65] (LE: 2a, GR: B).

Urine cultures are recommended in the following situations:

- Suspected acute pyelonephritis;
- Symptoms that do not resolve or recur within 2-4 weeks after the completion of treatment;
- Women who present with atypical symptoms [66, 67];
- Pregnant women, and

- Males with suspected UTI (LE: 4, GR: B).

A colony count of $\geq 10^3$ cfu/mL of uropathogens is microbiologically diagnostic in women who present with symptoms of acute uncomplicated cystitis [68] (LE: 3, GR: B).

Women who present with atypical symptoms of either acute uncomplicated cystitis or acute uncomplicated pyelonephritis, as well as those who fail to respond to appropriate antimicrobial therapy should be considered for additional diagnostic studies (LE: 4, GR: B).

Urological evaluation including rectal examination should always be carried out in men to rule out relevant complicating factors (LE: 4, GR: A).

3C.3.2 **Disease management**

Antibiotic therapy is recommended because clinical success is significantly more likely in women treated with antibiotics compared with placebo [69] (LE: 1a, GR: A). The choice of antibiotic therapy should be guided by [52]:

- spectrum and susceptibility patterns of the aetiological uropathogens;
- efficacy for the particular indication in clinical studies;
- tolerability and adverse reactions;
- adverse ecological effects;
- cost;
- availability.

According to these principles and the available susceptibility patterns in Europe, fosfomycin trometamol 3 g single dose, pivmecillinam 400 mg tid for 3 days, and nitrofurantoin macrocrystal 100 mg bid for 5 days, are considered as drugs of first choice in many countries, when available [70-72] (LE: 1a, GR: A) (Table 3). These regimens are recommended for women, but not for men. Most ESBL-producing *E. coli* are still susceptible to fosfomycin. However, in Spain a parallel increase in community use of fosfomycin and resistance to fosfomycin in ESBL-producing *E. coli* has been observed [73].

Alternative antibiotics include trimethoprim alone or combined with a sulphonamide, and the fluoroquinolone class. Co-trimoxazole (160/800 mg bid for 3 days) or trimethoprim (200 mg for 5 days) should only be considered as drugs of first choice in areas with known resistance rates for *E. coli* of < 20% [74, 75] (LE: 1b, GR: B). Despite still lower resistance rates in some areas, fluoroquinolones are not considered first choice because of adverse effects including negative ecological effects and selection of resistance (Table 3).

Aminopenicillins are no more suitable for empirical therapy because of the worldwide high *E. coli* resistance. Aminopenicillins in combination with a betalactamase inhibitor such as ampicillin/sulbactam or amoxicillin/slavulanic acid and oral cephalosporins are in general not so effective as short-term therapy and are not recommended for empirical therapy because of ecological collateral damage, but can be used in selected cases [76, 77].

Short courses of antimicrobial therapy can also be considered for the treatment of cystitis in pregnancy [78] (LE: 1a, GR: A), but not all antibiotics are suitable during pregnancy. In general penicillins, cephalosporins, fosfomycin, nitrofurantoin (not in case of G6P deficiency and during end of pregnancy), trimethoprim not in the first and sulphonamides not in the last trimester, can be considered.

In men a treatment duration of at least 7 days is recommended, preferably with TMP-SMX or a fluoroquinolone if in accordance with the susceptibility testing (LE: 4; GR: B).

In patients with renal insufficiency the choice of antimicrobials may be influenced by the decreased renal excretion. Most antibiotics, however, have a wide therapeutic index. No adjustment of dose is necessary until GFR < 20 mL/min, except antibiotics with nephrotoxic potential, e.g. aminoglycosides. Combination of loop diuretics (e.g. furosemide) and a cephalosporin is nephrotoxic. Nitrofurantoin and tetracyclines are contraindicated, but not doxycycline.

Table 3: Recommended antimicrobial therapy in acute uncomplicated cystitis in otherwise healthy women

Antibiotics	Daily dose	Duration of therapy	Comments
<i>First choice</i>			
Fosfomycin trometamol	3 g SD	1 day	
Nitrofurantoin macrocrystal	100 mg bid	5 days	avoid in G6PD deficiency
Pivmecillinam	400 mg tid	3 days	
<i>Alternatives</i>			
Ciprofloxacin	250 mg bid	3 days	not during pregnancy
Levofloxacin	250 mg qd	3 days	not during pregnancy
Ofloxacin	200 mg bid	3 days	not during pregnancy
Cephalosporin (e.g. cefadroxil)	500 mg bid	3 days	Or comparable (see Appendix 4.5)
<i>If local resistance pattern is known (E. coli resistance < 20%)</i>			
TMP	200 mg bid	5 days	TMP not in the first trimenon of pregnancy
TMP- SMX	160/800 mg bid	3 days	SMX not in the last trimenon of pregnancy

SD = single dose; G6PD = glucose-6-phosphate dehydrogenase; TMP = trimethoprim; SMX = sulphamethoxazole.

3C.3.3 Follow-up

Routine post-treatment urinalysis or urine cultures in asymptomatic patients are not indicated [27] (LE: 2b, GR: B), except in pregnant women, if asymptomatic bacteriuria is an issue of therapy (see Chapter 3B.5.3). In women whose symptoms do not resolve by the end of treatment, and in those whose symptoms resolve but recur within 2 weeks, urine culture and antimicrobial susceptibility tests should be performed (LE: 4, GR: B). For therapy in this situation, one should assume that the infecting organism is not susceptible to the agent originally used. Retreatment with a 7-day regimen using another agent should be considered (LE: 4, GR: C).

3C.4 Acute uncomplicated pyelonephritis in adults

3C.4.1 Diagnostic evaluation

3C.4.1.1 Clinical diagnosis

Acute pyelonephritis is suggested by flank pain, nausea and vomiting, fever (> 38°C), or costovertebral angle tenderness, and it can occur in the absence of symptoms of cystitis [79].

Pregnant women with acute pyelonephritis need special attention, because this kind of infection may have not only an adverse effect on the mother with anaemia, renal and respiratory insufficiency, but also on the unborn with more frequent preterm labour and preterm birth [80].

Most men with febrile UTI have a concomitant infection of the prostate as measured by transient increases of PSA and prostate volume [81]. Thus, urological evaluation should be carried out routinely in men with febrile UTI, pyelonephritis, or recurrent UTI, or whenever a complicating factor is suspected (LE: 4, GR: A).

In diabetic patients with acute pyelonephritis metabolic abnormalities, e.g. hypo- and hyperglycaemia, hyperosmolar dehydration, or ketoacidosis, need to closely be followed [57]. Diabetic patients may also develop progression of renal parenchymal infection sometimes caused by gas-forming organisms, with a high mortality (emphysematous pyelonephritis), characterised histologically by acute pyogenic infiltration with micro-abscesses and the development of acute renal failure [82].

The origin of the organisms may be haematogenous. Intrarenal abscesses may rupture, leading to a perinephric collection and a psoas abscess, which occasionally may be indolent. Papillary necrosis is common in diabetics, particularly in association with acute pyelonephritis, resulting in renal parenchymal scarring, although it is difficult to exclude obstruction by the sloughed papillae as the cause of the nephropathy.

The risk of chronic renal disease and renal insufficiency caused by pyelonephritis is low. Underlying lesions including vesicoureteral reflux, analgesic abuse, nephrolithiasis and obstruction of the urinary tract have to be observed. However, acute bacterial infection, including pyelonephritis, can dramatically influence the progression of a chronic renal disease and vice versa chronic renal failure can alter the severity of an infection [58].

3C.4.1.2 Differential diagnosis.

It is most important to differentiate by appropriate imaging very early between an acute uncomplicated and

complicated, mostly obstructive form of pyelonephritis, because the latter can very quickly lead to urosepsis.

3C.4.1.3 *Laboratory diagnosis*

Urinalysis (e.g. using a dipstick method), including the assessment of white and red blood cells and nitrites, is recommended for routine diagnosis [83] (LE: 4, GR: C). Colony counts $\geq 10^4$ cfu/mL of uropathogens are considered to be indicative of clinically relevant bacteriuria [84] (LE: 2b, GR: C).

3C.4.1.4 *Imaging diagnosis*

Evaluation of the upper urinary tract with ultrasound (US) should be performed to rule out urinary obstruction or renal stone disease (LE: 4, GR: C). Additional investigations, such as an unenhanced helical computed tomography (CT), excretory urography, or dimercaptosuccinic acid (DMSA) scanning, should be considered if the patient remains febrile after 72 h of treatment (LE: 4, GR: C). For diagnosis of complicating factors in pregnant women, US or magnetic resonance imaging (MRI) should be used preferentially to avoid radiation risk to the foetus (LE: 4, GR: B).

3C.4.2 *Disease management*

As a result of the lack of suitable surveillance studies, the spectrum and susceptibility patterns of uropathogens that cause uncomplicated cystitis can be used as a guide for empirical therapy [62] (LE: 4, GR: B). However, *S. saprophyticus* is less frequent in acute pyelonephritis as compared to acute cystitis (LE: 4, GR: B).

3C.4.2.1 *Mild and moderate cases*

In mild and moderate cases of acute uncomplicated pyelonephritis (see Table 4), oral therapy of 10-14 days is usually sufficient (LE: 1b, GR: B). A fluoroquinolone for 7-10 days can be recommended as first-line therapy if the resistance rate of *E. coli* is still < 10% [85] (LE: 1b, GR: A). If the fluoroquinolone dose is increased, the treatment can probably be reduced to 5 days [86, 87] (LE: 1b, GR: B). However, increasing numbers of fluoroquinolone-resistant *E. coli* in the community have already been found in some parts of the world, thus restricting the empirical use of fluoroquinolones, and fluoroquinolones are contraindicated during pregnancy.

A third-generation oral cephalosporin, such as cefpodoxime proxetil or ceftibuten, could be an alternative [88, 89] (LE: 1b, GR: B). However, available studies have demonstrated only equivalent clinical, but not microbiological, efficacy compared with ciprofloxacin.

As a result of increasing *E. coli* resistance rates >10%, cotrimoxazole is not suitable for empirical therapy in most areas, but it can be used after sensitivity has been confirmed through susceptibility testing [90] (LE: 1b, GR: B).

Co-amoxiclav is not recommended as a drug of first choice for empirical oral therapy of acute pyelonephritis (LE: 4, GR: B). It is recommended when susceptibility testing shows a susceptible Gram-positive organism (LE: 4, GR: C).

In communities with high rates of fluoroquinolone-resistant and ESBL-producing *E. coli* (> 10%), initial empirical therapy with an aminoglycoside or carbapenem has to be considered until susceptibility testing demonstrates that oral drugs can also be used (LE: 4, GR: B).

Table 4: Recommended initial empiric oral antimicrobial therapy in mild and moderate acute uncomplicated pyelonephritis

Oral Therapy in mild and moderate uncomplicated pyelonephritis			
Antibiotics	Daily dose	Duration of therapy	Reference
Ciprofloxacin	500-750 mg bid	7-10 days	[85]
Levofloxacin	500 mg qd	7-10 days	[91]
Levofloxacin	750 mg qd	5 days	[86, 87]
Alternatives (clinical but not microbiological equivalent efficacy compared with fluoroquinolones):			
Cefpodoxime proxetil	200 mg bid	10 days	[89]
Ceftibuten	400 mg qd	10 days	[88]
Only if the pathogen is known to be susceptible (not for initial empirical therapy):			
Trimethoprim-sulphamethoxazole	160/800 mg bid	14 days	[84]
Co-amoxiclav ^{1,2}	0.5/0.125 g tid	14 days	

Note: fluoroquinolones are contraindicated during pregnancy.

¹not studied as monotherapy for acute uncomplicated pyelonephritis.

²mainly for Gram-positive pathogens.

3C.4.2.2 Severe cases

Patients with severe pyelonephritis who cannot take oral medication because of systemic symptoms such as nausea and vomiting, have to be treated initially with one of the following parenteral antibiotics (Table 5).

Hospital admission should be considered if complicating factors cannot be ruled out by available diagnostic procedures and/or the patient has clinical signs and symptoms of sepsis (LE: 4, GR: B).

After improvement, the patient can be switched to an oral regimen using one of the antibacterials mentioned in Table 4, if active against the infecting organism, to complete the 1-2-week course of therapy (LE: 1b, GR: B).

Table 5: Recommended initial empirical parenteral antimicrobial therapy in severe acute uncomplicated pyelonephritis

Initial parenteral therapy in severe uncomplicated pyelonephritis		
After improvement, the patient can be switched to an oral regimen using one of the agents listed in Table 4 (if active against the infecting organism) to complete the 1-2-week course of therapy. Therefore, only daily dose and no duration of therapy are indicated.		
Antibiotics	Daily dose	Reference
Ciprofloxacin	400 mg bid	[85]
Levofloxacin ¹	250-500 mg qd	[91]
Levofloxacin	750 mg qd	[86]
Alternatives:		
Cefotaxime ²	2 g tid	
Ceftriaxone ^{1,4}	1-2 g qd	[92]
Ceftazidime ²	1-2 g tid	[93]
Cefepime ^{1,4}	1-2 g bid	[94]
Co-amoxiclav ^{2,3}	1.5 g tid	
Piperacillin/tazobactam ^{1,4}	2.5-4.5 g tid	[95]
Gentamicin ²	5 mg/kg qd	
Amikacin ²	15 mg/kg qd	
Ertapenem ⁴	1 g qd	[92]
Imipenem/cilastatin ⁴	0.5/0.5 g tid	[95]
Meropenem ⁴	1 g tid	[93]
Doripenem ⁴	0.5 g tid	[96]

Note: fluoroquinolones are contraindicated during pregnancy.

¹lower dose studied, but higher dose recommended by experts.

²not studied as monotherapy in acute uncomplicated pyelonephritis.

³mainly for Gram-positive pathogens.

⁴same protocol for acute uncomplicated pyelonephritis and complicated UTI (stratification not always possible).

In pregnant women with pyelonephritis outpatient management with appropriate antibiotics may also be considered, provided symptoms are mild and close follow-up is feasible [97, 98] (LE: 1b, GR: A). In more severe cases of pyelonephritis, hospitalisation and supportive care are usually required. After clinical improvement parenteral therapy can also be switched to oral therapy for a total treatment duration of 7-10 days (LE: 4, GR: B).

In men with febrile UTI, pyelonephritis, or recurrent infection, or whenever a complicating factor is suspected a minimum treatment duration of 2 weeks is recommended preferably with a fluoroquinolone since prostatic involvement is frequent [99] (LE: 2a, GR: B).

3C.4.3 Follow-up

Routine post-treatment urinalysis and urine cultures in an asymptomatic patient might not be indicated (LE: 4, GR: C), except in pregnant women, if asymptomatic bacteriuria is a treatment issue see Section 3B.5.3.

In patients whose pyelonephritis symptoms do not improve within 3 days, or resolve and then recur within 2 weeks, repeated urine culture and antimicrobial susceptibility tests and an appropriate investigation, such as renal US, CT or renal scintigraphy, should be performed (LE: 4, GR: B).

In patients with no urological abnormality, it should be assumed that the infecting organism is not susceptible to the agent originally used, and an alternative tailored treatment should be considered based on culture results (LE: 4, GR: B).

For patients who relapse with the same pathogen, the diagnosis of uncomplicated pyelonephritis should be reconsidered. Appropriate diagnostic steps are necessary to rule out any complicating factors (LE: 4, GR: C).

3C.5 Recurrent uncomplicated UTIs in adult women

3C.5.1 Diagnostic evaluation

Recurrent UTIs are common among young, healthy women, even though they generally have anatomically and physiologically normal urinary tracts [100] (LE: 2a). Common risk factors are given in Table 2.

Recurrent UTIs need to be diagnosed by urine culture (LE: 4, GR: A). Imaging of the upper urinary tract and cystoscopy are not routinely recommended for evaluation of women with recurrent UTIs [101] (LE: 1b, GR: B) but should be performed without delay in atypical cases. Also, residual urine should be excluded (LE: 4, GR: B).

Recurrent UTIs in men are not included here because this may be a sign of exacerbation from chronic bacterial prostatitis (see Chapter 3I). Also not included here are recurrent UTI due to complicating urological factors, such as urinary catheters, nephrolithiasis and neuropathic bladder voiding disturbances, among others.

3C.5.2 Disease management and follow-up

Prevention of rUTI includes i) counselling and behavioural modifications, i.e. avoidance of risk factors, ii) non-antimicrobial measures and iii) antimicrobial prophylaxis, which should be attempted also in this order. Urological risk factors need to be looked for and eliminated as far as possible. Significant residual urine should be treated optimally, which also includes clean intermittent catheterisation (CIC) when valued necessary.

3C.5.2.1 Risk factors and behavioural modifications

A number of measures such as fluid intake and personal hygiene behaviours (e.g. reduced fluid intake, habitual and post-coital delayed urination, wiping from back to front after defecation, douching and wearing occlusive underwear) have been suggested to increase the risk of UTI. However, studies that have explored these risk factors have consistently documented the lack of association with recurrent UTI.

In young healthy women, sexual intercourse is the risk factor most highly associated with rUTI. Others include spermicide use, having a new sex partner, having a mother with history of UTI, and having UTI during childhood.

The most common risk factors in postmenopausal women are given in Table 2. There is growing evidence that UTIs in children and adults are associated with genetic mutations that affect the innate immune system [54].

3C.5.2.2 Non-antimicrobial prophylaxis

There are many non-antimicrobial measures recommended for recurrent UTI but only a few result from well-designed studies and are therefore able to make evidence-based recommendations [102, 103].

Hormonal replacement

In postmenopausal women local, vaginal oestrogen replacement, but not oral oestrogen, showed a trend

towards preventing UTI recurrences, but vaginal irritation occurred in 6 - 20% of women [103, 104] (LE: 1b, GR: C).

Immunoactive prophylaxis

OM-89 (Uro-Vaxom®) is sufficiently well documented and has been shown to be more effective than placebo in several randomised trials with a good safety profile. Therefore, it can be recommended for immunoprophylaxis in female patients with recurrent uncomplicated UTI [103, 105, 106] (LE: 1a, GR: B). Efficacy in other groups of patients and relative to antimicrobial prophylaxis remains to be established.

The vaginal vaccine Urovac® slightly reduced UTI recurrence and primary immunisation followed by booster immunisation increased time to re-infection [103] (LE: 1a, GR: C).

For parenteral immunotherapeutic products on the market, larger phase III studies are still missing. In smaller phase II studies, StroVac® and Solco-Urovac® have been shown to be effective when administered with a booster cycle of the same agents (LE: 1a, GR: C).

For other immunotherapeutic products, no controlled studies are available. Therefore, no recommendations are possible.

Prophylaxis with probiotics (Lactobacillus sp)

Accessibility of clinically proven probiotics for UTI prophylaxis is currently not universal. Only the Lactobacillus strains specifically tested in studies should be considered for prophylaxis.

When commercially available, it is reasonable to consider the use of intravaginal probiotics that contain *L. rhamnosus* GR-1 and *L. reuteri* RC-14 for the prevention of recurrent UTI [107], and these products can be used once or twice weekly (LE: 4, GR: C). Vaginal application of *Lactobacillus crispatus* reduced the rate of recurrent UTI in pre-menopausal women in one study, and can also be used if available [108] (LE: 1b, GR: B).

Daily use of the oral product with strains GR-1 and RC-14 is worth testing given that it can restore the vaginal lactobacilli, compete with urogenital pathogens, and prevent bacterial vaginosis, a condition that increases the risk of UTI [102]. However, oral lactobacilli prophylaxis did not decrease UTI recurrence [103], therefore no recommendations are possible.

In summary, pooled data from meta-analyses of available RCTs show no convincing benefit of lactobacillus products as prophylaxis of recurrent UTI. However differences in effectiveness between available preparations suggest further trials are needed before any recommendation for use can be made. Recommendation: Do not use outside of investigational trials.

Prophylaxis with cranberry

Previous limited studies have suggested that cranberry (*Vaccinium macrocarpon*) is useful in reducing the rate of lower UTIs in women [109, 110]. A recent meta-analysis including 24 studies and comprising 4,473 participants showed however that cranberry products did not significantly reduce the occurrence of symptomatic UTI overall or for any of the following sub-groups: children with recurrent UTIs, older people, women with recurrent UTIs, pregnant women, cancer patients, or people with neuropathic bladder or spinal injury [111]. Due to these contradictory results, no recommendation of the daily consumption of cranberry products can be made.

Prophylaxis with d-mannose

In a recent randomised placebo-controlled non-blinded clinical trial, it was shown that a daily dose of 2g d-mannose was significantly superior to placebo and as effective as 50 mg nitrofurantoin in preventing recurrent UTI [112]. This is indicative but not sufficient for a recommendation. D-mannose should at the present time only be used within the frame of high quality clinical investigations.

Endovesical instillation

Endovesical instillation of hyaluronic acid and chondroitin sulphate have been used for glycosaminoglycan (GAG) layer replenishment in the therapy of interstitial cystitis, overactive bladder, radiation cystitis, and for prevention of recurrent UTI. A recent review of 27 clinical studies concluded that large-scale trials are urgently needed to underline the benefit of this type of therapy [113]. Therefore, no general recommendation is possible at this stage.

3C.5.2.3 Antimicrobial prophylaxis

Antimicrobial prophylaxis can be given continuously (daily, weekly) for longer periods of time (3-6 months), or as a single post-coital dose. Continuous or post-coital antimicrobial prophylaxis [114] for prevention of recurrent UTI should be considered only after counselling and behavioural modification has been attempted, and when non-antimicrobial measures have been unsuccessful (LE: 4, GR: B).

In appropriate women with recurrent uncomplicated cystitis, self-diagnosis and self-treatment with a short course regimen of an antimicrobial agent should be considered [115] (LE: 2b, GR: A). The choice of antibiotics is the same as for sporadic acute uncomplicated UTI (Table 3).

Postcoital prophylaxis should be considered in pregnant women with a history of frequent UTIs before onset of pregnancy, to reduce their risk of UTI [116] (LE: 2b, GR: B).

Continuous antimicrobial prophylaxis regimens for women with recurrent UTIs include e.g. nitrofurantoin (macrocrystal) 50 mg or 100 mg once daily, fosfomycin trometamol 3 g every 10 days, and during pregnancy e.g. cephalexin 125 mg or 250 mg or cefaclor 250 mg once daily [100].

In general, the choice of antibiotics should be based upon the identification and susceptibility pattern of the organism causing the UTI, the patient's history of drug allergies and the ecological collateral effects including bacterial selection of resistance by the chosen antimicrobial. Using these principles, several issues need to be considered:

- Ecological collateral effects mean that oral fluoroquinolones and cephalosporins are no longer recommended routinely, except in specific clinical situations.
- The worldwide increase of *E. coli* resistance against trimethoprim casts doubts on trimethoprim with or without a sulphonamide to be an effective prophylactic agent still.
- There are recent warnings by governmental agencies for the long-term prophylactic use of nitrofurantoin because of the rare but severe pulmonary and hepatic adverse effects [117].

Altogether this underlines the need for reconsidering long-term antibiotic prophylaxis in recurrent UTI and assess in each individual case effective alternative preventive measures.

3D COMPLICATED UTIs WITH UROLOGICAL AND NEPHROLOGICAL RISK FACTORS IN ADULTS

3D.1 Introduction

This chapter is based also on the EAU/ICUD publication on urogenital infections, Chapter 7 on UTI in nephropathies, transplant patients and immunosuppression, and on Chapter 8 on UTI in patients with underlying urological abnormalities [2].

A complicated UTI is an infection associated with a condition, such as a structural or functional abnormality of the genitourinary tract, or the presence of an underlying disease, which increase the risk of a more serious outcome than expected from UTI in individuals without identified risk factor (Chapter 3C) or of failing therapy. Examples of risk factors corresponding mainly to the category N,U, and C of the ORENUC classification are listed in Table 1.

A broad range of bacteria can cause a complicated UTI. The spectrum is much larger than in uncomplicated UTIs, and bacteria are more likely to be resistant to antimicrobials, especially in a treatment-related complicated UTI.

Enterobacteriaceae are the predominant pathogens, with *E. coli* being the most common. However, non-fermenters (e.g. *Pseudomonas aeruginosa*) and Gram-positive cocci (e.g. staphylococci and enterococci) may also play an important role, depending on the underlying conditions.

Treatment strategy depends on the severity of the illness and encompasses three goals: management of the urological abnormality, antimicrobial therapy, and supportive care when needed. Hospitalisation is often required. To avoid the emergence of resistant strains, therapy should be guided by urine culture whenever possible.

It is reasonable to measure the treatment effect after completion of surgical correction of a urological abnormality or medical correction of a risk factor and associated UTI, with a urine culture 1-2 weeks after completion of therapy and thereafter according to the clinical needs or surveillance purposes.

3D.2 Classification systems

Host-related risk factors for UTI in general, and complicated UTI in particular, are listed in Table 6. Complicated UTI can arise in a heterogeneous group of patients. However, neither patient age nor sex per se are part of the definition of a complicated UTI. With regard to prognosis and clinical studies, it is advisable to stratify complicated UTIs due to urological disorders into at least two groups [118]:

- Patients in whom the complicating factors could be eliminated by therapy, e.g. stone extraction, removal of an indwelling catheter corresponding to host risk factor U according to the ORENUC system (see Table 1).

- Patients in whom the complicating factor could not be or is not removed satisfactorily during therapy, e.g. permanent indwelling catheter, stone residues after treatment or neurogenic bladder corresponding to host risk factor C according to the ORENUC system (see Table 1).

Table 6: Factors that suggest a potential complicated UTI

The presence of an indwelling catheter, stent or splint (urethral, ureteral, renal) or the use of intermittent bladder catheterisation.
Post-void residual urine of > 100 mL.
An obstructive uropathy of any aetiology (upper and lower urinary tracts), e.g. bladder outlet obstruction (including neurogenic urinary bladder), stones and tumour.
Vesicoureteric reflux or other functional abnormalities.
Urinary tract modifications/deviation, such as an ileal loop or pouch.
Chemical or radiation injuries of the uroepithelium.
Peri- and postoperative UTI, including renal transplantation.

3D.3 Diagnostic evaluation

3D.3.1 Clinical presentation

A complicated UTI, in contrast to asymptomatic bacteriuria, also needs to be associated with clinical symptoms (e.g. dysuria, urgency, frequency, flank pain, costovertebral angle tenderness, suprapubic pain and fever), although in some clinical situations the symptoms may not be typical, e.g. in neuropathic bladder disturbances, catheter-associated UTI. Clinical presentation can vary from severe obstructive acute pyelonephritis with imminent urosepsis to a catheter-associated postoperative UTI, which might disappear spontaneously as soon as the catheter is removed. It also has to be recognised that symptoms, especially lower urinary tract symptoms (LUTS), are not only caused by UTIs but also by other urological disorders, such as benign prostatic hyperplasia (BPH) or transurethral resection of the prostate (TURP).

Apart from urological abnormalities, concomitant medical conditions, such as diabetes mellitus (10%) and renal failure, which can be related to urological abnormalities [119], are often present in a complicated UTI.

3D.3.2 Urine cultures

Significant bacteriuria in a complicated UTI is defined by counts of $\geq 10^5$ cfu/mL and $\geq 10^4$ cfu/mL, in the mid-stream urine (MSU) of women and men, respectively [84, 120]. If a straight catheter urine sample is taken, $\geq 10^4$ cfu/mL can be considered relevant. The requirement for pyuria is ≥ 10 white blood cells (WBC) per high-power field (x400) in the resuspended sediment of a centrifuged aliquot of urine or per mm³ in unspun urine. A dipstick method can also be used for routine assessment, including a leukocyte esterase test, haemoglobin and probably a nitrite reaction.

3D.3.3 Microbiology (spectrum and antibiotic resistance)

Patients with a complicated UTI, both community and hospital-acquired, tend to show a diversity of microorganisms with a higher prevalence of resistance against antimicrobials, and higher rates of treatment failure if the underlying abnormality cannot be corrected.

However, the presence of a resistant strain on its own is not enough to define a complicated UTI. Urinary abnormality (anatomical or functional) or the presence of an underlying disease predisposing to a UTI is also necessary.

A broad range of bacteria can cause a complicated UTI. The spectrum is much larger than with an uncomplicated UTI and the bacteria are more likely to be antibiotic-resistant (especially in a treatment-related complicated UTI) than those isolated in an uncomplicated UTI. *E. coli*, *Proteus*, *Klebsiella*, *Pseudomonas* and *Serratia sp.* and enterococci are the usual strains found in cultures. Enterobacteriaceae predominate (60-75%) [121-123], with *E. coli* as the most common pathogen; particularly if the UTI is a first infection. Otherwise, the bacterial spectrum may vary over time and from one hospital to another.

3D.3.4 Special types of complicated UTIs

Urinary stones: In the subset of complicated UTIs related to urinary stones, the frequency of *E. coli* and enterococci infection seem less important pathogens. In contrast, a greater portion of *Proteus* and *Pseudomonas sp.* [124] is found.

Of the urease-producing organisms, *Proteus*, *Providencia* and *Morganella sp.*, and *Corynebacterium urealyticum* are predominant, but *Klebsiella*, *Pseudomonas* and *Serratia sp.* and staphylococci are also urease producers to a certain extent.

Among patients with staghorn calculus disease, 88% were found to have a UTI at the time of diagnosis, with 82% of patients infected with urease-producing organisms [125]. The enzyme, urease, splits urea into carbon dioxide and ammonia. The resultant increase in ammonia in the urine injures the glycosaminoglycan layer, which in turn increases bacterial adherence [126] and enhances the formation of struvite crystals. These aggregate to form renal stones and incrustations on urinary catheters [127].

The pathogenic potential of coagulase-negative staphylococci and non-group D streptococci is controversial [63, 128]. Under certain circumstances, such as the presence of a stone or foreign bodies, staphylococci can be relevant pathogens. Otherwise, staphylococci are not so common in complicated UTIs (0-11%), according to published reports [122, 129].

Nephrectomy should be performed only as a last resort, because even residual renal function may be of vital importance (GR: B).

Urinary catheters: In catheter-associated UTIs, the distribution of microorganisms is similar [92], and biofilm has to be considered. Antimicrobial therapy may only be effective in the early stages of the infection [129]. For more details see Chapter 3F on catheter-associated UTIs.

Adult polycystic kidney disease (APCKD): UTI is a prominent complication of ADPKD, with symptomatic UTI being the presenting feature in 23-42% of patients, who are usually female [130]. It may be difficult to obtain a positive culture on standard laboratory media, but pyuria is common, particularly in the later stages of disease progression. Acute pyelonephritis is common and may originate from pyogenic infection in the cysts [131] (LE: 3). Puncture/aspiration of infected material from an infected cyst must be considered both for microbiological diagnosis and therapy (drainage). Polycystic disease is not to be confused with acquired renal cystic disease of the end-stage kidney, which has no predisposition to UTI.

3D.3.5 **Special types of renal infections**

Focal bacterial nephritis: This is restricted to one or several renal segments and usually resolves with appropriate medical treatment. In rare situations, especially in association with an obstruction, it may liquefy and form a renal abscess requiring drainage.

Renal abscess: They can rupture into the urinary tract or penetrate through the renal capsule to become a perinephric abscess.

Perinephric abscess: The clinical symptoms are chills, fever, back or abdominal pain, CVA tenderness, flank mass and redness, protection of the upper lumbar and paraspinal muscles. In bed-ridden patients, however, perinephric abscesses can present with few symptoms. Respiratory insufficiency, haemodynamic instability and paralytic ileus may predominate.

Emphsematous pyelonephritis: This is caused by gas-forming *E. coli*, *K. pneumoniae*, *E. cloacae* fermenting glucose. The contralateral kidney is often also affected. Papillary necrosis, intrarenal vascular thrombus, and renal infarction are often seen in pathology.

Xanthogranulomatous pyelonephritis: This is characterised by a chronic purulent, fatty inflammation of the renal parenchyma, the pelvis and the hilar tissue.

3D.3.6 **Complicated UTI after renal transplantation**

UTI is the most common infectious complication following kidney transplantation [132]. In a large database the cumulative incidence of UTI during the first six months after renal transplantation was 17% for both genders and at three years 60% for women and 47% for men [133]. Donor type (living vs. deceased) has conflicting evidence for UTI risk.

Symptomatic UTI after transplant has a wide clinical spectrum including acute cystitis, transplant pyelonephritis, and pyelonephritis of the native kidney. Risk factors include more intensive immunosuppression, extremes of age, diabetes mellitus, prolonged time on dialysis, abnormal or reconstructed lower urinary tract and prolonged use of urinary catheters and stents.

Typical signs and symptoms of UTI may be mimicked by other common post-transplant conditions including catheter induced bladder spasm, stent irritation, low volume defunctionalised bladder, polyuria due to early loss of urinary concentrating ability, urinary retention and fever/graft tenderness from acute rejection. Furthermore, common UTI features may not be evident. Immunosuppression can suppress fever, primarily through blockade of IL-1 and TNF. WBC counts may not be elevated due to bone marrow suppression. The transplanted kidney is denervated and may not be tender even in the face of pyelonephritis.

Typical uropathogens are commonly involved but UTIs may also be caused by commensal and

fastidious bacteria, fungus, mycobacteria and viruses. Some studies suggest post-transplant UTI has a negative impact on graft survival and function, although causality has not been established [132, 133].

3D.4 Disease management

Treatment strategy depends on the severity of the illness. Appropriate antimicrobial therapy and the management of the urological abnormality are mandatory. If needed, supportive care is given. Hospitalisation is often necessary depending on the severity of the illness.

3D.4.1 Choice of antibiotics

Empirical treatment of a symptomatic complicated UTI requires knowledge of the spectrum of possible pathogens and local antibiotic resistance patterns, as well as assessment of the severity of the underlying urological abnormality (including the evaluation of renal function).

Bacteraemia is usually reported too late to influence the choice of antibiotics. However, suspicion of bacteraemia must influence the empirical treatment. The severity of the associated illness and the underlying urological condition are still of utmost importance for prognosis.

Many therapeutic trials have been published on the use of specific antimicrobial therapies in complicated UTIs. Unfortunately, most reports are of limited use for the practical management of the patient in a day-to-day situation because of limitations such as:

- poor characterisation of the patient populations;
- unclear evaluation of the severity of the illness;
- nosocomial and community-acquired infections are not accurately distinguished;
- urological outcome is seldom taken into consideration.

Intense use of any antimicrobial, especially when used on an empirical basis in this group of patients with a high likelihood of recurrent infection, will lead to the emergence of resistant microorganisms in subsequent infections. Whenever possible, empirical therapy should be replaced by a therapy adjusted for the specific infective organisms identified in the urine culture. Therefore, a urine specimen for culture must be obtained before initiation of therapy, and the selection of an antimicrobial agent should be re-evaluated once culture results are available [123]. To date, it has not been shown that any agent or class of agents is superior in cases in which the infective organism is susceptible to the drug administered.

In patients with renal failure, whether related to a urological abnormality or not, appropriate dose adjustments have to be made after initiated treatment, usually by means of drug concentration monitoring.

If empirical treatment is necessary, the antibacterial spectrum of the antibiotic agent should include the most relevant pathogens (GR: A). A fluoroquinolone with mainly renal excretion, a Group 3a cephalosporin, or an aminoglycoside are recommended alternatives (LE: 1b, GR: B). In case of failure of initial therapy, or in case of clinically severe infection, a broader-spectrum antibiotic should be chosen that is also active against pseudomonas [134] (LE: 1b, GR: B), e.g. a Group 3b cephalosporin, an acylaminopenicillin (piperacillin) plus a BLI, or a carbapenem, with or without combination with an aminoglycoside (LE: 1b, GR: B). Local resistance pattern needs to be considered, which may result in different recommendations. The antibacterial treatment options are summarised in Table 7 and Appendix 4.3 (Recommendations for antimicrobial therapy in urology).

Patients can generally be treated as outpatients. In more severe cases (e.g. hospitalised patients), antibiotics have to be given parenterally. After a few days of parenteral therapy and clinical improvement, patients can be switched to oral treatment. Therapy has to be reconsidered when the infective strains have been identified and their susceptibilities are known. The successful treatment of a complicated UTI always combines effective antimicrobial therapy, optimal management of the underlying urological abnormalities or other diseases, and sufficient life-supporting measures.

3D.4.2 Duration of antibiotic therapy

Treatment for 7-14 days is generally recommended, but the duration should be closely related to the treatment of the underlying abnormality [84]. Sometimes, a prolongation for up to 21 days, according to the clinical situation, is necessary [120].

Table 7: Antimicrobial treatment options for empirical therapy

Antibiotics recommended for initial empirical treatment, if local resistance pattern is still < 20%
Fluoroquinolone
Aminopenicillin plus a BLI
Cephalosporin (Groups 3a)
Aminoglycoside
Antibiotics recommended for empirical treatment in case of initial failure, or for severe cases
Fluoroquinolone (if not used for initial therapy)
Piperacillin plus BLI
Cephalosporin (Group 3b)
Carbapenem
Antibiotics not recommended for empirical treatment
Aminopenicillins, e.g. amoxicillin, ampicillin
Trimethoprim-sulphamethoxazole (only if susceptibility of pathogen is known)
Fosfomycin trometamol

BLI = β -lactam inhibitor

3D.4.3 Specific treatment considerations

3D.4.3.1 Adult Polycystic kidney disease

In patients with APCKD, acute pyelonephritis by infected cysts may occur, presenting as recurrent pyelonephritis or even sepsis. Treatment requires a long course of high-dose systemic, preferably (if appropriate) fluoroquinolones, followed by suppressive therapy. Drainage may be required (see 3D.3.4). After transplantation, overall graft and patient survival rates do not differ between ADPKD and control groups [135] (LE: 2a). However, despite close monitoring, UTI and septicæmic episodes are still a significant cause of morbidity, such that bilateral nephrectomy may be the only option.

3D.4.3.2 Special types of complicated UTIs

Urinary stones: If a nidus of a stone or an infection remains, stone growth will occur. Complete removal of the stones and adequate antimicrobial therapy are both needed. Eradication of the infection will probably eliminate the growth of struvite calculi [136]. Long-term antimicrobial therapy should be considered if complete removal of the stone cannot be achieved [137].

Indwelling catheters: Current data do not support the treatment of ABU, either during short-term (< 30 days) or long-term catheterisation, because it will promote the emergence of resistant strains [138, 139]. In short-term catheterisation, antibiotics may delay the onset of bacteriuria, but do not reduce complications [140]. See Chapter 3F.

A symptomatic complicated UTI associated with an indwelling catheter is treated with an agent with as narrow a spectrum as possible, based on culture and sensitivity results. The optimal duration is not well established. Treatment durations that are too short as well as too long may cause the emergence of resistant strains. A 5 to 7-day course could be a reasonable compromise.

Spinal cord injury: In case of persistent UTIs and suspicion of urinary retention, a full urodynamic assessment to appraise bladder function is to be carried out. Priority is to ensure proper drainage of the bladder, preferably by clean intermittent catheterisation (CIC), to protect the urinary tract [141, 142].

It is generally accepted that ABU in patients with spinal cord injury should not be treated, even in cases of CIC, because it could be shown that deliberately induced *E. coli* ABU in these patients could prevent recurrences [45, 46]. For symptomatic episodes of infection in patients with spinal cord injury, only a few studies have investigated the most appropriate agent and duration of therapy. Currently, 7-10 days of therapy is most commonly used. There is no superiority of one agent or class of antimicrobials. Treatment or prophylaxis of asymptomatic bacteriuria in spinal cord patients does not decrease the frequency of subsequent symptomatic infections.

3D.4.3.3 Special types of renal infections

The special types of renal infections with abscess formation are not seen frequently. Conservative broad spectrum, antimicrobial therapy may be successful at the beginning of the infection or for abscesses of 3 cm or less (relative size) (see also 3D.3.5). Larger abscesses will usually need to be drained. In rare instances, only nephrectomy can cure the patient.

3D.4.3.4 UTI in renal transplantation

The need to correct uropathy or to remove a potential focus of infection in an end-stage disease kidney is more pressing in patients enlisted for renal transplantation. Even so, the results of nephrectomy for a scarred or hydronephrotic kidney may be disappointing.

There is a paucity of prospective controlled data that can guide UTI prophylaxis or therapy in terms of agent or duration, although most programs will routinely use prophylaxis for at least 6 months (GR: B). Post transplant UTI can be reduced by early removal or urinary foreign bodies, such as indwelling urinary catheter, ureteral stent (GR: C).

Bacteriocidal antibiotics should be preferred to bacteriostatic ones, which might be insufficient to cure the infection since the immune system cannot eradicate the dormant bacteria. Predisposing factors should be corrected if possible (e.g. optimal diabetic control, removal or change of stents and catheters, minimise immunosuppression based upon drug levels and clinical course).

Interactions exist between antibiotics used to treat post-transplant UTI and immunosuppressant drugs. Ciprofloxacin may raise calcineurin inhibitor (CNI) levels, but levofloxacin and ofloxacin usually do not [143]. Erythromycin and antifungal agents inhibit cytochrome P450 and increase CNI levels. Rifampin, imipenim and cephalosporins can reduce CNI levels. Nephrotoxic antibiotics (e.g. aminoglycosides, amphotericin) may have synergistic effects with CNIs, increasing renal damage.

UTI can co-exist with common post-transplant viral illnesses (e.g. cytomegalovirus). Transplant pyelonephritis may cause elevated serum creatinine, however reduced renal function should not be simply attributed to the infection without ruling out other causes (e.g. obstruction, rejection, drug toxicity). Ultimately, lack of response should prompt a biopsy to rule out rejection or other renal conditions (e.g. primary disease recurrence).

Asymptomatic bacteriuria post kidney transplant does not require therapy beyond standard prophylaxis (GR: C) [132].

3D.5 Follow-up

The greater likelihood of the involvement of resistant microorganisms in complicated UTIs is another feature of these infectious diseases. This is not a priori related to the urinary abnormality, but is related more to the fact that patients with a complicated UTI tend to have recurrent infection [123]. For these reasons, before and after the completion of the antimicrobial treatment, urine cultures must be obtained for the identification of the microorganisms and the evaluation of susceptibility testing.

3E SEPSIS SYNDROME IN UROLOGY (UROSEPSIS)

3E.1 Introduction

Patients with urosepsis should be diagnosed at an early stage, especially in the case of a complicated UTI. The systemic inflammatory response syndrome, known as SIRS (fever or hypothermia, hyperleukocytosis or leukopenia, tachycardia, tachypnoea), is recognised as the first event in a cascade to multi-organ failure (Figure 1). Mortality is considerably increased when severe sepsis or septic shock are present, although the prognosis of urosepsis is globally better than that of sepsis from other infectious sites.

The treatment of urosepsis calls for the combination of adequate life-supporting care, appropriate and prompt antibiotic therapy, adjunctive measures (e.g. sympathomimetic amines, hydrocortisone, blood glucose control) and the optimal management of urinary tract disorders (LE: 1a, GR: A). The drainage of any obstruction in the urinary tract is essential as first-line treatment (LE: 1b, GR: A). Urologists are recommended to treat patients in collaboration with intensive care and infectious diseases specialists (LE: 2a, GR: B).

Urosepsis is seen in both community-acquired and healthcare associated infections. Most nosocomial urosepsis can be avoided by measures used to prevent nosocomial infection, e.g. reduction of hospital stay, early removal of indwelling urethral catheters, avoidance of unnecessary urethral catheterisation, correct use of closed catheter systems, and attention to simple daily asepsis techniques to avoid cross-infection (LE: 2a, GR: B).

Urinary tract infections can manifest as bacteriuria with limited clinical symptoms, sepsis or severe sepsis, depending on localised or systemic extension. Sepsis is diagnosed when clinical evidence of infection is accompanied by signs of systemic inflammation (fever or hypothermia, tachycardia, tachypnoea, leukocyturia or leukopenia). Severe sepsis is defined by the presence of symptoms of organ dysfunction, and septic shock by the presence of persistent hypotension associated with tissue anoxia.

3E.2 Epidemiology, aetiology and pathophysiology

Urinary tract infections can manifest from bacteriuria with limited clinical symptoms to sepsis or severe sepsis, depending on localised and potential systemic extension. It is important to note that a patient can move from an almost harmless state to severe sepsis in very short time. Sepsis is diagnosed when clinical evidence of infection is accompanied by signs of systemic inflammation (fever or hypothermia, tachycardia, tachypnoea, leukocyturia or leukopenia). Severe sepsis is defined by the presence of symptoms of organ dysfunction, and septic shock by the presence of persistent hypotension associated with tissue anoxia.

Mortality associated to severe sepsis are reported in various rates depending on the organ source [144] with urinary tract sepsis generally having a lower mortality than that from other sources [145]. Sepsis is more common in men than in women [146]. In recent years, the overall incidence of sepsis arising from all sources has increased by 8.7% per year [144], but the associated mortality has decreased, which suggests improved management of patients (total in-hospital mortality rate fell from 27.8% to 17.9% from 1995 to 2000) [147]. Although sepsis due to fungal organisms from some sites has increased and Gram-positive bacteria have become the predominant pathogen overall, Gram-negative bacteria remain predominant in urosepsis.

In urosepsis, as in other types of sepsis, the severity depends mostly upon the host response. Patients who are more likely to develop urosepsis include: elderly patients; diabetics; immunosuppressed patients, such as transplant recipients; patients receiving cancer chemotherapy or corticosteroids; and patients with AIDS. Urosepsis also depends on local factors, such as urinary tract calculi, obstruction at any level in the urinary tract, congenital uropathy, neurogenic bladder disorders, or endoscopic manoeuvres. However, all patients can be affected by bacterial species that are capable of inducing inflammation within the urinary tract. Moreover, it is now recognised that SIRS may be present without infection (e.g. pancreatitis, burns, or non-septic shock) [148].

3E.3 Classification systems

For therapeutic purposes, the diagnostic criteria of sepsis should identify patients at an early stage of the syndrome, which should prompt urologists and intensive care specialists to search for and treat infection, apply appropriate therapy, and monitor for organ failure and other complications.

3E.4 Diagnostic evaluation

The clinical evidence of UTI is based on symptoms, physical examination, sonographic and radiological features, and laboratory data, such as bacteriuria and leukocyturia. The following definitions apply (Table 8):

- Sepsis is a systemic response to infection. The symptoms of SIRS which were initially considered to be 'mandatory' for the diagnosis of sepsis [148], are now considered to be alerting symptoms [149]. Many other clinical or biological symptoms must be considered.
- Severe sepsis is associated with organ dysfunction.
- Septic shock is persistence of hypoperfusion or hypotension despite fluid resuscitation.
- Refractory septic shock is defined by an absence of response to therapy.

Table 8: Clinical diagnostic criteria of sepsis and septic shock [148, 149]

Disorder	Definition
Infection	Presence of organisms in a normally sterile site that is usually, but not necessarily, accompanied by an inflammatory host response.
Bacteraemia	Bacteria present in blood as confirmed by culture. May be transient.
Systematic inflammatory response syndrome (SIRS)	Response to a wide variety of clinical insults, which can be infectious, as in sepsis but may be non-infectious in aetiology (e.g. burns, or pancreatitis). This systemic response is manifested by two or more of the following conditions: - Temperature > 38°C or < 36°C - Heart rate > 90 bpm - Respiratory rate > 20 breaths/min or PaCO ₂ < 32 mmHg (< 4.3 kPa) - WBC > 12,000 cells/mm ³ or < 4,000 cells/mm ³ or > 10% immature (band) forms
Sepsis	Activation of the inflammatory process due to infection.
Hypotension	Systolic blood pressure < 90 mmHg or a reduction of > 40 mmHg from baseline in the absence of other causes of hypotension.
Severe sepsis	Sepsis associated with organ dysfunction, hypoperfusion or hypotension. Hypoperfusion and perfusion abnormalities may include but are not limited to lactic acidosis, oliguria or acute alteration of mental status.
Septic shock	Sepsis with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to lactic acidosis, oliguria, or acute alteration in mental status. Patients who are on inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured.
Refractory septic shock	Septic shock that lasts for > 1 h and does not respond to fluid administration or pharmacological intervention.

3E.4.1 *Physiology and biochemical markers*

Microorganisms reach the urinary tract by way of the ascending, haematogenous, or lymphatic routes. For urosepsis to be established, the pathogens have to reach the bloodstream. The risk of bacteraemia is increased in severe UTIs, such as pyelonephritis and acute bacterial prostatitis, and is facilitated by obstruction of the urinary tract. *E. coli* remains the most prevalent microorganism. In several countries, some bacterial strains can be resistant to quinolones or third-generation cephalosporins. Some microorganisms are multiresistant, such as methicillin-resistant *Staphylococcus aureus* (MRSA), *P. aeruginosa* and *Serratia sp.* and therefore difficult to treat. Most commonly, the condition develops in compromised patients (e.g. those with diabetes or immunosuppression), with typical signs of generalised sepsis associated with local signs of infection. A fatal outcome is described in 20-40% of all patients.

3E.4.1.1 *Cytokines as markers of the septic response*

Cytokines are involved in the pathogenesis of sepsis syndrome. They are peptides that regulate the amplitude and duration of the host inflammatory response. They are released from various cells including monocytes, macrophages and endothelial cells, in response to various infectious stimuli. When they become bound to specific receptors on other cells, cytokines change their behaviour in the inflammatory response. The complex balance between pro- and anti-inflammatory responses is modified in severe sepsis. An immunosuppressive phase follows the initial pro-inflammatory mechanism. Other cytokines that are associated with sepsis are interleukins (ILs) (IL-1, -6, -8) and tumour necrosis factor (TNF)- α . Sepsis may indicate an immune system that is severely compromised and unable to eradicate pathogens or a non-regulated and excessive activation of inflammation, or both. Genetic predisposition is a probable explanation of sepsis in several patients. Mechanisms of organ failure and death in patients with sepsis remain only partially understood [145].

3E.4.1.2 *Procalcitonin is a potential marker of sepsis*

Procalcitonin is the propeptide of calcitonin, but is devoid of hormonal activity. Normally, levels are undetectable in healthy humans. During severe generalised infections (bacterial, parasitic and fungal) with systemic manifestations, procalcitonin levels may rise to > 100 ng/mL. In contrast, during severe viral infections or inflammatory reactions of non-infectious origin, procalcitonin levels show only a moderate or no increase. Procalcitonin monitoring may be useful in patients likely to develop a SIRS of infectious origin and to differentiate from a severe inflammatory status [150, 151] but can presently not be recommended as a diagnostic tool.

3E.5 Disease management

3E.5.1 Prevention

Septic shock is the most frequent cause of death for patients hospitalised for community-acquired and nosocomial infection (20-40%). Sepsis initiates the cascade that progresses to severe sepsis and then septic shock in a clinical continuum. Urosepsis treatment calls for a combination of treatment of the cause (obstruction of the urinary tract), adequate life-support care, and appropriate antibiotic therapy [145]. In such a situation, it is recommended that urologists collaborate with intensive care and infectious disease specialists for the best management of the patient.

3E.5.1.1 Preventive measures of proven or probable efficacy

The most effective methods to prevent nosocomial urosepsis are the same as those used to prevent other nosocomial infections [152, 153]:

- Isolation of all patients infected with multi-resistant organisms to avoid cross-infection.
- Prudent use of antimicrobial agents for prophylaxis and treatment of established infections, to avoid selection of resistant strains. Antibiotic agents should be chosen according to the predominant pathogens at a given site of infection in the hospital environment.
- Reduction in hospital stay. It is well known that long inpatient periods before surgery lead to a greater incidence of nosocomial infections.
- Early removal of indwelling urethral catheters, as soon as allowed by the patient's condition. Nosocomial UTIs are promoted by bladder catheterisation as well as by ureteral stenting [154]. Antibiotic prophylaxis does not prevent stent colonisation, which appears in 100% of patients with a permanent ureteral stent and in 70% of those temporarily stented.
- Use of closed catheter drainage and minimisation of breaks in the integrity of the system, e.g. for urine sampling or bladder wash-out.
- Use of least-invasive methods to release urinary tract obstruction until the patient is stabilised.
- Attention to simple everyday techniques to assure asepsis, including the routine use of protective, disposable gloves, frequent hand disinfection, and using infectious disease control measures to prevent cross-infections.

3E.5.1.2 Appropriate perioperative antimicrobial prophylaxis

For appropriate perioperative antimicrobial prophylaxis see Chapter 3N. The potential side-effects of antibiotics must be considered before their administration in a prophylactic regimen.

3E.5.1.3 Ineffective or counterproductive measures

- Instillation of antibiotic or antiseptic drugs into catheters and drainage bags.
- Use of urinary catheters with antimicrobial coatings [155]*.
- Continuous or intermittent bladder irrigations with antibiotics or urinary antiseptics that increase the risk of infection with resistant bacteria [152, 156].
- Routine administration of antimicrobial drugs to catheterised patients, which reduces the incidence of bacteriuria only for a few days and increases the risk of infection with multi-resistant bacteria [152, 156]. Its use may be reserved for immunosuppressed patients.

*Catheters coated or impregnated with antimicrobials may have efficacy in reduction of bacteriuria but this does not seem to translate to clinical benefit in terms of occurrence of symptomatic infection.

Figure 3: Clinical algorithm for the management of urosepsis

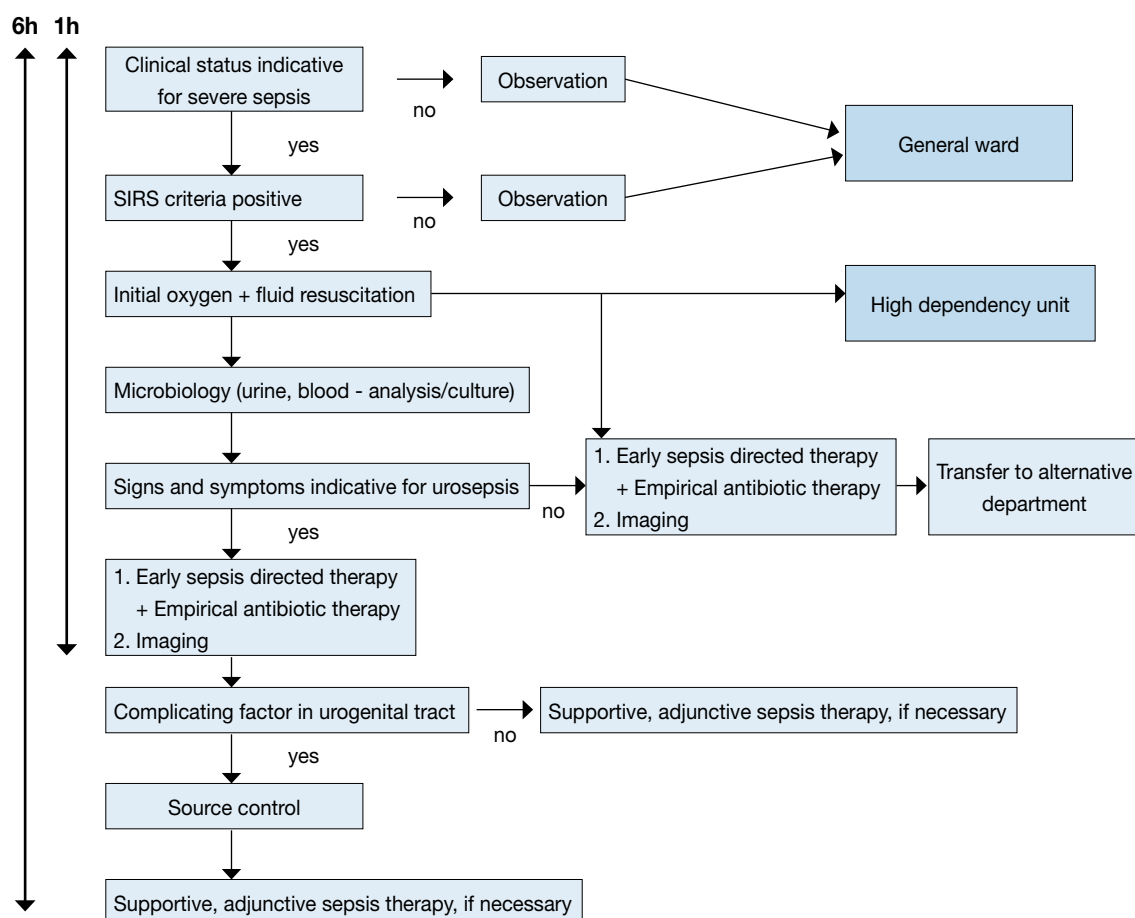


Table 9: Early sepsis therapy

Early sepsis therapy	
Central venous pressure (CVP)	8-12 mmHg
Mean arterial pressure (MAP)	65-90 mmHg
Central venous oxygen (CVO ₂)	≥ 70%
Haematocrit (HKT)	> 30 %
Urine output	> 40 mL/h

Table 10: Levels of therapy in sepsis

Levels of therapy in sepsis	
Causal therapy	1. Antimicrobial treatment 2. Source control
Supportive therapy	1. Haemodynamic stabilisation 2. Airways, respiration
Adjunctive therapy	1. Glucocorticosteroids 2. Intensified insulin therapy

3E.5.2.1 Relief of obstruction

Drainage of any obstruction in the urinary tract and removal of foreign bodies, such as urinary catheters or stones, should lead to resolution of symptoms and recovery. These are key components of the strategy. This condition is an absolute emergency.

3E.5.2.2 Antimicrobial therapy

Empirical initial treatment should provide broad antimicrobial coverage and should later be adapted on the

basis of culture results. The dosage of the antibiotic substances is of paramount importance in patients with sepsis syndrome and should generally be high, with the exception of patients in renal failure. Antimicrobials must be administered no later than 1 h after clinical assumption of sepsis (Figure 3). The antibacterial treatment options are summarised in Appendix 4.3 and 4.4.

3E.5.2.3 *Adjunctive measures*

The management of fluid and electrolyte balance is a crucial aspect of patient care in sepsis syndrome; particularly when the clinical course is complicated by shock [156, 157]. The use of human albumin is debatable. Early therapy aimed at restoring clinical indicators of vital organ above specific thresholds (goal-directed therapy) has been shown to reduce mortality [158]. Volæmic expansion and vasopressor therapy have a considerable impact on the outcome. Early intervention with appropriate measures to maintain adequate tissue perfusion and oxygen delivery by prompt institution of fluid therapy, stabilisation of arterial pressure, and providing sufficient oxygen transport capacity are highly effective.

Hydrocortisone (with a debate on dosage) is useful in patients with relative insufficiency in the pituitary gland-adrenal cortex axis (adrenocorticotropin test) [159].

Tight blood glucose control by administration of insulin doses up to 50 U/h is associated with a reduction in mortality [160].

The best strategy has been summarised and graded according to a careful evidence-based methodology in the recently published 'Surviving Sepsis Guidelines' [161].

In conclusion, sepsis syndrome in urology remains a severe situation with an appreciable mortality rate. A recent campaign, 'Surviving Sepsis Guidelines', aims to reduce mortality by 25% in the next few years [161]. Early recognition of the symptoms may decrease the mortality by timely treatment of urinary tract disorders, e.g. obstruction, or urolithiasis. Adequate life-support measures and appropriate antibiotic treatment provide the best conditions for improving patient survival. The prevention of sepsis syndrome is dependent on good practice to avoid nosocomial infections and using ABP and therapy in a prudent and well-accepted manner.

Acknowledgement

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3F CATHETER-ASSOCIATED UTIs

3F.1 Introduction

Based on the EAU Guidelines published in 2007 (ISBN-13:978-90-70244-59-0), the following text presents the findings of a comprehensive update produced as a collaborative effort by the ESIU (a full EAU section office), the Urological Association of Asia, the Asian Association of UTI/STD, the Western Pacific Society for Chemotherapy, the Federation of European Societies for Chemotherapy and Infection, and the International Society of Chemotherapy for Infection and Cancer. This text was recently published as "The European and Asian guidelines on management and prevention of catheter-associated urinary tract infections" [47]. Since the complete document is available online, only the abstract and a summary of the recommendations are presented here.

3F.2 Methods

The extensive literature regarding the development, therapy and prevention of catheter-associated UTIs (CAUTIs) was surveyed. Systematic searching involved: meta-analyses of RCTs available in Medline, the Cochrane Central Register of Controlled Trials, and also other relevant publications, rating them on the basis of their quality. Studies were identified through a PubMed search. The recommendations of the studies, rated according to a modification of the US Department of Health and Human Services (1992), give a close-to-evidence-based guideline for all medical disciplines, with special emphasis on urology, in which catheter care is an important issue.

3F.3 Classification systems

The survey found that the urinary tract is the commonest source of nosocomial infection, particularly when the bladder is catheterised (LE: 2a). Most CAUTIs are derived from the patient's own colonic flora (LE: 2b) and the catheter predisposes to UTI in several ways. The most important risk factor for the development of catheter-associated bacteriuria is the duration of catheterisation (LE: 2a). Most episodes of short-term catheter-

associated bacteriuria are asymptomatic and are caused by a single organism (LE: 2a). Further organisms tend to be acquired by patients who are catheterised for > 30 days.

3F.4 Diagnostic evaluation

The clinician should be aware of two priorities: the catheter system should remain closed and the duration of catheterisation should be minimal (GR: A). The use of nurse-based or electronic reminder systems to remove unnecessary catheters can decrease the duration of catheterisation and the risk of CAUTI (LE: 2a). The drainage bag should be always kept below the level of the bladder and the connecting tube (GR: B). In case of short-term catheterisation, routine prophylaxis with systemic antibiotics is not recommended (GR: B). There are sparse data about ABP in patients on long-term catheterisation, therefore, no recommendation can be made (GR: C). For patients using intermittent catheterisation, routine ABP is not recommended (GR: B). Antibiotic irrigation of the catheter and bladder is of no advantage (GR: A). Healthcare workers should be constantly aware of the risk of cross-infection between catheterised patients. They should observe protocols on hand washing and the need to use disposable gloves (GR: A).

3F.5 Disease management

A minority of patients can be managed with the use of the non-return (flip) valve catheters, thus avoiding the closed drainage bag. Such patients may exchange the convenience of on-demand drainage with an increased risk of infection. Patients with urethral catheters in place for > 10 years should be screened annually for bladder cancer (GR: C). Clinicians should always consider alternatives to indwelling urethral catheters that are less prone to causing symptomatic infection. In appropriate patients, suprapubic catheters, condom drainage systems and intermittent catheterisation are each preferable to indwelling urethral catheterisation (GR: B). While the catheter is in place, systemic antimicrobial treatment of asymptomatic catheter-associated bacteriuria is not recommended (GR: A), except for some special cases. Routine urine culture in an asymptomatic catheterised patient is also not recommended (GR: C) because treatment is in general not necessary. Antibiotic treatment is recommended only for symptomatic infection (GR: B). After initiation of empirical treatment, usually with broad-spectrum antibiotics based on local susceptibility patterns (GR: C), the choice of antibiotics might need to be adjusted according to urine culture results (GR: B). Long-term antibiotic suppressive therapy is not effective (GR: A).

The summary of recommendations in the present Guidelines is based on this extensive review [47] updated data from chapter 9 of Urological Infections [2] and a recent large scale study on catheters [155].

3F.6 Summary of recommendations

Recommendations		GR
<i>General aspects</i>		
1.	Written catheter care protocols are necessary.	B
2.	Health care workers should observe protocols on hand hygiene and the need to use disposable gloves between catheterised patients.	A
<i>Catheter insertion and choice of catheter</i>		
3.	An indwelling catheter should be introduced under antiseptic conditions.	B
4.	Urethral trauma should be minimised by the use of adequate lubricant and the smallest possible catheter calibre.	B
5.	Antibiotic-impregnated catheters may decrease the frequency of asymptomatic bacteriuria when used for a few days. There is, however, no evidence that they decrease symptomatic infection. Therefore, they cannot be recommended routinely.	B
6.	Silver alloy catheters have been shown in some studies to significantly reduce the incidence of asymptomatic bacteriuria, but only when used for < 1 week. There was weak evidence or contradictory results regarding the reduction of symptomatic UTI. More large scale clinical research is needed and no clear recommendation can be given.	B
<i>Prevention</i>		
7.	The catheter drainage system should remain closed.	A
8.	The duration of catheterisation should be minimal.	A
9.	Topical antiseptics or antibiotics applied to the catheter, urethra or meatus are not recommended.	A
10.	Benefits from prophylactic antibiotics and antiseptic substances have never been established, therefore, they are not recommended.	A

11.	Removal of the indwelling catheter after non-urological operation before midnight might be beneficial.	B
12.	Long-term indwelling catheters should be changed at intervals adapted to the individual patient, but must be changed before blockage is likely to occur. However, there is no evidence for the exact intervals of changing catheters.	B
13.	Chronic antibiotic suppressive therapy is not recommended.	A
14.	The drainage bag should always be kept below the level of the bladder and the connecting tube.	B
<i>Diagnostics</i>		
15.	Routine urine culture in asymptomatic catheterised patients is not recommended.	B
16.	Urine, and in septic patients, also blood for culture must be taken before any antimicrobial therapy is started.	C
17.	Febrile episodes are only found in < 10% of catheterised patients living in a long-term facility. It is therefore extremely important to rule out other sources of fever.	A
<i>Treatment</i>		
18.	While the catheter is in place, systemic antimicrobial treatment of asymptomatic catheter-associated bacteriuria is not recommended, except in certain circumstances, especially before traumatic urinary tract interventions.	A
19.	In case of asymptomatic candiduria, neither systemic nor local antifungal therapy is indicated, but removal of the catheter or stent should be considered.	A/C
20.	Antimicrobial treatment is recommended only for symptomatic infection.	B
21.	In case of symptomatic CAUTI, it might be reasonable to replace or remove the catheter before starting antimicrobial therapy if the indwelling catheter has been in place for > 7 days.	B
22.	For empirical therapy, broad-spectrum antibiotics should be given based on local susceptibility patterns.	C
23.	After culture results are available, antibiotic therapy should be adjusted according to pathogen sensitivity.	B
24.	In case of candiduria associated with urinary symptoms, or if candiduria is the sign of systemic infection, systemic therapy with antifungals is indicated.	B
25.	Bacteriuria after catheter removal in elderly patients does usually not require any treatment unless symptomatic.	C
<i>Alternative drainage systems</i>		
26.	There is limited evidence that postoperative intermittent catheterisation reduces the risk of bacteriuria compared with indwelling catheters. No recommendation can be made.	C
27.	In appropriate patients, a suprapubic, condom drainage system or intermittent catheter is preferable to an indwelling urethral catheter.	B
28.	There is little evidence to suggest that antibiotic prophylaxis decreases bacteriuria in patients using intermittent catheterisation, therefore, it is not recommended.	B
<i>Long-term follow up</i>		
29.	Patients with urethral catheters in place for > 10 years should be screened for bladder cancer.	C

3G UTIs IN CHILDREN

3G.1 Introduction

In children, UTIs are a frequent health problem, with the incidence only a little lower than that of upper respiratory and digestive infections. Incidence varies depending on age and sex. In the first year of life, mostly the first 3 months, UTI is more common in boys (3.7%) than in girls (2%), after which the incidence changes to 3% in girls and 1.1% in boys. Paediatric UTI is the most common cause of fever of unknown origin in boys aged < 3 years. The clinical presentation of UTI in infants and young children can vary from fever to gastrointestinal and lower or upper urinary tract symptoms.

Investigation should be undertaken after two episodes of UTI in girls and one in boys (GR: B). The objective is to rule out the unusual occurrence of obstruction, vesicoureteric reflux (VUR) and dysfunctional voiding, e.g. as caused by a neuropathic disorder.

Chronic pyelonephritic renal scarring develops very early in life due to the combination of a UTI, intrarenal reflux and VUR. It sometimes arises in utero due to dysplasia. Although rare, renal scarring may lead to severe long-term complications such as hypertension and chronic renal failure.

VUR is treated with long-term prophylactic antibiotics (GR: B). Surgical re-implantation or endoscopic treatment is reserved for the small number of children with breakthrough infection (GR: B).

For treatment of UTI in children, short courses are not advised and therefore treatment is continued for 5-7 days and longer (GR: A). If the child is severely ill with vomiting and dehydration, hospital admission is required and parenteral antibiotics are given initially (GR: A). For further information please refer to the EAU Paediatric Urology Guidelines.

3G.2 Epidemiology, aetiology and pathophysiology

The urinary tract is a common source of infection in children and infants. It represents the most common bacterial infection in children < 2 years of age [162] (LE: 2a). The outcome of a UTI is usually benign, but in early infancy, it can progress to renal scarring, especially when associated with congenital anomalies of the urinary tract. Delayed sequelae related to renal scarring include hypertension, proteinuria, renal damage and even chronic renal failure, which requires dialysis treatment in a significant number of adults [163] (LE: 2a).

The risk of UTI during the first decade of life is 1% in males and 3% in females [6]. It has been suggested that 5% of schoolgirls and up to 0.5% of schoolboys undergo at least one episode of UTI during their school life. The incidence is different for children < 3 months of age, when it is more common in boys. The incidence of ABU is 0.7-3.4% in neonates, 0.7-1.3% in infants < 3 months of age, and 0.2-0.8% in preschool boys and girls [6]. The incidence of symptomatic bacteriuria is 0.14% in neonates, with a further increase to 0.7% in boys and 2.8% in girls aged < 6 months. The overall recurrence rate for the neonatal period has been reported to be 25% [6, 164].

The common pathogenic sources are Gram-negative, mainly enteric, bacteria. Of these, *E. coli* is responsible for 90% of UTI episodes [165]. Gram-positive bacteria (particularly enterococci and staphylococci) represent 5-7% of cases. Hospital-acquired infections show a wider pattern of aggressive bacteria, such as *Klebsiella*, *Serratia* and *Pseudomonas sp.* Groups A and B streptococci are relatively common in new-born infants [166]. There is an increasing trend towards the isolation of *S. saprophyticus* in UTIs in children, although the role of this bacterium is still debatable [167].

The urinary tract is a sterile space with an impermeable lining. Retrograde ascent is the most common mechanism of infection. Nosocomial infection and involvement as part of a systemic infection are less common [168].

Obstruction and dysfunction are among the most common causes of urinary infection. Phimosis predisposes to UTI [169, 170] (LE: 2a). Enterobacteria derived from intestinal flora colonise the preputial sac, glandular surface and the distal urethra. Among these bacteria are strains of *E. coli* that express P fimbriae, which adhere to the inner layer of the preputial skin and to uroepithelial cells [171].

A wide variety of congenital urinary tract abnormalities can cause UTIs through obstruction, e.g. urethral valves, ureteropelvic junction obstruction or non-obstructive urinary stasis (e.g. prune belly syndrome, or VUR). More mundane but significant causes of UTIs include labial adhesion and chronic constipation [167].

Dysfunctional voiding in an otherwise normal child may result in infrequent bladder emptying aided by delaying manoeuvres, e.g. crossing legs, sitting on heels [172]. Neuropathic bladder dysfunction (e.g. spina bifida, or sphincter dyssynergia) may lead to post-void residual urine and secondary VUR [164].

The link between renal damage and UTIs is controversial. The mechanism in obstructive nephropathy is self-evident, but more subtle changes occur when there is VUR. Almost certainly, the necessary components include VUR, intrarenal reflux and UTI. These must all work together in early childhood when the growing kidney is likely to be susceptible to parenchymal infection. Later on in childhood, the presence of bacteriuria seems irrelevant to the progression of existing scars or the very unusual formation of new scars. Another confounding factor is that many so-called scars are dysplastic renal tissue which develop in utero [173].

Symptoms are non-specific, and vary with the age of the child and the severity of the disease. Epididymo-orchitis is extremely unusual. With scrotal pain and inflammation, testicular torsion has to be considered.

A UTI in neonates may be non-specific and with no localisation. In small children, a UTI may present with gastrointestinal signs, such as vomiting and diarrhoea. In the first weeks of life, 13.6% of patients with fever have a UTI [174]. Rarely, septic shock is the presentation. Signs of UTI may be vague in small children, but later on, when they are older than 2 years, frequent voiding, dysuria and suprapubic, abdominal or lumbar pain may appear with or without fever.

3G.3 Classification systems

UTIs may be classified as a first episode or recurrent, or according to severity (simple or severe).

Recurrent UTI may be subclassified into three groups [168]:

- *Unresolved infection*: subtherapeutic level of antimicrobial, non-compliance with treatment, malabsorption, resistant pathogens.

- *Bacterial persistence*: may be due to a nidus for persistent infection in the urinary tract. Surgical correction or medical treatment for urinary dysfunction may be needed.
- *Reinfection*: each episode is a new infection acquired from periurethral, perineal or rectal flora.

From the clinical point of view, severe and simple forms of UTIs should be differentiated because to some extent the severity of symptoms dictates the degree of urgency with which investigation and treatment are to be undertaken (Table 10).

Table 10: Clinical classification of UTIs in children

Severe UTI	Simple UTI
Fever > 39°C	Mild pyrexia
Persistent vomiting	Good fluid intake
Serious dehydration	Slight dehydration
Poor treatment compliance	Good treatment compliance

Severe UTI: Severe UTI is related to the presence of fever of > 39°C, the feeling of being ill, persistent vomiting, and moderate or severe dehydration.

Simple UTI: A child with a simple UTI may have only mild pyrexia, but is able to take fluids and oral medication. The child is only slightly or not dehydrated and has a good expected level of compliance. When a low level of compliance is expected, such a child should be managed as one with a severe UTI.

3G.4 Diagnostic evaluation

3G.4.1 Physical examination

It is mandatory to look for phimosis, labial adhesion, signs of pyelonephritis, epididymo-orchitis, and stigmata of spina bifida, e.g. hairy patch on the sacral skin. The absence of fever does not exclude the presence of an infective process.

3G.4.2 Laboratory tests

The definitive diagnosis of infection in children requires a positive urine culture [168, 175]. Urine must be obtained under bacteriologically reliable conditions when undertaking a urine specimen culture [176]. A positive urine culture is defined as the presence of > 100,000 cfu/mL of one pathogen. The urine specimen may be difficult to obtain in a child < 4 years old, and different methods are advised because there is a high risk of contamination [177, 178].

3G.4.2.1 Collection of the urine

Suprapubic bladder aspiration: This is the most sensitive method, even though urine may be obtained in 23-99% of cases [168, 177].

Bladder catheterisation: This is also a very sensitive method, even though there is the risk of introduction of nosocomial pathogens [168, 179].

Plastic bag attached to the genitalia: Prospective studies have shown a high incidence of false-positive results, ranging from 85 - 99% [168, 177]. It is helpful when the culture is negative [168, 177] and has a PPV of 15% [176]. To obtain a urine sample in the best condition in children < 2 years of age (girls and uncircumcised boys without sphincteric control), it is better to use suprapubic bladder aspiration or bladder catheterisation. In older children with sphincteric control, MSU collection is possible and reliable [177].

3G.4.2.2 Quantification of bacteriuria

The final concentration of bacteria in urine is directly related to the method of collection, diuresis, and method of storage and transport of the specimen [175]. The classical definition of significant bacteriuria of > 10⁵ cfu/mL is still used and depends on the clinical environment [175, 178].

The presence of pyuria (> 5 leukocytes per field) and bacteriuria in a fresh urine sample reinforce the clinical diagnosis of UTI [178].

In boys, when the urine is obtained by bladder catheterisation, the urine culture is considered positive with > 10⁴ cfu/mL. Even though Hoberman [180] has identified a microorganism in 65% of cases with colony counts between 10,000 and 50,000 cfu/mL, there was a mixed growth pattern suggesting contamination. In these cases, it is better to repeat the culture or to evaluate the presence of other signs, such

as pyuria, nitrites or other biochemical markers [175]. The collection of MSU or in a collecting bag of $\geq 10^5$ cfu/mL is considered positive [176] (Table 11).

Table 11: Criteria for UTI in children

Urine specimen from suprapubic bladder puncture	Urine specimen from bladder catheterisation	Urine specimen from midstream void
Any number of cfu/mL (at least 10 identical colonies)	$\geq 1,000$ -50,000 cfu/mL	$\geq 10^4$ cfu/mL with symptoms $\geq 10^5$ cfu/mL without symptoms

3G.4.2.3 Other biochemical markers

The presence of other biochemical markers in a urine sample are useful to establish the diagnosis of UTI [168]. The most frequent markers are nitrite and leukocyte esterase usually combined in a dipstick test.

Nitrite: This is the degradation product of nitrate in bacterial metabolism, particularly in Gram-negative bacteria. When an infection is caused by Gram-positive bacteria, the test may be negative [168, 176]. Limitations of the nitrite test include:

- not all uropathogens reduce nitrate to nitrite, e.g. *P. aeruginosa*, or enterococci;
- even nitrite-producing pathogens may show a negative test result, due to the short transit time in the bladder in cases of high diuresis and urine dilution, e.g. neonates;
- the nitrite test has a sensitivity of only 45-60%, but a very good specificity of 85-98% [168, 178, 181].

Leukocyte esterase: This is produced by the activity of leukocytes. The test for leukocyte esterase has a sensitivity of 48-86% and a specificity of 17-93% [168, 178, 180, 181].

A combination of nitrite and leukocyte esterase testing improves sensitivity and specificity, but carries the risk of false-positive results [181].

The dipstick test has become useful to exclude rapidly and reliably the presence of a UTI, provided both nitrite and leukocyte esterase tests are negative. If the tests are positive, it is better to confirm the results in combination with the clinical symptoms and other tests [178, 181].

Bacteriuria without pyuria may be found:

- in bacterial contamination;
- in colonisation (ABU);
- when collecting a specimen before the onset of an inflammatory reaction.

In such cases, it is advisable to repeat the urinalysis after 24 h to clarify the situation. Even in febrile children with a positive urine culture, the absence of pyuria may cast doubt on the diagnosis of UTI. Instead, ABU with a concomitant septic focus responsible for the febrile syndrome has to be considered.

Bacteriuria without pyuria is found in 0.5% of specimens. This figure corresponds well with the estimated rate of ABU in childhood [180, 182] (LE: 2a).

Pyuria without bacteriuria may be due to:

- incomplete antimicrobial treatment of UTI;
- urolithiasis and foreign bodies;
- infections caused by *M. tuberculosis* and other fastidious bacteria, e.g. *C. trachomatis*.

Thus, either bacteriuria or pyuria may not be considered reliable parameters to diagnose or exclude UTI. Their assessment can be influenced by other factors, such as the degree of hydration, method of specimen collection, mode of centrifugation, volume in which sediment is resuspended and subjective interpretation of results [183]. However, according to Landau et al. [184], pyuria in febrile children is indicative of acute pyelonephritis.

For all of these reasons, in neonates and children < 6 months of age, either pyuria, bacteriuria or the nitrite test, separately, have minimal predictive value for UTI [185, 186] (LE: 3). In contrast, the PPV of significant Gram staining with pyuria is 85% [180] (LE: 2b). In older children, pyuria with a positive nitrite test is more reliable for the diagnosis of UTI, with a PPV of 98%.

Combining bacteriuria and pyuria in febrile children, the findings of ≥ 10 WBC/mm³ and $\geq 50,000$ cfu/mL in a specimen collected by catheterisation are significant for a UTI, and discriminate between infection and contamination [180, 185].

C-reactive protein: Although non-specific in febrile children with bacteriuria, C-reactive protein seems to be useful in distinguishing between acute pyelonephritis and other causes of bacteriuria. It is considered

significant at a concentration > 20 µg/mL.

Urinary N-acetyl-b-glucosaminidase: This is a marker of tubular damage. It is increased in febrile UTI and may become a reliable diagnostic marker for UTIs, although it is also elevated in VUR [187].

IL-6: The clinical use of urinary concentrations of IL-6 in UTIs [188] is still at the research stage.

3G.4.3 Imaging of the urinary tract

A gold standard imaging technique has to be cost-effective, painless, safe, and have minimal or no radiation, as well as have the ability to detect any significant structural anomaly. Current techniques do not fulfil all such requirements.

3G.4.3.1 Ultrasound

Ultrasound (US) has become very useful in children because of its safety, speed and high accuracy in identifying the anatomy and size of the renal parenchyma and collecting system [189]. It is subjective and therefore operator-dependent, and gives no information on renal function. However, scars can be identified, although not as well as with Tc-99m DMSA scanning [189, 190] (LE: 2a). This technique has been shown to be very sensitive and excretory urography must be reserved only for when images need to be morphologically clarified [191] (LE: 2a).

3G.4.3.2 Radionuclide studies

Tc-99m DMSA is a radiopharmaceutical that is bound to the basement membrane of proximal renal tubular cells; half of the dose remains in the renal cortex after 6 h. This technique is helpful in determining functional renal mass and ensures an accurate diagnosis of cortical scarring by showing areas of hypoactivity, which indicates lack of function. A UTI interferes with the uptake of this radiotracer by the proximal renal tubular cells, and may show areas of focal defect in the renal parenchyma. A star-shaped defect in the renal parenchyma may indicate an acute episode of pyelonephritis. A focal defect in the renal cortex usually indicates a chronic lesion or a renal scar [192-194] (LE: 2a).

Focal scarring or a smooth uniform loss of renal substance as demonstrated by Tc-99m DMSA is generally regarded as being associated with VUR (reflux nephropathy) [195, 196]. However, Rushton et al. [197] have stated that significant renal scarring may develop, regardless of the existence or absence of VUR. Ransley and Risdon [198] have reported that Tc-99m DMSA shows a specificity of 100% and sensitivity of 80% for renal scarring.

The use of Tc-99m DMSA scanning can be helpful in the early diagnosis of acute pyelonephritis. About 50-85% of children show positive findings in the first week. Minimal parenchymal defects, when characterised by a slight area of hypoactivity, can resolve with antimicrobial therapy [199, 200]. However, defects lasting > 5 months are considered to be renal scarring [201] (LE: 2a).

Tc-99m DMSA scans are considered more sensitive than excretory urography and US in the detection of renal scars [202-205]. It remains questionable whether radionuclide scans can substitute echography as a first-line diagnostic approach in children with a UTI [206, 207].

3G.4.3.3 Cystourethrography

Conventional voiding cystourethrography (VCU): This is the most widely used radiological exploration for the study of the LUT and especially of VUR. It is considered mandatory in the evaluation of UTIs in children < 1 year of age. Its main drawbacks are the risk of infection, the need for retrogrades filling of the bladder, and the possible deleterious effect of radiation on children [208]. In recent years, tailored low-dose fluoroscopic VCU has been used for the evaluation of VUR in girls to minimise radiological exposure [209]. VCU is mandatory in the assessment of febrile childhood UTI, even in the presence of normal US. Up to 23% of these patients may reveal VUR [210].

Radionuclide cystography (indirect): This investigation is performed by prolonging the period of scanning after the injection of Tc-99m diethylene triamine pentaacetate (DTPA) or mercaptoacetyl triglycine (MAG-3) as part of dynamic renography. It represents an attractive alternative to conventional cystography, especially when following patients with reflux, because of its lower dose of radiation. Disadvantages are poor image resolution and difficulty in detecting LUT abnormalities [211, 212].

Cystosonography: Contrast-material-enhanced voiding US has been introduced for the diagnoses of VUR without irradiation [207, 212]. Further studies are necessary to determine the role of this new imaging modality in UTI.

3G.4.3.4 Additional imaging

Excretory urography remains a valuable tool in the evaluation of the urinary tract in children, but its use in UTIs is debatable unless preliminary imaging has demonstrated abnormalities that require further investigation. The major disadvantages in infants are the risks of side-effects from exposure to contrast media and radiation [213]. However, the role of excretory urography is declining with the increasing technical superiority of CT [214] and MRI. However, the indications for their use is still limited in UTI.

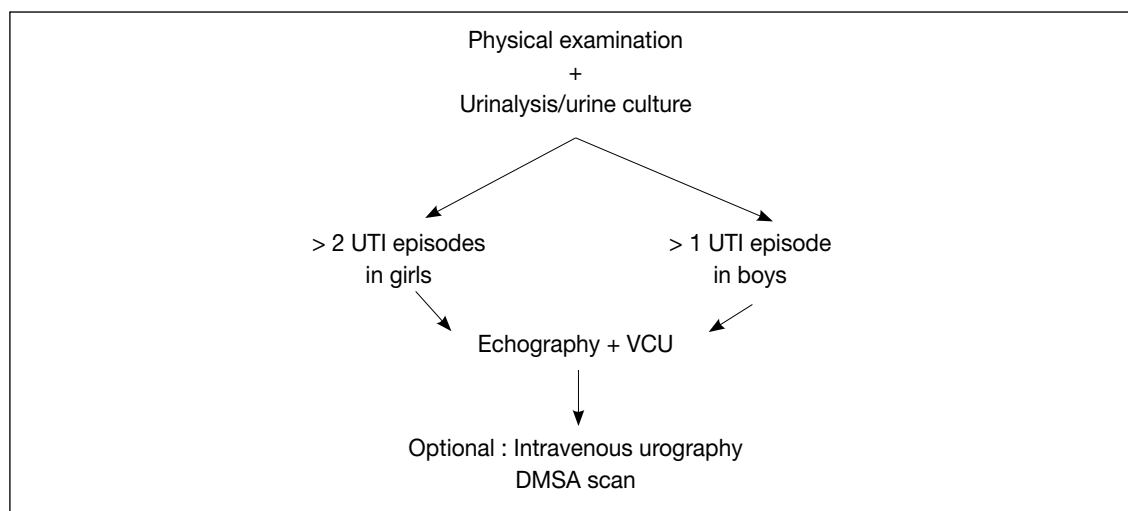
3G.4.3.5 Urodynamic evaluation

When voiding dysfunction is suspected, e.g. incontinence, residual urine, increased bladder wall thickness, urodynamic evaluation with uroflowmetry, (video) cystometry, including pressure flow studies, and electromyography should be considered.

3G.4.4 Schedule of investigation

Screening of infants for ABU is unlikely to prevent pyelonephritic scar formation, as these usually develop very early in infancy. Only a minority of children with a UTI have an underlying urological disorder, but when present, such a disorder can cause considerable morbidity. Thus, after a maximum of two UTI episodes in a girl and one in a boy, investigations should be undertaken (Figure 4), but not in the case of ABU [210-213, 215, 216]. The need for DTPA/MAG-3 scanning is determined by the US findings, particularly if there is suspicion of an obstructive lesion.

Figure 4: Schedule of investigation of a UTI in a child



DMSA = dimercaptosuccinic acid; UTI = urinary tract infection; VCU = voiding cystourethrography.

3G.5 Disease management

Treatment has four main goals:

- elimination of symptoms and eradication of bacteriuria in the acute episode;
- prevention of renal scarring;
- prevention of a recurrent UTI;
- correction of associated urological lesions.

3G.5.1 Severe UTIs

A severe UTI requires adequate parenteral fluid replacement and appropriate antimicrobial treatment, preferably with cephalosporins (third generation). If a Gram-positive UTI is suspected by Gram stain, it is useful to administer aminoglycosides in combination with ampicillin or amoxycillin/clavulanate [217] (LE: 2a). Antimicrobial treatment has to be initiated on an empirical basis, but should be adjusted according to culture results as soon as possible. In patients with an allergy to cephalosporins, aztreonam or gentamicin may be used. When aminoglycosides are necessary, serum levels should be monitored for dose adjustment. Chloramphenicol, sulphonamides, tetracyclines, rifampicin, amphotericin B and quinolones should be avoided. The use of ceftriaxone must also be avoided due to its undesired side effect of jaundice.

A wide variety of antimicrobials can be used in older children, with the exception of tetracyclines (because of tooth staining). Fluorinated quinolones may produce cartilage toxicity [218], but if necessary, may be used as second-line therapy in the treatment of serious infections, because musculoskeletal adverse events are of moderate intensity and transient [219, 220]. For a safety period of 24-36 h, parenteral therapy should be

administered. When the child becomes afebrile and is able to take fluids, he/she may be given an oral agent to complete the 10-14 days of treatment, which may be continued on an outpatient basis. This provides some advantages, such as less psychological impact on the child and more comfort for the whole family.

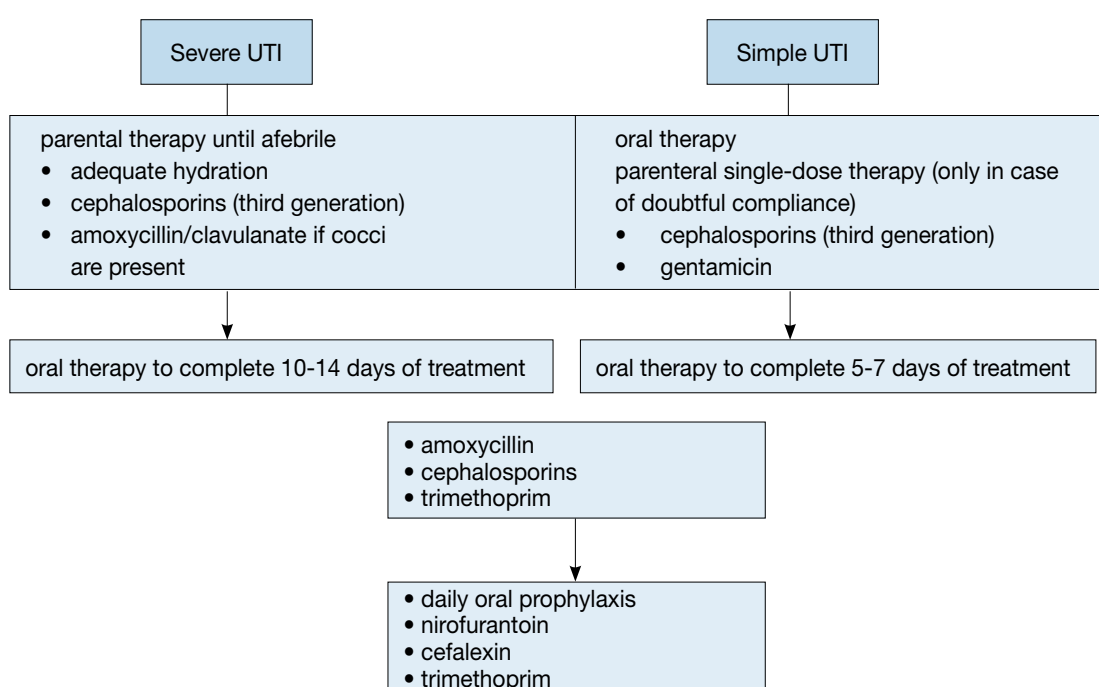
It is also less expensive, well tolerated and eventually prevents opportunistic infections [180]. The preferred oral antimicrobials are: trimethoprim (TMP), co-trimoxazole (TMP plus sulphamethoxazole), an oral cephalosporin, or amoxycillin/clavulanate. However, the indications for TMP are declining in areas with increasing resistance.

In children < 3 years of age, who have difficulty taking oral medications, parenteral treatment for 7-10 days seems advisable, with similar results to those with oral treatment [221].

If there are significant abnormalities in the urinary tract (e.g. VUR, or obstruction), appropriate urological intervention should be considered. If renal scarring is detected, the patient will need careful follow-up by a paediatrician in anticipation of sequelae such as hypertension, renal function impairment, and recurrent UTI.

An overview of the treatment of febrile UTIs in children is given in Figure 5 and the dosing of antimicrobial agents is outlined in Table 12 [222].

Figure 5: Treatment of febrile UTIs in children



3G.5.2 Simple UTIs

A simple UTI is considered to be a low-risk infection in children. Oral empirical treatment with TMP, an oral cephalosporin or amoxycillin/clavulanate is recommended, according to the local resistance pattern. The duration of treatment in uncomplicated UTIs treated orally should be 5-7 days [223, 224] (LE: 1b). A single parenteral dose may be used in cases of doubtful compliance and with a normal urinary tract [225] (LE: 2a). If the response is poor or complications develop, the child must be admitted to hospital for parenteral treatment [226].

3G.5.3 Prophylaxis

If there is an increased risk of pyelonephritis, e.g. VUR, and recurrent UTI, low-dose ABP is recommended [227, 228] (LE: 2a). It may also be used after an acute episode of UTI until the diagnostic work-up is completed. The most effective antimicrobial agents are: nitrofurantoin, TMP, cephalexin and cefaclor [227].

Acknowledgement

With our grateful thanks, the chapter on UTIs in children was updated also by Jorge Caffaratti Sfulcini, Paediatric Urology, Fundació Puigvert, Barcelona, Spain, as co-author.

Table 12: Dosing of antimicrobial agents in children aged 3 months to 12 years*

Antimicrobial agent	Application	Age	Total dose per day	No. of doses per day
Ampicillin	Intravenous	3-12 months	100-300 mg/kg BW	3
Ampicillin	Intravenous	1-12 years	60-150 (-300) mg/kg BW	3
Amoxycillin	Oral	3 months to 12 years	50-100 mg/kg BW	2-3
Amoxycillin/clavulanate	Intravenous	3 months to 12 years	60-100 mg/kg BW	3
Amoxycillin/clavulanate	Oral	3 months to 12 years	37.5-75 mg/kg BW	2-3
Cephalexin				
Treatment	Oral	3 months to 12 years	50-100 mg/kg BW	3
Prophylaxis	Oral	1-12 years	10 mg/kg BW	1-2
Cefaclor				
Treatment	Oral	3 months to 12 years	50-100 mg/kg BW	3
Prophylaxis	Oral	1-12 years	10 mg/kg BW	1-2
Cefixime	Oral	3 months to 12 years	8-12 mg/kg BW	1-2
Ceftriaxone	Intravenous	3 months to 12 years	50-100 mg/kg BW	1
Aztreonam	Intravenous	3 months to 12 years	(50)-100 mg/kg BW	3
Gentamicin	Intravenous	3-12 months	5-7.5 mg/kg BW	1-3
Gentamicin	Intravenous	1-2 years	5 mg/kg BW	1-3
Trimethoprim				
Treatment	Oral	1-12 years	6 mg/kg BW	2
Prophylaxis	Oral	1-12 years	1-2 mg/kg BW	1
Nitrofurantoin				
Treatment	Oral	1-12 years	3-5 mg/kg BW	2
Prophylaxis	Oral	1-12 years	1 mg/kg BW	1-2

BW = body weight. * Adapted from [222].

3H URETHRITIS

3H.1 Introduction

Inflammation of the urethra presents usually with symptoms of the LUT and must be distinguished from other infections of the LUT. For the purpose of these Guidelines, urethritis due to microbiological invasion and requiring antibiotic treatment is reviewed.

3H.2 Methods

These recommendations are based on a review of several European national guidelines updates and in line with the CDC on STD [229-232].

3H.3 Epidemiology, aetiology and pathogenesis

From a therapeutic and clinical point of view, gonorrhoeal urethritis (GU) has to be differentiated from non-gonococcal urethritis (NGU). In Central Europe, NGU is much more frequent than GU. NGU is common, but up to about 50% of cases have no defined aetiology [233]. There is a correlation between promiscuity and low socioeconomic status and the frequency of infections due to *Neisseria gonorrhoeae* and *C. trachomatis*. Infection is spread by sexual contact.

Pathogens include *N. gonorrhoeae* (NG), *C. trachomatis* (CT), *Mycoplasma genitalium* (MG) and *Trichomonas vaginalis* (TV), and *Ureaplasma urealyticum* (UU). The frequency of the different species varies between patient populations [233-238]. In a US study NGU with diagnosed aetiology were: CT in 22.3%, MG in 12.5%, TV in 2.5%, and UU in 24.0%, with multiple pathogens detected in 9.5% and no aetiology in [233]. *Mycoplasma hominis* probably does not cause urethritis. In most cases, however, *Mycoplasma* or *Ureaplasma* spp. are by asymptomatic colonisation of the urogenital tract.

Causative agents either remain extracellularly on the epithelial layer or penetrate into the epithelium (*N. gonorrhoeae* and *C. trachomatis*) and cause pyogenic infection. Although arising from urethritis, chlamydiae

and gonococci can spread further through the urogenital tract to cause epididymitis in men or cervicitis, endometritis and salpingitis in women. Recent evidence has suggested that *Mycoplasma genitalium* can also cause cervicitis and pelvic inflammatory disease in women [239] (LE: 3).

Mucopurulent or purulent discharge, alguria, dysuria and urethral pruritus are symptoms of urethritis. However, many infections of the urethra are asymptomatic.

3H.4 Diagnostic evaluation

A Gram stain of a urethral discharge or a urethral smear that shows more than five leukocytes per high power field ($\times 1,000$) and eventually, gonococci located intracellularly as Gram-negative diplococci, indicate pyogenic urethritis [240] (LE: 3, GR: B). The Gram stain is a rapid diagnostic test for evaluating urethritis. Laboratories should use validated nucleic acid amplification tests (NAATs) to detect chlamydia and gonorrhoea which are better than any of the other tests available for the diagnosis of chlamydial and gonococcal infections with respect to overall sensitivity, specificity, and ease of specimen transport [241]. *N. gonorrhoeae* and chlamydia cultures are mainly to evaluate treatment failures and monitor developing resistance to current treatment.

In all patients with urethritis, and when sexual transmission is suspected, the aim should be to identify the pathogenic organisms. If an amplification system is used for identifying the pathogens, the first voiding urine specimen can be taken instead of a urethral smear. *Trichomonas* sp. can usually be identified microscopically.

3H.5 Disease management

3H.5.1 Treatment of gonococcal urethritis

Table 13: Recommendations of antimicrobials for the treatment of gonorrhoea

As first choice treatment	
•	ceftriaxone, 1 g intramuscularly (with local anaesthetic) or intravenously as a single dose <u>plus</u>
•	azithromycin, 1.0-1.5 g (3 tablets a 0.5 g) orally as a single dose
•	If i.m. injection contraindicated and i.v. administration not possible: cefixime 800 mg p.o. (instead of ceftriaxone)
Alternative regimens, only if susceptibility is established	
•	cefixime, 400 mg p.o. as single dose; or
•	azithromycin 1.0-1.5 g p.o. as single dose.

As a result of the continuous spread of fluoroquinolone-resistant *N. gonorrhoeae*, this class of antibiotics is no longer recommended for the treatment of gonorrhoea, but could be used in case of proven susceptibility and in accordance with national guidelines. There is also an increase of resistance against cephalosporins in some areas, therefore knowledge of local susceptibility patterns is mandatory for the correct treatment of gonorrhoeal urethritis. Gonorrhoeae is frequently accompanied by chlamydial infection, therefore an active antichlamydial therapy should always be added.

3H.5.2 Treatment of chlamydial urethritis

Standard: azithromycin 1.0-1.5 g p.o. as single dose

Alternative: doxycycline 100 mg bid p.o. for 7 days

3H.5.3 Treatment of *Mycoplasma genitalium* urethritis

Standard: azithromycin 0.5 g p.o. day 1, 250 mg p.o. day 2-5

Alternative: moxifloxacin 400 mg q.d. for 5 days*

*because of reported failures, some experts recommend 10 to 14 days

3H.5.4 Treatment of *Ureaplasma urealyticum* urethritis

Standard: doxycycline 100 mg bid p.o. for 7 days

Alternative: azithromycin 1.0-1.5 g p.o. as single dose or clarithromycin 500 mg bid for 7 days (resistance against macrolides is possible)

3H.5.5 **Treatment of *Trichomonas vaginalis* urethritis**

Standard: metronidazole 2 g p.o. as single dose

In case of persistence: 4 g daily for 3-5 days

3H.5.6 **Treatment of non-gonococcal urethritis (NGU)***

Standard: doxycycline 100 mg bid p.o. for 7-10 days

Alternative: azithromycin 0.5 g p.o. day 1, 250 mg p.o. day 2-5

*if no agent could be identified

Doxycycline and azithromycin are considered to be equally effective in the treatment of chlamydial infections, however, infections with *M. genitalium* may respond better to azithromycin [242]. Erythromycin is less effective and causes more side effects. In pregnant women, fluoroquinolones and doxycycline are contraindicated, therefore, besides erythromycin and azithromycin, a regimen with amoxicillin 500 mg three times daily for 7 days is also recommended.

If therapy fails, one should consider treating infections by *T. vaginalis* and/or *M. genitalium* with a combination of metronidazole (2 g orally as single dose) and erythromycin (500 mg orally four times daily for 7 days). As in other STDs, the treatment of sexual partners is necessary.

3H.6 **Follow-up**

Patients should be followed-up for control of eradication or if symptoms persist or recur after completion of therapy. Patients should be instructed to abstain from sexual intercourse for 7 days after therapy is initiated, provided their symptoms have resolved and their sexual partners have been adequately treated. Reporting and tracing source should be done according to national routines and in cooperation with specialists in venereology whenever required. Persons who have been diagnosed with a new STD should receive testing for other STDs, including syphilis and HIV.

3I **BACTERIAL PROSTATITIS**

3I.1 **Introduction**

Bacterial prostatitis is a disease entity diagnosed clinically and by evidence of inflammation and infection localised to the prostate. According to the duration of symptoms, bacterial prostatitis is described as either acute or chronic, when symptoms persist for at least 3 months. It is recommended that European urologists use the classification suggested by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH), in which bacterial prostatitis with confirmed or suspected infection is distinguished from chronic pelvic pain syndrome (CPPS).

Acute bacterial prostatitis can be a serious infection. Parenteral administration of high doses of a bactericidal antibiotic is usually required, which may include a broad-spectrum penicillin, a third-generation cephalosporin, or a fluoroquinolone. All of these agents can be combined with an aminoglycoside for initial therapy. Treatment is required until there is defervescence and normalisation of infection parameters (LE: 3, GR: B). In less severe cases, a fluoroquinolone may be given orally for 10 days (LE: 3, GR: B).

In chronic bacterial prostatitis, and if infection is strongly suspected in CPPS, preferably a fluoroquinolone should be given for at least 4 weeks. In case of fluoroquinolone resistance or adverse reactions, trimethoprim can be given orally for a period of 4-12 weeks after the initial diagnosis. The patient should then be reassessed and antibiotics only continued if pre-treatment cultures are positive and/or the patient has reported positive effects from the treatment. A total treatment period of 4-6 weeks is recommended (LE: 3, GR: B). Patients with CPPS are treated empirically with numerous medical and physical modalities. The management of pain and other related symptoms are covered in the EAU Guidelines on Chronic Pelvic Pain [243].

3I.2 **Epidemiology, aetiology and pathogenesis**

Traditionally, the term prostatitis has included both acute and chronic bacterial prostatitis, in which an infective origin is accepted, and the term prostatitis syndrome or, more recently, CPPS, in which no infective agent can be found and whose origin is multifactorial and in most cases obscure.

Prostatitis and CPPS are diagnosed by symptoms and evidence of inflammation and infection localised to the prostate [244]. A causative pathogen, however, is detected by routine methods in only 5-10% of cases [245], and for whom antimicrobial therapy therefore has a rational basis. The remainder of patients are treated empirically with numerous medical and physical modalities. However, recent improvement

in classification and application of modern methods, including molecular biology, should allow proper systematisation of treatment [246-248].

This chapter reviews documented or suspected bacterial infections of the prostate (type I and II in Table 14).

31.3 Diagnostic evaluation

31.3.1 History and symptoms

According to the duration of symptoms, bacterial prostatitis is described as either acute or chronic, the latter being defined by symptoms that persist for at least 3 months [246-248]. The predominant symptoms are pain at various locations and LUTS (Tables 15 and 16) [249-251]. Chronic bacterial prostatitis is the most frequent cause of recurrent UTI in men [252].

Table 14: Classification of prostatitis and CPPS according to NIDDK/NIH [246-248]

Type	Name and description
I	Acute bacterial prostatitis
II	Chronic bacterial prostatitis
III	Chronic abacterial prostatitis - CPPS
IIIA	Inflammatory CPPS (white cells in semen/EPS/VB3)
IIIB	Non-inflammatory CPPS (no white cells in semen/EPS/VB3)
IV	Asymptomatic inflammatory prostatitis (histological prostatitis)

CPPS = chronic pelvic pain syndrome; EPS = expressed prostatic secretion; VB3 = voided bladder urine 3 (urine following prostatic massage).

Table 15: Localisation of pain in patients with prostatitis like symptoms*

Site of pain	Percentage of patients
Prostate/perineum	46%
Scrotum and/or testes	39%
Penis	6%
Urinary bladder	6%
Lower back	2%

*Adapted from Zermann et al. [251].

Table 16: LUTS in patients with prostatitis like symptoms*

Frequent need to urinate
Difficulty urinating, e.g. weak stream and straining
Pain on urination, or that increases with urination

*Adapted from Alexander et al. [250].

31.3.1.1 Symptom questionnaires

Symptoms appear to have a strong basis for use as a classification parameter in bacterial prostatitis as well as in CPPS [253]. Prostatitis symptom questionnaires have therefore been developed for the quantification of symptoms [253, 254]. They include the Chronic Prostatitis Symptom Index (CPSI), which was recently developed by the International Prostatitis Collaborative Network (IPCN), initiated by the NIH (USA) [255].

Although the CPSI has been validated, to date, its benefit in clinical studies is still uncertain. The questionnaire contains four questions regarding pain or discomfort, two regarding urination, and three related to QoL (see online only material 4.6).

31.3.2 Clinical findings

In acute prostatitis, the prostate may be swollen and tender on digital rectal examination (DRE). Prostatic massage is contraindicated. Otherwise, the prostate is usually normal on palpation. An essential consideration in the clinical evaluation is to exclude prostatic abscess.

In case of lasting symptoms ("chronic prostatitis" symptoms) CPPS as well as other urogenital and ano-rectal disorders must be taken into consideration.

Symptoms of chronic prostatitis or CPPS can mask prostate tuberculosis. Pyospermia and hematospermia in men in endemic regions or with a history of tuberculosis should be investigated for urogenital tuberculosis.

31.3.3 Urine cultures and expressed prostatic secretion

The most important investigation in the evaluation of the patient with acute prostatitis is MSU culture. If the patient presents with clinical signs suggestive of blood-stream infection, a blood culture should be taken using local protocol. In chronic bacterial prostatitis, quantitative bacteriological localisation cultures and microscopy of the segmented urine and of expressed prostatic secretion (EPS), as described by Meares and Stamey [244] are important investigations (see online only material 4.7).

The Enterobacteriaceae, especially *E. coli*, are the predominant pathogens in acute bacterial prostatitis (Table 17) [256]. In chronic bacterial prostatitis, the spectrum of strains is wider. The significance of intracellular bacteria, such as *C. trachomatis*, is uncertain [257]. In patients with immune deficiency or HIV infection, prostatitis may be caused by fastidious pathogens, such as *M. tuberculosis*, *Candida sp.* and rare pathogens, such as *Coccidioides immitis*, *Blastomyces dermatitidis*, and *Histoplasma capsulatum* [258]. In case of suspected prostate tuberculosis, the urine should be investigated for *Mycobacterium spp* by PCR technique.

Table 17: Most common pathogens in prostatitis

Aetiologically recognised pathogens*
<i>E. coli</i>
<i>Klebsiella sp.</i>
<i>Prot. mirabilis</i>
<i>Enterococcus faecalis</i>
<i>P. aeruginosa</i>
Organisms of debatable significance
Staphylococci
Streptococci
<i>Corynebacterium sp.</i>
<i>C. trachomatis</i>
<i>U. urealyticum</i>
<i>Myc. hominis</i>

*Adapted from Weidner et al. [245] and Schneider et al. [256].

31.3.4 Prostate biopsy

Perineal biopsies cannot be recommended as routine work-up and should be reserved only for research purposes. Transrectal prostate biopsy is not advisable in bacterial prostatitis (LE: 4, GR: C).

31.3.5 Other tests

Transrectal ultrasound (TRUS) may reveal intraprostatic abscesses, calcification in the prostate, and dilatation of the seminal vesicles but is unreliable and cannot be used as a diagnostic tool in prostatitis [259].

31.3.6. Additional investigations

31.3.6.1 Ejaculate analysis

An analysis of the ejaculate is not recommended for microbiological investigation due to the low sensitivity and specificity compared to the 2- or 3-glass tests. Ejaculate analysis is however frequently involved as part of the investigation of a generalised male accessory gland infection (MAGI) and it provides information about sperm quality. The EAU Panel believes that guidelines on prostatitis should not contain a set of differential diagnostic examinations. An experienced urologist should decide which investigations are relevant for each individual patient. Bladder outflow and urethral obstruction should always be considered and ruled out by uroflowmetry, retrograde urethrography, or endoscopy.

31.3.6.2 Prostate specific antigen (PSA)

Prostate specific antigen is often increased in acute bacterial prostatitis and other urogenital infections. If a patient has elevated PSA and evidence of prostatic inflammation, serum PSA will normalise after antimicrobial treatment for 4 weeks in about 50% of patients [260]. A delay of at least 3 months should be allowed before it can be assumed that a stable level of PSA has been reached. Measurement of free and total PSA adds no practical diagnostic information in prostatitis [261].

31.4 Disease management

31.4.1 Antibiotics

Antibiotics are life-saving in acute bacterial prostatitis and recommended in chronic bacterial prostatitis.

Acute bacterial prostatitis is a serious infection with fever, intense local pain, and general symptoms. Parenteral administration of high doses of bactericidal antibiotics, such as a broad-spectrum penicillin, a third-generation cephalosporin or a fluoroquinolone, should be administered. For initial therapy, any of these antibiotics may be combined with an aminoglycoside. After defervescence and normalisation of infection parameters, oral therapy can be substituted and continued for a total of 2-4 weeks [262].

The recommended antibiotics in chronic bacterial prostatitis, together with their advantages and disadvantages, are listed in Table 18 [263]. Fluoroquinolones, such as ciprofloxacin and levofloxacin, are considered drugs of choice because of their favourable pharmacokinetic properties [263] (LE: 2b, GR: B), their generally good safety profile, and antibacterial activity against Gram-negative pathogens, including *P. aeruginosa*. In addition, levofloxacin is active against Gram-positive and atypical pathogens, such as *C. trachomatis* and genital mycoplasmas (LE: 2b, GR: B).

The duration of antibiotic treatment is based on experience and expert opinion and is supported by many clinical studies [264]. In chronic bacterial prostatitis antibiotics should be given for 4-6 weeks after initial diagnosis. Relatively high doses are needed and oral therapy is preferred [263, 264] (LE: 3, GR: B). If intracellular bacteria have been detected or are suspected, tetracyclines or erythromycin should be given [263, 265] (LE: 2b, GR: B).

Table 18: Antibiotics in chronic bacterial prostatitis*

Antibiotic	Advantages	Disadvantages	Recommendation
Fluoroquinolones	Favourable pharmacokinetics	Depending on the substance	Recommend
	Excellent penetration into the prostate	Drug interaction	
	Good bioavailability	Phototoxicity	
	Equivalent oral and parenteral pharmacokinetics (depending on the substance)	Central nervous system adverse events	
	Good activity against typical and atypical pathogens and <i>P. aeruginosa</i>		
	In general, good safety profile		
Trimethoprim	Good penetration into prostate	No activity against <i>Pseudomonas</i> , some enterococci and some Enterobacteriaceae	Consider
	Oral and parenteral forms available		
	Relatively cheap		
	Monitoring unnecessary		
	Active against most relevant pathogens		
Tetracyclines	Cheap	No activity against <i>P. Aeruginosa</i>	Reserve for special indications
	Oral and parenteral forms available	Unreliable activity against coagulase-negative staphylococci, <i>E. coli</i> , other Enterobacteriaceae, and enterococci	
	Good activity against <i>Chlamydia</i> and <i>Mycoplasma</i>	Contraindicated in renal and liver failure	
		Risk of skin sensitisation	
	Macrolides	Reasonably active against Gram-positive bacteria	
Active against Chlamydia		Unreliable activity against Gram-negative bacteria	
Good penetration into prostate			
Relatively non-toxic			

*Adapted from Bjerklund Johansen et al. [263].

31.4.2 **Intraprostatic injection of antibiotics**

This treatment has not been evaluated in controlled trials and should not be considered [266, 267].

31.4.3 **Drainage and surgery**

Approximately 10% of men with acute prostatitis will experience urinary retention [268] which can be managed by suprapubic, intermittent or indwelling catheterisation. Suprapubic cystostomy placement is generally recommended. The use of catheterisation without evidence of retention may increase the risk of progression to chronic prostatitis [269]. Alpha-blocker treatment has also been recommended, but clinical evidence of benefit is poor.

In case of prostatic abscess, both drainage and conservative treatment strategies appear feasible [270]. The size may matter. In one study conservative treatment was successful if the abscess cavities were < 1 cm in diameter, while larger abscesses were better treated by single aspiration or continuous drainage [271]. Surgery should be avoided in the treatment of bacterial prostatitis.

3J **EPIDIDYMITIS AND ORCHITIS**

3J.1 **Introduction**

Epididymitis and orchitis are classified as acute or chronic processes according to the onset and clinical course. The most common type of orchitis, mumps orchitis, develops in 20-30% of post-pubertal patients with mumps virus infection. If mumps orchitis is suspected, a history of parotitis and evidence of IgM antibodies in the serum supports the diagnosis.

Epididymitis is almost always unilateral and relatively acute in onset. In young males it is associated with sexual activity and infection of the consort (LE: 3). The majority of cases in sexually active males aged < 35 years are due to sexually transmitted organisms, whereas in elderly patients, it is usually due to common urinary pathogens (LE: 3). Epididymitis causes pain and swelling, which begins in the tail of the epididymis, and may spread to involve the rest of the epididymis and testicular tissue. The spermatic cord is usually tender and swollen. It is imperative for the physician to differentiate between epididymitis and spermatic cord torsion as soon as possible using all available information.

The microbial aetiology of epididymitis can usually be determined by examination of a Gram stain of a urethral smear and/or an MSU for the detection of Gram-negative bacteriuria (LE: 3). A urethral swab and MSU should be obtained for microbiological investigation before antimicrobial therapy (GR: C). Antimicrobials should be selected on the empirical basis that in young, sexually active men, *C. trachomatis* is usually causative, and that in older men, the most common uropathogens are involved. Fluoroquinolones with activity against *C. trachomatis* (e.g. ofloxacin and levofloxacin), should be the drugs of first choice. If *C. trachomatis* has been detected, treatment could also be continued with doxycycline, 200 mg/day, for a total of at least 2 weeks. Macrolides may be used as alternative agents (GR: C). Supportive therapy includes bed rest, up-positioning of the testes and anti-inflammatory therapy. In case of *C. trachomatis* epididymitis, the sexual partner should also be treated (GR: C). Abscess forming epididymitis or orchitis needs surgical treatment. Chronic epididymitis can sometimes be the first clinical manifestation of urogenital tuberculosis.

3J.2 **Epidemiology, aetiology and pathophysiology**

There are no new data available concerning the incidence and prevalence of epididymitis. According to older data, acute epididymitis has been a major cause for admission to hospitals of military personnel [272] (LE: 3). Acute epididymitis in young men is associated with sexual activity and infection of the consort [273] (LE: 3).

The most common type of orchitis, mumps orchitis, develops in 20-30% of post-pubertal patients with mumps virus infection. The incidence depends upon the vaccination status of the population [274]. Primary chronic orchitis is a granulomatous disease, and a rare condition with uncertain aetiology that has been reported in about 100 cases in the literature [275].

Complications in epididymo-orchitis include abscess formation, testicular infarction, testicular atrophy, development of chronic epididymal induration and infertility [272].

Epididymitis caused by sexually transmitted organisms occurs mainly in sexually active males aged < 35 years [272, 276] (LE: 3). The majority of cases of epididymitis are due to common urinary pathogens, which are also the most common cause of bacteriuria [272, 276] (LE: 3). Bladder outlet obstruction and urogenital malformations are risk factors for this type of infection.

Typically, in epididymitis due to common bacteria and sexually transmitted organisms, the infection is spread from the urethra or bladder. In non-specific granulomatous orchitis, autoimmune phenomena are assumed to trigger chronic inflammation [275, 277]. Paediatric orchitis and mumps orchitis are of

haematogenous origin [277].

Epididymo-orchitis is also seen in systemic infections such as tuberculosis, lues, brucellosis and cryptococcus disease.

3J.3 Classification systems

Epididymitis (inflammation of the epididymis) causes pain and swelling which is almost always unilateral and relatively acute in onset. In some cases, the testes are involved in the inflammatory process (epididymo-orchitis). On the other hand, inflammatory processes of the testicle, especially virally induced orchitis, often involve the epididymis.

Orchitis and epididymitis are classified as acute or chronic processes according to the onset and clinical course. Chronic disease with induration develops in 15% of acute epididymitis cases. In the case of testicular involvement, chronic inflammation may result in testicular atrophy and the destruction of spermatogenesis [258, 272].

3J.4 Diagnostic evaluation

In acute epididymitis, the inflammation and swelling usually begin in the tail of the epididymis, and may spread to involve the rest of the epididymis and testicular tissue. The spermatic cord is usually tender and swollen. All men with epididymitis that is caused by sexually transmitted organisms have a history of sexual exposure, and the organisms can lie dormant for months before the onset of symptoms. If the patient is examined immediately after undergoing urinalysis, urethritis and urethral discharge may be missed because WBC and bacteria have been washed out of the urethra during urination.

The microbial aetiology of epididymitis can usually be determined by examination of a Gram stain of a urethral smear and/or an MSU for the detection of Gram-negative bacteriuria. The presence of intracellular Gram-negative diplococci on the smear correlates with infection with *N. gonorrhoeae*. The presence of only WBC on a urethral smear indicates the presence of non-gonorrhoeal urethritis. *C. trachomatis* is isolated in approximately two-thirds of these patients [272, 276] (LE: 3).

Ejaculate analysis according to WHO criteria including leukocyte analysis indicates persistent inflammatory activity. In many cases, transient decreased sperm counts and forward motility can be found. Azoospermia due to complete obstruction of both epididymides is a rare complication. If mumps orchitis is suspected, a history of parotitis and evidence of IgM antibodies in the serum supports the diagnosis. In about 20% of mumps orchitis cases, the disease occurs bilaterally in post-pubertal men with a risk of testicular atrophy and azoospermia [273] (LE: 3).

3J.4.1 Differential diagnosis

It is imperative for the physician to differentiate between epididymitis and spermatic cord torsion as soon as possible using all available information, including the age of the patient, history of urethritis, clinical evaluation and Doppler (duplex) scanning of testicular blood flow.

3J.5 Disease management

Only a few studies have measured the penetration of antimicrobial agents into the epididymis and testes in humans. Of these, the fluoroquinolones have shown favourable properties [278, 279] (LE: 2a).

Antimicrobials should be selected on the empirical basis that in young, sexually active men, *C. trachomatis* is usually causative, and that in older men, with BPH or other micturition disturbances, the most common uropathogens are involved. Studies that have compared microbiological results from puncture of the epididymis and from urethral swabs as well as urine have shown very good correlation. Therefore, before antimicrobial therapy, a urethral swab and MSU should be obtained for microbiological investigation (GR: C).

Again, fluoroquinolones, preferably those with activity against *C. trachomatis* (e.g. ofloxacin and levofloxacin), should be the drugs of first choice, because of their broad antibacterial spectra and their favourable penetration into the tissues of the urogenital tract. If *C. trachomatis* has been detected as an aetiological agent, treatment could also be continued with doxycycline, 200 mg/day, for at least 2 weeks. Macrolides may be used as alternative agents (GR: C).

Supportive therapy includes bed rest, up-positioning of the testes and antiphlogistic therapy. In young men, epididymitis can lead to permanent occlusion of the epididymal ducts and thus to infertility, therefore, one should consider antiphlogistic therapy with methylprednisolone, 40 mg/day, and reduce the dose by half every second day (GR: C).

In case of *C. trachomatis* epididymitis, the sexual partner should also be treated (GR: C). If uropathogens are found as causative agents, a thorough search for micturition disturbances should be carried out to prevent relapse (GR: C). Abscess-forming epididymitis or orchitis also needs surgical treatment. Chronic epididymitis can sometimes be the first clinical manifestation of urogenital tuberculosis.

3K Fournier's Gangrene

3K.1 Introduction

- Full, repeated surgical debridement should commence within 24 h of presentation (LE: 3; GR: B).
- Treatment with broad-spectrum antibiotics should be started on presentation, with subsequent refinement according to culture and clinical response (LE: 3; GR: B).
- Adjunctive treatment such as pooled immunoglobulin and hyperbaric oxygen are not recommended, except in the context of clinical trials (LE: 3; GR: C).

Fournier's gangrene is an aggressive and frequently fatal polymicrobial soft tissue infection of the perineum, peri-anal region, and external genitalia. It is an anatomical sub-category of necrotising fasciitis with which it shares a common aetiology and management pathway. Evidence regarding investigation and treatment is predominantly from case series and expert opinion (LE: 3/4).

3K.2 Diagnostic evaluation

Fournier's gangrene remains rare but its incidence is increasing with an ageing population and higher prevalence of diabetes, and emergence of multi-resistant pathogens. Typically there is painful swelling of the scrotum or perineum with severe sepsis. Examination shows small necrotic areas of skin with surrounding erythema and oedema. Crepitus on palpation and a foul-smelling exudate occurs with more advanced disease. Risk factors include immuno-compromised patients, most commonly diabetes or malnutrition, or a recent history of catheterisation, instrumentation or perineal surgery. In up to 40% of cases, the onset is more insidious with undiagnosed pain often resulting in delayed treatment. A high index of suspicion and careful examination, particularly of obese patients, is required.

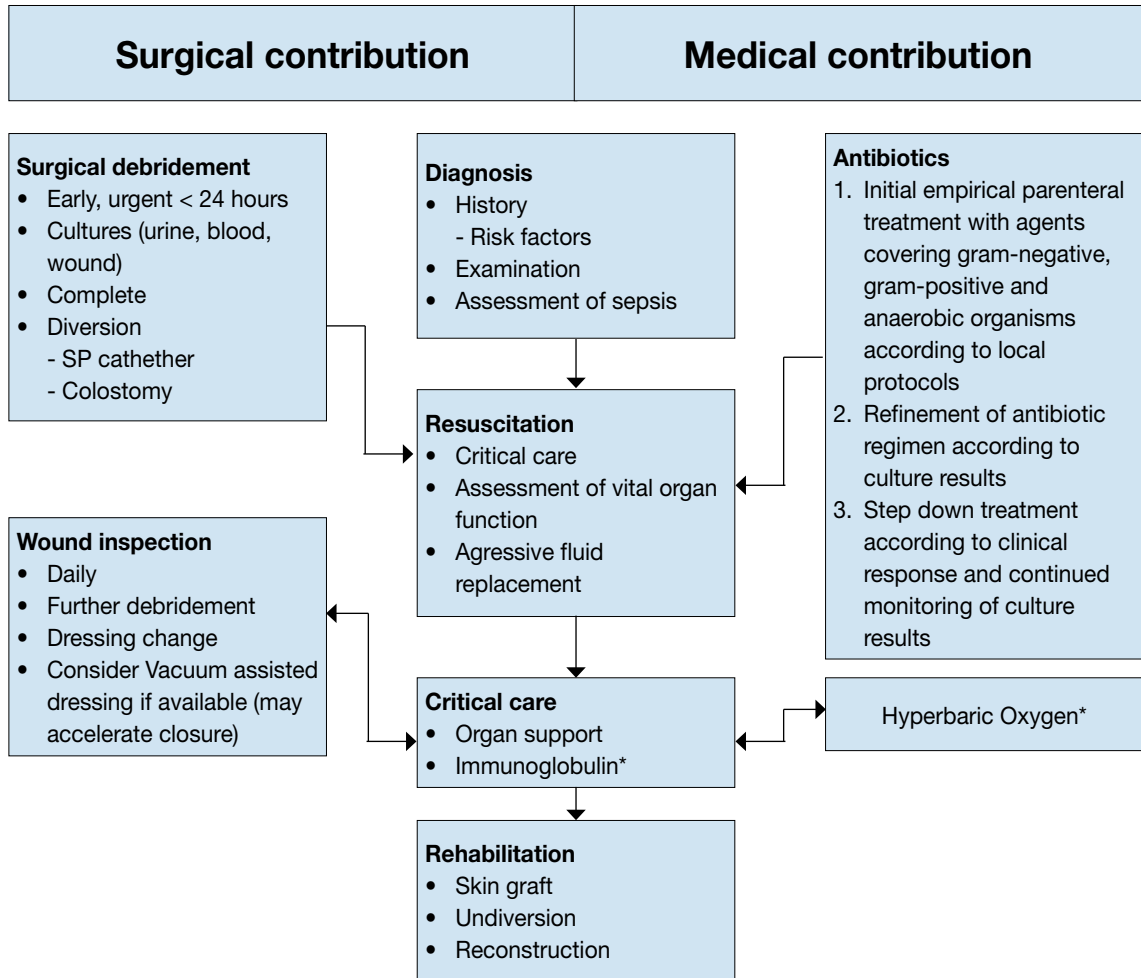
3K.2.1 Microbiology

Fournier's gangrene is typically a type 1 necrotising fasciitis that is polymicrobial in origin, including *S. aureus*, *Streptococcus* sp., *Klebsiella* sp., *E. coli* and anaerobes; involvement of *Clostridium* sp. is now less common. These organisms secrete endotoxins causing tissue necrosis and severe cardiovascular impairment. Subsequent inflammatory reaction by the host contributes to multi-organ failure and death if untreated.

3K.3 Disease management

The degree of internal necrosis is usually vastly greater than suggested by external signs, and consequently, adequate, repeated surgical debridement is necessary to save the patient's life (LE: 3, GR: B). Disease specific severity scoring systems do not appear superior to generic critical illness scores and are therefore not recommended for routine use (LE: 3, GR: C). Computed tomography or MRI can help define para-rectal involvement, suggesting the need for colostomy (LE: 3, GR: C). Consensus from case series suggests that surgical debridement should be early (< 24 h) and complete, because delayed and/or inadequate surgery results in higher mortality (LE: 3, GR: B). Concurrent parenteral antibiotic treatment should be given that covers all causative organisms and can penetrate inflammatory tissue (LE: 3, GR: B). This can then be refined following surgical cultures. The benefit of pooled immunoglobulin therapy and hyperbaric oxygen remains uncertain and should not be used routinely (LE: 3, GR: C). With aggressive early surgical and medical management, survival rates are > 70% depending upon patient group and availability of critical care (LE: 3). Following resolution, reconstruction using skin grafts is required [280-283].

Figure 6: Care pathway



*Use of immunoglobulin and hyperbaric oxygen therapy is of uncertain benefit.

3L SEXUALLY TRANSMITTED INFECTIONS

The classical bacteria that cause venereal diseases, e.g. gonorrhoea, syphilis, chancroid and inguinal granuloma, only account for a small proportion of all known sexually transmitted diseases (STDs) today. Other bacteria and viruses as well as yeasts, protozoa and epizoa must also be regarded as causative organisms of STD. Taken together, all STDs are caused by > 30 relevant pathogens. However, not all pathogens that can be sexually transmitted manifest genital diseases, and not all genital infections are exclusively sexually transmitted. At present, the reader is referred to the 2010 CDC STD Treatment Guidelines and later update [229].

The human immunodeficiency virus (HIV) causes a disease of the immune system leading to a vast panorama of complications and complex medical conditions also called acquired immunodeficiency syndrome (AIDS). The urogenital tract is rarely involved. The topic is beyond the scope of these Guidelines.

3M SPECIFIC INFECTIONS

Urogenital tuberculosis and bilharziasis are two infections that may affect the urogenital tract. Although not endemic in Europe, cases of urogenital tuberculosis are occasionally diagnosed in all communities. In a world of globalisation, travellers are regularly confronted with situations in which they may be infected. Guidelines on the diagnosis and management of these two infections have been published elsewhere [3, 4, 279, 284].

3M.1 Urogenital tuberculosis

Nearly one third of the world's population is estimated to be infected with *M. tuberculosis*. Moreover, tuberculosis is the most common opportunistic infection in AIDS patients. Urogenital tuberculosis is not very common but it is considered a severe form of extra-pulmonary tuberculosis. The diagnosis of urogenital tuberculosis is made based on culture studies by isolation of the causative organism; however, biopsy material on conventional solid media may occasionally be required. Drugs are the first-line therapy in urogenital tuberculosis. Treatment regimens of six months are effective in most patients. Although chemotherapy is the mainstay of treatment, surgery in the form of ablation or reconstruction may be unavoidable. Both radical and reconstructive surgery should be carried out in the first two months of intensive chemotherapy. The management should be done by, or in direct cooperation with, a specialist in the field of tuberculosis [4, 279, 284].

3M.2 Urogenital schistosomiasis

More than 200 million people worldwide are affected by bilharziasis, which is caused by *Schistosoma haematobium*. For travellers, precautions are most important. For the population in endemic areas, an integrated approach including health education is necessary. Effective pharmacological treatment is available [3].

3N PERIOPERATIVE ANTIBACTERIAL PROPHYLAXIS IN UROLOGY

3N.1 Introduction

The aim of antimicrobial prophylaxis in urological surgery is to decrease the load of microorganisms in the surgical field at the time of surgery in order to prevent infective complications resulting from diagnostic and therapeutic procedures. However, evidence for the best choice of antibiotics and prophylactic regimens is limited (Table 19).

Before surgery, it is essential to categorise the patients in relation to:

- The general health status according to American Society of Anaesthesiology (ASA) score P1-P5;
- The presence of general risk factors such as older age, diabetes mellitus, impaired immune system, malnutrition, extreme weight;
- The presence of specific endogenous or exogenous risk factors such as a history of UTI or urogenital infection, indwelling catheters, bacterial burden, previous instrumentation, genetic factors;
- The type of surgery and surgical field contamination burden;
- The expected level of surgical invasiveness, duration and technical aspects.

Only transrectal core prostate biopsy (LE: 1b, GR: A) and TUR-P (LE: 1a, GR: A) are well documented. There is no evidence for any benefits of antibiotic prophylaxis (ABP) in standard non-complicated endoscopic procedures and shockwave lithotripsy (SWL), although it is recommended in complicated procedures and patients with identified risk factors.

No ABP is recommended for clean operations, whereas a single or 1-day dose is recommended in clean-contaminated (urinary tract entered, breach of mucosal layer). The approach in contaminated operations varies with the type of procedure, the level of surgical site contamination and level of difficulty.

A urine culture is recommended prior to surgical interventions and the presence of bacteriuria controlled by directed pre-operative treatment of the detected pathogen (LE: 1b, GR A).

Antibiotic prophylaxis should be given as a single dose or a short course orally or parenterally. The administration route depends on the type of intervention and patient characteristics. Oral administration requires drugs that have good bioavailability. In the case of continuous close urinary drainage, prolongation of perioperative ABP is not recommended.

Many antibiotics are suitable for perioperative ABP, e.g. co-trimoxazole, second-generation cephalosporins, fluoroquinolones, aminopenicillins plus a beta-lactam inhibitor, and aminoglycosides. Broader-spectrum antibiotics including fluoroquinolones and carbapenem antibiotic group should however not be used or only cautiously in very selected cases. This applies also to the use of vancomycin.

The use of antimicrobials should be based on knowledge of the local pathogen profile and antibiotic susceptibility pattern. Best practice includes surveillance and an audit of infectious complications.

Table 19: Summary of level of evidence (LE) and grade of recommendation (GR) for peri-operative antibacterial prophylaxis in standard urological procedures
(for practical management refer to Tables 22-24 and text)

Procedure	LE	GR	Remarks	ABP
Diagnostic procedures				
Cystoscopy	1b	A	Low frequency of infections. Consider individual risk factors for UTI (i.e. BU, history of febrile UTI)	No
Urodynamic study	1a	A	Low frequency of infections. Consider individual risk factors for UTI (as for cystoscopy)	No
Trans-rectal core biopsy of prostate	1b	A	High risk of infection Assess carefully risk factors including risk of carrying resistant bacterial strains (i.e. fluoroquinolone resistance)	Yes
Diagnostic ureteroscopy	4	C	No available studies	Optional
Common endourological/endoscopic therapeutic procedures (examples)				
Fulguration of small bladder tumours	2b	C	As for cystoscopy	No
TUR-BT	2b	C	Poor data. No concern given to burden of tumour, i.e. size, multiplicity, necrosis	Optional See text
TUR-P	1a	A	High risk of febrile infection and sepsis. Control of BU/UTI and other risk factors prior to surgery	Yes
SWL (standard, no bacteriuria, no catheters, otherwise healthy)	1a	A	Low frequency of infections	No
SWL with risk factors for infection	1a	A	Increased risk of infection. Control of BU and risk factors	Yes
Ureteroscopy for stone management	2b	B (A)	Low frequency of infections but variable with stone position (i.e. proximal impacted stone). Control of BU and risk factors	Optional, related to difficulty/level
Percutaneous and retrograde intra-renal stone management	1b	A	High risk of febrile infection and sepsis	Yes
Common open and/or laparoscopic surgery (examples)				
<i>Clean operations (no opening/entering of the urinary tract)</i>				
Nephrectomy	3	C	SSI/WI poorly documented Secondary post-operative catheter-related BU/UTI	No
Planned scrotal surgery, vasectomy, surgery for varicocele	3	C	Conflicting data	No
Prosthetic implants	3	B	Limited documentation	Yes
<i>Clean-contaminated (opening/entering of the urinary tract)</i>				
Nephroureterectomy	3	B	Poor documentation Control of BU and other risk factors prior to surgery. Secondary post-operative catheter-related BU/UTI	Yes
Total (radical) prostatectomy	2a			
Uretero-pelvic junction repair	4	C		
Partial bladder resection	3			
<i>Clean-contaminated/contaminated (opening of bowel, urine deviation)</i>				
Cystectomy with urine deviation	2a	B	High risk of infection	Yes

ABP = antibiotic prophylaxis; BU = bacteriuria; SSI/WI = surgical site infection/wound infection;
SWL = extracorporeal shockwave lithotripsy; TUR-BT = transurethral resection of the bladder tumour;
TUR-P = transurethral resection of the prostate.

This section aims to clarify the current knowledge and to propose practical recommendations based on a few

existing systematic reviews [285, 286], available clinical studies, expert opinion and professional consensus. This section considers the recommendations of societies, such as the Paul Ehrlich Society for Chemotherapy, the corresponding working groups of the German Society of Urology [287], French Association of Urology [288], the Swedish Council on Health Technology Assessment [289], the Scottish Intercollegiate Guidelines Network [290] and an international consensus working group [2].

The EAU Guidelines Panel on urological infections has further presented a tentative classification of the urological procedures in relation to the level of contamination of the surgical site in order to facilitate the decision on ABP in the absence of evidence [291].

The Global Prevalence Infection in Urology studies (GPIU) have found that approximately 10% of urological patients had a healthcare-associated UTI [12]. Moreover, a review showed large discrepancies in the use of ABP in all types of procedures and between countries, and low compliance to the guidelines [292]. The marked increase in bacterial resistance development underscores the need for a stringent antibiotic policy throughout Europe and compliance to the recommendations [293].

3N.1.1 Goals of perioperative antibacterial prophylaxis

Antibiotic prophylaxis and therapy are two different issues. ABP aims to prevent healthcare-associated infections that result from diagnostic and therapeutic procedures. ABP is only one of several measures to prevent infections and can never compensate for poor hygiene and operative technique. In contrast, antibiotic therapy is the treatment of a clinically suspected or microbiologically proven infection.

The United States based CDC has presented definitions that are currently the most comprehensive, and are recommended for the evaluation of infectious complications [294]. These definitions have also been used in the GPIU point prevalence studies [12]. Revision of definitions and recommendations are under consideration, see chapter 2 in [2]. Table 20 illustrates the different types of infectious complications encountered in urological surgery.

Table 20: Main types of healthcare-associated infections (HAI) encountered in urological practice

Site of infection	Minor	Major
Surgical wound Incision/surgical site infection (SSI)	Superficial wound infection	Deep wound infection Wound rupture (abdominal dehiscence) Deep abdominal or surgical site abscess
UTI or organ-specific infection Include Catheter Associated UTI (CAUTI)	Asymptomatic bacteriuria (bacterial colonisation) Symptomatic lower UTI (cystitis)	Febrile UTI Pyelonephritis Renal abscess Peri-renal abscess
Blood stream	Bacteraemia without signs of systemic response	Sepsis with signs of systemic response (SIRS)
MAGI	Epididymitis (Orchitis)	Acute bacterial prostatitis (type I)
Other sites		Septic embolism Pneumonia Secondary bone infection

The endpoints of perioperative prophylaxis in urology are the infectious complications presented in Table 20 when directly related to surgery. This might be extended to ABU and even minor wound infections. Asymptomatic bacteriuria after TURP or other endourological procedures can disappear spontaneously and is usually of no clinical significance.

3N.2 Risk factors

Risk factors (Tables 21 and 1) are underestimated in most trials. However, they are important in the pre-operative assessment of the patient [291]. They are related to:

- The general health of the patient as defined by ASA score P1-P5;
- The presence of general risk factors such as older age, diabetes mellitus, impaired immune system, malnutrition, extreme weight;
- The presence of specific endogenous or exogenous risk factors such as a history of UTI or urogenital infection, indwelling catheters, bacterial burden, previous instrumentation, genetic factors;

- The type of surgery and surgical field contamination;
- The expected level of surgical invasiveness, duration and technical aspects.

The traditional classification of surgical procedures according to Cruse and Foord [295] into clean, clean-contaminated, contaminated, and infected/dirty operations applies to open surgery but not to endourological interventions. The present Guidelines consider the procedures entering the urinary tract and the breaching of the mucosa as clean-contaminated procedures because urine culture is not always a predictor of bacterial presence, and that the lower genitourinary tract is colonised by microflora, even in the presence of sterile urine [291, 296]. The presence of bacteriuria in an otherwise asymptomatic patient, revealed by a pre-operative culture, is indication of a contamination level (Table 23).

Table 21: Generally accepted risk factors for infectious complications

General risk factors	Special risk factors associated with an increased bacterial load
Older age	Long preoperative hospital stay or recent hospitalisation
Deficient nutritional status	History of recurrent urogenital infections
Impaired immune response	Surgery involving bowel segment
Diabetes mellitus	Colonisation with microorganisms
Smoking	Long-term drainage
Extreme weight	Urinary obstruction
Coexisting infection at a remote site	Urinary stone
Lack of control of risk factors	

The risk of infection varies with the type of intervention. The wide spectrum of interventions and recent advances in minimal invasive surgery further complicates the provision of clear-cut recommendations. Furthermore, the bacterial load, the duration and difficulty of the operation, the surgeon's skill, and perioperative bleeding may also influence the risk of infection [294-296]. For elective urological surgery, general and urinary tract specific risk factors must be controlled (i.e. bacteriuria, obstruction).

3N.3 Principles of antibiotic prophylaxis

Antibiotic prophylaxis aims at protecting the patient but not at the expense of promoting resistance. However, there is good evidence that intelligent use of prophylaxis can lower the overall consumption of antibiotics [297, 298]. It is essential to individualise the choice of ABP according to each patient's cumulative risk factors [299]. Urine culture prior to surgery is strongly recommended. Antibiotics cannot replace other basic measures to reduce infection [300-302].

3N.3.1 Timing

There is a given time frame during which ABP should be administered. Although the following guidelines are based on research into skin wounds [303] and clean-contaminated and contaminated bowel surgery, there is good reason to believe that the same findings apply to urological surgery. The optimal time for ABP is 1-2 h before instrumentation. Some studies on bowel surgery indicate similar results up to 3 h after the start of an intervention [304, 305].

For practical purposes, oral peri-operative ABP should be given approximately 1 hour before the intervention while intravenous ABP should be given about 30 minutes prior to incision, e.g. at the induction of anaesthesia. These timings allow the antibiotic to reach a peak concentration at the time of highest risk during the procedure, and an effective concentration shortly afterwards [306, 307].

3N.3.2 Route of administration

Oral administration is as effective as the intravenous route for antibiotics with sufficient bioavailability. This is recommended for most interventions when the patient can easily take the drug 1 h before intervention. In other cases, intravenous administration is recommended. Local irrigation of the operating field with antibiotics is not recommended.

3N.3.3 Duration of the regimen

For most procedures, duration of ABP has not yet been adequately addressed and rarely can a defined regimen be recommended. In principle, the duration of perioperative prophylaxis should be minimised, ideally to a single perioperative antibiotic dose. The prophylaxis should be prolonged only where there are significant risk factors (see Section 3N.2).

3N.3.4 **Choice of antibiotics**

No clear-cut recommendations can be given, as there are considerable variations in Europe regarding both bacterial spectra and susceptibility to different antibiotics. Antimicrobial resistance is usually higher in the Mediterranean region as compared with Northern European countries; resistance is correlated with an up to four-fold difference in sales of antibiotics [308]. Thus, knowledge of the local pathogen profile, susceptibility and virulence is mandatory in establishing local antibiotic guidelines. It is also essential to define the predominant pathogens for each type of procedure. When choosing an antimicrobial agent, it is necessary to consider the procedure-specific risk factors, contamination load, target organ, and the role of local inflammation.

In general, many antibiotics are suitable for perioperative antibacterial prophylaxis, e.g. co-trimoxazole, second-generation cephalosporins, aminopenicillins plus a BLI, aminoglycosides and fluoroquinolones. Broader-spectrum antibiotics such as fluoroquinolones, third generation cephalosporins and the carbapenem group should be used sparingly and reserved for treatment. This applies also to the use of vancomycin.

3N.3.5 **Prophylactic regimens in defined procedures**

All procedures are not alike. There is a large variation in invasiveness and risk for identically named interventions. The present Guidelines suggested a distribution of the different common diagnostic and therapeutic urological procedures in relation to the categories of surgical site contamination after adaptation to the urological context [291, 295]. The recommendations for ABP in standard urological surgery are summarised in Tables 22 and 23 [309-311].

3N.4 **Antimicrobial prophylaxis by procedure**

3N.4.1 **Diagnostic procedures**

3N.4.1.1 *Transrectal prostate biopsy*

Antimicrobial prophylaxis in core biopsy of the prostate is strongly recommended (LE: 1b, GR: A). However, the choice of regimens remains debatable. Most regimens used are effective, and recent studies have suggested that 1-day and even single doses are sufficient in low-risk patients [312-327] (LE: 1b, GR: A). The increase in fluoroquinolone resistance in the faecal flora has raised the question of appropriateness of the current recommendations [328, 329]. There is no clear-cut evidence-based alternative. In a recent review, it was recommended that men at risk for harbouring fluoroquinolone resistant strains should receive an alternate targeted regiment based on rectal swab finding [330]. Also several forms of bowel preparation are under investigation, although none has yet been shown to significantly impact on infection rates [330]. Each urologist must weigh the need for a prostate biopsy in relation to the risk, assess the individual risks factors including the risk of harbouring a resistant bacteria (e.g. ESBL) and consider the need for a rectal swab before the instrumentation [331].

3N.4.1.2 *Cystoscopy*

The frequency of infectious complications after cystoscopy, standard urodynamic studies and diagnostic simple ureteroscopy in otherwise healthy individuals is low [285, 332, 333]. In view of the very large number of cystoscopic examinations, the low infectious risk and the potential adverse effect on bacterial sensitivity, ABP is not recommended (LE: 1a, GR: A). However, bacteriuria, indwelling catheters, neurogenic LUTD and a history of urogenital infection are risk factors that must be considered [334-347] (LE: 1b, GR: A).

3N.4.2 **Endourological treatment procedures (urinary tract entered)**

3N.4.2.1 *TUR-BT*

There is little evidence for any benefit of ABP in TURB. The studies do not distinguish between simple fulguration (= cystoscopy) and large or multiple tumours, the presence of necrotic material or not. Therefore, the present Guidelines recommend a differentiation of type of tumour (Table 23) and the choice of ABP accordingly [285, 298, 348, 349] (LE: 2b, GR: C).

3N.4.2.2 *TUR-P*

Transurethral resection of the prostate is the best studied urological intervention. At least two meta-analyses of a large number of prospective, randomised and controlled studies, including several thousand patients, showed a marked benefit of ABP with a relative risk reduction of 65% and 77% for bacteriuria and septicaemia, respectively [285, 298, 348, 349] (LE: 1a, GR: A).

3N.4.2.3 *Ureteroscopy*

Well-conducted prospective controlled trials on ureteroscopy are lacking. It is reasonable, however, to distinguish low-risk procedures, such as simple diagnostic and distal stone treatment in otherwise healthy

individuals, from higher-risk procedures, such as treatment of proximal impacted stones with obstruction. These Guidelines recommend therefore a differentiation in degree of severity, stone anatomic position and patient related risk factors (Table 23), which is supported by a large database on URS [350].

3N.4.2.4 Percutaneous nephrolithotripsy

The risk of infection in PNL is high and use of ABP has been shown to significantly reduce the risk of infectious complications [351-359] (LE: 1b, GR: A). A single dose has shown to be sufficient [360]. Retrograde intra-renal stone treatment could be expected to have a similar risk profile [350].

3N.4.2.5 Shock-wave lithotripsy

No standard prophylaxis is recommended. However, control of bacteriuria and prophylaxis is recommended in cases of internal stent and treatment, due to the increased bacterial burden (e.g. indwelling catheter, nephrostomy tube, or infectious stones) [361-370] (LE: 1a-1b, GR: A) (Table 23).

Most antibiotic groups have been evaluated, such as fluoroquinolones, BLIs, including cephalosporins, and co-trimoxazole, but comparative studies are limited. It is recommended to direct the choice of an antibiotic on findings at urine culture.

3N.4.3 Laparoscopic surgery

There has been a lack of sufficiently powered studies in laparoscopic urological surgery. However, it seems reasonable to manage laparoscopic surgical procedures in the same manner as the corresponding open procedures (LE: 4, GR: C).

3N.4.4 Open or laparoscopic urological operations without opening of the urinary or genital tracts (clean procedures)

No standard ABP is recommended in clean operations [371-375] (LE: 3, GR: C).

3N.4.5 Open or laparoscopic urological operations with opening of the urinary tract (clean-contaminated procedures)

In cases of opening the urinary tract, a single perioperative parenteral dose of antibiotics is recommended (LE: 3, GR: C). This is valuable for standard procedures such as total (radical) prostatectomy [376-379]. In open enucleation of prostatic adenoma, the risk of postoperative infection is particularly high [380] (LE: 2b, GR: B).

3N.4.6 Open urological operations with bowel segment (clean-contaminated or contaminated procedures)

Antibiotic prophylaxis is recommended, as for clean-contaminated operations in general surgery. Single or 1-day dosage is recommended, although prolonged operation and other morbidity risk factors might support the use of a prolonged regimen, which should be < 72 h. The choice of antibiotic should focus on aerobic and anaerobic pathogens. Evidence is based on colorectal surgery (LE: 1a, GR: A), but experience is limited as for specific urological interventions [381-384] (LE: 2a, GR: B).

3N.4.7 Postoperative drainage of the urinary tract

When continuous urinary drainage is left in place after surgery, prolongation of perioperative antibacterial prophylaxis is not recommended, unless a complicated infection that requires treatment is suspected. Asymptomatic bacteriuria (bacterial colonisation) should only be treated after removal of the drainage tube if considered as necessary (LE: 3, GR: B).

3N.4.8 Implantation of prosthetic devices

When infectious complications occur in implant surgery, they are usually problematic and often result in removal of the prosthetic device. Diabetes mellitus is considered a specific risk factor for infection. Skin-related staphylococci are responsible for most infections. The antibiotics used must be chosen to target these strains [385-388] (LE: 2a, GR: B).

Table 22: Surgical wound classes modified from [295] and adapted to urological surgery.

Classification of urological procedures in relation to the different levels of surgical field contamination. The risk of wound infection or SSI expressed in percent (within brackets in left column) is that of classical wound infections without ABP and not bacteriuria or clinical UTI in urological surgery (modified from pg. 674-75 [2]). In this table some examples of open and laparoscopic procedures are given and the ABP basic principle.

Level of surgical site contamination	Description	Open or laparoscopic urological surgery (examples of procedures)	Principle of antibiotic prophylaxis (timing see 3N.3.1)
Clean (I) (1-4%)	Uninfected surgical site Urogenital tract not entered No evidence of inflammation No break in technique	Simple nephrectomy Planned scrotal surgery Vasectomy Varicocele	No
Clean-contaminated (IIA) (Not well studied)	Urogenital tract (UT) entered with no or little (controlled) spillage. No break in technique	Pelvic-ureteric junction repair Nephron-sparing tumour resection Total prostatectomy Bladder surgery, partial cystectomy	Single dose prior to (oral) or at surgery (i.v.)
Clean-contaminated (bowel) (IIB) (4-10%)	Gastrointestinal tract (GIT) entered with no or little (controlled) spillage. No break in technique	Urine diversion (small intestine) Orthotopic bladder replacement; ileal conduit	Single dose prior to (oral) or at surgery (i.v.)
Contaminated (IIIA) (10-15%)	UT and/or GIT entered, spillage of GI content; inflammatory tissue Presence of bacteriuria (UT) Major break in technique; Open, fresh accidental wounds	Urine diversion (large intestine) Spillage (small and large intestine) Concomitant GI disease Trauma surgery	Control of bacteriuria prior to surgery Single dose at Surgery Consider prolonged regime
Dirty (IV) (15-40%)	Pre-existing infection; viscera perforation Old traumatic wound	Drainage of abscess Large dirty trauma surgery	Treatment in accordance with pathogen's sensitivity

GIT = gastrointestinal tract; UT = urogenital tract.

Table 23: Classification of the different diagnostic and therapeutic endoscopic urological procedures in relation to the level of surgical field contamination.

Bacteriuria is a key factor to separate between clean-contaminated and contaminated surgical environment (modified from pg. 674-75 [2]).

Level of surgical field contamination	Bacteriuria	Diagnostic procedures	TUR-BT and TUR-P	URS PNL	SWL	Principle of antibiotic prophylaxis (timing see 3N.3.1)
Clean (I)*	No	Cystoscopy Urodynamic study	Fulguration of small bladder tumours (similar cystoscopy)	Diagnostic URS (simple) No history of UTI	Standard kidney or ureter stone, (no obstruction, no history of UTI)	No
Clean-contaminated (UT) (IIA)	No	Trans-perineal prostate biopsy	TUR-BT large tumour (no history of UTI), TUR-P (no identified RF) Controlled BU	Diagnostic URS (simple) Uncomplicated stone (no obstruction, no stent, not "impacted") History of UTI	Standard kidney or ureter, moderate obstruction and/or history of UTI	Single dose prior to (oral) or at surgery (i.v.)

Contaminated (UT=IIIA)	Yes	Trans-perineal prostate biopsy (history of UTI) Trans-rectal prostate biopsy	TUR-BT necrosis tumour Bacteriuria TUR-P in men with indwelling catheter or bacteriuria	Complicated stone (Moderate obstruction, "impacted")	Complex stone Obstruction Nephrostomy tube or JJ-stent present	Control of bacteriuria prior to surgery (3-5 days) Single dose at surgery. Consider prolonged regimen
Infected/Dirty (IV)	Yes	Prostate biopsy in men with catheter or UTI	Clinical UTI Drainage as required Emergency TUR-BT, TUR-P			Antibiotic Treatment according to sensitivity pattern

* Although the urinary tract/bladder is entered, the standard procedure, smooth and atraumatic, is considered in this model as clean in patients without bacteriuria and or history of infection after these procedures.

RF = risk factor; SWL = extracorporeal shockwave lithotripsy; TUR-BT = transurethral resection of the bladder tumour; TUR-P = transurethral resection of the prostate.

Table 24: Recommendations for perioperative antibiotic prophylaxis per type of procedure considering expected pathogens and individual risk factors (see 3N.3)

Procedure	Pathogens (expected)	Prophylaxis	Remarks	Choice of antimicrobial agents (when appropriate)
Diagnostic procedures				
Transrectal biopsy of the prostate	Enterobacteriaceae Anaerobes ¹	All patients Targeted alternative ²	Single dose effective in low-risk patients Consider prolonged course in high-risk patients (i.e. history of UGI)	Fluoroquinolones TMP ± SMX Targeted alternative ² Metronidazole? ¹
Cystoscopy Cystoscopy + fulguration Urodynamic study	Enterobacteriaceae Enterococci Staphylococci	No	Consider in high-risk patients (i.e. history UTI after procedure)	TMP ± SMX Cephalosporin group 2 Nitrofurantoin
Ureteroscopy	Enterobacteriaceae Enterococci Staphylococci	No	Consider in high-risk patients	
Endourological surgery and SWL				
SWL	Enterobacteriaceae Enterococci	No		TMP ± SMX Cephalosporin group 2 or 3 Aminopenicillin/BLI ^a
SWL with stent or nephrostomy tube	Enterobacteriaceae Enterococci	All patients	Risk patients	TMP ± SMX Cephalosporin group 2 or 3 Aminopenicillin/BLI ^a
Ureteroscopy for uncomplicated distal stone	Enterobacteriaceae Enterococci Staphylococci	No	Consider in risk patients	TMP ± SMX Cephalosporin group 2 or 3 Aminopenicillin/BLI Fluoroquinolones
Ureteroscopy of proximal or impacted stone and percutaneous stone extraction	Enterobacteriaceae Enterococci Staphylococci	All patients	Short course length to be determined Intravenous suggested at operation	TMP ± SMX Cephalosporin group 2 or 3 Aminopenicillin/BLI Fluoroquinolones

TUR-P	Enterobacteriaceae Enterococci	All patients	Low-risk patients and small-size prostate probably do not require prophylaxis	TMP ± SMX Cephalosporin group 2 or 3 Aminopenicillin/BLI
TUR-BT (For detail grading see Table 23)	Enterobacteriaceae Enterococci	No standard in minor procedures	Consider in high-risk patients, larger resection and in necrotic tumours	TMP ± SMX Cephalosporin group 2 or 3 Aminopenicillin/BLI
Open or laparoscopic urological surgery				
Clean operations	Skin-related pathogens, e.g. staphylococci Catheter-associated uropathogens	No	Consider in high-risk patients Short postoperative catheter requires no treatment	
Clean-contaminated (opening of urinary tract)	Enterobacteriaceae Enterococci Staphylococci	Recommended	Single perioperative course	TMP ± SMX Cephalosporin group 2 or 3 Aminopenicillin/BLI
Clean-contaminated/ contaminated (use of bowel segments)	Enterobacteriaceae Enterococci Anaerobes Skin-related bacteria	All patients	As for colonic surgery	Cephalosporin group 2 or 3 Metronidazole
Implant of prosthetic devices	Skin-related bacteria, e.g. staphylococci	All patients		Cephalosporin group 2 or 3 Penicillin (penicillinase stable)

¹The role of anaerobes in core biopsy of the prostate is not established and there is no evidence for metronidazole; ²Increasing fluoroquinolone resistance has to be assessed. ^a = gram-negative bacteria excluding *Pseudomonas aeruginosa*.

BLI = beta-lactamase inhibitor; SMX = sulphamethoxazole; TMP = trimethoprim; TUR-BT = transurethral resection of the bladder tumour; TUR-P = transurethral resection of the prostate.

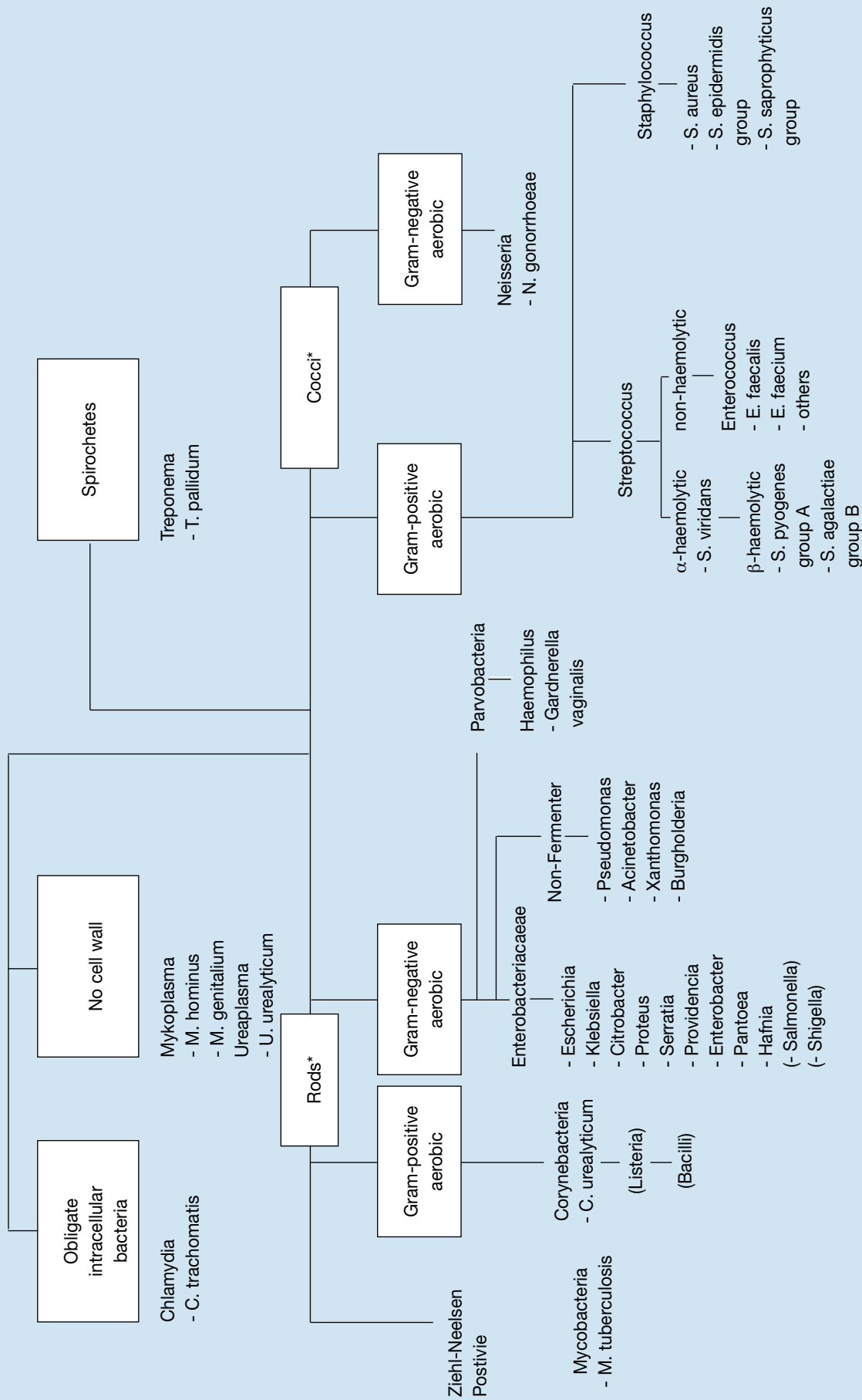
4. APPENDICES

4.1 Criteria for the diagnosis of UTI, as modified according to IDSA/European Society of Clinical Microbiology and Infectious Diseases guidelines [389-391]

Category	Description	Clinical features	Laboratory investigations
1	Asymptomatic bacteriuria	No urinary symptoms	> 10 WBC/mm ³ > 10 ⁵ cfu/mL* in two consecutive MSU cultures > 24 h apart
2	Acute uncomplicated UTI in women; acute uncomplicated cystitis in women	Dysuria, urgency, frequency, suprapubic pain, no urinary symptoms in 4 weeks before this episode	> 10 WBC/mm ³ > 10 ³ cfu/mL*
3	Acute uncomplicated pyelonephritis	Fever, chills, flank pain; other diagnoses excluded; no history or clinical evidence of urological abnormalities (ultrasonography, radiography)	> 10 WBC/mm ³ > 10 ⁴ cfu/mL*
4	Complicated UTI	Any combination of symptoms from categories 1 and 2 above; one or more factors associated with a complicated UTI (see text)	> 10 WBC/mm ³ > 10 ⁵ cfu/mL* in women > 10 ⁴ cfu/mL* in men, or in straight catheter urine in women
5	Recurrent UTI (antimicrobial prophylaxis)	At least three episodes of uncomplicated infection documented by culture in past 12 months: women only; no structural/functional abnormalities	< 10 ³ cfu/mL*

All pyuria counts refer to unspun urine. *Uropathogen in MSU culture.

4.2 Relevant bacteria for urological infections



*Anaerobic bacteria not considered.

4.3 Summary of recommendations for antimicrobial therapy in urology

Diagnosis	Most frequent pathogens/species	Initial, empirical antimicrobial therapy	Therapy duration
Asymptomatic bacteriuria	<i>E. coli</i> (low virulence) Other species can also be found	No treatment Exception: before urological surgery and during pregnancy (under debate)	3 – 5 days prior to surgery according to urine culture ¹
Cystitis, acute, sporadic (uncomplicated), in otherwise healthy women	<i>E. coli</i> <i>Klebsiella</i> sp. <i>Proteus</i> sp. Staphylococci	Fosfomycin trometamol Nitrofurantoin macrocrystal Pivmecillinam Alternative: Cephalosporin (group 1 or 2) TMP-SMX ² Fluoroquinolone ^{3,4}	Single 3 g dose/1 day 5 days 3-5 days 3 days 3 days 3 days
Pyelonephritis, acute, sporadic (febrile) (uncomplicated)	<i>E. coli</i> <i>Klebsiella</i> sp. <i>Proteus</i> sp. Other Enterobacteriaceae Staphylococci	Fluoroquinolone ³ Cephalosporin (group 3a) Alternative: Aminopenicillin/BLI Aminoglycoside TMP-SMX ⁵	7 – 10 days 10 days After improvement, switch to oral therapy according to sensitivity test
Febrile UTI with urological complicating factors	<i>E. coli</i> <i>Klebsiella</i> sp. <i>Proteus</i> sp. <i>Enterobacter</i> <i>Serratia</i> Other	Fluoroquinolone ³ Aminopenicillin/BLI Cephalosporin (group 3a) Aminoglycoside TMP-SMX ⁵	7-14 days As for Pyelonephritis 3-5 days after defervescence or control/elimination of complicating factor (drainage, surgery)
Healthcare associated complicated UTI	Enterobacteriaceae <i>Pseudomonas</i> sp.	In case of initial failure (<3 days) Fluoroquinolone (if not initially used)	As above
Urosepsis	High risk of multi-resistant strains Enterococci Staphylococci In case of Candida infection	Piperacillin/BLI Cephalosporin (group 3b) Carbapenem + Aminoglycoside Fluconazole Amphotericin B	Consider combination of two antibiotics in severe infections
Prostatitis, acute bacterial (febrile) Acute Epididymitis (febrile)	<i>E. coli</i> Other Enterobacteriaceae <i>Pseudomonas</i> sp. <i>Enterococcus faecalis</i>	Fluoroquinolone ² Cephalosporin (group 3a or b) Aminoglycoside TMP-SMX ⁵	Initial parenteral After improvement, switch to oral therapy according to sensitivity test 2 (-4) weeks
Prostatitis, chronic bacterial	Staphylococci	Fluoroquinolone ² Alternative to consider based on micro-organism: TMP-SMX Doxycycline Macrolide	Oral 4-6 weeks
Prostatitis, acute/chronic and Epididymitis caused by	<i>Chlamydia</i> sp <i>Ureaplasma</i> sp	Doxycycline Fluoroquinolone (e.g. ofloxacin, levofloxacin) Macrolide	7 (-14) days (Follow national guidelines if available)

¹ Bacteriuria is a risk factor, though no clear regimen has been defined in available literature. The given recommendation is a reasonable expert opinion

² Only in areas with resistance rate below 20% for *E. coli*

³ fluoroquinolones with mainly renal excretion

⁴ Avoid fluoroquinolones in acute sporadic cystitis whenever possible

⁵ When proven sensitivity

BLI = beta-lactamase inhibitor; SMX = sulphamethoxazole; TMP = trimethoprim.

4.4. Recommendations for antimicrobial prescription in renal failure

Antibiotic	GFR (mL/min)			Comments
	Mild 50-20	Moderate 20-10	Severe <10	
*Aciclovir	normal dose every 12 h	normal dose every 24 h	50% of normal dose every 24 h	Give post-HD
Aciclovir po		Herpes simplex: normal Herpes zoster: 800 mg Total Dissolved Solids tds	Herpes simplex: 200 mg bid Herpes zoster: 800 mg bd	Give post-HD
Amikacin	5-6 mg/kg 12 h	3-4 mg/kg 24 h HD: 5 mg/kg post HD and monitor levels	2 mg/kg 24-48 h	Give post-HD Monitor pre- and 1 h post-dose levels after 3 rd dose and adjust dose as required
Amoxicillin po	normal	normal	250 mg 8 h (normal)	Give post-HD
Amphotericin (Liposomal + lipid complex)	Amphotericin is highly NEPHROTOXIC. Consider using liposomal/lipid complex amphotericin. Daily monitoring of renal function (GFR) essential.			
Ampicillin IV	normal	250-500 mg 6 h	250 mg 6 h (500 mg 6 h)	Give post-HD
Benzylpenicillin	normal	75%	20-50% Max. 3.6 g/day (1.2 g qds)	Give post-HD Refer to microbiology for dosing in SBE
Caspofungin	normal	normal	normal	
Cefotaxime	normal	normal	1 g stat then 50%	Give post-HD
Cefradine	normal	normal	250 mg 6 h	Give post-HD
Ceftazidime	1 g 12 h	1 g 24 h	500 mg 24 h (1 g 24 h)	Give post-HD
Ceftriaxone	normal	normal	normal Max. 2 g/day	
Cefuroxime IV	normal	750 mg-1.5 g 12 h	750 mg 24 h (750 mg 12 h)	Give post-HD
Ciproflazin IV + po	normal	50%	50%	
Clarithromycin IV + po	normal	normal	50%	Give post-HD
Clindamycin IV + po	normal	normal	normal	
Co-amoxiclav IV (Augmentin)	normal	1.2 stat then 50% 12 h (1.2 g 12 h)	1.2 stat then 50% 24 h (1.2 g stat then 600 mg 12 h)	Give post-HD
Co-amoxiclav po (Augmentin)	normal	375-625 mg 12 h (375 mg 8 h)	375 mg 12 h (375 mg 8 h)	Give post-HD
*Co-trimoxazole IV	normal	Normal for 3/7 then 50%	50%	Give post-HD
Doxycycline	normal	normal	normal	All other tetracyclines contraindicated in renal impairment
Erythromycin IV + po	normal	normal	normal Max. 1.5 g/day (500 mg qds)	
*Ethambutol	normal	24-36 h	48 h	Give post-HD
	Monitor levels if GFR < 30 mL/min (contact Mirco)			
Flucloxacillin IV + po	normal	normal	normal Max. 4 g/day	

Fluconazole	normal	normal	50%	Give post-HD No adjustments in single-dose therapy required
*Flucytosine	50 mg/kg 12 h	50 mg/kg 24 h	50 mg/kg stat then dose according to levels	Give post-HD Levels should be monitored predialysis.
Fusidic acid	normal	normal	normal	
1) Gentamicin ONCE DAILY	GFR 10-40 mL/min 3 mg/kg stat (max. 300 mg) Check pre-dose levels 18-24 h after first dose Redose only when level < 1 mg/L		GFR < 10 mL/min 2 mg/kg (max. 200 mg) redose according to levels	BOTH METHODS Give post-HD Monitor blood levels
2) Gentamicin CONVENTIONAL	80 mg 12 h	80 mg 48 h	80 mg 24 h HD: 1-2 mg/kg Post-HD: redose according to levels	Once daily: pre only Conventional: pre and 1 h post level required
Imipenem	500 mg 8-12 h	250-500 mg bid	Risk of convulsions - use Meropenem: see <i>below</i>	Give post-HD
Isoniazid	normal	normal	200-300 mg 24 h	Give post-HD
Itraconazole	normal	normal	normal	
Levofloxacin	500 mg stat then 250 mg bid**	500 mg stat then 125 mg bid**	500 mg stat then 125 mg od	**Applies if full dose is 500 mg bid If full dose is 500 mg od, five reduced doses daily
Linezolid	normal	normal	normal	Give post-HD
Meropenem	12 h	50% 12 h	50% 24 h	Give post-HD
Metronidazole	normal	normal	12 h (normal)	Give post-HD
Nitrofurantoin	Do NOT use in renal impairment			
Penicillin V	normal	normal	normal	Give post-HD
Piperacillin/ Tazobactam (Tazocin)	4.5 g 8 h	4.5 g 12 h	4.5 g 12 h	Give post-HD
Pyrazinamide	normal	normal	normal	
Rifampicin	normal	normal	50-100%	
*Teicoplanin	100% 48 h	100% 72 h	100% 72 h	Dose reduction after day 3 of therapy
Tetracycline	See Doxycycline			
Trimethoprim	normal	Normal for 3/7 then 50% 18 h	50% 24 h	Give post-HD
Vancomycin	1 g od Check pre-dose level before 3 rd dose	1 g 48 h Check pre-dose level before 2 nd dose	1 g stat (or 15 mg/kg, up to max. 2 g). Recheck level after 4-5 days ONLY give subsequent dose when level < 12mg/L	Monitor pre-dose levels and adjust dose as required
Voriconazole	normal	normal	normal	Give post-HD

bid = twice daily; *GFR* = glomerular filtration rate; *HD* = haemodialysis; *od* = once daily; *po* = by mouth; *qds* = quantum dots; *qid* = four times daily; *SBE* = subacute bacterial endocarditis; *tds* = total dissolved solids.

4.5 Antibacterial agents

Groups	Agents
Trimethoprim-sulphonamide combinations	Trimethoprim, co-trimoxazole, co-tetroxoprim (trimethoprim plus sulfametrol)
Fluoroquinolones ^{1,2}	
Group 1	Norfloxacin, pefloxacin
Group 2	Enoxacin, fleroxacin, lomefloxacin, ofloxacin, ciprofloxacin
Group 3	Levofloxacin
Group 4	Gatifloxacin, moxifloxacin
Macrolides	Erythromycin, roxithromycin, clarithromycin, azithromycin
Tetracyclines	Doxycycline, minocycline, tetracycline
Fosfomycin	Fosfomycin sodium, fosfomycin trometamol ³
Nitrofurantoin ⁴	Nitrofurantoin
Penicillins	
Benzylpenicillin	Penicillin G
Phenoxyphenicillins	Penicillin V, propicillin, azidocillin
Isoxazolylpenicillins	Oxacillin, cloxacillin, dicloxacillin, flucloxacillin
Aminobenzylpenicillins ⁵	Ampicillin, amoxycillin, bacampicillin
Aminopenicillins/BLI ⁶	Ampicillin/sulbactam, amoxycillin/clavulanic acid ⁷
Acylaminopenicillins	Mezlocillin, piperacillin
±BLI ⁶	Piperacillin/tazobactam, sulbactam ⁶
Cephalosporins ¹	
Group 1 (oral)	Cefalexin, cefadroxil, cefaclor
Group 2 (oral)	Loracarbef, cefuroxime axetile
Group 3 (oral)	Cefpodoxime proxetile, cefetamet pivoxil, ceftibuten, cefixime
Group 1 (parenteral)	Cefazolin
Group 2 (parenteral)	Cefamandole, cefuroxime, cefotiam
Group 3a (parenteral)	Cefodizime, cefotaxime, ceftriaxone
Group 3b (parenteral)	Cefoperazone, ceftazidime
Group 4 (parenteral)	Cefepime, ceftipime
Group 5 (parenteral)	Cefoxitin
Monobactams	Aztreonam
Carbapenems	Imipenem, meropenem, ertapenem
Aminoglycosides	Gentamicin, netilmicin, tobramycin, amikacin
Glycopeptides	Vancomycin, teicoplanin
Oxazolidones	Linezolid

¹Classification according to the Paul Ehrlich Society for Chemotherapy [389-391].

²Only in adults, except pregnant and lactating women.

³Only in acute, uncomplicated cystitis as a single dose.

⁴Contraindicated in renal failure and in newborns.

⁵In cases of resistance, the pathogen is most likely to be a β -lactamase producer.

⁶BLIs can only be used in combination with β -lactam antibiotics.

⁷In solution, storage instability.

Further information regarding the different antibiotics are available in the online version.

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6. CONFLICT OF INTEREST

All members of the Urological Infections Guidelines Panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website. This Guidelines document was developed with the financial support of the EAU. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

Guidelines on Urinary Incontinence

M.G. Lucas (Chair), D. Bedretdinova (Guidelines Associate),
L.C. Berghmans, J.L.H.R. Bosch, F.C. Burkhard, F. Cruz,
A.K. Nambiar, C.G. Nilsson, A. Tubaro, R.S. Pickard

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1. INTRODUCTION

Urinary incontinence (UI) is an extremely common complaint in every part of the world. It causes a great deal of distress and embarrassment, as well as significant costs, to both individuals and societies. Estimates of prevalence vary according to the definition of incontinence and the population studied. However, there is universal agreement about the importance of the problem in terms of human suffering and economic cost.

1.1 Aim

These Guidelines from the European Association of Urology (EAU) Working Panel on Urinary Incontinence are written by urologists primarily for urologists, though we recognise that they are likely to be referred to by other professional groups. They aim to provide sensible and practical evidence-based guidance on the clinical problem of UI rather than an exhaustive narrative review. Such a review is already available from the International Consultation on Incontinence [1], and so the EAU Guidelines do not describe the causation, basic science, epidemiology and psychology of UI. The focus of these Guidelines is entirely on assessment and treatment reflecting clinical practice. The Guidelines also do not consider patients with UI caused by neurological disease, or in children, as this is covered by complementary EAU Guidelines [2, 3].

The EAU Panel knew that they would find little evidence for some issues and a lot of evidence for others. This difference, to some extent, reflects the greater funding available for industry-sponsored trials of drugs, the results of which are required for licensing in Europe and the USA. The less stringent regulatory requirements for the introduction of new devices or surgical techniques means that there are far fewer high-quality studies regarding these interventions. Although the lack of high-quality evidence means that judgements about the worth of interventions are prone to bias, the Panel took the view that clinicians still require some guidance concerning clinical practice. In these circumstances, we have summarised the available evidence and made recommendations based on expert opinion, with uncertainty reflected by a lower grade of recommendation.

The elderly

The panel decided to include a separate but complimentary set of recommendations referring to the elderly population within each section. Older people with UI deserve special consideration for a number of reasons. Physiological changes with natural ageing mean that all types of UI become more common with increasing age. Urinary incontinence commonly co-exists with other comorbid conditions, reduced mobility, and impaired cognition and may require specific interventions, such as assisted toileting.

For the elderly person expectations of assessment and treatment may need to be modified to fit in with specific circumstances, needs, and preferences, while taking into account any loss of capacity for consent. When the urologist is dealing with a frail elderly patient with urinary incontinence, collaboration with other healthcare professionals such as elderly care physicians is recommended.

1.1.1 **Use in different healthcare settings and by healthcare professionals**

The Panel recognises that a patient's first point of contact may not always be a urologist, and that the healthcare professional delivering specific treatments such as physiotherapy, may also not be a urologist. For this reason, some healthcare professionals may find that the Guidelines do not explain a particular topic in enough detail for their needs, e.g. delivery modalities for pelvic floor muscle training (PFMT).

1.2 Publication history

The 2012 edition of these Guidelines was completely rewritten using new methodology and based on new searches up to July 2011 and those carried out for ICUD and NICE (2006) documents.

The 2013 edition was updated with searches to September 2012 and included a new appendix on non obstetric fistula derived from the ICUD 2013, but the contained evidence has not yet been assessed according to the EAU methodology (see Appendix A available online at www.uroweb.org). In the 2014 edition additional searches were done for patient reported outcome measures (PROMS), urethral diverticulum, containment, prolapse reduction stress test, anticholinergic load, and mirabegron. In this 2015 edition searches were done on the 'Assessment and Diagnosis' chapter and on the subject of mirabegron in the 'Drug Treatment' chapter (Table 1).

A quick reference guide, presenting the main findings of the Urinary Incontinence Guidelines, is also available, as well as two scientific publications in the journal of the EAU, European Urology [4, 5]. All texts can be viewed and downloaded for personal use at the society website:

<http://www.uroweb.org/guidelines/online-guidelines/>.

This document was peer-reviewed prior to publication.

1.3 Panel composition

The EAU Urinary Incontinence Panel consists of a multidisciplinary group of experts, including urologists, a gynaecologist and a physiotherapist.

2. METHODS

References used in this text are graded according to their Level of Evidence (LE) and Guidelines are given a Grade of Recommendation (GR). In this 2015 EAU Guidelines compilation, all standard information on LE and GR has been taken out of the individual Guidelines topics for the sake of brevity. The methodology section (see the introduction chapter of the complete book) outlines the LE and GR criteria which are used throughout the Guidelines, according to a classification system modified from the Oxford Centre for Evidence-based Medicine Levels of Evidence.

This 2015 version has been updated and re-formatted according to the EAU template for non-oncology Guidelines, so that all Guidelines follow a similar format.

The current Guidelines provide:

- A clear pathway (algorithm) for common clinical problems. This can provide the basis for thinking through a patient's management and also for planning and designing clinical services.
- A brief but authoritative summary of the current state of evidence on clinical topics, complete with references to the original sources.
- Clear guidance on what to do or not to do, in most clinical circumstances. This should be particularly helpful in those areas of practice for which there is little or no high-quality evidence.

2.1 PICO questions

The 'PICO' framework was used to develop a series of clinical questions that would provide the basis of presentation of the guidelines [6, 7]. There are four elements to each clinical question:

- Population (P)
- Intervention (I)
- Comparison (C)
- Outcome (O)

The wording of each PICO is important because it informs the subsequent literature research. For each search, the EAU Panel listed every possible wording variation.

In these Guidelines, the four traditional domains of urological practice are presented as separate chapters, namely assessment and diagnosis, conservative management, drug therapy and surgical treatments.

In this third edition of these new EAU Guidelines for Urinary Incontinence, the Panel has focused largely on the management of a 'standard' patient. The Panel has referred in places to patients with 'complicated incontinence', by which we mean patients with associated morbidity, a history of previous pelvic surgery, surgery for UI, radiotherapy and women with associated genitourinary prolapse. This third edition does not review the prevention of UI, and the management of fistula (available online at the society website). These issues will be fully addressed using our standard methodology in future editions.

2.2 Search strategies

A number of significant narrative reviews, systematic reviews and guidance documents have been produced within the last few years. The Panel agreed that the literature searches carried out by these reviews would be accepted as valid. Thus, for each PICO question, a search was carried out with a start date that was the same as the cut-off date for the search associated with the most recent systematic review for the PICO topic. This pragmatic selection approach, while being a compromise and open to criticism, made the task of searching the literature for such a large subject area possible within the available resources. For each section, the latest cut-off date for the relevant search is indicated. Thus, for each PICO, a subsequent literature search was carried out (confined to Medline and Embase and to English language articles), which produced an initial list of abstracts. The abstracts were each assessed by two Panel members, who selected the studies relevant to the PICO question, and the full text for these were retrieved (Table 1).

Table 1: Initial list of abstracts	
Chapter	Latest 'cut-off' date for search
Assessment and diagnosis	<ul style="list-style-type: none"> - PROMS & Questionnaires: 30 April 2014 - Urinalysis and urinary tract infection: 1 May 2014 - Post-voiding residual volume: 12 May 2014 - Pad testing: 29 September 2014 - Urodynamics: 7 May 2014 - Imaging: 12 May 2014
Conservative therapy	28 June 2012 <ul style="list-style-type: none"> - Containment: 10 July 2013
Drug therapy	28 June 2012 <ul style="list-style-type: none"> - Anticholinergic load: 29 April 2013 - Mirabegron: 25 April 2014
Surgical therapy	9 July 2012 <ul style="list-style-type: none"> - POP & OAB: 29 April 2013 - Prolapse reduction stress test: 16 May 2013 - Urethral diverticulum: 7 May 2013

Each PICO was then assigned to a Panel member, who read the papers and extracted the evidence for incorporation into standardised evidence tables. From 2012 onwards we have used a purpose designed web based application in which original papers are downloaded and appraised online according to a standardised format which is based on Scottish Intercollegiate Guidelines Network (SIGN) documents. The web application is progressively populated with evidence appraisals which can be displayed in tabular format showing summaries of data quality as well as summaries of outcomes.

The existing evidence from previous systematic reviews and new evidence were then discussed for each PICO in turn at a Panel meeting generating consensus conclusions. To help standardise the approach, modified process forms (data extraction and considered judgment) from SIGN were used.

The quality of evidence for each PICO is commented on in the text, aiming to synthesise the important clinical messages from the available literature and is presented as a series of levels of evidence summaries in the EAU format as described in the Introduction chapter of the complete Guidelines book.

From the evidence summaries, the Panel then produced a series of action-based recommendations, again graded according to EAU standards. These grades aim to make it clear what the clinician should or should not do in clinical practice, not merely to comment on what they might do.

The Panel has tried to avoid extensive narrative text. Instead, algorithms are presented for both initial and specialised management of men and women with non-neurogenic UI. Each decision node of these algorithms is clearly linked back to the relevant evidence and recommendations.

It must be emphasised that clinical guidelines present the best evidence available to the Panel at the time of writing. There remains a need for ongoing re-evaluation of the current guidelines by the Panel. However, adherence to guideline recommendations will not necessarily result in the best outcomes for patients. Guidelines can never replace clinical expertise when making treatment decisions for individual patients; they aim to focus decisions by addressing key clinical questions, and provide a strong basis for management decisions. Clinical decisions must also take into account the patient's personal values, preferences and specific circumstances.

2.3 Terminology

Evidence summaries provide a succinct summary of what the currently available evidence tells us about an individual clinical question. They are presented according to the levels of evidence used by the EAU.

Recommendations have been deliberately written as 'action-based' sentences. The following words or phrases are used consistently throughout the Guidelines, as follows:

- **Consider** an action. This word is used when there is not enough evidence to say whether the action causes benefit or risk to the patient. However, in the opinion of the Panel, the action may be justified in some circumstances. Action is optional.
- **Offer** an action. This word is used when there is good evidence to suggest that the action is effective, or that, in the opinion of the Panel, it is the best action. Action is advisable.

- **Carry out (perform)** an action. **Do** something. This phrase is used when there is strong evidence that this is the only best action in a certain clinical situation. Action is mandatory.
- **Do not** perform (i.e. avoid) an action. This phrase is used when there is high-level evidence that the action is either ineffective or is harmful to the patient. Action is contraindicated.

3. DIAGNOSTIC EVALUATION

3.1 History and physical examination

Taking a careful clinical history is fundamental to the clinical process. Despite the lack of formal evidence, there is universal agreement that taking a history should be the first step in the assessment of anyone with UI. The history should include details of the type, timing and severity of UI, associated voiding and other urinary symptoms. The history should allow UI to be categorised into stress urinary incontinence (SUI), urgency urinary incontinence (UUI) or mixed urinary incontinence (MUI). It should also identify patients who need rapid referral to an appropriate specialist. These include patients with associated pain, haematuria, a history of recurrent urinary tract infection (UTI), pelvic surgery (particularly prostate surgery) or radiotherapy, constant leakage suggesting a fistula, voiding difficulty or suspected neurological disease. In women, an obstetric and gynaecological history may help to understand the underlying cause and identify factors that may impact on treatment decisions. The patient should also be asked about other ill health and for the details of current medications, as these may impact on symptoms of UI.

Similarly, there is little evidence that carrying out a clinical examination improves care, but wide consensus suggests that it remains an essential part of assessment of people with UI. It should include abdominal examination, to detect an enlarged bladder or other abdominal mass, and perineal and digital examination of the rectum (prostate) and/or vagina. Examination of the perineum in women includes an assessment of oestrogen status and a careful assessment of any associated pelvic organ prolapse (POP). A cough test may reveal SUI if the bladder is sufficiently full and pelvic floor contraction together with urethral mobility can be assessed digitally.

3.2 Patient questionnaires

This section includes symptom scores, symptom questionnaires, scales, indexes, PROMs and health-related quality of life (HRQoL) measures. The latter include generic or condition specific.

Questionnaires should have been validated for the language in which they are being used, and, if used for outcome evaluation, must have been shown to be sensitive to change. The methodology for questionnaire development was reviewed in the 5th International Consultation on Incontinence in 2012 [8].

3.2.1 Questions

- In patients with UI, can the use of Questionnaires/PROMS differentiate between stress, urgency and mixed incontinence, and does this differentiation impact on QoL after treatment?
- In adults with UI, does assessment using either urinary symptom or QoL questionnaires improve treatment outcome for UI?
- In adults with UI, does assessment of the patient perspective (concerns or expectations) improve patient outcomes, regarding either urinary symptoms or QoL, compared to no patient-reported assessment?

3.2.2 Evidence

Although many studies have investigated the validity and reliability of urinary symptom questionnaires and PROMs, most have taken place in adults without UI. This limits the extent to which results and conclusions from these studies can be applied in adults with UI. Some questionnaires (QUID, 3IQ) have potential to discriminate UI types in women [9, 10]. In men ICIQ-UI-SF score does not differentiate UI types [11].

Some are responsive to change and may be used to measure outcomes, though evidence on their sensitivity is inconsistent [12-14].

No evidence was found to indicate whether use of QoL or condition specific questionnaires have an impact on outcome of treatment.

The table shows a summary of the ICUD review 2012 with recent additions. Criteria on which questionnaires are assessed include validity, reliability and responsiveness to change.

	Category A (all 3 criteria fulfilled)*	Category B (2 criteria fulfilled)*	Category C (only 1 criterion fulfilled)*
Symptom measures and health related QOL measures	ICIQ-UI Short Form, ICIQFLUTS, ICIQ-MLUTS IIQ and IIQ-7, I-QOL (ICIQ-Uqol), ISS, KHQ, LIS (?-interview), N-QoL, OAB-q SF, OAB-q (ICIQ-OABqol), PFDI and PFDI-20, PFIQ and PFIQ-7, PRAFAB, UISS;	Contilife, EPIQ, LUTS tool IOQ, YIPS;	ABSST ISI, ISQ, UIHI, UIQ
Measure of patient satisfaction (patient's measure of treatment satisfaction)	BSW, OAB-S, OABSAT-q, TBS	PPQ	EPI, GPI, PSQ
Goal attainment scales		SAGA	
Screening tools (used to identify patients with UI)	B-SAQ, OAB-SS, OABV8, OAB-V3, QUID	ISQ, USP	3IQ, CLSS, MESA, PUF
patient symptom scale			
Assessment of symptom bother and overall bother	PPBC, UDI or UDI-6, LUSQ, PGI-I and PGI-S;	PFBQ, SSI and SII	PMSES, POSQ, UI-4
Assessment of the impact of urgency	IUSS, U-IIQ, UU Scale, U-UDI	PPIUS, SUIQ, UPScore, UPScale, UQ, USIQ-QOL, USIQ-S, USS	
Questionnaires to assess sexual function and urinary symptoms		FSFI, ICIQ-VS, PISQ, SQoL-F	SFQ
Treatment adherence measures		MASRI	

* Criteria on which questionnaires are assessed include validity, reliability and responsiveness to change.

3IQ = Three Incontinence Questions Questionnaire ABSST = Actionable Bladder Symptom Screening Tool B-SAQ = Bladder Self-Assessment Questionnaire BSW = Benefit, Satisfaction with treatment and Willingness CLSS = Core Lower Urinary Tract Symptom Score Contlife® = Quality of Life Assessment Questionnaire Concerning Urinary Incontinence EPIQ = Epidemiology of Prolapse and Incontinence Questionnaire FSFI = Female Sexual Function Index ICIQ = International Consultation on Incontinence Modular Questionnaire ICIQ-FLUTS = ICIQ-Female Lower Urinary Tract Symptoms ICIQ-MLUTS = ICIQ-Male Lower Urinary Tract Symptoms ICIQ-VS = International Consultation on Incontinence Questionnaire – Vaginal Symptoms IIQ (IIQ-7) = Incontinence Impact Questionnaire (short form) IOQ = Incontinence Outcome Questionnaire I-QOL (ICIQ-Uqol) = Urinary Incontinence-Specific Quality of Life Instrument ISI = Incontinence Severity Index ISQ = Incontinence Stress Index ISS = Incontinence Symptom Severity Index IUSS = Indevus Urgency Severity KHQ = King's Health Questionnaire LIS = Leicester Impact Scale LUSQ = Leicester Urinary Symptom Questionnaire LUTS Tool = Lower Urinary Tract Symptoms Tool MASRI = Medication Adherence Self-Report Inventory MESA = Medial Epidemiological and Social Aspects of Aging Questionnaire N-QoL = Nocturia Quality of Life Questionnaires OAB-q (ICIQ-OABqol) = Overactive Bladder Questionnaire OAB-S = Overactive Bladder Satisfaction measure OAB-SAT-q = OAB Satisfaction questionnaire OAB-SS = Overactive Bladder Symptom Score OAB-v3 = OAB short form OAB-v8 = OAB Awareness Tool	PFBQ = Pelvic Floor Bother Questionnaire PFDI (PFDI-20) = Pelvic Floor Distress Inventory (short form) PFIQ (PFIQ-7) = Pelvic Floor Impact Questionnaire (short form) PRAFAB = Protection, Amount, Frequency, Adjustment, Body image) PGI-I and PGI-S = Patient Global Impression of Severity and Improvement PISQ = Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire PMSES = Broome Pelvic Muscle Exercise Self-Efficacy Scale POSQ = Primary OAB Symptom Questionnaire PPBC = Patient Perception of Bladder Condition PPIUS = Patient's Perception of Intensity of Urgency Scale PPQ = Patient Preparation Questionnaire PUF = patient symptom scale (Pelvic Pain, Urgency and Frequency) QUID = Questionnaire for Urinary Incontinence Diagnosis SAGA = Self-Assessment Goal Achievement Questionnaire SQoL-F = Sexual Quality of Life - Female SSI and SII = Symptom Severity Index and Symptom Impact Index for Stress Incontinence in women SUIQ = Stress/Urgency Incontinence Questionnaire TBS = Treatment Benefit Scale UDI (UDI-6) = Urogenital Distress Inventory (-6) UI-4 = Urinary Incontinence -4 Questionnaire UIHI = Urinary Incontinence Handicap Inventory U-IIQ = Urge Incontinence Impact Questionnaire UIQ = Urinary Incontinence Questionnaire UISS = Urinary Incontinence Severity Score UPScale = Urgency Perception Scale UPScore = Urgency Perception Score UQ = Urgency Questionnaire USIQ-QOL = Urgency Severity & Intensity Questionnaire: Symptom Severity USIQ-S = Urgency Severity & Intensity Questionnaire: Quality of Life USP = Urinary Symptom Profile USS = Urinary Sensation Scale
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To date, there is no one questionnaire that fulfills all requirements for assessment of people with UI. The clinician must evaluate the tools that exist to use alone or in combination for assessment, and monitoring of treatment outcome [15].

The questionnaires can be found on the following internet resource sites: www.iciq.net, www.proqolid.org, www.mapi-institute.com, www.pfizerpatientreportedoutcomes.com, www.ncbi.nlm.nih.gov.

Evidence summary	LE
Validated condition specific symptom scores assist in the screening for, and categorisation of UI.	3
Validated symptom scores measure the severity of UI.	3
Both condition specific and general health status questionnaires measure current health status, and change following treatment.	3

Recommendation	GR
Use a validated and appropriate questionnaire when standardised assessment is required	B*

* Recommendation based on expert opinion.

3.3 Voiding diaries

Measurement of the frequency and severity of LUTS is an important step in the evaluation and management of lower urinary tract dysfunction, including UI. Voiding diaries are a semi-objective method of quantifying symptoms, such as frequency of urinary incontinence episodes. They also quantify urodynamic variables, such as voided volume and 24-hour or nocturnal total urine volume. Voiding diaries are also known as micturition time charts, frequency/volume charts and bladder diaries.

Discrepancy between diary recordings and the patient rating of symptoms, e.g. frequency or UI, can be useful in patient counselling. In addition, voided volume measurement can be used to support diagnoses, such as overactive bladder (OAB) or polyuria. Diaries can also be used to monitor treatment response and are widely used in clinical trials. In patients with severe UI, a voiding diary is unlikely to accurately report 24 hour urine output and so voided volume may be lower than total bladder capacity.

3.3.1 Questions

- In adults with UI, what are the reliability, diagnostic accuracy and predictive value of a voiding diary compared to patient history or symptom score?

3.3.2 Evidence

Two recent articles have suggested a consensus has been reached in the terminology used in voiding diaries [16, 17]:

- **Micturition time charts** record only the times of micturitions for a minimum of 24 continuous hours.
- **Frequency volume charts** record voided volumes and times of micturitions for a minimum of 24 hours.
- **Voiding diaries** include information on incontinence episodes, pad usage, fluid intake, degree of urgency and degree of UI.

Several studies have compared patients' preference for, and the accuracy of, electronic and paper voiding diaries in voiding dysfunction [18-22]. Several studies have compared shorter (3 or 5 days) and longer diary durations (7 days) [23-28].

Two studies have demonstrated the reproducibility of voiding diaries in both men and women [23, 28]. Further studies have demonstrated variability of diary data within a 24-hour period and compared voided volumes recorded in diaries with those recorded on uroflowmetry [29, 30]. Other studies have investigated the correlation between data obtained from voiding diaries and standard symptom evaluation [31-34].

Evidence summary	LE
Voiding diaries of 3-7 days duration are a reliable tool for the objective measurement of mean voided volume, daytime and night-time frequency and incontinence episode frequency.	2b
Voiding diaries are sensitive to change and are a reliable measure of outcome.	2b

Recommendations	GR
Ask patients with urinary incontinence to complete a voiding diary to evaluate co-existing storage and voiding dysfunction.	A
Use a diary duration of between 3 and 7 days.	B

3.4 Urinalysis and urinary tract infection

Reagent strip ('dipstick') urinalysis may indicate urinary tract infection (UTI), proteinuria, haematuria or glycosuria requiring further assessment. Refer to the Urological Infections Guideline for diagnosis and treatment of UTI [35].

3.4.1 Questions

- In adults with UI, what is the diagnostic accuracy of urinalysis to detect UTI?
- In adults with UI does treatment of UTI or asymptomatic bacteriuria cure or improve UI compared to no treatment?

3.4.2 Evidence

Urinalysis negative for nitrite and leucocyte esterase has high specificity to exclude UTI in people with UI [36] and despite lower sensitivity should be included, with urine culture when necessary, in the evaluation of all patients with UI. Urinary incontinence may occur during symptomatic UTI [37] and existing UI may worsen during UTI [38]. The rate and severity of UI was unchanged after eradication of asymptomatic bacteriuria in nursing home residents [39].

Evidence summary	LE
Urinalysis negative for nitrite and leucocyte esterase reliably excludes UTI.	1
UI may be a symptom during UTI.	3
The presence of a symptomatic UTI worsens symptoms of UI.	3
Elderly nursing home patients with UI do not benefit from treatment of asymptomatic bacteriuria.	2

Recommendations	GR
Do urinalysis as a part of the initial assessment of a patient with urinary incontinence.	A*
If a symptomatic urinary tract infection is present with urinary incontinence, reassess the patient after treatment.	A*
Do not routinely treat asymptomatic bacteriuria in elderly patients to improve urinary incontinence.	B

* Recommendation based on expert opinion.

3.5 Post-voiding residual volume

Post-voiding residual (PVR) volume is the amount of urine that remains in the bladder after voiding. It indicates poor voiding efficiency, which may result from a number of contributing factors. It is important because it may worsen symptoms and, more rarely, may be associated with UTI, upper urinary tract dilatation and renal insufficiency. Both bladder outlet obstruction and detrusor underactivity contribute to the development of PVR. Post-voiding residual can be measured by catheterisation or ultrasound (US). The prevalence of PVR is uncertain, partly because of the lack of a standard definition of an abnormal PVR volume.

3.5.1 Question

In adults with UI, what is the value of measuring PVR?

3.5.2 Evidence

Most studies investigating PVR have not included patients with UI. Although some studies have included women with UI and men and women with LUTS, they have also included children and adults with neurogenic UI. In general, the data on PVR can be applied with caution to adults with non-neurogenic UI. The results of studies investigating the best method of measuring PVR [40-45] have led to the consensus that US measurement of PVR is better than catheterisation.

In peri- and postmenopausal women without significant LUTS or pelvic organ symptoms, 95% of women had a PVR < 100 mL [46]. In women with UI, a PVR > 100 mL was found in 10% of cases [47]. Other research has found that a high PVR is associated with POP, voiding symptoms and an absence of SUI [46, 48-50].

In women with SUI, the mean PVR was 39 mL measured by catheterisation and 63 mL measured by US, with 16% of women having a PVR > 100 mL [47].

Evidence summary	LE
Lower urinary tract symptoms coexisting with UI are associated with a higher rate of post-voiding residual compared to asymptomatic subjects.	2

Recommendations	GR
Use ultrasound to measure post-voiding residual.	A
Measure post-voiding residual in patients with urinary incontinence who have voiding symptoms.	B
Measure post-voiding residual when assessing patients with complicated urinary incontinence.	C
Post-voiding residual should be monitored in patients receiving treatments that may cause or worsen voiding dysfunction.	B

3.6 Urodynamics

Urodynamic testing is widely used as an adjunct to clinical diagnosis, in the belief that it may help to provide or confirm diagnosis, predict treatment outcome, or facilitate discussion during a consultation. For all these

reasons, urodynamics is often performed prior to invasive treatment for UI. These Guidelines will focus on invasive tests, including multichannel cystometry, ambulatory monitoring and video-urodynamics, and different tests of urethral function, such as urethral pressure profilometry, Valsalva leak point pressure estimation and retrograde urethral resistance measurement.

3.6.1 **Question**

In adults with UI, what is the diagnostic accuracy and predictive value of uroflowmetry, i.e. the measurement of maximum urinary flow rate (Q_{max}), and urodynamic testing?

3.6.2 **Evidence**

3.6.2.1 *Variability*

In common with most physiological tests there is variability in urodynamics results. Numerous small studies of multichannel cystometry have been done over many years in differing populations. Whilst in healthy women the same session repeatability has been shown to be poor [51], in those with incontinence it may be acceptable [52]. Measurement of urethral closure pressure (MUCP) correlates poorly with incontinence severity [53] and there is conflicting evidence about its reproducibility [54, 55]. One method of recording MUCP cannot be compared meaningfully to another [56].

Abdominal or Valsalva leak point pressures may correlate to incontinence severity [57] but the tests are not standardised and there is no evidence about reproducibility.

No studies on the reliability of ambulatory monitoring were found.

3.6.2.2 *Diagnostic accuracy*

The diagnostic accuracy of urodynamics is assessed in terms of its correlation with clinical diagnosis and incontinence severity. The problem is that clinical diagnosis and urodynamic findings often do not correlate [58, 59], and normal healthy people may have urodynamic abnormalities.

The diagnostic accuracy of urethral pressure profilometry [53] and 'Urethral Retro resistance' is generally poor [60]. Urethral reflectometry may have greater diagnostic accuracy but its clinical role remains unclear [61].

Ambulatory urodynamics may detect unexpected physiological variance from normal more often than conventional cystometry, but the clinical relevance of this is uncertain [62, 63].

3.6.2.3 *Does urodynamics influence the outcome of conservative therapy*

A recent Cochrane review of seven RCTs showed that use of urodynamic tests increased the likelihood of prescribing drugs or avoiding surgery. However, there was no evidence that this influence on decision making altered the clinical outcome of treatment [64]. Subanalysis of an RCT comparing fesoterodine to placebo [65] and another dose finding study of botulinum toxin [66] showed no predictive value for treatment response, by the urodynamic diagnosis of DO.

3.6.2.4 *Does urodynamics influence the outcome of surgery for stress urinary incontinence?*

Post-hoc analysis of surgical RCTs has shown the risk of failure of SUI surgery is higher in women who have worse leakage or urodynamically demonstrable SUI [67].

A high quality RCT (n= 630) compared office evaluation alone to office evaluation and urodynamics in women with clinical demonstrable SUI about to undergo surgery for SUI. Whilst urodynamics changed the clinical diagnosis in 56% of women [68]) there was no difference in levels of UI or any secondary outcome at 12 months' follow-up after surgery [69]. Another similar study was closed with only 59 women [70] after finding no difference in outcome. It was then redesigned to randomise only women (N=109) in whom urodynamic findings were contradictory, to immediate surgery or treatment tailored to urodynamic findings. In this trial, performing immediate surgery irrespective of the result of urodynamics did not result in inferior outcomes [71].

In observational studies there is no consistent correlation between the result of urethral function tests and subsequent success or failure of SUI surgery.

3.6.2.5 *Does urodynamics help to predict complications of surgery?*

There have been no RCTs designed to answer this question.

The presence of pre-operative DO has consistently been associated with development of postoperative UUI.

Whilst post-hoc analysis of an RCT comparing the autologous fascial sling to Burch colposuspension showed inferior outcomes for women who suffered pre-operative urgency [72]. Pre-operative urodynamics failed to predict this outcome [73].

Whilst low pre-operative flow rate has been shown to correlate with post operative voiding dysfunction [74, 75], post hoc analysis of two high quality surgical trials showed that no pre-operative urodynamic parameter had the ability to predict post operative voiding dysfunction [76, 77].

3.6.2.6 Does urodynamics influence the outcome of surgery for detrusor-overactivity?

No studies were found on the relationship between urodynamic testing and subsequent surgical outcome for DO. However, most studies reporting surgical outcomes for DO have included only patients with urodynamically proven DO or DO incontinence.

3.6.2.7 Does urodynamics influence the outcome of treatment for post-prostatectomy urinary incontinence in men?

There are no RCTs examining the clinical usefulness of urodynamics in post-prostatectomy UI. Whilst urodynamics will distinguish causes of incontinence, its ability to predict outcome of surgery for incontinence for these men is uncertain [78, 79].

Evidence summary	LE
Most urodynamic parameters show variability within the same session and over time, and this limits their clinical usefulness.	3
Different techniques of measuring urethral function may have good test-retest reliability, but do not consistently correlate to other urodynamic tests or to the severity of UI.	3
There is limited evidence that ambulatory urodynamics is more sensitive than conventional urodynamics for diagnosing SUI or DO.	2
There may be inconsistency between history and urodynamic results.	3
Preliminary urodynamics can influence the choice of treatment for UI, but does not affect the outcome of conservative therapy or drug therapy for SUI.	1a
Preliminary urodynamics in women with uncomplicated, clinically demonstrable SUI does not improve the outcome of surgery for SUI.	1b
There is no evidence that urodynamic tests of urethral function predict outcome of surgery for SUI in women.	3
There is consistent low-level evidence that pre-operative DO is associated with poorer outcomes of mid-urethral sling surgery in women.	3
There is no evidence that urodynamics predicts the outcomes of treatment for post prostatectomy incontinence in men.	4

Recommendations	GR
(NB: Concerning only neurologically intact adults with urinary incontinence)	
Clinicians carrying out urodynamics in patients with urinary incontinence should: <ul style="list-style-type: none"> • Ensure that the test replicates the patient's symptoms. • Interpret results in the context of the clinical problem. • Check recordings for quality control. • Remember there may be physiological variability within the same individual. 	C
Advise patients that the results of urodynamics may be useful in discussing treatment options, although there is limited evidence that performing urodynamics will predict the outcome of treatment for urinary incontinence.	C
Do not routinely carry out urodynamics when offering conservative treatment for urinary incontinence.	B
Perform urodynamics if the findings may change the choice of invasive treatment.	B
Do not use urethral pressure profilometry or leak point pressure to grade severity of incontinence or predict the outcome of treatment.	C
Urodynamic practitioners should adhere to the standards laid out in the ICS document "Good Urodynamic Practice" [80].	C

3.7 Pad testing

Measurement of urine loss using an absorbent pad worn over a set period of time or during a protocol of physical exercise can be used to quantify the presence and severity of UI, and of response to treatment.

3.7.1 Question

- In adults with UI, what is the reliability, diagnostic accuracy and predictive value of pad testing?
- In adults with UI is one type of pad test better than another?

3.7.2 Evidence

The clinical usefulness of pad tests for people with UI has been assessed in two systematic reviews [81, 82]. A 1-hour pad test using a standardised exercise protocol and a diagnostic threshold of 1.4 g shows good specificity but lower sensitivity for symptoms of SUI and MUI. A 24-hour pad test using a threshold of 4.4 g is more reproducible but is difficult to standardise with variation according to activity level [83]. Pad test with a specific short graded exercise protocol also has diagnostic value but a negative test should be repeated or the degree of provocation increased [84]. The usefulness of pad tests in quantifying severity and predicting outcome of treatment is uncertain [81, 85] although early post-operative testing may predict future continence in men after prostatectomy [86]. Pad test is responsive to change following successful treatment [87]. There is no evidence that one type of pad test is superior to another.

Evidence summary	LE
A pad test can diagnose UI accurately.	2
Standardisation of bladder volume and degree of provocation improves reproducibility.	2
24 hours is sufficient duration for home-based testing balancing diagnostic accuracy and adherence.	2
Change in leaked urine volume on pad tests can be used to measure treatment outcome.	2

Recommendations	GR
Have a standardised duration and activity protocol for pad test.	B
Use a pad test when quantification of urinary incontinence is required.	C
Use repeat pad test after treatment if an objective outcome measure is required.	C

3.8 Imaging

Imaging improves our understanding of the anatomical and functional abnormalities that may cause UI. In clinical research, imaging is used to understand the relationship between conditions of the central nervous system (CNS) or of the lower urinary tract (LUT) and UI, and to investigate the relationship between lower urinary tract and pelvic floor imaging and treatment outcome.

Ultrasound (US) and magnetic resonance imaging (MRI) have replaced X-ray imaging. Ultrasound is preferred to MRI because of its ability to produce three-dimensional and four-dimensional (dynamic) images at lower cost and wider availability. Studies on LUT imaging in patients with UI often include an evaluation of surgical outcomes, making design and conduct of these trials challenging.

3.8.1 Questions

In adults with UI:

- What is the reliability and accuracy of imaging in the diagnosis of UI?
- Do the results of imaging influence the choice of treatment for UI?
- Do the results of imaging, help predict outcome of treatment for UI?
- Do the results of imaging help evaluate outcome of treatments for UI?

3.8.2 Evidence

Many studies have evaluated the imaging of bladder neck mobility by US and MRI, and concluded that UI cannot be identified by a particular pattern of urethrovesical movements [88]. In addition, the generalised increase in urethral mobility after childbirth does not appear to be associated with de novo SUI [89].

There is a general consensus that MRI provides good global pelvic floor assessment, including POP, defecatory function and integrity of the pelvic floor support [90]. However, there is a large variation in MRI interpretation between observers [91] and little evidence to support its clinical usefulness in the management of UI.

Studies have assessed the use of imaging to assess the mechanism of mid-urethral sling insertion for SUI. One study suggested that mid-urethral sling placement decreased mobility of the mid-urethra but not mobility of the bladder neck [92]. In addition, the position of mid-urethral slings with respect to the pubis has been associated with the cure of UI [93].

Several imaging studies have investigated the relationship between sphincter volume and function in women [94] and between sphincter volume and surgery outcome in men and women [95, 96]. In patients undergoing

radical prostatectomy, longer membranous urethra before and after surgery was associated with higher rate of continence [97]. However, no imaging test has been shown to predict the outcome of treatment for UI. Imaging of the pelvic floor can identify levator ani detachment and hiatus size, although there is little evidence of a relationship to clinical benefit after treatment of treating UI.

Detrusor wall thickness

As overactive bladder syndrome (OAB) has been linked to detrusor overactivity, it has been hypothesised that frequent detrusor contractions may increase detrusor/bladder wall thickness (DWT/BWT). However, there is no evidence if BWT/DWT imaging improves management OAB in real life practice. No consensus exists as to the relation between OAB and increased BWT/DWT [98-102].

Evidence summary	LE
Imaging can reliably be used to measure bladder neck and urethral mobility, although there is no evidence of clinical benefit for patients with UI.	2b
There is no consistent evidence that bladder (detrusor) wall thickness measurement is useful in the management of UI.	3

Recommendation	GR
Do not routinely carry out imaging of the upper or lower urinary tract as part of the assessment of urinary incontinence.	A

4. DISEASE MANAGEMENT

4.1 Conservative management

In clinical practice, it is a convention that non-surgical therapies are tried first because they usually carry the least risk of harm. They are often used in combination which makes it difficult to determine which components are effective. Containment devices play an important role, especially for individuals who prefer to avoid the risks of interventional treatments, or in whom active treatment is impossible for any reason.

4.1.1 Simple clinical interventions

4.1.1.1 Underlying disease/cognitive impairment

Urinary incontinence, especially in the elderly, can be worsened or caused by underlying diseases, especially conditions that cause polyuria, nocturia, increased abdominal pressure or CNS disturbances. These conditions include:

- cardiac failure [103]
- chronic renal failure
- diabetes [103, 104]
- chronic obstructive pulmonary disease [105]
- neurological disease including stroke and multiple sclerosis
- general cognitive impairment
- sleep disturbances, e.g. sleep apnoea
- obesity.

It is possible that correction of the underlying disease may reduce the severity of urinary symptoms. However, this is often difficult to assess as patients often suffer from more than one condition. In addition, interventions may be combined and individualised, making it impossible to decide which alteration in an underlying disease has affected a patient's UI.

4.1.1.1.1 Question

In adults with UI, does correcting an underlying disease or cognitive impairment improve UI compared to no correction of underlying disease?

4.1.1.1.2 Evidence

One study showed no correlation between earlier intensive treatment of type 1 diabetes mellitus and the prevalence of UI in later life versus conventional treatment [106].

Evidence summary	LE
Improved diabetic control does not improve UI.	3

4.1.1.2 *Adjustment of medication*

Although UI is listed as an adverse effect of many drugs in drug compendia, this mainly results from uncontrolled individual patient reports and post-marketing surveillance. Few controlled studies have used the occurrence of UI as a primary outcome or were powered to assess the occurrence of statistically significant UI or worsening rates against placebo. In most cases, it is therefore not possible to be sure that a drug causes UI.

In patients with existing UI, particularly the elderly, it may be difficult or impossible to distinguish between the effects of medication, comorbidity or ageing on UI.

Although changing drug regimens for underlying disease may be considered as a possible early intervention for UI, there is very little evidence of benefit [58]. There is also a risk that stopping or altering medication may result in more harm than benefit.

4.1.1.2.1 *Question*

In adults with UI, does adjustment of medication improve UI compared to no change in treatment?

4.1.1.2.2 *Evidence*

Oestrogenic drugs including conjugated equine oestrogens, oestradiol, tibolone and raloxifene, are used as hormone replacement therapy (HRT) for women with natural or therapeutic menopause. Studies of HRT with nonurogenital primary outcomes have looked for change in urinary continence in secondary analyses. Large trials using conjugated equine oestrogens showed a higher rate of development or worsening of UI compared to placebo [107-110]. In a single RCT use of raloxifene was not associated with development or worsening of UI [111]. Three small RCTs using oral oestriol or oestradiol as HRT for vulvovaginal atrophy suggested that UI symptoms were improved although the evidence was unclear [58, 112, 113].

Evidence summary	LE
There is very little evidence that alteration of medication can cure or improve symptoms of urinary incontinence.	3
Systemic hormone replacement therapy using conjugate equine estrogens in previously continent women increases the risk of developing UI and worsens pre-existing UI.	1a

Recommendations	GR
Take a drug history from all patients with urinary incontinence.	A
For women taking oral conjugated equine oestrogen as hormone replacement therapy who develop or worsen UI, suggest discussion of alternative hormone replacement therapies with the relevant clinician.	A
Advise women who are taking systemic oestradiol who suffer from UI, that stopping the oestradiol is unlikely to improve their incontinence.	A
Review any new medication associated with the development or worsening of urinary incontinence.	C

4.1.1.3 *Constipation*

Several studies have shown strong associations between constipation, UI and OAB. Constipation can be improved by behavioural, physical and medical treatments.

4.1.1.3.1 *Question*

Does treatment for constipation improve UI?

4.1.1.3.2 *Evidence*

One RCT found that a multimodal intervention in elderly patients, involving assisted toileting, fluid intake, etc, reduced the occurrence of UI and constipation, while behavioural therapy appeared to improve both [114]. An observational study comparing women with UI and women with pelvic organ prolapse (POP) to controls found that a history of constipation was associated with both prolapse and UI [115]. Two, large, cross-sectional population-based studies [116, 117] and two longitudinal studies [118, 119] showed that constipation was a risk factor for LUTS.

In conclusion, constipation appears to be associated with UI. However, there is no evidence to show whether or not treating constipation improves UI, although both constipation and UI appear to be improved by certain behavioural interventions.

Evidence summary	LE
There is a consistent association between a history of constipation and the development of UI and pelvic organ prolapse.	3
There is no evidence that treatment of constipation improves UI.	4
Multimodal behavioural therapy improves both constipation and UI in the elderly.	1b

Recommendation	GR
Adults with urinary incontinence who also suffer from constipation should be given advice about bowel management in line with good medical practice.	C

4.1.1.4 Containment

Containment is important for people with UI when active treatment does not cure the problem, or when it is not available or not possible. Some individuals may prefer to choose containment rather than undergo active treatment with its associated risks. This includes the use of absorbent pads, urinary catheters, external collection devices and penile clamps for men; and intravaginal devices for women. Studies of catheter use are not specific to patients with non-neurogenic UI. Detailed literature summaries can be found in the current ICUD monograph [1] and in European Association of Urological Nurses guidance documents [120-122]. A useful resource for health care professionals and patients can be found at:
<http://www.continenceproductadvisor.org/.org>

4.1.1.4.1 Question

For adults with UI, is one type of containment device better than another?

4.1.1.4.2 Evidence

One RCT involving elderly women in care comparing management with pads to indwelling urethral catheter found no difference in dependency level or skin integrity score at six months [123]. Use of an external sheath was compared with indwelling catheterisation over 30 days in an RCT involving elderly men resident in hospital [124]. There were no differences in bacteriuria or symptomatic UTI but the sheath was more comfortable. A short-term crossover RCT in men with UI found that disease specific QoL was better when using an external sheath and more men preferred it, compared to pads [125].

4.1.1.4.3 Question

For men or women with UI is one type of pad better than another?

4.1.1.4.4 Evidence

A systematic review of six RCTs comparing different types of pads found that pads filled with superabsorbent material were better than standard pads, whilst evidence that disposable pads were better than washable pads was inconsistent [126]. For men with light UI a randomised crossover trial found that a leaf-shaped type of pad was preferred to rectangular pads [127]. A series of three crossover RCTs examined performance of different pad designs for differing populations [128]. For women with light UI, disposable insert pads were most effective. In adults with moderate/severe incontinence, disposable pull-up pants were more effective for women, whilst for men disposable diapers were more effective during the day and washable diapers at night.

4.1.1.4.5 Question

For men or women with UI is one type of catheter or external collection device better than another?

4.1.1.4.6 Evidence

A Cochrane review summarised three RCTs comparing different types of long-term indwelling catheters and found no evidence that one catheter material or type of catheter was superior to another [129]. A systematic review of non-randomised studies found no differences in any UTI outcome or for upper urinary tract changes between use of suprapubic or urethral catheter drainage, but patients with suprapubic catheters were less likely to have urethral complications [130]. For people using intermittent catheterisation, a Cochrane review found no evidence that one type of catheter or regimen of catheterisation was better than another [131]. A Cochrane review summarising five trials comparing washout policies in adults with indwelling urinary catheters found inconsistent evidence of benefit [132].

A further Cochrane review summarising eight trials testing whether antibiotic prophylaxis was beneficial for adults using intermittent or indwelling catheterisation found it reduced incidence of symptomatic UTI but possible harms were not assessed [133].

A randomised crossover study comparing six different brands of sheath devices found that men preferred sheaths [134].

4.1.1.4.7 Question

For men and women with UI are external pressure devices more effective than standard treatment and is one device better than another?

4.1.1.4.8 Evidence

A crossover RCT in men with post-prostatectomy incontinence found a hinge-type penile clamp to be more effective than circular clamps for control of UI and was preferred by participants although it reduced penile blood flow [135].

A Cochrane review summarised seven trials comparing mechanical devices in women with UI finding limited evidence that SUI was reduced by intravaginal devices, no evidence on the effectiveness of intraurethral devices and that there was no difference in control of UI between intravaginal and intraurethral devices [136]. There was no difference in outcome at 12 months in women with SUI between vaginal pessary alone; PFMT alone; and vaginal pessary + PFMT though vaginal pessary was inferior to PFMT at three months for bother from UI.

Evidence summary	LE
Pads with greater absorbency are more effective.	1b
Hinge-type penile clamps control SUI in men.	2a
Vaginal devices control SUI in women.	2a
Vaginal devices are no better than PFMT for women with SUI.	2a
A sheath-type external collection device for men is better than pads for improvement in incontinence related QoL.	2a

Recommendations	GR
Ensure that adults with UI and/or their carers are informed regarding available treatment options before deciding on containment alone.	A*
Suggest use of disposable insert pads for women and men with light urinary incontinence.	A*
In collaboration with other healthcare professionals with expertise in UI help adults with moderate/severe urinary incontinence to select the individually best containment regimen considering pads, external devices and catheters, and balancing benefits and harms.	A*
Choice of pad from the wide variety of different absorbent materials and designs available should be made with consideration of the individual patient's circumstance, degree of incontinence and preference.	B

* Based on expert opinion.

4.1.2 Lifestyle interventions

Examples of lifestyle factors that may be associated with incontinence include obesity, smoking, level of physical activity and diet. Modification of these factors may improve UI.

4.1.2.1 Caffeine reduction

Many drinks contain caffeine, particularly tea, coffee and cola. Anecdotal evidence of urinary symptoms being aggravated by excessive caffeine intake has focused attention on whether caffeine reduction may improve UI. However, a cross-sectional population survey found no statistical association between caffeine intake and UI [137]. Lack of knowledge about caffeine content of different drinks has made the role of caffeine reduction in alleviating UI difficult to assess.

4.1.2.1.1 Question

In adults with UI, does caffeine reduction improve UI or QoL compared to no caffeine reduction?

4.1.2.1.2 Evidence

Four studies were found on the effect of caffeine reduction on UI [138-141]. They were of moderate quality and the results were inconsistent. The studies were mainly in women, so results can only be cautiously generalised

to men [139, 140]. One RCT showed that reducing caffeine intake as an adjunct to behavioural therapy resulted in reduced urgency but not reduced UI compared to behavioural therapy alone [139]. Another RCT found that reducing caffeine had no benefit for UI [140]. A further interventional study in the elderly showed borderline significance for the benefit of reducing caffeine intake on UI [141]. In a large prospective cohort study there was no evidence that caffeine reduction reduced the risk of progression of UI over 2 years [142].

Evidence summary	LE
Reduction of caffeine intake does not improve UI.	2
Reduction in caffeine intake may improve symptoms of urgency and frequency.	2

4.1.2.2 *Physical exercise*

Regular physical activity may strengthen the pelvic floor musculature and possibly decrease the risk of developing UI, especially SUI. However, it is also possible that heavy physical exercise may aggravate UI.

4.1.2.2.1 *Question*

Does physical exercise cause, improve or exacerbate UI in adults?

4.1.2.2.2 *Evidence*

The association between exercise and UI is unclear. Four studies [137, 143-145] in differing populations concluded that strenuous physical exercise increases the risk of SUI during periods of physical activity. There is also consistent evidence that physically active females and elite athletes experience higher levels of SUI than control populations [146-151]. On the other hand, the presence of UI may prevent women from taking exercise [152]. There is no evidence that strenuous exercise predisposes athletes to the development of SUI later in life [153]. Lower levels of UI have been observed in cohorts of women who undertake moderate exercise, but it remains unclear whether taking exercise can prevent development of UI [154, 155].

The elderly

Three RCTs in the elderly confirmed that exercise, as a component of a multidimensional regime including PFMT and weight loss, was effective in improving UI in women. It is not clear which component of such a scheme is most important [114, 156, 157].

Evidence summary	LE
Female athletes may experience UI during intense physical activity but not during common activities.	3
Strenuous physical activity does not predispose to UI for women later in life.	3
Moderate exercise is associated with lower rates of UI in middle-aged or older women.	2b

4.1.2.3 *Fluid intake*

Modification of fluid intake, particularly restriction, is a strategy commonly used by people with UI to relieve symptoms. Advice on fluid intake given by healthcare professionals should be based on 24-hour fluid intake and urine output measurements. From a general health point of view it should be advised that fluid intake should be sufficient to avoid thirst and that low or high 24-hour urine output should be investigated.

4.1.2.3.1 *Question*

In adults with UI, what is the effect of modifying fluid intake compared to not modifying fluid intake on symptoms and QoL?

4.1.2.3.2 *Evidence*

The few RCTs [140, 158, 159] provide inconsistent evidence. In most studies, the instructions for fluid intake were individualised and it is difficult to assess participant adherence to protocol. All available studies were in women.

A recent RCT [159] showed that a reduction in fluid intake by 25% improved symptoms in patients with OAB but not UI. Personalised fluid advice compared to generic advice made no difference to continence outcomes in people receiving antimuscarinics for OAB, according to an RCT comparing drug therapy alone to drug therapy with behavioural advice [160].

Evidence summary	LE
There is conflicting evidence on whether fluid modification changes symptoms of UI and QoL.	2

4.1.2.4 Obesity and weight loss

Obesity has been identified as a risk factor for UI in many epidemiological studies [137, 161]. There is evidence that the prevalence of both UUI and SUI increases proportionately with rising body mass index. The proportion of patients who undergo surgery for incontinence who are overweight or obese is higher than that of the general population.

4.1.2.4.1 Question

In adults with UI, does weight loss lead to an improvement in symptoms of UI or QoL?

4.1.2.4.2 Evidence

All the available evidence relates to women. The prevalence of UI in overweight individuals is well established [137, 161]. Obesity appears to confer a four-fold increased risk of UI [162].

Two systematic reviews plus 1 large RCT concluded that weight loss was beneficial in improving symptoms of UI [163-165]. Five further RCTs reported a similar beneficial effect on incontinence following surgical weight reduction programmes [166-170].

Two large studies in women with diabetes, for whom weight loss was the main lifestyle intervention showed UI did not improve but there was a lower subsequent incidence of UI among those who lost weight [166, 171]. There have been other cohort studies and case-control studies suggesting similar effects, including surgery for the morbidly obese [106, 165, 172-177]. For example, in a longitudinal cohort study, a weight loss of 5-10% was associated with a significant reduction in UI measured by pad test [178].

Evidence summary	LE
Obesity is a risk factor for UI in women.	1b
Weight loss (> 5%) in obese women improves UI.	1b
Weight loss in obese adults with diabetes mellitus reduces the risk of developing UI.	1b

4.1.2.5 Smoking

Smoking cessation is now a generalised public health measure. Smoking, especially if > 20 cigarettes per day, is considered to intensify UI.

4.1.2.5.1 Question

In adults with UI, does smoking cessation improve patient outcomes regarding either urinary symptoms or QoL compared to continued smoking?

4.1.2.5.2 Evidence

The effect of smoking cessation on UI was described as uncertain in a Cochrane review [164].

Evidence summary	LE
There is no evidence that smoking cessation will improve the symptoms of UI.	4

4.1.2.6 Recommendations for lifestyle interventions

Recommendations	GR
Encourage obese women suffering from any urinary incontinence to lose weight (> 5%).	A
Advise adults with urinary incontinence that reducing caffeine intake may improve symptoms of urgency and frequency but not incontinence.	B
Patients with abnormally high or abnormally low fluid intake should be advised to modify their fluid intake appropriately.	C
Counsel female athletes experiencing urinary incontinence with intense physical activity that it will not predispose to urinary incontinence in later life.	C
Patients with urinary incontinence who smoke should be given smoking cessation advice in line with good medical practice.	A

4.1.3 Behavioural and Physical therapies

Terminology relating to behavioural and physical therapies remains confusing because of the wide variety of ways in which treatment regimes and combinations of treatments have been delivered in different studies [179]. The terms are used here to encompass all those treatments which require a form of self-motivated personal

retraining by the patient and also includes those techniques which are used to augment this effect.

Approaches include bladder training (BT) and pelvic floor muscle training (PFMT), but terms such as bladder drill, bladder discipline and bladder re-education and behaviour modification are also used. Almost always in clinical practice, these will be introduced as part of a package of care including lifestyle changes, patient education and possibly some cognitive therapy as well. The extent to which individual therapists motivate, supervise and monitor these interventions is likely to vary but it is recognised that these influences are important components of the whole treatment package.

4.1.3.1 Bladder Training

Patients may be asked to void according to a fixed voiding schedule. Alternatively, patients may be encouraged to follow a schedule established by their own bladder diary/voiding chart (habit training). 'Timed voiding' is voiding initiated by the patient, while 'prompted voiding' is voiding initiated by the caregiver. Timed and habit voiding are recommended to patients who can void independently. Bladder training can be offered to any patient with any form of UI, as a first-line therapy for at least a short period of time. The ideal form or intensity of a BT programme for UI is unclear. It is also unclear whether or not BT can prevent the development of UI.

4.1.3.1.1 Questions

In adults with UI:

- Is BT better than no treatment for cure or improvement of UI?
- Is BT better than other conservative treatments for cure or improvement of UI?
- Does BT as an adjunct to other conservative treatments cure or improve UI?
- Are the benefits of BT durable in the longer term?
- Are there any patient groups for whom BT is more effective?

4.1.3.1.2 Evidence

There have been three systematic reviews on the effect of BT compared to standard care [58, 164, 180] confirming that BT is more effective than no treatment in improving UI. The addition of BT to anticholinergic therapy seems to confer no additional effect apart from the reduction of frequency and nocturia.

BT alone is inferior to a high-intensity programme of PFMT to improve SUI in elderly women [181]. Bladder training is better than intravaginal pessaries to control SUI, although the improvement may only be short-term.

Whatever the method of training used, any benefit of BT on UI is likely to be of short duration unless the BT programme is practised repeatedly. No adverse events have been reported with BT. Biofeedback combined with BT increased continence rates and improved MUI in two RCTs [180].

Evidence summary	LE
Behavioural interventions are effective for improvement of UI in women.	1b
The effectiveness of bladder training diminishes after the treatment has ceased.	2
The comparative benefit of bladder training and drugs for the improvement of UUI remains uncertain.	2
The combination of bladder training with antimuscarinic drugs does not result in greater improvement of UI but may have other benefits.	1b
Bladder training is better than pessary alone.	1b

For recommendations see section 4.1.3.5.

4.1.3.2 Pelvic floor muscle training (PFMT)

Pelvic floor muscle training is used to improve function of the pelvic floor, improving urethral stability. There is some evidence that improving pelvic floor function may inhibit bladder contraction in patients with OAB [182].

PFMT may be used to prevent UI, e.g. in childbearing women before birth, in men about to undergo radical prostatectomy, or as part of a planned recovery programme after childbirth or surgery. Most often, PFMT is used to treat existing UI, and may be augmented with biofeedback (using visual, tactile or auditory stimuli), surface electrical stimulation or vaginal cones.

4.1.3.2.1 Question

In adult men and women suffering from UI, does treatment with PFMT (given either alone or augmented with biofeedback, electrical stimulation or vaginal cones) improve or cure UI or improve QoL, compared to no treatment, sham treatment or other conservative treatments, e.g. bladder training, electrical stimulation or vaginal cones?

4.1.3.2.2 Evidence

In a recent UK Health Technology Appraisal (HTA), the role of PFMT in the care of women with SUI was analysed in direct comparisons of treatments and a mixed treatment comparison model, which compared different 'packages' of care [164]. This extensive meta-analysis reviewed data from 37 interventions and 68 direct comparisons, while the mixed treatment comparisons examined combinations of 14 different types of intervention from 55 separate trials. The mixed treatment comparison used both indirect and direct comparisons and may provide more accurate estimates of effect. Where relevant, the Technology Appraisal has influenced the evidence and recommendations in these Guidelines. The Agency for Healthcare Research and Quality (AHRQ) review of nonsurgical treatment of UI in adult women also included indirect comparison methods as well as conventional meta-analysis [180].

4.1.3.2.3 Efficacy of PFMT in SUI, UUI and MUI in women

This question has been addressed by several systematic reviews [164, 180, 183], all report inconsistency between studies because of poor reporting of technique and different outcome measures. Meta-analysis showed that PFMT was effective for cure or improvement of incontinence, and improvement in QoL. The effect applies in women with SUI, UUI and MUI though the effect in MUI is lower than in women with pure SUI. A Cochrane review comparing different approaches to delivery of PFMT (21 RCTs) concluded that increased intensity of delivery of the therapy improves response and that there is no consistent difference between group therapy and individualised treatment sessions [184]. No other consistent differences between techniques were found.

With regard to the durability of PFMT, another RCT reported 15-year follow-up outcomes of an earlier RCT, showing that long-term adherence to treatment was poor and half of patients had progressed to surgery [185].

Numerous systematic reviews have addressed the question of whether the effects of PFMT and BT are additive [164, 180, 186]. These reviews are confounded by differences in patient selection and have arrived at conflicting conclusions leaving uncertainty about the extent to which one treatment may augment the other. Similarly, there remains uncertainty about the additional value of biofeedback with systematic reviews reaching differing conclusions [180, 186].

Comparison of PFMT to other treatments was extensively reviewed by both AHRQ and the 2010 UK HTA [164, 180], which considered additional non-randomised data as part of a mixed treatment comparison. The UK HTA resulted in a number of different findings from those based solely on direct comparisons. In conclusion, the HTA, using a revised methodology, supported the general principle that greater efficacy was achieved by adding together different types of treatment and by increasing intensity.

4.1.3.2.4 PFMT in the elderly

The effect of PFMT in women with SUI does not seem to decrease with increased age: in trials with older women with SUI it appeared both primary and secondary outcome measures were comparable to those in trials focused on younger women [156, 181, 187].

4.1.3.2.5 PFMT and Radical prostatectomy

A Cochrane review concluded that there was no benefit at 12 months post-surgery for men who received postoperative PFMT for the treatment of post-prostatectomy urinary incontinence (PPI) and that the benefits of conservative treatment of PPI remain uncertain [188]. There have been further RCTs which leave uncertainty about whether or not PFMT leads to earlier recovery of continence [189-193]. Two additional RCTs have shown that written instructions alone offer similar levels of improvement to supervised PFMT [194, 195]. One RCT found that PFMT was helpful in men who had been incontinent for at least one year after prostatectomy, and who had had no previous therapy [196].

Evidence summary	LE
PFMT for Women with UI	
PFMT is better than no treatment for improving UI and QoL in women with SUI and MUI.	1
Higher-intensity, supervised treatment regimes, and the addition of biofeedback, confer greater benefit in women receiving PFMT.	1
Short-term benefits of intensive PFMT are not maintained at 15-year follow-up.	2
PFMT for post-prostatectomy UI	LE
PFMT does not cure UI in men post-prostatectomy.	1b
There is conflicting evidence as to whether PFMT speeds the recovery of continence following radical prostatectomy.	1b
There is conflicting evidence on whether the addition of bladder training, electrical stimulation or biofeedback increases the effectiveness of PFMT alone.	2
There is no evidence that pre-operative PFMT prevents UI following radical prostatectomy though it may lead to earlier recovery of continence.	2

For recommendations see section 4.1.3.5.

4.1.3.3 Prompted voiding

The term prompted voiding implies that carers, rather than the patient, initiate the decision to void and this applies largely to an assisted care setting.

Prompted voiding is the giving of positive reinforcement for requesting toileting assistance, either spontaneously or following verbal prompts from a caregiver. Two systematic reviews (9 RCTs) [197, 198]. Confirmed a positive effect on continence outcomes of prompted voiding in comparison to standard care [198].

Timed voiding is defined as fixed, pre-determined, time intervals between toileting, applicable for those with or without cognitive impairment. A Cochrane review of timed voiding reviewed two RCTs finding inconsistent improvement in continence compared with standard care in cognitively impaired adults [199].

Evidence summary	LE
Prompted voiding, either alone or as part of a behavioural modification programme, improves continence in elderly, care-dependent people.	1b

For recommendations see section 4.1.3.5.

4.1.3.3.1 Electrical stimulation

The details and methods of delivery of electrical stimulation vary considerably.

Electrical stimulation (ES) can also be combined with other forms of conservative therapy, e.g. PFMT and biofeedback. Electrical stimulation is often used to assist women who cannot initiate contractions to identify their pelvic floor muscles. Electrical stimulation is also used in patients with OAB and UUI, for detrusor inhibition. It has been suggested that ES probably targets the pelvic floor directly in SUI and the detrusor muscle or pelvic floor muscle or afferent innervation in UUI.

4.1.3.3.2 Question

In adults with UI, does treatment with ES improve or cure symptoms of UI or QoL compared to no treatment or sham treatment?

4.1.3.3.3 Evidence

Most evidence on ES refers to women with SUI. The topic has been included in two health technology appraisals [164, 180] and three systematic reviews [58, 200, 201].

The reviews include analysis of 15 trials and use different comparison methods, but conflict in their assessment of whether ES is more effective than sham stimulation and whether ES adds to the benefit of PFMT alone. Studies were considered to be of generally low quality, with a variety of stimulation parameters, treatment regimens and outcome parameters.

A systematic review reported two RCTs in which ES had been compared to oxybutynin in patients with UUI, showing similar efficacy [202].

A Cochrane review of ES in men with UI (6 RCTs) concluded that, in the short-term, there was limited evidence

of ES augmenting effectiveness of PFMT and there was better improvement of incontinence than with sham stimulation [203].

Electromagnetic stimulation has been promoted as an alternative to electrical stimulation but no evidence of effectiveness was found [204].

Evidence summary	LE
In adults with UI, there is inconsistent evidence whether ES is effective in improving UI compared to sham treatment or adds any benefit to PFMT.	1
The comparative benefit of electrical stimulation and antimuscarinic drugs, for improvement of patients with UUI, remains uncertain.	1

For recommendations see section 4.1.3.5.

4.1.3.4 Posterior tibial nerve stimulation

Electrical stimulation of the posterior tibial nerve (PTNS) delivers electrical stimuli to the sacral micturition centre via the S2-S4 sacral nerve plexus. Stimulation is done percutaneously with a fine, 34-G, needle, inserted just above the medial aspect of the ankle (P-PTNS). Transcutaneous stimulation is also available (T-PTNS). Treatment cycles typically consist of 12 weekly treatments of 30 minutes.

4.1.3.4.1 Question

In adults suffering from UUI, what is the clinical effectiveness of PTNS compared to sham treatment or alternative treatment such as antimuscarinic drugs?

4.1.3.4.2 Evidence

P-PTNS

The reviewed studies included two RCTs of PTNS against sham treatment [205, 206] and one comparing PTNS to tolterodine in patients with UUI [207]. The results of studies of PTNS in women with refractory UUI are consistent. Considered together, these results suggest that PTNS improves UUI in women who have had no benefit from antimuscarinic therapy or who are not able to tolerate these drugs. However, there is no evidence that PTNS cures UUI in women. In addition, PTNS is no more effective than tolterodine for improvement of UUI in women. In men there is insufficient evidence to make a conclusion about efficacy.

In patients who initially respond to PTNS, the improvement is maintained in some patients at 2 years with continued treatment (approximately monthly) [208].

T-PTNS

A small RCT compared transcutaneous PTNS plus standard treatment (PFMT and BT) with PFMT and BT alone in older women [209]. Women in the T-TPNS group were more likely to achieve Improvement at the end of therapy.

Evidence summary	LE
P-PTNS appears effective for improvement of UUI, in women who have had no benefit from antimuscarinic medication.	2b
P-PTNS is no more effective than tolterodine for improvement of UUI in women.	1b
No serious adverse events have been reported for P-PTNS in UUI.	3
There is limited evidence for effectiveness of T-PTNS.	2a

4.1.3.5 Recommendations for behavioural and physical therapies

Recommendations	GR
Offer supervised intensive PFMT, lasting at least 3 months, as a first-line therapy to women with stress urinary incontinence or mixed urinary incontinence.	A
PFMT programmes should be as intensive as possible.	A
Offer PFMT to elderly women with urinary incontinence.	B
Consider using biofeedback as an adjunct in women with stress urinary incontinence.	A
Offer instruction on PFMT to men undergoing radical prostatectomy to speed recovery of incontinence.	B
Offer bladder training as a first-line therapy to adults with urgency urinary incontinence or mixed urinary incontinence.	A
Use a trial of prompted voiding for adults with incontinence, who are cognitively impaired.	A
Do not offer electrical stimulation with surface electrodes (skin, vaginal, anal) alone for the treatment of stress urinary incontinence.	A
Consider offering electrical stimulation as an adjunct to behavioural therapy in patients with urgency urinary incontinence.	B
Do not offer magnetic stimulation for the treatment of incontinence or overactive bladder in adult women.	B
Do not offer PTNS to women or men who are seeking a cure for urgency urinary incontinence.	A
Offer, if available, P-PTNS as an option for improvement of urgency urinary incontinence in women who have not benefitted from antimuscarinic medication.	B
Support other healthcare professionals in use of rehabilitation programmes including prompted voiding for care of elderly care-dependent people with urinary incontinence.	A

PFMT = pelvic floor muscle training; P-PTNS = percutaneous posterior tibial nerve stimulation; T-PTNS = transcutaneous posterior tibial nerve stimulation.

4.1.4 Conservative therapy in mixed urinary incontinence

About one-third of women with UI have mixed urinary incontinence (MUI) with symptoms of both stress UI (SUI) and urgency UI (UUI), and this becomes more common with increasing age. In terms of evidence base, many studies include patients with MUI, but it is rare for these studies to provide a separate analysis of patients with MUI.

4.1.4.1 Question

In adults with MUI, is the outcome of conservative therapy different to that obtained with the same treatment in patients with either pure SUI or pure UUI?

4.1.4.2 Evidence

No specific systematic reviews were found that addressed the above question. However, a Cochrane report on pelvic floor muscle training (PFMT) [183] concluded that training was less likely to result in a cure in patients with MUI than in patients with pure SUI, though it is not clear from the report how this conclusion was reached.

A small RCT (n = 71) compared delivery of PFMT, with or without an instructive audiotape. It showed equal efficacy for different types of UI [210].

Following a RCT of PFMT, a review of 88 women available for follow-up at 5 years found that outcomes were less satisfactory in women with MUI than in women with pure SUI [211].

Evidence summary	LE
Pelvic floor muscle training appears less effective for MUI than for SUI alone.	2
Electrical stimulation is equally effective for MUI and SUI.	1b

4.1.4.3 Recommendations conservative therapy in mixed urinary incontinence

Recommendations	GR
Treat the most bothersome symptom first in patients with mixed urinary incontinence.	C
Warn patients with mixed urinary incontinence that the chance of success of pelvic floor muscle training is lower than for stress urinary incontinence alone.	B

4.2 Pharmacological management

4.2.1 Antimuscarinic drugs

Antimuscarinic (anticholinergic) drugs are currently the mainstay of treatment for UUI. They differ in their pharmacological profiles, e.g. muscarinic receptor affinity and other modes of action, in their pharmacokinetic properties, e.g. lipid solubility and half-life, and in their formulation.

The evaluation of cure or improvement of UI is made harder by the lack of a standard definition of improvement and the failure to use cure as a primary outcome. In general, systematic reviews note that the overall treatment effect of drugs is usually small but larger than placebo. Dry mouth is the commonest side effect, though constipation, blurred vision, fatigue and cognitive dysfunction may occur.

The immediate release (IR) formulation of oxybutynin is the prototype drug in the treatment of UUI. Oxybutynin IR provides maximum dosage flexibility, including an off-label 'on-demand' use. Immediate-release drugs have a greater risk of side effects than extended release (ER) formulations because of differing pharmacokinetics. A transdermal delivery system (TDS) and gel developed for oxybutynin gives a further alternative formulation.

4.2.1.1 Question

In adults with UUI, are antimuscarinic drugs better than placebo for improvement or cure of UUI and for the risk of adverse effects?

4.2.1.2 Evidence

Five systematic reviews of individual antimuscarinic drugs versus placebo were reviewed for this section [180, 212-215] as well as studies published since these reviews up until September 2013. Most studies included patients with a mean age of 55-60 years. Both female and male subjects were included in different studies but results cannot be generalised across sexes. Only short-term rates for improvement or cure of UUI are reported. The evidence reviewed was consistent, indicating that ER and IR formulations of antimuscarinics offer clinically significant short-term cure and improvement rates for UUI compared to placebo.

Cure of UI was deemed to be the most important outcome measure. Risk of adverse events was best represented by withdrawal from a trial because of adverse events although this does not reflect real life practice. Table 4 shows a summary of the findings from the most recent systematic review [180]. In summary, every drug where cure of UI was available shows superiority compared to placebo in achieving UI, but the absolute size of effect is small.

Table 4. Summary of cure rates and discontinuation rates of antimuscarinic drugs from RCTs which reported these outcomes [180]

Drug	No. of Studies	Patients	Relative risk (95% CI) (of curing UI)	Number needed to treat (95% CI) (to achieve one cure of UI)
Cure of incontinence				
Fesoterodine	2	2465	1.3 (1.1-1.5)	8 (5-17)
Oxybutynin (includes IR)	4	992	1.7 (1.3-2.1)	9 (6-16)
Propiverine (includes IR)	2	691	1.4 (1.2-1.7)	6 (4-12)
Solifenacin	5	6304	1.5 (1.4-1.6)	9 (6-17)
Tolterodine (includes IR)	4	3404	1.2 (1.1-1.4)	12 (8-25)
Trospium (includes IR)	4	2677	1.7 (1.5-2.0)	9 (7-12)
Discontinuation due to adverse events				
			Relative Risk (95% CI) (of discontinuation)	NNT (95% CI) (of one discontinuation)
Darifenacin	7	3138	1.2 (0.8-1.8)	
Fesoterodine	4	4433	2.0 (1.3-3.1)	33 (18-102)
Oxybutynin (includes IR)	5	1483	1.7 (1.1-2.5)	16 (8-86)
Propiverine (includes IR)	2	1401	2.6 (1.4-5)	29 (16-27)
Solifenacin	7	9080	1.3 (1.1-1.7)	78 (39-823)
Tolterodine (includes IR)	10	4466	1.0 (0.6-1.7)	
Trospium (includes IR)	6	3936	1.5 (1.1-1.9)	56 (30-228)

Darifenacin

The cure rates for darifenacin were not included in the AHRQ review. Continence rates were 29-33% for darifenacin compared to 17-18% for placebo [180].

Transcutaneous oxybutynin

Transdermal oxybutynin has shown a significant improvement in the number of incontinence episodes and micturitions per day versus placebo and other oral formulations but incontinence was not reported as an outcome [180].

Oxybutynin topical gel was superior to placebo for improvement of UUI with a higher proportion of participants being cured [180].

Evidence summary	LE
All formulations of Fesoterodine, Oxybutynin, Propiverine, Solifenacin, Tolterodine, Darifenacin and Trospium, provide a significantly better rate of cure or improvement of UUI compared to placebo.	1a
All formulations of Fesoterodine, Oxybutynin, Propiverine, Solifenacin, Tolterodine, Darifenacin and Trospium, result in higher rates of dry mouth compared to placebo.	1b

4.2.2 **Comparison of antimuscarinic agents**

Head-to-head comparison trials of the efficacy and side effects of different antimuscarinic agents are of interest for decision making in real life practice.

4.2.2.1 *Question*

In adults with UUI, does one type of antimuscarinic drug result in a greater likelihood of cure or improvement in UUI, and/or a greater improvement in QoL, and/or a lesser likelihood of adverse effects compared to an alternative antimuscarinic drug?

4.2.2.2 *Evidence*

There are over 40 RCTs and five systematic reviews [180, 202, 212, 214, 216]. Nearly all the primary studies were industry sponsored. Upward dose titration is often included in the protocol for the experimental arm, but not for the comparator arm.

In general, these studies have been designed for regulatory approval. They have short treatment durations (12 weeks) and a primary outcome of a change in OAB symptoms rather than a cure of, or an improvement in, UUI, which were generally analysed as secondary outcomes. The clinical utility of these trials in real life practice is questionable. Most trials were of low or moderate quality [214].

The 2012 AHRQ review included a specific section addressing comparisons of antimuscarinic drugs (Table 5).

Table 5: Comparison of antimuscarinic drugs as reviewed in the 2012 AHRQ review [180]

Experimental drug versus standard drug	No. of studies	Patients	Relative risk (95% CI) of curing UI
<i>Efficacy</i>			
Fesoterodine vs. tolterodine ER (continence)	2	3312	1.1 (1.04-1.16)
Oxybutynin ER vs. tolterodine ER (improvement)	3	947	1.11 (0.94-1.31)
Solifenacin vs. tolterodine ER	1	1177	1.2 (1.08-1.34)
Trospium vs. oxybutynin	1	357	1.1 (1.04-1.16)
<i>Discontinuation due to adverse events</i>			
			RR – 95% CI of discontinuation
Solifenacin vs. tolterodine ER	3	2755	1.28 (0.86-1.91)
Trospium vs. oxybutynin	2	2015	0.75 (0.52 -1.1)
Fesoterodine vs. tolterodine	4	4440	1.54 (1.21-1.97)

No antimuscarinic agent improved QoL more than another agent [214]. Dry mouth is the most prevalent adverse effect. Good evidence indicates that, in general, higher doses of any drug are likely to be associated

with higher rates of adverse events. Also, ER formulations of short-acting drugs, and longer-acting drugs are generally associated with lower rates of dry mouth than IR preparations [214, 216]. Oxybutynin IR showed higher rates of dry mouth than tolterodine IR and trospium IR, but lower rates of dry mouth than darifenacin, 15 mg daily [214, 216]. Overall, oxybutynin ER has higher rates of dry mouth than tolterodine ER, although the incidence of moderate or severe dry mouth were similar. Transdermal oxybutynin had a lower rate of dry mouth than oxybutynin IR and tolterodine ER, but had an overall higher rate of withdrawal due to an adverse skin reaction [214]. Solifenacin, 10 mg daily, had higher rates of dry mouth than tolterodine ER [214]. Fesoterodine, 8 mg daily, had a higher rate of dry mouth than tolterodine, 4 mg daily [217, 218]. In general, similar discontinuation rates were observed, irrespective of differences in the occurrence of dry mouth.*

**Doses have been given where the evidence relates to a specific dose level typically from trials with a dose escalation element.*

Evidence summary	LE
There is no consistent evidence that one antimuscarinic drug is superior to an alternative antimuscarinic drug for cure or improvement of UUI.	1a
The ER formulation of oxybutynin is superior to the ER and IR formulations of tolterodine for improvement of UUI.	1b
Solifenacin is more effective than tolterodine IR for improvement of UUI.	1b
Fesoterodine, 8 mg daily, is more effective than tolterodine ER, 4 mg daily, for cure and improvement of UUI, but with a higher risk of side effects.	1b
ER formulations and once-daily antimuscarinic drugs are generally associated with lower rates of dry mouth than IR preparations, although trial discontinuation rates are similar.	1b
Transdermal oxybutynin (patch) is associated with lower rates of dry mouth than oral antimuscarinic drugs, but has a high rate of withdrawal due to skin reaction.	1b
Oxybutynin IR or ER shows higher rates of dry mouth than the equivalent formulation of tolterodine.	1a
There is no evidence that any particular antimuscarinic agent is superior to another for improvement in QoL.	1a

4.2.3 **Antimuscarinic drugs versus non-drug treatment**

The choice of drug versus non-drug treatment of UUI is an important question.

4.2.3.1 *Question*

In adults with UUI, does one type of antimuscarinic drug result in a greater likelihood of cure or improvement in UUI and/or greater improvement in QoL, and/or lesser likelihood of adverse effects compared to an alternative non-drug treatment?

4.2.3.2 *Evidence*

More than 100 RCTs and high-quality reviews are available [202, 214, 215, 219-221]. Most of these studies were independent.

The US HTA [202] found that trials were of low- or moderate-quality. The main focus of the review was to compare the different drugs used to treat UUI. In one study, multicomponent behavioural modification produced significantly greater reductions in incontinence episodes compared to oxybutynin and higher patient satisfaction for behavioural versus drug treatment. One RCT showed a substantial benefit for sacral neuromodulation compared with medical therapy [222]. In men with storage LUTS, no difference in efficacy was found between oxybutynin and behavioural therapy [223]. The combination of BT and solifenacin in women with OAB conferred no additional benefit in terms of continence [224].

Two small RCTs [225, 226], reported a similar improvement in subjective parameters with either transcutaneous electrical nerve stimulation or T-PTNS. However, only oxybutynin treated patients showed significant improvements in objective urodynamic parameters (bladder capacity). The oxybutynin-treated group had more side effects. One study compared tolterodine ER to transvaginal/anal electrical stimulation without differences in UI outcomes [227]. One small RCT found that the addition of P-PTNS to tolterodine ER improved UI and QoL [228].

Evidence summary	LE
There is no consistent evidence to show superiority of drug therapy over behavioural therapy for treatment of UUI.	1b
Behavioural treatment has higher patient satisfaction than drug treatment.	1b
There is no consistent evidence to show superiority of drug therapy over PFMT for treatment of UUI.	1b

4.2.3.3 Recommendations for antimuscarinic drugs

Recommendations	GR
Offer IR or ER formulations of antimuscarinic drugs for adults with urgency urinary incontinence.	A
If IR formulations of antimuscarinic drugs are unsuccessful for adults with urgency urinary incontinence, offer ER formulations or longer-acting antimuscarinic agents.	A
Consider using transdermal oxybutynin if oral antimuscarinic agents cannot be tolerated due to dry mouth.	B
Offer and encourage early review (of efficacy and side effects) of patients on antimuscarinic medication for urgency urinary incontinence (< 30 days).	A

IR = immediate release; ER = extended release.

4.2.4 Antimuscarinic agents: adherence and persistence

Most studies on antimuscarinic medication are short term (12 weeks). Adherence in clinical trials is considered to be much higher than in real life practice.

4.2.4.1 Question

Do patients with UUI adhere to antimuscarinic drug treatment and persist with prescribed treatment in clinical practice?

4.2.4.2 Evidence

This topic has been reviewed for the development of these Guidelines [229]. Two recent open-label extensions of RCTs of fesoterodine 8 mg showed adherence rates at 2 years from 49-84% [230, 231]. The main drugs studied were oxybutynin and tolterodine IR and ER. Non-persistence rates were high for tolterodine at 12 months, and particularly high (68-95%) for oxybutynin.

'Median days to discontinuation' between < 30 days and 50 days were reported, with a maximum of 273 days, in a military health system where free medication was provided [232].

Data on adherence/persistence from open-label extension populations are questionable as these patients are self-selected to be compliant. Data from pharmacy databases is included in this section.

Several of the RCT trials tried to identify the factors associated with low/lower, adherence or persistence of antimuscarinic. These were identified as:

- low level of efficacy (41.3%)
- adverse events (22.4%)
- cost (18.7%), as higher adherence rates were observed when drugs were provided at no cost to the patient [232].

Other reasons for poor adherence included:

- IR versus ER formulations
- age (lower persistence among younger adults)
- unrealistic expectations of treatment
- gender distribution (better adherence/persistence in female patients)
- ethnic group (African-Americans and other minorities more likely to discontinue or switch treatment)

In addition, the source of data influenced the adherence figures.

Evidence summary	LE
More than half of patients will stop antimuscarinic agents within the first 3 months because of ineffectiveness, adverse events and cost.	2

4.2.5 **Antimuscarinic agents, the elderly and cognition**

Limited trials have been conducted in elderly people with UI. Issues include the multifactorial etiology of UI in the elderly, comorbidities such as cognitive impairment, the effect of co-medications and the risk of adverse events.

The effects of antimuscarinic agents on cognition have been studied in more detail.

4.2.5.1 *Question*

What is the comparative efficacy, and risk of adverse effects, particularly the cognitive impact, of treatment with antimuscarinic medication in elderly men and women with UI?

4.2.5.2 *Evidence*

Two systematic reviews are available [233, 234]. A community-based cohort study found a high incidence of cognitive dysfunction [235]. Other systematic reviews have included sections on the efficacy and safety of antimuscarinics in elderly patients [180, 214]. A systematic review in 2012 found inconclusive evidence as to the impact of antimuscarinics on cognition [236].

Very few trials specifically investigated the cognitive changes associated with antimuscarinic agents. In general, these trials have measured CNS side effects in a non-specific way and do not allow us to understand the impact on [237, 238].specific populations. There are studies on antimuscarinic effects in elderly persons [239], and in people with dementia with UI [240]. No specific studies exist in vulnerable patient populations at risk of cognitive dysfunction and deterioration of it while on antimuscarinics.

4.2.5.2.1 Oxybutynin

There is evidence that oxybutynin IR may cause/worsen cognitive dysfunction in adults although there is no consensus about it [237, 239, 241-245].

More rapid functional deterioration might result from the combined use of cholinesterase inhibitors with antimuscarinic agents in elderly patients with cognitive dysfunction [246].

4.2.5.2.2 Solifenacin

One pooled analysis [247] has shown that solifenacin does not increase cognitive impairment in the elderly. No age-related differences in the pharmacokinetics of solifenacin in different age groups was found although more frequent adverse events in subjects over 80 years old were observed. No cognitive effect on healthy elderly volunteers was shown [245]. In a subanalysis of a large trial, solifenacin 5-10 mg improved symptoms and QoL in people ≥ 75 years who had not responded to tolterodine [248]. In patients with mild cognitive impairment, over 65 years, solifenacin showed no difference in efficacy between age groups and a lower incidence of most side effects compared to oxybutynin IR [244, 249].

4.2.5.2.3 Tolterodine

No change in efficacy or side effects related to age have been reported, although a higher discontinuation rate was found for both tolterodine and placebo in elderly patients [237]. Two RCTs in the elderly found a similar efficacy and side effect profile to younger patients [250-253]. Post-hoc analysis has shown little effect on cognition. One non-randomised comparison showed lower rates of depression in elderly participants treated with tolterodine ER compared to oxybutynin IR [254].

4.2.5.2.4 Darifenacin

Two RCTs in the elderly population (one in patients with UI and the other in volunteers) concluded that darifenacin was effective with no risk of cognitive change, measured as memory scanning tests, compared to placebo [255, 256]. Another study on darifenacin and oxybutynin ER in elderly subjects concluded that the two agents had a similar efficacy, but that cognitive function was more often affected in the oxybutynin ER arm [239].

4.2.5.2.5 Trospium chloride

Trospium is not supposed to cross the blood-brain barrier in healthy individuals. Two (EEG) studies in healthy volunteers showed no effect from trospium whilst tolterodine caused occasional changes and oxybutynin caused consistent changes [257, 258]. No evidence as to the comparative efficacy and side effect profiles of trospium in different age groups is available. However, there is some evidence that trospium does not impair cognitive function [240, 259] and that it is effective compared to placebo in the elderly [260].

4.2.5.2.6 Fesoterodine

There is no evidence comparing the efficacy and side effects of fesoterodine in elderly and younger patients. Pooled analyses of the RCTs of fesoterodine confirmed the efficacy of the 8 mg but not the 4 mg dose in over-75-year olds [261]. Adherence was lower in the over-75 year-old group but the effect on mental status was not reported [230, 262, 263]. No difference between fesoterodine and placebo on cognitive function was reported in healthy older patients [264].

4.2.5.2.7 Duloxetine in the elderly

RCTs comparing duloxetine and placebo included women up to 85 years, but no age stratification of the results is available.

4.2.5.2.8 Mirabegron

No trials of mirabegron have yet been reported in the elderly population with UI.

4.2.5.2.9 Applicability of evidence to general elderly population

It is not clear how much the data from pooled analyses and subgroup analyses from large RCTs can be extrapolated to a general ageing population. Community-based studies of the prevalence of antimuscarinic side effects may be the most helpful [235].

When starting anticholinergics in elderly patients, mental function should be assessed objectively and monitored [265]. No consensus exists as to the best mental function test to detect changes in cognition [246, 261].

4.2.5.2.10 Anticholinergic load

A number of medications have anticholinergic effects and their cumulative effects on cognition should be considered [266].

4.2.5.2.11 Question

In older people suffering from UI what is the effect of anticholinergic burden (defined by anticholinergic cognitive burden scale, ACB) on cognitive function?

4.2.5.2.12 Evidence

There were no studies specifically in older people with UI, but evidence was available from observational cohort studies relating to the risk in a general population of older people.

Lists of drugs with anticholinergic properties are available from two sources [266, 267].

Two systematic reviews of largely retrospective cohort studies, showed a consistent association between longterm anticholinergic use and cognitive dysfunction [268, 269].

Longitudinal studies in older people over two to four years have found increased rate of decline in cognitive function for patients on definite and possible anticholinergics [270, 271].

Evidence summary	LE
All antimuscarinic drugs are effective in elderly patients.	1b
In older people, the cognitive impact of drugs which have anticholinergic effects, is cumulative, and increases with length of exposure.	3
There is inconsistent evidence as to whether oxybutynin IR may worsen cognitive function.	2
Solifenacin, darifenacin and fesoterodine have been shown not to cause increased cognitive dysfunction in elderly people.	1b
There is no evidence as to whether tolterodine and trospium chloride affect cognitive function.	3

4.2.5.2.13 Additional recommendations for antimuscarinic drugs in the elderly

Recommendations	GR
In older people being treated for urinary incontinence, every effort should be made to employ non-pharmacological treatments first.	C
Use antimuscarinic drugs with caution in elderly patients who are at risk of, or have, cognitive dysfunction.	B
In older people who are being prescribed antimuscarinic drugs for control of urinary incontinence, consider modifications to other medications to help reduce anticholinergic load.	C
Check mental function in patients on antimuscarinic medication if they are at risk of cognitive dysfunction.	C

4.2.6 **Mirabegron**

Mirabegron is the first clinically available beta 3 agonist, available from 2013. Beta 3 adrenoceptors are the predominant beta receptors expressed in the smooth muscle cells of the detrusor and their stimulation is thought to induce detrusor relaxation.

Mirabegron has undergone evaluation in industry-sponsored phase 2 and phase 3 trials. Two systematic reviews of all currently reported studies assessing the clinical effectiveness of mirabegron [272, 273] reported that mirabegron at doses of 25, 50 and 100 mg, results in significantly greater reduction in incontinence episodes, urgency episodes and micturition frequency/24 hrs than placebo, with no difference in the rate of common adverse events [272]. The placebo dry rates in most of these trials are between 35-40%, and 43 and 50% for mirabegron. In all trials the statistically significant difference is consistent only for improvement but not for cure of UI. Similar improvement in frequency of incontinence episodes and micturitions/24 hrs was found in people who had previously tried and those who had not previously tried antimuscarinic agents.

The most common treatment adverse events in the mirabegron groups were hypertension (7.3%), nasopharyngitis (3.4%) and UTI (3%) [272].

In a 12-month, active-controlled RCT of mirabegron 50/100 mg versus tolterodine ER 4 mg, the improvement in efficacy seen at 12 weeks was sustained at 12-month evaluation in all groups. The reported dry rates at 12 months were 43%, 45% and 45% for mirabegron 50 mg, 100 mg and tolterodine 4 mg respectively [274].

No risk of QTc prolongation on electrocardiogram [275] and raised intraocular pressure [276] were observed up to 100 mg dose. There is no significant difference in rate of side effects at different doses of mirabegron [274].

Evaluation of urodynamic parameters in men with combined BOO and OAB concluded that mirabegron (50 or 100 mg) did not adversely affect voiding urodynamic parameters compared to placebo [277].

Equivalent adherence was observed for tolterodine and mirabegron at 12 months (5.5% and 3.6%), although the incidence of dry mouth was significantly higher in the tolterodine group [274]. In mirabegron treated patients, improvement in objective outcome measures correlates directly with clinically relevant PROMs (OAB-q and PPBC) [278, 279].

Evidence summary	LE
Mirabegron is better than placebo for improvement of UUI symptoms	1a
There is no evidence that mirabegron is better than placebo for curing incontinence.	1b
Mirabegron is no more effective than tolterodine.	1b
Adrenergic-mediated side effects of mirabegron appear mild and not clinically significant in a trial setting.	1a
Discontinuation rates from mirabegron are similar to tolterodine in a trial setting.	1b

Recommendation	GR
Offer mirabegron to people with urgency urinary incontinence, but warn patients receiving mirabegron that the possible long-term side effects remain uncertain.	B

4.2.7 **Drugs for stress urinary incontinence**

Trials have focused on the effect of alpha-adrenoceptors in increasing the closure urethral pressure in women as a means of improving SUI.

A Cochrane review [280] found 22 trials of adrenergic drugs in women with predominant SUI in comparison to placebo or PFMT. Eleven of these trials involved phenylpropanolamine (withdrawn in some countries because of an increased risk of haemorrhagic stroke). The review found weak evidence that these drugs are better than placebo at improving UI in women. Comparative trials with PFMT gave inconsistent results. No new trials were published between 2007 and 2010. At present, these drugs are not licensed for use in UI.

Duloxetine inhibits the presynaptic re-uptake of the neurotransmitters, serotonin (5-HT) and norepinephrine (NE). In the sacral spinal cord, an increased concentration of 5-HT and NE in the synaptic cleft increases stimulation of 5-HT and NE receptors on the pudendal motor neurones, which in turn increases the resting tone and contraction strength of the urethral striated sphincter.

4.2.7.1 Questions

- In adults with SUI, does duloxetine cure or improve UI and/or improve QoL compared to no treatment?
- In adults with SUI, does duloxetine result in a greater cure or improvement of UI, or a greater improvement in QoL, or a lesser likelihood of adverse effects, compared to any other intervention?

4.2.7.2 Evidence

Duloxetine was evaluated as a treatment for female SUI or MUI in two systematic reviews [215, 280] of 10 RCTs, and one subsequent RCT. The typical dose of duloxetine was 80 mg daily, with dose escalation up to 120 mg daily allowed in one study, over a period of 8-12 weeks. One RCT extended the observation period up to 36 weeks and used the Incontinence Quality of Life (I-QoL) score as a primary outcome.

Improvement in UI compared to placebo was observed with no clear differences between SUI and MUI. One study reported cure for UI in about 10% of patients. An improvement in I-QoL was not found in the study using I-QoL as a primary endpoint. In a further study comparing duloxetine, 80 mg daily, with PFMT alone, PFMT + duloxetine, and placebo [281], duloxetine reduced leakage compared to PFMT or no treatment. Global improvement and QoL were better for combined therapy than no treatment. There was no significant difference between PFMT and no treatment.

Two open-label studies with a follow-up of 1 year or more evaluated the long-term effect of duloxetine in controlling SUI however both had high discontinuation rates [282, 283].

Duloxetine, 80 mg daily, which could be increased up to 120 mg daily, was investigated in a 12-week study in patients, who had OAB but not SUI [284]. Episodes of UUI were also significantly reduced by duloxetine.

One study [285] compared PFMT + duloxetine versus PFMT + placebo, for 16 weeks, followed by 8 weeks of PFMT alone in males with post-prostatectomy incontinence. Duloxetine + PFMT significantly improved UI, but the effect did not last to the end of the study, indicating that duloxetine only accelerates cure and does not increase the percentage of patients cured.

All studies had a high patient withdrawal rate of about 20-40% in short-term studies and up to 90% in long-term studies. Cause of the high withdrawal rate included lack of efficacy and high incidence of adverse events, including nausea and vomiting (40% or more of patients), dry mouth, constipation, dizziness, insomnia, somnolence and fatigue.

Evidence summary	LE
Duloxetine does not cure UI.	1a
Duloxetine, 80 mg daily improves SUI and MUI in women.	1a
Duloxetine causes significant gastrointestinal and CNS side effects leading to a high rate of treatment discontinuation.	1a
Duloxetine, 80 mg daily, can improve SUI in men.	1b
Duloxetine 80 mg - 120 mg daily can improve UUI in women.	1b

Recommendations	GR
Duloxetine should not be offered to women or men who are seeking a cure for their incontinence.	A
Duloxetine can be offered to women or men who are seeking temporary improvement in incontinence symptoms.	B*
Duloxetine should be initiated using dose titration because of high adverse effect rates.	A

* Downgraded based on expert opinion.

4.2.8 Oestrogen

Oestrogen treatment for UI has been tested using oral, transdermal and vaginal routes of administration. Available evidence suggests that vaginal oestrogen treatment with oestradiol and oestriol is not associated with the increased risk of thromboembolism, endometrial hypertrophy, and breast cancer seen with systemic administration [286-288]. Vaginal (local) treatment is primarily used to treat symptoms of vaginal atrophy in postmenopausal women.

4.2.8.1 Questions

- In women with UI, does oral (systemic) oestrogen cure or improve UI compared to no treatment?
- In women with UI, does vaginal (local) oestrogen cure or improve UI compared to no treatment or other active treatment?

4.2.8.2 Evidence

In women with SUI the use of oral conjugated equine estrogens, estradiol, or estrone showed no improvement [289-291]. Two placebo-controlled trials using sub-cutaneous estradiol or oral estriol showed no benefit for improvement of UI [292].

A recent Cochrane systematic review looked at the use of oestrogen therapy in postmenopausal women [286] given local oestrogen therapy. There is also a more recent narrative review of oestrogen therapy in urogenital diseases [293]. No new RCTs have been published up to September 2012. The Cochrane review (search date June 2012) found that vaginal oestrogen treatment improved symptoms of UI in the short-term [286]. The review found single, small, low quality trials comparing vaginal oestrogen treatment with phenylpropanolamine, PFMT, electrical stimulation and its use as an adjunct to surgery for SUI. Local oestrogen was less likely to improve UI than PFMT but no differences in UI outcomes were observed for the other comparisons. A single trial of local oestrogen therapy comparing a ring device to pessaries found no difference in UI outcomes although more women preferred the ring device. No adverse effects of vaginal administration of estradiol for vulvovaginal atrophy over 2 years was seen in one trial [294].

Vaginal oestrogen therapy can be given as conjugated equine oestrogen, oestriol or oestradiol in vaginal pessaries, vaginal rings or creams. Current data do not allow differentiation among the various types of oestrogens or delivery methods. The ideal treatment duration and the long-term effects are uncertain. One RCT compared oestradiol ring pessary with treatment with oxybutynin ER showing no difference in outcomes [295].

Evidence summary	LE
Vaginal oestrogen therapy improves UI for post-menopausal women.	1b
Oral oestrogen therapy does not improve UI.	1a
Vaginal oestrogen therapy in post-menopausal women may improve or cure UUI.	1a
There is no consistent evidence that vaginal oestrogen therapy cures SUI.	2
There is no evidence that one method of vaginal delivery is better than another	4
There is no evidence available on the neoadjuvant or adjuvant use of local oestrogens at the time of surgery for UI.	1a
There is no evidence that oestrogen therapy by non-vaginal route confers any improvement in UI.	1a

Recommendations	GR
Offer post-menopausal women with urinary incontinence vaginal oestrogen therapy particularly if other symptoms of vulvovaginal atrophy are present.	A
Do not offer oral (systemic) oestrogen replacement therapy as treatment for urinary incontinence.	A
Vaginal oestrogen therapy should be long-term and in an appropriate dose.	C

4.2.9 Desmopressin

Desmopressin is a synthetic analogue of vasopressin (also known as antidiuretic hormone). It can be taken orally, nasally or by injection. Desmopressin is most commonly used to treat diabetes insipidus and, when used at night, to treat nocturnal enuresis.

4.2.9.1 Questions

- In adults with UI, does desmopressin cure or improve UI and/or improve QoL compared to no treatment?
- In adults with UI, does desmopressin result in a lesser likelihood of adverse effects, compared to any other intervention?

4.2.9.2 Evidence

4.2.9.2.1 Improvement of incontinence

Few studies have examined the use of desmopressin exclusively for the treatment of UI. No evidence was found that demonstrated any effect on nocturnal incontinence. Two RCTs have compared desmopressin to placebo with daytime UI as an outcome measure. Improved continence was shown during the first 4 hours after taking desmopressin in women [296]. The continuous use of desmopressin improved frequency and urgency, but did not improve UI in men and women with OAB [297]. There is no evidence reporting desmopressin cure rates for UI and no evidence that compares desmopressin with other non-drug treatments for UI.

4.2.9.2.2 Monitoring for hyponatraemia

The use of desmopressin carries a risk of developing hyponatraemia (please refer to the EAU Guidelines on Male LUTS).

Evidence summary	LE
The risk of UI is reduced within 4 hours of taking oral desmopressin, but not after 4 hours.	1b
Continuous use of desmopressin does not improve or cure UI.	1b
Regular use of desmopressin may lead to hyponatraemia.	3

Recommendations	GR
Offer desmopressin to patients requiring occasional short-term relief from daytime urinary incontinence and inform them that this drug is not licensed for this indication.	B
Do not use desmopressin for long-term control of urinary incontinence.	A

4.2.10 Drug treatment in mixed urinary incontinence

4.2.10.1 Question

In adults with MUI, is the outcome of a drug treatment different to that with the same treatment in patients with either pure SUI or pure UUI?

4.2.10.2 Evidence

Many RCTs include patients with MUI with predominant symptoms of either SUI or UUI but few report outcomes separately for those with MUI compared to pure SUI or UUI groups.

Tolterodine

In an RCT of 854 women with MUI, tolterodine ER was effective for improvement of UUI, but not SUI suggesting that the efficacy of tolterodine for UUI was not altered by the presence of SUI [298]. In another study (n = 1380) tolterodine was equally effective in reducing urgency and UUI symptoms, regardless of whether there was associated SUI [299]. Similar results were found for solifenacin [300, 301].

Duloxetine

In one RCT of duloxetine vs. placebo in 588 women, subjects were stratified into either stress-predominant, urgency-predominant or balanced MUI groups. Duloxetine was effective for improvement of incontinence and QoL in all subgroups [302].

Duloxetine was found to have equal efficacy for SUI and MUI in an RCT (n = 553) following secondary analysis of respective subpopulations [303].

Evidence summary	LE
Limited evidence suggests that antimuscarinic drugs are effective for improvement of UUI component in patients with MUI.	2
Duloxetine is effective for improvement of both SUI and UUI in patients with MUI.	1b

Recommendations	GR
Treat the most bothersome symptom first in patients with mixed urinary incontinence.	C
Offer antimuscarinic drugs to patients with urgency-predominant mixed urinary incontinence.	A*
Consider duloxetine for patients with MUI unresponsive to other conservative treatments and who are not seeking cure.	B

4.3 Surgical management

In line with the recommendations from the UK National Institute for Healthcare and Clinical Excellence (NICE) [58] the Panel agreed that surgeons and centres performing surgery should:

- be properly trained in each procedure;
- not be trained by someone who is not surgically qualified;
- perform sufficient numbers of a procedure to maintain expertise of him/herself and the surgical team;
- be able to offer alternative surgical treatments;
- be able to deal with the complications of surgery;
- provide suitable arrangements for follow-up long-term if necessary.

The section considers surgical options for the following situations:

- Women with uncomplicated SUI. This means no history of previous surgery, no neurological lower urinary tract dysfunction (LUTD), no bothersome genitourinary prolapse, and not considering further pregnancy.
- Women with complicated SUI. Neurogenic LUTD is reviewed in the EAU Guidelines on Neurogenic Lower Urinary Tract Dysfunction [2].
- Associated genitourinary prolapse has been included in these Guidelines in terms of treating the incontinence, but no attempt has been made to comment on treatment of prolapse itself.
- Men with SUI, mainly in men with post-prostatectomy incontinence without neurological disease affecting the lower urinary tract.
- Patients with refractory DO incontinence.

The Panel has tried to acknowledge emerging techniques as they think appropriate and have made a strong recommendation (section 4.3.1.5.2) that new devices are only used as part of a structured research programme.

4.3.1 **Women with uncomplicated stress urinary incontinence**

4.3.1.1 *Mid-urethral slings*

Early clinical studies identified that slings should be made from monofilament, non-absorbable material, typically polypropylene, and constructed as a 1-2 cm wide mesh with a relatively large pore size (macroporous). Mid-urethral slings are now the most frequently used surgical intervention in Europe for women with SUI.

4.3.1.1.1 Questions

In women with SUI, what is the effectiveness in curing SUI and adverse effects at 1 year of:

- mid-urethral synthetic sling insertion compared to Burch colposuspension?
- one method of insertion of a mid-urethral synthetic sling compared to another method?
- one direction of insertion of a mid-urethral synthetic sling compared to another direction of insertion?

4.3.1.1.2 Evidence

For the purpose of these Guidelines, a new meta-analysis was performed.

Mid-urethral sling insertion compared to colposuspension

Thirteen RCTs (n = 1037) compared mid-urethral sling (retropubic) and colposuspension (open and laparoscopic). The meta-analysis found no difference in patient-reported cure rates at 12 months [304-314]. The overall patient-reported cure rate was 75%. There was weak evidence of higher clinician-reported cure rates at 12 months after mid-urethral sling (83%) compared to colposuspension (78%) [307-314]. However, longer term follow-up for up to 5 years reported no difference in effectiveness, though the numbers of participants lost to follow-up was high [87, 306]. Voiding dysfunction was more likely for colposuspension (relative risk 0.34, 95% CI 0.16-0.7) whilst bladder perforation was higher for the mid-urethral sling (15% vs. 9%, and 7% vs. 2%, respectively) [305, 307, 315-317].

Transobturator route versus retropubic route

The EAU Panel meta-analysis identified 34 RCTs (5786 women) comparing insertion of the mid-urethral sling by the retropubic and transobturator routes. There was no difference in cure rates at 12 months in either patient-reported or clinically reported cure rates (77% and 85%, respectively) [4]. Voiding dysfunction was less common (4%) following transobturator insertion compared to retropubic insertion (7%), as was the risk of bladder perforation (0.3%) or urethral perforation (5%). The risks of *de novo* urgency and vaginal perforation were 6% and 1.7%, respectively. Chronic perineal pain at 12 months after surgery was reported by 21 trials and meta-analysis showed a higher rate in women undergoing transobturator insertion (7%) compared to retropubic insertion (3%).

Insertion using a skin-to-vagina direction versus a vagina-to-skin direction

A Cochrane systematic review and meta-analysis found that the skin-to-vagina direction (top - down) for retropubic insertion of mid-urethral slings was less effective than the vagina-to-skin (bottom - up) direction and was associated with higher rates of voiding dysfunction, bladder perforation and vaginal erosion [318]. A further systematic review and meta-analysis found that the skin-to-vagina (outside in) direction of transobturator insertion of mid-urethral slings was equally effective compared to the vagina-to-skin route (inside out) using direct comparison. However, indirect comparative analysis gave weak evidence for a higher rate of voiding dysfunction and bladder injury [319].

4.3.1.2 Adjustability

4.3.1.2.1 Questions

- In women with SUI, does an adjustable sling cure SUI and improve QoL or does it cause adverse outcome(s)?
- How does an adjustable sling compare to other surgical treatments for SUI?

4.3.1.2.2 Evidence

There are no RCTs investigating outcome of adjustable sling insertion for women with SUI. There are limited data from cohort studies on adjustable tension slings with variable selection criteria and outcome definition. Few studies include sufficient numbers of patients or have a long enough follow-up to provide useful evidence. The available devices have differing designs, making it difficult to use existing data to make general conclusions about adjustable slings as a class of procedure.

4.3.1.3 Single-incision slings

4.3.1.3.1 Questions

- In women with SUI, do single-incision slings cure UI or improve QoL, or cause adverse outcomes?
- How does a single-incision sling compare to other surgical treatments for SUI?

4.3.1.3.2 Evidence

Although there have been many studies published on single-incision devices, it should be noted that there are significant differences in technical design between devices and it may be misleading to make general statements about them as a class of operations. It should also be noted that some devices have been withdrawn from the market (eg TVT Secur, Minitape), and yet evidence relating to these may be included in current meta analyses.

There was evidence to suggest single-incision slings are quicker to perform and cause less postoperative thigh pain, but there was no difference in the rate of chronic pain. There was not enough evidence to conclude any difference between single-incision slings in direct comparisons.

The most recent meta-analysis [320] and a reanalysis of the Cochrane review data by our panel (excluding TVT Secur data) have demonstrated that there was no difference in efficacy between available single incision devices and conventional mid-urethral slings. However, not all single incision devices have been subjected to RCT evaluation and it may be unsafe to assume that they are collectively technically similar devices.

Generalisability of evidence to adult women with SUI

Analysis of the population studied in trials included in this meta-analysis suggests that the evidence is generalisable to women, who have predominantly SUI, and no other clinically severe lower genitourinary tract dysfunction. The evidence is not adequate to guide choice of surgical treatment for those women with MUI, severe POP, or a history of previous surgery for SUI.

The results of the EAU Panel meta-analysis [4] were consistent with those of the Cochrane systematic review [318], except that in the EAU Panel meta-analysis the objective cure rates appeared slightly higher for retropubic (88%) compared to transobturator insertion (84%). The EAU Panel finding is consistent with an additional systematic review and meta-analysis [321] and the difference may result from the Panel's decision to only consider trial data with at least 12 months of follow-up.

Sexual function after mid-urethral tape surgery

A systematic review concluded there was a lack of RCTs addressing the effects of incontinence surgery on sexual function but noting a reduction in coital incontinence [322]. One recent RCT [323] and another cohort study [324] have shown that overall sexual activity improves after sling surgery.

SUI surgery in the elderly

There are no RCTs comparing surgical treatment in older versus younger women, although subgroup analyses

of some RCTs have included a comparison of older with younger cohorts. Definitions of “elderly” vary from one study to another so no attempt was made to define the term here. Instead, the Panel attempted to identify those studies which have addressed age difference as an important variable.

An RCT of 537 women comparing retropubic to transobturator tape, showed that increasing age was an independent risk factor for failure of surgery over the age of 50 [325]. An RCT assessing risk factors for the failure of TVT versus transobturator tension-free vaginal tape (TVT-O) in 162 women found that age is a specific risk factor (adjusted OR 1.7 per decade) for recurrence at 1 year [326]. In a subanalysis of a trial cohort of 655 women at 2 years’ follow-up, it was shown that elderly women were more likely to have a positive stress test at follow-up (OR 3.7, 95% CI 1.7-7.97), are less likely to report objective or subjective improvement in stress and urgency UI, and are more likely to undergo retreatment for SUI (OR 3.9, 95% CI 1.3-11.48). There was no difference in time to postoperative normal voiding [72].

Another RCT comparing immediate TVT versus no surgery (delayed TVT) in older women, confirmed efficacy of surgery in terms of QOL and satisfaction, but with higher complication rates [327].

A cohort study of 256 women undergoing inside-out transobturator tape reported similar efficacy in older versus younger women, but found a higher risk of de novo urgency in older patients [328].

Evidence summary	LE
Compared to colposuspension, the retropubic insertion of a mid-urethral synthetic sling gives equivalent patient-reported cure of SUI at 5 years.	1a
Mid-urethral synthetic sling inserted by either the transobturator or retropubic route gives equivalent patient-reported outcome at 12 months.	1a
The skin-to-vagina (top down) direction of retropubic insertion of mid-urethral sling is less effective than a vagina-to-skin (bottom up) direction.	1a
Mid-urethral sling insertion is associated with a lower rate of a new symptom of urgency, and voiding dysfunction, compared to colposuspension.	1a
The retropubic route of insertion is associated with a higher intra-operative risk of bladder perforation and a higher rate of voiding dysfunction than the transobturator route.	1a
The transobturator route of insertion is associated with a higher risk of chronic pain and vaginal erosion and extrusion at 12 months than the retropubic route.	1a
The skin-to-vagina direction of both retropubic and transobturator insertion is associated with a higher risk of postoperative voiding dysfunction.	1b
Adjustable mid-urethral synthetic sling devices may be effective for cure or improvement of SUI in women.	3
There is no evidence that adjustable slings are superior to standard mid-urethral slings.	4
The comparative efficacy of single-incision slings against conventional mid-urethral slings is uncertain.	1c
Operation times for insertion of single-incision mid-urethral slings are shorter than for standard retropubic slings.	1b
Blood loss and immediate postoperative pain are lower for insertion of single-incision slings compared with conventional mid-urethral slings.	1b
There is no evidence that other adverse outcomes from surgery are more or less likely with single-incision slings than with conventional mid-urethral slings.	1b
Older women benefit from surgical treatment for UI.	1
The risk of failure from surgical repair of SUI, or suffering adverse events, appears to increase with age.	2
There is no evidence that any surgical procedure has greater efficacy or safety in older women than another procedure.	4
In women undergoing surgery for SUI, coital incontinence is likely to improve.	3
Overall, sexual function is unlikely to deteriorate following SUI surgery.	3
There is no consistent evidence that the risk of postoperative sexual dysfunction differs between midurethral sling procedures.	3

**NB: Most evidence on single-incision slings is from studies using the tension-free vaginal tape secure (TVTS) device and although this device is no longer available, many women still have the device in place.*

4.3.1.4 *Open and laparoscopic surgery for stress urinary incontinence*

Open colposuspension was previously considered the gold standard surgical intervention for SUI, and was used as the comparator in RCTs of newer, less invasive, surgical techniques. These include laparoscopic techniques, which have enabled colposuspension to be performed with a minimally invasive approach.

Although the outcome of open and laparoscopic procedures should be considered in absolute terms, it is also important to consider any associated complications, adverse events and costs. The outcome parameters used to evaluate surgery for SUI have included:

- continence rate and number of incontinence episodes;
- general and procedure-specific complications;
- generic, specific (UI) and correlated (sexual and bowel) QoL.

4.3.1.4.1 *Question*

In women with SUI, what is the effectiveness of open and laparoscopic surgery, compared to other surgical procedures, measured in terms of cure or improvement of incontinence or QoL, or the risk of adverse events?

4.3.1.4.2 *Evidence*

Four systematic reviews were found, which covered the subject of open surgery for SUI, including 46 RCTs [2, 329-331], but no RCTs comparing any operation to a sham procedure.

Open colposuspension

The Cochrane review [332] included 46 trials (4738 women) having open colposuspension. In most of these trials, open colposuspension was used as the comparator to an experimental procedure. Consequently, for this review we have only considered the absolute effect of colposuspension, but have not reviewed all of these comparisons. No additional trials have been reported since this review.

Within the first year, complete continence rates of approximately 85-90% were achieved for open colposuspension, while failure rates for UI were 17% up to 5 years and 21% over 5 years. The re-operation rate for UI was 2%. Colposuspension was associated with a higher rate of development at 5 years of enterocele/vault/cervical prolapse (42%) and rectocele (49%) compared to tension-free vaginal tape (TVT) (23% and 32%, respectively). The rate of cystocele was similar in colposuspension (37%) and with TVT (41%).

Four trials compared Burch colposuspension to the Marshall Marchetti Krantz procedure and one trial evaluated Burch colposuspension with paravaginal repair. All showed fewer surgical failures up to 5 years with colposuspension but otherwise similar outcomes.

Anterior colporrhaphy

Anterior colporrhaphy is now considered an obsolete operation for UI. In a Cochrane review [330], 10 trials compared anterior colporrhaphy (385 women) with colposuspension (627 women). The failure rate for UI at follow-up of up to 5 years was worse for anterior colporrhaphy with a higher requirement for re-operation for incontinence.

Autologous fascial sling

The Cochrane review [330, 333] described 26 RCTs, including 2284 women undergoing autologous sling procedure in comparison to other operations.

There were seven trials of autologous fascial sling versus colposuspension. Except for one very high-quality study [334], most of the studies were of variable quality, with a few very small studies, and a short follow-up. The metaanalysis showed that fascial sling and colposuspension had a similar cure rate at 1 year. Colposuspension had a lower risk of voiding difficulty and UTIs, but a higher risk of bladder perforation.

In 12 trials of autologous fascial sling versus mid-urethral synthetic slings, the procedures showed similar efficacy. However, use of the synthetic sling resulted in shorter operating times and lower rates of complications, including voiding difficulty. Six trials compared autologous fascial slings with other materials of different origins, with results favouring traditional autologous fascial slings.

Laparoscopic colposuspension

The Cochrane review [329] identified 22 RCTs, of which 10 trials compared laparoscopic colposuspension to open colposuspension. No other trials have been identified. Although these procedures had a similar subjective cure rate, there was limited evidence suggesting the objective outcomes were less good for laparoscopic

colposuspension. However, laparoscopic colposuspension had a lower risk of complications and shorter duration of hospital stay.

In eight RCTs comparing laparoscopic colposuspension to mid-urethral slings, the subjective cure rates were similar, while the objective cure rate favoured the mid-urethral sling at 18 months. Complication rates were similar for the two procedures and operating times were shorter for the mid-urethral sling. Comparisons of colposuspension to mid-urethral sling are covered in section 4.3.1.1.

Evidence summary	LE
Open colposuspension and autologous fascial sling are similarly effective for cure of SUI in women.	1b
Laparoscopic colposuspension has similar efficacy to open colposuspension for cure of SUI and a similar risk of voiding difficulty or de novo urgency.	1a
Laparoscopic colposuspension has a lower risk of other complications and shorter hospital stay than open colposuspension.	1a
Autologous fascial sling has a higher risk of operative complications than open colposuspension, particularly voiding dysfunction and postoperative UTI.	1b

4.3.1.5 *Bulking agents*

4.3.1.5.1 Question

In women with SUI, does injection of a urethral bulking agent cure SUI or improve QoL, or cause adverse outcomes?

4.3.1.5.2 Evidence

There have been two Cochrane systematic reviews [335, 336] and one independent SR [337], which reported on 12 RCTs or quasi-RCTs of injectable agents. In general, the trials were only of moderate quality and small and many of them had been reported in abstract form. Wide confidence intervals meant a meta-analysis was not possible. Since the Cochrane review, two further RCTs have been reported [338, 339].

Each injectable product has been the subject of many case series. Short-term efficacy in reducing the symptoms of SUI has been demonstrated for all materials used. In 2006, NICE published an extensive review of these case series [340]. These case series have added very little to the evidence provided by RCTs. There has been only one placebo-controlled RCT, in which an autologous fat injection was compared with the placebo of a saline injection.

Comparison with open surgery

Two RCTs compared collagen injection to conventional surgery for SUI (autologous sling vs. silicon particles and collagen vs. assorted procedures). The studies reported greater efficacy but higher complication rates for open surgery. In comparison, collagen injections showed inferior efficacy but equivalent levels of satisfaction and fewer serious complications [58, 341].

Another trial found that a periurethral route of injection can carry a higher risk of urinary retention compared to a transurethral injection [342]. A recent small RCT found no difference in efficacy between mid-urethral and bladder neck injection of collagen [338].

Evidence summary	LE
Periurethral injection of bulking agent may provide short-term improvement in symptoms (3 months), but not cure, in women with SUI.	2a
Repeat injections to achieve therapeutic effect are often required.	2a
Bulking agents are less effective than colposuspension or autologous sling for cure of SUI.	2a
Adverse effect rates are lower compared to open surgery.	2a
There is no evidence that one type of bulking agent is better than another type.	1b
Transperineal route of injection may be associated with a higher risk of urinary retention compared to the transurethral route.	2b

Recommendations for surgery for uncomplicated stress urinary incontinence in women	GR
Offer the mid-urethral sling to women with uncomplicated stress urinary incontinence as the preferred surgical intervention whenever available.	A
Warn women who are being offered a retropubic insertion of midurethral sling about the relatively higher risk of peri-operative complications compared to transobturator insertion.	A
Warn women who are being offered transobturator insertion of mid-urethral sling about the higher risk of pain and dyspareunia in the longer term.	A

Warn women who are being offered a single-incision sling that long-term efficacy remains uncertain.	A
Do a cystoscopy as part of retropubic insertion of a mid-urethral sling, or if difficulty is encountered during transobturator sling insertion, or if there is a significant cystocele.	C
Offer colposuspension (open or laparoscopic) or autologous fascial sling to women with stress urinary incontinence if mid-urethral sling cannot be considered.	A
Warn women undergoing autologous fascial sling that there is a high risk of voiding difficulty and the need to perform clean intermittent self-catheterisation; ensure they are willing and able to do so.	C
Inform older women with stress urinary incontinence about the increased risks associated with surgery, including the lower probability of success.	B
Inform women that any vaginal surgery may have an impact on sexual function.	B
Only offer new devices, for which there is no level 1 evidence base, as part of a structured research programme.	A*
Only offer adjustable mid-urethral sling as a primary surgical treatment for stress urinary incontinence as part of a structured research programme.	A*
Do not offer bulking agents to women who are seeking a permanent cure for stress urinary incontinence.	A*

* Recommendation based on expert opinion.

4.3.2 **Complicated stress urinary incontinence in women**

This section will address surgical treatment for women who have had previous surgery for SUI, which has failed, or those women who have undergone previous radiotherapy affecting the vaginal or urethral tissues. Neurological lower urinary tract dysfunction is reviewed by the EAU Guidelines on Neurogenic Lower Urinary Tract Dysfunction [2]. Women with associated genitourinary prolapse are included in this edition (see section 4.3.3).

4.3.2.1 *Colposuspension or sling following failed surgery*

There may be persistent or recurrent SUI, or the development of de novo UUI. This means that careful evaluation including urodynamics becomes an essential part of the work-up of these patients.

4.3.2.1.1 Question

In women who have had failed surgery for SUI, what is the effectiveness of any second-line operation, compared to any other second-line operation, in terms of cure or improvement of UI, QoL or adverse events?

4.3.2.1.2 Evidence

Most of the data on surgery for SUI refer to primary operations. Even when secondary procedures have been included, it is unusual for the outcomes in this subgroup to be separately reported. When they are, the numbers of patients is usually too small to allow meaningful comparisons.

The 4th International Consultation on Incontinence includes a review of this topic [343] up till 2008 and the subject has also been reviewed by Ashok [344] and Lovatsis et al. [345]. A further literature review has been carried out since that time by the Panel.

Cochrane reviews of individual operative techniques have not included separate evaluation of outcomes in women undergoing second-line surgery. However, there is a current protocol to address this issue [346]. Only one RCT was found (abstract only) comparing TVT to laparoscopic colposuspension in women with recurrent SUI. This small study found similar cure rates and adverse events in the short-term for both procedures [317].

Post-hoc subgroup analysis of high-quality RCTs comparing one procedure to another have shown conflicting evidence of relative effectiveness [72, 85, 347, 348]. One large non-randomised comparative series suggested that cure rates after more than two previous operations were 0% for open colposuspension and 38% for fascial sling [349].

Several cohort studies have reported outcomes for TVT specifically for primary and secondary cases. Evidence on the effectiveness of second-line retropubic tapes conflicts with some series showing equivalent outcomes for primary and secondary cases [350, 351], whilst other research has shown inferior outcomes for secondary surgery [352, 353]. Other confounding variables make meaningful conclusions difficult.

Systematic review of older trials of open surgery for SUI suggest that the longer term outcomes of redo open colposuspension may be poor compared to autologous fascial slings [354]. Successful results have been reported from mid-urethral slings after various types of primary surgery, while good outcomes are reported for

both repeat TVT and for 'tightening' of TVT, but data are limited to small case series only.

Evidence summary	LE
There is conflicting evidence whether prior surgery for stress incontinence or prolapse results in inferior outcomes from repeat operations for SUI.	2
Most procedures will be less effective when used as a second-line procedure than when used for primary surgery.	2
In women who have had more than two procedures for SUI, the results of open colposuspension are inferior to autologous fascial sling.	2

4.3.2.2 External compression devices

External compression devices are still widely used in the treatment of recurrent SUI after the failure of previous surgery and if there is thought to be profound intrinsic failure of the sphincter mechanism, characterised by very low leak point pressures or low urethral closure pressures. This should be confirmed by urodynamic evaluation.

The two intracorporeal external urethral compression devices available are the adjustable compression therapy (ACT) device and the artificial urinary sphincter (AUS). Using ultrasound or fluoroscopic guidance, the ACT device is inserted by placement of two inflatable spherical balloons on either side of the bladder neck. Each volume of each balloon can be adjusted through a subcutaneous port placed within the labia majora. More recently, an adjustable artificial urinary sphincter (Flowsecure) has been introduced. It has the added benefit of 'conditional occlusion', enabling it to respond to rapid changes in intra-abdominal pressure.

4.3.2.2.1 Questions

- In women with SUI, does insertion of an external compressive device cure SUI, improve QoL or cause adverse outcomes?
- How do external compression devices compare to other surgical treatments for SUI?

4.3.2.2.2 Evidence

The major advantage of AUS over other anti-incontinence procedures is the perceived ability to be able to void normally [136]. However, voiding dysfunction is a known side effect, with a lack of data making it difficult to assess its importance. Because of significant differences in design between devices and in selection criteria between case series, results obtained with specific devices cannot be extrapolated generally to the use of adjustable devices. A recent consensus report has standardised the terminology used for reporting complications arising from implantation of materials into the pelvic floor region [17].

Artificial urinary sphincter (AUS)

A previous review of mechanical devices concluded that there was insufficient evidence to support the use of AUS in women [355].

There are a few case series in women, including four series (n = 611), with study populations ranging from 45 to 215 patients and follow-up ranging from 1 month to 25 years [356-359]. Case series have been confounded by varying selection criteria, especially the proportion of women who have neurological dysfunction or who have had previous surgery. Most patients achieved an improvement in SUI, with reported subjective cures in 59-88%. Common side effects included mechanical failure requiring revision (up to 42% at 10 years) and explantation (5.9-15%). In a retrospective series of 215 women followed-up for a mean of 6 years, the risk factors for failure were older age, previous Burch colposuspension and pelvic radiotherapy [359]. Peri-operative injury to the urethra, bladder or rectum was also a high-risk factor for explantation [357].

A newly introduced artificial sphincter using an adjustable balloon capacity through a self-sealing port, and stress responsive design, has been introduced to clinical use. A series of 100 patients reported 28% explantation at 4 years but the device has undergone redesign and more up-to-date evidence is awaited [360].

Early reports of laparoscopically implanted AUS do not have sufficient patient populations and/or sufficient follow-up to be able to draw any conclusions [361, 362].

Adjustable compression device (ACT)

There are four case series (n = 349), with follow-up ranging from 5 to 84 months [363-366]. Reported outcome ranged from 47% objective cure to 100% subjective improvement. However, most patients required adjustment to achieve continence and 21% required explantation.

Evidence summary	LE
Implantation of an artificial sphincter can improve or cure incontinence in women with SUI caused by sphincter insufficiency.	3
Implantation of the ACT device may improve complicated UI.	3
Complications, mechanical failure and device explantation often occur with both the artificial sphincter and the adjustable compression device.	3
Explantation is more frequent in older women and among those who have had previous Burch colposuspension or pelvic radiotherapy.	3

Recommendations for surgery for complicated stress urinary incontinence in women	GR
The choice of surgery for recurrent stress urinary incontinence should be based on careful evaluation of the individual patient including video-urodynamics.	C
Warn women with recurrent stress urinary incontinence, that the outcome of a surgical procedure, when used as a second-line treatment, is generally inferior to its use as a first-line treatment, both in terms of reduced efficacy and increased risk of complications.	C
Consider secondary synthetic sling, colposuspension or autologous sling as first options for women with complicated stress urinary incontinence.	C
Implantation of AUS or ACT for women with complicated stress urinary incontinence should only be offered in expert* centres.	C
Warn women receiving AUS or ACT that, even in expert centres, there is a high risk of complications, mechanical failure or a need for explantation.	C

AUS = artificial urinary sphincter; ACT = adjustable compression therapy.

* expert centres refers to the comments on surgeon volume in the introduction to the surgical chapter.

4.3.3 Women with both stress urinary incontinence and pelvic organ prolapse

There is a clear association between the presence of POP and SUI. Although the subject of prolapse is not part of the remit of these Guidelines, the extent to which it impacts on the management of SUI will be addressed. The aim is to assess the options available to women who require surgery for POP and who have associated UI (either symptomatic or after reduction of prolapse), and to assess the value of prophylactic antiincontinence surgery in women with no evidence of UI.

4.3.3.1 Questions

1. In women with POP and UI, does combined surgery for POP and SUI reduce the incidence of postoperative UI compared to POP surgery alone?
2. In continent women with POP, does combined surgery for POP and SUI reduce the incidence of postoperative de novo UI compared to POP surgery alone?
3. In women with POP and occult SUI, (i.e. seen only on prolapse reduction stress testing/urodynamics), does combined surgery for POP and SUI reduce the incidence of postoperative UI compared to POP surgery alone?
4. In women with POP and OAB, does surgery for POP improve OAB symptoms?
5. In adults with POP, what are the reliability, the diagnostic accuracy and predictive value of a prolapse reduction test to identify patients at risk for denovo SUI following prolapse repair?

4.3.3.2 Evidence

A Cochrane review in 2013 included sixteen trials concerning bladder function after surgery for pelvic organ prolapse [367]. After prolapse surgery 434 of 2125 women (20.4%) reported new subjective SUI in 16 trials. New voiding dysfunction was reported in 109 of 1209 (9%) women in 12 trials.

1. *In women with POP does combined surgery for POP and SUI reduce the incidence of postoperative UI compared to POP surgery alone?*

There are two well-designed RCTs relating to the prevalence of postoperative SUI in women who underwent prolapse surgery with and without an anti-incontinence procedure. Both of these trials involved women with POP who did not complain of symptoms of stress incontinence regardless of objective findings.

One trial compared abdominal sacrocolpopexy with and without Burch colposuspension [368], the other compared vaginal repair with and without a mid-urethral sling (3). In both trials addition of an anti-incontinence surgery reduced the risk of SUI at 12 months. In one trial there was a higher rate of adverse events reported in the combined surgery group [369]. This was also the finding of the Cochrane review and meta-analysis.

Two trials addressed postoperative SUI in patients who had had SUI preoperatively. Borstad et al., in a multicenter trial randomised women with POP and SUI to have a tension-free vaginal tape (TVT) at the time of prolapse repair or 3 months later, if they still had SUI. (n=53). One year after surgery there was no difference between the groups regarding continence, however, 44% of the women without initial TVT never required surgery and 29% were dry [370].

In contrast, Costantini et al. followed up women with POP and SUI randomised to abdominal POP repair with or without Burch colposuspension, (after a median of 97 months) finding that additional SUI surgery did not improve outcome [371]. On the contrary, a higher number of patients had de novo storage symptoms when a Burch colposuspension was performed.

In summary, it is difficult to generalise the results of trials using very different procedures to treat both POP and UI. It seems that with a combined procedure the rate of SUI postoperatively is lower. Studies using mid-urethral slings generally have shown more significant differences in UI outcomes with combined procedures than when other types of anti-incontinence procedure have been used. Individual patient characteristics may play the most important role in shaping treatment decisions. It must be taken into account that, although more women may be dry after combined surgery the risks of repeat surgery, should it become necessary, may outweigh the potential benefits.

2. *Continent women with POP*

The 2013 Cochrane review included 6 trials showing that postoperative incontinence rates at < 12 months were 19% in the combined surgery group vs. 32% in POP surgery alone. In this group of 438 women, undergoing continence surgery at the time of prolapse prevented 62 (14%) women from developing de novo SUI postprolapse surgery. A long-term update of a previously published RCT comparing POP surgery with or without Burch colposuspension in continent women suggested higher UI rates in women undergoing colposuspension [369].

3. *Women with POP and occult SUI*

The 2013 Cochrane review included five trials addressing this point. Overall, there was a significantly higher rate of postoperative patient-reported SUI with prolapse surgery alone compared with combined surgery.

4. *Women with POP and OAB*

There is evidence from 3 case series evaluating patients with concomitant OAB and pelvic organ prolapse assessing incontinence/OAB symptom scores postsurgical repair. Costantini et al. assessed the effect of posterior repair on OAB/DO and reported a 70-75% improvement rate in both parameters along with a 93% anatomic success rate [372].

Kummeling et al. assessed the effect of a modified laparoscopic sacrocolpopexy on urodynamic parameters and reported an improvement with no evidence to support a concomitant prophylactic colposuspension [373]. Lee et al. assessed the value of pre-op UDS and BOOI in predicting the degree of OAB symptoms post anterior prolapse repair. They reported a significant correlation between low pre-op BOOI and improvement in OAB symptom scores post-op [374].

5. *Prolapse reduction stress test (PRST)*

Data concerning PRST were made available from the CARE trial where significant differences were noted in the detection of urodynamic stress incontinence with prolapse reduction among the various methods studied ranging from 6% (pessary) to 30% (speculum). Manual, swab and forceps showed detection rates of 16%, 20% and 21%, respectively [375]. In the study by Duecy about one third of women were diagnosed with occult SUI using a pessary while two thirds were diagnosed with manual reduction of the prolapse [376]. In a further study occult SUI was only detected by a pessary test in 19% of patients, not by urodynamics, history or clinical examination [377].

Evidence summary	LE
<i>Women with prolapse + UI</i>	
Surgery for POP + SUI shows a higher rate of cure in the short-term than POP surgery alone.	1a
There is conflicting evidence on the relative benefit of combined surgery long-term.	1b
Combined surgery for POP+SUI carries a higher risk of adverse events.	1b
<i>Continent women with POP</i>	
Are at risk of developing UI postoperatively.	1a

The addition of a prophylactic anti-incontinence procedure reduces the risk of postoperative UI.	1b
The addition of a prophylactic anti-incontinence procedure increases the risk of adverse events.	1b
<i>Women with POP and OAB</i>	
There is some low-level inconsistent evidence to suggest that surgical repair of POP can improve symptoms of OAB.	3
<i>Women with prolapse and occult SUI</i>	
Surgery for POP + occult SUI shows a higher rate of cure in the short-term than POP surgery alone.	1a
Combined surgery for POP + SUI carries a higher risk of adverse events than POP surgery alone.	1b

Recommendations for women requiring surgery for bothersome POP who have symptomatic or unmasked stress urinary incontinence	GR
Offer simultaneous surgery for POP and stress urinary incontinence.	A
Warn women of the increased risk of adverse events with combined surgery compared to prolapse surgery alone.	A
Recommendations for women requiring surgery for bothersome POP without symptomatic or unmasked stress urinary incontinence	GR
Warn women that there is a risk of developing de novo stress urinary incontinence after prolapse surgery.	A
Inform women that the benefit of prophylactic stress urinary incontinence surgery is uncertain.	C
Warn women that the benefit of surgery for stress urinary incontinence may be outweighed by the increased risk of adverse events with combined surgery compared to prolapse surgery alone.	A

POP = pelvic organ prolapse.

* based on expert opinion.

4.3.4 Urethral diverticulum

A female urethral diverticulum is a sac-like protrusion made up by the entire urethral wall or only by the urethral mucosa laying between the periurethral tissues and the anterior vaginal wall. Urethral diverticulum give rise to a variety of symptoms that include pain, urgency, frequency, recurrent UTIs, vaginal discharge, dyspareunia, voiding difficulties or urinary incontinence.

1. *In a woman with the clinical suspicion of having an urethral diverticulum, what is the best test to confirm the diagnosis?*

No robust diagnostic accuracy studies address this question. However, a case series of 27 patients concluded that endoluminal (vaginal or rectal) MRI has better diagnostic accuracy than video cystourethrography VCUG [378]. In a case series of 60 subjects Pathi et al reported that the sensitivity, specificity, positive predictive value and negative predictive value of MRI is 100%, 83%, 92% and 100%, respectively [379]. Dwarkasing et al. also reports 100% specificity and sensitivity of MRI in a case series of 60 patients [380]. However, in a case series of 41 patients, a study reported 25% discrepancy between MRI and surgical findings [381].

2. *In a woman who has a bothersome urethral diverticulum, what is the relative effectiveness of available surgical treatments?*

4.3.4.1 Surgical treatment

No RCTs were found. Surgical removal is the most commonly reported treatment in contemporary cases series. However, recurrence may occur; Han et al. found a recurrence rate of 33% in U-shaped and of 60% in circumferential diverticulum within 1 year [382], Ingber et al. found a 10.7% recurrence rate in 122 women undergoing diverticulectomy, with a higher risk of recurrence in those with proximal or multiple diverticula or after previous pelvic surgery [383]. SUI may occur in up to 20% of women after diverticulectomy, requiring additional correction [384-387]. De novo SUI seems to be more common in proximal and in large size (>30 mm) diverticula.

Diverticula may undergo neoplastic alterations (6%) including invasive adenocarcinomas [388].

Evidence Statement	
MRI has good sensitivity and specificity for the diagnosis of urethral diverticula, however there is a risk of mis-diagnosis and missing potential intraluminal neoplastic change.	3
Surgical removal of symptomatic urethral diverticula provides good long-term results, however, women should be counselled of the risk of recurrence and de novo SUI.	3

Recommendation	GR
Symptomatic urethral diverticula should be completely surgically removed.	A*

4.3.5 **Men with stress urinary incontinence**

4.3.5.1 *Bulking agents in men*

Injection of bulking agents has been used to try and improve the coaptation of a damaged sphincter zone. Initial reports showed limited efficacy in treating incontinence following radical prostatectomy incontinence [389, 390].

4.3.5.1.1 Question

In men with post-prostatectomy incontinence or SUI, does injection of a urethral bulking agent cure SUI, improve QoL, or cause adverse outcomes?

4.3.5.1.2 Evidence

Most studies are case series with small sample sizes. Small cohort studies showed a lack of benefit using a number of different materials [391, 392]. However, polyacrylamide hydrogel resulted in limited improvement in QoL without curing the UI [391]. A Cochrane review on the surgical treatment of post-prostatectomy incontinence found only one study that fulfilled the inclusion criteria [393]. A prospective, randomised study compared the AUS to silicon particles (Macroplastique™) in 45 patients. Eighty-two per cent of patients receiving an AUS were continent compared to 46% receiving silicone particles. In patients with severe incontinence, outcome was significantly worse after silicon bulking injection.

Evidence summary	LE
There is no evidence that bulking agents cure post-prostatectomy incontinence.	2a
There is weak evidence that bulking agents can offer temporary, short-term, improvement in QoL in men with post-prostatectomy incontinence.	3
There is no evidence that one bulking agent is superior to another.	3

4.3.5.2 *Fixed male sling*

As well as external compression devices and bulking agents, slings have been introduced to treat postprostatectomy incontinence. Fixed slings are positioned under the urethra and fixed by a retropubic or transobturator approach. The tension is adjusted during the surgery and cannot be re-adjusted postoperatively.

For the restoration of continence by these male slings, two concepts are now being proposed:

- continence restoration by urethral compression (InVance®, Istop TOMS, Argus®)
- continence restoration by repositioning the bulb of urethra (AdVance) [394].

In principle, the AUS can be used for all degrees of post-prostatectomy incontinence, while male slings are advocated for mild-to-moderate UI. However, the definitions of mild and moderate UI are not clear. The definition of cure, used in most studies, was no pad use or one security pad per 24 hours. Some authors used a stricter criterion of less than 2 g urine loss in a 24-hour pad test [395].

4.3.5.2.1 Question

In men with post-prostatectomy SUI, does insertion of a fixed suburethral sling cure SUI, improve QoL, or cause adverse outcomes?

4.3.5.2.2 Evidence

Concerning the surgical treatment of post-prostatectomy incontinence, three recent literature reviews are available [396-398]. There are a large number of uncontrolled case series concerning men implanted with several types of slings [399, 400].

For the repositioning sling (AdVance), the benefit after a mean follow-up of 3 years has been published on 136 patients [401]. Earlier data were available from other cohort studies, totalling at least 614 patients with a mean follow-up of between 3 months and 3 years. Subjective cure rates for the device vary between 8.6% and 73.7%, with a mean of 49.5%. Radiotherapy was a negative prognostic factor [399]. Postoperative voiding dysfunction occurred in 5.7-1.3%, while erosions and chronic pain were uncommon (0-0.4%) [395, 401-403]. The overall failure rate was about 20%.

The previously available “InVance®” device has now been removed from the market in some countries.

Evidence summary	LE
There is limited short-term evidence that fixed male slings cure or improve post-prostatectomy incontinence in patients with mild-to-moderate incontinence.	3
Men with severe incontinence, previous radiotherapy or urethral stricture surgery may have less benefit from fixed male slings.	3
There is no evidence that one type of male sling is better than another.	3

4.3.5.3 Adjustable slings in males

Adjustability in male sling surgery attempts to adjust the tension of the sling postoperatively. Three main systems have been used in men: the Remeex® system, the Argus® system and the ATOMS system.

4.3.5.3.1 Question

In men with post-prostatectomy incontinence or SUI, does insertion of an adjustable suburethral sling cure or improve SUI, improve QoL, or cause adverse outcomes?

4.3.5.3.2 Evidence

There are no prospective RCTs. Most studies consist of prospective or retrospective case series, with variable follow-up and different definitions of success. Some have been published only as conference abstracts.

Remeex® system

For the Remeex® system, only two abstracts, with conflicting findings, have been published. One study followed 19 patients for nearly 7 years and reported 70% success, with no explants, infections or erosions. The second study followed 14 patients for 25 months. Only 36% of patients were satisfied and multiple re-adjustments were needed. Mechanical failure was reported in 21% [404].

Argus® system

Data on the Argus® system have been reported for 404 men, but only four series have reported on more than 50 patients [405, 406], with the longest follow-up being 2.4 years. Success rates varied between 17% and 91.6%, with a mean of 57.6% predominantly reporting a subjective cure. The number of implants requiring re-adjustment was reported as between 22.9% and 41.5% [406]. Infection of the device occurred in 5.4- 8% [405]. Erosions were reported in 5-10% [407]. Urethral perforations occurred in 2.7-16% [405]. Pain at the implant site was usually only temporary, but chronic pain has been reported [405, 407]. These complications resulted in explantation rates of 10-15% [406].

The ATOMS system consists of a mesh implant with an integrated adjustable cushion, which uses a titanium port left in the subcutaneous tissue of the lower abdomen for adjustment of cushion volume. Initial reports show objective cure rates of 60.5% and improvement rates of 23.7% but with the need for up to nine postoperative adjustments [408, 409].

Evidence summary	LE
There is limited evidence that adjustable male slings can cure or improve SUI in men.	3
There is limited evidence that early explantation rates are high.	3
There is no evidence that adjustability of the male sling offers additional benefit over other types of sling.	3

4.3.5.4 Compression devices in males

External compression devices can be divided into two types: circumferential and non-circumferential compression of the urethral lumen [396]. The artificial urinary sphincter (AUS) is the standard treatment for moderate-to-severe male SUI. Most data available on the efficacy and adverse effects of AUS implantation are from older retrospective cohort studies with RCTs not performed due to the lack of a comparator. Men considering insertion of an AUS should understand that if the ability of an individual to operate the pump is uncertain, it may not be appropriate to implant an AUS. There are several recognised complications of AUS implantation, e.g. mechanical dysfunction, urethral constriction by fibrous tissue, erosion and infection. The non-circumferential compression devices consist of two balloons placed close to the vesico-urethral anastomotic site. The balloons can be filled and their volume can be adjusted postoperatively through an intrascrotal port.

4.3.5.4.1 Question

In men with post-prostatectomy SUI, does insertion of an external compression device cure SUI, improve QoL, or cause adverse outcomes?

4.3.5.4.2 Evidence

Artificial urinary sphincter

Although the AUS is considered to be the standard treatment for men with SUI, there are two systematic reviews [393, 398] presenting limited evidence, of generally poor quality, except for one RCT comparing with bulking agents [389]. A continence rate of about 80% can be expected, while this may be lower in men who have undergone pelvic radiotherapy [396].

Trigo Rocha et al. published a prospective cohort study on 40 patients with a mean follow-up of 53 months, showing that from all urodynamic parameters, only low bladder compliance had a negative impact on the outcome [410]. Another retrospective study showed that no urodynamic factors adversely altered the outcome of AUS implantation [411].

The transcorporeal technique of placement can be used for repeat surgery but evidence of effectiveness is lacking [412]. The dual-cuff placement was introduced to treat patients who remained incontinent with a single 4 cm cuff in place. However, it has not improved control of UI, while the availability of a 3.5 cm cuff may have eliminated the need for a dual cuff [413, 414]. Patients who experienced complete continence after AUS implantation had a higher erosion risk [415]. One small series reported results of AUS implantation after failure of previous Advance sling, showing no difference in efficacy between secondary and primary implantation [416].

Non-circumferential compression device (ProAct®)

There have been trials to treat post-prostatectomy SUI by insertion of a device consisting of balloons with adjustable volume external to the proximal bulbar urethra. A prospective cohort study (n = 128) described the functional outcome as 'good' in 68%, while 18% of the devices had to be explanted [417]. A subgroup of radiotherapy patients only had 46% success and a higher percentage of urethral erosions.

A quasi-randomised trial comparing a non-circumferential compression device (ProAct®) with bone-anchored male slings found that both types of device resulted in similar improvement of SUI (68% vs. 65%, respectively) [418]. Other prospective series have shown that adverse events were frequent, leading to an explantation rate of 11-58% [398, 419-422]. A questionnaire study showed that 50% of patients were still bothered significantly by persistent incontinence [423].

Other designs of artificial sphincter remain the subject of ongoing evaluation though may have been introduced onto the market.

Evidence summary	LE
There is limited evidence that primary AUS implantation is effective for cure of SUI in men.	2b
Long-term failure rate for AUS is high although device replacement can be performed.	3
There are conflicting data on whether previous pelvic radiotherapy affects the outcome of AUS implantation.	3
Men who develop cognitive impairment or lose manual dexterity will have difficulty operating an AUS.	3
The usefulness of tandem-cuff placement is uncertain.	3
There is insufficient evidence to state whether one surgical approach for cuff placement is superior to another.	3
Very limited short-term evidence suggests that the non-circumferential compression device (ProACT®) is effective for treatment of post-prostatectomy SUI.	3
The non-circumferential compression device (ProACT®) is associated with a high failure and complication rate leading to frequent explantation.	3
The rate of explantation of the AUS because of infection or erosion remains high (up to 24% in some series).	3
Mechanical failure is common with the AUS.	3
Revision and reimplantation of AUS is possible after previous explantation or for mechanical failure.	3

Recommendations for surgery in men with stress urinary incontinence	GR
Only offer bulking agents to men with mild post-prostatectomy incontinence who desire temporary relief of incontinence symptoms.	C
Do not offer bulking agents to men with severe post-prostatectomy incontinence.	C
Offer fixed slings to men with mild-to-moderate * post-prostatectomy incontinence.	B
Warn men that severe incontinence, prior pelvic radiotherapy or urethral stricture surgery, may worsen the outcome of fixed male sling surgery.	C

Offer AUS to men with moderate-to-severe post-prostatectomy incontinence.	B
Implantation of AUS or ACT for men should only be offered in expert centres.	C
Warn men receiving AUS or ACT that, even in expert centres, there is a high risk of complications, mechanical failure or a need for explantation.	C
Do not offer non-circumferential compression device (ProACT®) to men who have had pelvic radiotherapy.	C

AUS = artificial urinary sphincter; ACT = artificial compression device.

* the terms mild and moderate post prostatectomy incontinence remain undefined.

4.3.6 **Surgical interventions for refractory detrusor-overactivity**

4.3.6.1 *Bladder wall injection of botulinum toxin A*

Onabotulinum toxin A (onabotA; BOTOX®) 100 U dissolved in 10 ml of saline and injected in 20 points of the bladder wall above the trigone (0.5 ml per injection site) is licenced in Europe to treat OAB with persistent or refractory UUI in adults of both gender, despite the small number of males included in the registration trials [424, 425]. Surgeons must realise that other doses of onabotA and other formulations of botulinum toxin A, abobotulinum toxinA and incobotulinum toxin A, are not licensed for use in UUI. Doses for OnabotA are not transposable to the other brands of botulinum toxin A. The continued efficacy of repeat injections is the rule but discontinuation rate may be high. The most important adverse events related to onabotA 100 U injection detected in the regulatory trials were UTI and an increase in PVR that may require clean intermittent catheterisation (CIC) [426].

4.3.6.1.1 Question

In adults with UUI, is bladder wall injection of onabotA better than no treatment for cure or improvement?

4.3.6.1.2 Evidence

Following a dose ranging study in which the 100U of onabotA was established as the ideal dose, two phase III trials randomised (1:1) 1105 OAB incontinent patients whose symptoms were not adequately managed with anticholinergics to receive bladder wall injections of onabotA (100 U) or saline. At baseline the population had in average more than 5 episodes of UUI, around 12 micturitions per day and small PVR. At week 12, in patients treated with onabotA UUI episodes/day were halved and number of micturitions/day reduced by more than 2. A total of 22.9% of the patients in the onabotA arm were fully dry, against 6.5% in the saline arm [427].

QoL was substantially improved in the onabotA arm, as shown by the more than 60% of positive responses in the TBS questionnaire at week 12, which doubled the positive responses in the saline arm. Cohort studies have shown the effectiveness of bladder wall injections of onabotA in the elderly and frail elderly [428], though the success rate might be lower and the PVR (> 150 mL) higher in this group.

A recent RCT compared onabotA injection 100 U to solifenacin (with dose escalation or switch to trospium possible in the solifenacin group) and showed a similar rates of improvement in UUI over the course of 6 months [429]. Patients receiving onabotA were more likely to have cure of UUI (27% vs. 13%, $p = 0.003$), but also had higher rates of urinary retention during the initial 2 months (5% vs. 0%) and of UTIs (33% vs. 13%). Patients taking antimuscarinics were more likely to have dry mouth.

Evidence summary	LE
A single treatment session of onabotulinum toxin A (100U) injected in the bladder wall is more effective than placebo at curing and improving UUI and QoL for up to 12 months.	1a
There is no evidence that repeated injections of onabotulinum toxin A have reduced efficacy.	3
There is a high risk of increased PVR when injecting elderly frail patients.	3
The risk of bacteruria after onabotulinum toxin A (100U) injection is high but the clinical significance of this remains uncertain.	1b
Onabotulinum toxin A 100 U is superior to solifenacin for cure of UUI.	1a
Long-term treatment with of onabotulinum toxin A may be associated with a high discontinuation rate.	2

Recommendations	GR
Offer bladder wall injections of onabotulinum toxin A (100 units) to patients with urgency urinary incontinence refractory to antimuscarinic therapy.	A
Warn patients of the limited duration of response, risk of UTI and the possible prolonged need to selfcatheterise (ensure that they are willing and able to do so) and risk of UTI.	A

UTI = urinary tract infection.

4.3.6.2 Sacral nerve stimulation (neuromodulation)

In the first stage of a two-stage implantation, an electrode is placed percutaneously under fluoroscopic control in the sacral foramen alongside a sacral nerve, usually S3. In earlier techniques, a temporary wire electrode was used. More recently, a permanent tined electrode has been used for a longer test phase. Patients, in whom selected symptoms of UUI are reduced by more than 50% during the test phase, are candidates for the full implant, including the pulse generator.

4.3.6.2.1 Question

In adults suffering from refractory UUI, what is the clinical effectiveness of sacral nerve neuromodulation compared to alternative treatments?

4.3.6.2.2 Evidence

All randomised studies suffer from the limitation that assessors and patients were not blind to the treatment allocation since all recruited subjects had to respond to a test phase before randomisation. A Cochrane review of the literature until March 2008 [430] identified three RCTs that investigated sacral nerve stimulation in patients with refractory UUI.

One study compared implantation to controls who stayed on medical treatment and received delayed implantation at 6 months. Fifty percent of the immediately implanted group had > 90% improvement in UUI at 6 months compared to 1.6% of the control group [222]. The other RCT [431] achieved similar results, although these patients had already been included in the first report [222]. However, Weil et al. [431] showed that the effect on generic QoL measured by the SF-36, was unclear as it differed between the groups in only one of the eight dimensions.

The results of 17 case series of patients with UUI, who were treated early in the experience with sacral nerve stimulation were reviewed [432]. After a follow-up duration of between 1 and 3 years, approximately 50% of patients with UUI demonstrated > 90% reduction in UI, 25% demonstrated 50-90% improvement, and another 25% demonstrated < 50% improvement. Two case series describing the outcome of sacral nerve neuromodulation, with a mean or median follow-up of at least 4 years [433, 434] reported continued success (> 50% improvement on original symptoms) by about 50 of patients available for follow-up. Cure rates for UUI were 15% [434].

Adverse events occurred in 50% of implanted cases, with surgical revision necessary in 33-41% [433, 434].

In a subanalysis of the RCT, the outcomes of UUI patients, with or without pre-implant DO, were compared. Similar success rates were found in patients with and without urodynamic DO [435].

Evidence summary	LE
Sacral nerve neuromodulation is more effective than continuation of failed conservative treatment for cure of UUI, but no sham controls have been used.	1b
In those patients who have been implanted, at longterm 50% improvement of UUI is maintained in at least 50% of patients and 15% may remain cured.	3
One-stage implantation. The use of tined, permanent electrodes results in more patients receiving the final implant than occurs with temporary test stimulation.	4

Recommendation	GR
If available, offer sacral nerve modulation to patients who have urgency urinary incontinence refractory to conservative therapy.	A

4.3.6.3 Cystoplasty/urinary diversion

4.3.6.3.1 Augmentation cystoplasty

In augmentation cystoplasty (also known as clam cystoplasty), a detubularised segment of bowel is inserted into the bivalved bladder wall. The distal ileum is the bowel segment most often used but any bowel segment can be used if it has the appropriate mesenteric length. One study did not find any difference between bivalving the bladder in the sagittal or in the coronal plane [436, 437].

There are no RCTs comparing bladder augmentation to other treatments for patients with UUI. Most often, bladder augmentation is used to correct neurogenic DO or small-capacity, low-compliant, bladders caused by fibrosis, tuberculosis, radiation or chronic infection.

The largest case series of bladder augmentation in a mixed population of ideopathic and neurogenic UII included 51 women [438]. At an average follow-up of 74.5 months, only 53% were continent and satisfied with the surgery, whereas 25% had occasional leaks and 18% continued to have disabling UII. It seems that the results for patients with idiopathic DO (58%) seemed to be less satisfactory than for patients with neurogenic UII (90%).

Adverse effects were common and have been summarised in a review over 5-17 years of more than 267 cases, 61 of whom had non-neurogenic UII [439]. In addition, many patients may require clean intermittent selfcatheterisation to obtain adequate bladder emptying (Table 7).

Table 7: Complications of bladder augmentation

Short-term complications	Affected patients (%)
Bowel obstruction	2
Infection	1.5
Thromboembolism	1
Bleeding	0.75
Fistula	0.4
Long-term complications	Affected patients (%)
Clean intermittent self-catheterisation	38
Urinary tract infection	70% asymptomatic; 20% symptomatic
Urinary tract stones	13
Metabolic disturbance	16
Deterioration in renal function	2
Bladder perforation	0.75
Change in bowel symptoms	25

4.3.6.3.2 Detrusor myectomy (bladder auto-augmentation)

Detrusor myectomy aims to increase bladder capacity and reduce storage pressures by incising or excising a portion of the detrusor muscle, to create a bladder mucosal 'bulge' or pseudodiverticulum. It was initially described as an alternative to bladder augmentation in children [440]. Two case series [441, 442], in adult patients with idiopathic and neurogenic bladder dysfunction, demonstrated poor long-term results caused by fibrosis of the pseudodiverticulum. This technique is rarely if ever used nowadays.

4.3.6.3.3 Urinary diversion

Urinary diversion remains a reconstructive option for patients, who decline repeated surgery for UI. However, there are no studies that have specifically examined this technique in the treatment of non-neurogenic UI [436].

Evidence summary summary	LE
There is limited evidence on the effectiveness of augmentation cystoplasty and urinary diversion in treatment of idiopathic DO.	3
Augmentation cystoplasty and urinary diversion are associated with high risks of short-term and long-term severe complications.	3
The need to perform clean intermittent self-catheterisation following augmentation cystoplasty is very common.	3
There is no evidence comparing the efficacy or adverse effects of augmentation cystoplasty with urinary diversion.	3
Detrusor myectomy is ineffective in adults with UI.	3

Recommendations	GR
Only offer augmentation cystoplasty to patients with detrusor overactivity incontinence who have failed conservative therapy, in whom the possibility of botulinum toxin and sacral nerve stimulation has been discussed.	C
Warn patients undergoing augmentation cystoplasty of the high risk of having to perform clean intermittent self-catheterisation; ensure they are willing and able to do so.	C
Do not offer detrusor myectomy as a treatment for urinary incontinence.	C
Only offer urinary diversion to patients who have failed less invasive therapies for the treatment of urinary incontinence and who will accept a stoma.	C

Warn patients undergoing augmentation cystoplasty or urinary diversion of the high risk of short-term and long-term complications, and the possible small risk of malignancy.	C
Life-long follow-up is recommended for patients who have undergone augmentation cystoplasty or urinary diversion.	C

4.3.7 **Surgery in patients with mixed urinary incontinence**

4.3.7.1 *Question*

In adults with MUI, is the outcome of surgery different to that obtained with the same treatment in patients with either pure SUI or pure UI?

4.3.7.2 *Evidence*

Many RCTs include both patients with pure SUI or pure UI and patients with MUI. However, very few RCTs report separate outcomes for MUI and pure UI groups.

Transvaginal obturator tape

In an RCT including 96 women with MUI, objective improvement was better for patients treated with transvaginal obturator tape + the Ingelman Sundberg operation versus patients treated with obturator tape alone [443].

Post-hoc analysis of the SISTER trial showed that in women undergoing either autologous fascial sling or Burch colposuspension, the outcomes were poorer for women with a concomitant complaint of pre-operative urgency [72]. A similar post-hoc review of another RCT comparing transobturator and retropubic mid-urethral slings showed that the greater the severity of pre-operative urgency the more likely that treatment would fail [85]. However, an earlier study had found that surgery provided similar outcomes, whether or not urgency was present prior to surgery (this study included only a few patients with urodynamic DO).

Case series tend to show poorer results in patients with MUI compared with those with pure SUI. In a case series of 192 women undergoing mid-urethral sling insertion, overall satisfaction rates were lower for women with mixed symptoms and detrusor overactivity on pre-operative urodynamics compared to those with pure SUI and normal urodynamics (75% vs. 98%, respectively) [444]. Comparison of two parallel cohorts of patients undergoing surgery for SUI, with and without DO, found inferior outcomes in women with MUI [445].

One cohort of 450 women, found that In urgency-predominant MUI, the success rate fell to 52% compared to 80% in stress-predominant MUI [446]. In a study with 1113 women treated with transvaginal obturator tape, SUI was cured equally in stress-predominant MUI or urgency-predominant MUI. However, women with stress-predominant MUI were found to have significantly better overall outcomes than women with urgency-predominant MUI [447].

Overall, the outcome for women with pre-existing urgency incontinence remains uncertain.

Evidence summary	LE
Women with MUI are less likely to be cured of their incontinence by SUI surgery than women with SUI alone.	1c
The response of pre-existing urgency symptoms to SUI surgery is unpredictable and symptoms may improve or worsen.	3

Recommendations	GR
Treat the most bothersome symptom first in patients with mixed urinary incontinence.	C
Warn patients with mixed urinary incontinence that surgery is less likely to be successful than surgery in patients with stress urinary incontinence alone.	A
Warn patients with mixed urinary incontinence that one single treatment may not cure UI; it may be necessary to treat other components of the incontinence problem as well as the most bothersome symptom.	A*

* upgraded following panel consensus.

4.3.8 **Surgery for urinary incontinence in the elderly**

There are no RCTs comparing surgical treatment in older versus younger women although subgroup analyses of some RCTs have included a comparison of older with younger cohorts.

An RCT of 537 women comparing retropubic to transobturator tape, showed that cure rates decreased and failure increased with each decade over the age of 50 [448]. An RCT assessing risk factors for failure of tension free vaginal tape (TVT) versus transobturator tension-free vaginal tape (TVT-O) in 162 women found that age is a specific risk factor (adjusted OR 1.7 per decade) for recurrence at 1 year [326]. In a subanalysis of the SISTER trial cohort of 655 women at 2 years of follow-up, it was shown that elderly women were more likely to have a positive stress test at follow-up (OR 3.7, 95% CI 1.7-7.97), are less likely to report objective or subjective improvement in stress and urgency UI, and are more likely to undergo retreatment for SUI (OR 3.9, 95% CI 1.3-11.48). There was no difference in time to normal postoperative voiding [72].

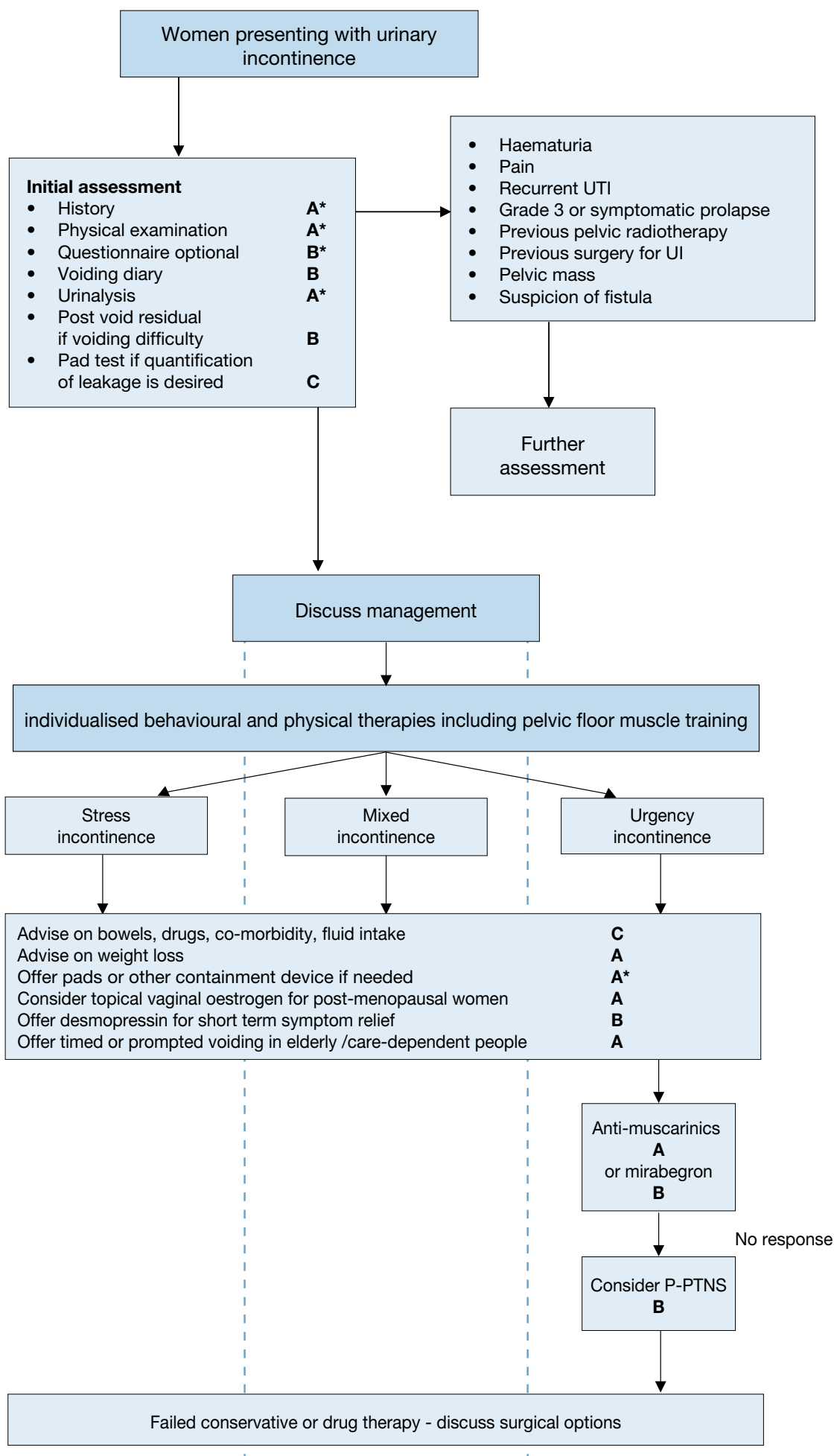
Another RCT compared immediate TVT versus delayed TVT in older women, confirming significant efficacy for the operated women, but the cohort as a whole suffered higher complication rates, particularly bladder perforation (22%) and urinary retention (13%) [327].

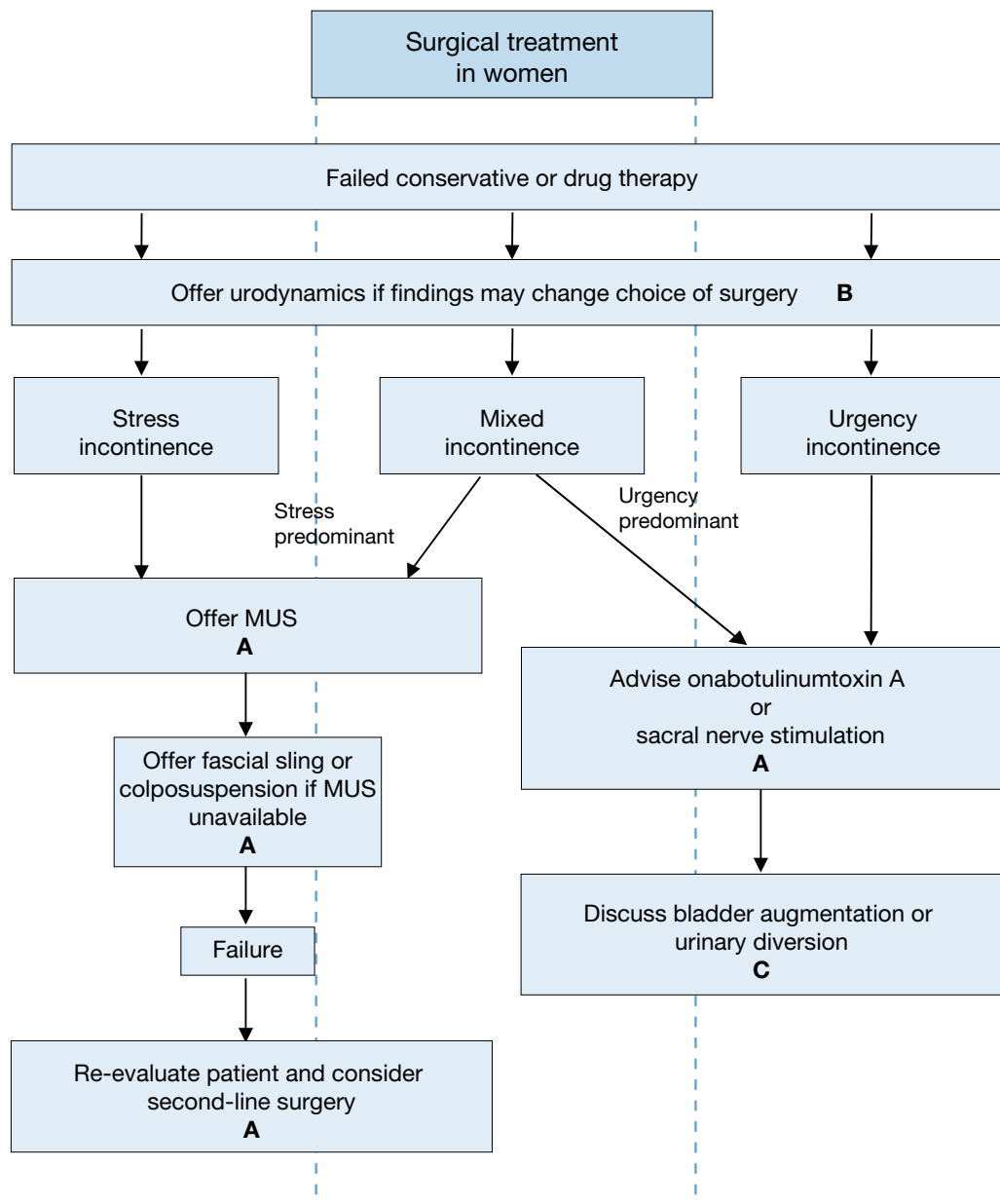
A cohort study of 256 women undergoing inside-out TVT-O reported similar efficacy in older versus younger women but there was a higher risk of de novo urgency in older patients [328].

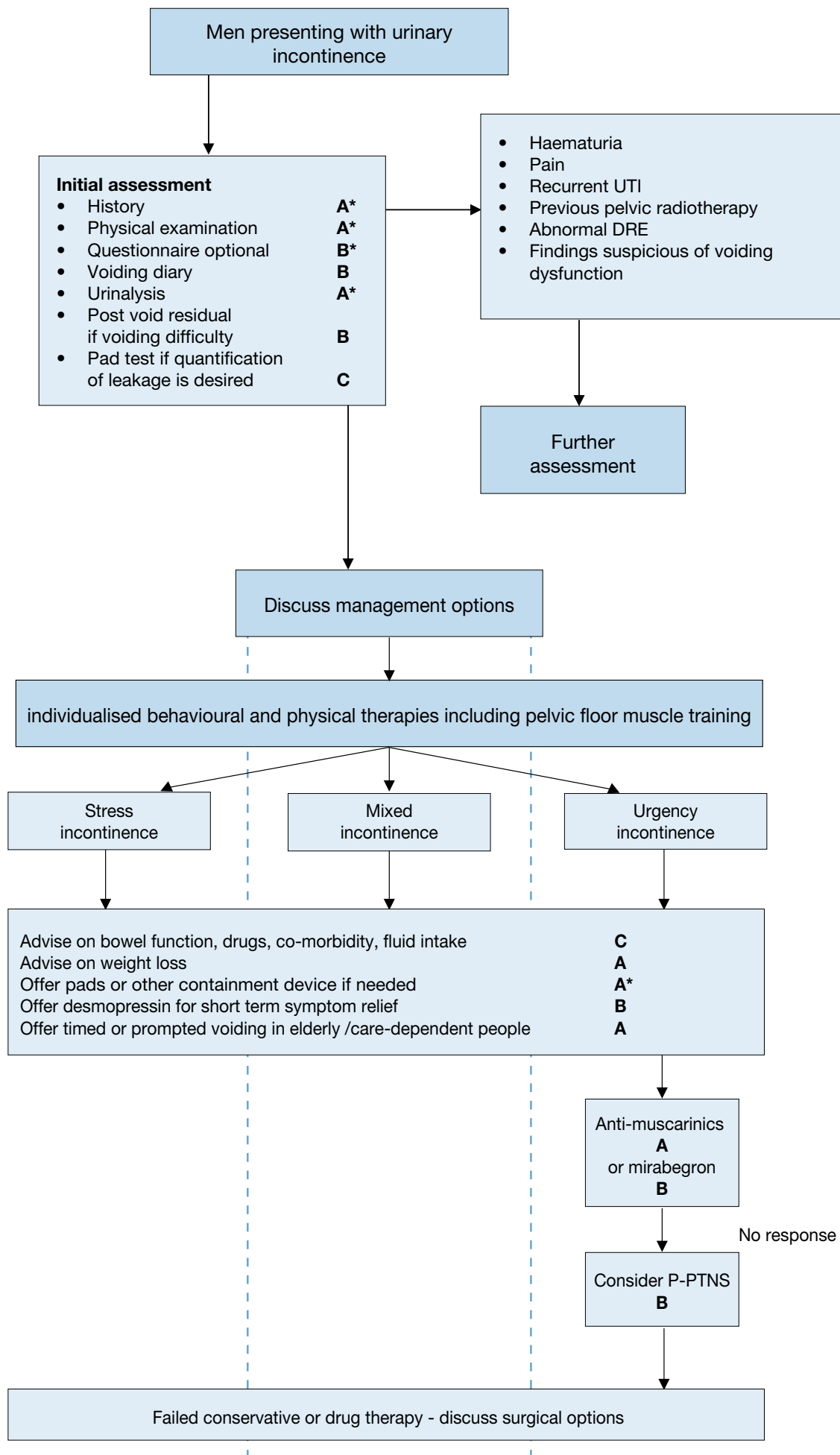
Cohort studies have shown the effectiveness of onabotulinum toxin A injections in the elderly and frail elderly [428, 449], although a comparison of cohort groups suggests that there is a lower success rate in the frail elderly and also a higher rate of increased PVR (> 150 mL) in this group.

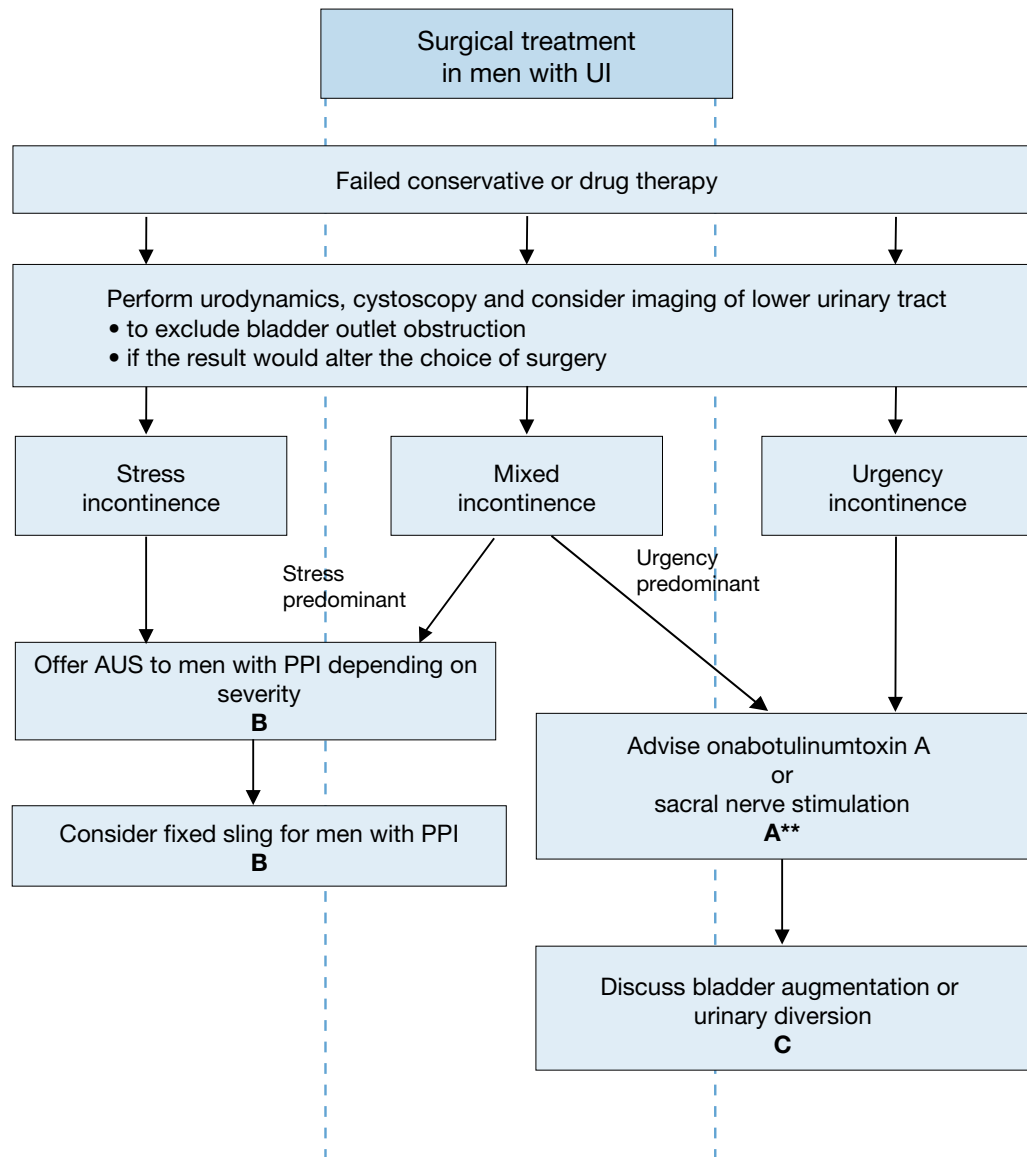
Evidence summary	LE
Older women benefit from surgical treatment for incontinence.	1
The risk of failure from surgical repair of SUI, or of suffering adverse events, appears to increase with age.	2
There is no evidence that any surgical procedure has greater efficacy or safety in older women than another procedure.	4

Recommendation	GR
Inform older women with urinary incontinence about the increased risks associated with surgery, (including onabotA injection), together with the lower probability of benefit.	B









**** Available evidence on onabotulinumtoxinA and sacral nerve stimulation refers mainly to women.**

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6. CONFLICT OF INTEREST

All members of the Urinary Incontinence Guidelines Panel have provided disclosure statements on all relationships that they have and that might be perceived to be a potential source of conflict of interest. This information is publically accessible through the European Association of Urology website. This Guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

Guidelines on Neuro-Urology

B. Blok (Co-chair), J. Pannek (Co-chair), D. Castro Diaz,
G. del Popolo, J. Groen, T. Gross (Guidelines Associate),
R. Hamid, G. Karsenty, T.M. Kessler, M.P. Schneider (Guidelines
Associate), L. 't Hoen (Guidelines Associate)

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1. INTRODUCTION

1.1 Aim

The European Association of Urology (EAU) Neuro-Urology Guidelines aim to provide information for clinical practitioners on the incidence, definitions, diagnosis, therapy, and follow-up of neuro-urological disorders. These Guidelines reflect the current opinion of experts in this specific pathology and thus represent a state-of-the-art reference for all clinicians, as of the publication date.

The terminology used and the diagnostic procedures advised throughout these Guidelines follow the recommendations for investigations on the lower urinary tract (LUT) as published by the International Continence Society (ICS) [1-4]. Readers are advised to consult the other EAU Guidelines which may address different aspects of the topics discussed in this document.

1.2 Publication history

The EAU published the first Neuro-Urology Guidelines in 2003 with updates in 2008, 2014 and 2015. In 2009, a review paper was published in European Urology [5].

Standard procedure for EAU Guidelines includes an annual assessment of newly published literature in the field to guide future updates. A shorter reference document, the Pocket Guidelines, is also available, both in print and as a mobile application, presenting the main findings of the Neuro-Urology Guidelines. These versions are abridged and therefore may require consultation with the full text version. All are available through the EAU website: <http://www.uroweb.org/guidelines/>.

For this 2015 print updates were made to:

- Chapter 3A: A new table summarising epidemiology of neuro-urological disorders has been added (Table 1) and text in this chapter has consequently been replaced.
- Chapter 3D: The sections on botulinum toxin sphincter injection (3D.2.5.4) and surgical treatment (3D.2.6) have been revised and updated.
- Chapter 3F: Sexual (dys)function and fertility has been revised and updated.

Additionally, the text has been significantly reduced so that only key information is included and re-formatted according to the EAU template for non-oncology Guidelines so that all Guidelines follow a similar format.

This document was peer-reviewed prior to publication.

1.3 Panel composition

The EAU Neuro-Urology Guidelines panel consists of an international multidisciplinary group of experts, including urologists specialised in the care of spinal cord injured (SCI) patients and a specialist in the field of urodynamic technologies.

1.4 Background

The function of the LUT is mainly storage and voiding of urine, which is regulated by the nervous system that coordinates the activity of the urinary bladder and bladder outlet. Any disturbance of the nervous system involved, including the peripheral nerves in the pelvis, can result in neuro-urological symptoms. Depending on the extent and location of the disturbance, a variety of different LUT changes might occur, which can be symptomatic or asymptomatic. Moreover, neuro-urological symptoms can cause a variety of long-term complications; the most dangerous being deterioration in renal function. Since symptoms and long-term complications do not correlate [6], it is important to identify patients with neuro-urological symptoms, and establish if they have a low or high-risk of subsequent complications.

According to current knowledge, elevated storage pressure in the bladder, either alone or combined with vesicoureteric reflux (VUR), is the most important risk factor for renal damage [7]. Sustained elevated storage pressure in the bladder is mainly due to a combination of increased detrusor activity during the storage phase (detrusor overactivity [DO] or low compliance), combined with detrusor-sphincter dyssynergia (DSD). The combination of these findings is usually caused by suprasacral infrapontine spinal lesions. Furthermore, elevated detrusor leak point pressure has been demonstrated to be a risk factor for renal deterioration in patients with meningocele [8]. Therefore, renal failure has been the leading cause of death in patients with SCI for a long time [9]. Even today, 26% of patients with meningocele who do not undergo urological treatment develop renal damage. Detrusor leak point pressure > 40 cm H₂O and low bladder compliance are the main risk factors for renal damage [10].

In recent years, adequate diagnosis and treatment of neuro-urological symptoms in patients with spinal cord lesions have improved the situation of these patients. Nowadays, respiratory diseases are the most frequent (21%) cause of death in patients with SCI [11].

In all other patients with neuro-urological symptoms, the risk of renal damage is significantly lower. However, in multiple sclerosis (MS), urodynamics and clinical symptoms may not correlate, which means that asymptomatic patients can present with abnormal urodynamic findings [12]. LUT symptoms do not always lead to urological evaluation in MS patients, even if the symptoms are troublesome [13]. Therefore, urological assessment is important [14]; although respiratory diseases are currently the leading cause of death in MS patients [15].

In Parkinson's disease (PD), neuro-urological disorders have not been reported as a significant cause of death. Moreover, patients with PD commonly suffer from overactive bladder without DSD [16], which does not seem to be as threatening to the upper urinary tract (UUT) as DO with DSD. In PD, urodynamic diagnosis of DO correlates well with diagnosis made by questionnaires [17]. Therefore, regular urodynamic follow-up might be less important in patients with PD compared with MS or SCI. The same is true for diabetes mellitus, which frequently leads to neuro-urological symptoms [18], but cardiovascular diseases are the main cause of death in these patients [19].

In summary, treatment and intensity of follow-up examinations are based on the type of neuro-urological disorder and the underlying cause.

2. METHODS

There is a need for ongoing re-evaluation of the information presented in the current Guidelines by an expert Panel. It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account.

Literature searches were carried out for all sections of the Neuro-Urology Guidelines. Focus of all searches was identification of all level 1 scientific papers (systematic reviews and meta-analyses of randomised controlled trials) in accordance with EAU methodology. If sufficient data was identified to answer the clinical question, the search was not expanded to include lower level literature. Searches were carried out in Medline and Embase on the Ovid platform. The searches used the controlled terminology of the respective databases.

References used in this text are graded according to their level of evidence (LE) and Guidelines are given a grade of recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [20]. The aim of grading recommendations is to provide transparency between the underlying evidence and the recommendation given. In this 2015 EAU Guidelines compilation, all standard information on LE and GR has been taken out of the individual Guidelines topics for the sake of brevity. The methodology section (see the introduction chapter of the complete book) outlines the LE and GR criteria which are used throughout the Guidelines.

3. THE GUIDELINE

3A EPIDEMIOLOGY, AETIOLOGY AND PATHOPHYSIOLOGY

3A.1 Introduction

Neuro-urological symptoms may be caused by various diseases and events affecting the nervous systems controlling the LUT. The resulting neuro-urological symptoms depend grossly on the location and the extent of the neurological lesion. There are no exact figures on the overall prevalence of neuro-urological disorders in the general population, but data are available on the prevalence of the underlying conditions and the relative risk of those for the development of neuro-urological symptoms. It is important to note that the majority of the data shows a very wide range of prevalence/incidence figures. This reflects the variability in the cohort (e.g. early or late stage disease) and the frequently smaller sample sizes, resulting in low level of evidence in most published data (summarised in Table 1).

Table 1: Epidemiology of Neuro-Urological Disorders

Suprapontine and pontine lesions and diseases		
Neurological Disease	Frequency in General Population	Type and Frequency of Neuro-Urological Symptoms
Cerebrovascular accident (Strokes)	450 cases/100,000/yr (Europe) [21] (10% of cardiovascular mortality)	Nocturia - OAB - UII - DO (other patterns less frequent) [22]. 57-83% of neuro-urological symptoms at 1 month post stroke, 80% of spontaneous recovery at 6 months [23]. Persistence of UI correlates with poor prognosis [24].
Dementias: Alzheimer's disease (80%), Vascular (10%), Other (10%)	6.4% of adults > 65 yrs [25, 26]	OAB - UII - DO 25% of incontinence in Alzheimer's disease, ≥ 25% in other dementias: Lewy body, NPH, Binswanger, Nasu-Hakola, Pick Disease [27]. Incontinence 3 times more frequent in geriatric patients with dementia than without (42.3/1000 women and 33.5/1000 men vs 19.6/1000 women, 18.6/1000 men) [28].
Parkinsonian syndrome Idiopathic Parkinson's disease (IPD): 75-80% of Parkinsonian syndromes	1.5% in > 65 yrs [29] 2nd neurodegenerative disease after Alzheimer's disease Prevalence: 150/100,000/yr Incidence: 20/100,000/yr	LUTS frequency 30% at onset, 70% after 5 yrs. Storage phase symptoms: Nocturia (60%) OAB - UII - DO [30].
Non-IPD: Parkinson's-plus (18%): Multi system atrophy (MSA), - Progressive supranuclear palsy, - Corticobasal degeneration, - Dementia with Lewy bodies.	MSA is the most frequent non-IPD.	OAB and DO at the initial phase, intrinsic sphincter deficiency and impaired contractility appear as the disease progress. Complications of neuro-urological symptoms (infections) account for a major cause of mortality in MSA [31].
Secondary Parkinson's (2%)		
Brain tumors	26.8/100,000/yr in adult (> 19 yrs) (17.9 benign, 8.9 malignant) [32].	Neuro-urological symptoms vary according to tumour location. Incontinence occurs mainly in frontal location (part of frontal syndrome or isolated in frontal location) [33]. Voiding dysfunction may occur in other location.
Mental retardation and cerebral palsy	Mental retardation other than cerebral palsy	Incontinence: In 65% of severe and profoundly retarded adult patients [35, 36]. DO and impaired contractility also reported.
<i>Intellectual disability in children is a very heterogenous group: including perinatal injury, materno-foetal infections, metabolic disease, genetic disorders and cerebral palsy</i>	Cerebral Palsy: 3.1-3.6/1,000 in children aged 8 yrs [34].	89% incontinence, 70% uninhibited detrusor contraction at urodynamic examination. Recurrent urinary tract infection and radiologic abnormalities in > 10% of cases.

Lesions and diseases between caudal brainstem and sacral spinal cord		
Spinal cord injury	Non-congenital SCI cases exceed 200,000 in the US with new cases 8/10,000/yr.	Suprasacral lesion leads to DO and DSD (95%). Lower lesions (sacral conus) lead to detrusor hypocontractility (83%) and to complete EUS denervation (60%) [37-39].
Myelomeningocele and nerve tube defects	Spina bifida and congenital nerve tube defects in G8 = 3-4/10,000 live birth/stillbirths with/without pregnancy termination [40]. Lumbar and lumbosacral form are the most common (60%).	Urethrovessical dysfunction in myelomeningocele is very high (90-97%). 50% of these children demonstrate DO. Low compliance is also frequent (alone/associated with can develop with time). Urethral behaviour varies from dyssynergia (50%), normal reflexes (25%) and denervation (25%) [41].
Lesions and diseases of the peripheral nervous system		
Lumbar spine Degenerative disease Disk prolapse	Male (5%) and female (3%) > 35 yrs have had a lumbosacral episode related to disc prolapse.	26% difficulty to void and acontractile detrusor at urodynamic testing. 14% frequent voiding while normal urodynamics testing [42]. Cauda equina lesions lead to detrusor hypocontractility (83%) and complete EUS denervation (60%) [37-39].
Lumbar canal stenosis	Incidence: approx. 5/100,000/yr More common: > 45 yrs, females.	27% significant LUTS (mainly difficulty to void) [42].
Iatrogenic pelvic nerve lesions	Rectum cancer Cervical cancer (multimodal therapy, radiotherapy and surgery) Endometriosis surgery	After APR: 50% urinary retention. After TME: 10-30% voiding dysfunction. Voiding phase dysfunction described. Voiding phase dysfunction if no nerve sparing approach.
Peripheral neuropathy Diabetes Other causes of peripheral neuropathy can cause neuro-urological symptoms: alcohol abuse, lumbosacral zona and genital herpes, Guillain Barré syndrome, porphyria, sarcoidosis.	In Europe, prevalence of pharmacologically treated diabetes ranges from 2.8-3.8%. 50% of patients will develop neuropathy, with 75-100% of these developing neuro-urological symptoms.	"Diabetic Cystopathy"[18, 43]. OAB and DO initially. Hyposensitive and hypocontractile detrusor at later phase.

Disseminated central diseases		
Multiple Sclerosis	<p>Prevalence: 1/1,000 adult in developed country, geographic variation (north > south).</p> <p>First neurological disorder in young adults [44].</p>	<p>80% of patients present neuro-urological symptoms after 10 yrs.</p> <p>10% of MS patients present voiding dysfunction at disease onset.</p> <p>DO due to suprapontine lesions most frequent dysfunction (> 60%).</p> <p>DSD due to spinal cord lesions in 25%.</p> <p>Hypocontractility in 20%.</p> <p>Dysfunction may change during the course of the disease [45].</p>

APR = abdominoperineal resection; DO = detrusor overactivity; DSD = detrusor sphincter dyssynergia; G8 = 8 most developed countries; IPD = idiopathic Parkinson's disease; LUTS = lower urinary tract symptoms; MSA = multi system atrophy; NPH = normal pressure hydrocephalus; OAB = overactive bladder; SCI = spinal cord injury; TME = total mesorectal excision; UUI = urinary urge incontinence.

3B CLASSIFICATION SYSTEMS

3B.1 Introduction

Several national and international guidelines have already been published for the care of patients with neuro-urological disorders [1, 46-48]. The ICS neuro-urological standardisation report [1] deals specifically with the standardisation of terminology and urodynamic investigation in neuro-urological patients. Other relevant definitions are found in the general ICS standardisation report [49].

Section 3B.2 lists the definitions from these references, partly adapted, and other definitions considered useful for clinical practice (Tables 2 and 3). For specific definitions relating to urodynamic investigation, the reader is referred to the appropriate ICS report [1].

3B.2 Definitions

Table 2: Definitions useful in clinical practice

Acontractility, detrusor	See below under voiding phase (Table 3)
Acontractility, urethral sphincter	See below under storage phase (Table 3)
Autonomic dysreflexia	Increase of sympathetic reflex due to noxious stimuli with symptoms or signs of headache, hypertension, flushing face, and perspiration
Capacity	See below under storage phase
Catheterisation, indwelling	Emptying of the bladder by a catheter that is introduced (semi-) permanently
Catheterisation, intermittent (IC)	Emptying of the bladder by a catheter that is removed after the procedure, mostly at regular intervals
• Aseptic IC	The catheters remain sterile, the genitals are disinfected or washed, and disinfecting lubricant might be used
• Clean IC	Disposable or cleansed re-usable catheters, genitals washed
• Sterile IC	Complete sterile setting, including sterile gloves, forceps, gown and mask
• Intermittent self-catheterisation	IC performed by the patient
Compliance, bladder	See below under storage phase
Condition	Evidence of relevant pathological processes
Diary, bladder	Record of times of micturitions and voided volumes, incontinence episodes, pad usage, and other relevant information

• Frequency volume chart (FVC)	Times of micturitions and voided volumes only
• Micturition time chart	Times of micturitions only
Filling rate, physiological	Below the predicted maximum: body weight (kg) /4 in mL/s [2, 50]
Hesitancy	Difficulty in initiating micturition; delay in the onset of micturition after the individual is ready to pass urine
Intermittency	Urine flow stops and starts on one or more occasions during voiding
Leak point pressure	See below under storage phase
Lower motor neuron lesion (LMNL)	Lesion at or below the S1-S2 spinal cord level
NLUTD	LUTD secondary to confirmed pathology of the nervous supply
Observation, specific	Observation made during specific diagnostic procedure
Overactivity, bladder	See below under symptom syndrome (Table 3)
Overactivity, detrusor	See below under storage phase
Rehabilitation, LUT	Non-surgical non-pharmacological treatment for LUTD
Sign	To verify symptoms and classify them
Sphincter, urethral, non-relaxing	See below under voiding phase
Symptom	Subjective indicator of a disease or change in condition, as perceived by the patient, carer, or partner that may lead the patient to seek help from healthcare professionals
Upper motor neuron lesion (UMNL)	Lesion above the S1-S2 spinal cord level
Voiding, balanced: In patients with neurourological disorders	Voiding with physiological detrusor pressure and low residual (< 80 mL or < 20% of bladder volume)
Voiding, triggered	Voiding initiated by manoeuvres to elicit reflex detrusor contraction by exteroceptive stimuli
Volume, overactivity	See below under storage phase

Table 3: Further definitions useful in clinical practice

Storage phase	
Maximum anaesthetic bladder capacity	Maximum bladder filling volume under deep general or spinal anaesthesia
Increased daytime frequency	Self-explanatory; the normal frequency can be estimated at about 8 times per day [51]
Nocturia	Waking at night one or more times to void
Urgency	The symptom of a sudden compelling desire to pass urine that is difficult to defer
Urinary incontinence	Any involuntary leakage of urine
• Stress urinary incontinence	On effort or exertion, or on sneezing or coughing
• Urgency urinary incontinence	Accompanied by or immediately preceded by urgency
• Mixed urinary incontinence	Associated with urgency but also exertion, effort, sneezing, or coughing
• Continuous urinary incontinence	
Bladder sensation	
<i>Normal</i>	
• Symptom and history	Awareness of bladder filling and increasing sensation up to a strong desire to void
• Urodynamics	First sensation of bladder filling, first desire to void, and strong desire to void at realistic bladder volumes
<i>Increased</i>	
• Symptom and history	An early and persistent desire to void
• Urodynamics	Any of the three urodynamic parameters mentioned under 'normal' persistently at low bladder volume
<i>Reduced</i>	
• Symptom and history	Awareness of bladder filling but no definite desire to void
• Urodynamics	Diminished sensation throughout bladder filling
Absent	
No sensation of bladder filling or desire to void	
Non-specific	Perception of bladder filling as abdominal fullness, vegetative symptoms, or spasticity

<i>Definitions valid after urodynamic confirmation only</i>	
Cystometric capacity	Bladder volume at the end of the filling cystometry
• Maximum cystometric capacity	Bladder volume at strong desire to void
• High-capacity bladder	Bladder volume at cystometric capacity far over the mean voided volume, estimated from the bladder diary, with no significant increase in detrusor pressure under non-anaesthetised condition
Normal detrusor function	Little or no pressure increase during filling: no involuntary phasic contractions despite provocation
Detrusor overactivity	Involuntary detrusor contractions during filling; spontaneous or provoked
• Phasic DO	Characteristic phasic contraction
• Terminal DO	A single contraction at cystometric capacity
• High pressure DO	Maximal detrusor pressure > 40 cm H ₂ O [1, 52]
• Overactivity volume	Bladder volume at first occurrence of DO
• Detrusor overactivity incontinence	Self-explanatory
Leak point pressure	
• Detrusor leak point pressure (DLPP)	Lowest value of detrusor pressure at which leakage is observed in the absence of abdominal strain or detrusor contraction
• Abdominal leak point pressure	Lowest value of intentionally increased intravesical pressure that provokes leakage in the absence of a detrusor contraction
Bladder compliance	Relationship between change in bladder volume (ΔV) and change in detrusor pressure (Δp_{det}): $C = \Delta V / \Delta p_{det}$ (mL/cm H ₂ O)
• Low bladder compliance	Compliance $C = \Delta V / \Delta p_{det} < 20$ mL/cm H ₂ O [53]
Break volume	Bladder volume after which a sudden significant decrease in bladder compliance is observed
Urethral sphincter acontractility	No evidence of sphincter contraction during filling, particularly at higher bladder volumes, or during abdominal pressure increase
Voiding phase	
• Slow stream	Reduced urine flow rate
• Intermittent stream (intermittency)	Stopping and starting of urine flow during micturition
• Hesitancy	Difficulty in initiating micturition
• Straining	Muscular effort to initiate, maintain, or improve urinary stream
• Terminal dribble	Prolonged final part of micturition when the flow has slowed to a trickle/dribble
<i>Definitions valid after urodynamic confirmation only</i>	
Normal detrusor function	Voluntarily initiated detrusor contraction that causes complete bladder emptying within a normal time span
Detrusor underactivity	Contraction of reduced strength/duration
Acontractile detrusor	Absent contraction
Non-relaxing urethral sphincter	Self-explanatory
Detrusor sphincter dyssynergia (DSD)	Detrusor contraction concurrent with an involuntary contraction of the urethra and/or periurethral striated musculature
Post-micturition phase	
Feeling of incomplete emptying (symptom only).	
Post-micturition dribble: involuntary leakage of urine shortly after finishing the micturition.	
Pain, discomfort or pressure sensation in the LUT and genitalia that may be related to bladder filling or voiding, may be felt after micturition, or be continuous.	
Symptom syndrome: combination of symptoms	
Overactive bladder syndrome: urgency with or without urgency incontinence, usually with frequency and nocturia.	
Synonyms: urgency syndrome, urgency-frequency syndrome.	

3C DIAGNOSTIC EVALUATION

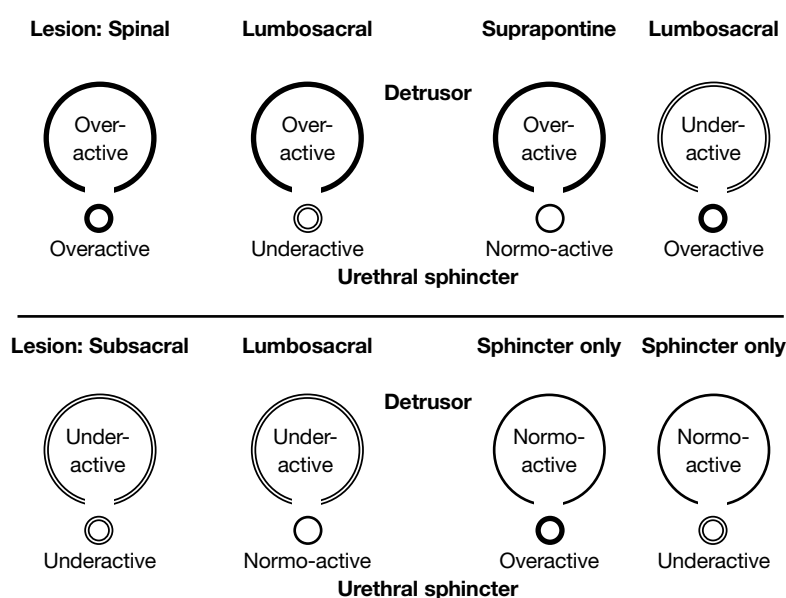
3C.1 Introduction

The normal physiological function of the LUT depends on an intricate interplay between the sensory and motor nervous systems. When diagnosing neuro-urological symptoms, the aim is to describe the type of dysfunction involved. A thorough medical history, physical examination and bladder diary are mandatory before any additional diagnostic investigations can be planned. Results of the initial evaluation are used to decide the patient's long-term treatment and follow-up.

3C.2 Classification systems

Several classification systems for neuro-urological symptoms have been proposed. The Madersbacher [54] (LE: 4) classification describes neuro-urological function in terms of the contraction state of the bladder and external urethral sphincter during filling and voiding phases, which can then be used to decide on the appropriate therapeutic approach [54] (Figure 1).

Figure 1: Madersbacher classification system [54] showing typical neurogenic lesions*



*Adapted from Madersbacher et al.

3C.3 The timing of diagnosis and treatment

Early diagnosis and treatment are essential in both congenital and acquired neuro-urological disorders [55]. This helps to prevent irreversible changes within the LUT, even in the presence of normal reflexes [56, 57] (LE: 3). Furthermore, urological symptoms can be the presenting feature of neurological pathology [58, 59] (LE: 3). Early intervention can prevent irreversible deterioration of the LUT and UUT [60] (LE: 3).

3C.4 Patient history

History taking should include past and present symptoms and disorders (Table 4). It is the cornerstone of evaluation, as the answers will aid in diagnostic investigations and treatment options.

- In non-traumatic neuro-urological patients with a slow insidious onset, history may find that the condition started in childhood or adolescence [61] (LE: 4).
- Urinary history consists of symptoms associated with both urine storage and evacuation.
- Bowel history is important because patients with neuro-urological symptoms may also have a related neuropathic lower gastrointestinal tract [62] (LE: 4).
- Sexual function may be impaired because of the neurological condition.
- Special attention should be paid to possible warning signs and symptoms (e.g. pain, infection, haematuria and fever) requiring further investigation.
- Patients with SCI usually find it difficult to report UTI-related symptoms accurately [1, 63, 64] (LE: 3).

Table 4: History taking in patients with suspected neuro-urological disorders*

Past history
Childhood through to adolescence and in adulthood
Hereditary or familial risk factors
Menarche (age); this may suggest a metabolic disorder
Obstetric history
History of diabetes; in some cases, correction will resolve the neurological problem
Diseases, e.g. syphilis, parkinsonism, multiple sclerosis, encephalitis
Accidents and operations, especially those involving the spine and central nervous system
Present history
Present medication
Lifestyle (smoking, alcohol and drugs); may influence urinary, sexual and bowel function
Quality of life
Specific urinary history
Onset of urological history
Relief after voiding; to detect the extent of a neurological lesion in the absence of obstructive uropathy
Bladder sensation
Initiation of micturition (normal, precipitate, reflex, strain, Credé)
Interruption of micturition (normal, paradoxical, passive)
Enuresis
Mode and type of voiding (catheterisation)
Frequency, volumes voided, incontinence, urge episodes
Bowel history
Frequency and faecal incontinence
Desire to defecate
Defecation pattern
Rectal sensation
Initiation of defecation (digitation)
Sexual history
Genital or sexual dysfunction symptoms
Sensation in genital area
Specific male: erection, (lack of) orgasm, ejaculation
Specific female: dyspareunia, (lack of) orgasm
Neurological history
Acquired or congenital neurological condition
Mental status and comprehension
Neurological symptoms (somatic and sensory), with onset, evolution and any treatment
Spasticity or autonomic dysreflexia (especially in lesions at or above level Th 6)
Mobility and hand function

* Adapted from Bors and Turner [61] (LE: 4; GR: C) and Stöhrer et al. [1] (LE: 4; GR: C).

3C.4.1 Bladder diaries

Bladder diaries provide data on the number of voids, volume voided, pad weight, incontinence and urge episodes. Although a 24-hour bladder diary (recording should be done for three consecutive days) is reliable in women with UI [65, 66] (LE: 3) and helpful in IC [1] (LE: 4), no research has been done on bladder diaries in neuro-urological patients. Nevertheless, bladder diaries are considered a valuable diagnostic tool.

3C.5 Quality of life

An assessment of the patient's present and expected future quality of life (QoL) is important to evaluate the effect of any therapy (or refrained from using) on this parameter. Despite the limitations associated with neurological diseases, adequate treatment with social independence is possible in most patients.

QoL is a very important aspect of the overall management of neuro-urological patients, e.g. to evaluate treatment related changes on a patient's QoL [67] (LE: 2a). The type of bladder management has been shown to affect health-related QoL (HRQoL) in patients with SCI [68]. Other research has also highlighted the importance of urological treatment and its impact on the urodynamic functionality of the neuro-urological patient in determining patient QoL [69].

QoL is related to an individual's ability to cope with a new life situation [70]. QoL can be influenced by several factors, including family support, coping ability, productivity, self-esteem, financial stability, education, and the physical and social environment [71] (LE: 3). Age, sex, ethnicity and the patient's acceptance of the condition also need to be considered when assessing QoL [72] (LE: 3).

Although several questionnaires have been developed to assess QoL, there are no specific QoL questionnaires for the neuro-urological patient. However, a validated specific tool for QoL in SCI and MS patients (Qualiveen®) appears to be a discriminative evaluation instrument [69, 73, 74]. A short-form is available [75] and various validated translations [76-79].

A patient's QoL can be assessed secondarily by generic HRQoL questionnaires, including the Incontinence Quality of Life Instrument (I-QOL), King's Health Questionnaire (KHQ), Short Form 36 Health Survey Questionnaire (SF-36), Euro Quality of Life-5 Domains (EQ-5D), Short Form 6D Health Survey Questionnaire (SF-6D), or the Health Utilities Index (HUI). In addition, the quality-adjusted life year (QALY) quantifies outcomes by weighing years of life spent in a specified health state by a factor representing the value placed by society or patients on the specific health state [80] (LE: 3).

3C.5.1 Recommendations

Recommendations	GR
Quality of life should be assessed when evaluating and treating the neuro-urological patient.	B
The available validated tools are Qualiveen®, a specific long-form and short-form tool for spinal cord lesion and multiple sclerosis patients. In addition, generic (SF-36) or specific tools for incontinence (I-QOL) questionnaires can be used.	B

I-QOL = incontinence quality of life instrument.

3C.6 Physical examination

In addition to a detailed patient history, attention should be paid to possible physical and mental handicaps with respect to the planned investigation. Neurological status should be described as completely as possible (Figure 1). Patients with very high neurological lesions may suffer from a significant drop in blood pressure when moved into a sitting or standing position. All sensations and reflexes in the urogenital area must be tested. Furthermore, detailed testing of the anal sphincter and pelvic floor functions must be performed (Figure 2). It is essential to have this clinical information to reliably interpret later diagnostic investigations.

3C.6.1 Autonomic dysreflexia

Autonomic dysreflexia (AD) is a sudden and exaggerated autonomic response to various stimuli in patients with SCI or spinal dysfunction. It can present in any type of suprasacral lesion but generally manifests above level Th 5-Th 6. The stimulus can be distended bladder or bowel. It can also be secondary to a noxious stimulus, e.g. infected toe nail or pressure sore. Hypertension is a relatively common manifestation of AD and can have life-threatening results if not properly managed [81-83] (LE: 3; GR: C).

Figure 2: The neurological status of a patient with neuro-urological symptoms must be described as completely as possible: (a) dermatomes of spinal cord levels L2-S4; (b) urogenital and other reflexes in the lower spinal cord.

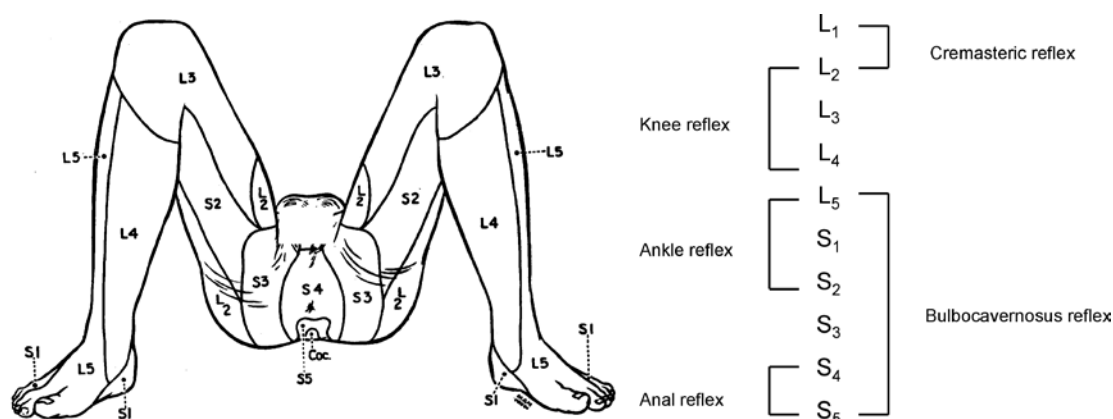


Table 5: Neurological items to be specified*

Sensations S2-S5 (both sides)
Presence (increased/normal/reduced/absent)
Type (light touch/pin prick)
Affected dermatomes
Reflexes (increased/normal/reduced/absent)
Bulbocavernosus reflex
Perianal/anal reflex
Knee and ankle reflexes
Plantar responses (Babinski)
Anal sphincter tone
Presence (increased/normal/reduced/absent)
Voluntary contractions of anal sphincter and pelvic muscles (increased/normal/reduced/absent)
Prostate palpation
Descensus (prolapse) of pelvic organs

*Adapted from Stöhrer et al. [1] (LE: 4; GR: C).

3C.6.2 Recommendations for history taking and physical examination*

History taking	GR
An extensive general history is mandatory, concentrating on past and present symptoms including urinary, sexual, bowel, and neurological functions.	A
Special attention should be paid to the possible existence of alarm signs, e.g. pain, infection, haematuria, fever, that warrant further specific diagnosis.	A
A specific history should be taken for each of the four mentioned functions.	A
Physical examination	
Individual patient handicaps should be acknowledged in planning further investigations.	A
The neurological status should be described as completely as possible. Sensations and reflexes in the urogenital area must all be tested.	A
The anal sphincter and pelvic floor functions must be tested.	A
Urinalysis, blood chemistry, bladder diary, residual and free flowmetry, incontinence quantification and urinary tract imaging should be performed.	A

* All grade A recommendations are based on panel consensus.

3C.7 Urodynamics

3C.7.1 Introduction

Urodynamic investigation is the only method that can objectively assess the (dys-) function of the LUT. In these patients, the invasive urodynamic investigation is even more provocative than in general patients. Any technical source of artifacts must be critically considered. It is essential to maintain the quality of the urodynamic

recording and its interpretation [2]. Same session repeat urodynamic investigations can be helpful in clinical decision making, since repeat measurements may yield completely different results [84].

In patients at risk for AD, it is advisable to measure blood pressure during the urodynamic study. The rectal ampulla should be empty of stool before the start of the investigation. All urodynamic findings must be reported in detail and performed, according to ICS technical recommendations and standards [1, 2, 85].

3C.7.2 **Urodynamic tests**

Free uroflowmetry and assessment of residual urine: This provides a first impression of the voiding function and is compulsory prior to planning any invasive urodynamics. For reliable information, it should be repeated at least 2-3 times [1, 2]. Possible pathological findings include a low flow rate, low voided volume, intermittent flow, hesitancy and residual urine. Care must be taken when assessing the results in patients unable to void in a normal position, as both flow pattern and rate may be modified by inappropriate positions.

Filling cystometry: This is the only method for quantifying the filling function (undertaken at a very slow rate ~20 mL/min). The status of LUT function must be documented during the filling phase. However, this technique has limited use as a solitary procedure. It is much more effective combined with bladder pressure measurement during micturition and even more effective in video-urodynamics.

The bladder should be empty at the start of filling. A physiological filling rate should be used with body-warm saline, as fast filling and room-temperature saline are provocative. Possible pathological findings include DO, low bladder compliance, abnormal bladder sensations, incontinence, and an incompetent or relaxing urethra.

Detrusor leak point pressure (DLPP) [52]: This appears to have no use as a diagnostic tool. Some positive findings have been reported [86, 87], but sensitivity is too low to estimate the risk to the UUT or for secondary bladder damage [88].

Pressure flow study: This reflects the co-ordination between detrusor and urethra or pelvic floor during the voiding phase. It is even more powerful if combined with filling cystometry and with video-urodynamics. LUT function must be recorded during the voiding phase. Possible pathological findings include detrusor hypocontractility, DSD, a high urethral resistance, and residual urine.

Most types of obstruction caused by neuro-urological disorders are due to DSD [89, 90], non-relaxing urethra, or non-relaxing bladder neck [1, 91, 92]. Pressure-flow analysis mostly assesses the amount of mechanical obstruction caused by the urethra's inherent mechanical and anatomical properties and has limited value in patients with neuro-urological disorders.

Electromyography (EMG): This reflects the activity of the external urethral sphincter, the peri-urethral striated musculature, the anal sphincter, and the striated pelvic floor muscles. Correct interpretation may be difficult due to artefacts introduced by other equipment. In the urodynamic setting, an EMG is useful as a gross indication of the patient's ability to control the pelvic floor. Possible pathological findings include inadequate recruitment upon specific stimuli (e.g. bladder filling, hyper-reflexive contractions, onset of voiding, coughing, Valsalva manoeuvre) suggesting a diagnosis of DSD.

Urethral pressure measurement: This has a very limited role in neuro-urological disorders. There is no consensus on parameters indicating pathological findings [93].

Video-urodynamics: This is the combination of filling cystometry and pressure flow study with imaging. It is the gold standard for urodynamic investigation in neuro-urological disorders [1]. Possible pathological findings include all those described in the cystometry and the pressure flow study sections, and any morphological pathology of the LUT and UUT.

Ambulatory urodynamics: This is the functional investigation of the urinary tract, which uses the predominantly natural filling of the urinary tract to reproduce the patient's normal activity [94]. Although this type of study might be considered when conventional urodynamics do not reproduce the patient's symptoms, the role in the neuro-urological patient needs to be determined.

Provocative tests during urodynamics: LUT function can be provoked by coughing, triggered voiding, or anal stretch. Fast-filling cystometry with cooled saline (the 'ice water test') will discriminate between upper and lower motor neuron lesions (UMNL/LMNL) [95, 96]. Patients with UMNL develop a detrusor contraction if the detrusor muscle is intact, while patients with LMNL do not. However, the test gives false-positive results in young children [97] and does not seem to fully discriminative in other types of patient [98].

Previously, a positive bethanechol test [99] (detrusor contraction > 25 cm H₂O) was thought to indicate detrusor denervation hypersensitivity and the muscular integrity of an acontractile detrusor. However, in practice, the test has given equivocal results. A variation of this method was reported using intravesical electromotive administration of the bethanechol [100], but there was no published follow-up.

3C.7.3 **Specialist uro-neurophysiological tests**

The following tests are advised as part of the neurological work-up:

- Electromyography (in a neurophysiological setting) of pelvic floor muscles, urethral sphincter and/or anal sphincter;
- Nerve conduction studies of pudendal nerve;
- Reflex latency measurements of bulbocavernosus and anal reflex arcs;
- Evoked responses from clitoris or glans penis;
- Sensory testing on bladder and urethra.

Other elective tests for specific conditions may become obvious during the work-up and urodynamic investigations.

3C.7.4 **Recommendations for urodynamics and uro-neurophysiology**

Recommendations	GR
The recording of a bladder diary is advisable.	A
Non-invasive testing is mandatory before invasive urodynamics is planned.	A
Urodynamic investigation is necessary to detect and specify lower urinary tract (dys-) function and help with formulating a management plan.	A
Same session repeat measurement can be helpful in clinical decision making.	C
Video-urodynamics is the gold standard for invasive urodynamics in neuro-urological patients. If this is not available, then a filling cystometry continuing into a pressure flow study should be performed.	A
A physiological filling rate and body-warm saline should be used.	A
Specific uro-neurophysiological tests are elective procedures.	C

3C.7.5 **Typical manifestations of neuro-urological disorders**

Table 6 lists typical signs indicating further neurological evaluation, as neuro-urological symptoms may be the presenting symptom [59].

Table 6: Typical findings in neuro-urological disorders

Filling phase
Hyposensitivity or hypersensitivity
Vegetative sensations
Low compliance
High-capacity bladder
Detrusor overactivity, spontaneous or provoked
Sphincter underactivity
Voiding phase
Detrusor underactivity or acontractility
Detrusor sphincter dyssynergia
Non-relaxing urethra
Non-relaxing bladder neck

3C.8 **Renal function**

In many patients with neuro-urological disorders, the UUT is at risk, particularly in patients who develop high detrusor pressure during the filling phase. Although effective treatment can reduce this risk, there is still a relatively high incidence of renal morbidity [56].

Caregivers must be informed of this condition and instructed to watch carefully for any signs or symptoms of a possible deterioration in the patient's renal function. If necessary, the renal function should be checked regularly.

3D DISEASE MANAGEMENT

3D.1 Introduction

The primary aims for treatment of neuro-urological symptoms and their priorities are [101, 102]:

- protection of the UUT;
- achievement of urinary continence;
- restoration of (parts of) the LUT function;
- improvement of the patient's QoL.

Further considerations are the patient's disability, cost-effectiveness, technical complexity, and possible complications [102].

Renal failure is the main mortality factor in SCI patients who survive the trauma [9, 103, 104].

Keeping the detrusor pressure during both the filling and voiding phases within safe limits significantly reduces the mortality from urological causes in these patients [105, 106] and has consequently become the golden rule in the treatment of patients with neuro-urological symptoms [101, 102].

In patients with high detrusor pressure during the filling phase (DO, low bladder compliance), treatment is aimed primarily at "conversion of an active, aggressive high-pressure bladder into a passive low-pressure reservoir" despite the resulting residual urine [101]. Reduction of the detrusor pressure contributes to urinary continence, and consequently to social rehabilitation and QoL. It is also pivotal in preventing UTI [9, 104]. Complete continence can however not always be obtained.

3D.2 Non-invasive conservative treatment

3D.2.1 Assisted bladder emptying - Credé manoeuvre, Valsalva manoeuvre, triggered reflex voiding

Incomplete bladder emptying is a serious risk factor for UTI, high intravesical pressure during the filling phase, and incontinence. Methods to improve the voiding process are therefore practiced.

Bladder expression (Credé manoeuvre) and voiding by abdominal straining (Valsalva manoeuvre): The downwards movement of the lower abdomen by suprapubic compression (Credé) or by abdominal straining (Valsalva) leads to an increase in intravesical pressure, and generally also causes a reflex sphincter contraction [107, 108]. The latter may increase bladder outlet resistance and lead to inefficient emptying. The high pressures created during these procedures are hazardous for the urinary tract [109, 110]. Their use should therefore be discouraged unless urodynamics show that the intravesical pressure remains within safe limits [107, 110-113].

Long-term complications are unavoidable for both methods of bladder emptying [108]. The already weak pelvic floor function may be further impaired, thus introducing or exacerbating already existing stress urinary incontinence (SUI) [110].

Triggered reflex voiding: Stimulation of the sacral or lumbar dermatomes in patients with UMNLS can elicit a reflex detrusor contraction [110]. The risk of high pressure voiding is present and interventions to decrease outlet resistance may be necessary [114]. Triggering can induce AD in patients with high level SCI (above Th 6) [115]. All assisted bladder emptying techniques require low outlet resistance. Even then, high detrusor pressures may still be present. Patients hence need dedicated education and close urodynamic and urological surveillance [110, 111, 113, 116].

Note: In the literature, including some of the references cited here, the concept "reflex voiding" is sometimes used to cover all three assisted voiding techniques described in this section.

External appliances: Social continence may be achieved by collecting urine during incontinence, for instance using pads [101, 117]. Condom catheters with urine collection devices are a practical method for men [117]. The infection risk must be closely observed [117]. The penile clamp is absolutely contraindicated in case of DO or low bladder compliance because of the risk of developing high intravesical pressure, and in case of significant reflux.

3D.2.2 Lower urinary tract rehabilitation

3D.2.2.1 Bladder rehabilitation including electrical stimulation

The term bladder rehabilitation summarises treatment options that aim to re-establish bladder function in patients with neuro-urological symptoms. Strong contraction of the urethral sphincter and/or pelvic floor, as well as anal dilatation, manipulation of the genital region, and physical activity inhibit micturition in a reflex manner [117, 118]. The first mechanism is affected by activation of efferent nerve fibres, and the latter ones are produced by activation of afferent fibres [88]. Electrical stimulation of the pudendal nerve afferents strongly inhibits the micturition reflex and detrusor contraction [119]. This stimulation might then support the restoration

of the balance between excitatory and inhibitory inputs at the spinal or supraspinal level [117, 120, 121]. Evidence for bladder rehabilitation using electrical stimulation in neurological patients is mainly based on pilot studies with small patient numbers.

Peripheral temporary electrostimulation: Percutaneous tibial nerve stimulation and external (e.g. penile/clitoral or intracavitary) temporary electrical stimulation suppress neurogenic DO during acute stimulation [122, 123]. Both techniques have also demonstrated sustained effects in patients with MS [124-126]. LUT function remained improved 2 years after transcutaneous electrical stimulation of the bladder in patients with SCI [127]. Electrostimulation also improved continence in children with MMC [128].

In MS patients, combining active neuromuscular electrical stimulation with pelvic floor muscle training and EMG biofeedback can achieve a substantial reduction of neuro-urological symptoms [129]. Furthermore, this treatment combination is significantly superior to electrostimulation alone. Biofeedback can be used for supporting the alleviation of neuro-urological symptoms [130].

Intravesical electrostimulation: Intravesical electrostimulation can increase bladder capacity and improve bladder compliance and bladder filling sensation in patients with incomplete SCI or MMC [131]. In patients with neurogenic detrusor underactivity, intravesical electrostimulation may also improve voiding and reduce residual volume [132, 133].

Chronic peripheral pudendal stimulation: A pilot study in patients with incomplete SCI showed that chronic peripheral pudendal stimulation (defined as 15 min, twice daily, during two weeks) may produce neuromodulatory effects in the brain. These effects are correlated with clinical improvement [134]. Semiconditional electrical stimulation of the dorsal penile nerve during 14-28 days improved bladder storage function in patients with SCI [135].

Repetitive transcranial magnetic stimulation: Although improvement of neuro-urological symptoms has been described in PD and MS patients, this technique is still under investigation [136, 137].

Summary: To date, bladder rehabilitation techniques are mainly based on electrical or magnetic stimulation. However, there is a lack of well-designed studies.

3D.2.3 **Drug treatment**

A single, optimal, medical therapy for neuro-urological symptoms is not yet available. Commonly, a combination of different therapies (e.g. intermittent catheterisation and antimuscarinic drugs) is advised to prevent urinary tract damage and improve long-term outcomes, particularly in patients with SCI with a suprasacral lesion or MS [110, 138-142].

3D.2.3.1 *Drugs for treatment of storage neuro-urological symptoms*

Antimuscarinic drugs: They are the first-line choice for treating neurogenic detrusor overactivity (NDO), increasing bladder capacity, reducing episodes of urinary incontinence secondary to NDO by the inhibition of parasympathetic pathways [5, 143-149].

Although antimuscarinic drugs have been used for many years to treat patients with NDO, the evidence is still limited [145, 146, 150], and the responses of individual patients to antimuscarinic treatment are variable. Only a recent meta-analysis has confirmed the clinical and urodynamic efficacy of antimuscarinic therapy compared to placebo in adult NDO [146]. In children, only oxybutynin is approved, despite prospective trials supporting the efficacy and tolerability of tolterodine, propiverine and solifenacin [151-153]. A prospective randomised study using fesoterodine in children with NDO is ongoing [154].

Higher doses or a combination of antimuscarinic agents may be an option to maximise outcomes in neurological patients [138, 140, 155-158] (LE: 3). However, these drugs have a high incidence of adverse events, which may lead to early discontinuation of therapy [146, 155, 157]. Dry mouth is the most frequent side effect.

Choice of antimuscarinic agent: Oxybutynin [5, 138, 140, 144-146, 149, 155, 156, 159-161], trospium [146, 157, 162], tolterodine [151, 163, 164] and propiverine [5, 146, 160, 165-168] are established, effective and well tolerated treatments even in long-term use (LE: 1a).

Darifenacin and solifenacin have been evaluated recently in NDO secondary to SCI and MS [146, 169-172] with results similar to other antimuscarinic drugs. A study using solifenacin in NDO due to Parkinson's disease is currently suspended [173]. The relatively new fesoterodine, an active metabolite of tolterodine, has also been introduced, even though to date there has been no published clinical evidence of its use in the treatment of neuro-urological disorders.

Side effects: Controlled release antimuscarinics have some minor side effects, e.g. dry mouth. It has been suggested that different ways of administration may help to reduce side effects. In a selected group of patients, transdermal oxybutynin was found to be well tolerated and effective [174-176]. Instead, although there are several studies reporting the efficacy and safety of intravesical oxybutynin, there are no standard protocols yet for its use [177-179]. Therefore, further research is needed into the use of alternative methods of administration, particularly long-term results (LE: 1b).

Other agents

Phosphodiesterase inhibitors (PDE5Is): In vivo and pilot studies seem to support that PDE5Is may become an alternative or adjunct to antimuscarinic treatment for NDO [180-182].

Beta₃-adrenergic receptor agonist: They have recently been introduced and evaluated in OAB, but clinical experience in neuro-urological patients is limited. Studies on safety and effectiveness in NDO are ongoing. In the future, combined therapy with antimuscarinics may be an attractive option [183-185].

3D.2.3.2 Drugs for voiding neuro-urological symptoms

Detrusor underactivity: Cholinergic drugs, such as bethanechol and distigmine, have been considered to enhance detrusor contractility and promote bladder emptying, but are not routinely used in clinical practice [186]. Only preclinical studies have documented the potential benefits of cannabinoid agonists on improving detrusor contractility administered intravesically [187, 188]. Conversely, a randomised controlled study on the use of oromucosal nabixinols (an endocannabinoid modulator), did not report any significant reduction of incontinence episodes in MS patients, although a statistically significant improvement in frequency, urgency and nocturia was documented [189].

Decreasing bladder outlet resistance: α -blockers (e.g. tamsulosin and naftopidil) seem to be effective for decreasing bladder outlet resistance, postvoid residual and autonomic dysreflexia [49]. Combination therapy with a cholinergic drug and an α -blocker appears to be more useful than monotherapy with either agent [190, 191].

Increasing bladder outlet resistance: Several drugs have shown efficacy in selected cases of mild stress urinary incontinence, but there are no high level evidence studies in neurological patients [149].

3D.2.4 Recommendations for drug treatments

Recommendations	LE	GR
For NDO, antimuscarinic therapy is the recommended first-line medical treatment.	1a	A
Alternative routes of administration (i.e., transdermal or intravesical) of antimuscarinic agents may be used.	2	A
Outcomes for NDO may be maximised by considering a combination of antimuscarinic agents.	3	B
To decrease bladder outlet resistance, alpha-blockers could be prescribed.	1b	A
For underactive detrusor, no parasympathomimetics should be prescribed.	1a	A
In neurogenic stress urinary incontinence, drug treatment should not be prescribed.	4	A

NDO = neurogenic detrusor overactivity.

3D.2.5 Minimal invasive treatment

3D.2.5.1 Catheterisation

Intermittent self- or third-party catheterisation [192, 193] is the preferred management for neuro-urological patients who cannot effectively empty their bladders [101, 117].

Sterile IC, as originally proposed by Guttman and Frankel [192], significantly reduces the risk of UTI and/or bacteriuria [117, 159, 194, 195] compared with clean IC introduced by Lapides et al. [193]. However, it cannot be considered a routine procedure [117, 195].

Aseptic IC is an alternative [101, 196] that provides a significant benefit by reducing external contamination of the catheter [197-199]. Contributing factors to contamination are insufficient patient education and the inherently greater risk of UTI in neuro-urological patients [117, 198, 200-202]. The average frequency of catheterisations per day is 4-6 times [203] and the catheter size most often used are between 12-16 Fr. In aseptic IC, an optimum frequency of 5 times showed a reduction of UTI [203]. Ideally, bladder volume at catheterisation should, as a rule, not exceed 400-500 mL.

Indwelling transurethral catheterisation and, to a lesser extent, suprapubic cystostomy are associated with a range of complications as well as an enhanced risk for UTI [112, 117, 204-211]. Both

procedures should therefore be avoided when possible.

Silicone catheters are preferred because they are less susceptible to encrustation and because of the high incidence of latex allergy in the neuro-urological patient population [212].

Recommendations for catheterisation

Recommendations	LE	GR
Intermittent catheterisation - whenever possible aseptic technique - should be used as a standard treatment for patients who are unable to empty their bladder.	3	A
Patients must be well instructed in the technique and risks of IC.	3	A
The catheter size should be 12-16 Fr.	4	B
Whenever possible, indwelling transurethral and suprapubic catheterisation should be avoided.	3	A

IC = intermittent catheterisation.

3D.2.5.2 Intravesical drug treatment

To reduce DO, anticholinergics can also be applied intravesically [213-216]. This approach may reduce adverse effects because the anticholinergic drug is metabolised differently [214] and a greater amount is sequestered in the bladder, even more than with electromotive administration [213].

The vanilloids, capsaicin and resiniferatoxin, desensitise the C-fibres and thereby decrease DO for a period of a few months until the sensation of these fibres has been restored [217-219]. The dosage is 1-2 mMol capsaicin in 100 mL 30% alcohol, or 10-100 nMol resiniferatoxin in 100 mL 10% alcohol for 30 minutes. Resiniferatoxin has about a 1,000-fold potency compared to capsaicin, with less pain during the instillation, and is effective in patients refractory to capsaicin. Clinical studies have shown that resiniferatoxin has limited clinical efficacy compared to botulinum toxin A (BTX-A) injections in the detrusor [218].

3D.2.5.3 Intravesical electrostimulation

Intravesical electrostimulation [220] enhances the sensation for bladder filling and urge to void and may restore the volitional control of the detrusor [221, 222]. Daily stimulation sessions of 90 minutes with 10 mA pulses of 2 ms duration at a frequency of 20 Hz [132, 222] are used for at least 1 week [132]. It appears that patients with peripheral lesions are the best candidates, that the muscle must be intact, and that at least some afferent connection between the detrusor and the brain must still be present [132, 222]. Also, the positioning of the stimulating electrodes and bladder filling are important parameters [223]. With these precautions, the results in the literature are still not unequivocal: both positive [131, 132, 221, 224] and negative [225, 226] (LE: 3) results have been reported.

3D.2.5.4 Botulinum toxin injections in the bladder

BTX-A causes a long-lasting but reversible chemical denervation that lasts for about 9 months [12, 227]. The toxin injections are mapped over the detrusor in a dosage that depends on the preparation used. BTX-A has been proven effective in patients with neuro-urological disorders in phase III RCTs [228-230]. Repeated injections seem to be possible without loss of efficacy [12, 230, 231]. Generalised muscular weakness is an occasional adverse effect [12, 229, 231]. Histological studies have not found ultrastructural changes after injection [232].

3D.2.5.5 Bladder neck and urethral procedures

Reduction of the bladder outlet resistance may be necessary to protect the UUT. This can be achieved by chemical denervation of the sphincter or by surgical interventions (bladder neck or sphincter incision or urethral stent). Incontinence may result and can be managed by external devices (see Section 3D.2.1).

BTX-A: This can be used to treat detrusor sphincter dyssynergia effectively by injection at a dose that depends on the preparation used. The dyssynergia is abolished for a few months, necessitating repeat injections. The efficacy of this treatment has been reported to be high and with few adverse effects [233-235]. However, a recent Cochrane report concluded that because of limited evidence future RCTs assessing the effectiveness of BTX injections also need to address the uncertainty about the optimal dose and mode of injection [236]. In addition, this therapy is not registered.

Balloon dilatation: Favourable immediate results were reported [237], but there are no further reports since 1994 so this method is no longer recommended.

Sphincterotomy: By staged incision, bladder outlet resistance can be reduced without completely losing the

closure function of the urethra [101, 117, 228]. Different techniques are used, and laser treatment appears to be advantageous [238, 239]. Sphincterotomy needs to be repeated at regular intervals in many patients [240], but it is efficient and does not cause severe adverse effects [101, 237]. Secondary narrowing of the bladder neck may occur, for which combined bladder neck incision might be considered [241].

Bladder neck incision: This is indicated only for secondary changes at the bladder neck (fibrosis) [101, 238]. This procedure is not recommended in patients with detrusor hypertrophy, which causes thickening of the bladder neck [101].

Stents: Implantation of urethral stents results in continence being dependent on adequate closure of the bladder neck [102]. The results are comparable with sphincterotomy and the stenting procedure has a shorter duration of surgery and hospital stay [242, 243]. However, the costs [101], possible complications and re-interventions [244, 245] are limiting factors in its use [246-249].

Increasing bladder outlet resistance: This can improve the continence condition. Despite early positive results with urethral bulking agents, a relative early loss of continence is reported in patients with neuro-urological disorders [102, 250, 251].

Urethral inserts: Urethral plugs or valves for management of (female) stress incontinence have not been applied in neuro-urological patients. The experience with active pumping urethral prosthesis for treatment of the underactive or acontractile detrusor was disappointing [252].

3D.2.5.6 Recommendations for minimal invasive treatment*

Recommendations	GR
Botulinum toxin injection in the detrusor is the most effective minimally invasive treatment to reduce neurogenic detrusor overactivity.	A
Bladder neck incision is effective in a fibrotic bladder neck.	B

*Recommendations for catheterisation are listed separately under Section 3D.2.5.1

3D.2.6 Surgical treatment

3D.2.6.1 Urethral and bladder neck procedures

Increasing the bladder outlet resistance has the inherent risk of causing high intravesical pressure during filling, which may become even higher during the voiding phase. Procedures to treat sphincteric incontinence are suitable only when the detrusor activity is, or can be, controlled, when no significant reflux is present. Moreover, these procedures require the urethra and bladder neck to be in good condition and mostly result in IC being performed after the procedure [102].

Urethral sling: Various materials have been used for this procedure with enduring positive results. The procedure is established in women with the ability to self-catheterise [102, 253-258]. In men there are a growing number of reports suggesting that both autologous and synthetic slings may also be an alternative [259-261].

Artificial urinary sphincter: This device has stood the test of time in patients with neuro-urological disorders [102]. It was introduced by Light and Scott [262] for this patient group, and the need for revisions [263] has decreased significantly with new generations of devices allowing one to obtain an acceptable long-term outcome [264-270].

Functional sphincter augmentation: By transposing the gracilis muscle to the bladder neck [271] or proximal urethra [272], there is a possibility of creating a functional autologous sphincter by electrical stimulation [271-273]. This opens the possibility of restoring control over the urethral closure.

Bladder neck and urethra reconstruction: The classical Young-Dees-Leadbetter [274] procedure for bladder neck reconstruction in children with bladder exstrophy, and Kropp urethra lengthening [275] improved by Salle [276], are established methods to restore continence provided that IC is practiced and/or bladder augmentation is performed [277].

Urethral inserts: See section 3D.2.5.5.

3D.2.6.2 Denervation, deafferentation, sacral neuromodulation

Sacral rhizotomy, also known as sacral deafferentation, has achieved some success in reducing detrusor overactivity [278-280], but nowadays, it is used mostly as an adjuvant to sacral anterior root stimulation (SARS) [281-285]. Alternatives to rhizotomy are sought in this treatment combination [286-288].

SARS is aimed at producing detrusor contraction. The technique was developed by Brindley [289] and is only applicable to complete lesions above the implant location, because its stimulation amplitude is over the pain threshold. The urethral sphincter efferents are also stimulated, but because the striated muscle relaxes faster than the smooth muscle of the detrusor, so-called "post-stimulus voiding" occurs. This approach has been successful in highly selected patients [282, 290, 291]. By changing the stimulation parameters, this method can also induce defecation or erection.

Sacral neuromodulation (SNM) [292] might be effective and safe for treating neuro-urological symptoms but there is a lack of RCTs and it is unclear which neurological patient is most suitable [293].

3D.2.6.3 Bladder covering by striated muscle

When the bladder is covered by striated muscle that can be stimulated electrically, or ideally that can be contracted voluntarily, voiding function can be restored to an acontractile bladder. The rectus abdominis [294] and latissimus dorsi [295] have been used successfully in patients with neuro-urological symptoms [296, 297].

3D.2.6.4 Bladder augmentation

The aim of auto-augmentation (detrusor myectomy) is to reduce detrusor overactivity or improve low bladder compliance. The advantages are: low surgical burden, low rate of long-term adverse effects, positive effect on patient QoL, and it does not preclude further interventions [101, 102, 298-304].

Replacing or expanding the bladder by intestine or other passive expandable coverage will reduce bladder compliance and at least reduce the pressure effect of detrusor overactivity [305]. Inherent complications associated with these procedures are: recurrent infection, stone formation, perforation or diverticula, possible malignant changes, and for intestine metabolic abnormality, mucus production and impaired bowel function [102, 306-308]. The procedure should be used with caution in patients with neuro-urological symptoms, but may become necessary if all less-invasive treatment methods have failed.

Bladder augmentation is a valid option to decrease detrusor pressure and increase bladder capacity, whenever more conservative approaches have failed. Several different techniques have been published, with comparable and satisfactory results [300, 309-317]. Bladder substitution to create a low-pressure reservoir is indicated in patients with a severely thick and fibrotic bladder wall [318, 319].

3D.2.6.5 Urinary diversion

When no other therapy is successful, urinary diversion must be considered for the protection of the UUT and for the patient's QoL [102, 320].

Continent diversion: This should be the first choice for urinary diversion. Patients with limited dexterity may prefer a stoma instead of using the urethra for catheterisation [102]. A continent stoma is created using various techniques. However, all of them have frequent complications, including leakage or stenosis [102, 321]. The short-term continence rates are > 80% and good protection of the UUT is achieved [102, 322-330]. For cosmetic reasons, the umbilicus is often used for the stoma site [326, 329-336].

Incontinent diversion: If catheterisation is impossible, incontinent diversion with a urine-collecting device is indicated. Ultimately, it could be considered in patients who are wheelchair bound or bed-ridden with intractable and untreatable incontinence, in patients with LUT destruction, when the UUT is severely compromised, and in patients who refuse other therapy [102]. An ileal segment is used for the deviation in most cases [102, 337-341].

Undiversion: Long-standing diversions may be successfully undiverted or an incontinent diversion changed to a continent one with the emergence of new and better techniques for control of detrusor pressure and incontinence [102]. The patient must be carefully counselled and must comply meticulously with the instructions [102]. Successful undiversion can then be performed [342].

Recommendations	LE	GR
In order to treat refractory detrusor overactivity, bladder augmentation is recommended. Detrusor myectomy is an acceptable alternative in highly selected cases.	3	A
In female patients with neurogenic stress urinary incontinence who are able to self-catheterise, placement of an autologous urethral sling should be used.	4	B
In male patients with neurogenic stress urinary incontinence, artificial urinary sphincter should be used.	3	A

3E URINARY TRACT INFECTION IN NEURO-UROLOGICAL PATIENTS

3E.1 Epidemiology, aetiology and pathophysiology

Urinary tract infection (UTI) is the onset of signs and/or symptoms accompanied by laboratory findings of a UTI (bacteriuria, leukocyturia and positive urine culture) [343]. There are no evidence-based cutoff values for the quantification of these findings. The published consensus is that a significant bacteriuria in persons performing IC is present with $> 10^2$ colony-forming units (cfu)/mL, $> 10^4$ cfu/mL in clean-void specimens and any detectable concentration in suprapubic aspirates. Regarding leukocyturia, 10 or more leukocytes in centrifuged urine samples per microscopic field (400x) are regarded as significant [343].

Individuals with neuro-urolological symptoms, especially those with SCI, may have other signs and symptoms in addition to or instead of traditional signs and symptoms of a UTI in able-bodied individuals. Other problems, such as autonomic dysreflexia, may develop or worsen due to a UTI [344]. The most common signs and symptoms suspicious of a UTI in those with neuro-urolological disorders are fever, new onset or increase in incontinence, including leaking around an indwelling catheter, increased spasticity, malaise, lethargy or sense of unease, cloudy urine with increased urine odour, discomfort or pain over the kidney or bladder, dysuria, or autonomic dysreflexia [344, 345].

3E.2 Diagnostic evaluation

The gold standard for diagnosis is urine culture and urinalysis. A dipstick test may be more useful to exclude than to prove UTI [346, 347]. As bacterial strains and resistance patterns in persons with neuro-urolological disorders may differ from those of able-bodied patients, microbiologic testing is mandatory [348].

3E.3 Disease management

Bacteriuria in patients with neuro-urolological disorders should not be treated. Treatment of asymptomatic bacteriuria results in significantly more resistant bacterial strains without improving the outcome [349]. UTI in persons with neuro-urolological disorders are by definition complicated UTI. Therefore, single-dose treatment is not advised. There is no consensus in the literature about the duration of treatment. It depends on the severity of the UTI and the involvement of kidneys and the prostate. Generally, a 5-7 day course of antibiotic treatment is advised, that can be extended up to 14 days according to the extent of the infection [349]. The choice of the antibiotic therapy should be based on the results of the microbiologic testing. If immediate treatment is mandatory (e.g. fever, septicaemia, intolerable clinical symptoms, extensive autonomic dysreflexia), the choice of treatment should be based on local and individual resistance profiles [350].

3E.3.1 Recurrent UTI

Recurrent UTI in patients with neuro-urolological disorders may indicate a suboptimal management of the underlying functional problem, e.g. high bladder pressure during storage and voiding, incomplete voiding or bladder stones. The improvement of bladder function, e.g. by treating detrusor overactivity by BTX-A injection in the detrusor [351], and the removal of bladder stones or other direct supporting factors, especially indwelling catheters, as early as possible, are mandatory [348].

3E.3.2 Prevention

If the improvement of bladder function and removal of foreign bodies/stones is not successful, additional UTI prevention strategies should be utilised. In men performing IC, the use of hydrophilic catheters is associated with a lower rate of UTI; in women this effect is not demonstrated [352]. Bladder irrigation has not been proven effective [353].

Various medical approaches have been tested as UTI prophylaxis in patients with neuro-urological disorders. The benefit of cranberry juice for the prevention of UTI could not be demonstrated in RCTs [354]. Methenamine hippurate is not effective in individuals with neuro-urological symptoms [355]. There is not sufficient evidence to support the use of L-methionine for urine acidification to prevent recurrent UTI [356]. There is only weak evidence that oral immunotherapy reduces bacteriuria in patients with SCI, and no evidence that recurrent UTI are reduced [357]. Low-dose, long-term, antibiotic prophylaxis cannot reduce UTI frequency, but increases bacterial resistance and is therefore not recommended [349].

A newly proposed application scheme of antibiotic substances for antibiotic prophylaxis provided positive results, but the results of this trial need to be confirmed in further studies [358]. Another possible future option, the inoculation of apathogenic *E. coli* strains into the bladder, has provided positive results in initial studies, but because of the paucity of data [359], cannot be recommended as a treatment option.

In summary, based on the criteria of evidence-based medicine, there is currently no preventive measure for recurrent UTI in patients with neuro-urological disorders that can be recommended without limitations. Therefore, individualised concepts should be taken into consideration, including immunostimulation, phytotherapy and complementary medicine [360]. Prophylaxis in patients with neuro-urological disorders is important to pursue, but since there are no data favouring one approach over another, prophylaxis is essentially a trial and error approach.

3E.4 Recommendations for the treatment of UTI

Recommendations	LE	GR
Asymptomatic bacteriuria in patients with neuro-urological disorders should not be treated.	4	A
The use of long-term antibiotics in recurrent UTIs should be avoided.	2a	A
In patients with recurrent UTI, treatment of neuro-urological symptoms should be optimised and foreign bodies (e.g. stones, indwelling catheters) should be removed from the urinary tract.	3	A
In patients with neuro-urological disorders, UTI prophylaxis must be individualised since there is no optimal prophylactic measure available.	4	C

UTI = urinary tract infection.

3F SEXUAL (DYS)FUNCTION AND FERTILITY

These Guidelines specifically focus on sexual dysfunction and infertility in patients with a neurological disease [361]. Non-neurogenic, male sexual dysfunction and infertility are covered in separate EAU Guidelines [362, 363]. Adopting a systematic approach, such as the PLISSIT model (Permission, Limited Information, Specific Suggestions and Intensive Therapy) [364], provides a framework for counselling and treatment involving a stepwise approach to the management of neurogenic sexual dysfunction.

3F.1 Erectile dysfunction

3F.1.1 Phosphodiesterase type 5 inhibitors

Phosphodiesterase type 5 inhibitors (PDE5Is) are recommended as first-line treatment in neurogenic erectile dysfunction (ED) [361]. All currently available PDE5Is appear to be effective and safe, although there are no high-evidence level studies in neuro-urological patients investigating efficacy and side effects across different PDE5Is, dosages and formulations. A recent network meta-analysis on a mixed ED population has suggested that tadalafil is the most effective agent [365]. Most common side effects of PDE5Is are headache, flushing, dyspepsia and nasal congestion, while PDE5Is may induce relevant hypotension in patients with tetraplegia/high-level paraplegia and multiple system atrophy [366, 367].

Several studies, including RCTs, show the efficacy and safety of PDE5Is for treating ED in patients with SCI [366, 368-371], MS [372-374], PD [375-377], diabetes mellitus [377-380], spina bifida [379] and after radical prostatectomy [381].

Most neuro-urological patients require long-term therapy for ED but some have a low compliance rate or stop therapy because of side effects [366, 367]. As a prerequisite for successful PDE5I-therapy, some residual nerve function is required to induce erection.

Since many patients with SCI use on-demand nitrates for the treatment of autonomic dysreflexia, they must be counselled that PDE5Is are contraindicated when using nitrate medication.

3F.1.2 **Mechanical devices**

Mechanical devices (vacuum tumescence devices and penile rings) may be effective but are less popular [382-386].

3F.1.3 **Intracavernous injections and intraurethral application**

Patients not responding to oral drugs may be offered intracavernous injections (alprostadil, papaverine and phentolamine) that have been shown to be effective in a number of neurological conditions, including SCI, MS, and diabetes mellitus [387-392], but their use requires careful dose titration and some precautions. Complications of intracavernous drugs include pain, priapism and corpora cavernosa fibrosis.

Intracavernous vasoactive drug injection is the first therapeutic option in patients taking nitrate medications, for whom there are concerns about drug interactions with PDE5Is, or in patients for whom PDE5Is are ineffective. The impact of intracavernous injections on ejaculation and orgasmic function, their early use for increasing the recovery rate of a spontaneous erection, and their effectiveness and tolerability in the long-term are unclear [366].

Intraurethral alprostadil application is an alternative but less effective route of administration [393].

3F.1.4 **Penile prostheses**

Penile prostheses may be considered for treatment of neurogenic ED when all conservative treatments have failed. Serious complications, including infection and prosthesis perforation, may occur in about 10% of patients, depending on implant type [394-396].

3F.1.5 **Recommendations for erectile dysfunction**

Recommendations	LE	GR
In neurogenic ED, oral PDE5Is are the recommended first-line medical treatment.	1b	A
In neurogenic ED, intracavernous injections of vasoactive drugs (alone or in combination) are the recommended second-line medical treatment.	3	A
In neurogenic ED, mechanical devices such as vacuum devices and rings can be effective and may be offered to patients.	3	B
In neurogenic ED, penile prostheses should be reserved for selected patients.	4	B

ED = erectile dysfunction; PDE5Is = phosphodiesterase type 5 inhibitors.

3F.2 **Male fertility**

Among the major conditions contributing to neurogenic infertility are pelvic and retroperitoneal surgery, diabetes mellitus, spina bifida, MS and SCI [397]. ED is managed as described previously. Retrograde ejaculation may be reversed by sympathomimetic agents contracting the bladder neck, including imipramine, ephedrine, pseudoephedrine, and phenylpropanolamine [397]. The use of a balloon catheter to obstruct the bladder neck may be effective in obtaining antegrade ejaculation [398]. If antegrade ejaculation is not achieved, the harvest of semen from the urine may be considered [397]. Prostatic massage is safe and easy to use for obtaining semen in men with lesions above T10 [399]. In several patients, vibrostimulation or transrectal electroejaculation are needed for sperm retrieval [397, 400-403]. Semen retrieval is more likely with vibrostimulation in men with lesions above T10 [404-406]. In men with SCI, especially at or above T6, AD might occur during sexual activity and ejaculation [407, 408]; patients at risk and fertility clinics must be informed and aware of this potentially life-threatening condition.

Surgical procedures, such as microsurgical epididymal sperm aspiration (MESA) or testicular sperm extraction (TESE), may be used if vibrostimulation and electroejaculation are not successful [409, 410]. Pregnancy rates in patients with SCI are lower than in the general population, but since the introduction of intracytoplasmic sperm injection (ICSI), men with SCI now have a good chance of becoming biological fathers [411-413].

3F.2.1 **Sperm quality and motility**

The following has been reported on sperm quality and motility:

- Vibrostimulation produces samples with better sperm motility than electrostimulation [402, 414].
- Electroejaculation with interrupted current produces better sperm motility than continuous current [415].
- Bladder management with clean IC may improve semen quality compared to indwelling catheterisation, reflex voiding or bladder expression [416].
- Sperm quality in men with SCI is enhanced by processing in able-bodied seminal plasma [417].
- Freezing of sperm is unlikely to improve fertility rates in men with SCI [400].

3F.2.2 Recommendations for male fertility

Recommendations	LE	GR
In men with SCI, vibrostimulation and transrectal electroejaculation are effective methods of sperm retrieval.	3	B
In men with SCI; MESA, TESE or ICSI may be used after failed vibrostimulation and/or transrectal electroejaculation.	3	B
In men with SCI, especially at or above T6, it is essential to counsel patients at risk and fertility clinics about the potentially life-threatening condition of autonomic dysreflexia.	3	A

SCI = spinal cord injury.

3F.3 Female sexuality

The most relevant publications on neurogenic female sexual dysfunction are in women with SCI and MS. After SCI, about 65-80% of women continue to be sexually active, but to a much lesser extent than before the injury, and about 25% report a decreased satisfaction with their sexual life [418-420]. Although sexual dysfunction is very common in women with MS, it is still often overlooked by medical professionals [421, 422].

The greatest physical barrier to sexual activity is urinary incontinence. Problems with positioning and spasticity affect mainly tetraplegic patients. Peer support may help to optimise the sexual adjustment of women with SCI in achieving a more positive self-image, self-esteem and feelings of being attractive to themselves and others [418, 423-425].

The use of specific drugs for sexual dysfunction is indicated to treat inadequate lubrication. Sildenafil may partially reverse subjective sexual arousal difficulties, while manual and vibratory clitoral stimulation may increase genital responsiveness [426, 427]. Although good evidence exists that psychological interventions are effective in the treatment of female hypoactive sexual desire disorder and female orgasmic disorder [428], there is a lack of high-evidence level studies in the neurological population.

Neurophysiological studies have shown that women with the ability to perceive T11-L2 pin-prick sensations may have psychogenic genital vasocongestion. Reflex lubrication and orgasm is more prevalent in women with SCI who have preserved the sacral reflex arc (S2-S5), even when it has not been shown in an individual woman that a specific level and degree of lesion is the cause of a particular sexual dysfunction. In SCI women with a complete lesion of the sacral reflex, arousal and orgasm may be evoked through stimulation of other erogenous zones above the level of lesions [429-431].

Women with SCI reported dissatisfaction with the quality and quantity of sexuality-related rehabilitation services and were less likely to receive sexual information than men [429, 432, 433].

3F.3.1 Recommendation for female sexuality

Recommendation	LE	GR
There is no effective medical therapy for the treatment of neurogenic sexual dysfunction in women.	4	A

3F.4 Female fertility

There are few studies on female fertility in neurological patients. More than a third (38%) of women with epilepsy had infertility and the relevant predictors were exposure to multiple (three or more) antiepileptic drugs, older age and lower education [434].

Although it seems that the reproductive capacity of women with SCI is only temporarily affected by SCI with cessation of menstruation for approximately 6 months after SCI [435], there are no high-evidence level studies. About 70% of sexually active women use some form of contraception after injury, but fewer women use the birth control pill compared to before their injury [436].

Women with SCI are more likely to suffer complications during pregnancy, labour and delivery compared to able-bodied women. Complications of labour and delivery include bladder problems, spasticity, pressure sores, anaemia, and AD [437, 438]. Obstetric outcomes include higher rates of Caesarean sections and an increased incidence of low birth-weight babies [436].

Epidural anaesthesia is chosen and effective for most patients with AD during labour and delivery [439, 440].

There is very little published data on women's experience of the menopause following SCI [441].

3F.4.1 Recommendation for female fertility

Recommendation	LE	GR
In women with a neurological disease, the management of fertility, pregnancy and delivery requires a multidisciplinary approach tailored to individual patient's needs and preferences.	4	A

3G FOLLOW-UP

3G.1 Introduction

Neuro-urological disorders are often unstable and the symptoms may vary considerably, even within a relatively short period. Regular follow-up is therefore necessary [46, 101, 305, 311, 338, 442-453].

Depending on the type of the underlying neurological pathology and the current stability of the neuro-urological symptoms, the interval between initial investigations and control diagnostics may vary and in many cases should not exceed 1-2 years. In high-risk neuro-urological patients this interval should be much shorter. Urinalysis should be performed regularly; the frequency to be guided by patient symptoms. The UUT should be checked by ultrasonography at regular intervals in high-risk patients; at least once every 6 months. In these patients, physical examination and urine laboratory should take place every year. Any significant clinical change warrants further, specialised, investigation.

3G.2 Recommendations for follow-up

Recommendations	LE	GR
In high-risk patients, the upper urinary tract should be assessed at least every six months.	4	A
In high-risk patients, physical examination, and urine laboratory should take place every year.	4	A
Any significant clinical changes should instigate further, specialised, investigation.	4	A
Urodynamic investigation is a mandatory baseline diagnostic and in high-risk patients, should be done at regular intervals.	3	A

3H CONCLUSIONS

Neuro-urological disorders have a multi-faceted pathology. They require an extensive and specific diagnosis before one can embark on an individualised therapy, which takes into account the medical and physical condition of the patient and the patient's expectations about his/her future.

The urologist or paediatric urologist can select from a wealth of therapeutical options, each with its own pros and cons. Notwithstanding the success of any therapy embarked upon, a close surveillance is necessary for the patient's entire life.

These Guidelines offer you expert advice on how to define the patient's neuro-urological symptoms as precisely as possible and how to select, together with the patient, the appropriate therapy. This last choice, as always, is governed by the golden rule: as effective as needed, as less invasive as possible.

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5. CONFLICT OF INTEREST

All members of the Neuro-Urology Guidelines Panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the EAU website. This guidelines document was developed with the financial support of the EAU. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

Guidelines on Urolithiasis

C. Türk (Chair), T. Knoll (Vice-chair), A. Petrik,
K. Sarica, A. Skolarikos, M. Straub, C. Seitz

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1. INTRODUCTION

1.1 Aims and scope

The European Association of Urology (EAU) Urolithiasis Guidelines Panel have prepared these guidelines to help urologists assess evidence-based management of stones/calculi and incorporate recommendations into clinical practice.

The document covers most aspects of the disease, which is still a cause of significant morbidity despite technological and scientific advances. The Panel is aware of the geographical variations in healthcare provision.

1.2 Panel composition

The EAU Urolithiasis Guidelines Panel consists of an international group of clinicians with particular expertise in this area. All experts involved in the production of this document have submitted potential conflict of interest statements.

1.3 Available publications

A quick reference document (Pocket guidelines) is available, both in print and in a number of versions for mobile devices. These are abridged versions which may require consultation together with the full text versions. Also a number of translated versions, alongside several scientific publications in European Urology and the Journal of Urology [1-3], are available. All documents can be accessed through the EAU website:

<http://www.uroweb.org/guidelines/online-guidelines/>.

1.4 Publication history and summary of changes

1.4.1 Publication history

The EAU published its first guidelines on Urolithiasis in 2000. This 2015 document presents a limited update of the 2014 publication of the EAU Urolithiasis Guidelines.

1.4.2 Summary of changes

Key changes for the 2015 publication:

- The literature for the complete document has been assessed and updated, whenever relevant and 46 new references have been included.
- A new introductory section was added to Section 3.1 (section Prevalence, aetiology, risk of recurrence), as well as a table. Additional data has been added to Table 1.2.
- Diagnostic imaging during pregnancy (section 3.3.3.1).

Recommendation	LE	GR
In pregnant women, ultrasound is the imaging method of choice.	1a	A*
In pregnant women, MRI should be used as a second-line imaging modality.	3	C
In pregnant women, low-dose CT should be considered as a last-line option. The exposure should be less than 0.05 Gy.	3	C

- In Section 3.4.1.2.1.1.1 - Conservative treatment (Observation) – a recommendation on the timing of patient follow-up has been included.

If renal stones are not treated, periodic evaluation is recommended (after 6 months and yearly thereafter).	A*
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- In Section: 3.4.1.3 - Indication for active stone removal of kidney stones - a new recommendation has been added.

Recommendation	LE	GR
Radiolucent stones may be dissolvable (See Section 3.4.1.2.1.1.2.1.3).	2a	B

- In Section 3.4.2.3.3 - Laparoscopic ureteral stone removal – a new recommendation has been included.

For ureterolithotomy, laparoscopy is recommended for large impacted stones when endoscopic lithotripsy or SWL has failed.	2	B
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- In Section 3.4.1.4.1 - Antibiotic treatment – a new recommendation has been included.

Recommendations	LE	GR
UTIs must be excluded or treated prior to endourologic stone removal.	1b	A
In all patients undergoing endourologic treatment, perioperative antibiotic prophylaxis is recommended.	1b	A*

- A new Figure (3.4.2) - Recommended treatment options (if indicated for active stone removal) - has been included.
- In Section 3.4.5 - Management of stones in patients with neurogenic bladder – the recommendation has been expanded.

Recommendation	GR
In myelomeningocele patients, latex allergy is common, thus appropriate measures need to be taken regardless of the treatment. For surgical interventions, general anesthesia remains the only option.	B

- An additional recommendation was included in Table 3.4.6 - Special problems in stone removal.

Horseshoe kidneys	• Acceptable stone free rates can be achieved with flexible ureteroscopy [335].
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- Figures 4.2 - Diagnostic and therapeutic algorithm for calcium oxalate stones - and 4.3 - Diagnostic and therapeutic algorithm for calcium phosphate stones - have updated reference values included.
- A new Section on Matrix stones has been added (4.12).
- In Table 4.6 - Pharmacological substances used for stone prevention - characteristics, specifics and dosage - Febuxostat for the treatment of hyperuricosuria and hyperuricaemia has been added.
- Section 4.4.4 - Recommendations for pharmacological treatment of patients with specific abnormalities in urine composition – a recommendation for Febustat has been added.

Hyperuricosuria	Allopurinol	1a	A
	Febuxostat	1b	A

- In Table 4.8 - Pharmacological treatment of renal tubular acidosis – additional alternatives for the treatment of hypercalciuria have been included.

2. METHODS

2.1 Data identification

For this 2015 print of the Urolithiasis guidelines, a scoping search, covering all content, was performed. Time frame of the search was August 2nd 2013 through August 11th 2014. This search was limited to level 1 evidence (systematic reviews [SRs] and meta-analyses of randomised controlled trials [RCTs]) and English language publications in peer-reviewed journals. Animal studies were excluded. The search identified 421 unique records.

Selection of the papers was done through a consensus meeting of the Panel held October 25-26th, 2014. Annual scoping searches will be repeated as a standard procedure.

In this 2015 EAU Guidelines compilation, all standard information on levels of evidence (LE) and grading of recommendations (GR) has been taken out of the individual guidelines topics for the sake of brevity. This information is included in the introductory section of this print.

2.2 Evidence sources

Searches were carried out in the Cochrane Library Database of Systematic Reviews, Cochrane Library of Controlled Clinical Trials, and Medline and Embase on the Ovid platform. The searches used the controlled terminology and the use of free text ensured search sensitivity.

2.3 Peer review

This document was subjected to double-blind peer review prior to publication.

2.4 Future plans

The EAU Urolithiasis guidelines panel aim to incorporate the results of a number of ongoing systematic reviews in their 2016 print update.

3. GUIDELINES

3.1 Prevalence, aetiology, risk of recurrence

3.1.1 Introduction

Stone incidence depends on geographical, climatic, ethnic, dietary and genetic factors. The recurrence risk is basically determined by the disease or disorder causing the stone formation. Accordingly, the prevalence rates for urinary stones vary from 1% to 20% [4]. In countries with a high standard of life such as Sweden, Canada or the US, renal stone prevalence is notably high (> 10%). For some areas an increase of more than 37% over the last 20 years is reported [5] (Table 3.1.1).

Table 3.1.1: Prevalence and incidence of urolithiasis from two European countries [6, 7]

	Germany 2000 (%)	Spain 2007 (%)
<i>Prevalence</i>	4.7	5.06
Females	4.0	NA
Males	5.5	NA
<i>Incidence</i>	1.47	0.73
Females	0.63	NA
Males	0.84	NA

Stones can be classified into those caused by: infection, or non-infectious causes (infection and non-infection stones); genetic defects [8]; or adverse drug effects (drug stones) (Table 3.1.2).

Table 3.1.2: Stones classified by aetiology*

Non-infection stones
• Calcium oxalate
• Calcium phosphate,
• Uric acid
Infection stones
• Magnesium ammonium phosphate
• Carbonate apatite
• Ammonium urate
Genetic causes
• Cystine
• Xanthine
• 2,8-dihydroxyadenine
Drug stones

*See Section 4.4.2

3.1.2 Stone composition

Stone composition is the basis for further diagnostic and management decisions. Stones are often formed from a mixture of substances. Table 3.1.3 lists the clinically most relevant substances and their mineral components.

Table 3.1.3: Stone composition

Chemical name	Mineral name	Chemical formula
Calcium oxalate monohydrate	Whewellite	$\text{CaC}_2\text{O}_4 \cdot \text{H}_2\text{O}$
Calcium oxalate dihydrate	Wheddelite	$\text{CaC}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$
Basic calcium phosphate	Apatite	$\text{Ca}_{10}(\text{PO}_4)_6 \cdot (\text{OH})_2$
Calcium hydroxyl phosphate	Carbonite apatite	$\text{Ca}_5(\text{PO}_3)_3(\text{OH})$
b-tricalcium phosphate	Whitlockite	$\text{Ca}_3(\text{PO}_4)_2$
Carbonate apatite phosphate	Dahllite	$\text{Ca}_5(\text{PO}_4)_3\text{OH}$
Calcium hydrogen phosphate	Brushite	$\text{PO}_4 \cdot 2\text{H}_2\text{O}$
Calcium carbonate	Aragonite	CaCO_3
Octacalcium phosphate		$\text{Ca}_8\text{H}_2(\text{PO}_4)_6 \cdot 5\text{H}_2\text{O}$
Uric acid	Uricite	$\text{C}_5\text{H}_4\text{N}_4\text{O}_3$
Uric acid dihydrate	Uricite	$\text{C}_5\text{H}_4\text{O}_3 \cdot 2\text{H}_2\text{O}$
Ammonium urate		$\text{NH}_4\text{C}_5\text{H}_3\text{N}_4\text{O}_3$
Sodium acid urate monohydrate		$\text{NaC}_5\text{H}_3\text{N}_4\text{O}_3 \cdot \text{H}_2\text{O}$
Magnesium ammonium phosphate	Struvite	$\text{MgNH}_4\text{PO}_4 \cdot 6\text{H}_2\text{O}$
Magnesium acid phosphate trihydrate	Newberyite	$\text{MgHPO}_4 \cdot 3\text{H}_2\text{O}$
Magnesium ammonium phosphate monohydrate	Dittmarite	$\text{MgNH}_4(\text{PO}_4) \cdot \text{H}_2\text{O}$
Cystine		$[\text{SCH}_2\text{CH}(\text{NH}_2)\text{COOH}]_2$
Gypsum	Calcium sulphate dihydrate Zinc phosphate tetrahydrate	$\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$ $\text{Zn}_3(\text{PO}_4)_2 \cdot 4\text{H}_2\text{O}$
Xanthine		
2,8-Dihydroxyadenine		
Proteins		
Cholesterol		
Calcite		
Potassium urate		
Trimagnesium phosphate		
Melamine		
Matrix		
Drug stones	<ul style="list-style-type: none"> • Active compounds crystallising in urine • Substances impairing urine composition (Section 4.11) 	
Foreign body calculi		

3.1.3 Risk groups for stone formation

The risk status of stone formers is of particular interest because it defines the probability of recurrence or regrowth, and is imperative for pharmacological treatment.

About 50% of recurrent stone formers have just one lifetime recurrence [6, 9]. Highly recurrent disease is observed in slightly more than 10% of patients. Stone type and disease severity determine low or high-risk of recurrence (Table 3.1.4) [10, 11].

Table 3.1.4: High-risk stone formers [10-17]

General factors
Early onset of urolithiasis (especially children and teenagers)
Familial stone formation
Brushite-containing stones ($\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$)
Uric acid and urate-containing stones
Infection stones
Solitary kidney (the kidney itself does not particularly increase the risk of stone formation, but prevention of stone recurrence is of more importance)
Diseases associated with stone formation
Hyperparathyroidism
Metabolic syndrome [17]
Nephrocalcinosis
Gastrointestinal diseases (i.e., jejunio-ileal bypass, intestinal resection, Crohn's disease, malabsorptive conditions, enteric hyperoxaluria after urinary diversion) and bariatric surgery [16]
Sarcoidosis
Genetically determined stone formation
Cystinuria (type A, B and AB)
Primary hyperoxaluria (PH)
Renal tubular acidosis (RTA) type I
2,8-Dihydroxyadeninuria
Xanthinuria
Lesch-Nyhan syndrome
Cystic fibrosis
Drugs associated with stone formation
Anatomical abnormalities associated with stone formation
Medullary sponge kidney (tubular ectasia)
Ureteropelvic junction (UPJ) obstruction
Calyceal diverticulum, calyceal cyst
Ureteral stricture
Vesico-uretero-renal reflux
Horseshoe kidney
Ureterocele

3.2 Classification of stones

Urinary stones can be classified according to size, location, X-ray characteristics, aetiology of formation, composition, and risk of recurrence [6, 18-20].

3.2.1 Stone size

Stone size is usually given in one or two dimensions, and stratified into those measuring up to 5, 5-10, 10-20, and > 20 mm in largest diameter.

3.2.2 Stone location

Stones can be classified according to anatomical position: upper, middle or lower calyx; renal pelvis; upper, middle or distal ureter; and urinary bladder. Treatment of bladder stones is not discussed here.

3.2.3 X-ray characteristics

Stones can be classified according to plain X-ray appearance [kidney-ureter-bladder (KUB) radiography] (Table 3.2.1), which varies according to mineral composition [20]. Non-contrast-enhanced computed tomography (NCCT) can be used to classify stones according to density, inner structure and composition, which can affect treatment decisions (Section 3.4.1.4.4) [19, 20].

Table 3.2.1: X-ray characteristics

Radiopaque	Poor radiopacity	Radiolucent
Calcium oxalate dihydrate	Magnesium ammonium phosphate	Uric acid
Calcium oxalate monohydrate	Apatite	Ammonium urate
Calcium phosphates	Cystine	Xanthine
		2,8-Dihydroxyadenine
		Drug-stones (Section 4.11)

Stratification of stones according to aetiology, composition and risk of recurrence is addressed in Section 3.1.

3.3 Diagnostic evaluation

3.3.1 Diagnostic imaging

The clinical situation will inform on the most appropriate imaging modality, which will differ for suspected ureteral stone or suspected renal stone.

Standard evaluation includes a detailed medical history and physical examination. Patients with ureteral stones usually present with loin pain, vomiting, and sometimes fever, but may also be asymptomatic [21].

Ultrasound (US) should be used as the primary diagnostic imaging tool, although pain relief, or any other emergency measures should not be delayed by imaging assessments. US is safe (no risk of radiation), reproducible and inexpensive. It can identify stones located in the calices, pelvis, and pyeloureteric and vesicoureteric junctions, as well as in patients with upper urinary tract dilatation. US has a sensitivity of 45% and specificity of 94% for ureteric stones and a sensitivity of 45% and specificity of 88% for renal stones [22].

The sensitivity and specificity of KUB radiography is 44-77% and 80-87%, respectively [23]. KUB radiography should not be performed if NCCT is considered [24], however, it is helpful in differentiating between radiolucent and radiopaque stones and for comparison during follow-up.

Recommendation	LE	GR
With fever or solitary kidney, and when diagnosis is doubtful, immediate imaging is indicated.	4	A*

*Upgraded following panel consensus.

3.3.1.1 Evaluation of patients with acute flank pain

NCCT has become the standard for diagnosing acute flank pain, and has replaced intravenous urography (IVU). NCCT can determine stone diameter and density. When stones are absent, the cause of abdominal pain should be identified. In evaluating patients with suspected acute urolithiasis, NCCT seems to be significantly more accurate than IVP [25].

Recommendation	LE	GR
Following initial US assessment, NCCT should be used to confirm stone diagnosis in patients with acute flank pain, because it is superior to IVU.	1a	A

IVU = intravenous urography; NCCT = non-contrast enhanced computed tomography.

NCCT can detect uric acid and xanthine stones, which are radiolucent on plain films, but not indinavir stones [26]. NCCT can determine stone density, inner structure of the stone and skin-to-stone distance; all of which affect extracorporeal shock wave lithotripsy (SWL) outcome [20, 27-29]. The advantage of non-contrast imaging must be balanced against loss of information on renal function and urinary collecting system anatomy, as well as higher radiation dose (Table 3.1).

Radiation risk can be reduced by low-dose CT [30]. In patients with body mass index (BMI) < 30, low-dose CT has been shown to have a sensitivity of 86% for detecting ureteric stones < 3 mm and 100% for calculi > 3 mm [31]. A meta-analysis of prospective studies [32] has shown that low-dose CT diagnosed urolithiasis with a pooled sensitivity of 96.6% (95% CI: 95.0-97.8) and specificity of 94.9% (95% CI: 92.0-97.0).

Table 3.3.1: Radiation exposure of imaging modalities [33-36]

Method	Radiation exposure (mSv)
KUB radiography	0.5-1
IVU	1.3-3.5
Regular-dose NCCT	4.5-5
Low-dose NCCT	0.97-1.9
Enhanced CT	25-35

Recommendation	LE	GR
If NCCT is indicated in patients with BMI < 30, use a low-dose technique.	1b	A

NCCT = non-contrast enhanced computed tomography.

3.3.1.2 Radiological evaluation of patients for whom further treatment of renal stones is planned

Recommendations	LE	GR
A contrast study is recommended if stone removal is planned and the anatomy of the renal collecting system needs to be assessed.	3	A*
Enhanced CT is preferable in complex cases because it enables 3D reconstruction of the collecting system, as well as measurement of stone density and skin-to-stone distance. IVU may also be used.	4	C

*Upgraded based on panel consensus.

CT – computed tomography; IVU = intravenous urography.

3.3.2 Diagnostics - metabolism-related

Each emergency patient with urolithiasis needs a succinct biochemical work-up of urine and blood besides imaging. At that point, no distinction is made between high- and low-risk patients for stone formation.

Table 3.3.2: Recommendations: basic laboratory analysis - emergency urolithiasis patients [11, 12, 37, 38]

Urine	GR
Dipstick test of spot urine sample	A*
• red cells	A
• white cells	
• nitrite	
• approximate urine pH	
Urine microscopy and/or culture	
Blood	
Serum blood sample	A*
• creatinine	A*
• uric acid	
• (ionised) calcium	
• sodium	
• potassium	
• Blood cell count	A*
• CRP	
If intervention is likely or planned: Coagulation test (PTT and INR).	A*

*Upgraded based on panel consensus.

CPR = C-reactive protein; INR = international normalised ratio; PTT = partial thromboplastin time.

3.3.2.1 Basic laboratory analysis - non-emergency urolithiasis patients

Biochemical work-up is similar for all stone patients. However, if no intervention is planned, examination of sodium, potassium, CRP, and blood coagulation time can be omitted.

Only patients at high-risk for stone recurrence should undergo a more specific analytical programme [11]. Stone-specific metabolic evaluation is described in Chapter 4.

The easiest means to achieve correct diagnosis is by analysis of a passed stone using a valid

method as listed below (see 3.2.2). Once mineral composition is known, the potential metabolic disorders can be identified.

3.3.2.2 Analysis of stone composition

Stone analysis should be performed in all first-time stone formers.

In clinical practice, repeat stone analysis is needed in the case of:

- recurrence under pharmacological prevention;
- early recurrence after interventional therapy with complete stone clearance;
- late recurrence after a prolonged stone-free period [39].

Patients should be instructed to filter their urine to retrieve a concrement for analysis. Stone passage and restoration of normal renal function should be confirmed.

The preferred analytical procedures are infrared spectroscopy (IRS) or X-ray diffraction (XRD) [40–42]. Equivalent results can be obtained by polarisation microscopy, but only in centres with expertise. Chemical analysis (wet chemistry) is generally deemed to be obsolete [40].

Recommendations	LE	GR
Always perform stone analysis in first-time formers using a valid procedure (XRD or IRS).	2	A
Repeat stone analysis in patients: <ul style="list-style-type: none"> • presenting with recurrent stones despite drug therapy; • with early recurrence after complete stone clearance; • with late recurrence after a long stone-free period because stone composition may change [38]. 	2	B

IRS = infrared spectroscopy; XRD = X-ray diffraction.

3.3.3 Diagnosis in special groups and conditions

3.3.3.1 Diagnostic imaging during pregnancy

In pregnant women diagnostic imaging (exposure to ionising radiation) might be associated with teratogenic risks and development of (childhood) malignancies. The risk for the child crucially depends on gestational age and amount of radiation delivered. X-ray imaging during the first trimester should be reserved for diagnostic and therapeutic situations in which alternative imaging methods have failed [43, 44].

Ultrasound (when necessary using change in renal resistive index and transvaginal/transabdominal US with a full bladder) has become the primary radiological diagnostic tool when evaluating pregnant patients suspected of renal colic [45].

Statement	LE
Normal physiological changes in pregnancy can mimic ureteral obstruction, therefore, US may not help to differentiate dilatation properly and has a limited role in acute obstruction.	3

Magnetic resonance imaging (MRI) can be used, as a second-line procedure, to define the level of urinary tract obstruction, and to visualise stones as a filling defect [46, 47].

Low dose CT protocols, or low dose CT scans reduce the radiation exposure and are currently recommended to be used judiciously in pregnant women as a last-line option [48, 49].

Recommendations	LE	GR
In pregnant women, ultrasound is the imaging method of choice.	1a	A*
In pregnant women, MRI should be used as a second-line imaging modality.	3	C
In pregnant women, low-dose CT should be considered as a last-line option. The exposure should be less than 0.05 Gy.	3	C

*Upgraded following panel consensus.

CT = computed tomography; MRI = magnetic resonance imaging.

3.3.3.2 Children

Paediatric patients with urinary stones have a high risk of recurrence, therefore, standard diagnostic procedures for high-risk patients apply (Section 3.1.3 and Chapter 4).

Statement	LE
In paediatric patients, the most common non-metabolic disorders are vesicoureteral reflux, ureteropelvic junction obstruction, neurogenic bladder, and other voiding difficulties [50].	4
Recommendations	GR
In all paediatric patients, efforts should be made to complete a metabolic evaluation based on stone analysis.	A
All efforts should be made to collect stone material that should then be analysed to classify the stone type.	A*

*Upgraded following panel consensus.

3.3.3.2.1 Diagnostic imaging

When selecting diagnostic procedures to identify urolithiasis in paediatric patients, it should be remembered that these patients might be uncooperative, require anaesthesia, or be sensitive to ionising radiation [51-53]. Again, the principle of ALARA (As Low As Reasonably Achievable) should be observed.

3.3.3.2.2 Ultrasound

Ultrasound (US) is the primary imaging technique [51] in paediatrics. Its advantages are absence of radiation and no need for anaesthesia.

Colour Doppler US shows differences in the ureteric jet [54] and resistive index of the arciform arteries of both kidneys, which are indicative of the grade of obstruction [55].

Nevertheless, US fails to identify stones in > 40% of paediatric patients [56-59] (LE: 4), and provides no information on renal function.

Statement	LE
US is the first choice for imaging in children and should include the kidney, filled bladder, and adjoining portions of the ureter [54-57, 60].	2a

3.3.3.2.3 Plain films (KUB radiography)

KUB radiography can help to identify stones and their radiopacity, and facilitate follow-up.

3.3.3.2.4 Intravenous urography (IVU)

The radiation dose for IVU is comparable to that for voiding cystourethrography (0.33 mSV) [61]. However, the need for contrast medium injection is a major drawback.

3.3.3.2.5 Helical computed tomography (CT)

Recent low-dose CT protocols have been shown to significantly reduce radiation exposure [36]. The principle of ALARA (as low as reasonably achievable) should always be observed. In adults it has a sensitivity of 94-100% and specificity of 92-100% [62].

In children, only 5% of stones escape detection by NCCT [54, 62, 63]. Sedation or anaesthesia is rarely needed with modern high-speed CT apparatus.

3.3.3.2.6 Magnetic resonance urography (MRU)

Magnetic resonance urography cannot be used to detect urinary stones. However, it might provide detailed anatomical information about the urinary collecting system, the location of an obstruction or stenosis in the ureter, and renal parenchymal morphology [64].

Recommendations	GR
In children, US is the first-line imaging modality when a stone is suspected.	B
If US does not provide the required information, KUB radiography (or NCCT) should be performed.	B

US = ultrasound; KUB = kidney, ureter, bladder; NCCT = non-contrast enhanced computed tomography.

3.4 Disease management

3.4.1 Management of patients with renal or ureteral stones

Treatment decisions for upper urinary tract calculi are based on several general aspects such as stone composition, stone size, and symptoms.

3.4.1.1 Renal colic

Pain relief

Pain relief is the first therapeutic step in patients with an acute stone episode [65, 66].

Non-steroidal anti-inflammatory drugs (NSAIDs) are effective in patients with acute stone colic [67, 68], and have better analgesic efficacy than opioids. Patients receiving NSAIDs are less likely to require further analgesia in the short-term.

Opioids, particularly pethidine, are associated with a high rate of vomiting compared to NSAIDs, and carry a greater likelihood of further analgesia being needed [69, 70] (see below). If an opioid is used, it is recommended that it is not pethidine.

Prevention of recurrent renal colic

Facilitation of passage of ureteral stones is discussed in Section 3.4.3.1.2.

For patients with ureteral stones that are expected to pass spontaneously, NSAID tablets or suppositories (e.g., diclofenac sodium, 100-150 mg/day, 3-10 days) may help reduce inflammation and the risk of recurrent pain [70-72]. Although diclofenac can affect renal function in patients with already reduced function, it has no functional effect in patients with normal kidney function [73] (LE: 1b).

In a double-blind, placebo-controlled trial, recurrent pain episodes of stone colic were significantly fewer in patients treated with NSAIDs (as compared to no NSAIDs) during the first 7 days of treatment [72]. Daily α -blockers reduce recurrent colic (LE: 1a) (Section 3.4.3.1.2).

If analgesia cannot be achieved medically, drainage, using stenting or percutaneous nephrostomy, or stone removal, should be performed.

Statement and recommendations for analgesia during renal colic

Statement	LE
For symptomatic ureteral stones, urgent stone removal as first-line treatment is a feasible option.	1b

Recommendations	GR
In acute stone episodes, pain relief should be initiated immediately.	A
Whenever possible, an NSAID should be the first drug of choice. e.g. diclofenac*, indomethacin or ibuprofen**.	A
Second choice: hydromorphone, pentazocine or tramadol.	C
Use α -blockers to reduce recurrent colics.	A

*Affects glomerular filtration rate (GFR) in patients with reduced renal function (LE: 2a).

**Recommended to counteract recurrent pain after ureteral colic.

3.4.1.2 Management of sepsis in obstructed kidney

The obstructed kidney with all signs of urinary tract infection (UTI) is a urological emergency. Urgent decompression is often necessary to prevent further complications in infected hydronephrosis secondary to stone-induced, unilateral or bilateral renal obstruction.

Decompression

Currently, there are two options for urgent decompression of obstructed collecting systems:

- placement of an indwelling ureteral stent;
- percutaneous placement of a nephrostomy tube.

There is little evidence to support the superiority of percutaneous nephrostomy over retrograde stenting for primary treatment of infected hydronephrosis. There is no good-quality evidence to suggest that ureteric stenting has more complications than percutaneous nephrostomy [74, 75].

Only one RCT [76] assessed decompression of acute infected hydronephrosis. The complications of percutaneous nephrostomy insertion have been reported consistently, but those of ureteric stent insertion are less well described [74]. Definitive stone removal should be delayed until the infection is cleared following a complete course of antimicrobial therapy.

Statement	LE
For decompression of the renal collecting system, ureteral stents and percutaneous nephrostomy catheters are equally effective.	1b

Recommendations	LE	GR
For sepsis with obstructing stones, the collecting system should be urgently decompressed, using percutaneous drainage or ureteral stenting.	1b	A
Definitive treatment of the stone should be delayed until sepsis is resolved.	1b	A

Further measures

Following urgent decompression of the obstructed and infected urinary collecting system, both urine- and blood samples should be sent for culture-antibiogram sensitivity testing, and antibiotics should be initiated immediately thereafter. The regimen should be re-evaluated in the light of the culture-antibiogram test. Intensive care might become necessary.

Recommendations	GR
Collect urine for antibiogram test following decompression.	A*
Start antibiotics immediately thereafter (+ intensive care if necessary).	
Re-evaluate antibiotic regimen following antibiogram findings.	

**Upgraded based on panel consensus.*

3.4.2 Specific stone management in Renal stones

The natural history of small, non-obstructing asymptomatic calculi is not well defined, and the risk of progression is unclear. There is still no consensus on the follow-up duration, and timing and type of intervention. Treatment options are observation, chemolysis or active stone removal.

3.4.2.1 Types of treatments

3.4.2.1.1 Conservative treatment (Observation)

Observation of renal stones, especially in calices, depends on their natural history (Section 3.4.2.2).

Statement	LE
It is still debatable whether renal stones should be treated, or whether annual follow-up is sufficient for asymptomatic caliceal stones that have remained stable for 6 months.	4

Recommendations	GR
If renal stones are not treated, periodic evaluation is recommended (after 6 months and yearly follow-up of symptoms and stone status [US, KUB or CT]).	A*

**Upgraded based on panel consensus.*

3.4.2.1.2 Pharmacological treatment

3.4.2.1.2.1 Percutaneous irrigation chemolysis

Today, percutaneous chemolysis is rarely used. Percutaneous irrigation chemolysis may be an option for infection- and uric acid stones [77, 78]. For dissolution of struvite stones, Suby's G solution (10% hemiacidrin; pH 3.5-4) can be used [79].

3.4.2.1.2.2 Oral chemolysis

Stones composed of uric acid, but not sodium or ammonium urate, can be dissolved by oral chemolysis. Prior stone analysis may provide information on stone composition. Urinary pH measurement and X-ray characteristics may provide information on the type of stone.

Oral chemolitholysis is based on alkalinisation of urine by application of alkaline citrate or sodium bicarbonate [78, 80]. The pH should be adjusted to 7.0-7.2. Within this range, chemolysis is more effective at a higher pH, which might lead to calcium phosphate stone formation.

Monitoring of radiolucent stones during therapy is the domain of US, however, repeat NCCT might be necessary.

In the case of uric acid obstruction of the collecting system, oral chemolysis in combination with urinary drainage is indicated [81]. A combination of alkalinisation with tamsulosin seems to achieve the highest SFRs for distal ureteral stones [81].

Recommendations	GR
The dosage of alkalisating medication must be modified by the patient according to urine pH, which is a direct consequence of such medication.	A
Dipstick monitoring of urine pH by the patient is required three times a day (at regular intervals). Morning urine must be included.	A

Careful monitoring of radiolucent stones during/after therapy is imperative.	A*
The physician should clearly inform the patient of the significance of compliance.	A

**Upgraded based on panel consensus.*

3.4.2.1.3 Extracorporeal shock wave lithotripsy (SWL)

Success depends on the efficacy of the lithotripter and the following factors:

- size, location (ureteral, pelvic or calyceal), and composition (hardness) of the stones (Section 3.4.3.2);
- patient's habitus (Section 3.4.2.2);
- performance of SWL (best practice, see below).

Each of these factors has an important influence on retreatment rate and final outcome of SWL.

3.4.2.1.3.1 Contraindications of extracorporeal shock wave lithotripsy

There are several contraindications to the use of extracorporeal SWL, including:

- pregnancy, due to the potential effects on the foetus [82];
- bleeding diatheses, which should be compensated for at least 24 h before and 48 h after treatment [83];
- uncontrolled UTIs;
- severe skeletal malformations and severe obesity, which prevent targeting of the stone;
- arterial aneurysm in the vicinity of the stone [84];
- anatomical obstruction distal to the stone.

3.4.2.1.3.2 Best clinical practice

Stenting

Routine use of internal stents before SWL does not improve SFR [85] (LE: 1b). A JJ stent reduces the risk of renal colic and obstruction, but does not reduce formation of steinstrasse or infective complications [86].

Pacemaker

Patients with a pacemaker can be treated with SWL, provided that appropriate technical precautions are taken; patients with implanted cardioverter defibrillators must be managed with special care (firing mode temporarily reprogrammed during SWL treatment). However, this might not be necessary with new-generation lithotripters [87].

Shock wave rate

Lowering shock wave frequency from 120 to 60-90 shock waves/min improves SFR [88-93]. Tissue damage increases with shock wave frequency [94-97].

Recommendation	LE	GR
The optimal shock wave frequency is 1.0-1.5 Hz.	1a	A

Number of shock waves, energy setting and repeat treatment sessions

The number of shock waves that can be delivered at each session depends on the type of lithotripter and shock wave power. There is no consensus on the maximum number of shock waves.

Starting SWL on a lower energy setting with stepwise power (and SWL sequence) ramping can achieve vasoconstriction during treatment [98], which prevents renal injury [99, 100]. Animal studies [101] and a prospective randomised study [102] have shown better SFRs (96% vs. 72%) using stepwise power ramping, but no difference has been found for fragmentation or evidence of complications after SWL, irrespective of whether ramping was used [103].

There are no conclusive data on the intervals required between repeated SWL sessions. However, clinical experience indicates that repeat sessions are feasible (within 1 day for ureteral stones).

Statement	LE
Clinical experience has shown that repeat sessions are feasible (within 1 day for ureteral stones).	4

Improvement of acoustic coupling

Proper acoustic coupling between the cushion of the treatment head and the patient's skin is important. Defects (air pockets) in the coupling gel reflect 99% of shock waves [104]. US gel is probably the most widely used agent available for use as a lithotripsy coupling agent [105].

Recommendation	LE	GR
Ensure correct use of the coupling agent because this is crucial for effective shock wave transportation.	2a	B

Procedural control

Results of treatment are operator dependent, and better results are obtained by experienced clinicians. During the procedure, careful imaging control of localisation contributes to outcome quality [106].

Recommendation	LE	GR
Maintain careful fluoroscopic and/or ultrasonographic monitoring during the procedure.		A*

**Upgraded based on panel consensus.*

Pain control

Careful control of pain during treatment is necessary to limit pain-induced movements and excessive respiratory excursions [107-109].

Recommendation	LE	GR
Use proper analgesia because it improves treatment results by limiting induced movements and excessive respiratory excursions.	4	C

Antibiotic prophylaxis

No standard antibiotic prophylaxis before SWL is recommended. However, prophylaxis is recommended in the case of internal stent placement ahead of anticipated treatments and in the presence of increased bacterial burden (e.g., indwelling catheter, nephrostomy tube, or infectious stones) [110-112].

Recommendation	LE	GR
In the case of infected stones or bacteriuria, antibiotics should be given prior to SWL.	4	C

Medical therapy after extracorporeal shock wave lithotripsy

MET after SWL for ureteral or renal stones can expedite expulsion and increase SFRs, as well as reduce additional analgesic requirements [113-121] (Section 3.4.2.1.2.1.2).

3.4.2.1.3.3 Complications of extracorporeal shock wave lithotripsy

Compared to PNL and URS, there are fewer overall complications with SWL [122, 123] (Table 3.4.1).

Table 3.4.1: SWL-related complications [124-138]

Complications			%	Ref.
Related to stone fragments	Steinstrasse		4 - 7	[124-126]
	Regrowth of residual fragments		21 - 59	[127, 128]
	Renal colic		2 - 4	[129]
Infectious	Bacteriuria in non-infection stones		7.7 - 23	[127, 130]
	Sepsis		1 - 2.7	[127, 130]
Tissue effect	Renal	Haematoma, symptomatic	< 1	[131]
		Haematoma, asymptomatic	4 - 19	[131]
	Cardiovascular	Dysrhythmia	11 - 59	[127, 132]
		Morbid cardiac events	Case reports	[127, 132]
	Gastrointestinal	Bowel perforation	Case reports	[133-135]
		Liver, spleen haematoma	Case reports	[135-138]

The relationship between SWL and hypertension or diabetes is unclear. Published data are contradictory and no conclusion can be reached [3, 139-141].

3.4.2.1.4 Endourology techniques for renal stone removal

3.4.2.1.4.1 Percutaneous nephrolithotomy (PNL)

PNL remains the standard procedure for large renal calculi. Different rigid and flexible endoscopes are available and the selection is mainly based on the surgeon's own preference. Standard access tracts are 24-30 F. Smaller access sheaths, < 18 French, were initially introduced for paediatric use, but are now increasingly popular in adults.

The efficacy of miniaturized systems seems to be high, but longer OR times apply and benefit compared to standard PNL for selected patients has yet to be demonstrated [142]. There is some evidence that smaller tracts cause less bleeding complications, but further studies need to evaluate this issue [143-146].

3.4.2.1.4.1.1 Contraindications

Patients receiving anticoagulant therapy must be monitored carefully pre- and postoperatively. Anticoagulant therapy must be discontinued before PNL [147].

Other important contraindications include:

- untreated UTI;
- tumour in the presumptive access tract area;
- potential malignant kidney tumour;
- pregnancy (Section 3.4.3.1).

3.4.2.1.4.1.2 Best clinical practice

Intracorporeal lithotripsy

Several methods for intracorporeal lithotripsy are available (the devices are discussed in Section 3.4.1.2.1.1.5). During PNL, ultrasonic and pneumatic systems are most commonly used for rigid nephroscopy. When using miniaturized instruments, laser lithotripsy is associated with lower stone migration than with pneumatic lithotripsy [148]. Flexible endoscopes require laser lithotripsy to maintain tip deflection and the Ho:YAG laser has become the standard, as for ureteroscopy [149]. Electrohydraulic lithotripsy (EHL) is highly effective, but is no longer considered as a first-line technique, due to possible collateral damage [150].

Recommendations	GR
Ultrasonic, ballistic and Ho:YAG devices are recommended for intracorporeal lithotripsy during PNL.	A*
When using flexible instruments, the Ho:YAG laser is currently the most effective device.	

*Upgraded based on panel consensus.

Preoperative imaging

Preprocedural evaluations are summarised in Section 3.3.1. In particular, PNL, US or CT of the kidney and the surrounding structures can provide information regarding interpositioned organs within the planned percutaneous path (e.g., spleen, liver, large bowel, pleura, and lung) [151].

Recommendation	GR
Preprocedural imaging, including contrast medium where possible or retrograde study when starting the procedure, is mandatory to assess stone comprehensiveness, view the anatomy of the collecting system, and ensure safe access to the renal stone.	A*

*Upgraded based on panel consensus.

Antibiotic therapy – see General recommendations and precautions for stone removal (See Section 3.4.1.4.1).

Positioning of the patient

Both prone and supine positions are equally safe.

Although the supine position confers some advantages, it depends on appropriate equipment being available to position the patient correctly, for example, X-ray devices and an operating table. Most studies cannot demonstrate an advantage of supine PNL in terms of OR time. In some series, stone-free rate is lower than for the prone position despite a longer OR time. Prone position offers more options for puncture and is therefore preferred for upper pole or multiple access [152-154]. The Urolithiasis Guidelines Panel will be setting up a systematic review to assess this topic.

Puncture

Colon interposition in the access tract of PNL can lead to colon injuries. Preoperative CT or intraoperative US allows identification of the tissue between the skin and kidney and lowers the incidence of bowel injury [155, 156].

Dilatation

Dilatation of the percutaneous access tract can be achieved using a metallic telescope, single (serial) dilators, or a balloon dilatator. The difference in outcomes is less related to the technology used than to the experience of the surgeon [155].

Nephrostomy and stents

The decision on whether or not to place a nephrostomy tube at the end of the PNL procedure depends on several factors, including:

- presence of residual stones;
- likelihood of a second-look procedure;
- significant intraoperative blood loss;
- urine extravasation;
- ureteral obstruction;
- potential persistent bacteriuria due to infected stones;
- solitary kidney;
- bleeding diathesis;
- planned percutaneous chemolitholysis.

Small bore nephrostomies seem to have advantages in terms of postoperative pain [157, 158].

Tubeless PNL is performed without a nephrostomy tube. When neither a nephrostomy tube nor a ureteral stent is introduced, the procedure is known as totally tubeless PNL. In uncomplicated cases, the latter procedure results in a shorter hospital stay, with no disadvantages reported [159-161].

Recommendation	LE	GR
In uncomplicated cases, tubeless (without nephrostomy tube) or totally tubeless (without nephrostomy tube and ureteral stent) PNL procedures provide a safe alternative.	1b	A

3.4.2.1.4.1.3 Complications

The most common postoperative complications associated with PNL are fever and bleeding, urinary leakage, and problems due to residual stones (Table 3.4.2).

Table 3.4.2: Complications following PNL [162]

Complications	Transfusion	Embolisation	Urinoma	Fever	Sepsis	Thoracic complication	Organ injury	Death	LE
(Range)	(0-20%)	(0-1.5%)	(0-1%)	(0-32.1%)	(0.3-1.1%)	(0-11.6%)	(0-1.7%)	(0-0.3%)	1a
N = 11,929	7%	0.4%	0.2%	10.8%	0.5%	1.5%	0.4%	0.05%	

Perioperative fever can occur, even with a sterile preoperative urinary culture and perioperative antibiotic prophylaxis, because the renal stones themselves may be a source of infection. Intraoperative renal stone culture may therefore help to select postoperative antibiotics [163, 164]. Intraoperative irrigation pressure < 30 mm Hg and unobstructed postoperative urinary drainage may be important factors in preventing postoperative sepsis. Bleeding after PNL may be treated by brief clamping of the nephrostomy tube. Super-selective embolic occlusion of the arterial branch may become necessary in the case of severe bleeding.

3.4.2.1.4.2 Ureterorenoscopy for renal stones (RIRS)

Technical improvements including endoscope miniaturisation, improved deflection mechanism, enhanced optical quality and tools, and introduction of disposables have led to an increased use of URS for both, renal and ureteral stones. Major technological progress has been achieved for retrograde intrarenal surgery (RIRS), [165-167]. Initial experience with digital scopes demonstrated shorter operation times due to the improvement in image quality [166-168]. For best clinical practice see Section 3.4.3.1.4.1.2 (Ureteral stones-URS).

Stones that cannot be extracted directly must be disintegrated. If it is difficult to access stones that need disintegration within the lower renal pole, it may help to displace them into a more accessible calyx [169].

Recommendation	GR
In case PNL is not an option, larger stones, even larger than 2 cm, may be treated with flexible URS. However, in that case there is a higher risk that a follow-up procedure and placement of a ureteral stent may be needed. In complex stone cases, open or laparoscopic approaches are possible alternatives.	B

GR = grade of recommendation; PNL = percutaneous nephrolithotomy; URS = ureterorenoscopy.

3.4.2.1.4.3 Open and laparoscopic surgery for removal of renal stones

Advances in SWL and endourological surgery (URS and PNL) have significantly decreased the indications for open or laparoscopic stone surgery [170-176]. There is a consensus that most complex stones, including partial and complete staghorn stones, should be approached primarily with PNL. Additionally, a combined approach with PNL and retrograde flexible uretero-renaloscopy (RIRS) may also be an appropriate alternative. However, if a reasonable number of percutaneous approaches are not likely to be successful, or if multiple, endourological approaches have been performed unsuccessfully, open or laparoscopic surgery may be a valid treatment option [177-180].

Recommendations	LE	GR
Laparoscopic or open surgical stone removal may be considered in rare cases in which SWL, URS, and percutaneous URS fail or are unlikely to be successful.	3	C
When expertise is available, laparoscopic surgery should be the preferred option before proceeding to open surgery, especially when the stone mass is centrally located.	3	C

3.4.2.2 Indication for active stone removal of renal stones [181]

- Stone growth;
- Stones in high-risk patients for stone formation;
- Obstruction caused by stones;
- Infection;
- Symptomatic stones (e.g., pain or haematuria);
- Stones > 15 mm;
- Stones < 15 mm if observation is not the option of choice.
- Patient preference;
- Comorbidity;
- Social situation of the patient (e.g., profession or travelling);
- Choice of treatment.

Statement	LE
Although the question of whether caliceal stones should be treated is still unanswered, stone growth, de novo obstruction, associated infection, and acute and/or chronic pain are indications for treatment [181-183].	3

The risk of a symptomatic episode or need for intervention seems to be ~10-25% per year, with a cumulative 5-year event probability of 48.5% [184-187]. A prospective RCT with > 2 years clinical follow-up reported no significant difference between SWL and observation when they compared asymptomatic caliceal stones < 15 mm in terms of SFR, symptoms, requirement for additional treatment, quality of life, renal function, or hospital admission [188]. Although some have recommended prophylaxis for these stones to prevent renal colic, haematuria, infection, or stone growth, conflicting data have been reported [184, 186, 189]. In a follow-up period of almost 5 years after SWL, two series have demonstrated that up to 25% of patients with small residual fragments needed treatment [128, 190].

Recommendations	GR
Renal stones should be treated in the case of growth, formation of de novo obstruction, associated infection, and acute or chronic pain.	A*
Comorbidity and patient preference need to be taken into consideration when making treatment decisions.	C

**Upgraded based on panel consensus.*

3.4.2.3 General recommendations and precautions for renal stone removal

3.4.2.3.1 Antibiotic therapy

Urinary tract infections should always be treated if stone removal is planned. In patients with clinically significant infection and obstruction, drainage should be performed for several days, via a stent or percutaneous nephrostomy, before starting stone removal.

Recommendation	GR
Urine culture or urinary microscopy is mandatory before any treatment is planned.	A*

**Upgraded following panel consensus.*

Perioperative antibiotic prophylaxis

For risk of infection following ureteroscopy and percutaneous stone removal, no clear-cut evidence exists [191]. In a review of a large database of patients undergoing percutaneous nephrolithotomy, it was found that in patients with negative baseline urine culture, antibiotic prophylaxis significantly reduced the rate of postoperative fever and other complications [192]. Single dose administration was found to be sufficient [193, 194].

Recommendations	LE	GR
UTIs must be excluded or treated prior to endourologic stone removal.	1b	A
In all patients, perioperative antibiotic prophylaxis is recommended.	1b	A*

UTI = urinary tract infection.

3.4.2.3.2 Antithrombotic therapy and stone treatment

Patients with a bleeding diathesis, or receiving antithrombotic therapy, should be referred to an internist for appropriate therapeutic measures before deciding on and during stone removal [195-199]. In patients with an uncorrected bleeding diathesis, the following are at elevated risk of haemorrhage or perinephritic haematoma (PNH) (high-risk procedures):

- SWL (hazard ratio of PNH up to 4.2 during anticoagulant/antiplatelet medication [200] [LE: 2];
- PNL;
- percutaneous nephrostomy;
- laparoscopic surgery;
- open surgery [195, 201, 202].

SWL is feasible and safe after correction of the underlying coagulopathy [203-205]. In the case of an uncorrected bleeding disorder or continued antithrombotic therapy, URS, in contrast to SWL and PNL, might offer an alternative approach since it is associated with less morbidity [147, 206-209]. Only data on flexible ureteroscopy is available which support the superiority of URS in the treatment of proximal ureteric stones [206, 210].

Recommendations	LE	GR
In patients at high-risk for complications (due to antithrombotic therapy) in the presence of an asymptomatic caliceal stone, active surveillance should be offered.		C
Temporary discontinuation, or bridging of antithrombotic therapy in high-risk patients, should be decided in consultation with the internist.	3	B
Antithrombotic therapy should be stopped before stone removal after weighing the thrombotic risk.	3	B
If stone removal is essential and antithrombotic therapy cannot be discontinued, retrograde (flexible) ureterorenoscopy is the preferred approach since it is associated with less morbidity.	2a	A*

*Upgraded based on panel consensus.

3.4.2.3.3 Obesity

Obesity can cause a higher risk due to anaesthesiological measurements, and a lower success rate after SWL and PNL.

3.4.2.3.4 Stone composition

Stones composed of brushite, calcium oxalate monohydrate, or cystine are particularly hard [27]. Percutaneous nephrolithotomy or RIRS are alternatives for removal of large SWL-resistant stones.

Recommendation	LE	GR
Consider the stone composition before deciding on the method of removal (based on patient history, former stone analysis of the patient or HU in unenhanced CT. Stones with medium density > 1,000 HU on NCCT are less likely to be disintegrated by SWL) [27].		
Radiolucent stones may be dissolvable (See Section 3.4.2.1.2.2).	2a	B

CT = computed tomography; HU = Hounsfield unit; NCCT = non-contrast enhanced computed tomography; SWL = shockwave lithotripsy.

3.4.2.3.5 Steinstrasse

Steinstrasse is an accumulation of stone fragments or stone gravel in the ureter, which does not pass within a reasonable period of time, and interferes with the passage of urine [211]. Steinstrasse occurs in 4-7% cases of SWL [126], and the major factor in steinstrasse formation is stone size [212].

Insertion of a ureteral stent before SWL prevents formation of steinstrasse in stones > 15 mm in diameter [213]. A major problem of steinstrasse is ureter obstruction, which can be silent in 23% of cases [125, 214].

When steinstrasse is asymptomatic, conservative treatment is an initial option. Medical expulsion therapy significantly increases stone expulsion and reduces the need for endoscopic intervention [215, 216].

Table 3.4.3: Treatment of steinstrasse

Asymptomatic	LE	Symptomatic	LE	Symptomatic + fever	LE
1. MET	1	1. URS	3	1. PCN	1
2. SWL	3	1. PCN	3	2. Stent	2
3. URS	3	1. SWL	3		
		2. Stent	3		

Numbers 1,2, and 3 indicate first, second and third choice (Panel consensus).

Statements	LE
Medical expulsion therapy increases the stone expulsion rate of steinstrasse [215].	1b
When spontaneous passage is unlikely, further treatment of steinstrasse is indicated.	4
SWL is indicated in asymptomatic and symptomatic cases, with no evidence of UTI, when large stone fragments are present [217].	4
Ureteroscopy is effective for the treatment of steinstrasse [218].	3
Placement of a percutaneous nephrostomy tube or ureteral stent is indicated for symptomatic ureteric obstruction with/without UTI.	4

Recommendations	LE	GR
Percutaneous nephrostomy is indicated for steinstrasse associated with urinary tract infection/fever.	4	C
Shockwave lithotripsy or ureterorenoscopy are indicated for steinstrasse when large stone fragments are present.	4	C

3.4.2.3 Selection of procedure for active removal of renal stones

3.4.2.3.1 Stones in renal pelvis or upper/middle calices

Shockwave lithotripsy, PNL and RIRS are available treatment modalities for renal calculi. While PNL efficacy is hardly affected by stone size, the SFRs after SWL or URS are inversely proportional to stone size [219-222]. Shockwave lithotripsy achieves good SFRs for stones up to 20 mm, except for those at the lower pole [221, 223]. Endourology is considered an alternative because of the reduced need of repeated procedures and consequently a shorter time until stone-free status is achieved. Stones > 20 mm should be treated primarily by PNL, because SWL often requires multiple treatments, and has the risk of ureteral obstruction (colic or steinstrasse) with the need for adjunctive procedures (Figure 3.4.1) [122]. Retrograde renal surgery cannot be recommended as first-line treatment for stones > 20 mm in uncomplicated cases as SFR is decreasing, and staged procedures have become necessary. However, it may be a first-line option in patients where PNL is not an option or contraindicated.

3.4.2.3.2 Stones in the lower renal pole

The stone clearance rate after SWL seems to be lower for stones in the inferior calyx than for other intrarenal locations. Although the disintegration efficacy of SWL is not limited compared to other locations, the fragments often remain in the calyx and cause recurrent stone formation. The reported SFR of SWL for lower pole calculi is 25-85%. The preferential use of endoscopic procedures is under discussion [122, 219-223].

The following can impair successful stone treatment by SWL:

- steep infundibular-pelvic angle;
- long calyx;
- narrow infundibulum (Table 3.4.4) [98, 224].

Further anatomical parameters cannot yet be established. The value of supportive measures such as inversion, vibration or hydration remains under discussion.

Table 3.4.4: Unfavourable factors for SWL success [98, 224-226]

Factors that make SWL less likely
Shockwave-resistant stones (calcium oxalate monohydrate, brushite, or cystine).
Steep infundibular-pelvic angle.
Long lower pole calyx (> 10 mm).
Narrow infundibulum (< 5 mm).

Shockwave lithotripsy for the lower pole is often disappointing, therefore, endourological procedures (PNL and RIRS) are recommended for stones > 15 mm. If there are negative predictors for SWL, PNL and RIRS might be a reasonable alternative, even for smaller calculi.

Retrograde renal surgery seems to have comparable efficacy to SWL [122, 223]. Recent clinical experience has suggested an advantage of URS over SWL, but at the expense of greater invasiveness. Depending on operator skills, stones up to 3 cm can be treated efficiently by RIRS [224, 227-229]. However, staged procedures are frequently required.

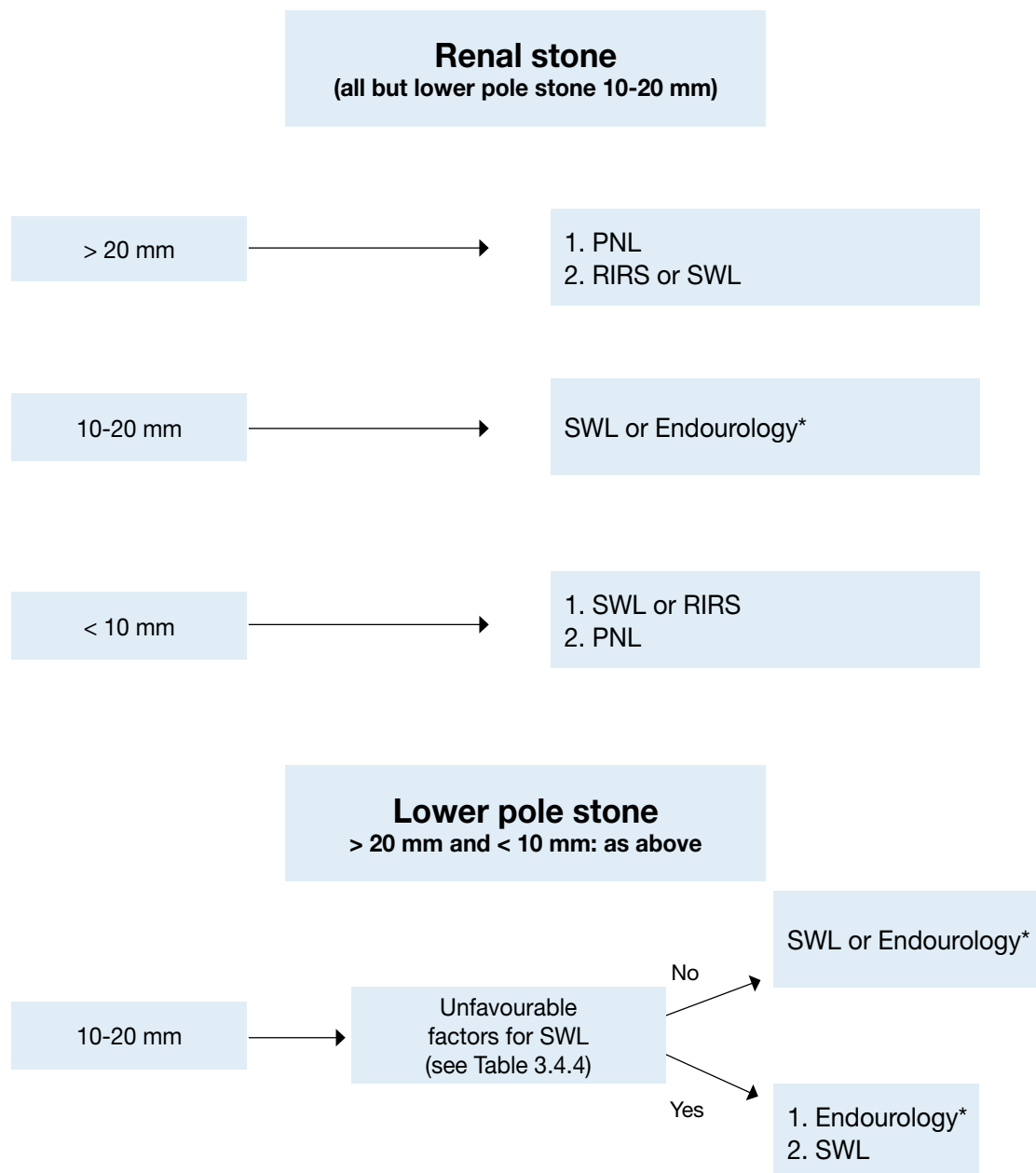
In complex stone cases, open or laparoscopic approaches are possible alternatives (see appropriate chapters).

3.4.2.3.3 Recommendations for the selection of procedures for active removal of renal stones

Recommendations	GR
SWL and endourology (PNL, RIRS) are treatment options for stones < 2 cm within the renal pelvis and upper or middle calices.	B
PNL should be used as first-line treatment of larger stones > 2 cm.	B
In case PNL is not an option, larger stones (> 2 cm) may be treated with flexible URS. However, in that case there is a higher risk that a follow-up procedure and placement of a ureteral stent may be needed.	B
For the lower pole, PNL or RIRS is recommended, even for stones > 1.5 cm, because the efficacy of SWL is limited (depending on favourable and unfavourable factors for SWL).	B

PNL = percutaneous nephrolithotomy; RIRS = retrograde renal surgery; SWL = shock wave lithotripsy; URS = ureterorenoscopy.

Figure 3.4.1: Treatment algorithm for renal calculi



*The term 'Endourology' encompasses all PNL and URS interventions.

SWL = shockwave lithotripsy; PNL = percutaneous nephrolithotomy; URS = ureterorenoscopy; SFR = stone-free rate; RIRS = retrograde renal surgery

3.4.3 **Specific stone management of Ureteral stones**

3.4.3.1 *Types of treatment*

3.4.3.1.1 Conservative treatment / observation

There are only limited data regarding spontaneous stone passage according to stone size [230]. It is estimated that 95% of stones up to 4 mm pass within 40 days [3].

Observation is feasible in informed patients who develop no complications (infection, refractory pain, deterioration of renal function).

Recommendations	LE	GR
In patients with newly diagnosed small* ureteral stones, if active removal is not indicated (Section 3.4.2.2), observation with periodic evaluation is an optional initial treatment.	1a	A
Appropriate medical therapy should be offered to these patients to facilitate stone passage during observation.		

*See stratification data [3].

Based on the analysis of available evidence, an exact cut-off size for stones that are likely to pass spontaneously cannot be provided; ≤ 10 mm may be considered a best estimate [3]. Therefore, the Panel decided not to include stone size in this recommendation and would rather limit “small”, suggesting ≤ 6 mm. The Panel is aware of the fact that spontaneous stone expulsion decreases with increasing stone size and that there are differences between individual patients.

3.4.3.1.2 Pharmacological treatment, Medical expulsive therapy (MET)

MET should only be used in informed patients. Treatment should be discontinued in case complications develop (infection, refractory pain, deterioration of renal function).

Meta-analyses have shown that patients with ureteral stones treated with α -blockers or nifedipine are more likely to pass stones with fewer colic episodes than those not receiving such therapy [72, 231].

Statement	LE
There is good evidence that MET accelerates spontaneous passage of ureteral stones and fragments generated with SWL, and limits pain [72, 216, 231-237].	1a

Medical agents

Tamsulosin is one of the most commonly used α -blockers [72, 232, 233]. However, one small study has suggested that tamsulosin, terazosin and doxazosin are equally effective, indicating a possible class effect [238]. This is also indicated by several trials demonstrating increased stone expulsion using doxazosin [72, 238, 239], terazosin [238, 240], alfuzosin [241-244] naftopidil [245, 246], and silodosin [247-249].

Statement	LE
Several trials have demonstrated an α -blocker class effect on stone expulsion rates.	1b

With regard to the class effect of calcium-channel blockers, only nifedipine has been investigated [72, 234-236, 250, 251] (LE = 1a).

Administration of tamsulosin and nifedipine is safe and effective in patients with distal ureteral stones with renal colic. However, tamsulosin is significantly better than nifedipine in relieving renal colic and facilitating and accelerating ureteral stone expulsion [236, 250, 251].

Based on studies with a limited number of patients [252, 253] (LE: 1b), no recommendation for the use of corticosteroids in combination with α -blockers in MET can be made.

Statement	LE
There is no evidence to support the use of corticosteroids as monotherapy for MET. Insufficient data exist to support the use of corticosteroids in combination with α -blockers as an accelerating adjunct [238, 252, 253].	1b

Recommendations for MET	LE	GR
For MET, α -blockers are recommended.	1a	A
Patients should be counseled regarding the attendant risks of MET, including associated drug side effects, and should be informed that it is administered off-label [†] .		A*
Patients, who elect for an attempt at spontaneous passage or MET, should have well-controlled pain, no clinical evidence of sepsis, and adequate renal functional reserve.		A
Patients should be followed once between 1 and 14 days to monitor stone position and assessed for hydronephrosis.	4	A*

[†] It is not known if tamsulosin harms the human foetus or if it is found in breast milk.

*Upgraded based on panel consensus.

**MET in children cannot be recommended due to the limited data in this specific population.

MET = medical expulsion therapy.

3.4.3.1.2.1 Factors affecting success of medical expulsive therapy (tamsulosin)

Stone size

Due to the high likelihood of spontaneous passage of stones up to ~5 mm, MET is less likely to increase the stone-free rate (SFR) [72, 233] (LE: 1b). However, MET does reduce the need for analgesics [72, 232] (LE: 1a).

Stone location

The vast majority of trials have investigated distal ureteral stones [72]. Two RCT assessed the effect of tamsulosin on spontaneous passage of proximal ureteral calculi <10 mm demonstrating stone migration to a more distal part of the ureter [254] and a significantly higher stone expulsion rate and shorter expulsion time for stones < 6 mm [255].

3.4.3.1.2.2 Medical expulsive therapy after extracorporeal shock wave lithotripsy (SWL)

One RCT and a meta-analysis have shown that MET after SWL for ureteral or renal stones can expedite expulsion and increase SFRs and reduce analgesic requirements [119, 237] (LE: 1a).

3.4.3.1.2.3 Medical expulsive therapy after ureteroscopy

MET following holmium:YAG laser lithotripsy increases SFRs and reduces colic episodes [256] (LE: 1b).

3.4.3.1.2.4 Medical expulsive therapy and ureteral stents (Section below)

3.4.3.1.2.5 Duration of medical expulsive therapy treatment

Most studies have had a duration of 1 month. No data are currently available to support other time-intervals.

3.4.3.1.2.6 Possible side-effects include retrograde ejaculation and hypotension [72]

3.4.3.1.3 SWL

Best clinical practice see Section 3.4.2.1.4.1.2 (renal stones).

Stenting

The 2007 AUA/EAU Guidelines on the management of ureteral calculi state that routine stenting is not recommended as part of SWL [3]. When the stent is inserted, patients often suffer from frequency, dysuria, urgency, and suprapubic pain [257].

Recommendation	LE	GR
Routine stenting is not recommended as part of SWL treatment of ureteral stones.	1b	A

SWL = shock wave lithotripsy.

3.4.3.1.4 Endourology techniques

3.4.3.1.4.1 Ureteroscopy (URS)

The current standard for rigid ureterorenoscopes are tip diameters of < 8 F. Rigid URS can be used for the whole ureter [3]. However, technical improvements, enhanced quality and tools as well as the availability of digital scopes also favour the use of flexible ureteroscopes in the ureter [165].

3.4.3.1.4.1.1 Contraindications

Apart from general problems, for example, with general anaesthesia or untreated UTIs, URS can be performed in all patients without any specific contraindications.

3.4.3.1.4.1.2 Best clinical practice in ureterorenoscopy (URS)

Access to the upper urinary tract

Most interventions are performed under general anaesthesia, although local or spinal anaesthesia is possible. Intravenous sedation is suitable for female patients with distal ureteral stones [258].

Antegrade URS is an option for large, impacted proximal ureteral calculi [259] (Section 3.4.2.6).

Safety aspects

Fluoroscopic equipment must be available in the operating room. We recommend placement of a safety wire, even though some groups have demonstrated that URS can be performed without it [260, 261].

Balloon and plastic dilators are available if necessary. If insertion of a flexible URS is difficult, prior rigid ureteroscopy can be helpful for optical dilatation. If ureteral access is not possible, insertion of a JJ stent followed by URS after 7-14 days offers an alternative procedure.

Recommendation	GR
Placement of a safety wire is recommended.	A*

**Upgraded based on panel consensus.*

Ureteral access sheaths

Hydrophilic-coated ureteral access sheaths, which are available in different calibres (inner diameter from 9 F upwards), can be inserted via a guide wire, with the tip placed in the proximal ureter.

Ureteral access sheaths allow easy multiple access to the upper urinary tract and therefore significantly facilitate URS. The use of ureteral access sheaths improves vision by establishing a continuous outflow, decreasing intrarenal pressure, and potentially reduces operating time [262, 263].

The insertion of ureteral access sheaths may lead to ureteral damage, whereas the risk was lowest in pre-stented systems [264]. No data on long-term consequences are available [264, 265]. Use of ureteral access sheaths depends on the surgeon's preference.

Stone extraction

The aim of URS is complete stone removal. "Dust and go" strategies should be limited to the treatment of large (renal) stones.

Stones can be extracted by endoscopic forceps or baskets. Only baskets made of nitinol can be used for flexible URS [266].

Recommendation	LE	GR
Stone extraction using a basket without endoscopic visualisation of the stone (blind basketing) should not be performed.	4	A*

**Upgraded based on panel consensus.*

Intracorporeal lithotripsy

The most effective lithotripsy system is the Ho:YAG laser, which has become the gold standard for ureteroscopy and flexible nephroscopy (Section 3.4.2.1.4.1.2), because it is effective for all stone types [267, 268]. Pneumatic and US systems can be used with high disintegration efficacy in rigid URS [269, 270].

However, stone migration into the kidney is a common problem, which can be prevented by placement of special antimigration tools proximal of the stone [271].

Recommendation	LE	GR
Ho:YAG laser lithotripsy is the preferred method for (flexible) URS.	3	B

Ho:YAG = holmium:yttrium-aluminium-garnet (laser); US = ultrasound.

Stenting before and after URS

Routine stenting is not necessary before URS. However, pre-stenting facilitates ureteroscopic management of stones, improves the SFR, and reduces complications [272].

Randomised prospective trials have found that routine stenting after uncomplicated URS (complete stone removal) is not necessary; stenting might be associated with higher postoperative morbidity [273-275]. A ureteric catheter with a shorter indwelling time (1 day) may also be used, with similar results [276].

Stents should be inserted in patients who are at increased risk of complications (e.g., ureteral trauma, residual fragments, bleeding, perforation, UTIs, or pregnancy), and in all doubtful cases, to avoid stressful emergencies. The ideal duration of stenting is not known. Most urologists favour 1-2 weeks after URS.

Alpha-blockers reduce the morbidity of ureteral stents and increase tolerability [277, 278]. A recently published

meta-analysis provides evidence for improvement of ureteral stent tolerability with tamsulosin [279].

Statements	LE
In uncomplicated URS, a stent need not be inserted.	1a
An α -blocker can reduce stent-related symptoms.	1a

3.4.3.1.4.1.3 Complications

The overall complication rate after URS is 9-25% [3, 280, 281]. Most are minor and do not require intervention. Ureteral avulsion and strictures are rare (< 1%). Previous perforations are the most important risk factor for complications.

3.4.3.1.4.2 Percutaneous antegrade ureteroscopy

Percutaneous antegrade removal of ureteral stones is a consideration in selected cases, i. e. large, impacted proximal ureteral calculi with dilated renal collecting system [284], or when the ureter is not amenable to retrograde manipulation [259, 285-288].

Recommendation	GR
Percutaneous antegrade removal of ureteral stones is an alternative when SWL is not indicated or has failed, and when the upper urinary tract is not amenable to retrograde URS.	A

SWL = shock wave lithotripsy; URS ureterorenoscopy

3.4.3.1.5 Laparoscopic ureteral stone removal

Few studies have reported laparoscopic stone removal (Section 3.4.2.1.4.3). These procedures are usually reserved for special cases, therefore, the reported data could not be used to compare procedures with each other or with SWL or URS. These more invasive procedures have yielded high SFRs.

For ureterolithotomy, laparoscopy is recommended for large impacted stones when endoscopic lithotripsy or SWL has failed.	2	B
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SWL = shock wave lithotripsy.

3.4.3.2 Indications for active removal of ureteral stones [3, 230, 282]

Indications for active removal of ureteral stones are:

- Stones with low likelihood of spontaneous passage;
- Persistent pain despite adequate analgesic medication;
- Persistent obstruction;
- Renal insufficiency (renal failure, bilateral obstruction, or single kidney).

3.4.3.2.1 General recommendations and precautions

3.4.3.2.1.1 Antibiotic treatment

The same considerations apply as in renal stone removal (Section 3.4.1.4.2).

Single dose administration was found to be sufficient as perioperative antibiotic prophylaxis [193, 194].

Recommendations	LE	GR
UTIs must be excluded or treated prior to endourologic stone removal.	1b	A
In all patients undergoing endourologic treatment, perioperative antibiotic prophylaxis is recommended.	1b	A*

UTI = urinary tract infection.

3.4.3.2.1.2 Obesity

Obesity can cause a lower success rate after SWL and PNL.

Statement	LE
In the case of severe obesity, URS is a more promising therapeutic option than SWL.	2b

3.4.3.2.1.3 Bleeding disorder

URS can be performed in patients with bleeding disorders, with a moderate increase in complications [147, 208]. Discontinuation of anticoagulant therapy should be weighed against the risk, in each individual patient.

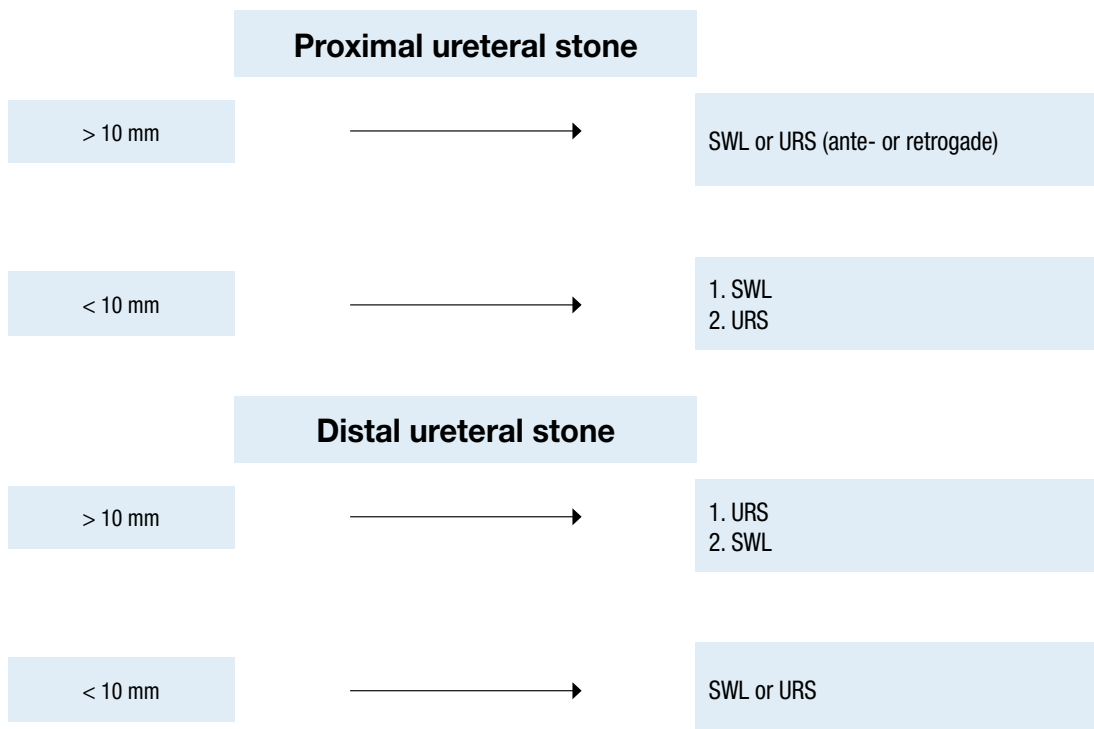
3.4.3.3 Selection of procedure for active removal of ureteral stones

Overall stone-free rates after URS or ESWL for ureteral stones are comparable. However, larger stones achieve

earlier stone-free status with URS. Although URS is effective for ureteric calculi, it has greater potential for complications. However, in the current endourological era, the complication rate and morbidity of ureteroscopy have been significantly reduced [283].

Patients should be informed that URS has a better chance of achieving stone-free status with a single procedure, but has higher complication rates [Sections 3.4.2.1.3.3 (Complications of SWL) and 3.4.3.1.4.1.3 (Complications of URS)].

Figure 3.4.2: Recommended treatment options (if indicated for active stone removal) (GR: A*)



**Upgraded following panel consensus.*

SWL = shockwave lithotripsy; URS = ureterorenoscopy.

3.4.4 Management of patients with residual stones

The clinical problem of residual renal stones is related to the risk of developing:

- new stones from such nidi (heterogeneous nucleation);
- persistent UTI;
- dislocation of fragments with/without obstruction and symptoms [128, 289, 290].

Recommendations	LE	GR
Identification of biochemical risk factors and appropriate stone prevention is particularly indicated in patients with residual fragments or stones [128, 290, 291].	1b	A
Patients with residual fragments or stones should be followed up regularly to monitor disease course.	4	C

Recurrence risk in patients with residual fragments after treatment of infection stones is higher than for other stones [291]. For all stone compositions, 21-59% of patients with residual stones required treatment within 5 years. Fragments > 5 mm are more likely than smaller ones to require intervention [128, 289, 292].

Table 3.4.5: Recommendations for the treatment of residual fragments

Residual fragments, stones (largest diameter)	Symptomatic residuals	Asymptomatic residuals	LE	GR
< 4-5 mm	Stone removal	Reasonable follow-up (dependent on risk factors)	4	C
> 6-7 mm	Stone removal			

3.4.4.1 Therapy

The indications for active removal of residual stones and selection of the procedure are based on the same criteria as for primary stone treatment (Section 3.4.2.4) and includes repeat SWL [293].

If intervention is not required, medical therapy according to stone analysis, patient risk group, and metabolic evaluation might help to prevent regrowth of residual fragments [294-296].

Statement	LE
For well-disintegrated stone material in the lower calix, an inversion therapy with simultaneous mechanical percussion maneuver under enforced diuresis may facilitate stone clearance [297].	1b

Recommendations	LE	GR
After SWL and URS, and in the presence of residual fragments, MET is recommended using an α -blocker to improve fragment clearance.	1a	A

SWL = shockwave lithotripsy; URS = ureteroscopy; MET = medical expulsive therapy

3.4.5 Management of specific patient groups

3.4.5.1 Management of urinary stones and related problems during pregnancy

Clinical management of a pregnant urolithiasis patient is complex and demands close collaboration between patient, radiologist, obstetrician and urologist. For diagnostic imaging see Section 3.3.1).

If spontaneous passage does not occur, or if complications develop (e.g., induction of premature labour), placement of a ureteral stent or a percutaneous nephrostomy tube is necessary [298-300]. Unfortunately, these temporising therapies are often associated with poor tolerance, and they require multiple exchanges during pregnancy, due to the potential for rapid encrustation. Ureteroscopy has become a reasonable alternative in these situations [301, 302]. Although feasible, retrograde endoscopic and percutaneous removal of renal stones during pregnancy remain an individual decision and should be performed only in experienced centres [303]. Pregnancy remains an absolute contraindication for SWL.

Statements	LE
If intervention becomes necessary, placement of a ureteral stent or a percutaneous nephrostomy tube are readily available primary options.	3
Ureteroscopy is a reasonable alternative to avoid long-term stenting/drainage.	1a
Regular follow-up until final stone removal is necessary due to the higher encrustation tendency of stents during pregnancy.	

Recommendation	GR
Conservative management should be the first-line treatment for all non-complicated cases of urolithiasis in pregnancy (except those that have clinical indications for intervention).	A

3.4.5.2 Management of stones in patients with urinary diversion

3.4.5.2.1 Aetiology

Patients with urinary diversion are at high risk for stone formation in the renal collecting system and ureter or in the conduit or continent reservoir [304-306]. Metabolic factors (hypercalciuria, hyperoxaluria and hypocitraturia), infection with urease-producing bacteria, foreign bodies, mucus secretion, and urinary stasis are responsible for stone formation [307] (Section 3.1.3). One study has shown that the risk for recurrent upper-tract stones in patients with urinary diversion subjected to PNL was 63% at 5 years [308].

3.4.5.2.2 Management

Smaller upper-tract stones can be treated effectively with SWL [286, 309]. In the majority, endourological techniques are necessary to achieve stone-free status [285]. In individuals with long, tortuous conduits or with

invisible ureter orifices a retrograde endoscopic approach might be difficult or impossible.

Statement	LE
The choice of access depends on the feasibility of orifice identification in the conduit or bowel reservoir. Whenever a retrograde approach is impossible, percutaneous access with antegrade URS is the alternative.	4

Recommendation	GR
PNL is the preferred treatment for removal of large renal stones in patients with urinary diversion, as well as for ureteral stones that cannot be accessed via a retrograde approach or that are not amenable to SWL.	A*

PNL = percutaneous nephrolithotomy; SWL = shockwave lithotripsy.

For stones in the conduit, a trans-stomal approach can be used to remove all stone material (along with the foreign body) using standard techniques, including intracorporeal lithotripsy and flexible endoscopes. Trans-stomal manipulations in continent urinary diversion must be performed carefully to avoid disturbance of the continence mechanism [310].

Before considering any percutaneous approach in these cases, CT should be undertaken to assess the presence of an overlying bowel, which could make this approach unsafe [311], and if present, an open surgical approach should be considered.

3.4.5.2.3 Prevention

Recurrence risk is high in these patients [308]. Metabolic evaluation and close follow-up of the patients are necessary to obtain the risk parameters for effective long-term prevention. Preventive measures include medical management of metabolic abnormalities, appropriate therapy of urinary infections, and hyperdiuresis or regular irrigation of continent reservoirs [312].

3.4.5.3 Management of stones in patients with neurogenic bladder

3.4.5.3.1 Aetiology, clinical presentation and diagnosis

Patients with neurogenic bladder develop urinary calculi because of additional risk factors such as bacteriuria, pelvicaliectasis, vesicoureteral reflux, renal scarring, lower urinary tract reconstruction, and thoracic spinal defect [313]. The main issues are urinary stasis and infection (Section 3.1.3). Indwelling catheters and surgical interposition of bowel segments for treatment of bladder dysfunction both facilitate UTI. Although calculi can form at any level of the urinary tract, they occur more frequently in the bladder; especially if bladder augmentation has been performed [314, 315].

Diagnosis of stones may be difficult and late in the absence of clinical symptoms due to sensory impairment and vesicourethral dysfunction. Difficulties in self-catheterisation should lead to suspicion of bladder calculi. Imaging studies are needed (US, CT) to confirm clinical diagnosis prior to surgical intervention.

3.4.5.3.2 Management

Management of calculi in patients with neurogenic bladder is similar to that described in Section 3.3.3. In MMC (myelomeningocele) patients, latex allergy is common, therefore, appropriate measures need to be taken regardless of the treatment [316]. Any surgery in these patients must be performed under general anaesthesia because of the impossibility of using spinal anaesthesia. Bone deformities often complicate positioning on the operating table [317]. The risk of stone formation after augmentation cystoplasty in immobile patients with sensory impairment can be significantly reduced by irrigation protocols [312].

For efficient long-term stone prevention in patients with neurogenic bladder, correction of the metabolic disorder, appropriate infection control, and restoration of normal storing/voiding function of the bladder are needed.

Statement	LE
Patients undergoing urinary diversion and/or suffering from neurogenic bladder dysfunction are at risk for recurrent stone formation.	3

Recommendation	GR
In myelomeningocele patients, latex allergy is common, thus appropriate measures need to be taken regardless of the treatment. For surgical interventions, general anesthesia remains the only option.	B

3.4.5.4 Management of stones in transplanted kidneys

3.4.5.4.1 Aetiology

Transplant patients depend on their solitary kidney for renal function. Impairment causing urinary stasis/obstruction therefore requires immediate intervention or drainage of the transplanted kidney. Risk factors in these patients are multifold:

- Immunosuppression increases the infection risk, resulting in recurrent UTIs.
- Hyperfiltration, excessively alkaline urine, renal tubular acidosis, and increased serum calcium caused by persistent tertiary hyperparathyroidism [318] are biochemical risk factors.

Stones in kidney allografts have a incidence of 0.2-1.7% [319-321].

Recommendation	LE	GR
In patients with transplanted kidneys, unexplained fever, or unexplained failure to thrive (particularly in children), US or NCCT should be performed to rule out calculi [322].	4	B

US = ultrasound; NCCT = non-contrast enhanced computed tomography.

3.4.5.4.2 Management

Treatment decisions for selecting the appropriate technique for stone removal from a transplanted kidney are difficult. Although management principles are similar to those applied in other single renal units [323-326], additional factors such as transplant function, coagulative status, and anatomical obstacles due to the iliacal position of the organ, directly influence the surgical strategy.

For large or ureteral stones, careful percutaneous access and subsequent antegrade endoscopy are more favourable. The introduction of small flexible ureteroscopes and the holmium laser has made ureteroscopy a valid treatment option for transplant calculi. However, one must be aware of potential injury to adjacent organs [327-329]. Retrograde access to transplanted kidneys is difficult due to the anterior location of the ureteral anastomosis, and ureteral tortuosity [330-332].

Statements	LE
Conservative treatment for small asymptomatic stones is only possible under close surveillance and in absolutely compliant patients.	
SWL for small calyceal stones is an option with minimal complication risk, but localisation of the stone can be challenging and SFRs are poor [333, 334].	4

Recommendation	GR
In patients with transplanted kidneys, all contemporary treatment modalities, including shockwave therapy, (flexible) ureteroscopy, and percutaneous nephrolithotomy are management options.	B
Metabolic evaluation should be completed after stone removal.	A*

*Upgraded following panel consensus.

3.4.5.4.3 Special problems in stone removal

Table 3.4.6: Special problems in stone removal

Caliceal diverticulum stones	<ul style="list-style-type: none"> • SWL, PNL (if possible) or RIRS. • Can also be removed using laparoscopic retroperitoneal surgery [335-339] • Patients may become asymptomatic due to stone disintegration (SWL), whilst well-disintegrated stone material remains in the original position due to narrow caliceal neck
Horseshoe kidneys	<ul style="list-style-type: none"> • Can be treated in line with the options described above [340] • Passage of fragments after SWL might be poor • Acceptable stone free rates can be achieved with flexible ureteroscopy [341]
Stones in pelvic kidneys	<ul style="list-style-type: none"> • SWL, RIRS, PNL or laparoscopic surgery • For obese patients, the options are RIRS, PNL or open surgery
Stones formed in a continent reservoir	<ul style="list-style-type: none"> • Section 3.4.4 • Each stone must be considered and treated individually

Patients with obstruction of the ureteropelvic junction	<ul style="list-style-type: none"> • When outflow abnormality requires correction, stones can be removed by PNL together with percutaneous endopyelotomy or open/laparoscopic reconstructive surgery • URS together with endopyelotomy with Ho:YAG. • Incision with an Acucise balloon catheter might be considered, provided the stones can be prevented from falling into the pelvi-ureteral incision [342-345].
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SWL = shockwave lithotripsy; PNL = percutaneous nephrolithotomy; URS = ureterorenoscopy;
RIRS = retrograde renal surgery

3.4.6 Management of urolithiasis in children

Rates of urolithiasis have increased in developed countries, and there has been a shift in the age group experiencing a first stone episode [6, 346, 347]. More than 1% of all urinary stones are seen in patients aged < 18 years. As a result of malnutrition and racial factors, paediatric urolithiasis remains an endemic disease in some areas (e.g., Turkey and the Far East); elsewhere, the rates are similar to those observed in developed countries [348-351].

For diagnostic procedures see Section 3.3.3.2.

3.4.6.1 Stone removal

Several factors must be considered when selecting treatment procedures for children. Compared to adults, children pass fragments more rapidly after SWL [40]. For endourological procedures, the smaller organs in children must be considered when selecting instruments for PNL or URS. Anticipation of the expected stone composition should be taken into account when selecting the appropriate procedure for stone removal (cystine stones are more resistant to SWL).

Statement	LE
Spontaneous passage of a stone is more likely in children than in adults [50].	4

3.4.6.1.1 Medical expulsive therapy (MET) in children

Medical expulsive therapy has already been discussed in Section 3.4.3.1.2 but not addressing children. Although the use of α -blockers is very common in adults, there are few data to demonstrate their safety and efficacy in children, however Tamsulosin seems to support stone passage [352, 353].

3.4.6.1.2 Extracorporeal shock wave lithotripsy

Extracorporeal shock wave lithotripsy remains the least-invasive procedure for stone management in children [354-358].

SFRs of 67-93% in short-term and 57-92% in long-term follow-up studies have been reported. In children, compared with adults, SWL can achieve more effective disintegration of large stones, together with swifter and uncomplicated discharge of large fragments [356, 359]. As in adults the slow delivery rate of shock waves may improve the stone clearance rates [359]. Stones located in calices, as well as abnormal kidneys, and large stones, are more difficult to disintegrate and clear. The likelihood of urinary obstruction is higher in such cases, and children should be followed closely for the prolonged risk of urinary tract obstruction. The retreatment rate is 13.9-53.9%, and the need for ancillary procedures and/or additional interventions is 7-33% [356, 358].

The need for general anaesthesia during SWL depends on patient age and the lithotripter used. General or dissociative anaesthesia is administered in most children aged < 10 years, to avoid patient and stone motion and the need for repositioning [356, 358]. With modern lithotripters, intravenous sedation or patient-controlled analgesia have been used in selected cooperative older children [360] (LE: 2b). There are concerns regarding the safety and potential biological effects of SWL on immature kidneys and surrounding organs in children. However, during short- and long-term follow-up, no irreversible functional or morphological side effects of high-energy shock waves have been demonstrated. In addition, when the potential deterioration of renal function is taken into account (although transient), restricting the number of shock waves and the energy used during each treatment session helps protect the kidneys [361-364].

If the stone burden requires a ureteral stent, alternative procedures should be considered. Ureteral stents are seldom needed following SWL of upper tract stones, ureteral pre-stenting decreases the SFR after initial treatment [354-356].

Statements	LE
In children, the indications for SWL are similar to those in adults, however, they pass fragments more easily.	3
Children with renal stones of a diameter up to 20 mm (~ 300 mm ²) are ideal candidates for SWL.	1b

3.4.6.1.3 Endourological procedures

Improvement in intracorporeal lithotripsy devices and development of smaller instruments facilitate PNL and URS in children.

3.4.6.1.3.1 Percutaneous nephrolithotripsy (PNL)

Preoperative evaluation and indications for PNL in children are similar to those in adults. Provided appropriate size instruments and US guidance are used, age is not a limiting factor, and PNL can be performed safely by experienced operators, with less radiation exposure, even for large and complex stones [365-368]. SFRs are between 68% and 100% after a single session, and increase with adjunctive measures, such as second-look PNL, SWL and URS [365].

As for adults, tubeless PNL is safe in children, in well-selected cases [369].

Statements	LE
For paediatric patients, the indications for PNL are similar to those in adults.	1a

Recommendation	GR
In children, PNL is recommended for treatment of renal pelvic or caliceal stones with a diameter > 20 mm (~ 300 mm ²).	C

PNL = percutaneous nephrolithotomy.

3.4.6.1.3.2 Ureteroscopy

Although SWL is still the first-line treatment for most ureteral stones, it is unlikely to be successful for stones > 10 mm in diameter, or for impacted, calcium oxalate monohydrate or cystine stones, or stones in children with unfavourable anatomy and in whom localisation is difficult [370, 371].

If SWL is not promising, ureteroscopy can be used. With the clinical introduction of smaller-calibre instruments, this modality has become the treatment of choice for medium and larger distal ureteric stones in children [370-373].

Different lithotripsy techniques, including ultrasonic, pneumatic and laser lithotripsy, are all safe and effective (Section 3.4.3.1.4.1.2) [374, 375].

Recommendation	LE	GR
For intracorporeal lithotripsy, the same devices as in adults can be used (Ho:Yag laser, pneumatic- and US lithotripters).	3	C

Flexible ureteroscopy has become an efficacious treatment for paediatric upper urinary tract stones. It might be particularly effective for treatment of proximal ureteral calculi and for stones < 1.5 cm in the lower pole calices [376-378].

3.4.6.1.3.3 Open or laparoscopic surgery

Most stones in children can be managed by SWL and endoscopic techniques. Therefore, the rate of open procedure has dropped significantly [379-381]. Indications for surgery include: failure of primary therapy for stone removal; very young children with complex stones; congenital obstruction that requires simultaneous surgical correction; severe orthopaedic deformities that limit positioning for endoscopic procedures; and abnormal kidney position [354, 355, 366]. Open surgery can be replaced by laparoscopic procedures in experienced hands [380, 381].

3.4.6.1.3.4 Special considerations on recurrence prevention

All paediatric stone formers need metabolic evaluation and recurrence prevention with respect to the detected stone type. In radiolucent stones oral chemolysis could be considered as an alternative to SWL [382]. In the case of obstructive pathology in association with the established metabolic abnormalities, treatment should not be delayed. Children are in the high-risk group for stone recurrence [383] (Chapter 4).

4. FOLLOW UP METABOLIC EVALUATION AND RECURRENCE PREVENTION

4.1 General metabolic considerations for patient work-up

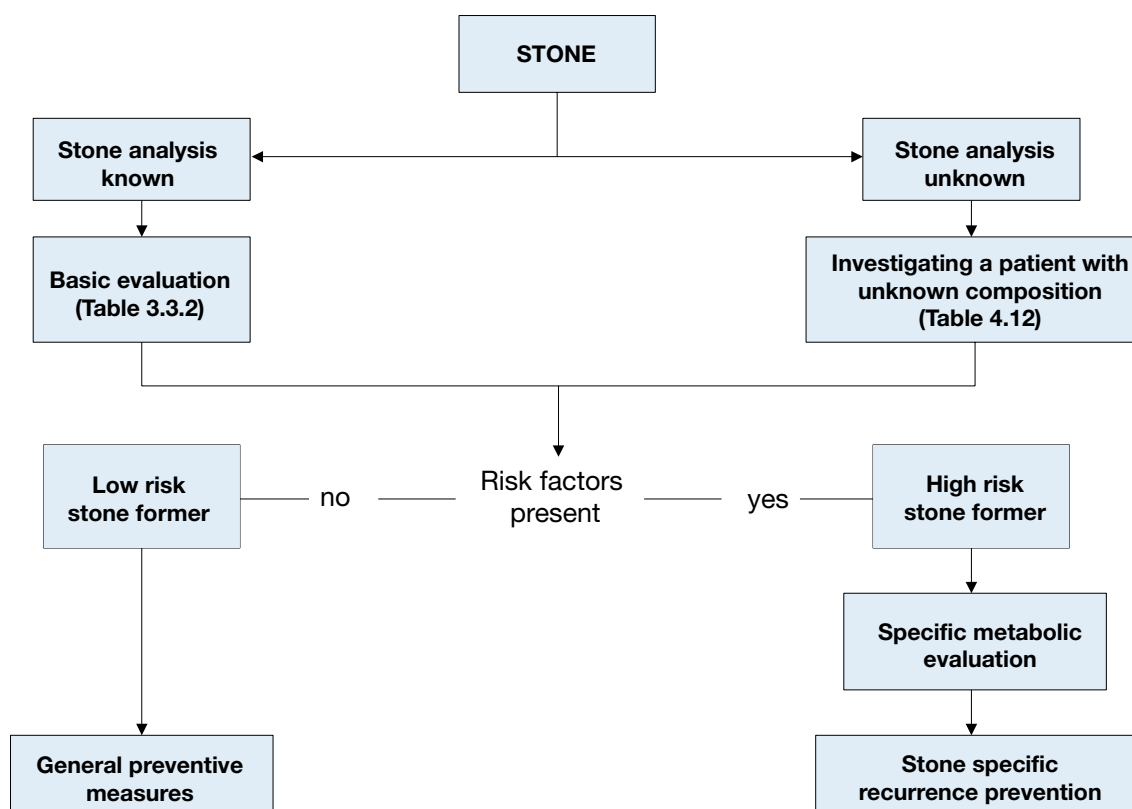
4.1.1 Evaluation of patient risk

After stone passage, every patient should be assigned to a low- or high-risk group for stone formation (Figure 4.1).

For correct classification, two items are mandatory:

- reliable stone analysis by infrared spectroscopy or X-ray diffraction;
- basic analysis (Section 3.3.2).

Figure 4.1 Assignment of patients to low- or high-risk groups for stone formation



Only high-risk stone formers require specific metabolic evaluation. Stone type is the deciding factor for further diagnostic tests. The different stone types include:

- calcium oxalate;
- calcium phosphate;
- uric acid;
- ammonium urate;
- struvite (and infection stones);
- cystine;
- xanthine;
- 2,8-dihydroxyadenine;
- drug stones;
- unknown composition.

4.1.2 Urine sampling

Specific metabolic evaluation requires collection of two consecutive 24-h urine samples [384, 385]. The collecting bottles should be prepared with 5% thymol in isopropanol or stored at $\leq 8^{\circ}\text{C}$ during collection with the risk of spontaneous crystallisation in the urine [386, 387]. Preanalytical errors can be minimised by carrying

out urinalysis immediately after collection. Alternatively boric acid (10 g powder per urine container) can also be used. The collecting method should be chosen in close cooperation with the particular laboratory. Urine pH should be assessed during collection of freshly voided urine four times daily [386, 388] using sensitive pH-dipsticks or a pH-meter.

Spot urine samples are an alternative method of sampling, particularly when 24-h urine collection is difficult, for example, in non-toilet trained children [389]. Spot urine studies normally link the excretion rates to creatinine [389], but these are of limited use because the results may vary with collection time and patients' sex, body weight and age.

4.1.3 **Timing of specific metabolic work-up**

For the initial specific metabolic work-up, the patient should stay on a self-determined diet under normal daily conditions and should ideally be stone free for at least 20 days [390].

Follow-up studies are necessary in patients taking medication for recurrence prevention [391]. The first follow-up 24-h urine measurement is suggested 8-12 weeks after starting pharmacological prevention of stone recurrence. This enables drug dosage to be adjusted if urinary risk factors have not normalised, with further 24-h urine measurements if necessary. Once urinary parameters have been normalised, it is sufficient to perform 24-h urine evaluation every 12 months. The panel realise that on this issue there is only very limited published evidence. The Urolithiasis Guidelines Panel aim to set up a systematic review on the ideal timing of the 24-hour urine collection.

4.1.4 **Reference ranges of laboratory values**

Tables 4.1 - 4.4 provide the internationally accepted reference ranges for the different laboratory values in serum and urine.

Table 4.1: Normal laboratory values for blood parameters in adults [388]

Blood parameter	Reference range	
Creatinine	20-100 µmol/L	
Sodium	135-145 mmol/L	
Potassium	3.5-5.5 mmol/L	
Calcium	2.0-2.5 mmol/L (total calcium)	
	1.12-1.32 mmol/L (ionised calcium)	
Uric acid	119-380 µmol/L	
Chloride	98-112 mmol/L	
Phosphate	0.81-1.29 mmol/L	
Blood gas analysis	pH	7.35-7.45
	pO ₂	80-90 mmHg
	pCO ₂	35-45 mmHg
	HCO ₃	22-26 mmol/L
	BE	±2 mmol/L

BE = base excess (loss of buffer base to neutralise acid).

4.1.5 **Risk indices and additional diagnostic tools**

Several risk indices have been developed to describe the crystallisation risk for calcium oxalate or calcium phosphate in urine [392-395]. However, clinical validation of these risk indices for recurrence prediction or therapy improvement is ongoing.

Table 4.2: Normal laboratory values for urinary parameters in adults

Urinary Parameters	Reference ranges and limits for medical attention
pH	Constantly > 5.8 (suspicious of RTA)
	Constantly > 7.0 (suspicious of infection)
	Constantly ≤ 5.8 (suspicious of acidic arrest)
Specific weight	> 1.010
Creatinine	7-13 mmol/day females
	13-18 mmol/day males
Calcium	> 5.0 mmol/day (see Fig. 4.2)
	≥ 8.0 mmol/day (see Fig. 4.2)
Oxalate	> 0.5 mmol/day (suspicious of enteric hyperoxaluria)
	≥ 1.0 mmol/day (suspicious of primary hyperoxaluria)
Uric acid	> 4.0 mmol/day (women), 5 mmol/day (men)
Citrate	< 2.5 mmol/day
Magnesium	< 3.0 mmol/day
Inorganic phosphate	> 35 mmol/day
Ammonium	> 50 mmol/day
Cystine	> 0.8 mmol/day

Table 4.3: Normal values for spot urine samples: creatinine ratios (solute/creatinine) in adults [396]

Parameter/Patient age	Ratio of solute to creatinine	units
Calcium	mol/mol	mg/mg
< 12 months	< 2.0	0.81
1-3 years	< 1.5	0.53
1-5 years	< 1.1	0.39
5-7 years	< 0.8	0.28
> 7 years	< 0.6	0.21
Oxalate	mmol/mol	mg/g
0-6 months	< 325-360	288-260
7-24 months	< 132-174	110-139
2-5 years	< 98-101	80
5-14 years	< 70-82	60-65
> 16 years	< 40	32
Citrate	mol/mol	g/g
0-5 years	> 0.25	0.42
> 5 years	> 0.15	0.25
Magnesium	mol/mol	g/g
	> 0.63	> 0.13
Uric acid	< 0.56 mg/dl (33 μmol/L) per GFR (ratio x plasma creatinine)	
> 2 years		

Table 4.4: Solute excretion in 24-h urine samples [396]**

Calcium excretion	Citrate excretion	Cystine excretion	Oxalate excretion	Urate excretion					
All age groups	< 0.1 mmol/kg/24 h < 4 mg/kg/24 h	All age groups	Boys > 1.9 mmol/1.73 m ² /24 h > 365 mg/1.73 m ² /24 h	< 10 y	< 55 μmol/1.73 m ² /24 h < 13 mg/1.73 m ² /24 h	All age groups	< 0.5 mmol/1.73 m ² /24 h < 45 mg / 1.73 m ² /24 h	< 1 y	< 70 μmol/kg/24 h < 13 mg/kg/24 h
			Girls > 1.6 mmol/1.73 m ² /24 h > 310 mg/1.73 m ² /24 h	> 10 y	< 200 μmol/1.73 m ² /24 h < 48 mg/1.73 m ² /24 h			1-5 y	< 65 μmol/kg/24 h < 11 mg/kg/24 h
								> 5 y	< 55 μmol/kg/24 h < 9.3 mg/kg/24 h

****24h urine parameters are diet and gender dependent and may vary geographically.**

4.2 General considerations for recurrence prevention

All stone formers, independent of their individual risk, should follow the preventive measures in Table 4.5. The main focus of these is normalisation of dietary habits and lifestyle risks. Stone formers at high risk need specific prophylaxis for recurrence, which is usually pharmacological treatment and based on stone analysis.

Table 4.5: General preventive measures

Fluid intake (drinking advice)	Fluid amount: 2.5-3.0 L/day Circadian drinking Neutral pH beverages Diuresis: 2.0-2.5 L/day Specific weight of urine: < 1010
Nutritional advice for a balanced diet	Balanced diet* Rich in vegetables and fibre Normal calcium content: 1-1.2 g/day Limited NaCl content: 4-5 g/day Limited animal protein content: 0.8-1.0 g/kg/day
Lifestyle advice to normalise general risk factors	BMI: retain a normal BMI level Adequate physical activity Balancing of excessive fluid loss

Caution: The protein need is age-group dependent, therefore protein restriction in childhood should be handled carefully.

* Avoid excessive consumption of vitamin supplements.

4.2.1 Fluid intake

An inverse relationship between high fluid intake and stone formation has been repeatedly demonstrated [397-399]. The effect of fruit juices is mainly determined by the presence of citrate or bicarbonate [400]. If hydrogen ions are present, the net result is neutralisation. However, if potassium is present, both pH and citrate are increased [401, 402]. One large fair-quality RCT randomly assigned men with more than one past renal stone of any type and softdrink consumption greater than 160 mL/day to reduced softdrink intake or no treatment. Although the intervention significantly reduced the risk for symptomatic recurrent stones (RR, 0.83 [CI: 0.71-0.98]), the level of evidence for this outcome was low because results were from only 1 trial." [399, 403].

4.2.2 Diet

A common sense approach to diet should be taken, that is, a mixed balanced diet with contributions from all food groups, but without any excesses [399, 404, 405].

Fruits, vegetables and fibres: fruit and vegetable intake should be encouraged because of the beneficial effects of fibre, although the role of the latter in preventing stone recurrences is debatable [406-409]. The alkaline content of a vegetarian diet also increases urinary pH.

Oxalate: excessive intake of oxalate-rich products should be limited or avoided to prevent high oxalate load [400], particularly in patients who have high oxalate excretion.

Vitamin C: although vitamin C is a precursor of oxalate, its role as a risk factor in calcium oxalate stone formation remains controversial [410]. However, it seems wise to advise calcium oxalate stone formers to avoid excessive intake.

Animal protein: should not be taken in excess [411, 412] and limited to 0.8-1.0 g/kg body weight. Excessive consumption of animal protein has several effects that favour stone formation, including hypocitraturia, low urine pH, hyperoxaluria and hyperuricosuria.

Calcium intake: should not be restricted unless there are strong reasons due to the inverse relationship between dietary calcium and stone formation [407, 413]. The daily requirement for calcium is 1000 to 1200 mg [12]. Calcium supplements are not recommended except in enteric hyperoxaluria, when additional calcium should be taken with meals to bind intestinal oxalate [399, 412, 414].

Sodium: the daily sodium (NaCl) intake should not exceed 3-5 g [12]. High intake adversely affects urine composition:

- calcium excretion is increased by reduced tubular reabsorption;
- urinary citrate is reduced due to loss of bicarbonate;
- increased risk of sodium urate crystal formation.

Calcium stone formation can be reduced by restricting sodium and animal protein [411, 412]. A positive correlation between sodium consumption and risk of first-time stone formation has been confirmed only in women [413, 415]. There have been no prospective clinical trials on the role of sodium restriction as an independent variable in reducing the risk of stone formation.

Urate: intake of purine-rich food should be restricted in patients with hyperuricosuric calcium oxalate [416, 417] and uric acid stones. Intake should not exceed 500 mg/day [12].

4.2.3 **Lifestyle**

Lifestyle factors may influence the risk of stone formation, for example, obesity [418] and arterial hypertension [419, 420].

4.2.4 **Recommendations for recurrence prevention**

Recommendations		LE	GR
The aim should be to obtain a 24-h urine volume ≥ 2.5 L.		1b	A
Hyperoxaluria	Oxalate restriction	2b	B
High sodium excretion	Restricted intake of salt	1b	A
Small urine volume	Increased fluid intake	1b	A
Urea level indicating a high intake of animal protein	Avoid excessive intake of animal protein.	1b	A

4.3 **Stone-specific metabolic evaluation and pharmacological recurrence prevention**

4.3.1 **Introduction**

Pharmacological treatment is necessary in patients at high-risk for recurrent stone formation. The ideal drug should halt stone formation, have no side effects, and be easy to administer. Each of these aspects is important to achieve good compliance. Table 4.6 highlights the most important characteristics of commonly used medication.

Table 4.6: Pharmacological substances used for stone prevention - characteristics, specifics and dosage

Agent	Rationale	Dose	Specifics and side effects	Stone type	Ref
Alkaline citrates	Alkalinisation Hypocitraturia Inhibition of calcium oxalate crystallisation	5-12 g/d (14-36 mmol/d) Children: 0.1-0.15 g/kg/d	Daily dose for alkalinisation depends on urine pH	Calcium oxalate Uric acid Cystine	[38, 399, 421-427]
Allopurinol	Hyperuricosuria Hyperuricaemia	100-300 mg/d Children: 1-3 mg/kg/d	100 mg in isolated hyperuricosuria Renal insufficiency demands dose correction	Calcium oxalate Uric acid Ammonium urate 2,8-Dihydroxyadenine	[428-432]
Calcium	Enteric hyperoxaluria	1000 mg/d	Intake 30 min before meals	Calcium oxalate	[412-414]
Captopril	Cystinuria Active decrease of urinary cystine levels	75-150 mg	Second-line option due to significant side effects	Cystine	[433, 434]
Febuxostat	Hyperuricosuria Hyperuricaemia	80-120 mg/d	Acute gout contraindicated, pregnancy, xanthine stone formation	Calcium oxalate Uric acid	[435, 436]
L-Methionine	Acidification	600-1500 mg/d	Hypercalciuria, bone demineralisation, systemic acidosis. No long-term therapy.	Infection stones Ammonium urate Calcium phosphate	[38, 437, 438]
Magnesium	Isolated hypomagnesiuria Enteric hyperoxaluria	200-400 mg/d Children: 6 mg/kg/d	Renal insufficiency demands dose correction. Diarrhoea, chronic alkali losses, hypocitraturia.	Calcium oxalate	[439, 440] low evidence
Sodium bicarbonate	Alkalinisation Hypocitraturia	4.5 g/d		Calcium oxalate Uric acid, Cystine	[441]
Pyridoxine	Primary hyperoxaluria	Initial dose 5 mg/kg/d Max. 20 mg/kg/d	Polyneuropathia	Calcium oxalate	[442]

Thiazide (Hydrochloro- thiazide)	Hypercalciuria	25-50 mg/d Children: 0.5-1 mg/kg/d	Risk for agent- induced hypotonic blood pressure, diabetes, hyperuricaemia, hypokalaemia, followed by intracellular acidosis and hypocitraturia	Calcium oxalate Calcium phosphate	[38, 439, 443-451]
Tiopronin	Cystinuria Active decrease of urinary cystine levels	Initial dose 250 mg/d Max. 2000 mg/d	Risk for tachyphylaxis and proteinuria.	Cystine	[452-455]

4.4 Calcium oxalate stones

The criteria for identification of calcium oxalate stone formers with high recurrence risk are listed in Section 3.1.2.

4.4.1 *Diagnosis*

Blood analysis requires measurement of creatinine, sodium, potassium, chloride, ionised calcium (or total calcium + albumin), uric acid, and parathyroid hormone (PTH) (and vitamin D) in the case of increased calcium levels.

Urinalysis requires measurement of urine volume, urine pH profile, specific weight, calcium, oxalate, uric acid, citrate, sodium and magnesium.

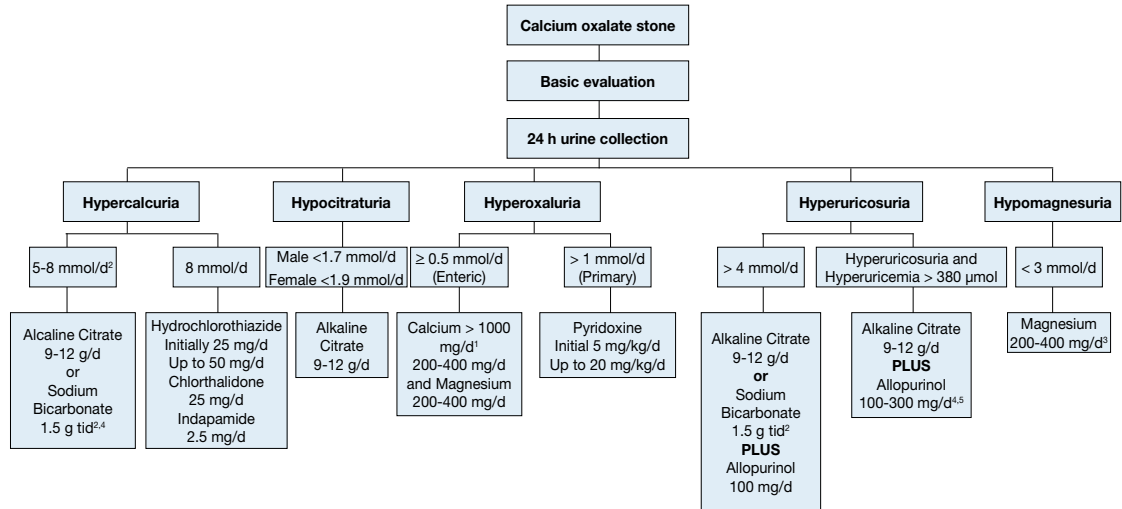
4.4.2 *Interpretation of results and aetiology*

The diagnostic and therapeutic algorithm for calcium oxalate stones is shown in Figure 4.2 [38, 399, 422-424, 428-430, 435, 439-441, 443-450, 456-460].

The most common metabolic abnormalities associated with calcium stone formation are hypercalciuria, which affects 30-60% of adult stone formers, and hyperoxaluria (26-67%), followed by hyperuricosuria (15-46%), hypomagnesuria (7-23%), and hypocitraturia (5-29%). However, ranges tend to differ based on ethnicity [456].

- Elevated levels of ionised calcium in serum (or total calcium and albumin) require assessment of intact PTH to confirm or exclude suspected hyperparathyroidism (HPT).
- "Acidic arrest" (urine pH constantly < 6) may promote co-crystallisation of uric acid and calcium oxalate. Similarly, increased uric acid excretion (> 4 mmol/day in adults or > 12 mg/kg/day in children) can act as a promoter.
- Urine pH levels constantly > 5.8 in the day profile indicate renal tubular acidosis (RTA), provided urinary tract infection (UTI) has been excluded. An ammonium chloride loading test confirms RTA and identifies RTA subtype (Section 4.6.5).
- Hypercalciuria may be associated with normocalcemia (idiopathic hypercalciuria, or granulomatous diseases) or hypercalcaemia (hyperparathyroidism, granulomatous diseases, vitamin D excess, or malignancy).
- Hypocitraturia (male <1.7 mmol/d, female < 1.9 mmol/d) may be idiopathic or secondary to metabolic acidosis or hypokalaemia.
- Oxalate excretion > 0.5 mmol/day in adults (> 0.37 mmol/1.73 m²/day in children) confirms hyperoxaluria.
 - o primary hyperoxaluria (oxalate excretion mostly ≥ 1 mmol/day), appears in three genetically determined forms;
 - o secondary hyperoxaluria (oxalate excretion ≥ 0.5 mmol/day, usually < 1 mmol/day), occurs due to intestinal hyperabsorption of oxalate or extreme dietary oxalate intake;
 - o mild hyperoxaluria (oxalate excretion 0.45-0.85 mmol/day), commonly found in idiopathic calcium oxalate stone formers.
- Hypomagnesuria (< 3.0 mmol/day) may be related to poor dietary intake or to reduced intestinal absorption (chronic diarrhoea).

Figure 4.2: Diagnostic and therapeutic algorithm for calcium oxalate stones



¹ Be aware of excess calcium excretion.

² tid = three times/day (24h).

³ No magnesium therapy for patients with renal insufficiency.

⁴ There is no evidence that combination therapy (thiazide + citrate) (thiazide + allopurinol) is superior to thiazide therapy alone [443, 450].

⁵ Febuxostat 80 mg/d.

4.4.3 Specific treatment

General preventive measures are recommended for fluid intake and diet. Hyperoxaluric stone formers should consume foods with low oxalate content, whereas hyperuricosuric stone formers benefit from daily dietary reduction of purine. Figure 4.2 summarises the diagnostic algorithm and the pharmacological treatment of calcium oxalate stones [38, 399, 422-424, 428-430, 435, 439-441, 443-450, 456-460]. There is only low level evidence on the efficacy of preventing stone recurrence through pre-treatment stone composition and biochemistry measures, or on-treatment biochemistry measures [399].

4.4.4 Recommendations for pharmacological treatment of patients with specific abnormalities in urine composition

Urinary risk factor	Suggested treatment	LE	GR
Hypercalcaemia	Thiazide + potassium citrate	1a	A
Hyperoxaluria	Oxalate restriction	2b	A
Enteric hyperoxaluria	Potassium citrate	3-4	C
	Calcium supplement	2	B
	Diet reduced in fat and oxalate	3	B
Hypocitraturia	Potassium citrate	1b	A
Hypocitraturia	Sodium bicarbonate if intolerant to potassium citrate	1b	A
Hyperuricosuria	Allopurinol	1a	A
	Febuxostat	1b	A
High sodium excretion	Restricted intake of salt	1b	A
Small urine volume	Increased fluid intake	1b	A
Urea level indicating a high intake of animal protein	Avoid excessive intake of animal protein	1b	A
No abnormality identified	High fluid intake	2b	B

4.5 Calcium phosphate stones

Some calcium phosphate stone formers are at high-risk of recurrence. Further information on identifying high-risk patients is given in Section 3.1.2.

Calcium phosphate mainly appears in two completely different minerals: carbonate apatite and brushite. Carbonate apatite crystallisation occurs at a pH ≥ 6.8 and may be associated with infection.

Brushite crystallises at an optimum pH of 6.5-6.8, at high urinary concentrations of calcium (> 8 mmol/day) and phosphate (> 35 mmol/day). Its occurrence is not related to UTI.

Possible causes of calcium phosphate stones include HPT, RTA and UTI; each of which requires different therapy.

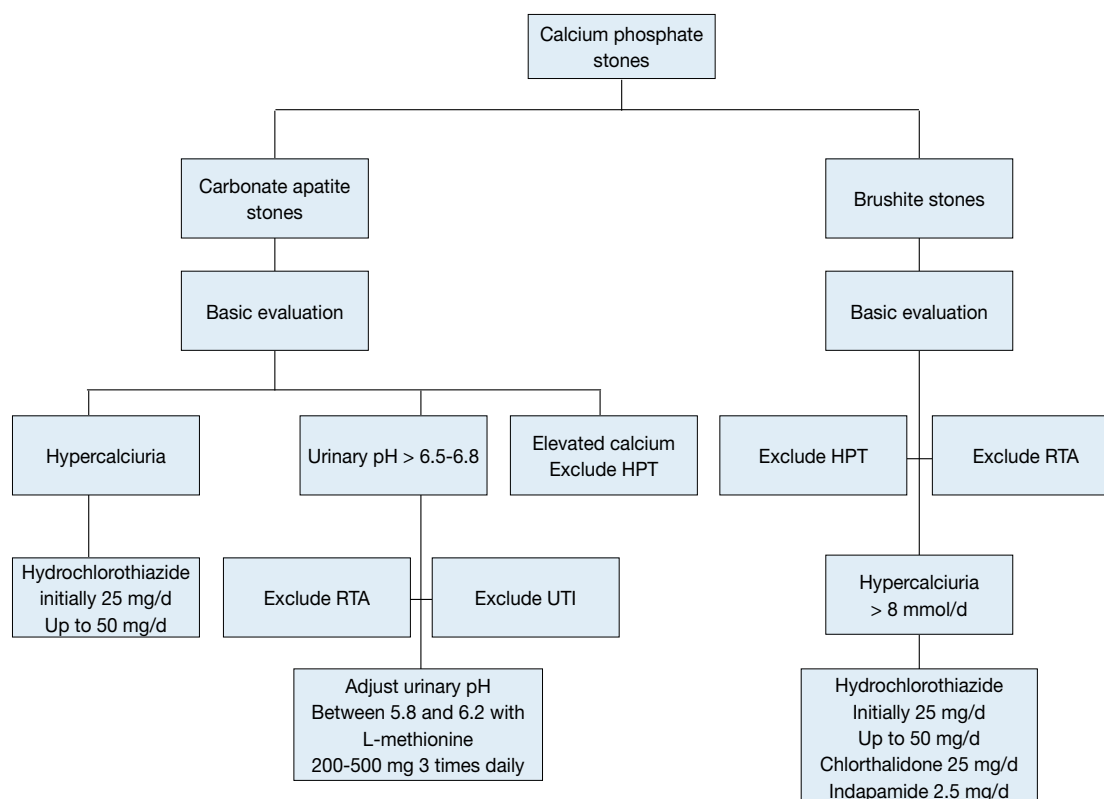
4.5.1 **Diagnosis**

Diagnosis requires blood analysis for: creatinine, sodium, potassium, chloride, ionised calcium (or total calcium + albumin), and PTH (in the case of increased calcium levels). Urinalysis includes measurement of: volume, urine pH profile, specific weight, calcium, phosphate and citrate.

4.5.2 **Interpretation of results and aetiology**

General preventive measures are recommended for fluid intake and diet. The diagnostic and therapeutic algorithm for calcium phosphate stones is shown in Figure 4.3.

Figure 4.3: Diagnostic and therapeutic algorithm for calcium phosphate stones



4.5.3 **Pharmacological therapy [38, 399, 443, 444, 448, 460]**

HPT and RTA are common causes of calcium phosphate stone formation. Although most patients with primary HPT require surgery, RTA can be corrected pharmacologically. If primary HPT and RTA have been excluded, pharmacotherapy for calcium phosphate calculi depends on effective reduction of urinary calcium levels using thiazides. If urine pH remains constantly > 6.2, urinary acidification with L-methionine may be helpful, however it is not commonly used and needs monitoring for systemic acidosis development. For infection-associated calcium phosphate stones, it is important to consider the guidance given for infection stones.

4.5.4 **Recommendations for the treatment of calcium phosphate stones**

Urinary risk factor	Suggested treatment	LE	GR
Hypercalciuria	Thiazide	1a	A
Inadequate urine pH	Acidification	3-4	C
UTI	Antibiotics	3-4	C

4.6 **Disorders and diseases related to calcium stones**

4.6.1 **Hyperparathyroidism [461-464]**

Primary HPT is responsible for an estimated 5% of all calcium stone formation. Renal stones occur in approximately 20% of patients with primary HPT. Elevated levels of PTH significantly increase calcium turnover,

leading to hypercalcaemia and hypercalciuria. Serum calcium may be mildly elevated and serum PTH within the upper normal limits, therefore, repeated measurements may be needed; preferably with the patient fasting. Stones of PTH patients may contain both calcium oxalate and calcium phosphate.

If HPT is suspected, neck exploration should be performed to confirm the diagnosis. Primary HPT can only be cured by surgery.

4.6.2 **Granulomatous diseases [465]**

Granulomatous diseases, such as sarcoidosis, may be complicated by hypercalcaemia and hypercalciuria secondary to increased calcitriol production. The latter is independent of PTH control, leading to increased calcium absorption in the gastrointestinal tract and suppression of PTH. Treatment focusses on the activity of the granulomatous diseases and may require steroids, hydroxychloroquine or ketoconazole. Treatment should be reserved for the specialist.

4.6.3 **Primary hyperoxaluria [442]**

Patients with primary hyperoxaluria (PH) should be referred to specialised centres, because successful management requires an experienced interdisciplinary team. The main therapeutic aim is to reduce endogenous oxalate production, which is increased in patients with PH. In approximately one-third of patients with PH type I, pyridoxine therapy normalises or significantly reduces urinary oxalate excretion. The goal of adequate urine dilution is achieved by adjusting fluid intake to 3.5-4.0 L/day in adults (children 1.5 L/m² body surface area) and following a circadian drinking regimen.

Therapeutic options for preventing calcium oxalate crystallisation include hyperdiuresis, alkaline citrates and magnesium. However, in end-stage renal failure, PH requires simultaneous liver-kidney transplantation.

Treatment regimens are:

- Pyridoxine in PH type I: 5-20 mg/kg/day according to urinary oxalate excretion and patient tolerance;
- Alkaline citrate: 9-12 g/day in adults, 0.1-0.15 meq/kg/day in children;
- Magnesium: 200-400 mg/day (no magnesium in the case of renal insufficiency).

Urinary risk factor	Suggested treatment	LE	GR
Primary hyperoxaluria	Pyridoxine	3	B

4.6.4 **Enteric hyperoxaluria [414, 466]**

Enteric hyperoxaluria is a particularly problematic condition in patients with intestinal malabsorption of fat. This abnormality is associated with a high risk of stone formation, and is seen after intestinal resection and malabsorptive bariatric surgery and in Crohn's disease and pancreas insufficiency. In addition to hyperoxaluria, these patients usually present with hypocitraturia due to loss of alkali. Urine pH is usually low, as are urinary calcium and urine volume. All these abnormalities contribute to high levels of supersaturation with calcium oxalate, crystalluria, and stone formation.

Specific preventive measures are:

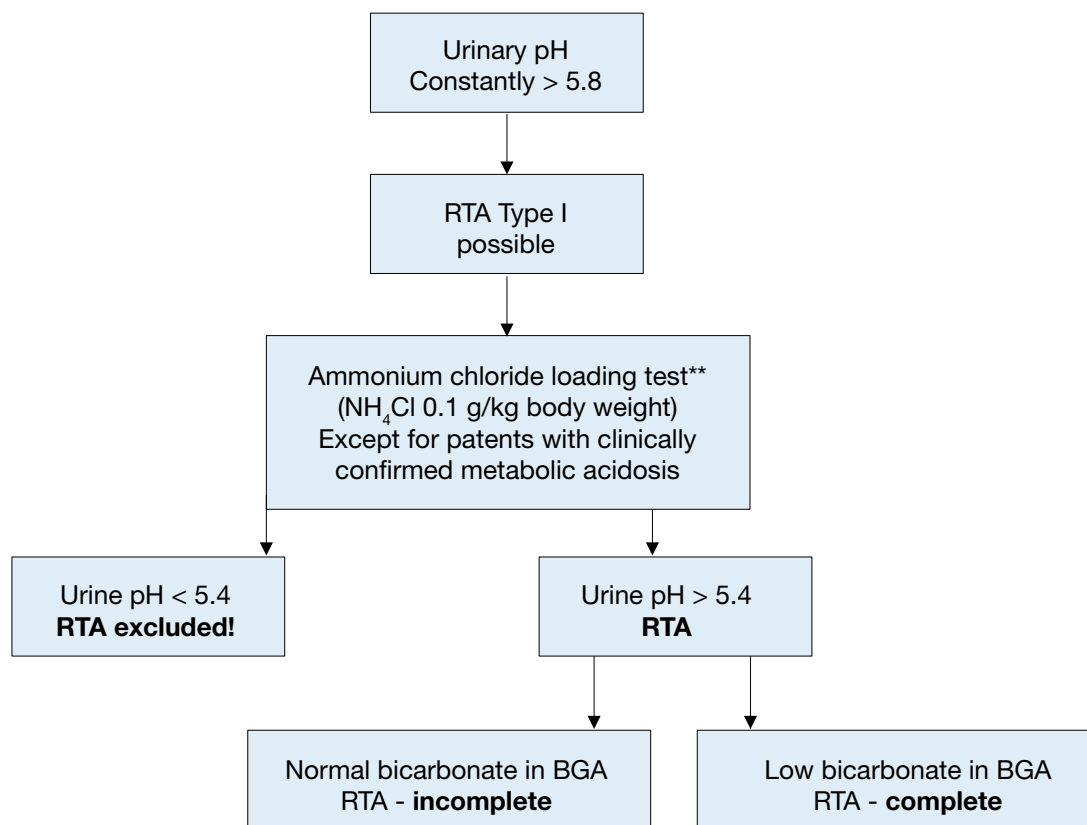
- Restricted intake of oxalate-rich foods;
- Restricted fat intake;
- Calcium supplementation at meal times to enable calcium oxalate complex formation in the intestine [414, 466];
- Sufficient fluid intake to balance intestinal loss of water caused by diarrhoea;
- Alkaline citrates to raise urinary pH and citrate.

Urinary risk factor	Suggested treatment	LE	GR
Enteric hyperoxaluria	Potassium citrate	3-4	C
	Calcium supplement	2	B
	Diet reduced in fat and oxalate	3	B
Small urine volume	Increased fluid intake	1b	A

4.6.5 **Renal tubular acidosis [467, 468]**

Renal tubular acidosis is caused by severe impairment of proton or bicarbonate handling along the nephron. Kidney stone formation most probably occurs in patients with distal RTA type I. Figure 4.4 outlines the diagnosis of RTA. Table 4.7 shows acquired and inherited causes of RTA.

Figure 4.4: Diagnosis of renal tubular acidosis



**** An alternative Ammonium Chloride loading test using NH₄Cl load with 0.05 g/kg body weight over 3 days might provide similar results and may be better tolerated by the patient. A second alternative in these cases could be the furosemide acidification test.**

Renal tubular acidosis can be acquired or inherited. Reasons for acquired RTA can be obstructive uropathy, recurrent pyelonephritis, acute tubular necrosis, renal transplantation, analgesic nephropathy, sarcoidosis, idiopathic hypercalciuria, primary parathyroidism, and drug-induced (e.g. zonisamide). Table 4.7 shows the inherited causes of RTA.

Table 4.7: Inherited causes of renal tubular acidosis

Type - inheritance	Gene/gene product/function	Phenotype
Autosomal dominant	SLC4A1/AE1/Cl-bicarbonate exchanger	Hypercalciuria, hypokalaemia, osteomalacia
Autosomal recessive with hearing loss	ATP6V1B1/B1 subunit of vacuolar H-ATPase/proton secretion	Hypercalciuria, hypokalaemia, rickets
Autosomal recessive	ATP6V0A4/A4 subunit of vacuolar H-ATPase/proton secretion	Hypercalciuria, hypokalaemia, rickets

The main therapeutic aim is restoring a normal acid-base equilibrium. Despite the alkaline pH of urine in RTA, alkalinisation using alkaline citrates or sodium bicarbonate is key to normalising the metabolic changes (intracellular acidosis) responsible for stone formation (Table 4.8). The alkali load reduces tubular reabsorption of citrate, which in turn normalises citrate excretion and simultaneously reduces calcium turnover. Therapeutic success can be monitored by venous blood gas analysis (base excess: ± 2.0 mmol/L) in complete RTA. If excessive calcium excretion (> 8 mmol/day) persists after re-establishing acid-base equilibrium, thiazides may lower urinary calcium excretion.

Table 4.8: Pharmacological treatment of renal tubular acidosis

Biochemical risk factor	Rationale for pharmacological therapy	Medication
Hypercalciuria	Calcium excretion > 8 mmol/day	Hydrochlorothiazide, - in adults: 25 mg/day initially, up to 50 mg/day - in children: 0.5-1 mg/kg/day Alternatives in adults: Chlorthalidone 25 mg/d Indapamide 2.5 mg/d
Inadequate urine pH	Intracellular acidosis in nephron	Alkaline citrate, 9-12 g/day divided in 3 doses OR Sodium bicarbonate, 1.5 g, 3 times daily

Urinary risk factor	Suggested treatment	LE	GR
Distal RTA	Potassium citrate	2b	B
Hypercalciuria	Thiazide + potassium citrate	1a	A

4.6.6 **Nephrocalcinosis [396]**

Nephrocalcinosis (NC) refers to increased crystal deposition within the renal cortex or medulla, and occurs alone or in combination with renal stones. There are various metabolic causes. The main risk factors are: HPT, PH, RTA, vitamin D metabolic disorders, idiopathic hypercalciuria and hypocitraturia, and genetic disorders, including Dent's disease, Bartter's syndrome and Medullary sponge kidney. The many causes of NC means there is no single standard therapy. Therapeutic attention must focus on the underlying metabolic or genetic disease, while minimising the biochemical risk factors.

4.6.6.1 **Diagnosis**

Diagnosis requires the following blood analysis: PTH (in the case of increased calcium levels), vitamin D and metabolites, vitamin A, sodium, potassium, magnesium, chloride, and blood gas analysis. Urinalysis should investigate: urine pH profile (minimum 4 times daily), daily urine volume, specific weight of urine, and levels of calcium, oxalate, phosphate, uric acid, magnesium and citrate.

4.7 **Uric acid and ammonium urate stones**

All uric acid and ammonium urate stone formers are considered to be at high risk of recurrence [12]. Uric acid nephrolithiasis is responsible for approximately 10% of renal stones [469]. They are associated with hyperuricosuria or low urinary pH. Hyperuricosuria may be a result of dietary excess, endogenous overproduction (enzyme defects), myeloproliferative disorders, tumour lysis syndrome, drugs, gout or catabolism [470]. Low urinary pH may be caused by decreased urinary ammonium excretion (insulin resistance or gout), increased endogenous acid production (insulin resistance, metabolic syndrome, or exercise-induced lactic acidosis), increased acid intake (high animal protein intake), or increased base loss (diarrhoea) [470].

Ammonium urate stones are extremely rare, comprising < 1% of all types of urinary stones. They are associated with UTI, malabsorption (inflammatory bowel disease and ileostomy diversion or laxative abuse), potassium deficiency, hypokalemia and malnutrition.

Suggestions on uric acid and ammonium urate nephrolithiasis are based on level 3 and 4 evidence.

4.7.1 **Diagnosis**

Figure 4.5 shows the diagnostic and therapeutic algorithm for uric acid and ammonium urate stones. Blood analysis requires measurement of creatinine, potassium and uric acid levels. Urinalysis requires measurement of urine volume, urine pH profile, specific weight of urine, and uric acid level. Urine culture is needed in the case of ammonium urate stones.

4.7.2 **Interpretation of results**

Uric acid and ammonium urate stones form under completely different biochemical conditions. Acidic arrest (urine pH constantly < 5.8) promotes uric acid crystallisation.

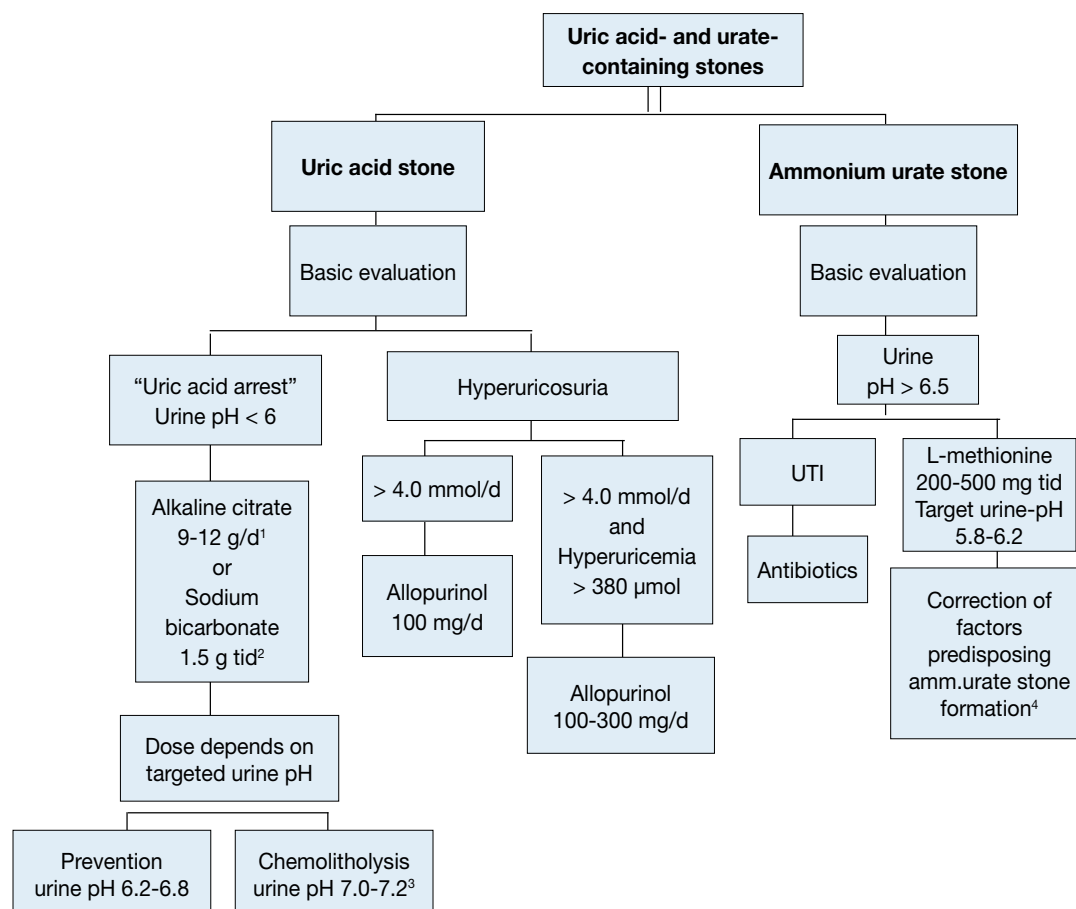
Hyperuricosuria is defined as uric acid excretion ≥ 4 mmol/day in adults or > 0.12 mmol/kg/day in children. Hyperuricaemia may be present, but there is only weak evidence for its association with stone formation.

Hyperuricosuric calcium oxalate stone formation can be distinguished from uric acid stone formation by: urinary pH, which is usually > 5.5 in calcium oxalate stone formation and < 5.5 in uric acid stone formation and occasional absence of hyperuricosuria in patients with pure uric acid stones [471, 472]. Ammonium urate crystals form in urine at pH > 6.5 , at high uric acid concentration and ammonium being present to serve as a cation [473-475].

4.7.3 Specific treatment

General preventive measures are recommended for fluid intake and diet. Hyperuricosuric stone formers benefit from purine reduction in their daily diet. Figure 4.5 describes pharmacological treatment [12, 389, 469-481]. For uric acid stones, allopurinol may change the stone composition distribution in patients with gout to a pattern similar to that in stone formers without gout [482].

Figure 4.5: Diagnostic and therapeutic algorithm for uric acid- and ammonium urate stones



¹ d: day.

² tid three times a day.

³ A higher pH may lead to calcium phosphate stone formation.

⁴ In patients with high uric acid excretion, Allopurinol may be helpful.

4.8 Struvite and infection stones

All infection-stone formers are deemed at high risk of recurrence.

Struvite stones represent 2-15% of the stones sent for analysis. Stones that contain struvite may originate de novo or grow on pre-existing stones, which are infected with urea-splitting bacteria [483]. There are several factors predisposing patients to struvite stone formation (Table 4.9) [484].

4.8.1 Diagnosis

Blood analysis requires measurement of creatinine, and urinalysis requires repeat urine pH measurements and urine culture.

Interpretation

Infection stones contain the following minerals: struvite and/or carbonate apatite and/or ammonium urate.

Urine culture typically provides evidence for urease-producing bacteria, which increase ammonia ions and develop alkaline urine (Table 4.10). Carbonate apatite starts to crystallise at a urine pH level of 6.8. Struvite only precipitates at pH > 7.2 [485, 486]. *Proteus mirabilis* accounts for more than half of all urease-positive UTIs [487, 488].

4.8.2 Specific treatment

General preventive measures are recommended for fluid intake and diet. Specific measures include complete surgical stone removal [484] short- or long-term antibiotic treatment [489], urinary acidification using methionine [437] or ammonium chloride [490], and urease inhibition [491, 492]. For severe infections, acetohydroxamic acid may be an option [491, 492] (Figure 4.6), however, it is not licensed/available in all European countries.

4.8.3 Recommendations for therapeutic measures of infection stones

Recommendations for therapeutic measures	LE	GR
Surgical removal of the stone material as completely as possible	3-4	A*
Short-term antibiotic course	3	B
Long-term antibiotic course	3	B
Urinary acidification: ammonium chloride, 1 g, 2 or 3 times daily	3	B
Urinary acidification: methionine, 200-500 mg, 1-3 times daily	3	B
Urease inhibition	1b	A

*Upgraded following panel consensus.

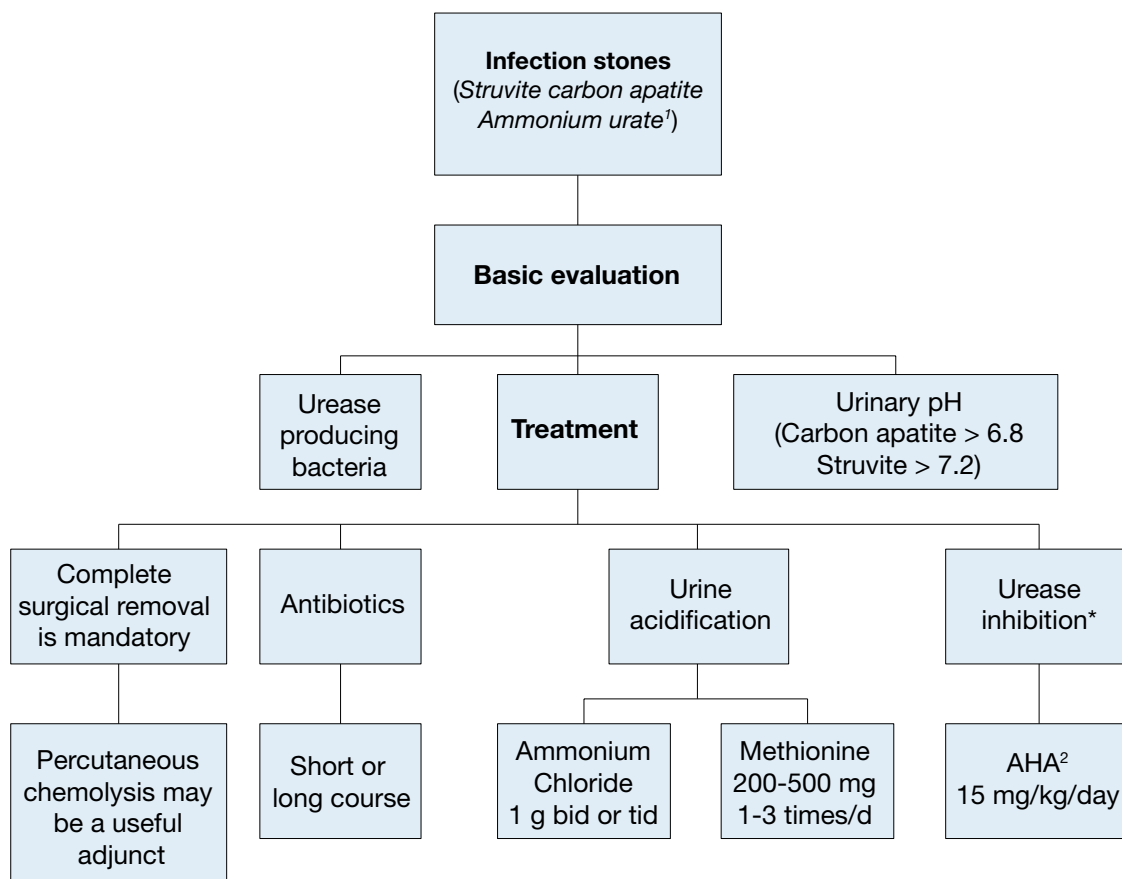
Table 4.9: Factors predisposing to struvite stone formation

Neurogenic bladder
Spinal cord injury/paralysis
Continent urinary diversion
Ileal conduit
Foreign body
Stone disease
Indwelling urinary catheter
Urethral stricture
Benign prostatic hyperplasia
Bladder diverticulum
Cystocele
Caliceal diverticulum
Ureteropelvic junction obstruction

Table 4.10: Most important species of urease-producing bacteria

Obligate urease-producing bacteria (> 98%)
<ul style="list-style-type: none">• <i>Proteus spp.</i>• <i>Providencia rettgeri</i>• <i>Morganella morganii</i>• <i>Corynebacterium urealyticum</i>• <i>Ureaplasma urealyticum</i>
Facultative urease-producing bacteria
<ul style="list-style-type: none">• <i>Enterobacter gergoviae</i>• <i>Klebsiella spp.</i>• <i>Providencia stuartii</i>• <i>Serratia marcescens</i>• <i>Staphylococcus spp.</i>
CAUTION: 0-5% of <i>Escherichia coli</i> , <i>Enterococcus spp.</i> and <i>Pseudomonas aeruginosa</i> strains may produce urease.

Figure 4.6: Diagnostic and therapeutic algorithm for infection stones



¹ Discussed with uric acid stones,

² Acetohydroxamic acid

* When nationally available.

bid = twice a day; tid = three times a day.

4.9 Cystine stones

Cystine stones account for 1-2% of all urinary stones in adults and 6-8% of the stones reported in paediatric studies [18, 493]. All cystine stone formers are deemed at high risk of recurrence.

4.9.1 Diagnosis

Blood analysis includes measurement of creatinine, and urinalysis includes measurement of urine volume, pH profile, specific weight, and cystine.

Interpretation

- Cystine is poorly soluble in urine and crystallises spontaneously within the physiological urinary pH range.
- Cystine solubility depends strongly on urine pH: at pH 6.0, the limit of solubility is 1.33 mmol/L.
- Routine analysis of cystine is not suitable for therapeutic monitoring.
- Regardless of phenotype or genotype of the cystinuric patient, the clinical manifestations are the same [494].
- There is no role for genotyping patients in the routine management of cystinuria [495, 496].
- Reductive therapy targets the disulphide binding in the cysteine molecule. For therapy monitoring, it is essential to differentiate between cystine, cysteine and drug-cysteine complexes. Only high-performance liquid chromatography (HPLC)-based analysis differentiates between the different complexes formed by therapy.
- Diagnosis is established by stone analysis. The typical hexagonal crystals are detectable in only 20-25% of urine specimens from patients with cystinuria [497].
- The cyanide nitroprusside colorimetric qualitative test detects the presence of cystine at a threshold concentration of 75 mg/L, with a sensitivity of 72% and specificity of 95%. False-positive results in patients with Fanconi's syndrome, homocystinuria, or those taking various drugs, including

- ampicillin or sulfa-containing medication [498, 499].
Quantitative 24-h urinary cystine excretion confirms the diagnosis in the absence of stone analysis. Levels above 30 mg/day are considered abnormal [500, 501].

4.9.2 **Specific treatment**

General preventative measures for fluid intake and diet are recommended. A diet low in methionine may theoretically reduce urinary excretion of cystine; however, patients are unlikely to comply sufficiently with such a diet. A restricted intake of sodium is more easily achieved and is more effective in reducing urinary cystine. Patients are usually advised to avoid sodium consumption > 2 g/day [502].

A high level of diuresis is of fundamental importance, aiming for a 24-h urine volume of ≥ 3 L [503]. A considerable fluid intake evenly distributed throughout the day is necessary.

4.9.2.1 *Pharmacological treatment of cystine stones*

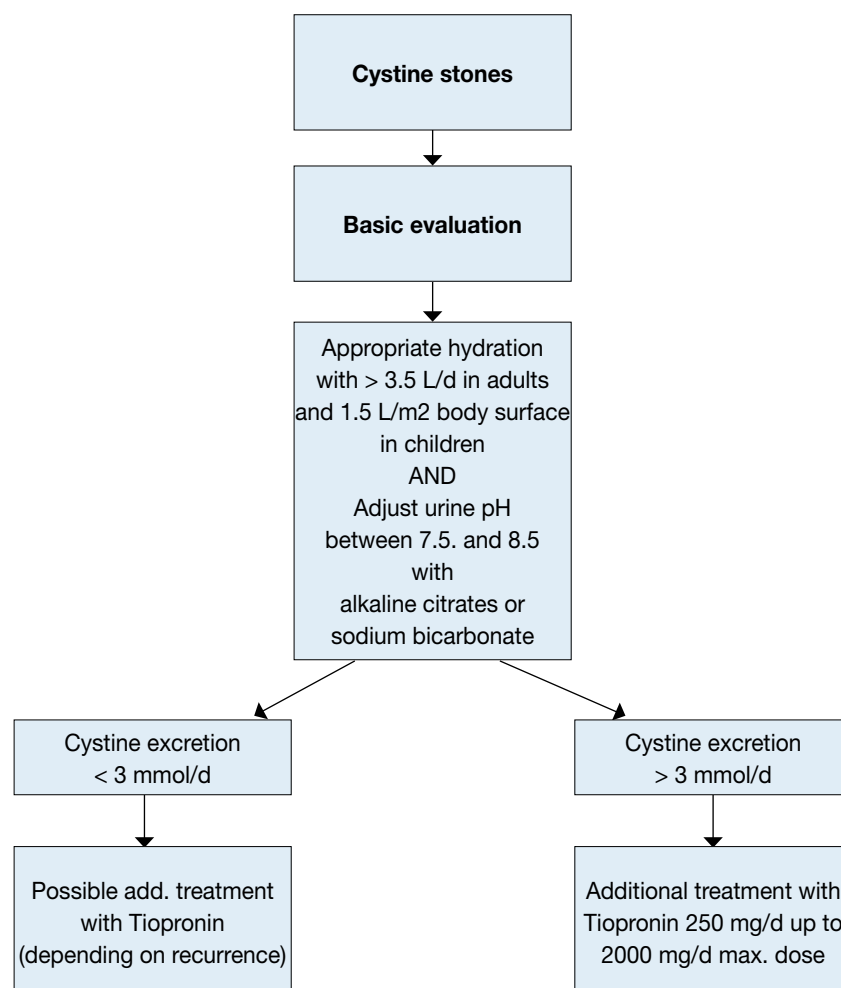
The main therapeutic option for avoiding cystine crystallisation is to maintain urine pH > 7.5, to improve cystine solubility and ensure appropriate hydration with a minimum of 3.5 L/day in adults, or 1.5 L/m² body surface area in children.

Free cystine concentration can be decreased by reductive substances, which act by splitting the disulphide binding of cysteine.

Tiopronin is currently the best choice for cystine reduction. However, side effects often lead to treatment termination, for example, when nephrotic syndrome develops, or poor compliance, especially with long-term use.

After carefully considering the risk of early tachyphylaxis, putting into place a dose-escape phenomenon for long-term use, and recurrence risk, tiopronin is recommended at cystine levels > 3.0 mmol/day or in the case of recurring stone formation, notwithstanding other preventive measures.

Figure 4.7: Metabolic management of cystine stones



4.9.3 Recommendations for the treatment of cystine stones

Therapeutic measures	LE	GR
Urine dilution High fluid intake recommended so that 24-h urine volume exceeds 3 L. Intake should be ≥ 150 mL/h.	3	B
Alkalinisation For cystine excretion < 3 mmol/day: potassium citrate 3-10 mmol 2 or 3 times daily, to achieve pH > 7.5 .	3	B
Complex formation with cystine For patients with cystine excretion > 3 mmol/day, or when other measures are insufficient: tiopronin, 250-2000 mg/day.	3	B

4.10 2,8-Dihydroxyadenine stones and xanthine stones [12]

All 2,8-Dihydroxyadenine and xanthine stone formers are considered to be at high-risk of recurrence. Both stone types are rare. Diagnosis and specific prevention are similar to those for uric acid stones.

4.10.1 2,8-Dihydroxyadenine stones

A genetically determined defect of adenine phosphoribosyl transferase causes high urinary excretion of poorly soluble 2,8-Dihydroxyadenine. High-dose allopurinol or febuxostat are important options, but should be given with regular monitoring.

4.10.2 Xanthine stones

Patients who form xanthine stones usually show decreased levels of serum uric acid. There is no available pharmacological intervention.

4.10.3 Fluid intake and diet

Recommendations for general preventive measures apply. Pharmacological intervention is difficult, therefore, high fluid intake ensures optimal specific weight levels of urine < 1.010 . A purine-reduced diet decreases the risk of spontaneous crystallisation in urine.

4.11 Drug stones [38]

Drug stones are induced by pharmacological treatment [504] (Table 4.11). Two types exist:

- stones formed by crystallised compounds of the drug;
- stones formed due to unfavourable changes in urine composition under drug therapy.

Table 4.11: Compounds that cause drug stones

Active compounds crystallising in urine
<ul style="list-style-type: none">• Allopurinol/oxypurinol• Amoxicillin/ampicillin• Ceftriaxone• Quinolones• Ephedrine• Indinavir• Magnesium trisilicate• Sulphonamides• Triamterene• Zonisamide
Substances impairing urine composition
<ul style="list-style-type: none">• Acetazolamide• Allopurinol• Aluminium magnesium hydroxide• Ascorbic acid• Calcium• Furosemide• Laxatives• Methoxyflurane• Vitamin D• Topiramate

4.12 Matrix Stones

Pure matrix stones are extremely rare with less than 70 cases described in the literature. They are more prevalent in females. The main risk factors are recurrent urinary tract infections, especially due to *Proteus mirabilis* or *Escherichia coli*, previous surgery for stone disease, chronic renal failure and haemodialysis. Complete endourological removal, frequently via the percutaneous approach, is critical. Given the rarity of matrix calculi a specific prophylactic regimen to minimize recurrence cannot be recommended. Eliminating infections and prophylactic use of antibiotics are most commonly proposed [505].

4.13 Unknown stone composition [11]

An accurate medical history is the first step towards identifying risk factors (Table 4.12).

Diagnostic imaging begins with ultrasound (US) examination of both kidneys to establish whether the patient is stone free. Stone detection by US should be followed by KUB and unenhanced multislice CT in adults to differentiate between calcium-containing and non-calcium stones.

Blood analysis demonstrates severe metabolic and organic disorders, such as renal insufficiency, HPT or other hypercalcaemic states and hyperuricaemia. In children, hyperoxalaemia is additionally screened.

Urinalysis is performed routinely with a dipstick test as described above. Urine culture is required if there are signs of infection.

Constant urine pH < 5.8 in the daily profile indicates acidic arrest, which may promote uric acid crystallisation. Persistent urine pH > 5.8 in the daily profile indicates RTA, if UTI is excluded.

Microscopy of urinary sediment can help to discover rare stone types, because crystals of 2,8-dihydroxyadenine, cystine and xanthine are pathognomonic for the corresponding disease. In cases in which the presence of cystine is doubtful, a cyanide nitroprusside colorimetric qualitative test can be used to detect the presence of cystine in urine, with a sensitivity of 72% and specificity of 95%. False-positive results are possible in patients with Fanconi's syndrome or homocystinuria, or in those taking various drugs, including ampicillin or sulfa-containing medication [498, 499].

Following this programme, the most probable stone type can be assumed and specific patient evaluation can follow. However, if any expelled stone material is available, it should be analysed by diagnostic confirmation or correction.

Table 4.12: Investigating patients with stones of unknown composition

Investigation	Rationale for investigation
Medical history	<ul style="list-style-type: none"> Stone history (former stone events, family history) Dietary habits Medication chart
Diagnostic imaging	<ul style="list-style-type: none"> Ultrasound in the case of a suspected stone Unenhanced helical CT (Determination of Hounsfield units provides information about the possible stone composition)
Blood analysis	<ul style="list-style-type: none"> Creatinine Calcium (ionised calcium or total calcium + albumin) Uric acid
Urinalysis	<ul style="list-style-type: none"> Urine pH profile (measurement after each voiding, minimum 4 times daily) Dipstick test: leukocytes, erythrocytes, nitrite, protein, urine pH, specific weight Urine culture Microscopy of urinary sediment (morning urine) Cyanide nitroprusside test (cystine exclusion)

Further examinations depend on the results of the investigations listed above.

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6. CONFLICT OF INTEREST

All members of the Urolithiasis Guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website: <http://www.uroweb.org/guidelines/online-guidelines/>. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

Guidelines on Paediatric Urology

S. Tekgül (Chair), H.S. Dogan,
E. Erdem (Guidelines Associate), P. Hoebeke, R. Kočvara,
J.M. Nijman (Vice-chair), C. Radmayr,
M.S. Silay (Guidelines Associate), R. Stein,
S. Undre (Guidelines Associate)



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1. INTRODUCTION

1.1 Aim

A collaborative working group consisting of members representing the European Society for Paediatric Urology (ESPU) and the European Association of Urology (EAU) has prepared these Guidelines to make a document available that may help to increase the quality of care for children with urological problems. This compilation document addresses a number of common clinical pathologies in paediatric urological practice, but covering the entire field of paediatric urology in a single guideline document is unattainable.

The majority of urological clinical problems in children are distinct and in many ways differ to those in adults. This publication intends to outline a practical and preliminary approach to paediatric urological problems. Complex and rare conditions that require special care with experienced doctors should be referred to designated centres where paediatric urology practice has been fully established and a multidisciplinary approach is available.

For quite some time, paediatric urology has informally developed, expanded, matured and established its diverse body of knowledge and expertise and may now be ready to distinguish itself from its parent specialties. Thus, paediatric urology has recently emerged in many European countries as a distinct subspecialty of both urology and paediatric surgery, and presents a unique challenge in the sense that it covers a large area with many different schools of thought and a huge diversity in management.

Knowledge gained by increasing experience, new technological advances and non-invasive diagnostic screening modalities has had a profound influence on treatment modalities in paediatric urology, a trend that is likely to continue in the years to come.

1.2 Publication history

The Paediatric Urology Guidelines were first published in 2001 with subsequent partial updates in 2005, 2006, 2008, 2009, 2010, 2011, 2012, 2013, 2014 and this 2015 publication which includes a number of updated chapters and sections as detailed below:

- 3A Phimosis: The literature has been updated
- 3B Cryptorchidism: The literature has been updated, minor text revisions made and one new recommendation added
- 3C Hydrocele: The literature has been updated
- 3D Acute scrotum in children: The literature has been updated and minor text revisions made
- 3E Hypospadias: The literature has been updated extensively
- 3G Varicocele in children and adolescents: The literature has been updated extensively
- 3H Urinary tract infections in children: The literature has been updated and minor revisions made to the text
- 3I Daytime lower urinary tract conditions: The literature has been updated, text revised and a recommendation added
- 3J Monosymptomatic enuresis: The literature has been updated, text revised and three recommendations added
- 3L Dilatation of the upper urinary tract: The literature has been updated
- 3O Obstructive pathology of renal duplication ureterocele and ectopic ureter: The literature has been updated
- 3Q Posterior urethral valves: The literature has been updated, minor revisions made to the text and some updates made to the recommendations

In addition, the text has been significantly reduced so that only key information is included and re-formatted according to the EAU template for non-oncology Guidelines, so that all Guidelines follow a similar format. This document was peer-reviewed prior to publication.

Standard procedure for EAU publications includes an annual scoping search to guide updates. A shorter reference document, the Pocket Guidelines, is also available, both in print and as a mobile application, presenting the main findings of the Paediatric Urology Guidelines. These versions are abridged and therefore may require consultation with the full text version. All are available through the EAU website: <http://www.uroweb.org/guidelines>.

2. METHODS

These Guidelines were compiled based on current literature following a systematic review using MEDLINE. Application of a structured analysis of the literature was not possible in many conditions due to a lack of well-designed studies. The limited availability of large randomised controlled trials (RCTs) - influenced also by the fact that a considerable number of treatment options relate to surgical interventions on a large spectrum of different congenital problems - means this document is largely a consensus document. Clearly there is a need for continuous re-evaluation of the information presented in this current document.

It must be emphasised that clinical guidelines present the best evidence available but following the recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, also taking into account individual circumstances and patient and parent preferences.

References used in this text are graded according to their Level of Evidence (LE) and Guidelines are given a Grade of Recommendation (GR). In this 2015 EAU Guidelines compilation, all standard information on LE and GR has been taken out of the individual Guidelines topics for the sake of brevity. The methodology section (see the introduction chapter of the complete book) outlines the LE and GR criteria which are used throughout the Guidelines, according to a classification system modified from the Oxford Centre for Evidence-based Medicine Levels of Evidence [1].

3. THE GUIDELINE

3A PHIMOSIS

3A.1 Epidemiology, aetiology and pathophysiology

At the end of the first year of life, retraction of the foreskin behind the glandular sulcus is possible in only about 50% of boys; this rises to approximately 89% by the age of 3 years. The incidence of phimosis is 8% in 6-7 year olds and just 1% in males aged 16-18 years [2].

3A.2 Classification systems

The phimosis is either primary with no sign of scarring, or secondary (pathological) to a scarring such as balanitis xerotica obliterans (BXO) [2]. BXO, also termed lichen sclerosus, has been recently found in 17% of boys younger than 10 years presenting with phimosis. The clinical appearance in children may be confusing and does not correlate with the final histopathological results. Chronic inflammation was the most common finding [3] (LE: 2b).

Phimosis has to be distinguished from normal agglutination of the foreskin to the glans, which is a more or less lasting physiological phenomenon with well-visible meatus and free partial retraction [4].

Paraphimosis must be regarded as an emergency situation: retraction of a too narrow prepuce behind the glans penis into the glanular sulcus may constrict the shaft and lead to oedema of the glans and retracted foreskin. It interferes with perfusion distally from the constrictive ring and brings a risk of preputial necrosis.

3A.3 Diagnostic evaluation

The diagnosis of phimosis and paraphimosis is made by physical examination.

If the prepuce is not retractable or only partly retractable and shows a constrictive ring on drawing back over the glans penis, a disproportion between the width of the foreskin and the diameter of the glans penis has to be assumed. In addition to the constricted foreskin, there may be adhesions between the inner surface of the prepuce and the glanular epithelium and/or a fraenum breve.

Paraphimosis is characterised by a retracted foreskin with the constrictive ring localised at the level of the sulcus, which prevents replacement of the foreskin over the glans.

3A.4 Disease management

Conservative treatment is an option for primary phimosis. A corticoid ointment or cream (0.05-0.1%) can be administered twice a day over a period of 20-30 days with a success rate of > 90% [5-8] (LE: 1b; GR: A). A recurrence rate up to 17% can be expected [9]. This treatment has no side effects and the mean bloodspot cortisol levels are not significantly different from an untreated group of patients [10] (LE: 1b). The hypothalamic-pituitary-adrenal axis was not influenced by local corticoid treatment [11]. Agglutination of the foreskin does not respond to steroid treatment [7] (LE: 2).

Operative treatment of phimosis in children is dependent on the parents' preferences and can be plastic or radical circumcision after completion of the second year of life. Alternatively, the Shang Ring may be used especially in developing countries [12]. Plastic circumcision has the objective of achieving a wide foreskin circumference with full retractability, while the foreskin is preserved (dorsal incision, partial circumcision). However, this procedure carries the potential for recurrence of the phimosis [13]. In the same session, adhesions are released and an associated fraenum breve is corrected by fraenulotomy. Meatoplasty is added if necessary.

An absolute indication for circumcision is secondary phimosis. In primary phimosis, recurrent balanoposthitis and recurrent urinary tract infections in patients with urinary tract abnormalities are indications for intervention [14-17] (LE: 2b; GR: B). Male circumcision significantly reduces the bacterial colonisation of the glans penis with regard to both non-uropathogenic and uropathogenic bacteria [18] (LE: 2b). Simple ballooning of the foreskin during micturition is not a strict indication for circumcision.

Routine neonatal circumcision to prevent penile carcinoma is not indicated. A recent meta-analysis could not find any risk in uncircumcised patients without a history of phimosis [19]. Contraindications for circumcision are: an acute local infection and congenital anomalies of the penis, particularly hypospadias or buried penis, because the foreskin may be required for a reconstructive procedure [20, 21]. Circumcision can be performed in children with coagulopathy with 1-5% of complications (bleeding) if haemostatic agents or diathermic knife are used [22, 23]. Childhood circumcision has an appreciable morbidity and should not be recommended without a medical reason and also taking into account epidemiological and social aspects [24-28] (LE: 1b; GR: B).

Treatment of paraphimosis consists of manual compression of the oedematous tissue with a subsequent attempt to retract the tightened foreskin over the glans penis. Injection of hyaluronidase beneath the narrow band; or 20% mannitol may be helpful to release the foreskin [29, 30] (LE: 3-4; GR: B-C). If this manoeuvre fails, a dorsal incision of the constrictive ring is required. Depending on the local findings, a circumcision is carried out immediately or can be performed in a second session.

3A.5 Follow-up

Any surgery done on prepuce requires an early follow-up of 4-6 weeks after surgery.

3A.6 Conclusions and recommendations on phimosis

Conclusion		
Treatment for phimosis usually starts after two years of age or according to parents' preference.		

Recommendations	LE	GR
In primary phimosis, conservative treatment with a corticoid ointment or cream is a first line treatment with a success rate of more than 90%.	1b	A
In primary phimosis, recurrent balanoposthitis and recurrent UTI in patients with urinary tract abnormalities are indications for active intervention.	2b	A
Secondary phimosis is an absolute indication for circumcision.	2b	A
Paraphimosis is an emergency situation and treatment must not be delayed. If manual reposition fails, a dorsal incision of the constrictive ring is required.	3	B
Routine neonatal circumcision to prevent penile carcinoma is not indicated.	2b	B

UTI = urinary tract infection.

3B CRYPTORCHIDISM

3B.1 Epidemiology, aetiology and pathophysiology

At one year of age, nearly 1% of all full-term male infants have cryptorchidism, which is the commonest congenital anomaly affecting the genitalia of newborn male infants [31].

3B.2 Classification systems

The most useful classification of cryptorchidism is into palpable and non-palpable testes, and clinical management is decided by the location and presence of the testes. Approximately 70% of all undescended testes are palpable [32].

- Retractable testes require only observation because they may become ascendant. Although they have

- completed their descent, a strong cremasteric reflex may cause their retention in the groin [33].
- Bilateral, non-palpable testes and any suggestion of sexual differentiation problems (e.g. hypospadias) require urgent, mandatory endocrinological and genetic evaluation [34] (LE: 3; GR: B).

3B.3 Diagnostic evaluation

Physical examination is the only way of differentiating between palpable or non-palpable testes. Usually there is no benefit in performing ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI) or angiography [35].

Clinical examination includes a visual description of the scrotum and assessment of the child in both the supine and crossed-leg positions. The examiner should inhibit the cremasteric reflex with his/her non-dominant hand, immediately above the symphysis in the groin region, before touching or reaching for the scrotum. The groin region may be “milked” towards the scrotum in an attempt to move the testis into the scrotum. This manoeuvre also allows an inguinal testis to be differentiated from enlarged lymph nodes that could give the impression of an undescended testis. A retractile testis can generally be brought into the scrotum, where it will remain until a cremasteric reflex (touching the inner thigh skin) retracts it into the groin [36].

A unilateral, non-palpable testis and an enlarged contralateral testis suggest testicular absence or atrophy, but this is not a specific finding and does not preclude surgical exploration. An inguinal, non-palpable testis requires specific visual inspection of the femoral, penile and perineal regions to exclude an ectopic testis. Diagnostic laparoscopy is the only examination that can reliably confirm or exclude an intra-abdominal, inguinal and absent/vanishing testis (non-palpable testis) [37]. Before carrying out laparoscopic assessment, examination under general anaesthesia is recommended because some, originally non-palpable, testes become palpable under anaesthetic conditions.

3B.4 Disease management

Treatment should be done as early as possible around one year of age, starting after six months and finishing preferably at 12 months of age, or 18 months at the latest [38-41]. This timing is driven by the final adult results on spermatogenesis and hormone production, as well as the risk for tumours.

3B.4.1 Medical therapy

Medical therapy using human chorionic gonadotrophin (hCG) or gonadotrophin-releasing hormone (GnRH) is based on the hormonal dependence of testicular descent, with maximum success rates of 20% [42, 43]. However, it must be taken into account that almost 20% of descended testes have the risk of reascending later.

Hormonal therapy for testicular descent has lower success rates, the higher the undescended testis is located. A total dose of 6000-9000 U hCG is given in four doses over a period of 2-3 weeks, depending on weight and age, along with GnRH, given for 4 weeks as a nasal spray at a dose of 1.2 mg/day, divided into three doses per day.

Medical treatment with GnRH may be beneficial before surgical orchidolysis and orchidopexy (dosage as described earlier) or afterwards (low intermittent dosages), in terms of increasing the fertility index, which is a predictor for fertility in later life [44]. Long-term follow-up data are still awaited. Nonetheless, it has been reported that hCG treatment may be harmful to future spermatogenesis through increased apoptosis of germ cells, including acute inflammatory changes in the testes and reduced testicular volume in adulthood. Therefore, the Nordic Consensus Statement on treatment of undescended testes does not recommend it on a routine basis because there is not sufficient evidence for a beneficial effect of hormonal treatment before or after surgery. However, this statement relied only on data from hormonal treatment using hCG [45, 46].

3B.4.2 Surgery

If a testis has not concluded its descent at the age of six months (corrected for gestational age) surgery should be performed within the subsequent year, with age 18 months the latest since histological examination of cryptorchid testes has revealed that undescended testes suffer a progressive loss of germ cells as well as Leydig cells [47].

Palpable testis

Surgery for a palpable testis includes orchidofuniculolysis and orchidopexy, via an inguinal approach, with success rates of up to 92% [48]. It is important to remove and dissect all cremasteric fibres to prevent secondary retraction. Alternatively a primary scrotal approach is also an option and has been documented to be of equal effectiveness in selected patients with a testis located distal to the external inguinal ring that can be mobilised adequately via a scrotal incision [49]. Associated problems, such as an open processus vaginalis, must be carefully dissected and closed. Any additional pathology has to also be taken care of, e.g. removal of an appendix testis. It is recommended that the testis is placed in a subdartos pouch. With regard to sutures,

there should be no fixation sutures or they should be made between the tunica vaginalis and the dartos musculature.

The lymph drainage of a testis that has undergone surgery for orchidopexy has been changed from iliac drainage to iliac and inguinal drainage (important in the event of later malignancy). Scrotal orchidopexy can also be an option in less-severe cases and when performed by surgeons with experience using that approach.

Non-palpable testis

A thorough examination once the boy is under general anaesthesia is recommended since a previously non-palpable testis might be identifiable and subsequently changed the surgical approach to a standard inguinal orchiopexy as described above. Otherwise laparoscopy or inguinal surgical exploration with possible laparoscopy should be attempted for non-palpable testes [50]. There is a significant chance of finding the testis via an inguinal incision. In rare cases, it is necessary to search into the abdomen if there are no vessels or vas deferens in the groin. Laparoscopy is the best way of examining the abdomen for a testis. In addition, either removal or orchidolysis and orchidopexy can be performed via laparoscopic access [51].

For boys aged ≥ 10 years with an intra-abdominal testis, with a normal contralateral testis, removal is an option because of the theoretical risk of later malignancy. In bilateral intra-abdominal testes, or in boys < 10 years, a one-stage or two-stage Fowler-Stephens procedure can be performed. In the event of a two-stage procedure, the spermatic vessels are laparoscopically clipped or coagulated proximal to the testis to allow development of collateral vasculature [52]. The second-stage procedure, in which the testis is brought directly over the symphysis and next to the bladder into the scrotum, can also be performed by laparoscopy or open surgery 6 months later. The testicular survival rate in the one-stage procedure varies between 50-60%, with success rates increasing up to 90% for the two-stage procedure [53, 54]. Microvascular autotransplantation can also be performed with a 90% testicular survival rate. However, the procedure requires skilled and experienced surgeons [53].

3B.5 Follow-up

Although boys with one undescended testis have a lower fertility rate, they have the same paternity rate as those with bilateral descended testes. Boys with bilateral undescended testes have lower fertility and paternity rates. Fertility rate is the number of offspring born per mating pair, individual or population, whereas paternity reflects the actual potential of fatherhood.

Boys with an undescended testis have an increased risk of developing testicular malignancy. Screening both during and after puberty is therefore recommended for these boys. A Swedish study, with a cohort of almost 17,000 men who were treated surgically for undescended testis and followed for ~210,000 person-years, showed that treatment for undescended testis before puberty decreased the risk of testicular cancer. The relative risk of testicular cancer among those who underwent orchidopexy before 13 years of age was 2.23 when compared with the Swedish general population; this increased to 5.40 for those treated at ≥ 13 years [55].

A systematic review and meta-analysis of the literature have also concluded that prepubertal orchidopexy may decrease the risk of testicular cancer and that early surgical intervention is indicated in children with cryptorchidism [56]. Boys with retractile testes do not need medical or surgical treatment, but require close follow-up until puberty.

3B.6 Recommendations for cryptorchidism

Recommendations	LE	GR
Boys with retractile testes do not need medical or surgical treatment, but require close follow-up until puberty.	2a	A
Surgical orchidolysis and orchidopexy should be concluded at the age of 12 months, or 18 months at the latest.	3	B
In the case of non-palpable testes and no evidence of disorders of sex development, laparoscopy still represents the gold standard because it has almost 100% sensitivity and specificity in identifying an intra-abdominal testis as well as the possibility for subsequent treatment in the same session.	1a	A
Hormonal therapy, either in an adjuvant or neo-adjuvant setting, is not standard treatment. Patients have to be evaluated on an individual basis.	2a	C
For an intra-abdominal testis in a 10-year-old boy or older, with a normal contralateral testis, removal is an option because of the theoretical risk of a later malignancy.	3	B
Male newborns with bilateal non-palpable testes should be evaluated for possible disorders of sex development.	1	A

3C HYDROCELE

3C.1 Epidemiology, aetiology and pathophysiology

Hydrocele is defined as a collection of fluid between the parietal and visceral layers of tunica vaginalis [57]. Pathogenesis of primary hydrocele is based on patency of processus vaginalis in contrast with secondary hydrocele. Incomplete obliteration of the processus vaginalis peritonei results in formation of various types of communicating hydrocele; a large open processus vaginalis allowing passage of abdominal viscera results in clinical hernia [58]. The exact time of spontaneous closure of the processus vaginalis is not known. It persists in approximately 80-94% of newborns and in 20% of adults [59]. If complete obliteration of the processus vaginalis occurs with patency of midportion, a hydrocele of the cord occurs. Scrotal hydroceles without associated patency of the processus vaginalis are encountered in newborns also [60]. Non-communicating hydroceles, based on an imbalance between the secretion and reabsorption of this fluid, are found secondary to minor trauma, testicular torsion, epididymitis, varicocele operation or may appear as a recurrence after primary repair of a communicating or non-communicating hydrocele.

3C.2 Diagnostic evaluation

The classic description of a communicating hydrocele is that of a hydrocele that vacillates in size, and is usually related to ambulation. It may be diagnosed by history and physical investigation. Transillumination of the scrotum makes the diagnosis in the majority of cases, keeping in mind that fluid-filled intestine and some prepubertal tumours such as teratomas may transilluminate as well [61, 62]. If the diagnosis is that of a hydrocele, there will be no history of reducibility and no associated symptoms; the swelling is translucent, smooth and usually non-tender. If there are any doubts about the character of an intrascrotal mass, scrotal ultrasound should be performed and has nearly 100% sensitivity in detecting intrascrotal lesions. Doppler ultrasound studies help to distinguish hydroceles from varicocele and testicular torsion, although these conditions may also be accompanied by a hydrocele.

3C.3 Disease management

In the majority of infants, the surgical treatment of hydrocele is not indicated within the first 12-24 months because of the tendency for spontaneous resolution [63] (LE: 2; GR: B). Little risk is taken by initial observation because progression to hernia is rare and does not result in incarceration [63]. Early surgery is indicated if there is suspicion of a concomitant inguinal hernia or underlying testicular pathology [64, 65] (LE: 2; GR: B). Persistence of a simple scrotal hydrocele beyond 24 months of age may be an indication for surgical correction. There is no evidence that this type of hydrocele risks testicular damage. The natural history of hydrocele is poorly documented beyond the age of 2 years and there is no good evidence to support current practice, according to a systematic review. Delaying surgery may reduce the number of procedures necessary without increasing morbidity [66].

The question of contralateral disease should be addressed by both history and physical examination at the time of initial consultation (LE: 2) [67]. In late-onset hydrocele, suggestive of a non-communicating hydrocele, there is a reasonable chance of spontaneous resolution (75%) and expectant management of 6-9 months is recommended [68]. In the paediatric age group, the operation consists of ligation of patent processus vaginalis via inguinal incision and the distal stump is left open, whereas in hydrocele of the cord the cystic mass is excised or unroofed [57, 62, 64] (LE: 4; GR: C). In expert hands, the incidence of testicular damage during hydrocele or inguinal hernia repair is very low (0.3%) (LE: 3; GR: B). Sclerosing agents should not be used because of the risk of chemical peritonitis in communicating processus vaginalis peritonei [62, 64] (LE: 4; GR: C). The scrotal approach (Lord or Jaboulay technique) is used in the treatment of a secondary non-communicating hydrocele.

3C.4 Recommendations for the management of hydrocele

Recommendations	LE	GR
In the majority of infants, surgical treatment of hydrocele is not indicated within the first 12-24 months due to the tendency for spontaneous resolution. Little risk is taken by initial observation because progression to hernia is rare.	2a	B
Early surgery is indicated if there is suspicion of a concomitant inguinal hernia or underlying testicular pathology.	2b	B
In case of doubts about the character of an intrascrotal mass, scrotal ultrasound should be performed.	4	C
In the paediatric age group, an operation would generally involve ligation of the patent processus vaginalis via inguinal incision. Sclerosing agents should not be used because of the risk for chemical peritonitis.	4	C

3D ACUTE SCROTUM IN CHILDREN

3D.1 Epidemiology, aetiology and pathophysiology

Acute scrotum is a paediatric urological emergency, most commonly caused by torsion of the testis or appendix testis, or epididymitis/epididymo-orchitis [69-74]. Other causes of acute scrotal pain are idiopathic scrotal oedema, mumps orchitis, varicocele, scrotal haematoma, incarcerated hernia, appendicitis or systemic disease (e.g. Henoch-Schönlein purpura) [75-87]. Trauma can also be a cause of acute scrotum as it can relate to post traumatic haematomas, testicular contusion, rupture dislocation or torsion [88-93]. Scrotal fat necrosis has also been reported to be an uncommon cause of mild-to-moderate scrotal pain in prepubertal overweight boys after exposure to cold [94].

Torsion of the testis occurs most often in the neonatal period and around puberty, whereas torsion of the appendix testes occurs over a wider age range. Acute epididymitis affects two age groups: < 1 year and 12-15 years [72, 95, 96]. Acute epididymitis is found most often (37-64.6%) in boys with acute scrotum [69, 70, 73, 74]. One study predicted the annual incidence of epididymitis around 1.2 per 1,000 children [97].

Perinatal torsion of the testis most often occurs prenatally. Perinatal torsion occurs after birth in 25% of the cases. Bilateral torsion comprises 11-21% of all perinatal cases [98]. Most cases are extravaginal in contrast to the usual intravaginal torsion, which occurs during puberty.

3D.2 Diagnostic evaluation

Patients usually present with scrotal pain, except in newborn torsion. The duration of symptoms is shorter in testicular torsion (69% present within 12 h) compared to torsion of the appendix testes (62%) and acute epididymitis (31%) [71, 72, 96].

In the early phase, location of the pain can lead to diagnosis. Patients with acute epididymitis experience a tender epididymis, whereas patients with testicular torsion are more likely to have a tender testicle, and patients with torsion of the appendix testis feel isolated tenderness of the superior pole of the testis [96].

An abnormal position of the testis is more frequent in testicular torsion than epididymitis [71]. Looking for absence of the cremasteric reflex is a simple method with 100% sensitivity and 66% specificity for testicular torsion [95, 99] (LE:3; GR: C).

Fever occurs often in epididymitis (11-19%). The classical sign of a "blue dot" was found only in 10-23% of patients with torsion of the appendix testis [70, 71, 95, 100].

In many cases, it is not easy to determine the cause of acute scrotum based on history and physical examination alone [69-74, 95, 100].

A positive urine culture is only found in a few patients with epididymitis [73, 95, 100, 101]. It should be remembered that a normal urinalysis does not exclude epididymitis. Similarly, an abnormal urinalysis does not exclude testicular torsion.

Doppler ultrasound is useful to evaluate acute scrotum, with 63.6-100% sensitivity and 97-100% specificity, and a positive predictive value of 100% and negative predictive value 97.5% [102-107] (LE: 3).

The use of Doppler ultrasound may reduce the number of patients with acute scrotum undergoing scrotal exploration, but it is operator-dependent and can be difficult to perform in prepubertal patients [104, 108]. It may also show a misleading arterial flow in the early phases of torsion and in partial or intermittent torsion. Of key importance, persistent arterial flow does not exclude testicular torsion. In a multicentre study of 208 boys with torsion of the testis, 24% had normal or increased testicular vascularisation [104]. Better results were reported using high-resolution ultrasonography (HRUS) for direct visualisation of the spermatic cord twist with a sensitivity of 97.3% and specificity of 99% [104, 109] (LE: 2; GR: C).

Scintigraphy and, more recently, dynamic contrast-enhanced subtraction MRI of the scrotum also provide a comparable sensitivity and specificity to ultrasound [110-113]. These investigations may be used when diagnosis is less likely and if torsion of the testis still cannot be excluded from history and physical examination. This should be done without inordinate delays for emergency intervention [100].

The diagnosis of acute epididymitis in boys is mainly based on clinical judgement and adjunctive investigation. However, it should be remembered that findings of secondary inflammatory changes in the absence of evidence of an extra-testicular nodule by Doppler ultrasound might suggest an erroneous diagnosis of epididymitis in children with torsion of appendix testes [114]. Prepubertal boys with acute epididymitis have an incidence of underlying urogenital anomalies of 25-27.6%. Complete urological evaluation in all children with acute epididymitis is still debatable [73, 95, 97].

Near-infrared spectroscopy has been used to diagnose testicular torsion in adults [115]. This non-invasive optical technique estimates the oxygenation of the spermatic cord tissue that is reduced in testicular torsion. However there is only one case report of its use in childhood in recent literature [116].

3D.3 Disease management

3D.3.1 Epididymitis

In prepubertal boys, the aetiology is usually unclear, with an underlying pathology of about 25%. A urine culture is usually negative, and unlike in older boys, a sexually transmitted disease is very rare.

Antibiotic treatment, although often started, is not indicated in most cases unless urinalysis and urine culture show a bacterial infection [97, 117]. Epididymitis is usually self-limiting and with supportive therapy (i.e. minimal physical activity and analgesics) heals without any sequelae (LE: 3; GR: C). However, bacterial epididymitis can be complicated by abscess or necrotic testis and surgical exploration is required [118].

Torsion of the appendix testis can be managed non-operatively with the use of anti-inflammatory analgesics (LE: 4; GR: C). During the six-week follow-up, clinically and with US, no testicular atrophy was revealed. Surgical exploration is done in equivocal cases and in patients with persistent pain [107].

3D.3.2 Testicular torsion

Manual detorsion of the testis is done without anaesthesia. It should initially be done by outwards rotation of the testis unless the pain increases or if there is obvious resistance. Success is defined as the immediate relief of all symptoms and normal findings at physical examination [119] (LE: 3; GR: C). Doppler ultrasound may be used for guidance [120].

Bilateral orchiopexy is still required after successful detorsion. This should not be done as an elective procedure, but rather immediately following detorsion. One study reported residual torsion during exploration in 17 out of 53 patients, including 11 patients who had reported pain relief after manual detorsion [119, 121].

3D.3.3 Surgical treatment

Testicular torsion is an urgent condition, which requires prompt surgical treatment. The two most important determinants of early salvage rate of the testis are the time between onset of symptoms and detorsion, and the degree of cord twisting [122]. Severe testicular atrophy occurred after torsion for as little as 4 h when the turn was $> 360^\circ$. In cases of incomplete torsion ($180\text{--}360^\circ$), with symptom duration up to 12 h, no atrophy was observed. However, an absent or severely atrophied testis was found in all cases of torsion $> 360^\circ$ and symptom duration > 24 h [123].

Early surgical intervention with detorsion (mean torsion time < 13 h) was found to preserve fertility [124]. Urgent surgical exploration is mandatory in all cases of testicular torsion within 24 h of symptom onset.

In patients with testicular torsion > 24 h, semi-elective exploration is necessary [122, 123] (LE: 3). There is still controversy on whether to carry out detorsion and to preserve the ipsilateral testis, or to perform an orchiectomy, in order to preserve contralateral function and fertility after testicular torsion of long duration (> 24 h).

A recent study in humans found that sperm quality was preserved after orchiectomy and orchidopexy in comparison to normal control men, although orchiectomy resulted in better sperm morphology [125].

During exploration, fixation of the contralateral testis is also performed. Recurrence after orchidopexy is rare (4.5%) and may occur several years later. There is no common recommendation about the preferred type of fixation and suture material; however, many urologists currently use a Dartos pouch orchidopexy with non-absorbable suture material [126].

External cooling before exploration and several medical treatments seem effective in reducing ischaemia-reperfusion injury and preserving the viability of the torsed and the contralateral testis [127–131].

3D.4 Follow-up

Patients would need a follow-up mainly for fertility issues, hormonal consequences and cancer.

3D.4.1 Fertility

The results vary and are conflicting. In one study, unilateral torsion of the testis seriously intervened with subsequent spermatogenesis in about 50% of the patients and produced borderline impairment in another 20% [122]. Although, 30% of affected testicles with mumps orchitis show a degree of atrophy, long-term outcome in terms of fertility is not conclusive [132].

3D.4.2 Subfertility

Subfertility is found in 36–39% of patients after torsion. Semen analysis may be normal in only 5–50% in long-term follow-up [122]. Early surgical intervention (mean torsion time < 13 h) with detorsion was found to preserve fertility, but a prolonged torsion period (mean 70 h) followed by orchiectomy jeopardised fertility [124].

Subfertility and infertility are consequences of direct injury to the testis after the torsion. This is

caused by the cut-off of blood supply, but also of the post-ischaemia-reperfusion injury that is caused after the detorsion when oxygen-derived free radicals are rapidly circulated within the testicular parenchyma [122].

3D.4.3 Androgen levels

Even though the levels of follicle-stimulating hormone (FSH), luteinising hormone (LH) and testosterone are higher in patients after testicular torsion compared to normal controls, endocrine testicular function remains in the normal range after testicular torsion [125].

3D.4.4 Testicular cancer

There may be a 3.2-fold increased risk of developing a testis tumour 6-13 years after torsion. However, two of nine reported cases had torsion of a tumour-bearing testis and four had a tumour in the contralateral testis [122].

3D.5 Recommendations for the treatment of acute scrotum in children

Recommendations	LE	GR
Acute scrotum is a paediatric urological emergency and intervention should not be delayed.		
Neonates with acute scrotum, and bilateral cases, should be treated as surgical emergencies. In neonates, the contralateral scrotum should also be explored.	3	C
Doppler ultrasound is a highly effective imaging tool to evaluate acute scrotum and comparable to scintigraphy and dynamic contrast-enhanced subtraction MRI.		
High-resolution ultrasonography is better for direct visualisation of spermatic cord twisting.	3	C
Torsion of the appendix testis can be managed conservatively but in equivocal cases and in patients with persistent pain, surgical exploration is indicated.		
Urgent surgical exploration is mandatory in all cases of testicular torsion within 24 h of symptom onset.	3	C

MRI = magnetic resonance imaging.

3E HYPOSPADIAS

3E.1 Epidemiology, aetiology and pathophysiology

3E.1.1 Risk factors

Risk factors associated with hypospadias are likely to be genetic, placental and/or environmental [133] (LE: 2b). Interactions between genetic and environmental factors may help explain non-replication in genetic studies of hypospadias. Single nucleotide polymorphisms seemed to influence hypospadias risk only in exposed cases [134] (LE: 2b; GR: B).

- An additional member with hypospadias is found in 7% of families [135].
- Endocrine disorders can be detected in rare cases.
- Babies of young or old mothers and babies with a low birth weight have a higher risk of hypospadias [135].
- A significant increase in the incidence of hypospadias over the last 20 years suggests a role for environmental factors (hormonal disruptors and pesticides) [136-139]. Though this information has been questioned recently [140].
- The use of oral contraceptives prior to pregnancy has not been associated with an increased risk of hypospadias in the offspring [141] (LE: 2a; GR: B).

A Dutch case-control study confirmed that genetic predisposition possibly plays a role in anterior and middle hypospadias, in contrast, the posterior phenotype was more often associated with pregnancy-related factors, such as primiparity, preterm delivery, and being small for gestational age. Hormone-containing contraceptive use after conception increased the risk of middle and posterior hypospadias, while multiple pregnancies were associated with the posterior form in particular [142] (LE: 2a).

3E.2 Classification systems

Hypospadias are usually classified based on the anatomical location of the proximally displaced urethral orifice:

- Distal-anterior hypospadias (located on the glans or distal shaft of the penis and the most common type of hypospadias);
- Intermediate-middle (penile);

- Proximal-posterior (penoscrotal, scrotal, perineal).
- The pathology may be much more severe after skin release.

3E.3 Diagnostic evaluation

It is important that hypospadias patients are diagnosed at birth (except for the megameatus intact prepuce variant).

Diagnosis includes a description of the local findings:

- Position, shape and width of the orifice;
- Presence of atretic urethra and division of corpus spongiosum;
- Appearance of the preputial hood and scrotum;
- Size of the penis;
- Curvature of the penis on erection.

The diagnostic evaluation also includes an assessment of associated anomalies, which are:

- Cryptorchidism (in up to 10% of cases of hypospadias);
- Open processus vaginalis or inguinal hernia (in 9-15%).

Severe hypospadias with unilaterally or bilaterally impalpable testis, or with ambiguous genitalia, require a complete genetic and endocrine work-up immediately after birth to exclude disorders of sex development (DSD), especially congenital adrenal hyperplasia.

Urine trickling and ballooning of the urethra requires exclusion of meatal stenosis. The relationship between the severity of the hypospadias and the associated anomalies of the upper- or lower urinary tract were not confirmed in a systematic literature review [143] (LE: 3).

3E.4 Disease management

Differentiation between functionally necessary and aesthetically feasible operative procedures is important for therapeutic decision-making.

The functional indications for surgery are:

- Proximally located meatus;
- Ventrally deflected or spraying urinary stream;
- Meatal stenosis;
- Curved penis.

The cosmetic indications, which are strongly linked to the psychology of the parent or future patient's psychology, are:

- Abnormally located meatus;
- Cleft glans;
- Rotated penis with abnormal cutaneous raphe;
- Preputial hood;
- Penoscrotal transposition;
- Split scrotum.

As all surgical procedures carry the risk of complications, thorough pre-operative counselling of the parents is crucial.

The therapeutic objectives are to correct the penile curvature, to form a neo-urethra of an adequate size, to bring the neomeatus to the tip of the glans, if possible, and to achieve an overall acceptable cosmetic appearance of the boy's genitalia [136] (LE: 4; GR: C) (Figure 1).

The use of magnifying spectacles and fine synthetic absorbable suture materials (6/0-7/0) is required. As in any penile surgery, an exceptional prudence should be adopted with the use of cautery. Knowledge of a variety of surgical reconstructive techniques, wound care and post-operative treatment are essential for a satisfactory outcome. Pre-operative hormonal treatment with local or parenteral application of testosterone, dihydrotestosterone or beta-chorionic gonadotropin is usually limited to patients with proximal hypospadias, a small appearing penis, reduced glans circumference or reduced urethral plate [144]. The effect of preoperative hormonal stimulation on operative outcomes after hypospadias repair remains unclear according to systematic review [145, 146].

3E.4.1 Age at surgery

The age at surgery for primary hypospadias repair is usually 6-18 (24) months [136] (LE: 4; GR: C). However, earlier repair between 4 and 6 months of age has been reported recently [147, 148] (LE: 3; GR: B). Age at surgery is not a risk factor for urethroplasty complication in prepubertal tubularised incised plate urethroplasty (TIP) repair [148] (LE: 2b).

3E.4.2 Penile curvature

If present, penile curvature is often released by degloving the penis (skin chordee) and by excision of the connective tissue of the genuine chordee on the ventral aspect of the penis in up to 70% [149]. The urethral plate has well vascularised connective tissue and does not cause curvature in most cases. The residual curvature is caused by corporeal disproportion and requires straightening of the penis, mostly using dorsal midline plication or orthoplasty or ventral corporotomies with or without grafting [150, 151] (LE: 2b; GR: B). No systematic review or meta-analyses related to this subject are currently available.

3E.4.3 Preservation of the well-vascularised urethral plate

The mainstay of hypospadias repair is preservation of the well-vascularised urethral plate and its use for urethral reconstruction has become standard practice in hypospadias repair [152]. Mobilisation of the corpus spongiosum/urethral plate and the bulbar urethra decreases the need for urethral plate transection [151] (LE: 2b; GR: B). Urethral plate elevation and urethral mobilization with TIP resulted in focal devascularization of the neourethra with symptomatic stricture development [153] (LE: 2b).

If the urethral plate is wide, it can be tubularised following the Thiersch-Duplay technique. If the plate is too narrow to be simply tubularised, it is recommended that a midline-relaxing incision of the plate, followed by reconstruction according to the Snodgrass-Orkiszewski technique, is performed in distal hypospadias, as well as in proximal hypospadias (though the complication rate is higher) [154-157].

The onlay technique is preferred in proximal hypospadias and if a plate is unhealthy or too narrow [149]. For distal forms of hypospadias, a range of other techniques are available (e.g. Mathieu, urethral advancement) [158] (LE: 2b; GR: B).

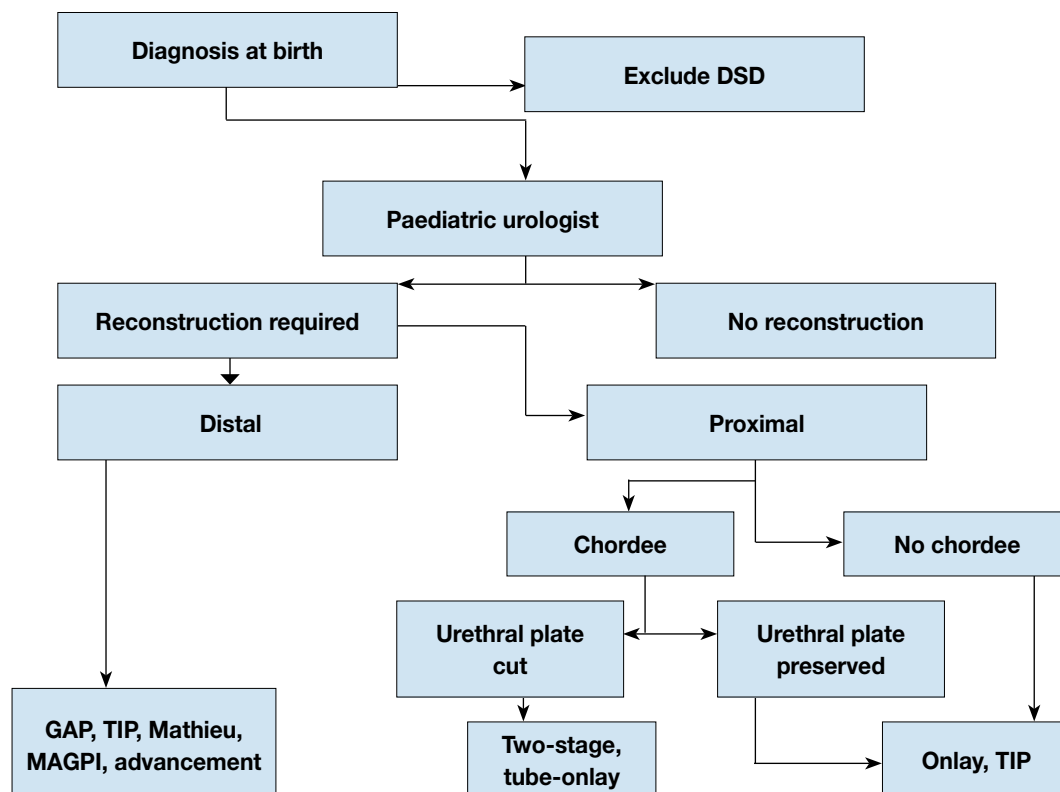
If the continuity of the urethral plate cannot be preserved, a modification of the tubularised flap, such as a tube-onlay, an inlay-onlay flap, or onlay flap on albuginea is used to prevent urethral stricture [159-161] (LE: 3). In this situation, as well as in severe scrotal or penoscrotal hypospadias, the Koyanagi technique or two-stage procedure may be preferable [162-164].

If preputial or penile skin is not available, or has signs of balanitis xerotica obliterans, a buccal mucosa graft is used in an onlay or two-stage repair [165, 166] (LE: 3; GR: C). The use of dorsal inlay skin grafts may allow an increased number of single-stage repairs to be performed [167].

3E.4.4 Re-do hypospadias repairs

For re-do hypospadias repairs, no definitive guidelines can be given. All the above-mentioned procedures are used in different ways and are often modified according to the individual needs of the patient.

Figure 1: Algorithm for the management of hypospadias



DSD = disorders of sex development; GAP = glans approximation procedure; TIP = tubularised incised plate urethroplasty; MAGPI = meatal advancement and glanuloplasty incorporated.

3E.4.5 Urethral reconstruction

Following formation of the neo-urethra, the procedure is completed by glansplasty and by reconstruction of the penile skin. If there is a shortage of skin covering, the preputial double-face technique or placement of the suture line into the scrotum may be used. In countries where circumcision is not routinely performed, preputial reconstruction can be considered. However, in the TIP repair, the parents should be advised that use of a preputial dartos flap reduces the fistula rate [154, 155] (LE: 2b; GR: B).

3E.4.6 Urine drainage and wound dressing

Urine is drained with a transurethral dripping stent, or with a suprapubic tube. Some surgeons use no drainage after distal hypospadias repair. Circular dressing with slight compression, as well as prophylactic antibiotics during surgery, are established procedures [168] (LE: 4; GR: C). Postoperative prophylaxis after hypospadias repair is controversial [169, 170] (LE: 2b).

A large variety of duration of stenting and dressing is described. No recommendation can be given due to the low level of evidence.

3E.4.7 Outcome

A literature review on distal TIP urethroplasty found significant clinical heterogeneity with some limitations to the comparability of the data; one should expect a predictable outcome with complication rates below 10% (fistula, meatal stenosis, dehiscence, recurrent ventral curvature, and haematoma) [171, 172]. A systematic review of the Mathieu and TIP repairs of distal hypospadias found similar incidence of fistula (3.4-3.6%), and higher incidence of meatal stenosis in TIP (3.0% versus 0.6% in Mathieu) after 6-12 months follow-up [173]. Another systematic review and meta-analysis found no difference in fistula, meatal stenosis or glans dehiscence, but better cosmesis in TIP repair [174].

The complication rate of TIP and onlay repairs of primary severe hypospadias is similar, 24% and 27%, respectively. It is higher in free graft and in preputial island tube urethroplasty [149]. Staged buccal mucosa graft requires a redo grafting in 13% of patients, after the second stage more than one third of patients have complications, mostly with some degree of graft fibrosis [175]. Low surgeon volume independently increases the risk of fistula, stricture or diverticulum repair [172] (LE: 3).

Ventral corporeal grafting for severe penile curvature gives good long-term results and safety for erectile function is reported [176] (LE: 2b).

3E.5 Follow-up

Long-term follow-up is necessary up to adolescence to detect urethral stricture, voiding dysfunctions and recurrent penile curvature. Up to half of complications requiring reoperation present after the first year postoperatively [177] (LE: 2b).

Overall, between 7% and 67% of patients operated on for hypospadias end up with an obstructive flow (24.6% in TIP). These children should be followed until adulthood to clarify the clinical significance. Spontaneous improvement has been described [178, 179] (LE: 2a). Urine flow is significantly lower in patients after hypospadias surgery, especially in those who had corrected chordee, than in controls, but without significant association with lower urinary tract symptoms (LUTS) [180] (LE: 2a).

Objective scoring systems have been developed in order to evaluate the results of hypospadias surgery (HOSE) [181] (LE: 2b) and cosmetic appearance (HOPE) [182] (LE: 2a). The Pediatric Penile Perception Score is a reliable instrument to assess penile self-perception in children after hypospadias repair, and for appraisal of the surgical result by parents and uninvolved urologists [183] (LE: 2a).

Adolescents and adults, who have undergone hypospadias repair in childhood, have a slightly higher rate of dissatisfaction with penile size, especially proximal hypospadias patients, but their sexual behaviour is not different from that of control subjects [184, 185] (LE: 2a-b).

3E.6 Conclusions and recommendations for the management of hypospadias

Conclusions	LE
The age at surgery for primary hypospadias repair is usually 6-18 (24) months.	4
The therapeutic objectives are to correct the penile curvature, to form a neo-urethra of an adequate size, to bring the neomeatus to the tip of the glans, if possible, and to achieve an overall acceptable cosmetic appearance.	4
The complication rate is about 10% in distal and 25% in proximal hypospadias repairs.	3
Sexual functions are usually well preserved.	2b

Recommendations	GR
At birth, isolated hypospadias has to be differentiated from disorders of sex development which are mostly associated with cryptorchidism or micropenis.	A
Differentiation between functionally necessary (functional indications) and aesthetically feasible operative procedures (psychological, cosmetic indications) is important for therapeutic decision-making. As all surgical procedures carry the risk of complications, thorough pre-operative counselling of the parents is crucial.	A
Original and modified tubularised incised plate urethroplasty has become the most frequent type of surgery for distal hypospadias; the onlay urethroplasty or two-stage procedures are used in more severe hypospadias. A treatment algorithm is presented (Figure 1).	B
Long-term follow-up is necessary up to adolescence to detect urethral stricture, voiding dysfunctions and recurrent penile curvature. New objective scoring systems help surgeons evaluate the functional and cosmetic outcome.	A

3F CONGENITAL PENILE CURVATURE

3F.1 Epidemiology, aetiology and pathophysiology

Penile curvature may be ventral, dorsal or lateral. Most ventral curvatures are associated with hypospadias due to chordee or ventral dysplasia of cavernous bodies [186]. Similarly, dorsal curvature is mostly associated with exstrophy/epispadias complex [187]. Isolated curvature is not frequent with an incidence of 0.6 % [188] (LE: 2) and is caused by asymmetry of the cavernous bodies [186, 189].

Curvature > 30° is considered clinically significant; curvature > 60° may interfere with satisfactory sexual intercourse in adulthood [190] (LE: 4).

3F.2 Diagnostic evaluation

Diagnosis is made during hypospadias or epispadias repair using an artificial erection [191]. The isolated anomaly is usually not recognised until later in childhood because the appearance of the penis is normal. The curvature is only observed during erections.

3F.3 Disease management

The treatment is surgical. An artificial erection is used to determine the degree of curvature and to check symmetry after the repair [191].

In hypospadias, chordee related to the tethering of the ventral skin and to the spongiosal pillars is first released. Only in a few cases, the penile curvature is caused by a short urethral plate, which should be cut. To repair the corporeal angulation in the isolated curvature, or curvature associated with hypospadias, different techniques of plication of corpora cavernosa (orthoplasty) are used [190].

In exstrophy/epispadias complex, a combination of complete release of the urethral body from the corpora and a different kind of corporoplasty with or without corporotomy is usually necessary to achieve a straight penis [192, 193].

3G VARICOCELE IN CHILDREN AND ADOLESCENTS

3G.1 Epidemiology, aetiology and pathophysiology

Varicocele is defined as an abnormal dilatation of testicular veins in the pampiniformis plexus caused by venous reflux. It is unusual in boys under 10 years of age and becomes more frequent at the beginning of puberty. It is found in 14-20% of adolescents, with a similar incidence during adulthood. It appears mostly on the left side (78-93% of cases). Right-sided varicoceles are less common; they are usually noted only when bilateral varicoceles are present and seldom occur as an isolated finding [194-196].

Varicocele develops during accelerated body growth and increased blood flow to the testes, by a mechanism that is not clearly understood. Genetic factors may be present. An anatomic abnormality leading to impaired venous drainage is expressed by the considerable prevalence of the left side condition where the internal spermatic vein drains into the renal vein. Varicocele can induce apoptotic pathways because of heat stress, androgen deprivation and accumulation of toxic materials. Severe damage is found in 20% of adolescents affected, with abnormal findings in 46% of affected adolescents. Histological findings are similar in children or adolescents and in infertile men. In 70% of patients with grade II and III varicocele, left testicular volume loss was found.

Several authors reported on reversal of testicular growth after varicocelectomy in adolescents [197, 198]. The average proportion of catch-up growth of 76.4% (range: 52.6-93.8%) has been found according to a recent meta-analysis [199] (LE: 2a). However, this may partly be attributable to testicular oedema associated with the division of lymphatic vessels [200] (LE: 2).

In about 20% of adolescents with varicocele, fertility problems will arise [201]. The adverse influence of varicocele increases with time. Improvement in sperm parameters has been demonstrated after adolescent varicocelectomy [202-204] (LE: 1).

3G.2 Classification systems

Varicocele is classified into 3 grades:

- Grade I - Valsalva positive (palpable at Valsalva manoeuvre only);
- Grade II - palpable (palpable without the Valsalva manoeuvre);
- Grade III - visible (visible at distance) [205].

3G.3 Diagnostic evaluation

Varicocele is mostly asymptomatic, rarely causing pain at this age. It may be noticed by the patient or parents, or discovered by the paediatrician at a routine visit. The diagnosis depends upon the clinical finding of a collection of dilated and tortuous veins in the upright posture; the veins are more pronounced when the patient performs the Valsalva manoeuvre. The size of both testicles should be evaluated during palpation to detect a smaller testis.

Venous reflux into the plexus pampiniformis is diagnosed using Doppler colour flow mapping in the supine and upright position [206]. Venous reflux detected on ultrasound only is classified as subclinical varicocele. To discriminate testicular hypoplasia, the testicular volume is measured by ultrasound examination or by orchidometer. In adolescents, a testis that is smaller by > 2 mL or 20% compared to the other testis is considered to be hypoplastic [207] (LE: 2).

Extension of Wilms tumour into the renal vein and inferior vena cava can cause a secondary varicocele. A renal ultrasound should be routinely added in prepubertal boys and in isolated right varicocele (LE: 4).

In order to assess testicular injury in adolescents with varicocele, supranormal FSH and LH responses to the luteinising hormone-releasing hormone (LHRH) stimulation test are considered reliable, because histopathological testicular changes have been found in these patients [203, 208].

3G.4 Disease management

There is no evidence that treatment of varicocele at paediatric age will offer a better andrological outcome than an operation performed later. Beneficial effect of pubertal screening and treatment for varicocele regarding chance of paternity has been questioned according to a corresponding questionnaire in adult patients [209] (LE: 4).

The recommended indication criteria for varicocelectomy in children and adolescents are [195]:

- varicocele associated with a small testis;
- additional testicular condition affecting fertility;
- bilateral palpable varicocele;
- pathological sperm quality (in older adolescents);
- symptomatic varicocele.

Testicular (left + right) volume loss in comparison with normal testes is a promising indication criterion, once the normal values are available [210]. Repair of a large varicocele, causing physical or psychological discomfort, may also be considered. Other varicoceles should be followed-up until a reliable sperm analysis can be performed (LE: 4).

Surgical intervention is based on ligation or occlusion of the internal spermatic veins. Ligation is performed at different levels:

- inguinal (or subinguinal) microsurgical ligation;
- suprainguinal ligation, using open or laparoscopic techniques [211-214].

The advantage of the former is the lower invasiveness of the procedure, while the advantage of the latter is a considerably lower number of veins to be ligated and safety of the incidental division of the internal spermatic at the suprainguinal level.

For surgical ligation, some form of optical magnification (microscopic or laparoscopic) should be used because the internal spermatic artery is 0.5 mm in diameter at the level of the internal ring [211, 213]. The recurrence rate is usually < 10%.

Lymphatic-sparing varicocelectomy is preferred to prevent hydrocele formation and testicular hypertrophy development and to achieve a better testicular function according to the LHRH stimulation test [200, 211, 212, 215] (LE: 2). The methods of choice are subinguinal or inguinal microsurgical (microscopic) repairs, or suprainguinal open or laparoscopic lymphatic-sparing repairs [211, 213, 216, 217]. Angiographic occlusion of the internal spermatic veins also meets these requirements. It is based on retrograde or antegrade sclerotisation of the internal spermatic veins [218, 219]. However, although this method is less invasive and may not require general anaesthesia, it is associated with radiation burden, which is less controllable in the antegrade technique. Available data on failure rates combine anatomical inaccessibility and recurrence [195, 218, 219] (LE: 2).

3G.5 Conclusions and recommendations

Varicocele becomes more frequent at the beginning of puberty and is found in 14-20% of adolescents. Fertility problems are expected in 20% of them.

Varicocele is examined in the standing position and classified into three grades. Venous reflux is diagnosed using Doppler colour flow mapping in the supine and upright position. In up to 70% of patients with grade II and III varicocele, left testicular volume loss is reported; in late adolescence the contralateral right testis may also become smaller.

Recommendations	LE	GR
There is no evidence that treatment of varicocele at paediatric age will offer a better andrological outcome than an operation performed later.		
Surgery is recommended for: <ul style="list-style-type: none"> - varicocele associated with a small testis; - additional testicular condition affecting fertility; - pathological sperm quality (in older adolescents); - bilateral palpable varicocele; - symptomatic varicocele. 	2	B

For surgical ligation, some form of optical magnification (microscopic or laparoscopic magnification) should be used.	2	B
Lymphatic-sparing varicocelectomy is preferred to prevent hydrocele formation and testicular hypertrophy.	2	A

3H URINARY TRACT INFECTIONS IN CHILDREN

3H.1 Epidemiology, aetiology and pathophysiology

Urinary tract infections (UTIs) represent the most common bacterial infection in children [220-222]. In neonates, the symptoms differ in many aspects from those in infants and children. The prevalence is higher; there is a male predominance; infections not caused by *Escherichia coli* are more frequent; and there is a higher risk of urosepsis [223-226].

The incidence varies depending on age and sex. One meta-analysis showed in the first three months of life UTIs were present in 7.5% of girls, 2.4% (CI: 1.4-3.5) of circumcised boys, and 20.1% (CI: 16.8-23.4) of uncircumcised boys, who presented with fever [224]. In the first year of life, UTIs are more common in boys (3.7%) than girls (2%). Later, the incidence of UTIs changes to ~3% in prepubertal girls and 1% in prepubertal boys [224-227].

E. coli is found in ~75% of UTIs and is more frequent in community-acquired than nosocomial. In the latter, *Klebsiella pneumoniae*, *Enterobacter spp.*, *Enterococcus spp.*, *Pseudomonas spp.* and *Candida spp.* are more frequent than in community-acquired UTIs. Neonatal UTI is frequently complicated by bacteraemia. In a retrospective study, 12.4% of blood cultures from neonates admitted for UTI were positive for bacteraemia [228], however, it is less frequent in community-acquired than in nosocomial UTI [228, 229].

3H.2 Classification systems

There are five widely used classification systems according to the site, episode, severity, symptoms and complicating factors. For acute treatment, site and severity are most important.

3H.2.1 Classification according to site

Lower urinary tract (cystitis) is an inflammatory condition of the urinary bladder mucosa with general signs and symptoms including infection, dysuria, frequency, urgency, malodorous urine, enuresis, haematuria, and suprapubic pain.

Upper urinary tract (pyelonephritis) is a diffuse pyogenic infection of the renal pelvis and parenchyma. The onset of pyelonephritis is generally abrupt. Clinical signs and symptoms include fever ($\geq 38^{\circ}\text{C}$), chills, costovertebral angle or flank pain, and tenderness. Older children may report cystitis symptoms along with fever/flank pain. Infants and children may have non-specific signs such as poor appetite, failure to thrive, lethargy, irritability, vomiting or diarrhoea.

3H.2.2 Classification according to episode [230]

The first UTI may be a sign of anatomical anomalies that may predispose to complications of UTI and potential renal damage [231]. Anatomical evaluation is recommended (see below). Recurrent infection can be divided into unresolved and persistent infection.

In unresolved infection, initial therapy is inadequate for elimination of bacterial growth in the urinary tract (inadequate therapy, inadequate antimicrobial urinary concentration [poor renal concentration/gastrointestinal malabsorption], and infection involving multiple organisms with differing antimicrobial susceptibilities).

Persistent infection is caused by re-emergence of bacteria from a site within the urinary tract coming from a nidus for persistent infection that cannot be eradicated (e.g. infected stones, non-functioning or poorly functioning kidneys/renal segments, ureteral stumps after nephrectomy, necrotic papillae in papillary necrosis, urachal cyst, urethral diverticulum, periurethral gland, vesicointestinal, rectourethral or vesicovaginal fistulas). The same pathogen is identified in recurrent infections, but episodes of sterile urine may occur during and shortly following antimicrobial treatment.

In reinfection, each episode can be caused by a variety of new infecting organisms, in contrast to bacterial persistence in which the same infecting organism is always isolated. However, the most common general pathogenic species is *E. coli*, which occurs in many different serotypes. Therefore, recurrent *E. coli* UTI does not equate to infection with the same organism.

3H.2.3 Classification according to severity

In simple UTI, children may have only mild pyrexia; are able to take fluids and oral medication; are only slightly or not dehydrated; and have a good expected level of compliance. When a low level of compliance is expected, such children should be managed as those with severe UTI.

In severe UTI, infection is related to the presence of fever of $> 39^{\circ}\text{C}$, the feeling of being ill, persistent vomiting, and moderate or severe dehydration.

3H.2.4 Classification according to symptoms

Asymptomatic bacteriuria indicates attenuation of uropathogenic bacteria by the host, or colonisation of the bladder by non-virulent bacteria that are incapable of activating a symptomatic response (no leukocyturia, no symptoms). Asymptomatic UTI includes leukocyturia but no other symptoms.

A symptomatic UTI, includes irritative voiding symptoms, suprapubic pain (cystitis), fever and malaise (pyelonephritis). Cystitis may represent early recognition of an infection destined to become pyelonephritis, or bacterial growth controlled by a balance of virulence and host response.

3H.2.5 Classification according to complicating factors [232]

In uncomplicated UTI, infection occurs in a patient with a morphologically and functionally normal upper and lower urinary tract, normal renal function and competent immune system. This category includes mostly isolated or recurrent bacterial cystitis and is usually associated with a narrow spectrum of infecting pathogens that are easily eradicated by a short course of oral antimicrobial agents. Patients can be managed on an outpatient basis, with an emphasis on documenting resolution of their bacteriuria, followed by elective evaluation for potential anatomical or functional abnormalities of the urinary tract.

All neonates, most patients with clinical evidence of pyelonephritis, and all children with known mechanical or functional obstructions of the urinary tract, are considered to have complicated UTI. Mechanical obstruction is commonly due to the presence of posterior urethral valves, strictures or stones, independent of their location. Functional obstruction often results from LUT dysfunction (LUTD) of either neurogenic or non-neurogenic origin and dilating vesicoureteral reflux. Patients with complicated UTI require hospitalisation and parenteral antibiotics. Prompt anatomical evaluation of the urinary tract is critical to exclude the presence of significant abnormalities [233]. If mechanical or functional abnormalities are present, adequate drainage of the infected urinary tract is necessary.

3H.3 Diagnostic evaluation

3H.3.1 Medical history

Medical history includes the question of a primary (first) or secondary (recurring) infection; possible malformations of the urinary tract (e.g. pre- or postnatal ultrasound screening); prior operation; family history; and whether there is constipation or presence of LUTS.

3H.3.2 Clinical signs and symptoms

Neonates with pyelonephritis or urosepsis can present with non-specific symptoms (failure to thrive, jaundice, hyperexcitability and without fever). UTI is the cause of fever in 4.1-7.5% of children who present to a paediatric clinic [234-236]. Septic shock is unusual, even with very high fever. Signs of a UTI may be vague and unspecific in small children, but later on, when they are > 2 years old, frequent voiding, dysuria and suprapubic, abdominal or lumbar pain can be detected.

3H.3.3 Physical examination

Physical examination includes a general examination of the throat, lymph nodes, abdomen (constipation, palpable and painful kidney, or palpable bladder), flank, the back (stigmata of spina bifida or sacral agenesis), genitalia (phimosis, labial adhesion, vulvitis, epididymo-orchitis), and temperature.

3H.3.4 Urine sampling, analysis and culture

Urine sampling has to be performed before any antimicrobial agent is administered. The technique for obtaining urine for urinalysis as well as culture affects the rate of contamination, which influences interpretation of the results. Especially in early infancy it can be challenging and depends on the mode of urine sampling [237].

3H.3.4.1 Urine sampling

Urine must be collected under defined conditions and investigated as soon as possible to confirm or exclude UTI, especially in children with fever.

In neonates, infants and non-toilet-trained children, there are four main methods with varying contamination rates and invasiveness to obtain urine in this age group:

(1) Plastic bag attached to the cleaned genitalia: This technique is most often used in daily practice. It is helpful when the culture results are negative. Also, if the dipstick is negative for both leukocyte esterase and nitrite, or microscopic analysis is negative for both pyuria and bacteriuria, UTI can be excluded without the need for confirmatory culture [238]. However, if the genitalia are not cleaned and culture is delayed, a high incidence of false-positive results (85-99%) can be found [239, 240].

(2) Clean-catch urine collection: The infant is placed in the lap of a parent or member of the nursing staff, who holds a sterile foil bowl underneath the infant's genitalia. The infant is offered oral fluids and urine collection is awaited [241]. This is time consuming and requires proper instruction of the parents. There seems to be a good correlation between the results of urine culture obtained by this method and suprapubic aspiration (SPA), with a false-positive rate of 5% and false-negative rate of 12% [241, 242]; however the contamination rate is higher compared to SPA [243].

(3) Bladder catheterisation: In female infants and also in neonates, this technique may be an alternative to SPA, however with a higher contamination rate [244]. In a prospective study using bladder catheterisation in febrile children aged ≤ 36 months, contamination was defined by multiple pathogens, non-pathogens, or colony counts $< 10,000$ cfu/mL. True UTI was found in 10% of children and 14% of the cultures were contaminated. Univariate analysis of potential predictors identified age < 6 months, difficult catheterisation, and uncircumcised boys. In children ≤ 6 months and uncircumcised boys a new, sterile catheter with each repeated attempt at catheterisation may lead to less contamination [245] otherwise SPA should be the method of choice.

(4) Suprapubic bladder aspiration: This is the most sensitive method to obtain an uncontaminated urine sample in this age group [245-247]. Using ultrasound to assess bladder filling, simplifies SPA and improves the diagnostic yield of obtaining a urine specimen from 60% to ~97% [246, 247]. Complications are rare and have been reported in only 0.22% of cases, ranging from transient haematuria to bowel perforation [248]. However, bladder puncture causes more pain than catheterisation in infants < 2 months old [249].

In older, toilet-trained, children who can void on command, after carefully retracting the foreskin and cleaning the glans penis in boys and spreading the labia and cleaning the periurethral area in girls, the use of clean catch, especially midstream urine, could be an acceptable technique for obtaining urine. After cleaning the urethral meatus and perineum with gauze and liquid soap twice, the risk of contamination was reduced from 23.9% (41/171) to 7.8% (14/171) in a randomised trial [250].

If the clinical situation necessitates, and for differential diagnosis of sepsis, it is most appropriate to obtain an adequate urine sample by catheterisation or SPA [242]. In infants, a bag can only be used if the dipstick is negative, otherwise the urine should be obtained through catheterisation or SPA. This is also recommended in children, who are severely ill and a UTI needs to be excluded or confirmed. Blood sampling is dependent on the clinical situation.

3H.3.4.2 Urinalysis

There are three methods that are commonly used for urinalysis:

(1) Dipsticks: These are appealing because they provide rapid results, do not require microscopy, and are ready to use. Leukocyte esterase (as a surrogate marker for pyuria) and nitrite (which is converted from dietary nitrates by most Gram-negative enteric bacteria in the urine) are the most frequent markers, and are usually combined in a dipstick test. The conversion of dietary nitrates to nitrites by bacteria takes approximately 4 h in the bladder [242, 251]. However, nitrite is not a very sensitive marker for infants, who empty their bladder frequently, and not all urinary pathogens reduce nitrate to nitrite. The test is helpful when the result is positive, because it is highly specific (i.e. there are few false-positive results) [242, 252].

Table 1: Sensitivity and specificity of component of urinalysis, alone and in combination [242]*

Test	Sensitivity (Range), %	Specificity (Range), %
Leukocyte esterase test	83 (67-94)	78 (64-92)
Nitrite test	53 (15-82)	98 (90-100)
Leukocyte esterase or nitrite test positive	93 (90-100)	72 (58-91)
Microscopy, white blood cells	73 (32-100)	81 (45-98)
Microscopy, bacteria	81 (16-99)	83 (11-100)
Leucocyte esterase test, nitrite test or microscopy positive	99.8 (99-100)	70 (60-92)

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(2) Microscopy: This is the standard method of assessing pyuria after centrifugation of the urine with a threshold of 5 white blood cells (WBCs) per high-power field (25 WBC/ μ L) [248]. In uncentrifuged urine, ≥ 10 WBC/ μ L has been demonstrated to be sensitive for UTI [253] and this could perform well in clinical situations [254]. However, this is rarely done in an outpatient setting.

(3) Flow imaging analysis technology: This is being used increasingly to classify particles in uncentrifuged urine specimens [255]. The numbers of WBCs, squamous epithelial cells and red cells correlate well with those found by manual methods [242].

3H.3.4.3 Urine culture

After negative results for dipstick, microscopic or automated urinalysis, urine culture is generally not necessary, especially if there is an alternative source of fever. If the dipstick result is positive, confirmation by urine culture is strongly recommended.

It is unclear what represents a significant UTI. In severe UTI, $> 10^5$ cfu/mL can be expected. However, the count can vary and be related to the method of specimen collection, diuresis, and time and temperature of storage until cultivation occurs [226]. The classical definition of $> 10^5$ cfu/mL of voided urine is still used to define a significant UTI [256, 257]. The recent American Academy of Pediatric Guidelines on Urinary tract infection suggest that the diagnosis should be on the basis of the presence of both pyuria and at least 50,000 cfu. However, some studies have shown that, in voided specimens, $\leq 10^4$ organisms may indicate a significant UTI [258, 259]. If urine is obtained by catheterisation, 1,000-50,000 cfu/mL is considered to be positive, and any counts obtained after SPA should be considered as significant. Mixed cultures are indicative of contamination.

Table 2: Criteria for UTI in children (adapted from the EAU Guidelines on Urological Infections [260])

Urine specimen from suprapubic bladder puncture	Urine specimen from bladder catheterisation	Urine specimen from midstream void
Any number of cfu/mL (at least 10 identical colonies)	$\geq 1,000$ -50,000 cfu/mL	$\geq 10^4$ cfu/mL with symptoms $\geq 10^5$ cfu/mL without symptoms

Pyuria without bacteriuria (sterile pyuria) may be due to incomplete antibiotic treatment, urolithiasis, or foreign bodies in the urinary tract, and infections caused by *Mycobacterium tuberculosis* or *Chlamydia trachomatis*.

3H.3.5 Imaging

3H.3.5.1 Ultrasound

Renal and bladder ultrasonography within 24 hours is advised in infants with febrile UTI to exclude obstruction of the upper and lower urinary tract. Abnormal results are found in ~15% of cases, and 1-2% have abnormalities that require prompt action (e.g. additional evaluation, referral, or surgery) [242]. In other studies, renal ultrasound revealed abnormalities in up to 37% of cases, whereas voiding cystourethrography (VCUG) showed vesicoureteral reflux (VUR) in 27% of cases [229]. Dilating VUR is missed by ultrasound in around one third of cases [261]. Post-void residual urine should be measured in toilet-trained children to exclude voiding abnormalities as a cause of UTI.

3H.3.5.2 Radionuclide scanning

Changes in dimercaptosuccinic acid (DMSA) clearance during acute UTI indicate pyelonephritis or parenchymal damage, correlated well with the presence of dilating reflux and the risk of further pyelonephritis episodes, breakthrough infections [262] and future renal scarring. DMSA scanning may be used as a first-line diagnostic procedure based on observations that dilating VUR occurs in almost all children with abnormal DMSA scan [261, 263]. These findings are different in neonates. After the first symptomatic, community-acquired UTI, the majority of renal units with VUR grade III or higher had normal early DMSA scanning [264]. See also Chapter 3M on VUR.

3H.3.5.3 Voiding cystourethrography

The gold standard to exclude or confirm VUR is VCUG. Due to the risk of renal scarring, VCUG is recommended after the first episode of febrile UTI in boys and girls depending on sex, age and clinical presentation (Figure 1 and Table 7) (see Chapter 3M). The timing of VCUG does not influence the presence or severity of VUR [265, 266]. Performance of early VCUG in patients with proven sterile urine does not cause any significant morbidity [267]. Another option is doing DMSA first, followed by VCUG if there is renal cortical uptake deficiency after UTI (see Chapter 3M).

3H.3.6 **Bladder and bowel dysfunction**

Bladder and bowel dysfunction (BBD) are risk factors for which each child with UTI should be screened upon presentation. Normalisation of micturition disorders or bladder over-activity is important to lower the rate of UTI recurrence. If there are signs of BBD at infection-free intervals, further diagnosis and effective treatment are strongly recommended [268-271]. Treatment of constipation leads to a decrease in UTI recurrence [272-274]. Therefore, exclusion of BBD is strongly recommended in any child with febrile and/or recurrent UTI, and it should be treated if there is evidence of BBD.

3H.4 **Disease management**

3H.4.1 **Administration route**

The choice between oral and parenteral therapy should be based on patient age; clinical suspicion of urosepsis; illness severity; refusal of fluids, food and/or oral medication; vomiting; diarrhoea; non-compliance; and complicated pyelonephritis (e.g. urinary obstruction). As a result of the increased incidence of urosepsis and severe pyelonephritis in newborns and infants aged < 2 months, parenteral antibiotic therapy is recommended. Electrolyte disorders with life-threatening hyponatraemia and hyperkalaemia based on pseudohypoadosteronism can occur in these cases [275, 276].

Parental combination treatment with ampicillin and an aminoglycoside (e.g. tobramycin or gentamicin) or respectively a third-generation cephalosporin achieves excellent therapeutic results (high efficacy of aminoglycosides, respectively cephalosporins against common uropathogens; enterococcus gap is closed with ampicillin). Compared to the division in two doses, a daily single dose of aminoglycosides is safe and effective [233, 277, 278].

The choice of agent is also based on local antimicrobial sensitivity patterns, and should later be adjusted according to sensitivity testing of the isolated uropathogen [242]. Especially in infancy, not all available antibiotics are approved by the national health authorities. In uncomplicated nephritis, both oral and parenteral treatment can be considered, because both are equally effective in children without urinary tract abnormalities. Some studies have demonstrated that once daily parenteral administration of gentamicin or ceftriaxone in a day treatment centre is safe, effective and cost-effective in children with UTI [277, 279, 280].

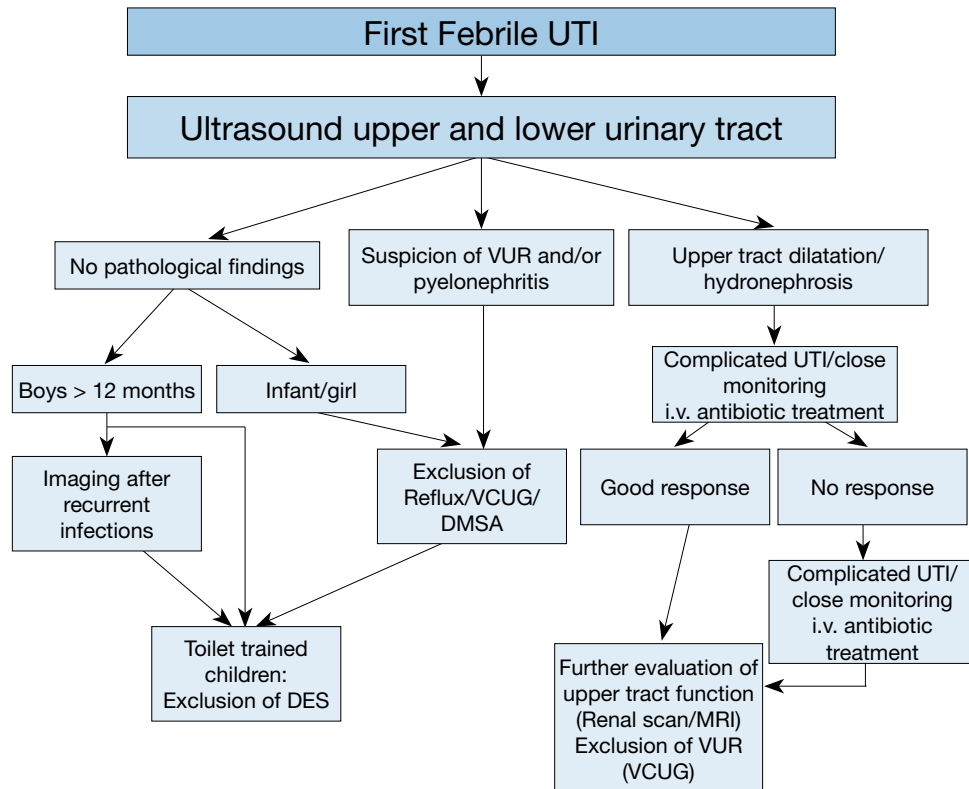
3H.4.2 **Duration of therapy**

Prompt adequate treatment of UTI can prevent the spread of infection and renal scarring. Outcomes of short courses (1-3 days) are inferior to those of 7-4-day courses [242]. In newborns and young infants with a febrile UTI, up to 20% may have a positive blood culture [228, 233]. In late infancy, there are no differences between strategies regarding the incidence of parenchymal scars, as diagnosed with DMSA scan [281]. Some recent studies using exclusively oral therapy with a third-generation cephalosporin (e.g. cefixime or ceftibuten) have demonstrated that this is equivalent to the usual 2-4 days intravenous therapy followed by oral treatment [278, 282-284]. Similar data have been shown for amoxicillin-clavulanate [285], however, these antibiotics are associated with increasing rates of resistance. If ambulatory therapy is chosen, adequate surveillance, medical supervision and, if necessary, adjustment of therapy must be guaranteed. In the initial phase of therapy, a close ambulant contact to the family is advised [286].

In complicated UTI, uropathogens other than *E. coli*, such as *Proteus mirabilis*, *Klebsiella spp.*, *Pseudomonas aeruginosa*, enterococci and staphylococci, are more often to be anticipated [233]. Parenteral treatment with broad-spectrum antibiotics is preferred. A temporary urinary diversion (suprapubiccystostomy or percutaneous nephrostomy) might be required in case of failure of conservative treatment in obstructive uropathy.

Acute focal bacterial nephritis (lobar nephronia) is a localised bacterial infection of the kidney that presents as an inflammatory mass without abscess formation. This may represent a relatively early stage of renal abscess. For the majority of children, the pathogenesis is related to ascending infection due to preexisting uropathy, especially vesicorenal reflux or urinary obstruction (megaureter). Prolonged intravenous antibiotic treatment is sufficient in most cases [287], and intravenous and oral therapy tailored to the pathogen identified in culture is recommended [288].

Figure 2: Algorithm for disease management of first febrile UTI



DES = dysfunctional elimination syndrome; DMSA = technetium⁹⁹-labelled dimercaptosuccinic acid; MRI = magnetic resonance imaging; UTI = urinary tract infection; VCUG = voiding cystourethrography; VUR = vesico-ureteral reflux.

3H.4.3 Antimicrobial agents

There is a great difference in the prevalence of antibiotic resistance of uropathogenic *E. coli* in different countries, with an alarmingly high resistance in Iran and Vietnam [289]. There are upcoming reports of UTIs caused by extended spectrum β -lactamase-producing enterobacteriaceae (ESBL) in children. In one study from Turkey, 49% of the children <1 year of age and 38% of those >1 year of age had ESBL-producing bacteria that were resistant to trimethoprim/sulfamethoxazole in 83%, to nitrofurantoin in 18%, to quinolones in 47%, and to aminoglycosides in 40% [290]. Fortunately, the outcome appears to be the same as for children with non-ESBL producing bacteria, despite the fact that initial intravenous empirical antibiotic therapy was inappropriate in one study [291].

Table 3: Frequently used antibacterial substances for the therapy of urinary tract infections in infants and children*

Chemotherapeutics	Daily dosage	Application	Comments
Parenteral cephalosporins			
Group 3a, e.g. cefotaxime	100-200 mg/kg (Adolesc.: 3-6 g)	i.v. in 2-3 D	
Group 3b, e.g. ceftazidime	100-150 mg/kg (Adolesc.: 2-6 g)	i.v. in 2-3 D	
Ceftriaxone	75 mg/kg	i.v. in 1 D	
Oral cephalosporins			
Group 3, e.g. ceftibuten	9 mg/kg (Adolesc.: 0.4 g)	p.o. in 1-2 D	
Group 3, e.g. cefixime	8-12 mg/kg (Adolesc.: 0.4 g)	p.o. in 1-2 D	
Group 2, e.g. cefpodoxime proxetil	8-10 mg/kg (Adolesc.: 0.4 g)	p.o. in 2 D	
Group 2, e.g. cefuroximaxetil	20-30 mg/kg (Adolesc.: 0.5-1 g)	p.o. in 3 D	
Group 1, e.g. cefaclor	50 -100 mg/kg (Adolesc.: 1.5-4 g)	p.o. in 2-3 D	
Trimethoprim or Trimethoprim/sulfamethoxazole	5-6 mg/kg 5-6 mg/kg (TMP-Anteil) (Adolesc.: 320 mg)	p.o. in 2 D p.o. in 2 D	
Ampicillin	100-200 mg/kgKG (Adolesc.: 3-6 g)	i.v. in 3 D	Ampicillin and Amoxicillin are not eligible for calculated therapy
Amoxicillin	50-100 mg/kg (Adolesc.: 1.5-6 g)	i.v. in 3-4 D p.o. in 2-3 D ¹ p.o. in 2-3 D	
Amoxicillin/clavulanic acid (parenteral)	60-100 mg/kg (Adolesc.: 3.6-6.6 g)	i.v. in 3 D	
Amoxicillin/clavulanic acid (oral)	45-60 mg/kg (Amoxicillinfraction) (Adolesc.: 1500 + 375 mg)	i.v. in 3 D p.o. in 3 D	
Piperacillin	300 mg/kg	p.o.in 3 D i.v. in 3-4 D	
Tobramycin	5 mg/kg (Adolesc.: 3-5 mg/kg, max. 0,4 g)	i.v. in 1 D	Drug monitoring
Gentamicin	5 mg/kg (Adolesc.: 3-5 mg/kg, max. 0,4g)	i.v. in 1 D	
Ciprofloxacin	Children and adolesc. (1-17 years of age): 20-30 mg/kg (max. D: 400 mg) (parenterally) Children and adolesc. (1-17 years of age): 20-40 mg/kg (max. D 750 mg) (orally)	i.v. in 3 D p.o. in 2 D	Approved in most European countries as second- or third line medication for complicated UTIs, "reserve-antibiotic"!
Nitrofurantoin	3-5 mg	p.o. in 2 D	Contraindicated in the case of renal insufficiency

* Reproduced with permission from the International Consultation on Urological Diseases (ICUD), International Consultation on Urogenital Infections, 2009. Copyright © by the European Association of Urology [292]. Dosage for adolescents in paracentesis, if differing. ¹ Infants 2 D, children 1-12 ys. 3 D.

Table 4: Recommendations for calculated antibacterial therapy of pyelonephritis dependent on age and severity of the infection*

Diagnosis	Proposal	Application	Duration of therapy	LE
Pyelonephritis during the first 0-6 months of life	Ceftazidime + Ampicillin ¹ or Aminoglycoside + Ampicillin ¹	3-7 days parenterally, for at least 2 days after defervescence, then oral therapy ² In newborns: parenteral therapy for 7-14 days, then oral therapy ²	10 (-14) days Newborns 14-21 days	4
Uncomplicated pyelonephritis after 6 months of age	Cephalosporin group 3 ²	Orally (initially parenterally, if necessary)	(7-)10 days	1
Complicated pyelonephritis/urosepsis (all ages)	Ceftazidime + Ampicillin ¹ or Aminoglycoside + Ampicillin ¹	7 days parenterally, then oral therapy ²	10-14 days	4

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¹ after receipt of microbiological findings (pathogen, resistance) adaptation of therapy.

² i.v.: e.g. cefotaxime; orally: e.g. cefpodoxime proxetil, ceftibuten, cefixime.

Table 5: Recommendations for antibacterial treatment in cystitis and cystourethritis
(Dosages for children up to 12 years of age)*

Chemotherapeutics	Daily dosage	Application
Oral cephalosporins		
Group 1, e.g. cefaclor	50 (-100) mg/kgbw	p.o. in 2-3 D
Group 1, e.g. cefalexin	50 mg/kgbw	p.o. in 3-4 D
Group 2, e.g. cefuroximaxetil	20-30 mg/kgbw	p.o. in 2 D
Group 2, e.g. cefpodoxime proxetil	8-10 mg/kgbw	p.o. in 2 D
Group 3, e.g. ceftibuten	9 mg/kgbw	p.o. in 1 D
Trimethoprim	5-6 mg/kgbw	p.o. in 2 D
Trimethoprim/sulfamethoxazole	5-6 mg/kgbw (TMP-fraction)	p.o. in 3 D
Amoxicillin/clavulanic acid	37.5-75 mg/kgbw (Amoxicillin-fraction)	p.o. in 3 D
Nitrofurantoin	3-5 mg/kgbw	p.o. in 2 D

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3H.4.4 Chemoprophylaxis

Long-term antibacterial prophylaxis should be considered in cases of high susceptibility to UTI and risk of acquired renal damage. Some recently published prospective, randomised studies do not support the efficacy of antibacterial prophylaxis [293-296]. The Australian PRIVENT study demonstrated risk reduction using trimethoprim-sulfamethoxazole in children from birth to 18 years of age who had at least one symptomatic UTI (19% of the placebo group and 13% of the antibiotic group) [282] (see also Chapter 3N on Urinary Stone Disease).

Table 6: Drugs for antibacterial prophylaxis*

Substance	Prophylactic dosage (mg/kgbw/D)	Limitations in neonates and infants
Trimethoprim**	1	Until 6 weeks of age
Trimethoprim Sulfamethoxazole	1-2 10-15	Not recommended under 2 months of age
Nitrofurantoin**	1	Until 3 months of age
Cefaclor	10	No age limitations
Cefixim	2	Preterms and newborns
Ceftibuten	2	***
Cefuroximaxetil	5	***

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** Substances of first choice are nitrofurantoin and trimethoprim. In exceptional cases, oral cephalosporin can be used. *** In Germany, ceftibuten is not approved for infants < 3 months old.

3H.4.5 Monitoring of UTI

With successful treatment, urine usually becomes sterile after 24 h, and leukocyturia normally disappears within 3-4 days. Normalisation of body temperature can be expected within 24-48 h after the start of therapy in 90% of cases. In patients with prolonged fever and failing recovery, treatment-resistant uropathogens or the presence of congenital uropathy or acute urinary obstruction should be considered. Immediate ultrasound examination is recommended in these cases.

Procalcitonin (among other laboratory inflammatory parameters such as C-reactive protein and leukocyte count) can be used as reliable serum marker for early prediction of renal parenchymal inflammation with first febrile UTI [297]. In patients with febrile UTI, serum electrolytes and blood cell counts should be obtained.

3H.5 Conclusions and recommendations for UTI in children

Conclusions
Urinary tract infection represents the most common bacterial infection in children < 2 years of age. The incidence varies depending on age and sex.
Classifications can be made according to the site, episode, severity, symptoms and complicating factors. For acute treatment, site and severity are most important.
The number of colony forming units (cfu) in the urine culture can vary and is related to the method of specimen collection, diuresis, and time and temperature of storage until cultivation occurs. The classical definition of > 10 ⁵ cfu/mL of voided urine is still used to define a significant UTI.

Recommendations		LE	GR
Diagnosis includes medical history, clinical signs and symptoms (signs of a UTI may be vague and unspecific in small children) as well as a physical examination (including a general examination as well as assessing the genitalia).		3	
Exclusion of bladder and assessing bowel dysfunction is strongly recommended in any child with febrile and/or recurrent UTI, and it should be treated if there is evidence of a dysfunctional elimination syndrome.		3	A
Urine sampling	Urine sampling with plastic bags is commonly used in daily practice. They are helpful only when the dipstick and/or the culture result are negative. There is a high risk of false-positive results.	3	B
	Clean-catch of urine could be an acceptable technique for obtaining urine only in toilet-trained children.	2b	B
	Bladder catheterisation is traumatic especially in boys. It may be an alternative to suprapubic bladder aspiration.	2b	B
	Suprapubic bladder aspiration is the most sensitive method to obtain an uncontaminated urine sample in an infant.	2a	B

Urinalysis	Dipsticks yield rapid results, but should be used with caution in infants who empty their bladder frequently as conversion of nitrates to nitrites by bacteria requires approximately 4 h.	2a	B
	Microscopic investigation is the standard method of assessing pyuria after centrifugation, but it is rarely done in an outpatient setting.	2a	B
	Flow imaging analysis is increasingly used to classify particles in uncentrifuged urine. The numbers of WBCs, squamous epithelial cells and red cells correlate well with manual methods.	3	B
Treatment	The choice between oral and parenteral therapy should be based on patient age; clinical suspicion of urosepsis; illness severity; refusal of fluids, food and/or oral medication; vomiting; diarrhoea; non-compliance; and complicated pyelonephritis (e.g., urinary obstruction).	3	B
	Long-term antibacterial prophylaxis should be considered in cases of high susceptibility to UTI and risk of acquired renal damage.		
	Parenteral therapy is advised when there is clinical suspicion of urosepsis; illness severity; refusal of fluids, food and/or oral medication; vomiting; diarrhoea; non-compliance; and complicated UTI.	2a	B
	As a result of the increased incidence of urosepsis and severe pyelonephritis in newborns and infants aged < 2 months, parenteral antibiotic therapy is recommended. In an emergency setting, i.v. fluid replacement is necessary.		
	Outcomes of short courses (1-3 days) are inferior to those of 7-4-day courses.	1b	B
	Oral therapy with a third-generation cephalosporin (e.g., cefixime or ceftibuten) may be equivalent to the usual 2-4 days intravenous therapy followed by oral treatment.		
	In complicated UTI, parenteral treatment with broad-spectrum antibiotics is indicated.		
Imaging	Renal and bladder ultrasonography is strongly recommended in infants with febrile UTI to exclude obstruction of the upper and lower urinary tract.	3	B
	Changes in DMSA clearance during acute UTI indicate pyelonephritis or parenchymal damage. If it is positive, reflux may be present.	2b	B
	VCUG is the gold standard to exclude or confirm VUR. Due to the risk of renal scarring, it is recommended after the first episode of febrile UTI in boys and girls. The timing of VCUG does not influence the presence or severity of VUR.	2a	B

DMSA = dimercaptasuccinic acid; UTI = urinary tract infections; VCUG = voiding cystourethography; VUR = vesicoureteral reflux; WBC = white blood cell.

31 DAYTIME LOWER URINARY TRACT CONDITIONS

31.1 Epidemiology, aetiology and pathophysiology

Following the newest terminology document by the International Children's Continence Society (ICCS), 'daytime lower urinary tract (LUT) conditions' is the new term used to group together functional incontinence problems in children [298]. After any possible underlying uropathy or neuropathy has been excluded, a problem of incontinence in children is grouped into the category of 'daytime LUT conditions'. Night-time wetting is known as 'enuresis'.

Due to the relationship between the bladder and bowel, concomitant bladder and bowel disturbances have been labeled as bladder bowel dysfunction (BBD). The use of the terms dysfunctional elimination syndrome (DES) or voiding dysfunction are discouraged. BBD is an umbrella term that can be sub-categorised into LUT dysfunction and bowel dysfunction.

Although exact data are unavailable, it is clear that the incidence of daytime LUT conditions is increasing. There exists a wide variation in reported prevalence ranging from 2% to 20% [299-303]. This wide variation might reflect the variation in definitions used. In recent studies, bowel dysfunction is observed in > 50 % of children suffering LUT dysfunction [304, 305].

31.2 Classification systems

Daytime LUT conditions are conditions that present with LUTS, including urge incontinence, weak stream, hesitancy, frequency and urinary tract infections without overt uropathy or neuropathy. Various functional disorders of the detrusor-sphincter complex may occur during the sophisticated early development of normal mechanisms of micturition control. LUT conditions are therefore thought to be the expression of incomplete or delayed maturation of the bladder sphincter complex. Normal daytime control of bladder function matures between 2 and 3 years of age, while night-time control is normally achieved between 3 and 7 years of age [299]. There are two main groups of LUTD, namely, filling-phase dysfunctions and voiding-phase dysfunctions.

31.2.1 *Filling-phase dysfunctions*

In filling-phase dysfunctions, the detrusor can be overactive, as in **overactive bladder (OAB)**, or underactive, as in **underactive (UAB)**. Some children habitually postpone micturition leading to **voiding postponement**.

31.2.2 *Voiding-phase (emptying) dysfunctions*

In voiding-phase (emptying) dysfunctions, interference with the sphincter and pelvic floor during detrusor contraction is the main dysfunction. The general terms for this condition are dysfunctional voiding or detrusor-sphincter discoordination. Different degrees of dysfunction are described, depending on the strength of interference with the sphincter and pelvic floor. Weak interference results in staccato voiding, while stronger interference results in interrupted voiding and straining, due to an inability to relax during voiding.

31.3 Diagnostic evaluation

A non-invasive screening, consisting of history-taking, clinical examination, uroflow, US and voiding diary, is essential to reach a diagnosis. The ICCS published a standardisation document for the diagnosis of LUTD [306]. In the paediatric age group, where the history is taken from both the parents and child together, a structured approach is recommended using a questionnaire. Many signs and symptoms related to voiding and wetting will be unknown to the parents and should be specifically requested, using the questionnaire as a checklist. A voiding diary is mandatory to determine the child's voiding frequency and voided volumes as well as the child's drinking habits. History-taking should also include assessment of bowel function. Some dysfunctional voiding scores have recently been developed and validated [307, 308]. For evaluation of bowel function in children, the Bristol Stool Scale is an easy-to-use tool [309, 310].

Upon clinical examination, genital inspection and observation of the lumbosacral spine and the lower extremities are necessary to exclude obvious uropathy and neuropathy. Uroflow with post-void residual evaluates the emptying ability, while an upper urinary tract ultrasound screens for secondary anatomical changes. A voiding diary provides information about storage function and incontinence frequency, while a pad test can help to quantify the urine loss.

In the case of resistance to initial treatment, or in the case of former failed treatment, re-evaluation is warranted and further video-urodynamic (VUD) studies may be considered. Sometimes, there are minor, underlying, urological or neurological problems, which can only be suspected using VUD. In these cases, structured psychological interviews to assess social stress should be added [311] (LE: 1b; GR: A).

In the case of anatomical problems, such as posterior urethral valve problems, syringocoeles, congenital obstructive posterior urethral membrane (COPUM) or Moormann's ring, it may be necessary to perform further cystoscopy with treatment. If neuropathic disease is suspected, MRI of the lumbosacral spine and medulla can help to exclude tethered cord, lipoma or other rare conditions.

31.4 Disease management

Treatment of LUTD consists of LUT rehabilitation, mostly referred to as urotherapy, meaning non-surgical, non-pharmacological, treatment of LUT function. It is a very broad therapy field, incorporating many treatments used by urotherapists and other healthcare professionals [312]. In case of comorbidity due to bowel problems it is advised to treat the bowel first, since bowel problems may sustain any bladder problems [309]. Urotherapy can be divided into standard therapy and specific interventions. It is strongly advised not to use terms such as "standard therapy" or "maintenance therapy" without defining the design of these treatments.

31.4.1 *Standard therapy*

Standard urotherapy is defined as non-surgical, non-pharmacological, treatment for LUTD. It can include the following components:

- Information and demystification, which includes explanation about normal LUT function and how a particular child deviates from normal function.
- Instruction about what to do about the problem, i.e. regular voiding habits, sound voiding posture, avoiding holding manoeuvres, etc.
- Lifestyle advice, regarding fluid intake, prevention of constipation, etc.

- Registration of symptoms and voiding habits using bladder diaries or frequency-volume charts.
- Support and encouragement via regular follow-up by the caregiver.

A success rate of 80% has been described for urotherapy programmes, independent of the components of the programme. However, the evidence level is low as most studies of urotherapy programmes are retrospective and non-controlled. A recently published multicentre controlled trial of cognitive treatment, placebo, oxybutynin, bladder and pelvic floor training did not report better results with oxybutynin and pelvic floor training compared to standard therapy [311] (LE: 1b; GR: A).

31.4.2 Specific interventions

As well as urotherapy, there are some specific interventions, including physiotherapy (e.g. pelvic floor exercises), biofeedback, alarm therapy and neurostimulation. Although good results with these treatment modalities have been reported, the level of evidence remains low, since only a few RCTs were published [272, 312-317]. In some cases, pharmacotherapy may be added. Antispasmodics and anticholinergics have been shown to be effective, though the level of evidence was low. Some studies on orthosympathomimetics have been published with a low level of evidence [318].

A few RCTs have been published, one on tolterodine showed safety but not efficacy [319], while another on propiverine showed both safety and efficacy [320] (LE: 1). The difference in results is probably due to study design. Despite the low level of evidence for the use of anticholinergics and antimuscarinics, their use is recommended (GR: B) because of the large number of studies reporting a positive effect on OAB symptoms.

Although α -blocking agents are used occasionally, an RCT showed no benefit [321]. Botulinum toxin injection seems promising, but can only be used off-label [322]. Other new treatment modalities such as sacral nerve stimulation are described in case series only and there is no evidence for their usefulness. These new treatment modalities can only be recommended for standard therapy resistant cases [323].

31.5 Recommendations for the treatment of daytime lower urinary tract conditions

Recommendations	LE	GR
Daytime LUTD in children are common and a stepwise treatment approach is recommended, starting with the least invasive approach.	4	B
Initial management consists of urotherapy involving: non-invasive training and re-education, and non-invasive neurostimulation.	2	B
Pharmacotherapy (mainly antispasmodics and anticholinergics) would be the next step.	1	C
In case of therapy resistance, re-evaluation will be required. This may consist of videourodynamics and MRI of lumbosacral spine, guiding to off-label treatment (e.g. some of the non-licensed drugs in children, botulinum toxin injection and sacral nerve stimulation). Such treatment should only be offered in highly experienced centres.	3	C

LUTD = lower urinary tract dysfunction; MRI = magnetic resonance imaging.

3J MONOSYMPTOMATIC ENURESIS

3J.1 Epidemiology, aetiology and pathophysiology

Enuresis is synonymous to intermittent nocturnal incontinence. It is a frequent symptom in children. With a prevalence of 5-10% at 7 years of age, it is one of the most prevalent conditions in childhood. With a spontaneous yearly resolution rate of 15%, it is considered relatively benign [324, 325]. Nocturnal enuresis is considered primary when a child has not yet had a prolonged period of being dry. The term "secondary nocturnal enuresis" is used when a child or adult begins wetting again after having stayed dry.

However, 7 out of 100 children wetting the bed at age 7 will take this condition into adulthood. As it is a stressful condition, which puts a high psychological burden on children resulting in low self-esteem, treatment is advised from the age of 6-7 years onwards. Treatment is unnecessary in younger children in whom spontaneous cure is likely. The child's mental status, family expectations, social issues and cultural background need to be considered before treatment can be started.

Genetically, enuresis is a complex and heterogeneous disorder. Loci have been described on chromosomes 12, 13 and 22 [326].

Three factors play an important pathophysiological role:

- high night-time urine output;

- night-time low bladder capacity or increased detrusor activity;
- arousal disorder.

Due to an imbalance between night-time urine output and night-time bladder capacity, the bladder can become easily full at night and the child will either wake up to empty the bladder or will void during sleep if there is a lack of arousal from sleep [324-326]. Recently, attention has been given to the chronobiology of micturition in which the existence of a circadian clock in kidney, brain and bladder [327] (LE: 1; GR: A).

3J.2 Classification systems

Enuresis is the condition describing the symptom of incontinence during night. Any wetting during sleep above the age of 5 years is enuresis. However, most importantly, there is a single symptom only. Children with other LUTS and enuresis are said to have non-monosymptomatic enuresis [324]. Thorough history-taking, excluding any other daytime symptoms, is mandatory before diagnosing monosymptomatic enuresis. Any associated urinary tract symptoms make the condition a 'daytime LUT condition' [326].

The condition is described as 'primary' when the symptom has always existed and the patient has not been dry for a period longer than 6 months. The condition is described as 'secondary', when there has been a symptom-free interval of 6 months.

3J.3 Diagnostic evaluation

The diagnosis is obtained by history-taking. In a patient with monosymptomatic enuresis, no further investigations are needed. A voiding diary, which records daytime bladder function and night-time urine output, will help to guide the treatment. An estimate of night-time urine production can be obtained by weighing diapers (nappies) in the morning and adding the volume of the morning void. Measuring the daytime bladder capacity gives an estimate of bladder capacity compared to normal values for age [328].

Ultrasound of the urinary tract is not recommended but, when available, it can be used to exclude underlying pathology. In most children, bedwetting is a familial problem, with most affected children found to have a history of bedwetting within the family. A urinary dipstick may help differentiate between true enuresis resulting from polyuria due to diabetes insipidus.

3J.4 Disease management

Before using alarm treatment or medication, simple therapeutic interventions should be considered.

3J.4.1 Supportive treatment measures

Explaining the condition to the child and the parents helps to demystify the problem. Eating and drinking habits should be reviewed, stressing normal fluid intake during the day and reducing fluid intake in the hours before sleep. Keeping a chart depicting wet and dry nights has been shown to be successful.

Counselling, provision of information, positive reinforcement, and increasing (and supporting) motivation of the child should be introduced first. A recent Cochrane review shows that simple behavioural interventions can be effective. However other proven therapies like enuresis alarm and tricyclic antidepressants are more effective [329] (LE:1a; GR: A).

3J.4.2 Alarm treatment

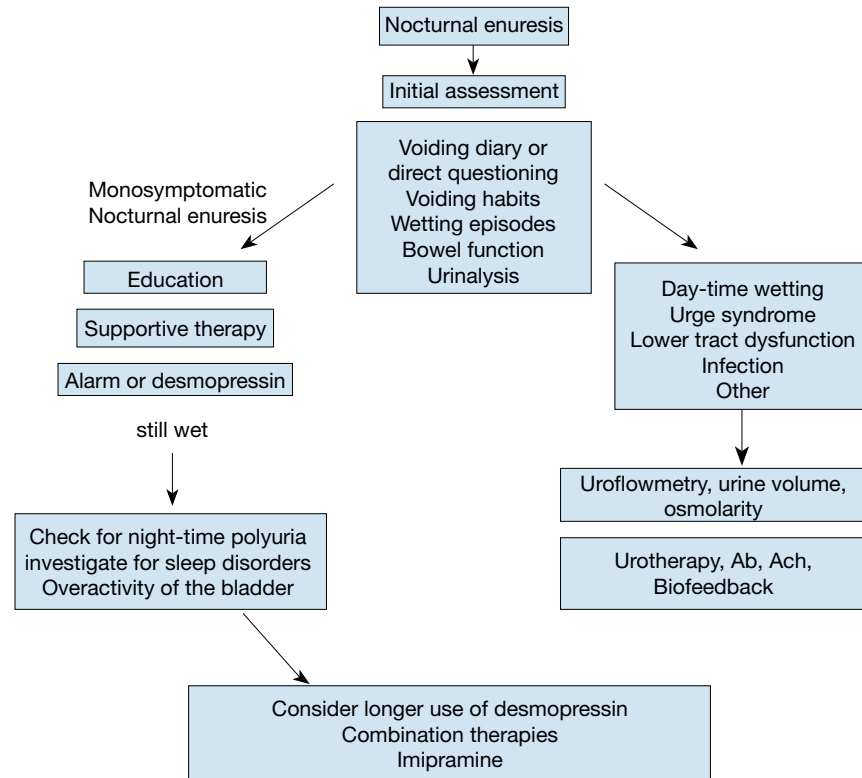
Alarm treatment is the best form for arousal disorder (LE: 1; GR: A). Initial success rates of 80% are realistic, with low relapse rates, especially when night-time diuresis is not too high and bladder capacity is not too low [330].

3J.4.3 Medication

In the case of high night-time diuresis, success rates of 70% can be obtained with desmopressin (DDAVP), either as tablets (200-400 µg), or as sublingual DDAVP oral lyophilisate (120-240 µg). A nasal spray is no longer recommended due to the increased risk of overdose [331, 332] (LE: 1; GR: A). However, relapse rates are high after DDAVP discontinuation [328] and recently, structured withdrawal has shown lower relapse rates [333] (LE: 1; GR: A).

In the case of small bladder capacity, treatment with antispasmodics or anticholinergics is possible [328]. However, when these medications are necessary, the condition is no longer considered to be monosymptomatic. Imipramine, which has been popular for treatment of the enuresis, achieves only a moderate response rate of 50% and has a high relapse rate. Furthermore, cardiotoxicity and death with overdose are described. Its use should therefore be discouraged as the first-line therapy [334] (LE: 1; GR: C).

Figure 3: Assessment and treatment of nocturnal enuresis



3J.5 Recommendations for the treatment of monosymptomatic enuresis

Recommendations	LE	GR
Chronobiology of micturition in which the existence of a circadian clock has been proven in kidney, brain and bladder and disturbances in this chronobiology play a major role in the pathophysiology of enuresis.	1	A
Treatment is unnecessary in younger children (< 5 years of age) in whom spontaneous cure is likely.	2	A
Voiding diaries or questionnaires should be used to exclude daytime symptoms.	2	A
A urine test is indicated to exclude the presence of infection or potential causes such as diabetes insipidus.	2	B
Supportive measures have limited success when used alone; they should be used in conjunction with other treatment modalities, of which pharmacological and alarm treatment are the two most important.	1	A
Alarm treatment is the best treatment for arousal disorder with low relapse rates. There may be family compliance problems.	1	A
For the treatment of night-time diuresis, desmopressin treatment has shown to be effective. The response rate is high around 70%; relapse rates are high.	1	A
Structured withdrawal of desmopressin improves relapse rates.	1	A
The choice of the treatment modality can be made during parental counselling. The parents should be well informed about the problem, and advantages and disadvantages of each of the two treatment modalities should be explained.	4	B

3K MANAGEMENT OF NEUROGENIC BLADDER IN CHILDREN

3K.1 Epidemiology, aetiology and pathophysiology

Neurogenic detrusor-sphincter dysfunction (NDSD) can develop as a result of a lesion at any level in the nervous system. This condition contributes to various forms of LUTD, which may lead to incontinence, UTIs, VUR, and renal scarring. Surgery may be required to establish adequate bladder drainage. If not managed properly, NDSD can potentially cause renal failure, requiring dialysis or transplantation. The main goals of treatment are prevention of urinary tract deterioration and achievement of continence at an appropriate age.

The management of neurogenic bladder sphincter dysfunction in children has undergone major changes over the years. Although nappies (diapers), permanent catheters, external appliances, Crede's manoeuvre and various forms of urinary diversion have been acceptable treatment methods, these are now reserved for only a small number of resistant patients. The introduction of clean intermittent catheterisation (IC) has revolutionised the management of children with neurogenic bladder. Not only has it made conservative management a very successful treatment option, but it has also made surgical creation of continent reservoirs a very effective treatment alternative, with a good outcome for quality of life and kidney protection [335-337].

Neurogenic bladder in children with myelodysplasia presents with various patterns of DSD within a wide range of severity. About 15% of neonates with myelodysplasia have no signs of neurourological dysfunction at birth. However, there is a high chance of progressive changes in the dynamics of neurological lesions with time. Even babies with normal neurourological function at birth have a one in three risk of developing either detrusor sphincter dyssynergia or denervation by the time they reach puberty. At birth, the majority of patients have normal upper urinary tracts, but nearly 60% of them develop upper tract deterioration due to infections, bladder changes and reflux [338-341].

The most common presentation at birth is myelodysplasia. The term myelodysplasia includes a group of developmental anomalies that result from defects in neural tube closure. Lesions may include spina bifida occulta, meningocele, lipomyelomeningocele, or myelomeningocele. Myelomeningocele is by far the most common defect seen and the most detrimental. Traumatic and neoplastic spinal lesions of the cord are less frequent in children. Additionally, different growth rates between the vertebral bodies and the elongating spinal cord can introduce a dynamic factor to the lesion. Scar tissue surrounding the cord at the site of meningocele closure can tether the cord during growth.

In occult myelodysplasia, the lesions are not overt and often occur with no obvious signs of neurological lesion. In nearly 90% of patients, however, a cutaneous abnormality overlies the lower spine, and this condition can easily be detected by simple inspection of the lower back [342].

Total or partial sacral agenesis is a rare congenital anomaly that involves absence of part or all of one or more sacral vertebrae. This anomaly can be part of the caudal regression syndrome, and must be considered in any child presenting with anorectal malformation (ARM). Patients with cerebral palsy may also present with varying degrees of voiding dysfunction, usually in the form of uninhibited bladder contractions (often due to spasticity of the pelvic floor and sphincter complex) and wetting.

Bladder sphincter dysfunction is poorly correlated with the type and spinal level of the neurological lesion.

3K.2 Classification systems

The purpose of any classification system is to facilitate the understanding and management of the underlying pathology. There are various systems of classification of neurogenic bladder.

Most systems of classification were formulated primarily to describe those types of dysfunction secondary to neurological disease or injury. Such systems are based on the localisation of the neurological lesion and the findings of the neurourological examination. These classifications have been of more value in adults, in whom neurogenic lesions are usually due to trauma and are more readily identifiable.

In children, the spinal level and extent of congenital lesion are poorly correlated with the clinical outcome. Urodynamic and functional classifications have therefore been more practical for defining the extent of the pathology and planning treatment in children.

The bladder and sphincter are two units working in harmony to make a single functional unit. The initial approach should be to evaluate the state of each unit and define the pattern of bladder dysfunction. According to the nature of the neurological deficit, the bladder and sphincter may be in either an overactive or inactive state:

- the bladder may be overactive with increased contractions, and low capacity and compliance, or inactive with no effective contractions;
- the outlet (urethra and sphincter) may be independently overactive causing functional obstruction, or paralysed with no resistance to urinary flow;

- these conditions may present in different combinations.

This is mainly a classification based on urodynamic findings. The understanding of the pathophysiology of disorders is essential to plan a rational treatment plan for each individual patient. In meningomyelocele, most patients will present with hyper-reflexive detrusor and dyssynergic sphincter, which is a dangerous combination as pressure is built up and the upper tract is threatened.

3K.3 Diagnostic evaluation

3K.3.1 Urodynamic studies

Since the treatment plan mainly depends upon a good understanding of the underlying problem in the LUT, a well-performed urodynamic study is mandatory in the evaluation of each child with neurogenic bladder.

As the bony level often does not correspond with the neurological defect present, and as the effect of the lesion on bladder function cannot be entirely determined by radiographic studies or physical examination, the information gained from a urodynamic study is priceless. A urodynamic study also provides the clinician with information about the response of the vesicourethral unit to therapy, as demonstrated by improvement or deterioration in follow-up.

It is important to determine several urodynamic parameters, including:

- the bladder capacity;
- the intravesical filling pressure;
- the intravesical pressure at the moment of urethral leakage;
- the presence or absence of reflex detrusor activity;
- the competence of the internal and external sphincteric mechanisms;
- the degree of coordination of the detrusor and sphincteric mechanisms;
- the voiding pattern;
- the post-voiding residual urine volume.

3K.3.1.1 Method of urodynamic study

There is very little comparative data evaluating the complexity and invasiveness of urodynamic testing for neurogenic bladders in children.

3K.3.1.2 Uroflowmetry

As uroflowmetry is the least invasive of all urodynamic tests, it can be used as an initial screening tool. It provides an objective way of assessing the efficiency of voiding, and, together with an ultrasonographic examination, the residual urine volume can also be determined. Unlike in children with non-neurogenic voiding dysfunction, uroflowmetry will rarely be used as a single investigational tool in children with neurogenic bladders, as it does not provide information for bladder storage, yet it may be very practical to monitor emptying in the follow-up. The main limitation of a urodynamic study is the need for the child to be old enough to follow instructions and void on request.

Recording of pelvic floor or abdominal skeletal muscle activity by electromyography (EMG) during uroflowmetry can be used to evaluate coordination between detrusor and the sphincter. As it is a non-invasive test, combined uroflowmetry and EMG may be very useful in evaluating sphincter activity during voiding [343-346] (LE: 3; GR: C).

3K.3.2 Cystometry

Although moderately invasive and dependent on a cooperative child, cystometry in children provides valuable information regarding detrusor contractility and compliance. The amount of information obtained from each study is related to the degree of interest and care given to the test.

It is important to be aware of the alterations in filling and emptying detrusor pressures as the infusion rates change during cystometry. Slow fill cystometry (filling rate < 10 mL/min) is recommended by the ICCS for use in children [347]. However, it has been suggested that the infusion rate should be set according to the child's predicted capacity, based on age and divided by 10 or 20 [325].

Several clinical studies using conventional artificial fill cystometry to evaluate neurogenic bladder in children have reported that conventional cystometry provides useful information for diagnosis and follow-up of children with neurogenic bladder [348-353]. All of the studies were retrospective clinical series and lacked comparison with natural fill cystometry, so that the grade of recommendation for an artificial cystometry in children with neurogenic bladder is not high (LE: 4). Additionally, there is evidence suggesting that natural bladder behaviour is altered during regular artificial filling cystometry [354-357].

Conventional cystometry in infants is useful for predicting future deterioration. Urodynamic parameters, such as low capacity and compliance and high leak-point pressures, are poor prognostic factors for future deterioration. Resolution of reflux is less likely to happen in such bladders [348, 352, 354] (LE: 4).

Although there are only a few studies on natural fill cystometry in children with neurogenic bladder, the results suggest that natural fill cystometry detects new findings compared with diagnoses delivered by conventional cystometry [355] (LE: 3). However, the comparison between natural fill and artificial fill cystometry has not been performed against a gold standard, making it difficult to conclude which study is a true reflection of natural bladder behaviour. Findings in the non-neurogenic adult population have questioned the reliability of natural fill cystometry, as natural fill cystometry has shown a high incidence of bladder overactivity in totally normal asymptomatic volunteers [358].

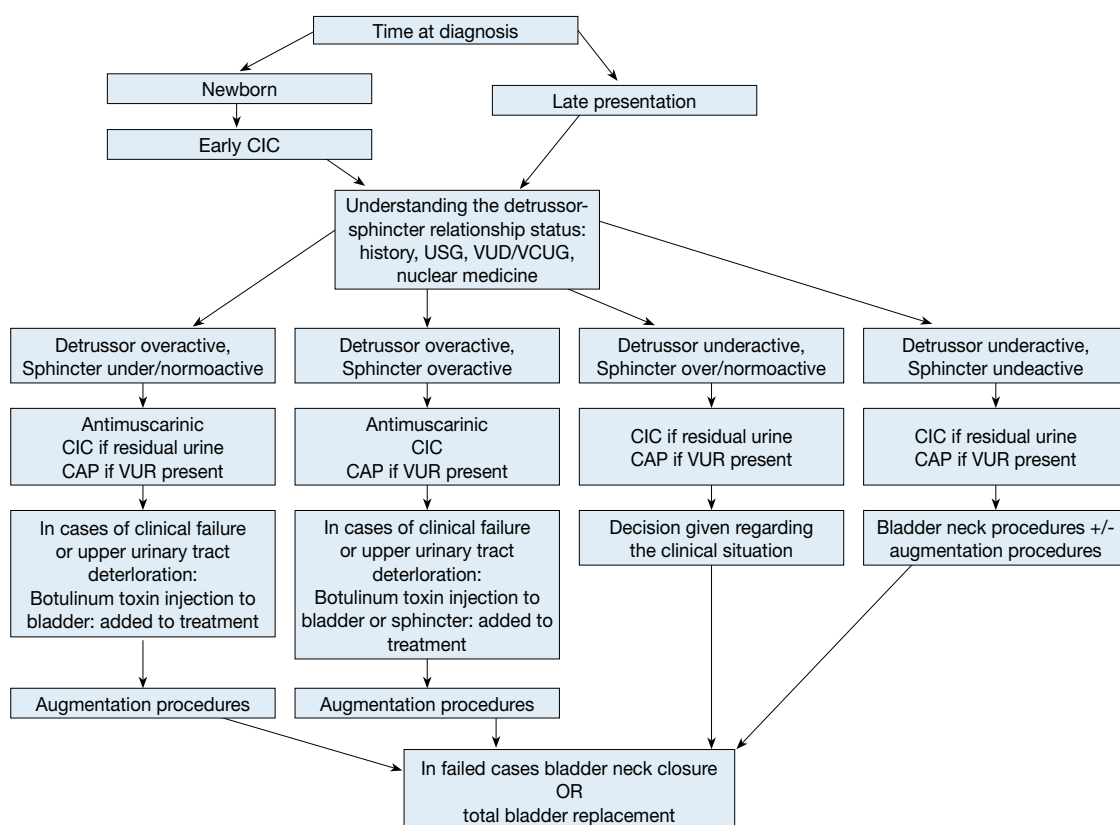
The main disadvantage of natural fill cystometry is that it is labour-intensive and time-consuming. Moreover, because of the transurethral catheter used during this study, false-positive findings caused by the catheter are possible. Especially in children, the recording of events is difficult and there is an increased risk of artefacts, which makes interpretation of the huge amount of data even more difficult. Natural fill cystometry remains a new technique in the paediatric population. More data need to be gathered in a standard way before it can be widely accepted [346].

The timing of the first urodynamic study is not clear. However, repeat studies should be done in a child with neurogenic bladder who are not responsive to the initial treatment or in whom a change in treatment or an intervention is planned.

3K.4 Disease management

The medical care of children with myelodysplasia with a neurogenic bladder requires constant observation and adaptation to new problems. In the first years of life, the kidneys are highly susceptible to back-pressure and infection. During this period, the emphasis is on documenting the pattern of NDSD, and assessing the potential for functional obstruction and VUR. A simple algorithm can be used for management of these patients (Figure 4).

Figure 4: Algorithm for the management of children with myelodysplasia with a neurogenic bladder



CAP = continuous antibiotic prophylaxis; CIC = clean intermittent catheterisation; USG = urinary specific gravity; VCUG = voiding cystourethrography; VUD = videourodynamic; VUR = vesicoureteric reflux.

3K.4.1 Investigations

An abdominal ultrasound obtained as soon as possible after birth will detect hydronephrosis or other upper genitourinary tract pathology. Following ultrasound, a VCUG, preferably a VUD study should be obtained to evaluate the LUT. Measurement of residual urine during both ultrasound and cystography should also be

done. These studies provide a baseline for the appearance of the upper and lower urinary tracts, can facilitate the diagnosis of hydronephrosis or VUR, and can help identify children at risk for upper genitourinary tract deterioration and impairment of renal function.

A urodynamic evaluation can be done after some weeks, and needs to be repeated at regular intervals, in combination with evaluation of the upper tract [359-361] (LE: 3; GR: B).

3K.4.2 Early management with intermittent catheterisation

Overwhelming experience gained over the years with early management of neurogenic bladder in infants has led to a consensus that children do not have upper tract deterioration when managed early with IC and anticholinergic medication. IC should be started soon after birth in all babies, especially in those with signs of possible outlet obstruction [271, 359, 362-369] (LE: 2; GR: B). Babies without any clear sign of outlet obstruction IC may be delayed but babies should be monitored for urinary tract infections and upper tract changes.

The early initiation of IC in the newborn period makes it easier for parents to master the procedure and for children to accept it as they grow older [370, 371].

Early management results in fewer upper tract changes, but also better bladder protection and lower incontinence rates. It has been suggested that increased bladder pressures due to detrusor sphincter dyssynergia cause secondary changes of the bladder wall. These fibroproliferative changes in the bladder wall may cause further loss of elasticity and compliance, resulting in a small non-compliant bladder with progressively elevated pressures.

Early institution of IC and anticholinergic drugs may prevent this in some patients [337, 369, 372] (LE: 3). The retrospective evaluation of patients has also shown that significantly fewer augmentations were required in patients with an early start of IC [363, 368] (LE: 4).

3K.4.3 Medical therapy

At present, oxybutynin, tolterodine, trospium and propiverine are the most frequently used drugs, with oxybutynin being the most studied. The dosage for oxybutynin is 0.1-0.3 mg/kg given three times daily.

Two different forms of tolterodine have been investigated in children with neurogenic bladder. The extended release formulation of tolterodine has been found to be as efficient as the instant release form, with the advantages of being single dosage and less expensive. Although the clinical outcome is encouraging, the level of evidence is low for anticholinergic medication because there are no controlled studies [372-379] (LE: 3; GR: B).

The use of medication to facilitate emptying in children with neurogenic bladder has not been well studied in the literature. A few studies investigating the use of α -adrenergic blockade in children with neurogenic bladder have reported a good response rate, but the studies lacked controls, and long-term follow-up is warranted [380] (LE: 4; GR: C).

Botulinum toxin injections: In neurogenic bladders that are refractory to anticholinergics, injection of botulinum toxin into the detrusor muscle is a novel treatment alternative. Initial promising results in adults have initiated its use in children. It has been shown that this treatment has beneficial effects on clinical and urodynamic variables. Complete continence was achieved in 65-87% of patients; in most studies mean maximum detrusor pressure was reduced to at least 40 cmH₂O and bladder compliance was increased to at least 20 cmH₂O/mL. However, findings are limited by the lack of controlled trials and most studies involved small patient numbers [322, 381-385].

Botulinum toxin seems to be more effective in bladders with obvious detrusor muscle overactivity, whereas non-compliant bladders without obvious contractions are unlikely to respond [386-391].

The most commonly used dose of botulinum toxin is 10 U/kg with a maximum dose of 200 units. No dose study has been performed in children and there is no evidence regarding the optimal dose. Currently, it is unclear how many times this treatment can be repeated, although repetitive treatment has been found to be safe in adults [322, 392-394].

Injection of botulinum toxin in therapy-resistant bladders appears to be an effective and safe treatment alternative (LE: 3; GR: C). Urethral sphincter botulinum-A toxin injection has been shown to be effective in decreasing urethral resistance and improve voiding. The evidence is still too low to recommend its routine use in decreasing outlet resistance, but it could be considered as an alternative in refractory cases [395, 396].

3K.4.4 Management of bowel incontinence

Children with neurogenic bladder have disturbances of bowel function as well as urinary function. Bowel incontinence in these children is frequently unpredictable. It is related to the turnover rate of faecal material in the anal area after evacuation, the degree of intactness of sacral cord sensation and motor function, and reflex

reactivity of the external anal sphincter [397].

Bowel incontinence is managed most commonly with mild laxatives, such as mineral oil, combined with enemas to facilitate removal of bowel contents. A regular and efficient bowel emptying regimen is often necessary to maintain faecal continence, and may have to be started at a very young age. With antegrade or retrograde enemas, most of these children will have decreased constipation problems and may attain some degree of faecal continence [398-402] (LE: 3).

Biofeedback training programmes to strengthen the external anal sphincter have not been shown to be more effective than a conventional bowel management programme in achieving faecal continence [403]. Electrostimulation of the bowel may also offer a variable improvement in some patients [404] (LE: 3; GR: C).

3K.4.5 Urinary tract infection

Urinary tract infections are common in children with neurogenic bladders. In the absence of reflux, UTIs should be treated symptomatically. There is strong evidence for not prescribing antibiotics to patients who have bacteriuria but no clinical symptoms. Although bacteriuria is seen in more than half of children on clean IC, patients who are asymptomatic do not need treatment [405-407] (LE: 3). Patients with VUR should usually be placed on prophylactic antibiotics to reduce the incidence of pyelonephritis, which can potentially lead to renal damage [408, 409].

3K.4.6 Sexuality

Sexuality, while not an issue in childhood, becomes progressively more important as the patient gets older. This issue has historically been overlooked in individuals with myelodysplasia. However, patients with myelodysplasia do have sexual encounters. Studies indicate that at least 15-20% of males are capable of fathering children and 70% of females can conceive and carry a pregnancy to term. It is therefore important to counsel patients about sexual development in early adolescence.

3K.4.7 Bladder augmentation

Children with a good response to anticholinergic treatment and an overactive sphincter may be continent between catheterisations. Bladder pressure and development of the upper urinary tract (UUT) will determine whether additional treatment is necessary.

Therapy-resistant overactivity of the detrusor, or small capacity and poor compliance, will usually need to be treated by bladder augmentation. A simple bladder augmentation using intestine may be carried out if there is any bladder tissue, a competent sphincter and/or bladder neck, and a urethra that can be catheterised.

Stomach is rarely used as an augmenting patch because of the associated complications [410]. Ileal or colonic patches are frequently used for augmenting the bladder, with either equally useful. Despite some advantages (e.g. avoiding mucus, decreased malignancy rate and fewer complications), alternative urothelium-preserving techniques, such as autoaugmentation and seromuscular cystoplasty, have not proven to be as successful as standard augmentation with intestine [411, 412].

A range of applications of engineered bladder tissues are at different stages of development. There have been a few pre-clinical trials; recent progress suggests that engineered bladder tissues may have an expanded clinical application in the future [413].

3K.4.8 Bladder outlet procedures

Children with detrusor overactivity, but with underactive sphincters, will be better for protecting their upper tracts, although they will be severely incontinent. Initial treatment is IC (as it might reduce the degree of incontinence and offers much better control over UTIs) with anticholinergic drugs. At a later age, the outlet resistance will be increased in order to render them continent. No medical treatment available has been validated to increase bladder outlet resistance. Alpha-adrenergic receptor stimulation of the bladder neck has not been very effective [414-419].

When conservative measures fail, surgical procedures need to be considered for maintaining continence. Although a simple augmentation is sufficient for most low-capacity, high-pressure bladders, augmentation with additional bladder outlet procedures is required when both the bladder and outlet are deficient. Bladder outlet procedures include bladder neck reconstruction or other forms of urethral reconstruction.

Various procedures can be used on the bladder neck to increase resistance, but all of them may complicate transurethral catheterisation. Augmentation with surgical closure of the bladder neck may be required primarily, or as a secondary procedure in certain rare clinical situations. In this situation, a continent stoma will be required. However, most surgeons prefer to leave the bladder neck and urethra patent as a safety precaution. Application of artificial urinary sphincters (AUS) in children is another option which gives a chance to the patient to void spontaneously. The largest paediatric series in the literature reports a continence rate over

85% [420]. However, the decision to implant an AUS in a child raises the issue of mechanical failure (>30%), revision of the functioning sphincter (>15%) and surgical complication (15%). Although, advancement of newer devices decreased these numbers [420].

3K.4.9 Continent stoma

Augmentation with an additional continent stoma is utilised primarily after failure of previous bladder outlet surgery. It is also advisable when an inability to catheterise transurethrally is likely. An abdominal wall continent stoma may be particularly beneficial to wheelchair-bound spina bifida patients, who often have difficulty with urethral catheterisation or are dependent on others to catheterise the bladder. For continence with augmentation and an abdominal wall stoma, an adequate bladder outlet mechanism is essential to maintain continence.

3K.4.10 Total bladder replacement

Total bladder replacement in anticipation of normal voiding in children is very rare, as there are infrequent indications for a total cystectomy, with preservation of the bladder outlet and a competent urethral sphincter. This type of bladder replacement is much more common in adult urological reconstruction. Any type of major bladder and bladder outlet construction should be performed in centres with sufficient experience of the surgical technique, and with experienced healthcare personnel to carry out post-operative follow-up [421-423].

3K.5 Follow-up

Neurogenic bladder patients require lifelong supervision, and the monitoring of renal and bladder function is extremely important. Periodic investigation of upper tract changes, renal function and bladder status is mandatory. Repeat urodynamic tests are therefore needed more frequently (every year) in younger children and less frequently in older children. From the urological viewpoint, a repeat urodynamic study is warranted when the patient has a change in symptoms or undergoes any neurosurgical procedure. In the case of any apparent changes in the UUT and LUT, or changes in neurological symptoms, a more detailed examination including urodynamics and spinal MRI is indicated.

Renal failure can progress slowly or occur with startling speed in these children. Patients who have undergone reconstructive procedures using intestine should be regularly followed up for complications such as infection, stone formation, reservoir rupture, metabolic changes, and malignancy [423].

The risk of malignancy in enteric augmentations has been reported to be higher than expected, and the risk increases with length of follow-up. Malignancy occurs in 0.6-2.8% of patients during median follow-up of 13-21 years [424-429]. In a study including 153 patients with a median follow-up time of 28 years [425], malignancy was found in 4.5%. The malignancy seemed to be associated with coexisting carcinogenic stimuli or with the inherent risk present with bladder exstrophy. Although there is poor data on follow-up schemes; after a reasonable follow-up time (e.g. 10 years), an annual diagnostic work-up including cystoscopy should be considered.

3L DILATATION OF THE UPPER URINARY TRACT (UPJ AND UVJ OBSTRUCTION)

3L.1 Epidemiology, aetiology and pathophysiology

Dilatation of the UUT remains a significant clinical challenge in deciding which patient will benefit from treatment.

Ureteropelvic junction (UPJ) obstruction is defined as impaired urine flow from the pelvis into the proximal ureter with subsequent dilatation of the collecting system and the potential to damage the kidney. It is the most common pathological cause of neonatal hydronephrosis [430]. It has an overall incidence of 1:1500 and a ratio of males to females of 2:1 in newborns.

Uterovesical junction (UVJ) obstruction is an obstructive condition of the distal ureter as it enters the bladder, commonly called a primary obstructive megaureter. Megaureters are the second most likely cause of neonatal hydronephrosis. They occur more often in males and are more likely to occur on the left side [431].

It can be very difficult to define 'obstruction' as there is no clear division between 'obstructed' and 'non-obstructed' urinary tracts. Currently, the most popular definition is that an obstruction represents any restriction to urinary outflow that, if left untreated, will cause progressive renal deterioration [432].

3L.2 Diagnostic evaluation

The widespread use of ultrasonography during pregnancy has resulted in a higher detection rate for antenatal hydronephrosis [433]. The challenge in the management of dilated UUT is to decide which child should be observed, which child should be managed medically, and which child requires surgical intervention. Despite the wide range of diagnostic tests, there is no single test that can accurately distinguish obstructive from non-obstructive cases (Figure 1).

3L.2.1 Antenatal ultrasound

Usually between the 16th and 18th weeks of pregnancy, the kidneys are visualised routinely, when almost all amniotic fluid consists of urine. The most sensitive time for foetal urinary tract evaluation is the 28th week. If dilatation is detected, ultrasound should focus on:

- laterality, severity of dilatation, and echogenicity of the kidneys;
- hydronephrosis or hydro-ureteronephrosis;
- bladder volume and bladder emptying;
- sex of the child;
- amniotic fluid volume [434].

3L.2.2 Postnatal ultrasound

Since transitory neonatal dehydration lasts about 48 hours after birth, imaging should be performed following this period of postnatal oliguria. However, in severe cases (bilateral dilatation, solitary kidney, oligohydramnios), immediate postnatal sonography is recommended [435]. Ultrasound should assess the anteroposterior diameter of the renal pelvis, calyceal dilatation, kidney size, thickness of the parenchyma, cortical echogenicity, ureters, bladder wall and residual urine.

3L.2.3 Voiding cystourethrogram

In newborns with identified UUT dilatation, the primary or important associated factors that must be detected include:

- vesicoureteral reflux (found in up to 25% of affected children) [436];
- urethral valves;
- ureterocele;
- diverticula;
- neurogenic bladder.

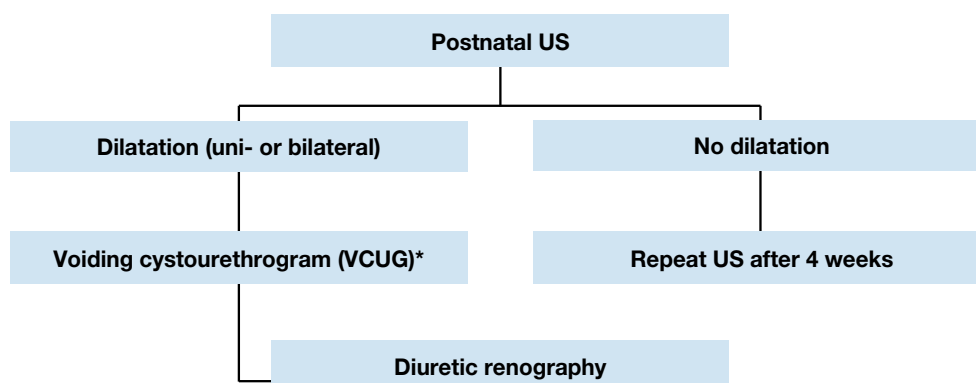
Conventional VCUG is the method of choice for primary diagnostic procedures [437].

3L.2.4 Diuretic renography

Diuretic renography is the most commonly used diagnostic tool to detect the severity and functional significance of problems with urine transport. ^{99m}Tc-MAG3 is the radionuclide of choice. It is important to perform the study under standardised circumstances (hydration, transurethral catheter) after the fourth and sixth weeks of life [438].

Oral fluid intake is encouraged prior to the examination. At 15 minutes before the injection of the radionuclide, it is mandatory to administer normal saline intravenous infusion at a rate of 15 mL/kg over 30 minutes, with a subsequent maintenance rate of 4 mL/kg/h throughout the whole time of the investigation [439]. The recommended dose of furosemide is 1 mg/kg for infants during the first year of life, while 0.5 mg/kg should be given to children aged 1 to 16 years, up to a maximum dose of 40 mg.

Figure 5: Diagnostic algorithm for dilatation of the upper urinary tract



* A diagnostic work-up including VCUG must be discussed with the parents, as it is possible that, even if reflux is detected, it may have absolutely no clinical impact. However, it should be borne in mind that reflux has been detected in up to 25% of cases of prenatally detected and postnatally confirmed hydronephrosis [436].

3L.3 Disease management

3L.3.1 Prenatal management

Counselling the parents of an affected child is one of the most important aspects of care. The prognosis is hopeful for a hydronephrotic kidney, even if it is severely affected, as it may still be capable of meaningful renal function. In contrast, a severely hypoplastic and dysplastic kidney has a much more hopeless outlook.

It is important to be able to tell the parents exactly when they will have a definitive diagnosis for their child and what this diagnosis will mean. In some cases, however, it will be immediately obvious that the child is severely affected; there will be evidence of massive bilateral dilatation, bilateral hypoplastic dysplasia, progressive bilateral dilatation with oligohydramnios, and pulmonary hypoplasia.

Intrauterine intervention is rarely indicated and should only be performed in well-experienced centres [440].

3L.3.2 UPJ obstruction

It is most important that management decisions are made on the basis of serial investigations that have used the same technique and have been performed by the same institution under standardised circumstances.

Symptomatic obstruction (recurrent flank pain, urinary tract infection) requires surgical correction using a pyeloplasty, according to the standardised open technique of Hynes and Anderson [441]. In experienced hands, laparoscopic or retroperitoneoscopic techniques and robot-assisted techniques have the same success rates as standard open procedures. In asymptomatic cases, conservative follow-up is the treatment of choice.

Indications for surgical intervention comprise impaired split renal function (< 40%), a decrease of split renal function of > 10% in subsequent studies, poor drainage function after the administration of furosemide, increased anteroposterior diameter on ultrasound, and grade III and IV dilatation as defined by the Society for Fetal Urology [442].

3L.3.3 Megaureter

The treatment options of secondary megaureters are reviewed in Chapter 3M.3.

3L.3.3.1 Nonoperative management

If a functional study reveals and confirms adequate ureteral drainage, conservative management is the best option. Initially, low-dose prophylactic antibiotics within the first year of life are recommended for the prevention of UTIs, although there are no existing prospective randomised trials evaluating the benefit of this regimen [443].

With spontaneous remission rates of up to 85% in primary megaureter cases, surgical management is no longer recommended, except for megaureters with recurrent UTIs, deterioration of split renal function and significant obstruction [444].

3L.3.3.2 Surgical management

In general, surgery is indicated for symptomatic children and if there is a drop in function in conservative follow-up and hydroureteronephrosis is increasing [445]. Data suggest that children with a ureteric diameter of > 10–15 mm are more likely to require intervention [446].

The initial approach to the ureter can be either intravesical, extravesical or combined. Straightening the ureter is necessary without devascularisation. Ureteral tapering should enhance urinary flow into the bladder. The ureter must be tapered to achieve a diameter for an antireflux repair. Several tailoring techniques exist, such as ureteral imbrication or excisional tapering [447]. Some institutions perform endoscopic stenting, but there is still no long-term data and no prospective randomised trials to confirm their outcome.

3L.4 Conclusion

The use of routine perinatal sonography has resulted in increased detection of hydronephrosis caused by UPJ or UVJ obstruction. Meticulous and repeat postnatal evaluation is mandatory to try to identify obstructive cases at risk of renal deterioration and requiring surgical reconstruction. Surgical methods are quite standardised and have a good clinical outcome.

3L.4.1 Conclusions and recommendations for UPJ-, UVJ-obstruction

Conclusions	LE
Nowadays, most hydronephrotic kidneys have already been diagnosed prenatally during a maternal ultrasound investigation.	2
Ureteropelvic junction obstruction is the leading cause of hydronephrotic kidneys (40%).	1

Recommendations	LE	GR
Postnatal investigations include serial ultrasound and subsequent diuretic renogram and sometimes VCUG.	2	B
A decision about surgical intervention should be based on the time course of the hydronephrosis and the impairment of renal function.	2	B
Indications for surgical intervention are an impaired split renal function due to obstruction or a decrease of split renal function in subsequent studies and increased anteroposterior diameter on the ultrasound, and grade IV dilatation as defined by the Society for Fetal Urology.	2	B
For ureteropelvic junction obstruction, the gold standard of treatment is pyeloplasty.	2	B
Most primary megaureters require no surgical intervention.	2	B

VCUG = voiding cystourethrography.

3M VESICoureTERIC REFLUX IN CHILDREN

The scientific literature for reflux disease is still limited and the level of evidence is generally low. Most of the studies are retrospective, include different patient groups, and have poor stratification of quality. Also, there is a high risk of presenting misleading results by combining different types of studies when systematically extracting data. Therefore, for reflux disease, it is unfortunately not possible to produce recommendations based on high-quality studies. The authors have assessed the current literature, but in the absence of conclusive findings, have provided recommendations based on panel consensus. These Guidelines aim to provide a practical approach to the treatment of VUR based on risk analysis.

3M.1 Epidemiology, aetiology and pathophysiology

Vesicoureteric reflux is an anatomical and/or functional disorder with potentially serious consequences, such as renal scarring, hypertension, and renal failure. Fortunately, patients with VUR present with a wide range of severity, and a good proportion of reflux patients do not develop renal scars and probably do not need any intervention [448]. VUR is a very common urological anomaly in children, with an incidence of nearly 1%.

The main goal in management is the preservation of kidney function, by minimising the risk of pyelonephritis. By defining and analysing the risk factors for each patient (i.e. age, sex, reflux grade, LUTD, anatomical abnormalities, and kidney status), it is possible to identify those patients with a potential risk of UTIs and renal scarring. Controversy persists over the optimal management of VUR, particularly the choice of diagnostic procedures, treatment (medical, endoscopic or surgical), and the timing of treatment.

Many children present without symptoms of UTI and because invasive diagnostic procedures are performed only when clinically indicated, the exact prevalence of VUR is unknown. However, the prevalence of VUR in non-symptomatic children has been estimated at 0.4-1.8% [449]. Among infants prenatally identified with hydronephrosis on ultrasonography (US), who were screened for VUR, the prevalence was 16.2% (7-35%) [450]. Siblings of children with VUR had a 27.4% (3-51%) risk of also having VUR, whereas the offspring of parents with VUR had a higher incidence of 35.7% (21.2-61.4%) [450].

However, reflux detected by sibling screening is associated with lower grades [450] and significantly earlier resolution [451]. When VUR is discovered in siblings after UTI, it is usually high grade and associated with a high incidence of reflux nephropathy, particularly if the sibling is male and the grade of reflux was high in the index patient [452, 453].

The incidence of VUR is much higher among children with UTIs (30-50%, depending on age). UTIs are more common in girls than boys due to anatomical differences. However, among all children with UTIs, boys are more likely to have VUR than girls (29% vs. 14%). Boys also tend to have higher grades of VUR diagnosed at younger ages, although their VUR is more likely to resolve [454-457].

There is a clear co-prevalence between LUTD and VUR [269]. LUTD refers to the presence of LUTS, including urge, urge incontinence, weak stream, hesitancy, frequency and UTIs, which reflect the filling and/or emptying dysfunction that may be accompanied with bowel problems [269]. Some studies have described a prevalence of 40-60% for VUR in children with LUTD [458]. A recently published Swedish reflux trial has demonstrated LUTD in 34% of patients, and subdivision into groups characteristic of children revealed that 9% had isolated overactive bladder and 24% had voiding phase dysfunction [459].

The spontaneous resolution of VUR is dependent on age at presentation, sex, grade, laterality, mode of clinical presentation, and anatomy [451]. Faster resolution of VUR is more likely with age < 1 year at presentation, lower grade of reflux (grade 1-3), and asymptomatic presentation with prenatal hydronephrosis or sibling reflux. The overall resolution rate is high in congenital high-grade VUR during the first years of life. In several Scandinavian studies, the complete resolution rate for high-grade VUR has been reported at > 25%,

which is higher than the resolution rate for VUR detected after infancy [460, 461].

The presence of renal cortical abnormality, bladder dysfunction, and breakthrough febrile UTIs are negative predictive factors for reflux resolution [462-464].

Dilating VUR increases the risk of developing acute pyelonephritis and renal scarring. Untreated recurrent UTIs may have a negative impact on somatic growth and medical status of the child. Evidence of renal scarring is present in 10-40% of children with symptomatic VUR, resulting from either congenital dysplasia and/or acquired post-infectious damage, which may have a negative impact on somatic growth and general wellbeing [465-467].

Higher grades of VUR present with higher rates of renal scars. Scar rates vary in different patient groups. In those with prenatal hydronephrosis, renal scarring occurs in ~10% of patients [468-473], whereas in patients with LUTD, this may increase up to 30% [467, 474, 475]. Renal scarring may adversely affect renal growth and function, with bilateral scarring increasing the risk of insufficiency. Reflux nephropathy (RN) may be the most common cause of childhood hypertension. Follow-up studies have shown that 10-20% of children with RN develop hypertension or end-stage renal disease [476].

3M.2 Diagnostic evaluation

The diagnostic work-up should aim to evaluate the overall health and development of the child, the presence of UTIs, renal status, the presence of VUR, and LUT function. A basic diagnostic work-up comprises a detailed medical history (including family history, and screening for LUTD), physical examination including blood pressure measurement, urinalysis (assessing proteinuria), urine culture, and serum creatinine in patients with bilateral renal parenchymal abnormalities.

The standard imaging tests include renal and bladder ultrasonography (US), VCUG and nuclear renal scans. The criterion standard in diagnosis of VUR is VCUG, especially at the initial work-up. This test provides precise anatomical detail and allows grading of VUR [477]. In 1985, the International Reflux Study Committee introduced a uniform system for the classification of VUR [478, 479] (Table 7). The grading system combines two earlier classifications and is based upon the extent of retrograde filling and dilatation of the ureter, renal pelvis and calyces on VCUG [479].

Radionuclide studies for detection of reflux have lower radiation exposure than VCUG, but the anatomical details depicted are inferior [480]. Recent studies on alternative imaging modalities for detection on VUR have yielded good results with voiding urosonography and magnetic resonance VCUG [481-483]. However, despite the concerns about ionising radiation and its invasive nature, conventional VCUG still remains the gold standard because it allows better determination of the grade of VUR (in a single or duplicated kidney) and assessment of the bladder and urethral configuration.

Table 7: Grading system for VUR on VCUG, according to the International Reflux Study Committee [479]

Grade I	Reflux does not reach the renal pelvis; varying degrees of ureteral dilatation
Grade II	Reflux reaches the renal pelvis; no dilatation of the collecting system; normal fornices
Grade III	Mild or moderate dilatation of the ureter, with or without kinking; moderate dilatation of the collecting system; normal or minimally deformed fornices
Grade IV	Moderate dilatation of the ureter with or without kinking; moderate dilatation of the collecting system; blunt fornices, but impressions of the papillae still visible
Grade V	Gross dilatation and kinking of the ureter, marked dilatation of the collecting system; papillary impressions no longer visible; intraparenchymal reflux

DMSA is the best nuclear agent for visualising the cortical tissue and differential function between both kidneys. DMSA is taken up by proximal renal tubular cells and is a good indicator of renal parenchyma function. In areas of acute inflammation or scarring, DMSA uptake is poor and appears as cold spots. DMSA scans are therefore used to detect and monitor renal scarring. A baseline DMSA scan at the time of diagnosis can be used for comparison with successive scans later during follow-up [479, 484]. DMSA can also be used as a diagnostic tool during suspected episodes of acute pyelonephritis [485]. Children with a normal DMSA scan during acute UTI have a low-risk of renal damage [485].

Video-urodynamic studies are only important in patients in whom secondary reflux is suspected, such as those with spina bifida or boys in whom VCUG is suggestive of posterior urethral valves. In the case of LUTS, diagnosis and follow-up can be limited to non-invasive tests (e.g. voiding charts, US, or uroflowmetry) [269]. Cystoscopy has a limited role in evaluating reflux, except for infravesical obstruction or ureteral anomalies that might influence therapy.

3M.2.1 **Infants presenting because of prenatally diagnosed hydronephrosis**

Ultrasound of the kidney and bladder is the first standard evaluation tool for children with prenatally diagnosed hydronephrosis. It is non-invasive and provides reliable information regarding kidney structure, size, parenchymal thickness and collecting system dilatation [486, 487].

Ultrasound should be delayed until after the first week after birth because of early oliguria in the neonate. It is essential to evaluate the bladder, as well as the kidneys. The degree of dilatation in the collecting system under US, when the bladder is both full and empty, may provide significant information about the presence of VUR. Bladder wall thickness and configuration may be an indirect sign of LUTD and reflux. The absence of hydronephrosis on postnatal ultrasound excludes the presence of significant obstruction; however, it does not exclude VUR.

Monitoring with careful US avoids unnecessary invasive and irradiating examinations. The first two US scans within the first 1-2 months of life are highly accurate for defining the presence or absence of renal pathology. In infants with two normal, successive scans, VUR is a rare entity, and if present it is likely to be low grade [468, 488]. The degree of hydronephrosis is not a reliable indicator for the presence of VUR, even though cortical abnormalities are more common in high-grade hydronephrosis [450]. The presence of cortical abnormalities on US (defined as cortical thinning and irregularity, as well as increased echogenicity) warrants the use of VCUG for detecting VUR [450]. DMSA provides more reliable and quantitative measurement of the degree of cortical abnormalities when first detected with US.

The use of VCUG is recommended in patients with US findings of bilateral high-grade hydronephrosis, duplex kidneys with hydronephrosis, ureterocele, ureteric dilatation, and abnormal bladders, because the likelihood of VUR is much higher. In all other conditions, the use of VCUG to detect reflux is optional [450, 470, 489, 490]. When infants who are diagnosed with prenatal hydronephrosis become symptomatic with UTIs, further evaluation with VCUG should be considered [490]. Patients with severe hydronephrosis and those whose hydronephrosis is sustained or progressive need further evaluation to exclude obstruction.

3M.2.2 **Siblings and offspring of reflux patients**

The screening of asymptomatic siblings and offspring is controversial. Some authors think that early identification of children with VUR may prevent episodes of UTI and therefore renal scarring, whereas others think that screening asymptomatic individuals is likely to result in significant over-treatment of clinically insignificant VUR.

The overall estimate for renal cortical abnormalities is 19.3% (11-54%), with 27.8% having renal damage in cohorts of symptomatic and asymptomatic children combined. In asymptomatic siblings only, the rate of renal damage is 14.4% (0-100%). Early screening and therefore early diagnosis and treatment appears to be more effective than late screening in preventing further renal damage [450, 452, 491, 492]. The lack of randomised clinical trials for screened patients to assess clinical health outcomes makes evidence-based guideline recommendations difficult.

3M.2.3 **Recommendations for paediatric screening of VUR**

The parents of children with VUR should be informed that siblings and offspring have a high prevalence of VUR.
--

If screening is performed, siblings should be screened by renal US. VCUG is recommended if there is evidence of renal scarring on US or a history of UTI.

In older children who are toilet-trained, there is no added value in screening for VUR.

US = ultrasound; UTI = urinary tract infection; VCUG = voiding cystourethrography; VUR = vesicoureteric reflux.

3M.2.4 **Children with febrile urinary tract infections**

A routine recommendation of VCUG at 0-2 years of age after the first proven febrile UTI is the safest approach as the evidence for the criteria to selecting patients for reflux detection is weak. Children with febrile infections and abnormal renal ultrasonographic findings may have higher risk of developing renal scars and they should all be evaluated for reflux [493]. If reflux is diagnosed, further evaluation has traditionally consisted of a DMSA scan.

An alternative “top-down” approach is also an option, as suggested by several studies in the literature. This approach carries out an initial DMSA scan close to the time of a febrile UTI, to determine the presence of pyelonephritis, which is then followed by VCUG if the DMSA scan reveals kidney involvement. A normal DMSA scan with no subsequent VCUG will fail to spot VUR in 5-27% of cases, with the missed VUR presumably being less significant. In contrast, a normal DMSA scan with no VCUG avoids unnecessary VCUG in > 50% of those screened [263, 494-496].

3M.2.5 **Children with lower urinary tract symptoms and vesicoureteric reflux**

Detection of LUTD is essential in treating children with VUR. It is suggested that reflux with LUTD resolves faster after LUTD correction, and that patients with LUTD are at higher risk for developing UTI and renal scarring [459, 497]. The coexistence of both conditions should be explored in any patient who has VUR. If there are symptoms suggestive of LUTD (e.g. urgency, wetting, constipation or holding manoeuvres), an extensive history and examination, including voiding charts, uroflowmetry and residual urine determination, will reliably diagnose underlying LUTD.

In LUTD, VUR is often low grade and US findings are normal, and there is no indication for performing VCUG in all children with LUTD, but the presence of febrile infections should be meticulously questioned. The coexistence of LUTD and VUR means it would be better to do a test covering both conditions, such as a videourodynamic study (VUDS). Any patient with LUTD and a history of febrile UTI should be investigated with a VUDS, if available. Furthermore, any child who fails standard therapy for LUTD should undergo urodynamic investigation. At this stage, combining a urodynamic study with VCUG is highly recommended.

3M.3 **Disease management**

There are two main treatment approaches: conservative (non-surgical) and surgical.

3M.3.1 **Non-surgical therapy**

The objective of conservative therapy is prevention of febrile UTI. It is based on the understanding that:

- VUR resolves spontaneously, mostly in young patients with low-grade reflux. Resolution is nearly 80% in VUR grades I and II and 30-50% in VUR grades III-V within 4-5 years of follow-up. Spontaneous resolution is low for bilateral high-grade reflux [498].
- VUR does not damage the kidney when patients are free of infection and have normal LUT function.
- There is no evidence that small scars can cause hypertension, renal insufficiency or problems during pregnancy. Indeed, these are possible only in cases of severe bilateral renal damage.
- The conservative approach includes watchful waiting, intermittent or continuous antibiotic prophylaxis, and bladder rehabilitation in those with LUTD [282, 497, 499-501].
- Circumcision during early infancy may be considered as part of the conservative approach because it is effective in reducing the risk of infection in normal children [502].

3M.3.1.1 *Follow-up*

Regular follow-up with imaging studies (e.g. VCUG, nuclear cystography, or DMSA scan) is part of the conservative management to monitor spontaneous resolution and kidney status. Conservative management should be dismissed in all cases of febrile breakthrough infections, despite prophylaxis, and intervention should be considered.

3M.3.1.2 *Continuous antibiotic prophylaxis*

The use of continuous antibiotic prophylaxis (CAP) and duration of follow-up during prophylaxis in reflux patients is another area of major controversy. It is clear that antibiotic prophylaxis may not be needed in every reflux patient [282, 503-505]. Trials show benefit of CAP is none or minimal in low-grade reflux. CAP is useful in patients with grade III and IV reflux in preventing recurrent infections but its use in preventing further renal damage is not proven. Toilet trained children and children with LUTD derive much better benefit from CAP [293-296, 506, 507].

It may be difficult and risky to select patients who do not need CAP. A safe approach would be to use CAP in most cases. Decision making may be influenced by the presence of risk factors for UTI, such as young age, high-grade VUR, status of toilet-training/LUTS, female sex, and circumcision status. Although the literature does not provide any reliable information about the duration of CAP in reflux patients, a practical approach would be to use CAP until after children have been toilet-trained and ensuring that there is no LUTD. CAP is mandatory in patients with LUTD and reflux. Active surveillance of UTI is needed after CAP is discontinued. The follow-up scheme and the decision to perform an antireflux procedure or discontinuation of CAP may also depend on personal preferences and the attitude of patients and parents. It is strongly advised that the advantages and disadvantages should be discussed in detail with the family.

3M.3.2 **Surgical treatment**

Surgical treatment can be carried out by endoscopic injection of bulking agents or ureteral reimplantation.

3M.3.2.1 *Subureteric injection of bulking materials*

With the availability of biodegradable substances, endoscopic subureteric injection of bulking agents has become an alternative to long-term antibiotic prophylaxis and open surgical intervention in the treatment of

VUR in children. Using cystoscopy, a bulking material is injected beneath the intramural part of the ureter in a submucosal location. The injected bulking agent elevates the ureteral orifice and the distal ureter, so that coaptation is increased. This results in narrowing of the lumen, which prevents reflux of urine into the ureter, while still allowing its antegrade flow.

Several bulking agents have been used over the past two decades, including polytetrafluoroethylene (PTFE or Teflon), collagen, autologous fat, polydimethylsiloxane, silicone, chondrocytes, and more recently, a solution of dextranomer/hyaluronic acid (Deflux).

Although the best results have been obtained with PTFE [508], due to concerns about particle migration, PTFE has not been approved for use in children [509]. Although they are all biocompatible, other compounds such as collagen and chondrocytes have failed to provide a good outcome. Deflux was approved by the US FDA in 2001 for the treatment of VUR in children. Initial clinical trials have demonstrated that this method is effective in treating reflux [510]. Studies with long-term follow-up have shown that there is a high recurrence rate which may rise as high as 20% in 2 years [503].

In a meta-analysis [511] of 5,527 patients and 8,101 renal units, the reflux resolution rate (by ureter) following one treatment for grades I and II reflux was 78.5%, 72% for grade III, 63% for grade IV, and 51% for grade V. If the first injection was unsuccessful, the second treatment had a success rate of 68% and the third treatment 34%. The aggregate success rate with one or more injections was 85%. The success rate was significantly lower for duplicated (50%) versus single (73%) systems, and neuropathic (62%) versus normal (74%) bladders.

Clinical validation of the effectiveness of antireflux endoscopy is currently hampered by the lack of methodologically appropriate studies. In the most recent prospective, randomised trials comparing three treatment arms: i) endoscopic injection; ii) antibiotic prophylaxis; iii) surveillance without antibiotic prophylaxis) in 203 children aged 1-2 years with grade III/IV reflux, endoscopic treatment gave the highest resolution rate of 71% compared to 39% and 47% for treatment arms II and III, respectively, after 2 years' follow-up. The recurrence rate at 2 years after endoscopic treatment was 20%. The occurrence of febrile UTIs and scar formation was highest in the surveillance group at 57% and 11%, respectively. New scar formation rate was higher with endoscopic injection (7%) compared with antibiotic prophylaxis (0%) [512]. Longer follow-up studies are needed to validate these findings.

3M.3.2.2 *Open surgical techniques*

Various intra- and extravesical techniques have been described for the surgical correction of reflux. Although different methods have specific advantages and complications, they all share the basic principle of lengthening the intramural part of the ureter by submucosal embedding of the ureter. All techniques have been shown to be safe with a low rate of complications and excellent success rates (92-98%) [513].

The most popular and reliable open procedure is cross trigonal reimplantation described by Cohen. The main concern with this procedure is the difficulty of accessing the ureters endoscopically if needed when the child is older. Alternatives are suprahialal reimplantation (Politano-Leadbetter technique) and infrahialal reimplantation (Glenn-Anderson technique). If an extravesical procedure (Lich-Gregoir) is planned, cystoscopy should be performed preoperatively to assess the bladder mucosa and the position and configuration of the ureteric orifices. In bilateral reflux, an intravesical antireflux procedure may be considered, because simultaneous bilateral extravesical reflux repair carries an increased risk of temporary postoperative urine retention [514]. Overall, all surgical procedures offer very high and similar success rates for correcting VUR.

3M.3.2.3 *Laparoscopy*

There have been a considerable number of case series of transperitoneal extravesical and pneumovesicoscopic intravesical ureteral reimplantation, which have shown the feasibility of the techniques. Various antireflux surgeries have been tried with the da Vinci Surgical System in an intravesicular or extravesicular manner. Today, robot-assisted laparoscopic approaches present comparable outcomes to their open surgical counterparts in terms of successful resolution of reflux. Further studies are needed to define the success rates, costs and benefits of both approaches [515, 516].

The major shortcoming of the new techniques seems to be the longer operative times, which hinder their wider acceptance. Also, laparoscopic approaches are more invasive than endoscopic correction and their advantages over open surgery are still debated. Therefore, at present, a laparoscopic approach cannot be recommended as a routine procedure. It can be offered as an alternative to the parents in centres where there is enough experience [502, 515, 517-523].

3M.3.3 Recommendations for the management of vesicoureteric reflux in childhood

Regardless of the grade of reflux or presence of renal scars, all patients diagnosed within the first year of life should be treated initially with CAP. During early childhood, the kidneys are at higher risk of developing new scars. Immediate, parenteral antibiotic treatment should be initiated for febrile breakthrough infections. Definitive surgical or endoscopic correction is the preferred treatment in patients with frequent breakthrough infections [520].

Surgical correction should be considered in patients with persistent high-grade reflux (grades IV/V). There is no consensus about the timing and type of surgical correction. The outcome of open surgical correction is better than endoscopic correction for higher grades of reflux, whereas satisfactory results can be achieved by endoscopic injection for lower grades.

There is no evidence that correction of persistent low-grade reflux (grades I-III) without symptoms and normal kidneys offers a significant benefit. These patients may be candidates for endoscopic treatment.

In all children presenting at age 1-5 years, CAP is the preferred option for initial therapy. For those with high-grade reflux or abnormal renal parenchyma, surgical repair is a reasonable alternative. In patients with lower grades of reflux and without symptoms, close surveillance without antibiotic prophylaxis may be an option.

A detailed investigation for the presence of LUTD should be performed in all children after toilet-training. If LUTD is found, the initial treatment should always be for LUTD.

If parents prefer definitive therapy to conservative management, surgical correction may be considered. Endoscopic treatment is an option for all children with low grades of reflux.

The traditional approach of initial medical treatment after diagnosis and shifting to interventional treatment in case of breakthrough infections and new scar formation needs to be challenged, because the treatment should be tailored to different risk groups.

The choice of management depends on the presence of renal scars, clinical course, grade of reflux, ipsilateral renal function, bilaterality, bladder function, associated anomalies of the urinary tract, age, compliance, and parental preference [517]. Febrile UTI, high-grade reflux, bilaterality, and cortical abnormalities are considered to be risk factors for possible renal damage. The presence of LUTD is an additional risk factor for new scars.

In high-risk patients who already have renal impairment, a more aggressive, multidisciplinary approach is needed.

CAP = continuous antibiotic prophylaxis; LUTD = lower urinary tract dysfunction; UTI = urinary tract infection.

Table 8: Management and follow-up according to different risk groups

Risk Groups	Presentation	Initial treatment	Comment	Follow-up
High	Symptomatic male or female patients after toilet-training with high-grade reflux (grades IV-V), abnormal kidneys and LUTD	Initial treatment is always for LUTD with CAP; intervention may be considered in cases of BT infections or persistent reflux	Greater possibility of earlier intervention	More aggressive follow-up for UTI and LUTD; full re-evaluation after 6 months
High	Symptomatic male or female patients after toilet-training with high-grade reflux (grade IV-V), abnormal kidneys and no LUTD	Intervention should be considered	Open surgery has better results than endoscopic surgery	Post-operative VCUG on indication only; follow-up of kidney status until after puberty
Moderate	Symptomatic male or female patients before toilet-training, with high-grade reflux and abnormal kidneys	CAP is the initial treatment. Intervention may be considered in cases of BT infections or persistent reflux	Spontaneous resolution is higher in males	Follow-up for UTI/hydronephrosis; full re-evaluation after 12-24 months
Moderate	Asymptomatic patients (PNH or sibling) with high-grade reflux and abnormal kidneys	CAP is the initial treatment. Intervention may be considered in cases of BT, infections or persistent reflux		Follow-up for UTI/hydronephrosis; full re-evaluation after 12-24 months
Moderate	Symptomatic male or female patients after toilet-training, with high-grade reflux and normal kidneys with LUTD	Initial treatment is always for LUTD with CAP. Intervention may be considered in cases of BT infections or persistent reflux	In case of persistent LUTD, despite urotherapy, intervention should be considered. The choice of intervention is controversial	Follow-up for UTI and LUTD, kidney status; full re-evaluation after successful urotherapy
Moderate	Symptomatic male or female patients after toilet-training with low-grade reflux, abnormal kidneys with or without LUTD	Choice of treatment is controversial. Endoscopic treatment may be an option. LUTD treatment should be given if needed		Follow-up for UTI, LUTD, and kidney status until after puberty
Moderate	All symptomatic patients with normal kidneys, with low-grade reflux, with LUTD	Initial treatment is always for LUTD with or without CAP		Follow-up for UTI and LUTD
Low	All symptomatic patients with normal kidneys, with low-grade reflux, with no LUTD	No treatment or CAP	If no treatment is given, parents should be informed about risk of infection	Follow-up for UTI
Low	All asymptomatic patients with normal kidneys with low-grade reflux	No treatment or CAP in infants	If no treatment is given, parents should be informed about risk of infection	Follow-up for UTI

BT = breakthrough; CAP = continuous antibiotic prophylaxis; LUTD = lower urinary tract dysfunction;
 PNH = prenatal diagnosed hydronephrosis.

3N URINARY STONE DISEASE

3N.1 Epidemiology, aetiology and pathophysiology

Paediatric stone disease is an important clinical problem in paediatric urology practice. Because of its recurrent nature, every effort should be made to discover the underlying metabolic abnormality so that it can be treated appropriately. Obtaining a stone-free state with interventional management and close follow-up are of the utmost importance.

Paediatric stone disease has its own unique features, which are different in both presentation and treatment compared to stone disease in adults. In contrast to adults with stone disease who are more likely to be male, boys and girls are affected almost equally. Most paediatric stones are located in the UUT. However, bladder stones are still common in underdeveloped areas of the world and are usually ammonium acid urate and uric acid stones, strongly implicating dietary factors [524].

The incidence and characteristics of stones show a wide geographical variation in children. Although urinary stone disease is generally considered to be a relatively rare disease, it is quite common in some parts of the world. Paediatric stone disease is endemic in Turkey, Pakistan and in some South Asian, African and South American states. However, recent epidemiological studies have shown that the incidence of paediatric stone disease is also increasing in the Western world [525, 526] especially in girls, Caucasian ethnicity, and older children [527]. In the UK and other European countries, 75% of calculi in children are composed of organic matrix and struvite, with many stone formations associated with *Proteus* infection and urinary tract anomalies [528].

3N.2 Classification systems

Urinary stone formation is the result of a complex process involving metabolic, anatomical factors and presence of infection.

3N.2.1 Calcium stones

Calcium stones are usually made from calcium oxalate or calcium phosphate. Supersaturation of calcium (hypercalciuria) and oxalate (hyperoxaluria) or decreased concentration of inhibitors, such as citrate (hypocitraturia), play a major role in the formation of calcium oxalate stones.

Hypercalciuria: This is defined by a 24-hour urinary calcium excretion of more than 4 mg/kg/day in a child weighing less than 60 kg. In infants younger than 3 months, 5 mg/kg/day is considered to be the upper limit of normal for calcium excretion [529].

Hypercalciuria can be classified as either idiopathic or secondary. Idiopathic hypercalciuria is diagnosed when clinical, laboratory, and radiographic investigations fail to delineate an underlying cause. Secondary hypercalciuria occurs when a known process produces excessive urinary calcium. In secondary (hypercalcaemic) hypercalciuria, a high serum calcium level may be due to increased bone resorption (hyperparathyroidism, hyperthyroidism, immobilisation, acidosis, metastatic disease) or gastrointestinal hyperabsorption (hypervitaminosis D) [530].

A good screening test for hypercalciuria compares the ratio of urinary calcium to creatinine. The normal calcium-to-creatinine ratio in children is less than 0.2. If the calculated ratio is higher than 0.2, repeat testing is indicated. Neonates and infants have a higher calcium excretion and lower creatinine excretion than older children [529, 530]. If the follow-up ratios are normal, then no additional testing for hypercalciuria is needed. However, if the ratio remains elevated, a timed 24-hour urine collection should be obtained and the calcium excretion calculated.

The 24-hour calcium excretion test is the criterion standard for the diagnosis of hypercalciuria. If calcium excretion is higher than 4 mg/kg/day (0.1 mmol/kg/day), the diagnosis of hypercalciuria is confirmed and further evaluation is warranted. Further evaluation includes levels of serum bicarbonate, creatinine, alkaline phosphatase, calcium, magnesium, pH, and parathyroid hormone. Freshly voided urine should be measured for pH [529-532]. A 24-hour urine collection should also be made to measure calcium, phosphorus, sodium, magnesium, citrate and oxalate. Meanwhile, dietary manipulations should be tried to normalise urine calcium [531].

Initial management is always to increase fluid intake and urinary flow. Dietary modification is a mandatory part of effective therapy. The child should be referred to a dietician to assess accurately the daily intake of calcium, animal protein, and sodium. Dietary sodium restriction is recommended as well as maintenance of calcium intake consistent with the daily needs of the child [533].

A brief trial of a low-calcium diet can be carried out to determine if exogenous calcium intake is contributing to high urinary calcium. However, great caution should be used when trying to restrict calcium intake for long periods (LE: 3; GR: B).

Hydrochlorothiazide and other thiazide-type diuretics may be used to treat hypercalciuria at a

dosage of 1-2 mg/kg/day [528, 534] (LE: 3; GR: C). In long-term use of thiazide-type diuretics, a decrease in hypocalciuric effect may be seen after the third month and may cause hypokalemia and hypocitraturia. Therefore, control of blood and serum values should be performed with regular intervals. Citrate therapy is also useful if citrate levels are low or if hypercalciuria persists, despite other therapies [528, 535] (LE: 4; GR: C).

Hyperoxaluria: Oxalic acid is a metabolite excreted by the kidneys. Only 10-15% of oxalate comes from diet. Normal school children excrete less than 50 mg (0.57 mmol)/1.73 m²/day [528, 536], while infants excrete four times as much. Hyperoxaluria may result from increased dietary intake, enteric hyperabsorption (as in short bowel syndrome) or an inborn error of metabolism.

In primary hyperoxaluria, one of the two liver enzymes that play a role in the metabolism of oxalate may be deficient. In primary hyperoxaluria there is increased deposition of calcium oxalate in the kidney and in urine. With increased deposition of calcium oxalate in the kidneys, renal failure may ensue in resulting deposition of calcium oxalate in other tissues. The diagnosis is made upon laboratory findings of severe hyperoxaluria and clinical symptoms. The definitive diagnosis requires liver biopsy to assay the enzyme activity.

Other forms of hyperoxaluria, as mentioned earlier, may be due to hyperabsorption of oxalate in inflammatory bowel syndrome, pancreatitis and short bowel syndrome. Yet, the majority of children who have high levels of oxalate excretion in urine may not have any documented metabolic problem or any dietary cause. This is known as idiopathic 'mild' hyperoxaluria, with urine oxalate levels elevated only mildly in these cases. The treatment of hyperoxaluria consists of the promotion of high urine flow, restriction of dietary oxalate and regular calcium intake. Pyridoxine may be useful in reducing urine levels, especially in primary hyperoxaluria [528, 536] (LE: 4; GR: C).

Hypocitraturia: Citrate is a urinary stone inhibitor. Citrate acts by binding to calcium and by directly inhibiting the growth and aggregation of calcium oxalate as well as calcium phosphate crystals. Thus, low urine citrate may be a significant cause of calcium stone disease. In adults, hypocitraturia is the excretion of citrate in urine of less than 320 mg/day (1.5 mmol/day) for adults; this value must be adjusted for children depending on body size [537, 538].

Hypocitraturia usually occurs in the absence of any concurrent symptoms or any known metabolic derangements. It may also occur in association with any metabolic acidosis, distal tubular acidosis or diarrhoeal syndromes.

Environmental factors that lower urinary citrate include a high protein intake and excessive salt intake. Many reports emphasise the significance of hypocitraturia in paediatric calcium stone disease. The presence of hypocitraturia ranges from 30% to 60% in children with calcium stone disease.

Due to the increased stone risk in hypocitraturia, the restoration of normal citrate levels is advocated to reduce stone formation. Although some studies have shown that citrate replacement therapy reduces the risk of stone formation in an adult population, there are few relevant studies in children. Hypocitraturia is treated by potassium citrate at a starting dose of 1 mEq/kg, given in two divided doses [538] (LE: 3; GR: B). The side effects of potassium citrate are very rare and most of the time they include non-specific gastrointestinal complaints. Potassium citrate should be used with caution in hyperkalemic and chronic renal failure conditions.

3N.2.2 **Uric acid stones**

Uric acid stones are responsible for urinary calculi in 4-8% of children. Uric acid is the end product of purine metabolism. Hyperuricosuria is the main cause of uric acid stone formation in children. A daily output of uric acid of more than 10 mg/kg/day is considered to be hyperuricosuria [528].

The formation of uric acid stones is mainly dependent on the presence of acidic urinary composition. Uric acid dissociation and solubility is strongly reduced at pH of less than 5.8. As the pH becomes more alkaline, uric acid crystals become more soluble and the risk of uric acid stone formation is reduced.

In the familial or idiopathic form of hyperuricosuria, children usually have normal serum uric acid levels. In other children, it can be caused by uric acid overproduction secondary to inborn errors of metabolism, myeloproliferative disorders or other causes of cell breakdown. Hyperuricosuria is also caused by high purine and protein intake. Although hyperuricosuria is a risk factor for calcium oxalate stone formation in adults, this does not appear to be a significant risk factor in children.

Uric acid stones are non-opaque stones. Plain X-rays are insufficient to show uric acid stones, and renal sonography and spiral CT are used for diagnosis.

Alkalinisation of urine is the mainstay of therapy and prevention for uric acid stones. Citrate preparations are useful as alkalinising agents. Maintaining a urine pH of 6 to 6.5 is sufficient to prevent uric acid stones [528]. In cases who failed with conservative measures with sustaining hyperuricosuria, stone recurrences or myeloproliferative diseases, allopurinol (10 mg/kg) may be used. This medication may cause several drug reactions (rash, diarrhoea, eosinophilia) and should be cautiously used in chronic renal failure patients.

3N.2.3 **Cystine stones**

Cystinuria is the cause of cystine stone formation and accounts for 2-6% of all urinary stones in children. Cystinuria is an incompletely recessive autosomal disorder characterised by failure of renal tubules to reabsorb four basic amino acids: cystine, ornithine, lysine and arginine.

Of these four amino acids, only cystine has poor solubility in urine, so that only cystine stones may form in the case of excessive excretion in urine. Cystine solubility is pH-dependent, with cystine precipitation beginning at pH levels < 7.0. Other metabolic conditions, such as hypercalciuria, hypocitraturia and hyperuricosuria, may accompany cystinuria, so leading to the formation of mixed-composition stones. Cystine stones are faintly radiolucent and may be difficult to show on regular radiograph studies. They are also hard in texture and more difficult to disintegrate by extracorporeal shock wave lithotripsy (SWL).

The medical treatment for cystine stones aims to reduce cystine saturation in urine and increase its solubility. The initial treatment consists of maintaining a high urine flow and the use of alkalinising agents, such as potassium citrate to maintain urine pH at above 7.0. If this treatment fails, the use of alpha-mercaptopropionyl glycine may reduce cystine levels in urine and prevent stone formation. Side effects of these drugs are mostly mild and include gastrointestinal complaints (alterations in taste and odour), fever, rash and can be associated with severe side effects, such as bone marrow depression, nephrotic syndrome and epidermolysis [539] (LE: 4; GR: C).

3N.2.4 **Infection stones (struvite stones)**

Infection-related stones constitute nearly 5% of urinary stones in children. Bacteria capable of producing urease enzyme (*Proteus*, *Klebsiella*, *Pseudomonas*) are responsible for the formation of such stones.

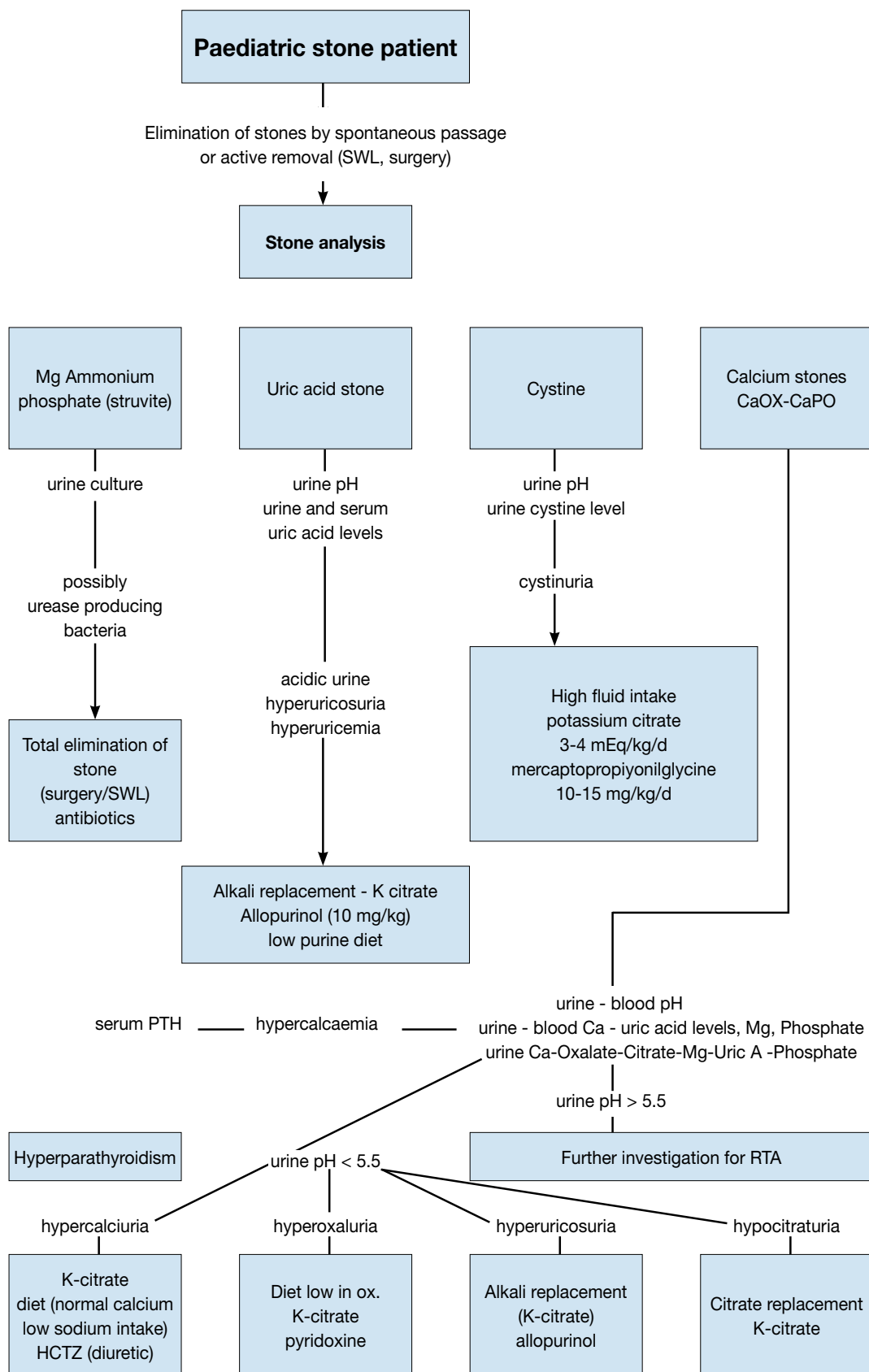
Urease converts urea into ammonia and bicarbonate, so alkalinising the urine and further converting bicarbonate into carbonate. In the alkaline environment, triple phosphates form, eventually resulting in a supersaturated environment of magnesium ammonium phosphate and carbonate apatite, which in turn leads to stone formation.

In addition to bacterial elimination, stone elimination is essential for treatment, as stones will harbour infection and antibiotic treatment will not be effective. Consideration should be given to investigating any congenital problem that causes stasis and infection. Genitourinary tract anomalies predispose to formation of such stones.

3N.3 **Diagnostic evaluation**

Presentation tends to be age-dependent, with symptoms such as flank pain and haematuria being more common in older children. Non-specific symptoms (e.g. irritability, vomiting) are common in very young children. Haematuria, usually gross, occurring with or without pain, is less common in children. However, microscopic haematuria may be the sole indicator and is more common in children. In some cases, urinary infection may be the only finding leading to radiological imaging in which a stone is identified [540, 541].

Figure 6: Algorithm for metabolic investigations in urinary stone disease in children



SWL = extracorporeal shockwave lithotripsy; HCTZ = hydrochlorothiazide; PTH = parathyroid hormone;
RTA = renal tubular acidosis.

3N.3.1 **Imaging**

Generally, ultrasonography should be used as a first study. Renal ultrasonography is very effective for identifying stones in the kidney. Many radiopaque stones can be identified with a simple abdominal flat-plate examination.

If no stone is found but symptoms persist, spiral CT scanning is indicated. The most sensitive test for identifying stones in the urinary system is non-contrast helical CT scanning. It is safe and rapid, with 97% sensitivity and 96% specificity [542-544] (LE: 2; GR: B). Intravenous pyelography is rarely used in children, but may be needed to delineate the caliceal anatomy prior to percutaneous or open surgery.

3N.3.2 **Metabolic evaluation**

Due to the high incidence of predisposing factors for urolithiasis in children and high stone recurrence rates, every child with urinary stone should be given a complete metabolic evaluation [524, 545, 546].

Metabolic evaluation includes:

- Family and patient history of metabolic problems.
- Analysis of stone composition (following stone analysis, metabolic evaluation can be modified according to the specific stone type).
- Electrolytes, BUN, creatinine, calcium, phosphorus, alkaline phosphatase, uric acid, total protein, carbonate, albumin, and parathyroid hormone (if there is hypercalcaemia).
- Spot urinalysis and culture, including ratio of calcium to creatinine.
- Urine tests, including a 24-hour urine collection for calcium, phosphorus, magnesium, oxalate, uric acid citrate, cystine, protein, and creatinine clearance.

Figure 6 provides an algorithm of how to perform metabolic investigations in urinary stone disease in children and how to plan medical treatment accordingly.

3N.4 **Disease management**

With the advance of technology stone management has changed from open surgical approach to endoscopic techniques that are less invasive. Deciding the form of treatment depends on the number, size, location, composition and anatomy of the urinary tract [545, 547, 548].

Currently, most paediatric stones can easily be managed by SWL. Endoscopic treatment can be applied easily for ureteric and bladder stones. Percutaneous removal of stones is also possible for kidney stones in children. Only a small portion of children will need an open surgical approach.

3N.4.1 **Extracorporeal shock wave lithotripsy**

Many reports confirm that SWL can be performed in children with no suspicion of long-term morbidity of the kidney [549-554].

The mean number of shock waves for each treatment is about 1800 and 2000 (up to 4000 if needed) and the mean power set varies between 14 kV and 21 kV. The use of ultrasonography and digital fluoroscopy has significantly decreased the radiation exposure and it has been shown that children are exposed to significantly lower doses of radiation compared to adults [547, 555, 556]. Concerns about anaesthesia do not seem to be a problem anymore because of advances in technique and medication, even in the infant period. The type of anaesthesia should be general or dissociative for children under 10 years of age, whereas conventional intravenous sedation or patient-controlled analgesia is an option for older children who are able to co-operate [557] (LE: 2b).

Stone-free rates are significantly affected by various factors. Regardless of the location, as the stone size increases, the stone-free rates decrease and re-treatment rate increases. The stone-free rates for < 1 cm, 1-2 cm, > 2 cm and overall, were reported as nearly 90%, 80%, 60% and 80%, respectively. As the stone size increases, the need for additional sessions increases [547, 555, 556, 558-562].

Localisation of the calculi has been described as a significant factor affecting the success rates in different studies. Stones in renal pelvis and upper ureter seem to respond better to SWL. In these mentioned sites, the stone clearance rates are nearly 90%. However, SWL was found to be less effective for caliceal stones particularly the lower caliceal stones. Several studies reported stone-free rates for isolated lower caliceal stones varying between 50% and 62% [563-566].

Shockwave lithotripsy can also be used to treat ureteral calculi. However, this is a more specific issue and with controversies. The success rates with SWL are less for distal ureteric stones. There may also be technical problems with localisation and focusing of ureteric stones in children [563-565, 567, 568].

The type of machine used has a strong effect on success rates and complications. First-generation machines can deliver more energy to a larger focal zone, resulting in higher fragmentation rates in a single therapy. However, general anaesthesia is usually required due to the intolerable discomfort associated with a

first-generation machine. Later-generation machines have a smaller focal zone and deliver less energy, and have a lower risk of pulmonary trauma. However, additional treatments may be needed with later-generation machines. The success rate is higher in younger children [561].

Although stenting does not affect stone clearance, overall complication rates are higher and hospital stay is longer in the unstented patient [560, 561]. Stenting is essential in solitary kidneys undergoing SWL treatment. Children with a large stone burden have a high risk of developing Steinstrasse and urinary obstruction and should be followed more closely for the risk of prolonged urinary tract obstruction after SWL. Post-SWL stent or nephrostomy tube placement may be needed in prolonged obstruction [546, 562].

The Hounsfield Unit (HU) of stone on noncontrast tomography has also been shown to be a predictor factor for success in children and SWL was found to be more successful in stones with HU less than 600 [569] and 1000 [570].

Complications arising from SWL in children are usually self-limiting and transient. The most common are:

- renal colic;
- transient hydronephrosis;
- dermal ecchymosis;
- urinary tract infection;
- formation of Steinstrasse;
- sepsis;
- rarely, haemoptysis.

In children with sterile pre-operative urine cultures, antibiotic prophylaxis to decrease infectious complications is not recommended [571]. However, every effort should be made to sterilise the urine before performing SWL, ureteroscopy (URS), or percutaneous nephrolithotomy (PCNL).

3N.4.2 **Percutaneous nephrolithotomy**

Shockwave lithotripsy is the first choice for treating most renal paediatric stones. However, percutaneous renal surgery can be used for larger and complex stones. Pre-operative evaluation, indication and surgical technique are similar in children compared to adults. In most cases, PCNL is used as monotherapy, but is also used as an adjunctive procedure to other therapies.

The use of adult-sized instruments, in association with an increased number of tracts and sheath size, seems to increase blood loss. However, the development of small-calibre instruments means that PCNL can be used in children. In children (particularly smaller children), PCNL has some advantages, such as smaller skin incision, single-step dilation and sheath placement, good working access for paediatric instruments, variable length, and lower cost [571, 572].

As monotherapy, PCNL is considerably effective and safe. The reported stone-free rates in the recent literature are between 86.9% and 98.5% after a single session. These rates increase with adjunctive measures, such as second-look PCNL, SWL and URS. Even in complete staghorn cases, a clearance rate of 89% has been achieved following a single session [573-578].

The most frequently reported complications of PCNL in children are bleeding, post-operative fever or infection, and persistent urinary leakage. Bleeding requiring transfusion in the modern series is reported in less than 10% [579-584] and is closely associated with stone burden, operative time, sheath size and the number of tracts [579, 585, 586]. In recent studies, post-operative infectious complications, such as fever with or without documented UTI, are reported as less than 15% [579-581, 583, 584, 587] and the origin of fever is not always found to be the infection. With the availability of smaller size instruments, miniaturised PCNL ('mini-perc') through a 13F or 14F sheath has become possible [572, 588, 589], with decreased transfusion rates [588]. This miniaturisation has been further developed into the technique of 'micro-perc' using a 4.85F 'all-seeing needle'. This technique is still experimental and enables the stone to be fragmented by a laser in situ and left for spontaneous passage [590]. A recent study revealed that microperc provides a similar stone-free rate with similar complication rates and a lower additional treatment rate compared with SWL in the treatment of kidney stone disease in children [591] (LE: 3, GR: B). As experience has accumulated in adult cases, new approaches have also started to be applied in children, including tubeless PCNL. This technique has been used in uncomplicated surgery for stones smaller than 2 cm, with patients left either with an indwelling catheter or double J stent in the ureter [582, 587] or totally tubeless [592].

The mean post-operative hospital stay is similar to adults. It is reported as 3-4 days in all published literature and is much shorter than open surgery. The less invasive nature of this technique has made it a promising alternative to open surgery for treating renal stones in children (LE: 2; GR: B).

3N.4.3 **Ureterorenoscopy**

The increasing availability of smaller size endourological equipment has made it possible to manage paediatric ureteral stones using endoscopic techniques.

The technique used in children is similar to the one used in adults. It is strongly recommended that guide wires are used and the procedure is performed using direct vision. Routine balloon dilation of ureterovesical junction and ureteral stenting are controversial. In general, ureteric dilatation is being performed much less and only in selected cases. There is a tendency to use hydrodilation more because it is similarly effective [571, 593-599] (LE: 3; GR: B).

Different lithotripsy techniques, including ultrasonic, pneumatic and laser lithotripsy, have all been shown to be safe and effective. Because of the smaller size of the probes, laser energy is easier to use in smaller instruments and is more useful for paediatric cases [574, 596, 598, 600-606].

All studies reporting the use of endoscopy for ureteric stones in children have clearly demonstrated that there is no significant risk of ureteric strictures or reflux with this mode of therapy (LE: 1; GR: A). A multi-institutional study on the use of semi-rigid ureteroscopy for ureteral calculi in children has revealed that the procedure is effective with a 90% stone-free rate and efficacy quotient. The study also focused on the factors affecting the complication rates. The authors found that although operating time, age, institutional experience, orifice dilation, stenting and stone burden were significant on univariate analysis, multivariate analysis revealed that operating time was the only significant parameter affecting the complication rate [607].

A recent literature review contains a growing number of case series on the use of flexible ureterorenoscopic interventions in children. Both intrarenal and ureteric stones can be treated using this approach [608-612]. In these series, the authors generally did not use active orifice dilation, but attempted to use a ureteral sheath where possible. However, an important problem was the inability to obtain retrograde access to the ureter in approximately half of the cases [609, 610]. This problem can be overcome by stenting and leaving the stent indwelling for passive dilation of the orifice, and performing the procedure in a second session. The success rates varied between 60 and 100%, with a negligible number of complications [608, 610-613]. The need for additional procedures was related to stone size [612]. A comparative study showed that RIRS had similar stone-free rate compared to ESWL after three months, with fewer sessions [614] (LE: 3, GR: B).

3N.4.4 **Open or laparoscopic stone surgery**

Most stones in children can be managed by SWL and endoscopic techniques. However, in some situations, open surgery is inevitable. Good candidates for open stone surgery include very young children with large stones and/or a congenitally obstructed system, which also requires surgical correction. Open surgery is also necessary in children with severe orthopaedic deformities that limit positioning for endoscopic procedures.

In centres with a well-established experience, a laparoscopic approach may be a good alternative for some cases as a last resort before open surgery. Suitable candidates include patients who have a history of previous failed endoscopic procedures, complex renal anatomy (ectopic or retrorenal colon), concomitant UPJ obstruction or caliceal diverticula, megaureter, or large impacted stones. Laparoscopic stone surgery via conventional or a robot-assisted transperitoneal or retroperitoneal approach can be attempted. However, there is very limited experience with these techniques and they are not routine therapeutic modalities [615-617].

Bladder stones in children can usually be managed by endoscopic techniques. Open surgery may also be used for very large bladder stones or for bladder stones caused by an anatomical problem. Recommendations for interventional management are given in Table 9.

Table 9: Recommendations for interventional management in paediatric stones

Stone size and localisation*	Primary treatment option	LE	GR	Secondary treatment options	Comment
Staghorn stones	PCNL	2	B	Open/SWL	Open/SWL Multiple sessions and accesses with PCNL may be needed. Combination with SWL may be useful.
Pelvis < 10 mm	SWL	1	A	RIRS/PCNL/MicroPerc	
Pelvis 10-20 mm	SWL	2	B	PCNL/RIRS/MicroPerc/Open	Multiple sessions with SWL may be needed. PCNL has similar recommendation grade.
Pelvis > 20 mm	PCNL	2	B	SWL/Open	Multiple sessions with SWL may be needed.
Lower pole calyx < 10 mm	SWL	2	B	RIRS/PCNL/MicroPerc	Anatomical variations are important for complete clearance after SWL.
Lower pole calyx > 10 mm	PCNL	2	B	SWL/ MicroPerc	Anatomical variations are important for complete clearance after SWL.
Upper ureteric stones	SWL	2	B	PCNL/URS/Open	
Lower ureteric stones	URS	1	A	SWL/Open	Additional intervention need is high with SWL.
Bladder stones	Endoscopic	2	B		Open is easier and with less operative time with large stones.

* Cystine and uric acid stones excluded. *PCNL* = percutaneous nephrolithostomy; *SWL* = shock-wave lithotripsy; *RIRS* = retrograde intrarenal surgery; *URS* = ureteroscopy.

3N.5 Conclusions and recommendations

Conclusions	LE
The incidence of stone disease in children is increasing.	2
Any child with urinary stone disease deserves metabolic and anatomical evaluation.	2
Treatment should be supported with medical treatment for the underlying metabolic abnormality if detected.	1
Open surgery for stone disease in children is an exceedingly rare requirement.	1
Surgical treatment is based on minimally invasive modalities.	1

Recommendations	LE	GR
In most cases, plain abdominal X-ray and ultrasonography is sufficient for diagnosis and follow-up.	2	B
Non-contrast CT may be required in cases with a doubtful diagnosis or complex cases requiring surgery.	2	B
The use of appropriately-sized instruments will decrease the number of complications in surgical treatment.	1	A

30 OBSTRUCTIVE PATHOLOGY OF RENAL DUPLICATION: URETEROCELE AND ECTOPIC URETER

30.1 Epidemiology, aetiology and pathophysiology

Ureterocele and ectopic ureter are the two main anomalies associated with complete renal duplication, but they also occur in a single system. At present, antenatal ultrasonography detects both conditions in the majority of cases if associated with obstruction, and diagnosis is confirmed after birth by further examination. Later in life, these anomalies are revealed by clinical symptoms: UTI, pain, calculus formation, disturbances of micturition, and urinary incontinence. There is a wide variation of symptoms in patients with ureterocele (from the asymptomatic patient to urosepsis, urinary retention and upper tract dilatation after birth).

30.1.1 Ureterocele

Ureterocele is 4-7 times more frequent in female than in male patients; the overall incidence in autopsies is around 1 in 4,000 children. Around 80% is associated with the upper pole ureter in duplicated systems and 20% in single systems. About 10% of ureteroceles are bilateral [618].

30.1.2 Ectopic ureter

Ectopic ureter is less frequent than ureterocele (10 in 19,046 autopsies), but is also more common in female patients (male to female ratio, 1:5). Some remain asymptomatic, therefore, the true incidence is difficult to determine [619]. Eighty per cent of ectopic ureters are associated with complete renal duplication; however, in male patients about 50% of ectopic ureters are associated with a single system [620].

30.2 Classification systems

30.2.1 Ureterocele

Ureterocele is a cystic dilatation that develops in the intravesical part of the submucosal ureter. The aetiology remains unclear [621-623]. A single-system ureterocele is associated with a kidney with one ureter, and in duplex systems, the ureterocele belongs to the upper pole.

Ureteroceles usually cause obstruction of the upper pole, but the degree of obstruction and functional impairment is variable according to the type of ureterocele and upper pole dysplasia. In the orthotopic form, there is often no or only mild obstruction, and frequently the function of the moiety is normal or slightly impaired, and the corresponding ureter may be dilated. Cystic renal dysplasia is also associated with a single system ureterocele [624, 625]. Vesicoureteral reflux can be observed in 50% on the ipsilateral side and 20% on the contralateral side. Reflux into the ureterocele is uncommon [626].

In the ectopic form, the upper pole is altered, frequently dysplastic, and hypo-functional or non-functional [627, 628]. The corresponding ureter is a megaureter. In the caeco-ureterocele (see definition below), the upper pole of the renal duplication is dysplastic and non-functional.

30.2.1.1 Ectopic (extravesical) ureterocele

If any portion of the ureterocele extends into the bladder neck or urethra, it is called an ectopic ureterocele. Ectopic ureterocele is the most common form of ureterocele (> 80%). It can be voluminous, dissociating the trigone and slipping into the urethra, and may prolapse through the urethral meatus (caeco-ureterocele). The ureterocele orifice is tight, and located in the bladder itself or below the neck. The ureter corresponding to the lower pole moiety is raised by the ureterocele and is frequently refluxing or compressed by the ureterocele, leading to an obstructive megaureter. A contralateral renal duplication is associated in 50% of cases. Occasionally, large ureteroceles are responsible for reflux or obstruction of the contralateral upper tract.

30.2.1.2 Orthotopic (intravesical) ureterocele

The intravesical or orthotopic ureterocele is completely located in the bladder. Intravesical ureteroceles are mostly combined with a single kidney system and account for about 15% of cases. It is seen more in older children or adults.

30.2.2 Ectopic ureter

The term ectopic ureter describes a ureter with the orifice located at the bladder neck, in the urethra, or outside the urinary tract. The ureter can drain the upper pole of a duplex or single system. There is a fundamental difference between the sexes. In boys, the ectopic orifice is never below the external sphincter.

In girls, the ureteral orifice may be located [629]:

- in the urethra, from the bladder neck to the meatus (35%);

- in the vaginal vestibule (34%);
- in the vagina (25%);
- in the uterus and Fallopian tube (6%).

In boys, the ureteral orifice may be located [629]:

- in the posterior urethra (47%);
- in the prostatic utricle (10%);
- in the seminal vesicles (33%);
- in the vas deferens or ejaculatory ducts (10%).

30.3 Diagnostic evaluation

30.3.1 Ureterocele

Prenatal ultrasound easily reveals voluminous obstructive ureteroceles [630, 631]. In cases with a small upper pole or a slightly obstructive ureterocele, prenatal diagnosis is difficult. If prenatal diagnosis is impossible, the following clinical symptoms, besides incidental findings, can reveal the congenital anomaly at birth or later:

- At birth, a prolapsed and sometimes strangulated ureterocele may be observed in front of the urethral orifice. In a newborn boy, it might cause acute urinary retention, simulating urethral valves.
- The early symptom of pyelonephritis in either sex may lead to the diagnosis.
- Later symptoms can include dysuria, recurrent cystitis and urgency.

In cases of prenatal diagnosis at birth, ultrasonography confirms the ureteral dilatation that ends at the upper pole of a renal duplication. It also demonstrates the presence of a ureterocele in the bladder, with a dilated ureter behind the bladder.

At this point, it is important to assess the function of the upper pole using nuclear renography of the region of interest. This is best assessed with DMSA [632-634]. Magnetic resonance urography may visualise the morphological status of the upper pole and lower moieties and of the contralateral kidney, but cannot reliably predict histology [635]. Based on the prevalence of high-grade reflux, VCUG is mandatory for identifying ipsilateral or contralateral reflux, and assessing the degree of intraurethral prolapse of the ureterocele [636]. Urethrocystoscopy may reveal the pathology in cases where it is difficult to make the differential diagnosis between ureterocele and ectopic megaureter.

30.3.2 Ectopic ureter

Most of the ectopic megaureters are diagnosed primarily by ultrasonography. In some cases, clinical symptoms can lead to diagnosis:

- In neonates: dribbling of urine, pyuria, and acute pyelonephritis.
- In young girls: permanent urinary incontinence besides normal voiding, or significant vaginal discharge as the equivalent of incontinence; an ectopic orifice may be found in the meatal region [637].
- In pre-adolescent boys: epididymitis is the usual clinical presentation and the seminal vesicle may be palpable.

Ultrasonography, radionuclide studies (DMSA), VCUG, MR urography, high-resolution MRI, and cystoscopy are the diagnostic tools to assess function, to detect reflux and rule out ipsilateral compression of the lower pole and urethral obstruction [638]. In some cases, the large ectopic ureter presses against the bladder and can look like a pseudo-ureterocele [639, 640].

Girls who present with lifelong minimal urinary incontinence, never being dry, normal bladder function, complete emptying, and normal US are very suspicious for ectopic ureter. This needs to be excluded or confirmed by further imaging (e.g. MRI). Filling the bladder with methylene blue and checking for clear urine output from the vagina can give clear evidence of extrasphincteric ureteral ectopia. This test is also helpful in confirming a vesicovaginal fistula (in this case blue fluid drains from the vagina).

30.4 Disease management

30.4.1 Ureterocele

The management is controversial with a choice between a non-operative approach, endoscopic decompression, ureteral reimplantation, partial nephroureterectomy, or complete primary reconstruction [641-646]. The choice of a therapeutic modality depends on the following criteria: clinical status of the patient (e.g. urosepsis); patient age; function of the upper pole; presence of reflux or obstruction of the ipsilateral or contralateral ureter; presence of bladder neck obstruction caused by ureterocele; intravesical or ectopic ureterocele; and parents' and surgeon's preferences [647]. When the diagnosis is made by ultrasound, prophylactic antibiotic treatment is indicated until a VCUG can be performed.

30.4.1.1 Early treatment

In the presence of febrile infection or obstruction at the bladder neck, immediate endoscopic incision or puncture of the ureterocele is recommended. In a clinically asymptomatic child with a ureterocele and a non- or hypofunctional upper pole, without significant obstruction of the lower pole and without bladder outlet obstruction, prophylactic antibiotic treatment is given until follow-up procedures are instigated.

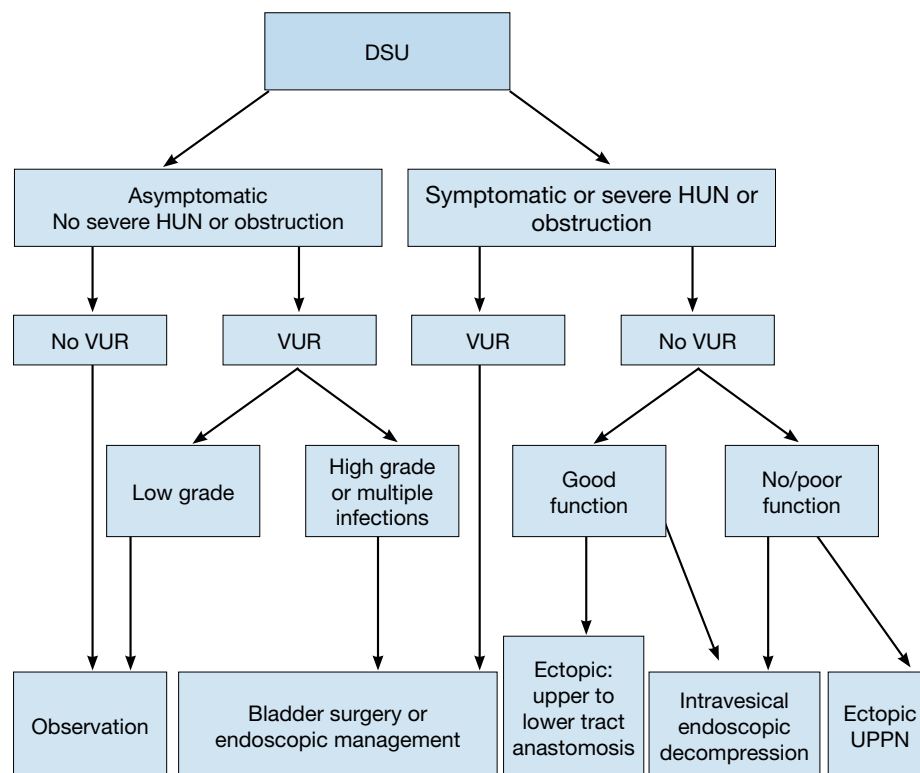
30.4.1.2 Re-evaluation

Conservative treatment may be adopted in asymptomatic patients without any bladder outlet obstruction, without severe hydroureteronephrosis of the ureterocele moiety or high-grade (over grade III) reflux [647, 648].

If decompression is effective and there is no reflux (~25% of cases and more often in intravesical ureterocele), the patient is followed-up conservatively. After an endoscopic incision, most of the children with an extravesical ureterocele (50-80%) need a secondary procedure, compared with only 18% of those with an intravesical ureterocele [620]. Secondary surgery is necessary if decompression is not effective, significant reflux is present, or there is obstruction of the ipsi- or contralateral ureters, and/or bladder neck obstruction or retained ureterocele [649].

Surgery may vary from upper pole nephrectomy to complete unilateral LUT reconstruction [626, 645, 650-653]. In an ectopic ureterocele with severe hydroureteronephrosis and without reflux, the primary upper tract approach without endoscopic decompression (partial upper-pole nephroureterectomy, pyelo/ureteropyelo/ureterostomy and upper-pole ureterectomy) gives up to an 80% chance of being the definitive treatment [647, 654].

Figure 7: Algorithm for the management of duplex system ureteroceles after the first 3-6 months of life [647]



DSU = duplex system ureterocele; ED = endoscopic decompression; HUN = hydroureteronephrosis; MCUG = micturating cystourethrography; UPPN = upper pole partial nephrectomy; VUR = vesicoureteric reflux to the lower pole.

Obstruction is considered to be the presence of non-refluxing dilatation of non-ureterocele-bearing moieties (especially of the lower pole) or of an obstructive drainage pattern on diuretic renography.

30.4.2 Ectopic ureter

In the majority of cases, the upper pole is dysplastic and heminephro-ureterectomy should be considered. Ureteral reconstruction (ureteral reimplantation/ ureteroureterostomy/ureteropyelostomy and upper-pole ureterectomy) is a therapeutic option in cases in which the upper pole has function worth preserving. Both

procedures can be performed through an open or laparoscopic approach [655-657]. In patients with bilateral single ectopic ureters (a very rare condition), an individual approach depending on the sex and renal and bladder function is necessary. Usually the bladder neck is insufficient in these patients [658-661].

30.5 Conclusions and recommendations for obstructive pathology of renal duplication: ureterocele and ectopic ureter

Conclusions
Ureterocele and ectopic ureter are associated with complete renal duplication, but they also occur in a single system.
In most cases, in young children (first years of life) diagnosis is done by ultrasonography.
In older children clinical symptoms will prompt assessment.
Management includes a conservative approach, endoscopic decompression, partial nephroureterectomy, or complete primary reconstruction. Choice of treatment will depend on: <ul style="list-style-type: none"> • clinical status of the patient (e.g., urosepsis); • patient age; • function of the upper pole; • presence of reflux or obstruction of the ipsilateral or contralateral ureter; • presence of bladder neck obstruction caused by ureterocele; • intravesical or ectopic ureterocele; • and parents' and surgeon's preferences.

Recommendations			LE	GR
Ureterocele	Diagnosis	Ultrasonography, radionuclide studies (MAG III/DMSA), VCUG, magnetic resonance urography, high-resolution MRI, and cystoscopy are the diagnostic tools to assess function, to detect reflux and rule out ipsilateral compression of the lower pole and urethral obstruction.	3	B
	Treatment	Choice of treatment will depend on symptoms, function and reflux as well on surgical and parenteral choices: observation, endoscopic decompression, ureteral reimplantation, partial nephroureterectomy, complete primary reconstruction. <ul style="list-style-type: none"> • In patients (single/duplex systems) with no hydronephrosis and no symptoms, the risk for renal injury is low and conservative treatment is a good option. • In patients with reflux, endoscopic treatment is an option; open reimplantation especially in dilating reflux provides better results. • In patients with an obstructing ureterocele, early endoscopic decompression is indicated. In half to two thirds of children with an extravesical ureterocele a secondary procedure is needed (compared to 20-25% of those with an intravesical ureterocele). • In patients with a non-functioning moiety and symptoms, heminephrectomy is indicated. 	3	B
Ectopic ureter	Diagnosis	Ultrasound, DMSA scan, VCUG, MRI should be used for a definitive diagnosis	3	B
	Treatment	Choice of treatment option will depend on the function of the upper urinary tract: <ul style="list-style-type: none"> • In poorly or non-functioning moieties (hemi-) nephroureterectomy is an definite solution. • In patients with a functioning renal moiety, ureteral reimplantation, ureteroureterostomy and ureteropyelostomy are reliable options, especially in cases in which the upper pole has function worth preserving. 	3	B

DMSA = dimercaptosuccinic acid; MRI = magnetic resonance imaging; VCUG = voiding cystourethrography.

3P DISORDERS OF SEX DEVELOPMENT

3P.1 Epidemiology, aetiology and pathophysiology

The formerly called 'intersex disorders' were recently the subject of a consensus document in which it was decided that the term 'intersex' should be changed to 'disorders of sex development' (DSD) [662, 663].

The new classification has arisen because of advances in knowledge of the molecular genetic causes of abnormal sexual development, controversies inherent to clinical management and ethical issues. Controversial and pejorative terminology, e.g. 'pseudohermaphroditism' and 'hermaphroditism', have been renamed according to the new pathophysiological insights. Furthermore, some conditions presenting with severe male genital malformation, such as penile agenesis, cloacal exstrophy, which could not be categorised, have also been included. The term 'disorders of sex development' is proposed to indicate congenital conditions with atypical development of chromosomal, gonadal or anatomical sex. This will also include the idiopathic micropenis which is added here as a separate heading in this chapter on DSD.

We refer to the consensus document as a general guideline, while this chapter will focus on what is relevant for the practising paediatric urologist. As the urologist is likely to be involved in both surgical and non-surgical neonatal work, this chapter will discuss the neonatal emergency and the diagnostic and therapeutic role of the paediatric urologist.

Overall, there is a low evidence base for the published literature on DSD. There are no RCTs and most studies are based on retrospective clinical descriptive studies (LE: 4) or are expert opinion. An exception is the risk of gonadal cancer, for which the LE is higher.

DSD can present as prenatal diagnosis, neonatal diagnosis and late diagnosis. Prenatal diagnosis can be based on karyotype or ultrasound findings, neonatal diagnosis is based on genital ambiguity and late diagnosis is made on early or delayed puberty. In this guideline focus is on the neonatal presentation where the paediatric urologist plays a major role. For late diagnosis we refer to endocrinology and gynaecology guidelines on precocious and delayed puberty where paediatric urologists play a minor role [664, 665].

The diagnosis and treatment of DSD requires a multidisciplinary approach, which should include geneticists, neonatologists, paediatric and adult endocrinologists, gynaecologists, psychologists, ethicists and social workers. Each team member should be specialised in DSD and a team should have enough new patients to ensure experience.

3P.1.1 *Micropenis*

Micropenis is a small but otherwise normally formed penis with a stretched length of < 2.5 SD below the mean [662, 663, 666]. Besides an idiopathic micropenis, two major causes of abnormal hormonal stimulation have been identified:

- Hypogonadotropic hypogonadism (due to an inadequate secretion of GnRH);
- Hypergonadotropic hypogonadism (due to failure of the testes to produce testosterone).

The penis is measured on the dorsal aspect, while stretching the penis, from the pubic symphysis to the tip of the glans [662]. The corpora cavernosa are palpated, the scrotum is often small, and the testes may be small and descended. Micropenis should be distinguished from buried and webbed penis, which is usually of normal size.

The initial evaluation has to define whether the aetiology of the micropenis is central (hypothalamic/pituitary) or testicular. A paediatric endocrinology work-up has to be carried out immediately. Karyotyping is mandatory in all patients with a micropenis. Endocrine testicular function is assessed (baseline and stimulated testosterone, LH and FSH serum levels). Stimulated hormone levels may also give an idea of the growth potential of the penis. In patients with non-palpable testes and hypogonadotropic hypogonadism, laparoscopy should be carried out to confirm vanishing testes syndrome or intra-abdominal undescended hypoplastic testes. This investigation can be delayed until the age of 1 year [663].

Pituitary or testicular insufficiency are treated by the paediatric endocrinologist. In patients with testicular failure and proven androgen sensitivity, androgen therapy is recommended during childhood and at puberty to stimulate the growth of the penis [667-670] (LE: 2; GR: B). In the presence of androgen insensitivity, good outcome of sexual function is questioned and gender conversion can be considered [671-673].

3P.2 Diagnostic evaluation

3P.2.1 *The neonatal emergency*

The first step is to recognise the possibility of DSD (Table 10) and to refer the newborn baby immediately to a tertiary paediatric centre, fully equipped with neonatal, genetics, endocrinology and paediatric urology units. At the paediatric centre, the situation should be explained to the parents fully and kindly. Registering and naming the newborn should be delayed as long as necessary.

3P.2.1.1 Family history and clinical examination

A careful family history must be taken followed by a thorough clinical examination (Table 11).

Table 10: Findings in a newborn suggesting the possibility of DSD (adapted from the American Academy of Pediatrics)

Apparent male
Severe hypospadias associated with bifid scrotum
Undescended testis/testes with hypospadias
Bilateral non-palpable testes in a full-term apparently male infant
Apparent female
Clitoral hypertrophy of any degree, non-palpable gonads
Vulva with single opening
Indeterminate
Ambiguous genitalia

Table 11: Diagnostic work-up of neonates with disorders of sex development

History (family, maternal, neonatal)
Parental consanguinity
Previous DSD or genital anomalies
Previous neonatal deaths
Primary amenorrhoea or infertility in other family members
Maternal exposure to androgens
Failure to thrive, vomiting, diarrhoea of the neonate
Physical examination
Pigmentation of genital and areolar area
Hypospadias or urogenital sinus
Size of phallus
Palpable and/or symmetrical gonads
Blood pressure
Investigations
Blood analysis: 17-hydroxyprogesterone, electrolytes, LH, FSH, TST, cortisol, ACTH
Urine: adrenal steroids
Karyotype
Ultrasound
Genitogram
hCG stimulation test
Androgen-binding studies
Endoscopy

ACTH = adrenocorticotrophic hormone; FSH = follicle-stimulating hormone; hCG = human chorionic gonadotrophin; LH = luteinising hormone; TST = testosterone.

3P.2.1.2 Choice of laboratory investigations

The following laboratory investigations are mandatory:

- Karyotype;
- Plasma 17-hydroxyprogesterone assay;
- Plasma electrolytes;
- Ultrasonography to evaluate the presence of Müllerian duct structures.

These investigations will provide evidence of congenital adrenal hyperplasia (CAH), which is the most frequently occurring DSD. If this evidence is found, no further investigation is needed. If not, then the laboratory work-up should proceed further.

The hCG stimulation test is particularly helpful in differentiating the main syndromes of 46XYDSD by evaluating Leydig cell potential. When testosterone metabolism is evaluated, the presence or absence of metabolites will help to define the problem. An extended stimulation can help to define phallic growth potential and to induce testicular descent in some cases of associated cryptorchidism.

3P.2.2 **Gender assignment**

This is a very complicated task. It should take place after a definitive diagnosis has been made. The idea that an individual is sex-neutral at birth and that rearing determines gender development is no longer the standard approach. Instead, gender assignment decisions should be based upon:

- age at presentation;
- fertility potential;
- size of the penis;
- presence of a functional vagina;
- endocrine function;
- malignancy potential;
- antenatal testosterone exposure;
- general appearance;
- psychosocial well-being and a stable gender identity;
- sociocultural aspect;
- parental opinions.

Each patient presenting with DSD should be assigned a gender as quickly as a thorough diagnostic evaluation permits. Minimal time needed is 48 hrs. During this period any referral to gender should be avoided, better to address the patient as “the child”, “your child”.

3P.2.3 **Role of the paediatric urologist**

The role of the paediatric urologist can be divided into a diagnostic role and a therapeutic role (Table 12). Each of these roles will be discussed briefly.

Table 12: Role of the paediatric urologist

Diagnostic role
<ul style="list-style-type: none">• Clinical examination• Ultrasound• Genitography• Cystoscopy• Diagnostic laparoscopy
Therapeutic role
<ul style="list-style-type: none">• Masculinising surgery• Feminising surgery• Gonadectomy

3P.2.3.1 *Clinical examination*

A thorough clinical examination in a neonate presenting with ambiguous genitalia is important. As well as a accurate description of the ambiguous genitalia, some detailed information should be given on palpability and localisation of the gonads. Information gathered by the various examinations described below should help the team to come to a final diagnosis.

Palpable gonad. If it is possible to feel a gonad, it is almost certainly a testis; this clinical finding therefore virtually excludes 46XXDSD.

Medical photography can be useful but requires sensitivity and consent [674].

Phallus. The phallus should be measured. A cotton bud placed at the suprapubic base of the implant of the stretched phallus allows for a good measurement of phallic length.

Urogenital sinus opening. The opening of the urogenital sinus must be well evaluated. Is there only one opening visible? Can a hymenal ring be seen? What does the fusion of the labioscrotal folds look like; do the folds show rugae or some discolouration?

3P.2.3.2 *Investigations*

Ultrasound can help to describe the palpated gonads or to detect non-palpable gonads. However, the sensitivity and specificity are not high. On ultrasound, the Müllerian structures can be evaluated. Is there a vagina? Are there some abdominal gonads? Is there a vaginal or utricular structure visible [675, 676]?

Genitography can provide some more information on the urogenital sinus. How low or how high is the confluence? Is there any duplication of the vagina? How does the urethra relate to the vagina?

General anaesthesia. In some cases, further examinations under general anaesthesia can be helpful. On cystoscopy, the urogenital sinus can be evaluated and the level of confluence between the bladder neck and the bladder. Cystoscopy can also be used to evaluate the vagina or utriculus, e.g. the presence of a cervix at the top of the vagina can be important information.

Laparoscopy is necessary to obtain a final diagnosis on the presence of impalpable gonads and on the presence of Müllerian structures. If indicated, a gonadal biopsy can be performed [677, 678].

3P.3 Disease management

Referring to the consensus document [662, 663], it is clear that the timing of surgery is much more controversial than it used to be.

The rationale for early surgery includes:

- beneficial effects of oestrogen on infant tissue;
- avoiding complications from anatomical anomalies;
- minimising family distress;
- mitigating the risks of stigmatisation and gender-identity confusion [679].

However, adverse outcomes have led to recommendations to delay unnecessary surgery to an age when the patient can give informed consent. Surgery that alters appearance is not urgent. Early surgery should be reserved for those patients with high confluent urogenital tracts, girls with severely masculinised genitalia and boys with undervirilised genitals. Vaginoplasty should be delayed until puberty and milder forms of masculinisation should not be treated surgically. Recently ESPU and SPU have taken a position in the debate on surgery for DSD [680].

3P.3.1 Feminising surgery

Clitororeduction. Reduction of an enlarged clitoris should be done with preservation of the neurovascular bundle. Clitoral surgery has been reported to have an adverse outcome on sexual function and should therefore be limited to severely enlarged clitorises [681, 682]. Informed parental consent should be obtained. Although some techniques that conserve erectile tissue have been described, the long-term outcome is unknown [683].

Separation of the vagina and the urethra is preserved for high confluence anomalies. Many techniques for urogenital sinus repair have been described, but their outcome has not been evaluated prospectively [684, 685].

Vaginoplasty should be performed during the teenage years. Every technique (self dilatation, skin or bowel substitution) has its specific advantages and disadvantages [686]. All carry a potential for scarring that would require further surgery before sexual function was possible.

Aesthetic refinements. The goals of genital surgery are to maximise anatomy to allow sexual function and romantic partnering. Aesthetics are important in this perspective. The reconstruction of minor labiae from an enlarged clitoral hood is an example of aesthetic refinement.

3P.3.2 Masculinising surgery

Hormone therapy early in life is advocated by many doctors. The level of evidence is low for restoration of normal penile size.

Hypospadias surgery. See section on hypospadias (Chapter 3E).

Excision of Mullerian structures. In the DSD patient assigned a male gender, Müllerian structures should be excised. There is no evidence on whether utricular cysts need to be excised.

Orchiopexy. See section on orchiopexy (Chapter 3B).

Phalloplasty. The increasing experience of phalloplasty in the treatment of female to male transsexual patients has led to reports about the reliability and feasibility of this technique. It has therefore become available to treat severe penile inadequacy in DSD patients.

Aesthetic refinements. These include correction of penoscrotal transposition, scrotoplasty and insertion of testicular prostheses.

Gonadectomy. Germ cell malignancy only occurs in patients with DSD who have Y-chromosomal material. The highest risk is seen in patients with gonadal dysgenesis and in patients with partial androgen insensitivity with intra-abdominal gonads (LE: 2). Intra-abdominal gonads of high-risk patients should be removed at the time of diagnosis [687] (GR: A).

3P.4 Guidelines for the treatment of disorders of sex development

Disorders of sex development (DSD) are an example of conditions for which a multidisciplinary approach is mandatory and gold standard. These children should be referred to experienced centres where neonatology, paediatric endocrinology, paediatric urology, child psychology and transition to adult care are guaranteed.
Any neonate presenting with ambiguous genitalia is an emergency since salt-loss in a 46XX CAH girl can be fatal.
Gender assignment is imminent and should be based on multidisciplinary consensus taking into account the latest knowledge.
Timing of surgery will be dependent on the severity of the condition and on the assigned sex.
- In severe anomalies in girls early surgical treatment is indicated.
- In less severe cases, in consultation with the parents, a more conservative approach might be followed.
- In boys the surgical correction will mainly consist of hypospadias repair and orchiopexy, so the timing will follow the recommendations for hypospadias repair and orchiopexy (from 6 months onwards and before 2 years of age).

3Q POSTERIOR URETHRAL VALVES

3Q.1 Epidemiology, aetiology and pathophysiology

Posterior urethral valves (PUV) are one of the few life-threatening congenital anomalies of the urinary tract found during the neonatal period. Despite optimal treatment, PUV in children may result in renal insufficiency in nearly one-third of cases [688-690]. PUV are found in 1 in 1,250 in a population undergoing foetal ultrasound screening [433]. An incidence of PUV of 1 in 5,000-12,500 live-births has been estimated [691, 692]. In one report, up to 46% of fetuses with a PUV diagnosis were terminated, indicating a possible decrease in incidence [693].

3Q.2 Classification systems

3Q.2.1 Urethral valve

Despite recent attempts to introduce new classification terms, such as 'congenital obstructive posterior urethral membrane' (COPUM) [694], the original classification by Hugh Hampton Young remains the most commonly used [695].

Hugh Hampton Young described three categories: type I, type II and type III. However, today, only type I and type III are found to be obstructive. As type II seems to be more like a fold and not obstructive, it is no longer referred to as a valve. Hampton Young's descriptions of type I and III are as follows:

Type I (90-95%). 'In the most common type there is a ridge lying on the floor of the urethra, continuous with the verumontanum, which takes an anterior course and divides into two fork-like processes in the region of the bulbo-membranous junction. These processes are continued as thin membranous sheets, direct upward and forward which may be attached to the urethra throughout its entire circumference. It is generally supposed that the valves have complete fusion anteriorly, leaving only an open channel at the posterior urethral wall. Yet, the fusion of the valves anteriorly may not be complete in all cases, and at this point a slight separation of the folds exists [695].'

Type III. 'There is a third type which has been found at different levels of the posterior urethra and which apparently bears no such relation to the verumontanum. This obstruction was attached to the entire circumference of the urethra, with a small opening in the centre [695].'

The transverse membrane described has been attributed to incomplete dissolution from the urogenital portion

of the cloacal membrane [696]. The embryology of the urethral valves is poorly understood. The membrane may be an abnormal insertion of the mesonephric ducts into the foetal cloaca [697].

3Q.3 Diagnostic evaluation

An obstruction above the level of the urethra affects the whole urinary tract in varying degrees.

- The prostatic urethra is distended and the ejaculatory ducts may be dilated due to urinary reflux. The bladder neck is hypertrophied and rigid.
- The hypertrophied bladder occasionally has multiple diverticula.
- Nearly all valve patients have dilatation of both upper urinary tracts. This may be due to the valve itself and the high pressure in the bladder, or due to obstruction of the ureterovesical junction by the hypertrophied bladder.
- If there is secondary reflux, the affected kidney functions poorly in most cases.

During prenatal ultrasonography screening, bilateral hydroureteronephrosis and a distended bladder are suspicious signs of a urethral valve. Also a thick-walled bladder and a dilated posterior urethra ('keyhole' sign) make a PUV likely. In one study, however, the keyhole sign was not found to be a reliable predictor ($p=0.27$) [698]. In the presence of increased echogenicity of the kidney, dilatation of the urinary tract and oligohydramnion, the diagnosis of a PUV should strongly be considered.

Voiding cystourethrogram (VCUG) confirms a PUV diagnosis. This study is essential whenever there is a question of an infravesical obstruction, as the urethral anatomy is well outlined during voiding. A secondary reflux is observed in at least 50% of patients with PUV [699]. Reflux is consistently associated with renal dysplasia in patients with PUV. It is generally accepted that reflux in the renal units acts as a 'pressure pop-off valve', which would protect the other kidney, leading to a better prognosis [700]. Other types of pop-off mechanism include bladder diverticula and urinary extravasation, with or without urinary ascites [701]. However, in the long-term, a supposed protective effect did not show a significant difference compared to other patients with PUV [702, 703].

Nuclear renography with split renal function is important to assess kidney function (DMSA or MAG III). Creatinine, blood urea nitrogen and electrolytes should be monitored closely during the first few days. A nadir creatinine of 80 $\mu\text{mol/L}$ is correlated with a better prognosis [690].

3Q.4 Disease management

3Q.4.1 Antenatal treatment

About 40-60% of PUV are discovered before birth [704]. The intrauterine obstruction leads to a decreased urine output, which could result in an oligohydramnios. Amniotic fluid is necessary for normal development of the lung and its absence may lead to pulmonary hypoplasia, causing a life-threatening problem. Intrauterine attempts have been made to treat a foetus with PUV.

As renal dysplasia is not reversible, it is important to identify those foetuses with good renal function. A sodium level below 100 mmol/L, a chloride value of < 90 mmol/L and an osmolarity below 200 mOsm/L found in three foetal urine samples gained on three different days are associated with a better prognosis [705].

The placing of a vesicoamniotic shunt has a complication rate of 21-59%, dislocation of the shunt occurs in up to 44%, mortality lies between 33% and 43%, and renal insufficiency is above 50% [705-707]. Although shunting is effective in reversing oligohydramnios, it makes no difference to the outcome and long-term results of patients with PUV [706, 707]. The PLUTO-trial (randomised study) could not prove a benefit of placing a shunt [708].

There are few papers reporting on foetal valve treatment. However, there is little evidence for the effectiveness of these interventions. Therefore this should be considered as an experimental intervention [709].

3Q.4.2 Postnatal treatment

Bladder drainage. If a boy is born with suspected PUV, drainage of the bladder and, if possible, an immediate VCUG is necessary. A neonate can be catheterised with a 3.5-5 F catheter. Balloon catheters are not available in this size. A VCUG is performed to see if the diagnosis is correct and whether the catheter is within the bladder and not in the posterior urethra. An alternative option is to place a suprapubic catheter, perform a VCUG and leave the tube until the neonate is stable enough to perform an endoscopic incision or resection of the valve.

Valve ablation. When the medical situation of the neonate has stabilised and the creatinine level decreased, the next step is to remove the intravesical obstruction. Small paediatric cystoscopes and resectoscopes are now available either to incise or to resect the valve at the 4-5, 7-8 or 12 o'clock position, or at all three positions, depending on the surgeon's preference. It is important to avoid extensive electrocoagulation,

as the most common complication of this procedure is stricture formation. One recently published study demonstrated a significant lower urethral stricture rate using the cold knife compared to diathermy [710]. Within the three months following initial treatment, a control VCUG or a re-look cystoscopy should demonstrate the effectiveness of the treatment, depending on the clinical course [711].

Vesicostomy. If the child is too small and/or too ill to undergo endoscopic surgery, a vesicostomy is used to drain the bladder temporarily. If initially a suprapubic tube has been inserted, this can be left in place for 6-12 weeks. Otherwise, a cutaneous vesicostomy provides an improvement or stabilisation of upper urinary tracts in over 90% of cases [712]. Although there has been concern that a vesicostomy could decrease bladder compliance or capacity, so far there are no valid data to support these expectations [713, 714].

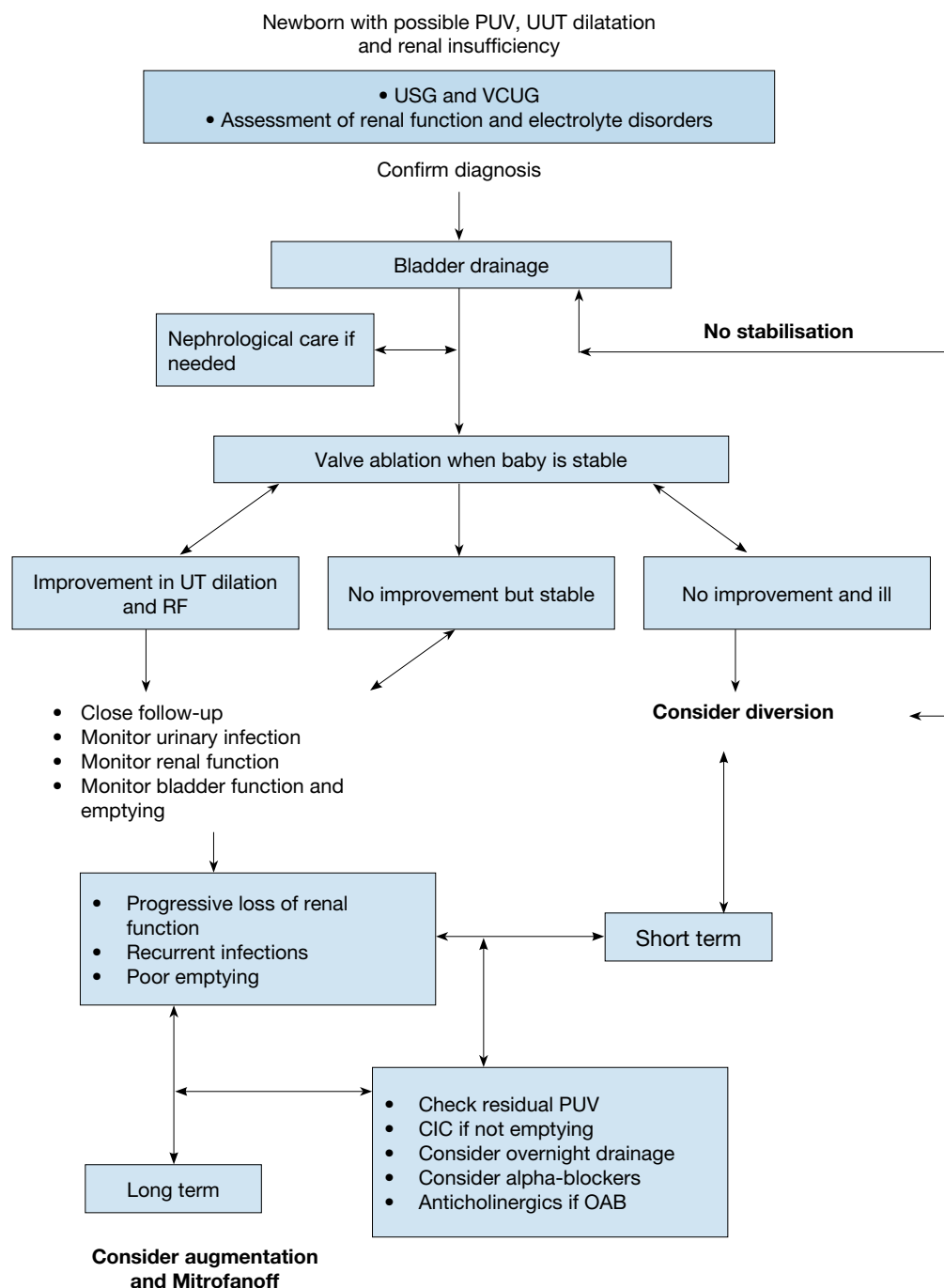
High diversion. If bladder drainage is insufficient to drain the upper urinary tract, high urinary diversion should be considered. Diversion may be suitable if there are recurrent infections of the upper tract, no improvement in renal function and/or an increase in upper tract dilatation, despite adequate bladder drainage. The choice of urinary diversion depends on the surgeon's preference for high loop ureterostomy, ring ureterostomy, end ureterostomy or pyelostomy, with each technique having advantages and disadvantages [715-717]. Reconstructive surgery should be delayed until the UUT has improved as much as can be expected.

Reflux is very common in PUV patients (up to 72%) and it is described bilaterally in up to 32% [718]. During the first months of life, antibiotic prophylaxis may be given especially in those with high-grade reflux [506] and in those with a phimosis, circumcision can be discussed in order to reduce the risk of urinary tract infections [719]. However, there are no randomised studies to support this for patients with PUV. High-grade reflux is associated with a poor functioning kidney and is considered a poor prognostic factor [688, 720]. However, early removal of the renal unit seems to be unnecessary, as long as it causes no problems. It may be necessary to augment the bladder and in this case the ureter may be used [721].

3Q.5 Follow-up

Life-long monitoring of these patients is mandatory, as bladder dysfunction ('valve bladder') is not uncommon and the delay in day- and night-time continence is a major problem [690, 699]. Poor bladder sensation and compliance, detrusor instability and polyuria (especially at night) and their combination are responsible for bladder dysfunction. In those with bladder instability, anticholinergic therapy can improve bladder function. However, with a low risk of reversible myogenic failure (3 out of 37 patients in one study) [722, 723]. In patients with poor bladder emptying α -blocker can be used to reduce the PVR urine, as demonstrated in one study with 42 patients using terazosin (mean PVR was reduced from 16 to 2 mL) [724] and in another study tamsulosin was effective [725]. Between 10% and 47% of patients may develop end-stage renal failure [688-690]. High creatinine nadir and severe bladder dysfunction are risk factors for renal replacement therapy [726]. Renal transplantation in these patients can be performed safely and effectively [727, 728]. Deterioration of the graft function is mainly related to lower urinary tract dysfunction [728, 729].

Figure 8: An algorithm providing information on assessment, treatment and follow up of newborns with possible PUV



CIC = clean intermittent catheterisation; OAB = overactive bladder; PUV = posterior urethral valve; RF = renal function; USG = urinary specific gravity; UT = urinary tract; UUT = upper urinary tract; VCUG = voiding cystourethrogram.

3Q.6 Summary

Posterior urethral valves (PUV) are one of the few life-threatening congenital anomalies of the urinary tract found during the neonatal period and despite optimal treatment result in renal insufficiency in nearly one-third of cases. Bilateral hydroureteronephrosis and a distended bladder are suspicious signs of a PUV in the neonates. A VCUG confirms a PUV diagnosis. Nuclear renography with split renal function is important to assess kidney function and serum creatinine nadir above 80 $\mu\text{mol/L}$ is correlated with a poor prognosis.

Postnatal treatment includes bladder drainage either transurethral or suprapubic and if the child is stable enough, endoscopic incision of the valve is performed. If a child is too small and/or too ill to undergo endoscopic surgery, a vesicostomy is an option for bladder drainage. If bladder drainage is insufficient to drain

the upper urinary tract, high urinary diversion should be considered.

In all patients life-long monitoring is mandatory, as bladder dysfunction is quite common and may cause progressive upper tract deterioration, if not managed properly. In the long run between 10% and 47% of patients may develop end-stage renal failure. Renal transplantation in these patients can be performed safely and effectively.

3Q.6.1 **Conclusions and recommendations posterior urethral valves**

PUV		LE	GR
Diagnosis	An ultrasound can indicate a PUV, but a VCUG is required to confirm the diagnosis. <ul style="list-style-type: none"> • Split renal function is to be assessed by DMSA scan or MAG III clearance. • Serum creatinine is the prognostic marker. 	3	B
Treatment antenatal	A vesico-amniotic shunt is effective in reversing oligohydramnios, but it has a relatively high complication rate. There is no difference in the renal outcome and long-term results.	1b	A
Treatment postnatal	After bladder drainage and stabilisation of the child, endoscopic valve ablation should be performed. <ul style="list-style-type: none"> • In case the child is too small, a vesicostomy is an option for bladder drainage. • If bladder drainage is insufficient to drain the UUT, and the patient remains unstable, high urinary diversion should be considered (see Fig. 8). 	3	B
Follow-up	Life-long monitoring is mandatory (bladder dysfunction; end-stage renal failure) in all patients. <ul style="list-style-type: none"> • Those with serum creatinine nadir above 80 µmol/L have a poor prognosis. Despite optimal treatment 10-47% of cases develop end-stage renal failure. • High creatinine nadir and severe bladder dysfunction are risk factors for renal replacement therapy. • Renal transplantation can safely be performed if bladder function is stable. 	3	B

DMSA = dimercaptosuccinic acid scan; VCUG = voiding cystourethrogram.

3R PAEDIATRIC UROLOGICAL TRAUMA

Trauma is the leading cause of morbidity and mortality in children and is responsible for more childhood deaths than the total of all other causes [730]. In about 3% of children seen at paediatric hospital trauma centres, there is significant involvement of the genitourinary tract [731]. This is caused by either blunt injuries from falls, car accidents, sports injuries, physical assault, and sexual abuse, or penetrating injuries, usually due to falls onto sharp objects or from gunshot or knife wounds.

3R.1 **Paediatric renal trauma**

3R.1.1 **Epidemiology, aetiology and pathophysiology**

In blunt abdominal trauma, the kidney is the most commonly affected organ, accounting for about 10% of all blunt abdominal injuries [730].

Children are more likely than adults to sustain renal injuries after blunt trauma because of their anatomy. Compared to an adult kidney, a child's kidney is larger in relation to the rest of the body and often retains foetal lobulations, so that blunt trauma is more likely to lead to a local parenchymal disruption. The paediatric kidney is also less well protected than the adult kidney. Children have less perirenal fat, much weaker abdominal muscles, and a less ossified and therefore much more elastic and compressible thoracic cage [732].

Blunt renal trauma is usually a result of sudden deceleration of the child's body, particularly due to sport accidents, falls, and contact with blunt objects. Deceleration or crush injuries result in contusion, laceration or avulsion of the less well-protected paediatric renal parenchyma.

3R.1.2 Classification systems

Renal injuries are classified according to the kidney injury scale of the American Association for the Surgery of Trauma (Table 13) [733].

Table 13: Renal injury classified according to the kidney injury scale of the American Association for the Surgery of Trauma [733]

Grade	Type of injury	Description
I	Contusion	Microscopic or gross haematuria
	Haematoma	Normal urological studies
II	Haematoma	Non-expanding subcapsular haematoma
	Laceration	Laceration of the cortex of < 1.0 cm
III	Laceration	Laceration > 1.0 cm without rupture of collecting system
IV	Laceration	Through the cortex, medulla and collecting system
V	Vascular	Vascular injury
	Laceration	Completely shattered kidney
	Vascular	Avulsion of the renal hilum

3R.1.3 Diagnostic evaluation

In a child who has sustained blunt abdominal trauma, renal involvement can often be predicted from the history, physical examination and laboratory evaluation. Renal involvement may be associated with abdominal or flank tenderness, lower rib fractures, fractures or vertebral pedicles, trunk contusions and abrasions, and haematuria.

3R.1.3.1 Haematuria

Haematuria may be a reliable finding. In severe renal injuries, 65% suffer gross haematuria and 33% microhaematuria, while only 2% have no haematuria at all [734].

The radiographic evaluation of children with suspected renal trauma remains controversial. Some centres rely on the presence of haematuria to diagnose renal trauma, with a threshold for renal involvement of 50 RBCs/HPF. Although this may be a reliable threshold for significant micro-haematuria in trauma, there have been many reports of significant renal injuries that manifest with little or even no blood in the urine [735]. It is therefore compulsory to consider all the clinical aspects involved, including the history, physical examination, consciousness of the child, overall clinical status and laboratory findings to decide on the diagnostic algorithm and whether or not a child needs further imaging studies.

3R.1.3.2 Blood pressure

It is important to consider that children, unlike adults, are able to maintain their blood pressure, even in the presence of hypovolaemia, due to compliance of the vascular tree and mechanisms for cardiac compensation [736].

Because blood pressure is an unreliable predictor of renal involvement in children, some centres recommend imaging of the urinary tract in children with any degree of haematuria following significant abdominal trauma.

3R.1.3.3 Choice of imaging method

Nowadays, computed tomography (CT) is the best imaging method for renal involvement in children. CT scanning is the cornerstone of modern staging of blunt renal injuries especially when it comes to grading the severity of renal trauma

CT scanning is quite rapid and usually performed with the injection of contrast media. To detect extravasation, a second series of images is necessary since the initial series usually finishes 60 seconds after injection of the contrast material and may therefore fail to detect urinary extravasation [737].

In acute trauma ultrasound may be used as a screening tool and for reliably following the course of renal injury. However, ultrasound is of limited value in the initial and acute evaluation of trauma. The standard IVP is a good alternative imaging method if a CT scan is not available. It is superior to ultrasound but not as good as CT scanning for diagnostic purposes.

3R.1.4 Disease management

The modern management of trauma is multidisciplinary, requiring paediatricians, emergency physicians, surgeons, urologists, and other specialties as required.

Non-surgical conservative management with bed rest, fluids and monitoring has become the

standard approach for treating blunt renal trauma. Even in high-grade renal injuries, a conservative approach is effective and recommended for stable children. However, this approach requires close clinical observation, serial CT scans, and frequent re-assessment of the patient's overall condition.

Absolute indications for surgery include persistent bleeding into an expanding or unconfined haematoma. Relative indications for surgery are massive urinary extravasation and extensive non-viable renal tissue [738].

3R.1.5 **Recommendations for the diagnosis and treatment of paediatric renal trauma**

Recommendations	GR
Imaging is recommended in all children who have sustained a blunt or penetrating trauma with any level of haematuria, especially when the history reveals a deceleration trauma, direct flank trauma or a fall from a height.	B
Rapid spiral CT scanning is the cornerstone in the diagnostic work-up and allows accurate staging.	B
Most injured kidneys can be managed conservatively.	B
Haemodynamic instability and a Grade V renal injury are absolute indications for surgical intervention.	A

3R.2 **Paediatric ureteral trauma**

Injuries to the ureter are rare. The ureter is well protected; the upper part is protected by its close approximation to the vertebral column and paraspinal muscles and the lower part by its route through the bony pelvis. In addition, the ureter is a small target, and both flexible and mobile. This also means that ureteral injuries are caused more often by penetrating trauma than blunt trauma [739]. Since the ureter is the sole conduit for urinary transport between the kidney and the bladder, any ureteral injury can threaten the function of the ipsilateral kidney.

3R.2.1 **Diagnostic evaluation**

Since there are no classical clinical symptoms suggestive of ureteral trauma, it is important to carry out a careful diagnostic work-up using different imaging modalities. Unfortunately, initial imaging studies, such as IVP and routine CT scans, are unreliable; a study of 11 disruptions of the ureteropelvic junction found that 72% had a normal or non-diagnostic IVP on initial studies [739]. Diagnostic accuracy of CT scanning can be improved by performing a delayed CT scan up to 10 minutes after injection of the contrast material [740]. The most sensitive diagnostic test is a retrograde pyelogram.

Quite a few patients present several days after the injury, when the urinoma produces flank and abdominal pain, nausea and fever.

Because the symptoms may often be quite vague, it is important to remain suspicious for a potential undiagnosed urinary injury following significant blunt abdominal trauma in a child.

3R.2.2 **Disease management**

Immediate repair during abdominal exploration is rare. Minimally invasive procedures are the method of choice, especially since many ureteral injuries are diagnosed late after the traumatic event. Percutaneous or nephrostomy tube drainage of urinomas can be successful, as well as internal stenting of ureteral injuries [741].

If endoscopic management is not possible, primary repair of partial lacerations should be followed by internal stenting. The management of complete lacerations, avulsions or crush injuries depends on the amount of ureter lost and its location. If there is an adequate healthy length of ureter, a primary ureteroureterostomy can be performed. If primary re-anastomosis is not achievable, distal ureteral injuries can be managed using a psoas bladder hitch, Boari flap or even nephropexy. Proximal injuries can be managed using transureteroureterostomy, autotransplantation or ureteral replacement with bowel of appendix [742].

3R.2.3 Recommendations for the diagnosis and treatment of paediatric ureteral trauma

Recommendations	GR
Retrograde pyelogram is the most sensitive diagnostic method and is the method of choice. However, in the initial phase of an injury, it is very likely that ureteral injuries will not be detected by routine imaging methods, including contrast-enhanced spiral CT.	A
Endoscopic treatment is the method of choice, such as internal stenting or drainage of a urinoma, either percutaneously or via a nephrostomy tube.	B
For distal and proximal ureteral injuries, open procedures are the methods of choice.	B
For distal injuries, they include direct re-anastomosis and ureteroneocystostomy.	B
For proximal injuries, they include transureteroureterostomy, ureteral replacement with bowel or appendix, or even autotransplantation.	B

3R.3 Paediatric bladder injuries

The paediatric bladder is less protected than the adult bladder, and is therefore more susceptible to injuries than the adult bladder, especially when it is full, due to:

- The paediatric bladder has a higher position in the abdomen and is exposed above the bony pelvis.
- The abdominal wall provides less muscular protection.
- There is less pelvic and abdominal fat surrounding the bladder to cushion it in trauma.

Blunt trauma is the most common cause of significant bladder injury. In adults, bladder injury is often associated with pelvic fractures. This is less common in children because the paediatric bladder sits above the pelvic ring. Thus, only 57% of children with pelvic fractures also had a bladder injury compared to 89% of adults [743].

3R.3.1 Diagnostic evaluation

The characteristic signs of bladder injury are suprapubic pain and tenderness, an inability to urinate, and gross haematuria (95% of injuries). Patients with a pelvic fracture and gross haematuria present with a bladder rupture in up to 45% of cases [744].

The diagnosis of bladder rupture can be difficult in some cases. The bladder should be imaged both when fully distended and after drainage using standard radiography or a CT scan. The best results can be achieved by retrograde filling of the bladder using a catheter. Despite advances in CT imaging, the bladder must still be filled to capacity to accurately diagnose a possible bladder injury [745].

Blunt injuries to the bladder are categorised as:

- Contusions with damage to the bladder mucosa or muscle, without loss of bladder wall continuity or extravasation, or,
- Ruptures, which are either intraperitoneal or extraperitoneal.

Intraperitoneal bladder ruptures are more common in children because of the bladder's exposed position and the acute increase in pressure during trauma. These cause the bladder to burst at its weakest point, i.e. the dome.

Extraperitoneal lesions occur in the lower half of the bladder and are almost always associated with pelvic fractures. A cystogram will show extravasation into the perivesical soft tissue in a typical flame pattern and the contrast material is confined to the pelvis.

3R.3.2 Disease management

Contusions usually present with varying degrees of haematuria and are treated with catheter drainage alone.

3R.3.2.1 Intraperitoneal injuries

The accepted management of intraperitoneal bladder ruptures is open surgical exploration and primary repair.

Post-operative drainage with a suprapubic tube is mandatory. Recent data suggest that transurethral drainage may be as effective, with fewer complications, resulting in shorter periods of diversion [746]. Usually, after about 7-10 days, a repeat cystogram is performed to ensure healing is taking place properly.

3R.3.2.2 Extraperitoneal injuries

Non-operative management with catheter drainage for 7-10 days alone is the method of choice for extraperitoneal bladder rupture. However, if there are bone fragments within the bladder, these must

be removed and the bladder must then be repaired and drained, according to the principles for treating intraperitoneal ruptures [747].

3R.3.3 **Recommendations for the diagnosis and treatment of paediatric bladder injuries**

Recommendations	GR
Retrograde cystography will allow for an accurate diagnosis, provided that the bladder has been filled full to its capacity and an additional film is taken after drainage.	A
Extraperitoneal bladder ruptures are usually managed conservatively with a transurethral catheter left in place for 7-10 days.	A
Intraperitoneal bladder ruptures require immediate surgical exploration and repair as well as postoperative drainage for 7-10 days.	A

3R.4 **Paediatric urethral injuries**

Except for the penile part of the urethra, the paediatric urethra is quite well protected. In addition, its shape and elasticity mean the urethra is seldom injured by trauma. However, a urethral injury should be suspected in any patient with a pelvic fracture or significant trauma to the perineum until confirmed otherwise by a diagnostic work-up.

3R.4.1 **Diagnostic evaluation**

Patients with suspected urethral trauma and pelvic fractures usually present with a history of severe trauma, often involving other organ systems.

Signs of urethral injury are blood at the meatus, gross haematuria, and pain during voiding or an inability to void. There may also be perineal swelling and haematoma involving the scrotum.

A rectal examination to determine the position and fixation of the prostate is important in any male with a suspected urethral injury. The prostate, as well as the bladder, may be displaced up out of the pelvis, especially in membranous urethral trauma.

Radiographic evaluation of the urethra requires a retrograde urethrogram. It is important to expose the entire urethral length, including the bladder neck. If a catheter has already been placed by someone else and there is suspected urethral trauma, the catheter should be left in place and should not be removed. Instead, a small infant feeding tube can be placed into the distal urethra along the catheter to allow the injection of contrast material for a diagnostic scan [748].

3R.4.2 **Disease management**

Since many of these patients are unstable, the urologist's initial responsibility is to provide a method of draining and monitoring urine output.

A transurethral catheter should only be inserted if there is a history of voiding after the traumatic event, and if a rectal and pelvic examination, as described above, has not suggested a urethral rupture. If the catheter does not pass easily, an immediate retrograde urethrogram should be performed.

A suprapubic tube may be placed in the emergency department percutaneously, or even in the operating room, if the patient has to undergo immediate exploration because of other life-threatening injuries.

There are often no associated injuries with a bulbous urethral or straddle injury and management is therefore usually straightforward. In these cases, a transurethral catheter is the best option for preventing urethral bleeding and/or painful voiding [749].

The initial management of posterior urethral injuries remains controversial, mainly regarding the long-term results with primary realignment compared to simple suprapubic drainage with later reconstruction. The main goals in the surgical repair of posterior urethral injuries are:

- Providing a stricture-free urethra.
- Avoiding the complications of urinary incontinence and impotence.

Suprapubic drainage and late urethral reconstruction was first attempted because immediate surgical repair had a poor outcome, with significant bleeding and high rates of incontinence (21%) and impotence in up to 56% of cases [750]. In adults, a study of the success rates of delayed repair reported re-structure rates of 11-30%, continence rates of 90-95% and impotence rates of 62-68% [751]. However, in children, there is much less experience with delayed repair. The largest paediatric series of delayed repair in 68 boys reported a success rate of 90% [752]. Another study reported strictures and impotence in 67% of boys, although all the boys were continent [751].

An alternative to providing initial suprapubic drainage and delayed repair is primary realignment of the urethra via a catheter. The catheter is usually put in place during open cystostomy by passing it from either the bladder neck or meatus and through the injured segment. In a series of 14 children undergoing this

procedure, this resulted in a stricture rate of 29% and incontinence in 7% [753].

3R.4.3 Guidelines for the diagnosis and treatment of paediatric trauma

Recommendations	GR
Imaging of the urethra with a retrograde urethrogram is mandatory in suspected urethral trauma.	A
Rectal examination is recommended to determine the position of the prostate.	B
Bulbous urethral injuries can usually be managed conservatively with a transurethral catheter.	B
There is still controversy about the optimal management for posterior urethral disruption. The options include primary reconstruction; primary drainage with a suprapubic catheter alone and delayed repair; primary re-alignment with a transurethral catheter.	C

3S POST-OPERATIVE FLUID MANAGEMENT

3S.1 Epidemiology, aetiology and pathophysiology

It is often stated that children are not simply small adults. Children are growing and developing organisms, with specific metabolic features. Compared to adults, children have a different total body fluid distribution, renal physiology and electrolyte requirements, as well as weaker cardiovascular compensation mechanisms [754]. As children are developing, they have a high metabolic rate and low fat and nutrient stores, which means they are more susceptible to metabolic disturbances caused by surgical stress [755]. The metabolic response to anaesthesia and surgery in infants and children is related to the severity of the operation [756].

3S.2 Disease management

3S.2.1 Pre-operative fasting

Pre-operative fasting has been advocated for elective surgery to avoid the complications associated with pulmonary aspiration during induction of anaesthesia. Table 14 gives the current guidelines for pre-operative fasting for elective surgery [757, 758].

Table 14: Pre-operative fasting times for elective surgery

Ingested material	Minimum fasting period (h)
Clear liquids	2
Breast milk	4
Infant formula	4 (< 3 months old) to 6 (> 3 months old)
Non-human milk	6
Light meal	6

Although hypoglycaemia is an important issue in children, research has shown that hypoglycaemia is uncommon if children are still fed up to 4 h before the induction of anaesthesia [759]. Newborns often have low glycogen stores and impaired gluconeogenesis, both of which can be helped by limiting the period of preoperative starvation and feeding with glucose-containing solutions. It is important to monitor blood glucose and to adjust the glucose supply continuously in neonates and those children who are small for their age, as this helps to prevent excessive fluctuation in blood glucose levels [760].

3S.2.2 Maintenance therapy and intra-operative fluid therapy

Generally, the anaesthetist is responsible for intra-operative management and the surgeon is responsible for post-operative instructions. The goal of intra-operative fluid management is to sustain homeostasis by providing the appropriate amount of parenteral fluid; this maintains adequate intravascular volume, cardiac output and oxygen delivery to tissues at a time when normal physiological functions have been altered by surgical stress and anaesthetic agents [760].

The fluids for maintenance therapy replace losses from two sources: insensible (evaporation) and urinary loss. They do not replace blood loss or third-space fluid loss into the interstitial space or gut. The main formulae for calculating the daily maintenance requirement for water have not changed in the past 50 years (Table 15) [761]. Calculations have shown that anaesthetised and non-anaesthetised children have similar fluid requirements [762].

The combination of maintenance fluid and electrolyte requirements results in a hypotonic electrolyte solution. The usual intravenous maintenance fluid given to children by paediatricians is one-quarter to one-third strength saline [763].

Table 15: Hourly and daily fluid requirements according to body weight

Body weight	Hourly	Daily
< 10 kg	4 mL/kg	100 mL/kg
10-20 kg	40 mL + 2 mL/kg; > 10 kg	1000 mL + 50 mL/kg; > 10 kg
> 20 kg	60 mL + 1 mL/kg; > 20 kg	1500 mL + 20 mL/kg; > 20 kg

The fasting deficit is calculated by multiplying the hourly maintenance fluid requirement by the number of hours of fluid restriction. It is recommended that 50% of the fasting deficit is replaced in the first hour and 25% in the second and third hours [764]. Berry (1986) proposed simplified guidelines for fluid administration according to the child's age and severity of surgical trauma [765] (Table 16).

Table 16: Intra-operative fluid management adapted for children fasted for 6-8 h, following the classical recommendation 'nil per oral after midnight'

Furman, et al. [764]			
Hour of fluid replacement	Maintenance fluid	Fasting deficit replacement	Persistent losses
First hour	As Table 14	50%	Third space + blood loss replacement
Second hour		25%	
Third hour		25%	
Berry [765]			
First hour	≤ 3 years: 25 mL/kg ≥ 4 years: 15 mL/kg		Blood replacement 1:1 with blood or colloid or 3:1 with crystalloids
All other hours	Maintenance volume = 4 mL/kg/h Maintenance + mild trauma = 6 mL/kg/h Maintenance + moderate trauma = 8 mL/kg/h Maintenance + severe trauma = 10 mL/kg/h		Blood replacement 1:1 with blood or colloid or 3:1 with crystalloids

** Reduce the amount of fluid given during the first hour if children are fasting for a shorter period of time, or if the child was already being given intravenous fluid prior to surgery.*

Five percent dextrose with one-quarter- to half-normal saline is often used as a maintenance fluid, while balanced salt solution or normal saline is used as replacement fluid. Blood losses are replaced with a 1:1 ratio of blood or colloid or a 3:1 ratio of crystalloid. However, the administration of a large volume of normal saline can cause dilutional acidosis or hyperchloremic acidosis, while a large volume of balanced salt solution, such as lactated Ringer's solution, can decrease serum osmolality, which is not beneficial in patients with decreased intracranial compliance. If appropriate, albumin, plasma, synthetic colloids, and blood should be administered [760].

Third-space losses may vary from 1 mL/kg/h for a minor surgical procedure to 15-20 mL/kg/h for major abdominal procedures, or even up to 50 mL/kg/h for surgery of necrotising enterocolitis in premature infants. Third-space losses should be replaced with crystalloids (normal saline or Ringer's lactate) [758].

Most of the fluids required during surgery are needed to replace fasting deficit or third-space losses, which are mainly extracellular fluids. Hydrating solutions should contain high concentrations of sodium and chloride and low concentrations of bicarbonate, calcium and potassium.

Intra-operative hypoglycaemia is rare in children. In contrast, hyperglycaemia is commonly encountered during anaesthesia and surgery. The replacement fluid should be free of dextrose or should not have > 1% dextrose. Current recommendations include the use of low-dextrose-containing solutions for maintenance fluid therapy, except in patients who are at high risk of hypoglycaemia [754, 763]. Intra-operative administration of glucose-free isotonic hydrating solutions should be the routine practice for most procedures in children over 4-5 years of age. In infants and young children, 5% dextrose solutions should be avoided, but it is appropriate to use 1% or 2% dextrose in lactated Ringer's solution [758].

3S.2.3 **Post-operative fluid management**

During the post-operative period, the fundamental principle is to monitor gastrointestinal function and to continue oral or enteral nutrition as much as possible [755], while remembering that withholding oral fluids post-operatively from children undergoing day surgery helps prevent vomiting [766]. In minor surgical procedures, intra-operative administration of large volumes of crystalloids is associated with a reduced incidence of post-operative nausea and vomiting after anaesthesia in both paediatric and adult patients [767]. Berry's fluid replacement guidelines can be followed, provided the child is given lactated Ringer's solution or polyionique B66, which has an osmolarity similar to plasma [768].

It is not obligatory to check serum chemistry after uncomplicated surgery in children with normal pre-operative renal and hepatic function. However, if oral intake has been postponed for > 24 h (e.g. as in intestinal surgery), there is an increased risk of electrolyte abnormalities, requiring further assessment and subsequent management, particularly with potassium. Post-operative findings, such as decreased bowel movements and ileus, may be signs of hypokalemia, which may be corrected with a solution of 20 mmol/L potassium and an infusion rate of not more than 3 mmol/kg/day. The potassium should be given via peripheral venous access if the duration of infusion is not expected to exceed 5 days, or via central venous access when long-term parenteral nutrition is necessary.

The goals of fluid therapy are to provide basic metabolic requirements and to compensate for gastrointestinal and additional losses. If hypovolemia is present, it should be treated rapidly. Hyponatremia is the most frequent electrolyte disorder in the post-operative period [768, 769]. This means that hypotonic fluid should not be routinely administered to hospitalised children because they have several stimuli for producing arginine vasopressin and are therefore at high risk for developing hyponatremia [758, 768, 770-773]. The preferred fluids for maintenance therapy are 0.45% saline with dextrose or isotonic fluids, in the absence of a specific indication for 0.25% saline. It is also advisable to administer isotonic fluids intra-operatively and also immediately post-operatively, albeit at two-thirds of the calculated maintenance rate in the recovery room. Fluid composition should balance high sodium requirements, energy requirements and solution osmolarity. The extra losses from gastric or chest tubes should be replaced with lactated Ringer's solution. Fluid that has been given to dilute medications must also be taken into account [758].

Children who undergo interventions to relieve any kind of obstructive diseases deserve particular attention, especially the risk of polyuria due to post-obstructive diuresis. In children who develop polyuria, it is important to monitor fluid intake and urine output, as well as renal function and serum electrolytes.

If necessary, clinicians should not hesitate in consulting with a paediatric nephrologist.

3S.2.4 **Post-operative fasting**

It has been reported that fasting reduces the risk of vomiting by up to 50% [766, 774, 775]. However, a study found that if children were freely allowed to drink and eat when they felt ready or requested it, the incidence of vomiting did not increase and the children felt happier and were significantly less bothered by pain than children who were fasting [776]. The mean times until first drink and first eating in the children who were free to eat or drink were 108 and 270 min, respectively, which were 4 h and 3 h earlier than in the fasting group.

Previous studies have suggested that gastric motility returns to normal 1 h after emergence from anaesthesia in children who have undergone non-abdominal surgery [777]. The first oral intake in children at 1 h after emergence from anaesthesia for minor surgery did not cause an increase in the incidence of vomiting, provided that the fluid ingested was at body temperature [778]. The EAU Panel members therefore recommend encouraging an early intake of fluid in children who have undergone minor or non-abdominal urological surgery.

3S.3 **Summary conclusions and recommendations**

Conclusion	LE
Children are not simply smaller physiological versions of adults. They have their own unique metabolic features, which must be considered during surgery.	2

Recommendations	GR
Pre-operative fasting periods for elective surgeries (up to 4 h) can be shorter than normally used.	B
Care should be taken for hyperglycaemia, which is common in children, compared to intra-operative hypoglycaemia, which is very rare. Fluids with lower dextrose concentrations should therefore be considered.	B
Avoid the routine use of hypotonic fluid in hospitalised children because they are at high risk of developing hyponatremia.	A

There is an increased risk of electrolyte abnormalities in children undergoing surgery. It is therefore essential to measure the baseline and daily levels of serum electrolytes, glucose, urea and/or creatinine in every child who receives intravenous fluids, especially in intestinal surgery (e.g. ileal augmentation), regardless of the type of solution chosen.	B
In patients treated with minor surgical procedures, early oral fluid intake should be encouraged.	A

3T POST-OPERATIVE PAIN MANAGEMENT IN CHILDREN: GENERAL INFORMATION

3T.1 Epidemiology, aetiology and pathophysiology

The provision of adequate pain control requires proper pain evaluation, accurate choice of drug and route of administration, and consideration of age, physical condition and type of surgery and anaesthesia [779]. However, there is still no standardised algorithm for management of post-operative pain in children [780]. There is an urgent need for a post-operative pain management protocol in children, particularly for guidance on the frequency of pain assessment, use of parenteral opioids, introduction of regional anaesthesia, and the application of rescue analgesics [781].

Traditional medical beliefs that neonates are incapable of experiencing pain have now been abandoned following recent and better understanding of how the pain system matures in humans, better pain assessment methods and a knowledge of the clinical consequences of pain in neonates [782-786]. Many studies have indicated that deficient or insufficient analgesia may be the cause of future behavioural and somatic sequelae [787-791]. Our current understanding of pain management in children depends fully on the belief that all children, irrespective of age, deserve adequate treatment.

3T.2 Diagnostic evaluation

Assessment of pain is the first step of pain management. Validated pain assessment tools are needed for this purpose and it is important to select the appropriate pain assessment technique. Several pain assessment tools have been developed according to the child's age, cultural background, mental status, communication skills and physiological reactions [792, 793].

One of the most important topics in paediatric pain management is informing and involving the child and parents during this process. Parents and patients can manage post-operative pain at home or in hospital if provided with the correct information. Parents and patients, if they are old enough, can actively take part in pain management in patient-family-controlled analgesia applications [794-799].

3T.3 Disease management

3T.3.1 Drugs and route of administration

Pre-emptive analgesia is an important concept that aims to induce the suppression of pain before neural hypersensitisation occurs [800]. Local anaesthetics or non-steroidal analgesics are given intra-operatively to delay post-operative pain and to decrease post-operative analgesic consumption. Analgesics must be titrated until an appropriate response is achieved. Opioids can be administered to children by the oral, mucosal, transdermal, subcutaneous, intramuscular or intravenous routes [796]. The combination of opioids with non-steroidal anti-inflammatory drugs (NSAIDs) or local anaesthetics (balanced or multimodal analgesia) can be used to increase the quality of analgesia and decrease undesired effects related to opioids [801]. The same combination of local anaesthetics, opioids, and non-opioid drugs used in adults can also be used in children taking into account their age, body weight and individual medical status.

The World Health Organization's 'pain ladder' is a useful tool for the pain management strategy [802]. A three-level strategy seems practical for clinical use. Post-operative management should be based on sufficient intra-operative pre-emptive analgesia with regional or caudal blockade followed by balanced analgesia.

Paracetamol and NSAIDs are the drugs of choice at the first level. As they become insufficient to prevent pain, weak and strong opioids are added to oral drugs to achieve balanced analgesia. Every institute must build their own strategy for post-operative analgesia. A proposed strategy for post-operative analgesia may be as follows:

1. Intra-operative regional or caudal block
2. Paracetamol + NSAID
3. Paracetamol + NSAID + weak opioid (e.g. tramadol or codeine)
4. Paracetamol + NSAID + strong opioid (e.g. morphine, fentanyl, oxycodone or pethidine)

Table 17: List of several drugs used in post-operative pain management in children [783, 791, 795, 860-862]

Name	Route of administration	Dose	Side effects	General remarks	Caution
Non-narcotics					
Acetaminophen	Rectal Oral Intravenous	40 mg/kg loading, 20 mg/kg/dose 4 times/day 15-40 mg/kg, followed by 30 mg/kg/8 h Propacetamol (prodrug)	Nephrotoxicity, hepatotoxicity (neonates)	Most common used analgesic Antipyretic effect Opioid-sparing effect Wide safety range	Slow onset time and variable absorption via the rectal route; dividing the vehicle is not recommended. Total dose should not exceed: 100 mg/kg for children; 75 mg/kg for infants; 60 mg/kg for term and preterm neonates > 32 weeks post-conceptual age; and 40 mg/kg for preterm neonates < 32 weeks post-conceptual age Safety not established for infants < 6 months old
Ibuprofen	Oral, rectal	4-10 mg/kg/dose 3-4 times/day		Better analgesic than paracetamol	
Diclofenac	Tablet, syrup, suppository	1-1.5 mg/kg 2-3 times/day	Nephrotoxicity, gastrointestinal disturbances	Better than ibuprofen	> 6 years old
Ketorolac	Oral, IV, IM	0.2-0.5 mg/kg every 6 h (48 h) Total dose < 2 mg/kg/day, maximum 5 days		Opioid-sparing effect	
Ketamine	Oral, rectal, IM, SC, IV, intraspinal	< 2 mg/kg (IM) < 1 mg/kg (IV, epidural)			
Metamizole, dipyrone	Oral, IM Oral drop	10-15 mg/kg/dose (max 40 mg/kg total) 10-15 mg/kg 1 drop/kg/dose, up to 4 times/day	Risk of agranulocytosis, not clarified definitely	Very effective antipyretic	Not approved in some countries including USA, Sweden, Japan and Australia
Narcotics					
Opioids			Nausea, vomiting, dyspepsia, constipation, urinary retention, respiratory depression, drowsiness, euphoria		
Tramadol (weak opioid)	Oral, rectal, IV, IM (dose can be repeated 4-6 times/day)	2-3 mg/kg/dose (oral, drop) 1-2 mg/kg/dose (oral, tablet) 1.5-3 mg/kg/dose (rectal) 0.75-2 mg/kg/dose (IM) 2-2.5 mg/kg/dose (IV) 0.1-0.25 mg/kg/h (continuous)	Nausea, vomiting, pruritus and rash	Does not inhibit prostaglandin synthesis	An IM injection is not recommended. Slow IV infusion. Be careful in patients taking psychoactive medications and with seizures

[illegible]

37.3.2 Circumcision

Circumcision without anaesthesia, irrespective of age, is not recommended. Circumcision requires proper pain management [803]. Despite this, adequate pain management is still below expectation [804]. Potential analgesic interventions during circumcision include the use of a dorsal penile nerve block (DPNB) or ring block, topical anaesthetics (e.g. lidocaine-prilocaine cream, or 4% liposomal lidocaine cream), a less painful clamp (e.g. Mogen clamp), a pacifier, sucrose, and swaddling, preferably in combination [805-809].

Although DPNB and topical anaesthetics seem to have a similar post-operative analgesic effect, DPNB is still the most preferred method [810] (LE: 1a). Ultrasonographic guidance may improve the results, with an increase in procedural time [811, 812]. Caudal blockade methods have similar efficacy compared to DPNB. However, parents should be informed about the more frequent incidence of post-operative motor weakness and micturition problems [813-818].

37.3.3 Penile, inguinal and scrotal surgery

Caudal block is the most studied method for analgesia following surgery for hypospadias. Several agents with different doses, concentrations and administration techniques have been used with similar outcomes [819-833]. Both single and combined use of these agents is effective [820, 821, 823, 824, 829, 831].

Penile blocks can be used for post-operative analgesia and have similar post-operative analgesic properties as caudal blocks [834]. Two penile blocks at the beginning and end of surgery seems to provide better pain relief [835]. Severe bladder spasms caused by the presence of the bladder catheter may sometimes cause more problems than pain and is managed with antimuscarinic medications.

For inguinoscrotal surgery, all anaesthetic methods, such as caudal blocks [307, 836-838], nerve block [839, 840], wound infiltration or instillation, and irrigation with local anaesthetics [841-843], have been shown to have adequate post-operative analgesic properties. Combinations may improve the results [844].

37.3.4 Bladder and kidney surgery

Continuous epidural infusion of local anaesthetics [845-847], as well as systemic (intravenous) application of analgesics [848], has been shown to be effective. Ketorolac is an effective agent that is underused. It decreases the frequency and severity of bladder spasms and the length of post-operative hospital stay and costs [837, 849-852].

Open kidney surgery is particularly painful because all three muscle layers are cut during conventional loin incision. A dorsal lumbotomy incision may be a good alternative because of the shorter post-operative hospital stay and earlier return to oral intake and unrestricted daily activity [853].

Caudal blocks plus systemic analgesics [854], and continuous epidural analgesia, are effective in terms of decreased post-operative morphine requirement after renal surgery [855, 856]. However, when there is a relative contraindication to line insertion, a less experienced anaesthetist is available, or parents prefer it [857], non-invasive regimens composed of intra-operative and post-operative analgesics may be the choice. Particularly in this group of patients, stepwise analgesia protocols can be developed [858]. For laparoscopic approaches, intraperitoneal spraying of local anaesthetic before incision of the perirenal fascia may be beneficial [859].

Table 18: A simple pain management strategy for paediatric urological surgery

Intensity of surgery	First step	Second step	Third step
Mild (inguinal, scrotal, penile)	Paracetamol and wound infiltration with local anaesthetics	NSAIDs	Regional block/weak opioid or IV strong opioid with small increments as rescue analgesia (e.g. nalbuphine, fentanyl, meperidine, morphine)
Moderate (lower abdominal)			Peripheral nerve block (single shot or continuous infusion)/opioid injection (IV PCA)
Severe (upper abdominal or lombotomy)			Epidural local/major peripheral nerve/plexus block/opioid injection (IV PCA)

IV PCA = intravenous patient-controlled analgesia.

3T.4 Conclusions and recommendations

Conclusions	LE
Neonates experience pain.	3
Pain may cause behavioural and somatic sequelae.	3
Every institute must develop their own well-structured strategy for post-operative analgesia.	4

Recommendations	GR
Pain must be prevented/treated in children of all ages.	B
Pain must be evaluated by age-compatible assessment tools.	B
Patients and parents must be informed accurately.	B
Pre-emptive analgesia is important and balanced analgesia should be used in order to decrease the side effects of opioids.	B

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5. CONFLICT OF INTEREST

All members of the Paediatric Urology Guidelines Panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website. This Guidelines document was developed with the financial support of the EAU. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

Guidelines on Urological Trauma

D.J. Summerton (Chair), N. Djakovic, N.D. Kitrey,
F.E. Kuehhas, N. Lumen, E. Serafetinidis, D.M. Sharma

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1. INTRODUCTION

1.1 Aims and objectives

The European Association of Urology (EAU) Guidelines Group for Urological Trauma prepared these guidelines in order to assist medical professionals in the management of urological trauma in adults. Paediatric trauma is addressed in the EAU Paediatric Urology Guidelines.

1.2 Panel composition

The EAU Urological Trauma Guidelines Panel consists of an international group of clinicians with particular expertise in this area.

1.2.1 Potential conflict of interest

The expert panel have submitted potential conflict of interest statements which can be viewed on the EAU website.

1.3 Available publications

A quick reference document (Pocket guidelines) is available, in print and in a number of versions for mobile devices. These are abridged versions which may require consultation together with the full text versions. Also a number of translated versions, alongside several scientific publications in European Urology, the Associations scientific journal are available [1-4]. All documents can be viewed free access through the EAU website: <http://www.uroweb.org/guidelines/online-guidelines/>.

1.4 Publication history and summary of changes

1.4.1 Publication history

The Urological Trauma Guidelines were first published in 2003. This 2015 document presents a limited update of the 2014 publication.

1.4.2 Summary of changes

The literature in the complete document has been assessed and updated, whenever relevant.

Key changes for the 2015 publication:

Figure 4.4.1 – Management of anterior urethral injuries in men, has been revised.

Conclusions and recommendations have been rephrased throughout the document.

2. METHODS

2.1 Evidence sources

The Urological Trauma guidelines are based on a review of the relevant literature, using on-line searches of the following databases: Medline, Embase, Cochrane, and other source documents published between 2002 and 2014. A critical assessment of the findings was made. The majority of publications on the subject are comprised of case reports and retrospective case series. The paucity of high-powered randomised controlled trials makes it difficult to draw meaningful conclusions. The panel recognises this critical limitation.

In this 2015 EAU Guidelines compilation, all standard information on levels of evidence (LE) and grading of recommendations (GR) has been taken out of the individual guidelines topics for the sake of brevity. This information is included in the introductory section of this print.

2.2 Peer review

This document was subjected to double-blind peer review prior to publication.

3. EPIDEMIOLOGY & CLASSIFICATION

3.1 Definition and Epidemiology

Trauma is defined as a physical injury or a wound to living tissue caused by an extrinsic agent. Trauma is the

sixth leading cause of death worldwide, accounting for 10% of all mortalities. It accounts for approximately 5 million deaths each year worldwide and causes disability to millions more [5, 6].

About half of all deaths due to trauma are in people aged 15-45 years and in this age group it is the leading cause of death [7]. Death from injury is twice as common in males than in females, especially from motor vehicle accidents (MVAs) and interpersonal violence. Trauma is therefore a serious public health problem with significant social and economic costs.

Significant variation exists in the causes and the effects of traumatic injuries between geographical areas, and between low, middle, and high-income countries. It should be noted that alcohol and drug abuse increase the rate of traumatic injuries by precipitating interpersonal violence, child and sexual abuse, and MVAs [8].

3.1.1 **Genito-Urinary Trauma**

Genito-urinary trauma is seen in both sexes and in all age groups, but is more common in males.

The kidney is the most commonly injured organ in the genito-urinary system and renal trauma is seen in up to 5% of all trauma cases [9, 10], and in 10% of all abdominal trauma cases [11]. In MVAs, renal trauma is seen after direct impact into the seatbelt or steering wheel (frontal crashes) or from body panel intrusion in side-impact crashes [12].

Ureteral trauma is relatively rare and mainly due to iatrogenic injuries or penetrating gunshot wounds – both in military and civilian settings [13].

Traumatic bladder injuries are usually due to blunt causes (MVA) and associated with pelvic fracture [14], although may also be a result of iatrogenic trauma.

The anterior urethra is most commonly injured by blunt or “fall-astride” trauma, whereas the posterior urethra is usually injured in pelvic fracture cases - the majority of which are seen in MVAs [15].

Genital trauma is much more common in males due to anatomical considerations and more frequent participation in physical sports, violence and war-fighting. Of all genito-urinary injuries, 1/3-2/3 involve the external genitalia [16].

3.2 **Classification of trauma**

Traumatic injuries are classified by the World Health Organization (WHO) into intentional (either interpersonal violence related, war-related or self-inflicted injuries), and unintentional injuries - mainly motor vehicle collisions, falls, and other domestic accidents. Intentional trauma accounts for approximately half of the trauma-related deaths worldwide [6]. A specific type of unintentional injury consists of iatrogenic injury which is created during therapeutic- or diagnostic procedures by healthcare personnel.

Traumatic insults are classified according to the basic mechanism of the injury into penetrating when an object pierces the skin, and blunt injuries.

Penetrating trauma is further classified according to the velocity of the projectile into:

1. High-velocity projectiles (e.g. rifle bullets - 800-1000 m/sec);
2. Medium-velocity projectiles (e.g. handgun bullets - 200-300 m/sec);
3. Low-velocity items (e.g. knife stab).

High-velocity weapons inflict greater damage because the bullets transmit large amounts of energy to the tissues. They form a temporary expansive cavitation that immediately collapses and creates shear forces and destruction in a much larger area than the projectile tract itself. Cavity formation disrupts tissue, ruptures blood vessels and nerves, and may fracture bones away from the path of the missile. In lower velocity injuries, the damage is usually confined to the track of the projectile.

Blast injury is a complex cause of trauma because it commonly includes both blunt and penetrating trauma, and may also be accompanied by a burn injury.

Several classifications are used to describe the severity and the features of a traumatic injury. The most common is the AAST (American Association for the Surgery of Trauma) injury scoring scale, which is widely used in renal trauma (see the relevant section) <http://www.aast.org/library/traumatools/injuryscoringscales.aspx> [17]. For the other urological organs, general practice is that injuries are described by their anatomical site and severity (partial/complete) and the elaborated AAST tables were therefore omitted from these guidelines.

3.3 **Initial evaluation and treatment**

The initial emergency assessment of the trauma patient is beyond the focus of these guidelines, and is usually carried out by emergency medicine and trauma specialised personnel. The first priority is stabilisation of the patient and treatment of associated life-threatening injuries. The initial treatment should include securing the

airway, controlling external bleeding and resuscitation of shock. In many cases, physical examination is carried out during stabilisation of the patient.

A direct history is obtained from conscious patients, while witnesses and emergency personnel can provide valuable information about unconscious or seriously injured patients. In penetrating injuries, important information includes the size of the weapon in stabbings, and the type and calibre of the weapon used in gunshot wounds. The medical history should be as detailed as possible, as pre-existing organ dysfunction can have a negative effect on trauma patient outcome [18, 19].

It is essential that all persons treating trauma patients are aware of the risk of hepatitis B and C infection. An infection rate of 38% was reported among males with penetrating wounds to the external genitalia [20]. In any penetrating trauma, tetanus vaccination should be considered according to the patient's vaccination history and the features of the wound itself (CDC tetanus wound management) [21].

4. UROGENITAL TRAUMA GUIDELINES

4.1 Renal Trauma

4.1.1 *Epidemiology, aetiology and pathophysiology*

4.1.1.1 *Definition and impact of the disease*

Renal trauma occurs in approximately 1-5% of all trauma cases [10, 22]. The kidney is the most commonly injured genitourinary organ, with a male to female ratio of 3:1 [23, 24]. Most injuries can be managed conservatively as advances in imaging and treatment strategies have decreased the need for surgical intervention and increased organ preservation [11, 25, 26].

4.1.1.2 *Mode of injury*

4.1.1.2.1 Blunt renal injuries

Blunt mechanisms include motor vehicle collision, falls, vehicle-associated pedestrian accidents, sports and assault. Traffic accidents are the major cause, accounting for almost half of blunt injuries [27]. A direct blow to the flank or abdomen during sports activities is another cause. Sudden deceleration or a crush injury may result in contusion or laceration of the parenchyma.

In general, renal vascular injuries occur in less than 5% of blunt abdominal trauma, while isolated renal artery injury is very rare (0.05-0.08%) [11] and renal artery occlusion is associated with rapid deceleration injuries.

4.1.1.2.2 Penetrating renal injuries

Gunshot and stab wounds represent the most common causes of penetrating injuries and tend to be more severe and less predictable than blunt trauma. In urban settings, the percentage of penetrating injuries can be as high as 20% or higher [28, 29]. Bullets have the potential for greater parenchymal destruction and are most often associated with multiple-organ injuries [30]. Penetrating injury produces direct tissue disruption of the parenchyma, vascular pedicles, or collecting system.

4.1.1.3 *Classification systems*

The most commonly used classification system is that of the American Association for the Surgery of Trauma (AAST) [17] (Table 4.1.1). This validated system has clinical and prognostic relevance and helps to predict the need for intervention [31-33]. It also predicts morbidity after blunt or penetrating injury and mortality after blunt injury [33].

Table 4.1.1: AAST renal injury grading scale

Grade*	Description of injury
1	Contusion or non-expanding subcapsular haematoma
	No laceration
2	Non-expanding peri-renal haematoma
	Cortical laceration < 1 cm deep without extravasation
3	Cortical laceration > 1 cm without urinary extravasation

4	Laceration: through corticomedullary junction into collecting system or Vascular: segmental renal artery or vein injury with contained haematoma, or partial vessel laceration, or vessel thrombosis
5	Laceration: shattered kidney or Vascular: renal pedicle or avulsion

**Advance one grade for bilateral injuries up to grade III.*

Proposals for changes include a substratification of the intermediate grade injury into grade 4a (low risk-cases likely to be managed non-operatively) and grade 4b (high risk-cases likely to benefit from angiographic embolisation, repair or nephrectomy), based on the presence of important radiographic risk factors, including peri-renal haematoma, intravascular contrast extravasation and laceration complexity [34], as well as a suggestion that grade 4 injuries comprise all collecting system injuries, including ureteropelvic junction (UPJ) injury of any severity and segmental arterial and venous injuries, while grade 5 injuries should include only hilar injuries, including thrombotic events [35].

4.1.2 **Diagnostic evaluation**

4.1.2.1 *Patient history and physical examination*

Vital signs should be recorded throughout the diagnostic evaluation. Possible indicators of major injury include a history of a rapid deceleration event (fall, high-speed motor vehicle accidents) or a direct blow to the flank. In the early resuscitation phase, special consideration should be given to pre-existing renal disease [36]. In patients with a solitary kidney, the whole functioning renal mass may be endangered [37, 38]. Pre-existing abnormality makes injury more likely following trauma. Hydronephrosis due to UPJ abnormality, calculi, cysts and tumours are the most commonly reported entities that may complicate a minor injury [38].

Physical examination may reveal an obvious penetrating trauma from a stab wound to the lower thoracic back, flanks and upper abdomen, or bullet entry or exit wounds. In stab wounds, the extent of the entrance wound may not accurately reflect the depth of penetration.

Blunt trauma to the back, flank, lower thorax or upper abdomen may result in renal injury. Haematuria, flank pain, ecchymoses, abrasions, fractured ribs, abdominal distension and/or a mass and tenderness raise the suspicion of renal involvement.

4.1.2.1.1 Recommendations for patient history and physical examination

	GR
Haemodynamic stability should be assessed upon admission.	A*
History should be taken from conscious patients, witnesses and rescue team personnel with regard to the time and setting of the incident.	A*
Past renal surgery, and known pre-existing renal abnormalities (UPJ obstruction, large cysts, lithiasis) should be recorded.	A*
A thorough physical examination should be made to rule out penetrating injury. Haematuria, flank pain, flank abrasions and bruising ecchymoses, fractured ribs, abdominal tenderness, distension or mass, could indicate possible renal involvement.	A*

**Upgraded following panel consensus.*

GR = grade of recommendation.

4.1.2.2 *Laboratory evaluation*

Urinalysis, haematocrit and baseline creatinine are the most important tests. Haematuria, either non-visible or visible is often seen, but is neither sensitive nor specific enough to differentiate between minor and major injuries [39].

Major injury, such as disruption of the UPJ, pedicle injuries, segmental arterial thrombosis and approximately 9% of patients with stab wounds and renal injury may occur without haematuria [40, 41]. Haematuria that is out of proportion to the history of trauma may suggest pre-existing pathology [42]. A urine dipstick is an acceptable reliable and rapid test to evaluate haematuria, however, the rate of false-negative results range from 3-10% [43].

Serial haematocrit determinations in combination with vital signs are used for continuous evaluation of the patient. A decrease in haematocrit and the requirement for blood transfusions are indirect signs of the rate of blood loss, and along with the patient's response to resuscitation, are valuable in the decision-making process. However, until evaluation is complete, it will not be clear whether this is due to renal trauma and/or associated injuries.

As most trauma patients are evaluated within 1 hour of injury, creatinine measurement reflects renal function prior to the injury. An increased creatinine level usually reflects pre-existing renal pathology.

4.1.2.2.1 Recommendations for laboratory evaluation

	GR
Urine from a patient with suspected renal injury should be inspected for haematuria (visually and by dipstick analysis).	A*
Creatinine levels should be measured to identify patients with impaired renal function prior to injury.	C

**Upgraded following panel consensus.*

GR = grade of recommendation.

4.1.2.3 Imaging: criteria for radiographic assessment

Decisions on radiographic imaging in cases of suspected renal trauma are based on the clinical findings and the mechanism of injury. Indications for radiographic evaluation are visible haematuria, non-visible haematuria with hypotension, or the presence of major associated injuries. However, patients with a history of rapid deceleration injury or clinical indicators of renal trauma also need immediate imaging to rule out ureteral avulsion or pedicle injury [44]. Patients with non-visible haematuria and no shock after blunt trauma have a low likelihood of concealing significant injury.

Patients with penetrating trauma to the torso have a high incidence of significant renal injuries. If there is such a suspicion on the basis of an entry or exit wound, imaging should be performed, regardless of the degree of haematuria [45].

4.1.2.3.1 Ultrasonography

Ultrasound (US) scans can detect lacerations, but cannot accurately assess their depth and extent. They do not provide functional information about excretion or urine leakage. Ultrasound is useful for the routine follow-up of parenchymal lesions or haematomas and for serial evaluation of stable injuries, as well as for assessment of the resolution of urinomas [39]. Ultrasound can also identify which patients require an aggressive radiological exploration to obtain a diagnosis [46]. Contrast-enhanced sonography is described as more sensitive, but it is not commonly used [47].

4.1.2.3.2 Intravenous pyelography

The use of intravenous pyelography (IVP) is recommended only when it is the only modality available [48]. IVP can be used to establish the presence or absence of one or both kidneys, clearly define the parenchyma and outline the collecting system. The most significant findings are non-function and extravasation. Non-function is a sign of extensive trauma to the kidney, pedicle injury, or a severely shattered kidney. Extravasation of the contrast medium implies a severe degree of trauma, involving the capsule, parenchyma and collecting system. Non-visualisation, contour deformity or contrast extravasation should prompt further radiological evaluation. The sensitivity of IVP is high (> 92%) for all grades of renal injury trauma [49].

4.1.2.3.3 One-shot intraoperative IVP

In unstable patients undergoing emergency laparotomy, IVP may provide information on the presence of a normal functioning contralateral kidney [50]. The technique consists of a bolus intravenous injection of 2 mL/kg of radiographic contrast followed by a single plain film taken after 10 minutes.

4.1.2.3.4 Computed tomography (CT)

CT is the best method for assessment of stable patients. CT is more sensitive and specific than IVP, ultrasonography or angiography, since it accurately defines the location of injuries, easily detects contusions and devitalised segments, visualises the entire retroperitoneum and any associated haematomas, and simultaneously provides a view of both the abdomen and pelvis. It demonstrates superior anatomical details, including the depth and location of lacerations and the presence of associated abdominal injuries, and establishes the presence and location of the contralateral kidney [49, 51].

Intravenous contrast should be administered for renal evaluation. A lack of contrast enhancement is a hallmark of pedicle injury. In cases where this typical finding is not demonstrated, central parahilar haematoma may also raise the possibility of pedicle injury. This sign should be considered even if the parenchyma is well enhanced [52]. Renal vein injury is difficult to diagnose, but the presence on CT of a large haematoma, medial to the kidney and displacing the vasculature, should raise the suspicion. Spiral CT provides fewer artefacts in the examination of patients who cannot co-operate adequately [53]. Three-dimensional post-processing modalities allow assessment of the vascular pedicle by CT angiography and improve the demonstration of complex lacerations of the parenchyma [54]. As injury to the collecting system may be missed

during routine spiral CT, in all cases of suspected trauma, repeat scans of the kidneys should be performed 10-15 minutes after contrast injection [55]. Most blunt ureteral and UPJ injuries can be identified with delayed excretory CT scans [56]. CT scanning is an essential diagnostic modality in patients with gunshot wounds who are being considered for non-operative management [57]. Missed injuries are common, but are mostly minor, and do not alter the patients' clinical course [58].

4.1.2.3.5 Magnetic resonance imaging (MRI)

MRI is not commonly used in this setup, although it is sensitive for the evaluation of blunt renal trauma [59]. MRI requires a longer imaging time and limits access to patients during the examination, and is therefore useful only if CT is not available, in patients with iodine allergy, or in cases where CT findings are equivocal [60].

4.1.2.3.6 Radionuclide scans

Radionuclide scans are generally used or required only in trauma patients with allergy to iodinated contrast material [49].

4.1.2.3.7 Recommendations for radiographic assessment

	GR
Blunt trauma patients with visible haematuria or non-visible haematuria and haemodynamic instability should undergo radiographic evaluation.	A*
Radiographic evaluation is recommended for all patients with a history of rapid deceleration injury and/or significant associated injuries.	B
All patients with or without haematuria after penetrating abdominal or lower thoracic injury require urgent renal imaging.	A*
Ultrasonography alone should not be used to set the diagnosis of renal injury as it cannot provide sufficient information. However, it can be informative during the primary evaluation of multitrauma patients and for the follow-up of recuperating patients.	C
A CT scan with enhancement of intravenous contrast material and delayed images is the gold standard for the diagnosis and staging of renal injuries in haemodynamically stable patients.	A

*Upgraded following panel consensus.

GR = grade of recommendation.

4.1.3 Disease management

4.1.3.1 Conservative management

4.1.3.1.1 Blunt renal injuries

Haemodynamic stability is the primary criterion for the management of all renal injuries. Non-operative management has become the treatment of choice for most renal injuries. In stable patients, this means supportive care with bed-rest and observation. Primary conservative management is associated with a lower rate of nephrectomies, without any increase in the immediate or long-term morbidity [61]. Hospitalisation or prolonged observation for evaluation of possible injury after a normal abdominal CT scan, when combined with clinical judgment, is unnecessary in most cases [62]. All grade 1 and 2 injuries, either due to blunt or penetrating trauma, can be managed non-operatively, whether due to blunt or penetrating trauma. For the treatment of grade 3 injuries, most studies support expectant treatment [63-65].

Most patients with grade 4 and 5 injuries present with major associated injuries, and consequently often undergo exploration and nephrectomy rates [66], although emerging data indicate that many of these patients can be managed safely with an expectant approach [67]. An initially conservative approach is feasible in stable patients with devitalised fragments [68], although these injuries are associated with an increased rate of complications and late surgery [69]. Patients diagnosed with urinary extravasation from solitary injuries can be managed without major intervention with a resolution rate of > 90% [67, 70]. Similarly, unilateral main arterial injuries are normally managed non-operatively in a haemodynamically stable patient with surgical repair reserved for bilateral artery injuries or injuries involving a solitary functional kidney. Conservative management is also advised in the treatment of unilateral complete blunt arterial thrombosis. However, a blunt arterial thrombosis in multiple trauma patients is usually associated with severe injuries and attempts of repair are usually unsuccessful [71].

4.1.3.1.2 Penetrating renal injuries

Penetrating wounds have traditionally been approached surgically. A systematic approach based on clinical, laboratory and radiological evaluation minimises the incidence of negative exploration without increasing

morbidity from a missed injury [72]. Selective non-operative management of abdominal stab wounds is generally accepted following complete staging in stable patients [65, 73]. If the site of penetration by the stab wound is posterior to the anterior axillary line, 88% of such injuries can be managed non-operatively [74]. Stab wounds producing major renal injuries (grade 3 or higher) are more unpredictable and are associated with a higher rate of delayed complications if treated expectantly [75].

Isolated grade 4 injuries represent a unique situation where treatment of the patient is based solely on the extent of the renal injury. Gunshot injuries should be explored only if they involve the hilum or are accompanied by signs of ongoing bleeding, ureteral injuries, or renal pelvis lacerations [76]. Minor low-velocity gunshot and stab wounds may be managed conservatively with an acceptably good outcome [77]. In contrast, tissue damage due to high-velocity gunshot injuries can be more extensive and nephrectomy may be required. Non-operative management of penetrating injuries in selected stable patients is associated with a successful outcome in approximately 50% of stab wounds and up to 40% of gunshot wounds [78-80].

4.1.3.1.3 Interventional radiology

Angiography with selective embolisation is the first-line option in the absence of other indications for immediate open surgery. The main indications for angiography are: embolisation for active haemorrhage, pseudo-aneurysm, and vascular fistulae [81]. Higher grade of renal injury is associated with an increased risk of failure for the first attempt and a need for repeat intervention [82]. However, initial and/or repeat embolisation for high grade injuries prevents nephrectomy in > 75% of these patients. Secondary open surgery after failed embolisation usually results in nephrectomy [83]. Embolisation is 3 times more likely to fail in penetrating trauma. However, with reports that conservative management of penetrating trauma is possible in selected cases, renal embolisation in the setting of failed conservative therapy for penetrating trauma must be critically considered [72]. In cases of severe multitrauma or high operative risk, the main artery may be embolised, either as a definitive treatment or to be followed by interval nephrectomy.

4.1.3.2 Surgical management

4.1.3.2.1 Indications for renal exploration

The need for renal exploration can be predicted by considering the type of injury, transfusion requirements, blood urea nitrogen (BUN), creatinine and injury grade [84]. However, the management of renal injury may also be influenced by the decision to explore or observe associated abdominal injuries [85].

Continuing haemodynamic instability unresponsive to aggressive resuscitation due to renal haemorrhage is an indication for exploration, irrespective of the mode of injury [72, 86]. Other indications include an expanding or pulsatile peri-renal haematoma identified at exploratory laparotomy performed for associated injuries. Persistent extravasation or urinoma are usually managed successfully with endourological techniques. Inconclusive imaging and a pre-existing abnormality or an incidentally diagnosed tumour may require surgery even after minor renal injury [42].

Grade 5 vascular injuries are regarded as an absolute indication for exploration, but parenchymal grade 5 patients who are stable at presentation may be safely treated conservatively [87-90]. In these patients, intervention is predicted by the need for continued fluid and blood resuscitation, peri-renal haematoma size > 3.5 cm and the presence of intravascular contrast extravasation [34].

4.1.3.2.2 Operative findings and reconstruction

The overall exploration rate for blunt trauma is less than 10% [86], and may be even lower as the conservative approach is increasingly adopted [91]. The goal of exploration following renal trauma are control of haemorrhage and renal salvage.

Most series suggest the transperitoneal approach for surgery [92, 93]. Access to the pedicle is obtained either through the posterior parietal peritoneum, which is incised over the aorta, just medial to the inferior mesenteric vein or by bluntly dissecting along the plane of the psoas muscle fascia, adjacent to the great vessels, and directly placing a vascular clamp on the hilum [94]. Stable haematomas detected during exploration for associated injuries should not be opened. Central or expanding haematomas indicate injuries of the renal pedicle, aorta, or vena cava and are potentially life-threatening [95].

In cases with unilateral arterial intimal disruption, repair can be delayed, especially in the presence of a normal contralateral kidney. However, prolonged warm ischaemia usually results in irreparable damage and renal loss. Entering the retroperitoneum and leaving the confined haematoma undisturbed within the perinephric fascia is recommended unless it is violated and cortical bleeding is noted; packing the fossa tightly with laparotomy pads temporarily can salvage the kidney [96]. Haemorrhage can occur while the patient is resuscitated, warmed, and awaits re-exploration, however, careful monitoring is sufficient. A brief period of controlled local urinary extravasation is unlikely to result in a significant adverse event or impact overall recovery. During the next 48 to 72 hours, CT scans can identify injuries and select patients for reconstruction or continued expectant management [97]. Ureteral stenting or nephrostomy diversion should be considered after

delayed reconstruction due to the increased risk of postoperative urinary extravasation.

Renal reconstruction is feasible in most cases. The overall rate of patients who undergo a nephrectomy during exploration is around 13%, usually in patients with penetrating injuries and higher rates of transfusion requirements, haemodynamic instability, and higher injury severity scores [98]. Other intra-abdominal injuries also slightly increase the need for nephrectomy [99]. Mortality is associated with overall severity of the injury and not often a consequence of the renal injury itself [100]. In gunshot injuries caused by a high-velocity bullet, reconstruction can be difficult and nephrectomy is often required [101]. Renorrhaphy is the most common reconstructive technique. Partial nephrectomy is required when non-viable tissue is detected. Watertight closure of the collecting system, if open, is desirable, although closing the parenchyma over the injured collecting system also has good results. If the capsule is not preserved, an omental pedicle flap or peri-renal fat bolster may be used for coverage [102]. The use of haemostatic agents and sealants in reconstruction can be helpful [103]. In all cases, drainage of the ipsilateral retroperitoneum is recommended.

Following blunt trauma, repair of vascular injuries (grade 5) is seldom, if ever, effective [104]. Repair should be attempted in patients with a solitary kidney or bilateral injuries [105], but is not used in the presence of a functioning contralateral kidney [26]. Nephrectomy for main artery injury has outcomes similar to those of vascular repair and does not worsen post-treatment renal function in the short-term.

4.1.3.2.3 Recommendations for conservative management

	GR
Following blunt renal trauma, stable patients should be managed conservatively with close monitoring of vital signs.	B
Isolated grade 1-3 stab and low-velocity gunshot wounds in stable patients, after complete staging, should be managed expectantly.	B
Indications for renal exploration include: <ul style="list-style-type: none">• haemodynamic instability;• exploration for associated injuries;• expanding or pulsatile peri-renal haematoma identified during laparotomy;• grade 5 vascular injury.	B
Radiological embolisation is indicated in patients with active bleeding from renal injury, but without other indications for immediate abdominal operation.	B
Intraoperatively, renal reconstruction should be attempted once haemorrhage is controlled and there is sufficient viable renal parenchyma.	B

GR = grade of recommendation.

4.1.4 Follow-up

The risk of complications in patients who have been treated conservatively increases with injury grade. Repeat imaging 2-4 days after trauma minimises the risk of missed complications, especially in grade 3-5 blunt injuries [106]. The usefulness of frequent CT scanning after injury has never been satisfactorily proved. CT scans should always be performed on patients with fever, unexplained decreased haematocrit or significant flank pain. Repeat imaging can be safely omitted for patients with grade 1-4 injuries as long as they remain clinically well [107].

Nuclear scans are useful for documenting and tracking functional recovery following renal reconstruction [108]. Follow-up should involve physical examination, urinalysis, individualised radiological investigation, serial blood pressure measurement and serum determination of renal function [68]. A decline in renal function correlates directly with injury grade; this is independent of the mechanism of injury and the method of management [109, 110]. Follow-up examinations should continue until healing is documented and laboratory findings have stabilised, although checking for latent renovascular hypertension may need to continue for years [111]. In general, the literature is inadequate on the subject of the long-term consequences of renal tissue trauma.

4.1.4.1 Complications

Early complications, occurring less than 1 month after injury, include bleeding, infection, perinephric abscess, sepsis, urinary fistula, hypertension, urinary extravasation and urinoma. Delayed complications include bleeding, hydronephrosis, calculus formation, chronic pyelonephritis, hypertension, arteriovenous fistula, hydronephrosis and pseudo-aneurysms. Delayed retroperitoneal bleeding may be life-threatening and selective angiographic embolisation is the preferred treatment [112]. Perinephric abscess formation is best managed by percutaneous drainage, although open drainage may sometimes be required. Percutaneous management of complications may pose less risk of renal loss than re-operation, when infected tissues make reconstruction difficult [86].

Renal trauma is a rare cause of hypertension, and is mostly observed in young men. The frequency of posttraumatic hypertension is estimated to be less than 5% [113, 114]. Hypertension may occur acutely as a result of external compression from peri-renal haematoma (Page kidney), or chronically due to compressive scar formation. Renin-mediated hypertension may occur as a long-term complication; aetiologies include renal artery thrombosis, segmental arterial thrombosis, renal artery stenosis (Goldblatt kidney), devitalised fragments and arteriovenous fistulae (AVF). Arteriography is informative in cases of post-traumatic hypertension. Treatment is required if the hypertension persists and could include medical management, excision of the ischaemic parenchymal segment, vascular reconstruction, or total nephrectomy [115].

Urinary extravasation after reconstruction often subsides without intervention as long as ureteral obstruction and infection are not present. Ureteral retrograde stenting may improve drainage and allow healing [116]. Persistent urinary extravasation from an otherwise viable kidney after blunt trauma often responds to stent placement and/or percutaneous drainage as necessary [117].

Arteriovenous fistulae usually present with delayed onset of significant haematuria, most often after penetrating trauma. Percutaneous embolisation is often effective for symptomatic AVF, but larger ones may require surgery [118]. Post-procedural complications include infection, sepsis, urinary fistula, and renal infarction [119]. The development of pseudo-aneurysm is a rare complication following blunt trauma. In numerous case reports, transcatheter embolisation appears to be a reliable minimally invasive solution [120]. Acute renal colic from a retained missile has been reported, and can be managed endoscopically if possible [121].

4.1.4.2 Recommendations for follow-up

	GR
Repeat imaging is recommended in cases of fever, flank pain, or falling haematocrit.	B
Nuclear scintigraphy is useful for documenting functional recovery.	C
First follow-up should be approximately 3 months after major renal injury with hospitalisation. Each follow-up should include: physical examination, urinalysis, individualised radiological investigation, serial blood pressure measurement and renal function tests.	C
Medical management and minimally invasive techniques should be the first choice for the management of complications.	C
Long-term follow-up should be decided on a case-by-case basis.	C

GR = grade of recommendation.

4.1.5 Renal injury in the multitrauma patient

Approximately 8-10% of blunt and penetrating abdominal injuries involve the kidneys. The incidence of associated injury in penetrating renal trauma ranges from 77% to 100%. Gunshot wounds are associated with adjacent organ injury more often than stab wounds. Most patients with penetrating renal trauma have associated adjacent organ injuries that may complicate treatment. In the absence of an expanding haematoma with haemodynamic instability, associated multiorgan injuries do not increase the risk of nephrectomy [29]. Blunt and penetrating injuries contribute equally to combined renal and pancreatic injury. Renal preservation is achieved in most patients, and the complication rate is 15% [122]. A similar rate of complications (16%) is reported in patients with simultaneous colon and renal injury [123]. Renal injuries seem to be rare in patients with blunt chest trauma [89].

4.1.5.1 Recommendations for multitrauma patient management

	GR
Multitrauma patients with associated renal injuries should be evaluated on the basis of the most significant injury.	C
In cases where surgical intervention is chosen, all associated abdominal injuries should be managed where appropriate simultaneously.	C
When deciding on conservative management all injuries should be considered independently.	C

GR = grade of recommendation.

4.1.6 Iatrogenic renal injuries

4.1.6.1 Introduction

Iatrogenic renal trauma (IRT) is rare, but can lead to significant morbidity.

4.1.6.2 Incidence and aetiology

The commonest causes of IRT are listed in Table 4.1.2 [124].

Table 4.1.2: Incidence and aetiology of commonest iatrogenic renal trauma during various procedures

Procedure	Haemorrhage	AVF	Pseudoaneurysm	Renal pelvis injury	Aortocaliceal fistula	Foreign body
Nephrostomy	+		+	+		
Biopsy	+ (0.5-1.5%)	+	+ (0.9%)			
PCNL	+	+		+		
Laparoscopic surgery (oncology)	+					
Open surgery (oncology)	+		+ (0.43%)			+
Transplantation	+	+	+		+	
Endopyelotomy	+			+		+
Endovascular procedure	+ (1.6%)					

AVF = arteriovenous fistulae; PCNL = percutaneous nephrolithotomy.

Large haematomas after biopsy (0.5-1.5%) are caused by laceration or arterial damage [125]. Renal artery and intraparenchymal pseudo-aneurysms (0.9%) may be caused by percutaneous biopsy, nephrostomy, and partial nephrectomy (0.43%) [126]. In PCNL, haemorrhage is the most dangerous IRT, especially when punctures are too medial or directly entering the renal pelvis. Other injuries include AVF or a tear in the pelvicaliceal system.

Iatrogenic renal injuries associated with renal transplantation include AVF, intrarenal pseudo-aneurysms, arterial dissection and arteriocaliceal fistulas. Pseudo-aneurysm is a rare complication of allograft biopsy. Although the overall complication rate following biopsy in transplanted kidneys is 9% (including haematoma, AVF, visible haematuria and infection), vascular complications requiring intervention account for 0.2-2.0% [127]. Predisposing factors include hypertension, renal medullary disease, central biopsies, and numerous needle passes [128]. Arteriovenous fistulae and pseudo-aneurysms can occur in 1-18% of allograft biopsies [125].

Extrarenal pseudo-aneurysms after transplantation procedures generally occur at the anastomosis, in association with local or haematogenous infection. Arterial dissection related to transplantation is rare and presents in the early postoperative period [129].

Iatrogenic renal trauma associated with endopyelotomy is classified as major (vascular injury), and minor (urinoma) [130]. Patients undergoing cryoablation for small masses via the percutaneous or the laparoscopic approach may have asymptomatic perinephric haematoma and self-limited urine leakage.

Vascular injury is a rare complication (1.6%) of endovascular interventions in contrast to patients with surgical injuries. The renal vessels are vulnerable mainly during oncological procedures [131]. Renal foreign bodies, with retained sponges or wires during open or endourological procedures, are uncommon.

4.1.6.3 Diagnosis

Haematuria is common after insertion of nephrostomies, but massive retroperitoneal haemorrhage is rare. Following percutaneous biopsy, AVF may occur with severe hypertension. A pseudo-aneurysm should be suspected if the patient presents with flank pain and decreasing haematocrit, even in the absence of haematuria.

During PCNL, acute bleeding may be caused by injury to the anterior or posterior segmental arteries, or late postoperative bleeding may be caused by interlobar and lower-pole arterial lesions, AVF and post-traumatic aneurysms [132]. Duplex ultrasound and CT angiography can be used to diagnose vascular injuries. A close watch on irrigation fluid input and output is required to ensure early recognition of fluid extravasation. Intra-operative evaluation of serum electrolytes, acid-base status, oxygenation, and monitoring of airway pressure are good indicators of this complication.

In arterial dissection related to transplantation, symptoms include anuria and a prolonged dependence on dialysis. Doppler ultrasound can demonstrate compromised arterial flow. Dissection can lead to thrombosis of the renal artery and/or vein.

After angioplasty and stent-graft placement in the renal artery, during which wire or catheters may enter the parenchyma and penetrate through the capsule, possible radiological findings include AVF, pseudo-aneurysm, arterial dissection and contrast extravasation. Common symptoms of pseudo-aneurysms are flank

pain and visible haematuria within 2 or 3 weeks after surgery [133]. Transplant AVF and pseudo-aneurysms may be asymptomatic or may cause visible haematuria or hypovolemia due to shunting and the 'steal' phenomenon, renal insufficiency, hypertension, and high output cardiac failure.

Patients with extrarenal pseudo-aneurysms (post-transplantation) may present with infection/bleeding, swelling, pain and intermittent claudication. Doppler ultrasound findings for AVFs include high-velocity, low-resistance, spectral waveforms, with focal areas of disorganised colour flow outside the normal vascular borders, and possibly a dilated vein [134]. Pseudo-aneurysms appear on ultrasound as anechoic cysts, with intracystic flow on colour Doppler.

Potential complications of retained sponges include abscess formation, fistula formation to the skin or intestinal tract, and sepsis. Retained sponges may look like pseudo-tumours or appear as solid masses. MRI clearly shows the characteristic features [135]. Absorbable haemostatic agents may also produce a foreign-body giant cell reaction, but the imaging characteristics are not specific. Retained stents, wires, or fractured Acucise cutting wires may also present as foreign bodies and can serve as a nidus for stone formation [136].

4.1.6.4 Management

If a nephrostomy catheter appears to transfix the renal pelvis, significant arterial injury is possible. The misplaced catheter should be withdrawn and embolisation may rapidly arrest the haemorrhage. CT can also successfully guide repositioning of the catheter into the collecting system [137]. Small subcapsular haematomas after insertion of nephrostomies resolve spontaneously, while AVF are best managed by embolisation. AVF and pseudo-aneurysms after biopsy are also managed by embolisation [138].

During PCNL, bleeding can be venous or arterial. In major venous trauma with haemorrhage, patients with concomitant renal insufficiency can be treated without open exploration or angiographic embolisation using a Council-tip balloon catheter [139]. In the case of profuse bleeding at the end of a PCNL, conservative management is usually effective. The patient should be placed in the supine position, clamping the nephrostomy catheter and forcing diuresis. Superselective embolisation is required in less than 1% of cases and has proved effective in more than 90% [140]. Short-term deleterious effects are more pronounced in patients with a solitary kidney, but long-term follow-up shows functional and morphological improvements [141]. Termination of PCNL if the renal pelvis is torn or ruptured is a safe choice. Management requires close monitoring, placement of an abdominal or retroperitoneal drain and supportive measures [142]. Most surgical venous injuries include partial lacerations that can be managed with various techniques, such as venorrhaphy, patch angioplasty with autologous vein, or an expanded polytetrafluoroethylene (ePTFE) graft [143]. If conservative measures fail in cases of pseudo-aneurysm and clinical symptoms or a relevant decrease in haemoglobin occurs, transarterial embolisation should be considered [144]. As the success rate is similar for initial and repeat interventions, a repeat intervention is justified when the clinical course allows this [82].

Traditionally, patients with postoperative haemorrhage following intra-abdominal laparoscopic surgery of the kidney require laparotomy. Pseudo-aneurysms and AVF are uncommon after minimally invasive partial nephrectomy, but can lead to significant morbidity. Temporary haemostasis occurs with coagulation and/or tamponade, but later degradation of the clot, connection with the extravascular space, and possible fistula formation within the collecting system may develop. Patients typically present with visible haematuria, even though they may also experience flank pain, dizziness and fever. Embolisation is the reference standard for both diagnosis and treatment in the acute setting, although CT can be used if the symptoms are not severe and/or the diagnosis is ambiguous. Reports have described good preservation of renal function after embolisation [145].

Endoluminal management after renal transplantation consists of stabilising the intimal flap with stent placement. Embolisation is the treatment of choice for a symptomatic transplant AVF or enlarging pseudo-aneurysm [146]. Superselective embolisation with a coaxial catheter and metallic coils helps to limit the loss of normal functioning graft tissue [147]. Failure of embolisation is associated with a high nephrectomy rate. The long-term outcome depends on the course of the transplant and the amount of contrast medium used during the procedure.

Surgical treatment for AVF consists of partial or total nephrectomy or arterial ligation, which results in loss of part of the transplant or the entire transplant. To date, surgery has been the main approach in the treatment of renal vascular injuries. In patients with retroperitoneal haematoma, AVF, and haemorrhagic shock, interventional therapy is associated with a lower level of risk compared to surgery [148]. Renal arteriography followed by selective embolisation can confirm the injury. In injuries during angioplasty and stent-graft placement, transcatheter embolisation is the first choice of treatment [149]. The treatment for acute iatrogenic rupture of the main renal artery is balloon tamponade. If this fails, immediate availability of a stent graft is vital [150]. The true nature of lesions caused by foreign bodies is revealed after exploration.

4.1.6.5 Statements and recommendations for iatrogenic renal injuries

Statements	LE
Iatrogenic renal injuries are procedure-dependent (1.8-15%).	3
Significant injury requiring intervention is rare.	3
The most common injuries are vascular.	3
Renal allografts are more susceptible.	3
Injuries occurring during surgery are rectified immediately.	3
Symptoms suggestive of a significant injury require investigation.	3

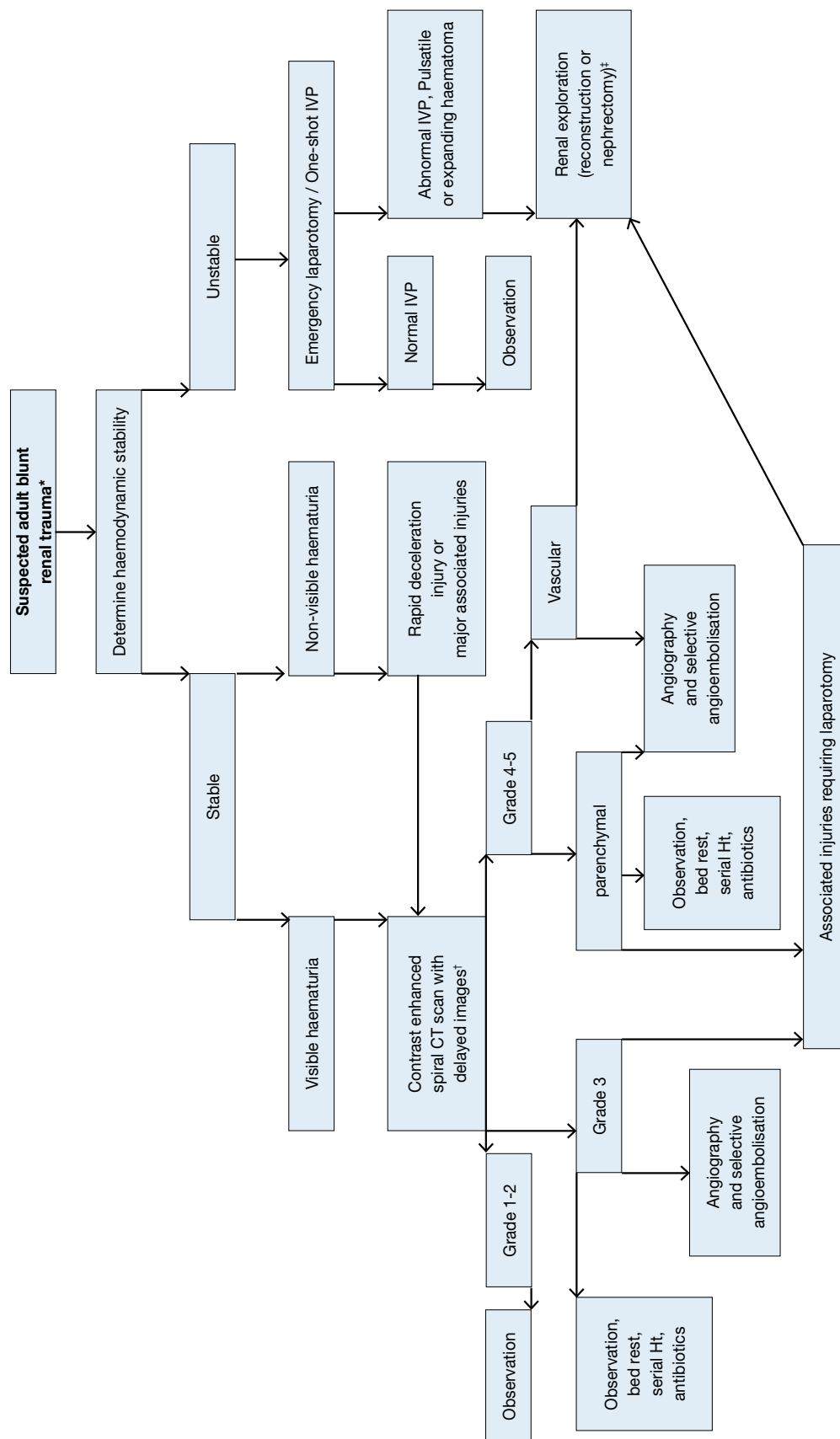
Recommendations	GR
Patients with minor injuries should be treated conservatively.	B
Severe or persistent injuries require intervention with embolisation.	B
In stable patients, a second embolisation should be considered in case of failure.	C

GR = grade; LE = level of evidence.

4.1.7 Algorithms

Figures 4.1.1 and 4.1.2 show the suggested treatment of blunt and penetrating renal injuries in adults.

Figure 4.1.1: Evaluation of blunt renal trauma in adults

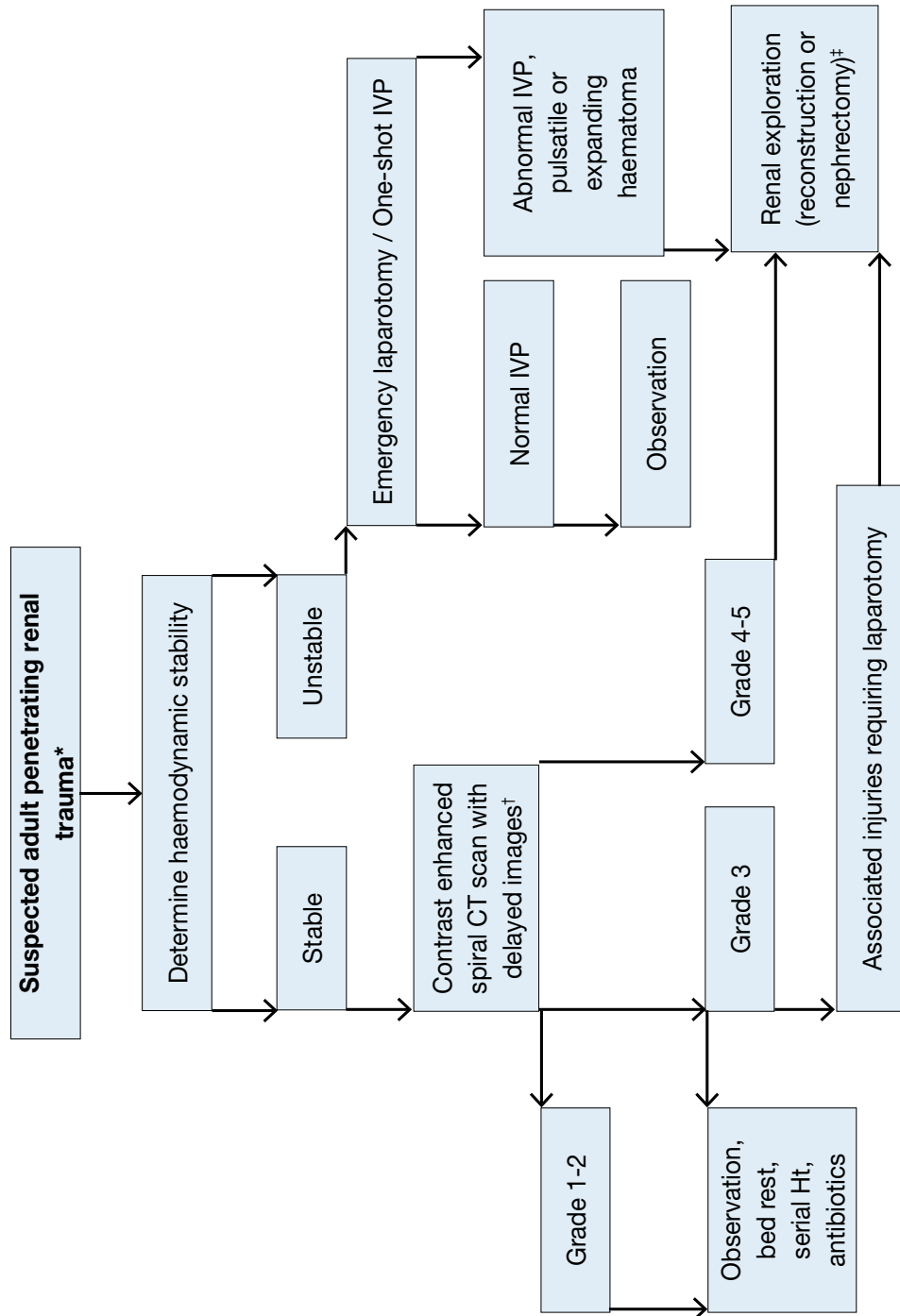


* Suspected renal trauma results from reported mechanism of injury and physical examination.

† Renal imaging: CT scans are the gold standard for evaluating blunt and penetrating renal injuries in stable patients. In settings where CT is not available, the urologist should rely on other imaging modalities (IVP, angiography, radiographic scintigraphy, MRI).

‡ Renal exploration: Although renal salvage is a primary goal for the urologist, decisions concerning the viability of the organ and the type of reconstruction are made during the operation.

Figure 4.1.2: Evaluation of penetrating renal trauma in adults



* Suspected renal trauma results from reported mechanism of injury and physical examination.

† Renal imaging: CT scans are the gold standard for evaluating blunt and penetrating renal injuries in stable patients. In settings where CT is not available, the urologist should rely on other imaging modalities (IVP, angiography, radiographic scintigraphy, MRI).

‡ Renal exploration: Although renal salvage is a primary goal for the urologist, decisions concerning the viability of the organ and the type of reconstruction are made during the operation.

4.2 Ureteral Trauma

4.2.1 Incidence

Trauma to the ureters is relatively rare because they are protected from injury by their small size, mobility, and the adjacent vertebrae, bony pelvis, and muscles. Iatrogenic trauma is the commonest cause of ureteral injury. It is seen in open, laparoscopic or endoscopic surgery and is often missed intraoperatively. Any trauma to the ureter may result in severe sequelae.

4.2.2 **Epidemiology, aetiology, and pathophysiology**

Overall, ureteral trauma accounts for 1-2.5% of urinary tract trauma [13, 151-153], and even higher rates in modern combat injuries [154]. Penetrating external ureteral trauma, mainly caused by gunshot wounds, dominates most of the modern series, both civilian and military [13, 151, 155]. About one-third of cases of external trauma to the ureters are caused by blunt trauma, mostly road traffic injuries [152, 153].

Ureteral injury should be suspected in all cases of penetrating abdominal injury, especially gunshot wounds, because it occurs in 2-3% of cases [151]. It should also be suspected in blunt trauma with deceleration mechanism, when the renal pelvis can be torn away from the ureter [151]. In external ureteral injuries, their distribution along the ureter varies between series, but it is more common in the upper ureter [13, 152, 153].

Iatrogenic ureteral trauma can result from various mechanisms: ligation or kinking with a suture, crushing from a clamp, partial or complete transection, thermal injury, or ischaemia from devascularisation [155-157]. It usually involves damage to the lower ureter [151, 155, 156, 158]. Gynaecological operations are the commonest cause of iatrogenic trauma to the ureters (Table 4.2.1), but it may also occur in colorectal operations, especially abdominoperineal resection and low anterior resection [159]. The incidence of urological iatrogenic trauma has decreased in the last 20 years [155, 160] due to improvements in technique, instruments and surgical experience.

Risk factors for iatrogenic trauma include conditions that alter the normal anatomy, e.g. advanced malignancy, prior surgery or irradiation, diverticulitis, endometriosis, anatomical abnormalities, and major haemorrhage [155, 159, 161]. Occult ureteral injury occurs more often than reported and not all injuries are diagnosed intraoperatively. In gynaecological surgery, if routine intraoperative cystoscopy is used, the detection rate of ureteral trauma is five times higher than usually reported [161, 162].

Table 4.2.1: Incidence of ureteral injury in various procedures

Procedure	Percentage %
Gynaecological [158, 162-164]	
Vaginal hysterectomy	0.02 – 0.5
Abdominal hysterectomy	0.03 – 2.0
Laparoscopic hysterectomy	0.2 – 6.0
Urogynaecological (anti-incontinence/prolapse)	1.7 – 3.0
Colorectal [157, 162, 165]	0.15 - 10
Ureteroscopy [160]	
Mucosal abrasion	0.3 – 4.1
Ureteral perforation	0.2 – 2.0
Intussusception/avulsion	0 – 0.3
Radical Prostatectomy [166]	
Open Retropubic	0.05 – 1.6
Robot-Assisted	0.05 – 0.4

4.2.3 **Diagnosis**

The diagnosis of ureteral trauma is challenging, therefore, a high index of suspicion should be maintained. In penetrating external trauma, it is usually made intraoperatively during laparotomy [167], while it is delayed in most blunt trauma and iatrogenic cases [155, 158, 168].

4.2.3.1 **Clinical diagnosis**

External ureteral trauma usually accompanies severe abdominal and pelvic injuries. Penetrating trauma is usually associated with vascular and intestinal injuries, while blunt trauma is associated with damage to the pelvic bones and lumbosacral spine injuries [152, 153]. Haematuria is an unreliable poor indicator of ureteral injury, as it is present in only 50-75% of patients [151, 155, 169].

Iatrogenic injury may be better noticed during the primary procedure, when intravenous dye (e.g. indigo carmine) is injected to exclude ureteral injury. It is usually noticed later, when it is discovered by subsequent evidence of upper tract obstruction, urinary fistulae formation or sepsis. The following clinical signs are characteristic of delayed diagnosis: flank pain, urinary incontinence, vaginal or drain urinary leakage, haematuria, fever, uraemia or urinoma. When the diagnosis is missed, the complication rate increases [151, 154, 168]. Early recognition facilitates immediate repair and provides better outcome [164, 170].

4.2.3.2 Radiological diagnosis

Extravasation of contrast medium in computerised tomography (CT) is the hallmark sign of ureteral trauma. However, hydronephrosis, ascites, urinoma or mild ureteral dilation are often the only signs. In unclear cases, a retrograde or antegrade urography is the gold standard for confirmation [155]. Intravenous pyelography, especially one-shot IVP, is unreliable in diagnosis, as it is negative in up to 60% of patients [151, 155].

4.2.4 Prevention of iatrogenic trauma

The prevention of iatrogenic trauma to the ureters depends upon the visual identification of the ureters and careful intraoperative dissection in their proximity [155-157]. The use of prophylactic preoperative ureteral stent insertion assists in visualisation and palpation and is often used in complicated cases (about 4% in a large cohort [171]). It is probably also advantageous in making it easier to detect ureteral injury [156]; however, it does not decrease the rate of injury [155]. Apart from its evident disadvantages (potential complications and cost), a stent may alter the location of the ureter and diminish its flexibility [156, 165]. Routine prophylactic stenting is generally not cost-effective [156]. Another form of secondary prevention is intraoperative cystoscopy after intravenous dye injection, which can provide confirmation of ureteral patency [158]. Routine cystoscopy has minimal risks and can markedly increase the rate of ureteral injury detection [162].

4.2.5 Management

Management of a ureteral trauma depends on many factors concerning the nature, severity and location of the injury. Immediate diagnosis of a ligation injury during an operation can be managed by de-ligation and stent placement. Partial injuries can be repaired immediately with a stent or urine diversion by a nephrostomy tube. Stenting is helpful because it provides canalisation and may decrease the risk of stricture [155]. On the other hand, its insertion has to be weighed against potentially aggravating the severity of the ureteral injury. Immediate repair of ureteral injury is usually advisable. However, in cases of unstable trauma patients, a 'damage control' approach is preferred with ligation of the ureter, diversion of the urine (e.g. by a nephrostomy), and a delayed definitive repair [172]. Injuries that are diagnosed late are usually treated first by a nephrostomy tube with or without a stent [155]. Retrograde stenting is often unsuccessful in this setting.

The endourological treatment of small ureteral fistulae and strictures is safe and effective in selected cases [173], but an open surgical repair is often necessary. The basic principles for any surgical repair of a ureteral injury are outlined in Table 4.2.2. Wide debridement is highly recommended for gunshot wound injuries due to the 'blast effect' of the injury.

4.2.5.1 Proximal and mid-ureteral injury

Injuries shorter than 2-3 cm can usually be managed by a primary uretero-ureterostomy [151]. When this approach is not feasible, a uretero-calycostomy should be considered. In extensive ureteral loss, a transuretero-ureterostomy is a valid option, where the proximal stump of the ureter is transposed across the midline and anastomosed to the contralateral ureter. The reported stenosis rate is 4% and intervention or revision occur in 10% of cases [174].

4.2.5.2 Distal ureteral injury

Distal injuries are best managed by ureteral reimplantation (ureteroneocystostomy) because the primary trauma usually jeopardises the blood supply to the distal ureter. The question of refluxing vs. non-refluxing ureteral reimplantation remains unresolved in the literature. The risk for clinically significant reflux should be weighed against the risk for ureteral obstruction.

A psoas hitch between the bladder and the ipsilateral psoas tendon is usually needed to bridge the gap and to protect the anastomosis from tension. The contralateral superior vesical pedicle may be divided to improve bladder mobility. The reported success rate is very high (97%) [174]. In extensive mid-lower ureteral injury, the large gap can be bridged with a tubularised L-shaped bladder flap (Boari flap). It is a time-consuming operation and not usually suitable in the acute setting. The success rate is reported to be 81-88% [175].

4.2.5.3 Complete ureteral injury

A longer ureteral injury can be replaced using a segment of the intestines, usually the ileum (ileal interposition graft). This should be avoided in patients with impaired renal function or known intestinal disease. Follow-up should include serum chemistry to diagnose hyperchloremic metabolic acidosis [176]. The long-term complications include anastomotic stricture (3%) and fistulae (6%) [177]. In cases of extensive ureteral loss or after multiple attempts of ureteral repair, the kidney can be relocated to the pelvis (autotransplantation). The renal vessels are anastomosed to the iliac vessels and a ureteral reimplantation is performed [178].

Table 4.2.2: Principles of surgical repair of ureteral injury

<ul style="list-style-type: none"> • Principles of surgical repair of ureteral injury • Debridement of necrotic tissue • Spatulation of ureteral ends • Watertight mucosa-to-mucosa anastomosis with absorbable sutures • Internal stenting • External drain • Isolation of injury with peritoneum or omentum
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Table 4.2.3: Reconstruction option by site of injury

Site of injury	Reconstruction options
Upper ureter	Uretero-ureterostomy
	Transuretero-ureterostomy
	Uretero-calycostomy
Mid ureter	Uretero-ureterostomy
	Transuretero-ureterostomy
	Ureteral reimplantation and a Boari flap
Lower ureter	Ureteral reimplantation
	Ureteral reimplantation with a psoas hitch
Complete	Ileal interposition graft
	Autotransplantation

4.2.6 Statements and recommendations for ureteral trauma

Statements	LE
Iatrogenic ureteral trauma gives rise to the commonest cause of ureteral injury.	3
Gunshot wounds account for the majority of penetrating ureteral injuries, while motor vehicle accidents account for most of blunt injuries.	3
Ureteral trauma usually accompanies severe abdominal and pelvic injuries.	3
Haematuria is an unreliable poor indicator of ureteral injury.	3
The diagnosis of ureteral trauma is often delayed.	2
Preoperative prophylactic stents do not prevent ureteral injury, but may assist in its detection.	2
Endourological treatment of small ureteral fistulae and strictures is safe and effective.	3
Major ureteral injury requires ureteral reconstruction following temporary urinary diversion.	3

Recommendations	GR
Visual identification of the ureters and meticulous dissection in their vicinity are mandatory to prevent ureteral trauma during abdominal and pelvic surgery.	A*
High level of suspicion for ureteral injury should be maintained in all abdominal penetrating trauma, and in deceleration-type blunt trauma.	A*
Preoperative prophylactic stents do not prevent ureteral injury and therefore it is recommended to be used in selected cases (based on risk factors and surgeon's experience).	B

*Upgraded following panel consensus.

GR= grade of recommendation; LE = level of evidence.

4.3 Bladder Trauma

4.3.1 Classification

A classification of bladder trauma can be made based on mode of action (Table 4.3.1).

Location of the bladder injury is important as it will guide further management:

- Intraperitoneal
- Extraperitoneal
- Combined intra-extraperitoneal

Table 4.3.1: Classification of bladder trauma based on mode of action

Non-iatrogenic trauma
• blunt
• penetrating
Iatrogenic trauma
• external
• internal
• foreign body

4.3.2 **Epidemiology, aetiology and pathophysiology**

4.3.2.1 *Non-iatrogenic trauma*

Motor vehicle traffic collisions are the most common cause of blunt bladder injury, followed by falls, industrial trauma/pelvic crush injuries and blows to the lower abdomen [14, 179, 180]. Between 60-90% of patients with bladder injuries caused by blunt trauma have associated pelvic fractures, and 44% of patients with bladder injuries have at least one other intra-abdominal injury [181]. Pelvic fractures are associated with bladder injuries in only 3.6% of cases [14]. The majority of ruptures are extraperitoneal, followed by intraperitoneal ruptures and combined intra- and extra-peritoneal ruptures [179, 181]. A combination of bladder and urethral injury is present in 4.1-15% of cases [14, 179].

Extraperitoneal ruptures are almost always associated with pelvic fractures [180]. The injury is usually caused by distortion of the pelvic ring, with shearing of the anterolateral bladder wall near the bladder base (at its fascial attachments), or by a 'counter-coup' that bursts opposite the fracture site. Occasionally, the bladder is directly perforated by a sharp bony fragment [179, 182]. The highest risk of bladder injury was found in disruptions of the pelvic circle with displacement > 1 cm, diastasis of the pubic symphysis > 1 cm and fractures of the rami pubis [14, 183]. An isolated acetabular fracture is not likely to be associated with bladder injury [183].

Intraperitoneal ruptures are caused by a sudden rise in intravesical pressure, secondary to a blow to the pelvis or lower abdomen. The bladder dome is the weakest point of the bladder and ruptures will usually occur there [179]. A full bladder is a risk factor for intraperitoneal ruptures [179].

Penetrating injuries, mainly gunshot wounds, are rare in the civilian setting [184].

4.3.2.2 *Iatrogenic bladder trauma (IBT)*

The bladder is the urological organ that most often suffers iatrogenic injury [185]. Table 4.3.2 shows the incidence of IBT during various procedures.

Table 4.3.2: Incidence of IBT during various procedures

Procedure	Percentage (%)
External	
<i>Obstetrics</i>	
Caesarean delivery [186, 187]	0.0016-0.94
<i>Gynaecology</i>	
Laparoscopic sterilisation [179]	0.02
Diagnostic laparoscopy [179]	0.01
Laparoscopic hysterectomy [188, 189] (benign)	0.5-2.0
Vaginal hysterectomy [188, 189] (benign)	0.44-6.3
Abdominal hysterectomy [188, 189] (benign)	0.73-2.5
<i>General surgery</i>	
Inguinal canal surgery [179, 190]	0.08-0.3
Abdominal cytoreductive surgery [191]	4.5
<i>Urology</i>	
Retropubic male sling [192]	8.0-50
Laparoscopic sacrocolpopexy [193]	1.9
Burch colposuspension [194, 195]	1.0-1.2
Midurethral sling (Transobturator route) [194, 196]	0-2.4
Midurethral sling (Retropubic route) [194, 196]	3.2-8.5
Pubovaginal sling [194]	2.8
Transvaginal mesh surgery [197, 198]	1.5-3.5

Anterior colporrhaphy [198]	0.5
TURB [199, 200]	3.5-58
TURP [179]	0.01

TURB = transurethral resection of the bladder; TURP = transurethral resection of the prostate.

External IBT occurs most often during obstetric and gynaecological procedures, followed by general surgical and urological interventions [185]. Main risk factors are previous surgery, inflammation and malignancy [185].

Internal IBT mainly occurs during transurethral resection of bladder tumour (TURB). Reported risk factors are larger tumours, older age, pretreated bladders (previous TURB, intravesical instillations) and location at the bladder dome [201, 202]. Monopolar TURB at the lateral wall with inadequate muscle relaxation and subsequent risk of stimulation of the obturator nerve, also increases the risk of perforation. Perforations requiring intervention are rare (0.16-0.57%) [201]. Extraperitoneal perforations are more frequent than intraperitoneal perforations [202, 203].

Intravesical foreign bodies include:

- Retained parts of endourologic equipment such as resectoscopes, ureteric stents or bladder catheters;
- Forgotten pieces of surgical gauze, sutures or staples used in pelvic procedures [204, 205];
- An unrecognised perforation or erosion of mesh used for correction of urinary incontinence or pelvic organ prolapse [204].

4.3.3 **Diagnostic evaluation**

4.3.3.1 *General evaluation*

The cardinal sign of bladder injury is visible haematuria [179, 180].

Non-iatrogenic bladder injury is strongly correlated with a combination of pelvic fracture and visible haematuria [206], and this combination is an absolute indication for further imaging [179, 206] (LE: 3). However, approximately 5-15% of patients with bladder rupture only have non-visible haematuria [183]. Existing data do not support lower urinary tract imaging in all patients with pelvic fracture or non-visible haematuria alone. In visible haematuria without pelvic fracture, non-visible haematuria with pelvic fracture and isolated non-visible haematuria, the decision for further imaging should be based on the presence of other clinical signs and symptoms and the site of maximal trauma [179]. Clinical signs and symptoms are summarised in Table 4.3.3.

Table 4.3.3: Clinical signs and symptoms of bladder injury

Signs and symptoms	Remarks
Haematuria [179, 180]	Visible = cardinal sign
Inability to void [179, 207]	
Abdominal tenderness [180]	
Suprapubic bruising [179, 207]	
Abdominal distension [179, 207]	In the case of urinary ascites
Swelling of scrotum, perineum, abdominal wall and/or thighs [179]	
Uraemia and elevated creatinine level [179]	Intraperitoneal rupture => reabsorption of urea nitrogen and creatinine
Entrance/exit wounds at lower abdomen, perineum or buttocks [184, 207]	In penetrating injuries

Signs of external IBT are extravasation of urine, visible laceration, clear fluid in the surgical field, appearance of the bladder catheter, and blood and/or gas in the urine bag during laparoscopy [179, 186]. Direct inspection is the most reliable method of assessing bladder integrity [185]. Intravesical instillation of methylene blue may be helpful [186]. If bladder perforation is close to the trigone, the ureteric orifices should be inspected [179, 185].

Internal IBT is suggested by cystoscopic identification of fatty tissue, a dark space between detrusor muscle fibres, or the visualisation of bowel [199]. Signs of major perforation are the inability to distend the bladder, a low return of irrigation fluid, and abdominal distension [208].

An IBT not recognised during surgery is more likely with laparoscopic procedures [185]. Clinical signs and symptoms include haematuria, abdominal pain, abdominal distension, ileus, peritonitis, sepsis, urine leakage from the wound, decreased urinary output, and increased serum creatinine [179, 185].

Symptoms of an intravesical foreign body include dysuria, recurrent urinary tract infection, frequency, urgency, haematuria, and perineal/pelvic pain [204]. Bladder calculi usually develop once the foreign body has been present > 3 months [204, 209].

4.3.3.2 Supplemental evaluation

4.3.3.2.1 Cystography

Cystography is the preferred diagnostic modality for non-iatrogenic bladder injury and for a suspected IBT in the post-operative setting [182, 185]. Both plain and CT cystography have a comparable sensitivity (90-95%) and specificity (100%) [180, 210]. In addition, CT cystography can diagnose other injuries or causes of abdominal pain [179].

Cystography must be performed using retrograde filling of the bladder with a minimum volume of 350 mL of dilute contrast material [182].

With intraperitoneal extravasation, free contrast medium is visualised in the abdomen, highlighting bowel loops and/or outlining abdominal viscera such as the liver [179, 211]. Extraperitoneal bladder injury is associated with flame-shaped areas of contrast extravasation in the perivesical soft tissues [179].

4.3.3.2.2 Cystoscopy

Cystoscopy is the preferred method for detection of intra-operative bladder injuries, as it may directly visualise the laceration. Cystoscopy can localise the lesion in relation to the position of the trigone and ureteral orifices [211]. A lack of bladder distension during cystoscopy suggests a large perforation.

Routine cystoscopy is advised at the end of a hysterectomy and every major gynaecological procedure [189]. Cystoscopy is recommended to detect perforation of the bladder (or urethra) following suburethral sling operations by the retropubic route [195, 212]. Routine cystoscopy after sling insertion through the obturator route is controversial because bladder injuries are rare but not impossible [195, 212]. Cystoscopy after transvaginal mesh procedures is preferable, but not mandatory [213].

Cystoscopy is preferred to diagnose a foreign body [205, 209].

4.3.3.2.3 Excretory phase of CT or IVP

Passive bladder filling by clamping the urinary catheter during the excretory phase of CT or IVP is not sufficient to exclude bladder injury [179, 182].

4.3.3.2.4 Ultrasound

Demonstration of intraperitoneal fluid or an extraperitoneal collection suggests intraperitoneal or extraperitoneal perforation, respectively. However, ultrasound alone is insufficient in the diagnosis of bladder trauma [179].

4.3.4 Disease management

4.3.4.1 Conservative management

Conservative treatment comprises clinical observation, continuous bladder drainage and antibiotics prophylaxis [179, 202]. This is the standard treatment for an uncomplicated extraperitoneal injury due to blunt trauma, after TURB or after other operations in which the injury was not recognised during surgery [179, 202, 207].

It is an option for an uncomplicated intraperitoneal injury after TURB or not recognised during surgery, but only in the absence of peritonitis and ileus [200, 211]. In addition to conservative treatment, placement of an intraperitoneal drain has been advocated, especially when the lesion is larger [208, 214].

4.3.4.2 Surgical management

The preferred method is two-layer vesicorrhaphy (mucosa-detrusor) with absorbable sutures [179, 185].

4.3.4.2.1 Blunt non-iatrogenic trauma

Although most extraperitoneal ruptures can be treated conservatively, bladder neck involvement, bone fragments in the bladder wall, concomitant rectal injury or entrapment of the bladder wall will necessitate surgical intervention [179, 207] (LE: 3). There is an increasing trend to treat pelvic ring fractures with open stabilisation and internal fixation with osteosynthetic material. During this procedure, an extraperitoneal rupture should be sutured concomitantly in order to reduce the risk of infection [179, 180]. Similarly, during surgical exploration for other injuries, an extraperitoneal rupture should be sutured concomitantly in order to reduce infective complications [180, 181].

Intraperitoneal ruptures should always be managed by formal surgical repair [179, 207] because intraperitoneal urine extravasation can lead to peritonitis, intra-abdominal sepsis and death [181] (LE: 3). Abdominal organs should be inspected for possible associated injuries and urinomas must be drained if detected. In the absence of other intra-abdominal injuries, laparoscopic suturing of the intraperitoneal rupture is possible [180].

4.3.4.2.2 Penetrating non-iatrogenic trauma

This requires emergency exploration, debridement of devitalised bladder muscle and primary bladder repair [184, 207] (LE: 3). A midline exploratory cystotomy is advised to inspect the bladder wall and the distal ureters [179, 184]. In gunshot wounds, there is a strong association with intestinal and rectal injuries, requiring faecal diversion [184]. Most gunshot wounds are associated with two transmural injuries (entry and exit wounds) and the bladder should be carefully checked for those two lesions [184].

4.3.4.2.3 Non-iatrogenic bladder trauma with avulsion of lower abdominal wall or perineum and/or bladder tissue loss

In these cases, direct closure of the traumatised bladder will lead to excessive tension, resulting in ischaemia and eventually breakdown of the repair. A bladder wall substitute is needed to repair the bladder defects and to restore the lower abdominal wall or perineum. A pedicled vastus lateralis myocutaneous flap has been proposed for this [200, 215].

4.3.4.2.4 Iatrogenic bladder trauma

Perforations recognised intra-operatively are primarily closed.

For bladder injuries not recognised during surgery or for internal injuries, a distinction must be made between intraperitoneal and extraperitoneal injuries. For intraperitoneal injuries, the standard of care is surgical exploration with repair [179, 211]. If surgical exploration is performed after TURB, the bowel must be inspected to rule out concomitant injury [201]. For extraperitoneal injuries, exploration is only needed for large perforations complicated by symptomatic extravescical collections. It requires drainage of the collection, with or without closure of the perforation [216].

If bladder perforation is encountered during midurethral sling or transvaginal mesh procedures, sling re-insertion and urethral catheterisation (1-2 days) should be performed [217].

4.3.4.2.5 Intravesical foreign body

For perforated or eroded meshes, the intravesical portion must be removed by open cystotomy or endoscopically [209, 218]. The choice depends on the surgeon's level of experience and the location of the mesh [209, 218]. For other types of foreign bodies, cystoscopic removal is performed and if this fails cystotomy is needed [205].

4.3.5 Follow-up

Continuous bladder drainage is required to prevent elevated intravesical pressure and to allow the bladder to heal [185, 219]. Conservatively treated bladder injuries (traumatic or external IBT) are followed by planned cystography scheduled to evaluate bladder healing, with catheter removal in case of absence of contrast extravasation [220]. The first cystography is planned 7-14 days after injury, depending on the extent of the laceration, and should be repeated thereafter in the case of an on-going leakage [220].

After operative repair of a simple injury in a healthy patient, the catheter can be removed after 7-10 days without need for a control cystography [204, 219] (LE: 2a). After repair of a complex injury (trigone involvement, ureteric reimplantation) or in the case of risk factors of wound healing (e.g. use of steroids, malnutrition), control cystography is advised [204, 219].

For conservatively treated internal IBT, a catheter duration of 5 and 7 days for extraperitoneal and intraperitoneal perforations, respectively, has been proposed [187, 188, 202, 203] (LE: 3).

4.3.6 Statements and recommendations for bladder injury

Statements	LE
Extraperitoneal bladder perforations are more common than intraperitoneal perforations.	3
The risk of bladder perforation during midurethral sling operations for stress urinary incontinence is lower for the obturator route compared to the retropubic route.	1a
The combination of pelvic fracture and visible haematuria is highly suggestive of bladder injury.	3

Recommendations	GR
Cystography is the preferred diagnostic modality for non-iatrogenic bladder injuries, and in suspected, iatrogenic, post-operative, bladder injuries.	B
Cystography (conventional or CT imaging) is required in the presence of visible haematuria and pelvic fracture.	B
Cystography should be performed with filling of the bladder with at least 350 mL of dilute contrast. Passive bladder filling by clamping the catheter during the excretory phase of CT or IVP is insufficient for diagnosis.	B
Cystoscopy is recommended after suburethral sling operations via the retropubic route and after major gynaecological operations. It is optional after any other type of sling procedure or transvaginal mesh procedure.	B
In the absence of bladder neck involvement and/or associated injuries that require surgical intervention, extraperitoneal bladder ruptures caused by blunt trauma are managed conservatively.	B
Intraperitoneal bladder ruptures by blunt trauma, and any type of bladder injury by penetrating trauma, must be managed by emergency surgical exploration and repair.	B
Conservative management is an option for small, uncomplicated, iatrogenic intraperitoneal bladder perforations.	C

GR= grade of recommendation; LE = level of evidence.

4.4 Urethral Trauma

4.4.1 Epidemiology, aetiology and pathophysiology

4.4.1.1 Iatrogenic urethral trauma

The most common type of urethral trauma seen in urological practice is iatrogenic, due to catheterisation, instrumentation, or surgery [221, 222]. New treatment methods and applied energy sources can also injure the urethra [223].

4.4.1.1.1 Transurethral catheterisation

Iatrogenic urethral trauma usually results from improper or prolonged catheterisation and accounts for 32% of strictures. Most of these strictures affect the bulbar urethra [223, 224], while the bladder neck is rarely affected in such cases [225].

The size and type of catheter used have an important impact on urethral stricture formation. Current data indicate that silicone catheters and small-calibre Foley catheters are associated with less urethral morbidity [226] (see Figure 4.4.3). Implementing training programmes may significantly decrease the incidence of such injuries, increase patients' safety and reduce the negative long-term effects [222, 227].

4.4.1.1.2 Transurethral surgery

Transurethral procedures are a common cause of iatrogenic urethral trauma. Factors that may influence the development of iatrogenic endoscopic urethral strictures include electrical dispersion generated by unipolar current and the diameter of the instruments used [228].

Predisposing factors most strongly associated with stricture formation in patients undergoing TURP are increased prostate volume, prostate cancer and the surgeon's experience [229].

Meatal strictures occur as a result of a mismatch between the size of the instrument and the diameter of the urethral meatus. Bulbar strictures occur due to insufficient insulation by the lubricant, causing the monopolar current to leak. To prevent strictures, lubricant gel should be applied carefully in the urethra.

The lubricant must be reapplied when the resection time is prolonged [230]. Internal urethrotomy must be performed before TURP if there are pre-existing meatal or urethral strictures [230].

There appears to be no relationship with the duration of the procedure or the method used (holmium laser or traditional TURP) on the rate of stricture formation [231].

4.4.1.1.3 Surgical treatment for prostate cancer

Urethral stricture following prostate cancer treatment can occur anywhere from the bladder neck to the urethral meatus. The rate of bladder neck constriction after radical prostatectomy varies with the definition of the stricture used and individual practice [232, 233]. The Cancer of the Prostate Strategic Urologic Research Endeavour (CaPSURE) database shows an incidence of urethral stricture after various forms of prostate cancer therapy of 1.1-8.4%. The risk is greatest after radical prostatectomy if combined with external-beam radiation therapy. In a multivariate analysis, primary treatment type, age, and obesity were found to be significant predictors for stricture development [232].

Robot-assisted prostatectomy also affects urinary function and the risk of iatrogenic trauma. Iatrogenic complications involving the bladder neck account for 2.2%, similar to the stricture rate found with conventional treatment for localised prostate cancer [234].

Anastomotic stricture is a complication in conventional laparoscopic prostatectomy. If prospective studies only are taken into account, there is no significant difference in the anastomotic stricture rates comparing laparoscopic and robot-assisted radical prostatectomy [235].

4.4.1.1.4 Radiotherapy for prostate cancer

The development of urinary fistulae has been reported after brachytherapy and radical prostatectomy, with incidences of 0.3-3.0% and 0-0.6%, respectively, with most fistulae involving the rectum [236, 237]. Brachytherapy is a recognised cause of strictures in patients with localised prostate cancer, as the CaPSURE study has shown [238]. Previous TURP increases the risk of stricture formation [239, 240].

4.4.1.1.5 Major pelvic surgery and cystectomy

Iatrogenic injuries to the urethra can be a complication of major pelvic procedures. Bladder and urethral catheterisation must therefore be carried out preoperatively to prevent these complications [241]. Radical cystectomy and subsequent urinary diversion may also cause urethral trauma [242]. Table 4.4.1 lists the most common causes of urethral trauma.

Table 4.4.1: Most common causes of iatrogenic urethral trauma

Procedure	Percentage
Catheterisation	32% of iatrogenic urethral strictures (52% bulbar urethra)
Urethral instrumentation for therapy and/or diagnosis	
Treatment for prostatic disease	1.1-8.4% urethral stricture rate
Transurethral surgery (e.g. TURB/TURP)	2.2-9.8% urethral stricture rate
Radical prostatectomy	0.5-32% bladder neck constriction; no difference between LRP and RALP (relative risk: 1.42; 95% confidence interval for relative risk, 0.40-5.06; p = 0.59)
Radiotherapy (percutaneous or brachytherapy)	6% urethral stricture rate, 0.3-3.0% urinary fistula rate
The greatest risk for urethral stricture is found in the combination of radical prostatectomy and EBRT	
Cryotherapy	
HIFU	
Treatment for bladder disease	
TURB	
Cystectomy	3.1% subneovesical obstruction, 1.2% neovesicourethral anastomotic strictures, 0.9% urethral strictures
Injury during major abdominal and pelvic operations	

TURB = transurethral resection of the bladder; TURP = transurethral resection of the prostate;

LRP = laparoscopic radical prostatectomy; RALP = robot-assisted laparoscopic radical prostatectomy;

EBRT = external-beam radiation therapy; HIFU = high-intensity focused ultrasound.

4.4.1.2 Non-iatrogenic urethral injuries

4.4.1.2.1 Anterior urethral injuries (in males)

Different causes of anterior injuries [243] are depicted in Table 4.4.2. Anterior urethral injuries are mainly caused by blunt trauma [243-245], with the bulbar urethra being the most common site injured [245, 246]. In these bulbar injuries, which are mostly 'straddle injuries' or kicks in the perineum, the bulb is compressed against the pubic symphysis, resulting in rupture of the urethra at this site [247].

Penetrating injuries of the penile or bulbar urethra are rare and usually caused by gunshot wounds [247-252]. Depending on the affected segment, penetrating injuries are usually associated with penile, testicular and/or pelvic injuries [249, 252].

Insertion of foreign bodies is another rare cause of anterior injury. It is usually a result of autoerotic stimulation or may be associated with psychiatric disorders [248]. Penile fractures account for 10-20% of anterior injuries [248]. In up to one-third of cases, the tear extends into the corpus spongiosum and urethra [253]. Urethral instrumentation is by far the most common cause of urethral trauma in the Western world and

can affect all segments of the anterior urethra [254, 255].

Table 4.4.2: Aetiology of urethral injury

Cause	Example
Blunt trauma	Vehicular accidents
	Fall astride ('straddle') e.g. on bicycle, fences, inspection covers
	Kicks in the perineum
Sexual intercourse	Penile fractures
	Urethral intraluminal stimulation
Penetrating trauma	Gunshot wounds
	Stab wounds
	Dog bites
	External impalement
	Penile amputations
Constriction bands	Paraplegia
Iatrogenic injuries	Endoscopic instruments
	Urethral catheters/dilators

4.4.1.2.2 Posterior urethral injuries (in males)

Injuries to the posterior urethra are most often related to pelvic fractures (about 72%) [254, 255], which themselves are usually caused by motor vehicle accidents [14, 221, 256]. Iatrogenic posterior injuries, due to irradiation or surgery to the prostate, are an increasing problem [254, 255], but appear to be less common than previously believed (3-25%) [243].

Surgically, these injuries are divided into either partial or complete ruptures. In complete ruptures, there is a gap between the disrupted ends of the urethra. The dismembered ends of the urethra retract and fibrous tissue fills the space between them [221]. There is no urethral wall in the scarred space and any lumen represents merely a fistulous tract between the urethral stumps [221]. Injury to the posterior urethra exclusively occurs in pelvic fractures with disruption of the pelvic ring [14]. The highest risk of urethral injury is in straddle fractures with a concomitant diastasis of the sacroiliac joint, followed by straddle fractures alone, and Malgaigne fractures [257]. Displaced fractures of the inferomedial pubic bone and pubic symphysis diastasis, together with their degree of displacement, are independent predictors of urethral injury [256]. Injuries of the bladder neck and prostate are rare [258] and they mostly occur at the anterior midline of both the bladder neck and prostatic urethra. It is more rare to find a complete transection of the bladder neck or an avulsion of the anterior part of the prostate [258].

Penetrating injuries of the pelvis, perineum or buttocks (mainly gunshot wounds) can also cause damage to the posterior urethra, but are extremely rare [259]. There is a high probability of associated injuries (80-90%), mainly intra-abdominal [184, 259].

Although urethral injuries themselves are not directly life-threatening [14, 243], the association with pelvic fractures and concomitant injuries of the thorax, abdomen and spine, may be life-threatening [14, 256].

Delayed morbidity of posterior urethral injuries includes strictures, incontinence and erectile dysfunction (ED), which may all have a detrimental effect on the quality of life [260]. Erectile dysfunction occurs in approximately 45% of patients after traumatic posterior urethral rupture [260, 261]. Strong predictors for ED are diastasis of the pubic symphysis [260-262], lateral displacement of the prostate [260, 263], a long urethral gap (> 2 cm) [260], a bilateral pubic rami fracture and a Malgaigne's fracture [260]. The assessment of sexual function and the definitive treatment (e.g. penile prosthesis) should be performed 2 years after the trauma because of the potential return of potency within that time [260].

4.4.1.3 Urethral injuries in females

Urethral injuries are very rare in females [244, 247]. Pelvic fractures are the main aetiology [244]. The injury is usually a partial longitudinal tear of the anterior wall associated with vaginal laceration [244, 248]. Urethral injuries in females which extend into the bladder neck may disrupt the normal continence mechanism [264].

4.4.2 Diagnosis in males and females

4.4.2.1 Clinical signs

Blood at the meatus is the cardinal sign of urethral injury [221]. The absence of it, however, does not rule out a urethral injury.

An inability to void (with a palpable distended bladder) is another classic sign and is often

associated with a complete rupture [221]. In addition, haematuria and pain on urination may be present. Urinary extravasation and bleeding may result in scrotal, penile and/or perineal swelling and ecchymosis, depending on the location and extent of the trauma [243, 248]. The presentation of these clinical symptoms may be delayed (> 1 hour) [221].

Rectal examination should always be done to exclude an associated rectal injury (up to 5% of cases) [265, 266] and may reveal a 'high-riding' prostate, which is an unreliable finding [221, 265]. Failure to detect a rectal injury will cause significant morbidity and even mortality [265]. A rectal injury is suggested by blood on the examining finger and/or a palpable laceration [265]. Another sign of urethral injury is difficulty or an inability to pass a urethral catheter [265].

A female urethral injury should be suspected from the combination of a pelvic fracture with blood at the vaginal introitus, vaginal laceration, haematuria, urethrorrhagia, labial swelling and/or urinary retention [244, 247, 248]. Vaginal examination is indicated to assess vaginal lacerations [265].

Symptoms of urethral lesions caused by improper catheterisation or instrumentation are penile and/or perineal pain (100%) and urethral bleeding (86%) [225]. Failure to diagnose accurately and treat urethral injuries may lead to significant long-term sequelae, mostly presenting as strictures [267, 268].

4.4.2.2 Further diagnostic evaluation

4.4.2.2.1 Retrograde urethrography

Retrograde urethrography is the standard diagnostic investigation for the acute evaluation of a male urethral injury [243]. A retrograde urethrography is conducted by injecting 20-30 mL of contrast material while occluding the meatus, with a balloon of a Foley catheter inflated in the fossa navicularis. Films should be taken in a 30°-oblique position, unless this is not possible because of the severity of the pelvic fractures and associated patient discomfort [243, 248]. In an unstable patient, retrograde urethrography should be postponed until the patient has been stabilised [184, 244].

A urethrogram allows for identification of the site of injury and assessment of the extent of any injury [244, 265]. Any extravasation outside the urethra is pathognomonic for urethral injury. However, the distinction between a complete and partial rupture is not always clear [221]. A typical image for incomplete rupture shows extravasation from the urethra which occurs while the bladder is still filling. A complete rupture is suggested by massive extravasation without bladder filling [221].

The following classification of urethral injuries is based on retrograde urethrography (Table 4.4.3) [243]:

Table 4.4.3: Staging of urethral injuries*

Anterior urethra
• Partial disruption
• Complete disruption
Posterior urethra
• Stretched but intact
• Partial disruption
• Complete disruption
• Complex (involves bladder neck/rectum)

*According to the 2004 Consensus Panel on Urethral Trauma [243].

4.4.2.2.2 Ultrasound, CT and MR imaging

In the acute phase, ultrasound (US) scanning is used for guiding the placement of a suprapubic catheter [243]. CT and rarely MRI are useful to evaluate concomitant injuries [243, 248].

4.4.2.2.3 Cystoscopy

Flexible cystoscopy is an option to diagnose (and manage) an acute urethral injury and may distinguish between complete- and incomplete rupture [243]. In addition, it may allow a guidewire to be passed into the bladder for early catheterisation [244, 269]. Flexible cystoscopy is also recommended above retrograde urethrography in suspected penile fracture-associated urethral injury [264, 270, 271]. In females, where the short urethra precludes adequate, radiological visualisation, urethroscopy and vaginoscopy are the diagnostic modalities of choice [243, 244].

4.4.2.3 Summary

Prior to deferred management, the combination of retrograde urethrography and antegrade cystourethrography

is standard [243]. The location and extent of the obliteration is diagnosed [243]. An MRI of the pelvis provides valuable additional information, which can help to determine the most appropriate surgical strategy [243, 263]. If the competence of the bladder neck is not clear upon antegrade cystourethrography, suprapubic cystoscopy is then advised [243].

4.4.3 Disease Management

4.4.3.1 Anterior urethral injuries

Anterior urethral injuries are usually not associated with other life-threatening injuries [244, 248]. Treatment decisions are based mainly on the type of injury (blunt, penile fracture associated or penetrating).

4.4.3.1.1 Blunt anterior urethral injuries

Blunt anterior urethral injuries are associated with spongiosal contusion, which makes it more difficult to evaluate the limits of urethral debridement in the acute phase. Acute or early urethroplasty is therefore not indicated [243]. The therapeutic options are suprapubic diversion or (a trial of) early endoscopic realignment with transurethral catheterisation [244]. Urinary diversion is maintained for 2 and 3 weeks for partial and complete ruptures, respectively [246].

Satisfactory urethral luminal recanalisation may occur in up to 68% after partial ruptures, but is rare after complete ruptures [246, 272].

4.4.3.1.2 Penile fracture-related anterior urethral injuries

In order to preserve erectile function, penile fractures require early exploration [247, 264, 273, 274]. The strategy consists of closing the tear in the cavernosal tunica albuginea, while the concomitant tear in the urethra is repaired at the same time [273]. In these circumstances, there is no substantial urethral tissue loss [275]. A small laceration can be repaired by simple closure, while a complete rupture requires an anastomotic repair [273, 274].

4.4.3.1.3 Penetrating anterior urethral injuries

Immediate exploration is advised, except when this is precluded by other life-threatening injuries [243]. Devitalised tissues should be debrided, although urethral and spongiosal debridement should be kept to a minimum due to the excellent vascularisation [252, 264]. For small lacerations and stab wounds, simple urethral closure might be sufficient [243]. Defects of up to 2-3 cm in length in the bulbar urethra, and up to 1.5 cm in the penile urethra, can be treated by spatulation of the urethral ends and primary anastomosis [244, 250, 252]. In the case of longer defects or apparent infection (particularly bite wounds), a staged repair with urethral marsupialisation and a suprapubic catheter is needed [250, 252]. Peri- and post-operative antibiotic treatment is also necessary [251].

4.4.3.2 Posterior urethral injuries

4.4.3.2.1 Blunt posterior urethral injuries

In posterior injuries, it is important to distinguish between complete and partial ruptures prior to treatment. The timing of the surgical intervention is classified as [243, 244]:

- Immediate: < 48 hours after injury (4.4.3.2.1.1);
- Delayed primary: 2 days to 2 weeks after injury (4.4.3.2.1.2);
- Deferred: > 3 months after injury (4.4.3.2.1.3).

4.4.3.2.1.1 Immediate management

Although urinary diversion is not essential during the first hours after trauma, many prefer to perform an early urinary diversion for three main reasons [221, 244]:

- To monitor urinary output, since this is a valuable sign of the haemodynamic condition and the renal function of the patient;
- To treat symptomatic retention if the patient is still conscious;
- To minimise urinary extravasation and its secondary effects, such as infection and fibrosis.

Insertion of a suprapubic catheter is always a good solution in urgent situations [243, 264]. However, insertion of a suprapubic catheter is not without risk, especially in the unstable trauma patient where the bladder is often displaced by the pelvic haematoma or because of poor bladder filling due to haemodynamic shock or concomitant bladder injury. In these circumstances, an attempt of urethral catheterisation can be carried out by experienced hands. It is extremely unlikely that the gentle passage of a urethral catheter will do any additional damage [221, 244, 248, 254, 255, 275]. If there is any difficulty, a suprapubic catheter should be placed under US guidance and direct vision [221].

4.4.3.2.1.1.1 Partial posterior urethral rupture

Partial tears of the posterior urethra can be managed with a suprapubic or urethral catheter [264]. Urethrography should be performed at 2-weekly intervals until healing has occurred [266, 276]. Injuries may heal without significant scarring or obstruction if managed by diversion alone [264]. A residual or subsequent stricture should be managed with:

- Internal urethrotomy if it is short and non-obliterative;
- Anastomotic urethroplasty, if it is long and dense, as is found with complete obliteration or after failed internal urethrotomy [272, 277].

4.4.3.2.1.1.2 Complete posterior urethral rupture

Acute definitive treatment options include:

- Immediate realignment: apposition of the urethral ends over a catheter (4.4.3.2.1.1.2.1);
- Immediate urethroplasty: suturing of urethral ends (4.4.3.2.1.1.2.2).

4.4.3.2.1.1.2.1 Immediate realignment

The aim of realignment is to correct severe distraction injuries rather than to prevent a stricture [264].

The reported benefits of realignment are:

- A lower stricture rate than with suprapubic catheter placement alone (where stricture formation is almost certain) [272, 277, 278];
- If scarring and subsequent stricture formation occurs, the restoration of urethral continuity is simplified. For short (< 2 cm), non-obliterative strictures, internal urethrotomy can be attempted, with a 50-90% success rate [272, 277, 279]. For longer strictures, or in the case of failure of an internal urethrotomy, urethroplasty is required [277].
- If urethroplasty is required later, it is technically easier when the prostate and urethra are well aligned [280].

Endoscopic realignment is the preferred technique 87-95 [244, 264]. Using a flexible/rigid cystoscope and biplanar fluoroscopy, a guidewire is placed inside the bladder. Over this, a catheter is placed into the bladder. If necessary, two cystoscopes can be used: one retrograde (per urethra) and one antegradely (suprapubic route through the bladder neck) [272, 277, 278]. The duration of catheter stay varies between 4 and 8 weeks among series [265, 272, 277, 278].

It is important to avoid traction on the Foley balloon catheter since it can damage the remaining sphincter mechanism at the bladder neck. Concomitant bladder neck or rectal injuries or presence of bony fragments inside the bladder must be repaired immediately.

The reasons for immediate repair of bladder neck and rectal injury are:

- Unrepaired bladder neck injury risks incontinence and infection of the pelvic fractures;
- Unrepaired rectal injury carries the obvious risk of sepsis and fistula. Early exploration is indicated to evacuate contaminated haematomas and to perform colostomy if necessary.

Immediate endoscopic realignment can also be performed when the patient is on the operating table for other surgery. Early endoscopic realignment (immediate or delayed primary, see below) is also possible in a stable patient without significant concomitant injuries [277, 278].

With modern endoscopic realignment procedures, acceptable complication rates have been reported for stricture formation (14-79%), incontinence (< 5%) and impotence (10-55%) [277, 278].

Differences between series in the rates of incontinence, impotence and re-stricture can be explained by differences in patient selection (severe vs. less severe trauma), a mix of partial and complete ruptures, and differences in follow-up duration. Furthermore, these differences make the comparison with other techniques difficult, especially with urethroplasty [265, 272, 277, 278].

4.4.3.2.1.1.2.2 Immediate urethroplasty

Immediate urethroplasty with suturing of the urethral ends is difficult because of poor visualisation and the inability to assess accurately the degree of urethral disruption, because of extensive swelling and ecchymosis. This might lead to extensive unjustified urethral debridement [244]. Another problem is the risk of uncontrolled bleeding following entry into the pelvic haematoma, which may result in uncontrolled re-bleeding [244]. Because of disturbingly high rates of impotence (56%), incontinence (21%) and strictures (69%) [276], immediate urethroplasty cannot be recommended and should only be done in experienced centres [281, 282].

4.4.3.2.1.1.3 Delayed primary treatment

Delayed treatment options include delayed primary realignment (4.4.3.2.1.2.1) and delayed primary urethroplasty (4.4.3.2.1.2.2).

4.4.3.2.1.1.3.1 Delayed primary realignment

In the absence of indications for immediate exploration, posterior urethral disruption can be managed in a delayed primary fashion. Delayed primary realignment requires the placement of a suprapubic tube at the time of initial injury, with endoscopic realignment performed within 14 days (i.e. before fibrosis begins). At that time, patients are stable and most of the pelvic bleeding has resolved [276, 278]. The aim and proposed benefits of delayed primary realignment are the same as mentioned for immediate realignment. Endoscopic realignment is also the preferred modality.

4.4.3.2.1.1.3.2 Delayed primary urethroplasty

Delayed primary urethroplasty is performed no later than 14 days after the initial injury i.e. before the start of the fibrotic process [283, 284]. If successful, it avoids a long period of suprapubic diversion [283]. It is restricted to stable patients with a short distraction defect, who are able to lie down in the lithotomy position [283]. Considering the limited accumulated experience with this approach, it cannot be generally recommended [283, 285, 286].

Supporters of early versus delayed intervention state that it does not affect the outcome of an eventual subsequent urethroplasty [281, 287]. However, some authors have reported worse outcomes of subsequent urethroplasty after failed initial urethral manipulation (realignment or urethroplasty) [282, 283, 288]. Due to this concern and the excellent results obtained with deferred urethroplasty, early realignment or urethroplasty should only be selectively performed in highly experienced centres [281, 282].

4.4.3.2.1.1.4 Deferred treatment

In the case of a complete rupture, treated with an initial period of 3 months' suprapubic diversion, obliteration of the posterior urethra is almost inevitable [221, 276]. Treatment options for these posterior urethral strictures are deferred urethroplasty (4.4.3.2.1.3.1) and deferred endoscopic optical incision (4.4.3.2.1.3.2).

4.4.3.2.1.1.4.1 Deferred urethroplasty

Deferred urethroplasty is the procedure of choice for the treatment of posterior urethral distraction defects [264]. After 3 months of suprapubic diversion, the pelvic haematoma is nearly always already resolved, the prostate has descended into a more normal position and the scar tissue has stabilised [283] and the patient is clinically stable and able to lie down in the lithotomy position [243, 244].

Most posterior urethral distraction defects are short and can be treated using a perineal anastomotic repair [243, 283]. The key objective of the operation is to achieve a tension-free anastomosis between two healthy urethral ends (i.e. after complete excision of any scar tissue) [264, 283].

After resection of fibrosis and spatulation of both healthy urethral ends, the gap between both ends is bridged by the so-called 'elaborated perineal approach', which is a series of consecutive manoeuvres, first described by Webster and Ramon [289] with reported success rates of 80-98% [290-292].

Most urethral stenoses are short and can be treated by mobilisation of the bulbar urethra, with or without separation of the corpora cavernosa [283]. This is in contrast to the situation in developing countries, where stenoses are more complex, and where additional manoeuvres, such as inferior pubectomy and supracrural rerouting or a combined abdominoperineal approach are needed more often [279, 291].

A number of situations may prevent the use of perineal anastomotic repair, either as an initial or as a salvage therapy. These situations probably represent < 5% of cases (Table 4.4.4) [293, 294].

Table 4.4.4: Circumstances that might preclude successful perineal anastomotic repair, either as an initial or as a salvage therapy [293, 294]

Circumstance	Alternative procedure
Distraction defects longer than 7-8 cm	A tubed interposition flap of penile or perineal skin can be used for reconstruction [295]. This is seldom required and most patients that require flap urethroplasties have previous failed repairs of posterior urethral rupture [264].
Fistulae	These might require a combined abdominoperineal approach to secure adequate closure [291].
Synchronous anterior urethral stricture	The presence of anterior urethral stricture may compromise the blood supply to the bulbar urethra following division of the bulbar arteries. These patients should be treated cautiously.
Urinary incontinence	The distal urethral sphincter mechanism can be defunctionalised by urethral distraction, so that urinary continence is maintained primarily by the proximal bladder neck sphincter. Concomitant bladder neck injury might increase incontinence and should require an abdominoperineal procedure to allow simultaneous bladder neck and urethral reconstruction [243, 264, 291].

Outcome after deferred urethroplasty is excellent with a stricture rate of around 10% [289, 296]. Deferred urethroplasty is unlikely to result in additional ED [283, 296]. Decompression of the erectile nerves after excision of the scar tissue might explain the amelioration of erectile function after urethroplasty [297]. Incontinence is rare with deferred urethroplasty (< 4%) [283] and is usually due to incompetence of the bladder neck [264, 291]. Standard therapy is a deferred urethroplasty at a minimum of 3 months after trauma, using a one-stage perineal approach whenever possible.

4.4.3.2.1.4.2 Deferred endoscopic treatment

Cold knife or laser core-through or cut-to-the light urethrotomy for complete urethral obliteration has been described. The results of this technique are poor [298, 299] and the procedure is therefore not recommended. For short, non-obliterative strictures following realignment or urethroplasty, direct vision urethrotomy can be performed [292] while in other cases, urethroplasty is warranted.

4.4.3.2.2 Penetrating posterior urethral injuries

The management of penetrating posterior urethral injuries is mainly dependent on associated injuries and the clinical condition of the patient [184, 259]. If possible, immediate exploration by the retropubic route and primary repair or realignment can be performed [184, 259, 264]. In the case of rectal injury, a diverting colostomy is necessary [184, 259]. Life-threatening associated injuries often preclude direct urethral repair. In those cases, suprapubic diversion with delayed abdominoperineal urethroplasty is advised [184, 252, 259].

4.4.3.2.2.1 Female urethral injuries

Proximal and mid-urethral disruptions require immediate exploration and primary repair using the retropubic and transvaginal routes, respectively, with primary suturing of the urethral ends. Concomitant vaginal lacerations are repaired transvaginally at the same time [244, 247, 265, 266]. Distal urethral injuries can be managed vaginally by primary suturing and closure of the vaginal laceration [244, 266]. In all of these operations, it is advisable to use a flap (e.g. Martius) to prevent urethrovaginal fistulas [300]. Nevertheless, distal urethral injuries can be left unrepaired and hypospadiac since they do not disrupt the sphincteric mechanism [244, 247, 265, 266].

4.4.3.2.2.1.1 Iatrogenic urethral injuries

Temporary stenting with an indwelling catheter is the conventional treatment option for an acute false passage [301], although its value in minor urethral injuries is unproven. In difficult cases, catheter insertion may be assisted by cystoscopy and guidewire placement [302], and suprapubic catheterisation is an alternative.

Endoscopic management, either with incision or resection, can successfully treat iatrogenic prostatic urethral strictures. Indwelling catheter placement or an open procedure (which is associated with increased morbidity) are alternatives [303].

Urethral lesions following radiotherapy are often more difficult to treat and may require complex reconstructive surgery [236, 237]. Section 4.4.4.1 lists the statements and recommendations regarding the iatrogenic causes of urethral trauma.

4.4.3.3 Treatment algorithms

The following algorithms are suggested for the treatment of anterior and posterior urethral injuries in men (Figures 4.4.1 and 4.4.2).

Figure 4.4.1: Management of anterior urethral injuries in men

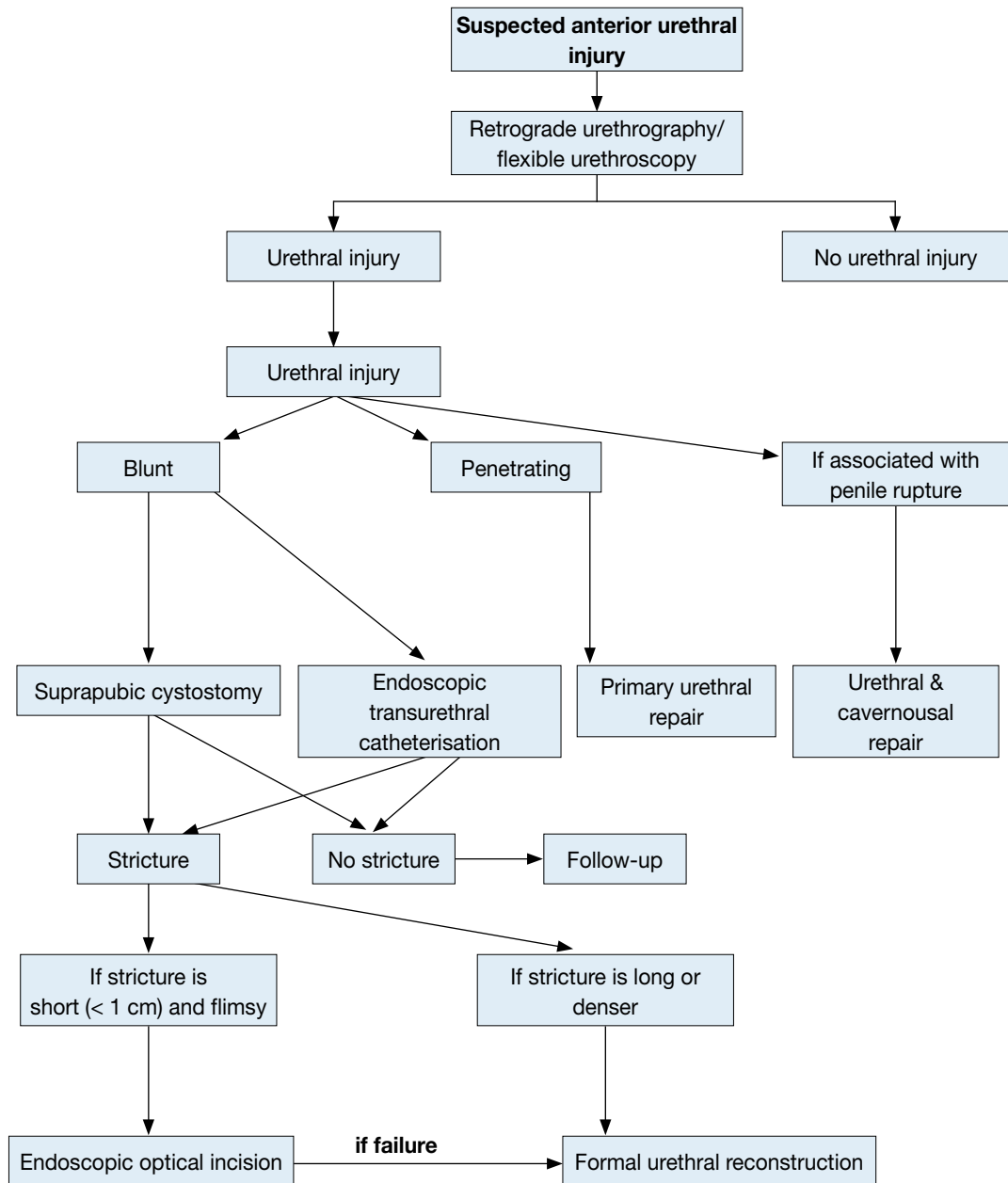


Figure 4.4.2: Management of posterior urethral injuries in men

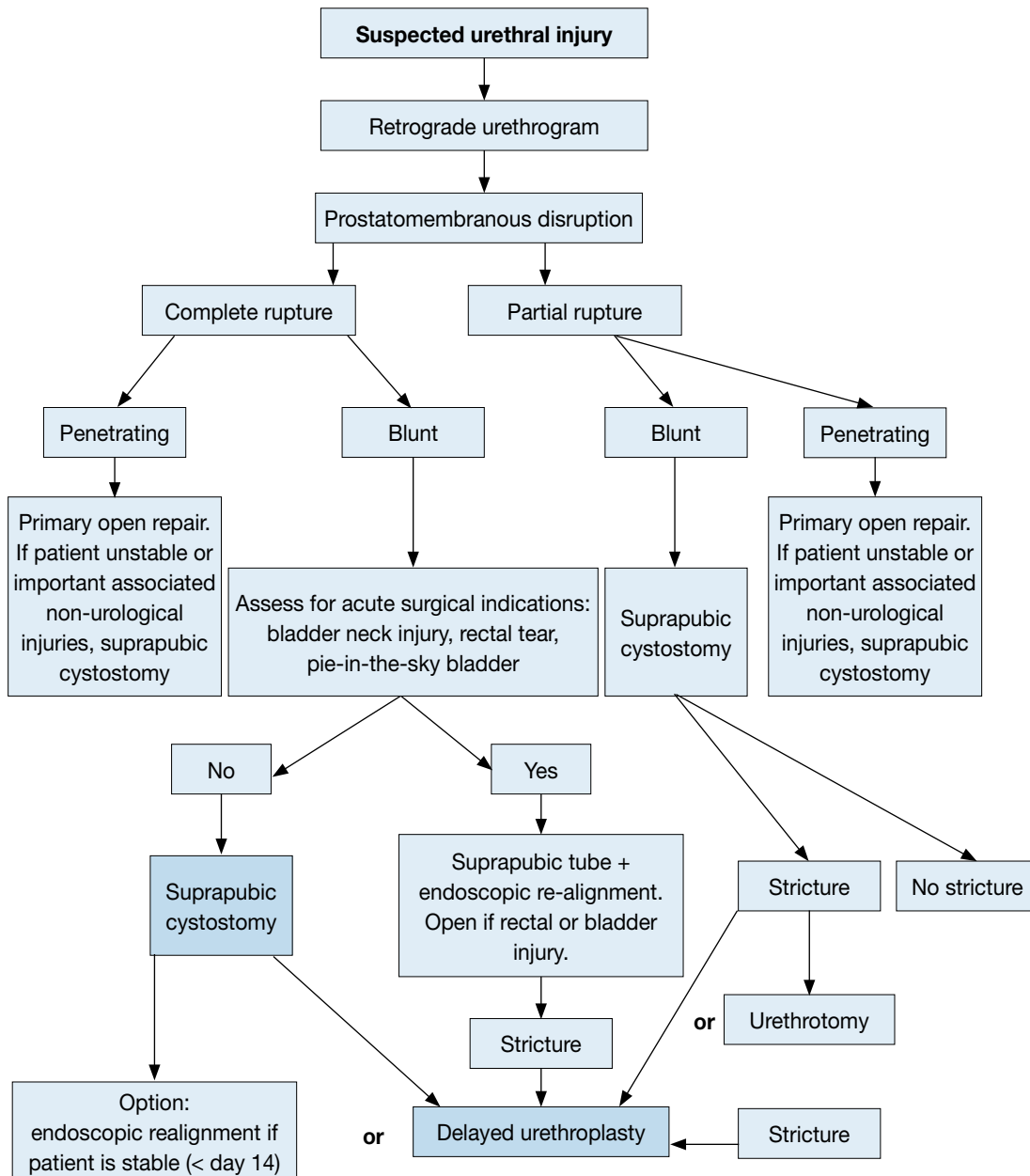


Figure 4.4.3: Treatment of iatrogenic urethral injury caused by improper insertion of a catheter

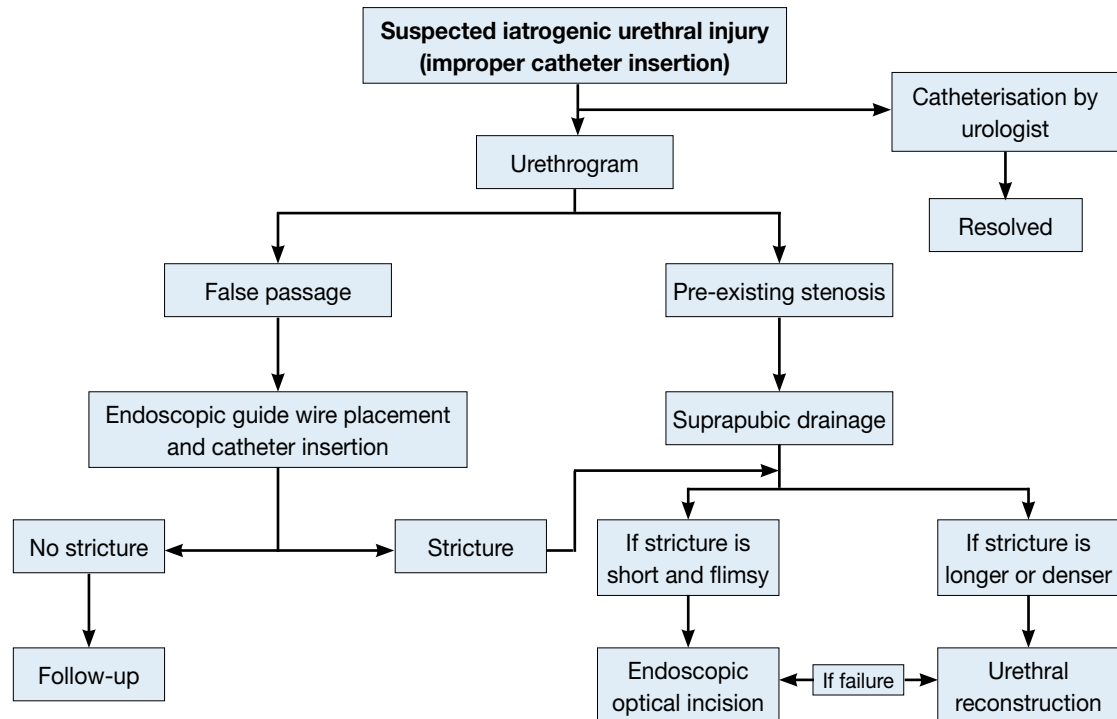
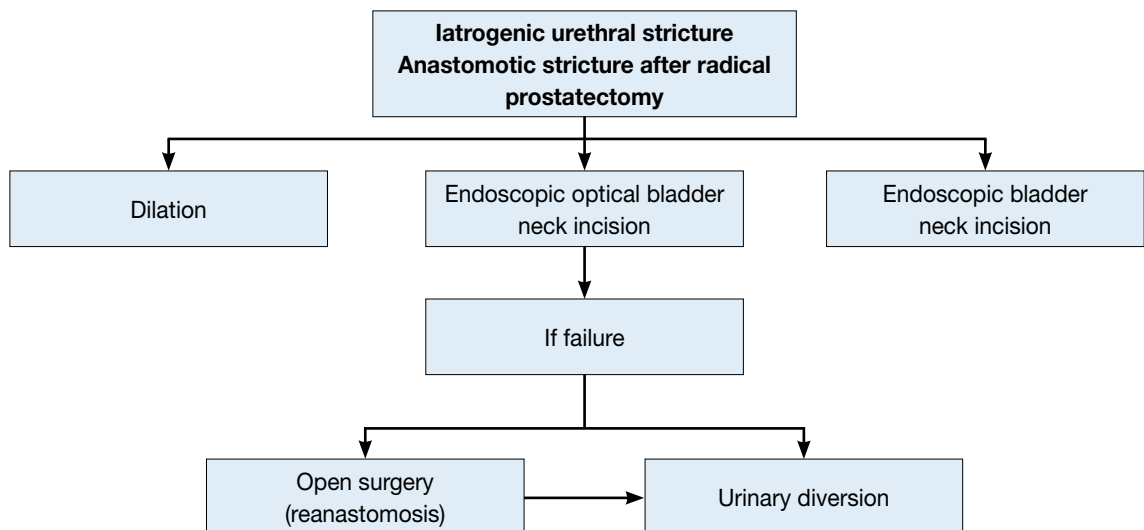


Figure 4.4.4: Treatment for stricture after radical prostatectomy



4.4.4 Statements and recommendation for urethral trauma

Statements	LE
Blunt trauma accounts for more than 90% of urethral injuries.	3
In penile fracture, the urethra is involved in 20% of cases.	4
The male posterior urethra is injured in 4-19% of pelvic fracture cases. In industrialised societies pelvic fracture-related injuries of the posterior urethra are the most common non-iatrogenic injuries.	3
Erectile dysfunction occurs in 20-60% of patients after traumatic urethral rupture.	3

Recommendations	GR
Retrograde urethrography is the gold standard for evaluating urethral injuries.	B
Delayed formal urethroplasty is the procedure of choice for the treatment of posterior urethral distraction defects.	B
Partial posterior urethral ruptures should be treated by urethral or suprapubic catheterisation.	C
Blunt anterior urethral injuries should be treated by suprapubic diversion.	C

GR= grade of recommendation; LE = level of evidence.

4.4.4.1 Statements and recommendations for iatrogenic urethral trauma

Statements	LE
Iatrogenic causes are the most common type of urethral injury in Europe, and therefore the most common cause of urethral stricture formation.	2a
Implementing training programmes on urinary catheter insertion significantly improves the rate of catheter-related complications.	2b
New technologies represent an additional source of urethral injury.	3

Recommendations	GR
Proper training should be provided to reduce the risk of traumatic catheterisation.	A
Urethral instrumentation should only be carried out when there are valid clinical indications.	A
When catheterisation is necessary, its duration should be kept to a minimum.	B

LE= level of evidence; GR = grade of recommendation.

4.5. Genital Trauma

4.5.1 Introduction and background

Genitourinary trauma is seen in both sexes and in all age groups. Of all urological injuries, 33-66% involve the external genitalia [16]. Genital trauma is much more common in males than in females, especially between the ages of 15 and 40 years. This is due to anatomical differences, increased frequency of road traffic accidents and increased participation in physical sports, war and violent crime.

Genital trauma is commonly caused by blunt injuries (80%). The risk of associated injuries to neighbouring organs (bladder, urethra, vagina, rectum and bowel) after blunt trauma is higher in females than in males. In males, blunt genital trauma frequently occurs unilaterally and only approximately 1% present as bilateral scrotal or testicular injuries [304].

Any kind of contact sport, without the use of necessary protective aids, may be associated with genital trauma. Off-road bicycling and motorbike riding (especially on motorbikes with a dominant petrol tank), rugby, football and hockey are all activities which are associated with blunt testicular trauma [305-308].

Penetrating injuries account for 20% of genitourinary trauma, with 40-60% of all penetrating genitourinary lesions involving the external genitalia [249, 309]. Thirty-five per cent of all genitourinary gunshot wounds involve the genitalia [304]. In a recent series of wartime genitourinary injuries, 71.5% of 361 operations involved the external genitalia - the majority caused by improvised explosive devices (IEDs) and other explosive ordinance, while smaller numbers of injuries were due to gunshot injuries [310]. In both males and females, penetrating genital injuries occur with other associated injuries in 70% of patients. In males, penetrating scrotal injuries affect both testes in 30% of cases compared with 1% in blunt scrotal injuries [304, 311].

Self-mutilation of the external genitalia has also been reported in psychotic patients and transsexuals [312]. Genital burns are rare in isolation, usually due to industrial flame or chemicals in adults, and all but the full thickness type are treated conservatively [313]. Both male and female genital piercings increase the risk for unexpected genital trauma [314]. Although there is an increased risk of Hepatitis B and C in genitally injured patients, there is no higher incidence of STDs in patients with genital piercing [314].

4.5.2 General principles and pathophysiology

In genital trauma, a urinalysis should be performed. The presence of visible- and/or non-visible requires a retrograde urethrogram in males. In females, flexible or rigid cystoscopy has been recommended to exclude urethral and bladder injury [315, 316]. In women with genital injuries and blood at the vaginal introitus, further gynaecological investigation is needed to exclude vaginal injuries [316]. The potential for significant injury

should never be discounted in those patients who may also have blood in the vaginal vault from menstruation. Complete vaginal inspection with specula is mandatory.

4.5.2.1 Gunshot wounds

In patients with genitalia injured by gunshot wounds, it is very useful to have information about the causative weapon, particularly the range, calibre and type of weapon. High-velocity missiles transmit large amounts of energy to the tissues and can produce trauma to structures outside the wound track. The passage of a missile creates an expansive cavity of sub-atmospheric pressure, which then collapses and creates shear forces and induction of other foreign bodies and (usually) infected material [16].

4.5.2.2 Bites

4.5.2.2.1 Animal bites

Although animal bites are common, bites injuring the external genital are rare. Wounds are usually minor, but have a risk of wound infection. The most common bacterial infection caused by a dog bite is *Pasturella multocida*, which accounts for up to 50% of infections [317]. Other commonly involved organisms are *Escherichia coli*, *Streptococcus viridans*, *Staphylococcus aureus*, *Eikenella corrodens*, *Capnocytophaga canimorsus*, *Veillonella parvula*, *Bacteroides* and *Fusobacterium* spp. [312, 317, 318].

The first choice of antibiotics is penicillin-amoxiclavulanic acid, followed by doxycycline, cephalosporin or erythromycin for 10-14 days [319-321]. The possibility of rabies infection must be considered. If rabies infection is suspected, vaccination should be considered taking into account the geographical location, animal involved, specific nature of the wound and the type of attack (provoked/unprovoked). Besides vaccination, local wound management is an essential part of post-exposure prophylaxis. High-risk patients should be vaccinated with human rabies immunoglobulin and human diploid cell vaccine [322, 323].

4.5.2.2.2 Human bites

Human bites are much less common, but infection should be considered, especially in risk groups. Since transmission of viral diseases may occur, risk assessment should be made. If appropriate, hepatitis B vaccine/immunoglobulin and/or HIV post-exposure prophylaxis should be offered. For further details, see Guidelines for the Management of Human Bite Injuries [324].

4.5.2.3 Sexual assault

Genital injury is often seen (42%) after sexual abuse, which must be considered when genital injuries present at any age [325]. In these cases, the examiner should be aware of the extraordinary emotional situation of the patient and the privacy of the patient respected. In suspicious cases, gynaecological and forensic support and advice is necessary. Swabs or vaginal smears should be taken for detection of spermatozoa [326] and local legal protocols followed closely. A thorough history and examination (in some cases under anaesthesia), photo documentation, and identification of forensic material may be important. In a recent report, only 38% of the forensic samples tested positive for an ejaculate and/or sperm. This may be due to delayed presentation or lack of vaginal/anal ejaculation [327, 328].

4.5.3 Organ-specific genital trauma

4.5.3.1 Penile trauma

4.5.3.1.1 Blunt penile trauma

Blunt trauma to the flaccid penis does not usually cause tearing of the tunica. In these cases, only subcutaneous haematoma with intact tunica albuginea may be seen.

4.5.3.1.1.1 Penile fracture

The most important and common presentation of blunt penile trauma is penile fracture. This results from trauma to the erect penis during sexual intercourse, masturbation, rolling over in bed (rarely) and as a result of self-inflicted bending to produce detumescence in some Middle Eastern Cultures-a practice known as 'taqaandan' (which, when translated, means 'to click') [329]. The most common mechanism of injury is when the penis slips out of the vagina and strikes against the symphysis pubis or perineum. Sixty per cent of cases occur during consensual intercourse [330], and is more likely when the partner is on top. Penile fracture is caused by rupture of the cavernosal tunica albuginea, and may be associated with subcutaneous haematoma and lesions of the corpus spongiosum or urethra in 10-22% [331, 332].

The thickness of the tunica albuginea in the flaccid state (approximately 2 mm) decreases in erection to 0.25-0.5 mm, and is therefore more vulnerable to traumatic injury [333, 334]. Penile fracture is associated with a sudden cracking or popping sound, pain and immediate detumescence. Local swelling of the penile shaft

develops quickly, due to enlarging haematoma. Bleeding may spread along the fascial layers of the penile shaft and extend to the lower abdominal wall if Buck's fascia is also ruptured. Sometimes, the rupture of the tunica may be palpable. Less severe penile injuries can be distinguished from penile fracture, as they are not usually associated with detumescence.

A thorough history and examination usually confirm the diagnosis, but in some cases imaging may be useful. Cavernosography, US or MRI [335-337] can identify lacerations of the tunica albuginea in unclear cases [338], or provide reassurance that the tunica is intact. If a concomitant urethral injury is suspected, a retrograde urethrogram (RUG) may be performed, even though flexible cystoscopy under anaesthesia during exploration/repair is more usually employed.

Subcutaneous haematoma, without associated rupture of the cavernosal tunica albuginea, does not require surgical intervention. In these cases, non-steroidal analgesics and ice-packs are recommended [339].

When a penile fracture is diagnosed, surgical intervention with closure of the tunica albuginea is recommended. The approach is usually through a circumferential incision proximal to the coronal sulcus which enables degloving the penis entirely. Increasingly, local longitudinal incisions centred on the area of fracture are currently used and further localisation may be gained with a flexible cystoscopy performed prior to incision, if urethral trauma is suspected and eventually proven.

Closure can be obtained by using absorbable sutures, with good long-term outcome, and protection of potency. Post-operative complications were reported in 9%, including superficial wound infection and impotence in 1.3% [330, 340]. The conservative management of penile fracture is not recommended. It increases complications, such as penile abscess, missed urethral disruption, penile curvature, and persistent haematoma requiring delayed surgical intervention [340]. Late complications after conservative management were fibrosis and angulations in 35%, and impotence in up to 62% [330, 340].

4.5.3.2 Penetrating penile trauma

Penetrating penile trauma is rarely seen in isolation. Most cases are associated with multiple injuries. Non-operative management is recommended in small superficial injuries with intact Buck's fascia [249]. In more significant penetrating penile injuries, surgical exploration and debridement of necrotic tissue is recommended. Even in extended injuries of the penis, primary alignment of the disrupted tissues may allow for acceptable healing because of the robust penile blood supply [312].

The principles of care are debridement of devitalised tissue, with the preservation of as much viable tissues as possible, haemostasis, diversion of urine in selected cases and the removal of foreign bodies. Tissues of questionable viability may be left for subsequent definitive surgery. If a subsequent immediate or delayed repair is needed, depending on the type of injury and the extent of tissue damage, it usually takes place 4-6 weeks after the trauma has occurred.

The surgical approach depends upon the site and extent of the injury, but a subcoronal incision with penile degloving usually gives good exposure. Initially, a defect in the tunica albuginea should be closed after copious irrigation. If there has been too much tissue loss, the defect can be repaired either immediately or after delay with a patch (either from an autologous saphenous vein or xenograft). If a concomitant urethral injury is suspected, a pre- or peri-operative urethrogram or cystoscopy is useful to diagnose any urethral involvement, to define its position, and to decide upon the incision used.

The elasticity of genital skin means it is usually possible to manage the loss of a moderate amount of penile skin. However, management is more difficult in extensive injuries with significant skin loss. The tissue chosen for reconstruction following trauma needs to provide good coverage and must be suitable for reconstruction. Split-thickness skin grafting provides good coverage and a dependable take that is reproducible and durable. However, split-thickness grafts contract more than full-thickness grafts and their use on the penile shaft should be kept to a minimum. In accordance, McAninch et al. recommended the use of skin grafts with thickness of at least 0.015 inch (0.4 mm) in order to reduce the risk of contraction [312]. Full-thickness skin grafting onto the penile shaft gives less contracture, a better cosmetic appearance and more resistance to trauma during intercourse, when eventually re-established [339]. The donor site may be taken from the abdomen, buttock, thigh or axilla and is chosen according to surgeon's preference and the pattern of injury.

In cases of extensive destruction of deeper tissues, or if later prosthetic placement is being considered, skin flaps, with their secure vascular supply can be used.

4.5.3.3 *Penile avulsion injuries and amputation*

Most injuries are self-inflicted, but some are a result of industrial accidents or assault. Acute management involves resuscitation of the patient, who may be compromised from massive blood loss, and preparation for surgical re-implantation of the penis if it has been recovered and is not too badly damaged. Surgical re-implantation should be considered for all patients and should be performed within 24 hours of amputation. If the injury occurred during a psychotic episode, early psychiatric advice and support should be sought.

The severed penis should be washed with sterile saline, wrapped in saline-soaked gauze, placed in a sterile bag and immersed in iced water. The penis must not come into direct contact with the ice. A pressure dressing or a tourniquet should be placed around the penile stump to prevent excessive blood loss. Re-attachment can be achieved in a non-microsurgical way, a technique which probably gives higher rates of post-operative urethral stricture and more problems with loss of sensation [341]. When operating microscopically, the corpora cavernosa and urethra are firstly aligned and repaired. Subsequently, the dorsal penile arteries, the dorsal vein and the dorsal nerves are anastomosed. The cavernosal arteries are generally too small to anastomose. The fascia and skin are closed in layers and both a urethral and a supra-pubic catheter are placed.

If the severed penis cannot be found, or is unsuitable for re-attachment, then the end should be closed as it is done in partial penectomy. Later reconstruction may be employed to lengthen the penis (e.g. suspensory ligament division and V-Y plasty, pseudo-glans formation with split-thickness skin grafting, etc). A delayed major reconstructive procedure, i.e. phalloplasty (either radial artery or pubic), is sometimes required for injuries which leave a very little or non-functioning penile stump.

4.5.4 **Scrotal trauma**

4.5.4.1 *Blunt scrotal trauma*

Blunt trauma to the scrotum can cause testicular dislocation, testicular haematocoele, testicular rupture and/or scrotal haematoma.

4.5.4.1.1 Testicular dislocation

Traumatic dislocation of the testicle occurs rarely. It is most common in victims of MVAs [342-345]. Bilateral dislocation of the testes has been reported in up to 25% of cases [343]. It can be either a subcutaneous dislocation with epifascial displacement of the testis or an internal dislocation. In the latter, the testis is positioned in the superficial external inguinal ring, inguinal canal or abdominal cavity. Traumatic dislocation of the testis is treated by manual replacement and secondary orchidopexy. If primary manual reposition cannot be performed, immediate orchidopexy is indicated.

4.5.4.1.2 Haematocoele

Conservative management is recommended in haematocoeles smaller than three times the size of the contralateral testis [346]. In large haematocoeles, non-operative management often fails, and delayed surgery (> 3 days) is often required. Patients with large haematocoeles have a higher rate of orchiectomy than patients who undergo early surgery, even in non-ruptured testes [304, 312, 347-349]. Early surgical intervention results in preservation of the testis in more than 90% of cases compared to delayed surgeries which result in orchiectomy in 45-55% of patients [349]. In addition, non-operative management is also associated with prolonged hospital stays. Therefore, large haematocoeles should be treated surgically, irrespective of the presence of testicular contusion or rupture. At the very least, the blood clot should be evacuated from the tunica vaginalis sac to relieve disability and hasten recovery. Patients initially treated non-operatively may eventually need delayed surgery if they develop infection or undue pain.

4.5.4.1.3 Testicular rupture

Testicular rupture is found in approximately 50% of cases of direct blunt scrotal trauma [349]. It may occur under intense, traumatic compression of the testis against the inferior pubic ramus or symphysis, resulting in a rupture of the tunica albuginea of the testis. A force of approximately 50 kg is necessary to cause testicular rupture [350]. Testicular rupture is associated with immediate pain, nausea, vomiting, and sometimes fainting.

The hemiscrotum is tender, swollen, and ecchymotic. The testis itself may be difficult to palpate.

High-resolution, real-time US with a high-resolution probe (minimum 7.5 MHz or higher) should be performed to determine intra- and/or extra-testicular haematoma, testicular contusion, or rupture [351-357, 358]. The literature is contradictory as to the usefulness of US compared to clinical examination alone. Some studies have reported convincing findings with a specificity of up to 98.6% [334]. Others reported poor specificity (78%) and sensitivity (28%) for the differentiation between testicular rupture and haematocoele, while accuracy is as low as 56% [352]. Colour Doppler-duplex US may provide useful information when used to evaluate

testicular perfusion. If scrotal US is inconclusive, testicular CT or MRI may be helpful [359]. However, these techniques did not specifically increase the detection rates of testicular rupture. It is therefore essential to surgically explore equivocal patients whenever imaging studies cannot definitively exclude testicular rupture. This involves exploration with evacuation of blood clots and haematoma, excision of any necrotic testicular tubules and closure of the tunica albuginea, usually with running absorbable sutures (e.g. 3/0 Vicryl).

4.5.4.2 *Penetrating scrotal trauma*

Penetrating injuries to the scrotum require surgical exploration with conservative debridement of non-viable tissue. Depending on the extent of the injury, primary reconstruction of the testis and scrotum can usually be performed. In complete disruption of the spermatic cord, realignment without vaso-vasostomy may be considered if surgically feasible [360]. Staged secondary microsurgical vaso-vasostomy can be performed after rehabilitation, although only a few cases have been reported [360]. If there is extensive destruction of the tunica albuginea, mobilisation of a free tunica vaginalis flap can be performed for testicular closure. If the patient is unstable or reconstruction cannot be achieved, orchiectomy is then indicated.

Prophylactic antibiotics are recommended after scrotal penetrating trauma, although data to support this approach is lacking. Tetanus prophylaxis is mandatory. Post-operative complications were reported in 8% of patients who underwent testicular repair after penetrating trauma [249].

Extended laceration of scrotal skin requires surgical intervention for skin closure. Due to the elasticity of the scrotum, most defects can be primarily closed, even if the lacerated skin is only minimally attached to the scrotum [312]. Local wound management with extensive initial wound debridement and washout is important for scrotal convalescence. In the case of extensive loss of genital tissue, e.g. IED blast injury, complex and staged reconstructive surgical procedures are often required [310].

4.5.5 *Genital trauma in females*

In females with blunt trauma to the external genitalia, imaging of the pelvis with US, CT, or MRI should be performed since additional injuries and extensive intra-pelvic haematomas are frequently expected [316, 326].

4.5.5.1 *Blunt vulvar injuries*

Blunt trauma to the vulva is rarely reported and usually presents as a large haematoma. The incidence of traumatic vulvar haematomas after vaginal deliveries has been reported as 1 in 310 deliveries [361]. Although blunt trauma to the female external genitalia is rarely reported, the presence of a vulvar haematoma is closely related to an increased risk of associated vaginal, pelvic or abdominal injuries. Goldman et al. reported that blunt injuries of the vulva and vagina were associated with pelvic trauma in 30%, after consensual intercourse in 25%, sexual assault in 20%, and other blunt trauma in 15% [315].

Blunt vulvar or perineal trauma may be associated with voiding problems and bladder catheterisation is usually required. Vulvar haematomas usually do not require surgical intervention, although they can cause a significant blood loss, which sometimes even requires blood transfusion. Data are scarce [362], but in haemodynamically stable women, non-steroidal anti-inflammatory medication and cold packs are generally successfully used. Yet, in cases of massive vulvar haematoma and haemodynamically unstable patients, surgical intervention with lavage and drainage is sometimes indicated [363].

Although antibiotics are often recommended after major vulvar trauma, there is no data to support this approach. It is important to emphasise that vulvar haematoma and/or blood at the vaginal introitus are indications for vaginal exploration under sedation or general anaesthesia. The aim is to identify possible associated vaginal and/or rectal injuries [316]. Flexible or rigid cystoscopy has been recommended to exclude urethral and bladder injury [315, 316]. In the case of vulvar laceration, suturing after conservative debridement is indicated. If there are associated injuries to the vagina, these can be repaired immediately by primary suturing.

4.5.6 *Conclusion and recommendations for genital trauma*

Conclusion	LE
Most genital injuries, in males and females, are caused by blunt trauma.	3

Recommendations	GR
In penile fracture, early surgical management, with closure of tunica albuginea, is recommended to enable good long-term outcome and preservation of potency.	B
In testicular trauma, surgical exploration is recommended in all cases of testicular rupture and in those with equivocal imaging.	B

GR= grade of recommendation; LE = level of evidence.

5. POLYTRAUMA, DAMAGE CONTROL AND MASS CASUALTY EVENTS

5.1 Introduction

Urological trauma is often associated with significant and higher priority injuries in the polytraumatised patient [364]. Lessons from civilian trauma networks, the battlefield, and mass casualty events have led to many advances in general trauma care [365, 366]. These include the widespread acceptance of damage control principles, trauma centralisation and recognition of the value of dedicated trauma teams. Urologists need to understand their role in the context of polytrauma with the ultimate aims of improving survivability and decreasing morbidity in these patients.

5.1.1 The development of major trauma centres

Multidisciplinary management of trauma patients has been shown to improve outcomes [367]. Major trauma patients initially managed in local hospitals are 1.5 to 5 times more likely to die than patients transported directly to specialist trauma centres. The reorganisation of care to these centres has been shown to reduce mortality by 25% and length of stay by four days [365]. Major trauma centres, which are expected to provide senior-led resuscitative trauma teams, dedicated trauma theatres, input from all major surgical specialties and interventional radiologists, have therefore been established worldwide. Urologists have an important role to play in this process [368].

5.1.1.1 Recommendations for polytrauma management

	LE	GR
Polytrauma patients are ideally managed in designated major trauma centres.	3	A
Urologists are to be involved in cases of associated urological injury.	4	A

GR= grade of recommendation; LE = level of evidence.

5.2 Damage control

Damage control is a life-saving strategy for severely injured patients that recognises the consequences of the lethal triad of trauma, i.e. hypothermia, coagulopathy and acidosis [369-371].

It is a prioritised three-phase approach:

- The first phase consists of rapid control of haemorrhage and wound contamination.
- The second phase involves resuscitation in the intensive care unit (ICU), with the goal of restoring normal temperature, coagulation, and tissue oxygenation.
- The third stage involves definitive surgery when more time-consuming reconstructive procedures are performed in the stabilised patient [372].

Identifying which patients benefit from the damage control mode requires critical decision-making by the trauma team leader. Prior preparedness and regular communication between the surgical, critical care and anaesthetic teams are vital [373]. Damage control principles have been successfully adopted in the context of civilian mass casualty events, military field surgery, and initial treatment in rural areas with long-range transfers [370, 374].

5.3 Management principles: polytrauma and associated urological injury

Urologists are often asked for advice in polytrauma patients, some of whom might be in a damage control phase of management. Fortunately, the management of urological trauma often involves the use of temporary measures, followed by later definitive surgery, which fits in well with these principles.

In the polytrauma setting, the urologist will usually work alongside the general/trauma surgeon. Procedures

should be directed at the rapid control of bleeding, debridement of dead and devitalised tissue, and minimizing urinary extravasation by simple diversionary measures. Complex reconstructive procedures, including organ preservation, are preferably delayed.

Examples where urological input is required in the polytraumatised patient include:

- Haemodynamically unstable patients with suspected intra-abdominal bleeding, who are transferred urgently to the operating theatre without any pre-operative imaging;
- Stable patients with suspected renal injuries-penetrating trauma to the upper abdomen/flanks/lower chest, or blunt abdominal trauma and visible haematuria;
- Patients with suspected urethral or bladder injury associated with pelvic fractures-blood at the urethral meatus and/or the inability to void;
- External genitalia injury associated with penetrating trauma (intra-abdominal injury).

5.3.1 **Statement and recommendation on management principles**

Statement	LE	GR
Damage control principles govern the management of the severely injured polytrauma patient.	4	
Recommendation		
Urologists are to understand their role in the damage control setting.	4	A

GR= grade of recommendation; LE = level of evidence.

5.4 **Urological injury management in polytrauma**

5.4.1 **Renal injury**

The incidence of multiorgan injury is high in penetrating trauma [29]. Most of these injuries can be managed without surgical exploration [26]. Renal exploration is required to control life-threatening bleeding [375]. The preservation of viable renal parenchyma is a secondary goal, with time-consuming renal reconstruction delayed until the patient is optimised [101].

At laparotomy, it is considered best practice not to explore the injured kidney if there is no active haemorrhage, even if delayed exploration is then necessary [75]. In unstable patients, packing the renal fossa and transferring the patient to the surgical ICU is the option of choice for damage control. A planned second-look laparotomy is then performed [172]. However, in patients with significant ongoing haemorrhage, speedy nephrectomy is required. It is recommended that the contralateral kidney should at least be palpated prior to nephrectomy [376].

In patients who are packed temporarily and who become sufficiently stable in the intensive setting, radiological assessment allows definitive management to begin. Computed tomography allows the kidney injury to be graded, documents the presence of a contralateral kidney, and helps to determine whether or not intervention (radiological or surgical) is necessary.

In patients who are haemodynamically unstable after the initial, acute-damage-control, laparotomy, or in patients with deteriorating haemodynamic parameters (indicating ongoing or delayed bleeding), the management options are angiographic embolisation of the bleeding kidney or re-operation. This decision should be made according to:

- The status of the patient;
- The presence of associated injuries (stapled bowel, packed liver or spleen), which may need re-operation irrespective of the renal injury;
- The availability of angioembolisation.

5.4.1.1 **Renal preservation**

Haemostatic techniques, many of which were developed for hepatic surgery and splenic trauma, can be used to control renal parenchymal bleeding. These techniques are not consistent with damage control principles and should only be considered in the rare casualty situation of a solitary kidney or bilateral renal injury.

These techniques are outlined below:

- Mattress sutures through the parenchyma, i.e. Renorrhaphy [172].
- Haemostatic agents, i.e. combined acellular matrix and fibrin sealants [103].
- Absorbable mesh kidney bags to maintain contact between renal parenchymal fragments [96].
- An intra-operative drain is left *in situ* to collect any urine that leaks following organ salvage.

5.4.1.2 Recommendations for the management of renal injury

	LE	GR
Life-threatening bleeding from renal injury is best managed by urgent nephrectomy.	4	B
Renal packing is an acceptable damage control option for haemorrhage.	4	B
Angioembolisation can be used immediately or can be delayed as a very effective haemostatic option.	4	B
Renal preservation is reserved primarily for patients with a solitary kidney.	4	B

GR= grade of recommendation; LE = level of evidence.

5.4.2 Ureteral injury

Ureteral injuries are primarily associated with penetrating intra-abdominal injury; although rapid deceleration injuries can also result in ureteropelvic disruption [155]. A high index of suspicion is required as these injuries are quite commonly missed [377]. The results of immediate ureteral reconstruction are generally satisfactory, but this is time-consuming and may not be appropriate in the polytraumatised patient. Diagnostic procedures, such as on-table IVP or retrograde ureteropyelography, to evaluate ureteral injuries are also not recommended in this setting.

If a ureteral injury is suspected but not clearly identified, a drain should be sited. If urine leaks post-operatively, a nephrostomy should be arranged. If a partial ureteral tear is identified (less than half a circumference) and the ureter is otherwise healthy, a double J-stent may be inserted over a guide wire through the tear, and the tear quickly closed with fine interrupted absorbable stitches.

When complete ureteral injuries are identified, definitive repair should not be performed. Dissection of the ureteral stumps should be avoided as it interferes with the blood supply. Temporary measures to control urine spillage should be performed:

- A single J or 8 French feeding tube is inserted into the ureter;
- The end of the disrupted proximal ureter is secured over the tube, which is exteriorised and secured to the skin.

The distal ureteral stump does not need to be ligated and any unnecessary manipulation should be avoided. Intra-operative placement of a nephrostomy tube is time-consuming and should be avoided [101, 172].

Tying off the injured ureteral segment and inserting a percutaneous nephrostomy post-operatively is a viable alternative [378]. Rarely, in cases with severe associated injuries of the ipsilateral kidney, nephrectomy is required.

5.4.2.1 Recommendations for the management of ureteral injury

	LE	GR
A high index of suspicion for ureteral injury in penetrating abdominal trauma is required.	4	A
Simple 'tube' urinary diversion is recommended if repair is not undertaken.	4	C

GR= grade of recommendation; LE = level of evidence.

5.4.3 Bladder trauma

In the acute polytrauma setting, a bladder injury should be treated with bladder drainage by a suprapubic and/or a urethral catheter. Later, definitive treatment can follow as necessary [179]. Ideally, large intraperitoneal bladder ruptures (often associated with unstable pelvic fractures) should be closed primarily and drained, as this will cope with both haemorrhage control and urinary contamination.

Examples of temporary measures that may be necessary include:

- The placement of externalised ureteral stents to provide external urinary drainage in extensive bladder rupture [172];
- Packing and/or arteriography and selective embolisation in unstable patients with severe bladder haemorrhage [172];
- The placement of a pelvic suction drain for urinary evacuation [172].

5.4.3.1 Recommendations for the management of bladder trauma

	LE	GR
Bladder injuries require urinary drainage by either the suprapubic or urethral route.	4	A
Complex bladder injuries in the setting of polytrauma may require temporary 'damage control' measures.	4	A

GR = grade of recommendation; LE = level of evidence.

5.4.4 Urethral injury

Urethral injury of any kind is not life-threatening, but the associated injuries are often severe. In this situation, wherever the location or extent of injury, drainage through a suprapubic or urethral catheter should be obtained without prior imaging [243].

5.4.4.1 Recommendation for the management of urethral injury

	LE	GR
Urethral injuries require urgent urinary drainage by either the suprapubic or urethral route.	4	A

GR= grade of recommendation; LE = level of evidence.

5.4.5 External genital injury

Traditionally, traumatic injuries of the external genitalia have a low priority and management is often deferred [379]. In the polytraumatised patient, the management of these injuries should be guided by the principles of haemorrhage control, debridement and urinary diversion (via a catheter). Delayed organ conservation is possible, particularly in testicular injury [380].

Temporary damage control measures that might be applicable include:

- Compression dressing of the penis [172];
- Packing of penetrating testicular injuries;
- Tampons for vulvar lacerations.

5.5 Mass casualty events

A mass casualty event is one in which the number of injured people is significantly higher than the number of available healthcare providers [381]. A mass casualty disaster does not therefore necessarily involve a large number of victims, but it is related to the disproportion between the number of victims and the size of the medical team available [382, 383].

There is little published data on the best way in which to handle these events. However, recent developments in both the military and civilian settings have led to greater survivability following major trauma [384]. Triage, communication and preparedness are important components for a successful response.

Potential mass casualty events include:

- Transportation systems accidents, e.g. road traffic, aircraft, shipping, railways;
- Natural disasters, e.g. earthquakes, hurricanes, floods, tsunamis;
- Industry, e.g. chemical spills, factory explosions and fires;
- Civilian terrorism.

5.5.1 Triage

Triage after mass casualty events is difficult and involves difficult moral and ethical considerations. Disaster triage requires differentiation of the few critically injured individuals who can be saved by immediate intervention from the many others with non-life-threatening injuries for whom treatment can be delayed. The ethical dilemmas that arise are primarily caused by having to decide who should be actively treated, or subsequently whether to stop treatment, because of injuries deemed unsurvivable or incompatible with survival in the home environment.

Triage sorts patients into four groups [385, 386]:

1. Patients with life-threatening injuries that require immediate intervention, presenting with airway compromise, breathing failure and/or circulatory compromise from ongoing external haemorrhage.
2. Patients with severe but non-life-threatening injuries, in whom treatment can be acceptably delayed, including those with major fractures, vascular injuries of the limbs and large soft tissue wounds.
3. 'Walking wounded', i.e. casualties with minimal injuries.

4. Patients who are so severely injured that treatment would require allocation of resources and time that would deny timely care to other patients with greater survivability. These patients are given minimal or no treatment, and are re-evaluated when resources become available. There is no absolute definition for this group because triage is individualised, according to the number and severity of casualties related to the available resources. The decision to implement this category is decided when sufficient information of the incident is available and is made at the highest level possible.

Triage should be performed at each stage from the pre-hospital setting to the emergency department and repeated as the clinical situation evolves. Ultimately, the individual in charge is responsible for directing specialty surgical teams, including urologists, and assigning them responsibility for specific patients as dictated by the specific injuries.

5.5.2 ***Urological role in the mass casualty setting***

Urological consultations during a mass casualty scenario should follow the principles outlined below:

1. Rule out under-triage by the surgeon in charge, and perform a rapid primary survey of every patient.
2. Avoid unnecessary imaging procedures such as CT scans and retrograde urethrography. These procedures should be performed later, after re-evaluation of the patient, and after mass casualty protocols have been suspended.
3. Treat unstable patients who are to have surgery using damage control principles.
4. Stable patients should be transferred to the surgical ward without imaging procedures. Re-evaluate if there is any change in their haemodynamic status, or when possible as dictated by the constraints of the mass casualty event.
5. 'Minimal acceptable' treatment for all urological injuries should be performed in order to transfer patients to the surgical wards and are outlined above in the Section 5.4 Urological injury management in polytrauma.

5.5.3 ***Statements and recommendations for mass casualty events***

Statements	LE
Recent large scale military conflicts have raised the standard of practice for trauma patients.	4
The centralisation of trauma and the establishment of trauma centres results in better outcomes for trauma patients.	3
Urologists have an important role to play in the management of polytrauma patients.	4

Recommendations	GR
Damage control surgery should be employed as the standard approach in the management of unstable trauma patients.	A
Medical teams should be well prepared to deal with polytrauma events.	A
All surgical sub-specialists involved in trauma management should be very familiar with the principles of triage and damage control.	A

GR= grade of recommendation; LE = level of evidence.

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7. CONFLICT OF INTEREST

All members of the Urological Trauma Guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: <http://www.uroweb.org/guidelines/online-guidelines/>. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

Guidelines on Chronic Pelvic Pain

D. Engeler (Chair), A.P. Baranowski, J. Borovicka,
A. Cottrell (Guidelines Associate), P. Dinis-Oliveira,
S. Elneil, J. Hughes, E.J. Messelink (Vice-chair),
A. van Ophoven, Y. Reisman, A.C. de C Williams

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1. INTRODUCTION

1.1 Aim

This guideline plays an important role in the process of consolidation and improvement of care for patients with abdominal and pelvic pain. From both literature and daily practice it has become clear that abdominal and pelvic pain are areas still under development. This guideline has been recognised as a cornerstone for important developments that have taken place in the past 10 years.

This guideline aims to expand the awareness of caregivers in the field of abdominal and pelvic pain, and to assist those who treat patients with abdominal and pelvic pain in their daily practice. The guideline is a useful instrument not only for urologists, but also for gynaecologists, surgeons, physiotherapists, psychologists and pain doctors.

1.1.1 Structure and scope

The panel wishes to take advantage of modern methods of delivering guideline information to clinicians dealing with these patients. We therefore plan to make a stepped information structure, in alignment with stepped care protocols. It is the vision of the panel to use new digital information sources like websites and apps to aid this process. Furthermore, the panel wishes to change the guideline according to the template used in all other non-oncology guidelines of the EAU. It has been recognised that structuring a guideline on chronic pain is quite different from structuring one on another subject. Multidisciplinary is of utmost importance and demands a broad view.

For the 2016 version the panel has made plans focussing on two important changes to the guideline. The first one is to rewrite the guideline in such a way that it is centred around pain instead of being organ centred. Chapters are now named after the organ or after the specialist that is consulted by the patient. For the 2016 edition of this guideline, pain will be the centre and every other information will be build around this central theme. The guideline will be partly theoretical to elucidate the importance of using a pain centred approach. The biggest part however, will deal with the practical approach in diagnostics, treatment and management of patients with abdominal and pelvic pain.

The second change the panel is working on is the way of presenting those practical aspects of pain. The guideline will, based on pain in the centre, lead the healthcare professional through the different steps in the process of dealing with abdominal and pelvic pain patients. One could say that it will be patient centred instead of complaint centred. Theoretical information will serve as background and can be read when needed. This second focus of updating will be of great importance for developing modern ways to make information available for the general practitioner who sees the patient in their office. It will contain red flags, associated conditions and available first line treatments. It should also be available for the medical specialist who gets a patient with chronic pain referred. The guideline will highlight necessary investigations and phenotyping, treatment options, decision making on whether a treatment is rational or not, and how and when to refer to a specialised pelvic pain centre. Caregivers who treat patients for pain related problems like myofascial and sexological dysfunctions will find help in making treatment plans and in the timing of referring back to specialised care. The guideline will also aid those involved in coaching self management and shared care.

1.2 Publication history

The EAU Guidelines on Chronic Pelvic Pain were first published in 2003 [1] which formed the basis of a scientific publication in European Urology in 2004 [2]. Also, in the 2003 edition the concept of Chronic Pelvic Pain Syndromes (CPPS) was introduced, which is now referred to as “pain as a disease process”. Partial updates of the CPP Guidelines were published in 2008 and formed the basis for another scientific publication in European Urology in the year 2010 [3, 4].

For the update in 2012 the Panel focussed on:

1. restructuring the text to emphasise the significance of holistic management of CPP;
2. addressing the changes in the management of CPPS based on the concept of pain as a disease process.

Two chapters were added at that time: Chapter 5 ‘Gastrointestinal aspects of chronic pelvic pain’ and Chapter 7 ‘Sexological aspects of chronic pelvic pain’.

In the 2014 edition minor revisions were made in the Chapters 5 ‘Gastrointestinal aspects of chronic pelvic pain’ and 8 ‘Psychological aspects of chronic pelvic pain’.

For the 2015 edition the Panel has worked on reduction of the text (about 35%). This was carried out to improve the readability of the document. We did a major reduction especially in Chapter 3 "Urological aspects of chronic pelvic pain". The subchapter on bladder pain syndrome was very critically revised and is now a comprehensive part of the guidelines. The fact that this part was so extensive shows that the roots of talking about abdominal and pelvic pain lies in the bladder, where Interstitial Cystitis was one of the first subjects addressed talking about pain in urology. The Panel has illustrated this in the publication in European Urology in 2013 [5].

Alongside the full text version, a quick reference document (Pocket Guidelines) is available, presenting key findings of the Chronic Pelvic Pain Guidelines. These reference documents follow the updating cycle of the underlying large texts. All available material can be viewed and downloaded for personal use at the EAU website. The EAU website also includes a selection of EAU Guidelines articles as well as translations produced by national urological associations: <http://www.uroweb.org/guidelines/online-guidelines/>.

This document was peer-reviewed prior to publication.

1.3 Panel composition

The panel of experts responsible for this document include five urologists, a neuro-urologist, two consultants in pain medicine, a gynaecologist, a psychologist, a gastroenterologist and two sexologists.

1.4 Methods

References used in this text are graded according to their Level of Evidence (LE) and Guidelines are given a Grade of Recommendation (GR). In this 2015 EAU Guidelines compilation, all standard information on LE and GR has been taken out of the individual Guidelines topics for the sake of brevity. The methodology section (see the introduction chapter of the complete book) outlines the LE and GR criteria which are used throughout the Guidelines, according to a classification system modified from the Oxford Centre for Evidence-based Medicine Levels of Evidence.

The 2012 full text update is based on a systematic review of literature using the Embase and Medline databases, the Cochrane Central Register of controlled trials and the PsycInfo and Bandolier databases to identify the best evidence from RCTs, Level of Evidence 1 (LE: 1), according to the rating schedule adapted from the Oxford Centre for Evidence-based Medicine Levels of Evidence (5). Where no (LE: 1) literature could be identified the search was moved down to the next lower level on the rating scale. Extensive use of free text ensured the sensitivity of the searches, resulting in a substantial body of literature to scan. Searches covered the period January 1995 and July 2011 and were restricted to English language publications.

Further updates of Chapter 5 'Gastrointestinal aspects of chronic pelvic pain' and Chapter 8 'Psychological aspects of chronic pelvic pain' in the 2014 edition were based on systematic reviews of the literature in the aforementioned databases including PsycInfo.

Initial list of abstracts	
<i>Chapter</i>	<i>Latest 'cut-off' date for search</i>
2 Chronic pelvic pain	16 May 2011
3 Urological aspects of chronic pelvic pain	
- Prostate pain syndrome	04 June 2011
- Bladder pain syndrome diagnosis	08 June 2011
- Bladder pain syndrome treatment	08 June 2011
- Scrotal pain syndrome	09 June 2011
- Urethral pain syndrome	09 June 2011
4 Gynaecological aspects of chronic pelvic pain	03 June 2011
5 Gastrointestinal aspect of chronic pelvic pain	14 January 2013
6 Peripheral nerve pain syndrome	17 May 2011
7 Sexological aspects of chronic pelvic pain	29 July 2011
8 Psychological aspects of chronic pelvic pain	16 January 2013
9 Pelvic floor function and chronic pelvic pain	08 June 2011
10 General treatment of chronic pelvic pain	29 June 2011

2. CHRONIC PELVIC PAIN

2.1 Introduction to chronic urogenital pain syndromes

Over the years much of the focus for CPP has been on peripheral-end-organ mechanisms, such as inflammatory or infective conditions. However, both animal and clinical research have indicated that many of the mechanisms for the CPP syndromes are based within the central nervous system (CNS). Although a peripheral stimulus such as infection may initiate the start of a CPP condition, the condition may become self-perpetuating as a result of CNS modulation, independent of the original cause. As well as pain, these central mechanisms are associated with several other sensory, functional, behavioural and psychological phenomena. It is this collection of phenomena that forms the basis of the pain syndrome diagnosis and individual phenomena need to be addressed in their own right through multispecialty and multidisciplinary care.

Although ongoing peripheral organ pathology can produce persistent and chronic pain, the main focus of these guidelines is on CPP syndromes in which no peripheral ongoing pathology (such as infection or neoplastic disease) is detected. The main exception is when pain is due to peripheral nerve damage, which will be discussed in Chapter 6.

2.2 Pain mechanisms - pain as a disease process

Chronic pelvic pain mechanisms may involve:

1. Ongoing acute pain mechanisms [6] (such as those associated with inflammation or infection), which may involve somatic or visceral tissue.
2. Chronic pain mechanisms, which especially involve the CNS [7].
3. Emotional, cognitive, behavioural and sexual responses and mechanisms [8-10]. These are covered in Chapters 7 and 8.

Table 1 illustrates some of the differences between the somatic and visceral pain mechanisms. They underlie some of the mechanisms that may produce the classical features of visceral pain; in particular, referred pain and hyperalgesia.

Table 1: Comparison between visceral and somatic pain

	Visceral pain	Somatic pain
Effective painful stimuli	Stretching and distension, producing poorly localised pain.	Mechanical, thermal, chemical and electrical stimuli, producing well localised pain.
Summation	Widespread stimulation produces significantly magnified pain.	Widespread stimulation produces a modest increase in pain.
Autonomic involvement	Autonomic features (e.g., nausea and sweating) frequently present.	Autonomic features less frequent.
Referred pain	Pain perceived at a site distant to the cause of the pain is common.	Pain is relatively well localised but well recognised.
Referred hyperalgesia	Referred cutaneous and muscle hyperalgesia is common, as is involvement of other visceral organs.	Hyperalgesia tends to be localised.
Innervation	Low density, unmyelinated C fibres and thinly myelinated A δ fibres.	Dense innervation with a wide range of nerve fibres.
Primary afferent physiology	Intensity coding. As stimulation increases, afferent firing increases with an increase in sensation and ultimately pain.	Two fibre coding. Separate fibres for pain and normal sensation.
Silent afferents	50-90% of visceral afferents are silent until the time they are switched on. These fibres are very important in the central sensitisation process.	Silent afferents present, but form a lower percentage.

Central mechanisms	Play an important part in the hyperalgesia, viscerovisceral, visceromuscular and muscovicisceral hyperalgesia. Sensations not normally perceived become perceived and non-noxious sensations become painful.	Responsible for the allodynia and hyperalgesia of chronic somatic pain.
Abnormalities of function	Central mechanisms associated with visceral pain may be responsible for organ dysfunction.	Somatic pain associated with somatic dysfunction, e.g., muscle spasm.
Central pathways and representation	As well as classical pathways, there is evidence for a separate dorsal horn pathway and central representation.	Classical pain pathways.

2.2.1 ***Ongoing peripheral visceral pain mechanisms as a cause of CPP***

In most cases of CPP, ongoing tissue trauma, inflammation or infection is not present [11-14]. However, conditions that produce recurrent trauma, infection or ongoing inflammation may result in CPP in a small proportion of cases. It is for this reason that the early stages of assessment include looking for these pathologies [15]. Once excluded, ongoing investigations for these causes are rarely helpful and indeed may be detrimental.

When acute pain mechanisms are activated by a nociceptive event, as well as direct activation of the peripheral nociceptor transducers, sensitisation of those transducers may also occur, thus magnifying the afferent signalling. Afferents that are not normally active may also become activated by the change, that is, there may be activation of the so-called silent afferents. Although these are mechanisms of acute pain, the increased afferent signalling is often a trigger for the chronic pain mechanisms that maintain the perception of pain in the absence of ongoing peripheral pathology (see below) [16, 17].

There are a number of mechanisms by which the peripheral transducers may exhibit an increase in sensibility.

1. Modification of the peripheral tissue, which may result in the transducers being more exposed to peripheral stimulation.
2. There may be an increase in the chemicals that stimulates the receptors of the transducers [18].
3. There are many modifications in the receptors that result in them being more sensitive.

In general, the effect of 1 and 2 is to lower the threshold and the effect of 3 is to increase responsiveness to external stimuli. Some of the chemicals responsible for the above changes may be released from those cells associated with inflammation, but the peripheral nervous system may also release chemicals in the form of positive and inhibitory loops [19].

2.2.2 ***Central sensitisation - spinal and higher mechanisms of visceral pain***

There are essentially three processes at the spinal cord level that are involved in central sensitisation [20]. Changes in existing protein activity (post-translational processing) are the earliest (within minutes); however, changes in genetic transcription of proteins and even structural changes in neuron connectivity may also have roles to play. These latter changes may occur within days [21].

2.2.3 ***Spinal mechanisms and visceral hyperalgesia***

Central sensitisation [21] is responsible for a decrease in threshold and increase in response duration and magnitude of dorsal horn neurons. It is associated with an expansion of the receptive field. As a result, sensitisation increases signalling to the CNS and amplifies what we perceive from a peripheral stimulus. As an example, for cutaneous stimuli, light touch would not normally produce pain, however, when central sensitisation is present, light touch may be perceived as painful (allodynia). In visceral hyperalgesia (so called because the afferents are primarily small fibres), visceral stimuli that are normally subthreshold and not usually perceived may be perceived. For instance, with central sensitisation, stimuli that are normally subthreshold may result in a sensation of fullness and a need to void the bladder or to defecate. Stimuli normally perceived may be interpreted as pain and stimuli that are normally noxious may be magnified (true hyperalgesia) with an increased perception of pain. As a consequence, one can see that many of the symptoms of the bladder pain syndrome (BPS) and irritable bowel syndrome (IBS) may be explained by central sensitisation. A similar explanation exists for the muscle pain of fibromyalgia.

2.2.4 *Supraspinal modulation of pain perception*

It is important to appreciate that nociception is the process of transmitting to centres involved in perception of information about a stimulus that has the potential to cause tissue damage. Pain is far more complex and involves activation of the nociceptive pathways but also the emotional response. Pain is defined by the International Association for the Study of Pain (IASP) as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” [22]. The brain may affect the modulation of pain pathways at the spinal cord level.

2.2.5 *Higher centre modulation of spinal nociceptive pathways*

It is now well accepted that there are both descending pain-inhibitory and descending pain-facilitatory pathways that originate from the brain [23].

Several neurotransmitters and neuromodulators are involved in descending pain-inhibitory pathways. The main contenders are the opioids, 5-hydroxytryptamine and noradrenaline.

2.2.6 *Neuromodulation and psychology*

Psychological processes of emotions, thought and behaviour involve networks rather than distinct centres. Some of these processes are sophisticated and others fundamental in evolutionary terms, and their interaction with pain processing is complex.

Various psychological processes affect pain neuromodulation at the higher level. Inhibiting or facilitating both the nociceptive signal reaching the consciousness and appraisal and interpretation of that signal; they will also modulate the response to the nociceptive message and hence the pain experience. Further, descending pathways represent cognitive, emotional and behavioural states at spinal and peripheral levels.

Functional Magnetic Resonance Imaging (fMRI) has indicated that the psychological modulation of visceral pain probably involves multiple pathways. For instance, mood and attentional focus probably act through different areas of the brain when involved in reducing pain [24].

This psychological modulation may act to reduce nociception within a rapid time frame but may also result in long-term vulnerability to chronic visceral pain, through long-term potentiation. This involvement of higher centre learning may be at both a conscious and subconscious level, and is clearly significant in the supratentorial neuroprocessing of nociception and pain. Long-term potentiation [25] may also occur at any level within the nervous system, so that pathways for specific or combinations of stimuli may become established, resulting in an individual being vulnerable to perceiving sensations that would not normally be experienced as painful.

Stress can modify the nervous system to produce long-term biological changes. These structural changes may be responsible for significant early life and adverse life events which are associated with chronic pain syndromes [26]. The patient should be asked about significant adverse life events, which may produce these biological responses, and also have an effect on a patient's psychological wellbeing [27-29].

2.2.7 *Autonomic nervous system*

There is good evidence that damaged afferent fibres may develop a sensitivity to sympathetic stimulation, both at the site of injury and more centrally, particularly the dorsal horns. In visceral pain, the efferent output of the CNS may be influenced by central changes (again, those changes may be throughout the neuraxis), and such modification of the efferent message may produce significant end-organ dysfunction. These functional abnormalities can have a significant effect on quality of life (QoL) and must be managed as appropriate.

2.2.8 *Endocrine system*

The endocrine system is involved in visceral function. Significant life events, and in particular, early life events may alter the development of the hypothalamic-pituitary-adrenal axis and the chemicals released. Increased vulnerability to stress may occur following such events and is thought to be partly due to increased corticotrophin-releasing hormone (CRH) gene expression. Upregulation of CRH has been implicated in several pain states such as rectal hypersensitivity to rectal distension. This model suggests an action of CRH on mast cells. A range of stress-related illnesses have been suggested, e.g. IBS and BPS. There is also evidence accumulating to suggest that the sex hormones also modulate both nociception and pain perception.

2.2.9 *Genetics and chronic pain*

An individual who has had one chronic pain syndrome is more likely to develop another. Family clusters of

pain conditions are also observed and animals can be bred that are more prone to an apparent chronic pain state. A whole range of genetic variations have been described that may explain the pain in certain cases; many of these are to do with subtle changes in transmitters and their receptors. However, the picture is more complicated in that development, environment and social factors also influence the situation.

2.3 Clinical paradigms and CPP

2.3.1 Referred pain

Referred pain is frequently observed and its identification is important for diagnosis and treatment. Referral is usually somatic to somatic, or visceral to somatic. However, there is no reason why pain cannot also be perceived within the area of an organ with the nociceptive signal having arisen from a somatic area. Referred pain may occur as a result of several mechanisms but the main theory is one of convergence-projection. In the convergence-projection theory, as an example, afferent fibres from the viscera and the somatic site of referred pain converge onto the same second order projection neurons. The higher centres receiving messages from these projection neurons are unable to separate the two possible sites from the origin of the nociceptive signal [12, 16, 30].

2.3.2 Referred pain to somatic tissues with hyperalgesia in the somatic tissues

Hyperalgesia refers to an increased sensitivity to normally painful stimuli. In patients that have passed a renal stone, somatic muscle hyperalgesia is frequently present, even a year after expulsion of the stone. Pain to non-painful stimuli (allodynia) may also be present in certain individuals. Somatic tissue hyperaesthesia is associated with urinary and biliary colic, IBS, endometriosis, dysmenorrhoea, and recurrent bladder infection. Vulvar pain syndromes are examples of cutaneous allodynia that, in certain cases, may be associated with visceral pain syndromes, such as BPS. Referred pain with hyperalgesia is thought to be due to central sensitisation of the converging viscerosomatic neurones. Central sensitisation also stimulates efferent activity that could explain the trophic changes that are often found in the somatic tissues.

2.3.3 Muscles and pelvic pain

In the urogenital pain syndromes, muscle tenderness and trigger points may be implicated as a source of pain. Central mechanisms are of great importance in the pathogenesis of this muscle hyperalgesia. The muscles involved may be a part of the spinal, abdominal or pelvic complex of muscles. It is not unknown for adjacent muscles of the lower limbs and the thorax to become involved. Pain may be localised to the trigger points but it is more often associated with classical referral patterns. As well as trigger points, inflammation of the attachments to the bones (enthesitis) and of the bursa (bursitis) may be found [31].

Certain postures affect the different muscles in different ways, and as a consequence, may exacerbate or reduce the pain. Stress has been implicated as both an initiator of pelvic myalgia and as a maintenance factor. As a result, negative sexual encounters may also have a precipitating effect [26].

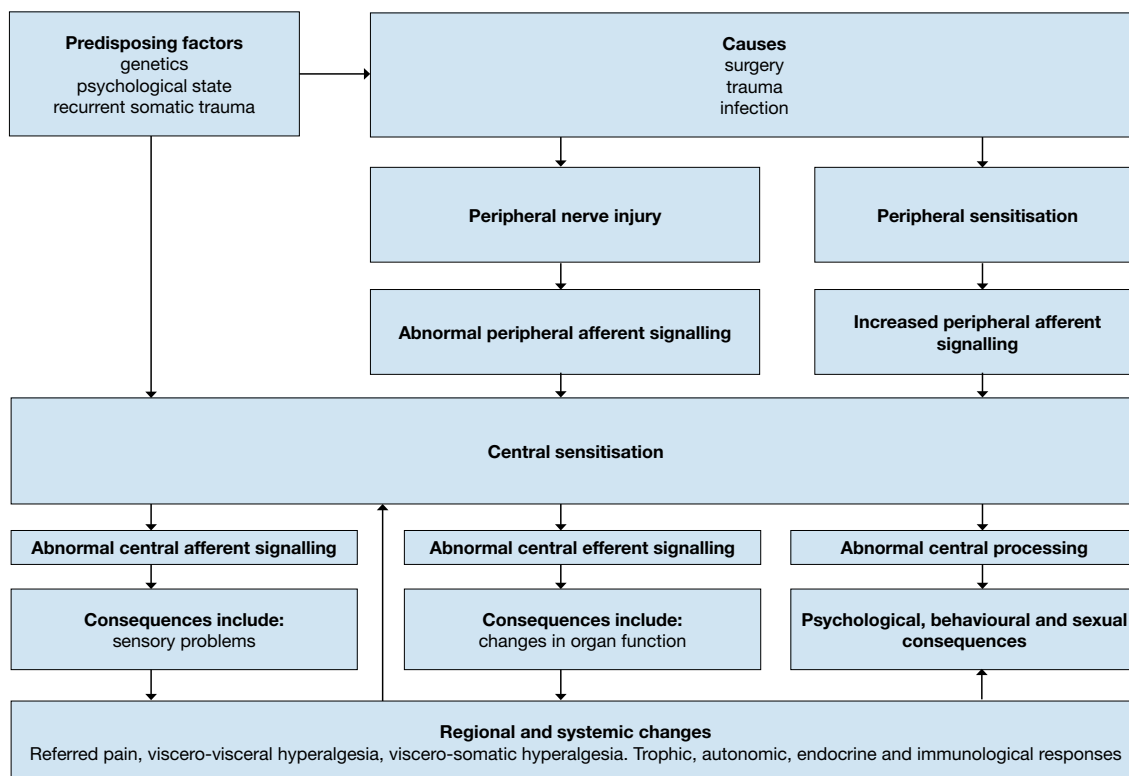
2.3.4 Visceral hyperalgesia

The increased perception of stimuli in the viscera is known as visceral hyperalgesia, and the underlying mechanisms are thought to be responsible for IBS, BPS and dysmenorrhoea. The mechanisms involved are often acute afferent input (e.g., due to infection) followed by long-term central sensitisation.

2.3.5 Viscero-visceral hyperalgesia

Viscero-visceral hyperalgesia is thought to be due to two or more organs with converging sensory projections and central sensitisation. For instance, overlap of bladder and uterine afferents or uterine and colon afferents.

Figure 1: Predisposing factors and causes associated with central and peripheral mechanisms



2.4 Classification of CPP syndromes

2.4.1 Importance of classification

It should be obvious to all that a condition cannot be treated unless it is defined. However, the reasons for classifying CPP go far beyond that.

Phenotyping

Phenotyping is describing the condition. For example, chronic bladder pain may be associated with the presence of Hunner's lesions and glomerulation on cystoscopy, whereas other bladder pain conditions may have a normal appearance on cystoscopy. These are two different phenotypes. The same is true for IBS, which may be subdivided into that with primarily diarrhoea or that with constipation. Phenotyping is based upon mechanisms when they are known (e.g., infection, ischaemic, autoimmune, or neuropathic). In the absence of well-defined mechanisms, describing the condition by its symptoms, signs and, where possible, by investigations, has been demonstrated to have clinical and research validity in many situations. When pain is the main symptom and pain as a disease process is considered the cause, the condition is often referred to as a pain syndrome – a well-defined collection of symptoms, signs and investigation results associated with pain mechanisms and pain perception as the primary complaint.

EAU classification of chronic pelvic pain syndromes is described in Table 2.

International Association for the Study of Pain (IASP) definitions, see: <http://www.iasp-pain.org>

Table 2: EAU classification of chronic pelvic pain syndromes

Axis I Region	Axis II System	Axis III End-organ as pain syndrome as identified from Hx, Ex and Ix	Axis IV Referral characteristics	Axis V Temporal characteristics	Axis VI Character	Axis VII Associated symptoms	Axis VIII Psychological symptoms
Chronic pelvic pain	Urological	Specific disease associated pelvic pain	Suprapubic Inguinal Urethral Penile/clitoral Perineal Rectal Back Buttocks Thighs	ONSET Acute Chronic ONGOING Sporadic Cyclical Continuous TIME Filling Emptying Immediate post Late post TRIGGER Provoked Spontaneous	Aching Burning Stabbing Electric	UROLOGICAL Frequency Nocturia Hesitance Dysfunctional flow Urge Incontinence GYNAECOLOGICAL Menstrual Menopause GASTROINTESTINAL Constipation Diarrhoea Bloating Urge Incontinence NEUROLOGICAL Dysaesthesia Hyperaesthesia Allodynia Hyperalgesia SEXUOLOGICAL Satisfaction Female dyspareunia Sexual avoidance Erectile dysfunction Medication MUSCLE Function impairment Fasciculation CUTANEOUS Trophic changes Sensory changes	ANXIETY About pain or putative cause of pain Catastrophic thinking about pain DEPRESSION Attributed to pain or impact of pain Attributed to other causes Unattributed PTSD SYMPTOMS Re-experiencing Avoidance
		OR Pelvic pain syndrome					
Chronic pelvic pain	Gynaecological	Prostate	Suprapubic Inguinal Urethral Penile/clitoral Perineal Rectal Back Buttocks Thighs	ONSET Acute Chronic ONGOING Sporadic Cyclical Continuous TIME Filling Emptying Immediate post Late post TRIGGER Provoked Spontaneous	Aching Burning Stabbing Electric	UROLOGICAL Frequency Nocturia Hesitance Dysfunctional flow Urge Incontinence GYNAECOLOGICAL Menstrual Menopause GASTROINTESTINAL Constipation Diarrhoea Bloating Urge Incontinence NEUROLOGICAL Dysaesthesia Hyperaesthesia Allodynia Hyperalgesia SEXUOLOGICAL Satisfaction Female dyspareunia Sexual avoidance Erectile dysfunction Medication MUSCLE Function impairment Fasciculation CUTANEOUS Trophic changes Sensory changes	ANXIETY About pain or putative cause of pain Catastrophic thinking about pain DEPRESSION Attributed to pain or impact of pain Attributed to other causes Unattributed PTSD SYMPTOMS Re-experiencing Avoidance
		Bladder					
		Scrotal Testicular Epididymal					
		Penile Urethral					
	Gastrointestinal	Postvasectomy					
		Vulvar Vestibular Clitoral					
		Endometriosis associated					
		CPPS with cyclical exacerbations					
	Peripheral nerves	Dysmenorrhoea					
		Irritable bowel					
		Chronic anal					
		Intermittent chronic anal					
	Sexological	Pudendal pain syndrome					
		Dyspareunia					
	Psychological	Pelvic pain with sexual dysfunction					
		Any pelvic organ					
	Musculo-skeletal	Pelvic floor muscle Abdominal muscle Spinal					
		Coccyx					

Hx = History; Ex = Examination; Ix = Investigation; PTSD = post-traumatic stress disorder.

2.4.2 **Pain syndromes**

The original EAU classification [2] was inspired by the IASP classification [22] and much work around what has become known as “pain as a disease” and its associated psychological, behavioural, sexual and functional correlates. After 10 years work developing the initial ideas, an updated version was accepted by IASP Council for publication in January 2012.

2.4.2.1 *Definition of chronic pelvic pain (CPP)*

Chronic pelvic pain is chronic or persistent pain perceived* in structures related to the pelvis of either men or women. It is often associated with negative cognitive, behavioural, sexual and emotional consequences as well as with symptoms suggestive of lower urinary tract, sexual, bowel, pelvic floor or gynaecological dysfunction. [*Perceived indicates that the patient and clinician, to the best of their ability from the history, examination and investigations (where appropriate) has localised the pain as being perceived in the specified anatomical pelvic area.]

In the case of documented nociceptive pain that becomes chronic/persistent through time, pain must have been continuous or recurrent for at least 6 months. That is, it can be cyclical over a 6-month period, such as the cyclical pain of dysmenorrhoea. Six months is arbitrary, however, it was chosen because 3 months was not considered long enough if cyclical pain conditions are included. If non-acute and central sensitisation pain mechanisms are well documented, then the pain may be regarded as chronic, irrespective of the time period. Cyclical pain is included in the classification and hence dysmenorrhoea needs to be considered as a chronic pain syndrome if it is persistent and associated with negative cognitive, behavioural, sexual, or emotional consequences.

Chronic pelvic pain may be subdivided into conditions with well-defined classical pathology (such as infection or cancer) and those with no obvious pathology. For the purpose of this classification, the term “specific disease-associated pelvic pain” is proposed for the former, and “chronic pelvic pain syndrome” for the latter. The following classification only deals with CPPS.

2.4.2.2 *Definition of chronic pelvic pain syndrome*

Chronic pelvic pain syndrome (CPPS) is the occurrence of CPP when there is no proven infection or other obvious local pathology that may account for the pain. It is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. CPPS is a subdivision of CPP.

2.4.2.2.1 Further subdivision of CPPS

Pain perception in CPPS may be focused within a single organ, more than one pelvic organ and even associated with systemic symptoms such as chronic fatigue syndrome (CFS), fibromyalgia (FM) or Sjögren's syndrome. When the pain is localised to a single organ, some specialists may wish to consider using an endorgan term such as BPS. The use of such a phrase with the terminology “syndrome” indicates that, although peripheral mechanisms may exist, CNS neuromodulation may be more important and systemic associations may occur. When the pain is localised to more than one organ site, the term CPPS should be used. Many, including some of the authors of this text, never subdivide by anatomy and prefer to refer to patients with pain perceived within the pelvis and no specific disease process as suffering from CPPS, subdivided by psychological and functional symptoms.

2.4.2.2.2 Psychological considerations for classification

Many CPPSs are associated with a range of concurrent negative psychological, behavioural and sexual consequences that must be described and assessed. Examples that need to be considered are depression, anxiety, fears about pain or its implications, unhelpful coping strategies, and distress in relationships. Both anxiety and depression can be significant important concomitant symptoms that are relevant to pain, disability and poor QoL. Catastrophic interpretation of pain has been shown to be a particularly salient variable, predicting patients' report of pain, disability, and poor QoL, over and above psychosocial variables such as depression or behavioural factors such as self-reported sexual dysfunction. It is suggested that CPPS sometimes creates a sense of helplessness that can be reported as overwhelming, and may be associated with the refractory nature of the patients' symptoms. It is important to note that many of these biopsychosocial consequences are common to other persistent pain problems but may show varying degrees of salience for any one individual suffering from CPPS. In all patients with CPPS, these consequences must be clearly described as part of the phenotype (where the term phenotype is used to indicate the observable characteristics of the syndrome).

2.4.2.2.3 Functional considerations for classification

Functional disorders, for the purpose of this document, are pathologies that have arisen secondary to changes in the control mechanisms of an organ or system. That is, they are disorders characterised by disturbance of function. As an example, slow colonic transit is a functional disorder of the bowel - the normal function of the bowel is not occurring as a result of changes in the mechanisms that produce defecation, and hence the bowel control is abnormal. The term is not used in the sense of a psychiatric functional disorder. Many CPPSs are associated with functional abnormalities at a local and even systemic level. These also need to be defined as a part of the phenotype. Functional pain disorders may not express significant pathology in the organs that appear responsible for the primary symptoms, but they are associated with substantial neurobiological, physiological and sometimes anatomical changes in the CNS.

2.5.2.2.4 Multisystem subdivision

It is recognised that the end-organ where the pain is perceived may not be the centre of pain generation. This classification is based upon the most effective accepted method of classifying and identifying different pain syndromes, that is, by site of presentation. It is argued that keeping the end-organ name in the classification is inappropriate because, in most cases, there are multisystemic causes and effects, with the result that symptoms are perceived in several areas. This is an area in which discussions are ongoing, and despite there being strong arguments for both keeping and dispensing with end-organ classification, the authors have not taken the umbrella approach of referring to all pain perceived in the pelvis as CPPS.

2.4.2.2.5 Dyspareunia

Dyspareunia is defined as pain perceived within the pelvis associated with penetrative sex. It tells us nothing about the mechanism and may be applied to women and men. It is usually applied to penile penetration, but is often associated with pain during insertion of any object. It may apply to anal as well as vaginal intercourse. It is classically subdivided into superficial and deep.

2.4.2.2.6 Perineal pain syndrome

Perineal pain syndrome is a neuropathic-type pain that is perceived in the distribution area of the pudendal nerve, and may be associated with symptoms and signs of rectal, urinary tract or sexual dysfunction. There is no proven obvious pathology. It is often associated with negative cognitive, behavioural, sexual and emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. Perineal pain syndrome should be distinguished from pudendal neuralgia, which is a specific disease associated with pelvic pain that is caused by nerve damage.

Specific pain syndromes are defined in the relevant chapters.

2.5 Conclusions and recommendations: CPP and mechanisms

Conclusions	LE
CPPS mechanisms are well defined and involve mechanisms of neuroplasticity and neuropathic pain.	2
The mechanisms of neuroplasticity and neuropathic pain result in increased perception of afferent stimuli which may produce abnormal sensations as well as pain.	1
End-organ function can also be altered by the mechanisms of neuroplasticity and neuropathic pain, so that symptoms of function can also occur.	1
CPP is associated with a high impact on QoL.	1
The diagnosis of a CPPS as a pain syndrome is essential as it encourages a holistic approach to management with multispecialty and multidisciplinary care.	2

Recommendations	GR
All of those involved in the management of CPP should have an understanding and training in CPPS pain mechanisms.	A
The early assessment of patients should involve not only investigations aimed at specific disease-associated pelvic pain but also assessment of functional, emotional, behavioural, sexual and other quality of life issues, such as effect on work and socialisation.*	A
CPPS patients should be managed in a multispecialty and multidisciplinary environment with consideration of all their symptoms.	A
Future classification should involve consideration of all three recommendations above.	A

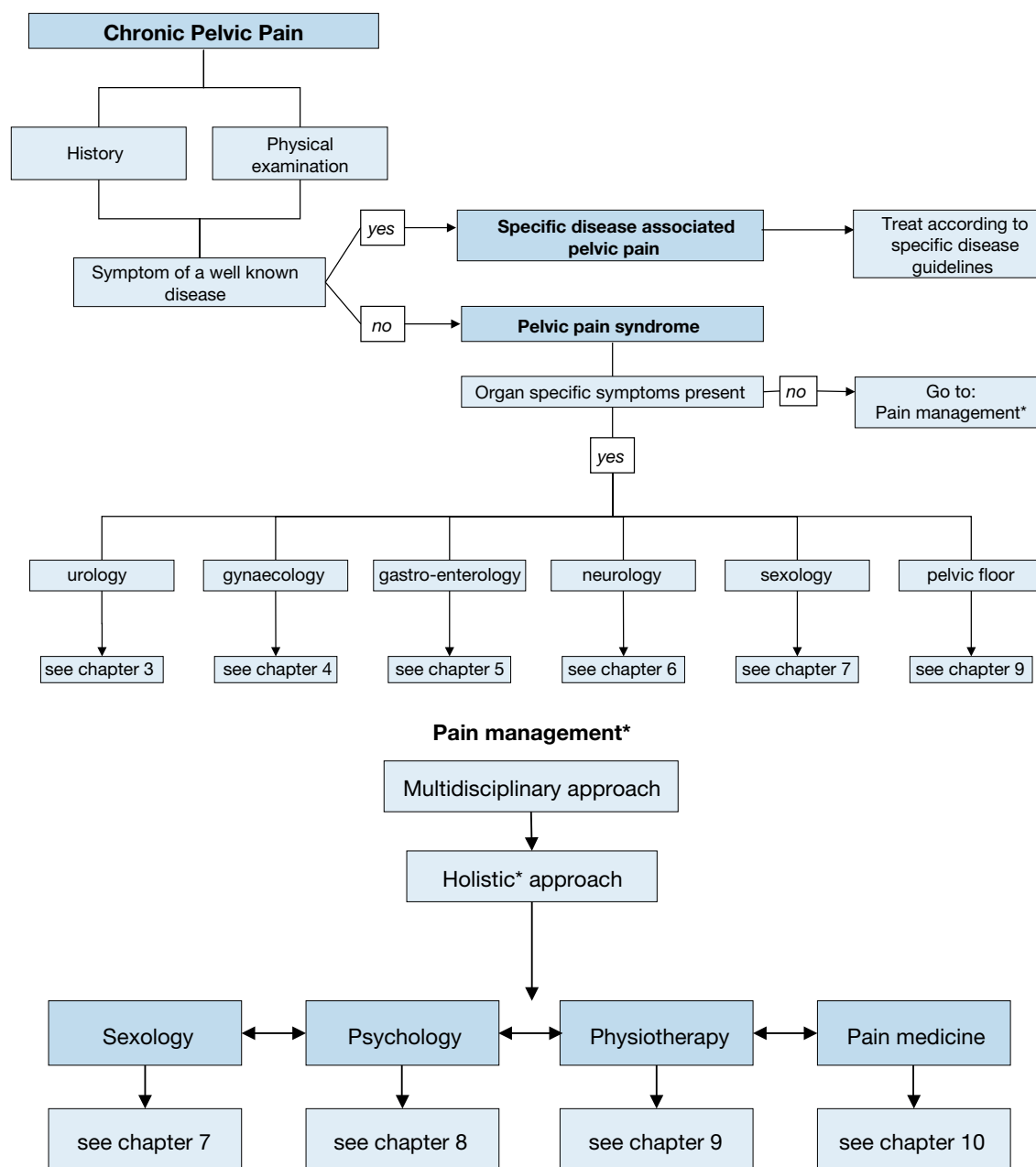
CPP = chronic pelvic pain; CPPS = chronic pelvic pain syndrome.

* Instruments for assessment see Chapter 8.

2.6 An algorithm for CPP diagnosis and treatment

The algorithm for diagnosing and treating CPP (Algorithm 1) has been developed to guide a physician through the process from diagnosis to management. A physician should follow the lines by answering the appropriate questions with yes or no. By doing this the clinician will end up at a box that refers to the chapter in this guideline that contains all the information needed. Because CPP is pain perceived in structures related to the pelvis, it is necessary to approach a patient diagnosed with CPP as a chronic pain patient. Confining the diagnosis to a specific organ may overlook multisystem functional abnormalities requiring individual treatment and general aspects of pain in planning investigation and treatment. This idea is easily recognised in the algorithm where the division in specific disease associated pain is made on one hand and pelvic pain syndrome on the other. The algorithm also illustrates that the authors advocate early involvement of a multidisciplinary pain team. In practice, this should mean that well-known diseases, e.g. 'true' cystitis and endometriosis, will be diagnosed and treated early. If treating such conditions does not reduce symptoms, or such well-defined conditions are not found, then further investigation may be necessary, depending on where the pain is localised. Every chapter of this guideline shows specific algorithms that assist the clinician in decisionmaking. It should be noted, however, that over-investigation may be as harmful as not performing appropriate investigations. The EAU algorithms introduce the concept of the 'minimum investigations' required to exclude a well-defined condition.

Algorithm 1: Diagnosing and treating CPP



**The term 'holistic' means consideration of the complete person, physically, psychologically, socially, and spiritually, in the management and prevention of disease.*

Figure 2: Phenotyping and assessment of CPP

Phenotyping	Assessment
Urology	Urinary flow, micturition diary, cystoscopy, ultrasound, uroflowmetry
Psychology	History of negative experiences, important loss, coping mechanism, depression
Organ specific	Ask for gynaecological, gastro-intestinal, ano-rectal, sexological complaints Gynaecological examination, rectal examination
Infection	Semen culture and urine culture, vaginal swab, stool culture
Neurological	Ask for neurological complaints (sensory loss, dysaesthesia). Neurological testing during physical examination: sensory problems, sacral reflexes and muscular function
Tender muscle	Palpation of the pelvic floor muscles, the abdominal muscles and the gluteal muscles

3. UROLOGICAL ASPECTS OF CHRONIC PELVIC PAIN

3.1 Introduction

In many of the patients with CPPS, pain is perceived predominantly in urological organs. Besides the known association of urological pelvic pain syndromes with negative psychological consequences [10] they are most frequently linked to functional disturbances of the lower urinary tract and sexuality. Multisystemic causes and effects lead to significant overlap of the different urological pain syndromes and they might be barely clinically distinguishable. Therefore, it has to be considered that some aspects of diagnosis and treatment addressed in the following subchapters may apply to all of them.

3.2 Prostate pain syndrome

3.2.1 Introduction

Chronic pain in the region of the prostate has been linked to the term “prostatitis” in the past, although there is a proven bacterial infection in only 10% of the cases [32]. The remaining 90% should be classified as prostate pain syndrome (PPS), based on the fact that there is no proven infection or other obvious pathology. If CPP cannot be clearly ascribed to the prostate or another organ of the pelvis, the condition is defined more generally as CPPS, as outlined in Chapter 2.

3.2.2 Definition

PPS is the occurrence of persistent or recurrent episodic pain over at least 3 out of the past 6 months (which is convincingly reproduced by prostate palpation). There is no proven infection or other obvious local pathology. PPS is often associated with negative cognitive, behavioural, sexual or emotional consequences [10], as well as with symptoms suggestive of lower urinary tract and sexual dysfunction [33, 34].

According to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) classification, this correlates to CP/CPPS (Cat. III). Laboratory diagnosis goes along with sterile specimen cultures and either significant, or insignificant, white blood cell counts in prostate-specific specimens (i.e. semen, expressed prostatic secretions and urine collected after prostate massage) [35]. At present, there are no clinically relevant diagnostic or therapeutic consequences arising from differentiating inflammatory from non-inflammatory PPS (according to NIH definition), therefore, they are considered here as one entity.

3.2.3 **Pathogenesis**

Pain is the main symptom in PPS. As a common feature of chronic pain syndromes, no single aetiological explanation has been found. One explanation [36] is that the condition probably occurs in susceptible men exposed to one or more initiating factor, which may be single, repetitive or continuous. Several of these potential initiating factors have been proposed, including infectious, genetic, anatomical, neuromuscular, endocrine, immune (including autoimmune), or psychological mechanisms. These factors may then lead to a peripheral self-perpetuating immunological inflammatory state and/or neurogenic injury, creating acute and then chronic pain. Based on the peripheral and the CNS, sensitisation involving neuroplasticity may lead to a centralised neuropathic pain state (see Chapter 2) [36]. This could also explain why tissue damage is not usually found in PPS. There is growing evidence for a neuropathic origin and association with CNS changes of pain in PPS.

3.2.4 **Epidemiology**

There is only limited information on the true prevalence of PPS in the population. As a result of significant overlap of symptoms with other conditions (e.g. benign prostate syndrome and BPS), purely symptom-based case definitions may not reflect the true prevalence of PPS [37, 38]. In the literature, numbers of the population-based prevalence of prostatitis symptoms are reported ranging from 1 – 14.2% [39, 40]. The risk of prostatitis increases with age (men aged 50-59 years have a 3.1-fold greater risk than those aged 20-39 years).

3.2.5 **Diagnosis**

Prostate pain syndrome is a symptomatic diagnosis, which is diagnosed from a history of pain perceived in the region of the prostate (convincingly reproduced by prostate palpation), and absence of other lower urinary tract pathology, for a minimum of 3 out of the past 6 months. This implies that specific disease-associated pelvic pain caused by bacterial infection, urogenital cancer, urinary tract disease, urethral stricture, and neurogenic disease of the bladder must be ruled out. A thorough history is an important first step in the evaluation of PPS. It should include type of pain and localisation. Pain is often reported in other pelvic areas outside the prostate such as perineum, rectum, penis, testicles and abdomen [41]. In addition, associated lower urinary tract symptoms (LUTS), sexual function, psychological, social and economic factors should be addressed.

Determination of the severity of disease, its progression and treatment response can be assessed only by means of a validated symptom-scoring instrument. QoL should also be measured because it can be very poor compared to other chronic diseases [42, 43]. In a study by Tripp et al. [10] more pain, pain-contingent rest, and urinary symptoms were associated with greater disability (also measured by self-report), and pain was predicted by depression and by catastrophising (helplessness subscale). Reliable, valid indexes of symptoms and QoL are the NIH-CPSI [41] and the International Prostate Symptom Score (I-PSS) [44]. These subjective outcome measures are recommended for the basic evaluation and therapeutic monitoring of patients in urological practice.

There is no diagnostic test for PPS, therefore, procedures are on the one hand directed towards identification and exclusion of specific diseases associated with pelvic pain, and on the other hand may be used for phenotypic description. Physical examination including digital rectal examination should be carried out. Muscle tenderness and trigger points in the pelvic floor should be noted. A post-void residual should be done. Prostate-specific antigen testing does not help to diagnose PPS but can exclude prostate cancer in patients at risk.

Laboratory diagnosis has been classically based on the four-glass test for bacterial localisation [45]. Besides sterile pre-massage urine (voided bladder urine-2), PPS shows < 10,000 cfu of uropathogenic bacteria in expressed prostatic secretions and insignificant numbers of leukocytes or bacterial growth in ejaculates. However, this test is too complex for use by practising urologists. Diagnostic efficiency may be enhanced cost-effectively by a simple screening procedure, that is, the two-glass test or pre-post-massage test (PPMT) [46, 47]. Overall, these tests help only a little in the diagnosis of PPS, because 8% of patients with suggested PPS have been found to have positive prostatic localisation cultures, similar to the percentage of asymptomatic [48]. A general algorithm for assessment and treatment of PPS is shown in Figure 3.

3.2.6 **Conclusions and recommendations: assessment/diagnosis PPS**

Conclusions	LE
PPS is associated with negative cognitive, behavioural, sexual, or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction.	2b
PPS has no known single aetiology.	3
Pain in PPS involves mechanisms of neuroplasticity and neuropathic pain.	2a
PPS has a high impact on QoL.	2b
Depression and catastrophic thinking are associated with more pain and poorer adjustment.	3
The prevalence of PPS-like symptoms is high in population-based studies (> 2%).	2b
Reliable instruments assessing symptom severity as well as phenotypic differences exist.	2b

Recommendations	GR
Specific diseases with similar symptoms must be excluded. It is therefore recommended to adapt diagnostic procedures to the patient and to aim at identifying them.	A
After primary exclusion of specific diseases, patients with symptoms according to the above definition should be diagnosed with prostate pain syndrome.	A
A validated symptom and quality of life scoring instrument, such as the NIH-CPSI, should be considered for initial assessment as well as for follow-up.	B
It is recommended to assess prostate pain syndrome associated negative cognitive, behavioural, sexual, or emotional consequences, as well as symptoms of lower urinary tract and sexual dysfunctions.	B

3.2.7 **Treatment**

There is a large discrepancy in the treatment effects reported in case series and controlled trials that results from a large placebo effect or publication bias. As a result of the multifactorial origin of PPS, one reason for treatment failure in some large randomised placebo-controlled trials may be the heterogeneity of the patient population. Thus, one strategy for improving treatment effects may be stratification of patient phenotypes. A prospective series of phenotypically directed treatment for PPS has shown significant improvement of symptoms and QoL [49]. Monotherapeutic strategies for the treatment of PPS may fail [50], therefore, most patients require multimodal treatment aimed at the main symptoms, and taking comorbidity into account. In the past 10 years, results from RCTs have led to advances in standard and novel treatment options.

3.2.7.1 *Alpha-blockers*

Positive results from RCTs of alpha-blockers, i.e. terazosin [51, 52], alfuzosin [53], doxazosin [54, 55], tamsulosin [56, 57], and silodosin [58] have led to widespread use of alpha-antagonists in the treatment of PPS in recent years. The most recent in-depth systematic review and network meta-analyses of alpha-blockers [59] have shown significant improvement in total symptom, pain, voiding, and QoL scores. In addition, they had a higher rate of favourable response compared to placebo [relative risk (RR) 1.4, 95% confidence interval (CI) 1.1-1.8, P=0.013].

However, treatment responsiveness, i.e. clinically perceptible or significant improvement, may be lower than expected from the change in mean symptom scores. Overall, alpha-blockers seem to have moderate but significant beneficial effects. This probably is not the case for long-standing PPS patients [60]. Future studies should show if longer duration of therapy or some sort of phenotypically directed (e.g. patients with PPS and relevant voiding dysfunction) treatment strategies will improve treatment outcomes.

3.2.7.2 *Antibiotic therapy*

Empirical antibiotic therapy is widely used because some patients have improved with antimicrobial therapy. Patients responding to antibiotics should be maintained on medication for 4-6 weeks or even longer. Unfortunately, culture, leukocyte and antibody status of prostate-specific specimens does not predict antibiotic response in patients with PPS [61], and prostate biopsy culture findings do not differ from those of healthy controls [62]. The only randomised placebo-controlled trials of sufficient quality have been done for oral antibiotic treatment with ciprofloxacin (6 weeks) [36], levofloxacin (6 weeks) [63], and tetracycline hydrochloride (12 weeks) [64]. The studies have been analysed in recently published meta-analyses [59, 65]. Although direct meta-analysis has not shown significant differences in outcome measures, network meta-analysis has suggested significant effects in decreasing total symptom, pain, voiding, and QoL scores compared with placebo. Combination therapy of antibiotics with alpha-blockers has shown even better outcomes in network meta-analysis. Despite significant improvement in symptom scores, antibiotic therapy did not lead to

statistically significant higher response rates [65]. In addition, sample sizes of the studies were relatively small and treatment effects were only modest and most of the time below clinical significance. It may be speculated that patients profiting from treatment have had some unrecognised uropathogens. If antibiotics are used, other therapeutic options should be offered after one unsuccessful course of a quinolone or tetracycline antibiotic over 6 weeks.

3.2.7.3 *Anti-inflammatory drugs*

For non-steroidal anti-inflammatory drugs, a trial with celecoxib the pain subscore, QoL subscore, and total NIH-CPSI score were in favour of the treatment arm vs. placebo, but effects were limited to the duration of therapy [66].

Two low-power placebo-controlled studies for zafirlukast, a leukotriene antagonist, and prednisone failed to show a benefit [67, 68]. More recently, a placebo-controlled phase IIa study of tanezumab, a humanised monoclonal antibody against the pain mediating neurotrophin, nerve growth factor, failed to demonstrate significant effect [69].

In a recent meta-analysis, two studies of NSAIDs [48, 66] and one with prednisolone [67] were pooled. Anti-inflammatory drugs were 80% more likely to have a favourable response than placebo. In an updated network meta-analysis with more restrictive inclusion criteria regarding documented outcome measures but a wider spectrum of drugs (including glycosaminoglycans, phytotherapy and tanezumab) a significant effect on total NIH-CPSI scores and treatment response rates could be demonstrated. Overall, a moderate treatment effect has been shown for anti-inflammatory drugs, but larger studies are needed for confirmation, and long-term side-effects have to be taken into account.

3.2.7.4 *Opioids*

Opioids produce modest pain relief in some patients with refractory PPS, although there are limited data on the long-term efficacy of opioids in non-cancer pain. Opioid treatment carries the risk of side-effects, reduced QoL, addiction, opioid tolerance and opioid-induced hyperalgesia [70]. Urologists should use opioids for PPS only in collaboration with pain clinics and with other treatments.

3.2.7.5 *5-alpha-reductase inhibitors*

Although a few small pilot studies with 5-alpha-reductase inhibitors supported the view that finasteride may improve voiding and pain, the first placebo-controlled randomised trial published in a peer-reviewed journal did not support this, but the study did lack power [71]. In another RCT, finasteride provided better amelioration of symptoms compared to saw palmetto over a 1-year period, but lacked a placebo-control arm [72]. A 6-month placebo-controlled study showed a non-significant tendency towards better outcome in favour of finasteride, possibly because of a lack of statistical power [73]. In a recently published study, NIH-CPSI scores decreased significantly in a subgroup of men enrolled in a prostate cancer risk reduction study treated with dutasteride compared to placebo [74]. Patients (n=427, age 50 to 75, elevated prostate-specific antigen) were included if they had significant "prostatitis-like" symptoms at baseline. Based on the evidence, 5-alpha-reductase inhibitors cannot be recommended for use in PPS in general, but symptom scores may be reduced in a restricted group of older men with an elevated PSA [74].

3.2.7.6 *Allopurinol*

There is insufficient evidence for the use of allopurinol in PPS [75, 76].

3.2.7.7 *Phytotherapy*

An adequately powered randomised placebo-controlled study of Cernilton, showed clinically significant symptom improvement over a 12-week period in inflammatory PPS patients (NIH Cat. IIIA) [77]. The effect was mainly based on a significant effect on pain. Quercetin, a polyphenolic bioflavonoid with documented antioxidant and anti-inflammatory properties, improved NIH-CPSI scores significantly in a small RCT [78]. In contrast, treatment with saw palmetto, most commonly used for benign prostatic hyperplasia, did not improve symptoms over a 1-year period [72]. In a systematic review and meta-analysis, patients treated with phytotherapy were found to have significantly lower pain scores than those treated with placebo [59]. In addition, overall response rate in network analysis was in favour of phytotherapy (RR: 1.6; 95% CI: 1.1-1.6).

3.2.7.8 *Pentosan polysulphate*

High-dose oral pentosan polysulphate (3x 300 mg/day), as for BPS, is able to improve clinical global assessment and QoL significantly over placebo in men with PPS, suggesting a possible common aetiology [79].

3.2.7.9 Muscle relaxants

Muscle relaxants (diazepam, baclofen) are claimed to be helpful in sphincter dysfunction or pelvic floor/perineal muscle spasm, but there have been only a few prospective clinical trials to support these claims. In a recent RCT, a triple combination of a muscle relaxant (tiocolchicoside), an anti-inflammatory drug (ibuprofen) and an alpha-blocker (doxazosin) was effective in treatment-naïve patients, but not superior to an alpha-blocker alone [55].

3.2.7.10 Pregabalin

Pregabalin is an antiepileptic drug that has been approved for use in chronic postherpetic neuralgia, fibromyalgia, and diabetic neuropathy. In an adequately powered randomised placebo-controlled study, which was the only report included in a recently published Cochrane review [80], a 6-week course of pregabalin (n = 218) compared to placebo (n = 106) did not result in a significant reduction of NIH-CPSI total score by at least 6 points [81].

3.2.7.11 Botulinum toxin A

A small randomised placebo- controlled study of perineal skeletal muscle injection (100 U) showed some effect in the global response assessment and the NIH-CPSI pain subdomain score. However, patient number was too low (13 in the BTX-A group and 16 in the placebo group), and follow-up was too short to draw definitive conclusions. Side-effects are unclear and it is advised to only use BTA within the context of a clinical trial.

3.2.7.12 Physical treatments

- *Electromagnetic therapy.* In a small, sham-controlled, double-blind study, 4 weeks electromagnetic therapy showed a significant, sustained effect over a 1-year period [82].
- *Microwave thermotherapy.* In uncontrolled studies significant symptomatic improvement has been reported from heat therapy, for example, transrectal and transurethral thermotherapy [83, 84]
- *Extracorporeal shock wave therapy.* A recent sham-controlled double-blind study of four times weekly perineal extracorporeal shock wave therapy (n = 30) showed significant improvement in pain, QoL, and voiding compared to the control group (n = 30) over 12 weeks [85]. Confirmatory studies are awaited because of an absent placebo-effect, which is very unusual in PPS trials.
- *Electroacupuncture.* In a small three-arm randomised trial, electroacupuncture was superior to sham treatment and advice and exercise alone [86]. In a recent prospective case series of 6 weeks of weekly electro-acupuncture of 97 patients with PPS, 92% showed significant improvement in total NIH-CPSI score. Based on these studies, no definitive conclusion can be drawn.
- *Posterior tibial nerve stimulation.* One sham-controlled medium-sized study (n = 89) demonstrated significant improvement in total NIH-CPSI score and visual analogue scale for pain [87].
- *Myofascial physical therapy.* A randomised feasibility trial of myofascial physical therapy including PPS (n = 21) and patients with BPS showed a clinical benefit compared to global therapeutic massage [88]. In the PPS group alone, there was no difference in the effect between the two treatment arms.

3.2.7.13 Surgical management

There is no evidence for surgical management, including transurethral incision of the bladder neck, radical transurethral resection of the prostate, or in particular, radical prostatectomy in the management of chronic pain in patients with PPS.

3.2.7.14 Psychological treatment

The evidence for psychological treatment is lacking, there is weak evidence for improvement of pain and QoL but not for some urinary symptoms. Details concerning appropriate treatment content and delivery are covered in Chapter 8.

3.2.8 Conclusions and recommendations: treatment of PPS

Conclusions	LE
Monotherapeutic treatment regimens in PPS may fail.	3
Phenotypically directed treatment may improve treatment success.	3
Alpha-blockers have moderate treatment effect regarding total pain-, voiding-, and QoL scores in PPS.	1a
Antimicrobial therapy has a moderate effect on total pain-, voiding-, and QoL scores in PPS.	1a
NSAIDs have moderate overall treatment effects on PPS.	1a
There are insufficient data on the effectiveness of steroids in PPS.	2b
There are insufficient data on the effectiveness of opioids in PPS.	4
There are insufficient data on the effectiveness of 5-alpha-reductase inhibitors in PPS.	2b
There are insufficient data on the effectiveness of allopurinol in PPS.	2b
Phytotherapy has some beneficial effect on pain and overall favourable treatment response in PPS.	1a
Pentosan polysulphate improves global assessment and QoL score in PPS.	1b
There are insufficient data on the effectiveness of muscle relaxants in PPS.	2b
Pregabalin is not effective for the treatment of PPS.	1b
BTX-A injection into the pelvic floor may have a modest effect in PPS.	2b
There are only limited data on the effectiveness of electromagnetic therapy in PPS.	2b
There are only limited data on the effectiveness of microwave thermotherapy in PPS.	3
Perineal extracorporeal shock wave therapy probably is effective for the treatment of PPS.	1b
There are limited data on the effectiveness of electro-acupuncture for the treatment of PPS.	2b
Posterior tibial nerve stimulation is probably effective for the treatment of PPS.	1b
There are insufficient data on the effectiveness of myofascial physical therapy for the treatment of PPS.	2b
There are limited data on lack of effectiveness of TUNA of the prostate for PPS.	2b
There are insufficient data supporting the use of other surgical treatments, such as transurethral incision of the bladder neck, transurethral resection of the prostate, or radical prostatectomy in patients with PPS.	3
Cognitive behavioural therapy designed for PPS may improve pain, and QoL.	3

Recommendations	GR
Consider multimodal and phenotypically directed treatment options for PPS.	B
Alpha-blockers are recommended for patients with a duration of PPS < 1 year.	A
Single use of antimicrobial therapy (quinolones or tetracyclines) is recommended in treatment-naïve patients over a minimum of 6 weeks with a duration of PPS < 1 year.	A
NSAIDs are recommended for use in PPS, but long-term side-effects have to be considered.	B
Allopurinol is not recommended for use in PPS.	B
Phytotherapy might be used in patients with PPS.	B
Consider high-dose pentosan polysulphate to improve symptoms and quality of life in PPS.	A
Pregabalin is not recommended for use in PPS.	A
Perineal extracorporeal shock wave therapy might be considered for the treatment of PPS.	B
Electro-acupuncture might be considered for the treatment of PPS.	B
Posterior tibial nerve stimulation might be considered for the treatment of PPS.	B
TUNA of the prostate is not recommended for the treatment of PPS.	B
For PPS with significant psychological distress, psychological treatment focussed on PPS should be attempted.	B

PPS = prostate pain syndrome; TUNA = transurethral needle ablation; NSAIDs = non-steroidal anti-inflammatory drugs.

Figure 3: Assessment and treatment of PPS

Assessment	Treatment	
Urine culture	Grade A recommended	Alpha-blockers when duration is < 1 year
Uroflowmetry		Single use antibiotics (6 weeks) when duration is < 1 year
Transrectal US prostate		High dose Pentosan polysulfate to improve QoL and symptoms
NIH-CPSI scoring list	Grade B recommended	NSAIDs. Be aware of long-term side effects
Phenotyping		Phytotherapy
Pelvic floor muscle testing		Perineal extracorporeal shock wave therapy
		Electroacupuncture
		Percutaneous tibial nerve stimulation (PTNS)
	Not recommended	Psychological treatment focused on the pain
		Allopurinol
		Pregabalin
		TransUrethral Needle Ablation (TUNA)

US = ultrasound.

3.3 Bladder pain syndrome

3.3.1 Introduction

BPS is the occurrence of persistent or recurrent pain perceived in the urinary bladder region, accompanied by at least one other symptom, such as pain worsening with bladder filling and day-time and/or night-time urinary frequency. There is no proven infection or other obvious local pathology. BPS is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction. The term BPS rather than interstitial cystitis (IC) was put forward by the International Society for the Study of BPS (ESSIC) and will be used in these guidelines. In accordance Classic IC (Hunner's lesion and inflammation) will be referred to as BPS type 3 C (See Chapter 2, section 2.4 'Definitions of CPP terminology').

3.3.2 Pathogenesis

An initial unidentified insult to the bladder, leading to urothelial damage, neurogenic inflammation and pain is thought to be the cause of BPS. However, BPS might be a local manifestation of a systemic disorder. No infection has as yet been implicated. Nevertheless, urinary infection is significantly more frequent during childhood and adolescence, in patients with BPS in adulthood [89]. Experimental induction of chronic pelvic pain by O-antigen deficient bacterial strains reinstates the bacterial hypothesis [90].

Pancystitis, with associated perineural inflammatory infiltrates, and mast cell count increase is an essential part of BPS type 3 C [91], but is scant in non-lesion BPS [92, 93] (24, 29).

Cystoscopic and biopsy findings in both lesion and non-lesion BPS are consistent with defects in the urothelial glycosaminoglycan (GAG) layer, which might expose submucosal structures to noxious urine components [94-101] and a consequent cytotoxic effect [102-104].

3.3.3 Epidemiology

Reports of BPS prevalence have varied greatly, along with the diagnostic criteria and populations studied. Recent reports range from 0.06% to 30% [105-114]. There is a female predominance of about 10:1 [111, 115-117] but possibly no difference in race or ethnicity [37, 118, 119]. The relative proportions of classic and non-lesion disease are unclear. Incidence in studies has ranged from 5 to 50% [120-124]. Evidence that BPS may have a genetic component has been presented in several studies, but may contribute to less than one third of total variation in susceptibility for BPS.

There is increasing evidence that children under 18 may also be affected, although prevalence figures are low thus, BPS cannot be excluded on the basis of age [125].

Bladder pain syndrome has significant economic costs. Direct annual costs in the USA have been estimated to be \$750 million [126].

3.3.4 Association with other diseases

An association has been reported between BPS and non-bladder syndromes such as fibromyalgia (FM), chronic fatigue syndrome (CFS), irritable bowel syndrome (IBS), vulvodynia, depression, panic disorders, migraine, sicca syndrome, temporomandibular joint disorder, allergy, asthma and systemic lupus erythematosus [127-133].

Risk of BPS correlates with a number of non-bladder syndromes in each patient [134]. Recent work showing non-lesion BPS to have significantly more FM, migraine, temporomandibular joint disorder and depression than BPS type 3C patients, emphasises the need for subtyping [135].

3.3.5 Diagnosis

Bladder pain syndrome should be diagnosed on the basis of pain, pressure or discomfort associated with the urinary bladder, accompanied by at least one other symptom, such as daytime and/or night-time increased urinary frequency, the exclusion of confusable diseases as the cause of symptoms, and if indicated, cystoscopy with hydrodistension and biopsy (Table 3, Algorithm 3) [15].

The nature of pain is key to disease definition:

- Pain, pressure or discomfort perceived to be related to the bladder, increasing with increasing bladder content.
- Located suprapubically, sometimes radiating to the groins, vagina, rectum or sacrum.
- Relieved by voiding but soon returns [136-140].
- Aggravated by food or drink [140].

BPS type 3 can lead to a small capacity fibrotic bladder with or without upper urinary tract outflow obstruction.

Symptom scores may help to assess the patient and act as outcome measures. The O'Leary-Sant Symptom Index, also known as the Interstitial Cystitis Symptom Index (ICSI) was validated in a large study [141].

Cystoscopy

Despite controversy on diagnostic or follow-up value of cystoscopy [142-146], this panel believes objective findings are important for diagnosis, prognosis and ruling out other treatable conditions (a standardised scheme of diagnostic criteria will also contribute to uniformity and comparability of different studies [147]). Endoscopically, BPS type 3 displays reddened mucosal areas often associated with small vessels radiating towards a central scar, sometimes covered by a small clot or fibrin deposit – the Hunner lesion [139]. The scar ruptures with increasing bladder distension, producing a characteristic water fall type of bleeding. There is a strong association between BPS type 3 C and reduced bladder capacity under anaesthesia [123, 139, 148]. Non-lesion disease displays a normal bladder mucosa at initial cystoscopy. The development of glomerulations after hydrodistension is considered to be a positive diagnostic sign, although they can be observed without BPS [149].

Biopsies are helpful in establishing or supporting the clinical diagnosis of both classic and non-lesion types of the disease [95, 147, 150-152]. Important differential diagnoses to exclude by histological examination are carcinoma in situ and tuberculous cystitis.

Table 3: ESSIC classification of BPS types according to results of cystoscopy with hydrodistension and biopsies [15]

	Cystoscopy with hydrodistension			
	Not done	Normal	Glomerulations ^a	Hunner's lesion ^b
Biopsy				
Not done	XX	1X	2X	3X
Normal	XA	1A	2A	3A
Inconclusive	XB	1B	2B	3B
Positive ^c	XC	1C	2C	3C

^aCystoscopy: glomerulations grade 2-3

^bLesion per Fall's definition with/without glomerulations

^cHistology showing inflammatory infiltrates and/or detrusor mastocytosis and/or granulation tissue and/or intrafascicular fibrosis.

Potassium chloride bladder permeability tests are no longer advised in current practice based on lack of evidence in the literature.

Phenotyping and biological markers

All putative biological markers to date have yet to be validated [97].

Recent work has indicated the need to phenotype BPS patients. UPOINT (Urinary, Psychosocial, Organ Specific, Inflammation, Neurological/Systemic, Tenderness) is an example of phenotyping which supports individualised therapy [153].

3.3.6 **Conclusions and recommendations: assessment and diagnosis BPS**

Conclusions	LE
BPS has no known single aetiology.	3
Pain in BPS does not correlate with bladder cystoscopic or histologic findings.	2a
BPS Type 3 C cannot be confirmed by non-invasive means.	2a
Lesion/non-lesion disease ratios of BPS are highly variable between studies.	2a
The prevalence of BPS-like symptoms is high in population-based studies.	2a
BPS associated non-bladder diseases are extremely prevalent, differ in BPS subtypes and correlate with BPS risk.	2a
BPS has a high impact on quality of life.	2a
There is significant overlap of symptoms with other conditions.	2a
Reliable instruments assessing symptom severity as well as phenotypical differences exist.	2a

Recommendations	GR
Specific diseases with similar symptoms must be excluded. It is therefore recommended to adapt diagnostic procedures to each patient and aim at identifying them.	A
After primary exclusion of specific diseases, patients with symptoms according to the above definition should be diagnosed with BPS by subtype and phenotype.	A
A validated symptom and quality of life scoring instrument should be considered for initial assessment as well as for follow-up.	B
BPS associated non-bladder diseases should be assessed systematically.	A
BPS associated negative cognitive, behavioural, sexual, or emotional consequences should be assessed.	A

BPS = Bladder pain syndrome.

3.3.7 **Medical treatment**

Analgesics. Urologists should preferably use analgesics in collaboration with pain clinics. For further information see Chapter 10. [70].

Corticosteroids are not recommended in the management of patients with BPS because of a lack of evidence.

Anti-allergics. Mast cells may play a role in BPS. Histamine is one of the substances released by mast cells. Histamine receptor antagonists have been used to block the H1 [154] and H2 [155] receptor subtypes, with variable results. A prospective placebo-controlled RCT of hydroxyzine or sodium pentosan polysulphate did not show a significant effect [156].

Amitriptyline. The tricyclic antidepressant amitriptyline alleviates symptoms in BPS, probably via blockade of acetylcholine receptors, inhibition of serotonin and noradrenalin reuptake, and blockade of histamine H1 receptors. It is also an anxiolytic agent [157]. Several reports have indicated amelioration after oral amitriptyline [116, 158, 159]. Amitriptyline has been shown to be beneficial when compared with placebo plus behavioural modification [160]. Drowsiness is a limiting factor with amitriptyline, and thus, nortriptyline is sometimes considered instead.

Pentosan polysulphate sodium (Elmiron) is thought to repair defects in the GAG layer. Subjective improvement of pain, urgency, frequency, but not nocturia, has been reported [161, 162]. Pentosan polysulphate sodium had a more favourable effect in BPS type 3C than in non-lesion disease [163]. Response was not dose dependent but related more to treatment duration. At 32 weeks, about half the patients responded. Combination therapy

showed a response rate of 40% compared to 13% with placebo. For patients with an initial minor response to pentosan polysulphate sodium, additional subcutaneous heparin was helpful [164].

Antibiotics have no role in BPS due to the lack of evidence.

Immunosuppressants. Azathioprine treatment has resulted in disappearance of pain and urinary frequency [165]. Initial evaluation of cyclosporin A (CyA) [166] and methotrexate [167] showed good analgesic effect but limited efficacy for urgency and frequency.

Gabapentin and Pregabalin are used in neuropathic pain as part of a broad multimodal management plan (see Chapter 10 General Treatment)

Tanezumab is a humanised monoclonal antibody that specifically inhibits nerve growth factor (NGF). It should only be used in clinical trials.

3.3.8 **Intravesical treatment**

Intravesical drugs are administered due to poor oral bioavailability establishing high drug concentrations at the target, with few systemic side-effects. Disadvantages include the need for intermittent catheterisation, which can be painful in BPS patients, cost, and risk of infection.

Local anaesthetics. There are sporadic reports of successful treatment of BPS with intravesical lidocaine [168, 169]. Alkalinisation of lidocaine improves its pharmacokinetics [170]. Combination of heparin, lidocaine and sodium bicarbonate gave immediate symptom relief in 94% of patients and sustained relief after 2 weeks in 80% [171]. Intravesical instillation of alkalinised lidocaine or placebo for five consecutive days resulted in significantly sustained symptom relief for up to 1 month [172].

Hyaluronic acid (hyaluronan) and Chondroitin sulphate are described to repair defects in the GAG layer. Despite the fact that intravesical GAG replenishment is in use for about 20 years for BPS/IC, most of the studies are uncontrolled and with a small number of patients. Based on the studies available there are differences by virtue of substance classes, whether they are natural GAG layer components, dosage formulations, or concentrations. More important, there are differences in proved efficacy. Only for chondroitin sulphate, a combination containing chondroitin sulfate and hyaluronic acid and pentosan polysulphate RCTs are published. It is well documented that intravesical instillations are a valuable and beneficial therapy, but distinct patient groups need to be confirmed by definite diagnostic findings [173].

Intravesical heparin. BPS patients were treated with heparin for 3 months, and over half had control of symptoms, with continued improvement after 1 year of therapy [174]. Kuo reported another trial of intravesical heparin for 3 months in women with frequency-urgency syndrome and a positive potassium test. Symptomatic improvement was reported in 80% of BPS patients [175]. Baykal et al. evaluated intravesical heparin plus dorsal tibial nerve stimulation in patients with refractory BPS. Voiding frequency, pain score and maximum cystometric capacity were significantly better after 2 and 12 months [176].

Dimethyl sulphoxide (DMSO) has been used in the past. There is insufficient current evidence to recommend its use.

Bacillus Calmette Guérin (BCG) has been used in the past but there is insufficient current evidence to recommend its use.

Vanilloids. There is little evidence to support their routine use and they should only be considered in a research environment.

3.3.9 **Interventional treatments**

Bladder distension. Although bladder hydrodistension is a common treatment for BPS, the scientific justification is scarce. It can be a part of the diagnostic evaluation, but has a limited therapeutic role.

Electromotive drug administration (EMDA) which enhances tissue penetration of ionised drugs by iontophoresis has been used in the research setting.

Transurethral resection (TUR), coagulation and laser. Endourological destruction of bladder tissue aims to eliminate urothelial, mostly Hunner, lesions. Since the 1970s resection and fulguration have been reported to

achieve symptom relief, often for more than 3 years [177, 178]. Prolonged amelioration of pain and urgency has been described for transurethral laser ablation as well [179].

Botulinum toxin A (BTX-A) may have an antinociceptive effect on bladder afferent pathways, producing symptomatic and urodynamic improvements [124]. Treatment with hydrodistension and hydrodistension plus intravesical BTX-A (onabotulinumtoxin A) has been compared [180]. There was symptomatic improvement in all patients. However, in the hydrodistension only group, 70% returned to their previous symptoms after 1 month, while in the BTX-A-treated patients, VAS score, and functional and cystometric bladder capacity improved at 3 months.

Trigonal-only injection seems effective and long-lasting because 87% of patients reported improvement after 3 months follow-up [181]. Over 50% reported continued benefit 9 months after the first treatment. When retreatment was needed, similar results were obtained. The authors concluded that this treatment is safe, effective and can be repeated.

Hyperbaric oxygen (HBO) is a safe and feasible therapeutic approach, with moderate effects on a small subgroup of BPS patients. Disadvantages include high cost, limited availability of treatment sites, and time-consuming treatment [182].

Neuromodulation. A comparison of sacral neuromodulation (SNM) vs. pudendal nerve stimulation (PNS), showed an overall 59% improvement in symptoms with PNS vs. 44% with SNM. Most patients who tested both a sacral and pudendal electrode chose PNS as the better site. Follow-up showed marked improvements in voiding variables and validated BPS symptom questionnaires. Over 90% of patients treated with neuromodulation stated that they would undergo implantation again [183]. Long-term results were verified in a retrospective study of patients from 1994 to 2008 [184]. Permanent SNM implantation was performed in patients who showed at least 50% improvement in symptoms with a temporary peripheral nerve evaluation test [184]. Median follow-up was 61.5 months. Good long-term success of SNM was seen in 72%, with a 28% explantation rate. The most frequent reason for explantation was poor outcome (54% of the failed patients). The revision rate was 50%. In a study of women who underwent permanent device implantation from 2002 to 2004 [185], mean pre-/postoperative pelvic pain and urgency/frequency scores were $21.61 \pm 8.6/9.22 \pm 6.6$, and mean pre-/postoperative visual analogue pain scale (VAPS) scores were $6.5 \pm 2.9/2.4 \pm 1.1$. Mean follow-up was 86 ± 9.8 months. Sacral neuromodulation showed adequate improvement for the symptoms of refractory BPS. Reoperation rate was 25%.

3.3.10 **Treatments of limited efficacy and absence of recent publications**

Cimetidine. There is limited data to suggest that Cimetidine improves symptoms of BPS in the short-term [186]. Compared with placebo for 3 months, cimetidine significantly improved symptom scores, pain and nocturia, although the bladder mucosa showed no histological changes in either group [187].

Prostaglandins. Misoprostol is a prostaglandin that regulates various immunological cascades. After 3 months of treatment with misoprostol, 14/25 patients had significantly improved, with 12 showing a sustained response after a further 6 months [188]. The incidence of adverse drug effects was 64%.

L-Arginine. Oral treatment with the NO synthase substrate L-arginine decreases BPS-related symptoms [189-191]. NO is elevated in patients with BPS [192]. However, others have not demonstrated symptomatic relief or changes in NO production after treatment [193, 194].

Anticholinergics. Oxybutynin is an anticholinergic drug used in overactive detrusor dysfunction. Intravesical oxybutynin combined with bladder training improves functional bladder capacity, volume at first sensation, and cystometric bladder capacity [195]. However, the effect on pain has not been reported.

Duloxetine inhibits both serotonin and noradrenaline reuptake. Duloxetine did not significantly improve symptoms of BPS [196]. Administration was safe, but tolerability was poor due to nausea. Based on these preliminary data, duloxetine cannot be recommended for treatment of BPS.

Clorpactin is a derivative of hypochloric acid previously used to treat BPS [197-201]. Due to high complication rates, clorpactin instillations can no longer be recommended [197, 198, 200, 202].

3.3.11 **Other treatments**

Diet. Scientific data are limited and dietary restriction alone does not produce complete symptomatic relief.

Acupuncture. Scientific evidence for acupuncture is often poor, with contradictory results from a few low evidence reports, with effects being limited and temporary.

3.3.12 **Surgical treatment**

BPS is benign and does not shorten life, thus operative procedures rank last in the therapeutic algorithm. There is no evidence it relieves pain. Surgery for refractory BPS is only appropriate as a last resort for patients with refractory end-stage disease. Major surgery should be preceded by thorough preoperative evaluation, with an emphasis on determining the relevant disease location and subtype. If surgery is considered, our advice is to refer the patient to a specialist center experienced in managing CPP in a MDT.

Four major techniques are common:

- Urinary diversion without cystectomy
- supratrigonal (i.e., trigone-sparing) cystectomy
- subtrigonal cystectomy
- radical cystectomy including excision of the urethra.

Urinary diversion without cystectomy. As early as 1967, Turner-Warwick reported that bladder augmentation without removal of the diseased tissue was not appropriate [203]. Reports that unresected BPS bladders cease to induce symptoms after loss of contact with urine are scarce [121, 204].

Supratrigonal cystectomy with subsequent bladder augmentation represents the most favoured continence-preserving surgical technique. Various intestinal segments have been used for trigonal augmentation [205-207].

Subtrigonal cystectomy. Subtrigonal resection has the potential of removing the trigone as a possible disease site, but at the cost of requiring ureteral reimplantation. Nurse et al. reported trigonal disease in 50% of their patients and blamed surgical failure on the trigone left in place [208]. In contrast, Linn et al. reported [209] six out of 17 patients being completely cured by supratrigonal resection [208]. A recent study on female sexuality after cystectomy and orthotopic ileal neobladder showed pain relief in all patients, but only one regained normal sexual activity [210].

Cystectomy with formation of an ileal conduit still ranks first in current US practice trends for BPS surgery [211]. For cosmetic reasons, continent diversion is preferred, particularly in younger patients. After orthotopic bladder augmentation, particularly when removing the trigone, voiding may be incomplete and require intermittent self-catheterisation. Patients considering these procedures must be capable of performing, accepting and tolerating self-catheterisation. For patients with BPS who develop recurrent pain in the augmented bladder or continent pouch after enterocystoplasty or continent urinary diversion, Elzawahri recommended retubularisation of a previously used bowel segment to form a urinary conduit [212]. It is important to note that pregnancies with subsequent lower-segment Caesarean section have been reported after ileocystoplasty [212, 213].

3.3.13 Conclusions and recommendations: treatment of BPS

Conclusions	LE
None of the present treatments affect all BPS subtypes or phenotypes.	4
Corticosteroids are not recommended for long-term treatment.	3
Hydroxyzine has limited efficacy in BPS.	3
Limited data exist on effectiveness of cimetidine in BPS.	2b
Amitriptyline is effective for pain and related symptoms of BPS.	1b
Oral pentosanpolysulphate sodium is effective for pain and related symptoms of BPS.	1a
Oral pentosanpolysulphate sodium plus subcutaneous heparin is effective for pain and related symptoms of BPS, especially in initially low responders to pentosanpolysulphate sodium alone.	1b
Insufficient data exist for the effectiveness of prostaglandins in BPS. Adverse effects are frequent.	3
Global response to cyclosporin A is superior to that of pentosanpolysulphate sodium, but associated with more adverse effects.	1b
Duloxetine shows no efficacy and tolerability is poor.	2b
Oxybutynin has limited effect on BPS pain, but data are scant.	3
Preliminary data showed effectiveness of quercetin alone and in multimodal uncontrolled studies.	3
Intravesical lidocaine plus sodium bicarbonate is effective in the short term.	1b
Intravesical pentosanpolysulphate sodium is effective, based on limited data, and may enhance oral treatment.	1b
There are limited data on the effectiveness of intravesical heparin.	3
Intravesical hyaluronic acid may have long-term effects in BPS patients with positive intravesical modified KCl test.	2b
Intravesical chondroitin sulphate may be effective according to non-randomised studies. Published RCTs are underpowered.	2b
There is insufficient current evidence for Intravesical DMSO.	1b
Intravesical submucosal BTX-A injection plus hydrodistension are significantly superior to hydrodistension alone.	1b
Only limited data exist on the effectiveness of BTX-A injection into the detrusor or trigone.	3
Intravesical BCG is not effective in BPS.	1b
Intravesical cloripactin has insufficient data to support effectiveness, and high complication rates.	3
Bladder distension should only be used as diagnostic.	3
Scarce data indicate electromotive drug administration may have a beneficial effect in some patients.	3
Transurethral resection (coagulation and laser) may be effective in BPS type 3C.	3
Sacral neuromodulation may be effective in BPS.	3
PNS is superior to SNM for treatment of BPS.	1b
Avoidance of some food and drink avoids pain triggering.	3
Acupuncture data are contradictory.	3
No definitive conclusion on the effectiveness of organ removal for BPS can be drawn based on the large variability of results.	3

Recommendations	GR
Offer subtype and phenotype-oriented therapy for the treatment of BPS.	A
Multimodal behavioural, physical and psychological techniques should always be considered alongside oral or invasive treatments of BPS.	A
Analgesics should be used preferably in collaboration with a pain clinic.	C
Corticosteroids are not recommended for long-term treatment.	C
Do not offer hydroxyzine for the treatment of BPS.	C
Consider cimetidine as a valid oral option before invasive treatments.	B
Administer amitriptyline for use in BPS.	A
Offer oral pentosanpolysulphate sodium for the treatment of BPS.	A
Treatment with oral pentosanpolysulphate sodium plus subcutaneous heparin is recommended especially in low responders to pentosanpolysulphate sodium alone.	A
Prostaglandins are not recommended. Insufficient data on BPS, adverse effects are considerable.	C
Cyclosporin A might be used in BPS but adverse effects are significant and should be carefully considered.	B
Duloxetine is not recommended for BPS treatment.	C

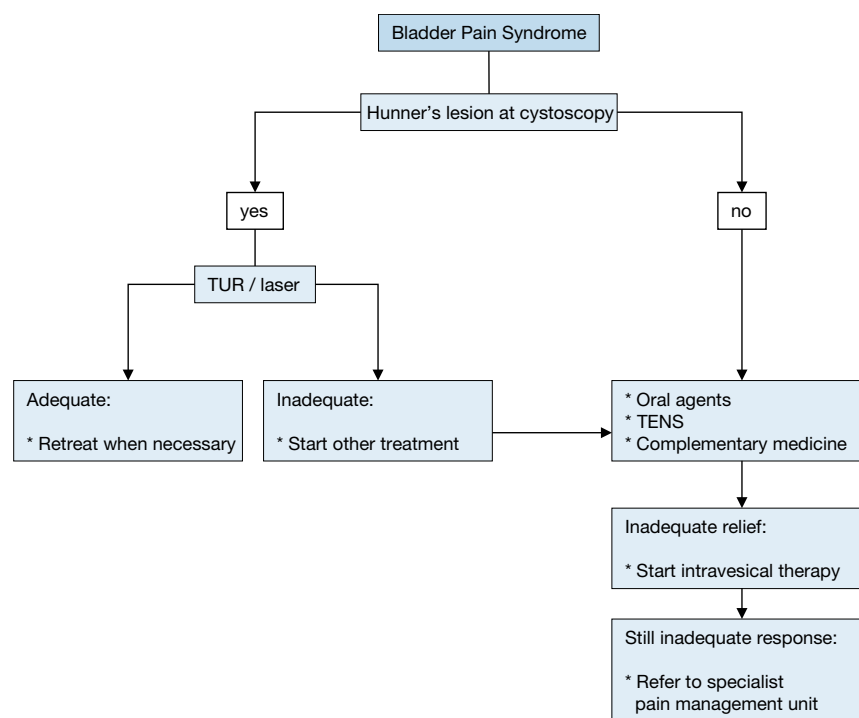
Oxybutynin might be considered for the treatment of BPS.	C
Gabapentin might be considered for oral treatment of BPS.	C
Administer intravesical lidocaine plus sodium bicarbonate prior to more invasive methods.	A
Administer intravesical pentosanpolysulphate sodium before more invasive treatment alone or combined with oral pentosanpolysulphate sodium.	A
Consider intravesical heparin before more invasive measures alone or in combination treatment.	C
Consider intravesical hyaluronic acid before more invasive measures.	B
Consider intravesical chondroitin sulphate before more invasive measures.	B
Consider intravesical bladder wall and trigonal injection of BTX-A if intravesical instillation therapies have failed.	C
Administer submucosal injection of BTX-A plus hydrodistension if intravesical instillation therapies have failed.	A
Intravesical therapy with BCG is not recommended in BPS.	A
Intravesical therapy with cloropactin is not recommended in BPS.	A
Bladder distension is not recommended as a treatment of BPS.	C
Consider transurethral resection (or coagulation or laser) of bladder lesions, but in BPS type 3 C only.	B
Neuromodulation might be considered before more invasive interventions.	B
Consider diet avoidance of triggering substances.	C
Acupuncture is not recommended.	C
All ablative organ surgery should be the last resort for experienced and BPS knowledgeable surgeons only.	A

DMSO = dimethyl sulphoxide; BPS = bladder pain syndrome.

Figure 4: Diagnosis and therapy of BPS

Assessment	Treatment	
Urine culture	Grade A recommended	Standard: Amitriptyline, Pentosanpolysulphate
Uroflowmetry		Intravesical: PPS, DMSO, onabotulinum toxin A plus hydrodistension
Cystoscopy with hydrodistension	Grade B recommended	
Bladder biopsy		Oral: Cimetidine, cyclosporin A
Micturition diary		Intravesical: hyaluronic acid, chondroitin sulphate
Pelvic floor muscle testing		Electromotive drug administration for intravesical drugs
Phenotyping		Neuromodulation, bladder training, physical therapy
		Psychological therapy
ICSI score list	Not recommended	Bacillus Calmette Guérin
		Intravesical Chlorpactin
		Hydroxyzine
	Other comments	Data on surgical treatment are largely variable
		Coagulation and laser only for Hunner's lesions

Algorithm 3: Treatment of BPS Type 3 C



3.4 Genital pain syndrome

3.4.1 Scrotal pain syndrome

Scrotal pain syndrome is the occurrence of persistent or recurrent episodic pain localised within the organs of the scrotum, and may be associated with symptoms suggestive of urinary tract or sexual dysfunction. There is no proven infection or other obvious local pathology. Scrotal pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction. Scrotal pain syndrome is a generic term and is used when the site of the pain is not clearly testicular or epididymal. The pain is not in the skin of the scrotum as such, but perceived within its contents, in a similar way to idiopathic chest pain.

3.4.2 Definitions

3.4.2.1 Testicular pain syndrome

Testicular pain syndrome is the occurrence of persistent or recurrent episodic pain perceived in the testes, and may be associated with symptoms suggestive of urinary tract or sexual dysfunction. There is no proven infection or other obvious local pathology. Testicular pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, and with symptoms suggestive of lower urinary tract and sexual dysfunction. Previous terms have included orchitis, orchialgia and orchiodynia. These terms are no longer recommended.

3.4.2.2 Epididymal pain syndrome

Epididymal pain syndrome is the occurrence of persistent or recurrent episodic pain perceived in the epididymis, and may be associated with symptoms suggestive of urinary tract or sexual dysfunction. There is no proven infection or other obvious local pathology. Epididymal pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, and with symptoms suggestive of lower urinary tract and sexual dysfunction.

3.4.3 Pathogenesis

Often scrotal pain is not associated with any specific pathology. Pain is perceived in the testes, epididymis, or the vas deferens.

3.4.3.1 Nerves

The ilioinguinal and genitofemoral and pundental nerves innervate the scrotum [214]. Any pathology or intervention at the origin or along the course of the nerves may result in pain perceived in the scrotum [215].

3.4.3.2 *Postvasectomy pain syndrome*

Postvasectomy scrotal pain syndrome occurs following vasectomy and is often associated with negative cognitive, behavioural, sexual or emotional consequences, and with symptoms suggestive of lower urinary tract and sexual dysfunction. Postvasectomy pain may be as frequent as 1% following vasectomy, possibly more frequent. The mechanisms are poorly understood and it is for that reason considered a special form of scrotal pain syndrome.

Incidence of postvasectomy pain is 2-20% among all men who have undergone a vasectomy [216]. In men with postvasectomy pain, 2-6% have a VAS score > 5 [217]. In a large cohort study of 625 men, the likelihood of scrotal pain after 6 months was 14.7%. The mean pain severity on a VAS score was 3.4/10. In the pain group, 0.9% had quite severe pain, noticeably affecting their daily life. In this cohort, different techniques were used to perform the vasectomy. The risk of postvasectomy pain was significantly lower in the no-scalpel vasectomy group (11.7% vs. the scalpel group 18.8%) [218].

3.4.3.3 *Post-inguinal hernia repair*

Chronic scrotal pain is a complication of hernia repair, but in trials it is seldom reported or it is put under the term chronic pain (not specified). In studies that have explicitly mentioned scrotal pain, there was a difference in incidence between laparoscopic and open hernia repair. In almost all studies, the frequency of scrotal pain was significantly higher in the laparoscopic than in the open group [215, 219]. In one particular study, there was no difference at 1 year but after 5 years, the open group had far fewer patients with scrotal pain [220].

3.4.4 **Diagnosis**

A physical examination is mandatory in patients with scrotal pain. Gentle palpation of each component of the scrotum is performed to search for masses and painful spots. A rectal examination is done to look for prostate abnormalities and to examine the pelvic floor muscles. Scrotal ultrasound (US) has limited value in finding the cause of the pain. In > 80% of patients, US does not show abnormalities that have clinical implications [221, 222]. If physical examination is normal, US can be performed to reassure the patient that there is no pathology that needs therapy (mainly surgery). Ultrasound can be used to diagnose hydroceles, spermatoceles, cysts and varicoceles. When abnormalities such as cysts are seen, this may play a role in therapeutic decision making.

3.4.5 **Treatment**

Treatment of chronic scrotal pain is based on the principles of treating chronic pain syndromes, described throughout these guidelines [223].

3.4.5.1 *Conservative treatment*

Conservative treatment should be in accordance with the principles described within this guideline (Chapters 9 and 10).

3.4.5.2 *Surgery*

The only surgical treatment that seems to be effective is microsurgical denervation which is for specific indications (see below). Epididymectomy may also be a choice in selected cases and orchiectomy is the last resort.

3.4.5.2.1 *Microsurgical denervation*

The three studies that have been carried out were cohort studies but their success rates were high. All studies are comparable on indication criteria, diagnostic methods and the surgical approach used. All had a follow-up of at least 20 months. Ultrasound showed no abnormalities and a spermatic cord block showed pain relief of > 50%.

Complete relief of pain is achieved in 71-96% and partial relief in 9-17%. Testicular atrophy was seen in 3-7% of the operated patients [224-226].

3.4.5.2.2 *Epididymectomy*

Evidence is conflicting around epididymectomy for scrotal pain and this should only be done as a part of a clinical trial.

3.4.5.2.3 *Orchiectomy*

There is no evidence to support orchiectomy and this should only be done within a clinical trial.

3.4.5.2.4 Vasovasostomy

In postvasectomy pain syndrome, a vasovasostomy might help to overcome the obstruction and thereby improve the pain. Some studies have shown good results but the quality of these studies was limited [227, 228].

3.4.6 Conclusions and recommendations: scrotal pain syndrome

Conclusions	LE
The nerves in the spermatic cord play an important role in scrotal pain.	2b
Ultrasound of the scrotal content does not aid in diagnostics nor treatment of scrotal pain.	2b
Postvasectomy pain is seen in a substantial number of men undergoing vasectomy.	2b
Scrotal pain is more often noticed after laparoscopic than after open inguinal hernia repair.	1b
Microsurgical denervation of the spermatic cord is an effective therapy for scrotal pain syndrome.	2b
Vasovasostomy is effective in postvasectomy pain.	2b
Orchiectomy is the last resort in treating scrotal pain syndrome.	4

Recommendations	GR
Start with general treatment options for chronic pelvic pain (see chapter 10).	A
Inform about the risk of postvasectomy pain when counselling patients planned for vasectomy.	A
To reduce the risk of scrotal pain, open instead of laparoscopic inguinal hernia repair is recommended.	A
It is recommended that during inguinal hernia repair all the nerves in the spermatic cord are identified.	A
For patients who are treated surgically, microsurgical denervation of the spermatic cord is recommended.	A
For patients who do not benefit from denervation it is recommended to perform epididymectomy.	B
We recommend that orchiectomy should not be done, unless all other therapies, including pain management assessment, have failed.	C

Figure 5: Assessment and treatment of scrotal pain syndrome

Assessment	Treatment
Semen culture	Grade A recommended
Uroflowmetry	
Ultrasound scrotum (see text)	
Pelvic floor muscle testing	
Phenotyping	
	Grade B recommended
	Grade C recommended
	Other comments

3.5 Urethral pain syndrome

3.5.1 Definition

Urethral pain syndrome is the occurrence of chronic or recurrent episodic pain perceived in the urethra, in the absence of proven infection or other obvious local pathology. Urethral pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. Urethral pain syndrome may occur in men and women.

3.5.2 Pathogenesis

Based on the definition, there is no well-known pathogenetic mechanism responsible for urethral pain syndrome. There are no data available to answer the question: "how common is dysuria in the presence of

negative rigorous investigation of the bladder and urethra?”. Some suggestions have been proposed. The intimate relation of the urethra with the bladder (both covered with urothelium) makes it plausible that pathology seen in the bladder is also found in the urethra and causes the same symptoms. This is the case in classifying urethral pain syndrome as a form of BPS. It is obvious that what might cause pain in the bladder could be responsible for urethral pain. Mechanisms thought to be basic for BPS also apply to the urethra. This means that the specific testing with potassium is used to support the theory of epithelial leakage [152, 229]. Urethral syndrome is supposed to be the same as BPS in that the epithelium is leaking, thereby causing pain. Another possible mechanism is the neuropathic hypersensitivity following urinary tract infection [230].

The relationship with gynaecological and obstetric aspects is unclear. In a small group of patients with urethral pain, it has been found that grand multiparity and delivery without episiotomy were more often seen in patients with urethral syndrome, using univariate analysis [231].

3.5.3 Treatment

There is no specific treatment that can be advised. Management should be multidisciplinary and multimodal [232]. Laser therapy of the trigonal region may be a specific treatment. One trial comparing two forms of laser reported good results, but did not compare with sham treatment [233]. The majority of publications on treatment of urethral pain syndrome have come from psychologists [230].

3.5.4 Conclusions and recommendations: urethral pain syndrome

Conclusions	LE
Urethral pain syndrome may be a part of BPS.	2a
Urethral pain may be neuropathic hypersensitivity following urinary tract infection.	2b
There is no specific treatment for urethral pain syndrome.	4
In patients with significant distress associated with bladder or urethral symptoms, psychological treatment may be worth using to reduce distress and thereby improve function and quality of life.	4

Recommendations	GR
Start with general treatment options for chronic pelvic pain (see chapter 10).	A
It is recommended that patients with urethral pain syndrome are treated in a multidisciplinary and multimodal programme.	B
When patients are distressed, it is recommended to refer them for pain-relevant psychological treatment to improve function and quality of life.	B

Figure 6: Assessment and treatment of urethral pain syndrome

Assessment	Treatment	
Uroflowmetry	Grade A recommended	General treatment options for chronic pelvic pain - <i>chapter 10</i>
Micturition diary		
Pelvic floor muscle testing	Grade B recommended	Treat in a multidisciplinary and multimodal programme
		Pain-relevant psychological treatment to improve QoL and function
Phenotyping		
	Other comments	Data on urethral pain are very sparse and of limited quality

4. GYNAECOLOGICAL ASPECTS OF CHRONIC PELVIC PAIN

4.1 Introduction

Chronic pelvic pain in urological and gynaecological practice is complex and difficult to treat. The aim is to define the aetiology and treat it appropriately. However, in 30% of cases, there is no definable cause and this poses a challenge [234].

4.2 Clinical history

A detailed medical history outlining the nature, frequency and site of pain; its relationship to precipitating factors and the menstrual cycle, may help define the aetiology. A menstrual and sexual history, including a history of sexually transmitted diseases, vaginal discharge, as well as previous sexual trauma is mandatory.

4.3 Clinical examination

Abdominal and pelvic examination to exclude gross pelvic pathology, as well as to demonstrate the site of tenderness is essential. Abnormalities in muscle function should also be sought. Clinical pelvic examination should be a single digit examination if possible. The usual bimanual examination can generate severe pain so the examiner must proceed with caution. Examining a woman with CPP is difficult, and many authors recommend that one should assess cutaneous allodynia along the dermatomes of the abdomen (T11-L1) and the perineum (S3, and the degree of tenderness should be recorded).

4.3.1 Investigations

Vaginal and endocervical swabs to exclude infection are recommended, and cervical cytology screening is advisable. Pelvic imaging can provide useful information about pelvic anatomy and pathology. Areas of tenderness detected during a transvaginal scan can help determine the possible presence of current or pre-existing visceral disease [235, 236]. Laparoscopy is perhaps the most useful invasive investigation to exclude gynaecological pathology [237, 238] and to assist in the differential diagnosis of CPP in women [239]. Often, it is combined with cystoscopy [240, 241] and/or proctoscopy to help identify the site of multi-compartment pain.

Psychological considerations around laparoscopy

There have been three diverse studies of laparoscopy. Elcombe et al. have shown that there was a distinct and lasting improvement in pain consequent of laparoscopy. Improvement was related to beliefs about pain and its meaning in terms of serious disease, and not to medical variables [242]. In another study, showing women a photograph of their pelvic contents taken during laparoscopy did not improve pain ratings/ beliefs about pain, than those who did not see a photograph [243]. Peters et al. compared standard clinical care of patients with CPP, where organic causes of pelvic pain were excluded first and diagnostic laparoscopy was routinely performed, with a second group, where an integrated approach was chosen from the beginning, with equal attention being given to somatic and psychological factors and laparoscopy was not routinely performed [244]. Both patient groups were similar in their characteristics. Evaluation of pain and function one year after therapy commenced revealed that the integrated approach improved pelvic pain parameters significantly more often than the standard approach, suggesting that equal attention to both organic and other causative factors is the best way forward [244].

4.4 Pain associated with well-defined conditions

4.4.1 Dysmenorrhoea

Menstrual pain or 'dysmenorrhoea' may be primary or secondary. Primary dysmenorrhoea classically begins at the onset of ovulatory menstrual cycles and tends to decrease following childbirth [239]. Secondary dysmenorrhoea suggests the development of a pathological process, such as endometriosis [238], adenomyosis [245] or pelvic infection, which need to be excluded.

Treatment

Simple analgesics and/or non-steroidal anti-inflammatory drugs (NSAIDs) [246], can be helpful if they are started before the onset of each menstrual cycle. Suppression of ovulation using combined or progesterone-only contraceptive tablets or the use of a levo-norgestrel intra-uterine device also reduces dysmenorrhoea. Dysmenorrhoea is a chronic condition and should be managed within a multidisciplinary pain management setting.

4.4.2 Infection

In premenopausal women, a history of pelvic inflammatory disease (PID) must be excluded. A patient's sexual

history should be taken along with swabs to exclude chlamydia and gonorrhoea infection. Bacterial and viral genital tract pathogens should also be excluded [247], as they can cause severe pelvic/vaginal/vulvar pain [248] and are associated with ulcerating lesions and inflammation, which may lead to urinary retention [249]. If there is any doubt about the diagnosis, laparoscopy may be helpful, as one of the differential diagnosis is endometriosis.

Treatment

Treatment of infection depends on the causative organisms. Subclinical chlamydial infection may lead to tubal pathology, and thus subfertility. Thus, screening for this organism in sexually active young women is essential to prevent this complication. Standard broad-spectrum antibiotics targeting Grampositive and negative organisms are normally recommended. Chronic PID is no longer common in developed countries, but still poses a significant problem for women in developing countries. Hospitalisation and opiates may be needed to achieve adequate analgesia.

4.4.3 Endometriosis and adenomyosis

The incidence of endometriosis is rising in the developed world. The precise aetiology is unknown, but an association with nulliparity is well known. A diagnosis is usually made when a history of secondary dysmenorrhoea and/or dyspareunia exists. On examination, there is often tenderness in the lateral vaginal fornices, reduced uterine mobility, tenderness in the recto-vaginal septum, and on occasion, adnexal masses. Laparoscopy is the most useful diagnostic tool [250-252].

Endometriotic lesions affecting the urinary bladder or causing ureteric obstructions can occur, as well as lesions affecting the bowel, which may lead to rectal bleeding in association with menstruation. Adenomyosis is associated with augmented pain during menses. It is diagnosed by an ultrasound scan of the uterus, which often shows cystic dilatation of the myometrium [253].

Treatment

Analgesics and NSAIDs are also helpful in easing pain during menses, along with the use of hormonal therapies. They modify the disease but do not cure it. Suppression with GnRH analogues may create an artificial menopause, although the resulting oestrogen deficiency can have marked long-term side-effects, such as reduced bone density and osteoporosis. Thus, these drugs are normally only used before surgery to improve surgical outcome. Extensive surgery for endometriosis is challenging and is still considered to be controversial, as there is at least one RCT showing no benefit in pain relief in the removal of early extensive endometriosis compared to sham surgery [254, 255].

A multidisciplinary surgical and pain management team should be integrated into the management pathway of women with endometriosis and pain. Pain in women with endometriosis is often not proportionate to the disease seen and has complex psycho-bio-social components. In patients with adenomyosis, the only curative surgery is hysterectomy but patients can benefit from hormonal therapy and analgesics.

4.4.4 Gynaecological malignancy

The spread of gynaecological malignancy of the cervix, uterine body or ovary will cause pelvic pain depending on the site of spread. Treatment is of the primary condition, but all physicians dealing with pelvic pain must be fully aware of the possibility of gynaecological malignancy.

4.4.5 Injuries related to childbirth

Trauma occurring at the time of childbirth may lead to CPP related to the site of injury. Female sexual dysfunction is perhaps the commonest presenting problem [256]. There is often a transient problem with oestrogen deficiency in the postpartum period and during breastfeeding, which can compound this situation. Denervation of the pelvic floor with re-innervation may also lead to dysfunction and pain.

Treatment

Treatment with a short course of hormone replacement cream can be beneficial. However, reassurance that the situation will improve on the cessation of breastfeeding is also helpful.

4.4.6 Pain associated with pelvic organ prolapse and prolapse surgery

Pelvic organ prolapse is often asymptomatic, unless it is so marked that it causes back strain, vaginal pain and skin excoriation [257]. Prolapse is often a disease of older women, and it is often associated with postmenopausal oestrogen deficiency, which may lead to pain associated with intercourse. Hormone replacement therapy is usually helpful. Specially designed supportive plastic vaginal devices or surgery may

also be helpful. Prolapse surgery may entail the use of non-absorbable mesh (usually in the form of “mesh kits”) [258-260]. Although they may have a role in supporting the vagina, they are also associated with several complications including bladder, bowel and vaginal trauma [259]. In a subset of these patients, chronic pain may ensue, because mesh insertion may cause nerve and muscle irritation [256].

Clinical evaluation

Patients should be fully evaluated clinically and may need specialised imaging, using contrast mediums if necessary, to make a diagnosis. Most patients can be treated by multidisciplinary pain management strategies, including psychology, or mesh-excisional surgery [261, 262], if appropriate.

4.5 Vaginal and vulvar pain syndromes

Pain in the vagina or the female external genital organs is most commonly due to infection or trauma, as a consequence of childbirth or surgery. Pain is usually a precedent to dyspareunia. When the pain persists for > 6 months, it can be diagnosed as “vulvodynia” or “chronic vaginal/vulvar pain syndrome” with no known cause. It is still a poorly understood condition, and thus difficult to treat.

There are two main subtypes of vulvodynia: generalised vulvodynia (GV), where the pain occurs in different areas of the vulva at different times; and vulvar vestibulitis (VV), where the pain is at the entrance of the vagina. In GV, the pain may be constant or occur occasionally, but touch or pressure does not initiate it, although it may make the pain worse. In VV, the pain is described as a burning sensation that comes on only after touch or pressure, such as during intercourse.

The causes of vulvodynia are many and include:

- History of sexual abuse
- History of chronic antibiotic use
- Hypersensitivity to yeast infections, allergies to chemicals or other substances
- Abnormal inflammatory response (genetic and non-genetic) to infection and trauma
- Nerve or muscle injury or irritation
- Hormonal changes

Although therapeutic options remain limited and require a multidisciplinary pain management approach, with psychological and physiotherapy input, they can be treated effectively with physiotherapy, stretching exercises and even botulinum toxin, though in the case of the latter the evidence is variable.

4.6 Managing chronic gynaecological pain in ill-defined conditions

In those where CPP is unrelated to any of the above well-defined conditions, it is often difficult to determine a therapeutic pathway other than a multi-disciplinary chronic abdomino-pelvic pain management plan. A Cochrane review suggests that there may be some evidence (moderate in nature) which supports the use of progestogens in such cases. Though efficacious, physicians need to be conversant with progestogenic side effects (e.g. weight gain, bloatedness-the most common adverse effects) which can stop some patients from accepting such medication. Gonadotrophins, such as goserelin, are also thought to help such pain. However, when compared with progestogens, their efficacy remains limited, as is the case when comparing gabapentin with amitriptyline. The quality of evidence is generally low and is drawn from single studies [263].

In patients with presumed adhesions, there is no consensus as to whether adhesiolysis should be performed to improve pain [264, 265].

4.7 Summary

Pain in association with urinary and gastrointestinal symptoms must be considered carefully. For example, patients with bladder pain quite often present with dyspareunia due to bladder base tenderness, so despite the dyspareunia being the focus it is the bladder component that is the main problem. Similarly, in those with anal pain it may be the evacuatory dysfunction that is the main culprit. Conditions, such as pelvic congestion have been cited as a cause of pelvic pain of unknown aetiology, but this diagnosis is not universally recognised [248, 249]. It is only when all the above conditions have been excluded that the physician may declare that the patient has ‘unexplained’ pelvic pain. Treating these patients remains a challenge for all physicians, but quite clearly the best results are obtained from a multidisciplinary approach that considers all possible causes.

4.7.1 Conclusions and recommendations: gynaecological aspects of chronic pelvic pain

Clinical state		LE
Clinical history and examination	Mandatory to making a diagnosis	2a
Investigations	Mandatory to making a diagnosis	2a
	Laparoscopy is well tolerated and does not appear to have negative psychological effects	1b
Pain associated with well-defined conditions	Dysmenorrhoea: effective therapeutic options	3
	Infection: effective therapeutic option	3
	Endometriosis: effective therapeutic options including medical and surgical care	1b
	Gynaecological malignancy: effective therapeutic options	3
	Injuries related to childbirth: effective therapeutic options	3
	Pain associated with pelvic organ prolapse: effective therapeutic options	3
Vaginal and vulvar pain syndrome	Diagnosis and therapeutic interventions	3
	Psychological treatment (CBT or supportive psychotherapy) can improve pain and sexual and emotional function	1b

Recommendations	GR
All women with pelvic pain should have a full gynaecological history and evaluation, and including laparoscopy is recommended to rule out a treatable cause (e.g. endometriosis).	A
Provide therapeutic options such as hormonal therapy or surgery in well-defined disease states.	B
Provide a multidisciplinary approach to pain management in persistent disease states.	B
Recommend psychological treatment for refractory chronic vulvar pain.	B
Use alternative therapies in the treatment of chronic gynaecological pelvic pain.	C

Figure 7: Assessment and treatment of gynaecological aspects in chronic pelvic pain

Assessment	Treatment	
Gynaecological examination	Grade A recommended	Laparoscopy to rule out treatable causes
Ultrasound		
Laparoscopy (see text)	Grade B recommended	Hormonal therapy in well defined states
		Multidisciplinary approach in persistent disease states
		Psychological treatment for refractory chronic vulvar pain

5. GASTROINTESTINAL ASPECTS OF CHRONIC PELVIC PAIN

5.1 Introduction

This chapter describes CPP perceived to be associated with the gastrointestinal tract, which is mainly due to functional disorders and cannot be explained by structural or specific well-defined diseases of the pelvis. Some points to note:

- There may be a considerable overlap of the gastrointestinal with other pelvic pain syndromes.
- Defined gastrointestinal conditions with specific structural defects and diseases may coexist.
- Behavioural changes such as straining can lead to organic diseases such as rectal prolapse, solitary rectal lesion syndrome, or pudendal nerve injury with consecutive faecal incontinence. Some structural gastrointestinal abnormalities (e.g., postpartum anal sphincter defects, or small rectoceles) are often observed in asymptomatic individuals and may be coincidental with the

gastrointestinal pelvic pain syndrome.

- Different diseases can aggravate previously asymptomatic functional disorders which may become symptomatic such as faecal incontinence in patients with diarrhoea of different origins or anal fissure in patients with dyssynergic defecation.
- Finally, we need to consider that all functional disorders such as anorectal pain are defined on the basis of retrospectively evaluated longstanding symptoms, which ideally would have been registered prospectively with symptom diaries [266, 267].

5.2 Clinical history

Functional anorectal disorders are diagnosed by symptoms, supplemented by objective findings. The predominant symptoms that patients are interviewed about are discomfort or pain in relation to their bowel habits, daily activities, and eating. A precise history of dysfunctional voiding or defecation should be asked, ideally applying symptom questionnaires for urinary and anorectal symptoms (e.g., Rome III questionnaire for anorectal pain). Excessive straining at most defecations, anal digitations in dyssynergic defecation, and a sensation of anal blockage may be found in patients with chronic anal pain. History of anxiety and depression with impaired QoL is often encountered in anorectal functional disorders and should be evaluated.

5.2.1 Clinical examination and investigations

At clinical examination, perianal dermatitis may be found as a sign of faecal incontinence or diarrhoea. Fissures may be easily overlooked and should be searched thoroughly in patients with anal pain. Rectal digital examination findings may show high or low anal sphincter resting pressure, a tender puborectalis muscle in patients with the Levator Ani Syndrome, and occasionally increased perineal descent. The tenderness during posterior traction on the puborectalis muscle differentiates between Levator Ani Syndrome and Unspecified Functional Anorectal Pain and is used in most studies as the main inclusion criterion. Dyssynergic (paradoxical) contraction of the pelvic muscles when instructed to strain during defecation is a frequent finding in patients with pelvic pain. Attention should be paid to anal or rectal prolapse at straining, and ideally during bimanual examination by the gynaecologist to diagnose an enterocele or cystocele.

5.2.2 Diagnostic assessment

The Rome III criteria for diagnosis of functional anorectal diseases include symptoms for each specific functional disorder as listed below. The gastrointestinal diagnostic assessment should be performed in an interdisciplinary manner, preferably at a pelvic floor centre by a dedicated team, and appropriate testing. The most frequently performed investigations are flexible rectosigmoidoscopy or colonoscopy, pelvic ultrasound, anorectal endosonography and anorectal manometry combined with anal electromyography (EMG) and balloon expulsion test. Three-dimensional anorectal ultrasound has become an indispensable readily available tool for the specialised proctologist. Perineal ultrasound offers the advantage of sphincter imaging without insertion of the transducer into the rectum.

Magnetic resonance imaging in conjunction with MR defecography has become the most valuable imaging technique to assess anorectal function dynamically. Magnetic resonance imaging studies outline simultaneously the anatomy of the pelvic floor and visualise different structural and functional pathologies, by applying dynamic sequences after filling of the rectum with a viscous contrast medium (e.g., ultrasound gel). The following pathologies can be visualised: pelvic floor descent, an abnormal anorectal angle while squeezing and straining, rectal intussusception, rectocele, enterocele and cystocele. However, limitations of MR defecography are the left lateral position and the limited space for the patient, which may reduce the ability to strain and hereby reduce the sensitivity of the method, underestimating the size of entero- and rectoceles as well as the amount of interception.

Surgical consultations should be available for all patients, plus referral to a urogynaecologist or urologist when indicated. Biofeedback treatment, botulinum toxin A injection, and percutaneous tibial nerve stimulation (PTNS) and sacral neuromodulation (SNM) should be available as a complementary therapeutic option to medical and surgical treatment.

5.3 Pain associated with well-defined conditions

5.3.1 Haemorrhoids

Chronic pelvic pain is rare in haemorrhoidal disease because endoscopic and surgical treatment is mostly effective in acute disease. The most frequent aetiology of pain without significant bleeding is thrombosed external haemorrhoids or an anal fissure. Haemorrhoidal pain on defecation associated with bleeding is usually due to prolapse or ulceration of internal haemorrhoids. Anaemia from haemorrhoidal bleeding is rare but may arise in patients on anticoagulation therapy, or those with clotting disorders. Different treatments of

haemorrhoids have been evaluated by two Cochrane reviews. Excisional haemorrhoidectomy (EH) has been compared to the less-invasive technique of rubber band ligation (RBL), and has been shown to increase pain, with more complications and time off work. However, despite these disadvantages of EH, complete long-term cure of symptoms is increased by surgery, and minor complications are accepted by patients [268]. Rubber band ligation is the choice of treatment for grade II haemorrhoids, whereas EH should be reserved for grade III haemorrhoids or recurrence after RBL [268]. New stapler techniques of haemorrhoidopexy are associated with a higher long-term risk of recurrence and prolapse compared to conventional EH. Further studies are needed [269].

5.3.2 **Anal fissure**

Anal fissures are tears in the distal anal canal and induce pain during and after defecation. The pain can last for several minutes to hours. Persistence of symptoms beyond 6 weeks or visible transversal anal sphincter fibres define chronicity. Fissures located off the midline are often associated with specific diseases such as Crohn's disease or anal cancer. Internal anal sphincter spasms and ischaemia are associated with chronic fissures. Medical therapy with nitrates and calcium channel blockers resulting in anal sphincter relaxation is more effective in children than in adults [270]. Recently, 2% diltiazem ointment has been shown to be superior to glyceryl trinitrate in terms of time to healing and recurrence rate in children with anal fissure [271]. In adults, 75 RCTs with 17 agents were analysed by a Cochrane review [270]. Nitroglycerin ointment (GTN), isosorbide mono & dinitrate, botulinum toxin A, diltiazem and nifedipine (calcium channel blockers) were found to be marginally better than placebo, but less efficacious than surgical sphincterotomy. Botulinum toxin A injection represents an alternative treatment option with a fissure healing rate which is comparable to topical diltiazem after 3 months [272]. Surgery with lateral-internal sphincterotomy is the most studied procedure but carries the risk of postoperative faecal incontinence, and may be replaced by fissure excision combined with botulinum toxin A or anal advancement flap [273].

5.3.3 **Proctitis**

Abdominal and pelvic pain in patients with inflammatory bowel disease and proctitis are often difficult to interpret. Faecal calprotectin may help to differentiate between inflammation and functional pain, to spare steroids. Tricyclic antidepressants at low dose can be effective in this situation when acute exacerbation has been ruled out [274, 275].

5.3.4 **Irritable bowel syndrome**

Although IBS can be associated with pelvic pain, the authors of these guidelines consider a full discussion of this topic beyond the scope of these guidelines. A number of high quality clinical guidelines address this topic [276, 277].

5.4. **Chronic anal pain syndrome**

5.4.1 **Diagnostic criteria**

Diagnostic criteria for chronic anal pain syndrome (chronic proctalgia) according to the Rome III criteria are as follows and must include all of the following:

1. Chronic or recurrent rectal pain or aching.
2. Episodes last at least 20 min.
3. Exclusion of other causes of rectal pain such as ischaemia, inflammatory bowel disease, cryptitis, intramuscular abscess and fissure, haemorrhoids, prostatitis, and coccygodynia.

These criteria should be fulfilled for the past 3 months with symptom onset at least 6 months before diagnosis [266].

The chronic anal pain syndrome includes the above diagnostic criteria and exhibits exquisite tenderness during posterior traction on the puborectalis muscle (previously called "Levator Ani Syndrome"). This common and debilitating condition is frustrating to treat. Pathophysiology of pain is thought to be due to overactivity of the pelvic floor muscles. Chiarioni et al. have recently published an RCT demonstrating that biofeedback treatment was superior to electrogalvanic stimulation and massage for treatment of the chronic anal pain syndrome. One hundred and fifty-seven patients who had at least weekly rectal pain were investigated, but only patients with tenderness on traction of the pelvic floor showed a significant treatment benefit. In patients with tenderness of the puborectalis muscle (Rome II: Highly likely Levator Ani Syndrome), 87% reported adequate relief after one month of biofeedback vs. 45% for electrogalvanic stimulation, and 22% for massage. These results were maintained at 12 months with adequate relief after nine sessions of biofeedback in 58% of the whole group (Rome II: Highly likely and Possible Levator Ani Syndrome), after galvanic stimulation in 27% and massage in 21% of patients. As previously described in dyssynergic defecation, the ability to expel a 50-ml water-

filled balloon and to relax pelvic floor muscles after biofeedback treatment were predictive of a favourable therapeutic outcome [278]. The pathophysiology of the chronic anal pain syndrome is therefore similar to that of dyssynergic defecation, and this favours the role of the pelvic floor muscles in the pathophysiology of both conditions. Other treatment modalities have been less successful.

5.4.2 *Botulinum toxin A in pelvic pain*

Chronic pelvic pain associated with spasm of the levator ani muscles and treatment of the puborectalis and pubococcygeus muscle by botulinum toxin A appears to be promising in some women, as shown in a pilot study (n = 12). The inclusion criteria were dependent only on vaginal manometry with overactivity of the pelvic floor muscles, defined as a vaginal resting pressure > 40 cm H₂O. Although dyspareunia and dysmenorrhea improved, non-menstrual pelvic pain scores were not significantly ameliorated [279]. In the following double-blinded, randomised, placebo-controlled trial, the same group defined pelvic floor myalgia according to the two criteria of tenderness on contraction and hypertension (> 40 cm H₂O) and included 60 women. In this larger study, non-menstrual pelvic pain was significantly improved compared to that treated with placebo (VAS score 51 vs. 22; P = 0.009). It was concluded therefore that botulinum toxin A is effective for reducing pelvic floor-muscle associated pain with acceptable adverse effects such as occasional urinary and faecal stress incontinence [280]. However, recently, a small RCT failed to show any benefit of botulinum toxin A [281].

5.4.3 *Sacral neuromodulation and percutaneous tibial nerve stimulation in pelvic pain*

In a large cohort of 170 patients with functional anorectal pain from the St. Mark's Hospital (Harrow, Middlesex, United Kingdom) sacral nerve stimulation was used in 3 patients (2 improved) while biofeedback was the most used modality with the greatest treatment effect in patients with defecatory dysfunction (29 patients, 17 improved) [282]. Sacral neuromodulation has been reported to be somewhat beneficial in two uncontrolled studies, showing improvement in about half the patients [283, 284]. Sacral neuromodulation may be a choice in patients with CPP who failed to respond to biofeedback and drug therapy. The less invasive percutaneous tibial nerve stimulation (PTNS) was tested in 12 women with CPP lasting for at least 6 months and showed an improvement in pain, quality of life and sexual life [285]. No "sham" SNM or PTNS control group were used in neither cited studies, which limits their value as an important placebo effect cannot be ruled out.

5.4.4 *Intermittent chronic anal pain syndrome*

Intermittent chronic anal pain syndrome (proctalgia fugax) consists of all the following diagnostic criteria, which should be fulfilled for 3 months and before 3 months:

1. Recurrent episodes of pain localised to the anus or lower rectum.
2. Episodes last from several seconds to minutes.
3. There is no anorectal pain between episodes.

Stressful life events or anxiety may precede the onset of the intermittent chronic anal pain syndrome. The attacks may last from a few seconds to as long as 30 min. The pain may be cramping, aching or stabbing and may become unbearable. However, most patients do not report it to their physicians and pain attacks occur less than five times a year in 51% of patients. Due to the short duration of the episodes, medical treatment and prevention is often not feasible. Inhaled beta-2 adrenergic agonist salbutamol was effective in an RCT in patients with frequent symptoms and shortened pain duration [286]. Other treatment options are topical diltiazem and botulinum toxin A [282]. However, there is still some controversy as regards the duration of pain of intermittent chronic and chronic anal pain syndrome. RCTs often use different definitions, extending the pain duration (with a shift to chronic pain) in order to include more patients and to better evaluate the study-drug action.

5.5 *Summary*

Chronic pelvic pain is an interdisciplinary entity needing multispeciality and multidisciplinary diagnostic assessment by a gastroenterologist, urologist, gynaecologist and pain teams as appropriate, with the input of physicians, psychologists and physiotherapists amongst others. Anorectal pain is investigated best by endoscopic and functional testing to rule out structural disease that can be treated specifically. Chronic pelvic pain due to functional disorders remains a therapeutic challenge that may respond to biofeedback therapy, electrogalvanic stimulation and botulinum toxin A in the case of Levator Ani Syndrome and defecatory disorders associated with pelvic pain.

5.5.1 Conclusions and recommendations: anorectal pain syndrome

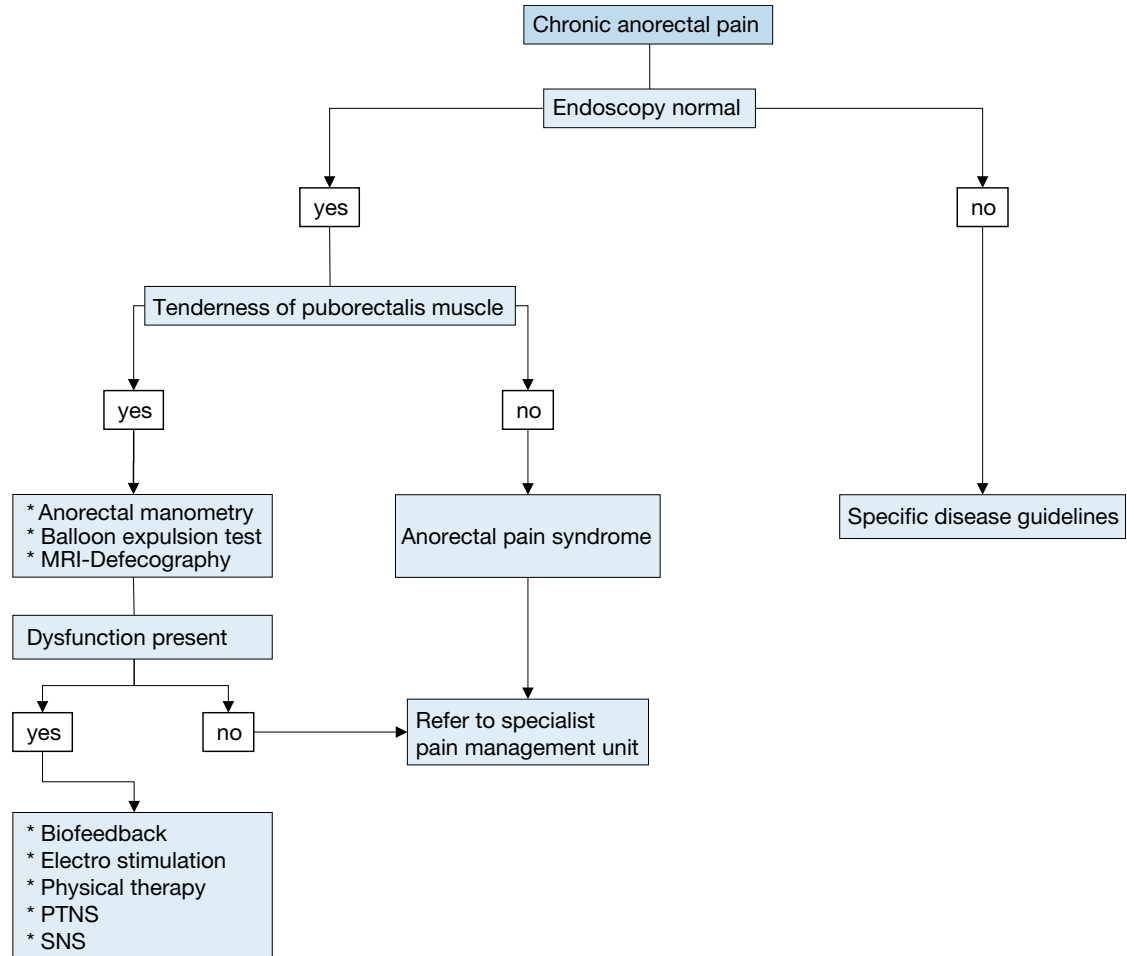
Conclusions on functional anorectal pain	LE
Tenderness on traction is the main criterion of the chronic anal pain syndrome.	1a
Biofeedback is the preferred treatment for the chronic anal pain syndrome.	1a
Electrogalvanic stimulation is less effective than biofeedback.	1b
Botulinum toxin is efficient in CPP with spasms.	1b
Percutaneous tibial nerve stimulation is effective in pelvic pain.	1b
Sacral neuromodulation is effective in pelvic pain.	3
Inhaled salbutamol is effective in intermittent chronic anal pain syndrome.	3

Recommendations for functional anorectal pain	GR
Functional testing is recommended in patients with anorectal pain.	A
Biofeedback treatment is recommended in patients with pelvic pain and dyssynergic defecation.	A
Botulinum toxin A and electrogalvanic stimulation can be considered in the chronic anal pain syndrome.	B
Percutaneous tibial nerve stimulation can be considered in the chronic anal pain syndrome.	B
Sacral neuromodulation should be considered in the chronic anal pain syndrome.	C
Inhaled salbutamol should be considered in the intermittent chronic anal pain syndrome.	C

Figure 8: Assessment and treatment of anorectal pain syndrome

Assessment	Treatment	
Endoscopy	Grade A recommended	Biofeedback treatment
Pelvic floor muscle testing		
Anorectal manometry	Grade B recommended	Botulinum toxin A in women with pelvic pain
Rectal balloon expulsion test		Electrogalvanic stimulation
		Percutaneous tibial nerve stimulation
MRI-defecography	Other comments	Sacral neuromodulation should be considered
		Inhaled salbutamol should be considered in intermittent anal pain syndrome

Algorithm 4: Diagnosis of chronic anorectal pain



6. PERIPHERAL NERVE PAIN SYNDROMES

6.1 Neuropathic pain

Much has been written on the subject of peripheral neuropathic pain [287-290] including its diagnosis and treatment. There are some fundamental principles that are worth considering:

1. Nerve injury is associated with changes both within the peripheral nervous system (PNS) and the central neural axis including the higher centres. These changes serve to produce an increasing disparity between stimulus and response (Chapter 2).
2. In the PNS, nerve damage may produce a neuroma that can provide a source of ongoing afferent central activity. The neuroma may be discreet and palpable to touch or en-passage and not palpable. Neuromas are sensitive and respond to: compression (e.g., by the surrounding tissue or digital pressure), temperature change and adrenergic stimulation. Sympathetic nerve fibres can grow into neuromas as well as the associated dorsal root ganglia, which may result in sensitivity to body adrenaline changes such as through mood and environment with subsequent changes in pain.
3. Windup is a progressive increase in centrally elicited action potentials per unit peripheral stimulus. A severe acute insult or a chronic repeated stimulus may result in a transient windup phenomenon becoming permanent. These long-term changes in central sensitisation are associated with dysfunction of the afferent sensory nervous system and perception, as well as efferent motor, vasomotor and pseudomotor activity within the pathways of the injured nerve [291].
4. These central changes may result in abnormal afferent processing for nerves other than those originally damaged, so that increased perception (pain, allodynia and hyperaesthesia) from an area greater than the expected pattern may occur. In the case of tissues with innervation that overlaps with an injured nerve, somatic and visceral hypersensitivity (e.g., sensory urge with increased

frequency of voiding/evacuation) may be perceived from those tissues.

Essentially, what may be considered a simple nerve injury may be magnified by the CNS so that a whole region may be involved and a non-specific regional pain syndrome may arise. There is also a suggestion that involvement of both the peripheral and CNS in the control of the endocrine and immunological system may also become abnormal. Certainly, there is a complex interaction between nerve injury, emotional well being, disability and widespread pain. A proportion of patients go on to develop CFS, FM and immunological disorders [134, 292, 293].

6.2 Anatomy

When considering pelvic pain mechanisms, nerves associated with the pelvis/genitalia are generally divided into thoraco-lumbar and sacral root afferents. The hypogastric plexus is mixed autonomic (sympathetic and parasympathetic) and may contain afferents associated with pain.

6.2.1 *The posterior subgluteal triangle nerves*

The posterior triangle area is the area defined superiorly by the upper border of the piriformis, inferiorly by the lower border of quadratus femoris, laterally by the greater trochanter and medially by the lateral border of the sacrum, the lateral borders of the sacrotuberous ligament and ischial tuberosity. This region contains the sciatic nerve, posterior femoral cutaneous nerve (which branches into the posterior cutaneous perineal branch and the cluneal nerves), the nerve to the obturator internus muscle, and the pudendal nerve. These nerves pass deep to the piriformis muscle and superficial to the superior gemellus and obturator internus muscles. Injury in this area may damage one or more of these nerves (Figure 9) [294-300].

6.2.2 *Branches of the pudendal nerve*

The pudendal nerve has its origins at the S2-S4 levels. S2 and S3 also contribute to the sciatic nerve and S4 to the coccygeal plexus and the anococcygeal nerves. The pudendal nerve has three main branches: the inferior anorectal nerve, the superficial perineal nerve (which terminates as cutaneous branches in the perineum and posterior aspect of the scrotum), and the deep perineal nerve, which is distributed to the pelvic structures (innervating parts of the bladder, prostate and urethra). This branch terminates as the dorsal nerve of the penis/clitoris, which innervates the glans. In addition to sensory branches, the pudendal nerve provides motor innervation to anal and urethral sphincters, as well as to the bulbospongiosus and ischiocavernosus muscles (involved in the bulbocavernosus response, orgasm and ejaculation). Autonomic fibres also pass with the pudendal nerve and are derived from the presacral parasympathetic as well as sympathetic fibres via the hypogastric plexi.

6.2.3 *Anatomical relations of the pudendal nerve*

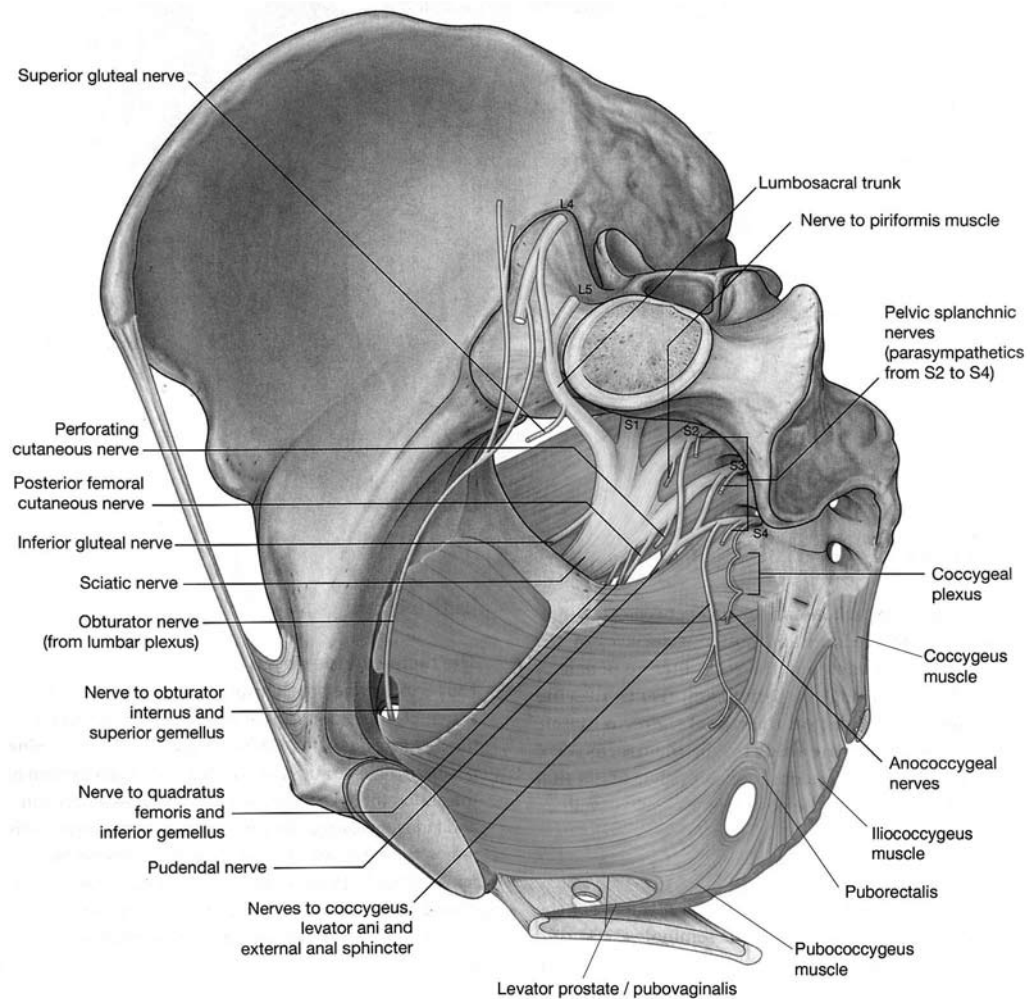
The anatomy may be variable, however, the three roots that form the pudendal nerve usually merge anterior to the sacrum and inferior to the piriformis muscle (Figure 9). The pudendal nerve leaves the pelvis via the greater sciatic notch to enter the subgluteal region. In the posterior subgluteal triangle (the area bordered by the inferior edge of the piriformis muscle, the sacrotuberous ligament medially and the upper border of the rectus femoris muscle inferiorly), the nerve emerges from under the inferior border of the piriformis muscle with its associated pudendal artery and veins; it is medial to the nerve innervating the obturator internus muscle, which is medial to the posterior femoral cutaneous nerve (which divides into its cutaneous branch but also the inferior cluneal nerves and perineal nerves), which is medial to the sciatic nerve. These anatomical relations are important for neurotracing techniques used for nerve blocks and because symptoms in those nerve territories also help with diagnosis [301-303].

The pudendal nerve leaves the subgluteal region as it wraps around the superficial surface of the ischial spine/sacrospinal ligament to re-enter the pelvis via the lesser sciatic notch (between the more ventral sacrospinal ligament and the more dorsal sacrotuberous ligaments) [294, 297]. This occurs 15% of the time at the entheses of the spine and the ligament; in 75% of the time, it is more medial, and in 10% it wraps around the spine. The sacrotuberous ligament may have a sharp superior border, be wide, and as a result, close to the spinosacral ligament, or be divided with the pudendal nerve passing through it. All of these features may predispose to nerve injury. As the pudendal nerve re-enters the pelvis below the levator muscles, it runs within a fascial canal medial to the internal obturator muscle (Alcock's canal).

The inferior anorectal branch may never be a true branch of the pudendal nerve, and may have its origins directly from the sacral roots. As a consequence, pain associated with pudendal nerve injury may not involve the anorectal area. Similarly, pain may only be perceived in the anorectal area if the main pudendal nerve is not involved. In 11% of cases, the inferior anorectal nerve pierces the sacrospinal ligament, possibly increasing the

risk of entrapment. Other variations of the anorectal branch exist with the nerve branching off from the main pudendal nerve at any point in the gluteal region or within the pelvis. In 56% of cases, the pudendal nerve is a single trunk as it re-enters the pelvis. Some people have two or three pudendal nerve trunks.

Figure 9: Anatomical relations of the pudendal nerve



Source: Drake, Vogel, & Mitchell: *GRAY's ANATOMY FOR STUDENTS*, 2004 Elsevier Inc.

6.2.4 **Afferent nerves and the genitalia**

- The afferents from the skin of the genitals pass via a complex of multiple sensory nerves and this makes the anatomical diagnosis of nerve injury as a cause of pain difficult.
- The anterolateral part of the scrotum/labia majora has afferents associated with the genitofemoral nerve primarily; there may also be some involvement of the ilioinguinal and iliohypogastric nerves.
- The posterior scrotal/labia branches of the pudendal nerve transmit sensation from the posterior scrotum/labia majora.
- The penis shaft is innervated on its dorsal surface by the genitofemoral, ilioinguinal and iliohypogastric nerves, and the ventral surface by the perineal branches of the posterior femoral cutaneous nerve and cutaneous branches of the pudendal nerve.
- The glans penis/clitoris is associated with the dorsal nerve of the penis/clitoris, the terminal branch of the pudendal nerve.
- All the nerves that are associated with the scrotum may also receive afferents from the testes, although classically, the nerves from the testes are usually associated with the genitofemoral nerve (thoracolumbar as opposed to sacral roots).
- The superficial branches of the pudendal's superficial perineal nerve and the perineal branch of the posterior femoral cutaneous nerve receive afferents from the perineal skin.
- Deeper afferents from the perineum and from some of the pelvic organs pass to the pudendal nerve via its deep perineal branch.

6.2.5 **Afferents in the autonomic plexus**

The pelvic plexus is associated with both the parasympathetic and sympathetic nerves, and as well as afferents associated with these pathways, afferents may travel back to the sacral and thoracolumbar roots with these autonomic nerves. Sites for injury and possible intervention may thus include: the ganglion impar, superior hypogastric plexus, inferior hypogastric plexus, and lumbar sympathetic trunk, as well as more central spinal root areas.

6.3 **Aetiology of nerve damage**

6.3.1 **Anterior groin nerves - aetiology of nerve damage**

The primary afferents of the anterior groin nerves enter the spinal cord at the thoracolumbar level (T10 to L3). Thoracolumbar spinal pathology and any pathology along the course of the nerve may result in neuropathic pain in the distribution of these nerves. As well as neoplastic disease, infection and trauma, surgical incisions and postoperative scarring may result in nerve injury [304].

6.3.2 **Pudendal neuralgia - aetiology of nerve damage**

Anatomical variations

Anatomical variations may predispose the patient to developing pudendal neuralgia over time or with repeated low-grade trauma (such as sitting for prolonged periods of time or cycling) [294, 297].

The pudendal nerve may be damaged due to local anatomical variation at the level of:

1. The piriformis muscle. For example, as part of a piriformis syndrome: in some cases, the nerve may pass through the muscle and hence be trapped; or in other cases, muscle hypertrophy or spasm is implicated.
2. The sacrospinous/sacrotuberous ligaments, possibly accounting for 42% of cases.
3. Within Alcock's canal (medial to the obturator internus muscle, within the fascia of the muscle), possibly accounting for 26% of cases.
4. Multiple levels in 17% of cases.

The site of injury determines the site of perceived pain and the nature of associated symptoms (e.g., the more distal the damage, the less likely the anal region will be involved).

6.3.3 **Surgery**

In orthopaedic hip surgery, pressure from the positioning of the patient, where the perineum is placed hard against the brace, can result in pudendal nerve damage [305, 306]. The surgery itself may also directly damage the nerve. Pelvic surgery such as sacrospinous colpopexy is clearly associated with pudendal nerve damage in some cases [307, 308]. In many types of surgery, including colorectal, urological and gynaecological, pudendal nerve injury may be implicated.

6.3.4 **Trauma**

Fractures of the sacrum or pelvis may result in pudendal nerve/root damage and pain. Falls and trauma to the gluteal region may also produce pudendal nerve damage if associated with significant tissue injury or prolonged pressure.

6.3.5 **Cancer**

Tumours in the presacral space must be considered. Tumours invading the pudendal nerve may occur and there may also be damage from surgery for pelvic cancer [298].

6.3.6 **Birth trauma**

This is more difficult to be certain about [295]. The pudendal neuralgia of birth trauma is thought to resolve in most cases over a period of months. However, rarely, it appears to continue as painful neuropathy. Multiple pregnancies and births may predispose to stretch neuropathy in later life.

6.3.7 **Elderly women**

Child birth and repeated abdominal straining associated with chronic constipation [309] are thought to predispose elderly women to postmenopausal pelvic floor descent and stretching of the pudendal nerve with associated pain. Changes in the hormone status may also be a factor. In the Urogenital Pain Management Centre, the commonest associations with pudendal neuralgia appear to be: history of pelvic surgery; prolonged sitting (especially young men working with computer technology); and postmenopausal older women.

6.4 Diagnosis for pudendal neuralgia

6.4.1 Differential diagnosis of other disorders

Other forms of neuropathic pain [310, 311].

As well as the pudendal nerve, there are several other nerves that may mimic the symptoms of pudendal neuralgia if they are damaged.

Inferior cluneal nerve. This is a branch of the posterior femoral cutaneous nerve. This nerve is prone to injury in the ischial region. Cluneal nerve injury produces a sensation of pain perceived more laterally than that for pudendal neuralgia.

Sacral nerve roots. The S2-S4 nerve roots may be involved. This is an important differential diagnosis as tumours must be excluded.

Cauda equina syndrome. Lumbar spinal pathology involving the cauda equina may result in an intractable neuropathic pain.

Ilioinguinal, iliohypogastric and genitofemoral nerves. Injury to these nerves or their roots may occur from thoracolumbar pathology, abdominal posterior wall conditions, surgery, and entrapment in the groin. The pain may extend into the groin, anterior perineum and scrotum/labia majorum. If the femoral branch of the genitofemoral nerve is involved, pain may extend into the inner thigh.

Referred spinal pain

Pain from thoracolumbar pathology may refer to the groin. Spinal pain may become associated with muscle hyperalgesia and trigger points. The muscle associated pain may spread to involve a range of muscles, including the pelvic floor muscles with resultant pelvic pain.

Musculoskeletal disorders

Trigger points associated with localised tenderness and pain may be detected in the piriformis, obturator internus, levator ani, bulbocavernosus and ischio cavernosus muscles, as well as the gluteal, adductor, rectus abdominus and spinal muscles. All of these may refer the pain to or close to the pelvis.

Pathology of the joints (sacroiliac, pubic symphysis, hip and spinal) may also refer into the pelvis.

Coccyx pain syndrome, a painful coccyx may occur for a number of reasons (Chapter 2).

6.4.2 Clinical presentation of pudendal neuralgia

6.4.2.1 Age

There is a wide age range, as one would expect with a condition that has so many potential causes. There is a suggestion that, the younger the patient, the better the prognosis. Essentially, the sooner the diagnosis is made, as with any compression nerve injury, the better the prognosis, and older patients may have a more protracted problem [312-314].

6.4.2.2 Sex

Six out of ten cases are observed in women.

6.4.2.3 History

A proportion of patients will be able to relate the onset of pain to an acute event such as surgery, sepsis or trauma, and occasionally, cycling for a prolonged period. Chronic injury is more frequent, such as associated with sitting for prolonged periods over time. Many will be idiopathic.

The pain is classically perceived in the perineum from anus to clitoris/penis. However, less-specific pain distribution may occur, and this may be due to anatomical variation, involvement of branches of the nerve rather than the main nerve, CNS central sensitisation, and consequently, the involvement of other organs and systems in a regional pain syndrome. Other nerves in the vicinity may also be involved, for example, inferior cluneal nerve and perineal branches of the posterior femoral cutaneous nerve. The musculoskeletal system may become involved, confusing the pain picture as aches and pains develop in the muscles due to immobility and disability, possibly magnified by the CNS changes.

Burning is the most predominant adjective used to describe the pain. Crushing and electric may also be used, indicating the two components - a constant pain often associated with acute sharp episodes. Many patients may have the feeling of a swelling or foreign body in the rectum or perineum, often described as a golf or tennis ball. The term pain has different meanings to patients and some would rather use the term discomfort or numbness.

Aggravating factors include any cause of pressure being applied, either directly to the nerve or indirectly to other tissue, resulting in pudendal traction. Allodynia is pain on light touch due to involvement of the CNS, and

may make sexual contact and the wearing of clothes difficult. These patients often remain standing, and as a consequence, develop a wide range of other aches and pains. Soft seats are often less well tolerated, whereas sitting on a toilet seat is said to be much better tolerated. If unilateral, sitting on one buttock is common. The pain may be exacerbated by bowel or bladder evacuation.

6.4.2.4 *Associated features*

Pudendal nerve damage may be associated with a range of sensory phenomena. In the distribution of the nerve itself, as well as unprovoked pain; the patient may have paraesthesia (pins and needles); dysaesthesia (unpleasant sensory perceptions usually but not necessarily secondary to provocation, such as the sensation of running cold water); allodynia (pain on light touch); or hyperalgesia (increased pain perception following a painful stimulus, including hot and cold stimuli). Similar sensory abnormalities may be found outside of the area innervated by the damaged nerve, particularly for the visceral and muscle hyperalgesia.

The cutaneous sensory dysfunction may be associated with superficial dyspareunia, but also irritation and pain associated with clothes brushing the skin. There may also be a lack of sensation and pain may occur in the presence of numbness. Visceral hypersensitivity may result in an urge to defecate or urinate. This is usually associated with voiding frequency, with small amounts of urine being passed. Pain on visceral filling may occur. Anal pain and loss of motor control may result in poor bowel activity, with constipation and/or incontinence. Ejaculation and orgasm may also be painful or reduced.

Many of those suffering from pudendal neuralgia complain of fatigue and generalised muscle cramps, weakness and pain. Being unable to sit is a major disability, and over time, patients struggle to stand and they often become bedbound. The immobility produces generalised muscle wasting, and minimal activity hurts. As a consequence of the widespread pain and disability, patients often have emotional problems, and in particular, depression. Patients with CPP are also often anxious and have the tendency to catastrophise. Depression, catastrophising and disability are all poor prognostic markers. Cutaneous colour may change due to changes in innervation but also because of neurogenic oedema. The patient may describe the area as swollen due to this oedema, but also to the lack of afferent perception.

6.4.2.5 *Clinical examination*

A full clinical examination of the spinal, muscular, nervous and urogenital systems is necessary to aid in diagnosis of pudendal neuralgia, especially to detect signs indicating another pathology. Often, there is little to find in pudendal neuralgia and frequently findings are non-specific. The main pathognomonic features are the signs of nerve injury in the appropriate neurological distribution, for example, allodynia or numbness. Tenderness in response to pressure over the pudendal nerve may aid the clinical diagnosis. This may be elicited by per rectal or per vaginal examination and palpation in the region of the ischeal spine and/or Alcock's canal. Muscle tenderness and the presence of trigger points in the muscles may confuse the picture. Trigger points may be present in a range of muscles, both within the pelvis (levator ani and obturator internus muscles) or externally (e.g., the piriformis, adductors, rectus abdominus or paraspinal muscles).

6.4.2.6 *Investigations*

Magnetic resonance imaging scans of the pelvis are usually normal although some practitioners claim them to be useful [315, 316]. However, MRI scans of the pelvis and spine (mid thoracic to coccyx) are considered essential to help with the differential diagnosis of pudendal neuralgia. Electrophysiological studies may reveal signs of perineal denervation, increased pudendal nerve latency, or impaired bulbocavernosus reflex [305, 312, 317-319]. However, for an abnormality to be detected, significant nerve damage is probably necessary. Pain may be associated with limited nerve damage, therefore, these investigations are often normal in patients thought to have pudendal neuralgia.

6.5 **Management of pain associated with nerve damage**

The approach to managing a patient with pain following nerve damage is similar irrespective of the nerve involved. There is a suggestion that early treatment has a better prognosis. The general principles are covered in chapter 10 of this document.

6.5.1 ***Pudendal neuralgia and injections***

The role of injections may be divided into two. First, an injection of local anaesthetic and steroid at the site of nerve injury may produce a therapeutic action. The possible reasons for this are related to the fact that steroids may reduce any inflammation and swelling at the site of nerve irritation, but also because steroids may block sodium channels and reduce irritable firing from the nerve [320]. The second possible benefit of local infiltration is diagnostic. It has already been indicated that when the pudendal nerve is injured there are several sites where this may occur. Differential block of the pudendal nerve helps to provide information in relation to the site where the nerve may be trapped [301-303, 315, 321-327].

Infiltration at the ischeal spine requires the use of a nerve stimulator/locator. Both motor (anal contraction) and sensory endpoints may be noted. The anatomical endpoint may be localised by fluoroscopy, computed tomography (CT) guidance, or the use of US. Ultrasound avoids any form of radiation, whereas CT guidance involves a significant amount of radiation. Currently, fluoroscopy is probably the imaging technique most frequently used because it is readily available to most anaesthetists that perform the block.

Currently, infiltration of the pudendal nerve within Alcock's canal is primarily undertaken with the use of CT. As well as injecting around the pudendal nerve, specific blocks of other nerves arising from the pelvis may be performed. Similarly, trigger point injections into tender areas within muscles may also be considered. Pulsed radiofrequency stimulation has also been suggested as a treatment [328].

6.5.2 **Pudendal neuralgia and surgery**

Decompression of an entrapped or injured nerve is a routine approach and probably should apply to the pudendal nerve as it applies to all other nerves. There are several approaches and the approach of choice probably depends upon the nature of the pathology. The most traditional approach is the transgluteal approach; however, a transperineal approach may be an alternative, particularly if the nerve damage is thought to be related to previous pelvic surgery [299, 300, 314, 315, 329-331].

Currently, there has been only one prospective randomised study [299]. This suggests that, if the patient has had the pain for < 6 years, 66% of patients will see some improvement with surgery (compared to 40% if the pain has been present for > 6 years). Surgery is by no means the answer for all patients. On talking to patients that have undergone surgery, providing the diagnosis was clear-cut, most patients are grateful to have undergone surgery but many still have symptoms that need management.

6.5.3 **Pudendal neuralgia and neuromodulation**

Pudendal neuralgia represents a peripheral nerve injury and as such should respond to neuromodulation by implanted pulse generators. However, it is important that the stimulation is perceived in the same site as the perceived pain. Spinal cord stimulation (SCS) may be effective for thoraco-lumbar afferents. However, it is difficult to obtain appropriate stimulation from SCS for the sacral nerves including pudendal. There is limited experience with sacral root stimulation and as a result stimulation for pudendal neuralgia should only be undertaken in specialised centres and in centres that can provide multidisciplinary care [332-335].

6.6 **Conclusions and recommendations: pudendal neuralgia**

Conclusions	LE
Multiple sensory and functional disorders within the region of the pelvis/urogenital system may occur as a result of injury to one or more of many nerves. The anatomy is complex.	2
There is no single aetiology for the nerve damage and the symptoms and signs may be few or multiple.	1
Investigations are often normal.	2
The peripheral nerve pain syndromes are frequently associated with negative cognitive, behavioural, sexual, or emotional consequences.	1
There are multiple treatment options with varying levels of evidence.	1

Recommendations	GR
It is important to rule out confusable diseases.	A
If a peripheral nerve pain syndrome is suspected, early referral should occur to an expert in the field, working within a multidisciplinary team environment.	B
Imaging and neurophysiology may help with the diagnosis, but the gold standard investigation is an image and nerve locator guided local anaesthetic injection.	B
Neuropathic pain guidelines are well established. Standard approaches to management of neuropathic pain should be utilised.	A

Figure 10: Assessment and treatment of peripheral nerve pain [317, 333, 336].

Assessment	Treatment	
Extended neurological tests	Grade A recommended	Refer to an expert when a peripheral nerve problem is suspected
Extended history on nature of pain	Grade B recommended	Imaging may be of help
Standardised Questionnaires		Neurophysiology may be of help
		Treatment is as for any other nerve injury http://publications.nice.org.uk/neuropathic-pain-the-pharmacological-management-of-neuropathic-pain-in-adults-in-non-specialist-cg96

7. SEXOLOGICAL ASPECTS OF CHRONIC PELVIC PAIN

7.1 Introduction

In general, human sexuality has three aspects - sexual function, sexual self-concept, and sexual relationships. Pain can affect self-esteem, one's ability to enjoy sex and relationships. Healthy sexuality is a positive and life-affirming part of being human. The capacity to experience optimal comfort and satisfaction in sexual expression also requires basic physical abilities. Essentially, these include intact sensory and motor processes, and the ability to move with ease.

Chronic pain may hinder the ability to move freely, and thus, may limit the positions one can get into to have sex. Second, chronic pain may affect the ability to respond sexually and conversely; in Chronic Pelvic Pain (CPP) the sex act can be associated with pain that can be inhibiting. Research on male sexual dysfunction highlights the importance of considering partners and the impact that male sexual problems have on their partners. Sexual dysfunction occurs in an interpersonal context and has implications for both partners in a relationship. Chronic pain also impacts the sexual and interpersonal functioning of couples; declines in sexual activity and reduced relationship satisfaction have been noted among patients with chronic pain and their partners [337, 338]. It is recommended that a biopsychosocial model of CPP should be incorporated into future research, and that research considers the role that sexual and relationship variables may play in couples' adjustment. The sexual-response cycle is divided into five phases: desire, arousal (excitement), plateau, orgasm and resolution. They are actually all part of a continuous process of sexual response. There is much variation among individuals, as well as between different sexual events and there are different models to describe the sexual responses [339].

During the sexual response cycle, the different phases are controlled by a different part of the brain and spinal cord. In each of these phases chronic pain and CPP in particular can cause disturbances [340].

- The Desire Phase begins in the "pleasure centres" of the brain and controls a person's sexual appetite or drive. Pain or even the fear of pain can decrease desire, making the person uninterested in sex. In some cases, however, having sex may actually help to relieve pain.
- The Arousal Phase is associated with the swelling of the blood vessels in a man's penis and in a woman's labia, vagina, and clitoris. This swelling causes an erection in the penis and in the clitoris and release of lubricating fluids. If a person experiences pain at the time of becoming excited, the excitement may be reversed, in a man the penis will become limp and in a woman the lubrication will stop, leading to dryness.
- The Orgasm Phase describes a genital reflex controlled by the spinal cord, which causes the genital muscles to contract, involuntarily releasing sexual tension and swelling that build up during the excitement phase. In some cases, pain prevents people from reaching this phase.

7.2 General considerations

Pelvic pain in women [341] and in men [342] is associated with significant sexual dysfunction. While chronic pain impacts all aspects of functioning, including work, family relationships, and social activities, the most frequent complaint cited by patients with CPP is sexual dysfunction [343]. Factors contributing to sexual

dysfunction in patients with chronic pain are multifactorial and contextual [344], and may be related to comorbidity with depression [345, 346], use of antidepressant medications [347], and relationship satisfaction [348], among many other factors. There are reports of increased rates of past sexual abuse which may have negative impact on sexual function [349, 350]. Chronic pelvic pain may have a higher association with sexual dysfunction than other types of chronic pain. CPP specifically involves areas intimately connected to sexuality, which may negatively impact one's body image and sexual self-esteem [351], and also affects both partners in the relationship [352].

7.3 Pelvic floor involvement in sexual function and dysfunction

The pelvic floor of the male appears to have some impact on sexual function, although its exact role is unclear. Erection is a neurovascular event in which the smooth and striated musculature of the corpora cavernosa and pelvic floor play a role in facilitating and maintaining the erection [353]. In ejaculation and orgasm the rhythmic contraction of the bulbocavernosus and ischiocavernosus muscles is perceived as pleasurable. Ejaculation is controlled by the sympathetic nervous system and performed with help of the pelvic floor muscles. Controlling the pelvic floor muscles may delay the onset of ejaculation through an active relaxation of the pelvic floor muscles. This is a learned technique, which may be mastered using pelvic floor biofeedback. Pelvic floor exercise and biofeedback for the treatment of both erectile dysfunction (ED) and premature ejaculation (PE) have been reported on in the literature. The effectiveness of physical therapy in treating sexual pain disorders has been reported upon in the literature also. Retrospective studies have reported a success rate of 77% [354, 355]. Goetsch recently reported her findings that physical therapy may serve as important adjunct to surgery for "vulvar vestibulitis" (vulvar pain syndrome) [356].

7.4 Chronic pelvic pain and sexual dysfunction in men

In the BACH study, Hu et al. found that men who reported having experienced sexual, physical, or emotional abuse had increased odds (1.7 compared to 3.3) for symptoms suggestive of CPP. The authors suggested that clinicians may wish to screen for abuse in men presenting with symptoms suggestive of CPP. Conversely, clinicians may wish to inquire about pelvic pain in patients who have experienced abuse [357]. A key feature of CPP is chronic pain. Chronic pain and its treatment can impair our ability to express sexuality. In a study in England 73% of patients with chronic pain had some degree of sexual problems as result of the pain [344]. These problems can occur because of several factors. Psychological factors like decrease in self-esteem, depression and anxiety can contribute to loss of libido. Physiological factors like fatigue, nausea and pain itself can cause sexual dysfunction. Pain medications (opioids, and the selective serotonin reuptake inhibitors, SSRI) can also decrease libido [358] and delay ejaculation. The number of studies on the effects of CPP on sexual function is limited. Sexual dysfunction is often ignored because of a lack of standardised measurements. At the present, the most commonly used tool is the international index of erectile function (IIEF) questionnaire [359]. Post-ejaculation pain is not mentioned in this questionnaire.

In the 1980s an association between CPP and sexual dysfunction was postulated. In 2 reviews the relation between PPS and health status, with influence on sexual activity, were addressed [360, 361]. In a Chinese study of men with CPP 1768 males completed the questionnaires. The overall prevalence of sexual dysfunction was 49%. Erectile dysfunction is the most investigated sexual dysfunction in PPS patients. The reported prevalence of ED ranges from 15.1% to 48%, varying with the evaluation tools and populations [362, 363]. Erectile dysfunction was prevalent in 27.4% of Italian men aged 25-50 [364], 15.2% among Turkish men (significantly higher than control group) [365] and 43% among Finnish men with PPS [366]. The prevalence of ED was found to be higher in young men with PPS than in the general population. According to other studies men with pelvic pain had a higher chance of suffering from ED [367, 368]. Recently, a significant correlation between "chronic prostatitis", CPP symptoms (measured by NIH-CPSI) and ED (measured by IIEF) was confirmed [369], while other studies using the same questionnaires were not able to confirm such a correlation [359, 370]. Some studies also report ejaculatory dysfunction, mainly premature ejaculation [342, 354, 362, 363].

A study from Turkey concerning the interaction between CPP and premature ejaculation (PE) according to intravaginal ejaculation latency time showed that 77% of men with PPS suffered from PE [365]. Screponi et al. reported the high incidence of prostatic inflammation symptoms in men with PE [371]. Premature ejaculation associated with CPP is hypothesised to be caused by infection or inflammation, thus treatment with antibiotics should reduce PE symptoms. In two studies antibiotic treatment has shown a significant increase in patient's IELT (intravaginal ejaculation latency time). Despite these improvements, the mean IELT was still very low and questionable. Before these results can be recommended, further placebo controlled studies are mandatory [372, 373]. Furthermore, there are reports which highlight the appearance of ejaculatory pain in patients with CPP [374] while some studies suggested CPP symptom improvement by increased ejaculatory frequency and sexual activity [375, 376].

The presence of pelvic pain may increase the risk for ED independent of age [338]. On the other hand, cross-sectional data suggest no improvement of lower urinary tract symptoms (LUTS) by an increased frequency of ejaculation [361]. In a study bridging the gap between LUTS and ED, Muller and Mulhall have speculated on the negative impact of PPS on QoL, leading to consecutive impairment of erectile function [377]. Although mental distress and impaired QoL related to illness could contribute to sexual dysfunction observed in patients with PPS, the presence of erectile and ejaculatory disorders is more frequently related to symptoms and imaging suggestive of a more severe inflammatory condition [342]. These arguments are important for the understanding of the close relationship between CPP symptoms, disturbed sexuality, impact on QoL, and psychological implications including depression [360-363, 378]. Sexual dysfunction heightens anger, frustration and depression, all of which place a strain on the relationship and the partner. The female partners of men with sexual dysfunction and depression often present with similar symptoms including pain upon intercourse and depressive symptoms. Men with CPP have reported a high frequency of sexual relationship dissolution and psychological symptoms, such as depression and suicidal thinking [360, 377]. Prostate pain syndrome patients reported greater sexual and relationship problems [360, 377, 379]. On the other hand, Smith et al. found that men with PPS did not report significantly decreased sexual satisfaction compared to controls [380]. There is consensus that therapeutic strategies reducing symptoms, especially against pelvic pain, are of relevance in relation to changes of sexuality. On the other hand, having sex and intimacy can yield positive experiences that will reduce the pain. The CNS plays an important role in this mechanism.

7.5 Chronic pelvic pain and sexual dysfunction in women

Chronic pelvic pain is a clinical condition that results from the complex interactions of physiological and psychological factors and has a direct impact on the social, marital, and professional lives of women. Chronic pelvic pain leads to substantial impairment in QoL and several sexual dysfunctions [381-384]. It seems reasonable to expect that pain, extreme fatigue, depressive mood and pain drugs will affect women's sexuality. Ter Kuile et al. found that women with CPP reported significantly more pain, depression, and anxiety symptoms and were physically more impaired than women in the control group. In comparison with controls, women with CPP reported significantly more sexual avoidance behaviour, non-sensuality, and complaints of "vaginismus" [385]. Chronic pelvic pain is more directly associated with sexual dysfunction than chronic pain at other sites. In one study of CPP patients' feelings and beliefs about their pain or illness, 40 out of 64 participants cited sexual dysfunction as one of the main problems the illness had caused, making it the most frequent complaint [386]. Collett and colleagues [387] also found that patients with CPP reported more sexual problems than women with any other type of chronic pain problem. The quality of intimate relationships is closely connected with sexual function [388]. Satisfaction with the sexual relationship appears to be associated with higher marital functioning [389]. In addition sexual dissatisfaction is related to sexual dysfunction. In cases in which one partner suffers from chronic pain, the ability of both partners to cope with the pain and the extent to which partners are supportive of the chronic pain sufferer have been found to be a predictor of sexual functioning [389].

In community-based studies in the UK [343], New Zealand [381] and Australia [390], a substantially larger proportion of the women with CPP reported dyspareunia (varying between 29% and 42%) than women without CPP (varying between 11% and 14%). Only a few studies have investigated sexual problems within clinical populations [387, 391, 392]. The study of Veritt et al. shows that all of the sexual function domains (desire, arousal, lubrication, orgasm, satisfaction, and pain) were significantly lower in women with CPP than in women without CPP [392]. In line with the results of the community based studies, patients with CPP reported more sexual problems such as dyspareunia, problems with desire or arousal and lubrication than women without CPP [391-393]. One study of patients enrolled in chronic pain treatment programs in England has reported that 73% had pain-related sexual problems [344]. Approximately two-thirds of patients in another study have reported reduced frequency in their sexual relations as a result of CPP [394]. One study demonstrated that CPP patients reported worse sexual function with regard to desire, arousal, lubrication, orgasm, satisfaction, and more frequent and severe pain with vaginal penetration than women without sexual dysfunction [395]. Maruta et al. interviewed 50 chronic pain sufferers and their spouses, of whom 78% of the pain sufferers and 84% of partners described deterioration, including cessation of their sex life [338]. In another study, in patients with back pain, half reported decreased frequency of sex since the onset of chronic pain [344]. The female sexual function index (FSFI) has been developed as a brief, multidimensional self-report instrument for assessing the key dimensions of sexual function in women, which includes desire, subjective arousal, lubrication, orgasm, satisfaction, and pain. The study of Veritt et al. showed that when FSFI was used, women with CPP reported worse sexual function in all subscales and total score than did women without CPP; the largest differences between women with CPP and without CPP were seen for the domains of pain and arousal; the correlations of FSFI corresponded well to each other; the total score and the subscales of the FSFI had high levels of internal consistency and test-retest reliability when assessed in a sample of women with CPP; and finally, that the

FSFI showed good ability to discriminate between women with and without CPP [396]. Some studies report a significant association between sexual abuse before the age of 15 years and later CPP [349]. It is suggested that there is increased frequency of sexual abuse or trauma history, anxiety and depression in women with CPP [396-400]. While the study of Fry et al. with 164 women with CPP show that child sexual abuse did not apparently differ in prevalence from that in the general population, which must throw into question previous assertions about its widespread and general role in CPP.

7.6 Treatment of sexual dysfunctions and CPP

Couples often benefit from early referral for relationship and sexual counselling during their treatment course [401]. Specific behavioural strategies for women who have urogenital complaints and female sexual dysfunction often include exploring alternatives to sexual intercourse (manual or oral pleasuring), different coital positions (female superior or side lying), and pacing, such as limiting thrusting to less than that causes pain. Planning for the time of intercourse is important, and scheduling a clinic visit after intercourse might be useful to identify specific sites and causes of postcoital flares. Other behavioural changes involve pre- and postcoital voiding, application of ice packs to the genital or suprapubic area [401, 402], and use of vaginal dilators before penile penetration. An alternative is to use natural dilators such as different fingers or sex toys. Hypoallergenic non-irritating lubricants can be used to reduce vulvar, urethra, and vaginal friction, and women with signs of vulvovaginal atrophy may benefit from introital application of minimally absorbed locally applied oestrogen cream [403]. In patients with an overactive pelvic floor, referral for physical therapy, myofascial release, and internal pelvic floor muscle massage may offer relief [340].

7.7 Summary

Problems with sexual function resulting from CPP have to be addressed and assessed by the healthcare professional. The attention directed toward these patients must be focused not only on the disease but also on the woman as a whole. As treatment solely of the underlying disease is not acceptable, the care of these suffering women should also address the emotional, sexual, and social problems that the disease causes.

7.8 Conclusions and recommendations: sexological aspects in CPP

Conclusions	LE
Chronic pain can lead to decline in sexual activity and satisfaction and may reduce relationship satisfaction.	2a
Patients who reported having sexual, physical or emotional abuse show a higher rate of reporting symptoms of PPS.	2b
Sexual dysfunctions are prevalent in patient with PPS.	2b
In men with PPS the most prevalent sexual complaints are erectile dysfunction and ejaculatory dysfunction.	3
In females with CPPS all sexual function domains are lower. The most reported dysfunctions are sexual avoidance, dyspareunia and "vaginismus".	2a
Vulvar pain syndrome is associated with BPS.	3
Women with BPS suffer significantly more from fear of pain, dyspareunia and less desire.	2a
Pelvic floor muscle function is involved in the excitement and orgasm phases of sexual response.	3
Chronic pain can cause disturbances in each of the sexual response cycle phases.	2b
Pelvic floor muscle physical therapy may offer relief of pain and reduction in sexual complaints.	2b

Recommendations	GR
Patients presenting with symptoms suggestive for chronic pelvic pain syndrome, should be screened for abuse, without suggesting a causal relation with the pain.	B
The biopsychosocial model should be applied in the evaluation of the effect of chronic pelvic pain syndrome on the sexual function of the patient.	B
The biopsychosocial model should be incorporated in research in the role of chronic pelvic pain in sexual dysfunction.	B
Offer behavioural strategies to the patient and his/her partner to cope with sexual dysfunctions.	B
Training of the pelvic floor muscles is recommended to improve quality of life and sexual function.	B

Figure 11: Assessment and treatment of sexological aspects in chronic pelvic pain

Assessment	Treatment	
History of sexual functioning	Grade A recommended	Refer to sexologist when sexual dysfunction or trauma is present
History of negative experiences		
Ask about abuse	Grade B recommended	Screen for sexual abuse
Psychiatric history		Use a bio-psycho-social model in treating the pain
History of relationship		Offer behavioural strategies to cope with sexual dysfunctions
		Offer partner treatment
		Refer for pelvic floor physiotherapy

8. PSYCHOLOGICAL ASPECTS OF CHRONIC PELVIC PAIN

This chapter addresses general issues concerning the psychological contribution to pelvic pain and its presenting problems, and assessment and treatment. The same areas are also covered in relation to CPP in women, as that is where psychology has focussed.

8.1 Understanding the psychological components of pain

8.1.1 *Neurophysiology of pain*

Models that integrate the psychological factors consistently found to be relevant in the maintenance of persistent pelvic and urogenital pain with current neurobiological understanding of pain are few but the quality is high. Symptom-related anxiety and central pain amplification may be measurably linked, as in IBS [404]. Bajaj et al. have demonstrated central sensitisation in symptomatic endometriosis (see Chapter 4) [405]. Decreases in gray matter (in the thalamus), characteristic of diverse chronic pains [406], has been shown in women with pelvic pain, associated with pain but not with endometriosis found in some of the sample [407]. Interestingly, central changes are evident in association with dysmenorrhea, increasingly recognised as a risk for female pelvic pain [408]. The various mechanisms of CNS facilitation, amplification, and failure of inhibition, mean that there is no simple relationship between physical findings, pain experienced, and resulting distress and restriction of activities.

However, difficult as it is to relieve chronic pain, the pain system is plastic and treatment attempts are not entirely unsuccessful.

8.1.2 *Sexual abuse and trauma*

Many studies have reported high rates of childhood sexual abuse in adults with persistent pain, usually in hospital samples, and particularly in women with pelvic pain [409]. However, all these studies are retrospective, and often of poor quality [410]. The only prospective investigation into the relationship between childhood sexual abuse, physical abuse, or neglect, and “medically unexplained pain”, including pelvic pain, used court records to establish a definite history, and compared with matched classmates [29]. The conclusions were that physically and sexually abused individuals were not at risk for increased pain, although those women with pain problems as adults were more likely to report earlier sexual or physical abuse or neglect.

The correlation between childhood victimisation and pain may be more about retrospective explanations for pain than about occurrence or extent of abuse. Controlling for depression also significantly weakens the relationship between childhood abuse and adult pain [411]. Disentangling the influences and inferences requires prospective studies or careful comparisons [26]. No studies have been found of sexual or physical abuse in childhood and pelvic pain in men, although such abuse has other adverse effects on psychological and physical health [412, 413].

8.1.3 *Interpreting psychological differences*

An important review [26] of CPP in women identifies as problematic the notion that women without physical findings to which pain can be causally attributed differ in psychological characteristics from women with

physical findings. It argues for better methodology, and for greater use of idiographic methods. In summary, women with pelvic pain often have other 'medically unexplained' symptoms, and current or lifetime anxiety and depression disorder; they may have a history of physical or sexual abuse in childhood but the significance of this for pelvic pain is unclear. Studies that invoke 'medically unexplained' or 'psychosomatic' or 'somatoform' disorders do not engage with current pain science, such as viscerovisceral cross sensitisation in relation to multiple pain sites [414], instead interpreting absence of physical findings to indicate psychological origins of the complaint [415, 416]. For instance, women with pelvic pain report more sexual and marital problems than those with migraine but are otherwise comparable (57). Some pain problems which affect sexual activity are diagnosed as sexual problems (e.g. 'dyspareunia') when pain is the central problem and not contingent on sexual activity alone [417]. Better integration of sexology and mainstream psychology for pelvic pain in both men and women is needed [418], building on a biopsychosocial formulation [370, 419].

8.2 Psychological assessment of pain

The report of anxiety, depression and sexual problems is sufficiently common for these to be important in assessment and in planning treatment, although they are often absent from treatment trials on the assumption that they will resolve with improvement in pain. Distress is best understood in the context of pain and of the meaning of pain to the individual. Additionally, impact on daily life and on QoL should be addressed (for suggested instruments in each of these domains see Turk et al. [420]).

Anxiety often refers to fears of missed pathology (particularly cancer) as the cause of pain, and to uncertainties about treatment and prognosis. A question such as that suggested by Howard [421], "What do you believe or fear is the cause of your pain?" is more suitable than a general anxiety questionnaire. Anticipated problems with urinary urgency and frequency when away from the home can also generate considerable anxiety of social disgrace.

Depression is also common in men and women with persistent pelvic pain [422]. A study comparing women with pelvic pain and men with urogenital pain with men and women with low back pain [351], after controlling for age and pain duration and severity, showed no differences in depression. However, there is a risk of diagnostic or standard assessment instruments attributing pain-related problems such as poor sleep to neurovegetative signs of depression [423, 424] where pain-related distress is often the cause [425]. Pain ratings themselves may be predicted by cognitive and emotional variables [10]. Furthermore, target outcomes of pain severity, distress and disability co-vary only partly, and improvement in one does not necessarily imply improvement in the others. Therefore, it is particularly important when the primary outcome is pain to anchor its meaning in a study such as that by Gerlinger et al. [426], who determined clinically important differences in pain in relation to overall satisfaction with treatment. There are many measures of restricted function, or disability, most suited to musculoskeletal pain and mobility problems rather than the difficulties of the individual with pelvic or urogenital pain, although specific measures such as the UPOINT are being developed [427], and generic QoL measures are useful.

8.3 Psychological issues in the treatment of pain

Providing information that is personalised and responsive to the patient's problems, conveying belief and concern, is a powerful way to allay anxiety [428]. Additional written information or direction to reliable sources is useful; practitioners tend to rely on locally produced material or pharmaceutical products of variable quality while endorsing the need for independent materials for patients [429].

Ideally, treatment arises from general principles and practice in the field of chronic pain, with specific study of the population of concern and design of appropriate treatment trials [430]. Curiously, in pelvic pain, the mainstream psychologically based treatments are overlooked in trial design for often rather idiosyncratic versions, published in single, often underpowered trials. It is hard to conclude anything from these, as is evidenced in sections of several other chapters. Psychological interventions may be directed at pain itself or at adjustment to pain - improved mood and function and reduced health care use with or without pain reduction. The major psychologically based treatment, cognitive behavioural therapy (CBT), the subject of several systematic reviews [431] produces small but consistent improvement in mood, disability, and cognitive set. Maintenance in the longer term is variable. An uncontrolled feasibility trial of CBT for men with CPP produced results consistent with these effects [432]. For less disabled and distressed patients, this can be delivered in part over the internet [433]. The crucial question, of what is the best choice of components in pelvic pain, is unanswered and possibly unanswerable given the complexity of variables, outcomes, and the difficulties in standardising treatments.

8.4 Female pelvic pain

8.4.1 *Psychological risk factors in development and maintenance of pelvic pain*

A thorough review from nearly 15 years ago [434] argues against division of aetiology into organic vs. psychogenic, and concludes that, given the methodological problems of many studies, the evidence for sexual abuse as a risk factor is uncertain. Pelvic pain and distress may be variously related, each as the consequence of the other, or arising independently; the same is true of painful bladder and distress [435]. The only systematic review [410] of risk factors for chronic non-cyclical pelvic pain in women included as well as medical variables: sexual or physical abuse (ORs from 1.51 to 3.49); psychological problems such as anxiety (OR: 2.28, 95% CI: 1.41- 3.70) and depression (OR: 2.69, 95% CI: 1.86-3.88); hysteria, i.e., multiple somatic problems (OR: 4.83, 95% CI: 2.50-9.33); and psychosomatic symptoms (OR: 8.01, 95% CI: 5.16-12.44). The terms hysteria and psychosomatic symptoms can best be understood as multiple somatic symptoms not associated with or indicative of any serious disease process, and personality variables are not reliably associated with pelvic pain in women. A comparison of clinic-attending women with diffuse abdominal/pelvic pain against those with vulvovaginal or cyclic pain found the former to report higher rates of lifetime trauma, but they also had more pelvic surgery, more non-pelvic symptoms and were more disabled by their pain [436]. Some of these risk factors are interrelated e.g. history of sexual abuse and depression, but cannot be disentangled. The most recent Diagnostic and Statistical Manual (DSM-V) puts more emphasis on pain [419, 437], but still subsumes female genital pain under sexual disorders. Issues of early trauma such as childhood sexual or physical abuse as a risk factor are addressed in section 8.1.2, but it is important to say that better quality studies, including one prospective study [29], have reported a weaker or no relationship, or not one which is specific to pelvic pain [410, 438-440]. However, another systematic review [413] has concluded that there is some evidence for a specific relationship between rape and CPP (and with fibromyalgia and functional gastrointestinal disorders). It is also important to recognise the possible role of recent sexual assault on the presentation of pelvic pain [409, 441].

There have been fewer studies of maintenance of or recovery from pelvic pain in relation to psychological factors. Weijenborg et al. found, in 25% of women treated surgically, recovery from pelvic pain over a mean 3 years follow-up was not predicted by pain variables at baseline, nor by a general measure of psychological distress or sociodemographic variables, or reports of childhood sexual abuse [442]. Studies that have described pelvic pain as medically unexplained or psychosomatic, due to the lack of physical findings, have been discarded, because such a distinction is unhelpful and inconsistent with known pain mechanisms [415]. Women experience diagnoses which assign their pain to psychological origin as scepticism about the reality or severity of their pain [443], undermining any therapeutic relationship [444]. Ehler et al. [445] have found that women with pelvic pain with and without laparoscopic findings do not differ from one another; only from pain-free controls, as anticipated by Savidge [26], but a large primary care study [446] showed doctors' tendency to attribute pelvic pain without obvious pathology to a psychological cause.

Anxiety and post-traumatic stress symptoms are common in some women with CPP [446, 447], and may account for substantial variance in health status and treatment use. Negative investigative findings do not necessarily resolve women's anxieties about the cause of pain [448, 449], and anxiety often focuses on what might be 'wrong' [450]. Depression may be related to pain in various ways, as described above. Until measures are available that are adequately standardised in patients with pain, anxiety and distress may be best assessed by questions about concerns about the cause of pain, its implications, and its consequences for everyday life [451]. Reference to the studies of the IMMPACT group [351] is recommended for guidance on outcome measures suitable for pain trials.

8.4.2 *Psychological factors in treatment of persistent pelvic pain*

A recent Cochrane systematic review and meta-analysis of non-surgical treatments for pelvic pain [263], excluding that due to endometriosis, IBS, and chronic PID [452] found five eligible trials of psychologically-based treatment, but they were diverse and not combined for analysis. Surprisingly, the single component treatments, counselling about ultrasound results [453], and emotional disclosure [454], showed improvements in pain, while three more standard multicomponent (including psychological) treatments for pain [244, 455, 456] did not. As surprisingly, only two measured mood improvement, and found no effects of psychological and physiotherapeutic treatment over gynaecological consultation [456], or for writing with vs without disclosure of distress [454]. The importance of multidisciplinary treatment is emphasised by several reviews [457, 458], and the need for high quality psychological treatment evaluation is underlined [457]. Several other reviews make positive comments on psychological involvement [459], and recommend addressing psychological concerns from the outset, directed at the pain itself, with the intended outcome of reducing its impact on life [404], or at adjustment to pain, with improved mood and function and reduced health care use, with or without pain reduction [405].

In the first category are relaxation and biofeedback methods of controlling and decreasing pain by reducing muscle tension, applied in mainly uncontrolled trials to pelvic floor retraining both in men and women. The only RCT applied a specific type of cognitively enhanced physical therapy to overall muscle tension, not to the pelvic floor, combined with normal gynaecological treatment compared with gynaecological treatment alone [456]. Pain was reduced by 50% and motor function improved in various aspects by 10 h of physical therapy, with particular attention to tension, relaxation and to the thoughts and emotions that generate tension. In the second category, multicomponent pain management, involving education, physical retraining, behavioural change, and increasing activity, relaxation and cognitive therapy, is often applied to mixed groups of chronic pain patients, including those with pelvic pain. A systematic review and meta-analysis which shows a good outcome for mixed chronic pain or back pain groups across pain experience, mood, coping, and activity, cannot with confidence be extrapolated to women with pelvic pain alone [460] although it is probably applicable.

The only RCT in CPP used elements of this approach in combination with medroxyprogesterone acetate (MPA) or placebo [455]. Combination of MPA and psychological therapy outperformed other treatment methods in the long-term, with nearly three quarters of women reporting > 50% pain relief. Several single treatments with benefits in other chronic pain or chronic health problems have been tried in pelvic pain: emotional disclosure by writing about pain (with writing about positive events as a control) [454] produced small differences on one measure of pain appraisal, particularly in women with more distress at baseline. Given the extent of problems associated with pelvic pain, this intervention on its own is unlikely to produce much change, but could be combined with other components described above. Finally, a small RCT of transcranial direct current stimulation compared to sham stimulation [461] produced greater pain reduction and improvement in disability in the treatment group, in the first week only.

8.5 Conclusions and recommendations: psychological aspects of CPP

Conclusions	LE
There is no evidence that distress generates complaints of pelvic pain, or that multiple symptoms suggest unreality of pain.	2b
Current or recent sexual abuse should be assessed as possible contributory factors in pelvic pain.	2a
Psychological intervention in general can produce benefits in pain, mood, and quality of life, depending on its content and focus.	1a
Psychologically informed physical therapy can improve pain and function.	1b
Combined exercise and cognitive behavioural therapy with medroxyprogesterone acetate can reduce pain in the majority of women with pelvic pain.	1b
Transcranial direct current stimulation may reduce pain in the short-term.	1b

Recommendations	GR
Psychological distress is common in pelvic pain in women, but should be interpreted in the context of pain.	A
Ask the patient what she/he thinks may be wrong to cause the pain, to allow the opportunity to inform and reassure as appropriate.	B
Try psychological interventions in combination with medical and surgical treatment, or alone.	A

Figure 12: Assessment and treatment of psychological aspects of chronic pelvic pain

Assessment	Treatment
Psychological history	Grade A recommended Interpret psychological distress in the context of pain Psychological interventions as adjuvant to other modalities
Investigate pain-related beliefs and behaviour	Grade B recommended Ask the patient what he or she believes may be the problem that causes the pain

9. PELVIC FLOOR FUNCTION AND CHRONIC PELVIC PAIN

9.1 Introduction

The pelvic floor is made up of muscles and fascia. The muscles usually function as a composite, although the anterior and posterior components may act in isolation. The pelvic floor has three functions: support, contraction and relaxation.

9.2 Function

In its resting state, the pelvic floor supports the bladder and the urethra in the anterior compartment, the uterus and the vagina in the middle compartment, and the rectum and the anus in the posterior compartment. When intra-abdominal pressure rises, the pelvic floor muscles respond with a contraction occurring simultaneously or before the pressure rise. Contraction of the pelvic floor muscles results in inward movement of the perineum and upward movement of the pelvic organs. There are two types of contraction that can be distinguished: a voluntary contraction and an involuntary contraction. These contractions not only maintain support of the pelvic organs, they also close the urethra, anus and vagina, thus avoiding loss of urine or stools. Contractions also form a defence against introduction of foreign objects into the anus or vagina, and in women, they can protect against sexual penetration.

Pelvic floor muscle relaxation results in a decrease or termination of the squeezing of the urethra, vagina and anus. The perineum and the pelvic organs return to their anatomical resting position. Relaxation of the pelvic floor muscles is needed for voiding, defecation and for sexual intercourse. The muscles of the pelvic floor are integrated in the total muscular girdle of the pelvis, yielding the stability needed for bearing the trunk. In turn, instability leads to compensatory pelvic floor muscle (over) activity.

9.3 Dysfunction

Pelvic floor dysfunction should be classified according to “The standardisation of terminology of pelvic floor muscle function and dysfunction” [462]. This is an international multidisciplinary report from the International Continence Society. By palpation of the pelvic floor muscles, the contraction and relaxation are qualified. Voluntary contraction can be absent, weak, normal or strong, and voluntary relaxation can be absent, partial or complete. Involuntary contraction and relaxation is absent or present.

Based on these signs, pelvic floor muscles can be classified as follows:

- non-contracting pelvic floor
- non-relaxing pelvic floor
- non-contracting, non-relaxing pelvic floor.

Based on symptoms and signs, the following conditions are possible:

- normal pelvic floor muscles
- overactive pelvic floor muscles
- underactive pelvic floor muscles
- non-functioning pelvic floor muscles.

Normal pelvic floor muscles relax during urination and contract during coughing. Overactive pelvic floor muscles do not relax during micturition, defecation or during sex and cause dysfunctional voiding, overactive bladder, constipation and dyspareunia [463]. Underactive pelvic floor muscles do not contract sufficiently to keep the patient dry. Non-functioning pelvic floor muscles do not show any activity and can cause every type of pelvic organ dysfunction. Overactivity tends to develop over a protracted period, with many causes. A psychological mechanism that is thought to play a role is that contraction of the pelvic floor muscles closes some of the exits of the body (anus and vagina), and helps to keep urine and stool inside. It gives women a defence mechanism against unwanted vaginal penetration of any type. The pelvic floor muscles also help to postpone micturition, which can be of benefit in a social or working environment. In summary, the pelvic floor muscles assist in adaptation to different situations in life.

9.4 Pelvic floor muscles and myofascial pain

Chronic pelvic pain can simply be a form of myalgia, due to misuse of muscles, in this case, the pelvic floor muscles. Studies in the field of chronic prostatitis support the idea that patients with CPP have more muscle spasm and increased muscle tone and pain when palpating the pelvic floor muscles [464]. Muscle relaxation can diminish spasm and pain [465]. Repeated or chronic muscular overload can activate trigger points in the

muscle. A report from the Chronic Prostatitis Cohort Study showed that 51% of patients with prostatitis and only 7% of controls had any muscle tenderness. Tenderness in the pelvic floor muscles was only found in the CPP group [466].

9.4.1 Muscular aspects

The relationship between muscular dysfunction (especially overactivity) and pelvic pain has been found in several studies. Rectal pain treated with pelvic floor muscle therapy is only relieved when patients learn to relax their pelvic floor muscles [278]. The vast majority (92.2%) of men visiting a tertiary centre for pelvic pain had dysfunction of the pelvic floor muscles. This finding was true regardless of evidence of inflammation (prostatitis or cystitis) [467]. This relationship has been found in chronic prostatitis [466], BPS [468] and vulvar pain [469]. Dysfunction of the pelvic floor directly affects function of the pelvic viscera and vice versa. Both systems can act as the primary signal to the spinal cord, with a cascade of reactions ascending to the CNS as a result. The muscle itself ends up with a diminished length, leading to restrictions even when it is in a relaxed state.

9.4.2 Neurological aspects

In 1999, the first ideas about the neurological aspects of the pelvic floor muscles in relation to CPP were published. The probability of CNS breakdown in the regulation of pelvic floor function was suggested as a mechanism for development of CPP. Of the patients presenting with pelvic pain, 88% had poor to absent pelvic floor function [470]. Basic studies on the role of neurogenic inflammation have also elucidated some important phenomena. Irritation of the prostate, bladder and pelvic floor muscles results in expression of C-fos-positive cells in the CNS. There appears to be convergence of afferent information onto central pathways. Once the central changes have become established, they become independent of the peripheral input that initiated them [471].

9.4.3 Myofascial trigger points

Repeated or chronic muscular overload can activate trigger points in the muscle. Trigger points are defined as hyperirritable spots within a taut band. Other criteria for trigger points are: recognition of the pain as 'familiar', and pain on stretching the muscle. Apart from pain, trigger points prevent full lengthening of the muscle, thereby restricting the range of movement. Pain as a result of these trigger points is aggravated by specific movements and alleviated by certain positions. Positions and movements in which the shortened muscle is stretched are painful. Patients know which activities and postures influence pain. Trigger points can be located within the pelvic floor muscles and in adjacent muscles such as the abdominal, gluteal and iliopsoas muscles. Pain is aggravated by pressure on the trigger point (e.g., pain related to sexual intercourse). Pain also worsens after sustained or repeated contractions (e.g., pain related to voiding or defecation).

9.5 Diagnostics of pelvic floor muscle function

Diagnosing pelvic floor muscle function in patients with CPP starts by taking a complete functional history of the pelvic organ function. The following items certainly should be addressed: lower urinary tract function, anorectal function, sexual function, gynaecological items, presence of pain and psycho-social aspects.

9.5.1 Pelvic floor testing

Pelvic floor muscle testing can be done by the medical doctor but a consultation of the pelvic floor physiotherapist is a good alternative. A vaginal or rectal examination is performed to assess the function of the pelvic floor muscles, according to the ICS report. This assessment has been tested and shows satisfactory face validity and intra-observer reliability. It can therefore be considered suitable for use in clinical practice [472]. Rectal examination is a good way to test the pelvic floor function in men [473].

In a cohort study of 72 men with CPP, the relationship between the locations of the trigger point and the referred pain was examined. Ninety percent of the patients showed tenderness in the puborectalis muscle and 55% in the abdominal wall muscles. Of the patients in whom trigger points were found in the puborectalis, 93% reported pain in the penis and 57% in the suprapubic region. Patients with trigger points in the abdominal muscles reported pain in the penis (74%), perineum (65%) and rectum (46%) [474].

9.6 Treatment of pelvic floor muscle pain

Treating pelvic floor overactivity and myofascial trigger points should be considered in the management of CPP. Treatment should be done by specialised physiotherapists who are trained not only in the musculoskeletal aspects of pain, but also in the psychological mechanisms and the role of the CNS in chronic pain.

9.6.1 Pelvic floor muscle exercise

For patients with CPP and dysfunction of the pelvic floor muscles, it is very helpful to learn how to relax the

muscles when the pain starts. By doing this, the circle of pain-spasm-pain can be interrupted. In the case of shortened muscles, relaxation alone is not enough. Stretching of the muscle is mandatory to regain length and function. Studies on physical therapy for pelvic floor pain syndrome have been sparse. A single blinded RCT with myofascial physical therapy and general massage was carried out in patients with prostate or bladder pain. The global response rate to treatment with massage was significantly better in the prostate than in the bladder pain group (57% vs. 21%). In the prostate pain group, there was no difference between the two treatment arms. In the bladder pain group, myofascial treatment did significantly better than the massage. Massage only improved complaints in the prostate pain group. The fact that the prostate pain group consisted of only men is mentioned as a possible confounding factor [475].

9.6.2 **Biofeedback and electrostimulation**

Biofeedback can be helpful in the treatment of pelvic floor pain in the process of recognising the action of the muscles. Visualising the action of the pelvic floor muscles by using biofeedback is revealing to many patients. Biofeedback should always be used in consultation with the patient. Special care should be taken when there is a history of negative physical or sexual experiences. The numbers of patients in most studies concerning biofeedback have been small but the results are promising. In a cohort study, 31 patients with CPPS participating in a pelvic floor biofeedback re-education programme were followed. The mean chronic prostatitis symptom index decreased from 23.6 to 11.4. They also measured the pelvic floor muscle activity by EMG using an anal probe. The resting amplitude was taken as a parameter for the ability to relax the pelvic floor muscles. This parameter was 4.9 μ V at the start and 1.7 μ V at the end of the treatment, so the relaxation improved markedly. There was also a correlation between the decline in EMG values and improvement in prostatitis symptom score [476]. In a study among patients with Levator Ani Syndrome, biofeedback was found to be the most effective therapy. Other modalities used were electrostimulation and massage. Adequate relief was reported by 87% in the biofeedback group, 45% for electrostimulation, and 22% for massage [278]. A review on biofeedback in pelvic floor dysfunction has shown that biofeedback is better than placebo or sham treatment. An odds ratio of 5.8 favouring biofeedback has been calculated based on three studies [477].

9.6.3 **Myofascial trigger point release**

Treatment of MTrP's can be done by manual therapy, dry needling and wet needling. The evidence for all the different treatments is weak, with most studies showing no significant difference between these techniques, though most studies were small and heterogeneous with regards to the patients and methods.

There is no evidence that manual techniques are more effective than no treatment [478]. Most studies of dry needling have compared with wet needling. Different systematic reviews have come to the conclusion that, although there is an effect of needling on pain, it is neither supported nor refuted that this effect is better than placebo [479]. Other reviews have concluded that the same is true for the difference between dry and wet needling [480, 481].

Physiotherapy. General muscular exercise may be beneficial in some BPS patients [482]. Transvaginal manual therapy of the pelvic floor musculature (Thiele massage) in BPS patients with high-tone dysfunction of the pelvic floor significantly improved several assessment scales [483]. Langford et al. examined the role of specific levator ani trigger point injections in women with CPP [484]. Each trigger point was identified by intravaginal palpation and injected with bupivacaine, lidocaine and triamcinolone. Seventy-two percent of women improved with the first trigger point injection, with 33% being completely pain-free. Efficacy and safety of pelvic floor myofascial physical therapy has been compared with global therapeutic massage in women with BPS; GRA rate was 59% and 26%, respectively. Pain, urgency and frequency ratings, and O'Leary-Sant IC Symptom and Problem Index decreased in both groups during follow-up, and did not differ significantly between the groups. This suggests that myofascial physical therapy is beneficial in women with BPS [485].

9.6.4 **Botulinum A toxin**

Botulinum A toxin (BTX-A) is an inhibitor of acetylcholine release at the neuromuscular junction and has a paralysing effect on striated muscles. BTX-A has been injected into trigger points. It is more expensive than lidocaine and has not been proven to be more effective [486]. Reviews do not support the injection of BTX-A into trigger points [487]. Pelvic floor muscle overactivity plays a role in CPP. BTX-A, as a muscle relaxant, can be used to reduce the resting pressure in the pelvic floor muscles. In women with high resting pressure in the pelvic floor muscles, it has been found that BTX-A lowers this pressure significantly. The magnitude of reduction was significantly higher than that in the placebo group. On the pain score (VAS), no intergroup differences were found in this relatively small randomised study [280]. BTX-A can also be injected at the sphincter level to improve urination or defecation. Relaxation of the urethral sphincter alleviates the bladder problems and secondarily the spasm. In a cohort study of 13 patients with CPP, BTX-A was injected into the

external urethral sphincter. Subjectively, 11 patients reported a substantial change in pain symptoms, from 7.2 to 1.6 on a VAS [488].

9.6.5 Pain management

The physiotherapist is part of the pain management team, together with the pain doctor and the psychologist. The therapeutic options for physiotherapists may not be the same in every country. Physiotherapists can either specifically treat the pathology of the pelvic floor muscles, or more generally treat myofascial pain if it is part of the pelvic pain syndrome. In most studies that have been done looking at the effect of physiotherapy in pelvic pain the treatment of the pelvic floor is only part of the pain management. In a review about physiotherapy in women with pelvic pain, it was concluded that recommendations for physiotherapy should be given with caution [489]. They found 6 RCT's of which three showed level 1b evidence with low risk of bias. One of these three found that Mensendieck somatocognitive therapy showed a pain reduction after 1 year follow-up of 64%. This approach consists of myofascial relaxation and tension, improving posture and movement in combination with CBT [456].

9.7 Conclusions and recommendations: pelvic floor function

Conclusions	LE
The ICS classification is suitable for clinical practice.	2a
Overactivity of the pelvic floor muscles is related to chronic pelvic pain, prostate, bladder and vulvar pain.	2a
Overactivity of the pelvic floor muscles is an input to the central nervous system causing central sensitisation.	2b
There is no accepted standard for diagnosing myofascial trigger points.	2a
There is a relation between the location of trigger point and the region where the pain is perceived.	3
Myofascial treatment is effective in prostate- and bladder pain syndrome.	1b
Biofeedback improves the outcome of myofascial therapy for pelvic floor dysfunction.	1a
Trigger point release is effective in treating muscle and referred pain, but there is no preference for this method over others.	1a

Recommendations	GR
The use of the ICS classification on pelvic floor muscle function and dysfunction is recommended.	A
In patients with chronic pelvic pain syndrome it is recommended to actively look for the presence of myofascial trigger points.	B
Apply pelvic floor muscle treatment as first line treatment in patients with chronic pelvic pain syndrome.	A
In patients with an overactive pelvic floor, biofeedback is recommended as therapy adjuvant to muscle exercises.	A
When myofascial trigger points are found, treatment by pressure or needling is recommended.	A

Figure 13: Assessment and treatment pelvic floor function

Assessment	Treatment	
Palpation of the muscles	Grade A recommended	Use the International Continence Society classification of dysfunction
Testing of pelvic floor function		Use biofeedback in combination with muscle exercises
Pelvic floor muscle EMG		Treat myofascial trigger points using pressure or needling
		Apply pelvic floor muscle therapy as first-line treatment
Test for myofascial trigger points	Grade B recommended	Look actively for the presence of myofascial trigger points
History of all the involved organs		
Standardised questionnaires	Other comments	The role and options of a physiotherapist may differ between countries

10. GENERAL TREATMENT OF CHRONIC PELVIC PAIN

10.1 Introduction

Chronic pelvic pain is well defined and involves multiple mechanisms as described in previous chapters. The management requires a holistic approach with biological, psychological and social components.

This chapter looks at general treatments for pain (both peripheral and central) and not the specific treatments mentioned in the Chapters 2 and 6.

Few studies have specifically looked at medications used in CPP [452], therefore, a wider look at the literature has been undertaken, further specific research is required. The agents concerned are divided for ease of description. Combinations often provide a greater benefit than individual agents. They may also allow lower individual dosages and thus minimise side-effects. The aim of using these drugs is to allow patients to improve their QoL. This is best measured by assessing their function as well as pain severity. If the use of these agents does not allow this, then they should be withdrawn. Unfortunately, the failure of one agent to provide benefit does not mean that there is an alternative. If the benefit is limited by side-effects, then the lowest effective dose should be found (by dose titration). Sometimes, patients will prefer a higher level of pain and have fewer side-effects. If the use of simple analgesics fails to provide adequate benefit, then consider using the neuropathic agents, if there is no improvement, consider involving a specialist pain management centre with an interest in pelvic pain.

10.2 Simple analgesics

Paracetamol (acetaminophen)

Paracetamol is a well-tolerated analgesic in a class of its own. This is an antipyretic analgesic with a central mechanism of action [490]. It is often available over the counter without prescription. There is evidence that paracetamol is beneficial in managing somatic and arthritic pain [491].

Non-steroidal anti-inflammatory agents (NSAIDs)

This group of agents is anti-inflammatory, antipyretic analgesics that act by inhibiting the enzyme cyclooxygenase (COX). They have a peripheral effect, hence their use in conditions involving peripheral or inflammatory mechanisms. They are commonly used for pelvic pain, many are available over the counter and are usually well tolerated. The evidence for their benefit in CPP is weak or non-existent and they do have side-effects, which may be significant. There is no good evidence to suggest one NSAID over another for pelvic pain.

For pelvic pain in which inflammatory processes are considered important, such as dysmenorrhoea [492], NSAIDs are more effective than placebo and paracetamol, but with a higher incidence of side-effects. For pelvic pain in which central mechanisms may be incriminated, such as endometriosis [246], then the evidence is lacking for NSAIDs despite their common use.

Guidelines for use of NSAIDs and COX-2 selective agents have been developed. They have more side-effects than paracetamol, including indigestion, headaches and drowsiness. At a practical level, NSAIDs could be considered as analgesics for patients with pelvic pain. They should be tried (having regard for the cautions and contraindications for use) and the patient reviewed for improvement in function as well as analgesia. If this is not achieved, or there are side-effects, then they should be withdrawn.

Neuropathic analgesics

These are agents that are not simple analgesics but used to modulate neuropathic or centrally mediated pain. There are several classes commonly used with a recognised benefit in pain medicine. They are taken on a regular basis rather than as required. They all have side-effects that limit their use in some patients.

In the UK, the National Institute for Health and Clinical Excellence (NICE) has reviewed the pharmacological management of neuropathic pain [493]. Further guidance is in progress for the management of neuropathic pain in the non-specialist setting.

Not all the agents are licensed for use in pain management but there is a history and evidence to demonstrate their benefit. The evidence for treatment of CPP is lacking but is present for other painful conditions. For this chapter, most of the evidence is from non-pelvic pain sources. The general method for using these agents is by titrating the dose against benefit and side-effects. The aim is for patients to have an improvement in their

QoL, which is often best assessed by alterations in their function. Side-effects frequently limit their use. It is common to use these agents in combination but studies comparing different agents against each other, or in combination, are lacking.

10.2.1 Antidepressants

10.2.1.1 Tricyclic antidepressants

The tricyclic antidepressants have multiple mechanisms of action, a long history of use in pain medicine and have been subjected to a Cochrane review [494]. This suggests that they are effective for neuropathic pain with numbers needed to treat (NNT) of approximately three.

Amitriptyline is the most commonly used member at doses from 10 to 75 mg/day (sometimes rising to 150 mg/day). This is titrated against benefit or side-effects and can be taken at night [493]. Nortriptyline and imipramine are used as alternatives.

10.2.1.2 Other antidepressants

Venlafaxine is a serotonin and noradrenalin reuptake inhibitor (SNRI). It is not licensed for managing neuropathic pain but there is evidence of its benefit in chronic pain [493]. There are cautions particularly in patients with heart disease. This is a drug best used by those familiar with its use.

Duloxetine is a newer SNRI antidepressant. It is used for depression, urinary stress incontinence and neuropathic pain. There is moderately strong evidence for a benefit in diabetic neuropathy and fibromyalgia at a dose of 60 mg/day [495]. Side-effects are common and may result in its discontinuation. Selective serotonin reuptake inhibitors (SSRIs) are antidepressants with fewer side-effects. They are effective for depression, but there have been insufficient studies to demonstrate their benefit in pelvic or neuropathic pain [494-496].

10.2.2 Anticonvulsants

Anticonvulsants are commonly used in the management of neuropathic pain. There have been general studies as well as some looking more particularly at pelvic pain. Individual agents have been systematically reviewed. Their use is suggested in the NICE Neuropathic Guidelines [493].

Carbamazepine has a long history of use in neuropathic pain. Evidence exists for its benefit [497]. Trials have tended to be of short duration, showing only moderate benefit. There are side-effects; some of which may be serious. More recently, developed agents are available with fewer serious side-effects, carbamazepine is no longer a first-choice agent. Gabapentin is commonly used for neuropathic pain and has been systematically reviewed [498]. It provides good quality relief with NNT of approximately six. Side-effects are common, notably drowsiness, dizziness and peripheral oedema. For upper dose levels, reference should be made to local formularies, and many clinicians do not routinely exceed 2.4 g/day in divided doses (most commonly three times daily). One study of women with CPP has suggested that gabapentin alone or in combination with amitriptyline provides better analgesia than amitriptyline alone [499].

Pregabalin is a commonly used neuromodulator with good evidence for its efficacy in some neuropathic conditions but the NNT varies depending on the condition [500]. The dose for benefit is in the range of 300 to 600 mg/day. The same systematic review found that doses less than 150 mg/day are unlikely to provide benefit. As with gabapentin, side-effects are relatively common and may not be tolerated by patients. Other anticonvulsants are available but not commonly used for managing pain.

10.2.3 Other agents

Other agents can be used in the management of neuropathic pain but they are best administered only by specialists in the management of pain and familiar with their use. They tend to be considered after the standard options have been exhausted. As with all good pain management, they are used as part of a comprehensive multidimensional management plan.

10.3 Opioids

Opioids are used for chronic non-malignant pain and may be beneficial for a small number of patients. Often patients will stop taking oral opioids due to side-effects or insufficient analgesia [501]. They should only be used in conjunction with a management plan and with consultation between clinicians experienced in their use. It is suggested that a pain management unit should be involved along with the patient and their primary care physician.

There are well established guidelines for the use of opioids in pain management as well as considering the potential risks [502]. There is also information available online for patients [503, 504].

There are several agents available in the group. They can be divided into weak (e.g., codeine, dihydrocodeine and tramadol) or strong opioids (e.g., morphine, oxycodone, fentanyl and hydromorphone).

Oral administration is preferable, but if poorly tolerated, a percutaneous (patch) route may have advantages. More invasive approaches are less commonly used and within the realms of specialist units. Side-effects are common and require active management.

There is a growing understanding of opioid-induced hyperalgesia; a situation in which patients taking opioids, paradoxically, become more sensitive to painful stimuli [505]. This is another reason for these drugs to be used in a controlled fashion for long-term management of non-malignant pain.

10.3.1 **Recommendations for use of opioids in chronic/non-acute urogenital pain**

Recommendations
All other reasonable treatments must have been tried and failed.
The decision to instigate long-term opioid therapy should be made by an appropriately trained specialist in consultation with another physician (including the patients and their family doctor).
Where there is a history or suspicion of drug abuse, a psychiatrist or psychologist with an interest in pain management and drug addiction should be involved.
The patient should undergo a trial of opioids.
The dose required needs to be calculated by careful titration.
<p>The patient should be made aware (and possibly give written consent):</p> <ul style="list-style-type: none"> • Opioids are strong drugs and associated with addiction and dependency. • Opioids will normally only be prescribed from one source (preferably the family doctor). • The drugs will be prescribed for fixed periods of time and a new prescription will not be available until the end of that period. • The patient may be subjected to spot urine and possibly blood checks to ensure that the drug is being taken as prescribed, and that non-prescribed drugs are not being taken. • Inappropriate aggressive behaviour associated with demanding the drug will not be accepted. • Hospital specialist review will normally occur at least once a year. • The patient may be requested to attend a psychiatric/psychological review. <p>Failure to comply with the above may result in the patient being referred to a drug dependency agency and the use of therapeutic, analgesic opioids being stopped</p>
<p>Morphine is the first-line opioid, unless there are contraindications to morphine or special indications for another drug.</p> <ul style="list-style-type: none"> • The drug should be prescribed in a slow-release/modified-release form. • Short-acting preparations are undesirable and should be avoided where possible. • Parenteral dosing is undesirable and should be avoided where possible.

10.3.2 **Morphine**

Morphine is the traditional gold standard and the opioid with which many physicians are most familiar. The aim is to use a slow or sustained release preparation starting with a low dose and titrating the dose every 3 days to 1 week against improvement in both function and pain. Side-effects should also be monitored and managed accordingly. Particular attention should be paid to the management of constipation.

10.3.3 **Other opioid agents**

There are a variety of agents available and some are mentioned below.

Transdermal fentanyl may be considered when oral preparations are restricted (e.g., ileostomy). It may also be beneficial when there are intolerable side-effects from other opioids.

Methadone has a long record of use as an opioid. There is a theoretical advantage of benefit with its N-methyl-D-aspartate receptor (NMDA) antagonist activity. This may be relevant in neuropathic pain [506].

Oxycodone may have greater efficacy than morphine in some situations, such as hyperalgesic states including visceral pain [507].

Analgesics with a dual mode of action may have a role in the management of chronic pain. Tramadol is an established analgesic with dual effects on opioid receptors and serotonin release. More recently, tapentadol,

has been released with opioid action and noradrenalin reuptake inhibition. It is too early to assess its real value in the armamentarium for pain management.

10.4 Nerve blocks

Nerve blocks for pain management are usually carried out by specialists in pain medicine as part of a broader management plan [508]. They may have a diagnostic or therapeutic role. Textbooks have been written on the subject and practitioners using them should be trained in appropriate patient selection, indications, risks and benefits. Many such interventions also require understanding and expertise in using imaging techniques to perform the blocks accurately.

Diagnostic blocks can be difficult to interpret due to the complex mechanisms underlying the painful condition or syndrome. Sustained but limited benefit may lead to more permanent procedures (e.g., radiofrequency procedures).

There is a weak evidence base for these interventions for chronic non-malignant pain.

10.5 Transcutaneous electrical nerve stimulation (TENS)

Despite the popularity of TENS and the number of trials undertaken, a systematic review has been unable to provide good evidence for or against its use in the management of chronic pain [509]. Further more, rigorous trials should be undertaken to provide some clarity for a commonly used intervention.

10.6 Neuromodulation in pelvic pain syndromes

The role of neuromodulation in the management of pelvic pain should only be considered by specialists in pelvic pain management. These techniques are only used as part of a broader management plan and require regular follow-up.

The research base is developing and the techniques broadening (e.g., spinal cord stimulation (SCS), sacral root stimulation, dorsal root ganglion stimulation or peripheral nerve stimulation). These are expensive interventions and thus many of the patients involved are refractory to other therapies. It is thus inappropriate to provide a detailed review of these techniques for this publication.

In the UK, guidance has been published for SCS in neuropathic pain [510]. This emphasises the comments above. This guidance suggests a trial period of stimulation before full implementation.

Neuromodulation is still finding its role in pelvic pain management. There has been growing evidence in small case series or pilot studies, but more detailed research is required [511]. Its role in overactive bladder and faecal incontinence is more robust but is limited for pain.

10.7 Summary

Chronic pelvic pain is a common complaint that is well defined and involves multiple mechanisms. Some of the conditions have clear management pathways but many do not. In these CPP syndromes, a holistic multidisciplinary team approach is required with active patient involvement.

This chapter focuses on general treatment of CPP, mainly drug therapy, and comments on other more invasive techniques. The latter are used in combination with other modalities. Many are aimed at the management of neuropathic pain or conditions in which central mechanisms are implicated.

At this stage in management, the involvement of trained clinicians with expertise in chronic pain management should be considered. Centres with a particular interest in pelvic pain do exist and involve clinicians from several specialties along with other healthcare professionals (e.g., physiotherapy, psychology, nursing and occupational therapy).

With any of the agents above, the aim is to assess pain relief, improvement in function, and side-effects. This should be done regularly while titrating and optimising drug dose. If there is no benefit, then the drug should be withdrawn.

Neuropathic agents are frequently used and often in combination. There is significant inter-patient variability in effect. Their use is often limited by side-effects that may be worse than any pain reduction.

Opioid drugs are used in this group of patients. Their role is limited and they should only be started in

consultation with all parties involved (including the patient's family practitioner). National guidelines exist and should be followed. There is growing understanding of the limitations of opioid use, and more recently, the paradoxical situation of opioid-induced hyperalgesia.

10.8 Recommendations for the medical and interventional treatment of CPP

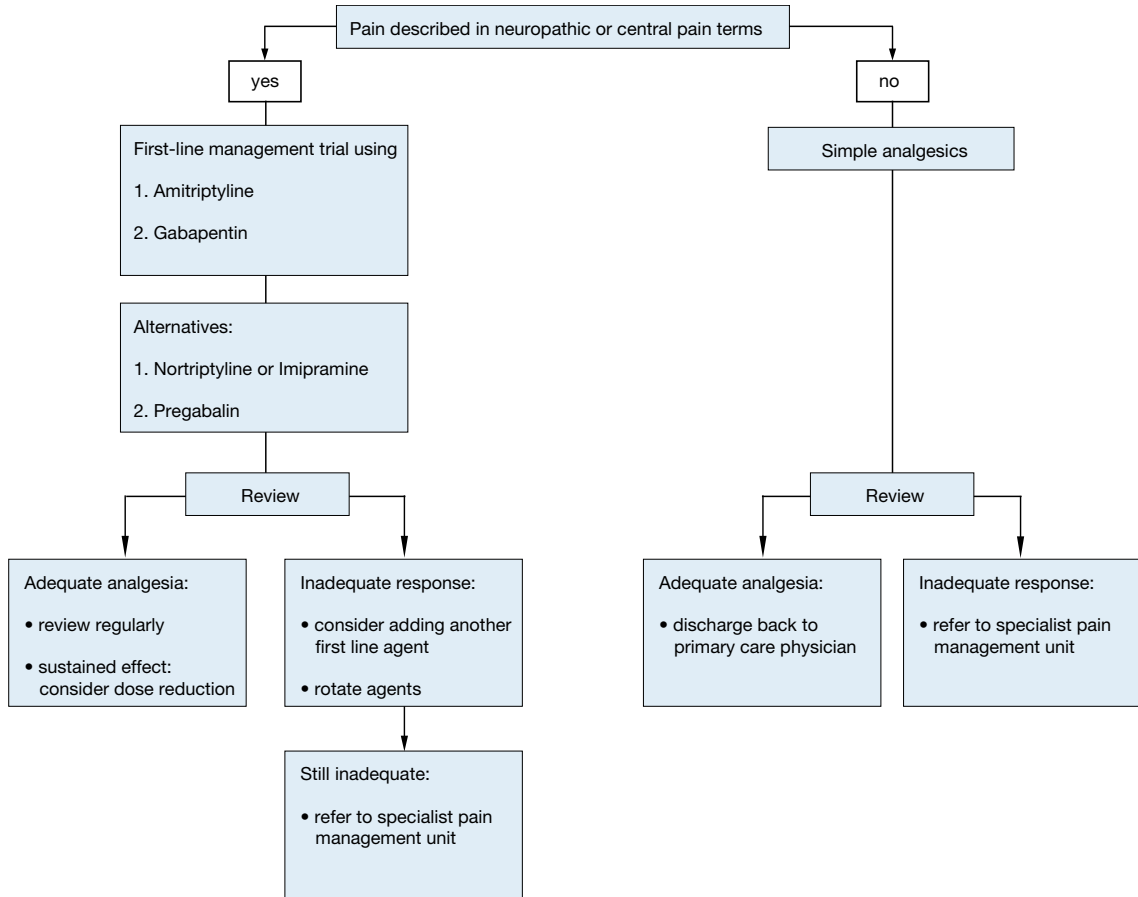
Agent	Pain Type	LE	GR	Comment
Paracetamol	Somatic pain	1a	A	Evidence based on arthritic pain with good benefit
NSAIDs	Pelvic pain with inflammatory process (e.g. dysmenorrhoea)	1a	A	Good evidence for their use
Antidepressants including tricyclic antidepressants, duloxetine and venlafaxine	Neuropathic pain	1a	A	Effective. No specific evidence for CPP
Anticonvulsants gabapentin, pregabalin	Neuropathic pain, fibromyalgia	1a	A	Effective
Gabapentin	Women with CPP	2b	B	Effective
Topical capsaicin	Neuropathic pain	1a	A	Some evidence of benefit
Opioids	Chronic non-malignant pain	1a	A	Beneficial in a small number of patients
Nerve blocks		3	C	Have a role as part of a broad management plan
TENS		1b	B	There is no good evidence for or against the use of TENS. Data covered chronic pain not just CPP and was insufficient regarding long-term treatment effects.
Neuromodulation	Pelvic pain	3	C	Role developing with increasing research

TENS = transcutaneous electrical nerve stimulation; CPP = chronic pelvic pain

Figure 14: General analgesic treatment of chronic pelvic pain

Assessment	Treatment	
General history	Grade A recommended	Paracetamol in somatic pain
Medications used		NSAID's when inflammation is present
Allergic reactions		Antidepressants (including TCA) in neuropathic pain
Use of alcohol		Anticonvulsants in neuropathic pain
Daily activities that will be affected		Topical Capsaicin in neuropathic pain
		Opioids in chronic non-malignant pain
	Grade B recommended	Gabapentin in women with CPP
	Other comments	Nerve blocks as part of a broad management plan
		Neuromodulation may become an option, increasing research

Algorithm 5: General management of CPP



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12. CONFLICT OF INTEREST

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Guidelines on Reporting and Grading of Complications after Urologic Surgical Procedures

D. Mitropoulos (Chair), W. Artibani, M. Graefen, M. Remzi,
M. Rouprêt, M.C. Truss

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1. INTRODUCTION

Evidence of variations in clinical practice, together with rising costs associated with constrained resources in most health care systems over the past decade, has triggered growing interest in evaluating the quality of our surgical work [1-3]. At present, the main methods of assessing surgical results for audit and quality assurance remain mortality and morbidity [4-6]. Thus measurement of morbidity requires an accurate definition of a surgical complication. Although the incidence of postoperative complications is still the most frequently used surrogate marker of quality in surgery [1, 3, 7], the direct cause-and-effect relationship between surgery and complications is often difficult to assess. This uncertainty carries a risk of underreporting surgical complications, with substantial consequences.

Most published articles focus only on positive outcomes (e.g. trilecta in prostate cancer after radical prostatectomy) [8]. There is a need to compare complications for each specific approach in a systematic, objective, and reproducible way. As yet, no definitions for complications or guidelines for reporting surgical outcomes have been universally accepted. Reporting and grading of complications in a structured fashion is only one aspect of the quality of outcome reporting. In 2002, Martin et al. proposed 10 criteria that should be met when reporting complications following surgery [9] (Table 1). Clavien and Dindo proposed a system for grading the severity of postoperative complications [10] that was subsequently revised and validated [11] (Table 2).

Table 1: Martin et al. criteria of accurate and comprehensive reporting of surgical complications [9]

Criteria	Requirement
Method of accruing data defined	Prospective or retrospective accrual of data are indicated
Duration of follow-up indicated	Report clarifies the time period of postoperative accrual of complications such as 30 days or same hospitalisation
Outpatient information included	Study indicates that complications first identified following discharge are included in the analysis
Definition of complications provided	Article defines at least one complication with specific inclusion criteria
Mortality rate and causes of death listed	The number of patients who died in the postoperative period of study are recorded together with cause of death
Morbidity rate and total complications indicated	The number of patients with any complication and the total number of complications are recorded
Procedure-specific complications included	
Severity grade utilised	Any grading system designed to clarify severity of complications including major and minor is reported
Length-of-stay data	Median or mean length of stay indicated in the study
Risk factors included in the analysis	Evidence of risk stratification and method used indicated by study

Table 2: Clavien-Dindo grading system for the classification of surgical complications [11]

Grades	Definitions
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Acceptable therapeutic regimens are: drugs such as antiemetics, antipyretics, analgesics, diuretics and electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than those allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade III-a	Intervention not under general anaesthesia
Grade III-b	Intervention under general anaesthesia
Grade IV	Life-threatening complication (including CNS complications: brain haemorrhage, ischaemic stroke, subarachnoid bleeding, but excluding transient ischaemic attacks) requiring IC/ICU management
Grade IV-a	Single organ dysfunction (including dialysis)
Grade IV-b	Multi-organ dysfunction

Grade V	Death of a patient
Suffix “d”	If the patient suffers from a complication at the time of discharge the suffix “d” (for disability) is added to the respective grade of complication. This label indicates the need for a follow-up to evaluate the complication fully.

Despite these proposals, no current standard guidelines or criteria exist for reporting surgical complications in the area of urology. It appears important that the urologic community create universally accepted criteria for reporting surgical morbidity and outcomes to establish the efficacy of surgical techniques and improve the quality of patient care [12]. Adopting an integrated method of characterising and reporting surgical morbidity has the potential to improve patient care on many levels:

- It enables better characterisation of surgical morbidity associated with various surgical techniques.
- It allows comparison of different surgical techniques, which is important due to the relative lack ($\leq 1\%$) of randomised trials in the urologic literature.
- It allows the physician to portray more accurately to patients the risks of a procedure versus other surgical or medical options.
- It allows better sequencing of multimodality approaches.
- It allows earlier recognition of the pattern of complications, thereby allowing for pre-emptive changes in care in an effort to decline the incidence.
- It allows better comparisons between individual surgeons or between institutional experiences.
- It allows identification of quality-of-care measures for benchmarking.

The aim of our work was to review the available reporting systems used for urologic surgical complications; to establish a possible change in attitude towards reporting of complications using standardised systems; to assess systematically the Clavien-Dindo system (currently widely used for the reporting of complications related to urologic surgical interventions); to identify shortcomings in reporting complications, and to present recommendations for the development and implementation of future reporting systems that focus on patient-centred outcomes. The panel did not take intraoperative complications into consideration, which may be addressed in a follow-up project.

1.1 Publication history

This article presents a republication of a scientific paper published in European Urology, the EAU scientific journal [13]. Prior to publication, the paper has been subjected to double blind peer review.

In the course of 2012 the authors aim to assess the usage and reproducibility of the proposed model for reporting of complications. These findings will be published upon completion of the assessment.

2. EVIDENCE ACQUISITION

Standardised systems for reporting and classification of surgical complications were identified through a systematic review of the literature. To establish a possible change in attitude towards reporting of complications related to urologic procedures and assessment of the Clavien-Dindo system in urology, two different strategies were used. For the first objective (reporting trends), papers reporting complications after urologic surgery published in European Urology, Journal of Urology, Urology, BJU International, and World Journal of Urology in 1999-2000 and 2009-2010 were reviewed. Selection criteria were the top five general urology journals (from major urologic societies) based on impact factor (IF) and English-language publications. The panel recognised that IF as a quality indicator was debatable but considered that it would have had no impact on the validity of the outcome of this review. Promising articles were identified initially through the tables of contents of the respective journals. All selected papers were full-text retrieved and assessed; papers not reporting complications and reviews were excluded from the analysis. Analysis was done based on a structured form, which was similar for each article and for each journal (Form 1).

Data identification for the second objective (systematic assessment of the Clavien-Dindo system currently used for reporting of complications related to urologic surgical interventions) involved a Medline/Embase search using *Clavien*, *urology*, and *complications* as keywords. This search produced 63 eligible papers reporting complications using the Clavien-Dindo system. A second search using the search engines of individual urologic journals and publishers that may identify Clavien or Dindo and urology within the full text of a paper produced

141 more papers. Thus the total number of eligible papers was 204. All selected papers were full-text retrieved for analysis, which was done based on a structured form (Form 2). All papers were evaluated by two authors independently, and in case of disagreement, the paper was presented to all members to reach consensus.

Form 1: Data extraction form to assess reporting of complications after urologic procedures using the Clavien-Dindo system

Study title:				
Published in:				
<input type="checkbox"/> European Urology	<input type="checkbox"/> Journal of Urology	<input type="checkbox"/> BJU International	<input type="checkbox"/> Urology	
<input type="checkbox"/> World Journal of Urology				
Year of publication:				
<input type="checkbox"/> 1999/2000	<input type="checkbox"/> 2009/2010	Volume	page	to
The study is a:				
<input type="checkbox"/> Case series	<input type="checkbox"/> Controlled study without randomisation Prospective, randomised trial			
<input type="checkbox"/> Meta-analysis				
Level of evidence (Oxford criteria, EAU modification):				
<input type="checkbox"/> 1a	<input type="checkbox"/> 1b	<input type="checkbox"/> 2a	<input type="checkbox"/> 2b	<input type="checkbox"/> 3
The study reports complications after (define the procedure):				
Did the authors use standardised criteria?				
<input type="checkbox"/> Yes <input type="checkbox"/> No				
In case standardised criteria were used, they were:				
<input type="checkbox"/> Predefined by authors <input type="checkbox"/> Clavien-Dindo system				
No of Martin criteria met:				
<input type="checkbox"/> 0-2	<input type="checkbox"/> 3/4	<input type="checkbox"/> 5/6	<input type="checkbox"/> 7/8	<input type="checkbox"/> 9/10

Form 2: Data extraction form to assess reporting of complications after urologic procedures using the Clavien-Dindo system

Study title:				
Published in:				
Year of publication: Volume: Page to				
The study is a:				
<input type="checkbox"/> Case series	<input type="checkbox"/> Controlled study without randomisation	<input type="checkbox"/> Prospective, randomised trial		
<input type="checkbox"/> Meta-analysis				
Level of evidence (Oxford criteria, EAU modification):				
<input type="checkbox"/> 1a	<input type="checkbox"/> 1b	<input type="checkbox"/> 2a	<input type="checkbox"/> 2b	<input type="checkbox"/> 3
No of Martin criteria met (0-10):				
The study reports complications after (define):				
In your opinion, was the Clavien-Dindo system used correctly?				
<input type="checkbox"/> Yes <input type="checkbox"/> No				
If NO, why not:				

3. EVIDENCE SYNTHESIS

3.1 Systems used to report surgical complications

The systematic review of the literature for standardised systems used for reporting and classification of surgical complications revealed five standardised systems (Table 3).

Table 3: Available classification systems for reporting of complications

Classification	Clinical validation	Simplicity	Severity grading
Clavien-Dindo	Yes	Easy	I-V
MSKCC	Yes	Easy	5
Accordion contracted extended	No	Easy	4 6
NSQIP	Yes	Complex	Major/minor
NCT-CTC	Yes	Complex	5

MSKCC = Memorial Sloan-Kettering Cancer Centre classification - modification of the original T92 Clavien classification [9, 14]; NSQIP = National Surgical Quality Improvement Programme [3]; NCT-CTC = National Cancer Institute Common Toxicity Criteria [17].

In 1992, Clavien et al. proposed a classification for complications of surgery and introduced a severity grading system called T92 [10], which was based on the main criterion of the intervention needed to resolve the complication. Four grades containing five levels of complications were described. In 2004, Dindo et al. introduced a modification of the T92 classification using five grades containing seven levels (Table 2) [11]. This modification was performed to add further precision and to characterise whether an intervention due to the complication led to general anaesthesia, intensive care unit admission, or organ failure, and again, it was based on the type of therapy required to treat the complication. This modified classification, which is known as the Clavien-Dindo system, was validated and tested for interobserver variation in 10 centres around the world [14]. The Clavien-Dindo system is widely used, with an exponential increase in recent years, especially in general surgery but also in urology (see Fig. 3 and 4). A few authors have adapted both systems to analyse specific procedures such as living donor liver and kidney transplantation, which has led to confusion [14].

A less extensive modification of the T92 system was made by Martin et al. [9, 15] and is referred to as the Memorial Sloan-Kettering Cancer Centre (MSKCC) severity grading system. Conceptually, it is very similar to T92 but differs in numbering (for details see Table 1 in Strasberg et al. [16]).

The Accordion classification was introduced in 2009 and represents a flexible system that can be used in studies of different size and complexity [17] (Table 4). It is available on an open Website (<http://www.accordionclassification.wustl.edu>).

Table 4: Accordion severity classification of postoperative complications: contracted and expanded classification [17]

Contracted classification	Expanded classification
<p>1. Mild complication Requires only minor invasive procedures that can be done at the bedside, such as insertion of intravenous lines, urinary catheters and nasogastric tubes, and drainage of wound infections. Physiotherapy and the following drugs are allowed: antiemetics, antipyretics, analgesics, diuretics and electrolytes.</p> <p>2. Moderate complication Requires pharmacological treatment with drugs other than those allowed for minor complications, for example, antibiotics. Blood transfusions and total parenteral nutrition are also included.</p> <p>3. Severe complication All complications requiring endoscopic or interventional radiology or re-operation, as well as complications resulting in failure of one or more organ systems.</p> <p>4. Death Postoperative death</p>	<p>1. Mild complication Requires only minor invasive procedures that can be done at the bedside, such as insertion of intravenous lines, urinary catheters and nasogastric tubes, and drainage of wound infections. Physiotherapy and the following drugs are allowed: antiemetics, antipyretics, analgesics, diuretics and electrolytes.</p> <p>2. Moderate complication Requires pharmacological treatment with drugs other than those allowed for minor complications, for example, antibiotics. Blood transfusions and total parenteral nutrition are also included.</p> <p>3. Severe: invasive procedure without general anaesthesia Requires management by an endoscopic, interventional procedure or re-operation* without general anaesthesia</p> <p>4. Severe: operation under general anaesthesia Requires management by an operation under general anaesthesia</p> <p>5. Severe: organ system failure[†]</p> <p>6. Death Postoperative death</p>

**An example would be wound re-exploration under conscious sedation and/or local anaesthetic.*

†Such complications would normally be managed in an increased acuity setting but in some cases patients with complications of lower severity might also be admitted to an ICU.

The National Surgical Quality Improvement Program was established in 1994 within the US Veterans Administration (VA) health care system, with the aim of identifying and reporting adverse events as one prerequisite for process improvement in health care [3]. The system is validated, outcome based, and uses data adjusted for patient preoperative risk. It allows comparison of the performance of different hospitals performing major surgery by the ratio of observed to expected (O/E) adverse events. Statistically low (O/E < 1) or high (O/E > 1) outliers are then identified to support continuous quality improvement activities. The annual use of this system has contributed to the improvement of the standard of surgical care and to lower 30-d mortality and morbidity rates for major noncardiac surgery within the VA.

The National Cancer Institute Common Toxicity Criteria (NCI-CTC) system [17] was first created in 1983, aimed at the recognition and grading of adverse effects of chemotherapy in cancer patients. The system was updated and expanded in 1998 (CTC v2.0), including acute effects of radiotherapy and limited criteria applicable to surgery. In 2003, Common Terminology Criteria for Adverse Events (CTCAE v3.0) was introduced for application to all possible modalities and is organised by organ system categories (all organs are included), with 370 different criteria. An adverse event is defined as any new finding or undesirable event that may not be attributed to treatment. Grading criteria are shown in Table 5. Late and acute effects criteria are merged into a single uniform system and applied without a predetermined time-based designation. The previously used “90-day rule” is not advised currently because each study is unique. The new CTC system was designed to be applied to all possible modalities, and it is organised by organ system categories (all organs are included) with 370 different criteria. The unexpected serious and life-threatening (grades 3 and 4) consequences of surgery are the focus of immediate surgical reporting. CTCAE v3.0 is available on the Cancer Therapy Evaluation Program Website (www.ctep.info.nih.gov).

Table 5: National Cancer Institute Common Toxicity Criteria grading system for the adverse effects of cancer treatment [17]

Grade	Definition of effects
Grade 1	Minimal and usually asymptomatic effects that do not interfere with functional endpoints (interventions or medications are generally not indicated for these minor effects).
Grade 2	Moderate, are usually symptomatic. Interventions such as local treatment or medications may be indicated (they may interfere with specific functions but not enough to impair activities of daily living).
Grade 3	Severe and very undesirable. There are usually multiple, disruptive symptoms (more serious interventions, including surgery or hospitalisation, may be indicated).
Grade 4	Potentially life threatening, catastrophic, disabling, or result in loss of organ, organ function, or limb.

Most recently, the International Urogynecological Association (IUGA) and the International Continence Society (ICS) have established a joint working group on terminology for complications related to the insertion of prostheses and grafts in female pelvic floor surgery [18]. The document proposes definitions of specific complications, distinguishing local complications, complications to surrounding organs, and systemic complications. New terms have been proposed and defined in detail such as contraction, prominence, separation, exposure, extrusion, perforation, dehiscence, and sinus tract formation. The classification is based on category, time, and site of complications, with the aim of summarising any of a large range of possible clinical scenarios into a code using as few as three numerals and three (or four) letters. Lowercase letters can be added, describing the presence and the type of pain. The ICS-IUGA classification appears at first sight to be complex and not immediately mastered, as outlined by the proponents. The main goal is to establish common language and to promote a homogeneous registry to improve the quality of pelvic floor surgical procedures using prostheses and grafts.

3.2 Attitude of urologists towards reporting complications

A total of 874 eligible papers of 1261 retrieved publications were included in the final analysis. The type of studies reporting complications did not vary between the two time frames selected (1999-2000 vs 2009-2010) ($p > 0.1$). Most of the papers identified were case studies (Fig. 1). However, a shift could be seen in the number of studies using most of the Martin criteria (Fig. 2), as well as in the number of studies using either standardised criteria or the Clavien-Dindo system to report complications (Fig. 3).

Fig. 1: Comparative distribution of papers reporting complications after urologic procedures by study type and time frame

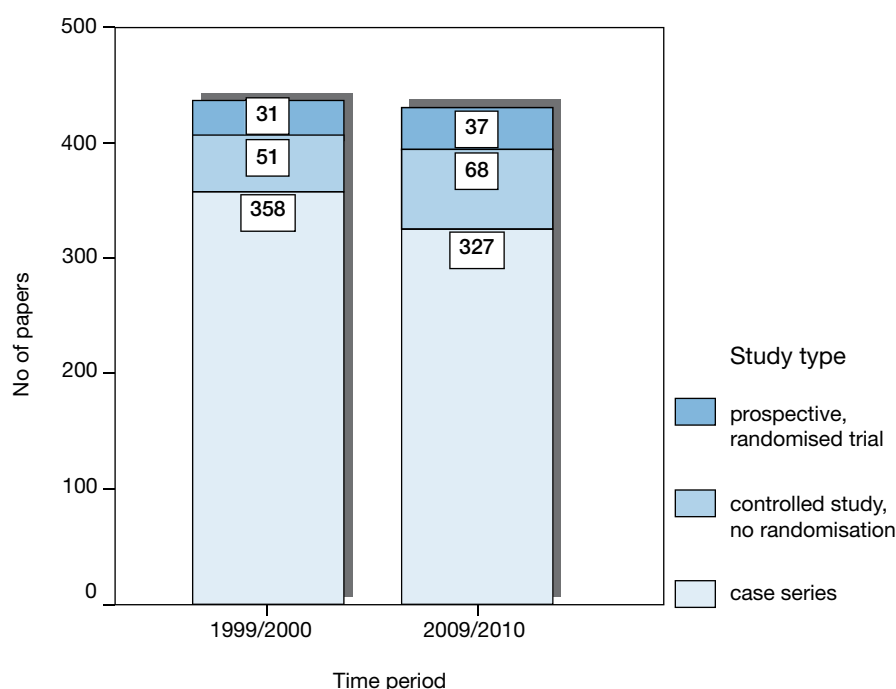


Fig. 2: Comparative distribution of papers reporting complications after urologic procedures by number of Martin criteria met and time frame

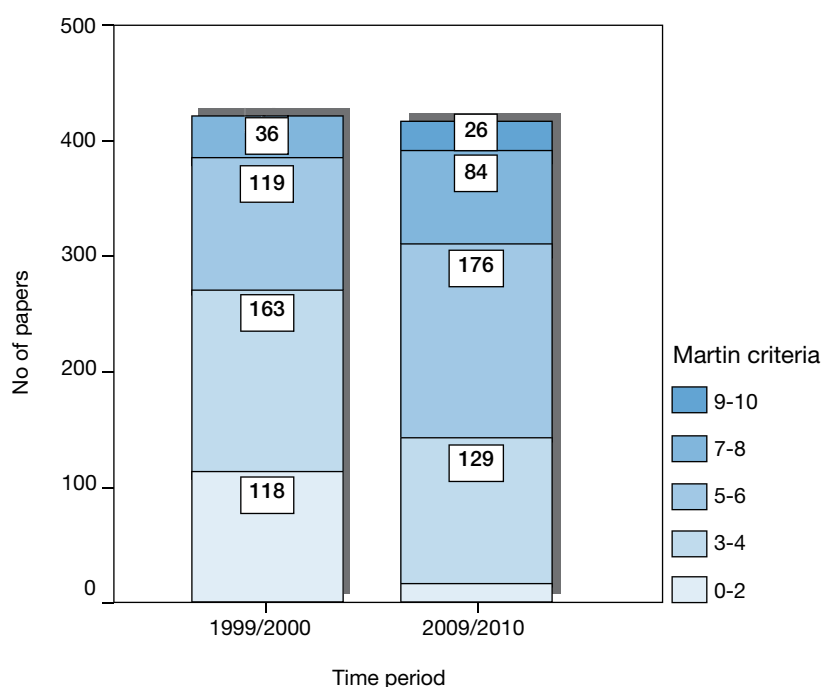
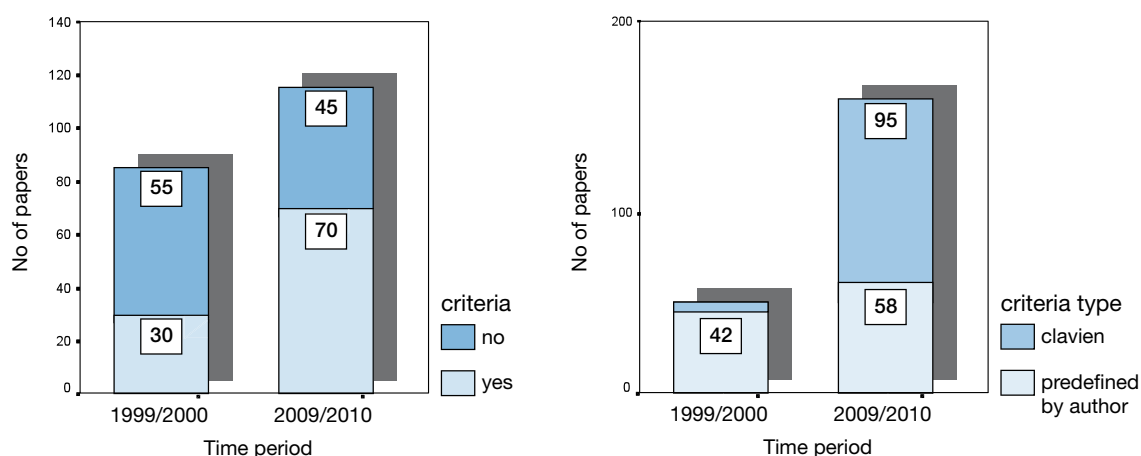


Fig. 3: Comparative distribution of papers reporting complications after urologic procedures by time frame and whether standardised criteria were used (left), and in case they were, whether the Clavien-Dindo system was used (right)



3.3 Assessment of the Clavien-Dindo system for reporting complications after urologic procedures

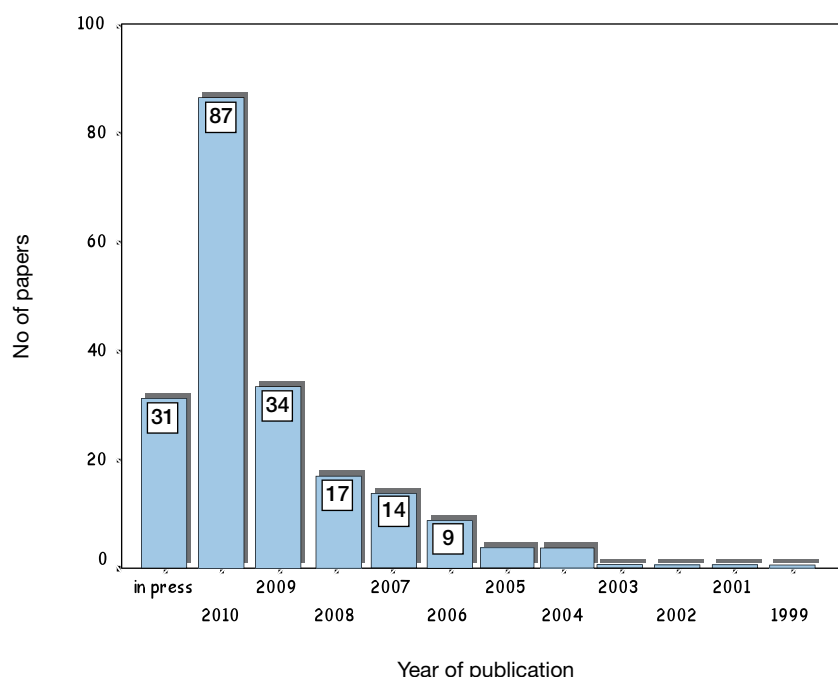
The literature search identified 204 papers published in:

- Urology 38
- Journal of Urology 37
- Journal of Endourology 35
- European Urology 34
- BJU International 19
- World Journal of Urology 15
- and several others 26

The number of papers using the Clavien-Dindo system to report complications after urologic surgical interventions showed an exponential increase (Fig. 4). Most of the studies identified were, again, case series, and 77.9% of the studies fulfilled ≥ 7 of the Martin criteria (range: 3-10; mean: 7.5; standard deviation: 1.5). The

vast majority of papers referred to novel technologies (laparoscopy/robot-assisted procedures), whereas only 13.2% of papers discussed open procedures. The Clavien-Dindo system was not properly used in 72 papers (35.3%): Eight times it was also used to report/grade intraoperative complications; six times the authors used their own modification of the Clavien-Dindo system; in 27 studies, the authors grouped complications into major (Clavien-Dindo ≥ 3) and minor without mentioning specific complications; and in 31 papers, the authors did not assign a grade to the complications reported.

Fig. 4: Distribution of studies using the Clavien-Dindo system to report complications after urologic procedures



3.4 Discussion

The definition of surgical complications still lacks standardisation, which hampers the interpretation of surgical performance and quality assessment [5, 7, 19]. Although many surgeons would argue that their subjective intuition is an appropriate guide to defining what a complication might be, the value of the surgeon's intuition is unreliable in many situations because it lacks objective criteria and depends heavily on the experience of the individual clinician [4, 7, 20]. Second, a surgical complication is not a fixed reality. Instead, it depends on the surgeon's level of skill, the surgeon's learning curve for the procedure, the patient's comorbidity and risk factors, and the facilities available. A surgical complication in a Western country may not be perceived or subjectively weighted as a surgical complication in rural or less developed countries. Similarly, a complication in 2011 may be seen as obsolete in a few years' time, with a better understanding of the pathophysiology of the underlying malady. As surgical techniques and equipment improve, what were once inevitable negative outcomes may acquire the status of mere surgical complications [2, 5, 7]. Finally, and paradoxically, the higher the expectation of the surgeon and patient, the more potential surgical complications occur [21, 22]. The clinical relevance of reporting surgical complications is primarily related to the fact that the dissemination of technology is very rapid, with current grades of recommendations based on the level of evidence in their corresponding studies. However, in the surgical field, randomised controlled trials with high levels of evidence are uncommon, and this limitation naturally leads to a low number of recommendations. We have to keep in mind that the guidelines can only rely on the surgical evidence. Thus there is a real discrepancy between the reality of daily surgical practice and the relevance of the low-grade recommendations produced in this area. However, the scientific quality of an article is not only related to its level of evidence. The use of more rigorous methodology and the consensus-related complications of surgical techniques will probably improve the quality of the surgical scientific literature. It is likely that this improvement will renew interest in daily clinical practice in the minds of surgeons. In addition, it will allow recommendations that avoid complications, clearly the most relevant issue in improving patient care.

In defining surgical complications, subjectivity cannot always be avoided, but it should be reduced as much as possible [4]. Additionally, different audiences (e.g. patients, nurses, health care providers, and third-party payers) and different surgical communities (e.g. urologists, orthopaedists, and vascular surgeons) view, define,

and perceive complications differently. Currently, no generally accepted standards or definitions exist with regard to the severity of surgical complications. Clavien-Dindo recommended the following definitions of surgical outcomes:

1. Surgical complication: any deviation from the ideal postoperative course that is not inherent in the procedure and does not comprise a failure to cure.
2. Failure to cure: diseases or conditions that remained unchanged after surgery.
3. Sequelae: conditions that are inherent in a procedure and thus would inevitably occur, such as scar formation or the inability to walk after an amputation.

Based on the review of the current literature, and with reference to the Accordion Severity Grading System [16], an appropriate definition of a complication is a combination of the following items: an event unrelated to the purposes of the procedure, an unintended result of the procedure, an event occurring in temporal proximity to the procedure, something causing a deviation from the ideal postoperative course, an event that induces a change in management, or something that is morbid (i.e. causes suffering directly by causing pain, or indirectly, by subjecting the patient to additional interventions).

In contrast to a complication, the sequelae of a procedure should be defined as an after-effect of that procedure. The risk of sequelae is inherent in the procedure (e.g. diabetes after pancreatic resection, rejection after transplantation, limp after amputation, dyspnoea after pneumonectomy, or impairment of renal function after tumour nephrectomy). Failure to cure should be defined as failure to attain or maintain the purpose of the procedure (e.g. failure to remove all stones during ureteroscopy or percutaneous stone surgery, tumour recurrence, stricture recurrence, or recurrence of patency when the purpose of the procedure is to occlude). Sequelae of procedures and failures to cure should be reported but presented separately from complications [14].

However, a complication that results in lasting disability is considered a sequela of a complication. Stroke or acute renal failure (ARF) occurring after a procedure is considered a complication and should be reported as such. However, long-term aphasia resulting from stroke or chronic renal failure after ARF is considered a sequela of that complication. Therefore, it should be reported in a special section devoted specifically to long-term disability.

Patients and their treating physicians do not necessarily mean the same thing when they use the term complication. Several studies have shown substantial discrepancies in the reporting of adverse events and sequelae of a treatment when the estimations of patients and physicians are compared [22]. The usual information on potential complications that patients can obtain before a surgical procedure can be taken from the available literature, the specific information given by the treating centre (i.e. home page or patient information brochures), or from direct discussion with the treating surgeon. This information has the potential to be biased from the definition of what is considered a complication, and a standardised system that is not only used for complication reports in the literature but also for patient counselling is important for a realistic estimation of outcomes. In the present literature, patients often report a higher frequency and severity of adverse events compared with that reported by their physicians [23]. However, in a recent randomised study, Steinsvik et al. showed that several adverse events, such as bowel problems, were overrated by the physician [24]. Overrating and especially underrating of complications by the treating physician leads to confusion and a discrepancy between patient expectation and reality.

Schroeck et al. evaluated variables associated with satisfaction and regret after open and robotic radical prostatectomy [21]. Patients who underwent robotic-assisted laparoscopic prostatectomy were more likely to be regretful and dissatisfied, which was not necessarily interpreted as caused by a worse outcome but potentially caused by the higher expectation associated with an innovative procedure. The authors therefore suggested that urologists should carefully portray the risks and benefits of new technologies during preoperative counselling to minimise regret and maximise satisfaction.

These examples support the notion that realistic counselling is crucial for the patient's decision-making process and for satisfaction with the achieved result. However, a standardised reporting system for surgical complications can only try to standardise the reporting of the intraoperative and perioperative morbidity of the procedure itself. Short-, mid- or long-term sequelae of a surgical procedure, such as erectile dysfunction or urinary incontinence following radical prostatectomy, are not covered by this classification and need to be reported with other validated tools.

Standardised classification and severity grading of surgical complications is essential for proper interpretation

of surgical outcome data, for comparing the surgical outcomes between institutions or individual surgeons, and for comparing techniques in case randomised trials are either lacking or difficult to perform (i.e. comparison of minimally invasive techniques with open surgery). The urologic community seems to conform to the current demands because recent studies have more often used standardised criteria to report complications (48.3% vs. 35.3%) (Fig. 3). In urologic oncology reports published from January 1995 to December 2005, the corresponding percentage was 33%, with only 19% (6% of the total) using a numerical complication severity grading system [12]. The Clavien-Dindo system has gained wide acceptance both in general surgery [14] and the urologic community (Fig. 3, and Fig. 4). Clinical databases designed and controlled by physicians may underreport complications [25]. Similarly, a disadvantage of the Clavien-Dindo system is its unreliability when recording is performed by residents, although, when captured, grading of complications was correct in 97% of the cases. Consequently, the authors have proposed that dedicated personnel should evaluate surgical outcomes [2]. Special attention should also be paid to proper use of the Clavien-Dindo system because it has not been designed/validated to grade intraoperative complications, and any modifications and revisions can be confusing [14].

Classification and severity grading of surgical complications is an important, albeit not the only criterion of quality when reporting surgical outcome. Approximately 40% of general surgery series and trials and 23% of studies reporting surgical complications in urologic oncology [2] fulfil seven or more Martin criteria. Interestingly, 77.9% of the papers that used the Clavien-Dindo system to report complications after urologic procedures fulfilled seven or more criteria, implying that its use contributes to higher quality reports.

Besides the efficiency of an individual surgeon and the function of an institution, surgical care outcomes also depend on the patient's preoperative risk factors [26]. Thus they should always be defined and used in the analysis and report. A substantial proportion of postoperative complications occur after hospital discharge [27]; extension of the length of postoperative observation may therefore be necessary. Other quality-of-care indicators are readmissions and reoperations [28] and should be included in both preliminary and final reports.

4. CONCLUSIONS

There is an urgent need for uniform reporting of complications after urologic procedures, which will aid all those involved in patient care and scientific publishing (authors, reviewers and editors). Urologists have considerably changed their attitude towards using standardised criteria when reporting complications, and there has been an exponential increase of the number of papers using the Clavien-Dindo system. However, a certain number of papers (35.3%) did not use it properly. When reporting the outcomes of urologic procedures, the committee proposes the following:

- Define your complications.
- Preferentially use a standardised system; the Clavien-Dindo grading system is highly recommended.
- When using the Clavien-Dindo system, provide a table of all complications and corresponding grades or list the complications by grade.
- Use the NCI-CTC system in multimodality treatment.
- Improve reporting of complications by following the revised quality criteria (Table 6).
- Define the method of accruing data: retrospective/prospective; through chart review/telephone interview/face-to-face interview/other.
- Define who collected the data: medical doctor/nurse/data manager/other, and whether he or she was involved in the treatment.
- Indicate the duration of follow-up: 30, 60, 90, or >90 d.
- Include outpatient information.
- Include mortality data and causes of death.
- Include definitions of complications.
- Define procedure-specific complications.
- Use a severity grading system (avoiding the distinction minor/major); the Clavien-Dindo system is recommended.
- Include risk factors: American Society of Anaesthesiologists score, Charlson score, Eastern Cooperative Oncology Group, other.
- Include readmissions and causes.
- Include reoperations, types and causes.
- Include the percentage of patients lost to follow-up.

- Finally, editors of urologic journals should demand the use of a standardised system to report complications after urologic surgery.

Table 6: Quality criteria for accurate and comprehensive reporting of surgical outcome

1. Define the method of accruing data:
retrospective _ prospective _ , through:
chart review _ telephone interview _ face to face interview _ other _
2. Define who collected the data:
medical doctor _ nurse _ data manager _ other _
and whether he/she was involved in the treatment: yes _ no _
3. Indicate the duration of follow-up:
30 days _ 60 days _ 90 days _ > 90 days _
4. Include outpatient information
5. Include mortality data and causes of death
6. Include definitions of complications
7. Define procedure-specific complications
8. Report intraoperative and postoperative complications separately
9. Use a severity grading system for postoperative complications (avoiding the distinction minor/major)
- Clavien-Dindo system is recommended
10. Postoperative complications should be presented in a table either by grade or by complication type
(specific grades should always be provided; grouping is not accepted)
11. Include risk factors
ASA score _ Charlson score _ ECOG _ other _
12. Include readmissions and causes
13. Include re-operations, types and causes
14. Include the percentage of patients lost to follow-up

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6. CONFLICT OF INTEREST

All members of the ad hoc EAU Guidelines working panel on Reporting and Grading of Complications after Urologic Surgical Procedures have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: <http://www.uroweb.org/guidelines/online-guidelines/>. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

EAU Standardised Medical Terminology for Urologic Imaging: **A Taxonomic Approach**

T. Loch (Chair), B. Carey, J. Walz, P.F. Fulgham

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1. INTRODUCTION

The continued development of new imaging techniques in urology has had considerable impact on both clinical practice and urologic research [1,2]. The clinical integration of these imaging techniques into urologic practice involves contributions from investigators and clinicians of varied backgrounds including physics and engineering, informatics, urology, and radiology. Each profession has its own jargon, a specialised language that allows for rapid and efficient communication between members of the same profession while minimising the potential for misunderstandings. Abbreviations are an extension of the jargon of each profession, and they enable health care professionals to document their work more easily and communicate quickly.

Abbreviations have generally been adopted on an ad hoc basis to accommodate the often conflicting demands of utilising brief context-sensitive phrases and combinations of letters with the challenging requirements of more rigid, computer software-driven, clinical and research practice; however, this jargon might lead to the problem of several terms for the same object. The differences in terminology and the lack of standardisation of the terminology can lead to confounders, errors, and misunderstandings as well as to loss of information and knowledge.

Most of this development and expansion of terminology has occurred in an unplanned and uncoordinated manner and has been adopted through common usage within specialities rather than by consensus agreement [3]. Various lists of abbreviations and terminologies have been produced by different speciality groups [4, 5]. During the review, it was found that a wide variety of terms were used for the same examination, for example, *Intravenous Urogram* (IVU) was also termed *Kidney, Ureter, Bladder (KUB) Urogram* or *Urography*.

Much of this usage has been driven by agreed common practice without reference to any unifying standard of methodology or taxonomy. Taxonomy is a general principle of scientific classification. Organisms are classified into a hierarchy of groupings. The order of ranking is usually from the more general to the more specific to describe and reflect a morphologic relationship [6].

There has been a general lack of international cooperation among different specialities and among different geographic locations for the same speciality. Confusion between the different requirements for digital archive coding systems and research may cause a lack of support to integrate data produced by everyone involved in urology imaging and further promote a diversity of interests.

The benefits of a shared nomenclature for literature research and communication among clinicians are obvious. The absence of agreed-on operational nomenclature will inevitably undermine the yield from literature review if different search terms are used. The aim of this work is to review the current nomenclature used for imaging in urology in clinical practice and in the published literature and to propose standardisation of terms using taxonomy.

2. METHODS

The list of terms used for urologic imaging was compiled from guidelines published by the European Association of Urology (EAU) [7], the American Urological Association (AUA) [8], and the American College of Radiology (ACR) [9]. These guidelines are regularly updated and based on extensive review of the current literature.

A review of the different guideline texts, which included the terminology and abbreviations found in the reference listings for each guideline, showed that the same examination might have a variety of names. As noted, IVU was also called *KUB urogram* or *urography*.

To investigate the terms used, the AUA and EAU guidelines and all of the urology-related ACR Appropriateness Criteria were downloaded into single directories. Using the advanced search feature of Acrobat Pro (CTRL-SHIFT-F; Adobe Systems Inc., San Jose, CA, USA), we searched for the terms, for example, *CT* or *computed tomography* (identical methodology for all other terms) and identified all of the various terms, abbreviations, and variants associated with them. Once the terms were identified, each term was then grouped by its operating characteristics. Specifically, terms were divided by the type of study (e.g., computed tomography [CT]), anatomic extent (e.g., area researched such as abdomen or pelvis), the use of contrast and phases, the technique or type of detector (e.g., multiphase, helical, low dose), and combined studies or fusions (e.g., positron emission tomography [PET], CT). Based on the frequency of use and expert consensus,

the terms were then placed in an *accepted* category or an *equivalent or similar* category. The categories were ranked by frequency of use within the documents. Imaging terms were grouped into broad categories based on technology (e.g., plain radiography, CT, ultrasound, magnetic resonance imaging [MRI], and nuclear medicine). Within each broad category, the imaging terms were further stratified based on the anatomic extent, contrast or phases, technique or modifiers, and combinations or fusions. Terms that had a high degree of utilisation were classified as *accepted*. Other terms were judged to be similar but were either infrequently used or contained modifiers requiring further explanation.

To construct a general methodology for nomenclature adaptation in medical terminology, we propose that a taxonomy-based approach would help define a more useful model that would be acceptable to all health professionals involved in urology.

2.1 Rationale for a taxonomic approach

The major advantage of a taxonomic approach to the classification of urologic imaging studies is that it provides a flexible framework for classifying the modifications of current imaging modalities and allows for the incorporation of new imaging modalities.

Adopting this hierarchical classification model (i.e., from the most general to the most detailed descriptions) should facilitate hierarchical searches of the medical literature using both general and very specific search terms.

3. RESULTS

Tables 1-7 summarise the findings of the systematic search for all major types of urologic imaging studies: ultrasound (US); CT; MRI; fluoroscopy; radiographs; PET, in combination with either CT (PET-CT) or MRI (PET MRI); and scintigraphy. In the tables, the most commonly used term is listed as the *accepted standard*, and less frequently used terms are listed under *glossary of other terms*, which should be replaced by the accepted standard.

Table 1: Taxonomic classification of ultrasound

	Root Name	Anatomic extent	Contrast/phases	Technique modifiers/postprocessing methods	Combinations/fusions
Accepted standard	Ultrasound US	Abdomen Kidney Ureter Bladder Penis Testis Scrotum Prostate Pelvis Vas Vessels	Noncontrast Contrast TRUS Transvaginal Transurethral Transvesical Intra-abdominal Transabdominal	Elastography C-TRUS/ANNA Histoscanning Doppler Colour Doppler Power Doppler Spectral Doppler Compound imaging Harmonic	MRI CT
Glossary of terms less widely acceptable (descending order based on use in current guidelines)	Ultrasonography Sonography	Endosonography Percutaneous			

ANNA = artificial neural network analysis; CT = computed tomography; C-TRUS = computerised transrectal ultrasound; MRI = magnetic resonance imaging; TRUS = transrectal ultrasound; US = ultrasound.

Example: "US, prostate, TRUS, C-TRUS/ANNA fused with MRI".

Table 2: Taxonomic classification for computed tomography

	Root Name	Anatomic extent	Contrast/phases	Technique modifiers	Combinations/fusions
Accepted standard	Computed tomography CT	Chest Abdomen Pelvis Abdomen and pelvis	Contrast Noncontrast urography	Multiphasic Multidetector	PET/CT
Glossary of terms less widely acceptable (descending order based on use in current guidelines)	Computer tomography Computer-aided tomography scan CAT scan CT scan Scan		Contrast-enhanced CT Noncontrast CT Nonenhanced CT Unenhanced CT Unenhanced spiral CT CT cystography CT angiography CT scout Intravenous CT angiography Three-phase helical CT	Multidetector row CT Single detector CT Multiphase CT Multiphasic CT Multiphasic CT urography Multiphasic CTU Low-dose CT Standard-dose CT Ultra-low-dose CT	

CAT = computer-aided tomography; CT = computed tomography; CTU = computed tomography urography; PET = positron emission tomography.

Example: "CT, renal arteries, contrast, multiphasic".

Table 3: Taxonomic classification for magnetic resonance imaging

	Root Name	Anatomic extent	Contrast/phases	Technique modifiers	Combinations/fusions
Accepted standard	Magnetic resonance imaging MRI	Whole body Abdomen Pelvis Genitals Prostate Kidney Testis Penis Urinary tract	T1 weighted (T1) T2 weighted (T2) Dynamic contrast enhanced Diffusion weighted imaging Spectroscopy Multiparametric	1.5 tesla (1.5T) 3 tesla (3T) 7 tesla (7T) Body array coil Rectal coil Surface coil	PET/MRI
Glossary of terms less widely acceptable (descending order based on use in current guidelines)	Magnetic resonance MR Nuclear magnetic resonance NMR		MRI urography Contrast-enhanced MRI Nonenhanced MRI Unenhanced MRI MRI cystography MRI angiography Functional MRI Molecular MRI Molecular imaging	Open-gantry MRI Regular-gantry MRI Interventional MRI Thermometrie	

DCE = dynamic contrast enhanced; DWI = diffusion weighted imaging; MP = multiparametric; MR = magnetic resonance; MRI = magnetic resonance imaging; NMR = nuclear magnetic resonance; PET = positron emission tomography.

Example: "MRI, prostate, T2, DCE, DWI, MP, 1.5T, surface coil".

Table 4: Taxonomic classification of fluoroscopy

	Root Name	Anatomic extent	Contrast/phases	Technique modifiers	Combinations/fusions
Accepted standard	Fluoroscopy	Chest Abdomen Pelvis Renal tracts	Noncontrast Contrast		CT fluoroscopy Intraoperative
Glossary of terms less widely acceptable (descending order based on use in current guidelines)	Fluorography				

CT = computed tomography.

Example: "Fluoroscopy, renal tract, contrast, intraoperative".

Table 5: Taxonomic classification of radiographs

	Root Name	Anatomic extent	Contrast/phases	Technique modifiers	Combinations/fusions
Accepted standard	Radiographs Plain x-rays Intravenous urogram	Chest Abdomen Pelvis Spine Extremities Renal tract	Conventional Digital	Antegrade Retrograde	CT-urogram
Glossary of terms less widely acceptable (descending order based on use in current guidelines)	Plain films Radiography KUB Intravenous Pyelogram Excretion Urography Nephrostogram	Kidneys, ureters, bladder Urethra Vas		Plain Radiography CT Ascending Descending	CT-KUB CT-nephrostogram CT-urethrogram

CT = computed tomography; IVU = intravenous urogram; KUB = kidney, ureter, and bladder.

Example: "IVU, renal tract, digital".

Table 6: Taxonomic classification of positron emission tomography in combination with either computed tomography or magnetic resonance imaging

	Root Name	Anatomic extent	Technique modifiers (isotope)
Accepted standard	Positron emission tomography–computed tomography PET-CT	Whole body Pelvis Kidney Bladder Prostate Abdomen Retroperitoneum	Fluorodeoxyglucose ¹¹ C-choline ¹⁸ F-fluorine Methionine Other (nonspecified)
Glossary of terms less widely acceptable (descending order based on use in current guidelines)	CT-PET FDG-PET ¹⁸ F-FDG-PET PET FDG-PET CT		
Accepted standard	Positron emission tomography magnetic resonance imaging PET MRI	Whole body Pelvis Kidney Bladder Prostate	FDG Choline Acetate
Glossary of terms not to be used (descending order based on use in current guidelines)	PET/MRI PET-MRI		fluoro deoxy glucose ¹⁸ F-choline ¹¹ C-acetate ¹⁸ F-acetate Other

¹⁸F-FDG-PET = ¹⁸fluorine-fluorodeoxyglucose positron emission tomography; CT = computed tomography;

FDG = fluorodeoxyglucose; MRI = magnetic resonance imaging; PET = positron emission tomography.

Example: "PET CT, Abdomen, ¹¹C- choline".

Table 7: Taxonomic classification of radiographs

	Root Name	Anatomic extent	Contrast/phases	Combinations/fusions
Accepted standard	Scintigraphy	Bone Kidney Testis Bladder	99m Technetium DMSA MAG3 DTPA	SPECT
Glossary of terms less widely acceptable (descending order based on use in current guidelines)	Radionuclide scintigraphy Nuclear scintigraphy Radiographic scintigraphy Isotope scintigraphy Radioisotope scintigraphy	Bone scan Bone scintigraphy Renal scintigraphy Renal cortical scintigraphy Isotope renogram Isotope renography Scrotum scintigraphy Scintigraphy of the testis Radioisotope cystography	Dimercaptosuccinic acid Mercaptuacetyltriglycine 3 Captopril scintigraphy	

99mTc = 99m technetium; DMSA = dimercaptosuccinic acid; MAG3 = mercaptuacetyltriglycine 3;

SPECT = single-photon emission computed tomography.

Example: "Scintigraphy, Bone, 99mTc".

4. DISCUSSION

4.1. Rationale for advocating the use of a unified nomenclature

In our review of the terminology used for imaging studies in clinical urologic practice, research, and publication, we found that terms used for the same studies were not uniform (Supplementary Tables 1-3). We found that there is no standardised or recommended terminology for these imaging studies. There are more general, ongoing efforts to standardise the different vocabularies used in health care.

The Unified Medical Language System (UMLS) [10] developed by the US National Library of Medicine is a set of files and software that link the major international terminologies into a common structure, allowing for efficient translation and interoperability. The UMLS currently includes vocabularies from about 140 different sources that can be used for the exchange of information.

The Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT) [11] is a reference terminology standard available through the UMLS consisting of concepts and terms and the interrelationships between them. The Health Terminology Standards Development Organisation is responsible for promoting the international adoption of SNOMED CT. It standardises the way health care terminology and data are recorded and aims to facilitate the coding, retrieval, analysis, aggregation, indexing, and exchange of clinical information across different health care entities. SNOMED CT was designed for use in software applications to represent clinically relevant information in a reliable and reproducible manner.

In a similar way, different professional groups have adopted varying terminology for similar imaging investigations. Our ability to communicate effectively across medical and scientific disciplines may be hindered by inconsistent use or inadvertent misinterpretation of commonly used abbreviations and acronyms. These terminology variations are evident across different health care systems in different countries and across individual disciplines of clinical and scientific interest.

There are a variety of abbreviations and synonyms for similar investigations, with overlapping definitions that can potentially confuse or misdirect clinicians and researchers (Supplementary Tables 1-3). The language of medicine is complex, and there is a justifiable need to avoid undue repetition and offer clarity to researchers and clinical specialists. Many abbreviations and acronyms that are readily understood within different professional disciplines may not be easily extrapolated to other areas of medical, and specifically urologic, practice.

The advent of the digital era in imaging has added a further layer of complexity to the terminology used for imaging procedures. The requirements of various digital systems to code and file huge volumes of imaging data has prompted the development of additional abbreviations and synonyms to organise and search for data within and between digital networks. Within these coding systems, individual studies are represented by specific identifiers, which are usually a combination of characters (letters and/or numbers) that have no meaning in themselves. This coded representation is then used in place of the natural language description of the concept for further computer or human processing. Standardised clinical vocabularies also generally include a coding system. An example of a coded system is MEDLINE's Medical Subject Headings [12].

Different professional groups (e.g., radiologists, urologists, health care providers) have ad hoc lists that have been adopted and incrementally amended in recent years. Large international databases such as

the Cochrane Library [13] and Medline [14] have guidelines for the use of abbreviations and acronyms without being prescriptive or exclusive. The Cochrane Library, for example, advises using abbreviations and acronyms only if they are widely known and states that not using them “would make literature reading tedious” [13].

4.2. Guidelines

Panels charged with writing clinical guidelines must evaluate the existing literature regarding medical practice and make judgments, first, about the quality of the data and, next, about the clinical effectiveness of the procedure, the risks and harms associated with the procedure, and the costs of the procedure.

Medical imaging is a complex technological procedure with many variables that affect efficacy, risk, and cost. It is difficult to evaluate the quality of the data when multiple terms describe the same imaging procedure and imaging procedures that share a common name but have vastly different operating characteristics (e.g., radiation dose, number of exposures).

Evaluations of existing guidelines from the EAU, the AUA, and the ACR have demonstrated wide variability in terms associated with imaging. We have attempted to define the range of terms within the existing guidelines and then proposed a strategy for naming these imaging studies. The proposed strategy should improve the ability to compare outcome data using similar methodologies and ultimately will encourage the use of consistent terminology when constructing new guidelines [15].

In an effort to unify the terminology used in the imaging of urologic conditions, this EAU Imaging Panel compiled a list of terms commonly used in clinical and investigative urology. The Panel focused on terms most relevant to urology. Not included within the scope of this document are more general terms related to the details of imaging. These were considered to be already well understood and documented in the literature of their respective fields. Finally, terms that were considered interchangeable without being ambiguous or requiring further clarification were not considered for this document.

5. CONCLUSIONS

The current list will form the basis for further discussion, development, and enhancement. The Expert Panel would like to stress that it has incorporated the most widely used terms across different specialties, avoiding any subjective selection of a term and aiming for objective selection of the most commonly used term for an imaging technique. Despite this, the proposed list (especially the glossary) is probably not complete. Consequently, the resulting list is not all-inclusive or comprehensive.

The proposed terminology is intended to promote unified nomenclature in both clinical and research settings. It is not intended to be used for administrative and billing purposes. Different Health Care Administrative systems already have different agreed terminologies based on individual requirements, and our tables are not intended to replace these.

It is anticipated that by adopting such a standardised terminology, all professional disciplines involved in the field of urologic imaging will benefit from better communication across specialties.

In particular, for those involved in research, unified terminology should enhance the yield of evidence from literature searches and thus help promote the dissemination of findings as different professional groups publish within their own literature bases using commonly agreed terminology.

5.1 Appendices

Appendix A. Practical points

Details should be carefully noted, for example, consistency of punctuation is essential so that the term is *IVU* and not *I.V.U.* Nonspecific terms such as *plain films* should not be used. It may generally be helpful to write the name of the abbreviation or acronym in full, immediately followed by the abbreviated version or acronym in brackets: *computed tomography (CT)*. A list of the most commonly used terms and abbreviations can be found online (<http://www.uroweb.org/guidelines/eau-standardised-medical-terminology-for-urologic-imaging/>).

Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at: Loch T, et al. EAU Standardised Medical Terminology for Urologic Imaging: A Taxonomic Approach. *Eur Urol* (2015), <http://dx.doi.org/10.1016/j.eururo.2014.08.014> Reprinted with permission by Elsevier®.

6. ACKNOWLEDGMENT STATEMENT

This document was externally peer reviewed by representatives from several organisations (National Institute of Clinical Excellence, the European Society of Urologic Imaging, ad hoc panel members of the American Urological Association and the American College of Radiology) as well as the current chairmen of the European Association of Urology (EAU) guideline panels.

This publication is the first approach addressing the issue of imaging terminology by the EAU Guidelines Office. The authors would like to thank the Guideline Office Board, the Panel Chairman, and the Central Office of the EAU for their constructive support during the process.

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8. CONFLICT OF INTEREST

All members of the EAU Guidelines Ad-hoc guidelines working group on Urological Imaging have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: <http://www.uroweb.org/guidelines/>. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided

ABBREVIATIONS 2015 EDITION

5-ARIs	5-alpha-reductase inhibitors
5-FU	5-fluorouracil
5-HT	5-hydroxytryptamine
AAST	American Association for the Surgery of Trauma
ABP	antibiotic prophylaxis
ABP	acute bacterial prostatitis
ABS-GEC-ESTRO	American Brachytherapy Society and the Groupe Européen de Curiethérapie-European Society of Therapeutic Radiation Oncology
ABU	asymptomatic bacteriuria
AC	adenocarcinoma
ACD-RCC	acquired cystic disease-associated RCC
ACE	angiotensin-converting enzyme
ACKD	acquired cystic kidney disease
ACT	adjustable compression therapy (device)
ACTH	adrenocorticotrophic hormone
AD	autonomic dysreflexia
ADL	activities of daily living
ADPKD	adult dominant polycystic disease
ADT	androgen-deprivation therapy
AFP	alpha-fetoprotein
AGS	adrenogenital syndrome
AHRQ	Agency for Healthcare Research and Quality
AIPE	Arabic Index of Premature Ejaculation
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
AMH	anti-Müllerian hormone
AML	angiomyolipoma
AMPA	amino-methylene-phosphonic acid
APCKD	adult polycystic kidney disease
AR	androgen receptor
ARF	acute renal failure
ARM	anorectal malformation
ART	assisted reproduction technique
ART	adjuvant radiotherapy
AS	active surveillance
ASA	American Society of Anesthesiologists
ASCO	American Society of Clinical Oncology
ASTRO	American Society for Therapeutic Radiology and Oncology
ATP	adenosine triphosphate
AUA	American Urological Association
AUC	area under curve
AUR	acute urinary retention
AUS	artificial urinary sphincter
AVF	arteriovenous fistulae
AVP	arginine vasopressin
BBD	bladder and bowel dysfunction
BC	bladder cancer
BCG	bacillus Calmette-Guérin
BCR	biochemical recurrence
BDFS	biochemical disease-free survival
BDNF	brain-derived neurotrophic factor
BEP	cisplatin, etoposide, bleomycin
BLI	β -lactamase inhibitor
BMD	bone mineral density
BMG	buccal mucosa grafts
BMI	body mass index
BMP	cisplatin, methotrexate and bleomycin
bNED	biochemically no evidence of disease

BOO(l)	bladder outlet obstruction (index)
BPE	benign prostatic enlargement
BPH	benign prostatic hyperplasia
BPO	benign prostatic obstruction
BPS	bladder pain syndrome
BS	bone scan
BSC	best supportive care
BT	bladder training
BT	brachytherapy
BTA	bladder tumour antigen
BTX	botulinum toxin
BTX-A	botulinum toxin A
BUN	blood urea nitrogen
BVM	bleomycin-vincristine-methotrexate
BWT	bladder wall thickness
BXO	balanitis xerotica obliterans
CAB	complete (or maximal or total) androgen blockade
CAD	coronary artery disease
CAD	complete androgen deprivation
CAG	cytosine-adenine-guanine
CAH	congenital adrenal hyperplasia
CaIX	carbonic anhydrase
CaPSURE	Cancer of the Prostate Strategic Urologic Research Endeavour
CAUTIs	catheter-associated urinary tract infections
CBAVD	congenital bilateral absence of the vas deferens
CBT	cognitive behavioural therapy
CCF	Cleveland Clinic Foundation
CCH	clostridium collagenase
CCI	Charlson Comorbidity Index
CF	chronic fatigue
CF	cystic fibrosis
CFS	chronic fatigue syndrome
CFU	colony forming unit
CFTR	cystic fibrosis transmembrane conductance regulator
Cg A	chromogranine A
CGA	comprehensive geriatric assessment
cGMP	cyclic guanosine monophosphate
CGRP	calcitonin gene-related peptide
CHF	congestive heart failure
chRCC	chromophobe renal cell cancer
CI	confidence interval
CIC	clean intermittent catheterisation
CIRS	Cumulative Illness Rating Scale
CIS	carcinoma <i>in situ</i>
CISCA	cisplatin, cyclophosphamide, and adriamycin
CISR-G	cumulative illness score rating-geriatrics
CKD	chronic kidney disease
CM	cisplatin, methotrexate
C _{max}	maximal concentration
CMV	cytomegalovirus
CN	cytoreductive nephrectomy
CNS	central nervous system
COLD	Cryo On-Line Data
CombAT	Combination of Avodart® and Tamsulosin
COPUM	congenital obstructive posterior urethral membrane
CPA	cyproterone acetate
CPP	chronic pelvic pain
CPPS	chronic pelvic pain syndrome
cPSA	complex PSA
CPSI	Chronic Prostatitis Symptom Index

CR	complete response
cRCC	clear cell renal cell cancer
CrCl	calculation of creatinine clearance
CRH	corticotrophin-releasing hormone
CRP	C-reactive protein
CRPC	castration-resistant prostate cancer
CRS	caudal regression syndrome
CRT	conformal radiotherapy
CS	clinical stage
CSAP	cryosurgical ablation of the prostate
CSS	cancer-specific survival
CT	computed tomography
CTC	circulating tumour cells
CTC AE	Common Terminology criteria for Adverse Events
CTU	computed tomography urography
CUETO	Club Urológico Español de Tratamiento Oncológico (Spanish Oncology Group)
CVA	cerebrovascular
CVD	cardiovascular disease
CyA	Cyclosporin A
DAN-PSS	Danish prostate symptom score
DARE	database of abstracts of reviews of effectiveness
DCE	dynamic contrast enhanced
DDAVP	desmopressin
DES	diethylstilbestrol
DFS	disease-free survival
DHT	dihydrotestosterone
DHTST	dihydrotestosterone
DICC	dynamic infusion cavernosometry or cavernosography
DLPP	detrusor leak point pressure
DMSA	dimercaptosuccinic acid
DMSO	dimethyl sulphoxide
DNIC	diffuse noxious inhibitory control
DO	detrusor overactivity
DRE	digital rectal examination
DRG	dorsal root ganglion
DSD	disorders of sex development
DSD	detrusor sphincter dyssynergia
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders IV-Text Revision
DSNB	dynamic sentinel node biopsy
DSS	disease-specific survival
DT	doubling time
DTPA	diethylenetriamine pentaacetate
DWI	diffusion-weighted imaging
DWT	detrusor wall thickness
EAA	European Academy of Andrology
EAU	European Association of Urology
EBL	estimated blood loss
EBM	evidence-based medicine
EBRT	external beam radiation therapy
ECOG	Eastern Cooperative Oncology Group
ED	erectile dysfunction
EEC	extracapsular extension of carcinoma
EF	erectile function
EGFR	epidermal growth factor receptor
eGFR	estimated glomerular filtration rate
EH	excisional haemorrhoidectomy
EHL	electrohydraulic lithotripsy
eLND	extended lymph node dissection
EMA	European Medicines Agency
EMDA	transdermal electromotive drug administration or electromotive drug administration

EMG	electromyography
eNOS	endothelial NOS
EORTC	European Organisation for Research and Treatment of Cancer
EORTC-GUCG	European Organisation for Research and Treatment of Cancer - Genito-Urinary Cancer Group
EP	etoposide, cisplatin
EPC	Early Prostate Cancer Trialists' Group
EPS	expressed prostatic secretion
ePTFE	expanded polytetrafluoroethylene
EQ	euro quality
ER	extended release
ERSPC	European Randomized Screening for Prostate Cancer
ES	electrical stimulation
ESR	erythrocyte sedimentation rate
ESSIC	International Society for the Study of BPS
ESWT	extracorporeal shock wave treatment
EUCAST	European Committee for Antimicrobial Susceptibility Testing
FACT	Functional Assessment of Cancer Therapy
FACT-P	Functional Assessment of Cancer Therapy-prostate
FAP	familial amyloidotic polyneuropathy
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FDG-PET	fluorodeoxyglucose-positron emission tomography
FISH	fluorescent <i>in situ</i> hybridisation
FIT	functional incidental training
FM	fibromyalgia
FNA	fine-needle aspiration
FNAB	fine-needle aspiration biopsy
FNAC	fine needle aspiration cytology
FS2S	first stage of two-stage (implantation of sacral neuromodulator)
FSH	follicle stimulating hormone
FSRT	fractionated stereotactic radiotherapy
FSSs	functional somatic syndromes
FVC	frequency volume chart
G6PD	glucose-6-phosphate dehydrogenase
GABA	gamma-aminobutyric acid
GAG	glycosaminoglycan
GAQ	General Assessment Questionnaire
GC	gemcitabine, cisplatin
G-CSF	granulocyte colony stimulating factor
GCT	germ cell tumour
GETUG	Groupe d'Etude des Tumeurs Uro-Génitales
GFR	glomerular filtration rate
GHQ	general health questionnaire
GI	gastrointestinal
GITS	gastrointestinal therapeutic system
GnRH	gonadotropin-releasing hormone
GR	grade of recommendation
GREAT	G-protein-coupled receptor affecting testis descent
GS	gleason score
GSSAB	Global Study of Sexual Attitudes and Behaviors
GU	genitourinary
GWAS	genome-wide association studies
HAD scale	hospital anxiety and depression scale
HAL	hexaminolaevulinic acid
HBO	hyperbaric oxygen
hCG	human chorionic gonadotropin
HD-MVAC	high-dose intensity MVAC
HDR	high-dose rate
HGPIN	high grade prostatic intraepithelial neoplasia

HIF	hypoxia inducible factor
HIFU	high-intensity focused ultrasound
HIV	human immunodeficiency virus
HLRCC	hereditary leiomyomatosis and renal cell cancer
HMG	human menopausal gonadotropin
HNPCC	hereditary non-polyposis colorectal carcinoma
Ho:YAG	holmium:yttrium-aluminium-garnet (laser)
HoLEP	holmium laser enucleation
HoLRP	holmium laser resection of the prostate
HOPE	hypospadias objective penile evaluation
HOSE	hypospadias objective scoring evaluation
HP	hyperprolactinemia
hpf	high-power field
HPLC	high-performance liquid chromatography
HPT	hyperparathyroidism
HPV	human papillomavirus
HR	hazard ratio
HRPC	hormone-refractory prostate cancer
HRQoL	health-related quality of life
HT	hormonal therapy
HUI	health utilities index
IAD	intermittent androgen deprivation
IARC	International Agency for Research on Cancer
IASP	Association for the Study of Pain
IBS	irritable bowel syndrome
IBT	iatrogenic bladder trauma
IC	intermittent catheterisation
ICCS	International Children's Continence Society
ICD-10	International Classification of Diseases-10
ICDB	Interstitial Cystitis Data Base
ICIQ	International Consultation on Incontinence Questionnaire
ICS	International Continence Society
ICSI	interstitial cystitis symptom index
ICSI	intracytoplasmic sperm injection
ICU	intensive care unit
IDSA	Infectious Diseases Society of America
IED	improvised explosive device
IELT	intravaginal ejaculatory latency time
IF	impact factor
IFIS	intra-operative floppy iris syndrome
IGCCCG	International Germ Cell Cancer Collaborative Group
IGCNU	intratubular germ cell neoplasia, unclassified type
IGRT	image-guided radiotherapy
IHH	Isolated hypogonadotrophic hypogonadism
IHH	Idiopathic hypogonadotrophic hypogonadism
IIEF	international index of erectile function
IKCWG	International Kidney Cancer Working Group
IL	interleukin
IMDC	International Metastatic Renal Cancer Database Consortium
IMRT	intensity modulated radiotherapy
INR	international normalised ratio
IPCN	International Prostatitis Collaborative Network
IPD	idiopathic parkinson's disease
IPE I	index of premature ejaculation
IPP	intravesical prostatic protrusion
IPSS	international prostate symptom score
I-QOL	incontinence quality of life
IR	Immediate release
IRS	infrared spectroscopy
IRT	iatrogenic renal trauma

ISSM	International Society for Sexual Medicine
ISSVD	Society for the Study of Vulvovaginal Disease
ISUP	International Society of Urological Pathology
ITGCN	intratubular germ cell neoplasia
ITGCNU	intratubular germ cell neoplasia of unclassified type
ITT	intent-to-treat
IU	international unit
IUGA	International Urogynecological Association
IVC	inferior vena cava
IVF	in vitro fertilisation
IVP	intravenous pyelogram
IVU	intravenous urography
JESS	joint expert speciation system
KHQ	King's health questionnaire
KUB	kidney ureter bladder
LAD	lymphadenectomy
LARP	laparoscopic radical prostatectomy
LDH	lactate dehydrogenase
LDR	low-dose rate
LE	level of evidence
LESS	laparoendoscopic single-site
LET	linear energy transfer
LH	luteinising hormone
LHRH	luteinising hormone releasing hormone
LMNL	lower motor neuron lesion
LN	lymph node
LND	lymph node dissection
LPN	laparoscopic partial nephrectomy
LPP	leak point pressure
LPP	laparoscopic pyeloplasty
LRN	laparoscopic radical nephrectomy
LRP	laparoscopic radical prostatectomy
LUT	lower urinary tract
LUTD	lower urinary tract dysfunction
LUTS	lower urinary tract symptoms
LVD	left ventricular dysfunction
MAB	maximal androgen blockade
MAG-3	mercaptoacethylglycine
MAGI	male accessory gland infection
MAPP	Multi-disciplinary Approach to the study of chronic Pelvic Pain research
MAR	mixed antiglobulin reaction
MBD	metastatic bone disease
M-CAVI	compared methotrexate/carboplatin/vinblastine
MESA	microsurgical epididymal sperm aspiration
MeSH	Medical Subject Headings
MET	metabolic equivalent system
MET	medical expulsive therapy
MFS	metastasis-free survival
MFSR	metastasis-free survival rate
MI	myocardial infarction
MIBC	muscle-invasive bladder cancer
mLND	modified inguinal lymphadenectomy
MMAS	Massachusetts Male Aging Study
MMC	mitomycin
MMC	myelomeningocele
MPA	medroxyprogesterone acetate
mpMRI	multiparametric magnetic resonance imaging
MPR	medication possession rate (drug adherence)
MRA	MRI biphasic angiography
MRC	Medical Research Council

MRI	magnetic resonance imaging
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
MRU	magnetic resonance urography
MS	multiple sclerosis
MSHQ-EJD	Male Sexual Health Questionnaire Ejaculatory Dysfunction
MSI	microsatellite instability
MSKCC	Memorial Sloan-Kettering Cancer Centre
MSU	mid-stream sample of urine
MTOPS	medical therapy of prostatic symptoms
MTS	cell proliferation assay
MUI	mixed urinary incontinence
MVA	methotrexate, vinblastine, adriamycin
MVAC	methotrexate, vinblastine, adriamycin and cisplatin
NAION	non-arteritic anterior ischemic optic neuropathy
NBSs	non-bladder syndromes
NC	nephrocalcinosis
NCCLS	National Committee for Clinical Laboratory Standards
NCCN	National Comprehensive Cancer Network
NCCT	non-contrast enhanced computed tomography
NCIC	National Cancer Institute of Canada
NCT-CTC	National Cancer Institute Common Toxicity Criteria
Nd:YAG	neodymium:yttrium-aluminum-garnet
NDO	neurogenic detrusor overactivity
NDSD	neurogenic detrusor-sphincter dysfunction
NGF	nerve growth factor
NHLS	National Health and Social Life Survey
NHT	neoadjuvant hormonal therapy
NICE	National Institute for Health and Clinical Excellence
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
NIH-CPSI	NIH Prostatitis Symptom Index
NLUTD	neurogenic lower urinary tract dysfunction
NMDA	N-methyl-D-aspartate
NMIBC	non-muscle-invasive bladder cancer
nNOS	neuronal nitric oxide synthase
NNT	number needed to treat
NO	nitric oxide
NOA	non-obstructive azoospermia
NOS	NO synthases
NPTR	nocturnal penile tumescence and rigidity
NPV	negative predictive value
NRS	nonrandomised studies
NS	nerve sparing
NSAA	non-steroidal anti-androgen
NSAIDs	non-steroidal anti-inflammatory drugs
NSF	nephrogenic systemic fibrosis
NSGCT	non-seminomatous germ cell tumour
NSQIP	National Surgical Quality Improvement Programme
NSRP	nerve-sparing radical prostatectomy
NVB	neurovascular bundle
NYHA	New York Heart Association
O/E	ratio of observed versus expected
OA	obstructive azoospermia
OAB	overactive bladder
OAT	oligo-astheno-teratozoospermia [syndrome]
OCAS	oral controlled absorption system
ODT	orally disintegrating tablet
ORC	open radical cystectomy
ORP	open retropubic radical prostatectomy
ORR	overall response rate

OS	overall survival
OSA	obstructive sleep apnoea
PA	para-aortic
PADUA	Preoperative Aspects and Dimensions Used for an Anatomical classification of renal tumours
PAG	periaqueductal grey
PCa	prostate cancer
PCN	percutaneous nephrostomy
PCNL	percutaneous nephrolithotomy
PCOS	prostate cancer outcomes study
PCP	<i>Pneumocystis carinii</i> pneumonia
PCPT	prostate cancer prevention trial
PCPTRC	prostate cancer prevention trial risk calculator
pCR	pathologically complete remissions
PCWG	prostate cancer working group
PD	Peyronie's disease
PD	Parkinson's disease
PD-1L	programmed death-1 ligand
PDD	photodynamic diagnosis
PDE5i	phosphodiesterase type 5 inhibitors
PDGF	platelet-derived growth factor
PDQ	Peyronie's disease-specific questionnaire
PE	premature ejaculation
PEDT	premature ejaculation diagnostic tool
PEI	cisplatin, etoposide, ifosfamide
PEP	premature ejaculation profile
PEPA	premature ejaculation prevalence and attitudes
PESA	percutaneous epididymal sperm aspiration
PET	positron emission tomography
PF	cisplatin and fluorouracil
PFMT	pelvic floor muscle training
PFS	pressure flow study
PFS	progression-free survival
PGD	pre-implantation genetic diagnosis
PH	primary hyperoxaluria
PHI	prostate health index
PICO	Population, Intervention, Comparison, Outcome
PID	pelvic inflammatory disease
PIN	prostatic intraepithelial neoplasia
PIRADS	prostate imaging reporting and data system
PIVOT	Prostate Cancer Intervention Versus Observation Trial
PLAP	placental alkaline phosphatase
PLCO	Prostate, Lung, Colorectal and Ovary
PLND	pelvic lymph node dissection
PMB	prostate mapping biopsy
PN	partial nephrectomy
PNE	percutaneous nerve evaluation
PNH	perinephritic hematoma
PNL	percutaneous litholapaxy
PNL	percutaneous nephrolithotomy
PNS	pubodendal nerve stimulation
POP	pelvic organ prolapse
POSEI	postoperative stress urinary incontinence
PPI	post-prostatectomy urinary incontinence
PPMT	pre-post-massage test
PPS	prostate pain syndrome
P-PTNS	percutaneous posterior tibial nerve stimulation
PPV	positive predictive value
pRCC	papillar renal cell cancer
PRISMA	preferred reporting items for systematic reviews and meta-analyses

PRO	patient reported outcome
PROMS	patient reported outcome measures
PS	performance status
PS	pathological stage
PSA	prostate specific antigen
PSADT	PSA doubling time
PSAV	PSA velocity
PSM	positive surgical margin
PTEN	phosphatase and tensin homolog
PTH	parathyroid hormone
PTNS	posterior tibial nerve stimulation
PTNS	percutaneous tibial nerve stimulation
PTT	partial thrombolastin time
PUNLMP	papillary urothelial neoplasms of low malignant potential
PUV	posterior urethral valves
PVB	cisplatin, vinblastine, bleomycin
PVR	post-voiding residual
PWS	Prader-Willi syndrome
QALY	quality-adjusted life year
Q_{ave}	average urinary flow rate
Q_{max}	maximum urinary flow rate
QoI	quality of life
QUALYs	quality-of-life-adjusted gain in life years
RALC	robot-assisted laparoscopic cystectomy
RALP	robot-assisted laparoscopic prostatectomy
RALRP	robot-assisted laparoscopic radical prostatectomy
RALS	robot-assisted laparoscopic sacrocolpopexy
RANKL	receptor activator of nuclear factor KB ligand
RARC	robot-assisted radical cystectomy
RARP	robot-assisted radical prostatectomy
RAT	renal angiomyomatous tumour
RBL	rubber band ligation
RC	radical cystectomy
RCC	renal cell cancer
RCT	randomised controlled trial
RECIST	Response Evaluation Criteria In Solid Tumours
REMS	Risk Evaluation and Mitigation Strategy
REST	renal epithelial and stromal tumours
RFA	radiofrequency ablation
RFS	recurrence-free survival
RIRS	retrograde renal surgery
RLPP	robot-assisted laparoscopic pyeloplasty
RN	reflux nephropathy
RN	radical nephrectomy
RNC	radionuclide cystography
RNU	radical nephroureterectomy
RP	radical prostatectomy
RPA	recursive partitioning analysis
RPLND	retroperitoneal lymph node dissection
RPN	robotic partial nephrectomy
RR	recurrent stones
RR	relative risk
RRN	robotic radical nephrectomy
RRP	radical retropubic prostatectomy
RT	radiotherapy
RTA	renal tubular acidosis
RTOG	Radiation Therapy Oncology Group
RTX	Resiniferatoxin
SAE	selective arterial embolisation
SARS	sacral anterior root stimulation

SAT	severe acute toxicity
SBRT	stereotactic body radiotherapy
SCC	squamous cell carcinoma
SCI	spinal cord injury
SDH	succinate dehydrogenase
SEER	surveillance, Epidemiology and End Results
SELECT	selenium and vitamin E cancer prevention trial
SEP	sexual encounter profile
SF	short form
SFR	stone free rate
SGA	standardised geriatric assessment
SHBG	sex hormone binding globulin
SIGN	Scottish Intercollegiate Guideline Network
SIOG	International Society of Geriatric Oncology
SIRS	systemic inflammatory response syndrome
SITUS	single-incision triangulated umbilical surgery
SMX	sulphamethoxazole
SNB	sentinel node biopsy
SNM	sacral neuromodulation
SPCG-4	Scandinavian Prostate Cancer Group Study Number 4
SR	systematic review
SR	sustained release
SRE	skeletal-related events
SRS	stereotactic radiosurgery
SRT	salvage radiotherapy
SRX	Sex region of the Y chromosome
SSI	surgical site infection
SSRI	selective serotonin reuptake inhibitor
SSRIs	selective serotonin reuptake inhibitors
STD	sexually transmitted disease
SUI	stress urinary incontinence
SV	seminal vesicle
SVI	seminal vesicle invasion
SWENOTECA	Swedish-Norwegian Testicular Cancer Project
SWL	shock wave lithotripsy
SWOG	Southwest Oncology Group
$t_{1/2}$	elimination half-life
TBT-O	transobturator tension-free vaginal tape
TC	testicular cancer
TC99m	technetium 99m
TCC	transitional cell carcinoma
Tc-MAG3 (99m)	technetium 99m mercaptoacetyltriglycine (MAG3)
TCS	testicular cancer survivor
TDS	testicular dysgenesis syndrome
TDS	transdermal delivery system
TEFNA	testicular fine-needle aspiration
TEMPE	topical eutectic mixture for premature ejaculation
TENS	transcutaneous electrical nerve stimulation
TESE	testicular sperm extraction
TGCT	testicular germ cell tumour
ThuLEP	tm:YAG laser enucleation of the prostate
ThuVaP	tm:YAG vaporisation of the prostate
ThuVaRP	tm:YAG vaporessection
ThuVEP	tm:YAG vapoenucleation
TIN	testicular intra-epithelial neoplasia
TIP	paclitaxel, cisplatin, and ifosfamide
TIP	tubularised incised plate urethroplasty
TIP	paclitaxel, ifosfamide, cisplatin
TK	tyrosine kinase
TKI	tyrosine kinase inhibitors

TM	testicular microlithiasis
T _{max}	time to maximum plasma concentration
TMP	trimethoprim
TNF	tumour necrosis factor
TNM	Tumour, Node, Metastasis (classification)
TPA	tissue plasminogen activator
T-PTNS	transcutaneous posterior tibial nerve stimulation
TRCC	MIT translocation renal cell carcinomas
TROG	Trans-Tasman Oncology Group
TRT	testosterone replacement therapy
TRUS	transrectal ultrasound
TS	testosterone supplementation
TS	tuberous sclerosis
TST	testosterone
TT	tumour thrombus
TTP	time to progression
TUIP	transurethral incision of the prostate
TUMT	transurethral microwave therapy
TUNA	transurethral needle ablation
TUR	transurethral resection
TURB	transurethral resection of the bladder
TURED	transurethral resection of the ejaculatory ducts
TURP	transurethral resection of the prostate
TVT	tension-free vaginal tape
TVTS	tension-free vaginal tape secure
TWOC	trial without catheter
UAB	underactive bladder
UC	urothelial carcinomas
UCB	urothelial carcinoma of the bladder
UDS	urodynamic study
UEBW	ultrasound-estimated bladder weight
UI	urinary incontinence
UICC	Union for International Cancer Control
ULN	upper limit of normal
UMNL	upper motor neuron lesion
UPJ	ureteropelvic junction
URR	urethral reflectometry
URS	ureterorenoscopy
US	ultrasound
US PSA	ultra-sensitive PSA
USPIOs	ultra-small particles of iron oxide
UTI	urinary tract infection
UTUC	upper tract urothelial carcinoma
UUI	urgency urinary incontinence
UUT	upper urinary tract
uUTI	uncomplicated urinary tract infection
UVJ	ureterovesical junction
VA	US Veterans Administration
VACURG	Veterans Administration Co-operative Urological Research Group
VAPS	visual analogue pain scale
VAS	visual analogue scale
VB1	first-voided urine
VB2	mid-stream urine
VB3	voided bladder urine-3
VBM	vinblastine, bleomycin, methotrexate
VC	vena cava
VCD	vacuum constriction devices
VCU	voiding cystourethrogram
VCUG	voiding cystourethrogram
VED	vacuum erection devices

VEGF	vascular endothelial growth factor
VeIP	vinblastine, ifosfamide, cisplatin
VHL	Von Hippel-Lindau
VIP	vasointestinal peptide
VIP (VP-16)	etoposide, ifosfamide, cisplatin
VR	vesicorenal reflux
VTT	venous tumour thrombus
VUR	vesicoureteric reflux
VUS	voiding urosonography
WBC	white blood cell
WBRT	whole brain radiotherapy
WHO	World Health Organization
WI	weighted imaging
WIT	warm ischaemia time
WW	watchful waiting
XRD	X-ray diffraction
ZA	zoledronic acid

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