Guidelines on

Muscle-invasive and Metastatic Bladder Cancer

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TABLE OF CONTENTS PAGE

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 it's 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***

Mandatory evaluations
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);
Optional evaluations
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

7.4.6 *Conclusions and recommendations for radical cystectomy and urinary diversion*

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

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

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***

Mandatory evaluations
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).
Optional evaluations
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 *in situ*: "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 $Ƶ = 0.983^{Y}$ (where Ƶ 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 chemonaïve 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 ≥ 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 supravesical 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 neobladdder)
		Ureteral catheter (UC) obstruction	5cc saline UC injection to avoid the obstruction Increase volume infusion to increase dieresis
		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'	*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.*		

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].

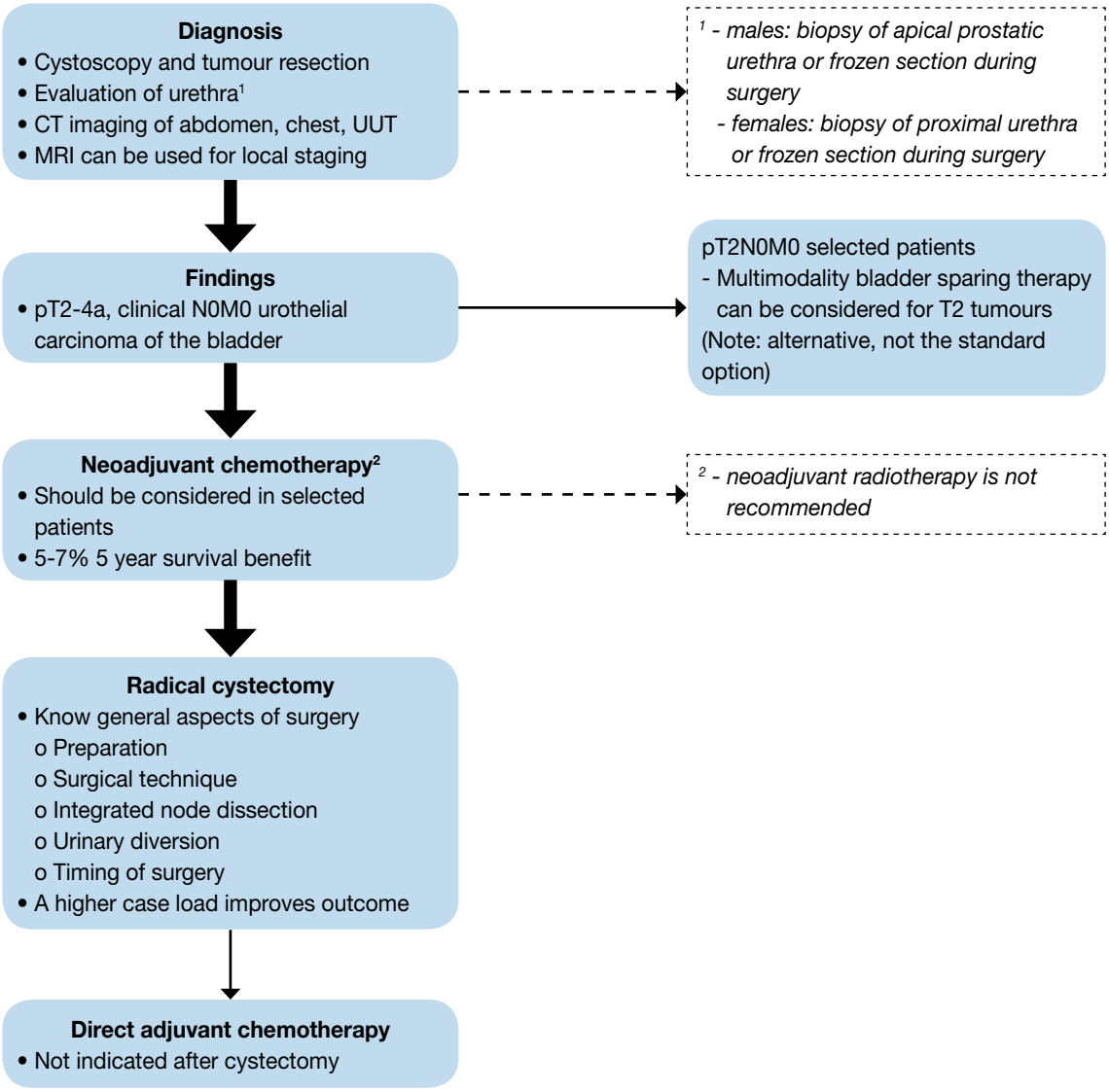
7.4.7 *Conclusions and recommendations for radical cystectomy and urinary diversion*

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 ≤ 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-KB 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 ≥ 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
First-line treatment for fit patients:	
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
First-line treatment in patients ineligible (unfit) for cisplatin:	
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
Second-line treatment:	
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***

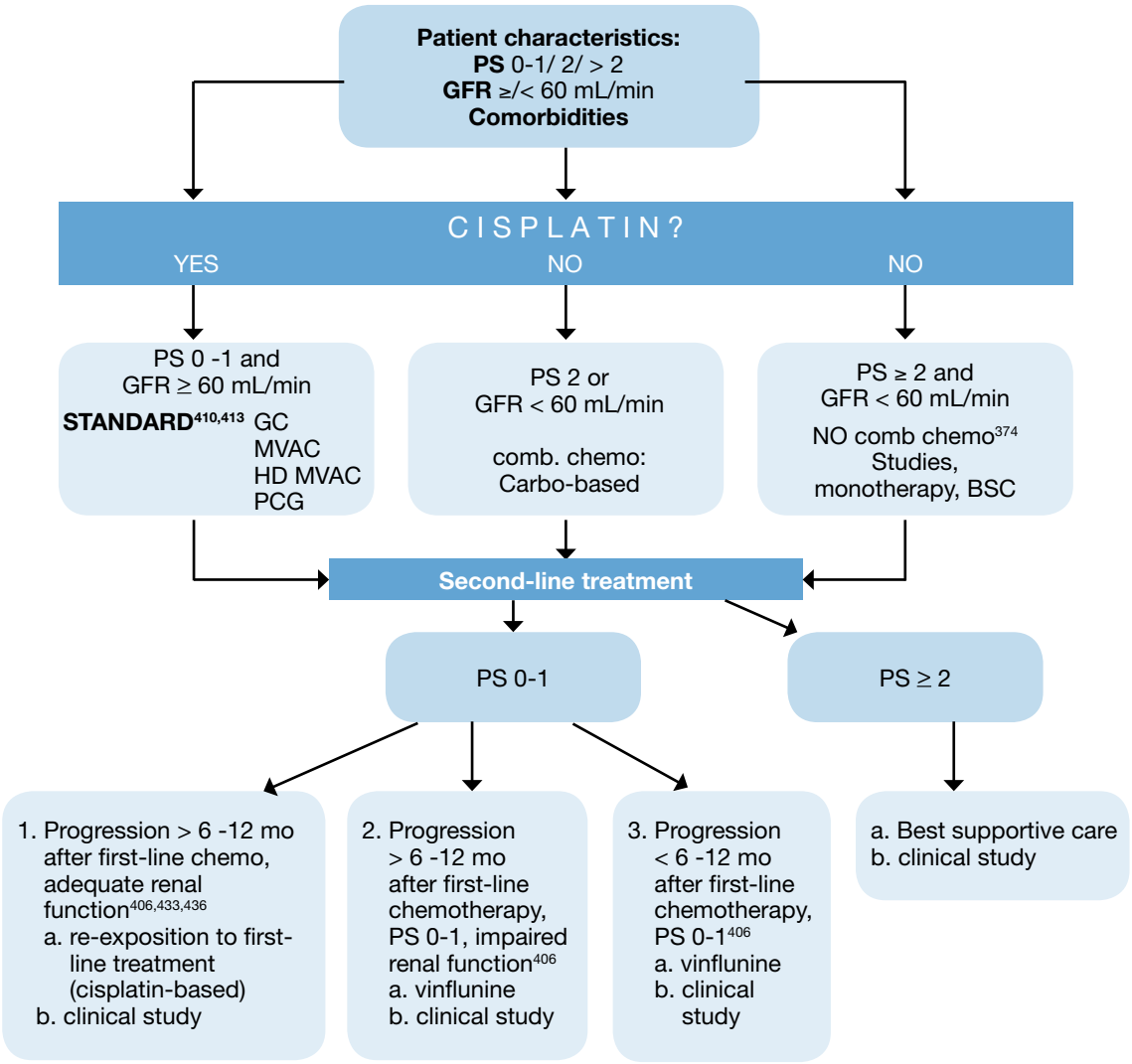
Modest disease control rates, with sporadic marked responses, in some patients with urothelial BC have led to the investigation of biomarkers for assessment of postoperative prognosis and the potential value of perioperative chemotherapy, and as predictors of response to chemotherapy or its monitoring. 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 = glomular 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 asymptomatically 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].

9. REFERENCES

1. Rouprêt M, Zigeuner R, Palou J, et al; members of the EAU Guidelines Panel on Non-muscle-invasive bladder cancer. Guidelines on upper urinary tract urothelial cell carcinoma. Edition presented at the EAU Annual Congress Madrid 2015. ISBN 978-90-79754- 80-9.
2. Babjuk M, Burger M, Zigeuner R, et al; members of the EAU Guidelines Panel on Non-muscle-invasive bladder cancer. Guidelines on Non-muscle-invasive bladder cancer (Ta, T1 and CIS). Edition presented at the EAU Annual Congress Madrid 2015. ISBN 978-90-79754- 80-9.
3. Gakis G, Witjes JA, Compérat E, et al; members of the EAU Guidelines Panel on Muscle-invasive and Metastatic Bladder Cancer. Guidelines on primary urethral carcinoma. Edition presented at the EAU Annual Congress Madrid 2015. ISBN 978-90-79754- 80-9.
4. Witjes JA, Compérat E, Cowan NC, et al. EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer: Summary of the 2013 Guidelines. Eur Urol 2014 Apr;65(4):778-92.
5. Bruins HM, Veskimae E, Hernandez V, et al. The impact of the extent of lymphadenectomy on oncologic outcomes in patients undergoing radical cystectomy for bladder cancer: a systematic review. Eur Urol 2014 Dec;66(6):1065-77.
6. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013 Jan;63:11-30.
7. Ploeg M, Aben KK, Kiemeney LA. The present and future burden of urinary bladder cancer in the world. World J Urol 2009 Jun;27(3):289-93.
8. Abdollah F, Gandaglia G, Thuret R, et al. Incidence, survival and mortality rates of stage-specific bladder cancer in United States: a trend analysis. Cancer Epidemiol 2013 Jun;37(3):219-25.
9. Freedman ND, Silverman DT, Hollenbeck AR, et al. Association between smoking and risk of bladder cancer among men and women. JAMA 2011 Aug;306(7):737-45.
10. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Tobacco smoke and involuntary smoking. IARC Monogr Eval Carcinog Risks Hum 2004;83:1-1438.
11. Brennan P, Bogillot O, Cordier S, et al. Cigarette smoking and bladder cancer in men: a pooled analysis of 11 case-control studies. Int J Cancer 2000 Apr;86(2):289-94.
12. Gandini S, Botteri E, Iodice S, et al. Tobacco smoking and cancer: a meta-analysis. Int J Cancer 2008 Jan; 122(1):155-64.
13. Pashos CL, Botteman MF, Laskin BL, et al. Bladder cancer: epidemiology, diagnosis, and management. Cancer Pract 2002 Nov-Dec;10(6):311-22.
14. Harling M, Schablon A, Schedlbauer G, et al. Bladder Cancer among hairdressers: a meta-analysis. Occup Environ Med 2010 May;67(5):351-8.
15. Weistenhofer W, Blaszkewicz M, Bolt HM, et al. N-acetyltransferase-2 and medical history in bladder cancer cases with a suspected occupational disease (BK 1301) in Germany. J Toxicol Environ Health A2008;71(13-14): 906-10.
16. Burger M, Catto JW, Dalbagni G, et al. Epidemiology and risk factors of urothelial bladder cancer. Eur Urol 2013 Feb;63(2):234-41.
17. Rushton L, Bagga S, Bevan R, et al. Occupation and cancer in Britain. Br J Cancer 2010 Apr;102:1428-37.
18. Chrouser K, Leibovich B, Bergstralh E, et al. Bladder cancer risk following primary and adjuvant external beam radiation for prostate cancer. J Urol 2006 Jul;174(1):107-10.
19. Nieder AM, Porter MP, Soloway MS. Radiation therapy for prostate cancer increases subsequent risk of bladder and rectal cancer: a population based cohort study. J Urol 2008 Nov;180(5):2005-9; discussion 2009-10.
20. Zelefsky MJ, Housman DM, Pei X, et al. Incidence of secondary cancer development after high-dose intensity-modulated radiotherapy and image-guided brachytherapy for the treatment of localized prostate cancer. Int J Radiat Oncol Biol Phys 2012 Jul;83(3):953-9.
21. Zamora-Ros R, Sacerdote C, Ricceri F, et al. Flavonoid and lignan intake in relation to bladder cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Br J Cancer 2014 Oct;111(9): 1870-80.
22. [No authors listed] Schistosomes, liver flukes and Helicobacter pylori. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon, 7-14 June, 1994. IARC Monogr Eval Carcinog Risks Hum 1994;61:1-241.
23. Gouda I, Mokhtar N, Bilal D, et al. Bilharziasis and bladder cancer: a time trend analysis of 9843 patients. J Egypt Natl Canc Inst 2007 Jun;19(2):158-62.

24. Salem HK, Mahfouz S. Changing Patterns (Age, Incidence, and Pathologic Types) of schistosoma-associated Bladder Cancer in Egypt in the Past Decade. Urology 2012 Feb;79(2):379-83.
25. Pelucchi C, Bosetti C, Negri E, et al. Mechanisms of disease: The epidemiology of bladder cancer. Nat Clin Pract Urol 2006 Jun;3(6):327-40.
26. Fajkovic H, Halpern JA, Cha EK, et al. Impact of gender on bladder cancer incidence, staging, and prognosis. World J Urol 2011 Aug;29(4):457-63.
27. Cárdenas-Turanzas M, Cooksley C, Pettaway CA, et al. Comparative outcomes of bladder cancer. Obstet Gynecol 2006 Jul;108(1):169-75.
28. McGrath M, Michaud DS, De Vivo I. Hormonal and reproductive factors and the risk of bladder Cancer in women. Am J Epidemiol 2006 Feb;163(3):236-44.
29. Scosyrev E, Noyes K, Feng C, et al. Sex and racial differences in bladder cancer presentation and mortality in the US. Cancer 2009 Jan;115(1):68-74.
30. Stenzl A. Words of wisdom. Re: sex and racial differences in bladder cancer presentation and mortality in the US. Eur Urol 2010 Apr;57(4):729.
31. Otto W, May M, Fritsche HM, et al. Analysis of sex differences in cancer-specific survival and perioperative mortality following radical cystectomy: results of a large German multicenter study of nearly 2500 patients with urothelial carcinoma of the bladder. Gend Med 2012 Dec;9(6):481-9.
32. Murta-Nascimento C, Silverman DT, Kogevinas M, et al. Risk of bladder cancer associated with family history of cancer: do low-penetrance polymorphisms account for the increase in risk? Cancer Epidemiol Biomarkers Prev 2007 Aug;16(8):1595-600.
33. Rothman N, Garcia-Closas M, Chatterjee N, et al. A multi-stage genome-wide association study of bladder cancer identifies multiple susceptibility loci. Nat Genet 2010 Nov;42(11): 978-84.
34. Kiemeney LA, Thorlacius S, Sulem P, et al. Sequence variant at 8q24 confers susceptibility to urinary bladder cancer. Nat Genet 2008 Nov; 40(11):1307-12.
35. Garcia-Closas M, Rothman N, Figueroa JD, et al. Common genetic polymorphisms modify the effect of smoking on absolute risk of bladder cancer. Cancer Res 2013 Apr;73(7):2211-20.
36. Stenzl A. Current concepts for urinary diversion in women. Eur Urol (EAU Update Series 1);2003:91-9.
37. Varinot J, Camparo P, Roupret M, et al. Full analysis of the prostatic urethra at the time of radical cystoprostatectomy for bladder cancer: impact on final disease stage. Virchows Arch 2009 Nov;455(5):449-53.
38. Hansel DE, Amin MB, Comperat E, et al. A contemporary update on pathology standards for bladder cancer: transurethral resection and radical cystectomy specimens. Eur Urol 2013 Feb;63(2):321-32.
39. Herr HW. Pathologic evaluation of radical cystectomy specimens. Cancer 2002 Aug;95(3):668-9.
40. Neuzillet Y, Soulie M, Larre S, et al. Positive surgical margins and their locations in specimens are adverse prognosis features after radical cystectomy in non-metastatic carcinoma invading bladder muscle: results from a nationwide case-control study. BJU Int 2013 Jun;111(8):1253-60.
41. Baltaci S, Adsan O, Ugurlu O, et al. Reliability of frozen section examination of obturator lymph nodes and impact on lymph node dissection borders during radical cystectomy: results of a prospective multicentre study by the Turkish Society of Urooncology. BJU Int 2011 Feb;107(4):547-53.
42. Jimenez RE, Gheiler E, Oskanian P, et al. Grading the invasive component of urothelial carcinoma of the bladder and its relationship with progression free survival. Am J Surg Pathol 2000 Jul;24(7):980-7.
43. Kapur P, Lotan Y, King E, et al. Primary adenocarcinoma of the urinary bladder: value of cell cycle biomarkers. Am J Clin Pathol 2011 Jun;135(6):822-30.
44. Ploeg M, Aben KK, Hulsbergen-van de Kaa CA, et al. Clinical epidemiology of nonurothelial bladder cancer: analysis of the Netherlands Cancer Registry. J Urol 2010 Mar;183(3):915-20.
45. Wasco MJ, Daignault S, Bradley D, et al. Nested variant of urothelial carcinoma: a clinicopathologic and immunohistochemical study of 30 pure and mixed cases. Hum Pathol 2010 Feb;41(2):163-71.
46. Mukesh M, Cook N, Hollingdale AE, et al. Small cell carcinoma of the urinary bladder: a 15-year retrospective review of treatment and survival in the Anglian Cancer Network. BJU Int 2009 Mar;103(6):747-52.
47. Leissner J, Koeppen C, Wolf HK. Prognostic significance of vascular and perineural invasion in urothelial bladder cancer treated with radical cystectomy. J Urol 2003 Mar;169:955-60.
48. Jensen JB, Høyer S, Jensen KM. Incidence of occult lymph-node metastasis missed by standard pathological examination in patients with bladder cancer undergoing radical cystectomy. Scan J Urol Nephrol 2011 Dec; 45(6)419-24.
49. Shariat SF, Karam JA, Lerner SP. Molecular markers in bladder cancer. Curr Opin Urol 2008 Jan;18(1):1-8.
50. Tiguert R, Lessard A, So A, et al. Prognostic markers in muscle invasive bladder cancer. World J Urol 2002 Aug; 20:190-5.
51. Sobin LH, Gospodariwicz M, Wittekind C (eds). TNM classification of malignant tumors. UICC International Union Against Cancer. 7th edn. Oxford: Wiley-Blackwell, 2009.
52. Fossa SD, Ous S, Berner A. Clinical significance of the 'palpable mass' in patients with muscleinfiltrating bladder cancer undergoing cystectomy after pre-operative radiotherapy. Br J Urol 1991 Jan;67(1):54-60.

53. Wijkström H, Norming U, Lagerkvist M, et al. Evaluation of clinical staging before cystectomy in transitional cell bladder carcinoma: a long-term follow-up of 276 consecutive patients. Br J Urol 1998 May;81(5):686-91.
54. Ploeg M, Kiemeney LA, Smits GA, et al. Discrepancy between clinical staging through bimanual palpation and pathological staging after cystectomy. Urol Oncol 2012 May-Jun;30(3):247-51.
55. Lokeshwar VB, Habuchi T, Grossman HB, et al. Bladder tumor markers beyond cytology: international consensus panel on bladder tumor markers. Urology 2005 Dec;66 (6 Suppl 1):35-63.
56. Raitanen M-P, Aine R, Rintala E, et al. FinnBladder Group. Differences between local and review urinary cytology and diagnosis of bladder cancer. An interobserver multicenter analysis. Eur Urol 2002 Mar;41(3):284-9.
57. Van Rhijn BW, van der Poel HG, van der Kwast Th. Urine Markers for bladder cancer surveillance: a systematic review. Eur Urol 2005 Jun;47(6):736-48.
58. Stenzl A, Burger M, Fradet Y, et al. Hexaminolevulinate guided fluorescence cystoscopy reduces recurrence in patients with non-muscle invasive bladder cancer. J Urol 2010 Nov;184(5):1907-13
59. Burger M, Grossman HB, Droller M, et al. Photodynamic diagnosis of non-muscle-invasive bladder cancer with hexaminolevulinate cystoscopy: a meta-analysis of detection and recurrence based on raw data. Eur Urol 2013 Nov;64(5):846-54.
60. Matzkin H, Soloway MS, Hardeman S. Transitional cell carcinoma of the prostate. J Urol 1991 Nov;146(5): 1207-12.
61. Mungan MU, Canda AE, Tuzel E, et al. Risk factors for mucosal prostatic urethral involvement in superficial transitional cell carcinoma of the bladder. Eur Urol 2005 Nov;48(5):760-3.
62. Kassouf W, Spiess PE, Brown GA, et al Prostatic urethral biopsy has limited usefulness in counselling patients regarding final urethral margin status during orthotopic neobladder reconstruction. J Urol 2008 Jul;180(1): 164-7;discussion 167.
63. Walsh DL, Chang SS. Dilemmas in the treatment of urothelial cancers of the prostate. Urol Oncol 2009 Jul-Aug; 27(4):352-7.
64. Lebret T, Herve JM, Barre P, et al. Urethral recurrence of transitional cell carcinoma of the bladder. Predictive value of preoperative latero-montanal biopsies and urethral frozen sections during prostatocystectomy. Eur Urol 1998;33(2):170-4.
65. Miladi M, Peyromaure M, Zerbib M, et al. The value of a second transurethral resection in evaluating patients with bladder tumours. Eur Urol 2003 Mar;43(3):241-5.
66. Jakse G, Algaba F, Malmström PU, et al. A second-look TUR in T1 transitional cell carcinoma: why? Eur Urol 2004 May;45(5):539-46.
67. Brauers A, Buettner R, Jakse G. Second resection and prognosis of primary high risk superficial bladder cancer: is cystectomy often too early? J Urol 2001 Mar;165(3):808-10.
68. Schips L, Augustin H, Zigeuner RE, et al. Is repeated transurethral resection justified in patients with newly diagnosed superficial bladder cancer? Urology 2002 Feb;59(2):220-3.
69. Grimm MO, Steinhoff Ch, Simon X, et al. Effect of routine repeat transurethral resection for superficial bladder cancer: a long-term observational study. J Urol 2003 Aug;170(2 Pt 1):433-7.
70. Divrik RT, Yildirim Ü, Zorlu F, et al. The effect of repeat transurethral resection on recurrence and progression rates in patients with T1 tumors of the bladder who received intravesical mitomycin: a prospective, randomized clinical trial. J Urol 2006 May;175(5):1641-4.
71. Jahnson S, Wiklund F, Duchek M, et al. Results of Second-look resection after primary resection of T1 tumour of the urinary bladder. Scand J Urol Nephrol 2005;39(3):206-10.
72. Damiano R, Di Lorenzo G, Cantiello F, et al. Clinicopathologic features of prostate adenocarcinoma incidentally discovered at the time of radical cystectomy: an evidence-based analysis. Eur Urol 2007 Sep;52(3):648-57.
73. Gakis G, Schilling D, Bedke J, et al. Incidental prostate cancer at radical cystoprostatectomy: implications for apex-sparing surgery. BJU Int 2010 Feb;105(4):468-71.
74. Jewett HJ. Proceedings: Cancer of the bladder. Diagnosis and Staging. Cancer 1973 Nov;32(5): 1072-4. [No abstract available]
75. Paik ML, Scolieri MJ, Brown SL, et al. Limitations of computerized tomography in staging invasive bladder cancer before radical cystectomy. J Urol 2000 Jun;163(6):1693-6.
76. Barentsz JO, Jager GJ, Witjes JA, et al. Primary staging of urinary bladder carcinoma: the role of MR imaging and a comparison with CT. Eur Radiol 1996;6(2):129-33.
77. Barentsz JO, Jager GJ, van Vierzen PB, et al. Staging urinary bladder cancer after transurethral biopsy: value of fast dynamic contrast-enhanced MR imaging. Radiology 1996 Oct;201(1):185-93.
78. Mallampati GK, Siegelman ES. MR imaging of the bladder. Magn Reson Imaging Clin N Am 2004 Aug;12(3): 545-55.
79. Rajesh A, Sokhi HK, Fung R, et al. Bladder cancer: evaluation of staging accuracy using dynamic MRI. Clin Radiol 2011 Dec;66(12):1140-5.
80. Thomsen HS. Nephrogenic systemic fibrosis: history and epidemiology. Radiol Clin North Am 2009 Sep; 47(5):827-31.

81. Kundra V, Silverman PM. Imaging in oncology from the University of Texas M. D. Anderson Cancer Center. Imaging in the diagnosis, staging, and follow-up of cancer of the urinary bladder. AJR Am J Roentgenol 2003 Apr:180(4):1045-54.
82. Kim B, Semelka RC, Ascher SM, et al. Bladder tumor staging: comparison of contrast-enhanced CT, T1- and T2-weighted MR imaging, dynamic gadolinium-enhanced imaging, and late gadolinium-enhanced imaging. Radiology 1994 Oct;193(1):239-45.
83. Kim JK, Park SY, Ahn HJ, et al. Bladder cancer: analysis of multi-detector row helical CT enhancement pattern and accuracy in tumor detection and perivesical staging. Radiology 2004 Jun;231(3):725-31.
84. Jager GJ, Barentsz JO, Oosterhof GO, et al. Pelvic adenopathy in prostatic and urinary bladder carcinoma: MR imaging with a three-dimensional TI-weighted magnetization-prepared-rapid gradient-echo sequence. AJR Am J Roentgenol 1996 Dec;167(6):1503-7.
85. Yang WT, Lam WW, Yu MY, et al. Comparison of dynamic helical CT and dynamic MR imaging in the evaluation of pelvic lymph nodes in cervical carcinoma. AJR Am J Roentgenol 2000 Sep;175(3): 759-66.
86. Kim SH, Kim SC, Choi BI, et al. Uterine cervical carcinoma: evaluation of pelvic lymph node metastasis with MR imaging. Radiology 1994 Mar;190(3):807-11.
87. Kim SH, Choi BI, Lee HP, et al. Uterine cervical carcinoma: comparison of CT and MR findings. Radiology 1990 Apr;175(1):45-51.
88. Oyen RH, Van Poppel HP, Ameye FE, et al. Lymph node staging of localized prostatic carcinoma with CT and CT-guided fine-needle aspiration biopsy: prospective study of 285 patients. Radiology 1994 Feb;190(2):315-22.
89. Barentsz JO, Engelbrecht MR, Witjes JA, et al. MR imaging of the male pelvis. Eur Radiol 1999;9(9):1722-36.
90. Dorfman RE, Alpern MB, Gross BH, et al. Upper abdominal lymph nodes: criteria for normal size determined with CT. Radiology 1991 Aug;180(2):319-22.
91. Swinnen G, Maes A, Pottel H, et al. FDG-PET/CT for the Preoperative Lymph Node Staging of Invasive Bladder Cancer. Eur Urol 2010 Apr;57(4):641-7.
92. Kibel AS, Dehdashti F, Katz MD, et al. Prospective study of [18F]fluorodeoxyglucose positron emission tomography/computed tomography for staging of muscle-invasive bladder carcinoma. J Clin Oncol 2009 Sep; 27(26):4314-20.
93. Lu YY, Chen JH, Liang JA, et al. Clinical value of FDG PET or PET/CT in urinary bladder cancer: a systemic review and meta-analysis. Eur J Radiol 2012 Sep;81(9):2411-6.
94. Vargas HA, Akin O, Schöder H, et al. Prospective evaluation of MRI, ^{11}C-acetate PET/CT and contrastenhanced CT for staging of bladder cancer. Eur J Radiol 2012 Dec;81(12):4131-7.
95. Cowan NC. CT urography for hematuria. Nat Rev Urol 2012 Mar;9(4):218-26.
96. Chow LC, Kwan SW, Olcott EW, et al. Split-bolus MDCT urography with synchronous nephrographic and excretory phase enhancement. AJR Am J Roentgenol 2007 Aug;189(2):314-22.
97. Cowan NC, Turney BW, Taylor NJ, et al. Multidetector computed tomography urography for diagnosing upper urinary tract urothelial tumour. BJU Int 2007 Jun;99(6):1363-70.
98. Fritz GA, Schoellnast H, Deutschmann HA, et al. Multiphasic multidetector-row CT (MDCT) in detection and staging of transitional cell carcinomas of the upper urinary tract. Eur Radiol 2006 Jun; 16(6):1244-52.
99. Maheshwari E, O'Malley ME, Ghai S, et al. Split-bolus MDCT urography: Upper tract opacification and performance for upper tract tumors in patients with hematuria. AJR Am J Roentgenol 2010 Feb;194(2):453-8.
100. Sudakoff GS, Dunn DP, Guralnick ML, et al. Multidetector computerized tomography urography as the primary imaging modality for detecting urinary tract neoplasms in patients with asymptomatic hematuria. J Urol 2008 Mar;179(3):862-7;discussion 867.
101. Wang LJ, Wong YC, Chuang CK, et al. Diagnostic accuracy of transitional cell carcinoma on multidetector computerized tomography urography in patients with gross hematuria. J Urol 2009 Feb;181(2):524-31; discussion 531.
102. Wang LJ, Wong YC, Huang CC, et al. Multidetector computerized tomography urography is more accurate than excretory urography for diagnosing transitional cell carcinoma of the upper urinary tract in adults with hematuria. J Urol 2010 Jan;183(1):48-55.
103. Jinzaki M, Matsumoto K, Kikuchi E, et al. Comparison of CT urography and excretory urography in the detection and localization of urothelial carcinoma of the upper urinary tract. AJR Am J Roentgenol 2011 May;196(5): 1102-9.
104. Van Der Molen AJ, Cowan NC, Mueller-Lisse UG, et al. CT Urography Working Group of the European Society of Urogenital Radiology (ESUR). CT urography: definition, indications and techniques. A guideline for clinical practice. Eur Radiol 2008 Jan;18(1):4-17.
105. Albani JM, Ciaschini MW, Streem SB, et al. The role of computerized tomographic urography in the initial evaluation of hematuria. J Urol 2007 Feb;177(2):644-8.
106. Gray Sears C, Ward JF, Sears ST, et al. Prospective comparison of computerized tomography and excretory urography in the initial evaluation of asymptomatic microhematuria. J Urol 2002 Dec;168(6):2457-60.

107. Girvin F, Ko JP. Pulmonary nodules: detection, assessment, and CAD. AJR Am J Roentgenol 2008 Oct;191(4):1057-69.
108. Heidenreich A, Albers P, Classen J, et al. Imaging studies in metastatic urogenital cancer patients undergoing systemic therapy: recommendations of a multidisciplinary consensus meeting of the Association of Urological Oncology of the German Cancer Society. Urol Int 2010;85(1):1-10.
109. Braendengen M, Winderen M, Fosså SD. Clinical significance of routine pre-cystectomy bone scans in patients with muscle-invasive bladder cancer. Br J Urol 1996 Jan;77(1):36-40.
110. Brismar J, Gustafson T. Bone scintigraphy in staging bladder carcinoma. Acta Radiol 1988 Mar-Apr; 29(2):251-2.
111. Lauenstein TC, Goehde SC, Herborn CU, et al. Whole-body MR imaging: evaluation of patients for metastases. Radiology 2004 Oct;233(1):139-48.
112. Schmidt GP, Schoenberg SO, Reiser MF, et al. Whole-body MR imaging of bone marrow. Eur J Radiol 2005 Jul;55(1):33-40.
113. Yang Z, Cheng J, Pan L, et al. Is whole-body fluorine-18 fluorodeoxyglucose PET/CT plus additional pelvic images (oral hydration-voiding-refilling) useful for detecting recurrent bladder cancer. Ann Nucl Med 2012 Aug; 26(7):571-7.
114. Maurer T, Souvatzoglou M, Kübler H, et al. Diagnostic efficacy of [11C]choline positron emission tomography/computed tomography compared with conventional computed tomography in lymph node staging of patients with bladder cancer prior to radical cystectomy. Eur Urol 2012 May; 61(5):1031-8.
115. Yoshida S, Koga F, Kobayashi S, et al. Role of diffusion-weighted magnetic resonance imaging in predicting sensitivity to chemoradiotherapy in muscle-invasive bladder cancer. Int J Radiat Oncol Biol Phys 2012 May; 83(1):e21-7.
116. Gamé X, Soulie M, Seguin P, et al. Radical cystectomy in patients older than 75 years: assessment of morbidity and mortality. Eur Urol 2001 May;39(5):525-9.
117. Clark PE, Stein JP, Groshen SG, et al. Radical cystectomy in the elderly: comparison of clinical outcomes between younger and older patients. Cancer 2005 Jul;104(1):36-43.
118. May M, Fuhrer S, Braun KP, et al. Results from three municipal hospitals regarding radical cystectomy on elderly patients. Int Braz J Urol 2007 Nov-Dec;33(6):764-73;discussion 774-6.
119. Lawrentschuk N, Colombo R, Hakenberg OW, et al. Prevention and management of complications following radical cystectomy for bladder cancer. Eur Urol 2010 Jun;57(6):983-1001.
120. Novara G, De Marco V, Aragona M, et al. Complications and mortality after radical cystectomy for bladder transitional cell cancer. J Urol 2009 Sep;182(3):914-21.
121. Rochon PA, Katz JN, Morrow LA, et al. Comorbid illness is associated with survival and length of hospital stay in patients with chronic disability. A prospective comparison of three comorbidity indices. Med Care 1996 Nov;34(11):1093-101.
122. Feinstein AR. The pre-therapeutic classification of co-morbidity in chronic disease. J Chronic Dis 1970 Dec; 23(7):455-468.
123. Zietman AL, Shipley WU, Kaufman DS. Organ-conserving approaches to muscle-invasive bladder cancer: future alternatives to radical cystectomy. Ann Med 2000 Feb;32(1):34-42.
124. Lughezzani G, Sun M, Shariat SF, et al. A population-based competing-risks analysis of the survival of patients treated with radical cystectomy for bladder cancer. Cancer 2011 Jan;117(1):103-9.
125. Froehner M, Brausi MA, Herr HW, et al. Complications following radical cystectomy for bladder cancer in the elderly. Eur Urol 2009 Sep;56(3):443-54.
126. de Groot V, Beckerman H, Lankhorst GJ, et al. How to measure comorbidity. a critical review of available methods. J Clin Epidemiol 2003 Mar;56(3):221-9.
127. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. J Am Geriatr Soc 1968 May;16(5):622-6. [No abstract available]
128. Kaplan MH, Feinstein AR. The importance of classifying initial co-morbidity in evaluating the outcome of diabetes mellitus. J Chronic Dis 1974 Sep;27(7-8):387-404. [No abstract available]
129. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373-83.
130. Greenfield S, Apolone G, McNeil BJ, et al. The importance of co-existent disease in the occurrence of postoperative complications and one-year recovery in patients undergoing total hip replacement. Comorbidity and outcomes after hip replacement. Med Care 1993 Feb;31(2):141-54.
131. Paleri V, Wight RG. Applicability of the adult comorbidity evaluation - 27 and the Charlson indexes to assess comorbidity by notes extraction in a cohort of United Kingdom patients with head and neck cancer: a retrospective study. J Laryngol Otol 2002 Mar;116(3):200-5.
132. Litwin MS, Greenfield S, Elkin EP, et al. Assessment of prognosis with the total illness burden index for prostate cancer: aiding clinicians in treatment choice. Cancer 2007 May;109(9):1777-83.
133. Mayr R, May M, Martini T, et al. Predictive capacity of four comorbidity indices estimating perioperative mortality after radical cystectomy for urothelial carcinoma of the bladder. BJU Int 2012 Sep;110(6 Pt B):E222-7.

134. Morgan TM, Keegan KA, Barocas DA, et al. Predicting the probability of 90-day survival of elderly patients with bladder cancer treated with radical cystectomy. J Urol 2011 Sep;186(3):829-34.
135. Abdollah F, Sun M, Schmitges J, et al. Development and validation of a reference table for prediction of postoperative mortality rate in patients treated with radical cystectomy: a population-based study. Ann Surg Oncol 2012 Jan;19(1):309-17.
136. Miller DC, Taub DA, Dunn RL, et al. The impact of co-morbid disease on cancer control and survival following radical cystectomy. J Urol 2003 Jan;169(1):105-9.
137. Koppie TM, Serio AM, Vickers AJ, et al. Age-adjusted Charlson comorbidity score is associated with treatment decisions and clinical outcomes for patients undergoing radical cystectomy for bladder cancer. Cancer 2008 Jun;112(11):2384-92.
138. Bolenz C, Ho R, Nuss GR, et al. Management of elderly patients with urothelial carcinoma of the bladder: guideline concordance and predictors of overall survival. BJU Int 2010 Nov;106(9):1324-9.
139. Yoo S, You D, Jeong IG, et al. Does radical cystectomy improve overall survival in octogenarians with muscle-invasive bladder cancer? Korean J Urol 2011 Jul;52(7):446-51.
140. Mayr R, May M, Martini T, et al. Comorbidity and performance indices as predictors of cancerindependent mortality but not of cancer-specific mortality after radical cystectomy for urothelial carcinoma of the bladder. Eur Urol 2012 Oct;62(4):662-70.
141. Hall WH, Ramachandran R, Narayan S, et al. An electronic application for rapidly calculating Charlson comorbidity score. BMC Cancer 2004 Dec;4:94.
142. Extermann M, Overcash J, Lyman GH, et al. Comorbidity and functional status are independent in older cancer patients. J Clin Oncol 1998 Apr;16(4):1582-7.
143. Blagden SP, Charman SC, Sharples LD, et al. Performance status score: do patients and their oncologists agree? Br J Cancer 2003 Sep;89(6):1022-7.
144. Weizer AZ, Joshi D, Daignault S, et al. Performance status is a predictor of overall survival of elderly patients with muscle invasive bladder cancer. J Urol 2007 Apr;177(4):1287-93.
145. Logothetis CJ, Finn LD, Smith T, et al. Escalated MVAC with or without recombinant human granulocyte-macrophage colony-stimulating factor for the initial treatment of advanced malignant urothelial tumors: results of a randomized trial. J Clin Oncol 1995 Sep;13(9):2272-7.
146. von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin,and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol 2000 Sep;18(17):3068-77.
147. Niegisch G, Fimmers R, Siener R, et al. Prognostic factors in second-line treatment of urothelial cancers with gemcitabine and paclitaxel (German Association of Urological Oncology trial AB20/99). Eur Urol 2011 Nov;60(5):1087-96.
148. Boström PJ, Kössi J, Laato M, et al. Risk factors for mortality and morbidity related to radical cystectomy. BJU Int 2009 Jan;103(2):191-6.
149. de Vries RR, Kauer P, van Tinteren H, et al. Short-term outcome after cystectomy: comparison of two different perioperative protocols. Urol Int 2012;88(4):383-9.
150. Malavaud B, Vaessen C, Mouzin M, et al. Complications for radical cystectomy. Impact of the American Society of Anesthesiologists score. Eur Urol 2001 Jan;39(1):79-84.
151. Haynes SR, Lawler PG. An assessment of the consistency of ASA physical status classification allocation. Anaesthesia 1995 Mar;50(3):195-9.
152. Cohen HJ, Feussner JR, Weinberger M, et al. A controlled trial of inpatient and outpatient geriatric evaluation and management. N Engl J Med 2002 Mar;346(12):905-12.
153. Balducci L, Yates J. General guidelines for the management of older patients with cancer. Oncology 2000 Nov;14(11A):221-7.
154. Castagneto B, Zai S, Marenco D, et al. Single-agent gemcitabine in previously untreated elderly patients with advanced bladder carcinoma: response to treatment and correlation with the comprehensive geriatric assessment. Oncology 2004;67(1):27-32.
155. Sylvester RJ, van der Meijden AP, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol 2006 Mar;49(3):466-5; discussion 475-7.
156. Duchek M, Johansson R, Jahnson S, et al. Members of the Urothelial Cancer Group of the Nordic Association of Urology. Bacillus Calmette-Guérin is superior to a combination of epirubicin and interferon-alpha2b in the intravesical treatment of patients with stage T1 urinary bladder cancer. A prospective, randomized, Nordic study. Eur Urol 2010 Jan;57(1):25-31.
157. Shelley MD, Court JB, Kynaston H, et al. Intravesical bacillus Calmette-Guerin versus mitomycin C for Ta and T1 bladder cancer. Cochrane Database Syst Rev 2003;(3):CD003231.

158. Sylvester RJ, Brausi MA, Kirkels WJ, et al. EORTC Genito-Urinary Tract Cancer Group. Long-term efficacy results of EORTC Genito-Urinary Group randomized phase 3 study 30911 comparing intravesical instillations of epirubicin, Bacillus Calmette-Guérin, and Bacillus Calmette-Guérin plus isoniazid in patients with intermediate- and high-risk stage Ta T1 urothelial carcinoma of the bladder. Eur Urol 2010 May;57(5):766-73.
159 Sylvester RJ, van der Meijden AP, Lamm DL. Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. J Urol 2002 Nov;168(5):1964-70.
160. Böhle A, Bock PR. Intravesical bacille Calmette-Guérin versus mitomycin C in superficial bladder cancer: formal meta-analysis of comparative studies on tumour progression. Urology 2004 Apr; 63(4):682-6.
161. Malmström PU, Sylvester RJ, Crawford DE, et al. An individual patient data meta-analysis of the longterm outcome of randomised studies comparing intravesical mitomycin C versus bacillus Calmette- Guérin for non-muscle-invasive bladder cancer. Eur Urol 2009 Aug;56(2):247-56.
162. Hautmann RE, Gschwend JE, de Petriconi RC, et al. Cystectomy for transitional cell carcinoma of the bladder: results of a surgery only series in the neobladder era. J Urol 2006 Aug;176(2):486-92.
163. Madersbacher S, Hochreiter W, Burkhard F, et al. Radical cystectomy for bladder cancer today-a homogeneous series without neoadjuvant therapy. J Clin Oncol 2003 Feb;21(4):690-6.
164. Stein JP, Lieskovsky G, Cote R, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol 2001 Feb;19(3):666-75.
165. Herr WH. The value of second transurethral resection in evaluating patients with bladder tumors. J Urol 1999 Jul;162(1):74-6.
166. van den Bosch S, Alfred Witjes J. Long-term cancer-specific survival in patients with high-risk, non-muscle-invasive bladder cancer and tumour progression: a systematic review. Eur Urol 2011 Sep;60(3):493-500.
167. Herr HW, Sogani PC. Does early cystectomy improve the survival of patients with high risk superficial bladder tumors? J Urol 2001 Oct;166(4):1296-9.
168. Pansadoro V, Emiliozzi P, de Paula F, et al. Long-term follow-up of G3T1 transitional cell carcinoma of the bladder treated with intravesical bacille Calmette-Guérin: 18-year experience. Urology 2002 Feb;59(2):227-31.
169. Margel D, Tal R, Golan S, et al. Long-term follow-up of patients with Stage T1 high-grade transitional cell carcinoma managed by Bacille Calmette-Guérin immunotherapy. Urology 2007 Jan;69(1):78-82.
170. Yates DR, Brausi MA, Catto JW, et al. Treatment options available for bacillus Calmette-Guérin failure in non-muscle-invasive bladder cancer. Eur Urol 2012 Dec;62(6):1088-96.
171. Solsona E, Iborra I, Dumont R, et al. The 3-month clinical response to intravesical therapy as a predictive factor for progression in patients with high risk superficial bladder cancer. J Urol 2000 Sep;164(3 Pt 1):685-9.
172. Herr HW, Dalbagni G. Defining bacillus Calmette-Guerin refractory superficial bladder tumours. J Urol 2003 May;169(5):1706-8.
173. Lerner SP, Tangen CM, Sucharew H, et al. Failure to achieve a complete response to induction BCG therapy is associated with increased risk of disease worsening and death in patients with high risk non-muscle invasive bladder cancer. Urol Oncol 2009 Mar-Apr;27(2):155-9.
174. Stein JP, Skinner DG. Radical cystectomy for invasive bladder cancer: long-term results of a standard procedure. World J Urol 2006 Aug;24(3):296-304.
175. Dalbagni G, Genega E, Hashibe M, et al. Cystectomy for bladder cancer: a contemporary series. J Urol 2001 Apr;165(4):1111-6.
176. Bassi P, Ferrante GD, Piazza N, et al. Prognostic factors of outcome after radical cystectomy for bladder cancer: a retrospective study of a homogeneous patient cohort. J Urol 1999 May;161(5): 1494-7.
177. Ghoneim MA, el-Mekresh MM, el-Baz MA, et al. Radical cystectomy for carcinoma of the bladder: critical evaluation of the results in 1,026 cases. J Urol 1997 Aug;158(2):393-9.
178. David KA, Milowsky MI, Ritchey J, et al. Low incidence of perioperative chemotherapy for stage III bladder cancer 1998 to 2003: a report from the National Cancer Data Base. J Urol 2007 Aug;178(2):451-4.
179. Porter MP, Kerrigan MC, Donato BM, et al. Patterns of use of systemic chemotherapy for Medicare beneficiaries with urothelial bladder cancer. Urol Oncol 2011 May-Jun;29(3):252-8.
180. Sánchez-Ortiz RF, Huang WC, Mick R, et al. An interval longer than 12 weeks between the diagnosis of muscle invasion and cystectomy is associated with worse outcome in bladder carcinoma. J Urol 2003 Jan;169(1):110-5;discussion 115.
181. Stein JP. Contemporary concepts of radical cystectomy and the treatment of bladder cancer. J Urol 2003 Jan;169(1):116-7.
182. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 2003 Aug;349(9):859-66.
183. Sherif A, Holmberg L, Rintala E, et al. Nordic Urothelial Cancer Group. Neoadjuvant cisplatinum based combination chemotherapy in patients with invasive bladder cancer: a combined analysis of two Nordic studies. Eur Urol 2004 Mar;45(3):297-303.

184. Sternberg CN, Pansadoro V, Calabrò F, et al. Can patient selection for bladder preservation be based on response to chemotherapy? Cancer 2003 Apr;97(7):1644-52.
185. Herr HW, Scher HI. Surgery of invasive bladder cancer: is pathologic staging necessary? Semin Oncol 1990 Oct;17(5):590-7. [No abstract available]
186. International Collaboration of Trialists; Medical Research Council Advanced Bladder Cancer Working Party (now the National Cancer Research Institute Bladder Cancer Clinical Studies Group); European Organisation for Research and Treatment of Cancer Genito-Urinary Tract Cancer Group; Australian Bladder Cancer Study Group; National Cancer Institute of Canada Clinical Trials Group; Finnbladder; Norwegian Bladder Cancer Study Group; Club Urologico Espanol de Tratamiento Oncologico Group, Griffiths G, Hall R, Sylvester R, et al. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. J Clin Oncol 2011 Jun;29(16):2171-7.
187. Bassi P PG, Cosciani S, Lembo A, et al. Neoadjuvant M-VAC chemotherapy of invasive bladder cancer: The G.U.O.N.E. multicenter phase III trial. Eur Urol 1998 (Suppl);33:142,abstr 567.
188. Sherif A, Rintala E, Mestad O, et al. Nordic Urothelial Cancer Group. Neoadjuvant cisplatinmethotrexate chemotherapy for invasive bladder cancer-- Nordic cystectomy trial 2. Scand J Urol Nephrol 2002;36(6):419-25.
189. Sengeløv L, von der Maase H, Lundbeck F, et al. Neoadjuvant chemotherapy with cisplatin and methotrexate in patients with muscle-invasive bladder tumours. Acta Oncol 2002;41(5):447-56.
190. Italian Bladder Cancer Study Group (GISTV). Neoadjuvant treatment for locally advanced bladder cancer: a randomized prospective clinical trial. J Chemother 1996;8(suppl 4):345-6.
191. Orsatti M, Curotto A, Canobbio L, et al. Alternating chemo-radiotherapy in bladder cancer: a conservative approach. Int J Radiat Oncol Biol Phys 1995 Aug;33(1):173-8.
192. Shipley WU, Winter KA, Kaufman DS, et al. Phase III trial of neoadjuvant chemotherapy in patients with invasive bladder cancer treated with selective bladder preservation by combined radiation therapy and chemotherapy: initial results of Radiation Therapy Oncology Group 89-03. J Clin Oncol 1998 Nov;16(11):3576-83.
193. Marcuello E, Tabernero JM, Villavicencio H, et al. A phase III trial of neoadjuvant chemotherapy (NCT) in patients (PTS) with invasive bladder cancer (IBC). Preliminary results: NCT improves pathological complete response rate. Eur J Cancer 1995;31A:S241, abstr 1155.
194. Cannobio L CA, Boccardo F, Venturini M, et al. A randomized study between neoadjuvant chemoradiotherapy (CT-RT) before radical cystectomy and cystectomy alone in bladder cancer. A 6 year follow-up. Proc Am Soc Clin Oncol 1995;14:245, abstr 654.
195. Abol-Enein H, El-Mekresh M, El-Baz M, et al. Neo-adjuvant chemotherapy in the treatment of invasive transitional bladder cancer. A controlled prospective randomized study. Br J Urol 1997;79 (Suppl 4):174.
196. Advanced Bladder Cancer Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. Lancet 2003 Jun;361(9373):1927-34.
197. Winquist E, Kirchner TS, Segal R, et al. Genitourinary Cancer Disease Site Group, Cancer Care Ontario Program in Evidence-based Care Practice Guidelines Initiative. Neoadjuvant chemotherapy for transitional cell carcinoma of the bladder: a systematic review and meta-analysis. J Urol 2004 Feb;171(2 Pt 1):561-9.
198. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. Eur Urol 2005 Aug;48(2):202-205;discussion 205-6.
199. Letocha H, Ahlström H, Malmström PU, et al. Positron emission tomography with L-methyl- 11Cmethionine in the monitoring of therapy response in muscle-invasive transitional cell carcinoma of the urinary bladder. Br J Urol 1994 Dec;74(6):767-74.
200. Nishimura K, Fujiyama C, Nakashima K, et al. The effects of neoadjuvant chemotherapy and chemoradiation therapy on MRI staging in invasive bladder cancer: comparative study based on the pathological examination of whole layer bladder wall. Int Urol Nephrol 2009 Dec;41(4):869-75.
201. Rosenblatt R, Sherif A, Rintala E, et al. Pathologic downstaging is a surrogate marker for efficacy and increased survival following neoadjuvant chemotherapy and radical cystectomy for muscle-invasive urothelial bladder cancer. Eur Urol 2012 Jun;61(6):1229-38.
202. Takata R, Katagiri T, Kanehira M, et al. Predicting response to methotrexate, vinblastine, doxorubicin, and cisplatin neoadjuvant chemotherapy for bladder cancers through genome-wide gene expression profiling. Clin Cancer Res 2005 Apr;11(7):2625-36.
203. Takata R, Katagiri T, Kanehira M, et al. Validation study of the prediction system for clinical response of M-VAC neoadjuvant chemotherapy. Cancer Sci 2007 Jan;98(1):113-7.
204. Barentsz JO, Berger-Hartog O, Witjes JA, et al. Evaluation of chemotherapy in advanced urinary bladder cancer with fast dynamic contrast-enhanced MR imaging. Radiology 1998 Jun;207(3):791-7.
205. Krajewski KM, Fougeray R, Bellmunt J, et al. Optimisation of the size variation threshold for imaging evaluation of response in patients with platinum-refractory advanced transitional cell carcinoma of the urothelium treated with vinflunine. Eur J Cancer 2012 Jul;48(10):1495-502.

206. Wallace DM, Raghavan D, Kelly KA, et al. Neo-adjuvant (pre-emptive) cisplatin therapy in invasive transitional cell carcinoma of the bladder. Br J Urol 1991Jun;67(6):608-15.
207. Font A, Saladie JM, Carles J, et al. Improved survival with induction chemotherapy in bladder cancer: preliminary results of a randomized trial. Ann Oncol 1994;5:71, abstr #355.
208. Martínez-Piñeiro JA, Gonzalez Martin M, Arocena F, et al. Neoadjuvant cisplatin chemotherapy before radical cystectomy in invasive transitional cell carcinoma of the bladder: a prospective randomized phase III study. J Urol 1995 Mar;153(3 Pt 2):964-73.
209. Rintala E, Hannisdahl E, Fosså SD, et al. Neoadjuvant chemotherapy in bladder cancer: a randomized study. Nordic Cystectomy Trial I. Scand J Urol Nephrol 1993;27(3):355-62.
210. Malmström PU, Rintala E, Wahlqvist R, et al. Five-year followup of a prospective trial of radical cystectomy and neoadjuvant chemotherapy: Nordic Cystectomy Trial I. The Nordic Cooperative Bladder Cancer Study Group. J Urol 1996 Jun;155(6):1903-6.
211. [No authors listed] Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscleinvasive bladder cancer: a randomised controlled trial. International collaboration of trialists. Lancet 1999 Aug;354(9178): 533-40.
212. Yuh BE, Ruel N, Wilson TG, et al. Pooled analysis of clinical outcomes with neoadjuvant cisplatin and gemcitabine chemotherapy for muscle invasive bladder cancer. J Urol 2013 May;189(5):1682-6.
213. Lee FC, Harris W, Cheng HH, et al. Pathologic Response Rates of Gemcitabine/Cisplatin versus Methotrexate/ Vinblastine/Adriamycin/Cisplatin Neoadjuvant Chemotherapy for Muscle Invasive Urothelial Bladder Cancer. Adv Urol 2013;2013:317190.
214. Dash A, Pettus JA 4th, Herr HW, et al. A role for neoadjuvant gemcitabine plus cisplatin in muscle-invasive urothelial carcinoma of the bladder: a retrospective experience. Cancer 2008 Nov;113(9):2471-7.
215. Weight CJ, Garcia JA, Hansel DE, et al. Lack of pathologic down-staging with neoadjuvant chemotherapy for muscle-invasive urothelial carcinoma of the bladder: a contemporary series. Cancer 2009 Feb;115(4):792-9.
216. Zaghloul MS. The need to revisit adjuvant and neoadjuvant radiotherapy in bladder cancer. Expert Rev Anticaner Ther 2010 Oct;10(10):1527-8.
217. El-Monim HA, El-Baradie MM, Younis A, et al. A prospective randomized trial for postoperative vs. preoperative adjuvant radiotherapy for muscle-invasive bladder cancer. Urol Oncol 2013 Apr;31(3): 359-65.
218. Widmark A, Flodgren P, Damber JE, et al. A systematic overview of radiation therapy effects in urinary bladder cancer. Acta Oncol 2003;42(5-6):567-81.
219. Granfors T, Tomic R, Ljungberg B. Downstaging and survival benefits of neoadjuvant radiotherapy before cystectomy for patients with invasive bladder carcinoma. Scand J Urol Nephrol 2009;43(4): 293-9.
220. Slack NH, Bross ID, Prout GR. Five-year follow-up results of a collaborative study of therapies for carcinoma of the bladder. J Surg Oncol 1977;9(4):393-405.
221. Smith JA, Crawford ED, Paradelo JC, et al. Treatment of advanced bladder cancer with combined preoperative irradiation and radical cystectomy versus radical cystectomy alone: a phase III intergroup study. J Urol 1997 Mar;157(3):805-7;discussion 807-8.
222. Ghoneim MA, Ashamallah AK, Awaad HK, et al. Randomized trial of cystectomy with or without preoperative radiotherapy for carcinoma of the bilharzial bladder. J Urol 1985 Aug;134(2):266-8.
223. Anderström C, Johanson S, Nilsson S, et al. A prospective randomized study of preoperative irradiation with cystectomy or cystectomy alone for invasive bladder carcinoma. Eur Urol 1983;9(3):142-7.
224. Blackard CE, Byar DP. Results of a clinical trial of surgery and radiation in stages II and III carcinoma of the bladder. J Urol 1972 Dec;108(6):875-8.
225. Huncharek M, Muscat J, Geschwind JF. Planned preoperative radiation therapy in muscle invasive bladder cancer; results of a meta-analysis. Anticancer Res 1998 May;18(3b):1931-4.
226. World Health Organization (WHO) Consensus Conference in Bladder Cancer, Hautmann RE, Abol- Enein H, Hafez K, Haro I, Mansson W, Mills RD, Montie JD, Sagalowsky AI, Stein JP, Stenzl A, Studer UE, Volkmer BG. Urinary diversion. Urology 2007 Jan;69(1 Suppl):17-49.
227. Figueroa AJ, Stein JP, Dickinson M, et al. Radical cystectomy for elderly patients with bladder carcinoma: an updated experience with 404 patients. Cancer 1998 Jul;83(1):141-7.
228. Geriatric Assessment Methods for Clinical Decision making. NIH Consensus Statement Online 1987 Oct 19-21;6(13):1-21 [access date Feb 2015].
229. Nielsen ME, Palapattu GS, Karakiewicz PI, et al. A delay in radical cystectomy of >3 months is not associated with a worse clinical outcome. BJU Int 2007 Nov;100(5):1015-20.
230. Ayres BE, Gillatt D, McPhail S, et al. A delay in radical cystectomy of >3 months is not associated with a worse clinical outcome. BJU Int 2008 Sep;102(8):1045.
231. Gore JL, Lai J, Setodji CM, et al. Mortality increases when radical cystectomy is delayed more than 12 weeks: results from a Surveillance, Epidemiology, and End Results-Medicare analysis. Cancer 2009 Mar;115(5):988-96.
232. Lebret T, Herve JM, Yonneau L, et al. After cystectomy, is it justified to perform a bladder replacement for patients with lymph node positive bladder cancer? Eur Urol 2002 Oct;42(4):344-9.

233. Stenzl A, Nagele U, Kuczyk M, et al. Cystectomy: technical considerations in male and female patients. EAU Update Series 2005 Sep;3:138-46.
234. Wallmeroth A, Wagner U, Moch H, et al. Patterns of metastasis in muscle-invasive bladder cancer (pT2-4): An autopsy study on 367 patients. Urol Int 1999;62(2):69-75.
235. Davies JD, Simons CM, Ruhotina N, et al. Anatomic basis for lymph node counts as measure of lymph node dissection extent: a cadaveric study. Urol 2013 Feb;81(2):358-63.
236. Jensen JB, Ulhøi BP, Jensen KM. Lymph node mapping in patients with bladder cancer undergoing radical cystectomy and lymph node dissection to the level of the inferior mesenteric artery. BJU Int 2010 Jul;106(2): 199-205.
237. Vazina A, Dugi D, Shariat SF, et al. Stage specific lymph node metastasis mapping in radical cystectomy specimens. J Urol 2004 May;171(5):1830-4.
238. Leissner J, Ghoneim MA, Abol-Enein H, et al. Extended radical lymphadenectomy in patients with urothelial bladder cancer: results of a prospective multicenter study. J Urol 2004 Jan;171(1):139-44.
239. Roth B, Wissmeyer MP, Zehnder P, et al. A new multimodality technique accurately maps the primary lymphatic landing sites of the bladder. Eur Urol 2010 Feb;57(2):205-11
240. Dorin RP, Daneshmand S, Eisenberg MS, et al. Lymph node dissection technique is more important than lymph node count in identifying nodal metastases in radical cystectomy patients: a comparative mapping study. Eur Urol 2011 Nov;60(5):946-52.
241. Wiesner C, Salzer A, Thomas C, et al. Cancer-specific survival after radical cystectomy and standardized extended lymphadenectomy for node-positive bladder cancer: prediction by lymph node positivity and density. BJU Int 2009 Aug;104(3):331-5.
242. Simone G, Papalia R, Ferriero M, et al. Stage-specific impact of extended versus standard pelvic lymph node dissection in radical cystectomy. Int J Urol 2013 Apr;20(4):390-7.
243. Holmer M, Bendahl PO, Davidsson T, et al. Extended lymph node dissection in patients with urothelial cell carcinoma of the bladder: can it make a difference? World J Urol 2009 Aug;27(4):521-6.
244. Poulsen AL, Horn T, Steven K. Radical cystectomy: extending the limits of pelvic lymph node dissection improves survival for patients with bladder cancer confined to the bladder wall. J Urol 1998 Dec;160(6 Pt 1): 215-9.
245. Jensen JB, Ulhøi BP, Jensen K. Extended versus limited lymph node dissection in radical cystectomy: Impact on recurrence pattern and survival. Int J Urol 2012 Jan;19(1):39-47.
246. Dhar NB, Klein EA, Reuther AM, et al. Outcome after radical cystectomy with limited or extended pelvic lymph node dissection. J Urol 2008 Mar;179(3):873-78.
247. Zlotta AR. Limited, extended, superextended, megaextended pelvic lymph node dissection at the time of radical cystectomy: what should we perform? Eur Urol 2012 Feb;61(2):243-4.
248. Zehnder P, Studer UE, Skinner EC, et al. Super Extended Versus Extended Pelvic Lymph Node Dissection in Patients Undergoing Radical Cystectomy for Bladder Cancer: A Comparative Study. J Urol 2011 Oct;186(4): 1261-8.
249. Brössner C, Pycha A, Toth A, et al. Does extended lymphadenectomy increase the morbidity of radical cystectomy? BJU Int 2004 Jan;93(1)64-6.
250. Finelli A, Gill IS, Desai MM, et al. Laparoscopic extended pelvic lymphadenectomy for bladder cancer: technique and initial outcomes. J Urol 2004 Nov;172(5 Pt 1);1809-12.
251. Abd El-Latif A, Miocinovic R, Stephenson AJ. Impact of extended versus standard lymph node dissection on overall survival among patients with urothelial cancer of bladder. J Urol 2012 May;187(4 Suppl): abstract #1752.
252. Abd El-Latif A, Miocinovic R, Stephenson AJ. Impact of extended (E) versus standard lymph node dissection (SLND) on post-cystectomy survival (PCS) among patients with LN-negative urothelial bladder cancer (UBC). J Urol 2011;185(4 Suppl):abstract #1896.
253. Abol-Enein H, Tilki D, Mosbah A. Does the extent of lymphadenectomy in radical cystectomy for bladder cancer influence disease-free survival? A Prospective Single-Center Study. Eur Urol 2011 Sep;60(3):572-7.
254. Dharaskar A, Kumar V, Kapoor R, et al. Does extended lymph node dissection affect the lymph node density and survival after radical cystectomy? Indian J Cancer 2011 April-June;48(2):230-3.
255. Abdollah F, Sun M, Schmitges J, et al. Stage-specific impact of pelvic lymph node dissection on survival in patients with non-metastatic bladder cancer treated with radical cystectomy. BJU Int 2012 Apr;109(8):1147-54.
256. Liu JJ, Leppert J, Shinghal R. Practice patterns of pelvic lymph node dissection for radical cystectomy from the veterans affairs central cancer registry (VACCR). J Urol 2011 May;185 (4S, Suppl), abstract #1404.
257. Isaka S, Okano T, Sato N, et al. [Pelvic lymph node dissection for invasive bladder cancer]. Nihon Hinyokika Gakkai Zasshi 1989 Mar:80(3):402-6. [Article in Japanese]
258. Miyakawa M, Oishi K, Okada Y, et al. [Results of the multidisciplinary treatment of invasive bladder cancer]. Kinyokika Kiyo 1986 Dec;32(12):1931-9. [Article in Japanese]
259. Simone G, Eneim HA, Ferreiro M, et al. Extended versus super-extended PLND during radical cystectomy: comparison of two prospective series. J Urol 2012 May;(187 4S Suppl):e708, abstract #1755.

260. Bostrom PJ, Mirtti T, Nurmi M, et al. Extended lymphadenectomy and chemotherapy offer survival advantage in muscle-invasive bladder cancer. Abstracts of the 2011 AUA Annual meeting. J Urol 2011 Apr;185(4):e640
261. Yuasa M, Yamamoto A, Kawanishi Y, et al. [Clinical evaluation of total cystectomy for bladder carcinoma: a ten-year experience]. Hinyokika Kiyo 1998 Jun;34(6):975-81. [Article in Japanese]
262. Karl A, Carroll PR, Gschwend JE, et al. The impact of lymphadenectomy and lymph node metastasis on the outcomes of radical cystectomy for bladder cancer. Eur Urol 2009 Apr;55(4):826-35.
263. Svatek R, Zehnder P. Role and extent of lymphadenectomy during radical cystectomy for invasive bladder cancer. Curr Urol Rep 2012 Apr;13(2)115-21.
264. Koppie TM, Vickers AJ, Vora K, et al: Standardization of pelvic lymphadenectomy performed at radical cystectomy: can we establish a minimum number of lymph nodes that should be removed? Cancer 2006 Nov;107(10):2368-74.
265. Fleischmann A, Thalmann GN, Markwalder R, et al. Extracapsular extension of pelvic lymph node metastases from urothelial carcinoma of the bladder is an independent prognostic factor. J Clin Oncol 2005 Apr;23(10): 2358-65.
266. Wright JL, Lin DW, Porter MP. The association between extent of lymphadenectomy and survival among patients with lymph node metastases undergoing radical cystectomy. Cancer 2008 Jun;112(11):2401-8.
267. Studer UE, Collette L. Morbidity from pelvic lymphadenectomy in men undergoing radical prostatectomy. Eur Urol 2006 Nov;50(5):887-9;discussion 889-92.
268. Chade DC, Laudone VP, Bochner BH, et al. Oncological outcomes after radical cystectomy for bladder cancer: open versus minimally invasive approaches. J Urol 2010 Mar;183(3):862-69.
269. Kasraeian A, Barret E, Cathelineau X, et al. Robot-assisted laparoscopic cystoprostatectomy with extended pelvic lymphadenectomy, extracorporeal enterocystoplasty, and intracorporeal enterourethral anastomosis: Initial Montsouris experience. J Endourol 2010 Mar;24(3):409-13.
270. Challacombe BJ, Bochner BH, Dasgupta P, et al. The role of laparoscopic and robotic cystectomy in the management of muscle-invasive bladder cancer with special emphasis on cancer control and complications. Euro Urol 2011;60(4):767-75.
271. Aboumarzouk OM, Hughes O, Narahari K, et al. Safety and feasibility of Laparoscopic Radical Cystectomy for the treatment of bladder cancer. J Endourol 2013 Sep;27(9):1083-95.
272. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009 Jul;6(7):e1000097.
273. Guillotreau J, Game X, Mouzin M, Doumerc N, Mallet R, Sallusto F, et al. Radical cystectomy for bladder cancer: morbidity of laparoscopic versus open surgery. J Urol 2009;181(2):554-9
274. Hemal AK, Kolla SB. Comparison of laparoscopic and open radical cystoprostatectomy for localized bladder cancer with 3-year oncological followup: a single surgeon experience. J Urol 2007;178(6):2340-3.
275. Basillote JB, Abdelshehid C, Ahlering TE, et al. Laparoscopic assisted radical cystectomy with ileal neobladder: a comparison with the open approach. J Urol 2004;172(2):489-93.
276. Gregori A, Galli S, Goumas I, et al. A cost comparison of laparoscopic versus open radical cystoprostatectomy and orthotopic ileal neobladder at a single institution. Archl Ital Urol Androl 2007 Sep;79(3):127-9.
277. Ha US, Kim SI, Kim SJ, et al. Laparoscopic versus open radical cystectomy for the management of bladder cancer: mid-term oncological outcome. Int J Urol 2010 Jan;17(1):55-61.
278. Haber GP, Crouzet S, Gill IS. Laparoscopic and robotic assisted radical cystectomy for bladder cancer: a critical analysis. Euro Urol 2008 Jul;54(1):54-62.
279. Porpiglia F, Renard J, Billia M, et al. Open versus laparoscopy-assisted radical cystectomy: results of a prospective study. J Endourol 2007 Mar;21(3):325-9.
280. Wang SZ, Chen Y, Lin HY, et al. Comparison of surgical stress response to laparoscopic and open radical cystectomy. World J Urol 2010 Aug;28(4):451-5.
281. Ng CK, Kauffman EC, Lee MM, et al. A comparison of postoperative complications in open versus robotic cystectomy. Eur Urol 2010 Feb;57(2):274-81.
282. Pruthi RS, Nix J, McRackan D, et al. Robotic-assisted laparoscopic intracorporeal urinary diversion. Eur Urol 2010 Jun;57:1013-21.
283. Haber GP, Campbell SC, Colombo JR, et al. Perioperative outcomes with laparoscopic radical cystectomy: “pure laparoscopic” and “open-assisted laparoscopic” approaches. Urology 2007 Nov;70(5):910-5.
284. Canda AE, Atmaca AF, Altinova S, et al. Robot-assisted nerve-sparing radical cystectomy with bilateral extended pelvic lymph node dissection (PLND) and intracorporeal urinary diversion for bladder cancer: initial experience in 27 cases. BJU Int 2012 Aug;110(3):434-44.
285. Pruthi RS, Nielsen ME, Nix J, et al. Robotic radical cystectomy for bladder cancer: surgical and pathological outcomes in 100 consecutive cases. J Urol 2010 Feb;183(2):510-4.
286. Hautmann RE. The oncologic results of laparoscopic radical cystectomy are not (yet) equivalent to open cystectomy. Curr Opin Urol 2009 Sep;19(5):522-6.

287. Cha EK, Wiklund NP, Scherr DS. Recent advances in robot-assisted radical cystectomy. Curr Opin Urol 2011 Jan;21(1):65-70.
288. Stenzl A. Bladder substitution. Curr Opin Urol 1999 May;9(3):241-5.
289. Azimuddin K, Khubchandani IT, Stasik JJ, et al. Neoplasia after reterosigmoidostomy. Dis Colon Rectum 1999 Dec;42(12):1632-8.
290. Gerharz EW, Turner WH, Kälble T, et al. Metabolic and functional consequences of urinary reconstruction with bowel. BJU Int 2003 Jan;91(2):143-9.
291. Madersbacher S, Studer UE. Contemporary cystectomy and urinary diversion. World J Urol 2002 Aug;20(3): 151-7.
292. Pruthi RS, Nielsen M, Smith A, et al. Fast track program in patients undergoing radical cystectomy: results in 362 consecutive patients. J Am Coll Surg 2010 Jan;210(1):93-9.
293. Kouba EJ, Wallen EM, Pruthi RS. Gum chewing stimulates bowel motility in patients undergoing radical cystectomy with urinary diversion. Urology 2007 Dec;70(6):1053-6.
294. Tanrikut C, McDougal WS. Acid-base and electrolyte disorders after urinary diversion. World J Urol 2004 Sep; 22(3):168-71.
295. Farnham SB, Cookson MS. Surgical complications of urinary diversion. World J Urol 2004 Sep;22(3):157-67.
296. Hautmann RE, Volkmer BG, Schumacher MC, et al. Long-term results of standard procedures in urology: the ileal neobladder. World J Urol 2006 Aug;24(3):305-14.
297. Hautmann RE, de Petriconi RC, Volkmer BG. Lessons learned from 1,000 neobladders: the 90-day complication rate. J Urol 2010 Sep;184(3):990-4; quiz 1235.
298. Stein JP, Ginsberg DA, Skinner DG. Indications and technique of the orthotopic neobladder in women. Urol Clin North Am 2002 Aug;29(3):725-34.
299. Hautmann RE, de Petriconi RC, Pfeiffer C, et al. Radical cystectomy for urothelial carcinoma of the bladder without neoadjuvant or adjuvant therapy: long-term results in 1100 patients. Eur Urol 2012 May;61(5):1039-47.
300. Jentzmik F, Schrader AJ, de Petriconi R, et al. The ileal neobladder in female patients with bladder cancer: long-term clinical, functional, and oncological outcome. World J Urol 2012 Dec;30(6):733-9.
301. Ahmadi H, Skinner EC, Simma-Chiang V, et al. Urinary functional outcome following radical cystoprostatectomy and ileal neobladder reconstruction in male patients. J Urol 2013 May;189(5):1782-8
302. Neuzillet Y, Yonneau L, Lebret T, et al. The Z-shaped ileal neobladder after radical cystectomy: an 18 years experience with 329 patients. BJU Int 2011 Aug;108(4):596-602.
303. Deliveliotis C, Papatsoris A, Chrisofos M, et al. Urinary diversion in high-risk elderly patients: modified cutaneous ureterostomy or ileal conduit? Urology 2005 Aug;66(2):299-304.
304. Kilciler M, Bedir S, Erdemir F, et al. Comparison of ileal conduit and transureteroureterostomy with ureterocutaneostomy urinary diversion. Urol Int 2006;77(3):245-50.
305. Pycha A, Comploj E, Martini T, et al. Comparison of complications in three incontinent urinary diversions. Eur Urol 2008 Oct;54:825-32.
306. Nieuwenhuijzen JA, de Vries RR, Bex A, et al. Urinary diversions after cystectomy: the association of clinical factors, complications and functional results of four different diversions. Eur Urol 2008 Apr;53:834-42;discussion 842-4.
307. Madersbacher S, Schmidt J, Eberle JM, et al. Long-term outcome of ileal conduit diversion. J Urol 2003 Mar;169(3):985-90.
308. Wood DN, Allen SE, Hussain M, et al. Stomal complications of ileal conduits are significantly higher when formed in women with intractable urinary incontinence. J Urol 2004 Dec;172(6 Pt 1):2300-3.
309. Neal DE. Complications of ileal conduit diversion in adults with cancer followed up for at least five years. Br Med J (Clin Res Ed) 1985 Jun;290(6483):1695-7.
310. Benson MC, Olsson CA. Continent urinary diversion. Urol Clin North Am 1999 Feb;26(1):125-47, ix.
311. Gerharz EW, Köhl UN, Melekos MD, et al. Ten years' experience with the submucosally embedded *in situ* appendix in continent cutaneous diversion. Eur Urol 2001 Dec;40(6):625-31.
312. Jonsson O, Olofsson G, Lindholm E, et al. Long-time experience with the Kock ileal reservoir for continent urinary diversion. Eur Urol 2001 Dec;40(6):632-40.
313. Wiesner C, Bonfig R, Stein R, et al. Continent cutaneous urinary diversion: long-term follow-up of more than 800 patients with ileocecal reservoirs. World J Urol 2006 Aug;24(3):315-8.
314. Wiesner C, Stein R, Pahernik S, et al. Long-term followup of the intussuscepted ileal nipple and the *in situ*, submucosally embedded appendix as continence mechanisms of continent urinary diversion with the cutaneous ileocecal pouch (Mainz pouch I). J Urol 2006 Jul;176(1):155-9;discussion 159-60.
315. Thoeny HC, Sonnenschein MJ, Madersbacher S, et al. Is ileal orthotopic bladder substitution with an afferent tubular segment detrimental to the upper urinary tract in the long term? J Urol 2002 Nov;168(5):2030-4; discussion 2034.
316. Leissner J, Black P, Fisch M, et al. Colon pouch (Mainz pouch III) for continent urinary diversion after pelvic irradiation. Urology 2000 Nov;56(5):798-802.

317. Simon J. Ectopia Vesicae (Absence of the anterior walls of the Bladder and the pubic abdominal parietes) Operation for directing the orifices of the ureteres into the rectum, temporary success. JAMA 1911;56:398.
318. Coffey R. Physiologic implantation of the severed ureter or common bile duct into the intestine. JAMA 1911;LVI(6):397-403.
319. Kälble T, Busse K, Amelung F, et al. Tumor induction and prophylaxis following different forms of intestinal urinary diversion in a rat model. Urol Res 1995;23(6):365-70.
320. Donat SM, Siegrist T, Cronin A, et al. Radical cystectomy in octogenarians—does morbidity outweigh the potential survival benefits? J Urol 2010 Jun;183(6):2171-7.
321 Hautmann RE, de Petriconi RC, Volkmer BG. 25 years of experience with 1,000 neobladders: longterm complications. J Urol 2011 Jun:185(6); 2207-12.
322. Stein JP, Dunn MD, Quek ML, et al. The orthotopic T pouch ileal neobladder: experience with 209 patients. J Urol 2004 Aug;172(2):584-7.
323. Abol-Enein H, Ghoneim MA. Functional results of orthotopic ileal neobladder with serous-lined extramural ureteral reimplantation: experience with 450 patients. J Urol 2001 May;165(5):1427-32.
324. Stein JP, Skinner DG. Results with radical cystectomy for treating bladder cancer: a 'reference standard' for high-grade, invasive bladder cancer. BJU Int 2003 Jul;92(1):12-7.
325. Yossepowitch O, Dalbagni G, Golijanin D, et al. Orthotopic urinary diversion after cystectomy for bladder cancer: implications for cancer control and patterns of disease recurrence. J Urol 2003 Jan;169(1):177-81.
326. Stein JP, Clark P, Miranda G, et al. Urethral tumor recurrence following cystectomy and urinary diversion: clinical and pathological characteristics in 768 male patients. J Urol 2005 Apr;173(4):1163-8.
327. Gerharz EW, Månsson A, Hunt S, et al. Quality of life after cystectomy and urinary diversion: an evidence based analysis. J Urol 2005 Nov;174(5):1729-36.
328. Hobisch A, Tosun K, Kinzl J, et al. Life after cystectomy and orthotopic neobladder versus ileal conduit urinary diversion. Semin Urol Oncol 2001 Feb;19(1):18-23.
329. Porter MP, Penson DF. Health related quality of life after radical cystectomy and urinary diversion for bladder cancer: a systematic review and critical analysis of the literature. J Urol 2005 Apr;173(4): 1318-22.
330. Gakis G, Jentzmik F, Schrader M, et al. [Benefits and risks of orthotopic neobladder reconstruction in female patients]. Aktuelle Urol 2011 Mar;42(2):109-14. [Article in German].
331. Stein JP, Penson DF, Wu SD, et al. Pathological guidelines for orthotopic urinary diversion in women with bladder cancer: a review of the literature. J Urol 2007 Sep;178(3 Pt 1):756-60.
332. Stein JP, Cote RJ, Freeman JA, et al. Indications for lower urinary tract reconstruction in women after cystectomy for bladder cancer: a pathological review of female cystectomy specimens. J Urol 1995 Oct;154(4):1329-33.
333. Vallancien G, Abou El Fettouh H, Cathelineau X, et al. Cystectomy with prostate sparing for bladder cancer in 100 patients: 10-year experience. J Urol 2002 Dec;168(6):2413-7.
334. Stenzl A, Sherif H, Kuczyk M. Radical cystectomy with orthotopic neobladder for invasive bladder cancer: a critical analysis of long term oncological, functional and quality of life results. Int Braz J Urol 2010 Sep-Oct; 36(5):537-47.
335. Porter MP, Gore JL, Wright JL. Hospital volume and 90-day mortality risk after radical cystectomy: a population-based cohort study. World J Urol 2011 Feb;29(1):73-7.
336. Hautmann RE, Abol-Enein H, Davidsson T, et al. ICUD-EAU International Consultation on Bladder Cancer 2012: urinary diversion. Eur Urol 2013 Jan;63(1):67-80.
337. Cookson MS, Chang SS, Wells N, et al. Complications of radical cystectomy for nonmuscle invasive disease: comparison with muscle invasive disease. J Urol 2003 Jun;169(1):101-4.
338. Sabir EF, Holmäng S, Liedberg F, et al. Impact of hospital volume on local recurrence and distant metastasis in bladder cancer patients treated with radical cystectomy in Sweden. Scand J Urol 2013 Dec;47(6):483-90.
339. Morgan TM, Barocas DA, Keegan KA, et al. Volume outcomes of cystectomy--is it the surgeon or the setting? J Urol 2012 Dec;188(6):2139-44.
340. Finks JF, Osborne NH, Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. N Engl J Med 2011 Jun;364(22):2128-37.
341. Eastham JA. Do high-volume hospitals and surgeons provide better care in urologic oncology? Urol Oncol 2009 Jul-Aug;27(4):417-21.
342. Shabsigh A, Korets R, Vora K, Cet al. Defining early morbidity of radical cystectomy for patients with bladder cancer using a standardized reporting methodology. Eur Urol 2009 Jan;55(1):164-74.
343. Shariat SF, Karakiewicz PI, Palapattu GS, et al. Outcomes of radical cystectomy for transitional cell carcinoma of the bladder: a contemporary series from the Bladder Cancer Research Consortium. J Urol 2006 Dec;176 (6 Pt 1):2414-22;discussion 2422.
344. Nuhn P, May M, Sun M, et al. External validation of postoperative nomograms for prediction of allcause mortality, cancer-specific mortality, and recurrence in patients with urothelial carcinoma of the bladder. Eur Urol 2012 Jan; 61(1):58-64.

345. Bruins HM, Huang GJ, Cai J, et al. Clinical outcomes and recurrence predictors of lymph node positive urothelial cancer after cystectomy. J Urol 2009 Nov;182(5):2182-7.
346. Ok JH, Meyers FJ, Evans CP. Medical and surgical palliative care of patients with urological malignancies. J Urol 2005 Oct;174(4 Pt 1):1177-82.
347. Ubrig B, Lazica M, Waldner M, et al. Extraperitoneal bilateral cutaneous ureterostomy with midline stoma for palliation of pelvic cancer. Urology 2004 May;63(5):973-5.
348. Zebic N, Weinknecht S, Kroepfl D. Radical cystectomy in patients aged > or = 75 years: an updated review of patients treated with curative and palliative intent. BJU Int 2005 Jun;95(9):1211-4.
349. El-Tabey NA, Osman Y, Mosbah A, et al. Bladder cancer with obstructive uremia: oncologic outcome after definitive surgical management. Urology 2005 Sep;66(3):531-5.
350. Nagele U, Anastasiadis AG, Merseburger AS, et al. The rationale for radical cystectomy as primary therapy for T4 bladder cancer. World J Urol 2007 Aug;25(4):401-5.
351. Ghahestani SM, Shakhssalim N. Palliative treatment of intractable hematuria in context of advanced bladder cancer: a systematic review. Urol J 2009 Summer;6(3):149-56.
352. Srinivasan V, Brown CH, Turner AG. A comparison of two radiotherapy regimens for the treatment of symptoms from advanced bladder cancer. Clin Oncol (R Coll Radiol) 1994;6(1):11-3.
353. Herr HW. Conservative management of muscle-infiltrating bladder cancer: prospective experience. J Urol 1987 Nov;138(5):1162-3.
354. Herr HW. Transurethral resection of muscle-invasive bladder cancer: 10-year outcome. J Clin Oncol 2001 Jan; 19(1):89-93.
355. Holmäng S, Hedelin H, Anderström C, et al. Long-term follow-up of all patients with muscle invasive (stages T2, T3 and T4) bladder carcinoma in a geographical region. J Urol 1997 Aug;158(2):389-92.
356. Solsona E, Iborra I, Collado A, et al. Feasibility of radical transurethral resection as monotherapy for selected patients with muscle invasive bladder cancer. J Urol 2010 Aug;184(2):475-80.
357. Whitmore WF Jr, Batata MA, Ghoneim MA, et al. Radical cystectomy with or without prior irradiation in the treatment of bladder cancer. J Urol 1977 Jul:118(1 Pt 2):184-7. [No abstract available]
358. Gospodarowicz MK, Blandy JP. Radiation therapy for organ-conservation for invasive bladder carcinoma. In: Vogelzang NJ, Scardino PT, Shipley WU, Coffey DS, eds. *Comprehensive Textbook of Genitourinary Oncology*. Lippincott: Williams and Wilkins, 2000; pp. 487-96.
359. Maciejewski B, Majewski S. Dose fractionation and tumor repopulation in radiotherapy for bladder cancer. Radiother Oncol 1991 Jul;21(3):163-70.
360. De Neve W, Lybeert ML, Goor C, et al. Radiotherapy for T2 and T3 carcinoma of the bladder: the influence of overall treatment time. Radiother Oncol 1995 Sep;36(3):183-8.
361. Milosevic M, Gospodarowicz M, Zietman A, et al. Radiotherapy for bladder cancer. Urology 2007 Jan;69 (1 Suppl):80-92.
362. Tonoli S, Bertoni F, De Stefani A, et al. Radical radiotherapy for bladder cancer: retrospective analysis of a series of 459 patients treated in an Italian institution. Clin Oncol (R Coll Radiol) 2006 Feb;18(1): 52-9.
363. Pollack A, Zagars GZ. Radiotherapy for stage T3b transitional cell carcinoma of the bladder. Semin Urol Oncol 1996 May;14(2):86-95.
364. Mameghan H, Fisher R, Mameghan J, et al. Analysis of failure following definitive radiotherapy for invasive transitional cell carcinoma of the bladder. Int J Radiat Oncol Biol Phys 1995 Jan;31(2):247-54.
365. Näslund I, Nilsson B, Littbrand B. Hyperfractionated radiotherapy of bladder cancer. A ten-year followup of a randomized clinical trial. Acta Oncol 1994;33(4):397-402.
366. Chung PW, Bristow RG, Milosevic MF, et al. Long-term outcome of radiation-based conservation therapy for invasive bladder cancer. Urol Oncol 2007 Jul-Aug;25(4):303-9.
367. Shelley MD, Barber J, Wilt T, et al. Surgery versus radiotherapy for muscle invasive bladder cancer. Cochrane Database Syst Rev 2002;(1):CD002079.
368. Scher HI, Yagoda A, Herr HW, et al. Neoadjuvant M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) effect on the primary bladder lesion. J Urol 1988 Mar;139(3):470-4.
369. Herr HW, Bajorin DF, Scher HI. Neoadjuvant chemotherapy and bladder-sparing surgery for invasive bladder cancer: ten-year outcome. J Clin Oncol 1998 Apr;16(4):1298-301.
370. Kachnic LA, Kaufman DS, Heney NM, et al. Bladder preservation by combined modality therapy for invasive bladder cancer. J Clin Oncol 1997 Mar;15(3):1022-9.
371. Als AB, Sengelov L, von der Maase H. Long-term survival after gemcitabine and cisplatin in patients with locally advanced transitional cell carcinoma of the bladder: focus on supplementary treatment strategies. Eur Urol 2007 Aug;52(2):478-86.
372. Sternberg CN, Yagoda A, Scher HI, et al. M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for advanced transitional cell carcinoma of the urothelium. J Urol 1988 Mar;139(3):461-9.
373. Logothetis CJ, Dexeus FH, Finn L, et al. A prospective randomized trial comparing MVAC and CISCA chemotherapy for patients with metastatic urothelial tumors. J Clin Oncol 1990 Jun;8(6):1050-5.

374. Loehrer PJ Sr, Einhorn LH, Elson PJ, et al. A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. J Clin Oncol 1992 Jul;10(7):1066-73.
375. Kaufman D, Raghavan D, Carducci M, et al. Phase II trial of gemcitabine plus cisplatin in patients with metastatic urothelial cancer. J Clin Oncol 2000 May;18(9):1921-7.
376. Stadler WM, Hayden A, von der Maase H, et al. Long-term survival in phase II trials of gemcitabine plus cisplatin for advanced transitional cell cancer. Urol Oncol 2002 Jul-Aug;7(4):153-7.
377. Moore MJ, Winquist EW, Murray N, et al. Gemcitabine plus cisplatin, an active regimen in advanced urothelial cancer: a phase II trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 1999 Sep;17(9):2876-81.
378. Bajorin DF, Dodd PM, Mazumdar M, et al. Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy. J Clin Oncol 1999 Oct;17(10):3173-81.
379. Herr HW, Donat SM, Bajorin DF. Post-chemotherapy surgery in patients with unresectable or regionally metastatic bladder cancer. J Urol 2001 Mar;165(3):811-4.
380. Ploussard G, Daneshmand S, Efstathiou JA, et al. Critical analysis of bladder sparing with trimodal therapy in muscle-invasive bladder cancer: a systematic review. Eur Urol 2014 Jul;66(1):120-37.
381. James N, Bryan RT, Viney R, Patel P, Hussain S. Bladder Cancer. In: Halperin E, Wazer D, Perez C, Brady L, editors. *Perez and Brady's Principles and Practice of Radiation Oncology*. Philadelphia: Lippincott Williams & Wilkins; 2012.
382. Tilki D, Shariat SF, Lotan Y, et al. Lymphovascular invasion is independently associated with bladder cancer recurrence and survival in patients with final stage T1 disease and negative lymph nodes after radical cystectomy. BJUInt 2013 Jun;111(8):1215-21.
383. Efstathiou JA, Spiegel DY, Shipley WU, et al. Long-term outcomes of selective bladder preservation by combined-modality therapy for invasive bladder cancer: the MGH experience. Eur Urol 2012 Apr;61(4):705-11.
384. Hoskin PJ, Rojas AM, Bentzen SM, et al. Radiotherapy with concurrent carbogen and nicotinamide in bladder carcinoma. J Clin Oncol 2010 Nov;28(33):4912-8.
385. Kaufman DS, Winter KA, Shipley WU, et al. Phase I-II RTOG study (99-06) of patients with muscle-invasive bladder cancer undergoing transurethral surgery, paclitaxel, cisplatin, and twice-daily radiotherapy followed by selective bladder preservation or radical cystectomy and adjuvant chemotherapy. Urology 2009 Apr;73(4):833-7.
386. Mak RH, Zietman AL, Heney NM, et al. Bladder preservation: optimizing radiotherapy and integrated treatment strategies. BJU Int 2008 Nov;102(9 Pt B):1345-53.
387. Huddart RA, Hall E, Hussain SA, et al. Randomized Noninferiority Trial of Reduced High-Dose Volume Versus Standard Volume Radiation Therapy for Muscle-Invasive Bladder Cancer: Results of the BC2001 Trial (CRUK/01/004). Int J Radiat Oncol Biol Phys 2013 Oct;87(2):261-9.
388. Ramani VA, Maddineni SB, Grey BR, et al. Differential complication rates following radical cystectomy in the irradiated and nonirradiated pelvis. Eur Urol 2010 Jun;57(6):1058-63.
389. Cohen SM, Goel A, Phillips J, et al. The role of perioperative chemotherapy in the treatment of urothelial cancer. Oncologist 2006 Jun;11(6):630-40.
390. Sylvester R, Sternberg C. The role of adjuvant combination chemotherapy after cystectomy in locally advanced bladder cancer: what we do not know and why. Ann Oncol 2000 Jul;11(7):851-6.
391. Donat SM, Shabsigh A, Savage C, et al. Potential impact of postoperative early complications on the timing of adjuvant chemotherapy in patients undergoing radical cystectomy: a high-volume tertiary cancer center experience. Eur Urol 2009 Jan;55(1):177-86.
392. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Adjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis of individual patient data. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Eur Urol 2005 Aug;48(2):189-199;discussion 199-201.
393. Leow JJ, Martin-Doyle W, Rajagopal PS, et al. Adjuvant chemotherapy for invasive bladder cancer: A 2013 updated systematic review and meta-analysis of randomized trials. Eur Urol 2014 Jul;66(1):42-54
394. Cognetti F, Ruggeri EM, Felici A, et al. Adjuvant chemotherapy with cisplatin and gemcitabine versus chemotherapy at relapse in patients with muscle-invasive bladder cancer submitted to radical cystectomy: an Italian, multicenter, randomized phase III trial. Ann Oncol 2012 Mar;23(3):695-700.
395. Paz-Ares LG, Solsona E, Esteban E, et al. Randomized phase III trial comparing adjuvant paclitaxel/ gemcitabine/cisplatin (PGC) to observation in patients with resected invasive bladder cancer: results of the Spanish Oncology Genitourinary Group (SOGUG) 99/01study [Abstract No:LBA4518]. Genitourinary Cancer Tract, 2010 ASCO Annual Meeting.
396. Stadler WM, Lerner SP, Groshen S, et al. Phase III study of molecularly targeted adjuvant therapy in locally advanced urothelial cancer of the bladder based on p53 status. J Clin Oncol 2011 Sep;29(25):3443-9.
397. Lehmann J, Franzaring L, Thuroff J, et al. Complete long-term survival data from a trial of adjuvant chemotherapy vs control after radical cystectomy for locally advanced bladder cancer. BJU Int 2006 Jan;97(1):42-7.

398. Bono A, Benvenuti C, Gibba A, et al. Adjuvant chemotherapy in locally advanced bladder cancer. Final analysis of a controlled multicentre study. Acta Urol Ital 1997;11(1):5-8.
399. Freiha F, Reese J, Torti FM. A randomized trial of radical cystectomy versus radical cystectomy plus cisplatin, vinblastine and methotrexate chemotherapy for muscle invasive bladder cancer. J Urol 1996 Feb;155(2): 495-9;discussion 499-500.
400. Stöckle M, Meyenburg W, Wellek S, et al. Adjuvant polychemotherapy of nonorgan-confined bladder cancer after radical cystectomy revisited: long-term results of a controlled prospective study and further clinical experience. J Urol 1995 Jan;153(1):47-52.
401. Studer UE, Bacchi M, Biedermann C, et al. Adjuvant cisplatin chemotherapy following cystectomy for bladder cancer: results of a prospective randomized trial. J Urol 1994 Jul;152(1):81-4.
402. Skinner DG, Daniels JR, Russell CA, et al. Adjuvant chemotherapy following cystectomy benefits patients with deeply invasive bladder cancer. Semin Urol 1990 Nov;8(4):279-84. [No abstract available]
403. Lehmann J, Retz M, Wiemers C, et al. Adjuvant cisplatin plus methotrexate versus methotrexate, vinblastine, epirubicin, and cisplatin in locally advanced bladder cancer: results of a randomized, multicenter, phase III trial (AUO-AB 05/95). J Clin Oncol 2005 Aug;23(22):4963-74.
404. Svatek RS, Shariat SF, Lasky RE, et al. The effectiveness of off-protocol adjuvant chemotherapy for patients with urothelial carcinoma of the urinary bladder. Clin Cancer Res 2010 Sep;16(17):4461-7.
405. Sternberg CN, Skoneczna I, Kerst JM, et al. Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open-label, randomised phase 3 trial. Lancet Oncol 2015 Jan;16(1):76-86.
406. von der Maase H, Sengelov L, Roberts JT, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol 2005 Jul;23(21):4602-8.
407. Sternberg CN. Perioperative chemotherapy in muscle-invasive bladder cancer to enhance survival and/or as a strategy for bladder preservation. Semin Oncol 2007 Apr;34(2):122-8.
408. Rosenberg JE, Carroll PR, Small EJ. Update on chemotherapy for advanced bladder cancer. J Urol 2005 Jul;174(1):14-20.
409. Sternberg CN, Vogelzang NJ. Gemcitabine, paclitaxel, pemetrexed and other newer agents in urothelial and kidney cancers. Crit Rev Oncol Hematol 2003 Jun;46(Suppl):S105-S15.
410. Bajorin DF, Dodd PM, Mazumdar M, et al. Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy. J Clin Oncol 1999 Oct;17(10):3173-81.
411. Bellmunt J, Albanell J, Paz-Ares L, et al; Spanish Oncology Genitourinary Group. Pretreatment prognostic factors for survival in patients with advanced urothelial tumors treated in a phase I/II trial with paclitaxel, cisplatin, and gemcitabine. Cancer 2002 Aug;95(4):751-7.
412. Sengeløv L, Kamby C, von der Maase H. Metastatic urothelial cancer: evaluation of prognostic factors and change in prognosis during the last twenty years. Eur Urol 2001 Jun;39(6):634-42.
413. De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/ carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol 2012 Jan;30(2):191-9.
414. Bellmunt J, Choueiri TK, Fougeray R, et al. Prognostic factors in patients with advanced transitional cell carcinoma of the urothelial tract experiencing treatment failure with platinum-containing regimens. J Clin Oncol 2010 Apr;28(11):1850-5.
415. Carles J, Suarez C, Mesia C, et al. Feasiblity study of gemcitabine and cisplatin administered every two weeks in patients with advanced urothelial tumors and impaired renal function. Clin Transl Oncol 2006 Oct;8(10):755-7.
416. Hussain SA, Palmer DH, Lloyd B et al. A study of split-dose cisplatin-based neo-adjuvant chemotherapy in muscle-invasive bladder cancer. Oncol Lett 2012 Apr;3(4):855-9.
417. Hussain SA, Stocken DD, Riley P, et al. A phase I/II study of gemcitabine and fractionated cisplatin in an outpatient setting using a 21-day schedule in patients with advanced and metastatic bladder cancer. Br J Cancer 2004 Aug;91(5):844-9.
418. Morales-Barrera R, Bellmunt J, Suarez C, et al. Cisplatin and gemcitabine administered every two weeks in patients with locally advanced or metastatic urothelial carcinoma and impaired renal function. Eur J Cancer 2012 Aug;48(12):1816-21.
419. Bamias A, Dafni U, Karadimou A, et al. Prospective, open-label, randomized, phase III study of two dose-dense regimens MVAC versus gemcitabine/cisplatin in patients with inoperable, metastatic or relapsed urothelial cancer: a Hellenic Cooperative Oncology Group study (HE 16/03). Ann Oncol 2013 Apr;24(4):1011-7.
420. Galsky MD, Krege S, Lin CC, et al. Cisplatin-based combination chemotherapy in septuagenarians with metastatic urothelial cancer. Urol Oncol 2014 Jan;32(1):30.e15-21.
421. De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer "unfit" for cisplatin-based chemotherapy: phase II--results of EORTC study 30986. J Clin Oncol 2009 Nov;27(33):5634-9.

422. Galsky MD, Hahn NM, Rosenberg J, et al. A consensus definition of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy. Lancet Oncol 2011 Mar;12(3):211-4. [No abstract available]
423. Galsky MD, Hahn NM, Rosenberg J, et al. Treatment of patients with metastatic urothelial cancer "unfit" for Cisplatin-based chemotherapy. J Clin Oncol 2011 Jun;29(17):2432-8.
424. Dash A, Galsky MD, Vickers AJ, et al. Impact of renal impairment on eligibility for adjuvant cisplatin-based chemotherapy in patients with urothelial carcinoma of the bladder. Cancer 2006 Aug;107(3):506-13.
425. Nogue-Aliguer M, Carles J, Arrivi A, et al. Gemcitabine and carboplatin in advanced transitional cell carcinoma of the urinary tract: an alternative therapy. Cancer 2003 May;97(9):2180-6.
426. Balducci L, Extermann M. Management of cancer in the older person: a practical approach. Oncologist 2000;5(3):224-37.
427. De Santis M, Bachner M. New developments in first- and second-line chemotherapy for transitional cell, squamous cell and adenocarcinoma of the bladder. Curr Opin Urol 2007 Sep;17(5):363-8.
428. Raj GV, Iasonos A, Herr H, et al. Formulas calculating creatinine clearance are inadequate for determining eligibility for Cisplatin-based chemotherapy in bladder cancer. J Clin Oncol 2006 Jul;24(19):3095-100.
429. von der Maase H. Gemcitabine in transitional cell carcinoma of the urothelium. Expert Rev Anticancer Ther 2003 Feb;3(1):11-9.
430. Yafi FA, North S, Kassouf W. First- and second-line therapy for metastatic urothelial carcinoma of the bladder. Curr Oncol 2011 February;18(1): e25-e34.
431. Bellmunt J, Petrylak DP. New therapeutic challenges in advanced bladder cancer. Semin Oncol 2012 Oct;39(5):598-607.
432. Gabrilove JL, Jakubowski A, Scher H, et al. Effect of granulocyte colony-stimulating factor on neutropenia and associated morbidity due to chemotherapy for transitional-cell carcinoma of the urothelium. N Engl J Med 1988 Jun;318(22):1414-22.
433. Bamias A, Aravantinos G, Deliveliotis C, et al. Hellenic Cooperative Oncology Group. Docetaxel and cisplatin with granulocyte colony-stimulating factor (G-CSF) versus MVAC with G-CSF in advanced urothelial carcinoma: a multicenter, randomized, phase III study from the Hellenic Cooperative Oncology Group. J Clin Oncol 2004 Jan;22(2):220-8.
434. Sternberg CN, de Mulder PH, Schornagel JH, et al; European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group. Randomized phase III trial Of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. J Clin Oncol 2001 May;19(10):2638-46.
435. Sternberg CN, de Mulder P, Schornagel JH, et al; EORTC Genito-Urinary Cancer Group. Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours. Eur J Cancer 2006 Jan;42(1):50-4.
436. Bellmunt J, von der Maase H, Mead GM, et al. Randomized phase III study comparing paclitaxel/ cisplatin/ gemcitabine and gemcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC Intergroup Study 30987. J Clin Oncol 2012 Apr;30(10):1107-13.
437. Galsky MD, Chen GJ, Oh WK, et al. Comparative effectiveness of cisplatin-based and carboplatinbased chemotherapy for treatment of advanced urothelial carcinoma. Ann Oncol 2012 Feb;23(2): 406-10.
438. Albers P, Siener R, Härtlein M, et al; German TCC Study Group of the German Association of Urologic Oncology. Gemcitabine monotherapy as second-line treatment in cisplatin-refractory transitional cell carcinoma - prognostic factors for response and improvement of quality of life. Onkologie 2002 Feb;25(1):47-52.
439. Sternberg CN, Calabrò F, Pizzocaro G, et al. Chemotherapy with an every-2-week regimen of gemcitabine and paclitaxel in patients with transitional cell carcinoma who have received prior cisplatin-based therapy. Cancer 2001 Dec;92(12):2993-8.
440. Meluch AA, Greco FA, Burris HA 3rd, et al. Paclitaxel and gemcitabine chemotherapy for advanced transitional-cell carcinoma of the urothelial tract: a phase II trial of the Minnie pearl cancer research network. J Clin Oncol 2001 Jun;19(12):3018-24.
441. Parameswaran R, Fisch MJ, Ansari RH, et al. A Hoosier Oncology Group phase II study of weekly paclitaxel and gemcitabine in advanced transitional cell (TCC) carcinoma of the bladder. Proc Am Soc Clin Oncol 2001; 200:abstr 798.
442. Guardino AE, Srinivas S. Gemcitabine and paclitaxel as second line chemotherapy for advanced urothelial malignancies. Proc Am Soc Clin Oncol 2002;21: abstr 2413.
443. Fechner G, Siener R, Reimann M, et al. Randomised phase II trial of gemcitabine and paclitaxel second-line chemotherapy in patients with transitional cell carcinoma (AUO Trial AB 20/99). Int J Clin Pract 2006 Jan; 60(1):27-31.
444. Kaufman DS, Carducci MA, Kuzel T, et al. Gemcitabine (G) and paclitaxel (P) every two weeks (GP2w):a completed multicenter phase II trial in locally advanced or metastatic urothelial cancer (UC). Proc Am Soc Clin Oncol 2002;21: abstr 767.

445. Calabrò F, Lorusso V, Rosati G, et al. Gemcitabine and paclitaxel every 2 weeks in patients with previously untreated urothelial carcinoma. Cancer 2009 Jun;115(12):2652-9.
446. Ko YJ, Canil CM, Mukherjee SD, et al. Nanoparticle albumin-bound paclitaxel for second-line treatment of metastatic urothelial carcinoma: a single group, multicentre, phase 2 study. Lancet Oncol 2013 Jul;14(8):769-76.
447. Albers P, Park SI, Niegisch G, et al. Randomized phase III trial of 2nd line gemcitabine and paclitaxel chemotherapy in patients with advanced bladder cancer: short-term versus prolonged treatment [German Association of Urological Oncology (AUO) trial AB 20/99]. Ann Oncol 2011 Feb;22(2):228-294.
448. Culine S, Theodore C, De Santis M, et al. A phase II study of vinflunine in bladder cancer patients progressing after first-line platinum-containing regimen. Br J Cancer 2006 May;94(10):1395-401.
449. Bellmunt J, Théodore C, Demkov T, et al. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. J Clin Oncol 2009 Sep;27(27):4454-61
450. Stadler WM. Gemcitabine doublets in advanced urothelial cancer. Semin Oncol 2002 Feb;29(1 Suppl3):15-9.
451. Hussain M, Vaishampayan U, Du W, et al. Combination paclitaxel, carboplatin, and gemcitabine is an active treatment for advanced urothelial cancer. J Clin Oncol 2001 May;19(9):2527-33.
452. Abe T, Shinohara N, Harabayashi T, et al. Impact of multimodal treatment on survival in patients with metastatic urothelial cancer. Eur Urol 2007 Oct;52(4):1106-13.
453. Bekku K, Saika T, Kobayashi Y, et al. Could salvage surgery after chemotherapy have clinical impact on cancer survival of patients with metastatic urothelial carcinoma? Int J Clin Oncol 2013 Feb;18(1):110-5.
454. Cowles RS, Johnson DE, McMurtrey MJ. Long-term results following thoracotomy for metastatic bladder cancer. Urology 1982 Oct;20(4):390-2.
455. de Vries RR, Nieuwenhuijzen JA, Meinhardt W, et al. Long-term survival after combined modality treatment in metastatic bladder cancer patients presenting with supra-regional tumor positive lymph nodes only. Eur J Surg 2009 Apr;35(4):352-5.
456. Dodd PM, McCaffrey JA, Herr H, et al. Outcome of postchemotherapy surgery after treatment with methotrexate, vinblastine, doxorubicin, and cisplatin in patients with unresectable or metastatic transitional cell carcinoma. J Clin 1999 Aug;17(8):2546-52.
457. Donat SM, Herr HW, Bajorin DF, et al. Methotrexate, vinblastine, doxorubicin and cisplatin chemotherapy and cystectomy for unresectable bladder cancer. J Urol 1996 Aug;156(2 Pt 1):368-71.
458. Gowardhan B, Mathers ME, Feggetter JG. Twenty-three years of disease-free survival following cutaneous metastasis from a primary bladder transitional cell carcinoma. Int J Urol 2004 Nov;11(11):1031-2.
459. Kanzaki R, Higashiyama M, Fujiwara A, et al. Outcome of surgical resection of pulmonary metastasis from urinary tract transitional cell carcinoma. Interact Cardiovasc Thorac Surg 2010 Jul;11(1):60-4.
460. Ku JH, Yeo WG, Park MY, et al. Metastasis of transitional cell carcinoma to the lower abdominal wall 20 years after cystectomy. Yonsei Med J 2005 Feb 28;46(1):181-3.
461. Lehmann J, Suttmann H, Albers P, et al. Surgery for metastatic urothelial carcinoma with curative intent: the German experience (AUO AB 30/05). Eur Urol 2009 Jun;55(6):1293-99.
462. Matsuguma H, Yoshino I, Ito H, et al. Is there a role for pulmonary metastasectomy with a curative intent in patients with metastatic urinary transitional cell carcinoma? Ann Thorac Surg 2011 Aug;92(2):449-53.
463. Miller RS, Freiha FS, Reese JH, et al. Cisplatin, methotrexate and vinblastine plus surgical restaging for patients with advanced transitional cell carcinoma of the urothelium. J Urol 1993 Jul;150(1):65-9.
464. Otto T, Krege S, Suhr J, et al. Impact of surgical resection of bladder cancer metastases refractory to systemic therapy on performance score: a phase II trial. Urology 2001 Jan;57(1):55-9.
465. Sarmiento JM, Wi MS, Piao Z, et al. Solitary cerebral metastasis from transitional cell carcinoma after a 14-year remission of urinary bladder cancer treated with gemcitabine: Case report and literature review. Surg Neurol Int 2012;3:82.
466. Tanis PJ, Zondervan P, van de Wiel BA, et al. Surgery for isolated lung metastasis in two patients with bladder cancer. Urology 2005 Oct;66(4):881.
467. Sweeney P, Millikan R, Donat M, et al. Is there a therapeutic role for post-chemotherapy retroperitoneal lymph nod dissection in metastatic transitional cell carcinoma of the bladder? J Urol 2003 Jun;169(6):2113-7.
468. Siefker-Radtke AO, Walsh GL, Pisters LL, et al. Is there a role for surgery in the management of metastatic urothelial cancer? The M.D. Anderson experience. J Urol 2004 Jan;171(1):145-8.
469. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. Cancer Treat Rev 2001 Jun;27(3):165-76. Review.
470. Aapro M, Abrahamsson PA, Body JJ, et al. Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel. Ann Oncol 2008 Mar;19(3):420-32.
471. Zaghloul MS, Boutrus R, El-Hossieny H, et al. A prospective, randomized, placebo-controlled trial of zoledronic acid in bony metastatic bladder cancer. Int J Clin Oncol 2010 Aug;15(4):382-9.

472. Henry DH, Costa L, Goldwasser F, et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. J Clin Oncol 2011 Mar;29(9):1125-32.
473. Rosen LS, Gordon D, Tchekmedyian NS, et al. Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: a randomized, Phase III, double-blind, placebo-controlled trial. Cancer 2004 Jun;100(12):2613-21.
474. Youssef RF, Mitra AP, Bartsch G Jr, et al. Molecular targets and targeted therapies in bladder cancer management. World J Urol 2009;27:9-20.
475. Shariat SF, Youssef RF, Gupta A, et al. Association of angiogenesis related markers with bladder cancer outcomes and other molecular markers. J Urol 2010;183:1744-50.
476. Song S, Wientjes MG, Gan Y, et al. Fibroblast growth factors: an epigenetic mechanism of broad spectrum resistance to anticancer drugs. Proc Natl Acad Sci USA 2000;97:8658-63.
477. Gomez-Roman JJ, Saenz P, Molina M, et al. Fibroblast growth factor receptor 3 is overexpressed in urinary tract carcinomas and modulates the neoplastic cell growth. Clin Cancer Res 2005 Jan;11(2 Pt 1):459-65.
478. Ioachim E, Michael MC, Salmas M, et al. Thrombospondin-1 expression in urothelial carcinoma: prognostic significance and association with p53 alterations, tumour angiogenesis and extracellular matrix components. BMC Cancer 2006 May;6:140.
479. Gallagher DJ, Milowsky MI, Ishill N, et al. Detection of circulating tumor cells in patients with urothelial cancer. Ann Oncol 2009 Feb:20(2):305-8.
480. Flaig TW, Wilson S, van Bokhoven A, et al. Detection of circulating tumor cells in metastatic and clinically localized urothelial carcinoma. Urology 2011 Oct;78(4):863-7.
481. Hoffmann AC, Wild P, Leicht C, et al. MDR1 and ERCC1 expression predict outcome of patients with locally advanced bladder cancer receiving adjuvant chemotherapy. Neoplasia 2010 Aug;12(8):628-36.
482. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol 1993 Mar;11(3):570-9.
483. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993 Mar;85(5):365-76.
484. Sogni F, Brausi M, Frea B, et al. Morbidity and quality of life in elderly patients receiving ileal conduit or orthotopic neobladder after radical cystectomy for invasive bladder cancer. Urology 2008 May;71(5):919-23.
485. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992 Jun;30(6):473-83.
486. Ware JE Jr, Keller SD, Gandek B, et al. Evaluating translations of health status questionnaires. Methods from the IQOLA project. International Quality of Life Assessment. Int J Technol Assess Health Care 1995 Summer;11(3):525-51.
487. Gilbert SM, Dunn RL, Hollenbeck BK, et al. Development and validation of the Bladder Cancer Index: a comprehensive, disease specific measure of health related quality of life in patients with localized bladder cancer. J Urol 2010 May;183(5):1764-9.
488. Ramirez A, Perrotte P, Valiquette L, et al. Exploration of health-related quality of life areas that may distinguish between continent diversion and ileal conduit patients. Can J Urol 2005 Feb;12(1):2537-42.
489. Månsson A, Caruso A, Capovilla E, et al. Quality of life after radical cystectomy and orthotopic bladder substitution: a comparison between Italian and Swedish men. BJU Int 2000 Jan;85(1):26-31.
490. Autorino R, Quarto G, Di Lorenzo G, et al. Health related quality of life after radical cystectomy: comparison of ileal conduit to continent orthotopic neobladder. Eur J Surg Oncol 2009 Aug;35(8): 858-64.
491. Månsson A, Davidsson T, Hunt S, et al. The quality of life in men after radical cystectomy with a continent cutaneous diversion or orthotopic bladder substitution: is there a difference? BJU Int 2002 Sep;90(4):386-90.
492. Wright JL, Porter MP. Quality-of-life assessment in patients with bladder cancer. Nat Clin Pract Urol 2007 Mar; 4(3):147-54.
493. Saika T, Arata R, Tsushima T, et al; Okayama Urological Research Group. Health-related quality of life after radical cystectomy for bladder cancer in elderly patients with an ileal conduit, ureterocutaneostomy, or orthotopic urinary reservoir: a comparative questionnaire survey. Acta Med Okayama 2007 Aug;61(4):199-203.
494. Hedgepeth RC, Gilbert SM, He C, et al. Body image and bladder cancer specific quality of life in patients with ileal conduit and neobladder urinary diversions. Urology 2010 Sep;76(3):671-5.
495. Dutta SC, Chang SC, Coffey CS, et al. Health related quality of life assessment after radical cystectomy: comparison of ileal conduit with continent orthotopic neobladder. J Urol 2002 Jul;168(1):164-7.
496. Hara I, Miyake H, Hara S, et al. Health-related quality of life after radical cystectomy for bladder cancer: a comparison of ileal conduit and orthotopic bladder replacement. BJU Int 2002 Jan;89(1):10-13.
497. Philip J, Manikandan R, Venugopal S, et al. Orthotopic neobladder versus ileal conduit urinary diversion after cystectomy - a quality-of-life based comparison. Ann R Coll Surg Engl 2009 Oct;91(7):565-9.

498. Roychowdhury DF, Hayden A, Liepa AM. Health-related quality-of-life parameters as independent prognostic factors in advanced or metastatic bladder cancer. J Clin Oncol 2003 Feb;21(4):673-8.
499. Hardt J, Filipas D, Hohenfellner R, et al. Quality of life in patients with bladder carcinoma after cystectomy: first results of a prospective study. Qual Life Res 2000 Feb;9(1):1-12.
500. Fosså SD, Aaronson N, Calais da Silva F, et al. Quality of life in patients with muscle-infiltrating bladder cancer and hormone-resistant prostatic cancer. Eur Urol 1989;16(5):335-9.
501. Mommsen S, Jakobsen A, Sell A. Quality of life in patients with advanced bladder cancer. A randomized study comparing cystectomy and irradiation-the Danish Bladder Cancer Study Group (DAVECA protocol 8201). Scand J Urol Nephrol Suppl 1989;125:115-20.
502. Fokdal L, Høyer M, von der Maase H. Radical radiotherapy for urinary bladder cancer: treatment outcomes. Expert Rev Anticancer Ther 2006 Feb;6(2):269-79.
503. Rödel C, Weiss C, Sauer R. Organ preservation by combined modality treatment in bladder cancer: the European perspective. Semin Radiat Oncol 2005 Jan;15(1):28-35.
504. Rödel C, Grabenbauer GG, Kühn R, et al. Combined-modality treatment and selective organ preservation in invasive bladder cancer: long-term results. J Clin Oncol 2002 Jul;20(14):3061-71.
505. Merseburger AS, Kuczyk MA. The value of bladder-conserving strategies in muscle-invasive bladder carcinoma compared with radical surgery. Curr Opin Urol 2007 Sep;17(5):358-62.
506. Rödel C, Weiss C, Sauer R. Trimodality treatment and selective organ preservation for bladder cancer. J Clin Oncol 2006;24(35):5536-44.
507. Lodde M, Palermo S, Comploj E, et al. Four years experience in bladder preserving management for muscle invasive bladder cancer. Eur Urol 2005 Jun;47(6):773-8;discussion 778-9.
508. Malkowicz SB, van Poppel H, Mickisch G, et al. Muscle-invasive urothelial carcinoma of the bladder. Urology 2007 Jan;69(1 Suppl):3-16.
509. Karakiewicz PI, Shariat SF, Palapattu GS, et al. Nomogram for predicting disease recurrence after radical cystectomy for transitional cell carcinoma of the bladder. J Urol 2006 Oct;176(4 Pt 1):1354-61; discussion 1361-2.
510. Shariat SF, Karakiewicz PI, Palapattu GS, et al. Nomograms provide improved accuracy for predicting survival after radical cystectomy. Clin Cancer Res 2006 Nov;12(22):6663-76.
511. Zaak D, Burger M, Otto W, et al. Predicting individual outcomes after radical cystectomy: an external validation of current nomograms. BJU Int 2010 Aug;106(3):342-8.
512. Giannarini G, Kessler TM, Thoeny HC, et al. Do the patients benefit form routine follow-up to detect recurrences after radical cystectomy an ileal orthotopic bladder substitution? Eur Urol 2010 Oct;58: 486-94.
513. Volkmer BG, Kuefer R, Bartsch GC Jr, et al. Oncological followup after radical cystectomy for bladder cancer-is there any benefit? J Urol 2009:181(4):1587-93.
514. Soukup V, Babjuk M, Bellmunt J, et al. Follow-up after surgical treatment of bladder cancer: A critical analysis of the literature. Eur Urol 2012 Aug:62(2):290-302.
515. Huguet J. Follow-up after radical cystectomy based on patterns of tumor recurrence and its risk factors. Actas Urol Esp 2013 Jun;37:376-382.
516. Ghoneim MA, Abdel-Latif M, el-Mekresh M, et al. Radical cystectomy for carcinoma of the bladder: 2,720 consecutive cases 5 years later. J Urol 2008 Jul;180(1):121-7.
517. Donat SM. Staged based directed surveillance of invasive bladder cancer following radical cystectomy: valuable and effective? World J Urol 2006;24(5):557-64.
518. Bochner BH, Montie JE, Lee CT. Follow-up strategies and management of recurrence in urologic oncology bladder cancer: invasive bladder cancer. Urol Clin North Am 2003 Nov;30(4):777-89.
519. Mathers MJ, Zumbe J, Wyler S, et al. Is there evidence for a multidisciplinary follow-up after urological cancer? An evaluation of subsequent cancers. World J Urol 2008 Jun;26(3):251-6.
520. Vrooman OP, Witjes JA. Follow-up of patients after curative bladder treatment: guidelines vs practice. Curr Opin Urol 2010 Sep;20(5):437-42.
521. Cagiannos I, Morash C. Surveillance strategies after definitive therapy of invasive bladder cancer. Can Urol Assoc J 2009 Dec;(6 Suppl 4):S237-42.
522. Stenzl A, Draxl H, Posch B, et al. The risk of urethral tumors in female bladder cancer: can the urethra be used for orthotopic reconstruction of the lower urinary tract? J Urol 1995 Mar;153(3 Pt 2):950-5.
523. Freeman JA, Tarter TA, Esrig D, et al. Urethral recurrence in patients with orthotopic ileal neobladders. J Urol 1996 Nov;156(5):1615-9.
524. Huguet J, Palou J, Serrallach M, et al. Management of urethral recurrence in patients with Studer ileal neobladder. Eur Urol 2003 May;43(5):495-8.
525. Nieder AM, Sved PD, Gomez P, et al. Urethral recurrence after cystoprostatectomy: implications for urinary diversion and monitoring. Urology 2004 Nov;64(5):950-4.
526. Varol C, Thalmann GN, Burkhard FC, et al. Treatment of urethral recurrence following radical cystectomy and ileal bladder substitution. J Urol 2004 Sep;172(3):937-42.

527. Lin DW, Herr HW, Dalbagni G. Value of urethral wash cytology in the retained male urethra after radical cystoprostatectomy. J Urol 2003 Mar;169(3):961-3.
528. Sherwood JB, Sagalowsky AI. The diagnosis and treatment of urethral recurrence after radical cystectomy. Urol Oncol 2006 Jul-Aug;24(4):356-61.
529. Slaton JW, Swanson DA, Grossman HB, et al. A stage specific approach to tumor surveillance after radical cystectomy for transitional cell carcinoma of the bladder. J Urol 1999 Sep;162(3 Pt 1):710-4.
530. Erckert M, Stenzl A, Falk M, et al. Incidence of urethral tumor involvement in 910 men with bladder cancer. World J Urol 1996;14(1):3-8.
531. Clark PE, Stein JP, Groshen SG, et al. The management of urethral transitional cell carcinoma after radical cystectomy for invasive bladder cancer. J Urol 2004 Oct;172(4 Pt 1):1342-7.
532. Picozzi S, Ricci C, Gaeta M, et al. Upper urinary tract recurrence following radical cystectomy for bladder cancer: a meta-analysis on 13,185 patients. J Urol 2012 Dec;188(6):2046-54.
533. Sanderson KM, Cai J, Miranda G, et al. Upper tract urothelial recurrence following radical cystectomy for transitional cell carcinoma of the bladder: an analysis of 1,069 patients with 10-year followup. J Urol 2007 Jun;177:2088-94.

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.