Multi-disciplinary Team (MDT) Guidance for Managing Bladder Cancer

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Produced by:

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- **Action on Bladder Cancer (ABC)**

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This guidance has been developed for healthcare professionals and multi-disciplinary teams with the following aims:

- To provide evidence-based guidance on the management options for superficial, muscle-invasive and advanced bladder cancer
- To ensure clarity on the role of the MDT on the management of superficial, muscle-invasive and advanced bladder cancer

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The Guidance has been compiled and edited from a multi-disciplinary panel with extensive experience in the management of patients with bladder cancer.

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Abbreviations

5-ALA: 5-aminolevulinic acid

BCG: bacillus Calmette-Guérin

BPT: bladder-preserving therapy

BSC: best supportive care

CI: confidence interval

CIS: carcinoma *in situ*

CR: complete response

CRT: chemoradiotherapy

CT: computed tomography

DC: docetaxel + cisplatin

DFS: disease-free survival

DRE: digital rectal examination

DSS: disease-specific survival

EAU: European Association of Urology

ECOG: Eastern Co-operative Oncology Group

EORTC: European Organization for the Research and Treatment of Cancer

GC: gemcitabine + cisplatin

GCb: gemcitabine + carboplatin

GCSF: granulocyte colony stimulating factor

GFR: glomerular filtration rate

HAL: hexaminolevulinic acid

HR: hazard ratio

IFN: interferon

LUTS: lower urinary tract symptoms

MDT: multi-disciplinary team

MMC: mitomycin C

MRC: Medical Research Council

MRI: magnetic resonance imaging

M-CAVI: methotrexate + vinblastine + carboplatin

M-VAC: methotrexate + vinblastine + cisplatin

NBI: narrow-band imaging

NMIBC: non-muscle invasive bladder cancer

OR: odds ratio

ORR: overall response rate

OS: overall survival

PDD: photodynamic diagnosis

PFS: progression-free survival

PR: partial response

PS: performance status

PSA: prostate-specific antigen

RCON: radiotherapy + carbogen + nicotinamide

RCP: Royal College of Pathologists

RCT: randomised controlled trial

RFS: recurrence-free survival

RR: relative risk

SD: stable disease

TB: tuberculosis

TCC: transitional cell carcinoma

TNM: tumour-node-metastasis

TTP: time to progression

TUR: transurethral resection

US: ultrasound

WHO: World Health Organization

Integrated Care and the Multi-disciplinary Team (MDT)

The provision of a consistent treatment strategy across a multi-disciplinary team (MDT), as well as the model of integrated care is increasingly being adapted as a valuable approach to overcome the fragmentation of patient management. In addition, an MDT provides an ideal framework to conduct audits and facilitate peer review.

The management strategies proposed for patients with non-muscle invasive bladder cancer (NMIBC), muscle invasive and advanced bladder cancer within the MDT can be successfully driven when the members of the MDT work together with ongoing support provided by the wider team (Table 1). The MDT can provide patients with treatment options that are specifically tailored to address their individual needs, such as disease state, co-morbid conditions and lifestyle. To ensure the success of the MDT approach, familiarity with the entire spectrum of management strategies is recommended.

Table 1: Proposed composition of the MDT in the non-muscle invasive, muscle invasive and advanced bladder cancer setting

• Urological surgeons	• Pathologists
• Clinical and medical oncologists*	• Urology and oncology nurse specialists
• MDT co-ordinator and administrative support	• Palliative care specialists
• Radiologists	

*Medical oncologist attendance is not necessary for low-risk superficial disease

The purpose of the treatment algorithms presented in this document is to provide a unique framework that can be adapted for the management of the three main types of bladder cancer: non-muscle invasive, muscle invasive and advanced transitional cell carcinoma (TCC) (Figure 1).[1] Management of the less common tumours such as squamous cell carcinomas or adenocarcinomas are not addressed within this document.

Figure 1: Summary of the definition of urinary bladder cancer stages *(adapted from the American Joint Committee on Cancer staging manual 2010)*[1]

NON-MUSCLE INVASIVE TCC	MUSCLE INVASIVE TCC	ADVANCED TCC (METASTATIC)
pTa/pTis/T1 N0 M0	T2/T3/T4 Nx/N0/N1 M0	Any T N2/N3 M1

T – Primary tumour

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
pTa	Non-invasive papillary carcinoma
pTis	Carcinoma in situ: 'flat tumour'
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
pT2a	Tumour invades superficial muscle (inner half)
pT2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue
pT3a	Microscopically
pT3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate (direct stromal invasion), uterus, vagina, pelvic wall, abdominal wall
pT4a	Tumour invades prostate, uterus or vagina
pT4b	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	Single positive node in primary drainage regions
N2	Multiple positive modes in primary drainage regions
N3	Common iliac node involvement

M – Distant metastasis

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

is: *in situ*; M: metastases; N; node; p: pathological; TCC: transitional cell carcinoma

Approach within the MDT

Key questions for the MDT

- Grade (World Health Organization [WHO])
- Tumour size
- Tumour Node Metastasis (TMN) stage
- New/recurrent
- Single/multiple
- Risk group if NMIBC
- Previous tumours
- Previous response to intravesical therapy
- Bladder symptoms/function
- Bladder diverticula diagnosis
- Bowel symptoms
- Bilateral hip prosthesis
- Hydronephrosis
- Renal function
- Age
- Co-morbidities
- Life expectancy
- Availability of appropriate clinical trials

The MDT plays an essential role in non-muscle invasive, muscle invasive and advanced bladder cancer management. However, it is often difficult to know which patients warrant discussion; thus it is essential to ensure that individual patients' details together with their diagnosis are available, as well as a record of any decisions that may have resulted from meetings. It is crucial that in order to fully discuss a particular patients' treatment plan, a member of the MDT team should have already seen the patient. As the majority of patients are sourced through pathology, relapses are more difficult to identify and as such patient identification continues to be a problem.

To ensure that all professional groups and appropriate disciplines contribute to, and participate in, decisions on the clinical management of patients, MDTs have repeatedly been endorsed as the principal way to do this.

One of the key concepts of integrated care is to support the role of the MDT (working as a single unit) but it should not be forgotten that the MDT has the freedom to clinically tailor management strategies for the specific needs of an individual patient.

Treatment strategies are influenced by the following:

- The stage of the bladder cancer, as well as the risk of disease progression, survival and patient characteristics, such as age and general fitness, influence the treatment strategy employed by the MDT. All these factors should be discussed to determine the most appropriate treatment modality for an individual patient. For example, age may be a restrictive factor in opting for surgery for some patients with bladder cancer.
- Patient preference should be discussed within the MDT and the MDT should ensure the involvement of the patient in determining the most appropriate treatment strategy.
- Patient case notes, pathology reports, laboratory test results and radiology data should be made available for discussion at the meeting.
- The inclusion of a patient in an appropriate clinical trial should also be considered.

Approach to the patient

Key points for discussion with the patient

- Likelihood of recurrence
- Likelihood of disease progression
- Treatment options
- Ability to tolerate general anaesthetic
- Fitness for radical radiotherapy
- Fitness for cystectomy
- Fitness for chemotherapy
- Patient preference
- Local disease control
- Major symptoms
- Life expectancy
- Palliative care
- Treatment side-effects
- Impact of treatment on quality of life
- Occupational exposure and advice
- Smoking history and cessation advice
- Diabetes and pioglitazone treatment
- Clinical trials

Patient expectations

The patient has the right to discuss their treatment strategy with appropriately trained members of the MDT

The occurrence of any potential side-effects associated with each treatment modality and the implications for future lifestyle changes should be discussed with the patient by the healthcare professional when determining an appropriate management option.

To ensure the patient and his/her partner, family and/or carers can make an informed decision, based upon the treatment options that are offered, all the points detailed above should be addressed. For example, the choice between radical radiotherapy and radical cystectomy may be influenced by a patient's anticipated effect of treatment on quality of life.

The available treatment modalities and the potential adverse effects they may have on lifestyle and quality of life should be discussed with all patients.

The lack of guidance for how healthcare professionals should effectively exchange clinical evidence supporting various treatment options to patients facing decisions is acknowledged. However, if recommendations are largely based on appropriate clinical studies and expert opinion, it is possible to achieve the five communication tasks when framing and communicating clinical evidence (Table 2).

Table 2: Exchange of clinical evidence with patients

1. Understand the patient's experience, expectations and preferences
2. Build partnerships between the patient and carer
3. Provide evidence, including uncertainties, and discuss adverse events
4. Provide and present recommendations
5. Check for understanding and agreement

Assessment and Diagnosis

Primary diagnosis

Symptoms

- Asymptomatic non-visible haematuria is generally the first sign of bladder cancer and is the most common finding in NMIBC.[2,3] It is microscopically present in almost all patients with cystoscopically detectable tumours.[4] However, it is an intermittent finding upon repeat testing.[5]
- Lower urinary tract symptoms (LUTS) such as urgency, increased urinary frequency and bladder pain may be associated with the presence of carcinoma *in situ* (CIS).[2,3]
- A key issue is the workup following presentation of haematuria or LUTS.

Screening

There is currently no evidence to support opportunistic screening for bladder cancer without a clinical reason.[6]

Urine cytology

- The diagnosis of a high-grade tumour or CIS can be made following cytological analysis of voided urine.[3]
- Urine cytology is highly specific (>90%) and has a reasonable sensitivity for detecting high-grade lesions /CIS (>60%).
- However, the sensitivity of urine cytology in detecting bladder cancers (especially low-grade NMIBC) in patients presenting with non-visible haematuria may be suboptimal; a negative test does not rule out malignancy. Urine cytology should therefore not be used as a diagnostic test in isolation.[7–9]

Urinary molecular biomarker tests

- Routine application of these tests has not been established to date.[3]
- Currently available molecular urinary biomarkers approved by the US Food and Drug Administration are the qualitative point-of-care tests (NMP22 Bladder Chek; bladder tumour antigen stat) and the laboratory-based tests (BTA TRAK; ImmunoCyt ; UroVysion).
    - The sensitivities of NMP22, ImmunoCyt and UroVysion are significantly higher than that of urine cytology.
    - However, the higher sensitivity comes at a price of reduced specificity. All three novel biomarkers and cytology were better at detecting more aggressive higher-risk tumours than less aggressive lower-risk tumours.[10]
- The clinical value of a novel urinary biomarker depends not only on its performance metrics but also the clinical context in which it is to be used.
    - As an adjunct in the primary detection of bladder cancer, such as in the haematuria clinic environment, the concern is that the lower specificity (higher false positive rate) of currently available urinary biomarkers would lead to unnecessary anxiety, further costly and invasive investigations and the potential dilemma of discharging a patient with a positive urinary biomarker test but negative diagnostic investigations.
    - The most promising arena for the use of novel contemporary biomarkers is likely to be as part of surveillance protocols in patients with a previous history of low- or intermediate-risk NMIBC. However, surveillance protocols utilising novel urinary biomarkers have not been validated in large prospective studies. Moreover, the cost-effectiveness and patient acceptability of such approaches needs further study.

White light cystoscopy

- Cystoscopy, guided by white light, has been the gold standard technique for the detection and follow-up of bladder cancer. However, the use of white light can lead to missing lesions that are not visible.[3]

Photodynamic diagnosis-assisted cystoscopy

- Photodynamic (fluorescence) diagnosis-assisted (PDD) cystoscopy with 5-aminolevulinic acid (5-ALA) or hexaminolevulinic acid (HAL) improves the detection of bladder tumours compared with conventional white-light cystoscopy (WLC), especially with respect to CIS and results in more complete resections.
    - HAL is an ester-derivative of 5-ALA with better bioavailability and a shorter instillation time. Only HAL is currently registered for PDD in bladder cancer patients.
- There are conflicting data on the effects of PDD on longer term outcomes.
    - The true added value of PDD in reducing tumour recurrence in routine practice is difficult to assess as studies vary in the use of immediate single- dose intravesical chemotherapy post-transurethral resection (TUR) and choice of photosensitiser (5-ALA or HAL).
    - The effects of PDD on time to progression (TTP) or survival remain to be demonstrated.
- PDD is most useful for detection of CIS and guiding biopsies in patients with positive cytology or a history of high-grade NMIBC.[3]
- PDD may also have a role to play in patients who have positive urine cytology, but negative WLC and negative upper urinary tract imaging.

Clinical evidence

- A systematic review and meta-analysis assessed the performance of PDD in 27 studies.[11] Most used 5-ALA (n=18) as the only photosensitising agent.
    - The median sensitivity for PDD was 92% (95% confidence interval [CI], 80–100) versus 71% (95% CI, 49–93) for WLC.
    - For higher-risk tumours, the median sensitivity of PDD was 89% (95% CI, 6–100) whereas for WLC it was 56% (95% CI, 0–100).
    - For lower-risk tumours, the median sensitivity of PDD and WLC were broadly similar; 92% (95% CI, 20–95) versus 95% (95% CI, 8–100), respectively.
    - However, the overall median specificity was less for PDD than for WLC; 57% (95% CI, 36–79) versus 72% (95% CI, 47–96).
    - In patient-based detection of bladder cancer across 4 studies using 5-ALA and 3 using HAL, the median (range) sensitivity and specificity for 5-ALA was 96% (64–100) and 52% (33–67) respectively, compared with 90% (53–96) sensitivity and 81% (43–100) specificity for HAL.
    - Four randomised controlled trials (RCTs) using 5-ALA reported clinical effectiveness. PDD at TUR resulted in fewer residual tumours at first check cystoscopy (relative risk [RR], 0.37; 95% CI, 0.20–0.69] and longer recurrence-free survival (RFS) (RR, 1.37; 95% CI, 1.18–1.59] than WLC.
- A meta-analysis of clinical studies has shown that an additional 20% of NMIBC (95% CI, 8–35) was detected using PDD compared with WLC, and an additional 39% of CIS cases (95% CI, 23–57).[12]
    - In addition, this analysis demonstrated improved RFS rates with PDD versus WLC (16–27% higher at 12 months and 12–15% higher at 24 months).
- More recently, 3 RCTs of PDD versus WLC have been published showing conflicting data on the clinical effectiveness of PDD.[13–15]
    - No benefit of PDD with 5-ALA was demonstrated for the detection of bladder tumours, recurrence rates or progression rates.[13]
    - Improved detection rates with 5-ALA assisted PDD did not translate into reduced recurrence rates at 12 months.[14]
    - PDD with HAL resulted in improved RFS at short-term follow-up (9 months) compared with WLC.[15]
        - This was a large trial (766 patients) in 28 centres in the USA, Canada and Europe. In this study, 16% of Ta and T1 tumours were detected solely with HAL-PDD.

Narrow-band imaging cystoscopy

- Narrow-band imaging (NBI) cystoscopy has been developed for use in both flexible and rigid cystoscopies. It increases contrast between normal and hypervascularised structures by filtering white light to 2 narrow bandwidths that are absorbed by haemoglobin.
- Several small non-randomised studies have shown promising results in terms of improved bladder tumour detection compared with WLC. More recently, NBI-assisted TUR was shown to reduce the residual tumour rate compared to a matched cohort.[16]
- However, the role of NBI cystoscopy as an aid to TUR and in surveillance needs further evaluation in RCTs.

Biopsy

- European Association of Urology (EAU) guidance recommends that on visualisation of the urothelium, abnormal areas should be biopsied, using either 'cold-cup' or resection loop methods.[3]
- In patients with positive urine cytology but no visible tumour or non-papillary tumour, biopsies from the trigone, bladder dome and bladder walls should be performed.[3] In this scenario, PDD improves detection of bladder tumour and could facilitate more targeted biopsies.

Histopathology

- Sufficient muscle tissue from biopsies is required for correct assignment of a T category.[3]
- In order to limit the variability in classifying and grading Ta and T1 tumours, it is recommended that the pathologist review the histological findings together with the urologist, in order to provide a clinical context.[17–19]
- Histopathologists in the UK are currently recommended to continue reporting the 1973 World Health organization (WHO) classification alongside the 2004 WHO classification and that results are compared through prospective audit of patient outcomes.
- Further details can be obtained in the standards and databases for reporting cancers prepared by the Royal College of Pathologists (RCP) and a published comment.[20,21]

Ultrasonography

- Transabdominal ultrasound (US) is a useful tool for investigation of haematuria. It permits detection of renal masses, intraluminal bladder masses and hydronephrosis.[3]

Computed tomography urography and Intravenous urography

- In many centres, computed tomography (CT) urography is now the investigation of choice compared with intravenous (IV) urography. However, the use of CT requires the exposure of the patient to an increased dose of radiation.
    - Urography is generally used to detect filling defects within the kidneys and ureters, which may indicate the presence of a tumour within the ureter.[22]
    - CT urography can also provide more comprehensive information including local tumour stage, the status of lymph nodes and neighbouring organs.
    - The diagnostic accuracy of CT urography has been estimated at around 90%; therefore, it should only be used in conjunction with cystoscopy and histology for the diagnosis of urinary tract cancers.[23,24]
- Routine urography is not advised in all patients at the time a primary bladder tumour has been detected.[25–29]
- Urography should, however, be considered in selected cases where the incidence of upper tract findings is higher, such as patients with trigonal tumours and those with high-risk or multifocal NMIBC.
    - The incidence of concomitant upper urinary tract TCC is low (1.8%), but in patients with trigonal tumours, the incidence is 7.5%.[30]
- The risk of upper urinary tract TCC recurrence during follow-up is more likely in patients with high-grade and multifocal NMIBC.[31]
    - In such patients, urography is also recommended during surveillance.[26,29,32,33]
    - Follow-up urography should only be considered in patients who are fit for upper tract intervention.
    - In such patients, the frequency of upper tract imaging surveillance has not been validated. There is no evidence to support annual imaging of the upper tract.
- Upper urinary tract CT or IV urography should be used as a surveillance tool in patients with high-risk NMIBC who have received bacillus Calmette Guérin (BCG), but the optimal frequency is unknown.

Functional tests and biochemistry

The following tests may be useful in the detection of advanced bladder cancer:

- Renal function test (glomerular filtration rate [GFR])
- Liver function test
- Full blood count
- Bone biochemistry

Determination of disease spread/staging

- Imaging modalities (CT and magnetic resonance imaging [MRI]) should be used for the staging of suspected muscle invasive bladder tumours, where this will influence treatment decisions.[24,34]

Local staging of invasive bladder cancer

- Both CT and MRI may be used for local staging of bladder cancer, but neither technique can detect tumours that have microscopically invaded perivesicular fat, i.e. Stage T3a.[35] Therefore they are used to detect T3b and more advanced tumours.
    - MRI is superior to CT in evaluating the T stage of suspected muscle invasive bladder cancer.[36–38]

Nodal involvement

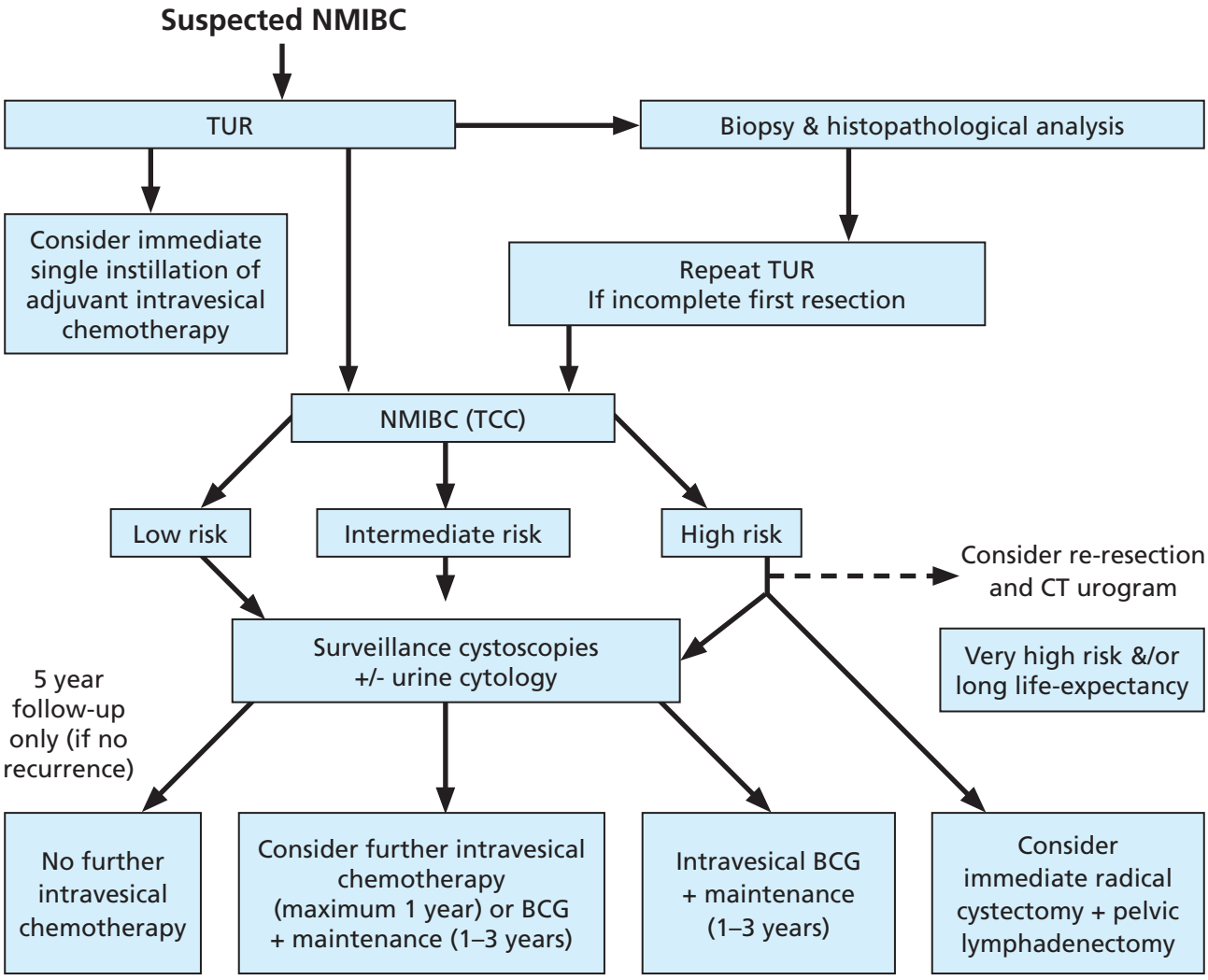
- The sensitivities of both CT and MRI in the detection of lymph node metastases are low.[24,35]

Distant metastases

- CT and MRI can be used to detect distant metastases within the lungs and liver.[34] Routine scanning of bone and brain is not recommended unless specific symptoms indicative of bone or brain metastases are present.[24]
- The use of US is not recommended in patients for whom a diagnosis of bladder cancer has already been established.
    - US may be used for the evaluation of metastases, in patients with contraindications to CT and/or MRI. However, its sensitivity compared with these other modalities is low.[39]

Non-muscle invasive bladder cancer: Management options

Figure 2: Algorithm for the primary management of non-muscle invasive bladder cancer *(adapted from Griffiths et al., 2012)*[40]



BCG: bacillus Calmette Guérin; NMIBC: non-muscle invasive bladder cancer; TCC: transitional cell carcinoma; TUR: transurethral resection

- The European Organization for the Research and Treatment of Cancer Genitourinary (EORTC GU) Group has carried out a large number of randomised trials in NMIBC patients, which has allowed the development of a risk assessment tool for recurrence and progression.[41]
- The annual risk of and cumulative risk of tumour recurrence and progression can be made using the EORTC scoring system, which combines data on previous tumour recurrence rate, number of tumours, tumour diameter, T stage, WHO grade and presence or absence of concomitant CIS.
- The web-based EORTC risk calculator can be downloaded from: http://www.eortc.be/tools/bladdercalculator/default.htm.
- It is recognised that the EORTC risk calculator may overestimate the risk of recurrence and progression in patients with high-risk NMIBC because in historical trials, re-resection was not standard practice, only 171 patients overall were treated with BCG and most of these patients had induction BCG without maintenance.
    - The Spanish Urological Club for Oncological Treatment (CUETO) has proposed a scoring model to stratify the risk of recurrence and progression in patients treated with BCG.[42]

Transurethral resection – first resection

Overview

- Transurethral resection (TUR) is the gold standard for the initial diagnosis and treatment of newly-diagnosed, apparently NMIBC.
- The adequacy of the initial TUR and the skills and experience of the surgeon may have a substantial impact on the recurrence rate at the first follow-up cystoscopy.
- Small tumours (<1 cm) can be resected en bloc.
- Larger tumours (>1 cm) should be resected so that at least exophytic tumour and deep (tumour base) biopsies are submitted in separate fractions.

Patient selection

- Newly-diagnosed NMIBC

Adverse effects of treatment

- Bleeding
- Infection
- Perforation of the bladder wall
- Clot retention

Clinical evidence

- The basic technique for TUR is illustrated in Wiesner et al., 2010.[43] It can be accessed at: http://onlinelibrary.wiley.com/doi/10.1111/j.1464-410X.2010.09387.x/pdf.
- TUR is used to remove the tumour and to obtain a biopsy specimen, which is subject to histopathological analysis to determine the tumour type, stage and grade. The pathological report should contain information on the type of specimen, tumour histology, growth pattern, grade and depth of invasion and the involvement of adjacent urothelium. Further details can be obtained in the standards and databases for reporting cancers prepared by the RCP.[21]
- Brausi et al. highlighted that the quality of the initial TUR performed by the individual surgeon may have a substantial impact on the local recurrence rate at the first follow-up cystoscopy. An overall evaluation of 2410 patients who participated in 7 studies revealed that 316 (13.1%) patients had a recurrence at the first follow-up cystoscopy.
    - When the data were analysed by the number of institutions who enrolled a median of 30 patients with a single tumour, local recurrence rates at the first cystoscopy check-up ranged from 3.5% to 20.6%, which suggested that the quality of the initial TUR was highly variable.[44]
- Removal of adequate detrusor muscle tissue is associated with a reduced risk of disease recurrence after the first TUR.[45]
    - In a study of 356 patients, the absence of detrusor muscle in tumours following first TUR was associated with an RR of recurrence at first follow-up cystoscopy (at 3 months) of 44% compared with 22% for tumours including detrusor muscle (odds ratio [OR], 2.9; 95% CI, 1.6–5.4; p=0.002).[45]
    - The presence of negative muscle tissue indicates a complete resection.[46]

Transurethral resection – second resection

Overview

- In many patients undergoing initial TUR, a subsequent second TUR performed 2–6 weeks later has demonstrated a high incidence of residual tumour.[46]
- Multiple tumours, poorly-defined tumours and CIS may contribute to an incomplete first resection.[46]
- Repeat TUR improves staging accuracy and can enhance treatment outcomes in NMIBC if all visible residual and suspected tumour is removed.[46]
- A second TUR should be performed when biopsies contain insufficient or no muscle tissue and/or inadequate separate exophytic tumour and tumour base fractions.
- For patients with pTa disease, if adequate biopsy samples have been obtained (i.e. muscle included) and macroscopic tumour clearance confirmed, a second TUR is generally unnecessary.
- For patients with pT1 disease, repeat TUR should also be considered, especially for high-grade tumours.

Adverse effects of treatment

- As per the first TUR.

Clinical evidence

- A prospective study randomised 210 patients with newly-diagnosed T1 bladder cancer to repeat TUR within 2–6 weeks of first TUR, or no repeat TUR. All patients received instillation of mitomycin C (MMC) within 24 hours of the first TUR.[47]
    - Second TUR resulted in a change of treatment strategy in 8 patients undergoing this procedure, due to changes in staging.
    - Presence of CIS or T2 tumour at second TUR was correlated with grade, size and numbers of the initial tumour.
    - Tumour-free status was confirmed histologically in 67% of this group of patients.
    - RFS was significantly higher in patients undergoing second TUR than in those not undergoing this procedure (5-year RFS, 59% versus 32%; p=0.0001).
- In an analysis of 1312 patients undergoing repeat TUR, around 50% of patients with low-grade tumours demonstrated residual disease.[46]
    - 25% of patients with T1 tumours following first TUR had residual disease on repeat TUR.
- Another analysis of 523 patients initially staged as T1, after repeat TUR 106 (20%) were upstaged to muscle invasive disease (T2).[48]
- In a separate study, 110 patients with newly-diagnosed NMIBC underwent repeat TUR.[49]
    - Cystoscopy prior to the second TUR was negative in 79 (78%) patients, but 14 of these were subsequently found to have residual disease.
    - Of the total 40 patients with residual disease at the second TUR, 22 had an identical stage to the first TUR, 9 had a lower stage and 9 had a higher stage of bladder tumour.
    - Of 76 patients with stage T1 cancer after the first TUR, 25 (33%) demonstrated residual disease at second TUR.

Immediate, single instillation of adjuvant intravesical chemotherapy

Overview

- Based on clinical evidence, a single instillation of adjuvant intravesical chemotherapy after the first TUR should be considered the standard of care for all NMIBC patients.
- There is strong evidence for the use of single-dose intravesical chemotherapy at first TUR, with the greatest benefit observed with low-grade, low-risk tumours.
- A meta-analysis conducted by the EORTC demonstrated that a single instillation of adjuvant intravesical chemotherapy immediately after TUR reduces the RR of local recurrence by 39% in all risk groups.[50]
- The single instillation of chemotherapy is thought to eradicate any tumour left behind after an incomplete first TUR and to destroy any circulating tumour cells that could implant at the resection site to prevent recurrence.
- Evidence suggests that the first instillation of adjuvant intravesical chemotherapy should be administered on the same day as the TUR, and ideally within 6 hours of the procedure.[50]
- The chemotherapeutic agents MMC, epirubicin and doxorubicin are all considered to have similar efficacy.[50]
- An immediate single instillation of adjuvant intravesical chemotherapy should be avoided when it is obvious or even suspected that the bladder wall is perforated.[51]

Patient selection

- First or repeat TUR after diagnosis of any NMIBC, if clinically safe to do so and the bladder is clear of any macroscopic disease.

Adverse effects of treatment

- Irritative bladder symptoms, including dysuria and frequency
- Haematuria
- Allergic skin reactions with MMC[52]
- Irritative bladder symptoms with epirubicin

Clinical evidence

- A meta-analysis of 7 RCTs (n=1476) compared one immediate post-operative instillation of adjuvant chemotherapy using MMC, epirubicin, doxorubicin or thiotepa, with TUR alone, to determine whether adjuvant chemotherapy decreased the risk of recurrence in patients with single and multiple Ta/T1 tumours.[50]
    - Recurrence data were available for 1476 patients at a median follow-up of 3.4 years.
    - Recurrence occurred in 48.4% of patients who had TUR alone and in 36.7% of patients receiving one post-operative instillation of chemotherapy. This was associated with a decreased risk of recurrence by 39% (OR, 0.61; 95% CI, 0.49–0.75; p<0.0001) versus TUR alone.
    - Patients with a single tumour (recurrence rate, 35.8%; OR, 0.61; 95% CI, 0.46–0.80; p=0.00050) or multiple tumours benefited (recurrence rate, 65.2%; OR 0.44; 95% CI, 0.18–1.02; p=0.06) from one immediate instillation of adjuvant chemotherapy compared with TUR alone.
    - However, in patients with multiple tumours, one instillation may be suboptimal and additional adjuvant treatment is necessary (discussed in more detail below).
    - For every 100 patients treated with a single instillation of adjuvant chemotherapy, 12 repeat TURs were avoided. Thus, 9 patients must be treated with a single instillation of adjuvant chemotherapy to prevent a recurrence. The cost of a TUR, anaesthesia and hospitalisation is probably more than 9 times that of one instillation of adjuvant chemotherapy.
- Kaasinen et al. found that the risk of recurrence doubled if the first instillation of MMC was not administered within 24 hours of TUR.[53]
- Bouffioux et al. demonstrated that when the first instillation of adjuvant chemotherapy was given within 24 hours after TUR with long-term maintenance chemotherapy, patients tended to have fewer recurrences than those who received treatment later than 24 hours.[54]

Follow-up of patients with low-risk NMIBC (low risk of recurrence and progression)

Overview

- In patients at low risk of recurrence and progression (EORTC recurrence and progression scores = 0), the probability of recurrence and progression at 1 year is 15% and 0.2%, respectively.[41]
- Data on the optimal follow-up regimen for patients with low-risk NMIBC is limited.
- EAU guidelines recommend that all patients with low-risk TaT1 tumours should have a follow-up cystoscopy at 3 months after the first resection. If recurrence-free at 3 months, the next cystoscopy is advised at 9 months, and then yearly for 5 years.[3]

Clinical evidence

- Oge et al. retrospectively evaluated the recurrence and progression rates of 120 patients with pTaG1/G2 and small (<4 cm) TCC.[55]
  - The recurrence rate was 6.5% at 3 months, and 6.7% and 3.6% at 6 and 9 months, respectively.
  - When the first 3-month follow-up cystoscopy was clear, the 6-, 9- and 12-month cystoscopy recurrence rates were 4.3%, 2.7% and 8%, respectively.
  - The progression rate was <1% for the first year.
- In a Scottish study utilising a prospective database, patients with TaG1 were followed for up to 20 years after TUR.[56]
  - The authors concluded that tumour status at 3 months was the strongest predictor of recurrence.
  - Of patients who had not experienced recurrence at 5 years, 98.3% remained tumour-free for 20 years.

Additional intravesical chemotherapy or BCG for patients with intermediate-risk NMIBC (intermediate or high risk of recurrence and intermediate risk of progression)

Overview

- The main priority in these patients is to reduce the risk of recurrence, although the risk of progression is not negligible.
- According to an analysis of 7 EORTC trials using the EORTC risk tables, the probability of recurrence at 1 and 5 years in patients with intermediate-risk TaT1 bladder cancer is 24–38% and 46–62%, respectively; the risk of progression to muscle invasive disease is estimated at 1–5% at 1 year and 6–17% at 5 years.[41]
- The prophylactic effect of a single instillation of chemotherapy after TUR lasts for 1–2 years.[52,57]
- The results of an EORTC and Medical Research Council (MRC) meta-analysis showed that adjuvant chemotherapy after TUR prevents disease recurrence; however, it has no apparent effect on disease progression.[58]
- The optimal duration and intensity of intravesical chemotherapy schedule is currently undefined.
- However, the available evidence does not support intravesical chemotherapy for more than 1 year.
- For prevention of recurrence, maintenance BCG is required to demonstrate superiority to MMC.[59]
- Current EAU guidelines recommend either a maximum of 1 year of intravesical chemotherapy or a minimum of 1 year of intravesical BCG.[3]
- The superior efficacy of BCG needs to be balanced against its increased toxicity.

Patient selection

- Recurrent pTaG1 TCC 2.
- pTaG1/G2 TCC and either >3 cm tumour diameter or multiple tumours.
- pT1G2 TCC and <3 cm tumour diameter and single tumour.

Adverse effects of treatment

- Irritative bladder symptoms. e.g. dysuria, urgency
- Haematuria
- Infection

Clinical evidence

- A meta-analysis of 5 studies conducted by the Japanese Urological Cancer Research Group, which included 1732 patients with NMIBC, revealed that the prophylactic effect of a single instillation of intravesical chemotherapy after TUR continued for a period of 500 days.[57]
- Two parallel randomised studies conducted by the EORTC highlighted that 1-year of monthly (15 instillations) maintenance chemotherapy was no more effective than 6 months (9 instillations) of treatment in reducing the recurrence rate when the first instillation was given immediately after TUR.[54]
- More recently, a Japanese randomised study of 150 patients with TaT1 bladder cancer demonstrated that long-term epirubicin therapy was more effective than short-term treatment after TUR in preventing recurrence.[60]
    - At 3 years, the recurrence rate was 14.8% in the group who received 1 year of epirubicin (19 instillations) compared with 36.1% in those who received 3 months of epirubicin (9 instillations) after TUR.
- The MRC has shown that five doses of adjuvant MMC is not superior to a single dose and that the treatment effect of a single dose lasts for at least 7 years.[61]
- In a prospective randomised study, Serretta et al. demonstrated that 10 monthly instillations of chemotherapy following a 6-week induction cycle of treatment (a total of 16 instillations) was not superior to the 6-week chemotherapy cycle (6 instillations) alone in terms of the recurrence-free rate, in 482 patients with Ta/T1 tumours (single, multiple or recurrent).[62]
    - At a median follow-up of 48 months (range, 3–78), recurrence rates were 29.6% for 6 instillations of chemotherapy versus 29.2% for 16 instillations of chemotherapy (p=0.43).
- In an earlier study, 495 patients with intermediate- to high-risk primary or recurrent bladder cancer (pTaG1/2, pT1G1–3) were randomised to 6 weekly instillations of MMC, 6 weekly instillations of BCG, or 6 weekly instillations followed for monthly instillations of MMC for 3 years.[63]
    - At a median follow-up of 2.9 years (range: 0–6.6), recurrence rates were 10.4% in the long-term MMC arm, 25.1% for BCG and 25.7% for 6 weekly instillations of MMC.
    - Three-year recurrence rates were 65.5%, 68.6% and 86.1% for BCG (p=0.0005 versus long-term MMC), 6 weekly instillations of MMC (p=0.0006 versus long-term MMC) and long-term MMC, respectively.
- In an individual patient data meta-analysis comparing BCG with MMC (n=2820), maintenance BCG resulted in a significant (32%) reduction in the risk of recurrence compared with MMC. In contrast, in studies where maintenance BCG was not given, there was a significant (28%) increase in risk of recurrence.[59]
- In a large RCT, BCG with maintenance significantly reduced the risk of progression/distant metastases (hazard ratio [HR], 0.63), overall survival (OS) (HR, 0.76) and disease-specific survival (DSS) (HR, 0.47) compared with intravesical epirubicin.[64]
    - The observed treatment benefit was at least as large, if not larger, in the intermediate-risk patients as compared with the high-risk patients. In this trial, high-risk patients did not undergo re-resection.

Follow-up of patients with intermediate-risk NMIBC

Overview

- Data on the optimal follow-up regimen for patients with intermediate-risk NMIBC is limited.
- EAU guidelines recommend that patients with TaT1 tumours at intermediate-risk of progression should have a follow-up schedule using cystoscopy and urinary cytology, which is dependent on the individual patient.[3]

Adjuvant BCG for high-risk NMIBC (high risk of recurrence or progression)

Overview

- The risk for tumour recurrence and progression to muscle invasive disease is high within this group of patients with NMIBC. According to an analysis of 7 EORTC trials using the EORTC risk tables, the probability of recurrence at 1 and 5 years in patients with high-risk TaT1 bladder cancer is 61% and 78%, respectively; the risk of progression to muscle invasive disease is estimated at 5–17% at 1 year and 17–45% at 5 years.[41]
- Patients who have multiple tumours at presentation and recurrence at 3 months have a 1-year risk of further recurrence of 90%.[65]
- Clinical evidence from a meta-analysis shows that when BCG is compared with a variety of strategies, the risk of progression from TaT1/CIS to muscle invasive disease is reduced provided maintenance instillations are given.[66] Similar findings were demonstrated for the subgroups of patients with CIS or papillary tumours.
- In studies and meta-analyses comparing BCG with intravesical chemotherapy in a combination of high-risk and intermediate-risk patients, contradictory results have been obtained with respect to the relative benefit of BCG on progression.[59,64,67]
- The optimum BCG maintenance regimen is not yet known. A commonly used schedule is that described by Lamm et al., who recommended 27 instillations over a 3-year period, i.e. administration once every 6 weeks.[68]
- Current EAU Guidelines for high-risk TaT1 TCC and also for CIS recommend at least 1 year of intravesical BCG.[3]
- The results of the Phase III trial EORTC 30962, which included intermediate-risk and selected high-risk (solitary tumour without CIS) patients, failed to demonstrate that 1 year of intravesical BCG was inferior to 3 years of intravesical BCG, or that 3 years of BCG was superior to 1 year of BCG.[69]
    - The best DFS was demonstrated in those patients who had received 3 years of BCG but this was not statistically significant.
    - A pragmatic approach should be therefore considered in these patients after 1 year of BCG, based on risk of progression and side-effects.

Patient selection

- pT1G2 and either >3 cm tumour diameter or multiple tumours.
- pTa/T1G3.
- CIS.
- Immunocompetent (avoid patients with leukaemia/lymphoma, Human Immunodeficiency Virus infection, organ transplant, and active and previous GU tuberculosis [TB]).
- Caution if previous pelvic radiotherapy >40 Gy.

Adverse effects of treatment

- Haematuria has been reported in 31–35% of patients.[70,71]
- BCG-induced cystitis has been reported in 3–54% of patients.[67,70–72]
- Systemic side-effects such as fever, general malaise and skin rash have been reported in 15–39% of patients.[70,73]
- BCG therapy may provoke both local and systemic side-effects and these can be serious in approximately 5% of treated patients. Only the systemic side-effects can be serious and life-threatening and require early systemic therapy.
    - It is therefore important to prevent complications and BCG instillation should be avoided after traumatic catheterisation, when frank haematuria persists after bladder biopsy, during the first 14 days after TUR and when irritative voiding symptoms or systemic upset persist after previous instillations of BCG.
- It is expected that with repeated instillation, patients will develop short-lived bladder irritative symptoms lasting 48–72 hours, associated with mild fever, arthralgia and even frank haematuria. Persistence of these symptoms is a warning to defer the next instillation until they have settled. Reduction to one-third of the dose could also be considered.
- Granulomatous prostatitis occurs in the majority of treated men, but it is usually asymptomatic and requires no treatment. In the small percentage of patients where this is symptomatic, high-dose fluoroquinolone antibiotics are recommended, along with suspension of intravesical therapy.[74]
- Epididymitis can be due to either BCG infection or more usual uropathogens. Therefore initial treatment with a quinolone antibiotic is appropriate. Isoniazid 300 mg daily for 6 weeks should be considered.
- Generalised polyarthritis, often associated with conjunctivitis, does occur and there is an association with the HLA-B27 genotype. As it is generally an allergic reaction, treatment with systemic steroids and/or isoniazid may be required and no further BCG therapy should be given. Referral to an appropriate physician should be considered.
- Miliary BCG infection affecting lungs, liver, kidneys and brain may rarely occur as may BCG septicaemia. If clinically suspected then there should not be a delay before the administration of triple anti-TB chemotherapy and high-dose systemic steroids. Blood testing for TB can help with more rapid diagnosis. The recommended treatment regimen is isoniazid 300 mg daily for 3 months, rifampicin 600 mg daily and ethambutol 1200 mg daily for 6 weeks and prednisolone 40 mg daily or greater IV during the acute stages.[67,75]

Clinical evidence

- A meta-analysis of 24 clinical trials with data relating to progression on 4863 patients was conducted by the EORTC. TUR + BCG was compared with either TUR alone or TUR + non-BCG treatment (control).[66]
    - At a median follow-up of 2.5 years (maximum of 15 years), 9.8% of patients receiving TUR + BCG progressed compared with 13.8% of control patients.
    - Overall, treatment with BCG was associated with a 27% reduction in tumour progression (OR, 0.73; 95% CI, 0.60–0.89; p=0.001).
    - Similar treatment effects were reported in the 2880 patients with only papillary tumours (OR, 0.68; 95% CI, 0.50–0.93; p=0.001) and in the 403 patients with CIS (OR, 0.65; 95% CI, 0.36–1.16; p=0.001).
    - Patients receiving maintenance BCG demonstrated a 37% reduction in tumour progression (OR, 0.63; 95% CI, 0.51–0.78; p=0.00004).
    - No reduction in tumour progression was reported in the 4 trials where maintenance BCG was not administered.
- The Phase III EORTC 30962 trial randomised 1355 patients to 1 year of full-dose BCG (1YFD), 3 years of full-dose BCG (3YFD), 1 year of one-third dose BCG (1Y3D) or 3 years of third-dose BCG (3Y3D).[69]
    - At a median follow-up of 7.1 years, 5-year DFS was 58.8% (1YFD), 54.5% (1Y3D), 64.2% (3YFD), and 62.6% (3Y3D).
    - The inferiority of the disease-free interval for 1Y3D versus 1YFD was not demonstrated.
    - FD BCG was not superior to one-third BCG (p=0.092).
    - 3 years of BCG was not superior to 1 year of BCG (p=0.059).
    - There were no differences between treatment groups for TTP or duration of survival.
- The South West Oncology Group 8507 study randomised 550 patients with recurrent Ta/T1 disease or CIS to induction + maintenance BCG therapy for 3 years (total 27 doses) or no maintenance (i.e. induction BCG therapy only).[68]
    - Median RFS was 76.8 months (95% CI, 64.3–93.2) with maintenance BCG versus 35.7 months (95% CI, 25.1–56.8) with no maintenance BCG (p<0.0001).
    - 5-year OS was 83% in the maintenance group compared with 78% in the no maintenance group.
- A meta-analysis of data from 9 trials involving 700 patients with CIS has demonstrated that BCG is associated with a superior response rate and reduction in disease recurrence when compared with chemotherapy (MMC, epirubicin, adriamycin).[76]
    - Complete response (CR) was achieved by 68.1% of patients receiving BCG versus 51.5% of patients receiving chemotherapy (OR, 0.53; p=0.0002).
    - Based on a median follow-up of 3.6 years, 161 of 345 patients receiving BCG (46.7%) had no evidence of disease compared with 93 of 355 patients on chemotherapy (26.2%), a reduction of 59% in the odds of treatment failure on BCG (OR, 0.41; p <0.0001).

BCG versus mitomycin C

- In an individual patient data meta-analysis of data from 9 clinical trials involving 2820 intermediate- and high-risk patients with Ta, T1 or CIS, TUR + BCG was compared with TUR + MMC. Median follow-up was 4.4 years (maximum 17.7 years).[59]
    - In the studies with BCG maintenance therapy (n=1324), a 32% reduction in the risk of recurrence was determined versus MMC (43.2% versus 57.9%; p<0.0001).
    - Notably, without maintenance BCG (n=1496), the risk of recurrence was increased versus MMC, by 28% (42.6% versus 31.8%; p=0.006).
    - There were no significant differences in progression, OS or DSS, irrespective if patients receiving BCG with maintenance were subanalysed.
- In a meta-analysis of data from 9 trials performed by Bohle & Bock (n=2410), median follow-up was 26 months (range, 11.5–50.4).[67]
    - When considering all treatment regimens, there was no significant difference between BCG and MMC in tumour progression (7.7% versus 9.4%; OR, 0.77; 95% CI, 0.57–1.03; p=0.081).
    - In the subgroup of patients receiving maintenance BCG therapy for at least 1 year, the risk of progression was significantly reduced compared with MMC (OR, 0.66; 95% CI, 0.47–0.94; p=0.02).
    - In patients not receiving maintenance BCG therapy, there were no differences between treatments in terms of disease progression (OR, 1.16; 95% CI, 0.65–2.07; p=0.61).
- In a meta-analysis involving 700 patients with CIS and where the overall median follow-up was 3.4 years, a reduction of 43% in the odds of treatment failure on BCG was shown provided BCG maintenance was given (OR, 0.57; p=0.04).[76]

BCG versus epirubicin

- In a large prospective RCT (837 eligible patients), intravesical epirubicin was compared with BCG alone and BCG + isoniazid in patients with intermediate- and high-risk Ta/T1 bladder cancer, following TUR. Patients received instillations of drug therapy immediately following TUR and 6 weekly doses, followed by 3 weekly instillations at months 3, 6, 12, 18, 24, 30 and 36 (27 in total). Median follow-up was 9.2 years.[64]
    - There were no differences between the two BCG groups for any outcome, so these data were combined.
    - BCG with maintenance significantly reduced the risk of progression/distant metastases (HR, 0.63), OS (HR, 0.76) and DSS (HR, 0.47) compared with intravesical epirubicin.[77]
    - In all patients the risk of recurrence was significantly reduced with BCG versus epirubicin (HR, 0.62; 95% CI, 0.50–0.76; p<0.001); similar results were achieved in intermediate-risk patients (n=497; HR, 0.59; 95% CI, 0.45–0.76; p<0.001). However, this was not true for the subgroup of high-risk patients (n=323; HR, 0.69; 95% CI, 0.48–1.05; p=0.09).
    - In all, intermediate- and high-risk patients, there were no significant differences between BCG and epirubicin for disease progression.
    - Disease-specific mortality was significantly reduced in intermediate-risk patients with BCG versus epirubicin (HR, 0.35; 95% CI, 0.14–0.86; p=0.02) but not in high-risk patients (HR, 0.60; 95% CI, 0.23–1.56; p=0.39).
- In a meta-analysis by the Cochrane Group, BCG was compared with epirubicin, using data from 5 clinical trials involving 1111 patients with TaT1 bladder cancer.[71] The meta-analysis did not include the large RCT described above.[64]
    - The incidence of recurrence was 35.5% with BCG versus 51.4% with epirubicin (RR, 0.69; 95% CI, 0.60–0.79; p<0.05)
    - There was no significant difference between treatments for the risk of disease progression. Progression to T2 or greater stage occurred in 8.02% of patients receiving BCG and 10.32% of patients receiving epirubicin (RR, 0.78; 95% CI, 0.54–1.13; p=0.19).
    - Results from only two trials were analysed for mortality data. There was no significant difference between BCG and epirubicin for overall mortality (RR, 0.86; 95% CI, 0.71–1.04), or for disease-specific mortality (RR, 0.94; 95% CI, 0.23–3.80).

Follow-up of patients with high-risk NMIBC

Overview

- All patients with NMIBC at high-risk of progression and those with CIS should have cystoscopy at 3–4 months after TUR. If this is negative, it should be repeated every 3–4 months for 2 years, then every 6 months for 5 years. After this period, annual cystoscopy is recommended and annual urinary cytology should be considered.

Primary radical cystectomy for patients with high-risk NMIBC

Overview

- Immediate radical cystectomy may be offered to patients at highest risk of tumour progression according to the EORTC calculator.[3]
- Residual T1 disease on restaging TUR is associated with early progression following induction BCG.[78]
- Retrospective series suggest immediate radical cystectomy provides a survival benefit over delayed surgery in BCG failures. However, the benefit is heterogeneous, and so is likely to include selection bias.[79]
- Higher percentages of micropapillary variant within TCC correlate with increasing adverse outcomes, including relative inefficacy of BCG.[80,81]

Patients failing to respond to adjuvant BCG therapy

Overview

- A change in approach should be undertaken for high-risk NMIBC patients who fail to respond to BCG within 6 months of initiating therapy.[82]
- Patients with refractory high-grade TCC, T1 TCC or CIS despite 2 induction courses of BCG (12 instillations) or 1 induction course followed by maintenance should be considered to have failed BCG treatment.
- Standard treatment should be radical cystectomy and delaying beyond this may lead to progression and advanced disease (discussed in more detail in the management options for muscle invasive bladder cancer).
- Radiotherapy has no place in the management of NMIBC that has failed to respond to BCG therapy.
- Some patients will be either unfit or unwilling to undergo cystectomy and could be offered other adjuvant therapies. The use of these is not well-established and therefore the risks need to be conveyed to the patient. These include:
- Device-assisted intravesical chemotherapy
    - microwave hyperthermia MMC (HT-MMC)
    - electromotive delivery of MMC (EMDA-MMC)
    - BCG combined with interferon-alpha (IFN-α)
    - Passive intravesical chemotherapy

Clinical evidence

HT-MMC

- Several single-arm proof-of-concept studies evaluating HT-MMC have included patients with disease recurrence after BCG induction therapy.
    - In the largest series to date, Nativ et al. used maintenance HT-MMC in 111 patients with NMIBC in whom BCG therapy had failed, including 77% with high-risk disease.[83]
    - This group reported recurrence-free rates of 85% and 56% at 12 and 24 months, respectively; 3% of the patients progressed to muscle invasive disease and 5% withdrew from treatment due to adverse events.

BCG + IFN-α

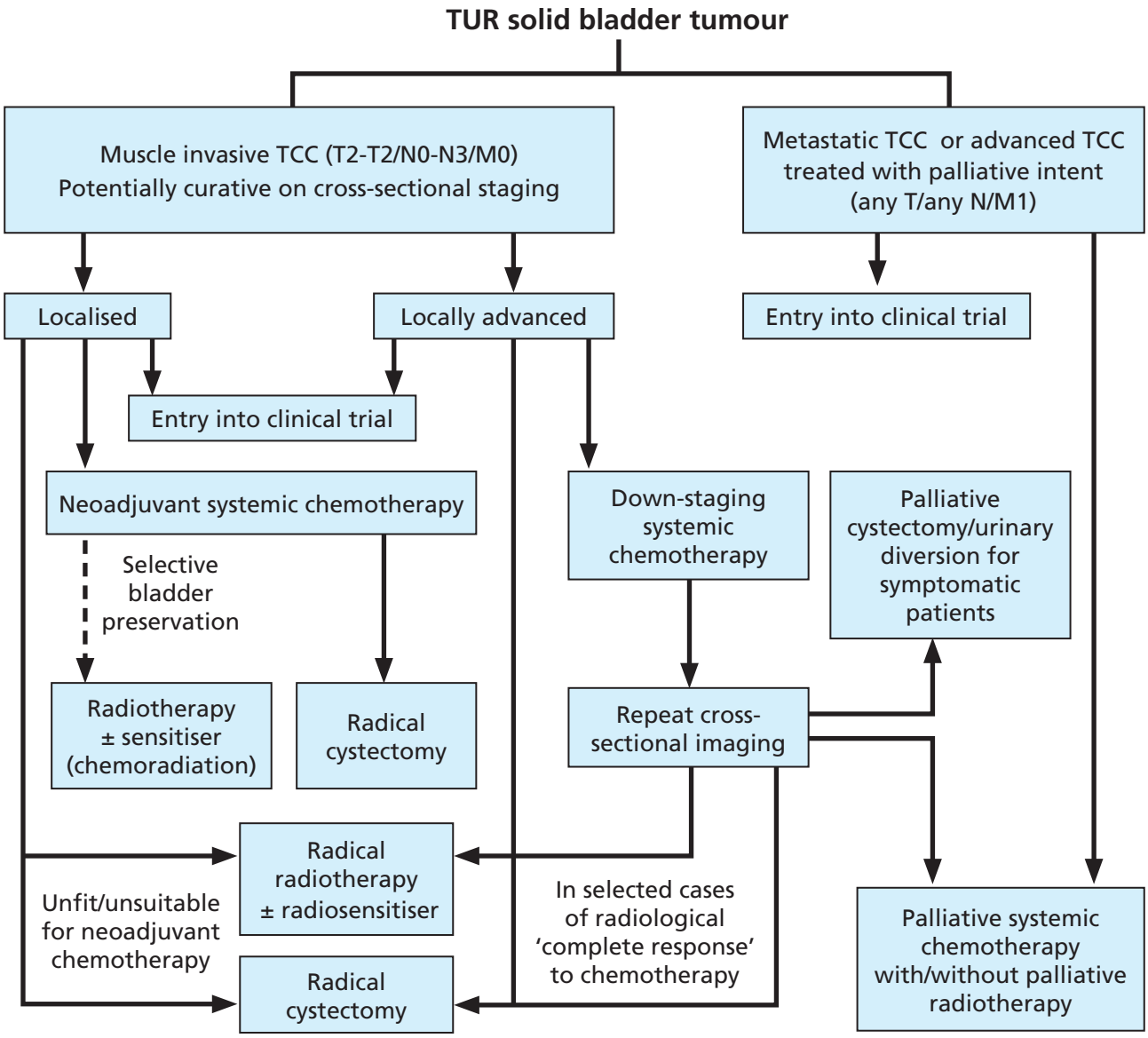
- In a study involving 40 patients who had failed previous therapy with BCG, treatment with 1/3 dose (27 mg) BCG + 50 MU IFN-α2B was initiated.[84]
    - At 12 months, 63% of patients were disease-free; at 24 months this was 53%.
- In a post-hoc analysis of data from 467 BCG-refractory patients entered in a Phase II clinical trial, the combination of low-dose BCG and 50 MU IFN-α demonstrated a disease-free survival (DFS) rate of 34% at 24 months.[85]

Passive intravesical chemotherapy

- A prospective randomised trial has compared intravesical gemcitabine and BCG in 80 patients with high-risk NMIBC who had previously failed 1 course of BCG therapy.[86] Treatment began 4–6 weeks after TUR, with either twice-weekly gemcitabine 2000 mg for 6 weeks, followed by weekly instillations for 3 weeks at months 3, 6 and 12 months; or BCG over a 6-week induction course and then weekly instillations for 3 weeks at months 3, 6 and 12 months.
    - At a median follow-up of around 15 months, 52.5% of patients receiving gemcitabine and 87.5% of patients receiving BCG experienced disease recurrence (p=0.002).
    - Disease progression was reported for 33% in the gemcitabine group and 37.5% of patients in the BCG group (p=0.12).
    - RFS at 24 months was significantly higher in the gemcitabine group than in the BCG group (19% versus 3%; HR, 0.15; 95% CI, 0.1–0.3; p<0.008).
- In a RCT comparing BCG with MMC, crossover treatment with MMC for BCG-refractory bladder cancer resulted in a 19% DFS at 24 months.[87]

Muscle invasive bladder cancer: Management options

Figure 3: Treatment algorithm for muscle invasive or advanced/metastatic bladder cancer *(adapted from Griffiths et al., 2012)*[40]



Radical treatments

Overview

- Chemotherapy may be used in a number of settings as part of a radical treatment plan for MIBC.
  - Neoadjuvant: the use of 3 cycles of cisplatin-based combination chemotherapy given **prior** to definitive local treatment with either radical cystectomy or radical radiotherapy to improve OS.
  - Down-staging: the use of 3–6 cycles of chemotherapy given to patients with locally advanced or node-positive, non-metastatic disease in an attempt to render the disease amenable to radical radiotherapy or cystectomy.
  - Synchronous chemoradiation: chemotherapy given **concurrently** with radical radiotherapy.
- There are no RCT data that support the superiority of radical cystectomy over radical radiotherapy, with respect to survival.
- When considering surgery, the morbidity associated with the procedure must be weighed against treatments that aim to preserve bladder and sexual function.
- There are concerns with using radical radiotherapy in muscle invasive bladder cancer: the disease may become inoperable, so that future surgery may be compromised, be more hazardous and at higher risk of complications and development of metastatic disease.
- It is therefore attractive to be able to identify at an early stage those patients in whom radiotherapy is likely to be successful, while offering immediate surgery to those patients in whom success is less likely.
- Patient preference and the presence or absence of co-morbidities should be considered when determining the appropriate treatment.
- In the BC2001 trial, synchronous chemoradiation was associated with a significantly prolonged RFS (but not OS) compared with radiotherapy alone.[88]

Patient selection

- A number of factors can result in the selection of either cystectomy or radical radiotherapy as the preferred treatment modality (Table 3). Where there are no clear medical indications for either treatment then patient choice becomes the dominant selection criteria.

Table 3. Factors favouring surgery or radiotherapy

Favours surgery	Favours radiotherapy
• Poor bladder function, especially small capacity • Widespread CIS or CIS remote from muscle invasive tumour • Large volume tumours • Multifocal disease • Pre-existing hydronephrosis (unless treated with stenting or nephrostomy) • Previous pelvic radiotherapy • Active inflammatory bowel disease • Severe lower urinary tract symptoms	• Unifocal disease • Maximum TUR • Good bladder capacity • Minimal or moderate lower urinary tract symptoms • No CIS distant to primary tumour • Unfit for surgery due to comorbidities • Patient preference

Clinical evidence for radical cystectomy versus radical radiotherapy

- A Cochrane review has compared radical surgery and radical radiotherapy for muscle invasive bladder cancer, using data from 3 trials (n=439).[89] **However, it must be noted that these data should be viewed with caution as they are somewhat out of date.**
  - Mean OS at 3 years was 45% for radical cystectomy and 28% for radical radiotherapy (OR, 1.91; 95% CI, 1.30–2.82).
  - Mean OS at 5 years was 36% for radical cystectomy and 20% for radical radiotherapy (OR, 1.85; 95% CI, 1.22–2.82).
  - There were 143 recurrences within the thoracic region, with a median of 1.3 years (range: 0.1–16.9). The same significant predictive factors as were identified for abdominal/pelvic recurrences were identified for thoracic recurrence.
  - However, only three historical trials were available for analysis, the patient numbers were small and many patients did not receive the treatment to which they were randomised.
  - The difference in OS may be attributable to several confounding variables, including selection bias. For example, patients treated with cystectomy were likely to have been younger and fitter than those having radiotherapy. Secondly, post-surgical tumours were more likely to have been staged pathologically rather than clinically, which frequently results in an increase in assigned stage for some patients.
  - Therefore, the data for cystectomy in these studies may not be applicable to the general population and comparisons with radical radiotherapy need to be interpreted with caution.
  - In addition, over 25 years has elapsed since the last patient was treated in these studies and significant improvements in radiotherapeutic and surgical techniques have taken place; these data may therefore be irrelevant to contemporary practice.
  - Hence an RCT comparing modern bladder-sparing therapy with state-of-the-art surgical techniques is required.
  - Recruitment of patients to studies was difficult due to clinician bias towards radical cystectomy

- In a series of 398 patients managed in Yorkshire (T2–T4, 96%), outcomes following radical cystectomy and radical radiotherapy were compared.[90]
    - 5-year OS was 36.5% (95% CI, 27.4–45.6) for radical cystectomy and 37.4% (95% CI, 32.3–42.6) for radical radiotherapy.
    - Following radical radiotherapy, 43.6% of patients experienced disease recurrence within the bladder and 18.8% underwent salvage cystectomy.
- In a UK series involving 169 patients treated between 1996–2000, there were no differences between radical radiotherapy and radical cystectomy for muscle invasive TCC in terms of OS, DSS and RFS at 5 years. This was despite the radiotherapy group being older (median age 75.3 years versus 68.2 years).[91]
    - In a more recent cohort (2002–2006), the median age of radiotherapy patients but not the cystectomy patients was higher than in the 1996–2000 cohort (78.4 years versus 75.3 years for radiotherapy and 67.9 years versus. 68.2 years for surgery).
    - The authors therefore concluded that although the patients undergoing radical cystectomy were significantly younger than the radiotherapy patients, treatment modality did not influence survival and radical radiotherapy is a viable treatment option.
- In a Swedish study, the adverse effects of radical radiotherapy and radical cystectomy in patients with muscle invasive bladder cancer were compared with each other and with healthy controls.[92]
    - The RR of urinary tract infections was significantly higher in the radiotherapy patients than in controls (22% versus 10%; RR, 2.0; 95% CI, 1.0–3.9).
    - The RR for night-time micturition with radiotherapy versus controls was 1.6 (95% CI, 1.2–2.0).
    - There were no differences between patients receiving radiotherapy and controls with respect to micturition urgency.
    - A total of 26% of patients receiving radiotherapy reported distress if their urinary symptoms persisted, compared with 13% of control subjects (RR, 1.9 (95% CI, 1.0–3.4).
    - There were no significant differences between radiotherapy and cystectomy in the frequencies of abdominal pain at least every month (22% versus 12%), diarrhoea at least once a month (35% versus 28%), faecal leakage at least once a month (17% versus 10%), and distress if gastrointestinal symptom-related problems persisted (32% versus 24%).
    - There were no significant differences between radiotherapy and cystectomy in the frequencies of sexual desire less than every month (68% versus 64%), erection difficulties (75% versus 92%), dissatisfaction with sex life (36% versus 67%), impairment to sex life due to urinary symptoms (19% versus 25%), and distress if urinary symptom-related sexual limitations persisted (32% versus 27%).

Radical cystectomy

Overview

- Radical cystectomy with bilateral pelvic iliac lymph node dissection is the standard treatment for muscle invasive bladder cancers.
- Incidental prostate cancer is a common finding following radical cystoprostatectomy.
- The presence of positive soft tissue surgical margins following radical cystectomy is a strong predictor of disease recurrence and survival.
- The pT stage of bladder tumours is a predictive factor for the presence of lymph node involvement at radical cystectomy.[93–95]
- There is currently no consensus regarding the extent of lymphadenectomy required for successful outcomes. However, the available data suggest that removal of at least 11 lymph nodes may be associated with more favourable outcomes.
- It should be ensured that the lymph nodes associated with the obturator fossa and the external and internal iliac vessels should be removed, up to the common iliac bifurcation.
- There is little evidence to support a more extensive field for lymphadenectomy in most patients, with the exception of confirmed node-positive disease.
- Patients should be informed of the urinary diversion techniques performed after radical cystectomy, which include an ileal conduit, a bladder reconstruction or a continent diversion.

Patient selection

- T2–T4a/N0-Nx/M0 tumours.
- Extensive papillary disease that cannot be controlled by TUR and intravesical therapy alone.
- Fitness for anaesthesia.
- Performance status (PS).
- Male patients should have an assessment of their prostate-specific antigen (PSA) concentration prior to surgery.

Adverse effects of treatment

- High risk of infection (~40%) and bleeding (~60%).[96,97]
- Early complications reported in 12–30% of patients.[90,93,97]
- Common complications include gastrointestinal, cardiovascular and pulmonary disorders and venous thromboembolism.[90,96]
- 30-day mortality of 2–4%.[90,93,96,97]
- 90-day mortality rates increase with patient age: ≤69 years, 2%; 70–79 years, 5.4%; 80 years, 9.2%.[98]

Clinical evidence

- In an analysis of data from 1388 patients undergoing radical cystectomy (T1–T3, 81%), a total of 493 patients (35.5%) had experienced at least 1 disease recurrence at a median follow-up of 14.3 years (range, 0.03–29.1).[99]
    - There were 67 disease recurrences within the upper urinary tract, at a median 3.1 years (range, 0.2–14.5) after surgery. A multivariate analysis of the data determined that pT4 tumours, positive ureteral margins, and multifocal tumours were significantly associated with upper urinary tract recurrences.
    - There were 388 disease recurrences within the abdomen/pelvis, at a median of 1.1 years (range, 0.1–17.3 years). A multivariate analysis of the data determined that pT3–T4 tumours, pNx, pN0 (+1–10 lymph nodes), pN1 + pN2, multifocal tumours and prostatic involvement were significantly associated with these recurrences.
- Stein et al. reported the long-term effects of radical cystectomy with pelvic lymph node dissection in 1054 patients with invasive bladder cancer.[93]
    - Overall, there were 27 (2.5%) perioperative deaths and 292 (28%) early complications.
    - RFS and OS at 5 years was 68% and 60%, respectively; and 66% and 43%, respectively, at 10 years.
    - Furthermore, in patients with muscle invasive (P2 and P3a), lymph node-negative tumours, 89% and 87%, and 78% and 76% had 5- and 10-year RFS rates, respectively.
- In a series of 432 patients undergoing radical cystectomy (pT2–T4, 64%; Grade 3, 95%), 27 (6%) developed a local recurrence and 78 (18%) developed a distant recurrence, with a mean time to recurrence of 13.6 months.[100]
    - 5-year DFS rates were: ≤pT1, 92%; pT2, 79%; pT3, 56%; pT4, 24%.
    - The mean number of lymph nodes removed was 10, and the mean number of positive lymph nodes was 3.8.
    - 5-year OS and DSS rates in node-positive patients were 22% and 40%, respectively. A positive lymph node percentage >30% was significantly associated with a worse prognosis (p=0.007).
- In a retrospective analysis of data from 4410 patients undergoing radical cystectomy with bilateral pelvic lymphadenectomy, positive soft tissue margins were identified in 278 cases (6.3%).[101]
    - 5-year RFS rates were 21.6% and 62.8% for patients with and without positive margins, respectively (p<0.001).
    - 5-year DSS rates were 26.4% and 69% for patients with and without positive margins, respectively (p<0.001).

Cystoprostatectomy

- On analysis of tissue from a series of 235 men undergoing radical cystoprostatectomy at a single centre over a 3-year period, 158 had evidence of prostate cancer (67%).[102]
    - A multivariate analysis demonstrated that the presence of CIS in the bladder, or tumours within the trigone and bladder neck were significantly associated with the presence of prostate cancer.
- In a separate series including 204 men undergoing radical cystoprostatectomy, 58 (28%) were found to have prostate cancer that was not predicted by preoperative PSA or digital rectal examination (DRE).[103]
    - In 18 cases the prostate cancer was considered to be clinically significant.
- In a series of 95 men undergoing radical cystoprostatectomy for invasive bladder cancer, 26 (27.4%) had incidental prostate cancer; 19 of these were unsuspected, based on preoperative PSA measurements and DRE.[104]
    - Seven of these patients were considered to have clinically significant prostate cancer.

Lymph node dissection

- A German retrospective analysis of data has assessed 477 patients with node-positive tumours (pN1–N2, M0) who had undergone radical cystectomy.[105]
    - T3 or higher stage tumours were found in 73% of patients and pN2 in 61% of patients.
    - The median number of lymph nodes removed was 12 (range, 1–66), and the median number of positive lymph nodes was 2 (range, 1–25).
    - With a median follow-up of 28 months (range, 2–240), for the overall study population, the 1-, 3- and 5-year DFS rates were 73%, 49% and 39%, respectively.
    - Patients with a positive lymph node percentage of ≤20% demonstrated a 5-year DFS of 46%, compared with 31% for patients with a positive lymph node percentage of >20% ($p<0.001$).
    - In a multivariate analysis, the number of lymph nodes removed was a significant predictor for reduced DFS, as was a positive lymph node percentage >20%.
- In a series of 171 consecutive patients undergoing radical cystectomy, pathological lymph node disease was found in 25 patients (17.2%) and the mean number of lymph nodes removed from all patients was approximately 14.[106]
    - 3-year DFS rates were 71% for node-negative disease and 40% for node-positive disease ($p<0.0001$).
    - The number of lymph nodes removed did not significantly impact on DFS in patients with node-negative disease. However, in patients with node-positive disease, the removal of ≥13 lymph nodes was associated with a longer DFS compared with the removal of <13 lymph nodes ($p=0.002$). However, it should be noted that the sample size in this group was small.
- In another series of 637 patients with T2–T4/N0/M0 bladder cancer, Herr evaluated the effect on survival of removing pre-defined quartiles of lymph nodes.[94]
    - In patients with node-negative disease, survival was significantly improved if ≥11 lymph nodes were removed versus ≤10 ($p=0.0001$).
    - In patients with node-positive disease, survival was significantly improved if ≥13 lymph nodes were removed versus ≤12 ($p=0.001$).

- In a previous study involving 302 patients undergoing radical cystectomy, at 5 years after surgery, 65% of patients who had ≥16 lymph nodes removed were alive and disease-free compared with 51% of patients who had ≤15 lymph nodes removed.[107]
    - For patients with stage pT1G3, pT2a and pT2b node-negative disease, 5-year DFS was 85% when ≥16 lymph nodes were removed versus 65% when ≤15 lymph nodes were removed ($p<0.01$).
    - In patients with pT3 or pT4 tumours, there was no effect on the number of lymph nodes removed on DFS.
- A prospective study in 400 consecutive patients with invasive bladder cancer randomised patients to either radical cystectomy with standard lymphadenectomy (up to the bifurcation of the common iliac vessels) or with extended lymphadenectomy (at the level of origin of the inferior mesenteric artery).[108]
    - A mean of 16 lymph nodes were removed with standard lymphadenectomy and 49 with extended lymphadenectomy.
    - 5-year DFS rates were 66.6% in the extended lymphadenectomy group versus 54.7% in the standard lymphadenectomy group ($p=0.043$).
    - In patients with node-positive disease (n=96), 5-year DFS rates were 48.0% in the extended lymphadenectomy group versus 28.2% in the standard lymphadenectomy group ($p=0.029$).
    - There were no differences between type of lymphadenectomy for 5-year DFS in node-negative patients.
- Another study has shown that in 117 patients with stage ≤pT3a tumours at radical cystectomy, extending lymph node dissection up to the bifurcation of the aorta was associated with an improved 5-year RFS rate versus lymph node dissection up to the bifurcation of the common iliac vessels (85% versus 64%; $p<0.02$). However, this was not the case for tumours >pT3.[109]

Urethrectomy

- EAU guidelines recommend that urethrectomy should be performed if positive surgical margins are present at the level of urethral dissection or within the bladder, the primary tumour is located at the bladder neck or in the urethra (in women), or if the tumour extensively infiltrates the prostate.[24]
- Factors predictive of urethral recurrence include the presence of distant CIS, high tumour stage and grade, multifocal recurrent tumours, trigonal or bladder neck invasion, prostatic urethral involvement and a positive urethral resection margin.[110]
- Factors that may protect against urethral recurrence include orthotopic bladder reconstruction and radical radiotherapy.

Synchronous chemoradiation/selective bladder preservation

Overview

- Patients with a good response to neoadjuvant chemotherapy can be offered radiotherapy rather than cystectomy.
- Modern bladder-preserving strategies are multi-faceted, aimed at maintaining a functional bladder, while maintaining similar survival rates radical cystectomy, but maintaining a good quality of life with a functioning native bladder.
- The discrepancy between clinical staging and pathological staging is an important confounding factor when comparing results of radical cystectomy with results of bladder preservation, as clinical staging is more likely to underestimate disease extent.
    - In 156 patients who had undergone radical cystectomy, Ficarra et al. found only 23% of clinically-staged T2 tumours to be pT2 at cystectomy, and 74% to be pT3/4.[111] There is thus an outcome bias in favour of surgical series, which have pathological staging data.
- The key factors for successful selective bladder preservation are:
    - Careful selection of patients, to increase the number of complete responders.
    - Meticulous cystoscopic follow-up to identify recurrent or persistent muscle invasive disease and candidates for early salvage cystectomy.
    - It is important to aim to reduce the amount of normal tissue in the irradiated area, especially as the small bowel may be used for reconstruction in the event of cystectomy.
- An initial maximal TUR is required, followed by neoadjuvant chemotherapy in appropriately selected patients. Radiation therapy either given alone or with synchronous chemotherapy is subsequently given to neoadjuvant chemotherapy responders, with early cystectomy for non-responders.
    - If maximal TUR has been performed longer than 6–8 weeks prior to neoadjuvant chemotherapy or radiotherapy, a repeat and complete TUR is recommended.
    - The ability to completely resect visible tumour is a strong predictor of CR as well as OS in univariate and multivariate analyses.[112]
- It has been suggested that in patients receiving chemoradiotherapy (CRT) following TUR, if this is unsuccessful, the associated delay until cystectomy allows disease progression and a worse prognosis than undergoing immediate cystectomy.
    - A systematic review of the literature suggests that there is a window of opportunity of less than 12 weeks between diagnosis of invasive disease and radical cystectomy.[113]
- Response to neoadjuvant chemotherapy is a strong prognostic marker, as pathological downstaging to pT0 disease is significantly associated with improved survival.
- Hydronephrosis is in general a poor prognostic indicator for patients with muscle invasive bladder cancer, irrespective of type of local treatment. Patients with hydronephrosis are in general excluded from bladder preservation protocols.[114]
- The optimal CRT regimen appears to be as per BC2001.

Patient selection

- T2–T4/N0–Nx/M0 tumours.
- Eastern Co-operative Oncology Group (ECOG) PS≤2.
- Absence of hydronephrosis.
- Unifocal disease (although not essential).
- Adequate renal function.
- Adequate white blood cell and platelet counts.
- Medical fitness for surgery/radiotherapy.
- Absence of extensive CIS.
- Node-negative disease on CT/MRI.

Adverse effects of treatment

- Acute side-effects include diarrhoea, tenesmus, proctitis, cystitis and lethargy.
- Late side-effects such as bladder fibrosis, second malignancies, haematuria and impotence.
- Platinum-associated toxicities, including myelosuppression and sepsis.
- Impaired sexual functioning has been reported in around 50% of men.[115]
- 40% of patients have concurrent BPH, which could have affect their urinary control after radiotherapy.
- A questionnaire-based study involved 29 patients who received bladder-preserving therapy (BPT), i.e. a combination of CRT and TUR, and 30 patients who had undergone radical cystectomy.[116]
    - Of the BPT group, 62% felt physically well, compared with 53% of the radical cystectomy group; 10% of the BPT group and 27% of the radical cystectomy group reported feeling ill.
    - A greater number of BPT patients were able to look after themselves compared with the cystectomy group.
    - Of the BPT patients, 28% were anxious and 24% were depressed; of the cystectomy patients, 57% were anxious and 47% were depressed.
    - The patients undergoing BPT reported dysuria (20%), daytime micturition frequency (44%), night-time micturition frequency (42%) and difficulty in controlling micturition (38%).
- In another study involving 32 patients with T2–T4a bladder cancer who had undergone TUR, chemotherapy and radiotherapy, at a median follow-up of 6.3 years (range, 1.6–14.9), 24 had normal bladder function.[115]
    - Urinary flow problems were reported by 6% of patients, urgency by 15%, problems with urinary control in 19%, and urinary leakage in 19%.
    - Post-void residual volume >100 ml was observed for 3 men and 1 woman.
    - Distress from urinary symptoms was reported by 50% of patients experiencing these.
    - Median bladder capacity was 400 ml in men.
    - Difficulty with bowel control occurred in 7 men and 3 women.
    - 59% of male subjects reported that they were satisfied with their sex life.
    - Physical functioning was comparable to US age-matched norms for men and women.

- Late pelvic toxicity following BPT was assessed in 157 patients with T2–T4a bladder cancer.[117]
    - At a median follow-up of 5.4 years (range, 2.0–13.2), 34 patients (22%) experienced late grade 1 pelvic toxicity, 16 (10%) developed late grade 2 pelvic toxicity, and 11 patients (7%) developed late grade 3 pelvic toxicity. No patients developed late grade 4 pelvic toxicity and there were no treatment-related deaths.
    - Median time to late grade 2 pelvic toxicity was 31.2 months (range, 9.2–137.8), and median time to late grade 3 pelvic toxicity was 22.1 months (range, 8.0–98.8).

Clinical evidence

- In the Phase III open-label BC2001 trial, 360 patients with T2–T4a MIBC were randomised to radiotherapy with concurrent fluorouracil + mitomycin C, or radiotherapy alone.[88]
    - 2-year RFS was 67% (95% CI, 59–74) with CRT and 54% (95% CI, 46–62) with radiotherapy alone (HR, 0.68; 95% CI, 0.48–0.96; p=0.03).
    - 5-year OS was 48% (95% CI, 40–55) with CRT and 35% (95% CI, 28–43) with radiotherapy alone (HR, 0.82; 95% CI, 0.63–1.09; p=0.16).
- In a retrospective analysis (1982–2000), 415 patients with T2–T4 or high-risk T1 disease received TUR followed by radiotherapy or CRT.[112]
    - A CR after initial therapy was achieved in 288 patients (72%), and of this subgroup, 186 had developed no recurrence of bladder tumours. Twenty-six patients demonstrated a non-invasive recurrence, 15 demonstrated a T1 recurrent tumour, 32 patients had a muscle invasive recurrence and 10 patients had a pelvic recurrence.
    - Eighty-three patients (20%) underwent radical cystectomy: 41 of the 110 incomplete responders to initial therapy and 42 patients with an initial CR who experienced a local relapse.
    - For patients with a preserved bladder, 5-year OS was 42% and 10-year OS was 27%. This compared with 50% and 32% 5- and 10-year OS for all patients.
    - For all patients with muscle invasive disease (T2–T4; 79%), 5-year OS was 45% and 10-year OS was 29%.
- In another series of 333 patients with bladder cancer (high-risk T1 or muscle invasive), following TUR patients received radiotherapy alone or platinum-based CRT.[118]
    - CR rates were 57% for radiotherapy and 80% for CRT (p<0.05).
    - 5-year DSS rates were 40% for radiotherapy, 64% for CRT with cisplatin and 54% for CRT with carboplatin.

- In a study involving 190 patients with T2–T4a bladder cancer, initial treatment was TUR plus CRT.[114]
  - A bladder preservation approach was utilised for those patients who demonstrated a CR following the induction phase of radiotherapy. This subgroup then received consolidation with additional concurrent chemotherapy and radiotherapy to a total dose of 65 Gy.
  - Patients with an incomplete response to TUR followed by chemotherapy and radiotherapy or progressive disease underwent radical cystectomy.
  - Sixty-six patients (35%) underwent radical cystectomy; 41 for an incomplete response and 25 as salvage therapy for invasive recurrent disease.
  - At a median follow-up of 6.7 years 5-year OS for patients with an intact bladder was 57% for T2 tumours and 35% for T3–T4 tumours (p=0.0008).
  - Ten-year OS for patients with an intact bladder was 50% for T2 tumours and 24% for T3–T4 tumours (p=0.0008).
  - For the 66 patients undergoing radical cystectomy, 5-year OS was 48% and 10-year OS was 41%
  - Of the patients demonstrating a CR after initial therapy, 60% developed no further bladder tumours, 24% developed a superficial recurrence and 16% developed an invasive tumour.
- In a phase II clinical study, patients with high-risk T1 or T2–T4 bladder cancer were treated with cisplatin-based CRT after TUR.[119]
  - At 6 months after completion of treatment, 79 patients (70%) achieved a CR and 21 patients demonstrated persistent or progressive disease; of these, 6 underwent salvage cystectomy.
  - Recurrence of invasive disease occurred in 11/79 patients with CR at 6 months (14%). Six of these underwent salvage cystectomy. Another 3 patients underwent cystectomy for persistent isolated NMIBC.
  - For the whole study population, 5-year RFS and DFS rates were 33% and 50%, respectively. In patients achieving a CR at 6 months, 5-year RFS and DFS rates were 44% and 68%, respectively.
  - The 5-year local control rate (free of both non-muscle invasive and muscle invasive recurrences) was 45% for all patients and 53% for those that achieved a CR at 6 months.
- In a phase II trial, 50 patients with T2–T3/N0/M0 bladder cancer received gemcitabine-based CRT following TUR.[120]
  - Of 47 patients undergoing post-treatment cystoscopy, 44 achieved a CR.
  - At a median follow-up of 36 months (range, 15–62), 36 patients were alive; 7 died as a result of metastatic bladder cancer, 5 died as a result of other diseases, and 2 died due to treatment-associated factors.
  - Four patients underwent salvage cystectomy.
  - The 3-year DSS rate was 82% and 3-year OS was 75%.
- In a study conducted in Canada, 340 patients with bladder cancer (T2–T4, 89%) received radical radiotherapy, cisplatin-based CRT, or neoadjuvant CRT.[121]
  - At a median follow-up of 7.9 years (range: 1.5 months–16.8 years), CR rate as assessed by cystoscopy was 64% for radical radiotherapy, 79% for CRT and 52% for neoadjuvant CRT.

- Sternberg et al. treated 104 patients with T2–T4 TCC with 3 cycles of methotrexate + vinblastine + cisplatin (M-VAC) given as a 2-weekly schedule with granulocyte colony stimulating factor (GCSF) (i.e. accelerated M-VAC) followed by TUR.122 Dependent on the response to chemotherapy, patients underwent TUR and partial cystectomy (i.e. bladder preservation) or radical cystectomy.
    - At a median follow-up of 56 months, in patients undergoing M-VAC and TUR, with or without subsequent partial cystectomy (63%), 5-year OS was 67%.
    - In the 52 patients undergoing M-VAC and TUR without partial cystectomy, 37 (71%) achieved a CR. Of this subgroup, 13 patients experienced superficial disease recurrence, 5 patients developed invasive disease, 12 patients developed metastatic disease and 3 patients developed both invasive and metastatic disease. 5-year OS was 67%.
    - Thirty-nine patients not achieving a CR to M-VAC and TUR underwent radical cystectomy. At a median follow-up of 45 months, 14 patients developed metastatic disease. The 5-year OS in this subgroup was 46%.
    - A total of 83 patients were downstaged following repeat TUR, including 48 (46%) to T0, 6 to Ta, 8 to Cis, 17 (16%) to T1 and 4 to T2 disease.

Radical radiotherapy

Overview

- Standard radiotherapy involves CT-planned external beam conformal radiotherapy using fractionation schedules such as 64 Gy in 32 fractions, over 6.5 weeks, or 55 Gy in 20 fractions over 4 weeks. The daily dose should be 1.8–2.0 Gy, with a maximum treatment duration of 6–7 weeks.[24]
- OS rates of 60% for T2 tumours, 45% for T3 tumours and 15% for T4 tumours have been reported with radical radiotherapy, similar to single institution series of radical cystectomy for MIBC.

Patient selection

- T2–T4/NX–N0 (N+ patients can be downstaged with adjuvant chemotherapy)/M0.
- Good bladder function.
- WHO PS ≤3.
- Maximal TUR.
- No hydronephrosis (unless treated).

Adverse effects of treatment

- Acute side-effects include diarrhoea, tenesmus, proctitis, cystitis and lethargy.
- Late side-effects such as bladder fibrosis, second malignancies, haematuria and impotence.
- Urinary complications occur in 5% of patients.[90]
- Increased risk of inoperable disease or more difficult and high-risk surgery.
- 30-day mortality of <1%.[90]
- Radiotherapy may impair the chance of bladder reconstruction.

Clinical evidence

- In an Italian study, a series of 459 patients with T1–T4/N0-Nx/M0 bladder cancer received a minimal radiation dose of 50–70 Gy.[123]
    - Treatment failure (defined as absence of CR at first cystoscopy) was observed in 218 patients (47.5%).
- Bell et al. evaluated the efficacy and morbidity of definitive EBR (40–65 Gy, median fractions, 20) in 120 patients with T1–T4 bladder cancer, over an 8-year period in the UK.[124]
    - Local recurrence developed in 77 (59%) patients, which was invasive in 36 (30%) patients.
    - The overall mortality rate was 52%.
    - Median OS at 5 years was 67% for T1 tumours, 37% for T2 tumours and 22% for T3 tumours.
    - Thirty-three (27%) patients underwent a salvage cystectomy.
- In the BCON study, 333 patients with T1G3–T4a bladder cancer were randomised to either radiotherapy in combination with carbogen and nicotinamide (RCON) to reduce the risk of hypoxia, or radiotherapy alone.[125]
    - Median OS was 54 months with RCON and 30 months with radiotherapy alone (p=0.04).
    - 3-year OS was 59% with RCON versus 46% with radiotherapy alone (p=0.04).
    - 3-year RFS was 52% for RCON and 41% for radiotherapy alone (p=0.06).

Neoadjuvant chemotherapy prior to definitive local treatment

Overview

- The use of neoadjuvant chemotherapy prior to radical radiotherapy or radical cystectomy in MIBC is associated with improvements in survival rates.[126]
- Neoadjuvant platinum-based combination chemotherapy is given prior to definitive local treatment with either radiotherapy or cystectomy in patients who have disease that is amenable to radical treatment. This is different to 'down-staging' chemotherapy, which may be given to reduce tumour bulk and nodal disease in patients who are not suitable for radical treatment initially but who may be rendered operable or encompassable in a radical radiotherapy field by the use of down-staging chemotherapy.

Patient selection

- T2–T4.
- NX/N0/N1.
- M0.
- PS 0–1.
- Creatinine clearance >50 ml/min.
- Fit for chemotherapy.
- Given the modest yet definite improvements in OS with neoadjuvant chemotherapy, patients aged >70 should be considered on a case-by-case basis.

Adverse effects of treatment

- Neuropathy
- Renal toxicity
- Tinnitus
- Anaemia
- Neutropenic sepsis
- Bleeding
- Nausea and vomiting
- Stomatitis
- Alopecia
- Fatigue

Clinical evidence

- A meta-analysis of 11 neoadjuvant chemotherapy clinical trials with data from 3005 patients has been completed by the Advanced Bladder Cancer Meta-analysis Collaboration.[126]
    - For all included trials, the risk of death was significantly reduced with neoadjuvant chemotherapy versus local treatment alone (HR, 0.89; 95% CI, 0.81–0.98; p=0.022).
    - However, when considering the type of chemotherapy regimen, platinum-based combinations were also significantly superior to local treatment alone (HR, 0.86; 95% CI, 0.77–0.95; p=0.003), whereas single-agent platinum was not (HR, 1.15; 95% CI, 0.90–1.47; p=0.26).
- With combination platinum therapy, this equated to an OS of 50% at 5 years.
    - Similar results were obtained for DFS, with an HR of death from cancer of 0.81 (95% CI, 0.74–0.89; p<0.0001) for all chemotherapy regimens.
    - Platinum-based combination therapy was also significantly superior to local treatment alone (HR, 0.78; 95% CI, 0.71–0.86; p<0.0001), whereas single-agent platinum was not (HR, 1.14; 95% CI, 0.83–1.55; p=0.42).
- Another neoadjuvant chemotherapy trial randomised 976 patients with T2–T4a bladder cancer to curative cystectomy or EBR alone or 3 cycles of neoadjuvant M-VAC chemotherapy prior to radical cystectomy or radiotherapy.[127]
    - At a median follow-up of 8 years, the risk of death was reduced by 16% (HR, 0.86; 95% CI, 0.72–0.99; p=0.037) for neoadjuvant M-VAC versus no neoadjuvant chemotherapy.
- This equated to a 10-year OS of 36%.
- A smaller retrospective study conducted in the UK assessed 80 patients with T2–T4a bladder cancer who had received accelerated M-VAC (aM-VAC; 3 cycles of methotrexate + vinblastine + cisplatin given as a 2-weekly schedule with GCSF) as neoadjuvant chemotherapy prior to either radical cystectomy or radical radiotherapy.[128]
    - Following neoadjuvant aM-VAC, 43% of patients scheduled for radical cystectomy were pT0; 12% had residual disease (pT2 or pT3); none had pT4 disease.
    - 19% of the surgically-managed patients had 1 or more affected pelvic lymph nodes following neoadjuvant aM-VAC.
    - The radiological overall response rate (ORR) following neoadjuvant aM-VAC was 83% (rCR, 32%; rPR, 51%).
    - At a median follow-up of 27.5 months, 32% of assessable patients (25/78) had experienced disease recurrence (either loco-regional or metastatic).
    - 2-year RFS was 65% and predicted median DFS >60 months.
    - 2-year OS was 77% and predicted median OS >5 years.

Neoadjuvant radiotherapy prior to radical cystectomy or radical radiotherapy

- The available evidence suggests that there is no benefit of neoadjuvant radiotherapy in patients with muscle invasive bladder cancer.
- The role of radiotherapy administered prior to cystectomy was compared with cystectomy alone in a meta-analysis of 5 RCTs.[129]
    - The authors calculated an OR of 0.94 (95% CI, 0.57–1.55), with no significant difference between treatments.

Adjuvant chemotherapy

- There are currently no data to support the use of adjuvant chemotherapy.
- A meta-analysis conducted by the Advanced Bladder Cancer Meta-analysis Collaboration evaluated data from 491 patients with T2–T4a bladder cancer included in six trials.[130]
    - When comparing adjuvant chemotherapy with no adjuvant treatment, there was a 25% relative reduction in the risk of death, equivalent to a 9% absolute improvement in survival (95% CI, 1–16; p=0.019) at 3 years.
    - When considering platinum-based chemotherapy versus no adjuvant therapy, there was a 29% relative reduction in the risk of death (HR, 0.71; 95% CI, 0.55–0.92; p=0.01).
    - However, these results are difficult to interpret, as there were multiple different regimens of chemotherapy used.

Advanced/metastatic bladder cancer: Management options

An overview of the treatment approach for patients with advanced bladder cancer is presented in Figure 3.

First-line systemic chemotherapy

Overview

- The M-VAC regimen or gemcitabine + cisplatin (GC) combination can be used for the first-line management of advanced bladder cancer.
- However, GC is associated with less toxicity than M-VAC.
- Standard M-VAC or accelerated M-VAC (aM-VAC; 3 cycles of methotrexate + vinblastine + cisplatin given as a 2-weekly schedule with GCSF) may be used
- Carboplatin-based therapy may be an option for patients 'unfit' for cisplatin therapy, due to comorbidities or suboptimal renal function.

Patient selection

- Cisplatin-based therapy: PS 0–1, Adequate renal function, CrCl >50 ml/min, calculated from Cockroft-Gault or EDTA.
- Carboplatin-based therapy: PS 2–3, CrCl 30–50 ml/min.
- Cisplatin or carboplatin: adequate liver and haematological function.
- No other significant comorbidities that would interfere with chemotherapy administration.
- Adequate renal function (GFR ≥60 ml/min; creatinine clearance ≥50 ml/min).
- Adequate liver function (according to enzyme tests).

Adverse effects of treatment

- GC has a better safety and tolerability profile than standard M-VAC, with a reduced frequency of grade 3/4 neutropenia, neutropenic fever, mucositis and alopecia occurring in GC-treated patients.
- M-VAC treatment is associated with substantial toxicity, including neutropenia, mucositis and toxic deaths.
- Side-effects may be problematic for older patients, who may also present with co-morbidities.
- The administration of granulocyte colony stimulating factor (GCSF) alongside M-VAC can improve its tolerability.
- Neuropathy
- Renal toxicity
- Tinnitus
- Anaemia
- Bleeding
- Nausea and vomiting
- Stomatitis
- Alopecia
- Fatigue

Clinical evidence

- In a randomised trial of 405 patients with advanced bladder cancer, after more than 5 years of follow-up, median OS was 15.2 months with M-VAC and 14.0 months with GC (HR, 1.09; 95% CI, 0.88–1.34; p=0.66).[131]
    - OS rates at 24 months (M-VAC, 31.0% versus GC, 25.0%), 48 months (M-VAC, 17.3% versus GC, 16.4%) and 60 months (M-VAC, 15.3% versus GC, 13.0%) were comparable.
    - There were no differences between treatments for PFS (HR, 1.09; 95% CI, 0.89–1.34; p=0.63) and median PFS was 8.3 months with M-VAC and 7.7 months with GC.
    - Toxicity with GC was substantially lower than with M-VAC. Grade 3/4 neutropenia, neutropenic fever, mucositis and alopecia occurred more frequently in patients who received M-VAC.
- The superiority of M-VAC compared with single-agent cisplatin has been demonstrated in a randomised trial of 269 patients with advanced bladder cancer.[132]
    - Median OS was 12.5 months for M-VAC versus 8.2 months for cisplatin (p=0.04).
    - However, M-VAC was associated with a greater toxicity, in particular leukopenia, mucositis and granulocytopenic fever.
    - Long-term follow-up confirmed that M-VAC was superior to single-agent cisplatin; however, at 6 years, only 3.7% of the patients randomised to M-VAC were alive and continuously disease-free.[133]

- In a separate study, aM-VAC was administered in 263 patients with advanced bladder cancer.[134]
  - aM-VAC achieved higher response rates than standard M-VAC (62% versus 50%, respectively; p=0.06).
  - Progression-free survival (PFS) was also significantly better with aM-VAC compared with standard M-VAC (9.1 months versus 8.2 months, respectively; HR, 0.75; 95% CI, 0.58–0.98; p=0.037).
  - At the 7-year update of this study, the 2- and 5- year OS rates were 36.7% and 21.8% for aM-VAC compared with 26.2% and 13.5% for standard M-VAC.[135]
  - Median OS was 15.1 months with aM-VAC versus 14.9 months with standard M-VAC (HR for mortality, 0.76; 95% CI, 0.58–0.99).
- In a Phase III trial, 220 patients with inoperable, metastatic or recurrent bladder cancer were randomised to aM-VAC or docetaxel + cisplatin with GCSF (DC).[136]
  - Median OS was 14.2 months with accelerated M-VAC compared with 9.3 months for DC (HR, 1.52; 95% CI, 1.11–2.08; p=0.0255).
  - Two-year OS rates were 28.6% with accelerated M-VAC versus 18.9% with DC.
  - Median TTP was 9.4 months in patients receiving accelerated M-VAC compared with 6.1 months in patients receiving DC (HR, 1.73; 95% CI, 1.24–2.42; p=0.0029).

Patients unfit for M-VAC or GC

- In a randomised Phase II study involving 178 patients with advanced bladder cancer and WHO PS 2 and/or impaired renal function (GFR >30 but <60 ml/min), treatment was either gemcitabine + carboplatin (GCb) or methotrexate, vinblastine and carboplatin (M-CAVI).[137]
  - CR rates were 3.4% with GCb and 4.6%, but ORRs were 38% with GCb and 20% with M-CAVI.
  - ORRs were lower for patients with both PS 2 and GFR <60 ml/min versus those with either PS >2 or GFR <60 ml/min (26.1% versus 39.5%).
  - Severe acute toxicity was reported for 12 patients (13.6%) of patients receiving GCb and 20 patients (23.0%) receiving M-CAVI.
  - Death associated with treatment toxicity occurred in 2 patients receiving GCb and 4 patients receiving M-CAVI.
  - Severe acute toxicity was also more common in patients with both these factors (26.1% versus 15.5% for patients with either PS >2 or GFR <60 ml/min).
- In a retrospective analysis of data, patients (n=15) with Stage IV bladder cancer received GCb for up to 6 cycles.[138]
  - A CR was observed in 1 patient, PRs in 9 patients, and SD in 1 patient.
  - Median OS was 9 months (95% CI, 7.4–10.6).

Second-line systemic therapy in metastatic disease

Overview

- There are no standard treatment regimens in this setting, but patients who have responded for 6 months to first-line treatment may be rechallenged with that regimen.
- Patients who received first-line GC can receive second-line M-VAC or aM-VAC.
- Clinical data also support the use of other agents, e.g. paclitaxel.
- A single RCT of vinflunine has shown a modest improvement compared with BSC; more clinical trials in this setting are needed.
- Ongoing studies are evaluating targeted therapies.

Patient selection

- PS 0–1.
- Life expectancy ≥12 weeks.
- Fit for further chemotherapy.
- Adequate haematological, renal and hepatic function (choice of agent dependent on renal function).

Adverse effects of treatment (as per first-line therapy)

- Haematological side-effects, including leukopenia, neutropenia, thrombocytopenia and anaemia
- Infusion-site reactions
- Alopecia
- Nausea, vomiting, constipation
- Stomatitis/mucositis
- Fatigue

Clinical evidence

- In a retrospective analysis, aM-VAC was evaluated in 45 patients with metastatic bladder cancer who had previously received gemcitabine + platinum chemotherapy (in the neoadjuvant, adjuvant or metastatic disease setting).[139]
    - In patients receiving gemcitabine + platinum in the metastatic setting (n=22), 1 achieved a CR, 9 achieved a PR and 6 demonstrated SD.
    - Median PFS in these patients was 4.0 months (95% CI, 2.9–5.2) and median OS was 5.7 months (95% CI, 2.8–8.7).
- Weekly paclitaxel has been evaluated in a Phase II trial involving 31 patients with recurrent or metastatic disease.[140]
    - PR was achieved by 3 patients (10%).
    - Median OS was 7.2 months and median TTP was 2.2 months.

- Patients (n=31) with recurrent or metastatic disease who had previously received M-VAC were treated with weekly paclitaxel and carboplatin in a Japanese Phase II trial.[141]
    - ORR was 32% (CR, 6%).
    - Median OS was 7.9 months and median PFS was 3.7 months.
- In a Phase II study, 60 patients with locally advanced or metastatic bladder cancer, who had received ≤1 previous chemotherapy regimen, received paclitaxel + GCb in 21-day cycles.[142]
    - The ORR was 43%, with 12% of patients achieving a CR.
    - Median PFS was 7.4 months at a median follow-up of 31 months.
    - Median OS was 11 months; 1- and 2-year OS was 46% and 27%, respectively.
- In another Phase II trial, 24 patients with advanced bladder cancer previously treated with M-VAC received gemcitabine + paclitaxel in 21-day cycles.[143]
    - ORR was 42% (CR was 8%).
    - Median OS was 12.4 months (95% CI, 0.5–30.2); 1- and 2-year OS was 52% and 11%, respectively.
    - Median PFS was 6.1 months (95% CI, 0.5–23.9).
- In a Phase II study, 57 patients with advanced bladder cancer who had previously received one course of treatment with platinum-based chemotherapy were treated with vinflunine for 2 cycles. If disease had progressed at this stage, treatment was halted; patients with stable disease (SD) received another 2 cycles and were reassessed; patients with a response could receive vinflunine until disease progression or unacceptable toxicity.[144]
    - Nine patients achieved a partial response (PR) and another 25 demonstrated SD.
    - Median duration of response was 9.1 months (95% CI, 4.2–15.0).
    - Median OS was 6.6 months (95% CI, 4.8–7.6) and median PFS was 3.0 months (95% CI, 2.4–3.8).
- Another Phase II study included 151 patients with metastatic bladder cancer who had progressed following platinum-based first-line chemotherapy.[145]
    - PR was achieved by 22 patients (14.6%) and another 64 patients (42.4%) achieved SD.
    - Median OS was 8.2 months (95% CI, 6.8–9.6) and PFS was 2.8 months (95% CI, 2.6–3.8).
- A subsequent Phase III study compared vinflunine + best supportive care (BSC) with BSC alone, in 370 patients with locally advanced or metastatic bladder cancer.[146]
    - Median OS was 6.9 months for vinflunine + BSC versus 4.6 months for BSC alone (HR for risk of death, 0.88; 95% CI, 0.69–1.12; p=0.287).
    - In the eligible patient population (patients not violating study entry criteria, n=357), median OS was 6.9 months for vinflunine + BSC versus 4.3 months for BSC alone (HR for risk of death, 0.78; 95% CI, 0.61–0.99; p=0.04)
    - Median PFS for all patients was 3.0 months for vinflunine + BSC versus 1.5 months for BSC alone (p=0.0012).
    - Sixteen patients receiving vinflunine + BSC achieved a PR compared with no patients in the BSC alone arm. No patients in either group achieved a CR.
    - SD rates were 46.5% with vinflunine + BSC and 27.1% with BSC alone.

Symptomatic/palliative treatments – patients unfit for chemotherapy

Overview

- In patients for whom a cure is not possible, a number of treatments are available that can alleviate pain and other symptoms such as haematuria, in order to improve quality of life.
- Quality of life is paramount – palliative radiotherapy offers good palliation of symptoms.
- Collaboration between MDT members and patients is paramount.

Clinical evidence

- The MRC trial BA09 compared the efficacy of 35 Gy in 10 fractions over 2 weeks with 21 Gy in 3 fractions over 10 days in 272 patients considered to be unsuitable for curative treatment due to disease stage or co-morbidity.[147]
    - The shorter, fractionated schedule of palliative radiotherapy (21 Gy in 3 fractions) was as effective as the 35 Gy in 10 fractions in providing overall symptomatic improvement (64% versus 71% respectively).
- In an earlier study, two regimens of radiotherapy were compared: (A) 1700 cGy in two fractions over 3 days and (B) 4500 cGy in 12 fractions over 26 days, in 41 patients with haematuria and localised pain.[148]
    - Resolution of haematuria was achieved by 59% of patients in Group A versus 16% in Group B.
    - Improvement in pain was achieved by 73% of patients in Group A compared with 37% in Group B.
    - However, median OS was 9.8 months in Group A and 14.5 months in Group B.
- In a retrospective analysis of data from 65 elderly patients (60–98 years) with symptomatic advanced bladder cancer, radiotherapy was administered in 6 Gy fractions, for a total dose of 30 or 36 Gy.[149]
    - At 1 month after completion of radiotherapy, 28 of 55 evaluable patients (51%) experienced complete symptom relief. An additional 7 patients achieved an improvement in their urinary symptoms.
- In a prospective clinical trial, 40 patients with bladder cancer and bony metastases underwent radiotherapy followed by randomisation to zoledronic acid or placebo, once a month, for 6 months.[150]
    - At the 1-year follow-up, the mean number of skeletal-related events (e.g. fractures, spinal compression) was 0.95 in the zoledronic acid group versus 2.05 in the placebo group (p=0.001).
    - Mean pain score was reduced with zoledronic acid versus placebo (mean score, 4.37 versus 2.95).
    - The 1-year OS was 36.3% for zoledronic acid compared with 0 for placebo.

Ongoing Support

- Regular communication between the MDT and the primary care team are key to providing ongoing support, and may include the following:
  - Provision of detailed discharge or out-patient summaries in a timely manner.
  - Rationale why a particular treatment option has been chosen.
  - Details of the patient's response to the chosen treatment.
  - Exchange of protocols.
  - Electronic educational resources.
  - Agreement on prescribing policies.
  - Provision of contact details for information exchange.
- In addition to the MDT and primary care team, the local patient support network, such as a partner or family member, should be included in the exchange of information and/or education process which may include patient information material.
  - Local charities can provide support and educational materials
- Patients should be able to access information regarding clinical trials.
- Community palliative care should be discussed at the appropriate time.

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