Guidelines on

Bladder Cancer Muscle-invasive and Metastatic

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1. INTRODUCTION

1.1 The guideline

The European Association of Urology (EAU) Guideline Panel for Muscle-invasive and Metastic Bladder Cancer (MIBC) has prepared these guidelines to help urologists assess the evidence-based management of MIBC and to incorporate guideline recommendations into their clinical practice. The EAU Guidelines Panel consists of an international multidisciplinary group of experts in this field.

It is evident that optimal treatment strategies for MIBC require the involvement of a specialist multidisciplinary team and a model of integrated care to avoid fragmentation of patient care.

1.2 Methodology

*1.2.1 **Data identification***

Comprehensive literature searches were designed for each section of the MIBC guideline with the help of an expert external consultant. Following detailed internal discussion, searches were carried out in the Cochrane Library database of Systematic Reviews, the Cochrane Library of Controlled Clinical Trials, and Medline and Embase on the Dialog-Datastar platform. The searches used the controlled terminology of the respective databases. Both MesH and EMTREE were analysed for relevant terms; urinary bladder neoplasms (Medline) and bladder cancer (Embase) were the narrowest single terms available.

Extensive use of free text ensured the sensitivity of the searches, although the subsequent concomitant workload for panel members having to assess the substantial body of literature greatly increased.

Search strategies covered the last 10 years for Medline and for Embase in most cases. Randomised controlled trial (RCT) strategies used were based on Scottish Intercollegiate Guidelines Network (SIGN) and Modified McMaster/Health Information Research Unit (HIRU) filters for RCTs, systematic reviews and practice guidelines on the OVID platform. Results of all searches were scan-read by panel members. In many cases there was a high 'numbers needed to read' due to the sensitivity of the search.

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

The level of evidence (LE) and grade of recommendation (GR) provided in this guideline follow the listings in Tables 1 and 2. The aim of grading the recommendations is to provide transparency between the underlying evidence and the recommendation given.

It should be noted, however, that when recommendations are graded, the link between the level of evidence and grade of recommendation is not directly linear. Availability of RCTs may not necessarily translate into a grade A recommendation where there are methodological limitations or disparity in published results.

Alternatively, absence of high level evidence does not necessarily preclude a grade A recommendation, if there is overwhelming clinical experience and consensus. In addition, there may be exceptional situations where corroborating studies cannot be performed, perhaps for ethical or other reasons and in this case unequivocal recommendations are considered helpful for the reader. The quality of the underlying scientific evidence - although a very important factor - has to be balanced against benefits and burdens, values and preferences and cost when a grade is assigned (2-4).

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

*1.2.2 **Publication history***

The EAU published a first guideline on bladder cancer in 2000. This document covered both superficial (non-muscle-invasive) bladder cancer and MIBC. As different treatment strategies are employed for these conditions it was decided to split these topics up, resulting in a first publication of the MIBC guideline in 2004, with subsequent updates in 2007, 2009, 2010 and this 2011 update. A quick reference document presenting the main findings is also available. All texts can be viewed and downloaded for personal use at the EAU website: http://www.uroweb.org/guidelines/online-guidelines/.

1.3 Summary of updated information

For all Sections, the literature has been assessed and the guideline updated whenever relevant information was available.

Of note is the inclusion of:

- Gender, race and socio-economic factors (Chapter 2)
- Diagnosis modalities, in particular radiological assessment (Diagnosis and Staging, Chapter 4)

- New data has been taken in the discussion on neoadjuvant chemotherapy (Chapter 6)
- New data has been taken in resulting in additional recommendations on oncological- and surgical outcomes, as well as a management algorithm on T2-T4a N0M0 urothelial bladder cancer (Chapter 7)
- A management algorithm is presented for the management on metastatic urothelial bladder cancer (Chapter 8).
- Pre-treatment of patients prior to cystectomy (Chapter 9)
- The section on multimodality, bladder-preserving strategies, was completely replaced (Chapter 10)
- New data has been taken in regarding the choice of chemotherapy regimen and the use of biomarkers (Chapter 12)
- The available new evidence on quality-of-life (Chapter 13).

1.4 Acknowledgements

The panel is grateful for the contribution of Prof. Dr. F. Algaba (urological pathologist) in assessing and revising section 3.2 concerning the histopathological grading of tumours. The support provided by research scientist Drs. J. Krabshuis has proved to be highly valuable in enhancing the methodological quality of this publication.

Table 1: Level of evidence*

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

**Modified from Sackett, et al. (1).*

Table 2: Grade of recommendation*

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

**Modified from Sackett, et al. (1).*

1.5 References

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2. EPIDEMIOLOGY AND RISK FACTORS

2.1 Epidemiology

Bladder cancer is the 9th most common cancer diagnosis worldwide, with more than 330,000 new cases each year and more than 130,000 deaths per year, with an estimated male:female ratio of 3.8:1.0 (1). At any point in time 2.7 million people have a history of urinary bladder cancer (1).

At the initial diagnosis of bladder cancer, 70% of cases are diagnosed as non-muscle-invasive bladder cancer (NMIBC) and approximately 30% as muscle-invasive disease. Among patients treated with radical cystectomy because of MIBC, 57% had muscle invasion at presentation, while 43% had been initially diagnosed with NMIBC that progressed despite organ-preserving treatment (2). Approximately one-third of patients diagnosed with MIBC have undetected metastasis at the time of treatment of the primary tumour (3), while 25% of patients subjected to radical cystectomy present with lymph node involvement at the time of surgery.

2.2 Risk factors for bladder cancer

*2.2.1 **Tobacco smoking***

Tobacco smoking is the most well-established risk factor for bladder cancer, causing 50-65% of male cases and 20-30% of female cases. A casual relationship has been established between an exposure to tobacco and cancer in studies in which chance, bias and confounding can be ruled out with reasonable confidence (4). The alleged carcinogenic constituents of tobacco smoke include arylamines, particularly the potent carcinogen 4-aminobiphenyl (4-ABP), polycyclic aromatic hydrocarbons (PAHs), N-nitroso compounds, heterocyclic amines, and various epoxides.

The incidence of bladder cancer is directly related to the duration of smoking and number of cigarettes smoked per day (5). The risk of bladder cancer is also higher in those who start smoking at a young age or who are exposed to environmental tobacco smoke during childhood (6). A recent meta-analysis looked at 216 observational studies on cigarette smoking and cancer from 1961 to 2003, with reported estimates for current and/or former smokers. The pooled risk estimates for bladder cancer demonstrated a significant association for both current and former smokers. In an analysis of 21 studies, the overall relative risk calculated for current smokers was 2.77 (95% confidence interval [CI]: 2.17-3.54), while an analysis of 15 studies showed that the overall relative risk calculated for former smokers was 1.72 (95% CI: 1.46-2.04) (7). An immediate decrease in the risk of bladder cancer was observed in those who stopped smoking. The reduction was about 40% within 1-4 years of quitting smoking and 60% after 25 years of cessation (5). The promotion of smoking cessation would result in the incidence of bladder cancer decreasing equally in men and women.

*2.2.2 **Occupational exposure to chemicals***

Occupational exposure is the second most important risk factor for bladder cancer. Work-related cases accounted for 20-25% of all bladder cancer cases in several series. The substances involved in chemical exposure have been benzene derivatives and arylamines (2-naphthylamine, 4-ABP, 4,4'-methylenedianiline and o-toluidine), and it is likely to occur in occupations in which dyes, rubbers, textiles, paints, leathers and chemicals are used (8). These chemicals have contributed minimally to the current incidence of bladder cancer in Western countries because of strict regulations. In fact, there has been a trend towards a decrease in bladder cancer due to occupational exposure, as indicated by a pooled analysis of 11 European case-control studies on bladder cancer between 1976 and 1996 (9).

An example of occupational exposure is that of aromatic amines. These established carcinogens for urothelium can be inactivated by a metabolic acetylation pathway. The presence of an NAT2 slow-acetylation genotype has been associated with a higher risk of bladder cancer (10), suggesting that patients who are slow acetylators may be more susceptible to bladder cancer than rapid acetylators.

Other risk factors include phenacetin, which was included in 1987 among proven human carcinogens by the International Agency for Research on Cancer (IARC). Some studies have suggested that the risk of bladder cancer due to phenacetin is dose dependent; however, the data concerning its metabolite acetaminophen are controversial (11).

*2.2.3 **Radiation therapy***

Increased rates of secondary bladder malignancies have been reported after external beam radiation therapy (EBRT) for gynaecological malignancies, with relative risks of 2 to 4 (12). A recent population cohort study identified 243,082 men treated for prostate cancer between 1988 and 2003 in the Surveillance, Epidemiology and End Results database (SEER) in the USA. The standardised incidence ratios for bladder cancer developing after radical prostatectomy (RP), EBRT, brachytherapy (BT), and EBRT-BT were 0.99, 1.42, 1.10 and 1.39, respectively, compared with the general US population. The increased risk of bladder cancer in patients

undergoing ERBT, BT or ERBT-BT should be taken into account during follow-up. As bladder cancer requires a long time to develop, patients treated with radiation at a young age are at highest risk and should be followed up closely (13).

2.2.4 ***Dietary factors***

Several dietary factors had been believed to be related to bladder cancer; however, a link remains controversial. Currently, there is limited evidence of a causal relationship between bladder cancer and dietary factors. A meta-analysis of 38 articles reporting data on diet and bladder cancer supported the hypothesis that vegetable and fruit intake reduced the risk of bladder cancer (14).

2.2.5 ***Chronic urinary tract infection***

Muscle-invasive bladder cancer, particularly invasive squamous cell carcinoma, is directly related to the presence of chronic urinary tract infection.

2.2.6 ***Bladder schistosomiasis***

Bladder schistosomiasis (bilharzia) has been considered a definitive cause of urinary bladder cancer with an associated five-fold risk. Schistosomiasis is the second most common parasitic infection after malaria, with about 600 million people exposed to infection in Africa, Asia, South America, and the Caribbean (15). Although there is a well-established relationship between squamous cell carcinoma of the bladder and schistosomiasis, the trends are changing for bladder cancer in endemic zones, such as Egypt. Data from the National Cancer Institute (NCI) Cairo, the largest tertiary cancer hospital in Egypt, showed that patients diagnosed in 2005 had a six-fold higher odds of developing transitional cell carcinoma compared with patients diagnosed in 1980 (16). The decline in the frequency of bladder cancer is related to a decline in the detection of bilharzia eggs in urine samples, probably due to better control of the disease in rural populations (17).

2.2.7 ***Chemotherapy***

The use of cyclophosphamide, an alkylating agent used for treatment of lymphoproliferative diseases and other non-neoplastic diseases, has been correlated with posterior development of MIBC with a period of latency of 6-13 years. Acrolein is a metabolite of cyclophosphamide and is responsible for the increase in the incidence of bladder cancer. This effect occurs independently of the association of haemorrhagic cystitis with the same treatment (18,19).

2.2.8 ***Synchronous and metachronous upper urinary tract tumours***

In some cases, there is an association between upper urinary tract tumours (UUTT) and bladder cancer. The incidence of UUTT after diagnosis of NMIBC has been reported to be between 1.7% and 26%. Although synchronous UUTT and NMIBC are uncommon, 46% are invasive.

In a retrospective review of 1,529 patients with primary non-muscle-invasive bladder carcinoma who underwent initial examination of the upper urinary tract with excretory urography, those with a tumour in the bladder trigone were almost 6 times more likely to develop a synchronous tumour in the upper urinary tract (20). Examination of the upper urinary tract only in patients with a tumour in the trigone or with multiple bladder tumours could diagnose 41% or 69% of UUTT, respectively.

In addition, the overall incidence of bladder cancer development after treatment of UUTT has been reported in the literature as 15-50%. No level 1 evidence from prospective randomised trials was available. Intraluminal tumour seeding and pan-urothelial field change effects have both been proposed to explain intravesical recurrences. In most cases, bladder cancer arises in the first 2 years after upper urinary tract-urothelial cell carcinoma (UUT-UCC) management. However the risk is life-long and repeat episodes are common. No variables can be used to predict future bladder cancer recurrence in UUT-UCC patients reliably. A history of bladder cancer prior to UUT-UCC management and upper tract tumour multifocality are the only commonly reported clinical risk factors in the current literature (21).

2.2.9 ***Gender***

In a retrospective study of patients who underwent radical cystectomy, it was demonstrated that women were more likely to be diagnosed with primary muscle-invasive disease than men (85% vs 51%) (2). It has been proposed that women are more likely to be older than men when diagnosed, with a direct effect on their survival. In addition, delayed diagnosis is more likely in women after haematuria is observed, because the differential diagnosis in women includes diseases more prevalent than bladder cancer (22).

Differences in the gender prevalence of bladder cancer may be due to other factors besides tobacco and chemical exposure. In a large prospective cohort study, post-menopausal status was associated with an increase in bladder cancer risk even after adjusting for smoking status. This result suggests that the differences in oestrogen and androgen levels between men and women could be responsible for some of the difference

in the gender prevalence of bladder cancer (23-25). Recently a study in Egyptian women was conducted and younger age at menopause (< 45y) was a factor associated with increasing risk of bladder cancer, while multiple pregnancies and use of oral contraceptives were associated with decreased odds of having bladder cancer. The magnitude of associations were higher in the urothelial carcinoma group (26).

*2.2.10 **Race and socio-economic status***

Limited data exists on this topic, but a study based on 13,234 cases diagnosed in the SEER database between 1979-2003 showed that survival time from diagnosis was significantly decreased among cancer cases in patients with low socioeconomic status (SES) compared with those with higher SES. Hazard ratios for all causes and cancer-specific mortality among blacks compared to whites for eight of the most common types of cancers combined lost statistical significance after adjusting for SES factors and treatments. But blacks still had unfavourable prognoses compared with whites even after adjustment for SES and treatment for tumours such as breast-, colorectal-, and urinary bladder cancer (27).

2.3 Conclusions about epidemiology and risk factors

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

2.4 Recommendation for risk factors

Recommendation

	GR
The most important primary prevention measure for MIBC is to eliminate active and passive smoking.	B

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3. CLASSIFICATION

3.1 Tumour, Node, Metastasis classification

The Tumour, Node, Metastasis (TNM) Classification of Malignant Tumours is the method most widely used to classify the extent of cancer spread. Recently a seventh edition was published, effective as of 2010 (1). There are no significant modifications to this for bladder cancer compared with the previous (2002) edition.

Table 3: 2009 TNM classification of urinary bladder cancer

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

3.2 Histological grading of non-muscle-invasive bladder tumours

In 1998, a new classification of non-invasive urothelial tumours was proposed by the World Health Organization (WHO) and the International Society of Urological Pathology (ISUP). It was published by the WHO in 2004 (2,3) (Table 4). Its major contribution is a detailed histological description of the various grades using specific cytological and architectural criteria. A website (http://www.pathology.jhu.edu/bladder) illustrating examples of various grades was developed to improve accuracy in using the system.

Table 4: WHO grading in 1973 and 2004 (2,3)

1973 WHO grading
• Urothelial papilloma
• Grade 1: well differentiated
• Grade 2: moderately differentiated
• Grade 3: poorly differentiated
2004 WHO grading
• Urothelial papilloma
• Papillary urothelial neoplasm of low malignant potential (PUNLMP)
• Low-grade papillary urothelial carcinoma
• High-grade papillary urothelial carcinoma

*3.2.1 **WHO grading***

The 2004 WHO grading differentiates between papilloma, papillary urothelial neoplasms of low malignant potential (PUNLMP), and low-grade and high-grade urothelial carcinomas.

The papilloma is composed of a delicate fibrovascular core covered by normal urothelium. A PUNLMP is defined as a papillary fibrovascular growth covered by proliferated urothelium exceeding the normal thickness. Although PUNLMPs have a negligible risk of progression, they are not completely benign and have a tendency to recur. The low-grade papillary urothelial carcinoma group includes all former grade 1 (WHO 1973) cases and some former grade 2 cases (if a variation of architectural and cytological features exist at high magnification).

Use of the 2004 WHO classification is recommended as this should result in a uniform diagnosis of tumours better classified according to risk potential. However, until the 2004 WHO classification has been validated by more clinical trials, tumours should be graded using both the 1973 and the 2004 WHO classifications (4).

Most clinical trials published so far on bladder tumours have been performed using the 1973 WHO classification, so this is used in the 2010 edition of the guidelines.

3.3 Pathology

*3.3.1 **Urologist handling of specimens***

In transurethral resection (TUR) specimens, the superficial and deep areas of the tumour must be sent to the pathology laboratory separately. If random biopsies of the flat mucosa have been carried out, each biopsy of the flat mucosa must also be sent separately.

In radical cystectomy the bladder fixation must be carried out as soon as possible. The pathologist must open the specimen from the urethra to the bladder dome and fix the specimen in formalin. In some circumstances this procedure can also be performed by the urologist. In a female cystectomy specimen, the length of the urethral segment removed en bloc with the specimen should be checked, preferably by the urological surgeon (5).

*3.3.2 **Pathologist handling of specimens***

Specimen handling should follow the general rules as published by a collaborative group of pathologists and urologists (6). It must be stressed that it may be very difficult to confirm the presence of a neoplastic lesion using gross examination of the cystectomy specimen after TUR or chemotherapy, so the entire retracted or ulcerated area must be included.

It is compulsory to study the urethra, the ureter, the prostate in men and the radial margins (7). In urethra-sparing cystectomy, the level of urethral dissection, completeness of the prostate specifically at the apex (in men), and the inclusion of the entire bladder neck and amount of adjacent urethra (in women) should be documented.

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

In invasive bladder cancer there are usually no cases of PUNLMP and low-grade carcinoma. All cases are high-grade urothelial carcinomas (grade II or grade III in WHO 1973). For this reason, no more prognostic information can be provided by grading muscle-invasive bladder cancer (8). However, some morphological subtypes can be important for helping with prognosis and treatment decisions:

- small-cell carcinomas;
- urothelial carcinomas with squamous and/or glandular partial differentiation;
- spindle cell carcinomas;
- some urothelial carcinomas with trophoblastic differentiation;
- micropapillary urothelial carcinoma;
- nested carcinoma.

For staging, TNM 2002/2009 (6th or 7th edition) is recommended. The pattern of muscular invasion can provide some prognostic information. Most cases show nodular or cordonal growth, but about 44% have an infiltrative pattern. According to some authors (8), the median survival time of a patient with an infiltrative pattern is lower than that for an individual with other pattern types (p = 0.06). Blood vessel invasion and lymph node infiltration have an independent prognostic significance (9). It seems that the pN category is closely related to the number of lymph nodes studied by the pathologist. For this reason, some authors have observed that more than nine lymph nodes have to be investigated to reflect pN0 appropriately (10).

New prognostic markers are under study (11). Currently, insufficient evidence exists to recommend the standard use of the prognostic marker p53 in high-risk muscle-invasive disease, as it will not yield sufficient data upon which to base treatment in an individual patient.

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

Mandatory evaluations
Depth of invasion (categories pT2 vs pT3a, pT3b or pT4)
Margins with special attention paid to the radial margin
Histological subtype, if it has clinical implications
Extensive lymph node representation (more than nine)
Optional evaluations
Bladder wall blood vessel invasion
Pattern of muscle invasion

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4. DIAGNOSIS AND STAGING

4.1 Primary diagnosis

4.1.1 Symptoms

Painless haematuria is a common finding. In addition, some patients complain of urgency, dysuria, increased frequency and pelvic pain. Pelvic pain and all the symptoms related to urinary tract obstruction are found in more advanced tumours.

4.1.2 Physical examination

Physical examination should include rectal and vaginal bimanual palpation. A palpable pelvic mass can be found in patients with locally advanced tumours. In addition, bimanual examination should be carried out before and after TUR to assess whether there is a palpable mass or if the tumour is fixed to the pelvic wall (1,2).

4.1.3 Bladder imaging

A bladder mass identified by diagnostic imaging such as ultrasonography (US), intravenous urography (IVU), computed tomography (CT) or magnetic resonance (MR) imaging should be confirmed with cystoscopy and histology.

4.1.4 Urinary cytology and urinary markers

Examination of a voided urine or bladder-washing specimen for exfoliated cancer cells has high sensitivity in high-grade tumours (LE: 3). It is therefore useful when a high-grade malignancy or carcinoma *in situ* (CIS) is present.

Positive urinary cytology may indicate a urothelial tumour anywhere in the urinary tract from the calix, through the ureters, into the bladder and proximal urethra. Cytological interpretation is user dependent (3). The evaluation can be hampered by low cellular yield, urinary tract infections, stones or intravesical instillations. In experienced hands, however, specificity exceeds 90% (4) (LE: 2b). Cytology should be performed on fresh urine with adequate fixation. Morning urine is not suitable as cytolysis may often be present. No urinary marker is registered specifically for the diagnosis of invasive bladder cancer. However, as most invasive tumours are of high grade the positive predictive value of markers may be greater (5).

4.1.5 Cystoscopy

The diagnosis of bladder cancer ultimately depends on cystoscopic examination of the bladder and histological evaluation of the resected tissue. In general, cystoscopy is initially performed in the office, using flexible instruments. If a bladder tumour has been visualised unequivocally in earlier imaging studies, such as CT, MR imaging, or US, a diagnostic cystoscopy may be omitted as the patient will undergo TUR for a histological diagnosis.

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

4.1.6 Transurethral resection (TUR) of invasive bladder tumours

The goal of TUR is to enable a correct diagnosis by the pathologist, which means including bladder muscle in the adequately sized resection biopsies.

The strategy of resection depends on the size of the lesion. Small tumours (less than 1 cm) can be resected en bloc, where the specimen contains the complete tumour plus a part of the underlying bladder wall including bladder muscle. Larger tumours have to be resected separately in fractions, which include the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle and the edges of the resection area. At least the deeper part of the resection specimen must be referred to the pathologist in a separate container to enable him to make a correct diagnosis. Cauterisation has to be avoided as much as possible during the resection to prevent tissue destruction.

4.1.7 Random bladder and (prostatic) urethral biopsy

Bladder tumours are often multifocal. Moreover tumours can be accompanied by CIS or dysplasia. These

lesions may present themselves as velvet-like, reddish areas, indistinguishable from inflammation, or may be not visible at all.

The biopsies from normal-looking mucosa in patients with bladder tumours, so-called random biopsies (R-biopsies) or selected site mucosal biopsies, are only recommended if fluorescent areas are seen with photodynamic diagnosis (PDD). Fluorescence cystoscopy is performed using filtered blue light after intravesical instillation of a photosensitiser, usually 5-aminolevulinic acid (5-ALA) or hexaminolaevulinate (HAL). It has been confirmed that fluorescence-guided biopsy and resection are more sensitive than conventional procedures in detecting malignant tumours, particularly CIS (6-8) (LE: 2a). However, false-positive results may be induced by inflammation, recent TUR or intravesical instillation therapy. Material obtained by random or directed biopsies must be sent for pathological assessment in separate containers.

The involvement of the prostatic urethra and ducts in male patients with bladder tumours has been reported. Although the exact risk is not known, it seems to be higher if the tumour is located on the trigone or bladder neck, in the presence of bladder CIS and in multiple tumours (9,10) (LE: 3). Identification of involvement of the prostatic urethra can be determined either at the time of primary TUR or by frozen section during the cystoprostatectomy procedure. Although a frozen section has a higher negative predictive value and is more accurate, neither technique is 100% sensitive (11-13).

*4.1.8 **Second resection***

There is a significant risk of residual tumour after the initial TUR (14,15) (LE: 1). Persistent disease was observed in 33-53% of patients (15-21). Moreover, the tumour may be understaged by the initial resection. There is a 10% probability that tumours initially staged as being of a lower stage are in fact muscle-invasive (16,17). Correct staging is extremely important since it will directly affect the treatment modality. A second TUR should always be performed when the initial resection has been incomplete, e.g. when multiple and/or large tumours are present, or when the pathologist has reported that the specimen contained no muscle tissue. Furthermore, a second TUR should be performed when a high-grade, non-muscle-invasive tumour or a T1 tumour has been detected at the initial TUR. There is no consensus about the strategy and timing of a second TUR. Most authors recommend resection at 2-6 weeks after the initial TUR. The procedure should include a resection of the primary tumour site.

*4.1.9 **Concomitant prostate cancer***

Ruling out progressive prostate cancer should be considered since 25-46% of patients submitted to cystectomy for bladder cancer (22,23) appear to have prostate cancer on final pathology. Unless the entire prostate is to be removed during cystectomy, any type of prostate cancer should be excluded.

*4.1.10 **Recommendations for primary assessment of presumably invasive bladder tumours***

Recommendations

	GR
Cystoscopy with description of the tumour (site, size, number and appearance) and mucosal abnormalities. A bladder diagram is recommended.	C
TUR in one piece for small tumours (< 1 cm), plus a deep resection with part from the underlying bladder muscle.	B
TUR in fractions (including muscle tissue) for larger tumours.	B
Biopsies of abnormal-looking urothelium. Biopsies from normal-looking mucosa when cytology is positive or when exophytic tumour is of nonpapillary appearance or in case of fluorescence if PDD is used.	C
Biopsy of the apical prostatic urethra in the case of bladder neck tumour, when bladder CIS is present or suspected or when abnormalities of prostatic urethra are visible.	C
Careful inspection with histological evaluation of the bladder neck and urethral margin, either prior to or at the time of cystoscopy in women undergoing a subsequent orthotopic neobladder.	C
A second TUR at 2-6 weeks after the initial resection when it was incomplete or when a high-grade or T1 tumour was detected.	B
The pathological report should specify the grade, the depth of tumour invasion and whether the lamina propria and muscle are present in the specimen.	C

4.2 Imaging for staging in verified bladder tumours

Imaging is indicated only if there is a clinical consequence. The treatment and prognosis for invasive bladder cancer is determined by tumour stage and grade (24). Tumour staging must be accurate for selecting the correct treatment in clinical practice. The use of CT and MR imaging has largely replaced other imaging modalities for staging of invasive bladder cancer.

The purpose of imaging for staging invasive bladder cancer is to:

- Assess the extent of local tumour invasion
- Detect tumour spread to lymph nodes
- Detect tumour spread to the upper urinary tract and other distant organs (liver, lung, bones, peritoneum, pleura, adrenal gland and others).

*4.2.1 **Local staging of invasive bladder cancer***

Both CT and MR imaging may be used for assessment of local invasion (25) but they are unable to detect microscopic invasion of perivesical fat (T3a) (26). The aim of CT and MR imaging is therefore to detect T3b disease or higher.

4.2.1.1 MR imaging for local staging of invasive bladder cancer

Magnetic resonance imaging has superior soft tissue contrast resolution compared with CT, but poorer spatial resolution. In studies performed before the availability of CT imaging, MR imaging was reported to be more accurate for local assessment. The accuracy of MR imaging for primary tumour staging varies from 73% to 96% (mean 85%). These values were 10-33% (mean 19%) higher than those obtained with CT (27).

Fast dynamic contrast-enhanced MR imaging helps to differentiate bladder tumour from surrounding tissues because enhancement of the tumour occurs earlier than the normal bladder wall due to neovascularisation (28,29). Fast dynamic MR imaging with images acquired at one image per second helps to distinguish tumour from postbiopsy reaction (28).

In 2006 a link was established between gadolinium-based contrast agents (Gd-CA) and nephrogenic systemic fibrosis (NSF) which may result in a fatal or debilitating systemic fibrosis. It is widely accepted that patients with reduced (eGFR < 60 ml/min) or severely reduced (eGFR < 30 ml/min) renal function are at risk of developing NSF and in such patients the use of non-ionic linear Gd-CAs should be avoided (gadodiamide, gadopentetate dimeglumine, and gadoversetamide). Some centres advocate the use of stable macrocyclic contrast agents (gadobutrol, gadoterate meglumine, or gadoteridol) in these circumstances whilst others suggest using iodinated contrast media and performing contrast enhanced CT (30) (LE: 4).

4.2.1.2 CT imaging for local staging of invasive bladder cancer

The advantages of CT include shorter acquisition time, wider coverage in a single breath hold, and lower susceptibility to various patient factors.

Computed tomography imaging is unable to differentiate between stages Ta to T3a, but it is useful clinically for detecting invasion into the perivesical fat (T3b) and adjacent organs. The accuracy of CT in determining extravesical tumour extension varies from 55% to 92% (31) and increases with more advanced disease (32).

A study by Kim, et al. to determine the accuracy of CT for detection and staging of bladder cancer showed that CT had lower sensitivity (89%) and higher specificity (95%) compared to MR imaging for diagnosis of perivesical invasion, while the cancer detection rate and overall accuracy for perivesical invasion were similar (33). These findings are explained by better visualisation of perivesical fat invasion on MR imaging, but because only mild inflammation around bladder cancers mimics perivesical invasion, this results in overstaging with MR imaging.

*4.2.2 **Imaging of nodal involvement***

The assessment of nodal status based simply on size is limited by the inability of both CT and MR imaging to identify metastases in normal sized or minimally enlarged nodes. Sensitivities for detection of lymph node metastases are low, ranging from 48% to 87%. Specificities are also low as nodal enlargement may be due to benign pathology. Overall, the results of CT and MR imaging for detection of lymph node metastases in a variety of primary pelvic tumours are similar (34-38). Pelvic nodes greater than 8 mm and abdominal nodes greater than 10 mm in maximum short axis diameter (MSAD) should be regarded as enlarged on CT and MR imaging (39,40).

Currently there is no evidence for routine use of positron emission tomography (PET) CT in nodal staging of BC, although the method has been evaluated with varying results in small prospective trials (41,42).

4.2.3 *Extravesical urothelial carcinoma*

Multidetector computed tomography urography is the preferred imaging modality for the diagnosis and staging of upper urinary tract and bladder cancer (43,44). Computed tomography imaging has a higher diagnostic accuracy for urothelial cancers than IVU (LE: 2b), but has the disadvantage of higher radiation exposure (45-48).

4.2.4 *Distant metastases other than lymph nodes*

Prior to any treatment aimed at cure, it is essential to evaluate the presence of distant metastases. CT and MR imaging are the diagnostic tools of choice to detect metastases to lung and liver. Metastases to bones or brain at presentation of invasive bladder cancer are rare. Bone scan and additional brain imaging are therefore not routinely indicated unless the patient has specific symptoms or signs to suggest bone or brain metastases (49,50). MR imaging is more sensitive and specific for diagnosing bone metastases than bone scintigraphy (51,52) (LE: 2b).

4.2.5 *Conclusions for staging of verified bladder tumour*

Conclusions	LE
Imaging is used for formal staging only if it will make a difference to the selection of treatment options.	
MRI is the preferred modality if the patient is evaluated for radical treatment. CT due to its higher specificity may be equivalent to MRI regarding local staging.	
CT is recommended if there is suspicion of locally advanced or metastatic disease precluding radical treatment.	2b-3

4.2.6 *Recommendations for staging of verified bladder tumour*

Recommendations

	GR
For optimal T-staging, either MR imaging with fast dynamic contrast-enhancement or CT with contrast enhancement are recommended for patients considered suitable for radical treatment.	B
For patients with confirmed muscle-invasive bladder cancer, CT of the chest, abdomen and pelvis is the optimal form of staging, including CT urography for complete examination of the upper urinary tracts. If CT is not available, lesser alternatives are excretory urography and a chest X-ray.	B

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5. TREATMENT FAILURE OF NON-MUSCLE INVASIVE BLADDER CANCER

5.1 High-risk non-muscle-invasive urothelial carcinoma

The recurrence and progression rate of NMIBC is strongly associated with tumour grade and invasion into the lamina propria. The progression to T2 tumours varies from 6% to 25% in Ta and from 27% to 48% in T1 tumours of all grades. Inter- and intra-observer varying abilities in grading as well as staging and completeness of TUR are key variables confounding the results of present long-term studies of TUR, with or without intravesical therapy.

The understaging error in TaT1 tumours of 35% to 62% presented in large cystectomy series is due to the presence of recurrent tumours of largely unknown pre-cystectomy therapy and the lack of a second TUR (1-3) (LE: 3). The latter identifies 24% to 49% T2 tumours diagnosed initially as non-muscle-invasive tumours (4,5) (LE: 3). However, in spite of these disadvantages, recent meta-analyses have shown that intravesical therapy with Bacillus Calmette-Guerin (BCG) maintenance therapy prevents recurrence (6,7), but not progression. So far, no significant overall- or disease-specific survival advantages have been proven compared to no intravesical therapy (8-10) (LE: 1).

The disease progression rate is low in patients with small tumours (< 3 cm) and without associated CIS. Twenty

per cent of patients progress within 5 years, with approximately 90% of patients keeping their intact bladder during follow-up of up to 10 years (11) (LE: 2). However, in a recently published prospective multicentre trial, the progression rate was significantly lower than previously reported, even when the presence of concomitant CIS was considered. This was probably due to the combination of a second resection prior to inclusion in the trial and maintenance treatment as part of the protocol (12) (LE: 1b).

Initial cystectomy can be considered based on tumour multiplicity, size, concomitant *in situ* cancer, and urothelial tumour of the prostatic urethra (13) (GR: C). Although the percentage of patients with primary TaT1 tumours and the indication for cystectomy in TaT1 tumours is not specified in large cystectomy series, the 10-year recurrence-free survival is approximately 80% and similar to TUR and BCG maintenance therapy (1,3,14,15) (LE: 3). In case of recurrent TaT1, mostly associated with CIS, the understaging at time of cystectomy is 34%, but the 10-year survival is not significantly different for patients with pT1 and pT2 tumours (16) (LE: 3). This is in contrast to an earlier report indicating a significant worse outcome for patients with previous TUR(s) (17) (LE: 3).

Undoubtedly, patients with muscle-invasive recurrence are best treated with radical cystectomy. However, the outcome in terms of presence of lymph node metastases and cancer-free survival may be inferior to patients with the same tumour stage, but who receive radical cystectomy at first presentation (18) (LE: 3).

There is uncertainty about the treatment of patients who develop tumour recurrence in spite of BCG therapy because of different BCG therapy schedules and the absence of a uniform definition of BCG failure. It has been indicated that the recurrence (persistence) of tumour at 9 months in spite of BCG therapy is associated with a 30% chance of invasive tumours and death due to metastatic disease (19) (LE: 3). Solsona, et al. demonstrated that 80% of patients who had persistent disease at 3 months progressed to muscle invasive disease (20) (LE: 3). In addition, adequate tissue sampling from the prostatic urethra is an essential factor in considering the outcome of conservative treatment, since urethral tumours are associated with a significant decrease in tumour-free survival (21) (LE: 3). However, with careful selection and surveillance a durable complete response can be achieved also in patients diagnosed with superficial bladder transitional cell carcinoma involving the prostatic urethra (22). Based on these findings, cystectomy should be performed in appropriate patients at least at 9 months, because additional BCG therapy yields a response rate of only 27% to 51% and of unknown duration (23,24) (GR: C). Salvage chemotherapy is associated with limited response and should not be offered (25,26) (LE: 3).

Patients with superficial disease recurring within 2 years of initial TUR plus BCG therapy have a better outcome than patients who already have muscle-invasive disease indicating that cystectomy should be performed at first recurrence, even in case of superficial disease (LE: 3; GR: C) (18).

5.2 Carcinoma *in situ*

Primary CIS confined to the bladder is treated with intravesical BCG, yielding a complete response rate of 83-93% (27,28) (LE: 2). CIS associated with TaT1 is treated according to the overt tumour.

Approximately 50% of patients develop recurrent disease with muscle invasion or extravesical tumour (27,29) (LE: 2). Between 11% and 21% die of the disease within 5-7 years after an initial complete response (27,30) (LE: 2). Non-responders or incomplete responders have a significant risk of tumour progression of 33% to 67% (20,31) (LE: 2). Cystectomy should be performed in patients with an incomplete response at 9 months, tumour recurrence within the bladder, or extravesical recurrence (GR: B).

5.3 Recommendations for treatment failure of NIMBC

Recommendations

	GR
In patients with high-grade TaT1-tumours, a complete TUR and intravesical therapy is recommended (*see* EAU guidelines for non-muscle-invasive bladder cancer [32]).	B
In all T1 tumours at high risk of progression (i.e. high grade, multifocality, CIS, and tumour size, as outlined in the EAU guidelines for non-muscle-invasive bladder cancer [32]), immediate radical cystectomy is an option.	B
In all T1 patients failing intravesical therapy, cystectomy should be performed.	B

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6. NEOADJUVANT CHEMOTHERAPY

The standard treatment for patients with muscle-invasive bladder cancer is radical cystectomy. However, this 'gold standard' only provides 5-year survival in about 50% of patients (1-5). In order to improve these unsatisfactory results, the use of peri-operative chemotherapy has been explored since the 1980s.
There are many advantages of neoadjuvant chemotherapy, i.e. administering chemotherapy to patients with operable urothelial carcinoma of the urinary bladder before the planned definitive surgery (or radiation), including:

- Chemotherapy is delivered at the earliest time-point, when the burden of micrometastatic disease is expected to be low;
- Potential reflection of in vivo chemosensitivity;
- Tolerability of chemotherapy is expected to be better before cystectomy rather than after it;
- Hypothetically patients with micrometastatic disease might respond to neoadjuvant therapy and reveal favourable pathological status determined mainly by negative lymph node status and negative surgical margins.

The disadvantages of neoadjuvant chemotherapy include:

- For clinical staging with CT or MR imaging, over- and under-staging is likely to happen with a staging accuracy of only 70% (6,7). Overtreatment is the possible negative consequence;
- Delayed cystectomy might compromise the outcome in patients not sensitive to chemotherapy (8,9).

The side-effects of neoadjuvant chemotherapy affecting outcome of surgical morbidity need to be considered. In one randomised trial (10), the same distribution of post-operative complications grade 3-4 was seen in both trial arms (10). However, generally, pre-operative anaemia and neuropathy was more common in the chemotherapy group. In the combined Nordic trials NCS1+NCS2, (n = 620), neoadjuvant chemotherapy did not have any major adverse effect on the percentage of performable cystectomies. In the intention to treat analysis, the cystectomy-frequency was 86% in the experimental arm and 87% in the control arm. Still, in crude figures, 218 of 306 experimental and cystectomised patients received all 3 chemotherapy cycles (71%). Further 23 patients 1 or 2 cycles and 3 patients with greater than 25% dose reduction of cisplatin, translating into 78% receiving any neoadjuvant treatment (11).

Several randomised phase III trials investigated the question of whether or not neoadjuvant chemotherapy improved survival, with conflicting results (12-28). Most patients were $\leq$ 70 years old, had a performance status (PS) of 0-1 and a creatinine clearance of > 50-60 mL/minute, due to the kind of chemotherapy (single-agent cisplatin or cisplatin combination chemotherapy) scheduled.

Differences in trial design were mainly the type of chemotherapy (i.e. single-agent cisplatin or combination chemotherapy) and the number of cycles planned. From the statistical point of view, the studies differed in size, patient characteristics (e.g. clinical T-stages included), and the kind of definitive treatment allowed (cystectomy or radiotherapy or both).

Because of the lack of clarity, even though a considerable number of randomised trials had been performed, three meta-analyses were undertaken to answer the very important question of whether or not neoadjuvant chemotherapy prolongs survival (29-31).

- The first meta-analysis, published in 2003 (29), included 10 randomised trials (except for results of the INT 0080-study [20]) and showed a 13% reduction in the risk of death, equivalent to 5% absolute benefit at 5 years (increased overall survival from 45% to 50%).
- The second meta-analysis, published in 2004 (30), included 11 of 16 randomised trials with overall survival data of 2,605 patients. A statistically significant decrease in the risk of death (10%) was seen, corresponding to an absolute improvement in overall survival of 5% (from 50% to 55%).
- In the most recent meta-analysis, published in 2005 (32), with updated independent patient data of 11 randomised trials (3005 patients), a statistically significant survival benefit in favour of neoadjuvant chemotherapy was also seen. The results of this analysis confirmed the previously published data and showed 5% absolute improvement in survival at 5 years. The Nordic combined trial showed an absolute benefit of 8% in survival at 5 years and 11% in the clinical T3 subgroup, translating into nine patients needed to treat (11). Of note, only cisplatin combination chemotherapy with at least one additional chemotherapeutic agent resulted in a meaningful benefit (29,31); the regimens tested were MVA(E)C, CMV, CM, cisplatin/adriamycin, cisplatin/5-fluorouracil (5-FU), and CarboMV. To date, it is unknown if more modern chemotherapy regimens are as effective.

The presence of micrometastases is postulated to be lower in smaller tumours (T2) compared to more extensive tumours (T3b-T4b). T4 stage tumours are prone to a higher degree of clinical understaging because macrometastic nodal deposits are detected more often in post-cystectomy specimens of these extensive

tumours (32). Further data is in support of neoadjuvant chemotherapy in the subgroup of T2b-T3b tumours (former classification T3), which has been shown to provide a modest but substantial improvement in long-term survival and significant downstaging.

6.1 Conclusions for neoadjuvant chemotherapy

Conclusions	LE
Neoadjuvant cisplatin-containing combination chemotherapy improves overall survival by 5-7% at 5 years, irrespective of the type of definitive treatment used.	1a
Neoadjuvant chemotherapy has its limitations regarding patient selection, current development of surgical technique, and current chemotherapy combinations.	

6.2 Recommendations for neoadjuvant chemotherapy

Recommendations

	GR
Neoadjuvant cisplatin-containing combination chemotherapy should be considered in muscle-invasive bladder cancer, irrespective of further treatment.	A
Neoadjuvant chemotherapy is not recommended in patients with PS ≥ 2 and/or impaired renal function.	B

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7. RADICAL SURGERY AND URINARY DIVERSION

7.1 Removal of the tumour-bearing bladder

7.1.1 ***Background***

Radical cystectomy is the standard treatment for localised muscle-invasive bladder cancer in most countries of the Western Hemisphere (1,2). New interest in quality-of-life issues has increased the trend toward bladder preservation treatment modalities, like radio- and/or chemotherapy (*see* Chapters 9 and 10). Performance status and age influence the choice of primary therapy, as well as type of urinary diversion with cystectomy being reserved for younger patients without concomitant disease and better performance status. The value of assessing overall health before recommending and proceeding with surgery was emphasised in a recent multivariate analysis, which demonstrated an association between co-morbid disease and adverse pathological and survival outcome following radical cystectomy (3).

There is still controversy about age, radical cystectomy and the type of urinary diversion. Cystectomy is associated with the greatest risk reduction in disease-related and non-disease related death in patients older than 80 years (3). The largest retrospective single-institution study on cystectomy to date demonstrated that patients above 80 years did have an increased postoperative morbidity but not an increased mortality. Some patients even successfully underwent a neobladder procedure in this group, but the majority of patients were treated with an ileal conduit diversion (4).

7.1.2 ***Timing and delay of cystectomy***

In a retrospective series of 153 patients with a clear indication for radical surgery of locally advanced bladder cancer, a delay of treatment beyond 90 days of primary diagnosis caused a significant increase in extravesical disease (81 vs 52%) (5).

The delay of cystectomy not only affects the outcome but also the type of urinary diversion. In organconfined urothelial cancer of the bladder the average time from the primary diagnosis to cystectomy was 12.2 months in neobladder and 19.1 months in ileal conduit patients. It was even more striking for those patients who had an organ confined invasive cancer diagnosed; in neobladder patients the average time to surgery was 3.1 and in ileal conduit patients 15.1 months (6). Similar results have been observed in a series of 247 patients where superior recurrence-free survival and overall survival was significantly better in those treated within the 90 day period compared to others who were treated after a longer period (7).

7.1.3 ***Indications***

Traditionally radical cystectomy is recommended for patients with muscle-invasive bladder cancer T2-T4a, N0-Nx, M0 (1). Other indications include high-risk and recurrent superficial tumours, BCG-resistant Tis, T1G3 (*see* Chapter 5), as well as extensive papillary disease that cannot be controlled with TUR and intravesical therapy alone.

Salvage cystectomy is indicated for non-responders to conservative therapy, recurrences after bladder sparing treatments, non-urothelial carcinomas (these tumours respond poorly to chemo- and

radiotherapy) and as a purely palliative intervention for e.g. fistula formation, pain or recurrent macrohaematuria (*see* Section 8.1 Palliative cystectomy).

7.1.4 ***Technique and extent***

Radical cystectomy includes the removal of the bladder and adjacent organs, that is prostate and seminal vesicles in men, and uterus and adnexa in women (8). The inclusion of the entire prostate in male patients, and the extent of urethrectomy and vaginal resection in female patients, however, has recently been questioned (9,10).

Various techniques of partial prostate-sparing cystoprostatectomy in male patients with localised tumours have been proposed and results of series with a longer follow-up have been published (11-13). A randomised study comparing patients with and without remnant portions of the prostate is lacking and will be difficult to perform. Autopsy studies as well as studies looking at the unsuspected incidence of prostate cancer in cystoprostatectomy specimens suggest that in approximately 23-54% of patients a prostate cancer is found in the cystoprostatectomy specimen. Up to twenty-nine percent of these cancers may be clinically significant, locally recurrent or even metastatic in patients with prostatic tissue preserving radical cystectomy (14-16).

Furthermore urothelial cancer in the prostate was detected in 32 and 33% (69/240 cases and 77/235 cases, resp.) of patients undergoing radical cystoprostatectomy (15,17). In another study 50/121 of the cystoprostatectomy specimens (41%) removed for urothelial cancer had unsuspected prostate cancer. Twenty-four of these 50 tumours (48%) were clinically significant. In the same study 58/121 patients (48%) had urothelial carcinoma in the prostate of which 19 (33%) had apical involvement (18). Overall in the above mentioned series only 26 to 33% of the patients undergoing cystoprostatectomy for bladder cancer had neither prostate cancer nor prostatic urothelial cancer in the specimen.

However, by individualising the indication to spare seminal vesicles and the prostatic capsule in a group of 31 patients the oncological risk was small with a high probability of preserving potency (19).

Radical cystectomy also includes the dissection of regional lymph nodes. There is a substantial amount of literature about the extent of lymphadenectomy. Yet, data regarding its clinical significance are controversial. In retrospective studies extended lymphadenectomy (removal of the obturator, internal, external, common iliac and presacral nodes as well as nodes at the aortic bifurcation) has been reported to improve survival in patients with muscle-invasive bladder cancer. The curative value of lymph node dissection, however, is still unknown and a standardised lymph node dissection has yet to be defined (20-22).

There are several localisation studies with regards to lymphadenectomy (23,24) which demonstrated both retrospectively and prospectively that lymph nodes in bladder cancer patients are not found outside the pelvis if the pelvic lymph nodes are free of tumour. Furthermore progression free survival as well as overall survival might be correlated with the amount of lymph nodes removed during surgery. Removal of more than 15 lymph nodes has been postulated to be both sufficient for the evaluation of the lymph node status as well as beneficial for overall survival in retrospective studies (21,24,25). Inter-individual differences in the number of pelvic and retroperitoneal lymph nodes and difficulties in processing of the removed tissue by pathologists were not taken into account in these studies (20).

A distal ureteral segment (length not specified) should be resected and in case of bladder CIS a frozen section for evaluation of the surgical margins should be performed (8,26). Urethrectomy is recommended if there are positive margins at the level of urethral dissection, positive margins anywhere on the bladder specimen (in both sexes), if the primary tumour is located at the bladder neck or in the urethra (in women), or if tumour extensively infiltrates the prostate (1,27,28).

7.1.5 ***Laparoscopic/robotic-assisted laparoscopic cystectomy (RALC)***

Laparoscopic cystectomy and RALC have been shown to be feasible both in male and female patients (29,30). Both cystectomy and lymphadenectomy have been done in small series, according to the same principles used in cystectomy and anterior exenteration for several decades now (31). However, these techniques are still experimental because of the limited number of cases reported, an absence of long-term oncological and functional outcome data, and a possible selection bias (32,33).

Laparoscopic intracorporeal construction of urinary diversion with or without robotic assistance has been tested in small series only (32,34). It is a challenging and lengthy procedure with the current technical equipment available and must therefore be regarded experimental. Laparoscopic cystectomy and pelvic lymphadenectomy (with or without robotic assistance), with extracorporeal construction of urinary diversion, is an option for surgical treatment (LE: 3).

7.2 Urinary diversion after radical cystectomy

From an anatomical standpoint three alternatives are presently used after cystectomy:

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

Different types of segments of the intestinal tract have been used to reconstruct the urinary tract, including the stomach, ileum, colon, and the appendix (36). Several studies have compared certain aspects of health-related quality of life, such as sexual function, urinary continence and body image, in patient cohorts with different types of urinary diversion. However, further research is needed on pre-operative tumour stage and functional situation, socio-economic status, time interval to primary surgery, etc.

*7.2.1 **Preparations for surgery***

For cystectomy, general preparations are necessary as for any other major pelvic and abdominal surgery. If the urinary diversion is constructed from gastrointestinal segments, the length or size of the respective segments and their pathophysiology when storing urine must be considered (37). Despite the necessary interruption and re-anastomosis of bowel, a formal bowel preparation may not be necessary (38). Furthermore, bowel recovery time has been reduced by the use of early mobilisation, early oralisation and gastrointestinal stimulation with metoclopramide and chewing gum (39).

Patients undergoing continent urinary diversion have to be motivated both to learn about their diversion and to be manually skilful in manipulating their diversion. Contra-indications to more complex forms of urinary diversion include:

- Debilitating neurological and psychiatric illnesses.
- Limited life expectancy.
- Impaired liver or renal function.
- Transitional cell carcinoma of the urethral margin or other surgical margins.

Relative contraindications specific for an orthotopic neobladder are high-dose preoperative radiation therapy, complex urethral stricture disease, and severe urethral sphincter-related incontinence (40-42).

*7.2.2 **Ureterocutaneostomy***

Ureteral diversion to the abdominal wall is the simplest form of cutaneous diversion. It is considered as a safe procedure. It is therefore preferred in older, or otherwise compromised, patients, who need a supravesical diversion (43,44). However, others have demonstrated that, in carefully selected elderly patients, all other forms of wet and dry urinary diversions, including orthotopic bladder substitutions, are possible (4).

Technically either one ureter to which the other shorter one is attached end-to-side is connected to the skin (transuretero-ureterocutaneostomy) or both ureters are directly anastomosed to the skin. Due to the smaller diameter of the ureters, stoma stenosis has been observed more often than in intestinal stomas (43).

In a recent retrospective comparison with short or median follow-up of 16 months the diversion-related complication rate was considerably lower for ureterocutaneostomy compared to an ileal or colon conduit (45). Despite the limited comparative data available it has to be taken into consideration however, that older data and clinical experience suggest stricturing on skin level and ascending urinary tract infection are more frequent complications as compared to ileal conduit. In a retrospective study comparing various forms of intestinal diversion, ileal conduits had fewer late complications than continent abdominal pouches or orthotopic neobladders (46).

*7.2.3 **Ileal conduit***

The ileal conduit is still an established option with well-known/predictable results. However, up to 48% of the patients develop early complications including urinary tract infections, pyelonephritis, uretero-ileal leakage and stenosis (46). The main complications in long-term follow-up studies are stomal complications in up to 24% of cases and functional and/or morphological changes of the upper urinary tract in up to 30% (47-49). An increase in complications was seen with increased follow-up in the Berne series of 131 patients followed for a minimum of 5 years (median follow-up 98 months) (47): the rate of complications increased from 45% at 5 years to 94% in those surviving longer than 15 years. In the latter group, 50% and 38% of the patients developed upper urinary tract changes and urolithiasis, respectively.

7.2.4 ***Continent cutaneous urinary diversion***

A low-pressure detubularised ileal reservoir can be used as a continent cutaneous urinary diversion for selfcatheterisation; gastric, ileocecal and sigma pouches have also been described (50-52). Different anti-reflux techniques can be used (8). Most patients have a well-functioning reservoir with daytime and night time continence approaching 93% (53). A stomal stenosis in 23.5% of patients with appendix stoma and 15% with an efferent intussuscepted ileal nipple was observed in a study reviewing retrospectively the results of more than 800 patients. Stone formation in the pouch occurred in 10% of patients (53-55). In a small series of previously irradiated female patients incontinence and stomal stenosis was 18% (8/44 patients) (56).

7.2.5 ***Ureterocolonic diversion***

The oldest and most common form was primarily a refluxive and later an antirefluxive connection of ureters into the intact rectosigmoideum (uretero[recto]sigmoidostomy) (57,58). Most of the indications for this procedure have become obsolete due to a high incidence of upper urinary tract infections and the long-term risk of developing colon cancer (59,60). Bowel frequency and urge incontinence were additional side-effects of this type of urinary diversion. However, it may be possible to circumvent the above-mentioned problems by interposing a segment of ileum between ureters and rectum or sigmoid in order to augment capacity and to avoid a direct interaction between urothelium, colonic mucosa, together with faeces and urine (61).

7.2.6 ***Orthotopic neobladder***

An orthotopic bladder substitution to the urethra is now commonly used both in men and women.

Contemporary reports document the safety and long-term reliability of this procedure. In several large centres, this has become the diversion of choice for most patients undergoing cystectomy (1,42,62). The terminal ileum is the gastrointestinal segment most often used for bladder substitution and there is less experience with ascending colon, including caecum, and the sigmoid (1). The emptying of the reservoir anastomosed to the urethra requires abdominal straining, intestinal peristalsis and sphincter relaxation. Early and late morbidity in up to 22% of the patients is reported (63,64). Long-term complications include diurnal (8-10%) and nocturnal incontinence (20-30%), ureterointestinal stenosis (3-18%), urinary retention (4-12%) both in males and female patients, metabolic disorders and vitamin B12 deficiency in series with 1054 and more than 1,300 patients (42,65). In a recent study, which compared cancer control and patterns of disease recurrence in neobladder and conduit patients, no cancer-specific survival difference could be identified between the two groups when adjusting for pathological stage (66). Urethral recurrence in neobladder patients seems rare (1.5-7% for both male and female patients) (42,67). These results indicate that the choice of a neobladder both in male and female patients does not compromise the oncological outcome of cystectomy. It remains debatable whether a neobladder is better for quality of life compared to a non-continent urinary diversion (68-70).

Various forms of upper tract reflux protection, including a simple isoperistaltic tunnel, an ileal intussusception, a tapered ileal prolongation implanted subserosally, and a direct (sub)mucosal or subserosal ureteral implantation, have been described (55,64). According to the reported long-term results, the upper urinary tract is protected sufficiently by either method.

In conclusion, standard radical cystectomy in male patients with bladder neoplasms includes removal of the entire bladder, prostate, seminal vesicles, distal ureters (length of the segment undefined), and corresponding lymph nodes (extent undefined) (LE: 2b). Currently, it is not possible to recommend a particular type of urinary diversion. However, most institutions will prefer ileal orthotopic neobladders and ileal conduits based on clinical experience (9,71). In selected patients, ureterocutaneostomy is surgically the least-burdensome type of diversion (LE: 3). Recommendations related to radical cystectomy and urinary diversion are listed in section 7.6.2.

7.3 Morbidity and mortality

In a recent comprehensive long-term study (n = 1054), peri-operative mortality was reported in 3% of cases, and early complications, defined as any complication within 3 months of surgery, in 28% (62,65). Late morbidity is usually due to the type of urinary diversion (*see above*). Early morbidity associated with radical cystectomy for NMIBC (at high risk for disease progression) is similar and not less than that associated with muscle-invasive tumours (72). In general, a lower morbidity and mortality has been observed by surgeons and by hospitals with a higher case load and therefore more experience (73).

7.4 Survival

Research findings have demonstrated good survival outcomes:

- According to a multi-institutional database of 888 consecutive patients undergoing cystectomy and lymphadenectomy for bladder cancer, the outcome at 5 years was 58% for a mean recurrence-free survival and 66% for bladder cancer-specific survival (74).
- The recurrence-free and overall survival in a large single centre study of 1,054 male and female patients was 68% and 66% at 5 years and 60% and 43%, at 10 years, respectively (2).
- In node-positive patients, 10-year disease-specific and overall survival rates in another study have been reported to be 27.7% and 20.9%, respectively (75). In this cohort, 10-year disease-specific and overall survival rates were 72.9% versus 49.1% for organ-confined disease (defined as ≤ pT3a), and 33.3% versus 22.8% for non-organ-confined disease (75).
- In another study, 5-year recurrence-free survival was 76% in patients with pT1 tumours, 74% for pT2, 52% in pT3, and 36% in pT4 tumours (76). Tumour stage and nodal involvement are the only independent predictors of survival (77).

7.5 Conclusions on urinary diversion after radical cystectomy

Conclusions	LE
Cystectomy is the preferred curative treatment for localised bladder.	3
A higher case load reduces morbidity and mortality of cystectomy.	3
Radical cystectomy includes removal of regional lymph nodes, the anatomical extent of which has not been sufficiently defined.	3
Radical cystectomy in both sexes must not include the removal of the entire urethra in all cases, which may then serve as outlet for an orthotopic bladder substitution.	3
Terminal ileum and colon are the intestinal segments of choice for urinary diversion.	3
The type of urinary diversion does not affect oncological outcome.	3
Laparoscopic and robotic-assisted laparoscopic cystectomy is feasible but still investigational.	3

7.6 Recommendations for radical cystectomy and urinary diversion

*7.6.1 **Recommendations for radical cystectomy***

Recommendations

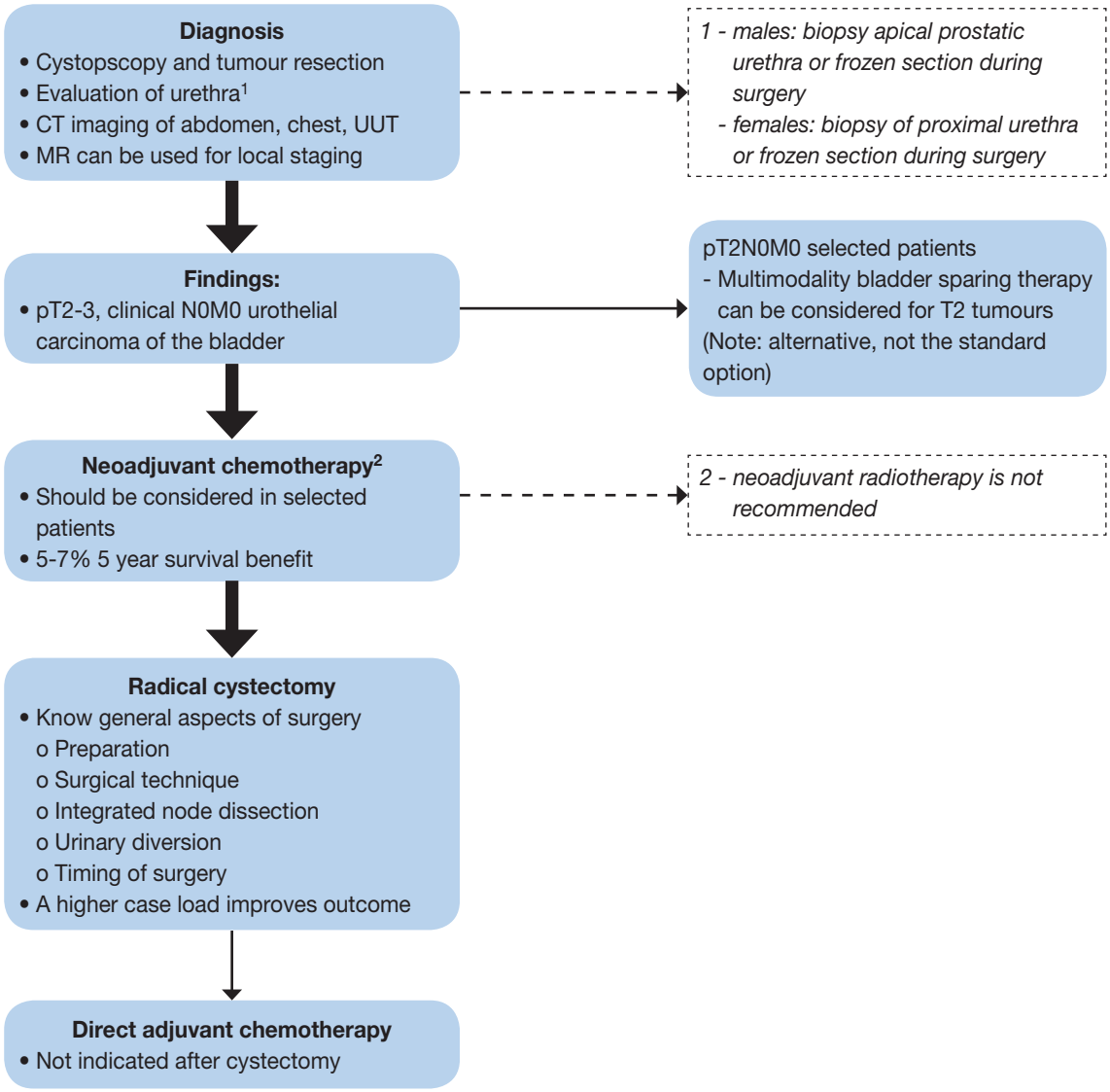
	GR
Radical cystectomy is recommended in T2-T4a, N0 M0, and high risk non-muscle-invasive BC (as outlined above).	A*
A delay in cystectomy increases the risk of progression and cancer-specific death.	B
No pre-operative radiotherapy should be administered.	A
Lymph node dissection should be an integral part of cystectomy, but the extent of the dissection has not been established.	B
Preservation of the urethra is reasonable if margins are negative. If no bladder substitution is attached, the urethra must be checked regularly.	B
Laparoscopic and robot-assisted laparoscopic cystectomy may be options. However, current data have not sufficiently proven the advantages or disadvantages of laparoscopic cystectomy.	C
Before cystectomy, the patient should be counselled adequately regarding all possible alternatives, and the final decision should be based on a consensus between patient and surgeon.	B
Pre-operative bowel preparation is not mandatory, 'fast track' measurements reduce the time of bowel recovery.	C
An orthotopic bladder substitute should be offered to male and female patients lacking any contraindications and who have no tumour in the urethra and at the level of urethral dissection.	B

**Upgraded following panel consensus*

7.6.2 *Recommendations regarding outcome after surgery*

Oncological outcome	GR
For patients with inoperable locally advanced tumours (T4b), primary radical cystectomy is a palliative option and not recommended as a curative treatment.	C
In patients with invasive bladder cancer older than 80 years cystectomy is an option.	C
For palliative cystectomy, surgery-related morbidity and quality of life should be weighed against other options.	C
Surgical outcome	
Surgical complications of cystectomy and urinary diversion should be reported in a uniform grading system. Currently, the best-adapted, graded system for cystectomy is the Clavien grading system.	B
Co-morbidity, age, previous treatment for bladder cancer or other pelvic diseases, surgeon and hospital volume of cystectomy, and type of urinary diversion influence surgical outcome.	B

Figure 1: Flowchart on the management for T2-T4a N0M0 urothelial bladder cancer



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8. NON-RESECTABLE TUMOURS

8.1 Palliative cystectomy for muscle-invasive bladder carcinoma

For patients with inoperable locally advanced tumours (T4b, invading the pelvic or abdominal wall), radical cystectomy is not usually a therapeutic option (1). Treatment of these patients remains a clinical challenge. These patients are candidates for palliative treatments, such as palliative radiotherapy.

Inoperable locally advanced tumours may be accompanied by several debilitating symptoms, including bleeding, pain, dysuria and urinary obstruction. There are several treatment options for patients with these symptoms. In advanced bladder cancer complicated by bleeding, cystectomy with urinary diversion is the most invasive treatment. It carries the greatest morbidity and should be considered only if there are no other options (1).

In patients with locally advanced pelvic cancer and urinary bladder involvement, palliative radical cystectomy with urinary diversion using intestinal segments is usually performed for the relief of symptoms such as pain, recurrent bleeding, urgency and fistula formation (2).

Zebic, et al. (2005) (3) retrospectively analysed patients aged ≥ 75 years, who had received radical cystectomies with either curative or palliative intent. The indications for palliative cystectomy were advanced pelvic malignancy with severe irritating voiding symptoms, severe pain and recurrent macrohaematuria requiring blood transfusions (3). Zebic, et al. (2005) concluded that elderly people have a greater risk of peri-operative morbidity and mortality, especially those with very advanced pelvic malignancies, who have undergone palliative cystectomy (3).

Advanced MIBC can be associated with ureteral obstruction. In invasive tumours, the mechanism of ureteral obstruction is probably caused by a combination of mechanical blockage by the tumour and invasion of ureteral orifices by tumour cells interfering with ureteral peristalsis. Bilateral ureteral obstruction, or unilateral obstruction to a solitary functioning kidney, can result in uraemia. Treatment of such patients is still a dilemma. El-Tabey, et al. (2005) (4) retrospectively reviewed the records of patients who presented with bladder cancer and obstructive uraemia. Patients with inoperable locally advanced bladder tumours (23 patients, 37.7%) were treated with permanent nephrostomy tubes to relieve obstruction; radical cystectomy was not an option. Ten patients underwent surgery (26.3%); palliative cystectomy without lymphadenectomy was carried out for advanced nodal involvement in four patients and for locally advanced disease infiltrating the pelvic wall in six patients. In all 10 patients, local pelvic recurrence was reported within the first year of follow-up (4).

In another study, post-operative outcome was reported for primary radical cystectomy in 20 T4 bladder cancer patients (of which seven cases were T4b). The authors concluded that primary cystectomy for T4 bladder cancer was technically feasible and had a very tolerable therapy-related morbidity and mortality (5).

8.2 Conclusions on non-resectable tumours

Primary radical cystectomy in T4b bladder cancer is not a curative option.
If there are symptoms, radical cystectomy may be a therapeutic/palliative option.
Intestinal or non-intestinal forms of urinary diversion can be used with or without palliative cystectomy.

8.3 Recommendations for non-resectable tumours

Recommendations

	LE	GR
For patients with inoperable locally advanced tumours (T4b), primary radical cystectomy is not a curative option.		B
The indication for performing a palliative cystectomy is symptom relief.		
Morbidity of surgery and quality of life should be weighed against other options.	3	B

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9. NEOADJUVANT RADIOTHERAPY IN MUSCLE-INVASIVE BLADDER CANCER

9.1 Pre-operative radiotherapy

*9.1.1 **Retrospective studies***

Several retrospective studies have looked at the effect of pre-operative radiotherapy in patients with bladder cancer.

- The largest retrospective series (n = 526) showed that pre-operative radiotherapy at a dose of 50 Gy resulted in down-staging in 73% of cT3 patients versus 29% of patients who were not given preoperative radiotherapy (1,2). Local control improved from 72% to 91% in pT3b patients (n = 91), but not in pT2 or pT3a patients, while overall survival improved from 40% to 52%.
- The results of a non-randomised study comparing 40 Gy versus 5-20 Gy versus no radiotherapy showed that only 40 Gy pre-operative radiotherapy reduced the risk of local recurrence from 27% to 11% and improved survival from 21% to 63% (3).
- Overall, nearly all retrospective studies of pre-operative radiotherapy at doses of 40-50 Gy, followed after 4-6 weeks by cystectomy, showed (1-9):
  - down-staging of the tumour stage (40-65% of patients)
  - lower risk of local recurrence (10-42%)
  - improved survival (11-12%).
- Some studies showed that an improvement in local control was highest for T3b tumours (2-4).
- Other studies showed that achievement of a pathological complete remission (pCR) was a prognostic factor for survival (3-5).
- One retrospective study (5) found no significant increase in toxicity due to pre-operative radiotherapy (10% versus 3%).

*9.1.2 **Randomised studies***

There have been five published randomised studies investigating pre-operative radiotherapy.

- The largest randomised trial (n = 234 evaluable patients) administered pre-operative radiotherapy at a dose of 45 Gy in fractions of 1.8-2.2 Gy in muscle-invasive tumours. The results showed a significant increase in pCR (9% to 34%) in favour of pre-operative radiotherapy and no significant increase in 5-year survival of 33% to 45% (10). In patients not given adjuvant chemotherapy, survival was significantly better than in patients given pre-operative radiotherapy (25-52%). pCR was a prognostic factor for better survival. A major limitation was the exclusion from the analysis of almost 50% of patients because they did not receive the planned treatment.
- The Southwest Oncology Group (SWOG) trial (n = 124), which used a pre-operative dose of 5 x 4 Gy, did not show a survival advantage (11).
- An Egyptian study in patients with bladder cancer caused by bilharzia (predominantly squamous cell carcinoma, n = 92) showed a significant survival advantage for > T3 tumours, but a marginal and non-significant difference for the whole group (12).
- A small, randomised study of 44 patients (13) showed a significant increase in pCR (18-55%) and a small increase in 5-year survival (61-72%, not significant), but the results were limited by a small patient population and differing radiotherapy schedules (32-54 Gy).
- In another small, three-armed study (n = 72), patients were randomised between surgery, surgery with pre-operative radiotherapy (45 Gy in 4-5 weeks) and radiotherapy alone (50-60 Gy in 4-6 weeks) (14). Pre-operative radiotherapy resulted in 24% of patients achieving pCR. There were no significant differences in survival or toxicity between the three arms.
- There was no reported increase in toxicity due to pre-operative radiotherapy in any of the above-mentioned studies.
- The effect on the local recurrence rate was not specifically documented in any of the studies.
- Three of the randomised studies looked at down-staging and found an increase in pCR following preoperative radiotherapy from 9% to 34% (10), 0% to 24% (14) and from 18% to 55% (13).
- Local recurrences were not reported (10,14), nor were they similar in any of the randomised studies (13).
- All five randomised studies looked at survival. The largest study found a significant survival advantage from 25% to 52% in those patients who did not receive adjuvant chemotherapy (10). The Egyptian study found a survival advantage only for T3 patients or higher (12). No study found a significant survival advantage for the whole group.
- A meta-analysis of the randomised trials on the value of pre-operative radiotherapy showed an odds

ratio for the difference in 5-year survival of 0.71 (95% CI: 0.48-1.06). However, the meta-analysis was potentially biased by the many patients in the largest trial, who did not receive the planned treatment. When the results of the largest trial were excluded, the odds ratio became 0.95 (95% CI: 0.57-1.55), indicating that improved survival with pre-operative radiotherapy had not been proven (15,16).

*9.1.3 **Effect of pre-treating patients with neoadjuvant radiotherapy before cystectomy***

A recent study compared the long-term outcome of pre-treating patients before cystectomy with neoadjuvant radiotherapy (n = 90) versus not pre-treating with radiotherapy (n = 97). The clinical stage of tumours was T1-3. Down-staging to T0 after cystectomy occurred in 7% (7/97) without radiotherapy versus 57% (51/90) with radiotherapy. In cT3 tumours, these results were 0% (0/16) versus 59% (19/34), respectively. Down-staging resulted in a longer PFS. In cT3 tumours, there was also a significant longer disease-specific survival. However, the results are limited by the small patient numbers and the retrospective nature of the study.

Another recent retrospective study on neoadjuvant radiotherapy also found a survival advantage, though the results were also limited (17).

9.2 Conclusions for pre-operative radiotherapy

Conclusions	LE
It is not proven that pre-operative radiotherapy for operable muscle-invasive bladder cancer increases survival.	2
Pre-operative radiotherapy for operable muscle-invasive bladder cancer, using a dose of 45-50 Gy in fractions of 1.8-2 Gy results in down-staging after 4-6 weeks.	2
Pre-operative radiotherapy with a dose of 45-50 Gy in fractions of 1.8-2 Gy does not seem to significantly increase toxicity after surgery.	3
There are suggestions in older literature that pre-operative radiotherapy decreases local recurrence of muscle-invasive bladder cancer.	3

9.3 Recommendations for pre-operative radiotherapy

Recommendations

	GR
Pre-operative radiotherapy is not recommended to improve survival.	B
Pre-operative radiotherapy for operable muscle-invasive bladder cancer results in tumour downstaging after 4-6 weeks.	B

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10. BLADDER-SPARING TREATMENTS FOR LOCALISED DISEASE

10.1 Transurethral resection of bladder tumour (TURB)

When patients, with an initially invasive bladder cancer, presenting with pT0 or pT1 status at second resection are selected for transurethral resection of bladder tumour (TURB) alone, about half of them will have to undergo radical cystectomy for recurrent muscle-invasive cancer, with a disease-specific death rate ranging up to 47% within this group (1,2).

A disease-free status at re-staging TUR appears to be crucial in making the decision not to perform radical cystectomy (3,4). Transurethral resection alone is only possible as a therapeutic option if tumour growth is limited to the superficial muscle layer and if re-staging biopsies are negative for residual tumour (5). Transurethral resection alone should only be considered as a therapeutic option, when the patient is unfit for cystectomy or a multimodality bladder-preserving approach, or refuses open surgery (6).

10.1.1 ***Conclusion and recommendation for TURB***

Conclusion and recommendation	LE	GR
TUR alone is not a curative treatment option in most patients.	2a	B

10.1.2 ***References***

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10.2 External beam radiotherapy

The target field usually comprises the bladder only, with a safety margin of 1.5-2 cm to allow for unavoidable organ movements (1-4). Any beneficial effect with larger pelvic fields has not been demonstrated. The target dose for curative radiotherapy for bladder cancer is 60-66 Gy, with a subsequent boost using external radiotherapy or interstitial brachytherapy. The daily dose is usually 1.8-2 Gy, and the course of radiotherapy should not extend beyond 6-7 weeks to minimise the repopulation of cancer cells. The use of modern standard radiotherapy techniques results in major, related, late morbidity of the urinary bladder or bowel in less than 5% of tumour-free patients (5-9). As well as the response to radiotherapy, important prognostic factors for outcome include:

- tumour size;
- hydronephrosis;
- completeness of the initial TURB.

Overall 5-year survival rates in patients with muscle-invasive bladder cancer range between 30% and 60%, with a cancer-specific survival rate of 20% and 50%, with or without a complete response following radiotherapy, respectively (10-14).

Prognostic factors for success were investigated in an Italian single institution series of 459 irradiated patients, including approximately 30% of unfit T1 patients, with 4.4 years average follow-up. Significant factors were found to be:

- age;
- T category (for all end points);
- tumour dose (only for failure-free survival) in a multivariate survival analysis (15).

Based on available trials, a Cochrane analysis has demonstrated that radical cystectomy has an overall survival benefit compared to radiotherapy (16).

External radiotherapy can be an alternative treatment in patients unfit for radical surgery, as demonstrated in a group of 92 elderly or disabled patients with T2-4 N0-1 M0 bladder cancer and a median age of 79 years. The total dose given was 55 Gy in 4 weeks. The cystoscopic complete remission rate at 3 months was 78%, 3-year local control rate 56%, and 3-year overall survival 36%. Pre-treatment bladder capacity was demonstrated in 81% of patients (17).

10.2.1 ***Conclusions on external beam radiotherapy***

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

10.2.2 ***Recommendation for external beam radiotherapy***

Recommendation

	GR
There is evidence that radiotherapy alone is less effective than curative therapy (surgery or trimodality treatment).	B

10.2.3 ***References***

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10.3 Chemotherapy

Chemotherapy alone rarely produces durable complete responses. In general, a clinical complete response rate of up to 56%, as reported in some series, must be weighed against a staging error of > 60% (1-2). Response to chemotherapy is a prognostic factor for treatment outcome and eventual survival (3), though it may be confounded by patient selection.

Several groups have reported the effect of chemotherapy on resectable tumours (neoadjuvant approach), as well as unresectable primary tumours (4-7). Neoadjuvant chemotherapy with 2-3 cycles of MVAC or CMV has led to a downstaging of the primary tumour in different prospective series (4-6). Pathological complete responses of bladder primary tumours were reached in 12-50% of patients after MVAC and in 12-22% of patients after gemcitabine/ cisplatin (GC) in phase II and phase III trials (4-6,8-16). Contemporary series with GC followed by radical cystectomy reported inferior pT0 rates, which may have been related to a lack of dose density and inappropriate delay of surgery (17).

As for bladder preservation, response is evaluated by cystoscopy and CT imaging only, followed by close surveillance. This approach is prone to an immanent staging error, which can put the patient at risk for local recurrence and/or consecutive metastatic disease.

For very selected patients, a bladder-conserving strategy with TUR of the bladder and systemic cisplatin-based chemotherapy, preferably with MVAC, may allow long-term survival with intact bladder (18). However, this approach cannot be recommended for routine use.

*10.3.1 **Conclusion and recommendation for chemotherapy for bladder tumours***

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

Recommendation

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

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10.4 Multimodality bladder-preserving strategy

A trimodality treatment approach for muscle-invasive bladder cancer consists of TUR for the primary tumour followed by a combination of local radiation therapy and systemic chemotherapy (1-5). Radical cystectomy and multimodality bladder-preserving strategies have never been directly compared and patients in multimodality series are highly selected (5-7). For example: small T2 tumours only without CIS. No hydronephrosis. A T0

status at repeat TUR after the initial transurethral resection of the primary tumour, followed by chemotherapy in combination with radiotherapy, was identified as a prognostically important variable. However, even the latter patients are at a life-long risk of developing intravesical tumour recurrences with the need for meticulous surveillance and multiple invasive procedures.

With this approach, a radical cystectomy is only performed in cases where the restaging cystoscopy following initial therapy fails to demonstrate a complete response (CR). Cisplatin, together with the addition of 5-fluorouracil (5-FU), demonstrated a CR and bladder preservation rates of up to 70-80% and 50-60%, respectively (5). Although the long-term survival rates observed with a trimodality treatment approach are apparently equal to those following radical cystectomy (5,6,8-10), both treatment approaches have not been directly compared to date. The combined use of radiation therapy and chemotherapy rarely induces severe (Grade ≥ 3) late toxicity (11). The addition of further cytotoxic drugs improves the clinical response and bladder preservation rate but increases acute (Grade 3-4) toxicity (12).

For the 30-40% of patients who need to undergo radical cystectomy either as non-responders to initial therapy or due to the long-term diagnosis of muscle-invasive disease, the disease-specific survival rate is worse and decreases to 20-50% after 5 years of follow-up (5,6). It remains unclear whether this is due to higher biological aggressiveness in this subgroup of bladder cancers or if it results from delay of surgical therapy impacting on the patient's clinical prognosis (13-17).

Non-muscle-invasive bladder cancer recurrences typically occur at a frequency of 14-40% during the first 12-24 months, with intravesical disease recurring as late as 5-10 years following initial trimodality therapy (5,6,8-10). With the bladder remaining a potential source of tumour recurrence, the patient must be highly compliant, and must be informed about the need for life-long follow-up and the possibility of multiple repeat TUR interventions. In addition, urinary incontinence and voiding dysfunction affects 11-14% of males and 17-45% of females with a native intact bladder (18).

*10.4.1 **Conclusion on multimodality treatment***

Conclusion	**LE**
Multimodality treatment can achieve long term survival rates in highly selected patients.	3

*10.4.2 **Recommendations for multimodality treatment***

Recommendations

	GR
TURB alone is not a curative treatment option in most patients.	B
Radiotherapy alone is less effective than surgery.	B
Chemotherapy alone is not recommended as primary therapy for localised bladder cancer.	A
Multimodality treatment is an alternative in selected, well-informed and compliant patients for whom cystectomy is not considered for medical or personal reasons.	B

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11. ADJUVANT CHEMOTHERAPY

Adjuvant chemotherapy for patients after radical cystectomy with pT3/4 and/or lymph node positive (N+) disease without clinically detectable metastases (M0) is under debate (1,2). The benefits of chemotherapy in the adjuvant setting include:

- Chemotherapy is administered after accurate pathological staging.
- Overtreatment in patients at low risk for micrometastases is avoided.
- No delay in definitive surgical treatment, especially in patients not sensitive to chemotherapy.

The drawbacks of adjuvant chemotherapy are:

- Assessment of in vivo chemosensitivity of the tumour is not possible.
- Delay or intolerability of chemotherapy, due to post-operative morbidity.

There is not enough evidence in favour of the routine use of adjuvant chemotherapy (2,8). To date, there have been only five published randomised trials of adjuvant chemotherapy (3-7) and one meta-analysis (8), with updated individual patient data from six trials and a total of only 491 patients for survival analysis. Furthermore, all these trials were suboptimal with serious deficiencies, including low sample size (underpowered), substandard chemotherapy, early stopping of patient entry, and flaws in design and statistical analysis, including irrelevant endpoints or a lack of recommendations concerning salvage chemotherapy for relapse or metastases (2). The data are not convincing enough to give an unequivocal recommendation for the use of adjuvant chemotherapy.

From the evidence so far available, it is unclear whether immediate adjuvant chemotherapy or chemotherapy at the time of relapse is superior or if the two approaches are equivalent with respect to the endpoint overall survival. In recent trial updates, cisplatin-based combination chemotherapy was able to produce long-term disease-free survival, even in metastatic disease, albeit mainly in patients with lymph node metastases only and with a good performance status (9-11).

Patients with extravesical and/or node positive disease following cystectomy should be enrolled in clinical trials whenever possible. In non-protocol-eligible patients, adjuvant cisplatin-based chemotherapy is an option provided the patient is well informed about the scarce data available.

Published trials of randomised adjuvant chemotherapy have used three to four cycles of CMV (cisplatin, methotrexate, vinblastine), CISCA (cisplatin, cyclophosphamide, and adriamycine), MVA(E)C (methotrexate, vinblastine, adriamycine or epirubicine, and cisplatin) and CM (cisplatin, methotrexate) (12). There is no evidence that more modern or carboplatin-containing chemotherapy combinations are as effective. Patients ineligible for cisplatin should not receive adjuvant chemotherapy.

11.1 Conclusion and recommendation for adjuvant chemotherapy

Conclusion	LE
Adjuvant chemotherapy is under debate. Neither randomised trials nor a meta-analysis have provided sufficient data to support the routine use of adjuvant chemotherapy.	1a

Recommendation

	GR
Adjuvant chemotherapy is advised within clinical trials, but not for routine use because it has not been studied sufficiently.	A

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12. METASTATIC DISEASE

Approximately 30% of patients with urothelial cancer present with muscle-invasive disease; about half will relapse after radical cystectomy depending on the pathological stage of the primary tumour and the nodal status. Local recurrence accounts for about 30% of relapses, whereas distant metastases are more common. About 10-15% of patients are already metastatic at diagnosis (1). Before the development of effective chemotherapy, patients with metastatic urothelial cancer rarely exceeded the median survival of 3-6 months (2).

12.1 Prognostic factors and treatment decisions

Bladder cancer is a chemosensitive tumour. Response rates differ with respect to patient-related factors and pre-treatment disease. Prognostic factors for response and survival have been established. In a multivariate analysis, Karnofsky PS of 80% or less and the presence of visceral metastases were independently prognostic of poor survival after treatment with MVAC (methotrexate, vinblastine, adriamycine and cisplatin). These so-called 'Bajorin' prognostic factors (3) have also been validated for newer combination chemotherapies (4,5) and are crucial for assessing phase II study results and stratifying phase III trials (6,7). Additional data on the prognostic value of elevated alkaline phosphatase and the number of disease sites (more or less than three) were generated prospectively (8). A retrospective analysis showed that, in elderly patients, an ECOG (Eastern Cooperative Oncology Group) PS 2-3 and a haemoglobin level of < 10 mg/dL were independent predictors of poor survival (9). Age itself has no impact on response or toxic events (9).

12.1.1 ***Comorbidity in metastatic disease***

Comorbidity is defined as „the presence of one or more diseases in addition to an index disease". Patients with a history of cancer have an average of three co-morbid conditions and co-morbidity is the rule, rather than the

exception. Incidence and prevalence of co-morbidity increase with age. However, despite the importance of co-morbidity in clinical practice, it has not gained a considerable role in clinical trials, medical statistics and clinical practice (10). Co-morbidities are an important predictor of clinical outcome (11).

In multiple publications, co-mobidities proved predictive in 1-5 year mortality rates, which was true only in part for age and sex.

Source	N	Comorbidity	Predictive capacity
Charlson[12]	218	+	5-year mortality
Inouye[13]	318	+	2-year mortality
Lee[14]	8009	+	4-year mortality
Walter[15]	1427	+	1-year mortality

Comorbidity increases with age. However, chronologic age does not necessarily correlate with functional impairment. Physiologic impairment varies substantially between individuals. A number of definitions exist trying to establish how to select patients better as potentially “fit” or “unfit” candidates for chemotherapy. Age itself is not among them.

The EORTC conducted the first randomized phase II/III trial for „unfit“ TCC patients (16). Their definition of „fit“ and „unfit“ for cisplatin is:
„fit“: GFR ≥ 60 ml/min and PS 0-1
„unfit“: GFR < 60 ml/min and /or PS 2

In addition to renal function impairment and decreased performance status, co-morbidities that caution or preclude the use of cisplatin are cardiovascular diseases, congestive heart failure, neuropathy and severe presbyacusis. For urothelial cancer, more than 50% of patients are not eligible for cisplatin based chemotherapy (17-20).

Patient selection for systemic chemotherapy is key, not only in urinary cancer treatment. There are a number of tools, which, so far, have not been able to solve this dilemma. Performance status is not accurate enough, particular in patients > 75 years of age.

For measuring functional status, the comprehensive geriatric assessment (CGA) has proven to be more sensitive than the mere estimate of the physician (21). The CGA would most likely be helpful but, as yet, has not been validated for urothelial cancer patients.

As for comorbidity, the Charlson score is not used as a standard. Renal function assessment is of utmost importance in the urothelial cancer population. Calculated creatinine clearance (crcl) with current formulas tends to under-estimate crcl in pts > 65 years compared to measured crcl (17,22).

The CGA includes: functional status, co-morbidities, socio- economic circumstances, cognition, emotional perception, co-medication, nutrition and geriatric syndrome (23).

Notwithstanding the clear advantages of this tool (description of physiologic aging, detection of reversible problems and issues, cognitive function assessment) the drawbacks preventing its widespread use in clinical practice is the fact that it is a resource intensive activity (both for time and staff involvement).

This tool could potentially be the basis of a more user-friendly, accurate, questionnaire. However, validation in studies will be needed before standard use can be recommended.

12.2 Single-agent chemotherapy

Varying response rates of single-agent first-line chemotherapy have been reported with only 12% for cisplatin compared to MVAC (7), 12% for carboplatin (24), 42% for paclitaxel (25), 31% for docetaxel (26), 29% for methotrexate, 19% for adriamycin, 15% for epirubicin, 13% for mitomycin C, 35% for 5-FU, 14% for vinblastine, 29% for ifosfamide and 8% for cyclophosphamide (27,28). The most robust single-agent data is a response rate of about 25% for gemcitabine for first- and second-line use in several, larger-sized, phase II trials (29-36).

Responses with single agents are usually short-lived and complete responses are rare. Of note, no long-term disease-free survival has been reported with single-agent chemotherapy. The median survival in such patients is only about 6-9 months. Patients with PS WHO 3-4, with or without additional negative prognostic factors, are not expected to benefit from combination chemotherapy. The most appropriate approach for this patient group

is best supportive care or, at most, single-agent chemotherapy.

12.3 Standard first-line chemotherapy for 'fit' patients

Cisplatin-containing combination chemotherapy has been the standard of care since the late 1980s. MVAC has been proven superior to cisplatin monotherapy and CISCA (cisplatin, cyclophosphamide and adriamycine) (7,37) and, more recently, to cisplatin/docetaxel (38). MVAC and gemcitabine/cisplatin (GC) have prolonged survival up to 14.8 and 13.8 months, respectively (39-41). The lower toxicity of GC (41), however, has resulted in GC increasingly becoming a new standard regimen (41).

Neither of the two combinations was proven to be superior over the other, but equivalence was not tested, with response rates of 46% and 49% for MVAC and GC, respectively. The long-term survival results confirmed the anticipated equivalence of the two regimens (8). The major difference between the above-mentioned combinations was toxicity, with GC being less toxic (41). MVAC is better tolerated with the use of GCSF (38,42).

High-dose intensity MVAC (HD-MVAC) with GCSF is less toxic and more efficacious than standard MVAC in terms of dose density, complete response and 2-year survival rate. However, there is no significant difference in median survival between the two regimens (43,44).

All disease sites have been shown to respond to cisplatin-based combination chemotherapy, but have been reported most often in lymph nodes. A response rate of 66% and 77% with MVAC and HD-MVAC, respectively, has been reported in retroperitoneal lymph nodes versus 29% and 33% at extranodal sites (43). The sites of disease also have an impact on long-term survival. In lymph-node-only disease, 20.9% of patients were alive at 5 years compared to only 6.8% of patients with visceral metastases (8).

Further intensification of treatment using new triplets, dose-dense schedules or adding targeted therapies is still being investigated. These approaches should be reserved for clinical trials and are not suitable for routine use (45,46).

12.4 Carboplatin-containing chemotherapy in 'fit' patients

Carboplatin-containing chemotherapy is not proven to be equivalent to cisplatin combinations. However, it is probably inferior and therefore should not be considered interchangeable or standard. The only randomised phase III study of carboplatin-containing chemotherapy had a disappointing response rate of only 28.2% in the investigational arm (paclitaxel/carboplatin) compared to MVAC and had to be closed down early because of a low accrual rate. There is therefore no evidence that this doublet might have adequate efficacy for first-line use (47).

Various carboplatin versus cisplatin combination chemotherapies in randomised phase II trials have produced lower complete response rates and a shorter overall survival for the carboplatin arms (48-50).

12.5 Non-platinum combination chemotherapy

Gemcitabine and paclitaxel combinations in different schedules have been studied as both first- and second-line treatments. Apart from severe pulmonary toxicity with a weekly schedule of both drugs, this combination has been well tolerated and produced response rates between 38% and 60% in both lines. As there has not been a randomised comparison to standard cisplatin chemotherapy, non-platinum combination-chemotherapy is not recommended for first-line use in patients who are fit enough (36,51-57).

12.6 Chemotherapy in patients 'unfit' for cisplatin

Up to 50% of patients are ineligible for cisplatin-containing chemotherapy, either because of a poor PS and/or impaired renal function, or because of co-morbidity preventing high-volume hydration (58,59). The first randomized phase II/III trial in this setting was conducted by the European Organisation for Research and Treatment of Cancer and compared methotrexate/carboplatin/vinblastine (M-CAVI) and carboplatin/gemcitabine (Carbo/Gem) in patients unfit for cisplatin. Both regimens were active. Severe acute toxicity (SAT) was 13.6% in patients given Carbo/Gem versus 23% on M-CAVI, while the overall response rate was 42% on Carbo/Gem and 30% on M-CAVI. Further analysis showed that in patients with PS 2 and impaired renal function, combination chemotherapy provides limited benefit (60). The overall response rate and SAT were both 26% for the former group, and 20% and 24%, respectively, for the latter group (60). Recent phase III data has confirmed these results.

12.7 Second-line treatment

Second-line chemotherapy data are highly variable and prognostic factors are unclear in this setting. Suggested prognostic factors include the choice of first-line chemotherapy (peri-operative/metastatic), prior chemosensitivity, duration of response to first-line treatment, presence of visceral metastases, PS and the

'Bajorin'-prognostic factors. Until recently, there was no defined chemotherapy standard in this setting. Re-exposition 12 months or more after response to a prior chemotherapeutic regimen is a reasonable strategy.

Second-line response rates of paclitaxel (weekly), docetaxel, oxaliplatin, ifosfamide, topotecan, lapatinib, gefitinib and bortezomib range between 0% and 13% in small phase II trials (61-69). Although gemcitabine has also shown excellent response rates in second-line use (29,33-36), most patients already receive this drug as part of their front-line treatment.

In a phase II trial, pemetrexed 500 mg/m2, given every 3 weeks, showed a promising response rate of 28% and manageable toxicity with the addition of vitamin B12 and folinic acid supplementation and dexamethasone prophylaxis (70). The excellent response rate could not be confirmed by a second, smaller sized trial (71).

Paclitaxel/gemcitabine showed response rates of 38-60%, depending on pre-treatment response and indication of prior chemotherapy. Unfortunately, no adequate randomised phase III trial has been conducted to assess the true value of this second-line combination (2,52,56).

Vinflunine, a novel third-generation vinca alkaloid, has shown objective response rates of 18% and disease control in 67% (72). A phase III trial of vinflunine plus best supportive care (BSC) randomised against BSC alone in patients progressing after first-line treatment with platinum-containing combination chemotherapy for metastatic disease was published recently (73). The results showed modest activity (overall response rate, 8.6%), a clinical benefit with a favourable safety profile and, most importantly, a survival benefit in favour of vinflunine, which was statistically significant in the eligible patient population (not in the ITT population). For second-line treatment in advanced or metastatic urothelial cancer, this trial reached the highest level of evidence ever reported. Currently, vinflunine is the only approved second-line treatment; any other treatment should take place in the context of clinical trials.

12.8 Low-volume disease and post-chemotherapy surgery

With cisplatin-containing combination chemotherapy, excellent response rates may be obtained in patients with lymph node metastases only, good PS and an adequate renal function, including a high degree of complete responses, with up to 20% of patients achieving long-term disease-free survival (8,44,74,75). Stage migration may play a role in this positive prognostic development.

A retrospective study of post-chemotherapy surgery after a partial or complete response indicated that post-chemotherapy surgery may contribute to long-term disease-free survival in selected patients (76-78).

12.9 Bisphosphonates

The prevalence of metastatic bone disease (MBD) in patients with advanced/metastatic urothelial cancer has been reported to be 30-40% (79). Skeletal complications due to MBD have a detrimental effect on pain and quality of life and are also associated with increased mortality (80). Bisphosphonates reduce and delay skeletal-related events due to bone metastases by inhibiting bone resorption. Therefore, patients with MBD, irrespective of the cancer type, should be considered for biphosphonate treatment (80).

To date, only one, but so far not peer-reviewed, published, randomised placebo-controlled phase III trial has confirmed the beneficial effect of zoledronic acid in the treatment of bone metastases from urothelial cancer. Urothelial cancer patients treated with zoledronic acid experienced a decrease in skeletal-related events, an improvement of their quality of life and of their one year overall survival. Zoledronic acid is the only biphosphonate, which has been studied (81) and approved for the treatment of MBD in all tumour types. Biphosphonate treatment should be accompanied by calcium and vitamin D supplementation. Dosing regimens should follow respective regulatory recommendations and adjusted according to pre-existing medical conditions (80).

12.10 Conclusions for metastatic disease

Conclusion	LE
Performance status and the presence or absence of visceral metastases are independent prognostic factors for survival. These factors are at least as important as the type of chemotherapy administered.	3
Cisplatin-containing combination chemotherapy is able to achieve a median survival of up to 14 months, with long-term disease-free survival reported in about 15% of patients with nodal disease and good performance status.	1b
Single-agent chemotherapy provides low response rates of usually short duration.	2a
Carboplatin-combination chemotherapy is less effective than cisplatin-based chemotherapy in terms of complete response and survival.	2a
Non-platinum combination chemotherapy has produced substantial responses in first- and secondline use, but has not been tested against standard chemotherapy in fit patients or in a purely unfit patient group.	2a
To date, there is no defined standard chemotherapy for 'unfit' patients with advanced or metastatic urothelial cancer.	2b
Vinflunine reached the highest level of evidence ever reported for second-line use.	1b
Post-chemotherapy surgery after a partial or complete response may contribute to long-term disease-free survival.	3
Zoledronic acid is the only bisphosphonate studied and approved for all cancer types including urothelial cancer, which has been shown to reduce and delay skeletal-related events in metastatic bone disease.	2a

12.11 Recommendations for metastatic disease

Recommendations

	GR
Prognostic factors should guide the treatment selection.	B
First-line treatment for "fit" patients:	
Use cisplatin-containing combination chemotherapy with GC, MVAC, preferably with GCSF, or HD-MVAC with GCSF.	A
Carboplatin and non-platinum combination chemotherapy is *not* recommended.	B
First-line treatment in patients ineligible ('unfit") for cisplatin:	
Use carboplatin combination chemotherapy or single agents.	C
For cisplatin-ineligible patients ('unfit') with either PS 2 or impaired renal function, or with 0-1 poor Bajorin prognostic factors, first-line treatment is carboplatin-containing combination chemotherapy, preferably with gemcitabine/carboplatin.	A
Second-line treatment:	
In patients progressing after platinum-based combination chemotherapy for metastatic disease vinflunine should be offered, which has the highest level of evidence to date, or clinical trials of other treatments.	A*

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

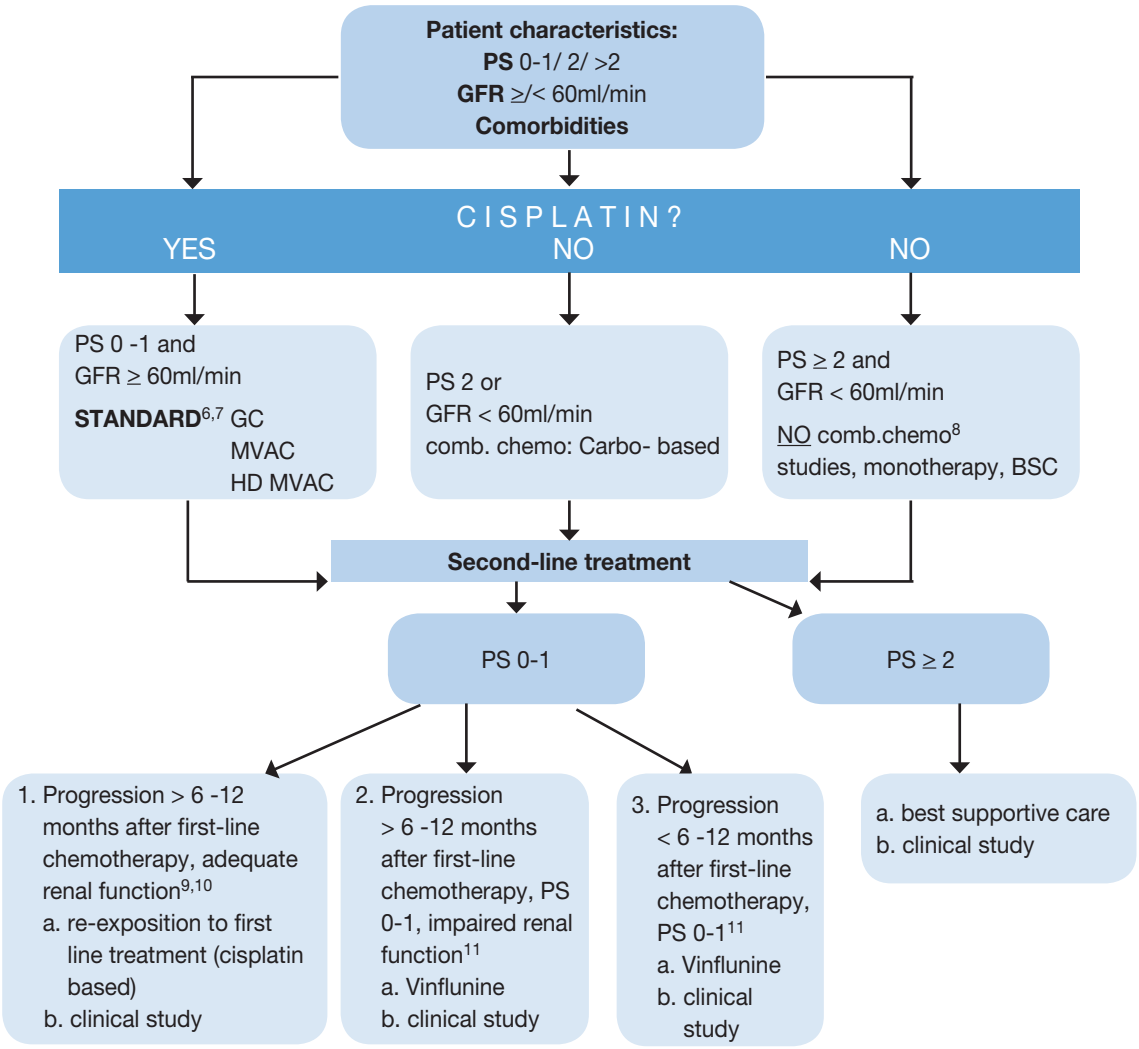
12.12 Biomarkers

Statistically, relatively modest, disease control rates, but sporadically, remarkable responses in some patients with urothelial bladder cancer have led to investigation of biomarkers for assessment of prognosis after surgery and as an indication for chemotherapy or for its monitoring. Most of the biomarkers were associated with tumour angiogenesis. To date, small studies, usually retrospective, have investigated microvessel density, altered p53 tumour expression (82), serum vascular endothelial growth factor (83), urinary and tissue basic fibroblast growth factor (84), urinary (wild type and mutant) and tissue fibroblast growth factor receptor-3 (85), and more recently thrombospondin-1 (86), the detection of circulating tumour cells (87) and multi-drug resistance gene expression (88). Although a few biomarkers have shown potential, none has sufficient evidence to support their clinical routine use (LE: 3).

Recommendation on the use of biomarkers	GR
Currently, no biomarkers can be recommended in daily clinical practice since they have no impact on predicting outcome, treatment decisions or monitoring therapy in invasive bladder cancer.	A*

**Upgraded following panel consensus.*

Figure 2: Flowchart for the management of metastatic urothelial cancer



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13. QUALITY OF LIFE

13.1 Introduction

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

Several questionnaires have been validated for assessing HRQoL in patients with bladder cancer, including FACT (Functional Assessment of Cancer Therapy)-G (1), EORTC QLQ-C30 (2), EORTC QLQ-BLM (muscle invasive bladder cancer module) (3), and SF (Short Form)-36 (4,5). A psychometric test, such as the FACT-BL, should be used for recording bladder cancer morbidity. New intensive interviewing techniques have added valuable information to our knowledge of HRQoL, which greatly depends on patients' individual preferences in life (6).

Unfortunately, most retrospective studies do not evaluate the association between HRQoL and bladder cancer-specific issues after cystectomy, such as day and night-time incontinence or potency. Furthermore, important co-variables, such as a patient's age, mental status, coping ability and gender, have only rarely been considered (7,8). It remains difficult to predict the impact of post-therapeutic symptoms because of individual differences in symptom tolerance.

13.2 Choice of urinary diversion

There is controversy about which type of urinary diversion is best for a patient's HRQoL (9). Some studies have not demonstrated any difference in HRQoL (8,10,11). Nevertheless, most patients stated that, given a choice, they would still opt for an orthotopic diversion rather than an ileal conduit (12). Another recent study has shown that, although urinary function is better in conduit patients, the urinary bother is the same in both diversion groups, resulting in the same HRQoL evaluation (13).

Due to improved surgical techniques in orthotopic bladder substitution, some recent studies are supportive of continent bladder substitutes (3,14-17). Two studies have shown a statistically significant difference in HRQoL in favour of neo-bladders (17,18). Patients with an orthotopic substitution had significantly better physical function and a more active lifestyle compared to patients with an ileal conduit. It is important to note that HRQoL parameters are independent prognostic factors for overall survival (19). Patients with a continent bladder-substitute generally score more favourably than those with an incontinent diversion, as judged by body image, social activity and physical function (13,14,20).

13.3 Non-curative or metastatic bladder cancer

In non-curative or metastatic bladder cancer, HRQoL is reduced because of associated micturition problems, bleeding, pain and therefore disturbance of social and sexual life (21). There is limited literature describing HRQoL in bladder cancer patients receiving palliative care (25), but there are reports of bladder-related symptoms relieved by palliative surgery (22), radiotherapy (23), and/or chemotherapy (24).

Alternative definitive treatments of muscle-invasive bladder cancer, e.g. trimodality bladder-sparing procedures, have shown similar survival times compared to cystectomy. However, the impact on HRQoL has been controversial (26-31).

13.4 Conclusions on HRQoL in bladder cancer

Conclusions	LE
There is no randomised, prospective HRQoL study that evaluates different forms of definitive treatment for invasive bladder cancer.	
The overall HRQoL after cystectomy remains good in most patients studied, whichever type of urinary diversion is used. Some data suggests that continent diversions give a better HRQoL, but this is controversial.	2b

13.5 Recommendations for HRQoL in bladder cancer

Recommendations

	GR
If HRQoL in patients with muscle-invasive bladder cancer is assessed validated questionnaires should be used.	B
Continent urinary diversions should be offered for reasons of HRQoL, whenever a patient's age, co-morbidities, tumour variables and coping ability are suitable.	C
Pre-operative patient information, patient selection, surgical techniques, and careful post-operative follow-up are the cornerstones for achieving good long-term results.	C
Patient education and active participation in treatment decisions is the key to post-operative satisfaction + personality.	C

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14. FOLLOW-UP

An appropriate schedule for disease monitoring should be based on:
- natural timing of recurrence;
- probability of disease recurrence;
- functional deterioration at particular sites;
- possibilities of treatment of a recurrence (1).

Nomograms on cancer specific survival following radical cystectomy have been developed and externally validated, however, their wider use cannot be recommended prior to further data (2-4).

Contemporary cystectomy series have demonstrated a 5-15% probability of pelvic recurrence. Most recurrences manifest during the first 24 months, often within 6-18 months after surgery. However, late recurrences have occurred up to 5 years after cystectomy. Again, pTN and pN were predictive of the development of pelvic recurrence.

Patients have a poor prognosis after pelvic recurrence. Even with treatment, median survival ranges from 4-8 months following diagnosis. Definitive therapy can sometimes provide prolonged survival, but in most cases provides significant palliation of symptoms. Treatment is with systemic chemotherapy, local surgery or radiotherapy.

14.1 Site of recurrence

14.1.1 ***Distant recurrences***

Distant recurrences are seen in up to 50% of patients treated with cystectomy. Most recurrences occur in the first 24 months, although progression has been observed after more than 10 years (5). Again, pTN and pN were risk factors (6).

The most likely sites for distant recurrences are the lungs, liver and bones (7). Upper urinary tract recurrence is rarely seen (2-7%). However, when it develops, it usually does so within 22-40 months after cystectomy (1,7-9). Surveillance regimens often fail to detect tumours before symptoms develop. Radical nephro-ureterectomy can provide prolonged survival (8).

14.1.2 ***Secondary urethral tumours***

The incidence of secondary urethral tumours is 5-17% and is particularly likely to occur at 1-3 years after surgery. Prophylactic urethrectomy at the time of cystectomy is no longer justified in most patients. In men, the most important risk factor for development of urethral recurrence is prostatic stromal invasion (21-64%) (10-12).

In women, the risk factor is disease at the bladder neck (13). Many studies have demonstrated that the risk of urethral recurrence after orthotopic diversion (0.9-4%) (10,14-16) is significantly less than after nonorthotopic diversion (6.4-11.1%) (10,15).

There is little data and agreement about urethral follow-up, with some recommending routine surveillance urethral wash cytology and urine cytology (14), and others doubting the need for routine urethral surveillance (14,17-19). Urethral washes and urine cytology do not appear to have any effect on survival (17,20,21).

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

- In CIS of the urethra, BCG instillations have shown success rates of 83% (16).
- In invasive disease, urethrectomy should be performed if the urethra is the only site of disease.
- In distant disease, systemic chemotherapy is indicated (7).

*14.1.3 **Conclusions and recommendations for specific recurrence sites***

Site of recurrence	Conclusion	LE	Recommendation	GR
Secondary urethral tumour	Staging and treatment should be done as for primary urethral tumour	3	Local conservative treatment is possible for non-invasive tumour	C
			In isolated invasive disease, urethrectomy should be performed	B
			Urethral washes and cytology are not recommended	A
Pelvic recurrence	Poor prognosis Treatment should be individualised depending on the local extent of tumour	2b	Radiotherapy, chemotherapy and possibly surgery are options for treatment, either alone or in combination	C
Upper urinary tract			Specific upper urinary tract imaging is only indicated in case of clinical symptoms	
			Radical nephrectomy can provide prolonged survival	

Variant 2: Invasive TCC with or without cystectomy*

Radiological procedure	Rating scale[1]	Comments	Relative radiation level*
X-ray chest	9		Minimum
CT urography	8		High
X-ray abdomen loopogram	8	In patients with an ideal loop postcystectomy	Medium
X-ray intravenous urography	5	Utilization of intravenous urography has continued to decline with the increasingly widespread use of CT urography	Medium
MR imaging abdomen and pelvis without and with contrast	5	See ESUR guidelines on contrast media version 7.0 (22)	None
CT abdomen and pelvis with contrast	5	Appropriate if CT urography is not available. Visceral/nodal status evaluated during CT urography	High
CT chest with contrast	3	Performed if chest X-ray is equivocal	Medium
US pelvis (bladder)	3		None
FDG-PET whole body indicated for suspected or nodal metastasis	2	Indicated for suspected nodal or distant metastasis	High
After 5 years of follow-up, oncological surveillance can be stopped and surveillance continued with functional surveillance			

[1]1 is least appropriate; 9 is most appropriate

[*]Adapted from: American College of Radiology. Follow-up Imaging of Bladder Carcinoma. Date of origin: 1996; Last review date: 2000.

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15. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

ARCO	accelerated radiotherapy with carbogen
ARCON	accelerated radiotherapy with carbogen nicotinamide
ASCO	American Society of Clinical Oncology
5-ALA	5-aminolaevulinic acid
4-ABP	4-aminobiphenyl
BC	bladder cancer
BT	brachytherapy
BCG	Bacille Calmette-Guérin
CGA	comprehensive geriatric assessment
CI	confidence interval
CIS	carcinoma *in situ*
CISCA	cisplatin, cyclophosphamide plus adriamycin
CM	cisplatin, methotrexate
CMV	cisplatin, methotrexate plus vinblastine
CT	computed tomography
EAU	European Association of Urology
EBRT	external beam radiation therapy
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
FACT	Functional Assessment of Cancer Therapy
5-FU	5-Fluorouracil
GC	gemcitabine plus cisplatin
GFR	glomerular filtration rate
GCSF	granulocyte colony stimulating factor
HAL	hexaminolaevulinate
HD-MVAC	high-dose methotrexate, vinblastine, adriamycin plus cisplatin
HIRU	Health Information Research Unit
HRQL	health-related quality of life
IARC	International Agency for Research on Cancer
IPD	independent patient data
ISUP	International Society of Urological Pathology
IVU	Intravenous urography
MCV	methrotrexate, cisplatin and vinblastine
MiM-BC	Muscle-invasive and metastatic bladder cancer
MRC	Medical Research Council (UK)
MR(I)	magnetic resonance (imaging)
MVAC	methotrexate, vinblastine, adriamycin plus cisplatin
MVA(E)C	methotrexate, vinblastine, adriamycine or epirubicine, and cisplatin
NAT	N-acetyltransferase
NMIBC	non-muscle-invasive bladder cancer
NSF	nephrogenic systemic fibrosis
OS	overall survival
PAHs	polycyclic aromatic hydrocarbons
pCR	pathological complete remission
PDD	photodynamic diagnosis
PET	positron emission tomography
PS	performance status
PUNLMP	papillary urothelial neoplasms of low malignant potential
RALC	robotic-assisted laparoscopic cystectomy
R-biopsies	random biopsies
RCT	randomised controlled trial
SEER	Surveillance Epidemiology and End Results
SES	socio-economic status
SF-36	Short Form-36
SIGN	Scottish Intercollegiate Guidelines Network
SWOG	Southwest Oncology Group
TCC	transitional cell carcinoma

TNM	Tumour, Node, Metastasis
TUR	transurethral resection
TURB	transurethral resection of bladder tumour
UICC	Union International Contre le Cancer
UC	urethrocystoscopy
US	ultrasonography
UUTT	upper urinary tract tumours
UUT-UCC	upper urinary tract-urothelial cell carcinoma (UUT-UCC)
WHO	World Health Organization

Conflict of interest
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