Guidelines on

Muscle-invasive and Metastatic Bladder Cancer

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1. INTRODUCTION

1.1 Background

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

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

The Muscle-invasive and Metastatic Bladder Cancer guidelines are one of four EAU guidelines documents addressing bladder cancer (EAU Guidelines on Non-muscle-invasive (Ta, T1 and CIS) bladder cancer, EAU Guidelines on upper urinary tract urothelial cell carcinomas and EAU Guidelines on primary urethral carcinoma) which, together, present a comprehensive overview of the management of urothelial neoplasms (1-3).

1.2 Methodology

*1.2.1 **Data identification***

The recommendations provided in the current guidelines are based on literature searches performed by the expert panel members. A systemic literature search was performed for the systematic review of the role and extent of lymphadenectomy during radical cystectomy for cN0M0 muscle-invasive bladder cancer (see Chapter 7: Radical surgery and urinary diversion).

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

The level of evidence (LE) and grade of recommendation (GR) provided in these guidelines follow the listings in Tables 1 and 2 (4). 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. The availability of randomized controlled trials (RCTs) does not necessarily translate into a grade A recommendation where there are methodological limitations or a disparity in published results.

Alternatively, the 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. In this situation, unequivocal recommendations are considered helpful for the reader. The quality of the underlying scientific evidence (although a very important factor) must be balanced against benefits and burdens, values and preferences, and cost when a grade of recommendation is assigned (5-7).

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 (4).*

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 (4).*

The EAU Guidelines Office does not perform cost assessments or review local/national preferences in a systematic fashion. However, whenever this data is available, the expert panels will include the information.

1.2.2 Publication history

The EAU published its first guidelines on bladder cancer in 2000. This document covered both superficial (non-muscle-invasive) bladder cancer and MIBC. Since these conditions require different treatment strategies, it was decided to give each condition its own guidelines, resulting in the first publication of the MIBC guidelines in 2004, with subsequent updates in 2007, 2009, 2010, 2011, 2012, 2013 and this 2014 update. A quick reference document presenting the main findings is also available alongside several scientific publications (8-11).

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 this 2014 update, the following changes should be noted:

Chapter 2: Epidemiology and risk factors The literature has been updated. Section 2.3, Genetic factors, is a new section. The conclusions and recommendations have stayed the same for Chapter 2.
Chapter 3: Classification The literature has been updated, particularly Section 3.3, with the inclusion of additional morphological subtypes and new information on substaging in node-negative disease after cystectomy.
Chapter 4: Diagnosis and staging Section 4.1.8, Second resection, was revised. No other changes have been made.
Chapter 6: Neoadjuvant chemotherapy The literature for this chapter has been updated and the text was reformatted.
Chapter 7: Radical surgery and urinary diversion All the literature has been updated for this entire chapter. Section 7.1.6, Radical cystectomy, includes the key findings of a finalized systematic review on the extent of lymph node dissection. The literature for Section 7.1.7, Laparoscopic/robotic-assisted laparoscopic cystectomy, has been updated and a new recommendation has been included in favour of open radical cystectomy.
Chapter 8: Non-resectable tumours This chapter has been condensed. No further changes were made.
Chapter 9: Pre-operative radiotherapy in muscle-invasive bladder cancer This chapter has been condensed. No further changes were made.
Chapter 11: Adjuvant chemotherapy The literature has been updated for the entire chapter. The text has been condensed.
Chapter 12: Metastatic disease The literature for this chapter has been updated and the text has been condensed.
Chapter 14: Follow-up Additional data has been included. In particular, Section 14.1.1, Local recurrence, and Section 14.1.2, Distant recurrences, have been revisited. A new section on post-cystectomy UTUC recurrences is included.

1.4 Potential conflict of interest statement

The expert panel have submitted potential conflict of interest statements which can be viewed on the EAU website: http://www.uroweb.org/guidelines/.

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2. EPIDEMIOLOGY AND RISK FACTORS

2.1 Epidemiology

Bladder cancer is the ninth most commonly diagnosed cancer worldwide, with more than 380,000 new cases each year and more than 150,000 deaths per year, and an estimated male-female ratio of 3.8:1.0 (1). At any one time, 2.7 million people have a history of urinary bladder cancer (2).

Recently, overall and stage-specific age-adjusted incidence rates of bladder cancer have been analysed in the U.S. (5 year survival and mortality rates between 1973 and 2009). Although the analysis of the Surveillance, Epidemiology and End Results (SEER) database implies some limitations it is worrying to note that in the last 30 years the mortality rate associated with bladder cancer has not changed substantially, highlighting gaps in diagnosis, monitoring and management of these patients (3).

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 bladder cancer (MIBC). Among patients treated with radical cystectomy because of MIBC, 57% had muscle invasion at presentation, while 43% were initially

diagnosed with NMIBC that progressed despite organ-preserving treatment (4). Approximately one-third of patients diagnosed with MIBC have undetected metastases at the time of treatment for the primary tumour (5), while 25% of patients who undergo 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 (6). A causal relationship has been established between exposure to tobacco and cancer in studies in which chance, bias, and confounding can be ruled out with reasonable confidence (7).

The incidence of bladder cancer is directly related to the duration of smoking and the number of cigarettes smoked per day (8). 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 (9). 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 to 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 to 2.04) (10). 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 (8). Encouraging people to stop smoking 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 have accounted for 20-25% of all bladder cancer cases in several series. The substances involved in chemical exposure include benzene derivatives and aryl amines (2-naphthylamine, 4-ABP, 4,4'-methylenedianiline, and o-toluidine), and it is likely to occur in occupations in which dyes, rubbers, textiles, paints, leathers, and chemicals are used (11). The risk of bladder cancer due to occupational exposure to carcinogenic aromatic amines is significantly greater after 10 years or more of exposure; the mean latency period usually exceeds 30 years (12,13). The chemicals involved have contributed minimally to the current incidence of bladder cancer in Western countries because of strict regulations. Importantly, in recent years, the extent and pattern of occupational exposure have changed because awareness has prompted safety measures and population based studies established the occupational attribution for men to bladder cancer to be 7.1%, while no such attribution was discernible for women (14,15).

An example of occupational exposure is that of aromatic amines. These are established carcinogens for urothelium and 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 (16), suggesting that patients who are slow acetylators may be more susceptible to bladder cancer than rapid acetylators.

Other risk factors include phenacetin, which the International Agency for Research on Cancer (IARC) included in 1987 among proven human carcinogens. 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 (17).

*2.2.3 **Radiotherapy***

Increased rates of secondary bladder malignancies have been reported after external-beam radiotherapy (EBRT) for gynaecological malignancies, with relative risks of 2-4 (18). A recent population cohort study identified 243,082 men treated for prostate cancer between 1988 and 2003 in the SEER database 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, in comparison with the general U.S. population. The increased risk of bladder cancer in patients undergoing ERBT, BT, or ERBT-BT should be taken into account during follow-up, although the likelihood of mortality was described as very low in a recent study (19). It has recently been proposed that patients who have received radiotherapy for prostate cancer with modern modalities such as intensity-modulated radiotherapy (IMRT) may have lower rates of in-field bladder and rectal secondary malignancies (20). Nevertheless, since longer follow-up data are not yet available, and as bladder cancer requires a long period to develop, patients treated with radiation and with a long life-expectancy are at highest risk and should be followed up closely (20).

2.2.4 ***Dietary factors***

Several dietary factors have been considered to be related to bladder cancer; however, the links remain 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 reduces the risk of bladder cancer (21). For bladder cancer, there appears to be no association between dietary transfatty acid (TFA) intake and an increased risk, as observed for prostate cancer (22).

2.2.5 ***Bladder schistosomiasis***

Bladder schistosomiasis (bilharzia) is the second most common parasitic infection after malaria, with about 600 million people exposed to infection in Africa, Asia, South America, and the Caribbean (23). 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) in Cairo, the largest tertiary cancer hospital in Egypt, showed that patients diagnosed in 2005 had a six-fold higher chance of developing urothelial carcinoma in comparison with patients diagnosed in 1980 (24). This shift from squamous cell carcinoma to urothelial carcinoma is attributed to a decline in the detection of bilharzia eggs in urine samples, probably due to better control of the disease in rural populations (25,26).

2.2.6 ***Chronic urinary tract infection***

Muscle-invasive bladder cancer, particularly invasive squamous cell carcinoma, has been linked to the presence of chronic urinary tract infection (UTI) distinct from schistosomiasis. A direct association between bladder cancer and UTIs has been observed in several case-control studies, which have reported a two-fold increased risk of bladder cancer in patients with recurrent UTIs in some series. However, some of these results may be attributed to recall bias (27). Furthermore, to date, no clear relationship between any bacterial or viral infection and bladder cancer has been established in prospective studies (28). However, an increased risk of bladder cancer has been described in patients with long-term indwelling catheters (29).

2.2.7 ***Chemotherapy***

The use of cyclophosphamide, an alkylating agent used to treat lymphoproliferative diseases and other non-neoplastic diseases, has been correlated with subsequent development of MIBC, with a latency period 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 (30) and was counteracted with concomitant application of mercapto-ethanesulfonate (MESNA) (31).

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

In some cases, there is an association between upper tract urothelial carcinoma (UTUC) and bladder cancer. The incidence of UTUC after a diagnosis of NMIBC has been reported to be between 1.7% and 26%. Although synchronous UTUC and NMIBC are uncommon, 46% of UTUCs 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 six times more likely to develop a synchronous tumour in the upper urinary tract (32).

Examination of the upper urinary tract alone in patients with a tumour in the trigone or with multiple bladder tumours was capable of diagnosing 41% or 69% of UTUCs, respectively. In multiple and high-risk tumours, there is an increased risk of tumour recurrence in the upper urinary tract. Carcinoma *in situ* (CIS) in the bladder is an important risk factor for subsequent upper urinary tract recurrence (33). It has been shown in various studies that tumour involvement of the distal ureter at RC is an independent risk factor for metachronous upper urinary tract (mUUT) recurrence (34,35), with an approximate 2.6-fold increase in the relative risk (35).

The overall incidence of bladder cancer developing after treatment for UTUC has been reported in the literature as 15-50%. Level 1 evidence from prospective randomised trials is not yet 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 UTUC management. However, the risk is life-long, and repeat episodes are common. No variables can be used to predict future bladder cancer recurrence in UTUC patients reliably. A history of bladder cancer prior to UTUC management and upper tract tumour multifocality are the only commonly reported clinical risk factors in the current literature (36).

2.2.9 ***Gender***

In a retrospective study of patients who had undergone radical cystectomy, it was found that women were more likely to be diagnosed with primary muscle-invasive disease than men (85% vs. 51%) (4). It has been suggested that women are more likely to be older than men when diagnosed, with a direct effect on their

survival. In addition, delayed diagnosis is more likely in women after haematuria is observed, as the differential diagnosis in women includes diseases that are more prevalent than bladder cancer (37).

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, postmenopausal status was associated with an increase in bladder cancer risk, even after adjustment for smoking status. This result suggests that the differences in oestrogen and androgen levels between men and women may be responsible for some of the difference in the gender prevalence of bladder cancer (38-40). Recently, a study of Egyptian women found that younger age at menopause (< 45 y) was a factor associated with an increasing risk of bladder cancer, while multiple pregnancies and use of oral contraceptives were associated with decreased odds of having bladder cancer. The strength of the associations was greater in the urothelial carcinoma group (41). Another finding is that female gender has a significant negative impact on cancer-specific survival in patients who are younger and have lymphovascular invasion, possibly suggesting different clinical phenotypes (42). A large German retrospective multicentre study including 2,483 patients submitted to radical cystectomy, showed that cancer-specific mortality was higher in female patients. This difference was more pronounced in earlier time periods. These findings could suggest different tumour biology and potentially unequal access to timely radical cystectomy in earlier periods because of reduced awareness of bladder cancer in women (43).

2.2.10 ***Ethnic and socioeconomic status***

There are limited data on this topic, but a study based on 13,234 cases diagnosed in the SEER database in the period 1979-2003 showed that the survival time from diagnosis was significantly lower 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 in comparison with whites for eight of the most common types of cancer combined lost statistical significance after adjustment for SES factors and treatments.

However, blacks still had unfavourable prognoses in comparison with whites even after adjustment for SES and treatment for tumours such as breast, colorectal, and urinary bladder cancer (44).

2.3. Genetic factors

There is growing evidence that genetic susceptibility factors and family associations may influence the incidence of bladder cancer. The relationship between family history of cancer and risk of bladder cancer was examined in the Spanish Bladder Cancer Study. It was found that family history of cancer in first-degree relatives was associated with an increased risk of bladder cancer; the association being stronger among younger patients. Shared environmental exposure was recognised as a potentially confounding factor (45). These results support the hypothesis that genetic factors play a role in the aetiology of bladder cancer.

Genome-wide association studies (GWAS) of bladder cancer identified several susceptibility loci associated with bladder cancer risk (46,47). Polymorphisms in two carcinogen-metabolizing genes, NATS and GSTM1, have been related to bladder cancer risk, and furthermore they have demonstrated, together with UGT1A6, to confer additional risk to exposure of carcinogens such as tobacco smoking (48).

2.4 Conclusions and recommendations for epidemiology and risk factors

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

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

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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. A seventh edition was published, effective as of 2010 (1) (Table 3). There are no significant modifications in it for bladder cancer, compared with the previous edition (2002).

Table 3: TNM classification of urinary bladder cancer (2009)

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

3.2 Histological grading of non-muscle-invasive bladder tumours

A new classification of non-invasive urothelial tumours was proposed by the World Health Organization (WHO) and the International Society of Urological Pathology (ISUP) in 1998. 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 web site (http://www.pathology.jhu.edu/bladder) illustrating examples of various grades has been developed to improve accuracy in using the system.

Table 4: World Health Organization grading for urothelial papilloma 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
Flat lesions
Hyperplasia (flat lesion without atypia or papillary aspects)
Reactive atypia (flat lesion with atypia)
Atypia of unknown significance
Urothelial dysplasia
Urothelial CIS is always high-grade

Papillary lesions
Urothelial papilloma (completely benign lesion)
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.

Papilloma is composed of a delicate fibrovascular core covered by normal urothelium. PUNLMP is defined as a papillary fibrovascular growth covered with 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 (4). The low-grade papillary urothelial carcinoma group includes most former grade 1 (WHO 1973) cases and some former grade 2 cases (if there is variation in the architectural and cytological features at high magnification).

Use of the 2004 WHO classification is recommended, because it should result in a uniform diagnosis of tumours better classified according to their risk potential. However, until the 2004 WHO classification has been validated by further clinical trials, tumours should be graded using both the 1973 and the 2004 WHO classifications (5). Most clinical trials published so far on bladder tumours have been performed using the 1973 WHO classification, therefore, this is the classification used in the 2014 edition of these guidelines.

3.3 Pathology

*3.3.1 **Handling of specimens by urologists***

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

In radical cystectomy, bladder fixation must be carried out as soon as possible. The pathologist must open the specimen from the urethra to the bladder dome and fix the specimen in formalin. In some circumstances, this procedure can also be performed by the urologist. In a female cystectomy specimen, the length of the urethral segment removed en bloc with the specimen should be checked, preferably by the urological surgeon (6).

*3.3.2 **Handling of specimens by pathologists***

Specimen handling should follow the general rules as published by a collaborative group of pathologists and urologists (7,8). It must be stressed that it may be difficult to confirm the presence of a neoplastic lesion using gross examination of the cystectomy specimen after TURB or chemotherapy, so the entire retracted or ulcerated area must be included.

It is mandatory to study the urethra, ureter and prostate in men and the radial margins (9). In urethra-sparing cystectomy, the level of urethral dissection, completeness of the prostate specifically at the apex (in men), and inclusion of the entire bladder neck and amount of adjacent urethra (in women) should be documented. All lymph node specimens should be provided in their totality, in clearly labelled containers. In doubtful cases, or if there is adipose differentiation of the lymph node, the entire specimen should be included.

Lymph nodes should be counted and measured on slides. In addition, capsular bursting and the percentage of lymph-node invasion should be reported, as well as vascular emboli. If there is metastatic spread into the perivesical fat without real lymph node structures (capsule, and subcapsular sinus), this localization should still be classified as N+.

Fresh frozen sections may help to determine the treatment strategy. A recent study confirmed the reliability of fresh frozen sections of obturator lymph nodes, but similar studies are needed to confirm these results (10). As yet, fresh frozen sections have mainly been used in the setting of clinical studies.

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

In muscle-invasive bladder cancer, there are no cases of PUNLMP or low-grade carcinoma. All cases are high-grade urothelial carcinomas. For this reason, no further prognostic information can be provided by grading the lesions (11). However, some morphological subtypes can be helpful in assessing the prognosis and treatment options. The following differentiation is currently used:

1. Urothelial carcinoma (> 90% of all cases)
2. Urothelial carcinoma with squamous and/or glandular partial differentiation (12,13)
3. Micropapillary urothelial carcinoma

4. Nested carcinoma (14)
5. Large cell nested
6. Urothelial carcinoma with small tubules
7. Microcystic urothelial carcinoma
8. Lymphoepithelioma-like urothelial carcinoma
9. Lipoid-rich urothelial carcinoma
10. Clear-cell (glycogen-rich) urothelial carcinoma
11. Rhabdoid urothelial carcinoma
12. Plasmocytoid urothelial carcinoma
13. Sarcomatoid urothelial carcinoma
14. Undifferentiated urothelial carcinoma (including with giant cell/trophoblastic-like giant cell/osteoclast-like giant cell differentiation)
15. Squamous cell carcinoma
16. Adenocarcinoma
17. Neuroendocrine carcinoma (small-cell carcinoma, large-cell neuroendocrine carcinoma, and carcinoid) (15)

Detection of any of the variants listed above from 3 to 15 is a poor prognostic factor (8,15-17). Frequent metastases and high tumour stage have been reported for these variants, together with a substantial risk of understaging in these tumours (16,18). Small-cell carcinoma must be treated differently and has to be mentioned (19).

For staging, TNM 2002 (6th edition) or TNM 2010 (7th edition) is recommended, because both editions are identical for staging bladder cancer. Blood vessel invasion and lymph node infiltration have an independent prognostic significance (20). It appears that the pN category is closely related to the number of lymph nodes studied by the pathologist (21). For this reason, some authors have reported that more than nine lymph nodes have to be investigated in order to reflect pN0 appropriately (22).

3.3.4 ***pT2 substaging in node-negative disease after cystectomy***

In 1997, the American Joint Committee on Cancer (AJCC) updated the TNM staging system and introduced substaging for the T2 tumour stage (23). The latest version was published in 2009, but without any changes from the previous 2002 version (1).

Substratification of the T2 tumour stage is intended to provide better risk assessment for follow-up strategies and to improve counselling of patients for adjuvant treatment options (24). In TURB specimens, due to the resection technique used, only invasion up to pT2b can be diagnosed with certainty. Staging cannot be performed beyond pT2, thus, no substaging of pT2a/b should be done on TURB (25).

pT3 stage is defined as tumour invasion into the perivesical fat, either microscopically or macroscopically. The presence of adipose tissue on transurethral resection of the bladder (TURB) is not a predictor of the pT3 stage, because adipose tissue can be found in the lamina propria and normal detrusor muscle (26).

In patients with node-negative, pT2a-T2b bladder cancer, later research has challenged the prognostic importance of substratifying pT2 tumours into those involving either the inner half of the detrusor muscle (T2a) or the outer half (T2b). Research has suggested consolidating the two substages into one (27-29). However, this research was limited by the extent of lymphadenectomy and the numbers of retrieved lymph nodes, which were not reported accurately, and which may have biased the final survival analysis (29). In addition, analysis of the results has not excluded patients with non-urothelial cell carcinoma and those who underwent neoadjuvant chemotherapy (27,28).

A multicentre series has attempted to overcome these limitations. The study included 565 patients with pT2 urothelial bladder carcinoma and reported significant differences in survival between the two substages in node-negative pT2 disease (30). These findings were confirmed by a single-centre Egyptian cohort, which included 1,737 patients with pT2 bladder cancer; 54% of whom had squamous cell carcinoma (31). Furthermore, significant differences in recurrence-free and cancer-specific survival were confirmed in a single-centre series of patients with pT2 urothelial carcinoma of the bladder treated with extended pelvic lymphadenectomy (32). In addition, pT2 substaging has recently been incorporated into prognostic models designed to predict upstaging and recurrence after radical cystectomy.

Another multicentre study has suggested using a weighted prognostic model for patients with node-negative pT2 bladder cancer. Among various independent risk factors (presence of high-grade disease or lymphovascular invasion), pT2 substaging is the strongest one for recurrence-free survival (33). This finding was confirmed in a large single-centre series including 948 patients with cT2N0M0 bladder carcinoma, in which pT2

substaging was also found to be predictive of the risk of recurrence (34,35). In conclusion, the present data support the current approach using substratification of node-negative pT2 bladder cancer and can be used to tailor the need for adjuvant treatment.

*3.3.5 **pT3 substaging in node-negative disease after cystectomy***

Recent studies have suggested that there is no difference in outcome between pT3a and pT3b urothelial carcinoma in cases with negative lymph nodes (27,36,37). Only one study has shown a better outcome for pT3aN0 patients (30).

*3.3.6 **pT4 substaging after cystectomy***

Extension of CIS into the ducti and acini of the prostate must be considered as CIS, and involvement of the gastrointestinal tract as pT4 (38).

New prognostic markers are under investigation (29). Currently, there is insufficient evidence to recommend the standard use of the prognostic marker p53 in high-risk muscle-invasive disease, because it does not provide sufficient data on which to base treatment in an individual patient.

*3.3.7 **Recommendations for assessing tumour specimens***

Mandatory evaluations
Histological subtype
Depth of invasion
Resection margins, including CIS
Extensive lymph-node representation
Optional evaluation
Lymphovascular invasion

CIS = carcinoma in situ.

3.4 Recommendations for the classification of muscle-invasive bladder cancer

Recommendations	LE	GR
The AJCC substratification into node-negative pT2 bladder cancer is of prognostic value after radical cystectomy in patients who have not undergone neoadjuvant chemotherapy.	3	B
The pathological depth of muscle invasion should be reported by the pathologist in patients with node-negative pT2 bladder cancer after cystectomy.	3	B

AJCC = American Joint Committee on Cancer

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4. DIAGNOSIS AND STAGING

4.1 Primary diagnosis

*4.1.1 **Symptoms***

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

*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 under anaesthesia should be carried out before and after TURB, to assess whether there is a palpable mass or if the tumour is fixed to the pelvic wall (1,2). However, considering the discrepancy between bimanual examination and pT stage after

cystectomy (11% clinical overstaging and 31% clinical understaging), some caution is suggested with the interpretation of bimanual examination (3).

*4.1.3 **Bladder imaging***

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

*4.1.4 **Urinary cytology and urinary markers***

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

Positive urinary cytology may originate from a urothelial tumour located anywhere in the urinary tract. Evaluation of cytology specimens can be hampered by low cellular yield, UTIs, stones or intravesical instillations, but for experienced readers, specificity exceeds 90% (4,5) (LE: 2b). However, negative cytology does not exclude tumour. Cytology should be performed on fresh urine with adequate fixation. Early morning urine is not suitable as cytolysis may often be present. There is no known urinary marker specific for the diagnosis of invasive bladder cancer (6).

*4.1.5 **Cystoscopy***

Ultimately, the diagnosis of bladder cancer is made by cystoscopy and histological evaluation of 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 computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound (US), diagnostic cystoscopy may be omitted and the patient can proceed directly to TURB for histological diagnosis.

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

The use of photodynamic diagnosis could be considered, especially if a T1 high-grade tumour is present, to find associated CIS. The additional presence of CIS may lead to a modified treatment plan (see Section 5.1). Photodynamic diagnosis is highly sensitive for the detection of CIS; with experience, the rate of false-positive results may be similar to that with regular white-light cystoscopy (7).

*4.1.6 **Transurethral resection of invasive bladder tumours***

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

The strategy of resection depends on the size of the lesion. Small tumours (< 1 cm in diameter) can be resected *en bloc*, where the specimen contains the complete tumour plus a part of the underlying bladder wall including muscle. Larger tumours need to be resected separately in parts, which include the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle, and the edges of the resection area. At least the deeper part of the resection specimen must be referred to the pathologist in a separate labelled container to enable him/her to make a correct diagnosis. It is desirable to avoid cauterisation as much as possible during resection to prevent tissue destruction. In cases in which photodynamic diagnosis is used, fluorescing areas should be biopsied in order to detect primary or associated CIS lesions. Fluorescence endoscopy should not be used in the first 6 weeks after any instillation therapy due to a higher rate of false-positive results.

*4.1.7 **Random bladder and prostatic urethral biopsy***

Bladder tumours are often multifocal and can be accompanied by CIS or dysplasia. These lesions may present themselves as velvet-like, reddish areas, indistinguishable from inflammation, or may not be visible at all.

The biopsies from normal-looking mucosa in patients with invasive bladder tumours, so-called random biopsies (R-biopsies) show a low yield (8). Fluorescence cystoscopy is performed using filtered blue light after intravesical instillation of a photosensitiser, such as 5-aminolevulinic acid (5-ALA), and more recently, hexaminolaevulinate (HAL), following approval by the European Medicines Agency. It has been confirmed that fluorescence-guided biopsy and resection are more sensitive than conventional procedures in detecting malignant tumours, particularly CIS (9-12) (LE: 2a). However, false-positive results may be induced by inflammation, or recent TURB or intravesical instillation therapy. A recent multicentre, prospective, international trial showed that, in experienced hands, the rate of false-positive results is no higher than that seen for regular, white-light cystoscopy (7). 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 men with bladder tumours has been reported. The exact risk is not known, but it seems to be higher if the tumour is located on the trigone or bladder neck, in the presence of bladder CIS, and in multiple tumours (13,14) (LE: 3). Involvement of the prostatic urethra can be determined either at the time of primary TURB or by frozen section during the cystoprostatectomy procedure. A frozen section has a higher negative predictive value and is more accurate (15-17).

*4.1.8 **Second resection***

In the case of high-grade non-muscle-infiltrative tumour, residual disease is observed in 33-53% of patients (18-24). In order to reduce the risk of understaging (19,20), a second TURB resection is often required to determine the future treatment strategy.

In consultation with the patient, orthotopic neobladder should be considered in case reconstructive surgery does not expose the patient to excessive risk (as determined by comorbidity and age). Age greater than 80 years is often considered to be the threshold after which neobladder reconstruction is not recommended, however, there is no exact age for strict contraindication. In most large series coming from experienced centres, the rate of orthotopic bladder substitution after cystectomy for bladder tumour is up to 80% for men and 50% for women (25-28). Nevertheless, no randomized controlled studies comparing conduit diversion with neobladder or continent cutaneous diversion have been performed.

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

When there are positive lymph nodes, orthotopic neobladder can nevertheless be considered in case of N1 involvement (metastasis in a single node in the true pelvis) but not for N2 or N3 tumours (29).

Oncological results after orthotopic neobladder substitution or conduit diversion are similar in terms of local or distant metastasis recurrence, but secondary urethral tumours seem less common in patients with neobladder compared with those with conduits or continent cutaneous diversions (30).

*4.1.9 **Concomitant prostate cancer***

Ruling out prostate cancer is important because 25-46% of patients undergoing cystectomy for bladder cancer (31,32) have prostate cancer confirmed by histopathological analysis of resected specimens.

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

(For general information on the assessment of bladder tumours, see EAU Guidelines on Non-muscle-invasive Bladder cancer [33]).

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

4.2 Imaging for staging MIBC

The treatment and prognosis for MIBC is determined by tumour stage and grade (34). In clinical practice, CT and MRI are the imaging techniques used. The purpose of using imaging for staging MIBC is to determine prognosis and provide information to assist treatment selection. Tumour staging must be accurate to ensure the correct choice of treatment is made.

Imaging parameters required for staging MIBC are:

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

4.2.1 ***Local staging of MIBC***

Both CT and MRI may be used for assessment of local invasion, but they are unable to diagnose accurately microscopic invasion of perivesical fat (T3a) (35). The principal aim of CT and MRI is therefore to detect T3b disease or higher.

4.2.1.1 MRI for local staging of invasive bladder cancer

Magnetic resonance imaging has superior soft tissue contrast resolution compared with CT, but poorer spatial resolution. In studies performed before the availability of multidetector CT, MRI was reported as more accurate in local assessment. The accuracy of MRI for primary tumour staging varies from 73% to 96% (mean 85%). These values were 10-33% (mean 19%) higher than those obtained with CT (36). Dynamic contrast-enhanced (DCE) MRI may help to differentiate bladder tumour from surrounding tissues or post-biopsy reaction, because enhancement of the tumour occurs earlier than that of the normal bladder wall, due to neovascularisation (37-39).

In 2006, a link was established between the use of gadolinium-based contrast agents and nephrogenic systemic fibrosis (NSF), which may result in fatal or severely debilitating systemic fibrosis. Patients with impaired renal function are at risk of developing NSF and the non-ionic linear gadolinium-based contrast agents should be avoided (gadodiamide, gadopentetate dimeglumine and gadoversetamide). A stable macrocyclic contrast agent should be used (gadobutrol, gadoterate meglumine or gadoteridol). Alternatively, contrast-enhanced CT could be performed using iodinated contrast media (40) (LE: 4).

4.2.1.2 CT imaging for local staging of MIBC

The advantages of CT include high spatial resolution, shorter acquisition time, wider coverage in a single breath hold, and lower susceptibility to variable patient factors. Computed tomography is unable to differentiate between stages Ta and T3a tumours, but it is useful for detecting invasion into the perivesical fat (T3b) and adjacent organs. The accuracy of CT in determining extravesical tumour extension varies from 55% to 92% (41) and increases with more advanced disease (42).

4.2.2 ***Imaging of lymph nodes in MIBC***

Assessment of lymph node metastases based solely on size is limited by the inability of both CT and MRI to identify metastases in normal-sized or minimally enlarged nodes. The sensitivity for detection of lymph node metastases is low (48-87%). Specificity is also low because nodal enlargement may be due to benign disease. Overall, CT and MRI show similar results in the detection of lymph node metastases in a variety of primary pelvic tumours (43-48). Pelvic nodes > 8 mm and abdominal nodes > 10 mm in maximum short-axis diameter, detected by CT or MRI, should be regarded as pathologically enlarged (49,50).

Currently, there is no evidence supporting the routine use of positron emission tomography (PET) in the nodal staging of bladder cancer, although the method has been evaluated with varying results in small prospective trials (51-54).

4.2.3 ***Upper urinary tract urothelial carcinoma***

Excretory-phase CT urography is the imaging technique with the highest diagnostic accuracy for upper urinary tract urothelial carcinoma (UTUC) and has replaced conventional intravenous urography and US as the first-line imaging test for investigating high-risk patients (55). The sensitivity of CT urography for UTUC is reported to range from 0.67 to 1.0 and specificity from 0.93 to 0.99, depending on the technique used (56-63). Attention to technique is therefore important for optimum results.

For UTUC detected by CT urography, a biopsy for histopathological confirmation of diagnosis is recommended to eliminate false-positive results and to provide information regarding the grade of the tumour to aid in the choice of treatment (57,58,64-66). The biopsy is usually performed ureteroscopically.

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

Prior to any curative treatment, it is essential to evaluate the presence of distant metastases. Computed tomography and MRI are the diagnostic techniques of choice to detect lung and liver metastases. Bone and brain metastases are rare at the time of presentation of invasive bladder cancer. A bone scan and additional brain imaging are therefore not routinely indicated unless the patient has specific symptoms or signs to suggest bone or brain metastases (67,68). Magnetic resonance imaging is more sensitive and specific for diagnosing bone metastases than bone scintigraphy (69,70) (LE: 2b).

4.2.5 ***Future developments***

Evidence is accruing in the literature suggesting that fluorodeoxyglucose (FDG)-PET/CT might have potential

clinical use for staging metastatic bladder cancer (71,72) but there is no consensus as yet. The results of further trials are awaited before a recommendation can be made. Recently, the first study was published showing the superior feasibility of diffusion-weighted imaging (DWI) over T2-weighted and DCE MRI for assessing the therapeutic response to induction chemotherapy against MIBC (73). The high specificity of DWI indicates that it is useful for accurate prediction of a complete histopathological response, allowing better patient selection for bladder-sparing protocols. Results from prospective studies are awaited.

4.2.6 ***Conclusions and recommendations for staging in MIBC***

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

DWI = diffusion-weighted imaging; FDG-PET/CT = fluorodeoxyglucose-positron emission tomography

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

CT = computed tomography; MRI = magnetic resonance imaging; UTUC = upper urinary tract urothelial carcinoma

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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 non-muscle invasive bladder cancer (NMIBC) is strongly associated with several factors as described in the EORTC risk calculator. According to this calculator, the risk of progression after 5 years ranges from 6 to 45% for high-risk tumours. However, in a prospective, multicentre trial, the progression rate was significantly lower than previously reported, even when the presence of concomitant CIS was considered. This was probably due to the combination of a second resection, prior to inclusion in the trial and maintenance treatment as part of the protocol (1). For example, recent meta-analyses have demonstrated that Bacillus Calmette-Guérin (BCG) therapy prevents the risk of tumour recurrence (2,3).

Two other meta-analyses have shown that BCG therapy decreases the risk of tumour progression (4,5) but so far, no significant overall- or disease-specific survival advantages have been shown, as compared to no intravesical therapy (4-6).

As also reported in the EAU NMIBC guidelines, there are reasons to consider cystectomy in selected patients with NMIBC (7).

There is a risk of an understaging error in Ta, T1 tumours of 35-62% presented in large cystectomy series. This seems due to the presence of persisting or recurrent tumours due to the lack of a second TURB or re-TURB and the absence of neoadjuvant therapy (8-10). Second TURB identifies 24-49% of T2 tumours that have been diagnosed initially as non-muscle-invasive tumours (11,12). Progression to MIBC significantly decreases cancer-specific survival (CSS). In a review of 19 trials and 3,088 patients, CSS after progression from NMIBC to MIBC was 35%, which is significantly worse compared to patients with MIBC without a history of NMIBC. This underlines the need to recommend early radical treatment, such as f.i. radical cystectomy, in case of intravesical therapy failure (7,13,14).

According to the EAU NMIBC Guidelines, it is reasonable to propose immediate radical cystectomy to those patients with non-muscle-invasive tumour who are at highest risk of progression (13). These are:

- multiple and/ or large (> 3 cm) T1, high-grade (G3) tumours;
- T1, high-grade (G3) tumours with concurrent CIS;
- recurrent T1, high-grade (G3) tumours;
- T1G3 and CIS in prostatic urethra;
- micropapillary variant of urothelial carcinoma.

Although the percentage of patients with primary Ta, T1 tumours and the indication for cystectomy in Ta, T1 tumours is not specified in large cystectomy series, the 10-year recurrence-free survival rate is ~80% and similar to that with TURB and BCG maintenance therapy (7,9,15,16) (LE: 3).

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

- whenever muscle-invasive tumour is detected during follow-up;
- if high-grade, non-muscle-invasive tumour is present at both 3 and 6 months;
- high-grade recurrence after BCG (more recurrences, Ta → T1 or upgrading, appearance of CIS).

Patients with disease recurrence within 2 years of initial TURB plus BCG therapy have a better outcome than patients who already have muscle-invasive disease, indicating that cystectomy should be performed at first recurrence, even in non-muscle-invasive disease (14) (LE: 3; GR: C).

There are now several bladder-preservation strategies available that can be categorised as immunotherapy, chemotherapy, device-assisted therapy, and combination therapy (17). However, experience is limited and treatments other than radical cystectomy must be considered oncologically inferior at the present time (18-20).

5.2 Recommendations for treatment failure of non-muscle-invasive bladder cancer

Recommendations	GR
In all T1 tumours at high risk of progression (i.e., high grade, multifocality, CIS, and tumour size, as outlined in the EAU guidelines for non-muscle-invasive bladder cancer [7]), immediate radical treatment is an option.	C
In all T1 patients failing intravesical therapy, radical treatment should be offered.	B

CIS = carcinoma in situ

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6. NEOADJUVANT CHEMOTHERAPY

6.1 Introduction

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 perioperative chemotherapy has been explored since the 1980s. Despite large-scale randomized phase III studies and a high level of evidence supporting its use, neoadjuvant chemotherapy is still infrequently used (6,7).

There are many **advantages and disadvantages** of administering chemotherapy before planned definitive surgery to patients with operable muscle-invasive urothelial carcinoma of the bladder, with clinically negative nodes (cN0):

- Chemotherapy is delivered at the earliest time-point, when the burden of micrometastatic disease is expected to be low.
- Potential reflection of *in vivo* chemosensitivity.
- Tolerability of chemotherapy and patient compliance are expected to be better before rather than after cystectomy.
- Patients might respond to neoadjuvant therapy and reveal a favourable pathological status, determined mainly by achieving pT0, a negative lymph node status, and negative surgical margins.
- Delayed cystectomy might compromise the outcome in patients not sensitive to chemotherapy (8,9), although published studies on the negative effect of delayed cystectomy only entail series of chemonaive patients. There are no trials or large patient series indicating that delayed surgery, due to neoadjuvant chemotherapy, has a negative impact on survival.

Neoadjuvant chemotherapy does not seem to affect the outcome of surgical morbidity. In one randomised trial (10), the same distribution of grade 3-4 postoperative complications was seen in both trial arms (10). 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, while 71% of patients received all three chemotherapy cycles (11).

- Clinical staging using bimanual palpation, CT or MRI may often result in over- and understaging and have a staging accuracy of only 70% (12,13). Overtreatment is the possible negative consequence.
- Neoadjuvant chemotherapy should only be used in patients who are eligible for cisplatin combination chemotherapy, because other combinations (or monotherapies), are inferior in metastatic bladder cancer and have not been tested adequately in the neoadjuvant setting (14-27).

6.2 The role of imaging and biomarkers to identify responders

In small published series, attempts have been made to identify the responders among patients undergoing neoadjuvant chemotherapy, suggesting that the response after two cycles of neoadjuvant chemotherapy is related to outcome. To date, no firm conclusions can be made (28,29).

The meaning of stable disease after two cycles of neoadjuvant chemotherapy still has to be defined. To identify progression during neoadjuvant chemotherapy, imaging is being used in many centres, notwithstanding the lack of published data to support its relevance.

For patients who respond to neoadjuvant chemotherapy, and especially those who show a complete response (pT0 N0), neoadjuvant chemotherapy has a major positive impact on overall survival (OS) (30).

The overtreatment of non-responders and patients in the non-target population (i.e. patients without micrometastatic disease) are major drawbacks of neoadjuvant (and adjuvant) chemotherapy. Ideally, preoperative identification of responders utilizing tumour molecular profiling in TURB specimens would guide the use of neoadjuvant chemotherapy (31,32) (see Biomarker chapter).

In addition, imaging methods for the early identification of responders during treatment have been explored. So far, neither PET, CT nor conventional MRI can accurately predict response (28,29). Fast DCE MRI

was compared with conventional MRI before and after two, four and six cycles of MVAC (33). The differences concerning response to MVAC were not significant. The authors concluded that after two cycles, DCE MRI helped to detect 13 of 14 responders and all eight non-responders. However, these results need to be confirmed and validated in larger studies.

In general, in the metastatic setting, measurable lesions are evaluated according to response criteria (34). In the neoadjuvant setting, the only measurable lesion is the primary tumour itself, and in the adjuvant setting, no measurable lesions are present.

6.3 Summary of available data

Several randomised phase III trials have addressed the question of whether neoadjuvant chemotherapy improves survival, with conflicting results (14-24,35-40).

The main differences in trial design were the type of chemotherapy (i.e. single-agent cisplatin or combination chemotherapy) and the number of cycles planned. From the statistical point of view, the studies differed in size, patient characteristics (e.g. clinical T-stages included) and the type of definitive treatment allowed (cystectomy and/or radiotherapy). Patients had to be fit for cisplatin. As a result of the lack of clarity, even though a considerable number of randomised trials had been performed, three meta-analyses were undertaken to answer the important question of whether neoadjuvant chemotherapy prolongs survival (25-27).

- The first meta-analysis, published in 2003 (25), included 10 randomised trials (except for results of the INT 0080-study [16]) and showed a 13% reduction in the risk of death, equivalent to 5% absolute benefit at 5 years [increased overall survival (OS) from 45% to 50%).
- The second meta-analysis, published in 2004 (26), included 11 of 16 randomised trials with OS data from 2,605 patients. There was a significant decrease in mortality risk of 10%, which corresponded to an absolute improvement in OS of 5% (from 50% to 55%).
- In the most recent meta-analysis, published in 2005 (27), with updated independent patient data from 11 randomised trials (3,005 patients), there was a significant survival benefit in favour of neoadjuvant chemotherapy. 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). Only cisplatin combination chemotherapy with at least one additional chemotherapeutic agent resulted in a meaningful therapeutic benefit (25,27); 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 updated analysis of the largest randomised phase III trial (14) with a median follow-up of 8 years confirmed the former results and provided some additional interesting findings:

- 16% reduction in mortality risk;
- Improvement in 10-year survival from 30% to 36% with neoadjuvant CMV;
- Benefit with regard to distant metastases;

No benefit for locoregional control and locoregional disease-free survival, with the addition of neoadjuvant CMV independent of the definitive treatment.

The presence of micrometastases is postulated to be lower in smaller tumours (T2) compared to more extensive tumours (T3b-T4b). T4 stage tumours are prone to a higher degree of clinical understaging because macrometastatic nodal deposits are detected more often in post-cystectomy specimens of these extensive tumours (41). Further data support the use 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 (30).

6.4 Conclusions and recommendations for neoadjuvant chemotherapy

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

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

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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 MIBC in most western countries (1,2). Recent interest in patients' quality of life (QoL) has increased the trend toward bladder preservation treatment modalities, such as radio- and/or chemotherapy (see Chapters 9 and 10). Performance status (PS) and age influence the choice of primary therapy, as well as the type of urinary diversion, with cystectomy being reserved for younger patients without concomitant disease and with a better PS. The value of assessing overall health before recommending and proceeding with surgery was emphasised in a multivariate analysis (3). The analysis found an association between comorbidity and adverse pathological and survival outcome following radical cystectomy (3). PS and comorbidity have a different impact on treatment outcome and must be evaluated independently (4).

Controversy remains 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 aged > 80 years (3). The largest, retrospective, single-institution study on cystectomy to date found that patients aged > 80 years had increased postoperative morbidity but not increased mortality. Although some patients successfully underwent a neobladder procedure, most patients were treated with an ileal conduit diversion (5).

It is particularly important to evaluate the function and QoL of elderly patients using a standardised geriatric assessment, as well as carrying out a standard medical evaluation (see Section 7.1.4) (6).

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

A retrospective series of 153 patients, with a clear indication for radical surgery of locally advanced bladder cancer, found that patients treated > 90 days after the primary diagnosis showed a significant increase in extravesical disease (81 vs 52%) (7).

Delay in cystectomy affects treatment outcome and the type of urinary diversion. In organ-confined urothelial cancer of the bladder, the average time from primary diagnosis to cystectomy was 12.2 months in patients who received a neobladder and 19.1 months in those who received an ileal conduit. This was even more noticeable with organ-confined invasive cancer; the average time to surgery was 3.1 months with a neobladder and 15.1 months with an ileal conduit (8). Similar results have been observed in a series of 247 patients: recurrence-free survival and OS were significantly better in patients treated before 90 days compared to others treated after 90 days (9).

*7.1.3 **Indications***

Traditionally, radical cystectomy was recommended for patients with MIBC 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 TURB and intravesical therapy alone.

Salvage cystectomy is indicated for non-responders to conservative therapy, recurrence after bladder-sparing treatment, and non-urothelial carcinoma (these tumours respond poorly to chemo- and radiotherapy). It is also used as a purely palliative intervention, including in fistula formation, for pain or recurrent visible haematuria (macrohaematuria) (see Section 8.1 Palliative cystectomy).

*7.1.4 **MIBC and comorbidity***

Complications related to radical cystectomy may be directly related to pre-existing comorbidity as well as the surgical procedure, bowel anastomosis, or urinary diversion. A significant body of literature has evaluated the usefulness of age as a prognostic factor for radical cystectomy (10-12). Advanced age has been identified as a risk factor for complications due to radical cystectomy, although chronological age is less important than biological age. Other risk factors for morbidity include prior abdominal surgery, extravesical disease, and prior radiotherapy (13), while an increased body mass index is associated with a higher rate of wound dehiscence and hernia (14).

7.1.4.1 Evaluation of comorbidity

Rochon et al. have shown that evaluation of comorbidity provides a better indicator of life expectancy in MIBC than patient age (15). The evaluation helps to identify the medical conditions likely to interfere with, or have an impact on, treatment and the evolution and prognosis of MIBC (16).

The value of assessing overall health before recommending and proceeding with surgery was emphasised by Zietman et al. who demonstrated an association between comorbidity and adverse pathological and survival outcome following radical cystectomy (17). Similar results were found for the impact of comorbidity on cancer-specific and other-cause mortality in a population-based competing risk analysis of > 11,260 patients from the SEER registries. Age carried the highest risk for other-cause mortality but not for increased cancer-specific death, while the stage of locally advanced tumour was the strongest predictor for decreased cancer-specific survival (18). Stratifying elderly patients according to their risk-benefit profile using a multidisciplinary approach will help to select patients most likely to benefit from radical surgery and to optimise treatment outcomes (19). Unfortunately, most series evaluating radical cystectomy do not include indices of comorbidity in the patient evaluation.

7.1.4.2 Comorbidity scales

A range of comorbidity scales have been developed (20); six of which have been validated (LE: 3):

- Cumulative Illness Rating Scale (CIRS) (21);
- Kaplan-Feinstein index (22);
- Charlson Comorbidity Index (CCI) (23);
- Index of Coexistent Disease (ICD) (24);
- ACE-27 (25);
- Total Illness Burden Index (TIBI) (26).

The CCI ranges from 0 to 30 according to the importance of comorbidity described at four levels and is calculated by healthcare practitioners from the patients' medical records. The score has been widely studied

in patients with bladder cancer and found to be an independent prognostic factor for perioperative mortality (27,28), overall mortality (29), and cancer-specific mortality (30-33). Only the age-adjusted version of the CCI was correlated with both cancer-specific and other-cause mortality (34).

The ICD evaluates 14 possible comorbidities and is also calculated from the patients' medical records.

The CIRS quantifies the severity of organic disease in 14 systems and is calculated from the medical records. Nurses and doctors have been shown to provide comparable calculations of CIRS (35). Although CIRS has been validated in elderly patients (36,37), it has not been validated in bladder cancer treatment.

The Kaplan-Feinstein index evaluates patient comorbidity as a cumulative score. Depending on the level of damaging effect on body organs, all diseases and their complications are classified as 'mild', 'moderate' and 'severe'. In total 12 comorbidities using a score from 0 to 3 are included: 0, no problem; 1, light and non-chronic decompensated comorbidity; 2, significant decompensation; and 3, severe decompensation. Healthcare practitioners calculate the Kaplan-Feinstein index score from medical records.

The TIBI evaluates 16 diseases across 110 items. The TIBI questionnaire is completed by the patients themselves. The TIBI was initially validated in a cohort of patients with type 2 diabetes. The TIBI was then correlated to QoL, age, number of days spent in bed during the previous 3 months, and reduced mobility in a cohort of 1,638 men with prostate cancer (38). None of ICD, CIRS, Kaplan-Feinstein index and TIBI has been validated in the setting of bladder cancer treatment.

Performances of the CCI and the Adult Comorbidity Evaluation Index (ACE-27) are approximately equivalent (LE: 3). The age-adjusted CCI (Table 4) is the most widely used comorbidity index in cancer for estimating long-term survival and is easily calculated (39).

Table 4: Calculation of the Charlson Comorbidity Index

Number of points	Conditions
1 point	50-60 years Myocardial infarction Heart failure Peripheral vascular insufficiency Cerebrovascular disease Dementia Chronic lung disease Connective tissue disease Ulcer disease Mild liver disease Diabetes
2 points	61-70 years Hemiplegia Moderate to severe kidney disease Diabetes with organ damage Tumours of all origins
3 points	71-80 years Moderate to severe liver disease
4 points	81-90 years
5 points	> 90 years
6 points	Metastatic solid tumours AIDS

Interpretation

1. Calculate Charlson Score or Index = i

a. Add comorbidity score to age score

b. Total denoted as 'i' in the Charlson Probability calculation (see below). i = sum of comorbidity score to age score.

2. Calculate Charlson Probability (10-year mortality)

a. Calculate $Y = 10^{(i \times 0.9)}$

b. Calculate Z = 0.983Y (where Z is the 10-year survival)

Health assessment of oncology patients must be supplemented by measuring their activity level. Extermann et al. have shown that there is no correlation between morbidity and competitive activity level (4). Eastern

Cooperative Oncology Group (ECOG) PS scores and Karnofsky index have been validated to measure patient activity (LE: 3) (40). PS is correlated with patient OS after radical cystectomy (32,41) and palliative chemotherapy (42-44).

The ASA score has been validated to assess, prior to surgery, the risk of postoperative complications. In the bladder cancer setting, ASA scores ≥ 3 are associated with major complications (45,46), particularly those related to the type of urinary diversion (Table 7.1) (47).

Table 7.1: ASA score (48)

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

According to a consensus conference of the National Institutes of Health, the aim of the Standardized Geriatric Assessment (SGA) is to discover, describe and explain the many problems of elderly people, to catalogue their resources and strengths, to assess individual service needs, and to develop a coordinated plan of care. The SGA is thus a medico-psycho-social index.

The SGA can be carried out by means of several protocols. These protocols differ in the completeness of diagnostic research. The protocol is the most complete Comprehensive Geriatric Assessment (CGA) (49). The CGA is suited to the care of cancer patients (50). In bladder cancer, the CGA has been used to adapt gemcitabine chemotherapy in previously untreated elderly patients with advanced bladder carcinoma (51).

The Senior Adult Oncology Program proposed by Balducci et al. presents a less-comprehensive evaluation than an SGA (52). Even though these protocols identify previously unrecognised geriatric medical and social problems, their usefulness has not been clearly demonstrated (53). Similarly, the CGA, when performed in patients in general medicine, does not alter the risk of hospitalisation or death within 2 years of the evaluation (54). To provide benefit to patients, the CGA should be associated with the management problems it identifies (55).

7.1.4.3 Conclusions and recommendations for comorbidity scales

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

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

*7.1.5 **References***

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7.1.6 ***Radical cystectomy: technique and extent***

In men, standard radical cystectomy includes removal of the bladder, prostate, seminal vesicles, distal ureters, and regional lymph nodes. In women, standard radical cystectomy includes removal of the bladder, entire urethra and adjacent vagina, uterus, distal ureters, and regional lymph nodes (1). Currently, there are substantial data on the extent of lymphadenectomy. Controversies in evaluating the clinical significance of lymphadenectomy are related to two main aspects of nodal dissection: therapeutic procedure and/or staging instrument.

Two important autopsy investigations for radical cystectomy have been performed so far. The first investigation showed that in 215 patients with MIBC and nodal dissemination, the frequency of metastasis was 92% in regional (perivesical or pelvic), 72% in retroperitoneal, and 35% in abdominal lymph nodes. There was also a significant correlation between nodal metastases and concomitant distant metastases ($P < 0.0001$). Approximately 47% of the patients had both nodal metastases and distant dissemination and only 12% of the patients had nodal dissemination as the sole metastatic manifestation (2). The second autopsy investigation focussed on the nodal yield when super-extended pelvic lymph node dissection (LND) was performed. Substantial inter-individual differences were found with counts ranging from 10 to 53 nodes (3). These findings demonstrate the limited utility of node count as a surrogate for extent of dissection.

Regional lymph nodes have been shown to consist of all pelvic lymph nodes below the bifurcation of the aorta (4-8). Mapping studies have also found that skip lesions at locations above the bifurcation of the aorta, without more distally located lymph node metastases, are rare (8,9).

The extent of LND has not been established to date. Standard lymphadenectomy in bladder cancer patients involves removal of nodal tissue cranially up to the common iliac bifurcation, with the ureter being the medial border, and including the internal iliac, presacral, obturator fossa and external iliac nodes (10). Extended lymphadenectomy includes all lymph nodes in the region of the aortic bifurcation, and presacral and common iliac vessels medial to the crossing ureters. The lateral borders are the genitofemoral nerves, caudally the circumflex iliac vein, the lacunar ligament and the lymph node of Cloquet, as well as the area described for standard lymphadenectomy (10-14). A super-extended lymphadenectomy extends cranially to the level of the inferior mesenteric artery (15,16).

In order to assess how and if cancer outcome is influenced by the extent of lymphadenectomy in patients with clinical N0M0 MIBC, a systematic review of the literature was undertaken, as outlined in detail elsewhere (17). Four independent reviewers performed abstract and full-text screening, data abstraction, and risk of bias assessment. Out of 1,692 abstracts retrieved and assessed, 19 studies fulfilled the review criteria and were included (10-14,16,18-30). All five studies comparing LND versus no LND reported a better oncological outcome for the former group. Seven out of 12 studies comparing (super-)extended with limited or standard LND reported a beneficial outcome for (super-)extended in at least a subset of patients. No difference in outcome was reported between extended and super-extended LND in the two high-volume-centre studies identified (16,28).

Two other reviews reported similar findings. Karl (31) concluded that more limited pelvic LND was associated with suboptimal staging as well as poorer outcome compared with standard or extended LND, in patients with node-positive or node-negative disease. Svatek and colleagues (32) concluded that extended LND with complete skeletonisation of all pelvic structures up to the mid-upper third of the common iliac vessels was superior to limited LND. However, all of these identified studies suffered from significant methodological limitations and were prone to biases, thereby compromising the quality and reliability of the evidence. Further data from on-going randomized trials on the therapeutic impact of extent of lymphadenectomy are awaited.

It has been suggested that progression-free survival as well as OS might be correlated with the number of lymph nodes removed during surgery, although there are no data from randomized controlled trials on the minimum number of lymph nodes that should be removed. Nevertheless, survival rates increase with the number of dissected lymph nodes (33). Removal of at least 10 lymph nodes has been postulated as sufficient for evaluation of lymph node status, as well as being beneficial for OS in retrospective studies (34-36). In conclusion, extended LND might have a therapeutic benefit compared to less-extensive LND, but due to bias, no firm conclusions can be drawn (17).

*7.1.7 **Laparoscopic/robotic-assisted laparoscopic cystectomy***

Laparoscopic cystectomy and robotic-assisted laparoscopic cystectomy (RALC) are feasible both in male and female patients (37,38).

Laparoscopic cystectomy is a technically challenging procedure that requires a high level of skill and has a long learning curve (39). Recently, Aboumarzouk and co-workers conducted a systematic review in line with both Cochrane and PRISMA guidelines (40,41). All the included studies were observational cohort studies with no randomization, and all reported experience with laparoscopic compared with open cystectomy (42-49). A total of 427 patients were included: 211 underwent laparoscopic cystectomy with extracorporeal reconstruction, and 216 were in the open cystectomy group. Patients in the laparoscopy group were significantly younger than those in the open cystectomy group. The laparoscopic group had significantly longer operative times, but less

blood loss, less time to oral intake, less analgesic requirement, and shorter length of hospital stay. Patients who underwent open cystectomy developed significantly more minor complications than those who were treated laparoscopically. There was no difference between the two groups regarding LND yields, major complications, positive margins, pathological results, local recurrence, or distant metastases. However, there were significantly more positive nodes in the open cystectomy group. The main limitation of this meta-analysis was the inclusion of non-randomized observational studies with small patient cohorts. Only five of the studies had > 20 patients and all the studies had cohorts with < 50 patients. This led to a substantial risk of bias in the results. Another limitation was the age selection bias.

Laparoscopic cystectomy and RALC data often suffer from selection bias including younger patients, lower stage of disease, and minimal comorbidity compared to most contemporary studies of open cystectomy (50-55). To date, laparoscopic cystectomy and RALC still need to be considered experimental because of the limited number of cases reported, absence of long-term oncological and functional outcome data, and possible selection bias (50,56).

Laparoscopic intracorporeal construction of urinary diversion (with or without robotic assistance) has been tested in small series only (51-53,56). It is a challenging and lengthy procedure with the currently available equipment and must therefore be regarded as experimental. Furthermore, there are no long-term results available. Laparoscopic cystectomy and pelvic lymphadenectomy (with or without robotic assistance), with extracorporeal construction of urinary diversion, is an option for surgical treatment only in experienced centres (LE: 3).

7.1.8 ***References***

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7.2 Urinary diversion after radical cystectomy

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

- Abdominal diversion, such as an 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 appendix (1). Several studies have compared certain aspects of health-related QoL, such as sexual function, urinary continence and body image, in patient cohorts with different types of urinary diversion. However, further research is needed on preoperative tumour stage and functional situation, socioeconomic status, and time interval to primary surgery.

*7.2.1 **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 (2). Despite the necessary interruption and re-anastomosis of bowel, a formal bowel preparation may not be necessary (3). Furthermore, bowel recovery time has been reduced by the use of early mobilisation, early oralisation, and gastrointestinal stimulation with metoclopramide and chewing gum (4).

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

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

Relative contraindications specific for an orthotopic neobladder are high-dose preoperative radiotherapy, complex urethral stricture disease, and severe urethral sphincter-related incontinence (5-7).

7.2.1.1 Patient selection for orthotopic diversion

Radical cystectomy and urinary diversion are the two steps of one operation. However, the literature uniformly reports the complications of radical cystectomy, while ignoring the fact that most complications are diversion related (8). Age alone is not a criterion for offering continent diversion (9,10). Comorbidity, cardiac and pulmonary function, and cognitive function are all important factors that should be considered, along with the patient's social support and preference.

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 (11,12). 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 (13). 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 (11).

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 ileal or colon conduit (14). Despite the limited comparative data available, however, it must be taken into consideration that older data and clinical experience suggest ureter stenosis on skin level and ascending UTI are more frequent complications in comparison with those with ileal conduit diversion. In a retrospective study comparing various forms of intestinal diversion, ileal conduits had fewer late complications than continent abdominal pouches or orthotopic neobladders had (15).

7.2.3 ***Ileal conduit***

The ileal conduit is still an established option with well-known/predictable results. However, up to 48% of patients develop early complications including UTIs, pyelonephritis, ureteroileal leakage and stenosis (15). 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% (16-18). 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) (16): the rate of complications increased from 45% at 5 years to 94% in those surviving > 15 years. In the latter group, 50% of patients developed upper urinary tract changes and 38% developed urolithiasis.

7.2.4 ***Continent cutaneous urinary diversion***

A low-pressure detubularised ileal reservoir can be used as a continent cutaneous urinary diversion for self-catheterisation; gastric, ileocecal and sigma pouches have also been described (19-21). Different antireflux techniques can be used (22). Most patients have a well-functioning reservoir with day-time and night-time continence approaching 93% (23). In a retrospective study of > 800 patients, stomal stenosis was seen in 23.5% of patients with an appendix stoma and 15% of those with an efferent intussuscepted ileal nipple (23). Stone formation in the pouch occurred in 10% of patients (23-25). In a small series of previously irradiated female patients, incontinence and stomal stenosis was seen in eight of 44 patients (18%) (26).

7.2.5 ***Ureterocolonic diversion***

The oldest and most common form of ureterocolonic diversion was primarily a refluxive and later an antirefluxive connection of ureters to the intact rectosigmoid colon (uretero- or rectosigmoidostomy) (27,28). Most indications for this procedure have become obsolete due to a high incidence of upper UTIs and the long-term risk of developing colon cancer (29,30). Bowel frequency and urge incontinence are additional adverse effects of this type of urinary diversion. However, it may be possible to circumvent the above-mentioned problems by interposing a segment of ileum between the ureters and rectum or sigmoid in order to augment capacity and avoid direct contact between the urothelium and colonic mucosa, as well as faeces and urine (31).

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 (7,32,33). In elderly patients (> 80 years), however, it is rarely performed, even in high-volume expert centres (34,35).

The terminal ileum is the gastrointestinal segment most often used for bladder substitution and there is less experience with the ascending colon, including the caecum, and the sigmoid (32). 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 (36,37). In two studies with 1,054 and 1,300 patients (7,38), long-term complications included diurnal (8-10%) and nocturnal (20-30%) incontinence, ureterointestinal stenosis (3-18%), metabolic disorders, and vitamin B12 deficiency. In a recent study that compared cancer control and patterns of disease recurrence in patients with neobladder and ileal conduit, there was no difference in cancer-specific survival between the two groups when adjusting for pathological stage (39). Urethral recurrence in neobladder patients seems rare (1.5-7% for both male and female patients) (7,40). These results indicate that neobladder in male and female patients does not compromise the oncological outcome of cystectomy. It remains debatable whether neobladder is better for QoL compared to non-continent urinary diversion (41-43).

Various forms of upper urinary tract reflux protection, including a simple isoperistaltic tunnel, ileal intussusception, tapered ileal prolongation implanted subserosally, and direct (sub)mucosal or subserosal ureteral implantation, have been described (25,37). According to the 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 (segment length 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 prefer ileal orthotopic neobladders and ileal conduits, based on clinical experience (44,45). In selected patients, ureterocutaneostomy is surgically the least burdensome type of diversion (LE: 3). Recommendations related to radical cystectomy and urinary diversions are listed in section 7.5.

7.3 Morbidity and mortality

In two long-term studies, and one population-based cohort study, the perioperative mortality was reported as 1.2-3% at 30 days and 2.3-5.7% at 90 days (46-49). In a large single-centre series, early complications (within 3 months of surgery) were seen in 58% of patients (49). Late morbidity is usually due to the type of urinary diversion (see also above) (50,51). Early morbidity associated with radical cystectomy for NMIBC (at high risk for disease progression) is similar and no less than that associated with muscle-invasive tumours (52). In general, lower morbidity and (perioperative) mortality have been observed by surgeons and in hospitals with a higher caseload and therefore more experience (53-56).

7.4 Survival

According to a multi-institutional database of 888 consecutive patients undergoing radical cystectomy for bladder cancer, the 5-year recurrence-free survival was 58% and the cancer-specific survival was 66% (57). Recent external validation of postoperative nomograms for bladder-cancer-specific mortality showed similar results, with 5-year OS of 45% and cancer-specific survival of 62% (58).

Recurrence-free survival and OS in a large single-centre study of 1,054 patients was 68% and 66% at 5 years and 60% and 43%, at 10 years, respectively (59). The 5-year recurrence-free survival in node-positive patients who underwent cystectomy was considerably less at 34-43% (59-61). However, in patients with a low level of lymph node metastasis, the survival is better.

In a surgery only study, the 5-year recurrence-free survival was 76% in patients with pT1 tumours, 74% for pT2, 52% for pT3, and 36% for pT4 (59). Another study reported 10-year disease-specific survival and OS rates of 72.9% versus 49.1% for organ-confined disease (defined as pT $\leq$ 3a), and 33.3% versus 22.8% for non-organ-confined disease (62).

A trend analysis according to the 5-year survival and mortality rates of bladder cancer in the United States, between 1973 and 2009 with a total of 148,315 bladder cancer patients, revealed an increased stage-specific 5-year survival rate for all stages, except for metastatic disease (63). However, no changes in mortality were recorded among localized and regional stage. In patients with visceral metastases an increase in mortality rates was observed, but differences were minor, and hardly of any clinical importance.

7.5 Conclusions and recommendations for radical cystectomy and urinary diversion

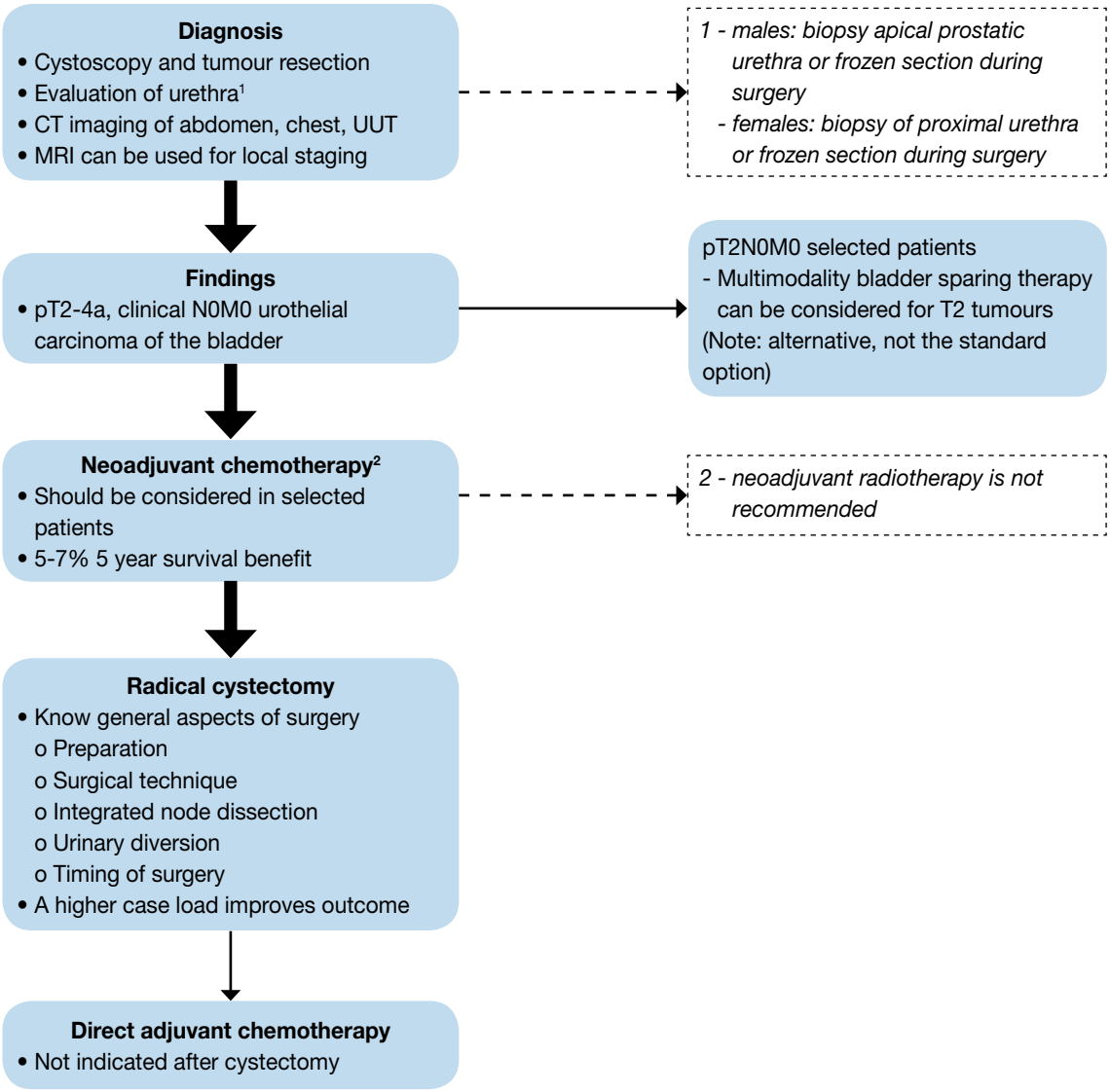
Conclusions	LE
For MIBC, radical cystectomy is the curative treatment of choice.	3
A higher case load reduces morbidity and mortality of cystectomy.	3
Radical cystectomy includes removal of regional lymph nodes.	3
There are data to support that extended LND (vs. standard or limited LND) improves survival after radical cystectomy.	3
Radical cystectomy in both sexes must not include removal of the entire urethra in all cases, which may then serve as outlet for an orthotopic bladder substitution. The terminal ileum and colon are the intestinal segments of choice for urinary diversion.	3
The type of urinary diversion does not affect oncological outcome.	3
Laparoscopic cystectomy and robotic-assisted laparoscopic cystectomy are feasible but still investigational. Current best practice is open radical cystectomy.	3
In patients aged > 80 years with MIBC, cystectomy is an option.	3
Surgical outcome is influenced by comorbidity, age, previous treatment for bladder cancer or other pelvic diseases, surgeon and hospital volumes of cystectomy, and type of urinary diversion.	2
Surgical complications of cystectomy and urinary diversion should be reported using a uniform grading system. Currently, the best-adapted, graded system for cystectomy is the Clavien Grading System.	2

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

**Upgraded following EAU Working Panel consensus.*

LND = lymph node dissection; MIBC = muscle-invasive bladder cancer.

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



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

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8. NON-RESECTABLE TUMOURS

8.1 Palliative cystectomy for muscle-invasive bladder carcinoma

Locally advanced tumours (T4b, invading the pelvic or abdominal wall) may be accompanied by several debilitating symptoms, including bleeding, pain, dysuria and urinary obstruction. These patients are candidates for palliative treatments, such as palliative radiotherapy. 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 these cases, 'palliative radical cystectomy' with urinary diversion is usually performed for symptom relief (2).

Zebic et al. (2005) (3) retrospectively analyzed 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 visible haematuria requiring blood transfusions (3). The study reported a greater risk of peri-operative morbidity and mortality in the elderly, especially those with very advanced pelvic malignancies, who had undergone palliative cystectomy.

Locally advanced MIBC can be associated with ureteral obstruction due to a combination of mechanical blockage by the tumour and invasion of ureteral orifices by tumour cells, interfering with ureteral peristalsis. Bilateral ureteral obstruction, or unilateral obstruction to a solitary functioning kidney, can result in uraemia. El-Tabey et al. retrospectively reviewed the records of patients who had presented with bladder cancer and obstructive uraemia (4). In 23 patients, radical cystectomy was not an option and obstruction was relieved using permanent nephrostomy tubes. Another 10 patients underwent palliative cystectomy, but local pelvic recurrence occurred in all 10 patients within the first year of follow-up. Another study reported post-operative outcome following primary radical cystectomy in 20 patients with T4 bladder cancer (including seven cases of T4b). The study showed that primary cystectomy for T4 bladder cancer was technically feasible and associated with a very tolerable therapy-related morbidity and mortality (5).

8.2 Conclusions and recommendations for non-resectable tumours

Conclusions
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.

Recommendations	LE	GR
In patients with inoperable locally advanced tumours (T4b), primary radical cystectomy is a palliative option and cannot be offered as curative treatment.		B
In patients with symptoms palliative cystectomy may be offered.		
Prior to any further interventions, surgery-related morbidity and quality of life should be fully discussed with the patient.	3	B

8.3 Supportive care

Severe localized problems can occur in patients with invasive, non-operable, bladder cancer and in those who have not undergone cystectomy because of metastatic disease. These problems include pain, bleeding, voiding problems and obstruction of the upper urinary tract (UUT).

*8.3.1 **Obstruction of the UUT***

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

*8.3.2 **Bleeding and pain***

In the case of bleeding, the patient must first be screened for coagulation disorders or the patient's use of anticoagulant drugs must be reviewed. Transurethral (laser) coagulation may be difficult in a bladder full of tumour or with a bleeding tumour. Intravesical rinsing of the bladder with 1% silver nitrate or 1-2% alum can be effective (6). It can usually be done without any anaesthesia. The instillation of formalin (2.5-4% during 30 minutes) is a more aggressive and more painful procedure, requiring general or regional anaesthesia. Formalin instillation has a higher risk of side-effects, e.g. bladder fibrosis, but is more likely to control the bleeding (6). Vesicoureteral reflux should be excluded to prevent renal complications.

Radiation therapy is another common strategy for control of bleeding, and is also used to control pain. An older study reported control of haematuria in 59% of patients and pain control in 73% (7). Irritative bladder and bowel complaints due to irradiation are possible, but are usually mild. Non-conservative options are embolization of specific arteries in the small pelvis, with success rates as high as 90% (6). Radical surgery is a last resort and includes cystectomy and diversion (*see above* Section 8.1).

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9. PRE-OPERATIVE RADIOTHERAPY IN MUSCLE-INVASIVE BLADDER CANCER

In contrast to the literature on pre-operative radiotherapy for MIBC, there is very little data discussing adjuvant radiotherapy after radical cystectomy. The research is outdated and mostly relevant to non-urothelial cancer. However, advances in technology, allowing more precise targeting and reducing damage to surrounding tissue, may result in this option being tried again in the future (1). A recent RCT in 100 patients, comparing pre-operative versus post-operative radiotherapy and radical cystectomy, showed comparable OS, DFS and complication rates (2). Approximately half of these patients had UC, while the other half had squamous cell carcinoma.

9.1 Pre-operative radiotherapy

*9.1.1 **Retrospective studies***

Several retrospective studies, all published many years ago in the 20th century, looked at the effect of pre-operative radiotherapy in patients with bladder cancer. Nearly all the retrospective studies of pre-operative radiotherapy at doses over 40 Gy, followed after 4-6 weeks by cystectomy, showed down-staging, improved local control, especially in T3b tumours, and an improved survival, especially in complete responders to radiotherapy (references available upon request). However, these results cannot be used as a basis for modern Guideline advice because of major study limitations, including concomitant chemotherapy, different approaches to surgery and node dissection, different forms of radiotherapy, and the age of some of the data, including some more than 50 years old. This conclusion was supported by a systemic review in 2003 (3).

However, there has been a more recent retrospective study in 2009, which compared the long-term outcome of pre-operative (n=90) versus no pre-operative (n=97) radiotherapy and cystectomy (4). 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 were limited by the small patient numbers and the retrospective nature of the study.

*9.1.2 **Randomized studies***

There have been six published randomized studies investigating pre-operative radiotherapy, although again from several decades ago. In the largest randomized trial, pre-operative radiotherapy at a dose of 45 Gy was used in patients with muscle-invasive tumours (5). There was a significant increase in pCR (9% to 34%) in favour of pre-operative radiotherapy, which was also a prognostic factor for better survival. The overall survival data was difficult to interpret because chemotherapy was used in a subset of patients and more than 50% of patients (241/475) did not receive the planned treatment and were not used for the final analyses. Two smaller studies using a dose of 20 Gy did not show a survival advantage, or only a small advantage in ≥ T3 tumours (6,7). Two other small trials confirmed down-staging after pre-operative radiotherapy (8,9).

A meta-analysis of the above five randomized trials showed an odds ratio for the difference in 5-year survival of 0.71 (95% CI: 0.48-1.06) in favour of pre-operative radiotherapy (10). However, the meta-analysis was potentially biased by the patients in the largest trial who were not given the planned treatment. When the largest trial was excluded, the odds ratio became 0.94 (95% CI: 0.57-1.55) showing that improved survival with pre-operative radiotherapy had not been proven.

A sixth RCT was not included in the meta-analysis since its methods deviated from all the other RCTs and the follow-up period was only 2 years (11).

9.2 Conclusions and recommendations for pre-operative radiotherapy

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

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

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10. BLADDER-SPARING TREATMENTS FOR LOCALIZED 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 mortality rate of up to 47% within this group (1,2).

A disease-free status at re-staging TURB appears to be crucial in making the decision not to perform radical cystectomy (3,4). A prospective study by Solsona et al. (3), which included 133 patients with a radical TURB and negative biopsies, has recently reported a 15-year follow-up (5). Patients had regular cystoscopy and biopsies and were treated additionally according to their findings. Only 6.7% were understaged during the initial TURB, 30% had recurrent NMIBC and went on to intravesical therapy, and 30% (n=40) progressed, of which 27 died of bladder cancer. After 5, 10 and 15 years, respectively, the results showed a cancer-specific survival (CSS) of 81.9%, 79.5%, and 76.7%, and a progression-free survival (PFS) with an intact bladder of 75.5%, 64.9%, and 57.8%.

TURB 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 (6). TURB 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 (7).

*10.1.1 **Recommendation for TURB***

Recommendation	LE	GR
Transurethral resection of bladder tumour (TURB) 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 (EBRT)

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 minimize 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 MIBC range between 30% and 60%, depending on whether they show a complete response (CR) following radiotherapy. Cancer-specific survival rates are between 20% and 50% (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 in a multivariate survival analysis to be:

- age;
- T category (for all end points);
- tumour dose (only for failure-free survival) (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).

Similar long-term results were reported by Chung et al. (18). A total of 340 patients with MIBC were treated with EBRT alone, EBRT with concurrent chemotherapy, or neoadjuvant chemotherapy followed by EBRT. The overall CR was 55% and the 10-year DSS and OS were 35% and 19%, respectively. Complete response was 64% after EBRT alone, 79% after concurrent chemotherapy (n=36), and 52% after neoadjuvant chemotherapy (n=57), although in this last group most patients had T3 and T4 tumours. Younger age, lower tumour stage and absence of CIS were associated with a significant improvement in survival. For example, in the T2 group, the 5-year OS was 44% and DSS was 58%. A relapse within 2 to 3 years was a bad prognostic sign. The authors concluded that EBRT monotherapy was an option only in highly selected patients.

*10.2.1 **Conclusions and recommendation for external beam radiotherapy***

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

Recommendation	GR
Surgical intervention or multimodality treatment are the preferred curative therapeutic approaches because they are more effective than radiotherapy alone.	B

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10.3 Chemotherapy

Chemotherapy alone rarely produces durable CRs. In general, a clinical CR rate of up to 56%, as reported in some series, must be weighed against a staging error of > 60% (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 methotrexate, vinblastine, adriamycin plus cisplatin (MVAC) or cisplatin, methotrexate plus vinblastine (CMV) has led to a down-staging of the primary tumour in different prospective series (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 imminent 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 TURB 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 muscle-invasive bladder tumours***

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

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

*10.3.2 **References***

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10.4 Multimodality bladder-preserving treatment

Recent organ-preservation strategies combine TURB, chemotherapy and radiation (1,2). The rationale for performing TURB and radiation is to achieve local tumour control. Application of systemic chemotherapy, most commonly as methotrexate, cisplatin and vinblastine (MCV), aims at the eradication of micrometastasis. Many protocols use cisplatin and/or 5-FU and, recently, gemcitabine with radiation, because of their established role as radiosensitizers. Cisplatin-based chemotherapy in combination with radiotherapy, following TURB, results in a CR of 60-80%.

In a small, phase 1-2 study the value of gemcitabine in multimodality treatment was emphasised, with a 5- year OS of 70.1% and DSS of 78.9% (3).

Another study with a mean follow-up of 42 months compared TURB + radiochemotherapy (n=331) with TURB + radiotherapy (n=142) (4). The overall CR was high (70.4%). However, the radiochemotherapy group had a clear survival advantage (median survival 70 months) compared to the radiotherapy group (median survival 28.5 months). Long-term results were dependent on stage, lymphatic invasion (LVI), residual tumour status and initial response at re-staging TURB.

The importance of the radicalism of the initial TURB was also confirmed in a Japanese study with 82 patients treated with TURB and chemoradiotherapy (5). The initial pCR rate was relatively low (39%) in the absence of a radical initial TURB. Still, clinical CR (84%) and survival data were high (5-year OS 77.7%; 5 year PFS 64.5%), although this included salvage treatment. Primary cT2 patients showed a significant improvement in survival compared to cT3-4 and recurrent cases.

Several smaller series have confirmed the potential of multimodality protocols (6-9). Five-year OS rates of about 70% were reported. However, protocols and patient selection differed for each study. Recurring patients and patients with tumours progressing from NMIBC to MIBC usually did badly. Low stage and complete TURB remain important prognostic variables. It is recommended that early cystectomy should be performed in individuals who have not achieved a CR following combination therapy. About 40-45% of these

patients may survive with an intact bladder at 4-5 years (2).

A comparable long-term survival rate of 50-60% at 5-year follow-up is reported by both multimodality bladder-preserving trials and cystectomy series. However, these therapeutic approaches have never been directly compared and patients in multimodality series are highly selected (2,10-12).

A bladder-preserving multimodality strategy requires very close multidisciplinary co-operation and a high level of patient compliance. Even if a patient has shown a CR to a multimodality bladder-preserving strategy, the bladder remains a potential source of recurrence. About half of all patients can be expected to survive with their native bladder intact. A T0 status at repeat TURB after the initial transurethral resection of the primary tumour, followed by chemotherapy in combination with radiotherapy, has been identified as a prognostically important variable. However, patients with this status still remain at life-long risk of developing intravesical tumour recurrences and require meticulous surveillance and multiple invasive procedures. It has been postulated that a delay in radical cystectomy due to an initial bladder-preserving approach increases the risk of lymph node metastases to a lymph node-positive rate of 26%, so that cystectomy becomes necessary due to treatment failure.

*10.4.1 **Conclusions and recommendations for multimodality treatment in MIBC***

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

Recommendations	**GR**
Transurethral resection of bladder tumour alone cannot be offered as a standard curative treatment option in most patients.	B
Radiotherapy alone is less effective than surgery and is only recommended as a therapeutic option when the patient is unfit for cystectomy or a multimodality bladder-preserving approach.	B
Chemotherapy alone is not recommended as primary therapy for MIBC.	A
Surgical intervention or multimodality treatments are the preferred curative therapeutic approaches as they are more effective than radiotherapy alone.	B
Multimodality treatment could be offered as an alternative in selected, well-informed, well-selected and compliant patients, especially for whom cystectomy is not an option.	B

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11. ADJUVANT CHEMOTHERAPY

Adjuvant chemotherapy after radical cystectomy for patients with pT3/4 and/or lymph node positive (N+) disease without clinically detectable metastases (M0) is under debate (1,2) and still infrequently used (3).

The general benefits of adjuvant chemotherapy include:
- Chemotherapy is administered after accurate pathological staging, therefore treatment in patients at low risk for micrometastases is avoided.
- No delay in definitive surgical treatment.

The drawbacks of adjuvant chemotherapy are:
- Assessment of *in vivo* chemosensitivity of the tumour is not possible and overtreatment is an unavoidable problem.
- Delay or intolerability of chemotherapy, due to postoperative morbidity (4).

There is limited evidence from adequately conducted and accrued randomized phase III trials in favour of the routine use of adjuvant chemotherapy (2,5-10). Individual patient data from six randomised trials (11-15) of adjuvant chemotherapy were included in one meta-analysis (5) with 491 patients for survival analysis (unpublished data from Otto et al, were included in the analysis). All these trials were suboptimal with serious deficiencies, including small sample size (underpowered), early cessation of patient entry, and flaws in design and statistical analysis, including irrelevant endpoints or a lack of recommendations concerning salvage chemotherapy for relapse or metastases (2). In these trials, three or four cycles of CMV (cisplatin, methotrexate and vinblastine), CISCA (cisplatin, cyclophosphamide, and adriamycin), MVA(E)C (methotrexate, vinblastine, adriamycin or epirubicin, and cisplatin) and CM (cisplatin and methotrexate) were used (16), and one trial (14) used cisplatin monotherapy. These data were not convincing enough to give an unequivocal recommendation for the use of adjuvant chemotherapy.

In a more recent meta-analysis (6), an additional three studies were included (7-9). However, the patient number in this meta-analysis of nine trials was only 945, and none of the trials were fully accrued and no individual patient data were used (6). For one trial, only an abstract was available at the time of the meta-analysis (8), and none of the included trials by themselves were significantly positive for overall survival (OS) in favour of adjuvant chemotherapy. In two of the trials, more modern chemotherapy regimens were used (gemcitabine/cisplatin and paclitaxel/gemcitabine cisplatin) (7,8). The hazard ratio (HR) for OS was 0.77 and there was a

trend towards an OS benefit when including all nine trials. The effect was stronger for disease-free survival (DFS) (HR: 0.66; 95% CI: 0.48-0.92) and when stratified for the ratio of nodal positivity (HR: 0.64; 95% CI: 0.45-0.91). The background of this finding was a heterogeneity in outcomes observed between the included studies. After stratification of the studies by the ratio of node positivity, no further heterogeneity was identified. The HR for DFS associated with adjuvant cisplatin-based chemotherapy in studies with higher nodal involvement was 0.39 (95% CI: 0.28-0.54), compared with 0.89 (95% CI: 0.69-1.15) in studies with less nodal involvement.

Furthermore, a retrospective cohort analysis that included 3,974 patients after cystectomy and lymph node dissection showed an OS benefit in high-risk subgroups (extravesical extension and nodal involvement) (17).

From the currently available evidence, it is still unclear whether immediate adjuvant chemotherapy or chemotherapy at the time of relapse is superior, or if the two approaches are equivalent with respect to the endpoint of OS. Cisplatin-based combination chemotherapy results in long-term DFS, even in metastatic disease, mainly in patients with lymph node metastases only, and with a good performance status (18-20). With the most recent meta-analysis, the positive role of adjuvant chemotherapy for bladder cancer has been strengthened, however, still with a poor level of evidence (6). In patients who are eligible for cisplatin combination chemotherapy, adjuvant chemotherapy is a reasonable option. The patients should be informed about potential chemotherapy options before radical cystectomy, including neoadjuvant and adjuvant chemotherapy, and the limited evidence for adjuvant chemotherapy.

11.1 Conclusion and recommendations for adjuvant chemotherapy

Conclusion	LE
Neither randomised trials nor two meta-analyses have provided sufficient data to support the routine use of adjuvant chemotherapy.	1a

Recommendations	GR
Adjuvant chemotherapy should only be given within clinical trials, whenever possible.	A
Adjuvant cisplatin based combination chemotherapy may be offered to patients with pN+ disease if no neoadjuvant chemotherapy has been given.	C

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12. METASTATIC DISEASE

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

12.1 Prognostic factors and treatment decisions

Outcome of chemotherapy depends on patient-related factors and pretreatment disease. Prognostic factors for response and survival have been established. In a multivariate analysis, Karnofsky performance status (PS) of ≤ 80% and presence of visceral metastases were independent prognostic factors of poor survival after treatment with MVAC (methotrexate, vinblastine, adriamycin and cisplatin). These so-called Bajorin prognostic factors (3) have also been validated for newer combination chemotherapy regimens (4,5) and carboplatin combinations (6). These prognostic factors are crucial for assessing phase II study results and stratifying phase III trials (7,8).

For patients refractory to or progressing shortly after platinum-based combination chemotherapy, four prognostic groups have been established, based on three adverse factors that have been developed in patients treated with vinflunine and that have been validated in an independent data set: Hb < 10 g/dL; presence of liver metastases; and ECOG PS ≥ 1 (9).

*12.1.1 **Comorbidity in metastatic disease***

Comorbidity is defined as “the presence of one or more disease(s) in addition to an index disease” (see Chapter 7). Comorbidity increases with age. However, chronological age does not necessarily correlate with functional impairment. There are several definitions by which patients can be selected as potentially fit or unfit for chemotherapy, but age is not among them (10).

*12.1.2 **Not eligible for cisplatin (unfit)***

The European Organisation for Research and Treatment of Cancer (EORTC) conducted the first randomised phase II/III trial for urothelial carcinoma patients who were unfit for cisplatin chemotherapy (11). The EORTC definitions were:

- fit: GFR ≥ 60 mL/min and PS 0 or 1
- unfit: GFR < 60 mL/min and/or PS 2.

A recent international survey among bladder cancer experts (12) was the basis for a consensus statement on how to classify patients unfit for cisplatin-based chemotherapy. At least one of the following criteria has to be present: PS > 1; GFR < 60 mL/min; grade ≥ 2 audiometric loss and peripheral neuropathy; and New York Heart Association (NYHA) class III heart failure (13).
More than 50% of patients with urothelial cancer are not eligible for cisplatin-based chemotherapy (14-17).

Renal function assessment is of utmost importance in patients with urothelial cancer. Calculation of creatinine clearance (CrCl) (24-h urine collection) with current formulae tends to underestimate clearance in patients aged > 65 years compared to measured CrCl (14,18).

12.2 Single-agent chemotherapy

Response rates to single-agent, first-line chemotherapy have varied. The most robust data have shown a response rate of about 25% for first- and second-line gemcitabine in several phase II trials (19,20). 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 6-9 months. Patients with WHO PS 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 (BSC) 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 (for a review see [21]). MVAC and gemcitabine/cisplatin (GC) prolonged survival to up to 14.8 and 13.8 months, respectively, compared to monotherapy and older combinations. Neither of the two combinations is superior to the other, but equivalence has not been tested. Response rates were 46% and 49% for MVAC and GC, respectively. The long-term survival results have confirmed the anticipated equivalence of the two regimens (22). The major difference between the above-mentioned combinations is toxicity. The lower toxicity of GC (23) has resulted in it becoming a new standard regimen (24). MVAC is better tolerated when combined with granulocyte colony-stimulating factor (G-CSF) (24,25).

High-dose intensity MVAC (HD-MVAC) with G-CSF is less toxic and more efficacious than standard MVAC in terms of dose density, complete response, and 2-year survival rate. However, there is no significant difference in median survival between the two regimens (26,27).

In general, all disease sites have been shown to respond to cisplatin-based combination chemotherapy, but

responses 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 (26). The disease sites also have an impact on long-term survival. In lymph-node-only disease, 20.9% of patients were alive at 5 years compared to only 6.8% of patients with visceral metastases (22).

Further intensification of treatment using the new PCG triple regimen (paclitaxel, cisplatin and gemcitabine) did not result in a significant improvement in OS in the intent-to-treat (ITT) population of a large randomised phase III trial, comparing PCG triple regimen to GC (28). However, the overall response rate (ORR) was higher with the triple regimen (56% vs. 44%; P = 0.0031), and the trend for OS improvement in the ITT population (15.8 vs. 12.7 months; HR = 0.85, P = 0.075) became significant in the eligible population. Adding paclitaxel to GC did not induce major additional side effects. G4 neutropenia was more common (35.8% vs. 20% for GC), as was febrile neutropenia (13.2% vs. 4.3%), and the need for G-CSF was higher (17% vs. 11%). GC alone caused more grade 4 thrombocytopenia and thrombocytopenia-induced bleeding (11.4% vs. 6.8%). PCG is one additional option for first-line treatment of UC.

12.4 Carboplatin-containing chemotherapy in fit patients

Carboplatin-containing chemotherapy is not equivalent to cisplatin combinations, and should not be considered interchangeable or standard. Several randomised phase II trials of carboplatin versus cisplatin combination chemotherapy have produced lower CR rates and shorter OS for the carboplatin arms (29).

12.5 Non-platinum combination chemotherapy

Different combinations of gemcitabine and paclitaxel have been studied as first- and second-line treatments. Apart from severe pulmonary toxicity with a weekly schedule of both drugs, this combination is well tolerated and produces response rates between 38% and 60% in both lines. Non-platinum combination chemotherapy has not been compared to standard cisplatin chemotherapy in randomised trials, therefore, it is not recommended for first-line use in cisplatin eligible patients (30-37).

12.6 Chemotherapy in patients unfit for cisplatin

Up to 50% of patients are ineligible for cisplatin-containing chemotherapy (13). The first randomised phase II/III trial in this setting was conducted by EORTC and compared methotrexate/carboplatin/vinblastine (M-CAVI) and carboplatin/gemcitabine (GemCarbo) in patients unfit for cisplatin. Both regimens were active. Severe acute toxicity (SAT) was 13.6% in patients treated with GemCarbo versus 23% with M-CAVI, while the ORR was 42% for GemCarbo and 30% for M-CAVI. Further analysis showed that in patients with PS 2 and impaired renal function, combination chemotherapy provided limited benefit (11). The ORR and SAT were both 26% for the former group, and 20% and 24%, respectively, for the latter group (11). Recent phase III data have confirmed these results (6).

12.7 Second-line treatment

Second-line chemotherapy data are highly variable and prognostic factors have been established recently (see 12.1, [9]). A reasonable strategy may be to re-challenge former cisplatin-sensitive patients if progression occurs at least 6-12 months after first-line cisplatin-based combination chemotherapy.

Second-line response rates of paclitaxel (weekly), docetaxel, nab-paclitaxel (38) oxaliplatin, ifosfamide, topotecan, pemetrexed, lapatinib, gefitinib and bortezomib have ranged between 0% and 28% in small phase II trials (20). Although gemcitabine has also shown excellent response rates in second-line use, most patients already receive this drug as part of their front-line treatment (19).

Paclitaxel/gemcitabine have shown response rates of 38-60%, depending on patient selection. No randomised phase III trial with an adequate comparator arm has been conducted to assess the true value and OS benefit of this second-line combination (2,36,39).

Vinflunine, a novel third-generation vinca alkaloid, has shown objective response rates of 18% and disease control in 67% of patients (40). A recent randomised phase III trial has compared vinflunine plus BSC against BSC alone in patients progressing after first-line treatment with platinum-containing combination chemotherapy for metastatic disease (41). The results showed a modest ORR (8.6%), a clinical benefit with a favourable safety profile and, most importantly, a survival benefit in favour of vinflunine, which was statistically significant in the eligible patient population (not in the ITT population). For second-line treatment of advanced or metastatic urothelial cancer, this trial reached the highest level of evidence ever reported. Currently, vinflunine is the only approved second-line treatment; 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 but no other metastases, good PS, and adequate renal function, including a high number of CRs, with up to 20% of patients achieving long-term disease-free survival (22,27,42,43). Stage migration may play a role in this positive prognostic development. A retrospective study of post-chemotherapy surgery after a partial or complete response has indicated that surgery may contribute to long-term disease-free survival in selected patients (44-46).

12.9 Treatment of bone metastases

The prevalence of metastatic bone disease (MBD) in patients with advanced/metastatic urothelial cancer is 30-40% (47). Skeletal complications due to MBD have a detrimental effect on pain and QoL and are also associated with increased mortality (48). Bisphosphonates reduce and delay skeletal-related events (SREs) due to bone metastases by inhibiting bone resorption. In a small pilot study in patients with bladder cancer, SREs caused by bone metastases were delayed (49). Denosumab is a fully human monoclonal antibody that binds to and neutralises RANKL (receptor activator of nuclear factor-$_{K}$B ligand), thereby inhibiting osteoclast function and preventing generalised bone resorption and local bone destruction. Denosumab is not inferior to zoledronic acid (ZA) in preventing or delaying SREs in patients with advanced MBD, including patients with urothelial carcinoma (50). Denosumab has recently been approved by the European Medicines Agency (EMA) for treatment of patients with bone metastases from solid tumours. Patients with MBD, irrespective of the cancer type, should be considered for bone-targeted treatment (48).

Patients treated with ZA or denosumab should be informed about possible side effects and receive prophylactic treatment for jaw osteonecrosis and hypocalcaemia, which is more common with denosumab. Aggressive calcium and vitamin D supplementation is recommended. Dosing regimens of ZA should follow regulatory recommendations and should be adjusted according to pre-existing medical conditions (51). For denosumab, no dose adjustments are required for variations in renal function.

12.10 Conclusions and recommendations for metastatic disease

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

Recommendations	GR
First-line treatment for fit patients:	
Use cisplatin-containing combination chemotherapy with GC, PCG, MVAC, preferably with G-CSF, or HD-MVAC with G-CSF.	A
Carboplatin and non-platinum combination chemotherapy is not recommended.	B
First-line treatment in patients ineligible (unfit) for cisplatin:	
Use carboplatin combination chemotherapy or single agents.	C

For cisplatin-ineligible (unfit) patients, with PS2 or impaired renal function, as well as those with 0 or 1 poor Bajorin prognostic factors and impaired renal function, treatment with carboplatin-containing combination chemotherapy, preferably with gemcitabine/carboplatin is indicated.	A
Second-line treatment:	
In patients progressing after platinum-based combination chemotherapy for metastatic disease, vinflunine should be offered. Alternatively, treatment within a clinical trial setting may be offered.	A*
Zoledronic acid or denosumab is recommended for treatment of bone metastases.	B

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

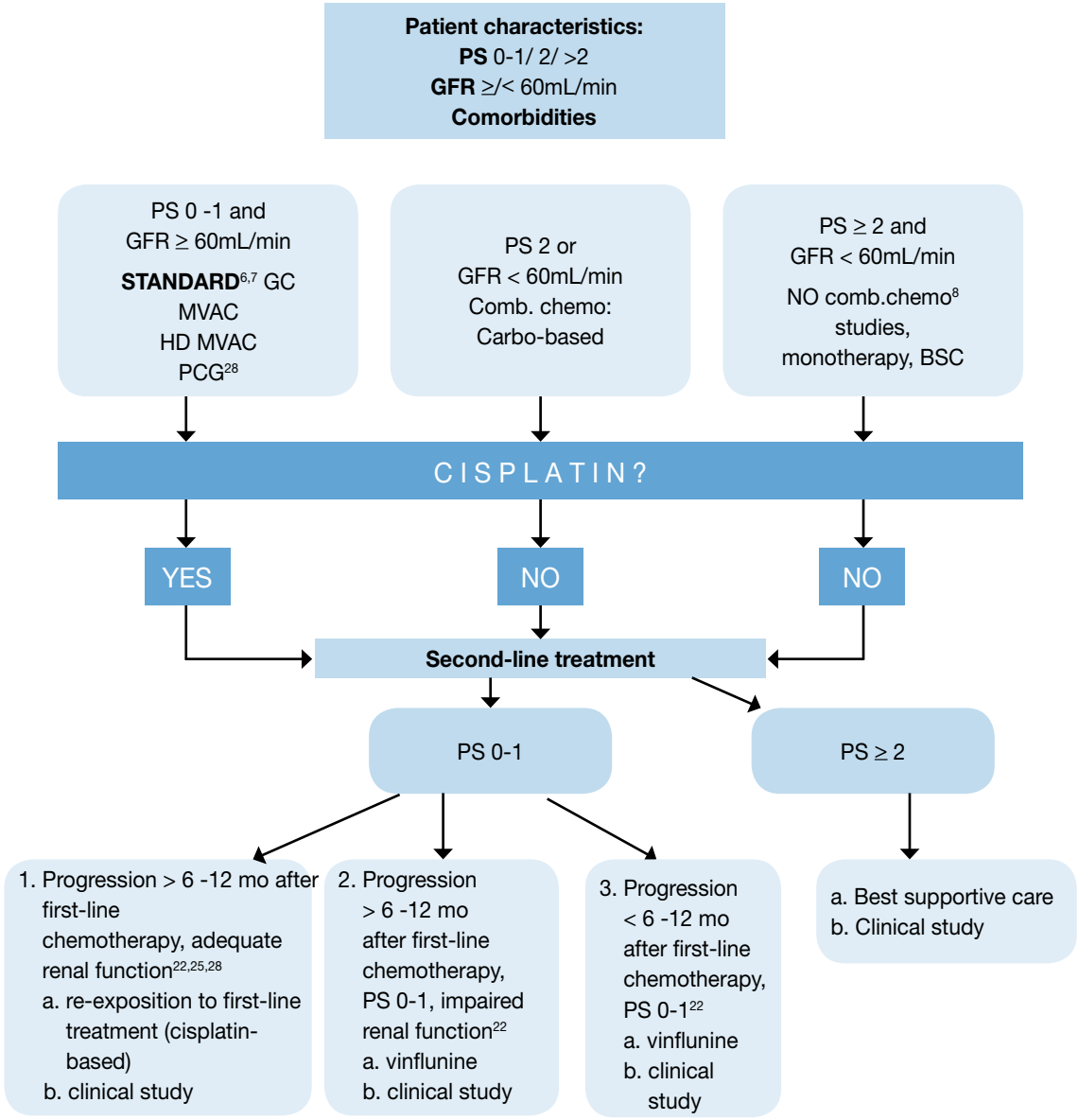
12.11 Biomarkers

Modest disease control rates, with sporadic marked responses, in some patients with urothelial bladder cancer have led to the investigation of biomarkers for assessment of postoperative prognosis and the potential value of perioperative chemotherapy, and as predictors of response to chemotherapy or its monitoring. Most of the biomarkers are associated with tumour angiogenesis. Small studies, usually retrospective, have investigated microvessel density, altered p53 tumour expression (52), serum vascular endothelial growth factor (53), urinary and tissue basic fibroblast growth factor (54), urinary (wild-type and mutant) and tissue fibroblast growth factor receptor-3 (55), and more recently, thrombospondin-1 (56), circulating tumour cells (57,58), and multidrug resistance gene expression (59). Although a few biomarkers have shown potential, none has sufficient evidence to support its routine clinical use (LE: 3).

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

**Upgraded following panel consensus.*

Figure 2: Flowchart for the management of metastatic urothelial cancer



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

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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) and recently the BCI questionnaire specifically designed and validated for bladder cancer patients (6).

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 (7).

Unfortunately, most retrospective studies do not evaluate the association between HRQoL and bladder cancer-specific issues after cystectomy, such as day-time and night-time incontinence or potency. Furthermore, important co-variables, such as a patient's age, mental status, coping ability and gender, have rarely been considered (8,9). 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 (10). Some studies have not demonstrated any difference in HRQoL (9,11,12). Nevertheless, most patients stated that, given a choice, they would still opt for an orthotopic diversion rather than an ileal conduit (13). Another study reported that, although urinary function is better in conduit patients, the urinary bother is the same in both diversion groups, resulting in the same HRQoL evaluation (14).

Due to improved surgical techniques in orthotopic bladder substitution, some recent studies are supportive of continent bladder substitutes (3,15-18). Two studies have shown a statistically significant difference in HRQoL in favour of neobladders (18,19). 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 (20). Patients with a continent bladder-substitute generally scored more favourably than those with an incontinent diversion, as judged by

body image, social activity and physical function (14,15,21).

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 (22). There is limited literature describing HRQoL in bladder cancer patients receiving palliative care (23), but there are reports of bladder-related symptoms relieved by palliative surgery (24), radiotherapy (25), and/or chemotherapy (26).

Alternative definitive treatments of MIBC, e.g. trimodality bladder-sparing procedures, have shown similar survival times compared to cystectomy. However, the impact on HRQoL has been controversial (26-32).

13.4 Conclusions and recommendations for HRQoL

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

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

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

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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 and site of recurrence;
- functional monitoring after urinary diversion;
- 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).

Surveillance protocols are commonly based on patterns of recurrence observed from retrospective series. The diagnosis of asymptomatic recurrence based on routine oncologic follow-up has been discussed and results from retrospective series are controversial (5,6). Importantly, these retrospective series use different follow-up regimens and different follow-up imaging techniques which made the final analysis and elaboration of conclusive recommendations difficult. Prospective trials demonstrating the effectiveness of follow-up after RC and, more importantly, its impact on overall survival, are lacking (7).

14.1 Site of recurrence

*14.1.1 **Local recurrence***

Local recurrence can be considered a recurrence in soft tissues at the original surgical site or lymph nodes in the area of the LND. Lymph node involvement above the aortic bifurcation can be considered metastatic recurrence (5).

Contemporary cystectomy series have demonstrated 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. Pathological stage and lymph node status were predictive of the development of pelvic recurrence, as well as positive margins, the extent of LND and the use of perioperative chemotherapy (8).

Patients have a poor prognosis after pelvic recurrence. Even with treatment, the 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 (7).

14.1.2 ***Distant recurrences***

Distant recurrences are seen in up to 50% of patients treated with cystectomy. Again, pTN and pN were risk factors (9). Systemic recurrence is more common in locally advanced disease (pT3-pT4) ranging 32-62% and in patients with lymph node involvement (range 52-70%) (10).

The most likely sites for distant recurrences are lymph nodes, lungs, liver and bones (11). Near 90% of distant recurrences will appear in the first 3 years after RC and mainly in the first 24 months, although late recurrences have been described after more than 10 years. Median survival of patients with progressive disease treated with platinum-based chemotherapy ranges between 9-26 months (12-14).

Despite periodic monitoring, more than half of the metastases are diagnosed after the appearance of symptoms.

The value of monitoring in the diagnosis of asymptomatic metastases and its impact on survival is highly questionable. There are series that do not demonstrate any impact on survival in spite of using protocols for routine monitoring, although others argue that the diagnosis of asymptomatic metastases, especially lung metastases, slightly improves patient survival (5,6). In this respect we must also consider the possibility of longer survival in patients with minimal metastatic disease undergoing multimodal treatment, including metastasectomy. There have been reported survival rates of 28-33% at 5 years in patients undergoing resection of metastases after objective response to chemotherapy (15,16).

14.1.3 ***Post-cystectomy urothelial tumour recurrences***

The incidence of new urethral tumours after radical cystectomy is 1.5-6.0% in males, with a mean recurrence-free interval of 13.5-39.0 months and a median survival of 28-38 months, of which > 50% died because of systemic disease.

Secondary urethral tumours are particularly likely to occur at 1-3 years after surgery. Prophylactic urethrectomy at the time of cystectomy is no longer justified in most patients. Independent predictors for urethral recurrence are: cystectomy for NMIBC, prostate involvement, and a history of previously recurrent NMIBC (7).

In women, the main risk factor is disease at the bladder neck (17). Many studies have demonstrated that the risk of urethral recurrence after orthotopic diversion (0.9-4.0%) (18-21) is significantly less than after non-orthotopic diversion (6.4-11.1%) (18,20).

There is little data and agreement about urethral follow-up, with some authors recommending routine surveillance with urethral wash cytology and urine cytology (21), and others doubting the need for routine urethral surveillance (19,22-24). Urethral washes and urine cytology do not appear to have any effect on survival (22,25,26). However, there is a significant survival advantage in males with urethral recurrence diagnosed asymptomatically versus symptomatically, so follow-up of the male urethra is indicated in those patients at risk of urethral recurrence (7).

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% (21).
- In invasive disease, urethrectomy should be performed if the urethra is the only site of disease.
- In distant disease, systemic chemotherapy is indicated (11).

Upper urinary tract tumours (UTUC) occur in 1.8-6.0% of cases in contemporary series and represent the most common sites of late recurrence (3 years of disease-free survival following radical cystectomy). The median OS is 10-55 months, and 60-67% of patients will die of metastatic disease (7).

A recent meta-analysis found that 38% of UTUC recurrences were diagnosed by follow-up investigation, whereas in the remaining 62% diagnosis was based on symptoms. When urine cytology was used in surveillance, the rate of primary detection was 7% and with UUT imaging it was 29.6% (27). This meta-analysis concluded that patients with non-invasive cancer are twice as likely to have a UTUC lesion as patients with invasive disease; multifocality increases the risk of recurrence by 3-fold while positive ureteral or urethral margins increase the recurrence risk by 7-fold. Radical nephro-ureterectomy can provide prolonged survival (28).

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

Site of recurrence	Conclusion	LE	Recommendation	GR
Local recurrence	Poor prognosis			
	Treatment should be individualized depending on the local extent of tumour	2b	Radiotherapy, chemotherapy and possibly surgery are options for treatment, either alone or in combination	C
Distant recurrence	Poor prognosis	2b	Chemotherapy is the first option, and consider individualized cases for metastatectomy in case of unique metastasis site	C
Upper urinary tract recurrences			See EAU guidelines on Upper Urinary Tract Carcinomas (29)	
Secondary urethral tumour	Staging and treatment should be done as for primary urethral tumour	3	Local conservative treatment is possible for non-invasive tumour	C
			In isolated invasive disease, urethrectomy should be performed	B
			Urethral washes and cytology are not recommended	A

Although general recommendations cannot be advised, based on high level of evidence a closer follow-up could be considered in patients with locally advanced disease or lymph node involvement. The suggested follow-up includes 4-monthly CT scans during the first year, six-monthly until the third year and after this period monitoring by annual imaging.

14.1.5 ***Follow-up of functional outcomes and complications***

Apart from the oncologic surveillance, patients submitted to urinary diversion deserve functional follow-up. Urinary-diversion related complications are detected in 45% of patients during the first 5 years of follow-up. This rate increases with time being more than 54% after 15 years of follow-up. Long-term follow-up of functional outcomes are desirable (7) (LE: 3). Follow-up may stop after 15 years.

The functional complications are diverse and include: vitamin b12 deficiency, metabolic acidosis, worsening of renal function, urinary infections, urolithiasis, stenosis of uretero-intestinal anastomosis, stoma complications in patients with ileal conduit and in patients with neobladder continence problems and emptying dysfunctions (7).

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15. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

ACE	Adult Comorbidity Evaluation Index
AJCC	American Joint Committee on Cancer
5-ALA	5-aminolevulinic acid
ASA (score)	American Society of Anesthesiologists
BC	bladder cancer
BCG	Bacillus Calmettte-Guérin
BSC	best supportive care
BT	brachytherapy
CCI	Charlson Comorbidity Index
CGA	comprehensive geriatric assessment
CI	confidence interval
CISCA	cisplatin, cyclophosphamide, and adriamycin
CIRS	Cumulative Illness Rating Scale
CIS	carcinoma *in situ*
CM	cisplatin, methotrexate
CMV	cytomegalovirus
cNO	clinically negative nodes
CR	complete response
CrCl	calculation of creatinine clearance
CSS	cancer-specific survival
CT	computed tomography
DCE	dynamic contract enhanced
DSS	disease-specific survival
DWI	diffusion-weighted imaging
ECOG	Eastern Cooperative Oncology Group
EAU	European Association of Urology
EBRT	external-beam radiotherapy
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
ESUR	European Society of Urogenital Radiology
FACT	Functional Assessment of Cancer Therapy
FDG-PET/CT	fluorodeoxyglucose-positron emission computed tomography
G-CSF	granulocyte colony stimulating factor
GC	gemcitabine, cisplatin
GFR	glomular filtration rate
GR	grade of recommendation
GWAS	genome-wide association studies
HAL	hexaminolaevulinate
HD-MVAC	high-dose intensity MVAC
HRQoL	health-related quality of life
IARC	International Agency for Research on Cancer
ICD	Index of Coexistent Disease
IMRT	intensity-modulated radiotherapy
ISUP	International Society of Urological Pathology
ITT	intent-to-treat
IVU	intravenous urography
LE	level of evidence
LND	lymph node dissection
M-CAVI	compared methotrexate/carboplatin/vinblastine
MCV	methotrexate, cisplatin and vinblastine
MBD	metastatic bone disease
MD CT	multidetector computed tomography
MDCTU	multidetector computed tomography urography
MESNA	mercapto-ethanesulfonate
MIBC	muscle-invasive bladder cancer
MRI	magnetic resonance imaging
mUUT	metachronous upper urinary tract

MVA	methotrexate, vinblastine, adriamycin
MVAC	methotrexate, vinblastine, adriamycine and cisplatin
NCI	National Cancer Institute
NMIBC	non-muscle-invasive bladder cancer
NSF	nephrogenic systemic fibrosis
NYHA	New York Heart Association Functional Classification
ORR	overall response rate
OS	overall survival
PCR	pathological complete remission
PET	positron emission tomography
PET/CT	positron emission tomography, computed tomography
PFS	progression-free survival
PS	performance status
PUNLMP	papillary urothelial neoplasm of low malignant potential
QoL	quality-of-life
RALC	robotic-assisted laparoscopic cystectomy
RANKL	receptor activator of nuclear factor-$_{\kappa}$B ligand
RC	radical cystectomy
RCT	randomized controlled trial
RP	radical prostatectomy
SAT	severe acute toxicity
SEER	Surveillance, Epidemiology and End Results database
SES	socioeconomic status
SGA	standardized geriatric assessment
SREs	skeletal-related events
SWOG	Southwest Oncology Group
TFA	transfatty acid
TIBI	Total Illness Burden Index
TNM	Tumour, Node, Metastasis (classification)
TUR	transurethral resection
TURB	transurethral resection of bladder tumour
UC	urothelial carcinoma
US	ultrasound
UTI	urinary tract infection
UTUC	upper tract urothelial carcinoma
UUT	upper urinary tract
WHO	World Health Organisation
ZA	zoledronic acid

Conflict of interest
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