

EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer

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1. INTRODUCTION

1.1 Aims and scope

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

Separate EAU guidelines documents are available addressing upper urinary tract tumours [1], non-muscle-invasive bladder cancer (TaT1 and carcinoma *in situ*) [2], and primary urethral carcinomas [3].

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel Composition

The EAU Guidelines Panel consists of an international multidisciplinary group of clinicians, including urologists, a pathologist, a radiologist and an oncologist.

All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website Uroweb: <http://uroweb.org/guideline/bladder-cancermuscle-invasive-and-metastatic/?type=panel>.

1.3 Available publications

A quick reference document (Pocket Guidelines) is available, both in print and in a number of versions for mobile devices. These are abridged versions which may require consultation together with the full text version.

Several scientific publications are available (the most recent paper dating back to 2016 [4]), as are a number of translations of all versions of the EAU MIBC Guidelines. All documents are accessible through the EAU website: <http://uroweb.org/guideline/bladder-cancer-muscle-invasive-and-metastatic/>.

1.4 Publication history and summary of changes

1.4.1 Publication history

The EAU published its first guidelines on bladder cancer in 2000. This document covered both superficial (non-muscle-invasive) bladder cancer and MIBC. Since these conditions require different treatment strategies, it was decided to give each condition its own guidelines, resulting in the first publication of the MIBC Guidelines in 2004. This 2017 document presents a limited update of the 2016 version.

1.4.2 Summary of changes

New relevant references have been identified through a structured assessment of the literature and incorporated in the various chapters of the 2017 EAU NMIBC Guidelines.

Key changes in the 2017 print are:

- Section 3.2.6 Gender - This section has been expanded with additional data.
- Section 5.1.4 Urinary cytology and urinary markers - This section has been expanded with additional data.
- Section 6.2.4 Prognostic markers - A new section has been included.
- Section 7.4.4.1 Preparations for surgery - A new section on pain management has been included as well as additional data on estimated glomerular filtration rate.
- Section 7.4.4.2.1 Ureterocutaneostomy - This section has been expanded with additional data.
- Table 7.6 Management of neobladder morbidity - Additional information has been added.
- Section 7.8.10 Role of immunotherapy - This is a new section.

1.4.2.1 Change in summary of evidence

7.8.11 Summary of evidence and recommendations for metastatic disease

7.8.11 Summary of evidence for metastatic disease	LE
PD-L1 inhibitor atezolizumab has been FDA approved for patients that have progressed during or after previous platinum-based chemotherapy based on the results of a phase-II trial.	2a

2. METHODS

2.1 Data identification

For the 2017 MIBC Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature.

A broad and comprehensive literature search, covering all sections of the MIBC Guideline was performed. The search was limited to English language publications. Databases searched included Medline, EMBASE and the Cochrane Libraries, covering a time frame between July 1st 2015 and April 5th 2016. A total of 2,298 unique records were identified, retrieved and screened for relevance. A detailed search strategy is available online: <http://uroweb.org/guideline/bladder-cancer-muscle-invasive-andmetastatic/?type=appendices-publications>.

References used in this text are assessed according to their level of evidence (LE) and Guidelines are given a grade of recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [5]. Additional methodology information can be found in the general Methodology section of this print, and online at the EAU website: <http://uroweb.org/guidelines/>.

A list of Associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

No separate peer-review was done for the 2017 print of the MIBC Guidelines.

2.3 Future goals

Topics considered for inclusion in the 2018 update of the MIBC Guidelines:

- Diagnostics - haematuria

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Bladder cancer (BC) is the 7th most commonly diagnosed cancer in the male population worldwide, whilst it drops to 11th when both genders are considered [6]. The worldwide age-standardised incidence rate (per 100,000 person/years) is 9.0 for men and 2.2 for women [6]. In the European Union, the age-standardised incidence rate is 19.1 for men and 4.0 for women [6, 7]. In Europe, the highest age-standardised incidence rate has been reported in Belgium (31 in men and 6.2 in women) and the lowest in Finland (18.1 in men and 4.3 in women) [6, 7].

Worldwide, the BC age-standardised mortality rate (per 100,000 person/years) was 3.2 for men vs. 0.9 for women in 2012 [6, 7]. Bladder cancer incidence and mortality rates vary across countries due to differences in risk factors, detection and diagnostic practices, and availability of treatments. The variations are, however, also partly caused by the different methodologies used in the studies and the quality of data collection [8, 9].

The incidence and mortality of BC has decreased in some registries, possibly reflecting the decreased impact of causative agents [9, 10].

Approximately 75% of patients with BC present with a disease confined to the mucosa (stage Ta, carcinoma *in situ* [CIS]) or submucosa (stage T1). In younger patients (< 40) this percentage is even higher [11]. Patients with TaT1 and CIS have a high prevalence due to long-term survival in many cases and lower risk of cancer-specific mortality compared to T2-4 tumours [7, 8, 12].

3.2 Aetiology

3.2.1 Tobacco smoking

Tobacco smoking is the most well-established risk factor for BC, causing 50-65% of male cases and 20-30% of female cases [13]. A causal relationship has been established between exposure to tobacco and cancer in studies in which chance, bias and confounding can be discounted with reasonable confidence [14].

The incidence of BC is directly related to the duration of smoking and the number of cigarettes smoked per day [15]. A meta-analysis looked at 216 observational studies on cigarette smoking and cancer published between 1961 and 2003, and the pooled risk estimates for BC demonstrated a significant association for both current

and former smokers [16]. Recently, an increase in risk estimates for current smokers relative to never smokers has been described suggesting this could be due to changes in cigarette composition [13]. An immediate decrease in the risk of BC was observed in those who stopped smoking. The reduction was about 40% within one to four years of quitting smoking and 60% after 25 years of cessation [15]. Encouraging people to stop smoking would result in the incidence of BC decreasing equally in men and women.

3.2.2 **Occupational exposure to chemicals**

Occupational exposure is the second most important risk factor for BC. Work-related cases accounted for 20-25% of all BC cases in several series and it is likely to occur in occupations in which dyes, rubbers, textiles, paints, leathers, and chemicals are used [17]. The risk of BC due to occupational exposure to carcinogenic aromatic amines is significantly greater after ten years or more of exposure; the mean latency period usually exceeds 30 years [18, 19]. Population-based studies established the occupational attribution for BC in men to be 7.1%, while no such attribution was discernible for women [8, 20].

3.2.3 **Radiotherapy**

Increased rates of secondary bladder malignancies have been reported after external-beam radiotherapy (EBRT) for gynaecological malignancies, with relative risks of 2-4 [21]. In a population-based cohort study, the standardised incidence ratios for BC developing after radical prostatectomy (RP), EBRT, brachytherapy (BT), and EBRT-BT were 0.99, 1.42, 1.10, and 1.39, respectively, in comparison with the general U.S. population [22].

It has recently been proposed that patients who have received radiotherapy (RT) for prostate cancer with modern modalities such as intensity-modulated radiotherapy (IMRT) may have lower rates of in-field bladder- and rectal secondary malignancies [23]. Nevertheless, since longer follow-up data are not yet available, and as BC requires a long period to develop, patients treated with radiation and with a long life-expectancy are at a higher risk of developing BC [23].

3.2.4 **Dietary factors**

Several dietary factors have been considered to be related to BC; however, the links remain controversial. The European Prospective Investigation into Cancer and Nutrition (EPIC) study is an on-going multicentre cohort study designed to examine the association between diet, lifestyle, environmental factors and cancer. They found no links between BC and fluid intake, red meat, vegetable and fruit consumption, and only recently they have described an inverse association between dietary intake of flavonols and lignans and the risk of BC, in particular aggressive tumours [24].

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

Bladder schistosomiasis (bilharzia) is the second most common parasitic infection after malaria, with about 600 million people exposed to infection in Africa, Asia, South America, and the Caribbean [25]. There is a well-established relationship between schistosomiasis and urothelial carcinoma of the bladder, which can progress to squamous cell carcinoma (SCC), however, a better control of the disease is decreasing the incidence of SCC of the bladder in endemic zones such as Egypt [26, 27].

Similarly, invasive SCC has been linked to the presence of chronic urinary tract infection (UTI) distinct from schistosomiasis. A direct association between BC and UTIs has been observed in several case-control studies, which have reported a two-fold increased risk of BC in patients with recurrent UTIs in some series. However, some of these results may be attributed to recall bias [28].

3.2.6 **Gender**

Although men are more likely to develop BC than women, women present with more advanced disease and have worse survival rates. A meta-analysis including nearly 28,000 patients shows that female gender was associated with a worse survival outcome (HR: 1.20; 95% CI: 1.09-1.32) compared to male gender after radical cystectomy (RC) [29]. This finding had already been presented in a descriptive Nation-Wide Analysis based on 27,773 Austrian patients. After their analysis the authors found that cancer-specific-survival (CSS) was identical for pT1-tumours in both sexes, while women had a worse CSS in both age cohorts (< 70 years and ≥ 70 years) with higher tumour stages [30]. However this higher mortality is questioned once both genders receive the same therapy. In the population-based study from the Ontario Cancer Registry analysing all patients with BC treated with cystectomy or radical RT between 1994 and 2008, no differences in overall survival (OS), mortality and outcomes were found between males and females following radical therapy [31].

A population-based study from the MarketScan databases suggests that a possible reason for worse survival in the female population may be that women experienced longer delays in diagnosis than men, as the differential diagnosis in women includes diseases that are more prevalent than BC [32].

Furthermore, differences in the gender prevalence of BC may be due to other factors besides tobacco and chemical exposure. In a large prospective cohort study, post-menopausal status was associated

with an increase in BC risk, even after adjustment for smoking status. This result suggests that the differences in oestrogen and androgen levels between men and women may be responsible for some of the difference in the gender prevalence of BC [33-35].

3.2.7 Genetic factors

There is growing evidence that genetic susceptibility factors and family association may influence the incidence of BC. The relationship between family history of cancer and risk of BC was examined in a Spanish BC study showing that family history of cancer in first-degree relatives was associated with an increased risk of BC; the association being stronger among younger patients. Shared environmental exposure was recognised as a potentially confounding factor [36]. Recent studies detected genetic susceptibility with independent loci, which are associated with BC risk [37].

Genome-wide association studies (GWAS) of BC identified several susceptibility loci associated with BC risk [38, 39].

3.2.8 Summary of evidence and recommendations for epidemiology and risk factors

Summary of evidence	LE
Worldwide, bladder cancer is the 11 th most commonly diagnosed cancer.	2a
Several risk factors connected with the risk of bladder cancer diagnosis have been identified.	3
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 (BT), or a combination of EBRT and BT, must be taken into account during patient follow-up. As bladder cancer requires time to develop, patients treated with radiation at a young age are at the greatest risk and should be followed up closely.	3

Recommendations	GR
The principal preventable risk factor for MIBC 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

3.3 Pathology

3.3.1 Handling of transurethral resection and cystectomy specimens

In transurethral resection (TUR), a snap frozen specimen from the tumour and normal looking bladder wall should be taken, if possible. Separate specimens should be taken from the superficial and deep areas of the tumour and sent to the pathology laboratory separately, in case the outcome will impact on treatment decisions. If random biopsies of the flat mucosa are taken, each biopsy specimen of the flat mucosa should also be sent separately.

In RC, 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 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 [40].

Specimen handling should follow the general rules as published by a collaborative group of pathologists and urologists [41, 42]. It must be stressed that it may be very difficult to confirm the presence of a neoplastic lesion using gross examination of the cystectomy specimen after TUR or chemotherapy, so the entire retracted or ulcerated area should be included.

It is compulsory to study the urethra, the ureters, the prostate in men and the radial margins [43]. In urethra-sparing cystectomy; the level of urethral dissection, completeness of the prostate, specifically at the apex (in men), and the inclusion of the entire bladder neck and amount of adjacent urethra, uterus and vaginal top (in women) should be inked and documented.

All lymph node (LN) specimens should be provided in their totality, in clearly labelled containers. In case of doubt, or adipose differentiation of the LN, the entire specimen is to be included. LNs should be counted and measured on slides, capsular extension and percentage of LN invasion should be reported as well as vascular embols [44, 45]. In the case of metastatic spread in the perivesical fat without real LN structures (capsule, subcapsular sinus), this localisation should nevertheless be considered as N+.

A meta-analysis indicated that LN density is an independent predictor of clinical outcome (HR OS: 1.45; 95% CI: 1.11-1.90) [46].

Positive margins in the peripelvic fat tissue (soft tissue margins), should be inked by the pathologist for evaluation. Positive margins decrease CSS in cases of pN0M0 urothelial carcinomas [47].

In rare cases, fresh frozen sections may be helpful to determine treatment strategy. A recent study confirmed the reliability of fresh frozen sections of obturator LNs, but further studies are warranted to confirm these results [48].

3.3.2 Pathology of muscle-invasive bladder cancer

In MIBC all cases are high-grade urothelial carcinomas. For this reason, no prognostic information can be provided by grading MIBC [49]. However, identification of some morphological subtypes may be important for prognostic reasons and treatment decisions [50, 51]. Recently, an update of the World Health Organization (WHO) grading was published [52] however, the data presented in these guidelines are based on the 2004 WHO classification [53]. Currently the following differentiations are used:

1. urothelial carcinoma (more than 90% of all cases);
2. urothelial carcinomas with partial squamous and/or glandular differentiation [54, 55];
3. micropapillary and microcystic urothelial carcinoma;
4. nested variant [56] (including large nested variety);
5. lymphoepithelioma;
6. plasmocytoid, giant cell, signet ring, diffuse, undifferentiated;
7. some urothelial carcinomas with trophoblastic differentiation;
8. small-cell carcinomas [57];
9. sarcomatoid carcinomas.

3.3.3 Recommendations for the assessment of tumour specimens

Recommendations	GR
Record the depth of invasion (categories pT2a and pT2b, pT3a and pT3b or pT4).	A*
Record margins with special attention paid to the radial margin, prostate, ureter, urethra and peritoneal fat and uterus and vaginal top.	
Record the number of lymph nodes (LNs) and number of positive LNs.	
Record lymphatic or blood vessel invasion and extranodal extension.	
Record the presence of carcinoma <i>in situ</i> .	

*Upgraded following panel consensus.

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Pathological staging

For staging, the Tumour, Node, Metastasis (TNM) classification (2017, 8th edition) is recommended [58]. Blood and lymphatic vessel invasion and LN infiltration have an independent prognostic significance [59]. It seems that the pN category is closely related to the number of LNs studied by the pathologist [58]. New prognostic markers are under study (see Section 6.2.4 Prognostic Markers).

4.2 Tumour, node, metastasis classification

The TNM classification of malignant tumours is the method most widely used to classify the extent of cancer spread [50-52, 58, 60] (Table 4.1).

Table 4.1: TNM classification of urinary bladder cancer [58]

T - Primary Tumour	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma <i>in situ</i> : “flat tumour”
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
T2a	Tumour invades superficial muscle (inner half)
T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue:
T3a	microscopically
T3b	macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostate stroma, seminal vesicles, uterus, or vagina
T4b	Tumour invades pelvic wall or abdominal wall
N - Regional Lymph Nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N2	Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N3	Metastasis in a common iliac lymph node(s)
M - Distant Metastasis	
M0	No distant metastasis
M1a	Non-regional lymph nodes
M1b	Other distant metastasis

5. DIAGNOSTIC EVALUATION

5.1 Primary diagnosis

5.1.1 Symptoms

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

5.1.2 Physical examination

Physical examination should include rectal and vaginal bimanual palpation. A palpable pelvic mass can be found in patients with locally advanced tumours. In addition, bimanual examination under anaesthesia should be carried out before and after transurethral resection of the bladder (TURB), to assess whether there is a palpable mass or if the tumour is fixed to the pelvic wall [61, 62]. 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 [63].

5.1.3 Bladder imaging

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

5.1.4 Urinary cytology and urinary markers

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

However, 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% [64, 65] (LE: 2b). However, negative cytology does not exclude a tumour. There is no known urinary marker specific for the diagnosis of invasive BC [66].

A standardised reporting system redefining urinary cytology diagnostic categories was published in 2016 by the Paris Working Group [67]:

- Adequacy of urine specimens (Adequacy);
- Negative for high-grade urothelial carcinoma (Negative);
- Atypical urothelial cells (AUC);
- Suspicious for high-grade urothelial carcinoma (Suspicious);
- High-grade urothelial carcinoma (HGUC);
- Low-grade urothelial neoplasia (LGUN).

5.1.5 **Cystoscopy**

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

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

The use of PDD could be considered if a T1 high-grade tumour is present, to identify associated CIS. Presence of CIS may lead to a modified treatment plan (see Section 7.1). Photodynamic diagnosis is highly sensitive for the detection of CIS, but in experienced hands, the rate of false-positive results may be similar to that with regular white-light cystoscopy [68].

5.1.6 **Transurethral resection of invasive bladder tumours**

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

The strategy of resection depends on the size of the lesion. Small tumours (< 1 cm in diameter) can be resected *en bloc*, where the specimen contains the complete tumour plus a part of the underlying bladder wall including muscle. Larger tumours need to be resected separately in parts, which includes the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle, and the edges of the resection area. At least the deeper part of the resection specimen must be referred to the pathologist in a separate labelled container to enable him/her to make a correct diagnosis. In cases in which RT is considered and CIS is to be excluded, PDD can be used [69].

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 [70, 71] (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 [72-74].

5.1.7 **Second resection**

In the case of high-grade non-muscle-infiltrative tumour, residual disease is observed in 33-53% of patients [75-81]. In order to reduce the risk of understaging [76, 77], a second TURB resection is often required to determine the future treatment strategy.

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

5.1.8 **Concomitant prostate cancer**

Prostate cancer is found in 25-46% of patients undergoing cystectomy for BC [82, 83]. The impact on survival is unknown but the impact on surgical treatment is limited.

5.1.9 Summary of evidence and specific recommendations for the primary assessment of presumably invasive bladder tumours

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

Summary of evidence	LE
Currently, treatment decisions cannot be based on molecular markers.	3

Recommendations	GR
During cystoscopy, describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities. A bladder diagram is recommended.	C
Take a biopsy of the prostatic urethra for cases of bladder neck tumour, when bladder carcinoma <i>in situ</i> 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.	C
Take a biopsy at the time of the second resection, if no biopsy was taken during the initial procedure.	C
In women undergoing subsequent orthotopic neobladder construction, obtain procedural information (including histological evaluation) of the bladder neck and urethral margin, either prior to or at the time of cystoscopy.	C
Specify the grade, depth of tumour invasion, and whether the lamina propria and muscle tissue are present in the specimen in the pathological report.	C

5.2 Imaging for staging of MIBC

The treatment and prognosis of MIBC is determined by tumour stage and grade [84, 85]. In clinical practice, CT and MRI are the imaging techniques used. The purpose of using imaging for staging MIBC is to determine prognosis and provide information to assist treatment selection. Tumour staging must be accurate to ensure that the correct choice of treatment is made. Imaging parameters required for staging MIBC are:

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

5.2.1 Local staging of MIBC

Both CT and MRI may be used for assessment of local invasion, but they are unable to accurately diagnose microscopic invasion of perivesical fat (T2 vs. T3a) [86]. The principal aim of CT and MRI is therefore to detect T3b disease, or higher.

5.2.1.1 MRI for local staging of invasive bladder cancer

Magnetic resonance imaging has superior soft tissue contrast resolution compared with CT, but poorer spatial resolution. In studies performed before the availability of multidetector CT, MRI was reported as more accurate in local assessment. The accuracy of MRI for primary tumour staging varies from 73% to 96% (mean 85%). These values were 10-33% (mean 19%) higher than those obtained with CT [87]. Dynamic contrast-enhanced (DCE) MRI may help to differentiate bladder tumour from surrounding tissues or evaluate post-biopsy reaction, because enhancement of the tumour occurs earlier than that of the normal bladder wall, due to neovascularisation [88-90].

In 2006, a link was established between the use of gadolinium-based contrast agents and nephrogenic systemic fibrosis (NSF), which may result in fatal or severely debilitating systemic fibrosis. Patients with impaired renal function are at risk of developing NSF and the non-ionic linear gadolinium-based contrast agents should be avoided (gadodiamide, gadopentetate dimeglumine and gadoversetamide). A stable macrocyclic contrast agent should be used (gadobutrol, gadoterate meglumine or gadoteridol). Contrast-enhanced CT using iodinated contrast media should be considered as an alternative [91] (LE: 4).

5.2.1.2 CT imaging for local staging of MIBC

The advantages of CT include high spatial resolution, shorter acquisition time, wider coverage in a single breath hold, and lower susceptibility to variable patient factors. Computed tomography is unable to differentiate between stages from Ta to T3a tumours, but it is useful for detecting invasion into the perivesical fat (T3b) and adjacent organs. The accuracy of CT in determining extravesical tumour extension varies from 55% to 92% [92] and increases with more advanced disease [93].

5.2.2 **Imaging of lymph nodes in MIBC**

Assessment of LN 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 LN 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 LN metastases in a variety of primary pelvic tumours [94-99]. 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 [100, 101]. Currently, there is no evidence supporting the routine use of positron emission tomography (PET) in the nodal staging of BC, although the method has been evaluated with varying results in small prospective trials [102-105].

5.2.3 **Upper urinary tract urothelial carcinoma**

Excretory-phase CT urography is the imaging technique with the highest diagnostic accuracy for upper urinary tract urothelial carcinoma (UTUC) and has replaced conventional intravenous urography and US as the first-line imaging test for investigating high-risk patients [106]. The sensitivity of CT urography for UTUC is reported to range from 0.67 to 1.0 with a specificity from 0.93 to 0.99, depending on the technique used [107-114]. Attention to technique is therefore important for optimal 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 [108, 109, 115-117]. The biopsy is usually performed endoscopically.

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

Prior to any curative treatment, it is essential to evaluate the presence of distant metastases. Computed tomography and MRI are the diagnostic techniques of choice to detect lung [118] and liver metastases [119], respectively. Bone and brain metastases are rare at the time of presentation of invasive BC. A bone scan and additional brain imaging are therefore not routinely indicated unless the patient has specific symptoms or signs to suggest bone or brain metastases [120, 121]. Magnetic resonance imaging is more sensitive and specific for diagnosing bone metastases than bone scintigraphy [122, 123] (LE: 2b).

5.2.5 **Future developments**

Evidence is accruing in the literature suggesting that fluorodeoxyglucose (FDG)-PET/CT might have potential clinical use for staging metastatic BC [124, 125], 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 [126]. The high specificity of DWI indicates that it is useful for accurate prediction of a complete histopathological response, allowing better patient selection for bladder-sparing protocols. Results from prospective studies are awaited.

5.2.6 **Summary of evidence and recommendations for staging in muscle-invasive bladder cancer**

Summary of evidence	LE
Imaging as part of staging in muscle-invasive bladder cancer (MIBC) provides information about prognosis and assists in selection of the most appropriate treatment.	2b
There are currently insufficient data on the use of diffusion-weighted imaging (DWI) and fluorodeoxyglucose- positron emission tomography/computed tomography (FDG-PET/CT) in MIBC to allow a recommendation to be made.	

Recommendations	GR
In patients with confirmed MIBC, use computed tomography (CT) of the chest, abdomen and pelvis as the optimal form of staging. Include excretory-phase CT urography for complete examination of the upper urinary tract.	B
Diagnose upper urinary tract urothelial carcinoma (UTUC) using excretory-phase CT urography rather than magnetic resonance (MR) urography as excretory-phase CT urography has greater diagnostic accuracy and is associated with less cost, and greater patient acceptability.	C
Use MR urography when CT urography is contraindicated for reasons related to contrast administration or radiation dose.	C
Perform endoscopically-guided biopsy for histopathological confirmation of pre-operative diagnosis of UTUC.	C
Use CT or magnetic resonance imaging (MRI) for staging locally advanced or metastatic disease in patients in whom radical treatment is considered.	B
Use CT to diagnose pulmonary metastases. CT and MRI are generally equivalent for diagnosing local disease and distant metastases in the abdomen.	C

6. PROGNOSIS

6.1 Introduction

The treatment and prognosis for MIBC is mainly determined by tumour and nodal stage [85]. The pathological report will inform on histological type, lymphovascular invasion, presence of CIS, positive margins and extranodal extension. In clinical practice, CT and MRI are the imaging techniques used.

6.2 MIBC and comorbidity

Complications related to RC 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 RC [127-129].

Advanced age has been identified as a risk factor for complications of RC, although chronological age is less important than biological age. Other risk factors for morbidity include prior abdominal surgery, extravesical disease, and prior RT [130]. Female gender, an increased body mass index (BMI) and lower pre-operative albumin levels are associated with a higher rate of parastomal hernias [131].

Low pre-operative serum albumin is also associated with impaired wound healing, gastrointestinal complications and a decrease of recurrence-free and OS after RC [132, 133]. Therefore, it could be used as a prognostic biomarker for patients undergoing RC.

6.2.1 Evaluation of comorbidity

Rochon *et al.* have shown that evaluation of comorbidity provides a better indicator of life expectancy in MIBC than patient age [134]. 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 [135].

The value of assessing overall health before recommending and proceeding with surgery was emphasised by Zietman *et al.*, who have demonstrated an association between comorbidity and adverse pathological and survival outcome following RC [136]. 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 Surveillance, Epidemiology, and End Results (SEER) registries. Age carried the highest risk for other-cause mortality but not for increased cancer-specific death, while the stage of locally advanced tumour was the strongest predictor for decreased CSS [137]. 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 [138]. Unfortunately, most series evaluating RC do not include indices of comorbidity in the patient evaluation.

6.2.2 Comorbidity scales, anaesthetic risk classification and geriatric assessment

A range of comorbidity scales has been developed [139]; six of which have been validated [140-145] (LE: 3). The Charlson Comorbidity Index (CCI) ranges from 0 to 30 according to the importance of comorbidity described at four levels and is calculated by healthcare practitioners based on patients' medical records. The score has been widely studied in patients with BC and found to be an independent prognostic factor for peri-operative mortality [146, 147], overall mortality [148], and cancer-specific mortality [149-152]. Only the age-adjusted version of the CCI was correlated with both cancer-specific and other-cause mortality [153]. The age-

adjusted CCI (Table 6.1) is the most widely used comorbidity index in cancer for estimating long-term survival and is easily calculated [154].

Table 6.1: Calculation of the Charlson Comorbidity Index

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

Interpretation

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 [155]. The Eastern Cooperative Oncology Group (ECOG) PS scores and Karnofsky index have been validated to measure patient activity [156] (LE: 3). Performance score is correlated with patient OS after RC [151] and palliative chemotherapy [157-159].

1. Calculate Charlson Comorbidity 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 = Y)
 - a. Calculate $Y = 10^{(i \times 0.9)}$
 - b. Calculate $Z = 0.983^Y$ (where Z is the 10-year survival)

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 co-ordinated plan of care. The SGA can be carried out by means of several protocols. These protocols differ in the completeness of diagnostic research. The most complete protocol is the Comprehensive Geriatric Assessment (CGA) [160] which is tailored to the care of cancer patients [161]. In BC, the CGA has been used to adapt gemcitabine chemotherapy in previously untreated elderly patients with advanced BC [162].

6.2.3 Summary of evidence and recommendations for comorbidity scales

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

Recommendations	GR
Base the decision on bladder-sparing treatment or radical cystectomy in elderly/geriatric patients with invasive bladder cancer on tumour stage and comorbidity.	B
Assess comorbidity by a validated score, such as the Charlson Comorbidity Index. The American Society of Anesthesiologists (ASA) score should not be used in this setting (see section 7.4.4.1).	B

6.2.4 Prognostic markers

6.2.4.1 Tumour location

Location of the tumour at the bladder trigone has shown to be associated with an increased likelihood (OR 1.83 95% CI: 1.11-2.99) of nodal metastasis and decreased survival (OR 1.68; 95% CI: 1.11-2.55) [84].

6.2.4.2 Molecular markers

The performance of current commercially available pathological prognostic markers points to the relevance of including molecular prognostic markers into clinical practice [163], but so far very few studies have addressed this topic. At present, insufficient evidence exists to recommend the standard use of prognostic marker p53 in high-risk muscle-invasive disease, as it will not yield sufficient data upon which to base treatment in an individual patient [164].

Recent publications demonstrated four main molecular groups of BC:

- basal BC with the basal and claudin low-type group;
- luminal BC with luminal and p53-like subtype.

The basal group, which can have sarcomatoid aspects and shows an over-expression of epidermal growth factor receptor 3 (EGFR3), is chemosensitive, the luminal type displays an over-expression of fibroblast growth factor receptor 3 (FGFR3), epidermal growth factor receptor (ERBB2[↑] and ERBB3), and is chemotherapy resistant [50, 51, 165].

In 2014, the Cancer Genome Atlas (TCGA) project in BC reported on the integrated genomic analysis of the first 131 MIBC patients, identifying genes that are mutated in a significant proportion of BCs, several of which were not previously reported [166]. Profiling studies have also reported on validated biomarker panels that predict prognosis and can be used to identify patients who may benefit from more aggressive therapy [167]. In the coming years, expanding knowledge of BC carcinogenesis may change our management of the disease.

7. DISEASE MANAGEMENT

7.1 Treatment failure of non-muscle invasive bladder cancer

7.1.1 High-risk non-muscle-invasive urothelial carcinoma

The recurrence and progression rate of non-muscle invasive BC (NMIBC) strongly correlates with the factors as described in the European Organisation for Research and Treatment of Cancer (EORTC) risk calculator [168]. According to this calculator, the risk of progression after five years is 45% for high-risk tumours. In 2015, however, the EORTC group presented new nomograms based on two large phase III trials with a median follow up of 7.4 years. With one to three years of maintenance bacillus Calmette-Guérin (BCG), the risk for progression at five years was much lower: 19.3% for T1G3 tumours [169].

Meta-analyses have demonstrated that BCG-therapy prevents the risk of tumour recurrence [170] and the risk of tumour progression [171, 172] but so far, no significant overall- or disease-specific survival advantages have been shown, as compared to no intravesical therapy [171-173]. The EAU NMIBC Guidelines present data supporting cystectomy in selected patients with NMIBC.

Large cystectomy series show a risk of an understaging error in TaT1 tumours of 35-62%. This may be caused by the presence of persisting or recurrent tumours due to omission of a second TURB or re-TURB, and the absence of neoadjuvant therapy [174-176]. Second TURB identifies upstaging to > T2 tumours in 10-20% of patients [177, 178].

Progression to MIBC significantly decreases CSS. In a review of nineteen trials including 3,088 patients, CSS after progression from NMIBC to MIBC was 35%, which is significantly worse compared to patients with MIBC without a history of NMIBC. This underlines the need to recommend early radical treatment, such as RC, in case of intravesical therapy failure [2, 179, 180].

According to the EAU NMIBC Guidelines, it is reasonable to propose immediate RC to patients with non-muscle-invasive tumour who are at highest risk of progression [168, 181-183]. Risk factors are any of the following:

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

Subgroup of highest-risk tumours:

- T1G3/high-grade associated with concurrent bladder CIS;
- multiple and/or large T1G3/HG and/or recurrent T1G3/high-grade;
- T1G3/high-grade with CIS in the prostatic urethra;
- unusual histology of urothelial carcinoma;
- lymphovascular invasion;
- BCG failures.

Although the percentage of patients with primary TaT1 tumours and the indication for cystectomy in TaT1 tumours is not specified in large cystectomy series, the ten-year recurrence-free survival rate is 80% and similar to that of TURB and BCG maintenance therapy [2, 175, 184, 185] (LE: 3).

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

- whenever muscle-invasive tumour is detected during follow-up;
- if high-grade, non-muscle-invasive papillary tumour is present at three months;
- if CIS (without concomitant papillary tumour) is present at both three and six months;
- if high-grade tumour appears during BCG therapy [186];
- high-grade recurrence after BCG (recurrence of high-grade/grade 3 [WHO 1973/2004] tumour after completion of BCG maintenance, despite an initial response).

Patients with disease recurrence within two 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 [187] (LE: 3; GR: C).

There are now several bladder-preservation strategies available; immunotherapy, chemotherapy, device-assisted therapy, and combination therapy [188]. However, experience is limited and treatments other than RC must be considered oncologically inferior at the present time [188].

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

Recommendations	GR
Consider immediate radical treatment in all T1 tumours at high risk of progression (i.e., high grade, multifocality, carcinoma <i>in situ</i> , and tumour size, as outlined in the EAU Guidelines for Non-muscle-invasive Bladder Cancer).	C
Offer radical treatment to all T1 patients failing intravesical therapy.	B

7.2 **Neoadjuvant chemotherapy**

7.2.1 **Introduction**

The standard treatment for patients with MIBC is RC. However, RC only provides five-year survival in about 50% of patients [176, 189-192]. To improve these results, neoadjuvant chemotherapy (NAC) has been used since the 1980s [193, 194].

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

- Chemotherapy is delivered at the earliest time-point, when the burden of micrometastatic disease is expected to be low.
- Potential reflection of *in-vivo* chemosensitivity.
- Tolerability of chemotherapy and patient compliance are expected to be better pre-cystectomy.
- Patients might respond to NAC and reveal a favourable pathological status, determined mainly by achieving pT0, pN0 and negative surgical margins.
- Delayed cystectomy might compromise the outcome in patients not sensitive to chemotherapy [195, 196], although published studies on the negative effect of delayed cystectomy only include chemo-naïve patients. There are no trials indicating that delayed surgery, due to NAC, has a negative impact on survival.

- Neoadjuvant chemotherapy does not seem to affect the outcome of surgical morbidity. In one randomised trial the same distribution of grade 3-4 post-operative complications was seen in both treatment arms [197]. In the combined Nordic trials (n = 620), NAC did not have a major adverse effect on the percentage of performable cystectomies. The cystectomy frequency was 86% in the experimental arm and 87% in the control arm, 71% received all three chemotherapy cycles [198].
- Clinical staging using bimanual palpation, CT or MRI may often result in over- and understaging and have a staging accuracy of only 70% [199, 200]. Overtreatment is a possible negative consequence.
- Neoadjuvant chemotherapy should only be used in patients eligible for cisplatin combination chemotherapy; other combinations (or monotherapies) are inferior in metastatic BC and have not been fully tested in a neoadjuvant setting [197, 201-213].

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

Data from small imaging studies, aiming to identify responders in patients treated with NAC, suggest that response after two cycles of treatment is related to outcome. So far, neither PET, CT, nor conventional MRI or DCE MRI can accurately predict response [214-217]. In addition, the definition of stable disease after two cycles of NAC is still undefined. To identify progression during NAC, imaging is being used in many centres, notwithstanding the lack of supporting evidence.

For responders to NAC, especially in those with a complete response (pT0 N0), treatment has a major positive impact on OS [218]. The overtreatment of non-responders and patients in the non-target population (i.e. patients without micrometastatic disease) are major drawbacks. Pre-operative identification of responders based on molecular tumour profiling in TURB specimens might guide the use of NAC [219, 220] (see Section 7.8.12 - Biomarkers).

7.2.3 **Summary of available data**

Several randomised phase III trials addressed the potential survival benefit of NAC administration, with conflicting results [197, 201-210, 221-226]. The main differences in trial designs were the type of chemotherapy (i.e. single-agent cisplatin or combination chemotherapy) and the number of cycles provided. Patients had to be fit for cisplatin. Since these studies differed considerably for patient numbers, patient characteristics (e.g. clinical T-stages included) and the type of definitive treatment offered (cystectomy and/or RT), pooling of results was not possible.

Three meta-analyses were undertaken to establish if NAC prolongs survival [211-213]. In the most recent meta-analysis, published in 2005 [213], with updated patient data from 11 randomised trials (n = 3,005), a significant survival benefit was shown in favour of NAC. The results of this analysis confirmed the previously published data and showed a 5% absolute improvement in survival at five years.

The Nordic combined trial showed an absolute benefit of 8% survival at five years and 11% in the clinical T3 subgroup, translating into nine patients needed to treat [198]. Only cisplatin combination chemotherapy with at least one additional chemotherapeutic agent resulted in a meaningful therapeutic benefit [211, 213]; the regimens tested were methotrexate, vinblastine, adriamycin plus cisplatin (MVA(E)C), cisplatin, methotrexate plus vinblastine (CMV), cisplatin and methotrexate (CM), cisplatin/adriamycin, cisplatin/5-fluorouracil (5-FU), and carboplatin, methotrexate, vinblastine (CarboMV).

More modern chemotherapeutic regimens such as gemcitabine/cisplatin have shown similar pT0/pT1 rates as methotrexate, vinblastine, adriamycin plus cisplatin (MVAC) in the most recent retrospective series and pooled data analyses, but have not been used in randomised controlled trials (RCTs) [227-230]. The updated analysis of the largest randomised phase III trial [201] with a median follow-up of eight years confirmed previous results and provided some additional interesting findings:

- 16% reduction in mortality risk;
- improvement in ten-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 [198]. Data support the use of NAC in the T2b-T3b tumour subgroup (former classification T3), and has shown a modest, but substantial, improvement in long-term survival as well as significant downstaging [218].

7.2.4 Summary of evidence and recommendations for neoadjuvant chemotherapy

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

Recommendations	GR
Offer neoadjuvant chemotherapy (NAC) for T2-T4a, cN0M0 bladder cancer. In this case, always use cisplatin-based combination therapy.	A
Do not offer NAC to patients who are ineligible for cisplatin-based combination chemotherapy.	A

7.3 Pre- and post-operative radiotherapy in muscle-invasive bladder cancer

7.3.1 Post-operative radiotherapy

There are only very limited, old, data on adjuvant RT after RC. However, advances in targeting, and reducing the damage to surrounding tissue, may yield better results in the future [231]. A recent RCT in 100 patients, comparing pre-operative vs. post-operative RT and RC, showed comparable OS, DFS and complication rates [232]. Approximately half of these patients had urothelial cancer (UC), while the other half had SCC. In locally advanced BC (T3-T4, N0/N1, M0), the local recurrence rate seems to decrease with post-operative RT [233].

7.3.2 Pre-operative radiotherapy

7.3.2.1 Retrospective studies

Older data and retrospective studies alone cannot provide an evidence base for modern guideline recommendations due to the major study limitations, which include concomitant chemotherapy and differences between surgery and RT. This conclusion was supported by a 2003 systemic review [234]. A retrospective study from 2015 [235] did show a decreased cause-specific mortality and overall mortality for pre-operative RT in clinical T2b and T3 patients only. Another recent retrospective study with pre-operative RT in clinical T1-3 tumours showed that downstaging to T0 tumours occurs in > 50% of the irradiated patients, as compared to < 10% of patients without having received pre-operative RT [236]. Additionally, downstaging resulted in a longer progression-free survival (PFS).

7.3.2.2 Randomised studies

Six randomised studies have been published so far, investigating pre-operative RT, although all are from several decades ago. In the largest trial, pre-operative RT at a dose of 45 Gy was used in patients with muscle-invasive tumours resulting in a significant increase in pathological complete response (pCR) (9% to 34%) in favour of pre-operative RT, which was also a prognostic factor for survival [237]. The OS data were difficult to interpret since chemotherapy was used in a subset of patients only and more than 50% of patients (241/475) did not receive the planned treatment and were excluded from the final analyses. Two smaller studies using a dose of 20 Gy showed only a small survival advantage in \geq T3 tumours [238, 239]. Two other small trials confirmed downstaging after pre-operative RT [240, 241].

A meta-analysis of the five randomised trials showed a difference in five-year survival of (OR: 0.71; 95% CI: 0.48-1.06) in favour of pre-operative RT [242]. However, the meta-analysis was potentially biased by the patients in the data from largest trial who were not given the planned treatment. When the largest trial was excluded, the OR became 0.94 (95% CI: 0.57-1.55), which is not significant.

7.3.3 Summary of evidence and recommendations for pre- and post-operative radiotherapy

Summary of evidence	LE
No data exist to support that pre-operative radiotherapy (RT) for operable muscle-invasive bladder cancer (MIBC) increases survival.	2a
Pre-operative RT for operable MIBC, using a dose of 45-50 Gy in fractions of 1.8-2 Gy, results in downstaging after four-six weeks.	2
Limited high-quality evidence supports the use of pre-operative RT to decrease the local recurrence of MIBC after radical cystectomy.	3

Recommendations	GR
Do not offer pre-operative radiotherapy (RT) to improve survival.	A
Offer pre-operative RT for operable MIBC since it can result in tumour downstaging after four to six weeks.	C

7.4 Radical surgery and urinary diversion

7.4.1 Removal of the tumour-bearing bladder

7.4.1.1 Introduction

Radical cystectomy is the standard treatment for localised MIBC in most Western countries [176, 243]. Recent interest in patients' quality of life (QoL) has promoted the trend toward bladder-preserving treatment modalities, such as radio- and/or chemotherapy (see Sections 7.2 and 7.6). Performance status (PS) and age influence the choice of primary therapy, as well as the type of urinary diversion, with cystectomy being reserved for younger patients without concomitant disease and with a better PS. The value of assessing overall health before recommending and proceeding with surgery was emphasised in a multivariate analysis [149]. The analysis found an association between comorbidity and adverse pathological- and survival outcome following RC [149]. Performance status and comorbidity have a different impact on treatment outcomes and must be evaluated independently [155].

Controversy remains regarding age, RC 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 [149]. The largest, retrospective, single-institution study on cystectomy to date found that patients aged > 80 years had increased post-operative morbidity, but not increased mortality. Although some patients successfully underwent a neobladder procedure, most patients were treated with an ileal conduit diversion [244].

It is particularly important to evaluate functioning and QoL of elderly patients using a standardised geriatric assessment, as well as carrying out a standard medical evaluation (see Section 6.2) [245].

7.4.2 Timing and delay of cystectomy

Nielsen *et al.* reported that a delay of RC > 3 months in three American centres was not associated with a worse clinical outcome [246]. Ayres *et al.* investigated whether a delay > 3 months would have the same effect in the United Kingdom [247]. Initially they found, in agreement with Nielsen *et al.*, that cystectomy within 90 days of diagnosis had no effect on OS for MIBC (n = 955). However, analysis of T2 tumours showed a statistically significant survival benefit if patients had surgery within 90 days of diagnosis (n = 543; HR: 1.40; 95% CI: 1.10-1.79). A population-based study from the USA SEER database analysed patients who underwent a cystectomy between 1992 and 2001, also concluded that a delay of more than twelve weeks has a negative impact on outcome and should be avoided [248].

7.4.2.1 Indications

Traditionally, RC was recommended for patients with MIBC T2-T4a, N0-Nx, M0 [243]. Other indications include high risk and recurrent superficial tumours, BCG-resistant Tis, T1G3 (see Section 7.1), as well as extensive papillary disease that cannot be controlled with TURB and intravesical therapy alone.

Salvage cystectomy is indicated in non-responders to conservative therapy, recurrence after bladder-sparing treatment, and non-urothelial carcinoma (these tumours respond poorly to chemotherapy and RT). It is also used as a purely palliative intervention, including for fistula formation, pain and recurrent visible haematuria (macrohaematuria) (see Section 7.5.1 - Palliative cystectomy).

When there are positive LNs, in the case of N1 involvement (metastasis in a single node in the true pelvis) orthotopic neobladder can still be considered, but not in N2 or N3 tumours [249].

7.4.3 **Radical cystectomy: technique and extent**

In men, standard RC includes removal of the bladder, prostate, seminal vesicles, distal ureters, and regional LNs. Prostate-sparing cystectomy is an option in a subset of carefully selected patients with BC without involvement of the prostatic urethra and without prostate cancer. This procedure is oncologically safe with good functional results as long as it is performed in an experienced centre [250]. In women, standard RC includes removal of the bladder, entire urethra and adjacent vagina, uterus, distal ureters, and regional LNs [251]. 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 studies for RC have been performed so far. The first study 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 LNs. 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 [252]. The second autopsy study focused on the nodal yield when super-extended pelvic LN dissection (LND) was performed. Substantial inter-individual differences were found with counts ranging from 10 to 53 nodes [253]. These findings demonstrate the limited utility of node count as a surrogate for extent of dissection.

Regional LNs have been shown to consist of all pelvic LNs below the bifurcation of the aorta [254-258]. Mapping studies have also found that skipping lesions at locations above the bifurcation of the aorta, without more distally located LN metastases, is rare [258, 259].

The extent of LND has not been established to date. Standard lymphadenectomy in BC 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 [260]. Extended lymphadenectomy includes all LNs 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 LN of Cloquet, as well as the area described for standard lymphadenectomy [260-264]. A super-extended lymphadenectomy extends cranially to the level of the inferior mesenteric artery [265, 266].

In order to assess how and if cancer outcome is influenced by the extent of lymphadenectomy in patients with clinical N0M0 MIBC, a SR of the literature was undertaken [267]. Out of 1,692 abstracts retrieved and assessed, nineteen studies fulfilled the review criteria [260-264, 266, 268-280]. All five studies comparing LND vs. no LND reported a better oncological outcome for the LND group. Seven out of twelve studies comparing (super-)extended with limited or standard LND reported a beneficial outcome for (super)extended in at least a subset of patients which is in concordance with several other recently performed meta-analyses [281, 282]. No difference in outcome was reported between extended and super-extended LND in the two high-volume-centre studies identified [266, 278]. Further data from on-going randomised trials on the therapeutic impact of the extent of lymphadenectomy are awaited.

It has been suggested that PFS as well as OS might be correlated with the number of LNs removed during surgery, although there are no data from RCTs on the minimum number of LNs that should be removed. Nevertheless, survival rates increase with the number of dissected LNs [283]. Removal of at least ten LNs has been postulated as sufficient for evaluation of LN status, as well as being beneficial for OS in retrospective studies [284-286]. In conclusion, extended LND might have a therapeutic benefit compared to less-extensive LND, but due to study bias, no firm conclusions can be drawn [267].

7.4.3.1 *Pelvic organ preservation techniques in men: oncological and functional outcomes*

Different approaches have been described to improve voiding and sexual function in patients undergoing RC for BC. No consensus exists regarding which approach preserves function best. Concern remains regarding the impact of "sparing-techniques" on oncological outcomes.

To determine the effect of sexual function-preserving cystectomy (SPC) on functional and oncological outcomes a SR was undertaken [287].

Four main types of sexual-preserving techniques have been described:

1. **Prostate sparing cystectomy:** part or the whole prostate is preserved including seminal vesicles, vas deferens and neurovascular bundles.
2. **Capsule sparing cystectomy:** the capsule or peripheral part of the prostate is preserved with adenoma

(including prostatic urethra) removed by TURP or *en bloc* with bladder. Seminal vesicles, vas deferens and neurovascular bundles are also preserved.

3. **Seminal sparing cystectomy:** seminal vesicles, vas deferens and neurovascular bundles are preserved.
4. **Nerve sparing cystectomy:** the neurovascular bundles are the only tissue left in place.

Out of 8,517 screened abstracts twelve studies recruiting a total of 1,098 patients (823 in the intervention group vs. 275 in the control group) were identified, including nine comparative studies (one RCT and two retrospective non-RCTs with matched pair design [250, 288-297] and three single-arm case series [298-300]. Sexual function-preserving cystectomy described included prostate-, capsule-, seminal vesicle- and nerve-sparing techniques. In the majority of cases, the open surgical approach was used and the urinary diversion of choice was an orthotopic neobladder. Median follow-up was longer than three years in nine studies, with three studies presenting results at a median follow-up longer than five years.

The majority of the studies included patients who were potent pre-operatively with organ-confined disease without tumour in the bladder neck and/or prostatic urethra. Prostate cancer was ruled out in all of the SPC techniques, except in those performing nerve-sparing cystectomy.

Oncological outcomes did not differ between groups in any of the comparative studies that measured local recurrence, metastatic recurrence, DSS and OS, at a median follow-up of three to five years. Local recurrence after SPC was commonly defined as any urothelial cancer (UC) recurrence below the iliac bifurcation within the pelvic soft tissue and ranged from 1.2-61.1% vs. 16-55% in the control group. Metastatic recurrence ranged from 0-33.3%.

For those techniques preserving prostatic tissue (prostate or capsule sparing) rates of incidental prostate cancer in the intervention group ranged from 0 to 15%. In no case, incidental prostate cancer with Gleason score ≥ 8 was reported.

Sexual outcomes were evaluated using validated-questionnaires (International Index of Erectile Function [IIEF], Erection Hardness Scale [EHS], Bladder Cancer Index [BCI]) in eight studies. Post-operative potency was significantly better in patients who underwent any type of sexual-preserving technique compared to conventional RC ($p < 0.05$), ranging 80-90%, 50-100% and 29-78% for prostate-, capsule- or nerve-sparing techniques, respectively. Data did not show superiority of any sexual-preserving technique.

Urinary continence, defined as the use of no pads in the majority of studies, ranged from 88 to 100% (day-time continence) and from 31-96% (night-time continence) in the prostate-sparing cystectomy patients. No major impact was shown with regard to continence rates for any of the three approaches.

The evidence base suggests that these procedures may yield better sexual outcomes than standard cystectomy without compromising oncological outcomes. However, the overall quality of the evidence was moderate, and hence if a sexual-preserving technique is offered, patients must be carefully selected, counselled and closely monitored.

7.4.3.1.1 Summary of evidence and recommendations for sexual-preserving techniques in men

Summary of evidence	LE
The majority of patients motivated to preserve their sexual function will benefit from sexual-preserving techniques.	2
None of the sexual-preserving techniques (prostate/capsule/seminal/nerve sparing) have shown to be superior and no particular technique can be recommended.	

Recommendations	LE	GR
Offer sexual-preserving techniques to men motivated to preserve their sexual function since the majority will benefit.	2	B
Select patients based on: <ul style="list-style-type: none"> • organ-confined disease; • absence of any kind of tumour at the level of the prostate, prostatic urethra or bladder neck. 	2	A
Do not offer sexual-preserving cystectomy as standard therapy for muscle-invasive bladder cancer.		C

7.4.3.2 Pelvic organ preservation techniques in women: oncological and functional outcomes

Sexual and voiding dysfunction in female patients is prevalent after RC and orthotopic neobladder. Patients' QoL has promoted the trend toward pelvic organ-preserving techniques. Better imaging modalities, increased knowledge of the function of the pelvic structures and improved surgical techniques has enabled less destructive methods for treating high-risk BC. These techniques involve preserving the neurovascular bundle, vagina, uterus or variations of any of the stated techniques.

A SR was conducted to evaluate the advantages and disadvantages of sexual-function preserving RC and orthotopic neobladder for female patients [301].

After screening 11,941 abstracts, fifteen studies recruiting a total of 874 patients were eligible for inclusion. Three papers had a matched pair study design, and the remainder of the included studies were retrospective surgical series with small case numbers and a high risk of selection bias favouring less advanced cancers.

Sexual outcomes were reported in seven studies with 167/194 patients (86%) having resumed sexual activity within six months post-operatively, with median patients' sexual satisfaction scores of 88.5%, ranging from 80% to 100%.

Survival outcomes were reported in seven studies on 197 patients, with a mean follow-up of between 12 and 132 months. At three and five year, CSS was 70-100% and OS was 65-100%. Positive surgical margins were reported in six studies, ranging from 0 to 13.7%. Local and metastatic recurrence rates were reported as ranging between 0-13% and 0-16.7%, respectively. Mean time to local recurrence was seven months.

Eleven studies reported continence outcomes. Overall daytime and nighttime continence was 58-100% and 42-100%, respectively. Overall self-catheterisation rate was 9.5-78%.

Although, this SR provides the best evidence currently available, including basically all reported cases, the data remains immature. Most studies were retrospective and non-comparative with small numbers of patients included, meaning that any estimates are uncertain and likely to be biased. Heterogeneity in outcome definition, measurement and reporting hampers the usefulness of the current evidence base. The overall risk of bias was high across all studies. However, for well-selected patients, sparing female reproductive organs during RC appears to be oncologically safe and provides improved functional outcomes.

7.4.3.2.1 Summary of evidence and recommendations for sexual-preserving techniques in women

Summary of evidence	LE
Data regarding pelvic organ-preserving radical cystectomy for female patients remain immature.	3

Recommendations	LE	GR
Offer sexual-preserving techniques to female patients motivated to preserve their sexual function since the majority will benefit.	3	C
Select patients based on: <ul style="list-style-type: none"> • organ-confined disease; • absence of tumour in bladder neck or urethra. 		C
Do not offer pelvic organ-preserving radical cystectomy for female patients as standard therapy for muscle-invasive bladder cancer.		C

7.4.3.3 Laparoscopic/robotic-assisted laparoscopic cystectomy

Due to data limitations, until recently, laparoscopic radical cystectomy (LRC) and robot-assisted radical cystectomy (RARC) were considered as investigational procedures for which no advantages could be shown as compared to open surgery. Most of the available studies suffered from patient selection bias (age, stage).

A number of new publications have become available (cut-off date for the literature search was Oct 1st, 2015), in particular on RARC; a SR [302], a consensus panel report [303], an RCT from the Memorial Sloan Kettering Cancer Center (MSKCC) group [304] a SR on oncologic and functional outcomes after RARC [305] and a retrospective review on the recurrence patterns after open radical cystectomy (ORC) and RARC [306]. Since there is a continuous flow of reports on RARC, this text section and the recommendations will be subject to significant updates in the coming years.

For the methodology of the SR we refer to the manuscript [302]. In short, out of 1,071 abstracts assessed, 105 studies were selected as meeting the inclusion criteria. Of the 105 papers 102 had a level of evidence of 4, and only three publications had a level of evidence of 2b.

For RARC with urinary diversion, the mean operative time was six to seven hours. Although the intracorporeal technique is more demanding, operating times are comparable, most likely reflecting more experience with the procedure. The operation time decreased over time, but remained longer than for ORC. The average operative time for ORC is listed as 297 minutes in the three higher quality RCTs, which still seems relatively long.

In the comparative studies, mean length of hospital stay for RARC decreases with time and experience, and is 1 to 1.5 days shorter as compared to ORC. In the RCT's however, operative time and length of hospital stay showed no significant difference for either procedure. Blood loss and transfusion rate favour RARC. Intraoperative, 30-day complication rate and mortality were similar for RARC and ORC, but complication grade and grade 3, 90-day, complication rates favoured RARC. Overall complication rates were reported as > 50% which illustrates that cystectomy and diversion remains major surgery. Complication rates did not change with time or experience.

A major limitation of this review is the low level of evidence of the included studies. Of the three RCT's, only one was adequately powered and there was no correction for baseline characteristics (selection bias). In some of the larger series in the review 59-67% of tumours are < pT2 tumours. In the largest RCT 91.5% were clinically < T2 and 71.7% pathologically < T2 [304] compared to a large series of ORC (n = 1,054) 47% of included patients had a < pT2 tumour [176].

The Pasadena Consensus Panel (a group of experts on RC, lymphadenectomy and urinary reconstruction) reached similar conclusions as the Novara review based on the same methodology and literature [303]. They presented similar outcomes comparing RARC and ORC for operative endpoints, pathological and intermediate oncological endpoints (positive surgical margins and LN yield), functional endpoints and complication outcomes. Additionally, RARC was associated with increased costs, although there are ergonomic advantages for the surgeon, as compared to laparoscopic radical cystectomy (LRC). For both techniques surgeons' experience and institutional volume strongly predicted outcome. According to the literature, proficiency is reached after 20-250 cases. However, the Pasadena Consensus Panel performed statistical modelling and came to the conclusion that 30 cases should be enough to achieve proficiency in RARC, but they also concluded that challenging cases (high BMI, post chemo- or RT, pelvic surgery, T4 or bulky tumours or positive nodes) should be performed by experienced robotic surgeons only. Experience is defined as a high volume centre, > 30 RARCs/year and experience in ORC.

In the only sufficiently powered RCT, comparing ORC (n = 58) vs. RARC (n = 60) and open diversion, the primary endpoint was an advantage in 90 days grade 2-5 complications for RARC [304]. Since the complication rates were similar (62% for RARC vs. 66% for ORC), the trial was closed after a planned interim analysis. Robotic-assisted radical cystectomy resulted in less blood loss but had a longer operative time and higher costs. Length of hospital stay, pathology, and QoL were similar. Limitations of this study are lack of long-term outcomes and limited experience in RARC as compared to ORC in this group of patients. A similar health-related QoL (HRQoL) was also found in an initial report of a prospective RCT comparing ORC and RARC [307]. Similar functional and oncological outcomes with five years follow up were also reported by Yuh *et al.* [305]. Ngyuyen *et al.* also reported that RARC was not an independent predictor of recurrence after surgery in a retrospective review of 383 consecutive patients [306].

Most reviewed series used extracorporeal reconstruction which leaves room for improvement.

Although an intracorporeal neobladder is a very complex robotic procedure [308] the choice for neobladder or cutaneous diversion, must not depend on the surgical approach.

For LRC, a recent review came to similar conclusions as described for RARC [308]. The review included sixteen eligible studies on LRC. As compared to ORC, LRC had a significantly longer operative time, fewer overall complications, blood transfusions and analgesic use, less blood loss and a shorter length of hospital stay. However, the review was limited by the inherent limitations of the included studies. Although this review also showed better oncological outcomes, these appeared comparable to ORC series in the largest LRC multicentre study to date [308].

7.4.3.3.1 Summary of evidence and recommendations for laparoscopic/robotic-assisted laparoscopic cystectomy

Summary of evidence	LE
Robot-assisted radical cystectomy (RARC) provides longer operative time (1-1.5 hours), major costs, but shorter length of hospital stay (1-1.5 days) and less blood loss compared to open radical cystectomy (ORC).	1
RARC series suffer from a significant stage selection bias as compared to ORC.	1
Grade 3, 90-day complication rate is lower with RARC.	2
Most endpoints, if reported, including intermediate term oncological endpoint and quality of life are not different between RARC and ORC.	2
Surgeons experience and institutional volume are considered the key factor for outcome of both RARC and ORC, not the technique.	2
Recommendations on how to define challenging patients and an experienced RARC surgeon are still under discussion.	3
The use of neobladder after RARC still seems under-utilised, and functional results of intracorporeally constructed neobladders should be studied.	4

Recommendations	GR
Inform the patient of the advantages and disadvantages of open radical cystectomy (ORC) and robot-assisted radical cystectomy (RARC) to allow selection of the proper procedure.	C
Select experienced centres, not specific techniques, both for RARC and ORC.	B
Beware of neobladder under-utilisation and outcome after RARC.	C

7.4.4 Urinary diversion after radical cystectomy

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

- abdominal diversion, such as an ureterocutaneostomy, ileal or colonic conduit, and various forms of a continent pouch;
- urethral diversion, which includes various forms of gastrointestinal pouches attached to the urethra as a continent, orthotopic urinary diversion (neobladder, orthotopic bladder substitution);
- rectosigmoid diversions, such as uretero-(ileo-)rectostomy.

Different types of segments of the intestinal tract have been used to reconstruct the urinary tract, including the stomach, ileum, colon and appendix [309]. Several studies have compared certain aspects of HRQoL, such as sexual function, urinary continence and body image, in patient cohorts with different types of urinary diversion. However, further research is needed on pre-operative tumour stage and functional situation, socio-economic status, and time interval to primary surgery.

7.4.4.1 Preparations for surgery

The ASA score has been validated to assess the risk of post-operative complications prior to surgery. In the BC setting, ASA scores ≥ 3 are associated with major complications [132, 310], particularly those related to the type of urinary diversion (Table 7.4) [311]. However, the ASA score is not a comorbidity scale and should not be used as such.

Table 7.4: ASA score [312]

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 hours, with or without surgery.

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

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

When there are positive LNs, orthotopic neobladder can nevertheless be considered in the case of N1 involvement (metastasis in a single node in the true pelvis) but not for N2 or N3 tumours [313].

Oncological results after orthotopic neobladder substitution or conduit diversion are similar in terms of local or distant metastasis recurrence, but secondary urethral tumours seem less common in patients with neobladder compared to those with conduits or continent cutaneous diversions [314].

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 [315]. Despite the necessary interruption and re-anastomosis of bowel, a formal bowel preparation may not be necessary [316]. Bowel recovery time can be reduced by the use of early mobilisation and early oralisation, gastrointestinal stimulation with metoclopramide and chewing gum [317]. Patients treated according to the “fast tract”/ERAS (Early Recovery After Surgery) protocol have shown to score better on the emotional and physical functioning scores and suffer less from wound healing disorders, fever and thrombosis [318].

A cornerstone of the ERAS protocol is post-operative pain management which involves significantly reducing the use of opioids; offering opioids mainly as breakthrough pain medication. Instead of patient-controlled analgesia (PCA) and epidural opioids, most patients receive high-dose acetaminophen and/or ketorolac, starting intra-operatively. Patients on ERAS experience more pain as compared to patients on a traditional protocol (VAS 3.1 vs. 1.1, $p < 0.001$), but post-operative ileus decreased from 22% to 7.3% ($p = 0.003$) [319].

A multicentre randomised placebo-controlled trial showed that patients receiving alvimopan, a peripherally acting μ -opioid receptor antagonist, experienced quicker bowel recovery compared to patients receiving placebo [320]. However, this drug is, as yet, not approved in Europe.

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

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

Relative contraindications specific for an orthotopic neobladder are high-dose pre-operative RT, complex urethral stricture disease, and severe urethral sphincter-related incontinence [321].

7.4.4.2 Patient selection for orthotopic diversion

Radical cystectomy and urinary diversion are the two steps of one operation. However, the literature uniformly reports complications of RC, while ignoring the fact that most complications are diversion related [322]. Age alone is not a criterion for offering continent diversion [321, 323]. Comorbidity, cardiac and pulmonary function, and cognitive function, are all important factors that should be considered, along with the patient's social support and preference.

Age > 80 years is often considered to be the threshold after which neobladder reconstruction is not recommended. However, there is no exact age for a strict contraindication. In most large series from experienced centres, the rate of orthotopic bladder substitution after cystectomy for bladder tumour is up to 80% in men and 50% in women [324-327]. Nevertheless, no RCTs comparing conduit diversion with neobladder or continent cutaneous diversion have been performed.

Recently, a retrospective study including 1,383 patients showed that the risk of a decline in estimated glomerular filtration rate (eGFR) did not significantly differ after ileal conduit vs. neobladder in patients with pre-operative chronic kidney disease 2 (eGFR 60-89 mL/min/1.73 m²) or 3a (eGFR 45-59 mL/min/1.73 m²) [328]. Only age and anastomotic strictures were found to be associated with a decline in eGFR.

7.4.4.2.1 Ureterocutaneostomy

Ureteral diversion to the abdominal wall is the simplest form of cutaneous diversion. Operating time, complication rate, stay at intensive care and length of hospital stay are lower in patients treated with

ureterocutaneostomy as compared to ileal conduit [329]. Therefore, in older, or otherwise compromised, patients who need a supravescical diversion, ureterocutaneostomy is the preferred procedure [330, 331]. Quality of life, which was assessed using the Bladder Cancer Index, showed equal urinary bother and function for patients treated with ileal conduit and ureterocutaneostomy [329].

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 [244]. Technically, either one ureter, to which the other shorter one is attached end-to-side, is connected to the skin (transureteroureterocutaneostomy) or both ureters are directly anastomosed to the skin. Due to the smaller diameter of the ureters, stoma stenosis has been observed more often than in intestinal stomas [330].

In a retrospective multicentre study peri-operative morbidity was evaluated for urinary diversion using bowel as compared to ureterocutaneostomy. Patients selected for a ureterocutaneostomy were older and had a higher ASA score, while their mean Charlson score was lower (4.2 vs. 5.6, $p < 0.001$) [332].

Despite the limited comparative data available, it must be taken into consideration that older data and clinical experience suggest ureter stenosis at the skin level and ascending UTI are more frequent complications in ureterocutaneostomy compared to an 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 [333].

7.4.4.2.2 Ileal conduit

The ileal conduit is still an established option with well-known/predictable results. However, up to 48% of patients develop early complications including UTIs, pyelonephritis, ureteroileal leakage and stenosis [333]. The main complications in long-term follow-up studies are stomal complications in up to 24% of cases and functional and/or morphological changes of the UUT in up to 30% [334-336]. An increase in complications was seen with longer follow-up in the Berne series of 131 patients who were followed for a minimum of five years (median follow-up 98 months) [337]; the rate of complications increased from 45% at five years to 94% in those surviving > 15 years. In the latter group, 50% of patients developed UUT changes and 38% developed urolithiasis.

7.4.4.2.3 Continent cutaneous urinary diversion

A low-pressure detubularised ileal reservoir can be used as a continent cutaneous urinary diversion for self-catheterisation; gastric, ileocecal and sigma pouches have also been described [338-340]. Different anti-reflux techniques can be used [341]. Most patients have a well-functioning reservoir with day-time and night-time continence approaching 93% [342]. 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 [342]. Stone formation in the pouch occurred in 10% of patients [341-343]. In a small series of previously irradiated female patients, incontinence and stomal stenosis was seen in 8/44 patients (18%) [344].

7.4.4.2.4 Ureterocolonic diversion

The oldest and most common form of ureterocolonic diversion was primarily a refluxive and later an anti-refluxive connection of ureters to the intact rectosigmoid colon (uretero-rectosigmoidostomy) [345, 346]. 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 [313, 314]. 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 [347].

7.4.4.2.5 Orthotopic neobladder

An orthotopic bladder substitution to the urethra is now commonly used both in men and women. Contemporary reports document the safety and long-term reliability of this procedure. In several large centres, this has become the diversion of choice for most patients undergoing cystectomy [189, 243, 321]. In elderly patients (> 80 years), however, it is rarely performed, even in high-volume expert centres [348, 349]. The terminal ileum is the gastrointestinal segment most often used for bladder substitution. There is less experience with the ascending colon, including the caecum, and the sigmoid [243]. 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 [350, 351]. In two studies with 1,054 and 1,300 patients [321, 352], long-term complications included diurnal (8-10%) and nocturnal (20-30%) incontinence, ureterointestinal stenosis (3-18%), metabolic disorders, and vitamin B12 deficiency. In a recent study that compared cancer control and patterns of disease recurrence in patients with neobladder and ileal conduit, there was no

difference in CSS between the two groups when adjusting for pathological stage [353]. Urethral recurrence in neobladder patients seems rare (1.5-7% for both male and female patients) [321, 354]. 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 [355-357].

Various forms of UUT reflux protection, including a simple isoperistaltic tunnel, ileal intussusception, tapered ileal prolongation implanted subserosally, and direct (sub)mucosal or subserosal ureteral implantation, have been described [341, 351]. According to the long-term results, the UUT is protected sufficiently by either method.

In conclusion, standard RC in male patients with bladder neoplasms includes removal of the entire bladder, prostate, seminal vesicles, distal ureters (segment length undefined), and corresponding LNs (extent undefined) (LE: 2b). In female patients, standard RC includes removal of the entire bladder, urethra and adjacent vagina, uterus, distal ureters, and corresponding LNs.

A detailed investigation of the bladder neck prior to RC is important for women who are scheduled for an orthotopic bladder substitute [358]. In women undergoing RC the rate of concomitant urethral malignancy has been reported to range from 12-16% [359]. Localisation of the primary tumour at the bladder neck correlated strongly with concomitant urethral malignancy. Additionally, the tumours were at higher risk of advanced stage and nodal involvement [360].

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 [361, 362]. In selected patients, such as patients with a single kidney, ureterocutaneostomy is surgically the least burdensome type of diversion (LE: 3). Recommendations related to RC and urinary diversions are listed in section 7.5.

7.4.5 Morbidity and mortality

In three long-term studies, and one population-based cohort study, the peri-operative mortality was reported as 1.2-3.2% at 30 days and 2.3-8.0% at 90 days [189, 322, 324, 363, 364]. In a large single-centre series, early complications (within three months of surgery) were seen in 58% of patients [322]. Late morbidity was usually linked to the type of urinary diversion (see also above) [325, 365]. Early morbidity associated with RC for NMIBC (at high risk for disease progression) is similar and no less than that associated with muscle-invasive tumours [366]. In general, lower morbidity and (peri-operative) mortality have been observed by surgeons and in hospitals with a higher case load and therefore more experience [363, 367-371].

Table 7.6: Management of neobladder morbidity (30-64%) [372].

CLAVIEN System		Morbidity	Management
Grade I	Any deviation from the normal post-operative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs such as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.	Immediate complications:	
		Post-operative ileus	Nasogastric intubation (usually removed at J1) Chewing gum Avoid fluid excess and hypovolemia (provoke splanchnic hypoperfusion)
		Post-operative nausea and vomiting	Antiemetic agent (decrease opioids) Nasogastric intubation
		Urinary infection	Antibiotics (ATB), no ureteral catheter removal Check the 3 drainages (ureters and neobladder)
		Ureteral catheter obstruction	Inject 5cc saline in the ureteral catheter to resolve the obstruction Increase volume infusion to increase diuresis
		intra-abdominal urine leakage (anastomosis leakage)	Check drainages and watchful waiting
		Anaemia well tolerated	Martial treatment (give iron supplement)
		Late complications:	
		Non compressive lymphocele	Watchful waiting
		Mucus cork	Cough Indwelling catheter to remove the obstruction
		Incontinence	Urine analysis (infection), echography (post-void residual) Physiotherapy
		Retention	Drainage and self-catheterisation education
		Grade II	Requiring pharmacological treatment with drugs other than those allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Pulmonary embolism	Heparinotherapy ³		
Pyelonephritis	ATB and check kidney drainage (nephrostomy if necessary)		
Confusion or neurological disorder	Neuroleptics and avoid opioids		
Grade III	Requiring surgical, endoscopic or radiological intervention	Ureteral catheter accidentally dislodged	Indwelling leader to raise the ureteral catheter
		Anastomosis stenosis (7%)	Renal drainage (ureteral catheter or nephrostomy)
		Ureteral reflux	No treatment if asymptomatic
III-a	Intervention not under general anaesthesia	Compressive lymphocele	Transcutaneous drainage or intra-operative marsupialisation (cf grade III)
III-b	Intervention under general anaesthesia	Ileal anastomosis leakage	Ileostomy, as soon as possible
		Evisceration	Surgery in emergency
		Compressive lymphocele	Surgery (marsupialisation)

Grade IV	Life-threatening complication (including central nervous system complications: brain haemorrhage, ischaemic stroke, subarachnoid bleeding, but excluding transient ischaemic attacks) requiring intensive care/ intensive care unit management.	Rectal necrosis	Colostomy
		Neobladder rupture	Nephrostomy and indwelling catheter/surgery for repairing neobladder
		Severe sepsis	ATB and check all the urinary drainages and computed tomography scan in emergency
IV-a	Single organ dysfunction (including dialysis)	Non-obstructive renal failure	Bicarbonate/aetiology treatment
IV-b	Multi-organ dysfunction	Obstructive pyelonephritis and septicaemia	Nephrostomy and ATB
Grade V	Death of a patient		
Suffix 'd'	<i>If the patient suffers from a complication at the time of discharge, the suffix "d" (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.</i>		

¹ A recent SR showed that peri-operative blood transfusion (PBT) in patients who undergo RC correlates with increased all-cause mortality, cancer specific mortality and cancer recurrence. The authors hypothesised that this may be caused by the suggested immunosuppressive effect of PBT. The foreign antigens in transfused blood induce immune suppression, which may lead to tumour cell spread, tumour growth and reduced survival in already immunosuppressed cancer patients. As other possible causes for this finding increased post-operative infections and blood incompatibility were mentioned [373].

² Intraoperative tranexamin acid infusion reduces peri-operative blood transfusion rates from 57.7% to 31.1%. There was no increase seen in peri-operative venous thromboembolism [374].

³ Hammond and co-workers reviewed 20,762 cases of venous thromboembolism (VTE) after major surgery and found cystectomy patients to have the second highest rate of VTE among all cancers studied [375]. These patients benefit from 30 days low-molecular-weight heparin prophylaxis. Subsequently, it was demonstrated that BMI > 30 and non-urothelial BCs are independently associated with VTE after cystectomy. In these patients extended (90 days) heparin prophylaxis should be considered [376].

7.4.6 Survival

According to a multi-institutional database of 888 consecutive patients undergoing RC for BC, the five-year recurrence-free survival was 58% and the CSS was 66% [377]. Recent external validation of post-operative nomograms for BC-specific mortality showed similar results, with bladder-CSS of 62% [378].

Recurrence-free survival and OS in a large single-centre study of 1,054 patients was 68% and 66% at five years and 60% and 43%, at ten years, respectively [176]. However, the five-year recurrence-free survival in node-positive patients who underwent cystectomy was considerably less at 34-43% [175, 176, 379]. In a surgery-only study, the five-year recurrence-free survival was 76% in patients with pT1 tumours, 74% for pT2, 52% for pT3, and 36% for pT4 [176].

A trend analysis according to the five-year survival and mortality rates of BC in the U.S.A., between 1973 and 2009 with a total of 148,315 BC patients, revealed an increased stage-specific five-year survival rate for all stages, except for metastatic disease [380].

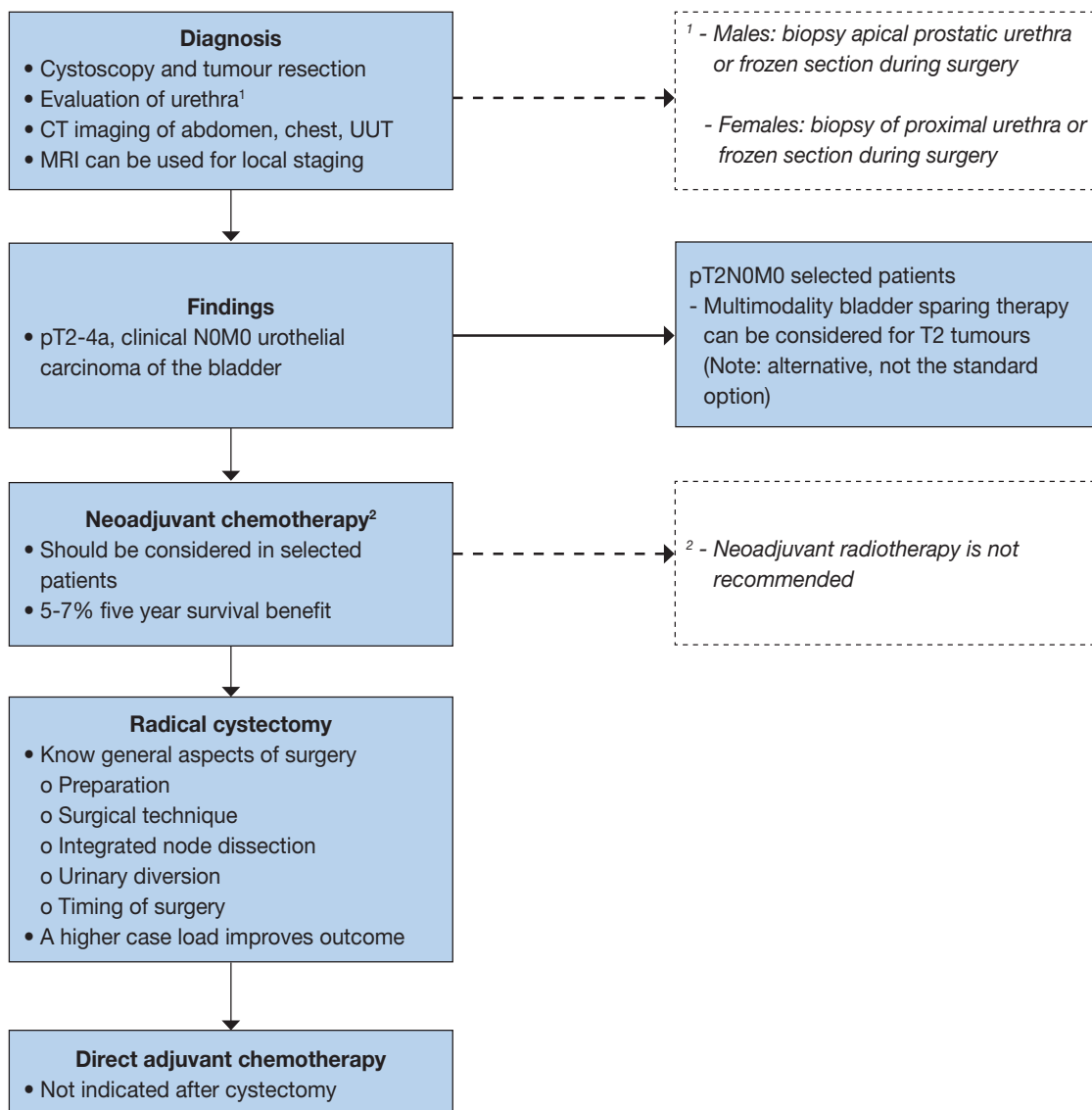
7.4.7 Summary of evidence and recommendations for radical cystectomy and urinary diversion

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

Recommendations	GR
Do not delay cystectomy for > 3 months as it increases the risk of progression and cancer-specific mortality.	B
Before cystectomy, fully inform the patient about the benefits and potential risks of all possible alternatives. The final decision should be based on a balanced discussion between the patient and the surgeon.	B
Offer an orthotopic bladder substitute or ileal conduit diversion to male and female patients lacking any contraindications and who have no tumour in the urethra or at the level of urethral dissection.	B
Do not offer pre-operative radiotherapy when subsequent cystectomy with urinary diversion is planned.	A
Pre-operative bowel preparation is not mandatory. "Fast track" measurements may reduce the time of bowel recovery.	C
Offer radical cystectomy in T2-T4a, N0M0, and high-risk non-MIBC (as outlined above).	A*
Perform a lymph node dissection as an integral part of cystectomy.	A
Preserve the urethra if margins are negative.	B
Check the urethra regularly if no bladder substitution is attached.	B

*Upgraded following EAU Working Panel consensus.

7.1: Flow chart for the management of T2-T4a N0M0 urothelial bladder cancer



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

7.5 Unresectable tumours

7.5.1 Palliative cystectomy for muscle-invasive bladder carcinoma

Locally advanced tumours (T4b, invading the pelvic or abdominal wall) may be accompanied by several debilitating symptoms, including bleeding, pain, dysuria and urinary obstruction. These patients are candidates for palliative treatments, such as palliative RT. Palliative cystectomy with urinary diversion carries the greatest morbidity and should be considered for symptom relief only if there are no other options [381-383].

Locally advanced MIBC can be associated with ureteral obstruction due to a combination of mechanical blockage by the tumour and invasion of ureteral orifices by tumour cells. In a series of 61 patients with obstructive uraemia, RC was not an option in 23 patients, and obstruction was relieved using permanent nephrostomy tubes [384]. Another ten patients underwent palliative cystectomy, but local pelvic recurrence occurred in all ten patients within the first year of follow-up. Another small study (n = 20) showed that primary cystectomy for T4 BC was technically feasible and associated with a very tolerable therapy-related morbidity and mortality [385].

7.5.1.1 Recommendations for unresectable tumours

Recommendations	GR
Offer radical cystectomy as a palliative treatment to patients with inoperable locally advanced tumours (T4b).	B
Offer palliative cystectomy in patients with symptoms.	B

7.5.2 Supportive care

7.5.2.1 Obstruction of the UUT

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

7.5.2.2 Bleeding and pain

In the case of bleeding, the patient must be screened first 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 [386]. It can usually be done without any anaesthesia. The instillation of formalin (2.5-4% for 30 minutes) is a more aggressive and painful procedure, requiring anaesthesia. Formalin instillation has a higher risk of side-effects, e.g. bladder fibrosis, but is more likely to control the bleeding [386]. 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% [387]. Irritative bladder and bowel complaints due to irradiation are possible, but are usually mild. Non-conservative options are embolisation of specific arteries in the small pelvis, with success rates as high as 90% [386]. Radical surgery is a last resort and includes cystectomy and diversion (see above Section 7.5.1).

7.6 Bladder-sparing treatments for localised disease

7.6.1 Transurethral resection of bladder tumour (TURB)

Transurethral resection of bladder tumour alone in patients with muscle-invasive bladder tumours is only possible as a therapeutic option if tumour growth is limited to the superficial muscle layer and if re-staging biopsies are negative for residual (invasive) tumour [388]. In general, about half will still have to undergo RC for recurrent muscle-invasive cancer with a disease-specific mortality rate of up to 47% within this group [389]. A disease-free status at re-staging TURB appears to be crucial in making the decision not to perform RC [390, 391]. A prospective study by Solsona *et al.*, which included 133 patients with radical TURB and re-staging negative biopsies, reported a fifteen-year follow-up [391]. Thirty per cent had recurrent NMIBC and went on to intravesical therapy, and 30% (n = 40) progressed, of which 27 died of BC. After five, ten and fifteen years the results showed a CSS of 81.9%, 79.5%, and 76.7%, respectively and PFS rates with an intact bladder of 75.5%, 64.9%, and 57.8%, respectively.

In conclusion, TURB alone should only be considered as a therapeutic option for muscle-invasive disease after radical TURB, when the patient is unfit for cystectomy or a multimodality bladder-preserving approach, or refuses open surgery [392].

7.6.1.1 Recommendation for transurethral resection of bladder tumour

Recommendation	LE	GR
Do not offer transurethral resection of bladder tumour alone as a curative treatment option as most patients will not benefit.	2a	B

7.6.2 External beam radiotherapy (EBRT)

Current RT techniques with soft-tissue matching result in superior bladder coverage and a reduced integral dose to the surrounding tissues. The target dose for curative RT in BC is 60-66 Gy, with a subsequent boost using external RT or interstitial RT. The use of modern standard RT techniques results in major, related, late morbidity of the urinary bladder or bowel in less than 5% of tumour-free patients [393]. Acute diarrhoea is even more reduced with intensity-modulated RT [394]. Important prognostic factors for outcome include response to

RT, tumour size, hydronephrosis and completeness of the initial TURB. Additional prognostic factors reported were age and stage [395].

In 2007 long-term results were reported by Chung *et al.* [396]. A total of 340 patients with MIBC were treated with EBRT alone, EBRT with concurrent chemotherapy, or NAC followed by EBRT. The overall CR was 55% and the ten-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 NAC (n = 57). Younger age, lower tumour stage and absence of CIS were associated with a significant improvement in survival.

A 2002 Cochrane analysis demonstrated that RC has an OS benefit compared to RT [397], although this was not the case in a 2014 retrospective review using a propensity score analysis [398].

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

7.6.2.1 Summary of evidence and recommendation for external beam radiotherapy

Summary of evidence	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
Do not offer radiotherapy alone as primary therapy for localised bladder cancer.	B

7.6.3 Chemotherapy

Chemotherapy alone rarely produces durable complete remissions. In general, a clinical CR rate of up to 56%, as reported in some series, which must be weighed against a staging error of > 60% [399, 400]. Response to chemotherapy is a prognostic factor for treatment outcome and eventual survival [199], 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 [197, 226, 401, 402]. Neoadjuvant chemotherapy with 2-3 cycles of MVAC or CMV has led to a downstaging of the primary tumour in different prospective series [197, 226, 401]. Pathological complete responses of primary bladder tumours were reached in 12-50% of patients after MVAC and in 12-22% of patients after gemcitabine/cisplatin (GC) in phase II and phase III trials [197, 226, 401, 403-410].

Contemporary series with GC followed by RC reported inferior pT0 rates, which may have been related to a lack of dose density and inappropriate delay of surgery [230].

For highly selected patients, a bladder-conserving strategy with TURB and systemic cisplatin-based chemotherapy, preferably with MVAC, may allow long-term survival with intact bladder [199]. However, this approach cannot be recommended for routine use.

7.6.3.1 Summary of evidence and recommendation for chemotherapy for muscle-invasive bladder tumours

Summary of evidence	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
Do not offer chemotherapy alone as primary therapy for localised bladder cancer.	A

7.6.4 Multimodality bladder-preserving treatment

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

are targeted by platinum-based combination chemotherapy and this topic is covered in the section on NAC (see Section 7.2). The aim of multimodality therapy is to preserve the bladder and QoL, without compromising outcome. A collaborative review addressed this approach [411].

There are no completed RCTs to compare the outcome of MMT with the gold standard, RC, but this approach has been shown to be superior to RT alone [412, 413]. Many of the reported series have differing characteristics as compared to the large surgical series which typically have median ages in the mid-late 60s compared to mid-70s for some large RT series (reviewed in [412]). In the case of MMT, two distinct patterns of care may be distinguished: treatment aimed at patients fit for cystectomy and treatment aimed at older, less fit patients. For the former category MMT presents selective bladder preservation. In that case, the initial step is a radical TURB, where as much tumour as possible should be resected. This implies that proper patient selection (T2 tumours, no CIS) is critical [414]. For patients who are not candidates for cystectomy, less stringent criteria can be applied, though extensive CIS and poor bladder function should both be regarded as strong contraindications.

Following TURB and staging, treatment comprises EBRT with concurrent radiosensitising drugs. Two schedules are in common use worldwide: a split dose format with interim cystoscopy is used in North America [414] whilst single-phase treatment is more commonly used elsewhere [412]. For radiosensitising chemotherapy, cisplatin [415] or mitomycin C plus 5-fluorouracil (5-FU) can be used [412], but also other schedules have been used. In particular, hypoxic cell sensitisation with nicotinamide and carbogen has been evaluated in a large phase III trial [416]. In a recent phase I trial gemcitabine was used [417]. The regimen was well tolerated with promising results.

With MMT, five-year CSS and OS rates are achieved from 50-82% and from 36-74% respectively [393, 412, 415, 416, 418-420]. Salvage cystectomy rates are 10-30% [412, 415, 420]. There are data that major complication rates are similar for salvage and primary cystectomy [421]. The majority of recurrences post-MMT are non invasive and can be managed conservatively [412]. The collaborative review comes to the conclusion that there are accumulating data suggesting that bladder preservation with MMT leads to acceptable outcomes and therefore may be considered a reasonable treatment option in well-selected patients as compared to RC [422]. It should also be considered in all patients where surgery is contraindicated, either relatively or absolutely as the factors that determine fitness for surgery and chemoradiotherapy differ.

A bladder-preserving multimodality strategy requires very close multidisciplinary co-operation and a high level of patient compliance. Even if a patient has shown a CR to a multimodality bladder-preserving strategy, the bladder remains a potential source of recurrence, hence long-term bladder monitoring is essential and patients should be counselled that this will be required. A recent subanalysis from two RTOG trials looked at CR (T0) and near CR (Ta or Tis) after MMT [423]. After a median follow up of 5.9 years 41/119 (35%) of these patients experienced a bladder recurrence, and fourteen required a salvage cystectomy. There was no difference between complete and near-complete responders.

7.6.4.1 Summary of evidence and recommendations for multimodality treatment in muscle-invasive bladder cancer

Summary of evidence	LE
In a highly selected patient population, long-term survival rates of multimodality treatment are comparable to those of early cystectomy.	2b

Recommendations	GR
Offer surgical intervention or multimodality treatments as primary curative therapeutic approaches since they are more effective than radiotherapy alone.	B
Offer multimodality treatment as an alternative in selected, well-informed and compliant patients, especially for whom cystectomy is not an option.	B

7.7 Adjuvant chemotherapy

Adjuvant chemotherapy after RC for patients with pT3/4 and/or LN positive (N+) disease without clinically detectable metastases (M0) is still under debate [421, 424] and is still infrequently used [193].

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 intolerance of chemotherapy, due to post-operative morbidity [425].

There is limited evidence from adequately conducted and accrued randomised phase III trials in favour of the routine use of adjuvant chemotherapy [424, 426-431]. Individual patient data from six randomised trials [420, 432-435] of adjuvant chemotherapy were included in one meta-analysis [426] 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 [424]. In these trials, three or four cycles of CMV, cisplatin, cyclophosphamide, and adriamycin (CISCA), methotrexate, vinblastine, adriamycin or epirubicin, and cisplatin (MVA(E)C) and cisplatin and methotrexate (CM) were used [436], and one trial used cisplatin monotherapy [434]. These data were not convincing enough to give an unequivocal recommendation for the use of adjuvant chemotherapy.

In a 2014 meta-analysis [427], an additional three studies were included [428-430]. However, only 945 patients were included in this meta-analysis of nine trials, and none of the trials were fully accrued and no individual patient data were used [427]. For one trial, only an abstract was available at the time of the meta-analysis [429], and none of the included trials by themselves were significantly positive for OS in favour of adjuvant chemotherapy. In two of the trials, more modern chemotherapy regimens were used (gemcitabine/ cisplatin and paclitaxel/gemcitabine and cisplatin) [428, 429]. The 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 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 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 LND showed an OS benefit in high-risk subgroups (extravesical extension and nodal involvement) [HR: 0.75; CI: 0.62-0.90] [437]. The most recent publication of the so far largest RCT (EORTC 30994), although not fully accrued, showed a significant improvement of PFS for immediate compared with deferred treatment (HR: 0.54; 95% CI: 0.4-0.73, $p < 0.0001$), there was, however, no significant OS benefit [438].

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 LN metastases only, and with a good PS [407, 439, 440]. In the most recent meta-analysis, the positive role of adjuvant chemotherapy for BC has been strengthened, however, still with a poor level of evidence [427]. Patients should be informed about potential chemotherapy options before RC, including neoadjuvant and adjuvant chemotherapy, and the limited evidence for adjuvant chemotherapy.

7.7.1 Recommendation for adjuvant chemotherapy

Recommendation	GR
Offer adjuvant cisplatin-based combination chemotherapy to patients with pT3/4 and/or pN+ disease if no neoadjuvant chemotherapy has been given.	B

7.8 Metastatic disease

7.8.1 Introduction

Half of the patients with muscle-invasive UC relapse after RC, 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 [441]. Before the development of effective chemotherapy, patients with metastatic UC rarely had a median survival that exceeded three-six months [442].

7.8.1.1 Prognostic factors and treatment decisions

Prognostic factors are crucial for assessing phase II study results and stratifying phase III trials [405, 409].

In a multivariate analysis, Karnofsky PS of $\leq 80\%$ and presence of visceral metastases were independent prognostic factors of poor survival after treatment with MVAC [409]. They have also been validated for newer combination chemotherapy regimens [443-445].

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 [446]. Cisplatin, has also been administered in patients with a GFR as low as 40 mL/min., using different schedules. The respective studies were mostly small size phase I and II trials [447-450]. In one phase III trial the cut off for cisplatin eligibility was ≥ 50 mL/min [451].

7.8.1.2 *Comorbidity in metastatic disease*

Comorbidity is defined as “the presence of one or more disease(s) in addition to an index disease” (see Section 6.2.1). Comorbidity increases with age. However, chronological age does not necessarily correlate with functional impairment. Different evaluation systems are being used to screen patients as potentially fit or unfit for chemotherapy, but age alone should not be used to base treatment selection on [452].

7.8.1.3 *Not eligible for cisplatin (unfit)*

The EORTC conducted the first randomised phase II/III trial for urothelial carcinoma patients who were unfit for cisplatin chemotherapy [453]. The EORTC definitions were GFR < 60 mL/min and/or PS 2.

An international survey among BC experts [454] 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; peripheral neuropathy; and New York Heart Association (NYHA) class III heart failure [455].

More than 50% of patients with UC are not eligible for cisplatin-based chemotherapy [456-459].

Renal function assessment in UC is of utmost importance for treatment selection. Calculation of creatinine clearance (CrCl) (24-h urine collection) with current formulae tend to underestimate clearance in patients aged > 65 years compared to measured CrCl [456, 460].

7.8.2 *Single-agent chemotherapy*

Response rates to single-agent, first-line chemotherapy vary. The most robust data have shown a response rate of about 25% for first- and second-line gemcitabine in several phase II trials [461, 462]. Responses with single agents are usually short-lived, complete responses are rare and no long-term DFS has been reported. The median survival in such patients is only six-nine months.

7.8.3 *Standard first-line chemotherapy for fit patients*

Cisplatin-containing combination chemotherapy has been the standard of care since the late 1980s (for a review see [463]). Methotrexate, vinblastine, adriamycin plus cisplatin MVAC and 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 [439]. The major difference between the above-mentioned combinations is toxicity. The lower toxicity of GC [158] has resulted in it becoming a new standard regimen [464]. Methotrexate, vinblastine, adriamycin plus cisplatin is better tolerated when combined with granulocyte colony-stimulating factor (G-CSF) [464, 465].

High-dose intensity MVAC (HD-MVAC) combined with G-CSF is less toxic and more efficacious than standard MVAC in terms of dose density, complete response, and two-year survival rate. However, there is no significant difference in median survival between the two regimens [466, 467]. In general, all disease sites have been shown to respond to cisplatin-based combination chemotherapy. A response rate of 66% and 77% with MVAC and HD-MVAC, respectively, has been reported in retroperitoneal LNs vs. 29% and 33% at extranodal sites [466]. The disease sites also have an impact on long-term survival. In lymph-node-only disease, 20.9% of patients were alive at five years compared to only 6.8% of patients with visceral metastases [439].

Further intensification of treatment using the new paclitaxel, cisplatin and gemcitabine (PCG) triple regimen 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 [468]. 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. Grade 4 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%). Gemcitabine/cisplatin alone caused more G4 thrombocytopenia and thrombocytopenia-induced bleeding (11.4% vs. 6.8%). Paclitaxel, cisplatin and gemcitabine is an additional option for first-line treatment of UC.

7.8.4 Carboplatin-containing chemotherapy for fit patients

Carboplatin-containing chemotherapy is not equivalent to cisplatin combinations, and should not be considered interchangeable or standard. Several randomised phase II trials of carboplatin vs. cisplatin combination chemotherapy have produced lower CR rates and shorter OS for the carboplatin arms [469].

7.8.5 Non-platinum combination chemotherapy

Different combinations of gemcitabine and paclitaxel have been studied as first- and second-line treatments. Apart from severe pulmonary toxicity with a weekly schedule of both drugs, this combination is well tolerated and produces response rates between 38% and 60% in both lines. Non-platinum combination chemotherapy has not been compared to standard cisplatin chemotherapy in randomised trials, therefore, it is not recommended for first-line use in cisplatin-eligible patients [470-477].

7.8.6 Chemotherapy in patients unfit for cisplatin

Up to 50% of patients are ineligible for cisplatin-containing chemotherapy [455]. The first randomised phase II/III trial in this setting was conducted by the EORTC and compared methotrexate/carboplatin/vinblastine (M-CAVI) and carboplatin/gemcitabine (GemCarbo) in patients unfit for cisplatin. Both regimens were active. Severe acute toxicity (SAT) was 13.6% in patients treated with GemCarbo vs. 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 [453]. The ORR and SAT were both 26% for the former group, and 20% and 24%, respectively, for the latter group [453]. Phase III data have confirmed these results [445].

7.8.7 Second-line treatment

Second-line chemotherapy data are highly variable and prognostic factors have been established recently (see Section 7.8.1.1) [446]. A reasonable strategy may be to re-challenge former cisplatin-sensitive patients if progression occurs at least six to twelve months after first-line cisplatin-based combination chemotherapy. Second-line response rates of paclitaxel (weekly), docetaxel, nab-paclitaxel [478] oxaliplatin, ifosfamide, topotecan, pemetrexed, lapatinib, gefitinib and bortezomib have ranged between 0% and 28% in small phase II trials [462, 479, 480]. 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 [461].

Paclitaxel/gemcitabine studies have shown response rates of 38-60%. No randomised phase III trial with an adequate comparator arm has been conducted to assess the true value and OS benefit of this second-line combination [442, 476, 481].

Vinflunine, a novel third-generation vinca alkaloid, provided promising results in phase II trials [482]. A randomised phase III trial compared vinflunine plus best supportive care (BSC) against BSC alone in patients progressing after first-line treatment with platinum-containing combination chemotherapy for metastatic disease [483]. 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 UC, this trial reached the highest level of evidence ever reported. Currently, in Europe, vinflunine is the only approved second-line treatment. Vinflunine has not been approved for this indication in the United States.

7.8.8 Low-volume disease and post-chemotherapy surgery

With cisplatin-containing combination chemotherapy, excellent response rates may be obtained in patients with LN 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 DFS [439, 467, 484, 485]. The role of surgery after chemotherapy is still unclear. Although some studies suggest a survival benefit and QoL improvement, the level of evidence supporting this practice is very limited [486-500]. A retrospective study of post-chemotherapy surgery after a partial or complete response has indicated that surgery may contribute to long-term DFS in selected patients [410, 501, 502].

7.8.9 **Treatment of bone metastases**

The prevalence of metastatic bone disease (MBD) in patients with advanced/metastatic UC is 30-40% [503]. Skeletal complications due to MBD have a detrimental effect on pain and QoL and are also associated with increased mortality [504]. Bisphosphonates reduce and delay skeletal-related events (SREs) due to bone metastases by inhibiting bone resorption. In a small pilot study in patients with BC, SREs caused by bone metastases were delayed [505]. Denosumab is a fully human monoclonal antibody that binds to and neutralises RANKL (receptor activator of nuclear factor- κ B ligand), thereby inhibiting osteoclast function and preventing generalised bone resorption and local bone destruction. Denosumab is not inferior to zoledronic acid (ZA) in preventing or delaying SREs in patients with advanced MBD, including patients with UC [506]. 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 [504].

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 [507]. For denosumab, no dose adjustments are required for variations in renal function.

7.8.10 **Role of immunotherapy**

Immunomodulatory therapies using checkpoint inhibition, particularly with antibodies directed against the programmed cell death-1 (PD-1) protein or its ligand (PD-L1) have been tested. Atezolizumab, the first PD-L1 inhibitor was approved by the US Food and Drug Administration (FDA) in May 2016 for patients that have progressed during or after previous platinum-based chemotherapy. In a phase-II two-cohort study including 310 patients, the objective response rate was 15% independent of the expression of PD-L1. Progression-free survival was 2.1 and OS was 7.9 months. According to the expression level of PD-L1 numbers for response rate, PFS and OS were greater for patients with high expression but responses occurred also in patients with no expression of PD-L1. The toxicity profile of atezolizumab was favourable. Results of the phase III trial (NCT02302807) comparing atezolizumab with second-line chemotherapy are pending [508, 509].

7.8.11 **Summary of evidence and recommendations for metastatic disease**

Summary of evidence	LE
In a first-line setting, performance status (PS) and the presence or absence of visceral metastases are independent prognostic factors for survival.	1b
In a second-line setting, negative prognostic factors are: liver metastasis, PS \geq 1 and low haemoglobin (< 10 g/dL)	1b
Cisplatin-containing combination chemotherapy can achieve median survival of up to 14 months, with long-term disease-free survival reported in ~15% of patients with nodal disease and good PS.	1b
Single-agent chemotherapy provides low response rates of usually short duration.	2a
Carboplatin combination chemotherapy is less effective than cisplatin-based chemotherapy in terms of complete response and survival.	2a
Non-platinum combination chemotherapy produces substantial responses in first- and second-line settings.	2a
Non-platinum combination chemotherapy has not been tested against standard chemotherapy in patients who are fit or unfit for cisplatin combination chemotherapy.	4
There is no defined standard chemotherapy for unfit patients with advanced or metastatic urothelial cancer (UC).	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 in selected patients.	3
Zoledronic acid and denosumab have been approved for all cancer types including UC, because they reduce and delay skeletal related events in metastatic bone disease.	1b
PD-L1 inhibitor atezolizumab has been FDA approved for patients that have progressed during or after previous platinum-based chemotherapy based on the results of a phase-II trial.	2a

Recommendations	GR
First-line treatment for fit patients:	
Use cisplatin-containing combination chemotherapy with GC, MVAC, preferably with G-CSF, HD-MVAC with G-CSF or PCG.	A
Do not use carboplatin and non-platinum combination chemotherapy.	B
First-line treatment in patients ineligible (unfit) for cisplatin:	
Use carboplatin combination chemotherapy or single agents.	C
For cisplatin-ineligible (unfit) patients, with performance status 2 or impaired renal function, as well as those with 0 or 1 poor Bajorin prognostic factors and impaired renal function, offer carboplatin-containing combination chemotherapy, preferably with gemcitabine/carboplatin.	B
Second-line treatment:	
Offer vinflunine to patients progressing after platinum-based combination chemotherapy for metastatic disease. Alternatively, offer treatment within a clinical trial setting.	A*
Offer zoledronic acid or denosumab to treat bone metastases.	B

* Grade A recommendation is weakened since the key studies did not reach statistical significance.

GC = gemcitabine plus cisplatin; G-CSF = granulocyte colony-stimulating factor; MVAC = methotrexate, vinblastine, adriamycin plus cisplatin; HD MVAC = high-dose methotrexate, vinblastine, adriamycin plus cisplatin; PCG = paclitaxel, cisplatin, gemcitabine.

7.8.12 Biomarkers

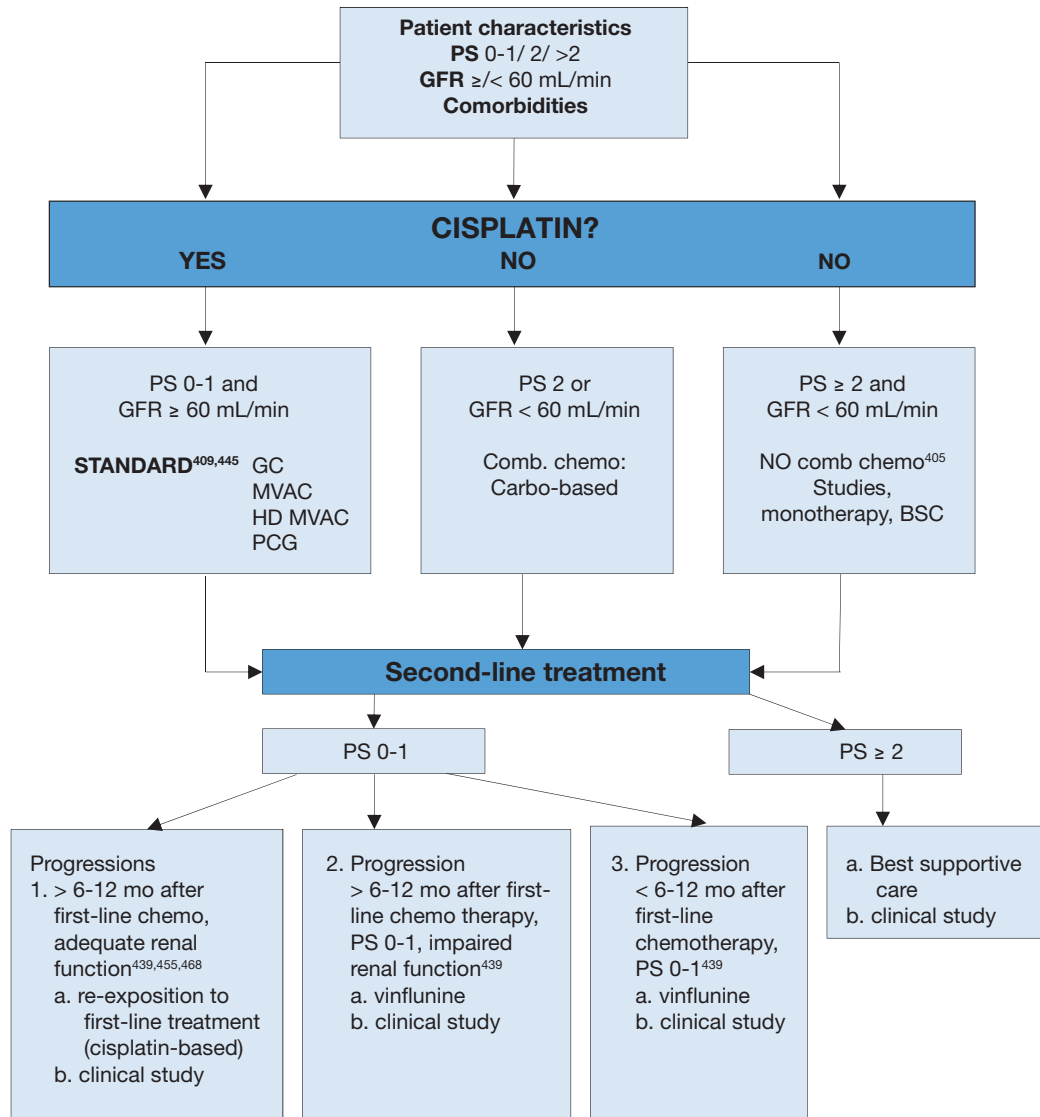
Modest disease control rates, with sporadic marked responses, in some patients with UC have led to the investigation of biomarkers for assessment of post-operative prognosis and the potential value of peri-operative chemotherapy, and as predictors of response to chemotherapy or its monitoring. Most of the biomarkers are associated with tumour angiogenesis. Small studies, usually retrospective, have investigated microvessel density, altered p53 tumour expression [510], serum vascular endothelial growth factor [511], urinary and tissue basic fibroblast growth factor [512], urinary (wild-type and mutant) and tissue fibroblast growth factor receptor-3 [513], and more recently, thrombospondin-1 [514], circulating tumour cells [515, 516], and multidrug resistance gene expression [517]. Although a few biomarkers have shown potential, as yet, there is insufficient evidence to support their routine clinical use (LE: 3).

7.8.12.1 Recommendation for the use of biomarkers

Recommendation	GR
Do not use biomarkers in daily clinical practice since they have no impact on predicting outcome, treatment decisions, or monitoring therapy in muscle-invasive bladder cancer.	A*

*Upgraded following panel consensus.

Figure 7.2: Flow chart for the management of metastatic urothelial cancer



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

7.9 Quality of life

7.9.1 Introduction

The evaluation of HRQoL considers physical, psychological, emotional and social functioning.

Several questionnaires have been validated for assessing HRQoL in patients with BC, including FACT (Functional Assessment of Cancer Therapy)-G [518], EORTC QLQ-C30 [519], EORTC QLQ-BLM (muscle-invasive BC module) [520], and SF (Short Form)-36 [521, 522] and recently the BCI questionnaire specifically designed and validated for BC patients [523].

A psychometric test, such as the FACT-BL, should be used for recording BC morbidity. New intensive interviewing techniques have added valuable information to our knowledge of HRQoL, which greatly depends on patients' individual preferences [524].

7.9.2 Choice of urinary diversion

There is controversy about which type of urinary diversion is best for a patient's HRQoL [243]. Most patients stated that, given a choice, they would still opt for an orthotopic diversion rather than an ileal conduit [525]. Another study reported that, although urinary function is better in conduit patients, at long-term follow up (> 1 year) the urinary bother is the same in both diversion groups .

A SR based on 18 studies showed a slight, but not significant, better QoL in patients with an orthotopic diversion [526]. However, analysing only the studies comparing exclusively ileal conduit vs. ileal orthotopic neobladder, the advantage in QoL of the latter group was significant.

Due to improved surgical techniques in orthotopic bladder substitution, some recent studies are supportive of continent bladder substitutes [362, 520, 527]. Patients with an orthotopic substitution had significantly better physical function and a more active lifestyle compared to patients with an ileal conduit. It is important to note that HRQoL parameters are independent prognostic factors for OS [528]. 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 [527, 529]. Note that all studies investigated mostly male patients. Also of interest is the urinary bother in female neobladder. Bartsch and co-workers found in 56 female patients day-time and night-time incontinence rates of respectively 29.6% and 35.2%. Thirty-five patients (62.5%) performed clean intermittent catheterisation, which is much worse compared to male neobladder patients. Moreover, patients with non-organ-confined disease ($p = 0.04$) and patients with a college degree ($p = 0.001$) showed worse outcome on HRQoL scores [530].

Nevertheless, the HRQoL outcome is most likely a result of good patient selection. An older more isolated patient is probably better served with an ileal conduit whereas a younger patient with more interest in body image and sexuality is better off with an orthotopic diversion.

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

In non-curative or metastatic BC, HRQoL is reduced because of associated micturition problems, bleeding, pain and therefore disturbance of social and sexual life [531]. There is limited literature describing HRQoL in BC patients receiving palliative care [532], but there are reports of bladder-related symptoms relieved by palliative surgery [385], RT [533], and/or chemotherapy [534].

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 [136, 393, 535-538].

7.9.4 **Summary of evidence and recommendations for health-related quality of life**

Summary of evidence	LE
No randomised, prospective health-related quality of life (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 better HRQoL has not been sufficiently substantiated.	
Important determinants of (subjective) quality of life are a patient's personality, coping style and social support.	

Recommendations	GR
Use validated questionnaires to assess HRQoL in patients with MIBC.	B
Offer a continent urinary diversion unless a patient's comorbidities, tumour variables and coping abilities present clear contraindications.	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
Encourage patients to actively participate in the decision-making process.	
Provide clear and exhaustive information on all potential benefits and side-effects, allowing patients to make informed decisions.	A

8. FOLLOW-UP

8.1 Introduction

An appropriate schedule for disease monitoring should be based on:

- natural timing of recurrence;
- probability and site of recurrence;
- functional monitoring after urinary diversion;
- possible treatment of recurrence [539].

Nomograms on CSS following RC have been developed and externally validated. However, their wider use cannot be recommended until further data becomes available [540, 541].

Surveillance protocols are commonly based on patterns of recurrence observed from retrospective series. Diagnosis of asymptomatic recurrence based on routine oncological follow-up and results from retrospective studies are controversial [542, 543]. Importantly, these retrospective studies use different follow-up regimens and imaging techniques that make final analysis and conclusive recommendations difficult. Prospective trials demonstrating the effectiveness of follow up after RC and its impact on OS are lacking [544].

8.2 Site of recurrence

8.2.1 Local recurrence

Local recurrence takes place in soft tissues at the original surgical site or LNs in the area of LND. Lymph node involvement above the aortic bifurcation can be considered metastatic recurrence [542].

Contemporary cystectomy has a 5-15% probability of pelvic recurrence. Most recurrence manifests during the first 24 months, often within six to eighteen months after surgery. However, late recurrence can occur up to five years after cystectomy. Pathological stage and LN status are predictive for pelvic recurrence, as well as positive margins, extent of LND, and peri-operative chemotherapy [545].

Patients have poor prognosis after pelvic recurrence. Even with treatment, the median survival ranges from four to eight months following diagnosis. Definitive therapy can prolong survival, but mostly provides significant palliation of symptoms. Treatment comprises systemic chemotherapy, local surgery, or RT [544].

8.2.2 Distant recurrence

Distant recurrence is seen in up to 50% of patients treated with cystectomy. Stage and nodal involvement are risk factors [546]. Systemic recurrence is more common in locally advanced disease (pT3/4), ranging from 32 to 62%, and in patients with LN involvement (range 52-70%) [547].

The most likely sites for distant recurrence are LNs, lungs, liver and bone. Nearly 90% of distant recurrence appears within the first three years after RC, mainly in the first two years, although late recurrence has been described after > 10 years. Median survival of patients with progressive disease treated with platinum-based chemotherapy is 9-26 months [548-550].

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

The value of monitoring in diagnosis of asymptomatic metastases and its impact on survival is questionable. Some studies have demonstrated no impact on survival despite using routine monitoring, although others have suggested that diagnosis of asymptomatic metastases, especially in the lungs, improves survival [542, 543]. Consideration must also be given to the possibility of longer survival in patients with minimal metastatic disease undergoing multimodal treatment, including metastasectomy. There are reports of survival rates of 28-33% at five years in patients undergoing resection of metastases after objective response to chemotherapy [495, 502].

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

Secondary urethral tumours are likely to occur at one to three years after surgery. Prophylactic urethrectomy at cystectomy is no longer justified in most patients. Independent predictors for urethral recurrence are: cystectomy for NMIBC, prostate involvement, and history of recurrent NMIBC [544].

In women, the main risk factor is bladder neck disease. Many studies have demonstrated that the risk of urethral recurrence after orthotopic diversion (0.9-4.0%) [551-554] is significantly less than after non-orthotopic diversion (6.4-11.1%) [545, 551, 553].

There is limited data and agreement about urethral follow-up, with some recommending routine surveillance with urethral wash and urine cytology [554], and others doubting the need for routine urethral surveillance [552, 555, 556]. Urethral washes and urine cytology do not appear to affect survival [555, 557]. However, there is a significant survival advantage in men with urethral recurrence diagnosed asymptotically vs. symptomatically, so follow-up of the male urethra is indicated in patients at risk of urethral recurrence [544].

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

- in urethral CIS, BCG instillations have success rates of 83% [554];
- in invasive disease, urethrectomy should be performed if the urethra is the only site of disease;
- in distant disease, systemic chemotherapy is indicated [558].

Upper urinary urothelial carcinomas occur in 1.8-6.0% of cases and represent the most common sites of late recurrence (three years DFS following RC). Median OS is 10-55 months, and 60-67% of patients die of metastatic disease [544].

A meta-analysis found that 38% of UTUC recurrence was diagnosed by follow-up investigation, whereas in the remaining 62%, diagnosis was based on symptoms. When urine cytology was used in surveillance, the rate of primary detection was 7% and 29.6% with UUT imaging [559]. This meta-analysis concluded that patients with non-invasive cancer are twice as likely to have UTUC as patients with invasive disease. Multifocality increases the risk of recurrence by three-fold, while positive ureteral or urethral margins increase the risk by seven-fold. Radical nephroureterectomy can prolong survival [560].

8.2.3 Summary of evidence and recommendations for specific recurrence sites

Site of recurrence	Summary of evidence	LE	Recommendation	GR
Local recurrence	Poor prognosis. Treatment should be individualised depending on the local extent of tumour.	2b	Offer radiotherapy, chemotherapy and possibly surgery as options for treatment, either alone or in combination.	C
Distant recurrence	Poor prognosis.	2b	Offer chemotherapy as the first option, and consider metastasectomy in case of unique metastasis site.	C
Upper urinary tract recurrence	Multifocal disease (non-muscle-invasive bladder cancer/carcinoma <i>in situ</i> or positive ureteral margins).		See EAU guidelines on Upper Urinary Tract Urothelial Carcinomas.	
Secondary urethral tumour	Staging and treatment should be done as for primary urethral tumour.	3	Use local conservative treatment for non-invasive tumour.	C
			Offer urethrectomy in isolated invasive disease.	B
			Do not use urethral washes and cytology.	A

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

Patients with multifocal disease, NMIBC with CIS or positive ureteral margins are at higher risk of developing UTUC which can develop late (> 3 years). In those cases, monitoring of the UUT is mandatory during follow-up. Computed tomography is to be used to assess the UUT [559].

8.3 Follow-up of functional outcomes and complications

Apart from oncological surveillance, patients having undergone a urinary diversion deserve functional follow up. Complications related to urinary diversion are detected in 45% of patients during the first five years of follow up.

This rate increases over time, and exceeds 54% after fifteen years of follow up. Therefore, long-term follow up of functional outcomes is desirable [544] (LE: 3), and may stop after fifteen years.

The functional complications are diverse and include: vitamin B12 deficiency, metabolic acidosis, worsening of

renal function, urinary infections, urolithiasis, stenosis of uretero-intestinal anastomosis, stoma complications in patients with ileal conduit, neobladder continence problems, and emptying dysfunction [544]. Especially in women, approximately two-thirds need to catheterise their neobladder, while almost 45% do not void spontaneously at all [530]. Recently a 21% increased risk of fractures was described as compared to no cystectomy, due to chronic metabolic acidosis and subsequent long-term bone loss [561].

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10. CONFLICT OF INTEREST

All members of the Muscle-invasive and Metastatic Bladder Cancer Guidelines Working Group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website: <https://uroweb.org/guideline/bladder-cancer-muscle-invasive-and-metastatic/?type=panel>.

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