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) has prepared these guidelines to help urologists assess the evidence-based management of MIBC and to incorporate guideline recommendations into their clinical practice.

Separate EAU guidelines documents are available addressing upper urinary tract tumours [1], non-muscle-invasive bladder cancer (Ta,T1 and carcinoma *in situ*) [2], and primary urethral carcinomas [3].

1.2 Panel Composition

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

All experts involved in the production of this document have submitted potential conflict of interest statements.

1.3 Available publications

A quick reference document (Pocket guidelines) is available, both in print and in a number of versions for mobile devices. These are abridged versions which may require consultation together with the full text versions. Several scientific publications are available (the most recent paper dating back to 2014 [4]), as are a number of translations of all versions of the EAU MIBC Guidelines. All documents are accessible through the EAU website Uroweb: http://www.uroweb.org/guidelines/online-guidelines/.

1.4 Publication history and summary of changes

*1.4.1 **Publication history***

The EAU published its first guidelines on bladder cancer in 2000. This document covered both superficial (non-muscle-invasive) bladder cancer and MIBC. Since these conditions require different treatment strategies, it was decided to give each condition it's own guidelines, resulting in the first publication of the MIBC guidelines in 2004. This 2015 document presents a limited update of the 2014 version.

*1.4.2 **Summary of changes***

The literature in the complete document has been assessed and updated, whenever relevant.
Key changes for the 2015 publication:

- Section 7.4.2 on timing and delay of cystectomy was revised.
- Section 7.4.4.2.5 on orthotopic neobladder; additional information on female patients has been included.
- A table on the management of neobladder morbidity (Table 7.1) has been added.
- Section 7.6.4 on multimodality bladder-preserving treatment was completely revised.

Recommendations have been rephrased and added to throughout the current document:

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

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

7.2.4 ***Conclusions and recommendations for neoadjuvant chemotherapy***

Conclusions	**LE**
Neoadjuvant chemotherapy has its limitations regarding patient selection, current development of surgical techniques, and current chemotherapy combinations.	3

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

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

7.6.2.1 *Conclusions and recommendation for external beam radiotherapy*

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

Recommendation	GR
Radiotherapy alone is not recommended as primary therapy for localised bladder cancer.	B

2. METHODS

2.1 Data identification

The recommendations provided in the current guidelines are based on literature searches performed by the expert panel members. A systemic literature search was performed for the systematic review of the role and extent of lymphadenectomy during radical cystectomy for cN0M0 muscle-invasive bladder cancer (see Section 7.4: Radical surgery and urinary diversion [5].

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

In this 2015 EAU Guidelines compilation, all standard information on levels of evidence (LE) and grading of recommendations (GR) has been taken out of the individual guidelines topics for the sake of brevity. This information is included in the introductory section of this print.

2.2 Peer review

This document was subjected to double-blind peer review prior to publication.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Bladder cancer (BC) is the ninth most commonly diagnosed cancer worldwide, with more than 380,000 new cases each year and more than 150,000 deaths per year, and an estimated male-female ratio of 3.8:1.0 [6]. At any one time, 2.7 million people have a history of urinary BC [7].

Recently, overall and stage-specific age-adjusted incidence rates of bladder cancer have been analysed in the U.S. (5-year survival and mortality rates between 1973 and 2009). Although the analysis of the Surveillance, Epidemiology and End Results (SEER) database implies some limitations, it is worrying to note that in the last 30 years the mortality rate associated with BC has not changed substantially, highlighting gaps in diagnosis, monitoring and management of these patients [8].

3.2 Aetiology

3.2.1 *Tobacco smoking*

Tobacco smoking is the most well-established risk factor for BC, causing 50-65% of male cases and 20-30% of female cases [9]. A causal relationship has been established between exposure to tobacco and cancer in

studies in which chance, bias and confounding can be discounted with reasonable confidence [10].

The incidence of BC is directly related to the duration of smoking and the number of cigarettes smoked per day [11]. A meta-analysis looked at 216 observational studies on cigarette smoking and cancer from 1961 to 2003, and the pooled risk estimates for BC demonstrated a significant association for both current and former smokers [12]. Recently, an increase in risk estimates for current smokers relative to never smokers has been described suggesting this could be due to changes in cigarette composition [9]. An immediate decrease in the risk of BC was observed in those who stopped smoking. The reduction was about 40% within 1-4 years of quitting smoking and 60% after 25 years of cessation [11]. Encouraging people to stop smoking would result in the incidence of BC decreasing equally in men and women.

*3.2.2 **Occupational exposure to chemicals***

Occupational exposure is the second most important risk factor for BC. Work-related cases have accounted for 20-25% of all BC cases in several series. The substances involved in chemical exposure include benzene derivatives and aryl amines (2-naphthylamine, 4-ABP, 4,4'-methylenedianiline, and o-toluidine), and it is likely to occur in occupations in which dyes, rubbers, textiles, paints, leathers, and chemicals are used [13]. The risk of BC due to occupational exposure to carcinogenic aromatic amines is significantly greater after 10 years or more of exposure; the mean latency period usually exceeds 30 years [14, 15]. The chemicals involved have contributed minimally to the current incidence of BC in Western countries because of strict regulations. Importantly, in recent years, the extent and pattern of occupational exposure have changed because awareness has prompted safety measures, and population-based studies established the occupational attribution for BC in men to be 7.1%, while no such attribution was discernible for women [16, 17].

*3.2.3 **Radiotherapy***

Increased rates of secondary bladder malignancies have been reported after external-beam radiotherapy (EBRT) for gynaecological malignancies, with relative risks of 2-4 [18]. In a population cohort study, the standardised incidence ratios for BC developing after radical prostatectomy (RP), EBRT, brachytherapy (BT), and EBRT-BT were 0.99, 1.42, 1.10, and 1.39, respectively, in comparison with the general U.S. population [19]. It has recently been proposed that patients who have received radiotherapy for prostate cancer with modern modalities such as intensity-modulated radiotherapy (IMRT) may have lower rates of in-field bladder- and rectal secondary malignancies [20]. Nevertheless, since longer follow-up data are not yet available, and as BC requires a long period to develop, patients treated with radiation and with a long life-expectancy are at a higher risk of developing BC [20].

*3.2.4 **Dietary factors***

Several dietary factors have been considered to be related to BC; however, the links remain controversial. The EPIC study is an on-going multicentre cohort study designed to examine the association between diet, lifestyle and environmental factors and cancer. They found no links between BC and fluid intake, red meat, vegetable and fruit consumption, and only recently they have described an inverse association between dietary intake of flavonols and lignans and the risk of BC, in particular aggressive tumours [21].

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

Bladder schistosomiasis (bilharzia) is the second most common parasitic infection after malaria, with about 600 million people exposed to infection in Africa, Asia, South America, and the Caribbean [22]. There is a well-established relationship between schistosomiasis and squamous cell carcinoma of the bladder, although a better control of the disease is decreasing the incidence of squamous carcinoma of the bladder in endemic zones such as Egypt [23, 24].

Similarly, invasive squamous cell carcinoma has been linked to the presence of chronic urinary tract infection (UTI) distinct from schistosomiasis. A direct association between BC and UTIs has been observed in several case-control studies, which have reported a two-fold increased risk of BC in patients with recurrent UTIs in some series. However, some of these results may be attributed to recall bias [25].

*3.2.6 **Gender***

Although men are more likely to develop BC than women, women present with more advanced disease and have worse survival [26].

It has been suggested that women are more likely to be older than men when diagnosed, with a direct effect on their survival. In addition, delayed diagnosis is more likely in women after haematuria is observed, as the differential diagnosis in women includes diseases that are more prevalent than BC [27].

Differences in the gender prevalence of BC may be due to other factors besides tobacco and chemical

exposure. In a large prospective cohort study, postmenopausal status was associated with an increase in BC risk, even after adjustment for smoking status. This result suggests that the differences in oestrogen and androgen levels between men and women may be responsible for some of the difference in the gender prevalence of BC [28-30]. A large German retrospective multicentre study including 2,483 patients submitted to radical cystectomy showed that cancer-specific mortality was higher in female patients. This difference was more pronounced in earlier time periods. These findings could suggest different tumour biology and potentially unequal access to timely radical cystectomy in earlier periods because of reduced awareness of BC in women [31].

*3.2.7 **Genetic factors***

There is growing evidence that genetic susceptibility factors and family associations may influence the incidence of BC. The relationship between family history of cancer and risk of BC was examined in the Spanish Bladder Cancer Study. It was found that family history of cancer in first-degree relatives was associated with an increased risk of BC; the association being stronger among younger patients. Shared environmental exposure was recognised as a potentially confounding factor [32]. These results support the hypothesis that genetic factors play a role in the aetiology of BC.

Genome-wide association studies (GWAS) of BC identified several susceptibility loci associated with BC risk [33, 34]. Polymorphisms in two carcinogen-metabolizing genes, NATS and GSTM1, have been related to BC risk, and furthermore they have demonstrated, together with UGT1A6, to confer additional risk to exposure of carcinogens such as tobacco smoking [35].

*3.2.8 **Conclusions and recommendations for epidemiology and risk factors***

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

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

GR = grade of recommendation; LE = level of evidence.

3.3 Pathology

*3.3.1 **Handling of transurethral resection and cystectomy specimens***

In transurethral resection (TUR) specimens, the superficial and deep areas of the tumour should be sent to the pathology laboratory separately, in case the outcome will impact on treatment decisions. If random biopsies of the flat mucosa are taken, each biopsy specimen of the flat mucosa should also be sent separately.

In radical cystectomy, bladder fixation must be carried out as soon as possible. The pathologist must open the specimen from the urethra to the bladder dome and fix the specimen in formalin. In some circumstances this procedure can also be performed by the urologist. In a female cystectomy specimen, the length of the urethral segment removed en bloc with the specimen should be checked, preferably by the urological surgeon [36].

Specimen handling should follow the general rules as published by a collaborative group of pathologists and urologists [37, 38]. It must be stressed that it may be very difficult to confirm the presence of a neoplastic lesion using gross examination of the cystectomy specimen after TUR or chemotherapy, so the entire retracted or ulcerated area should be included.

It is compulsory to study the urethra, the ureters, the prostate in men and the radial margins [39]. In urethra-sparing cystectomy, the level of urethral dissection, completeness of the prostate specifically at the apex (in men), and the inclusion of the entire bladder neck and amount of adjacent urethra, uterus and vaginal top (in women) should be documented.

All lymph node specimens should be provided in their totality, in clearly labelled containers. In case of doubt, or adipous differentiation of the lymph node, the entire specimen is to be included.

Lymph nodes should be counted and measured on slides, capsular effraction and percentage of lymph node invasion should be reported as well as vascular embols. In the case of metastatic spread in the perivesical fat without real lymph node structures (capsule, subcapsular sinus), this localisation should nevertheless be considered as N+.

Positive margins in the peripelvic fat tissue (soft tissue margins), should be inked by the pathologist for evaluation. Positive margins have decreased cancer-specific survival (CSS) in cases of pNOM0 urothelial carcinomas [40].

In selected cases, fresh frozen sections may be helpful to determine treatment strategy. A recent study confirmed the reliability of fresh frozen sections of obturator lymph nodes, but similar studies are warranted to confirm these results [41].

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

In muscle-invasive BC there are usually no cases of PUNLMP and low-grade carcinoma. All cases are high-grade urothelial carcinomas (grade II or grade III). For this reason, no more prognostic information can be provided by grading muscle-invasive BC [42]. However, some morphological subtypes can be important in helping with prognosis and treatment decisions. Currently the following differentiation is used:

1. urothelial carcinoma (more than 90% of all cases);
2. urothelial carcinomas with squamous and/or glandular partial differentiation [43, 44];
3. micropapillary urothelial carcinoma;
4. nested carcinoma [45];
5. some urothelial carcinomas with trophoblastic differentiation;
6. small-cell carcinomas [46];
7. spindle cell carcinomas.

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

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

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Pathological staging

For staging, TNM 2002/2009 (6th or 7th edition) is recommended (both editions are identical for BC). The pattern of muscular invasion can provide some prognostic information. Most cases show nodular or cordonal growth, but about 44% have an infiltrative pattern. According to some authors [42], the median survival time of a patient with an infiltrative pattern is lower than that for an individual with other pattern types ($p = 0.06$). Blood vessel invasion and lymph node infiltration have an independent prognostic significance [47]. It seems that the pN category is closely related to the number of lymph nodes studied by the pathologist [48]. For this reason, some authors have observed that more than nine lymph nodes have to be investigated to reflect pN0 appropriately [49].

New prognostic markers are under study [50]. Currently, insufficient evidence exists to recommend the standard use of the prognostic marker p53 in high-risk muscle-invasive disease, as it will not yield sufficient

data upon which to base treatment in an individual patient.

4.2 Tumour, node, metastasis classification

The tumour, node, metastasis (TNM) classification of malignant tumours is the method most widely used to classify the extent of cancer spread. A seventh edition was published, effective as of 2010 [51] (Table 4.1). There are no significant modifications in it for BC, compared with the previous edition (2002).

Table 4.1: TNM classification of urinary bladder cancer [51]

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

5. DIAGNOSTIC EVALUATION

5.1 Primary diagnosis

*5.1.1 **Symptoms***

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

*5.1.2 **Physical examination***

Physical examination should include rectal and vaginal bimanual palpation. A palpable pelvic mass can be found in patients with locally advanced tumours. In addition, bimanual examination under anaesthesia should be carried out before and after TURB, to assess whether there is a palpable mass or if the tumour is fixed to the pelvic wall [52, 53]. However, considering the discrepancy between bimanual examination and pT stage after cystectomy (11% clinical overstaging and 31% clinical understaging), some caution is suggested with the interpretation of bimanual examination [54].

*5.1.3 **Bladder imaging***

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

5.1.4 Urinary cytology and urinary markers

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

Positive urinary cytology may originate from a urothelial tumour located anywhere in the urinary tract. Evaluation of cytology specimens can be hampered by low cellular yield, UTIs, stones or intravesical instillations, but for experienced readers, specificity exceeds 90% [55, 56] (LE: 2b). However, negative cytology does not exclude tumour. There is no known urinary marker specific for the diagnosis of invasive BC [57].

5.1.5 Cystoscopy

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

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

The use of photodynamic diagnosis could be considered, especially if a T1 high-grade tumour is present, to find associated CIS. The additional presence of CIS may lead to a modified treatment plan (see Section 7.1). Photodynamic diagnosis is highly sensitive for the detection of CIS, but in experienced hands, the rate of false-positive results may be similar to that with regular white-light cystoscopy [58].

5.1.6 Transurethral resection of invasive bladder tumours

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

The strategy of resection depends on the size of the lesion. Small tumours (< 1 cm in diameter) can be resected *en bloc*, where the specimen contains the complete tumour plus a part of the underlying bladder wall including muscle. Larger tumours need to be resected separately in parts, which include the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle, and the edges of the resection area. At least the deeper part of the resection specimen must be referred to the pathologist in a separate labelled container to enable him/her to make a correct diagnosis. In cases in which radiotherapy is considered and CIS is to be excluded, photodynamic diagnosis can be used [59].

The involvement of the prostatic urethra and ducts in men with bladder tumours has been reported. The exact risk is not known, but it seems to be higher if the tumour is located on the trigone or bladder neck, in the presence of bladder CIS, and in multiple tumours [60, 61] (LE: 3). Involvement of the prostatic urethra can be determined either at the time of primary TURB or by frozen section during the cystoprostatectomy procedure. A frozen section has a higher negative predictive value and is more accurate [62-64].

5.1.7 Second resection

In the case of high-grade non-muscle-infiltrative tumour, residual disease is observed in 33-53% of patients [65-71]. In order to reduce the risk of understaging [66, 67], a second TURB resection is often required to determine the future treatment strategy.

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

5.1.8 Concomitant prostate cancer

Prostate cancer is found in 25-46% of patients undergoing cystectomy for BC [72, 73]. The impact on survival is unknown, however, the impact on surgical treatment is limited.

5.1.9 Specific recommendations for the primary assessment of presumably invasive bladder tumours

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

Conclusion	LE
Currently, treatment decisions cannot be based on molecular markers.	3

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

CIC = carcinoma in situ; GR = grade of recommendation; LE = level of evidence.

5.2 Imaging for staging of MIBC

The treatment and prognosis of MIBC is determined by tumour stage and grade [74]. In clinical practice, CT and MRI are the imaging techniques used. The purpose of using imaging for staging MIBC is to determine prognosis and provide information to assist treatment selection. Tumour staging must be accurate to ensure that the correct choice of treatment is made. Imaging parameters required for staging MIBC are:

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

*5.2.1 **Local staging of MIBC***

Both CT and MRI may be used for assessment of local invasion, but they are unable to accurately diagnose microscopic invasion of perivesical fat (T2 versus T3a) [75]. The principal aim of CT and MRI is therefore to detect T3b disease or higher.

5.2.1.1 MRI for local staging of invasive bladder cancer

Magnetic resonance imaging has superior soft tissue contrast resolution compared with CT, but poorer spatial resolution. In studies performed before the availability of multidetector CT, MRI was reported as more accurate in local assessment. The accuracy of MRI for primary tumour staging varies from 73% to 96% (mean 85%). These values were 10-33% (mean 19%) higher than those obtained with CT [76]. Dynamic contrast-enhanced (DCE) MRI may help to differentiate bladder tumour from surrounding tissues or post-biopsy reaction, because enhancement of the tumour occurs earlier than that of the normal bladder wall, due to neovascularisation [77-79].

In 2006, a link was established between the use of gadolinium-based contrast agents and nephrogenic systemic fibrosis (NSF), which may result in fatal or severely debilitating systemic fibrosis. Patients with impaired renal function are at risk of developing NSF and the non-ionic linear gadolinium-based contrast agents should be avoided (gadodiamide, gadopentetate dimeglumine and gadoversetamide). A stable macrocyclic contrast agent should be used (gadobutrol, gadoterate meglumine or gadoteridol). Contrast-enhanced CT using iodinated contrast media should be considered as an alternative [80] (LE: 4).

5.2.1.2 CT imaging for local staging of MIBC

The advantages of CT include high spatial resolution, shorter acquisition time, wider coverage in a single breath hold, and lower susceptibility to variable patient factors. Computed tomography is unable to differentiate between stages from Ta to T3a tumours, but it is useful for detecting invasion into the perivesical fat (T3b) and adjacent organs. The accuracy of CT in determining extravesical tumour extension varies from 55% to 92% [81] and increases with more advanced disease [82].

*5.2.2 **Imaging of lymph nodes in MIBC***

Assessment of lymph node metastases based solely on size is limited by the inability of both CT and MRI to identify metastases in normal-sized or minimally enlarged nodes. The sensitivity for detection of lymph node metastases is low (48-87%). Specificity is also low because nodal enlargement may be due to benign disease. Overall, CT and MRI show similar results in the detection of lymph node metastases in a variety of primary pelvic tumours [83-88]. Pelvic nodes > 8 mm and abdominal nodes > 10 mm in maximum short-axis diameter, detected by CT or MRI, should be regarded as pathologically enlarged [89, 90].

Currently, there is no evidence supporting the routine use of positron emission tomography (PET) in the nodal staging of BC, although the method has been evaluated with varying results in small prospective trials [91-94].

5.2.3 Upper urinary tract urothelial carcinoma

Excretory-phase CT urography is the imaging technique with the highest diagnostic accuracy for upper urinary tract urothelial carcinoma (UTUC) and has replaced conventional intravenous urography and US as the first-line imaging test for investigating high-risk patients [95]. The sensitivity of CT urography for UTUC is reported to range from 0.67 to 1.0 and specificity from 0.93 to 0.99, depending on the technique used [96-103]. Attention to technique is therefore important for optimum results.

For UTUC detected by CT urography, a biopsy for histopathological confirmation of diagnosis is recommended to eliminate false-positive results and to provide information regarding the grade of the tumour to aid in the choice of treatment [97, 98, 104-106]. The biopsy is usually performed endoscopically.

5.2.4 Distant metastases at sites other than lymph nodes

Prior to any curative treatment, it is essential to evaluate the presence of distant metastases. Computed tomography and MRI are the diagnostic techniques of choice to detect lung [107] and liver metastases [108], respectively. Bone and brain metastases are rare at the time of presentation of invasive BC. A bone scan and additional brain imaging are therefore not routinely indicated unless the patient has specific symptoms or signs to suggest bone or brain metastases [109, 110]. Magnetic resonance imaging is more sensitive and specific for diagnosing bone metastases than bone scintigraphy [111, 112] (LE: 2b).

5.2.5 Future developments

Evidence is accruing in the literature suggesting that fluorodeoxyglucose (FDG)-PET/CT might have potential clinical use for staging metastatic BC [113, 114], but there is no consensus as yet. The results of further trials are awaited before a recommendation can be made. Recently, the first study was published showing the superior feasibility of diffusion-weighted imaging (DWI) over T2-weighted and DCE MRI for assessing the therapeutic response to induction chemotherapy against MIBC [115]. The high specificity of DWI indicates that it is useful for accurate prediction of a complete histopathological response, allowing better patient selection for bladder-sparing protocols. Results from prospective studies are awaited.

5.2.6 Conclusion and recommendations for staging in MIBC

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

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

CT = computed tomography; DWI = diffusion-weighted imaging; FDG-PET/CT = fluorodeoxyglucose-positron emission tomography; GR = grade of recommendation; LE = level of evidence; MIBC = muscle-invasive bladder cancer; MRI = magnetic resonance imaging; UTUC = upper urinary tract urothelial carcinoma.

6. PROGNOSIS

6.1 Introduction

The treatment and prognosis for MIBC is determined by tumour stage and grade [74]. In clinical practice, CT and MRI are the imaging techniques used.

6.2 MIBC and comorbidity

Complications related to radical cystectomy may be directly related to pre-existing comorbidity as well as the surgical procedure, bowel anastomosis, or urinary diversion. A significant body of literature has evaluated the usefulness of age as a prognostic factor for radical cystectomy [116-118]. Advanced age has been identified as a risk factor for complications in the case of radical cystectomy, although chronological age is less important than biological age. Other risk factors for morbidity include prior abdominal surgery, extravesical disease, and prior radiotherapy [119], while an increased body mass index is associated with a higher rate of wound dehiscence and hernia [120].

*6.2.1 **Evaluation of comorbidity***

Rochon et al. have shown that evaluation of comorbidity provides a better indicator of life expectancy in MIBC than patient age [121]. The evaluation helps to identify the medical conditions likely to interfere with, or have an impact on, treatment and the evolution and prognosis of MIBC [122].

The value of assessing overall health before recommending and proceeding with surgery was emphasised by Zietman et al., has demonstrated an association between comorbidity and adverse pathological and survival outcome following radical cystectomy [123]. Similar results were found for the impact of comorbidity on cancer-specific and other-cause mortality in a population-based competing risk analysis of > 11,260 patients from the SEER registries. Age carried the highest risk for other-cause mortality but not for increased cancer-specific death, while the stage of locally advanced tumour was the strongest predictor for decreased CSS [124]. Stratifying elderly patients according to their risk-benefit profile using a multidisciplinary approach will help to select patients most likely to benefit from radical surgery and to optimise treatment outcomes [125]. Unfortunately, most series evaluating radical cystectomy do not include indices of comorbidity in the patient evaluation.

*6.2.2 **Comorbidity scales, anaesthetic risk classification and geriatric assessment***

A range of comorbidity scales has been developed [126]; six of which have been validated [127-132] (LE: 3).

The Charlson Comorbidity Index (CCI) ranges from 0 to 30 according to the importance of comorbidity described at four levels and is calculated by healthcare practitioners from the patients' medical records. The score has been widely studied in patients with BC and found to be an independent prognostic factor for perioperative mortality [133, 134], overall mortality [135], and cancer-specific mortality [136-139]. Only the age-adjusted version of the CCI was correlated with both cancer-specific and other-cause mortality [140].

The age-adjusted CCI (Table 6.1) is the most widely used comorbidity index in cancer for estimating long-term survival and is easily calculated [141].

Table 6.1: Calculation of the Charlson Comorbidity Index

Number of points	Conditions
1 point	50-60 years Myocardial infarction Heart failure Peripheral vascular insufficiency Cerebrovascular disease Dementia Chronic lung disease Connective tissue disease Ulcer disease Mild liver disease Diabetes
2 points	61-70 years Hemiplegia Moderate to severe kidney disease Diabetes with organ damage Tumours of all origins

3 points	71-80 years Moderate to severe liver disease
4 points	81-90 years
5 points	> 90 years
6 points	Metastatic solid tumours AIDS

Interpretation

1. Calculate Charlson Score or Index = i
a. Add comorbidity score to age score
b. Total denoted as 'i' in the Charlson Probability calculation (see below). i = sum of comorbidity score to age score
2. Calculate Charlson Probability (10-year mortality)
a. Calculate $Y = 10^{(i \times 0.9)}$
b. Calculate $Ƶ = 0.983^{Y}$ (where Ƶ is the 10-year survival)

Health assessment of oncology patients must be supplemented by measuring their activity level. Extermann et al. have shown that there is no correlation between morbidity and competitive activity level [142]. Eastern Cooperative Oncology Group (ECOG) PS scores and Karnofsky index have been validated to measure patient activity [143] (LE: 3). PS is correlated with patient OS after radical cystectomy [138, 144] and palliative chemotherapy [145-147].

The ASA score has been validated to assess the risk of postoperative complications prior to surgery. In the BC setting, ASA scores ≥ 3 are associated with major complications [148, 149], particularly those related to the type of urinary diversion (Table 6.2) [150]. However, the ASA score is not a comorbidity scale and should not be used as such.

Table 6.2: ASA score [151]

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

According to a consensus conference of the National Institutes of Health, the aim of the Standardized Geriatric Assessment (SGA) is to discover, describe and explain the many problems of elderly people, to catalogue their resources and strengths, to assess individual service needs, and to develop a coordinated plan of care. The SGA can be carried out by means of several protocols. These protocols differ in the completeness of diagnostic research. The protocol is the most complete Comprehensive Geriatric Assessment (CGA) [152]. The CGA is suited to the care of cancer patients [153]. In BC, the CGA has been used to adapt gemcitabine chemotherapy in previously untreated elderly patients with advanced bladder carcinoma [154].

6.2.3 Conclusions and recommendations for comorbidity scales

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

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

ASA = American Society of Anesthesiologists; GR = grade of recommendation; LE = level of evidence.

7. DISEASE MANAGEMENT

7.1 Treatment failure of non-muscle-invasive bladder cancer

*7.1.1 **High-risk non-muscle-invasive urothelial carcinoma***

The recurrence and progression rates of non-muscle-invasive BC (NMIBC) is strongly associated with several factors as described in the EORTC risk calculator [155]. According to this calculator, the risk of progression after 5 years ranges from 6 to 45% for high-risk tumours. However, in a prospective, multicentre trial, the progression rate was significantly lower than previously reported, even when the presence of concomitant CIS was considered. This was probably due to the combination of a second resection, prior to inclusion in the trial and maintenance treatment as part of the protocol [156]. Meta-analyses have demonstrated that Bacillus Calmette-Guérin (BCG) therapy prevents the risk of tumour recurrence [157, 158].

Two other meta-analyses have shown that BCG therapy decreases the risk of tumour progression [159, 160] but so far, no significant overall- or disease-specific survival advantages have been shown, as compared to no intravesical therapy [159-161].

As also reported in the EAU NMIBC guidelines, there are reasons to consider cystectomy in selected patients with NMIBC [2].

There is a risk of an understaging error in Ta, T1 tumours of 35-62% presented in large cystectomy series. This seems due to the presence of persisting or recurrent tumours due to the lack of a second TURB or re-TURB and the absence of neoadjuvant therapy [162-164]. Second TURB identifies 24-49% of T2 tumours that have been diagnosed initially as non-muscle-invasive tumours [67, 165]. Progression to MIBC significantly decreases cancer-specific survival (CSS). In a review of 19 trials including 3,088 patients, CSS after progression from NMIBC to MIBC was 35%, which is significantly worse compared to patients with MIBC without a history of NMIBC. This underlines the need to recommend early radical treatment, such as f.i. radical cystectomy, in the case of intravesical therapy failure [2, 166, 167].

According to the EAU NMIBC Guidelines, it is reasonable to propose immediate radical cystectomy to those patients with non-muscle-invasive tumour who are at highest risk of progression [166]. These are:

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

**low grade is a mixture of G1 and G2.*

** high grade is a mixture of some G2 and all G3.

Although the percentage of patients with primary Ta, T1 tumours and the indication for cystectomy in Ta, T1 tumours is not specified in large cystectomy series, the 10-year recurrence-free survival rate is ~80% and similar to that with TURB and BCG maintenance therapy [2, 163, 168, 169] (LE: 3).

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

- whenever muscle-invasive tumour is detected during follow-up;
- if high-grade, non-muscle-invasive papillary tumour is present at 3 months;
- if CIS (without concomitant papillary tumour) is present at both 3 and 6 months;
- If high-grade tumour appears during BCG therapy;
- high-grade recurrence after BCG (Recurrence of high-grade/grade 3 [WHO 2004/1973] tumour after completion of BCG maintenance, despite an initial response).

Patients with disease recurrence within 2 years of initial TURB plus BCG therapy have a better outcome than patients who already have muscle-invasive disease, indicating that cystectomy should be performed at first recurrence, even in non-muscle-invasive disease [167] (LE: 3; GR: C).

There are now several bladder-preservation strategies available that can be categorised as immunotherapy, chemotherapy, device-assisted therapy, and combination therapy [170]. However, experience is limited and treatments other than radical cystectomy must be considered oncologically inferior at the present time [171-173].

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

Recommendations	GR
In all T1 tumours at high risk of progression (i.e., high grade, multifocality, CIS, and tumour size, as outlined in the EAU guidelines for non-muscle-invasive bladder cancer [2]), immediate radical treatment is an option.	C
In all T1 patients failing intravesical therapy, radical treatment should be offered.	B

CIS = carcinoma in situ; GR = grade of recommendation.

7.2 Neoadjuvant chemotherapy

*7.2.1 **Introduction***

The standard treatment for patients with muscle-invasive BC is radical cystectomy. However, this gold standard only provides 5-year survival in about 50% [164, 174-177]. To improve these unsatisfactory results, neoadjuvant chemotherapy (NAC) has been used since the 1980s [178, 179].

There are many advantages and disadvantages of administering chemotherapy before planned definitive surgery to patients with operable muscle-invasive urothelial carcinoma of the bladder and cN0M0:

- Chemotherapy is delivered at the earliest time-point, when the burden of micrometastatic disease is expected to be low.
- Potential reflection of in vivo chemosensitivity.
- Tolerability of chemotherapy and patient compliance are expected to be better pre-cystectomy.
- Patients might respond to NAC and reveal a favourable pathological status, determined mainly by achieving pT0, pN0 and negative surgical margins.
- Delayed cystectomy might compromise the outcome in patients not sensitive to chemotherapy [180, 181], although published studies on the negative effect of delayed cystectomy only entail series of chemonaïve patients. There are no trials indicating that delayed surgery, due to NAC, has a negative impact on survival.
- Neoadjuvant chemotherapy does not seem to affect the outcome of surgical morbidity. In one randomised trial the same distribution of grade 3-4 postoperative complications was seen in both trial arms [182].

In the combined Nordic trials (n = 620), NAC did not have any major adverse effect on the percentage of performable cystectomies. The cystectomy frequency was 86% in the experimental arm and 87% in the control arm, 71% received all three chemotherapy cycles [183].

- Clinical staging using bimanual palpation, CT or MRI may often result in over- and understaging and have a staging accuracy of only 70% [184, 185]. Overtreatment is a possible negative consequence.
- NAC should only be used in patients eligible for cisplatin combination chemotherapy; other combinations (or monotherapies) are inferior in metastatic BC and have not been tested adequately in the neoadjuvant setting [182, 186-198].

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

In small published series entailing imaging, attempts to identify the responders among patients undergoing NAC, suggested that response after two cycles of treatment is related to outcome. To date, no firm conclusions can be made [199, 200]. The definition of stable disease after two cycles of NAC is still undefined. To identify progression during NAC, imaging is being used in many centres, notwithstanding the lack of supporting evidence.

For responders to NAC, especially in those with a complete response (pT0 N0), treatment has a major positive impact on overall survival (OS) [201]. The overtreatment of non-responders and patients in the non-target population (i.e. patients without micrometastatic disease) are major drawbacks of NAC. Preoperative

identification of responders utilizing tumour molecular profiling in TURB specimens might guide the use of NAC [202, 203] (see Section 7.8.11 - Biomarkers). In addition, imaging methods for the early identification of responders during treatment have been explored. So far, neither PET, CT, nor conventional MRI or DCE MRI can accurately predict response [199, 200, 204, 205].

*7.2.3 **Summary of available data***

Several randomised phase III trials have addressed the question of NAC improving survival, with conflicting results [182, 186-195, 206-211]. The main differences in trial design were the type of chemotherapy (i.e. single-agent cisplatin or combination chemotherapy) and the number of cycles planned. From the statistical point of view, the studies differed in size, patient characteristics (e.g. clinical T-stages included) and the type of definitive treatment allowed (cystectomy and/or radiotherapy). Patients had to be fit for cisplatin. As a result of the lack of clarity, even though a considerable number of randomised trials had been performed, three meta-analyses were undertaken to answer the important question of whether NAC prolongs survival or not [196-198].

In the most recent meta-analysis, published in 2005 [198], with updated patient data from 11 randomised trials (3,005 patients), a significant survival benefit was shown in favour of NAC. The results of this analysis confirmed the previously published data and showed a 5% absolute improvement in survival at 5 years. The Nordic combined trial showed an absolute benefit of 8% survival at 5 years and 11% in the clinical T3 subgroup, translating into nine patients needed to treat [183]. Only cisplatin combination chemotherapy with at least one additional chemotherapeutic agent resulted in a meaningful therapeutic benefit [196, 198]; the regimens tested were MVA(E)C, CMV, CM, cisplatin/adriamycin, cisplatin/5-fluorouracil (5-FU), and CarboMV. More modern chemotherapy regimens like gemcitabine/cisplatin have shown similar pT0/pT1 rates as MVAC in the most recent retrospective series and pooled data analysis, but have not been used in randomised controlled trials [212-215].

The updated analysis of the largest randomised phase III trial [186] with a median follow-up of 8 years confirmed previous results and provided some additional interesting findings:

- 16% reduction in mortality risk;
- Improvement in 10-year survival from 30% to 36% with neoadjuvant CMV;
- Benefit with regard to distant metastases; No benefit for locoregional control and locoregional disease-free survival, with the addition of neoadjuvant CMV independent of the definitive treatment.

The presence of micrometastases is postulated to be lower in smaller tumours (T2) compared to more extensive tumours (T3b-T4b). T4 stage tumours are prone to a higher degree of clinical understaging because macrometastatic nodal deposits are detected more often in post-cystectomy specimens of these extensive tumours [183]. Further data support the use of NAC in the T2b-T3b tumour subgroup (former classification T3), which has shown to provide a modest but substantial improvement in long-term survival and significant downstaging [201].

*7.2.4 **Conclusions and recommendations for neoadjuvant chemotherapy***

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

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

GR = grade of recommendation; LE = level of evidence; OS = overall survival.

7.3 Pre- and postoperative radiotherapy in muscle-invasive bladder cancer

There is very limited and only older data on adjuvant radiotherapy after radical cystectomy. However, advances in targeting, reducing damage to surrounding tissue, may yield better results in the future [216]. A recent RCT in 100 patients, comparing pre-operative versus post-operative radiotherapy and radical cystectomy, showed comparable OS, DFS and complication rates [217]. Approximately half of these patients had UC, while the other half had squamous cell carcinoma.

*7.3.1 **Pre-operative radiotherapy***

7.3.1.1 Retrospective studies

Several old and retrospective studies reporting on pre-operative radiotherapy at doses over 40 Gy, followed after 4-6 weeks by cystectomy, showed down-staging, improved local control, especially in T3b tumours, and an improved survival, especially in complete responders to radiotherapy (references available upon request). However, these results cannot be used as a basis for modern Guideline advice due to major study limitations, including concomitant chemotherapy and differences in surgery and radiotherapy. This conclusion was supported by a 2003 systematic review [218]. A more recent retrospective study compared the long-term outcome of pre-operative versus no pre-operative radiotherapy in clinical T1-3 tumours [219]. Down-staging to T0 after cystectomy occurred in 7% (7/97) without radiotherapy versus 57% (51/90) with radiotherapy. In cT3 tumours, these results were 0% (0/16) versus 59% (19/34), respectively. Down-staging resulted in a longer PFS.

7.3.1.2 Randomised studies

Six randomised studies were published investigating pre-operative radiotherapy, although again from several decades ago. In the largest trial, pre-operative radiotherapy at a dose of 45 Gy was used in patients with muscle-invasive tumours [220]. There was a significant increase in pCR (9% to 34%) in favour of pre-operative radiotherapy, which was also a prognostic factor for better survival. The OS data was difficult to interpret because chemotherapy was used in a subset of patients and > 50% of patients (241/475) did not receive the planned treatment and were excluded for the final analyses. Two smaller studies using a dose of 20 Gy did not show a survival advantage or only a small advantage in ≥ T3 tumours [221, 222]. Two other small trials confirmed down-staging after pre-operative radiotherapy [223, 224].

A meta-analysis of the above five randomised trials showed an odds ratio for the difference in 5-year survival of 0.71 (95% CI: 0.48-1.06) in favour of pre-operative radiotherapy [225]. However, the meta-analysis was potentially biased by the patients in the largest trial who were not given the planned treatment. When the largest trial was excluded, the odds ratio was 0.94 (95% CI: 0.57-1.55, which is not significant).

*7.3.2 **Conclusions and recommendations for pre- and postoperative radiotherapy***

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

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

GR = grade of recommendation; LE = level of evidence; MIBC = muscle-invasive bladder cancer.

7.4 Radical surgery and urinary diversion

*7.4.1 **Removal of the tumour-bearing bladder***

7.4.1.1 Introduction

Radical cystectomy is the standard treatment for localised MIBC in most Western countries [164, 226]. Recent interest in patients' quality of life (QoL) has promoted the trend toward bladder-preserving treatment modalities, such as radio- and/or chemotherapy (see Sections 7.2 and 7.6). Performance status (PS) and age influence the choice of primary therapy, as well as the type of urinary diversion, with cystectomy being reserved for younger patients without concomitant disease and with a better PS. The value of assessing overall health before recommending and proceeding with surgery was emphasised in a multivariate analysis [136]. The analysis found an association between comorbidity and adverse pathological and survival outcome following radical cystectomy [136]. Performance status and comorbidity have a different impact on treatment outcomes and must be evaluated independently [142].

Controversy remains regarding age, radical cystectomy and the type of urinary diversion. Cystectomy is associated with the greatest risk reduction in disease-related and non-disease-related death in patients aged > 80 years [136]. The largest, retrospective, single-institution study on cystectomy to date found that patients aged > 80 years had increased postoperative morbidity, but not increased mortality. Although some patients successfully underwent a neobladder procedure, most patients were treated with an ileal conduit diversion [227].

It is particularly important to evaluate the function and QoL of elderly patients using a standardised geriatric assessment, as well as carrying out a standard medical evaluation (see Section 6.2) [228].

*7.4.2 **Timing and delay of cystectomy***

Nielsen et al. reported that a delay of radical cystectomy > 3 months in three American centres, was not associated with a worse clinical outcome [229]. Ayres et al. investigated whether a delay > 3 months would have the same effect in England [230]. Initially they found, in agreement with Nielsen et al, that cystectomy within 90 days of diagnosis had no effect on OS for MIBC (n = 955). However, analysis of T2 tumours showed a statistically significant survival benefit if patients had surgery within 90 days of diagnosis (n = 543; HR 1.40, 95% CI 1.10-1.79). A population-based study from the US SEER-database analysed patients who underwent a cystectomy between 1992 and 2001, also concluded that a delay of more than 12 weeks has a negative impact on outcome and should be avoided [231].

7.4.2.1 Indications

Traditionally, radical cystectomy was recommended for patients with MIBC T2-T4a, N0-Nx, M0 [226]. Other indications include high-risk and recurrent superficial tumours, BCG-resistant Tis, T1G3 (see Section 7.1), as well as extensive papillary disease that cannot be controlled with TURB and intravesical therapy alone. Salvage cystectomy is indicated in non-responders to conservative therapy, recurrence after bladder-sparing treatment, and non-urothelial carcinoma (these tumours respond poorly to chemo- and radiotherapy). It is also used as a purely palliative intervention, including in fistula formation, for pain or recurrent visible haematuria (macrohaematuria) (see Section 7.5.1 - Palliative cystectomy).

When there are positive lymph nodes, in the case of N1 involvement (metastasis in a single node in the true pelvis) orthotopic neobladder can still be considered, but not in N2 or N3 tumours [232].

*7.4.3 **Radical cystectomy: technique and extent***

In men, standard radical cystectomy includes removal of the bladder, prostate, seminal vesicles, distal ureters, and regional lymph nodes. In women, standard radical cystectomy includes removal of the bladder, entire urethra and adjacent vagina, uterus, distal ureters, and regional lymph nodes [233]. Controversies in evaluating the clinical significance of lymphadenectomy are related to two main aspects of nodal dissection: therapeutic procedure and/or staging instrument.

Two important autopsy investigations for radical cystectomy have been performed so far. The first investigation showed that in 215 patients with MIBC and nodal dissemination, the frequency of metastasis was 92% in regional (perivesical or pelvic), 72% in retroperitoneal, and 35% in abdominal lymph nodes. There was also a significant correlation between nodal metastases and concomitant distant metastases ($P < 0.0001$). Approximately 47% of the patients had both nodal metastases and distant dissemination and only 12% of the patients had nodal dissemination as the sole metastatic manifestation [234]. The second autopsy investigation focussed on the nodal yield when super-extended pelvic lymph node dissection (LND) was performed. Substantial inter-individual differences were found with counts ranging from 10 to 53 nodes [235]. These findings demonstrate the limited utility of node count as a surrogate for extent of dissection.

Regional lymph nodes have been shown to consist of all pelvic lymph nodes below the bifurcation of the aorta [236-240]. Mapping studies have also found that skip lesions at locations above the bifurcation of the aorta, without more distally located lymph node metastases, are rare [240, 241].

The extent of LND has not been established to date. Standard lymphadenectomy in bladder cancer patients involves removal of nodal tissue cranially up to the common iliac bifurcation, with the ureter being the medial border, and including the internal iliac, presacral, obturator fossa and external iliac nodes [242]. Extended lymphadenectomy includes all lymph nodes in the region of the aortic bifurcation, and presacral and common iliac vessels medial to the crossing ureters. The lateral borders are the genitofemoral nerves, caudally the circumflex iliac vein, the lacunar ligament and the lymph node of Cloquet, as well as the area described for standard lymphadenectomy [242-246]. A super-extended lymphadenectomy extends cranially to the level of the inferior mesenteric artery [247, 248].

In order to assess how and if cancer outcome is influenced by the extent of lymphadenectomy in patients with clinical N0M0 MIBC, a systematic review of the literature was undertaken [5]. Out of 1,692 abstracts retrieved and assessed, 19 studies fulfilled the review criteria and were included [242-246, 248-261]. All five studies comparing LND versus no LND reported a better oncological outcome for the former group. Seven out of 12 studies comparing (super-)extended with limited or standard LND reported a beneficial outcome for (super-) extended in at least a subset of patients. No difference in outcome was reported between extended and super-extended LND in the two high-volume-centre studies identified [248, 259].

Two other reviews reported that more limited pelvic LND was associated with suboptimal staging as well as poorer outcome compared with standard or extended LND [262, 263]. However, all of these identified studies suffered from significant methodological limitations and were prone to bias, thereby compromising the quality and reliability of the evidence. Further data from on-going randomised trials on the therapeutic impact of the extent of lymphadenectomy are awaited.

It has been suggested that progression-free survival as well as OS might be correlated with the number of lymph nodes removed during surgery, although there are no data from randomised controlled trials on the minimum number of lymph nodes that should be removed. Nevertheless, survival rates increase with the number of dissected lymph nodes [264]. Removal of at least 10 lymph nodes has been postulated as sufficient for evaluation of lymph node status, as well as being beneficial for OS in retrospective studies [265-267]. In conclusion, extended LND might have a therapeutic benefit compared to less-extensive LND, but due to bias, no firm conclusions can be drawn [5].

7.4.3.1 Laparoscopic/robotic-assisted laparoscopic cystectomy

Laparoscopic cystectomy and robotic-assisted laparoscopic cystectomy (RALC) are feasible both in male and female patients [268, 269].

Laparoscopic cystectomy is a technically challenging procedure that requires a high level of skill and has a long learning curve [270]. Recently, Aboumarzouk and co-workers conducted a systematic review in line with both Cochrane and PRISMA guidelines [271, 272]. All the included studies were observational cohort studies with no randomisation, and all reported experience with laparoscopic compared with open cystectomy [273-280]. A total of 427 patients were included: 211 underwent laparoscopic cystectomy with extracorporeal reconstruction, and 216 were included in the open cystectomy group. Patients in the laparoscopy group were significantly younger than those in the open cystectomy group. The laparoscopic group had significantly longer operative times, but less blood loss, less time to oral intake, less analgesic requirement, and shorter length of hospital stay. Patients who underwent open cystectomy developed significantly more minor complications than those treated laparoscopically. There was no difference between the two groups regarding LND yields, major complications, positive margins, pathological results, local recurrence, or distant metastases. However, there were significantly more positive nodes in the open cystectomy group. The main limitation of this meta-analysis was the inclusion of non-randomised observational studies with small patient cohorts. Only five of the studies had > 20 patients and all the studies had cohorts with < 50 patients. This led to a substantial risk of bias in the results. Another limitation was the age selection bias.

Laparoscopic cystectomy and RALC data often suffer from selection bias including younger patients, lower stage of disease, and minimal comorbidity compared to most contemporary studies of open cystectomy [281-286]. To date, laparoscopic cystectomy and RALC still need to be considered experimental because of the limited number of cases reported, absence of long-term oncological and functional outcome data, and possible selection bias [281, 287].

Laparoscopic intracorporeal construction of urinary diversion (with or without robotic assistance) has been tested in small series only [282-284, 286]. It is a challenging and lengthy procedure with the currently available equipment and must therefore be regarded as experimental. Furthermore, there are no long-term results available. Laparoscopic cystectomy and pelvic lymphadenectomy (with or without robotic assistance), with extracorporeal construction of urinary diversion, is an option for surgical treatment only in experienced centres [287] (LE: 3).

*7.4.4 **Urinary diversion after radical cystectomy***

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

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

- Rectosigmoid diversions, such as uretero- (ileo-)rectostomy.

Different types of segments of the intestinal tract have been used to reconstruct the urinary tract, including the stomach, ileum, colon and appendix [288]. Several studies have compared certain aspects of health-related QoL, such as sexual function, urinary continence and body image, in patient cohorts with different types of urinary diversion. However, further research is needed on preoperative tumour stage and functional situation, socioeconomic status, and time interval to primary surgery.

7.4.4.1 Preparations for surgery

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

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

When there are positive lymph nodes, orthotopic neobladder can nevertheless be considered in the case of N1 involvement (metastasis in a single node in the true pelvis) but not for N2 or N3 tumours [289].

Oncological results after orthotopic neobladder substitution or conduit diversion are similar in terms of local or distant metastasis recurrence, but secondary urethral tumours seem less common in patients with neobladder compared to those with conduits or continent cutaneous diversions [290].

For cystectomy, general preparations are necessary as for any other major pelvic and abdominal surgery. If the urinary diversion is constructed from gastrointestinal segments, the length or size of the respective segments and their pathophysiology when storing urine must be considered [291]. Despite the necessary interruption and re-anastomosis of bowel, a formal bowel preparation may not be necessary [292]. Furthermore, bowel recovery time has been reduced by the use of early mobilisation, early oralisation, and gastrointestinal stimulation with metoclopramide and chewing gum [293].

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

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

Relative contraindications specific for an orthotopic neobladder are high-dose preoperative radiotherapy, complex urethral stricture disease, and severe urethral sphincter-related incontinence [294-296].

7.4.4.2 Patient selection for orthotopic diversion

Radical cystectomy and urinary diversion are the two steps of one operation. However, the literature uniformly reports the complications of radical cystectomy, while ignoring the fact that most complications are diversion related [297]. Age alone is not a criterion for offering continent diversion [296, 298]. Comorbidity, cardiac and pulmonary function, and cognitive function are all important factors that should be considered, along with the patient's social support and preference.

Age > 80 years is often considered to be the threshold after which neobladder reconstruction is not recommended, however, there is no exact age for strict contraindication. In most large series from experienced centres, the rate of orthotopic bladder substitution after cystectomy for bladder tumour is up to 80% for men and 50% for women [299-302]. Nevertheless, no randomised controlled studies comparing conduit diversion with neobladder or continent cutaneous diversion have been performed.

7.4.4.2.1 Ureterocutaneostomy

Ureteral diversion to the abdominal wall is the simplest form of cutaneous diversion. It is considered a safe procedure. It is therefore preferred in older, or otherwise compromised, patients, who need a supravesical diversion [303, 304]. However, others have demonstrated that, in carefully selected elderly patients, all other forms of wet and dry urinary diversions, including orthotopic bladder substitutions, are possible [227]. Technically, either one ureter, to which the other shorter one is attached end-to-side, is connected to the skin (transureteroureterocutaneostomy) or both ureters are directly anastomosed to the skin. Due to the smaller diameter of the ureters, stoma stenosis has been observed more often than in intestinal stomas [303].

In a retrospective comparison with short or median follow-up of 16 months, the diversion-related complication rate was considerably lower for ureterocutaneostomy compared to ileal or colon conduit [305]. Despite the limited comparative data available, however, it must be taken into consideration that older data and clinical experience suggest ureter stenosis at the skin level and ascending UTI are more frequent complications in comparison to those with ileal conduit diversion. In a retrospective study comparing various forms of intestinal diversion, ileal conduits had fewer late complications than continent abdominal pouches or orthotopic neobladders [306].

7.4.4.2.2 Ileal conduit

The ileal conduit is still an established option with well-known/predictable results. However, up to 48% of patients develop early complications including UTIs, pyelonephritis, ureteroileal leakage and stenosis [306]. The main complications in long-term follow-up studies are stomal complications in up to 24% of cases and functional and/or morphological changes of the UUT in up to 30% [307-309]. An increase in complications was seen with increased follow-up in the Berne series of 131 patients followed for a minimum of 5 years (median follow-up 98 months) [307]: the rate of complications increased from 45% at 5 years to 94% in those surviving > 15 years. In the latter group, 50% of patients developed UUT changes and 38% developed urolithiasis.

7.4.4.2.3 Continent cutaneous urinary diversion

A low-pressure detubularised ileal reservoir can be used as a continent cutaneous urinary diversion for self-catheterisation; gastric, ileocecal and sigma pouches have also been described [310-312]. Different antireflux techniques can be used [233]. Most patients have a well-functioning reservoir with day-time and night-time continence approaching 93% [313]. In a retrospective study of > 800 patients, stomal stenosis was seen in 23.5% of patients with an appendix stoma and 15% of those with an efferent intussuscepted ileal nipple [313]. Stone formation in the pouch occurred in 10% of patients [313-315]. In a small series of previously irradiated female patients, incontinence and stomal stenosis was seen in eight of 44 patients (18%) [316].

7.4.4.2.4 Ureterocolonic diversion

The oldest and most common form of ureterocolonic diversion was primarily a refluxive and later an antirefluxive connection of ureters to the intact rectosigmoid colon (uretero-rectosigmoidostomy) [317, 318]. Most indications for this procedure have become obsolete due to a high incidence of upper UTIs and the long-term risk of developing colon cancer [289, 290]. Bowel frequency and urge incontinence are additional adverse effects of this type of urinary diversion. However, it may be possible to circumvent the above-mentioned problems by interposing a segment of ileum between the ureters and rectum or sigmoid in order to augment capacity and avoid direct contact between the urothelium and colonic mucosa, as well as faeces and urine [319].

7.4.4.2.5 Orthotopic neobladder

An orthotopic bladder substitution to the urethra is now commonly used both in men and women. Contemporary reports document the safety and long-term reliability of this procedure. In several large centres, this has become the diversion of choice for most patients undergoing cystectomy [174, 226, 296]. In elderly patients (> 80 years), however, it is rarely performed, even in high-volume expert centres [320, 321].

The terminal ileum is the gastrointestinal segment most often used for bladder substitution. There is less experience with the ascending colon, including the caecum, and the sigmoid [226]. Emptying of the reservoir anastomosed to the urethra requires abdominal straining, intestinal peristalsis, and sphincter relaxation. Early and late morbidity in up to 22% of the patients is reported [322, 323]. In two studies with 1,054 and 1,300 patients [296, 324], long-term complications included diurnal (8-10%) and nocturnal (20-30%) incontinence, ureterointestinal stenosis (3-18%), metabolic disorders, and vitamin B12 deficiency. In a recent study that compared cancer control and patterns of disease recurrence in patients with neobladder and ileal conduit, there was no difference in CSS between the two groups when adjusting for pathological stage [325]. Urethral recurrence in neobladder patients seems rare (1.5-7% for both male and female patients) [296, 326]. These results indicate that neobladder in male and female patients does not compromise the oncological outcome of cystectomy. It remains debatable whether neobladder is better for QoL compared to non-continent urinary diversion [327-329].

Various forms of UUT reflux protection, including a simple isoperistaltic tunnel, ileal intussusception, tapered ileal prolongation implanted subserosally, and direct (sub)mucosal or subserosal ureteral implantation, have been described [315, 323]. According to the long-term results, the UUT is protected sufficiently by either method.

In conclusion, standard radical cystectomy in male patients with bladder neoplasms includes removal of the

entire bladder, prostate, seminal vesicles, distal ureters (segment length undefined), and corresponding lymph nodes (extent undefined) (LE: 2b). In female patients, standard radical cystectomy includes removal of the entire bladder, urethra and adjacent vagina, uterus, distal ureters, and corresponding lymph nodes.

A detailed investigation of the bladder neck prior to radical cystectomy is important for women who are scheduled for an orthotopic bladder substitute [330]. In women undergoing radical cystectomy the rate of concomitant urethral malignancy has been reported to range around 12-16% [331]. Localisation of the primary tumour at the bladder neck correlated strongly with concomitant urethral malignancy. Additionally, the tumours were at higher risk of advanced stage and nodal involvement [332].

Currently, it is not possible to recommend a particular type of urinary diversion. However, most institutions prefer ileal orthotopic neobladders and ileal conduits, based on clinical experience [333, 334]. In selected patients, f.i. patients with a single kidney, ureterocutaneostomy is surgically the least burdensome type of diversion (LE: 3). Recommendations related to radical cystectomy and urinary diversions are listed in section 7.5.

*7.4.5 **Morbidity and mortality***

In two long-term studies, and one population-based cohort study, the perioperative mortality was reported as 1.2-3% at 30 days and 2.3-5.7% at 90 days [174, 297, 299, 335]. In a large single-centre series, early complications (within 3 months of surgery) were seen in 58% of patients [297]. Late morbidity is usually due to the type of urinary diversion (see also above) [300, 336]. Early morbidity associated with radical cystectomy for NMIBC (at high risk for disease progression) is similar and no less than that associated with muscle-invasive tumours [337]. In general, lower morbidity and (perioperative) mortality have been observed by surgeons and in hospitals with a higher caseload and therefore more experience [338-341].

Table 7.1: Management of neobladder morbidity (30-64%) [342].

CLAVIEN System		Morbidity	Management
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs such as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.	**Immediate complications:**	
		Post-operative ileus	Nasogastric intubation (usually removed at J1) Chewing gum Avoid fluid excess and hypovolemia (provoke splanchnic hypoperfusion)
		Postoperative Nausea and Vomiting	Antiemetic agent (decrease opioids) Nasogastric intubation
		Urinary infection	ATB, no ureteral catheter removal Check the 3 drainages (ureters and neobladdder)
		Ureteral catheter (UC) obstruction	5cc saline UC injection to avoid the obstruction Increase volume infusion to increase dieresis
		Intra abdominal urine leakage (anastomosis leakage)	Check drainages and watchful waiting
		Anaemia well tolerated	Martial treatment (give iron supplement)
		Late complications:	
		Non compressive lymphocele	Watchful waiting
		Mucus cork	Cough Indwelling catheter to remove the obstruction

		Incontinence	Urine analysis (infection), echography (post-void residual) Physiotherapy
		Retention	Drainage and self-catheterisation education
Grade II	Requiring pharmacological treatment with drugs other than those allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.	Anaemia badly tolerated or if myocardial cardiopathy history	Transfusion
		Pulmonary embolism	Heparinotherapy
		Pyelonephritis	ATB and check kidney drainage (nephrostomy if necessary)
		Confusion or neurological disorder	Neuroleptics and avoid opioids
Grade III	Requiring surgical, endoscopic or radiological intervention	UC accidentally dislodged	Indwelling leader to raise the UC
		Anastomosis stenosis (7%)	Renal drainage (ureteral catheter or nephrostomy)
		Ureteral reflux	No treatment if asymptomatic
III-a	Intervention not under general anaesthesia	Compressive lymphocele	Transcutaneous drainage or intraoperative marsupialisation (cf grade III)
III-b	Intervention under general anaesthesia	Ileal anastomosis leakage	Ileostomy ASAP
		Evisceration	Surgery in emergency
		Compressive lymphocele	Surgery (marsupialisation)
Grade IV	Life-threatening complication (including CNS complications: brain haemorrhage, ischaemic stroke, subarachnoid bleeding, but excluding transient ischaemic attacks) requiring IC/ICU management.	Rectal necrosis	Colostomy
		Neobladder rupture	Nephrostomy and indwelling catheter / surgery for repairing neobladder
		Severe sepsis	ATB and check all the urinary drainages and CT Scan in emergency
IV-a	Single organ dysfunction (including dialysis)	Non obstructive renal failure	Bicarbonate / aetiology treatment
IV-b	Multi-organ dysfunction	Obstructive pyelonephritis and septicaemia	Nephrostomy and ATB
Grade V	Death of a patient		
Suffix 'd'	*If the patient suffers from a complication at the time of discharge, the suffix "d" (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.*		

ASAP = as soon as possible; ATB = antibiotics; CNS = central nervous system; CT = computed tomography; IC = intensive care; ICU = intensive care unit; UC = urethral catheter.

7.4.6 ***Survival***

According to a multi-institutional database of 888 consecutive patients undergoing radical cystectomy for BC, the 5-year recurrence-free survival was 58% and the CSS was 66% [343]. Recent external validation of postoperative nomograms for bladder-cancer-specific mortality showed similar results, with bladder-cancer-specific survival of 62% [344].

Recurrence-free survival and OS in a large single-centre study of 1,054 patients was 68% and 66% at 5 years and 60% and 43%, at 10 years, respectively [164]. However, the 5-year recurrence-free survival in node-positive patients who underwent cystectomy was considerably less at 34-43% [163, 164, 345]. In a surgery-only study, the 5-year recurrence-free survival was 76% in patients with pT1 tumours, 74% for pT2, 52% for pT3, and 36% for pT4 [164].

A trend analysis according to the 5-year survival and mortality rates of BC in the United States, between 1973 and 2009 with a total of 148,315 BC patients, revealed an increased stage-specific 5-year survival rate for all stages, except for metastatic disease [8].

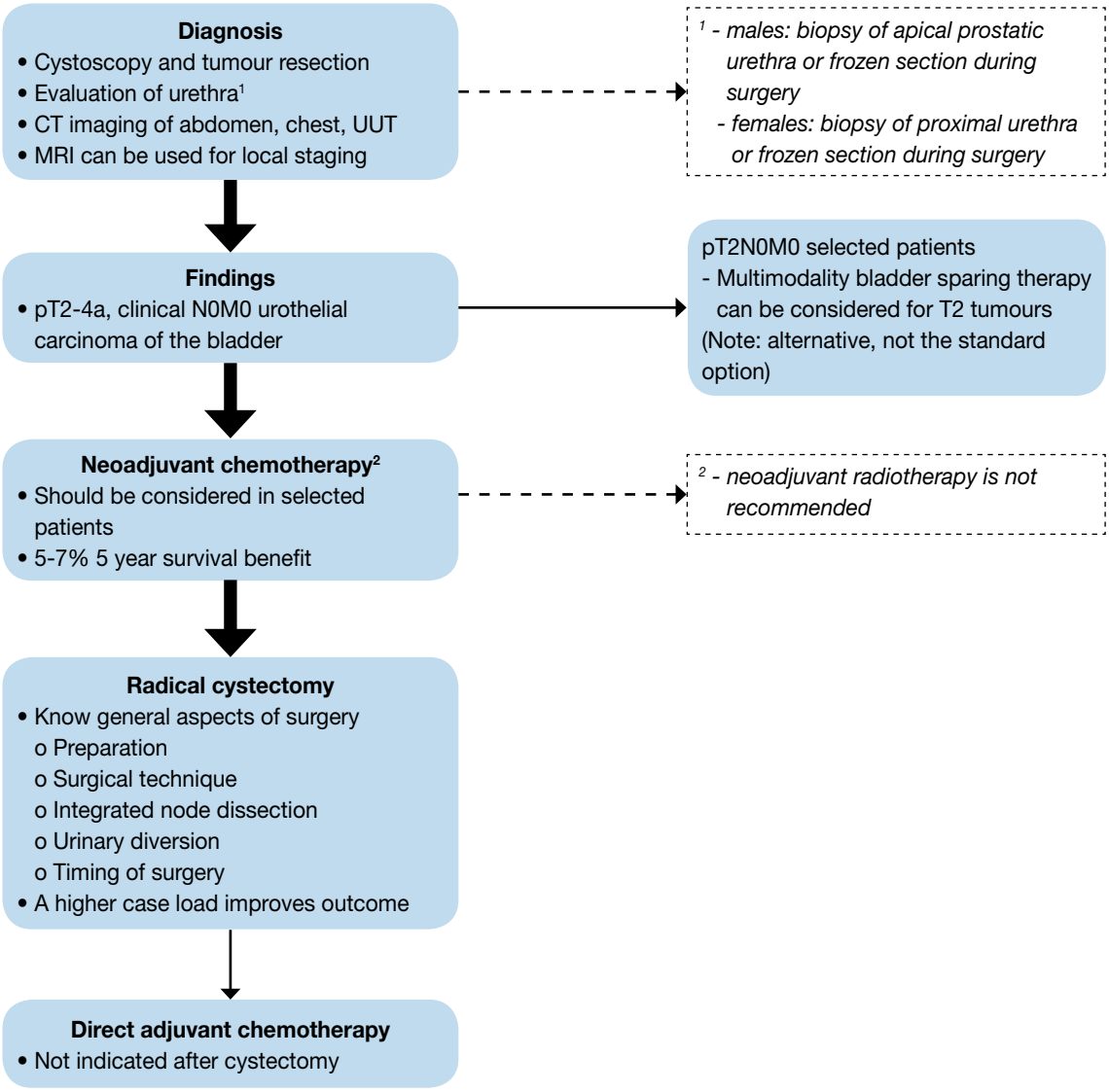
7.4.7 *Conclusions and recommendations for radical cystectomy and urinary diversion*

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

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

**Upgraded following EAU Working Panel consensus.*
GR = grade of recommendation; LE = level of evidence; LND = lymph node dissection; MIBC = muscle-invasive bladder cancer.

Figure 7.1: Flowchart for the management of T2-T4a N0M0 urothelial bladder cancer



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

7.5. Unresectable tumours

*7.5.1 **Palliative cystectomy for muscle-invasive bladder carcinoma***

Locally advanced tumours (T4b, invading the pelvic or abdominal wall) may be accompanied by several debilitating symptoms, including bleeding, pain, dysuria and urinary obstruction. These patients are candidates for palliative treatments, such as palliative radiotherapy. Palliative cystectomy with urinary diversion carries the greatest morbidity and should be considered for symptom relief only if there are no other options [346-348].

Locally advanced MIBC can be associated with ureteral obstruction due to a combination of mechanical blockage by the tumour and invasion of ureteral orifices by tumour cells. In a series of 61 patients with obstructive uraemia, radical cystectomy was not an option in 23 patients, and obstruction was relieved using permanent nephrostomy tubes [349]. Another 10 patients underwent palliative cystectomy, but local pelvic recurrence occurred in all 10 patients within the first year of follow-up. Another small (n = 20) study showed that primary cystectomy for T4 BC was technically feasible and associated with a very tolerable therapy-related morbidity and mortality [350].

7.5.1.1 Recommendations for unresectable tumours

Recommendations	GR
In patients with inoperable locally advanced tumours (T4b), primary radical cystectomy is a palliative option.	B
In patients with symptoms, palliative cystectomy may be offered.	

GR = grade of recommendation.

7.5.2 ***Supportive care***

7.5.2.1 Obstruction of the UUT

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

7.5.2.2 Bleeding and pain

In the case of bleeding, the patient must first be screened for coagulation disorders or the patient's use of anticoagulant drugs must be reviewed. Transurethral (laser) coagulation may be difficult in a bladder full of tumour or with a bleeding tumour. Intravesical rinsing of the bladder with 1% silver nitrate or 1-2% alum can be effective [351]. It can usually be done without any anaesthesia. The instillation of formalin (2.5-4% during 30 minutes) is a more aggressive and more painful procedure, requiring anaesthesia. Formalin instillation has a higher risk of side-effects, e.g. bladder fibrosis, but is more likely to control the bleeding [351]. Vesicoureteral reflux should be excluded to prevent renal complications.

Radiation therapy is another common strategy for control of bleeding, and is also used to control pain. An older study reported control of haematuria in 59% of patients and pain control in 73% [352]. Irritative bladder and bowel complaints due to irradiation are possible, but are usually mild. Non-conservative options are embolisation of specific arteries in the small pelvis, with success rates as high as 90% [351]. Radical surgery is a last resort and includes cystectomy and diversion (see above Section 7.5.1).

7.6 Bladder-sparing treatments for localised disease

7.6.1 ***Transurethral resection of bladder tumour (TURB)***

TURB alone in patients with muscle-invasive bladder tumours is only possible as a therapeutic option if tumour growth is limited to the superficial muscle layer and if re-staging biopsies are negative for residual (invasive) tumour [353]. In general about half will still have to undergo radical cystectomy for recurrent muscle-invasive cancer with a disease-specific mortality rate of up to 47% within this group [354]. A disease-free status at re-staging TURB appears to be crucial in making the decision not to perform radical cystectomy [355, 356]. A prospective study by Solsona et al., which included 133 patients with a radical TURB and re-staging negative biopsies, has recently reported a 15-year follow-up [356]. 30% had recurrent NMIBC and went on to intravesical therapy, and 30% (n = 40) progressed, of which 27 died of BC. After 5, 10 and 15 years the results showed a CSS of 81.9%, 79.5%, and 76.7%, and a progression-free survival (PFS) with an intact bladder of 75.5%, 64.9%, and 57.8%, respectively.

In conclusion, TURB alone should only be considered as a therapeutic option for muscle-invasive disease after radical TURB, when the patient is unfit for cystectomy or a multimodality bladder-preserving approach, or refuses open surgery [357].

7.6.1.2 Recommendation for transurethral resection of bladder tumour

Recommendation	LE	GR
Transurethral resection of bladder tumour alone is not a curative treatment option in most patients.	2a	B

GR = grade of recommendation; LE = level of evidence.

7.6.2 ***External beam radiotherapy (EBRT)***

The target field usually comprises the bladder only, with a safety margin of 1.5-2 cm to allow for unavoidable organ movements [358]. Any beneficial effect with larger pelvic fields has not been demonstrated. The target dose for curative radiotherapy for BC is 60-66 Gy, with a subsequent boost using external radiotherapy or interstitial brachytherapy. The course of radiotherapy should not extend beyond 6-7 weeks to minimise the repopulation of cancer cells [359, 360]. The use of modern standard radiotherapy techniques results in major,

related, late morbidity of the urinary bladder or bowel in less than 5% of tumour-free patients [361]. As well as the response to radiotherapy, important prognostic factors for outcome include tumour size, hydronephrosis and completeness of the initial TURB. Additional prognostic factors found in a recent single institution study (n = 459, including 30% of unfit T1 patients) were age and stage [362]. Overall, 5-year survival rates in patients with MIBC range between 30% and 60%, depending on whether they show a complete response (CR) following radiotherapy. Cancer-specific survival rates are between 20% and 50% [360, 363-365]. Similar long-term results were reported by Chung et al. [366]. A total of 340 patients with MIBC were treated with EBRT alone, EBRT with concurrent chemotherapy, or neoadjuvant chemotherapy followed by EBRT. The overall CR was 55% and the 10-year DSS and OS were 35% and 19%, respectively. Complete response was 64% after EBRT alone, 79% after concurrent chemotherapy (n = 36), and 52% after neoadjuvant chemotherapy (n = 57). Younger age, lower tumour stage and absence of CIS were associated with a significant improvement in survival.

Based on available trials, a Cochrane analysis has demonstrated that radical cystectomy has an OS benefit compared to radiotherapy [367].

Similar long-term results were reported by Chung et al. [366]. A total of 340 patients with MIBC were treated with EBRT alone, EBRT with concurrent chemotherapy, or neoadjuvant chemotherapy followed by EBRT. The overall CR was 55% and the 10-year DSS and OS were 35% and 19%, respectively. Complete response was 64% after EBRT alone, 79% after concurrent chemotherapy (n = 36), and 52% after neoadjuvant chemotherapy (n = 57). Younger age, lower tumour stage and absence of CIS were associated with a significant improvement in survival.

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

7.6.2.1 Conclusions and recommendation for external beam radiotherapy

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

Recommendation	**GR**
Radiotherapy alone is not recommended as primary therapy for localised bladder cancer.	B

GR = grade of recommendation; LE = level of evidence.

7.6.3 ***Chemotherapy***

Chemotherapy alone rarely produces durable CRs. In general, a clinical CR rate of up to 56%, as reported in some series, must be weighed against a staging error of > 60% [368, 369]. Response to chemotherapy is a prognostic factor for treatment outcome and eventual survival [184], though it may be confounded by patient selection.

Several groups have reported the effect of chemotherapy on resectable tumours (neoadjuvant approach), as well as unresectable primary tumours [182, 211, 370, 371]. Neoadjuvant chemotherapy with 2-3 cycles of methotrexate, vinblastine, adriamycin plus cisplatin (MVAC) or cisplatin, methotrexate plus vinblastine (CMV) has led to a down-staging of the primary tumour in different prospective series [182, 211, 370]. Pathological complete responses of primary bladder tumours were reached in 12-50% of patients after MVAC and in 12-22% of patients after gemcitabine/cisplatin (GC) in phase II and phase III trials [182, 211, 370, 372-379]. Contemporary series with GC followed by radical cystectomy reported inferior pT0 rates, which may have been related to a lack of dose density and inappropriate delay of surgery [215].

For highly selected patients, a bladder-conserving strategy with TURB and systemic cisplatin-based chemotherapy, preferably with MVAC, may allow long-term survival with intact bladder [184]. However, this approach cannot be recommended for routine use.

7.6.3.1 Conclusion and recommendation for chemotherapy for muscle-invasive bladder tumours

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

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

GR = grade of recommendation; LE = level of evidence.

*7.6.4 **Multimodality bladder-preserving treatment***

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

Micrometastasis is targeted by platinum-based combination chemotherapy which is covered in Section 7.2 on neoadjuvant chemotherapy. The aim of multimodality therapy is to preserve the bladder and QoL, without compromising outcome. A collaborative review addressed this approach [380].

There are no completed randomised controlled trials to compare the outcome of MMT with the gold standard, radical cystectomy. Many of the reported series have differing characteristics to the large surgical series which typically have median ages in the mid-late 60s compared to mid-70s for some large radiotherapy series (reviewed in [381]). In the case of MMT, two distinct patterns of care may be distinguished: treatment aimed at patients fit for cystectomy and treatment aimed at older, less fit patients. For the former category, MMT is a selective bladder preservation option. In that case the initial step is a radical TURB, where as much tumour as possible should be resected. This implies that appropriate patient selection (T2 tumours, no CIS) is critical [382]. For patients who are not candidates for cystectomy, less stringent criteria can be applied, although extensive CIS and poor bladder function should both be regarded as strong contraindications.

Following TURBT and staging, treatment then comprises EBRT with concurrent radiosensitising drugs. Two schedules are in common use worldwide: a split dose format with interim cystoscopy is used in North America [383], whilst single phase treatment is more commonly used elsewhere (reviewed in [381]). A typical schedule for single phase radiotherapy would be either 64-66 Gy in 32-33 fractions or 55 Gy in 20 fractions, generally to the bladder plus tumour only. For radiosensitising chemotherapy cisplatin [383] or mitomycin C plus 5-fluorouracil [381] can be used, but other schedules have also been used. In particular, hypoxic cell sensitisation with nicotinamide and carbogen has been evaluated in a large phase 3 trial [384]. With MMT, 5-year CSS and OS rates of 50% to 82% and from 36% to 74% were achieved, respectively [361, 381, 383-387]. Salvage cystectomy rates are 10-30% [381, 383, 387]. There are data to show that major complication rates are similar for salvage and primary cystectomy [388]. The majority of recurrences post-MMT are non-invasive and can be managed conservatively [381].

The collaborative review came to the conclusion that there are accumulating data to suggest that bladder preservation with MMT leads to acceptable outcomes and therefore may be considered a reasonable treatment option in well-selected patients as compared to radical cystectomy. It should also be considered in all patients where surgery is contraindicated, either relatively or absolutely as the factors that determine fitness for surgery and chemoradiotherapy differ.

A bladder-preserving multimodality strategy requires very close multidisciplinary co-operation and a high level of patient compliance. Even if a patient has shown a CR to a multimodality bladder-preserving strategy, the bladder remains a potential source of recurrence, hence long-term bladder monitoring is essential and patient counselling is required.

7.6.4.1 Conclusions and recommendations for multimodality treatment in MIBC

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

Recommendations	GR
Surgical intervention or multimodality treatments are the preferred curative therapeutic approaches as they are more effective than radiotherapy alone.	B
Multimodality treatment could be offered as an alternative in selected, well-informed and compliant patients, especially for whom cystectomy is not an option.	B

GR = grade of recommendation; LE = level of evidence.

7.7 Adjuvant chemotherapy

Adjuvant chemotherapy after radical cystectomy for patients with pT3/4 and/or lymph node positive (N+) disease without clinically detectable metastases (M0) is under debate [389, 390] and still infrequently used [178].

The general benefits of adjuvant chemotherapy include:

- Chemotherapy is administered after accurate pathological staging, therefore treatment in patients at low risk for micrometastases is avoided;
- No delay in definitive surgical treatment.

The drawbacks of adjuvant chemotherapy are:

- Assessment of in vivo chemosensitivity of the tumour is not possible and overtreatment is an unavoidable problem;
- Delay or intolerability of chemotherapy, due to postoperative morbidity [391].

There is limited evidence from adequately conducted and accrued randomised phase III trials in favour of the routine use of adjuvant chemotherapy [390, 392-397]. Individual patient data from six randomised trials [398-402] of adjuvant chemotherapy were included in one meta-analysis [392] with 491 patients for survival analysis (unpublished data from Otto et al, were included in the analysis). All these trials were suboptimal with serious deficiencies, including small sample size (underpowered), early cessation of patient entry, and flaws in design and statistical analysis, including irrelevant endpoints or a lack of recommendations concerning salvage chemotherapy for relapse or metastases [390]. In these trials, three or four cycles of CMV (cisplatin, methotrexate and vinblastine), CISCA (cisplatin, cyclophosphamide, and adriamycin), MVA(E)C (methotrexate, vinblastine, adriamycin or epirubicin, and cisplatin) and CM (cisplatin and methotrexate) were used [403], and one trial used cisplatin monotherapy [401]. These data were not convincing enough to give an unequivocal recommendation for the use of adjuvant chemotherapy.

In a more recent meta-analysis [393], an additional three studies were included [394-396]. However, the patient number in this meta-analysis of nine trials was only 945, and none of the trials were fully accrued and no individual patient data were used [393]. For one trial, only an abstract was available at the time of the meta-analysis [395], and none of the included trials by themselves were significantly positive for overall survival (OS) in favour of adjuvant chemotherapy. In two of the trials, more modern chemotherapy regimens were used (gemcitabine/cisplatin and paclitaxel/gemcitabine and cisplatin) [394, 395]. The hazard ratio (HR) for OS was 0.77 and there was a trend towards an OS benefit when including all nine trials. The effect was stronger for disease-free survival (DFS) (HR: 0.66; 95% CI: 0.48-0.92) and when stratified for the ratio of nodal positivity (HR: 0.64; 95% CI: 0.45- 0.91). The background of this finding was a heterogeneity in outcomes observed between the included studies. After stratification of the studies by the ratio of node positivity, no further heterogeneity was identified. The HR for DFS associated with adjuvant cisplatin-based chemotherapy in studies with higher nodal involvement was 0.39 (95% CI: 0.28-0.54), compared with 0.89 (95% CI: 0.69-1.15) in studies with less nodal involvement.

Furthermore, a retrospective cohort analysis that included 3,974 patients after cystectomy and lymph node dissection showed an OS benefit in high-risk subgroups (extravesical extension and nodal involvement) [HR: 0.75; CI 0.62-0.90] [404]. The most recent publication of the so far largest RCT (EORTC 30994), although not fully accrued, showed a significant improvement of PFS for immediate compared with deferred treatment (HR 0.54, 95% CI 0.4-0.73, $p < 0.0001$), there was, however, no significant OS benefit [405].

From the currently available evidence, it is still unclear whether immediate adjuvant chemotherapy or chemotherapy at the time of relapse is superior, or if the two approaches are equivalent with respect to the endpoint of OS. Cisplatin-based combination chemotherapy results in long-term DFS, even in metastatic disease, mainly in patients with lymph node metastases only, and with a good performance status [376, 406, 407]. With the most recent meta-analysis, the positive role of adjuvant chemotherapy for BC has been strengthened, however, still with a poor level of evidence [393]. Patients should be informed about potential chemotherapy options before radical cystectomy, including neoadjuvant and adjuvant chemotherapy, and the limited evidence for adjuvant chemotherapy.

7.7.1 Recommendations for adjuvant chemotherapy

Recommendations	GR
Adjuvant cisplatin-based combination chemotherapy can be offered to patients with pT3/4 and/or pN+ disease if no neoadjuvant chemotherapy has been given.	C

GR = grade of recommendation.

7.8 Metastatic disease

*7.8.1 **Introduction***

Half of the patients with muscle-invasive urothelial cancer (UC) relapse after radical cystectomy, depending on the pathological stage of the primary tumour and the nodal status. Local recurrence accounts for 30% of relapses, whereas distant metastases are more common. Ten to fifteen percent of patients are already metastatic at diagnosis [408]. Before the development of effective chemotherapy, patients with metastatic urothelial cancer rarely had a median survival that exceeded 3-6 months [409].

7.8.1.1 Prognostic factors and treatment decisions

Prognostic factors are crucial for assessing phase II study results and stratifying phase III trials [374, 410]. In a multivariate analysis, Karnofsky performance status (PS) of ≤ 80% and presence of visceral metastases were independent prognostic factors of poor survival after treatment with MVAC (methotrexate, vinblastine, adriamycin and cisplatin [378]. They have also been validated for newer combination chemotherapy regimens [411-413].

For patients refractory to, or progressing shortly after, platinum-based combination chemotherapy, four prognostic groups have been established, based on three adverse factors that have been developed in patients treated with vinflunine and that have been validated in an independent data set: Hb < 10 g/dL; presence of liver metastases; and ECOG PS ≥ 1 [414]. Cisplatin, using different schedules, has also been administered in patients with a GFR down to 40 mL/min. The respective studies were mostly small sized phase I and II trials [415-418]. One phase III trial used a cut off for cisplatin eligibility of ≥ 50 mL/min [419].

7.8.1.2 Comorbidity in metastatic disease

Comorbidity is defined as “the presence of one or more disease(s) in addition to an index disease” (see Section 6.2.1). Comorbidity increases with age. However, chronological age does not necessarily correlate with functional impairment. There are several definitions by which patients can be selected as potentially fit or unfit for chemotherapy, but age is not among them [420].

7.8.1.3 Not eligible for cisplatin (unfit)

The European Organisation for Research and Treatment of Cancer (EORTC) conducted the first randomised phase II/III trial for urothelial carcinoma patients who were unfit for cisplatin chemotherapy [421]. The EORTC definitions were GFR < 60 mL/min and/or PS 2.

An international survey among BC experts [422] was the basis for a consensus statement on how to classify patients unfit for cisplatin-based chemotherapy. At least one of the following criteria has to be present: PS > 1; GFR ≤ 60 mL/min; grade ≥ 2 audiometric loss and peripheral neuropathy; and New York Heart Association (NYHA) class III heart failure [423].

More than 50% of patients with urothelial cancer are not eligible for cisplatin-based chemotherapy [424-427].

Renal function assessment in UC is of utmost importance for treatment selection. Calculation of creatinine clearance (CrCl) (24-h urine collection) with current formulae tend to underestimate clearance in patients aged > 65 years compared to measured CrCl [424, 428].

*7.8.2 **Single-agent chemotherapy***

Response rates to single-agent, first-line chemotherapy vary. The most robust data have shown a response rate of about 25% for first- and second-line gemcitabine in several phase II trials [429, 430]. Responses with single agents are usually short-lived, complete responses are rare and no long-term disease-free survival has been reported. The median survival in such patients is only 6-9 months.

*7.8.3 **Standard first-line chemotherapy for fit patients***

Cisplatin-containing combination chemotherapy has been the standard of care since the late 1980s (for a review see [431]). MVAC and gemcitabine/cisplatin (GC) prolonged survival to up to 14.8 and 13.8 months, respectively, compared to monotherapy and older combinations. Neither of the two combinations is superior to the other, but equivalence has not been tested. Response rates were 46% and 49% for MVAC and GC, respectively. The long-term survival results have confirmed the anticipated equivalence of the two regimens [406]. The major difference between the above-mentioned combinations is toxicity. The lower toxicity of GC [146] has resulted in it becoming a new standard regimen [432]. MVAC is better tolerated when combined with granulocyte colony-stimulating factor (G-CSF) [432, 433].

High-dose intensity MVAC (HD-MVAC) with G-CSF is less toxic and more efficacious than standard MVAC in terms of dose density, complete response, and 2-year survival rate. However, there is no significant difference in median survival between the two regimens [434, 435].

In general, all disease sites have been shown to respond to cisplatin-based combination chemotherapy. A response rate of 66% and 77% with MVAC and HD-MVAC, respectively, has been reported in retroperitoneal lymph nodes versus 29% and 33% at extranodal sites [434]. The disease sites also have an impact on long-term survival. In lymph-node-only disease, 20.9% of patients were alive at 5 years compared to only 6.8% of patients with visceral metastases [406].

Further intensification of treatment using the new PCG triple regimen (paclitaxel, cisplatin and gemcitabine) did not result in a significant improvement in OS in the intent-to-treat (ITT) population of a large randomised phase III trial, comparing PCG triple regimen to GC [436]. However, the overall response rate (ORR) was higher with the triple regimen (56% vs. 44%; P = 0.0031), and the trend for OS improvement in the ITT population (15.8 vs. 12.7 months; HR = 0.85, P = 0.075) became significant in the eligible population. Adding paclitaxel to GC did not induce major additional side effects. G4 neutropenia was more common (35.8% vs. 20% for GC), as was febrile neutropenia (13.2% vs. 4.3%), and the need for G-CSF was higher (17% vs. 11%). GC alone caused more grade 4 thrombocytopenia and thrombocytopenia-induced bleeding (11.4% vs. 6.8%). PCG is one additional option for first-line treatment of UC.

7.8.4 ***Carboplatin-containing chemotherapy for fit patients***

Carboplatin-containing chemotherapy is not equivalent to cisplatin combinations, and should not be considered interchangeable or standard. Several randomised phase II trials of carboplatin versus cisplatin combination chemotherapy have produced lower CR rates and shorter OS for the carboplatin arms [437].

7.8.5 ***Non-platinum combination chemotherapy***

Different combinations of gemcitabine and paclitaxel have been studied as first- and second-line treatments. Apart from severe pulmonary toxicity with a weekly schedule of both drugs, this combination is well tolerated and produces response rates between 38% and 60% in both lines. Non-platinum combination chemotherapy has not been compared to standard cisplatin chemotherapy in randomised trials, therefore, it is not recommended for first-line use in cisplatin eligible patients [438-445].

7.8.6 ***Chemotherapy in patients unfit for cisplatin***

Up to 50% of patients are ineligible for cisplatin-containing chemotherapy [423]. The first randomised phase II/III trial in this setting was conducted by the EORTC and compared methotrexate/carboplatin/vinblastine (M-CAVI) and carboplatin/gemcitabine (GemCarbo) in patients unfit for cisplatin. Both regimens were active. Severe acute toxicity (SAT) was 13.6% in patients treated with GemCarbo versus 23% with M-CAVI, while the ORR was 42% for GemCarbo and 30% for M-CAVI. Further analysis showed that in patients with PS 2 and impaired renal function, combination chemotherapy provided limited benefit [421]. The ORR and SAT were both 26% for the former group, and 20% and 24%, respectively, for the latter group [421]. Recent phase III data have confirmed these results [413].

7.8.7 ***Second-line treatment***

Second-line chemotherapy data are highly variable and prognostic factors have been established recently (see Section 7.8.1.1) [414]. A reasonable strategy may be to re-challenge former cisplatin-sensitive patients if progression occurs at least 6-12 months after first-line cisplatin-based combination chemotherapy.

Second-line response rates of paclitaxel (weekly), docetaxel, nab-paclitaxel [446] oxaliplatin, ifosfamide, topotecan, pemetrexed, lapatinib, gefitinib and bortezomib have ranged between 0% and 28% in small phase II trials [430]. Although gemcitabine has also shown excellent response rates in second-line use, most patients already receive this drug as part of their front-line treatment [429].

Paclitaxel/gemcitabine studies have shown response rates of 38-60%. No randomised phase III trial with an adequate comparator arm has been conducted to assess the true value and OS benefit of this second-line combination [409, 444, 447].

Vinflunine, a novel third-generation vinca alkaloid, provided promising results in phase II trials [448]. A randomised phase III trial compared vinflunine plus best supportive care (BSC) against BSC alone in patients progressing after first-line treatment with platinum-containing combination chemotherapy for metastatic disease [449]. The results showed a modest ORR (8.6%), a clinical benefit with a favourable safety profile and, most importantly, a survival benefit in favour of vinflunine, which was statistically significant in the eligible patient population (not in the ITT population). For second-line treatment of advanced or metastatic urothelial cancer, this trial reached the highest level of evidence ever reported. Currently, vinflunine is the only approved second-line treatment.

7.8.8 Low-volume disease and post-chemotherapy surgery

With cisplatin-containing combination chemotherapy, excellent response rates may be obtained in patients with lymph node but no other metastases, good PS, and adequate renal function, including a high number of CRs, with up to 20% of patients achieving long-term disease-free survival [406, 435, 450, 451]. The role of surgery after chemotherapy is still unclear. Although some studies suggest a survival benefit and QOL improvement, the level of evidence supporting this practice is very limited [452-466]. A retrospective study of post-chemotherapy surgery after a partial or complete response has indicated that surgery may contribute to long-term disease-free survival in selected patients [379, 467, 468].

7.8.9 Treatment of bone metastases

The prevalence of metastatic bone disease (MBD) in patients with advanced/metastatic urothelial cancer is 30-40% [469]. Skeletal complications due to MBD have a detrimental effect on pain and QoL and are also associated with increased mortality [470]. Bisphosphonates reduce and delay skeletal-related events (SREs) due to bone metastases by inhibiting bone resorption. In a small pilot study in patients with BC, SREs caused by bone metastases were delayed [471]. Denosumab is a fully human monoclonal antibody that binds to and neutralises RANKL (receptor activator of nuclear factor-KB ligand), thereby inhibiting osteoclast function and preventing generalised bone resorption and local bone destruction. Denosumab is not inferior to zoledronic acid (ZA) in preventing or delaying SREs in patients with advanced MBD, including patients with urothelial carcinoma [472]. Denosumab has recently been approved by the European Medicines Agency (EMA) for treatment of patients with bone metastases from solid tumours. Patients with MBD, irrespective of the cancer type, should be considered for bone-targeted treatment [470].

Patients treated with ZA or denosumab should be informed about possible side effects and receive prophylactic treatment for jaw osteonecrosis and hypocalcaemia, which is more common with denosumab. Aggressive calcium and vitamin D supplementation is recommended. Dosing regimens of ZA should follow regulatory recommendations and should be adjusted according to pre-existing medical conditions [473]. For denosumab, no dose adjustments are required for variations in renal function.

7.8.10 Conclusions and recommendations for metastatic disease

Conclusions	**LE**
In a first-line setting, PS and the presence or absence of visceral metastases are independent prognostic factors for survival.	1b
In a second-line setting, negative prognostic factors are: liver metastasis, PS ≥ 1 and low haemoglobin (< 10 g/dL).	1b
Cisplatin-containing combination chemotherapy can achieve median survival of up to 14 months, with long-term disease-free survival reported in ~15% of patients with nodal disease and good PS.	1b
Single-agent chemotherapy provides low response rates of usually short duration.	2a
Carboplatin combination chemotherapy is less effective than cisplatin-based chemotherapy in terms of complete response and survival.	2a
Non-platinum combination chemotherapy produces substantial responses in first- and second-line settings.	2a
Non-platinum combination chemotherapy has not been tested against standard chemotherapy in patients who are fit or unfit for cisplatin combination chemotherapy.	4
There is no defined standard chemotherapy for unfit patients with advanced or metastatic urothelial cancer.	2b
Vinflunine reaches the highest level of evidence ever reported for second-line use.	1b
Post-chemotherapy surgery after partial or complete response may contribute to long-term disease-free survival.	3
Zoledronic acid and denosumab have been approved for all cancer types including urothelial cancer, because they reduce and delay skeletal related events in metastatic bone disease.	1b

Recommendations	GR
First-line treatment for fit patients:	
Use cisplatin-containing combination chemotherapy with GC, PCG, MVAC, preferably with G-CSF, or HD-MVAC with G-CSF.	A
Carboplatin and non-platinum combination chemotherapy is not recommended.	B
First-line treatment in patients ineligible (unfit) for cisplatin:	
Use carboplatin combination chemotherapy or single agents.	C
For cisplatin-ineligible (unfit) patients, with PS2 or impaired renal function, as well as those with 0 or 1 poor Bajorin prognostic factors and impaired renal function, treatment with carboplatin-containing combination chemotherapy, preferably with gemcitabine/carboplatin is indicated.	B
Second-line treatment:	
In patients progressing after platinum-based combination chemotherapy for metastatic disease, vinflunine should be offered. Alternatively, treatment within a clinical trial setting may be offered.	A*
Zoledronic acid or denosumab is recommended for treatment of bone metastases.	B

** Grade A recommendation is weakened by a problem of statistical significance.*
GC = gemcitabine plus cisplatin; G-CSF = granulocyte colony-stimulating factor; GR = grade of recommendation; MVAC = methotrexate, vinblastine, adriamycin plus cisplatin; HD MVAC = high-dose methotrexate, vinblastine, adriamycin plus cisplatin; LE = level of evidence; PS = performance status; PCG = paclitaxel, cisplatin, gemcitabine.

*7.8.11 **Biomarkers***

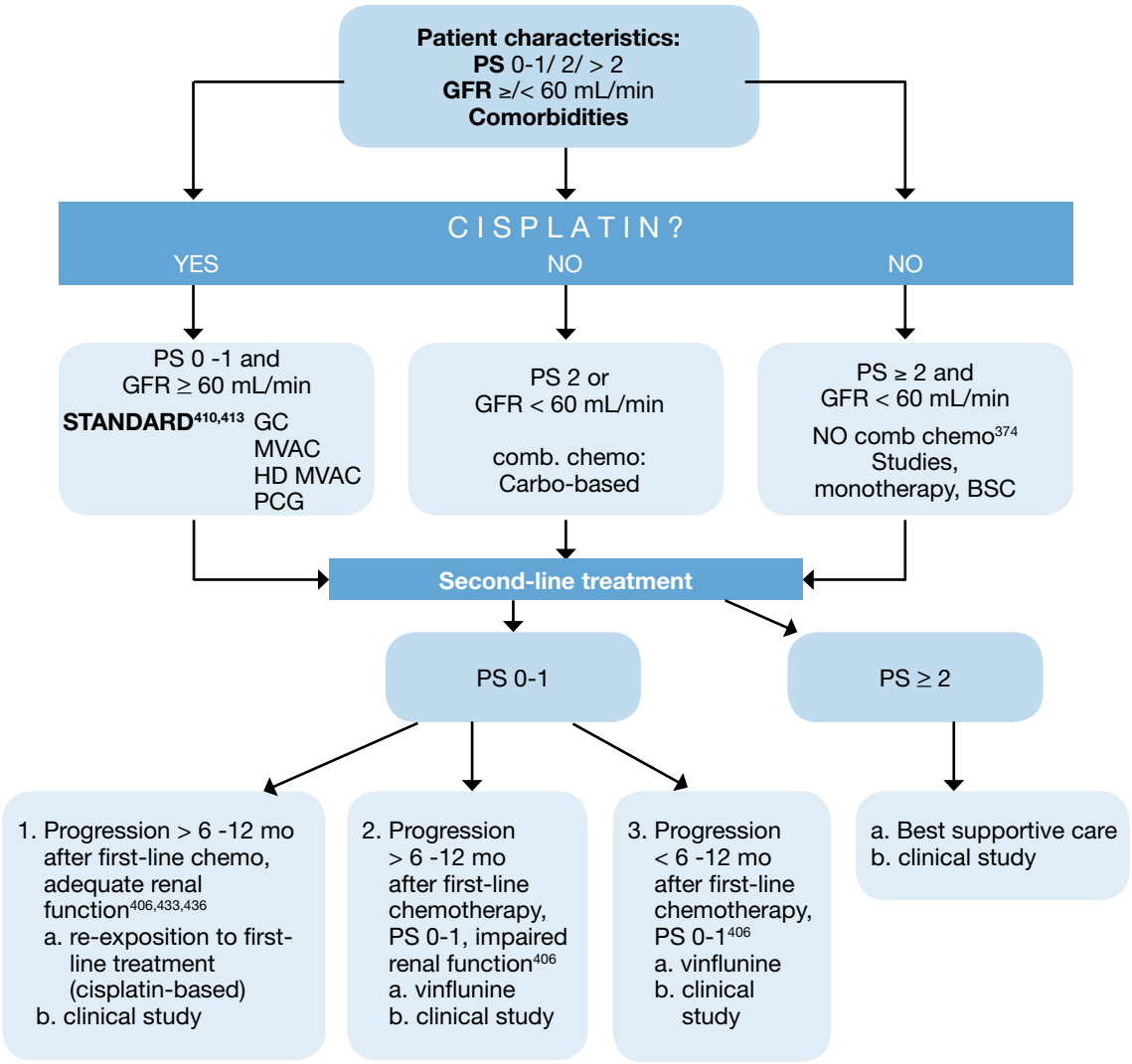
Modest disease control rates, with sporadic marked responses, in some patients with urothelial BC have led to the investigation of biomarkers for assessment of postoperative prognosis and the potential value of perioperative chemotherapy, and as predictors of response to chemotherapy or its monitoring. Most of the biomarkers are associated with tumour angiogenesis. Small studies, usually retrospective, have investigated microvessel density, altered p53 tumour expression [474], serum vascular endothelial growth factor [475], urinary and tissue basic fibroblast growth factor [476], urinary (wild-type and mutant) and tissue fibroblast growth factor receptor-3 [477], and more recently, thrombospondin-1 [478], circulating tumour cells [479, 480], and multidrug resistance gene expression [481]. Although a few biomarkers have shown potential, as yet, there is insufficient evidence to support its routine clinical use (LE: 3).

7.8.11.1 Recommendation on the use of biomarkers

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

**Upgraded following panel consensus.*
GR = grade of recommendation.

Figure 7.2: Algorithm for the management of metastatic urothelial cancer



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

7.9 Quality of life

7.9.1 Introduction

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

Several questionnaires have been validated for assessing HRQoL in patients with BC, including FACT (Functional Assessment of Cancer Therapy)-G [482], EORTC QLQ-C30 [483], EORTC QLQ-BLM (muscle-invasive bladder cancer module) [484], and SF (Short Form)-36 [485, 486] and recently the BCI questionnaire specifically designed and validated for BC patients [487].

A psychometric test, such as the FACT-BL, should be used for recording BC morbidity. New intensive interviewing techniques have added valuable information to our knowledge of HRQoL, which greatly depends on patients' individual preferences in life [488].

Unfortunately, most retrospective studies do not evaluate the association between HRQoL and BC-specific issues after cystectomy, such as day-time and night-time incontinence or potency. Furthermore, important co-variables, such as a patient's age, mental status, coping ability and gender, have rarely been considered [489, 490]. It remains difficult to predict the impact of post-therapeutic symptoms because of individual differences in symptom tolerance.

7.9.2 Choice of urinary diversion

There is controversy about which type of urinary diversion is best for a patient's HRQoL [226]. Some studies have not demonstrated any difference in HRQoL [490-492]. Nevertheless, most patients stated that, given a choice, they would still opt for an orthotopic diversion rather than an ileal conduit [493]. Another study reported that, although urinary function is better in conduit patients, the urinary bother is the same in both diversion groups, resulting in the same HRQoL evaluation [494].

Due to improved surgical techniques in orthotopic bladder substitution, some recent studies are supportive of continent bladder substitutes [334, 484, 495-497]. Patients with an orthotopic substitution had significantly better physical function and a more active lifestyle compared to patients with an ileal conduit. It is important to note that HRQoL parameters are independent prognostic factors for OS [498]. Patients with a continent bladder-substitute generally scored more favourably than those with an incontinent diversion, as judged by body image, social activity and physical function [494, 495, 499].

7.9.3 Non-curative or metastatic bladder cancer

In non-curative or metastatic BC, HRQoL is reduced because of associated micturition problems, bleeding, pain and therefore disturbance of social and sexual life [500]. There is limited literature describing HRQoL in BC patients receiving palliative care [501], but there are reports of bladder-related symptoms relieved by palliative surgery [350], radiotherapy [502], and/or chemotherapy [503].

Alternative definitive treatments of MIBC, e.g. trimodality bladder-sparing procedures, have shown similar survival times compared to cystectomy. However, the impact on HRQoL has been controversial [123, 361, 503-507].

7.9.4 Conclusions and recommendations for HRQoL

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

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

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

8. FOLLOW-UP

8.1 Introduction

An appropriate schedule for disease monitoring should be based on:
- natural timing of recurrence;
- probability and site of recurrence;
- functional monitoring after urinary diversion;
- possible treatment of recurrence [508].

Nomograms on cancer-specific survival following radical cystectomy have been developed and externally validated. However, their wider use cannot be recommended prior to further data [509-511].

Surveillance protocols are commonly based on patterns of recurrence observed from retrospective series. Diagnosis of asymptomatic recurrence based on routine oncological follow-up and results from retrospective studies are controversial [512, 513]. Importantly, these retrospective studies use different follow-up regimens and imaging techniques that make final analysis and conclusive recommendations difficult. Prospective trials demonstrating the effectiveness of follow-up after RC and its impact on overall survival (OS) are lacking [514].

8.2 Site of recurrence

*8.2.1 **Local recurrence***

Local recurrence takes place in soft tissues at the original surgical site or lymph nodes in the area of LND. Lymph node involvement above the aortic bifurcation can be considered metastatic recurrence [512].

Contemporary cystectomy has a 5-15% probability of pelvic recurrence. Most recurrence manifests during the first 24 months, often within 6-18 months after surgery. However, late recurrence can occur up to 5 years after cystectomy. Pathological stage and lymph node status are predictive for pelvic recurrence, as well as positive margins, extent of LND, and perioperative chemotherapy [515].

Patients have poor prognosis after pelvic recurrence. Even with treatment, the median survival ranges from 4 to 8 months following diagnosis. Definitive therapy can prolong survival, but mostly provides significant palliation of symptoms. Treatment includes systemic chemotherapy, local surgery, or radiotherapy [514].

*8.2.2 **Distant recurrence***

Distant recurrence is seen in up to 50% of patients treated with cystectomy. Stage and nodal involvement are risk factors [516]. Systemic recurrence is more common in locally advanced disease (pT3/4), ranging from 32 to 62%, and in patients with lymph node involvement (range 52-70%) [517].

The most likely sites for distant recurrence are lymph nodes, lungs, liver and bone [518]. Nearly 90% of distant recurrence appears within the first 3 years after RC, mainly in the first 2 years, although late recurrence has been described after > 10 years. Median survival of patients with progressive disease treated with platinum-based chemotherapy is 9-26 months [519-521].

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

The value of monitoring in the diagnosis of asymptomatic metastases and its impact on survival is questionable. Some studies have demonstrated no impact on survival despite using routine monitoring, although others have suggested that diagnosis of asymptomatic metastases, especially in the lungs, improves survival [512, 513]. We must also consider the possibility of longer survival in patients with minimal metastatic disease undergoing multimodal treatment, including metastasectomy. There are reports of survival rates of 28-33% at 5 years in patients undergoing resection of metastases after objective response to chemotherapy [461, 468].

*8.2.3 **Post-cystectomy urothelial tumour recurrence***

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

Secondary urethral tumours are likely to occur at 1-3 years after surgery. Prophylactic urethrectomy at cystectomy is no longer justified in most patients. Independent predictors for urethral recurrence are: cystectomy for NMIBC, prostate involvement, and history of recurrent NMIBC [514].

In women, the main risk factor is bladder neck disease [522]. Many studies have demonstrated that the risk of urethral recurrence after orthotopic diversion (0.9-4.0%) [523-526] is significantly less than after non-orthotopic diversion (6.4-11.1%) [523, 525].

There are limited data and agreement about urethral follow-up, with some recommending routine surveillance with urethral wash and urine cytology [526], and others doubting the need for routine urethral surveillance [524, 527-529]. Urethral washes and urine cytology do not appear to affect survival [527, 530, 531]. However, there is a significant survival advantage in men with urethral recurrence diagnosed asymptomatically versus symptomatically, so follow-up of the male urethra is indicated in patients at risk of urethral recurrence [514].

Treatment is influenced by local stage and grade of urethral occurrence:
- in urethral CIS, BCG instillations have success rates of 83% [526];
- in invasive disease, urethrectomy should be performed if the urethra is the only site of disease;
- in distant disease, systemic chemotherapy is indicated [518].

Upper urinary urothelial carcinomas (UTUC) occur in 1.8-6.0% of cases and represent the most common sites of late recurrence (3 years disease-free survival following RC). Median OS is 10-55 months, and 60-67% of patients die of metastatic disease [514].

A recent meta-analysis found that 38% of UTUC recurrence was diagnosed by follow-up investigation, whereas in the remaining 62%, diagnosis was based on symptoms. When urine cytology was used in surveillance, the rate of primary detection was 7% and 29.6% with UUT imaging [532]. This meta-analysis concluded that patients with non-invasive cancer are twice as likely to have UTUC as patients with invasive disease. Multifocality increases the risk of recurrence by threefold, while positive ureteral or urethral margins increase the risk by sevenfold. Radical nephroureterectomy can prolong survival [533].

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

Site of recurrence	Conclusion	LE	Recommendation	GR
Local recurrence	Poor prognosis. Treatment should be individualised depending on the local extent of tumour.	2b	Radiotherapy, chemotherapy and possibly surgery are options for treatment, either alone or in combination.	C
Distant recurrence	Poor prognosis.	2b	Chemotherapy is the first option, and consider individualised cases for metastasectomy in the case of a unique metastasis site.	C
Upper urinary tract recurrence	Multifocal disease (NMIBC/ CIS or positive ureteral margins.		See EAU guidelines on Upper Urinary Tract Carcinomas [1].	
Secondary urethral tumour	Staging and treatment should be done as for primary urethral tumour.	3	Local conservative treatment is possible for non-invasive tumour.	C
			In isolated invasive disease, urethrectomy should be performed.	B
			Urethral washes and cytology are not recommended.	A

Although general recommendations are not advised based on high level of evidence, closer follow-up could be considered in patients with locally advanced disease or lymph node involvement. The suggested follow-up includes 4-monthly CT scans during the first year, 6-monthly until the 3rd year, and annual imaging thereafter.

In patients with multifocal disease, NMIBC with CIS or positive ureteral margins are at higher risk of developing UTUC which can develop late (> 3 years). In those cases, monitoring of the UUT is mandatory during follow-up. Computed tomography should be used to assess the UUT [532].

8.3 Follow-up of functional outcomes and complications

Apart from oncological surveillance, patients submitted for urinary diversion deserve functional follow-up. Complications related to urinary diversion are detected in 45% of patients during the first 5 years follow-up.

This rate increases over time, and exceeds 54% after 15 years follow-up. Therefore, long-term follow-up of functional outcomes is desirable [514] (LE: 3), and may stop after 15 years.

The functional complications are diverse and include: vitamin B12 deficiency, metabolic acidosis, worsening of renal function, urinary infections, urolithiasis, stenosis of uretero-intestinal anastomosis, stoma complications in patients with ileal conduit, neobladder continence problems, and emptying dysfunction [514].

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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: http://www.uroweb.org/guidelines/. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.