EAU Guidelines on

Muscle-invasive and Metastatic Bladder Cancer

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European Association of Urology

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1. INTRODUCTION

1.1 Aims and scope

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

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

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

1.2 Panel Composition

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

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

1.3 Available publications

A quick reference document (Pocket Guidelines) is available, both in print and as an app for iOS and Android devices. These are abridged versions which may require consultation together with the full text version.

Several scientific publications are available (the most recent paper dating back to 2017 [4]), as are a number of translations of all versions of the EAU MIBC Guidelines. All documents are accessible through the EAU website: http://uroweb.org/guideline/bladder-cancer-muscle-invasive-and-metastatic/.

1.4 Publication history and summary of changes

*1.4.1 **Publication history***

The EAU published its first guidelines on BC in 2000. This document covered both NMIBC and MIBC. Since these conditions require different treatment strategies, it was decided to give each condition its own guidelines, resulting in the first publication of the MIBC Guidelines in 2004. This 2019 document presents a limited update of the 2018 version.

*1.4.2 **Summary of changes***

New relevant references have been identified through a structured assessment of the literature and incorporated in the various chapters of the 2019 EAU MIBC Guidelines.

Key changes in the 2019 print are:

- Section 6.3 Prognostic markers – this section was revised, to include new data. Based on the current data, no recommendation can be provided.
- Figures 7.1: Flow chart for the management of T2-T4a N0M0 urothelial BC was adapted.
- Section 7.2 Neoadjuvant therapy – this section was revised and restructured. A new recommendation was added.

*7.2.4 **Summary of evidence and guidelines for neoadjuvant therapy***

Summary of evidence	LE
Currently immunotherapy with checkpoint inhibitors is tested in phase II and III trials. First results are promising.	

Recommendation	Strength rating
Only offer neoadjuvant immunotherapy to patients within a clinical trial setting.	Strong

- New Section 7.4.7 – Impact of hospital and surgeon volume on treatment outcomes, has been included. This section is based on the findings of a systematic review (SR) on 'The impact of the annual hospital and surgeon radical cystectomy volume for BC on peri-operative outcomes and long-term oncological outcomes' [5];

- Section 7.6.2 External beam radiotherapy (EBRT) - this section was revised, to include new data. The recommendations did not change.
- Section 7.6.4 Multimodality bladder-preserving treatment - this section was revised, to include new data. The recommendations did not change.
- Section 7.7 Adjuvant therapy - this section was revised, to include new data. A new recommendation was included.

7.7.3 ***Guideline for adjuvant therapy***

Recommendation	Strength rating
Offer immunotherapy with a checkpoint inhibitor only in a clinical trial setting.	Strong

- Section 7.8 Metastatic disease – this section was revised, to include new data, resulting in changes to both the Summary of evidence and the recommendations.

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

Summary of evidence	LE
Post-chemotherapy surgery after partial or complete response may contribute to long-term disease-free survival in selected patients.	3
PD-1 inhibitor pembrolizumab has been approved for patients with advanced or metastatic urothelial cancer ineligible for cisplatin-based first-line chemotherapy based on the results of a phase II trial but use of pembrolizumab is restricted to PD-L1 positive patients.	2a
PD-L1 inhibitor atezolizumab has been approved for patients with advanced or metastatic urothelial cancer ineligible for cisplatin-based first-line chemotherapy based on the results of a phase II trial but use of atezolizumab is restricted to PD-L1 positive patients.	2a

Recommendations	Strength rating
First-line treatment for cisplatin-eligible patients	
Use cisplatin-containing combination chemotherapy with GC, MVAC, preferably with G-CSF, HD-MVAC with G-CSF or PCG.	Strong
Do not offer carboplatin and non-platinum combination chemotherapy.	Strong
First-line treatment in patients ineligible (unfit) for cisplatin	
Offer checkpoint inhibitors pembrolizumab or atezolizumab depending on PDL-1 status.	Strong
Offer carboplatin combination chemotherapy if PD-L1 is negative.	Weak
Second-line treatment	
Offer checkpoint inhibitor (pembrolizumab) to patients progressing during or after platinum-based combination chemotherapy for metastatic disease. Alternatively, offer treatment within a clinical trial setting.	Strong
Offer zoledronic acid or denosumab for supportive treatment in case of bone metastases.	Weak
Only offer vinflunine to patients for metastatic disease as second-line treatment if immunotherapy or combination chemotherapy is not feasible. Alternatively, offer vinflunine as third- or subsequent treatment line.	Weak

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

- Figure 7.2: Flow chart for the management of metastatic urothelial cancer was adapted.
- Section 7.9 Quality of life - this section was revised to include new data. However, the recommendations did not change.

Summary of evidence	LE
Compared to non-cancer controls, the diagnosis and treatment of bladder cancer has a negative impact on health-related quality of life (HRQoL).	2a

2. METHODS

2.1 Data identification

For the 2019 MIBC Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the MIBC Guideline was performed. The search was limited to English language publications. Databases searched included Medline, EMBASE and the Cochrane Libraries, covering a time frame between June 2nd 2017 and June 1st, 2018. A total of 1,676 unique records were identified, retrieved and screened for relevance. Forty-four new publications have been included in the 2019 print. A detailed search strategy is available online: http://uroweb.org/guideline/bladdercancer-muscle-invasive-andmetastatic/?type=appendices-publications.

For each recommendation within the guidelines there is an accompanying online strength rating form, the basis of which is a modified GRADE methodology [6, 7] which addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [8];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [9]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences. The strength rating forms will be available online.

Additional information can be found in the general Methodology section of this print, and online at the EAU website; http://www.uroweb.org/guideline/. A list of Associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Peer-review

The 2019 MIBC Guidelines have not been peer reviewed.

*2.2.1 **Lay review***

Post publication, the 2018 MIBC Guidelines were shared with seven patients treated for MIBC. Their comments were requested, but not limited to:

- the overall tone of the guidelines content;
- any missing information;
- any information considered incorrect;
- any information which is not presented in a clear fashion;
- any text which is considered redundant and should be omitted;
- any text section that should be more detailed.

Common comments across reviewers:

- In general, the overall tone of the text was considered informational and instructive, but the language used obviously targets medical professionals, which make certain parts of the text difficult to understand for lay persons. The use of the many abbreviations is considered an additional hindrance, as are the methodological elements. In case the EAU are considering producing a lay version of this text, the language needs to be adapted and clear instructions are to be provided.
- It is difficult for lay reviewers to comment on what may be omitted since, in their opinion, they lack the expertise.
- Some sections, such as 'Recurrent disease' and 'Markers' denote areas where less evidence is available. Consequently, the available data is less systematically presented which makes these sections more difficult to understand.
- There is an interest whether screening for BC is a consideration.
- In particular 'follow up', 'quality of life' and 'survivorship aspects' should be elaborated on; providing additional information on what may be expected after treatment is considered very helpful for patients and their families. Also lifestyle elements would be of relevance (healthy living, "what to do to prevent cancer"). For this section, in particular, involvement of patients in the text development was

considered missing. Transparency about the process of patient involvement in guidelines development was considered most relevant.

The MIBC Guidelines Panel is most grateful for the unique insights and guidance provided by the lay reviewers.

2.3 Future goals

Topics considered for inclusion in the 2020 update of the MIBC Guidelines:

- a SR on 'What is the importance of urothelial and non-urothelial histological variants of BC in predicting oncological outcomes in patients with muscle-invasive and metastatic BC?' [10];
- development of a diagnostic pathway for the assessment of visible and non-visible haematuria;
- inclusion of data based on the EAU-ESMO Consensus Conference on Urothelial Carcinoma;
- participation in developing strategies to ensure meaningful participation of patients in the development and implementation of the MIBC Guidelines.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Bladder cancer (BC) is the 7th most commonly diagnosed cancer in males, whilst it drops to 11th when both genders are considered [11]. The worldwide age-standardised incidence rate (per 100,000 person/years) is 9.0 for men and 2.2 for women [11]. In the European Union, the age-standardised incidence rate is 19.1 for men and 4.0 for women [8]. In Europe, the highest age-standardised incidence rate has been reported in Belgium (31 in men and 6.2 in women) and the lowest in Finland (18.1 in men and 4.3 in women) [8, 11].

Worldwide, the BC age-standardised mortality rate (per 100,000 person/years) was 3.2 for men vs. 0.9 for women in 2012 [8, 11]. Bladder cancer incidence and mortality rates vary across countries due to differences in risk factors, detection and diagnostic practices, and availability of treatments. The variations are, however, also partly caused by the different methodologies used in the studies and the quality of data collection [12, 13].

The incidence and mortality of BC has decreased in some registries, possibly reflecting the decreased impact of causative agents [13, 14].

Approximately 75% of patients with BC present with disease confined to the mucosa (stage Ta, carcinoma *in situ* [CIS]) or submucosa (stage T1). In younger patients (< 40 years) this percentage is even higher [15]. Patients with TaT1 and CIS have a high prevalence due to long-term survival in many cases and lower risk of cancer-specific mortality (CSM) compared to T2-4 tumours [8, 12, 16].

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 [17]. 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 [18].

The incidence of BC is directly related to the duration of smoking and the number of cigarettes smoked per day [19]. A meta-analysis looked at 216 observational studies on cigarette smoking and cancer published between 1961 and 2003, and the pooled risk estimates for BC demonstrated a significant association for both current and former smokers [20]. 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 [18]. An immediate decrease in the risk of BC was observed in those who stopped smoking. The reduction was about 40% within one to four years of quitting smoking and 60% after 25 years of cessation [19]. Encouraging people to stop smoking would result in the incidence of BC decreasing equally in men and women [17].

*3.2.2 **Occupational exposure to chemicals***

Occupational exposure is the second most important risk factor for BC. Work-related cases accounted for 20-25% of all BC cases in several series and it is likely to occur in occupations in which dyes, rubbers, textiles, paints, leathers, and chemicals are used [21]. The risk of BC due to occupational exposure to carcinogenic aromatic amines is significantly greater after ten years or more of exposure; the mean latency period usually exceeds 30 years [22, 23]. Population-based studies established the occupational attribution for BC in men to be 7.1%, while no such attribution was discernible for women [12, 24].

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 [25]. In a population-based cohort study, the standardised incidence ratios for BC developing after radical prostatectomy (RP), EBRT, brachytherapy, and EBRT-brachytherapy were 0.99, 1.42, 1.10, and 1.39, respectively, in comparison with the general U.S. population [26].

It has recently been proposed that patients who have received radiotherapy (RT) for prostate cancer with modern modalities such as intensity-modulated radiotherapy (IMRT) may have lower rates of in-field bladder- and rectal secondary malignancies [27]. 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 [27].

3.2.4 *Dietary factors*

Several dietary factors have been related to BC; however, the links remain controversial. The European Prospective Investigation into Cancer and Nutrition (EPIC) study is an on-going multicentre cohort study designed to examine the association between diet, lifestyle, environmental factors and cancer. They found no links between BC and fluid intake, red meat, vegetable and fruit consumption and only recently an inverse association between dietary intake of flavonoids and lignans and the risk of aggressive BC tumours has been described [28].

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 [29]. There is a well-established relationship between schistosomiasis and urothelial carcinoma (UC) of the bladder, which can progress to squamous cell carcinoma (SCC), however, better control of the disease is decreasing the incidence of SCC of the bladder in endemic zones such as Egypt [30, 31].

Similarly, invasive SCC has been linked to the presence of chronic urinary tract infection (UTI) distinct from schistosomiasis. A direct association between BC and UTIs has been observed in several case-control studies, which have reported a two-fold increased risk of BC in patients with recurrent UTIs in some series. However, some of these results may be attributed to recall bias [32].

3.2.6 *Gender*

Although men are more likely to develop BC than women, women present with more advanced disease and have worse survival rates. A meta-analysis including nearly 28,000 patients shows that female gender was associated with a worse survival outcome (hazard ratio [HR]: 1.20; 95% CI: 1.09-1.32) compared to male gender after radical cystectomy (RC) [33]. This finding had already been presented in a descriptive Nation-Wide Analysis based on 27,773 Austrian patients. After their analysis the authors found that cancer-specific-survival (CSS) was identical for pT1-tumours in both sexes, while women had a worse CSS in both age cohorts (< 70 years and ≥ 70 years) with higher tumour stages [34]. However, this higher mortality is questionable once both genders receive the same therapy. In a population-based study from the Ontario Cancer Registry analysing all patients with BC treated with cystectomy or radical RT between 1994 and 2008, no differences in overall survival (OS), mortality and outcomes were found between males and females following radical therapy [35].

A population-based study from the MarketScan databases suggests that a possible reason for worse survival in the female population may be that women experienced longer delays in diagnosis than men, as the differential diagnosis in women includes diseases that are more prevalent than BC [36].

Furthermore, differences in the gender prevalence of BC may be due to other factors besides tobacco and chemical exposure. In a large prospective cohort study, post-menopausal status was associated with an increase in BC risk, even after adjustment for smoking status. This result suggests that the differences in oestrogen and androgen levels between men and women may be responsible for some of the difference in the gender prevalence of BC [37-39].

3.2.7 *Genetic factors*

There is growing evidence that genetic susceptibility factors and family association may influence the incidence of BC. A recent population-based study of cancer risk in relatives and spouses of UC patients showed an increased risk for first- and second-degree relatives, and suggests genetic or environmental roots independent of smoking-related behaviour [40]. Shared environmental exposure was recognised as a potentially confounding factor [41]. Recent studies detected genetic susceptibility with independent loci, which are associated with BC risk [42].

Genome-wide association studies (GWAS) of BC identified several susceptibility loci associated with BC risk [43, 44].

3.2.8 *Summary of evidence and guidelines for epidemiology and risk factors*

Summary of evidence	LE
Worldwide, bladder cancer is the 11th most commonly diagnosed cancer.	2a
Several risk factors associated with bladder cancer diagnosis have been identified.	3
Active and passive tobacco smoking continues to be the main risk factor, while the exposure-related incidence is decreasing.	2a
The increased risk of developing bladder cancer in patients undergoing external-beam radiotherapy (EBRT), brachytherapy, or a combination of EBRT and brachytherapy, must be considered during patient follow-up. As bladder cancer requires time to develop, patients treated with radiation at a young age are at the greatest risk and should be followed up closely.	3

Recommendations	Strength rating
Council patients to stop active and avoid passive smoking.	Strong
Inform workers in potentially hazardous workplaces of the potential carcinogenic effects of a number of recognised substances, including duration of exposure, and latency periods. Protective measures are recommended.	Strong

3.3 Pathology

3.3.1 *Handling of transurethral resection and cystectomy specimens*

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

In RC, bladder fixation must be carried out as soon as possible. The pathologist must open the specimen from the urethra to the bladder dome and fix the specimen. In some circumstances this procedure can also be performed by the urologist. In a female cystectomy specimen, the length of the urethral segment removed *en bloc* with the specimen should be checked, preferably by the urological surgeon [45].

Specimen handling should follow the general rules as published by a collaborative group of pathologists and urologists [46, 47]. 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 [48]. In urethra-sparing cystectomy; the level of urethral dissection, completeness of the prostate, specifically at the apex (in men), and the inclusion of the entire bladder neck and amount of adjacent urethra, uterus and vaginal top (in women) should be inked and documented.

All lymph node (LN) specimens should be provided in their totality, in clearly labelled containers. In case of doubt, or adipose differentiation of the LN, the entire specimen is to be included. Lymph nodes should be counted and measured on slides, capsular extension and percentage of LN invasion should be reported as well as vascular embols [49, 50]. In the case of metastatic spread in the perivesical fat without real LN structures (capsule, subcapsular sinus), this localisation should nevertheless be considered as N+.

Positive margins in the peripelvic fat tissue (soft tissue margins), should be inked by the pathologist for evaluation. Positive margins decrease CSS in cases of pN0M0 UCs [51].

In rare cases, fresh frozen sections may be helpful to determine treatment strategy. The reliability of fresh frozen sections of obturator LNs was confirmed in a study, but further research is needed to confirm these results [52].

3.3.2 *Pathology of muscle-invasive bladder cancer*

All MIBC cases are high-grade UCs. For this reason, no prognostic information can be provided by grading MIBC [53]. However, identification of some morphological subtypes may be important for prognostic reasons and treatment decisions [54, 55]. Recently, an update of the World Health Organization (WHO) grading was published [56], however, the data presented in these guidelines are based on the 2004 WHO classification [57].

Currently the following differentiations are used:

1. urothelial carcinoma (more than 90% of all cases);
2. urothelial carcinomas with partial squamous and/or glandular differentiation [58, 59];
3. micropapillary and microcystic UC;
4. nested variant [60] (including large nested variety);
5. lymphoepithelioma;
6. plasmocytoid, giant cell, signet ring, diffuse, undifferentiated;
7. some UCs with trophoblastic differentiation;
8. small-cell carcinomas [61];
9. sarcomatoid carcinomas.

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

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

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Pathological staging

For staging, the Tumour, Node, Metastasis (TNM) Classification (2017, 8th edition) is recommended [62]. Blood and lymphatic vessel invasion and LN infiltration have an independent prognostic significance [63, 64]. It seems that the pN category is closely related to the number of LNs studied by the pathologist [62].

4.2 Tumour, node, metastasis classification

The TNM classification of malignant tumours is the method most widely used to classify the extent of cancer spread [54-56, 62, 65] (Table 4.1).

Table 4.1: TNM Classification of urinary bladder cancer [62]

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 regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)	
N3	Metastasis in a common iliac lymph node(s)	
M - Distant Metastasis		
M0	No distant metastasis	
	M1a	Non-regional lymph nodes
	M1b	Other distant metastasis

5. DIAGNOSTIC EVALUATION

5.1 Primary diagnosis

*5.1.1 **Symptoms***

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

*5.1.2 **Physical examination***

Physical examination should include rectal and vaginal bimanual palpation. A palpable pelvic mass can be found in patients with locally advanced tumours. In addition, bimanual examination under anaesthesia should be carried out before and after transurethral resection of the bladder (TURB), to assess whether there is a palpable mass or if the tumour is fixed to the pelvic wall [66, 67]. 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 [68].

*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***

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

However, positive urinary cytology may originate from a urothelial tumour located anywhere in the urinary tract. Evaluation of cytology specimens can be hampered by low cellular yield, UTIs, stones or

intravesical instillations, but for experienced readers, specificity exceeds 90% [69, 70] (LE: 2b). However, negative cytology does not exclude a tumour. There is no known urinary marker specific for the diagnosis of invasive BC [71].

A standardised reporting system redefining urinary cytology diagnostic categories was published in 2016 by the Paris Working Group [72]:

- adequacy of urine specimens (Adequacy);
- negative for high-grade UC (Negative);
- atypical urothelial cells (AUC);
- suspicious for high-grade UC (Suspicious);
- high-grade UC (HGUC);
- low-grade urothelial neoplasia (LGUN).

*5.1.5 **Cystoscopy***

Ultimately, the diagnosis of BC is made by cystoscopy and histological evaluation of resected tissue. If a bladder tumour has been visualised unequivocally by 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 and resection. Currently, there is no evidence for the role of photodynamic diagnosis (PDD) in the standard diagnosis of invasive BC.

A careful description of the cystoscopic findings is necessary. This should include documentation of the site, size, number, and appearance (papillary or solid) of the tumours, as well as a description of any mucosal abnormalities [73]. The use of a bladder diagram is recommended.

The use of PDD could be considered if a T1 high-grade tumour is present, to identify associated CIS. Presence of CIS may lead to a modified treatment plan (see Section 7.1). Photodynamic diagnosis is highly sensitive for the detection of CIS and in experienced hands the rate of false-positive results may be similar to that with regular white-light cystoscopy [64, 74].

*5.1.6 **Transurethral resection of invasive bladder tumours***

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

The strategy of resection depends on the size of the lesion. Small tumours (< 1 cm in diameter) can be resected *en bloc*, where the specimen contains the complete tumour plus a part of the underlying bladder wall including muscle. Larger tumours need to be resected separately in parts, which includes the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle, and the edges of the resection area. At least the deeper part of the resection specimen must be referred to the pathologist in a separate labelled container to enable them to make a correct diagnosis. In cases in which RT is considered and CIS is to be excluded, PDD can be used [75].

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, with concomitant bladder CIS, and in the case of multiple tumours [76, 77] (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 [78-80].

*5.1.7 **Second resection***

In the case of high-grade non-muscle-infiltrative tumour, residual disease is observed in 33-53% of patients [81-87]. In order to reduce the risk of understaging [82, 83], a second TURB resection is often required to determine subsequent treatment strategy.

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

*5.1.8 **Concomitant prostate cancer***

Prostate cancer is found in 21-50% of male patients undergoing radical cystectomy for BC [88-91]. Incidentally discovered clinically significant prostatic adenocarcinoma did not alter survival [90, 91].

5.1.9 *Summary of evidence and guidelines for the primary assessment of presumably invasive bladder tumours*

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

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

Recommendations	Strength rating
Describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities during cystoscopy. Use a bladder diagram.	Strong
Take a biopsy of the prostatic urethra in cases of bladder neck tumour, when bladder carcinoma *in situ* 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.	Strong
Take a biopsy at the time of the second resection, if no biopsy was taken during the initial procedure.	Strong
In women undergoing subsequent orthotopic neobladder construction, obtain procedural information (including histological evaluation) of the bladder neck and urethral margin, either prior to, or at the time of cystoscopy.	Strong
Specify the grade, depth of tumour invasion, and whether the lamina propria and muscle tissue are present in the specimen in the pathology report.	Strong

5.2 Imaging for staging of MIBC

The treatment and prognosis of MIBC is determined by tumour stage and grade [92, 93]. In clinical practice, CT and MRI are the imaging techniques used. The purpose of using imaging for staging MIBC is to determine prognosis and provide information to assist treatment selection. Tumour staging must be accurate to ensure that the correct choice of treatment is made. Imaging parameters required for staging MIBC are:

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

5.2.1 *Local staging of MIBC*

Both CT and MRI may be used for assessment of local invasion, but they are unable to accurately diagnose microscopic invasion of perivesical fat (T2 vs. T3a) [94]. The principal aim of CT and MRI is 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%). A meta-analysis of seventeen studies showed a 91% sensitivity and 96% specificity for 3.0-T device MRI combined with diffusion-weighted imaging (DWI) to differentiate ≤ T1 tumours from ≥ T2 tumours before surgery [95]. These values were 10-33% (mean 19%) higher than those obtained with CT [96]. Dynamic contrast-enhanced (DCE) MRI may help to differentiate bladder tumour from surrounding tissues, in particular in patients where organ-preserving cystectomy is considered. Magnetic resonance imaging may evaluate post-biopsy reaction, because enhancement of the tumour occurs earlier than that of the normal bladder wall due to neovascularisation [97-99].

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 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 can be considered as an alternative [100] (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 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% [101] and increases with more advanced disease [102].

5.2.2 Imaging of lymph nodes in MIBC

Assessment of LN metastases based solely on size is limited by the inability of both CT and MRI to identify metastases in normal-sized or minimally enlarged nodes. The sensitivity for detection of LN metastases is low (48-87%). Specificity is also low because nodal enlargement may be due to benign disease. Overall, CT and MRI show similar results in the detection of LN metastases in a variety of primary pelvic tumours [96, 103-107]. 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 [108, 109].

Positron emission tomography combined with CT is increasingly being used in clinical practice and its exact role continues to be evaluated [110].

5.2.3 Upper urinary tract urothelial carcinoma

5.2.3.1 Computed tomography urography

Computed tomography urography has the highest diagnostic accuracy of the available imaging techniques [111]. The sensitivity of CT urography for UTUC is 0.67-1.0 and specificity is 0.93-0.99 [112].

Rapid acquisition of thin sections allows high-resolution isotropic images that can be viewed in multiple planes to assist with diagnosis without loss of resolution. Epithelial “flat lesions” without mass effect or urothelial thickening are generally not visible with CT.

The secondary sign of hydronephrosis is associated with advanced disease and poor oncological outcome [113, 114]. The presence of enlarged LNs is highly predictive of metastases in UTUC [115].

5.2.3.2 Magnetic resonance urography

Magnetic resonance urography is indicated in patients who cannot undergo CT urography, usually when radiation or iodinated contrast media are contraindicated [116]. The sensitivity of MR urography is 0.75 after contrast injection for tumours < 2 cm [116]. The use of MR urography with gadolinium-based contrast media should be limited in patients with severe renal impairment (< 30 mL/min creatinine clearance), due to the risk of NSF. Computed tomography urography is generally preferred to MR urography for diagnosing and staging UTUC.

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 [117] and liver metastases [118], 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 [119, 120]. Magnetic resonance imaging is more sensitive and specific for diagnosing bone metastases than bone scintigraphy [121, 122] (LE: 2b).

5.2.5 Future developments

Evidence is accruing in the literature suggesting that ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT might have potential clinical use for staging metastatic BC [123, 124], 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 DWI over T2-weighted and DCE MRI for assessing the therapeutic response to induction chemotherapy against MIBC [125]. The high specificity of DWI indicates that it is useful for accurate prediction of a complete histopathological response, allowing better patient selection for bladder-sparing protocols. Results from prospective studies are awaited.

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

Summary of evidence	**LE**
Imaging as part of staging in muscle-invasive bladder cancer (MIBC) provides information about prognosis and assists in selection of the most appropriate treatment.	2b
There are currently insufficient data on the use of diffusion-weighted imaging (DWI) and ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) in MIBC to allow for a recommendation to be made.	
The diagnosis of upper tract urothelial carcinoma depends on CT urography and ureteroscopy.	2

Recommendations	Strength rating
In patients with confirmed MIBC, use computed tomography (CT) of the chest, abdomen and pelvis as the optimal form of staging.	Strong
Perform a CT urography for upper tract evaluation and for staging.	Strong
For upper tract evaluation, use diagnostic ureteroscopy and biopsy only in cases where additional information will impact treatment decisions.	Strong
Use magnetic resonance urography when CT urography is contraindicated for reasons related to contrast administration or radiation dose.	Strong
Use CT or magnetic resonance imaging (MRI) for staging locally advanced or metastatic disease in patients in whom radical treatment is considered.	Strong
Use CT to diagnose pulmonary metastases. Computed tomography and MRI are generally equivalent for diagnosing local disease and distant metastases in the abdomen.	Strong

6. PROGNOSIS

6.1 Introduction

Both patient and tumour characteristics impact on the prognosis of patients with MIBC. Treatment and prognosis for MIBC are mainly based on tumour and nodal stage [93].

6.2 MIBC and comorbidity

Complications related to RC may be directly related to pre-existing comorbidity as well as the surgical procedure, bowel anastomosis, or urinary diversion. A significant body of literature has evaluated the usefulness of age as a prognostic factor for RC, although chronological age is less important than biological age [126-128]. Controversy remains regarding age, RC and the type of urinary diversion. Radical cystectomy is associated with the greatest risk reduction in disease-related and non-disease-related death in patients aged > 80 years [129].

The largest retrospective study on RC in septuagenarians and octogenarians based on data from the National Surgical Quality Improvement Program database (n = 1,710) showed no significant difference for wound, cardiac, or pulmonary complications. However, the risk of mortality in the octogenarians compared to the septuagenarians is higher (4.3% vs. 2.3%) [130]. Although some octogenarians successfully underwent a neobladder procedure, most patients were treated with an ileal conduit diversion.

It is important to evaluate functioning and quality of life (QoL) of elderly patients using a standardised geriatric assessment, as well as carrying out a standard medical evaluation [131].

Sarcopenia has been shown to be an independent predictor for OS and CSS in a large multicentre study with patients undergoing RC for BC [132]. Other risk factors for morbidity include prior abdominal surgery, extravesical disease, and prior RT [133]. Female gender, an increased body mass index (BMI) and lower pre-operative albumin levels are associated with a higher rate of parastomal hernias [134].

Low pre-operative serum albumin is also associated with impaired wound healing, gastrointestinal complications and a decrease of recurrence-free and OS after RC [135, 136]. Therefore, it could be used as a prognostic biomarker for patients undergoing RC.

*6.2.1 **Evaluation of comorbidity***

Rochon *et al.* have shown that evaluation of comorbidity provides a better indicator of life expectancy in MIBC than patient age [137]. Evaluation of comorbidity helps to identify the medical conditions likely to interfere with, or have an impact on, treatment and the evolution and prognosis of MIBC [138].

The value of assessing overall health before recommending and proceeding with surgery was emphasised by Zietman *et al.*, who have demonstrated an association between comorbidity and adverse pathological and survival outcomes following RC [139]. Similar results were found for the impact of comorbidity on cancer-specific and other-cause mortality in a population-based competing risk analysis of > 11,260 patients from the Surveillance, Epidemiology, and End Results (SEER) registries. Age carried the highest risk for other-cause mortality but not for increased cancer-specific death, while the stage of locally advanced tumour was the strongest predictor for decreased CSS [140]. 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 [141]. Unfortunately, most series evaluating RC do not include indices of comorbidity in the patient evaluation.

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

A range of comorbidity scales has been developed [142], six of which have been validated [143-148] (LE: 3). The Charlson Comorbidity Index (CCI) ranges from 0 to 30 according to the importance of comorbidity described at four levels and is calculated by healthcare practitioners based on patients' medical records. The score has been widely studied in patients with BC and found to be an independent prognostic factor for peri-operative mortality [149, 150], overall mortality [151], and CSM [129, 152-154]. Only the age-adjusted version of the CCI was correlated with both cancer-specific and other-cause mortality [155]. 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 [156].

Table 6.1: Calculation of the Charlson Comorbidity Index

Number of points	Conditions
1	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	61-70 years
	Hemiplegia
	Moderate to severe kidney disease
	Diabetes with organ damage
	Tumours of all origins
3	71-80 years
	Moderate to severe liver disease
4	81-90 years
5	> 90 years
6	Metastatic solid tumours
	AIDS

Interpretation

1. Calculate Charlson Comorbidity Score or Index = i
    a. Add comorbidity score to age score
    b. Total denoted as 'i' in the Charlson Probability calculation (see below).
       i = sum of comorbidity score to age score
2. Calculate Charlson Probability (10-year mortality = Y)
    a. Calculate $Y = 10^{(i \times 0.9)}$
    b. Calculate $Ƶ = 0.983^{Y}$ (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 [157]. The Eastern Cooperative Oncology Group (ECOG) performance status (PS) scores and Karnofsky index have been validated to measure patient activity [158] (LE: 3). Performance score is correlated with patient OS after RC [153] and palliative chemotherapy [159-161].

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 most complete protocol is the Comprehensive Geriatric Assessment (CGA) [162] which is tailored to the care of cancer patients [163]. In BC, the CGA has been used to adapt gemcitabine chemotherapy in previously untreated elderly patients with advanced BC [164].

6.2.3 *Summary of evidence and guidelines for comorbidity scales*

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

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

6.3 Prognostic markers

6.3.1 *Clinical and histopathological parameters*

The most important histopathological prognostic variables after RC and LN dissection are tumour stage and LN status [165]. In addition, other histopathological parameters of the RC specimen have been associated with prognosis.

The value of lymphovascular invasion was reported in a SR and meta-analysis including 78,000 patients from 65 studies treated with RC for BC [166]. Lymphovascular invasion was present in 35% of the patients and correlated with a 1.5-fold higher risk of recurrence and cancer mortality, independent of pathological stage and peri-operative chemotherapy. This correlation was even stronger in those patients with node-negative disease [167].

In a SR and meta-analysis including 23 studies and over 20,000 patients, the presence of concomitant CIS in the RC specimen was associated with a higher odds ratio (OR) of ureteral involvement (pooled OR: 4.51, 2.59-7.84). Concomitant CIS was not independently associated with OS, recurrence-free survival (RFS) and DSS survival in all patients, but in patients with organ-confined disease concomitant CIS was associated with worse RFS (pooled HR: 1.57, 1.12-2.21) and CSM (pooled HR: 1.51, 1.001-2.280) [168].

Tumour location has been associated with prognosis. Tumours located at the bladder neck or trigone of the bladder appear to have an increased likelihood of nodal metastasis (OR: 1.83 95% CI: 1.11-2.99) and have been associated with decreased survival [92, 165].

Prostatic urethral involvement at the time of RC was also found to be associated with worse survival outcomes. In a series of 995 patients, prostatic involvement was recorded in 31% of patients. The five-year CSS in patients with CIS of the prostatic urethra was 40%, whilst the prognosis of patients with UC invading the prostatic stroma was worse with a five-year CSS of only 12% [169].

In patients with LN-positive disease a SR and meta-analysis reported that LN density, defined as the ratio of positive LNs to the number of LNs removed, was independently associated with OS (HR: 1.45; 95%, CI: 1.11-1.90) [170]. It has been suggested that LN density outperforms the AJCC-TNM staging system for LN-positive disease in terms of prognostic value [171]. However, in spite of these studies supporting the use of LN density, LN density relies on the number of LNs removed which, in turn, is subject to surgical and pathological factors. This makes the concept of LN density difficult to apply uniformly.

Biomarkers such as C-reactive protein, lymphocyte-monocyte ratio (LMR), or platelet-lymphocyte ratio (PLR) have been investigated. Recently neutrophil-to-lymphocyte ratio (NLR) has emerged as a prognostic factor in UUT tumours [1] and other non-urological malignancies. In a pooled analysis of 21 studies analysing the prognostic role of NLR in BC, the authors correlated elevated pre-treatment NLR with OS, RFS and DFS in both localised and metastatic disease [172]. In contrast, a secondary analysis of the SWOG 8710 trial, a randomised phase III trial that assessed cystectomy ± neoadjuvant chemotherapy (NAC) in patients with MIBC, suggests that NLR is neither a prognostic nor predictive biomarker for OS in MIBC, nor could an OS benefit from NAC be demonstrated [173].

Several studies have already demonstrated that systemic inflammation correlates with worse prognosis in several malignancies.

*6.3.2 **Molecular markers***

6.3.2.1 Molecular groups based on the Cancer Genome Atlas (TCGA) cohort

It has been attempted to classify UC from a molecular point of view. Four major systems exist:

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

The basal group, which can have sarcomatoid aspects and shows an over-expression of epidermal growth factor receptor 3 (EGFR3), is chemosensitive, the luminal type displays an over-expression of fibroblast growth factor receptor 3 (FGFR3), epidermal growth factor receptor (ERBB2↑ and ERBB3), and is chemotherapy resistant [54, 55, 174].

These molecular classifications have been updated in the last four years, as have the TCGA and the Lund classifications [175, 176]. According to their molecular appearance urothelial carcinomas react differently to different therapies [175, 177]. Warrick *et al.* found that intratumoural molecular heterogeneity and great somatic mutation burden could also be related to therapeutic response [178]. However, molecular classification of MIBC is still evolving and treatment according to the molecular subtype is not a standard yet. In the coming years, new insights into BC carcinogenesis may change our management of the disease.

6.3.2.2 Other molecular markers

The performance of current commercially available pathological prognostic markers points to the relevance of including molecular prognostic markers in clinical practice [179], but so far very few studies have addressed this topic. At present, insufficient evidence exists to recommend the standard use of prognostic marker p53 in high-risk muscle-invasive disease, as it will not yield sufficient data to base treatment on in an individual patient [180].

Beyond the recently developed molecular classification for MIBC, as yet, no other molecular markers can be considered for use in standard clinical practice although several markers (mainly predictive markers assessing response to NAC) are now being evaluated, such as tumour mutation burden (TMB), DNA damage response (DDR) gene defects and mismatch repair defects or microsatellite instability [178]. Further research is needed to establish their role as predictive and prognostic markers in patient selection.

7. DISEASE MANAGEMENT

7.1 Treatment failure of non-muscle invasive bladder cancer

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

In 2015 the European Organisation for Research and Treatment of Cancer (EORTC) group presented new nomograms based on two large phase III trials with a median follow-up of 7.4 years. These showed that with one to three years of maintenance Bacillus Calmette-Guérin (BCG), the risk for progression at five years was 19.3% for T1G3 tumours [181]. Meta-analyses have demonstrated that BCG-therapy prevents the risk of tumour recurrence [182] and the risk of tumour progression [183, 184], but so far, no significant overall- or disease-specific survival advantages have been shown, as compared to no intravesical therapy [183-185]. The EAU NMIBC Guidelines present data supporting cystectomy in selected patients with NMIBC.

Large cystectomy series show a risk of an understaging error in TaT1 tumours of 35-62%. This may be caused by the presence of persisting or recurrent tumours due to omission of a second TURB or re-TURB, and the absence of neoadjuvant therapy [186-188]. Second TURB identifies upstaging to > T2 tumours in 10-20% of patients [189, 190]. Residual T1 disease in second TURB is associated with a higher recurrence and progression rate, as well as with a higher CSM [191].

Progression to MIBC has been shown to significantly decrease CSS. In a review of nineteen trials including 3,088 patients, CSS after progression from NMIBC to MIBC was 35%, which is significantly worse compared to patients with MIBC without a history of NMIBC. Although all studies reflect these findings, a large retrospective Canadian study showed that even progressive patients had a slightly better outcome [192]. High-grade T1 disease remains a dangerous disease, which underlines the need to recommend early radical treatment, such as RC, in case of intravesical therapy failure [2, 193].

According to the EAU NMIBC Guidelines, it is reasonable to propose immediate RC to patients with non-muscle-invasive tumours who are at highest risk of progression [194-196]. Risk factors are any of the following:

- T1 tumours;
- G3 (high grade) tumours;
- CIS;
- multiple, recurrent and large (> 3 cm) TaG1G2/low-grade tumours (all features must be present).

Subgroup of highest-risk tumours:
- T1G3/high-grade associated with concurrent bladder CIS;
- multiple and/or large T1G3/high grade and/or recurrent T1G3/high-grade;
- T1G3/high-grade with CIS in the prostatic urethra;
- some forms of variant histology of UC;
- lymphovascular invasion;

Although the percentage of patients with primary TaT1 tumours and the indication for cystectomy in TaT1 tumours is not specified in large cystectomy series, the ten-year RFS rate is 80% and similar to that of TURB and BCG maintenance therapy [2, 187, 197, 198] (LE: 3).

Radical cystectomy is also strongly recommended in patients with a muscle-invasive tumour detected during follow up, in BCG-refractory tumours, BCG relapse and BCG unresponsive tumours, which are defined in the NMIBC guideline as [2]:

BCG-refractory tumour:
- if T1 high-grade/G3, non-muscle-invasive papillary tumour is present at three months;
- if Ta high-grade/G3 or CIS (without concomitant papillary tumour) is present at both three and six months (after a second induction course or the first maintenance course of BCG);
- if high-grade tumour appears during BCG therapy [199];

BCG-relapsing tumour:
- recurrence of high-grade/ G3 (WHO 1973/2004) tumour after completion of BCG maintenance, despite an initial response).

BCG unresponsive:
- Bacillus Calmette-Guérin-refractory or T1 BCG relapse within six months or CIS within twelve months of last BCG exposure.

Patients with disease recurrence within two years of initial TURB plus BCG therapy have a better outcome than patients who already have muscle-invasive disease, indicating that cystectomy should be performed at first recurrence, even in non-muscle-invasive disease [200] (LE: 3).

There are now several bladder-preservation strategies available; immunotherapy, chemotherapy, device-assisted therapy, and combination therapy [201]. However, experience is limited and treatments other than RC must be considered oncologically inferior at the present time [201].

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

Recommendations	Strength rating
Discuss immediate radical treatment in all T1 tumours at high risk of progression (i.e. high grade, multifocality, carcinoma *in situ*, and tumour size, as outlined in the EAU Guidelines for Non-muscle-invasive Bladder Cancer).	Strong
Offer radical treatment to all patients presenting with T1 tumours failing intravesical therapy.	Strong

7.2 Neoadjuvant therapy

*7.2.1 **Introduction***

The standard treatment for patients with urothelial MIBC and MIBC with variant histologies is RC. However, RC only provides five-year survival in about 50% of patients [188, 202-205]. To improve these results, cisplatin-based NAC has been used since the 1980s [188, 202-207].

*7.2.2 **Role of cisplatin-based chemotherapy***

There are theoretical advantages and disadvantages of administering chemotherapy before planned definitive surgery to patients with resectable muscle-invasive UC of the bladder and cN0M0 disease:
- Chemotherapy is delivered at the earliest time-point, when the burden of micrometastatic disease is expected to be low.
- Potential reflection of *in-vivo* chemosensitivity.
- Tolerability of chemotherapy and patient compliance are expected to be better pre-cystectomy.
- Patients might respond to NAC and reveal a favourable pathological status, determined mainly by achieving pT0, pN0 and negative surgical margins.
- Delayed cystectomy might compromise the outcome in patients not sensitive to chemotherapy [208,

209], although published studies on the negative effect of delayed cystectomy only include chemo-naïve patients. There are no trials indicating that delayed surgery due to NAC has a negative impact on survival.

- Neoadjuvant chemotherapy does not seem to affect the outcome of surgical morbidity. In one randomised trial the same distribution of grade 3-4 post-operative complications was seen in both treatment arms [210]. In the combined Nordic trials (n = 620), NAC did not have a major adverse effect on the percentage of performable cystectomies. The cystectomy frequency was 86% in the experimental arm and 87% in the control arm with 71% of patients receiving all three chemotherapy cycles [211].
- Clinical staging using bimanual palpation, CT or MRI may result in over- and understaging and have a staging accuracy of only 70% [68]. Overtreatment is a possible negative consequence.
- Neoadjuvant chemotherapy should only be used in patients eligible for cisplatin combination chemotherapy; other combinations (or monotherapies) are inferior in metastatic BC and have not been fully tested in a neoadjuvant setting [210, 212-220].

7.2.2.1 Summary of available data

Several randomised phase III trials addressed the potential survival benefit of NAC administration [210, 212-217, 221-225]. The main differences in trial designs were the type of chemotherapy (i.e. single-agent cisplatin or combination chemotherapy) and the number of cycles provided. Patients had to be fit for cisplatin. Since these studies differed considerably for patient numbers, patient characteristics (e.g. clinical T-stages included) and the type of definitive treatment offered (cystectomy and/or RT), pooling of results was not possible.

Three meta-analyses were undertaken to establish if NAC prolongs survival [218-220]. In a meta-analysis, published in 2005 [220] with updated patient data from eleven randomised trials (n = 3,005), a significant survival benefit was shown in favour of NAC.

The most recent meta-analysis included four additional randomised trials, and used the updated results from the Nordic I, Nordic II, and BA06 30894 trials, consisting of information for 427 new patients and updated information for 1,596 patients. The results of this analysis confirmed the previously published data and showed an 8% absolute improvement in survival at five years with a number needed-to-treat of 12.5 [226].

Only cisplatin combination chemotherapy with at least one additional chemotherapeutic agent resulted in a meaningful therapeutic benefit [218, 220]; the regimens tested were methotrexate, vinblastine, adriamycin (epirubicin) plus cisplatin (MVA(E)C), cisplatin, methotrexate plus vinblastine (CMV), cisplatin and methotrexate (CM), cisplatin/adriamycin, and cisplatin/5-fluorouracil (5-FU) [227].

The updated analysis of a large randomised phase III trial [212] with a median follow-up of eight years confirmed previous results and provided additional findings:

- 16% reduction in mortality risk;
- improvement in ten-year survival from 30% to 36% with neoadjuvant CMV;
- benefit with regard to distant metastases;
- no benefit for locoregional control and locoregional DFS, with the addition of neoadjuvant CMV independent of the definitive treatment.

More modern chemotherapeutic regimens such as gemcitabine/cisplatin have shown similar pT0/pT1 rates as methotrexate, vinblastine, adriamycin plus cisplatin (MVAC) in retrospective series and pooled data analyses, but have not been used in randomised controlled trials (RCTs) [227-230]. Recently modified dose-dense MVAC (ddMVAC) was tested in two small single arm phase II studies demonstrating high rates of pathologic complete remission [231, 232]. Moreover, a large cross-sectional analysis showed higher rates of downstaging and pathological complete response for ddMVAC [233].

It is unclear, if patients with non-urothelial carcinoma histology can also benefit from NAC. A retrospective analysis demonstrated that patients with neuroendocrine tumours had improved OS and lower rates of non-organ-confined disease when receiving NAC. In case of micropapillary differentiation, sarcomatoid differentiation and adenocarcinoma, lower rates of non-organ confined disease were found, but no statistically significant impact on OS. Patients with SCC did not benefit from NAC [234].

A retrospective analysis assessed the use of NAC in MIBC based on data from the U.S. National Cancer Database [235]. Only 19% of all patients received NAC before radical cystectomy (1,619 of 8,732 patients) and no clear survival advantage for NAC following propensity score adjustment was found despite efforts to include patients based on SWOG 8710 study criteria [210]. Therefore, these results have to be interpreted with caution, especially since there is no information about the type of NAC applied, however, these findings emphasise the importance of pragmatically designed studies that reflect real-life practice.

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

Data from small imaging studies aiming to identify responders in patients treated with NAC suggest that

response after two cycles of treatment is related to outcome. Although multiparametric (mp) MRI has the advantage of better resolution of the bladder wall tissue planes as compared to CT without radiation exposure, it is not ready yet for standard patient care. However, bladder mpMRI may be useful to inform on tumour stage after TUR and response to NAC [236]. So far neither PET, CT, conventional MRI or DCE MRI can accurately assess treatment response [237-240]. In addition, the definition of stable disease after two cycles of NAC is still undefined. To identify progression during NAC, imaging is being used in many centres, notwithstanding the lack of supporting evidence.

For responders to NAC, especially in those with a complete response (pT0 N0), treatment has a major positive impact on OS [241]. Therefore, reliable predictive markers to identify patients most likely to benefit from treatment are needed. Molecular tumour profiling might guide the use of NAC in the future [242, 243] (see Section 7.8.12 - Biomarkers).

*7.2.4 **Role of neoadjuvant immunotherapy***

Checkpoint inhibitors have shown significant benefit in patients with unresectable and metastatic BC in the salvage setting and in platinum-ineligible PD-L1+ patients as first-line treatment. A number of PD1/PD-L1 inhibitors have received regulatory approval and are currently being tested in several ongoing phase II trials whilst phase III trials are accruing. The initial data from two phase II trials with pembrolizumab and atezolizumab show promising results [244].

*7.2.5 **Summary of evidence and guidelines for neoadjuvant therapy***

Summary of evidence	LE
Neoadjuvant cisplatin-containing combination chemotherapy improves overall survival (OS) (8% at five years).	1a
Neoadjuvant treatment of responders and especially patients who show complete response (pT0 N0) has a major impact on OS.	2
Currently immunotherapy with checkpoint inhibitors is tested in phase II and III trials. Initial results are promising.	
There are still no tools available to select patients who have a higher probability of benefitting from NAC. In the future, genetic markers, in a personalised medicine setting, might facilitate the selection of patients for NAC and differentiate responders from non-responders.	
Neoadjuvant chemotherapy has its limitations regarding patient selection, current development of surgical techniques, and current chemotherapy combinations.	3

Recommendations	Strength rating
Offer neoadjuvant chemotherapy (NAC) for T2-T4a, cN0M0 bladder cancer. In this case, always use cisplatin-based combination therapy.	Strong
Do not offer NAC to patients who are ineligible for cisplatin-based combination chemotherapy.	Strong
Only offer neoadjuvant immunotherapy to patients within a clinical trial setting.	Strong

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

*7.3.1 **Post-operative radiotherapy***

The data on adjuvant RT after RC are very limited and old. However, advances in targeting and reducing the damage to surrounding tissue, may yield better results in the future [245]. A RCT, comparing pre-operative vs. post-operative RT and RC (n = 100), showed comparable OS, DFS and complication rates [246]. Approximately half of these patients had urothelial cancer (UC), while the other half had SCC. In locally advanced BC (T3-T4, N0/N1, M0), the local recurrence rate seems to decrease with post-operative RT [247].

*7.3.2 **Pre-operative radiotherapy***

7.3.2.1 Retrospective studies

Older data and retrospective studies alone cannot provide an evidence base for modern guideline recommendations due to major study limitations, which include concomitant chemotherapy and differences between surgery and RT. This conclusion was supported by a 2003 SR [248]. A retrospective study from 2015 [249] showed decreased cause-specific mortality and overall mortality for pre-operative RT in clinical T2b and T3 patients only. Another retrospective study with pre-operative RT in clinical T1-3 tumours showed that downstaging to T0 tumours occurs in > 50% of the irradiated patients, as compared to < 10% of patients who did not receive pre-operative RT [250]. Additionally, downstaging resulted in a longer progression-free survival (PFS).

7.3.2.2 *Randomised studies*

To date, six randomised studies have been published, investigating pre-operative RT, although all are from several decades ago. In the largest trial, pre-operative RT at a dose of 45 Gy was used in patients with muscle-invasive tumours resulting in a significant increase in pathological complete response (9% to 34%) in favour of pre-operative RT, which was also a prognostic factor for survival [251]. The OS data were difficult to interpret since chemotherapy was used in a subset of patients only and more than 50% of patients (241/475) did not receive the planned treatment and were excluded from the final analyses. Two smaller studies using a dose of 20 Gy showed only a small survival advantage in ≥ T3 tumours [252, 253]. Two other small trials confirmed downstaging after pre-operative RT [254, 255].

A meta-analysis of the five randomised trials showed a difference in five-year survival (OR: 0.71; 95% CI: 0.48-1.06) in favour of pre-operative RT [256]. However, the meta-analysis was potentially biased by data from the largest trial in which patients were not given the planned treatment. When the largest trial was excluded from the analysis, the OR became 0.94 (95% CI: 0.57-1.55), which was not significant.

7.3.3 ***Summary of evidence and guidelines for pre- and post-operative radiotherapy***

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

Recommendations	**Strength rating**
Do not offer pre-operative radiotherapy (RT) for operable MIBC since it will only result in downstaging, but will not improve survival.	Strong
Do not offer pre-operative RT when subsequent radical cystectomy with urinary diversion is planned.	Strong

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 [188, 257]. Recent interest in patients' QoL has promoted the trend toward bladder-preserving treatment modalities, such as radio- and/or chemotherapy (see Section 7.6). Performance status and life expectancy influence the choice of primary management, as well as the type of urinary diversion, with cystectomy being reserved for patients with a longer life expectancy without concomitant disease and a better PS. The value of assessing overall health before proceeding with surgery was emphasised in a multivariate analysis [129]. The analysis found an association between comorbidity and adverse pathological- and survival outcomes following RC [129]. Performance status and comorbidity have a different impact on treatment outcomes and must be evaluated independently [157].

7.4.1.2 *Radical cystectomy: timing*

An analysis of the Netherlands Cancer Registry showed that a delay of RC > 3 months was not associated with a worse clinical outcome [258]. Previously, Ayres *et al.* also found that in the United Kingdom 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) [259]. A population-based study from the U.S. SEER database analysed patients who underwent a cystectomy between 2001 and 2011 and concluded that a delay of more than twelve weeks has a negative impact on outcome and should be avoided [260]. Moreover, the SEER analysis did not show any significant utilisation and timing differences between men and women.

7.4.2 ***Radical cystectomy: indications***

Traditionally, RC was recommended for patients with MIBC T2-T4a, N0-Nx, M0 [257]. Other indications include high risk and recurrent non-muscle-invasive tumours, BCG-refractory, BCG-relapsing and BCG-unresponsive, T1G3 tumours (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-UC (these tumours respond poorly to chemotherapy and RT). It is also used as a purely palliative intervention, including for fistula formation, pain and recurrent visible haematuria (see Section 7.5.1 - Palliative cystectomy).

When there are positive LNs, in the case of N1 involvement (metastasis in a single node in the true pelvis) orthotopic neobladder can still be considered, but not in N2 or N3 tumours [261].

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

In men, standard RC includes removal of the bladder, prostate, seminal vesicles, distal ureters, and regional LNs. Prostate-sparing cystectomy is an option in a subset of carefully selected patients with BC without involvement of the prostatic urethra and without prostate cancer. This procedure is oncologically safe with good functional results as long as it is performed in an experienced centre [262]. In women, standard RC includes removal of the bladder, entire urethra and adjacent vagina, uterus, distal ureters, and regional LNs [263]. Controversies in evaluating the clinical significance of lymphadenectomy are related to two main aspects of nodal dissection: therapeutic procedure and/or staging instrument.

Two important autopsy studies for RC have been performed so far. The first study showed that in 215 patients with MIBC and nodal dissemination, the frequency of metastasis was 92% in regional (perivesical or pelvic), 72% in retroperitoneal, and 35% in abdominal LNs. There was also a significant correlation between nodal metastases and concomitant distant metastases ($p < 0.0001$).

Approximately 47% of the patients had both nodal metastases and distant dissemination and only 12% of the patients had nodal dissemination as the sole metastatic manifestation [264]. The second autopsy study focused on the nodal yield when super-extended pelvic LN dissection (LND) was performed. Substantial inter-individual differences were found with counts ranging from 10 to 53 nodes [265]. These findings demonstrate the limited utility of node count as a surrogate for extent of dissection.

Regional LNs have been shown to consist of all pelvic LNs below the bifurcation of the aorta [266-270]. Mapping studies have also found that skipping lesions at locations above the bifurcation of the aorta, without more distally located LN metastases, is rare [270, 271].

The optimal extent of LND has not been established to date. Standard lymphadenectomy in BC patients involves removal of nodal tissue cranially up to the common iliac bifurcation, with the ureter being the medial border, and including the internal iliac, presacral, obturator fossa and external iliac nodes [272]. Extended lymphadenectomy includes all LNs in the region of the aortic bifurcation, and presacral and common iliac vessels medial to the crossing ureters. The lateral borders are the genitofemoral nerves, caudally the circumflex iliac vein, the lacunar ligament and the LN of Cloquet, as well as the area described for standard lymphadenectomy [272-276]. A super-extended lymphadenectomy extends cranially to the level of the inferior mesenteric artery [277, 278].

In order to assess how and if cancer outcome is influenced by the extent of lymphadenectomy in patients with clinical N0M0 MIBC, a SR of the literature was undertaken [279]. Out of 1,692 abstracts retrieved and assessed, nineteen studies fulfilled the review criteria [272-276, 278, 280-292]. All five studies comparing LND vs. no LND reported a better oncological outcome for the LND group. Seven out of twelve studies comparing (super) extended with limited or standard LND reported a beneficial outcome for (super) extended LND in at least a subset of patients which is in concordance with the findings of several other meta-analyses [293, 294]. No difference in outcome was reported between extended and super-extended LND in the two high-volume-centre studies identified [278, 290]. A prospective randomised phase III study including 401 patients with a median follow-up of 43 months recently reported [295]. Extended LND failed to show a significant advantage over limited LND in RFS, CSS, and OS. Results from another large RCT on the therapeutic impact of the extent of lymphadenectomy are expected shortly.

It has been suggested that PFS as well as OS might be correlated with the number of LNs removed during surgery. Although there are no data from RCTs on the minimum number of LNs that should be removed, survival rates increase with the number of dissected LNs [296]. Removal of at least ten LNs has been postulated as sufficient for evaluation of LN status, as well as being beneficial for OS in retrospective studies [297-299]. Submitting separate nodal packets instead of *en bloc* has shown significant increased total LN yield, but did not result in an increased number of positive LNs, making LN density an inaccurate prognosticator [300]. In conclusion, extended LND might have a therapeutic benefit compared to less extensive LND, but due to study bias no firm conclusions can be drawn [135, 279].

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

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

To determine the effect of sexual function-preserving cystectomy (SPC) on functional and oncological outcomes the EAU MIBC Panel undertook a SR [301].

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

1. **Prostate sparing cystectomy:** part of or the whole prostate is preserved including seminal vesicles, vas deferens and neurovascular bundles.
2. **Capsule sparing cystectomy:** the capsule or peripheral part of the prostate is preserved with adenoma (including prostatic urethra) removed by TURP or *en bloc* with the bladder. Seminal vesicles, vas deferens and neurovascular bundles are also preserved.
3. **Seminal sparing cystectomy:** seminal vesicles, vas deferens and neurovascular bundles are preserved.
4. **Nerve-sparing cystectomy:** the neurovascular bundles are the only tissue left in place.

Twelve studies recruiting a total of 1,098 patients were identified, including nine comparative studies [262, 302-311] and three single-arm case series [312-314]. In the majority of cases, the open surgical approach was used and the urinary diversion of choice was an orthotopic neobladder. Median follow-up was longer than three years in nine studies, with three studies presenting results with a median follow-up longer than five years.

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

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

For techniques preserving prostatic tissue (prostate- or capsule-sparing), rates of incidental prostate cancer in the intervention group ranged from 0-15%. In no case was incidental prostate cancer with ISUP grade ≥ 4 reported.

Post-operative potency was significantly better in patients who underwent any type of sexual-preserving technique compared to conventional RC ($p < 0.05$), ranging from 80-90%, 50-100% and 29-78% for prostate-, capsule- or nerve-sparing techniques, respectively. Data did not show superiority of any sexual-preserving technique.

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

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

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

Summary of evidence	**LE**
The majority of patients motivated to preserve their sexual function will benefit from sexual-preserving techniques.	2a
None of the sexual-preserving techniques (prostate/capsule/seminal/nerve-sparing) have shown to be superior, and no particular technique can be recommended.	3

Recommendations	Strength rating
Do not offer sexual-preserving cystectomy to men as standard therapy for muscle-invasive bladder cancer.	Strong
Offer sexual-preserving techniques to men motivated to preserve their sexual function since the majority will benefit.	Strong
Select patients based on: • organ-confined disease; • absence of any kind of tumour at the level of the prostate, prostatic urethra or bladder neck.	Strong

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

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

A SR was conducted to evaluate the advantages and disadvantages of sexual-function preserving RC and orthotopic neobladder in female patients [315]. After screening 11,941 abstracts, fifteen studies recruiting a total of 874 patients were eligible for inclusion. Three papers had a matched pair study design, and the remainder of the included studies were retrospective surgical series with small case numbers and a high risk of selection bias favouring less advanced cancers.

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

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

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

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

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

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

Recommendations	Strength rating
Do not offer pelvic organ-preserving radical cystectomy to women as standard therapy for muscle-invasive bladder cancer.	Strong
Offer sexual-preserving techniques to women motivated to preserve their sexual function since the majority will benefit.	Weak
Select patients based on: • organ-confined disease; • absence of tumour in bladder neck or urethra.	Strong

7.4.3.3 Laparoscopic/robotic-assisted laparoscopic cystectomy

Due to data limitations, until recently, laparoscopic radical cystectomy (LRC) and robot-assisted radical cystectomy (RARC) were considered as investigational procedures for which no advantages could be shown as compared to open surgery. Most of the available studies suffered from patient selection bias (age, stage). However, since there is now a continuous flow of reports on RARC, this section of the text and the recommendations contained therein will be subject to significant updates in the coming years. A number of

new publications have recently become available on RARC; a SR [316], a consensus panel report [317], a RCT from the Memorial Sloan Kettering Cancer Center (MSKCC) group [318], a SR on oncologic and functional outcomes after RARC [319] and a retrospective review on recurrence patterns after open radical cystectomy (ORC) and RARC [320].

For the methodology of the SR we refer to the manuscript by Novara *et al.* [316]. In short, out of 1,071 abstracts assessed, 105 studies were selected as meeting the inclusion criteria. Of the 105 papers 102 had a level of evidence of 4 (expert opinion), and only three publications had a level of evidence of 2b.

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

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

A major limitation of this review is the low level of evidence of the included studies. Of the three RCT's, only one was adequately powered and there was no correction for baseline characteristics (selection bias). In some of the larger series in the review 59-67% of tumours are < pT2 tumours. In the largest RCT 91.5% were clinically < T2 and 71.7% pathologically < T2 [318] compared to a large series of ORC (n = 1,054) 47% of included patients had a < pT2 tumour [188].

The Pasadena Consensus Panel (a group of experts on RC, lymphadenectomy and urinary reconstruction) reached similar conclusions as the Novara review based on the same methodology and literature [317]. They presented similar outcomes comparing RARC and ORC for operative endpoints, pathological and intermediate oncological endpoints (positive surgical margins and LN yield), functional endpoints and complication outcomes. Additionally, RARC was associated with increased costs, although there are ergonomic advantages for the surgeon, as compared to LRC. For both techniques, surgeons' experience and institutional volume strongly predicted outcome. According to the literature, proficiency is reached after 20-250 cases. However, the Pasadena Consensus Panel performed statistical modelling and came to the conclusion that 30 cases should be enough to achieve proficiency in RARC, but they also concluded that challenging cases (high BMI, post chemotherapy or RT, pelvic surgery, T4 or bulky tumours, or positive nodes) should be performed by experienced robotic surgeons only. Experience is defined as a high volume centre, > 30 RARCs/year and experience in ORC. Safety after radiotherapy was confirmed by a small (n = 46) retrospective study [321]. In experienced hands the percentage of 90-day (major) complications after robotic cystectomy was independent of previous RT.

In the only sufficiently powered RCT, comparing ORC (n = 58) vs. RARC (n = 60) and open diversion, the primary endpoint was an advantage in 90-day grade 2-5 complications for RARC [318]. Since the complication rates were similar (62% for RARC vs. 66% for ORC), the trial was closed after a planned interim analysis. Robotic-assisted radical cystectomy resulted in less blood loss but had a longer operative time and higher costs. Length of hospital stay, pathology, and QoL were similar. Limitations of this study are lack of long-term outcomes and limited experience in RARC as compared to ORC in this group of patients. Similar health-related quality of life (HRQoL) was also reported in an initial report of a prospective RCT comparing ORC and RARC [322]. Similar functional and oncological outcomes with five years follow-up were reported by Yuh *et al.* [319]. Nguyen *et al.* reported that RARC was not an independent predictor of recurrence after surgery in a retrospective review of 383 consecutive patients [320]. Most reviewed series used extracorporeal reconstruction which leaves room for improvement.

Although an intracorporeal neobladder is a very complex robotic procedure [323], the choice for neobladder or cutaneous diversion must not depend on the surgical approach.

For LRC, a recent review came to similar conclusions as described for RARC [323]. The review included sixteen eligible studies on LRC. As compared to ORC, LRC had a significantly longer operative time, fewer overall complications, blood transfusions and analgesic use, less blood loss and a shorter length of hospital stay. However, the review was limited by the inherent limitations of the included studies. Although this review also showed better oncological outcomes, these appeared comparable to ORC series in the largest LRC multicentre study to date [323].

The CORAL study was a small single centre RCT comparing open (n = 20) vs. robotic (n = 20) vs. laparoscopic (n = 19) cystectomy [324]. The 30-day complication rate was significantly higher in the open arm (70%) compared to the laparoscopic arm (26%). There was no difference between the 90-day Clavien-graded complication rates in the three study arms. Limitations of this study include the small and below target sample size, three different, although experienced, surgeons, and cross over between arms.

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

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

Recommendations	Strength rating
Inform the patient of the advantages and disadvantages of open radical cystectomy (ORC) and robot-assisted radical cystectomy (RARC) to allow selection of the proper procedure.	Strong
Select experienced centres, not specific techniques, both for RARC and ORC.	Strong

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

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

- abdominal diversion, such as an uretero-cutaneostomy, 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 [325]. Several studies have compared certain aspects of HRQoL, such as sexual function, urinary continence and body image, in patient cohorts with different types of urinary diversion. However, further research is needed on pre-operative tumour stage and functional situation, socio-economic status, and time interval to primary surgery.

7.4.4.1 Patient selection and preparations for surgery

The ASA score has been validated to assess the risk of post-operative complications prior to surgery. In the BC setting, ASA scores ≥ 3 are associated with major complications [135, 326], particularly those related to the type of urinary diversion (Table 7.4) [327]. However, the ASA score is not a comorbidity scale and should not be used as such.

Table 7.4: ASA score [328]

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

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

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

When there are positive LNs, orthotopic neobladder can nevertheless be considered in the case of N1 involvement (metastasis in a single node in the true pelvis) but not for N2 or N3 tumours [261].

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 [329].

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 [330]. Despite the necessary interruption and re-anastomosis of bowel, a formal bowel preparation may not be necessary [331]. Bowel recovery time can be reduced by the use of early mobilisation and early oralisation, gastrointestinal stimulation with metoclopramide and chewing gum [332]. Patients treated according to the “fast tract”/ERAS (Early Recovery After Surgery) protocol have shown to score better on the emotional and physical functioning scores and suffer less from wound healing disorders, fever and thrombosis [333].

A cornerstone of the ERAS protocol is post-operative pain management which involves significantly reducing the use of opioids; offering opioids mainly as breakthrough pain medication. Instead of patient-controlled analgesia (PCA) and epidural opioids, most patients receive high-dose acetaminophen and/or ketorolac, starting intra-operatively. Patients on ERAS experience more pain as compared to patients on a traditional protocol (Visual Analogue Scale 3.1 vs. 1.1, $p < 0.001$), but post-operative ileus decreased from 22% to 7.3% ($p = 0.003$) [334].

A multicentre randomised placebo-controlled trial showed that patients receiving alvimopan, a peripherally acting μ-opioid receptor antagonist, experienced quicker bowel recovery compared to patients receiving placebo [335]. However, this drug is, as yet, not approved in Europe.

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

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

Relative contraindications specific for an orthotopic neobladder are high-dose pre-operative RT, complex urethral stricture disease, and severe urethral sphincter-related incontinence [336].

7.4.4.2 Different types of urinary diversion

Radical cystectomy and urinary diversion are the two steps of one operation. However, the literature uniformly reports complications of RC, while ignoring the fact that most complications are diversion related [337]. Age alone is not a criterion for offering continent diversion [336, 338]. Comorbidity, cardiac and pulmonary function,

and cognitive function, are all important factors that should be considered, along with the patient's social support and preference.

Age > 80 years is often considered to be the threshold after which neobladder reconstruction is not recommended. However, there is no exact age for a strict contraindication. In most large series from experienced centres, the rate of orthotopic bladder substitution after cystectomy for bladder tumour is up to 80% in men and 50% in women [339-342]. Nevertheless, no RCTs comparing conduit diversion with neobladder or continent cutaneous diversion have been performed.

A retrospective study including 1,383 patients showed that the risk of a decline in estimated glomerular filtration rate (eGFR) did not significantly differ after ileal conduit vs. neobladder in patients with pre-operative chronic kidney disease 2 (eGFR 60-89 mL/min/1.73 m^2) or 3a (eGFR 45-59 mL/min/1.73 m^2) [343]. Only age and anastomotic strictures were found to be associated with a decline in eGFR.

7.4.4.2.1 Uretero-cutaneostomy

Ureteral diversion to the abdominal wall is the simplest form of cutaneous diversion. Operating time, complication rate, stay at intensive care and length of hospital stay are lower in patients treated with uretero-cutaneostomy as compared to ileal conduit [344]. Therefore, in older, or otherwise compromised, patients who need a supravesical diversion, uretero-cutaneostomy is the preferred procedure [345, 346]. Quality of life, which was assessed using the Bladder Cancer Index (BCI), showed equal urinary bother and function for patients treated with ileal conduit and uretero-cutaneostomy [344]. 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 [347].

Technically, either one ureter, to which the other shorter one is attached end-to-side, is connected to the skin (trans-uretero-cutaneostomy) 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 [345].

In a retrospective multicentre study peri-operative morbidity was evaluated for urinary diversion using bowel as compared to uretero-cutaneostomy. Patients selected for a uretero-cutaneostomy were older and had a higher ASA score, while their mean Charlson score was lower (4.2 vs. 5.6, $p < 0.001$) [348].

Despite the limited comparative data available, it must be taken into consideration that older data and clinical experience suggest ureter stenosis at the skin level and ascending UTI are more frequent complications in uretero-cutaneostomy compared to an ileal conduit diversion. In a retrospective study comparing various forms of intestinal diversion, ileal conduits had fewer late complications than continent abdominal pouches or orthotopic neobladders [349].

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 [349]. 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% [350-352]. An increase in complications was seen with longer follow-up in the Berne series of 131 patients who were followed for a minimum of five years (median follow-up 98 months) [353]; the rate of complications increased from 45% at five years to 94% in those surviving > 15 years. In the latter group, 50% of patients developed UUT changes and 38% developed urolithiasis.

7.4.4.2.3 Continent cutaneous urinary diversion

A low-pressure detubularised ileal reservoir can be used as a continent cutaneous urinary diversion for self-catheterisation; gastric, ileocecal and sigma pouches have also been described [354-356]. Different anti-reflux techniques can be used [357]. Most patients have a well-functioning reservoir with day-time and night-time continence approaching 93% [358]. 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 [358]. Stone formation in the pouch occurred in 10% of patients [357-359]. In a small series of previously irradiated female patients, incontinence and stomal stenosis was seen in 8/44 patients (18%) [360].

7.4.4.2.4 Ureterocolonic diversion

The oldest and most common form of ureterocolonic diversion was primarily a refluxive and later an anti-refluxive connection of ureters to the intact rectosigmoid colon (uretero-rectosigmoidostomy) [361, 362]. 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 [329, 363]. Bowel frequency and urge incontinence are additional adverse effects of this type of urinary diversion. However, it may be possible to circumvent these 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 [364].

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 [202, 257, 336]. However, in elderly patients (> 80 years), it is rarely performed, even in high-volume expert centres [365, 366]. 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 [257]. 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 patients is reported [367, 368]. In two studies with 1,054 and 1,300 patients [336, 369], long-term complications included diurnal (8-10%) and nocturnal (20-30%) incontinence, ureterointestinal stenosis (3-18%), metabolic disorders, and vitamin B12 deficiency. A study comparing cancer control and patterns of disease recurrence in patients with neobladder and ileal conduit showed no difference in CSS between the two groups when adjusting for pathological stage [370]. Urethral recurrence in neobladder patients seems rare (1.5-7% for both male and female patients) [336, 371]. 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 [372, 373].

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 [357, 368]. According to the long-term results, the UUT is protected sufficiently by either method.

A detailed investigation of the bladder neck prior to RC is important for women who are scheduled for an orthotopic bladder substitute [374]. In women undergoing RC the rate of concomitant urethral malignancy has been reported to range from 12-16% [375]. 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 [376].

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 [377, 378]. In selected patients, such as patients with a single kidney, uretero-cutaneostomy is surgically the least burdensome type of diversion (LE: 3). Recommendations related to RC and urinary diversions are listed in Section 7.5.

*7.4.5 **Morbidity and mortality***

In three long-term studies, and one population-based cohort study, the peri-operative mortality was reported as 1.2-3.2% at 30 days and 2.3-8.0% at 90 days [202, 337, 339, 379, 380]. In a large single-centre series, early complications (within three months of surgery) were seen in 58% of patients [337]. Late morbidity was usually linked to the type of urinary diversion (see also above) [340, 381]. Early morbidity associated with RC for NMIBC (at high risk for disease progression) is similar and no less than that associated with muscle-invasive tumours [382]. In general, lower morbidity and (peri-operative) mortality have been observed by surgeons and in hospitals with a higher case load and therefore more experience [379, 383-387].

Table 7.6: Management of neobladder morbidity (30-64%) [388]

CLAVIEN System		Morbidity	Management
Grade I	Any deviation from the normal post-operative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs such as antiemetics, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.	**Immediate complications:**	
		Post-operative ileus	Nasogastric intubation (usually removed at J1) Chewing gum Avoid fluid excess and hypovolemia (provoke splanchnic hypoperfusion)
		Post-operative nausea and vomiting	Antiemetic agent (decrease opioids) Nasogastric intubation
		Urinary infection	Antibiotics (ATB), no ureteral catheter removal Check the 3 drainages (ureters and neobladdder)
		Ureteral catheter obstruction	Inject 5 cc saline in the ureteral catheter to resolve the obstruction Increase volume infusion to increase diuresis
		Intra-abdominal urine leakage (anastomosis leakage)	Check drainages and watchful waiting
		Anaemia well tolerated	Martial treatment (give iron supplement)
		Late complications:	
		Non compressive lymphocele	Watchful waiting
		Mucus cork	Cough Indwelling catheter to remove the obstruction
		Incontinence	Urine analysis (infection), echography (post-void residual) Physiotherapy
		Retention	Drainage and self-catheterisation education
Grade II	Requiring pharmacological treatment with drugs other than those allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.	Anaemia badly tolerated or if myocardial cardiopathy history	Transfusion[1,2]
		Pulmonary embolism	Heparinotherapy[3]
		Pyelonephritis	ATB and check kidney drainage (nephrostomy if necessary)
		Confusion or neurological disorder	Neuroleptics and avoid opioids
Grade III	Requiring surgical, endoscopic or radiological intervention	Ureteral catheter accidentally dislodged	Indwelling leader to raise the ureteral catheter
		Anastomosis stenosis (7%)	Renal drainage (ureteral catheter or nephrostomy)
		Ureteral reflux	No treatment if asymptomatic
III-a	Intervention not under general anaesthesia	Compressive lymphocele	Transcutaneous drainage or intra-operative marsupialisation (cf grade III)
III-b	Intervention under general anaesthesia	Ileal anastomosis leakage	Ileostomy, as soon as possible
		Evisceration	Surgery in emergency
		Compressive lymphocele	Surgery (marsupialisation)

Grade IV	Life-threatening complication (including central nervous system complications: brain haemorrhage, ischaemic stroke, subarachnoid bleeding, but excluding transient ischaemic attacks) requiring intensive care/ intensive care unit management.	Rectal necrosis	Colostomy
		Neobladder rupture	Nephrostomy and indwelling catheter/surgery for repairing neobladder
		Severe sepsis	ATB and check all the urinary drainages and 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.*		

[1] *A SR showed that peri-operative blood transfusion (PBT) in patients who undergo RC correlates with increased overall mortality, CSM and cancer recurrence. The authors hypothesised that this may be caused by the suggested immunosuppressive effect of PBT. The foreign antigens in transfused blood induce immune suppression, which may lead to tumour cell spread, tumour growth and reduced survival in already immunosuppressed cancer patients. As other possible causes for this finding increased post-operative infections and blood incompatibility were mentioned [389]. Buchner and co-workers showed similar results in a retrospective study. The five-year CSS decreased in cases where intra-operative blood transfusion (CSS decreased from 67% to 48%) or post-operative blood transfusion (CSS decreased from 63% to 48%) were given [390].*

[2] *Intra-operative tranexamin acid infusion reduces peri-operative blood transfusion rates from 57.7% to 31.1%. There was no increase seen in peri-operative venous thromboembolism [391].*

[3] *Hammond and co-workers reviewed 20,762 cases of venous thromboembolism (VTE) after major surgery and found cystectomy patients to have the second highest rate of VTE among all cancers studied [392]. These patients benefit from 30 days low-molecular-weight heparin prophylaxis. Subsequently, it was demonstrated that BMI > 30 and non-urothelial BCs are independently associated with VTE after cystectomy. In these patients extended (90 days) heparin prophylaxis should be considered [393].*

7.4.6 ***Survival***

According to a multi-institutional database of 888 consecutive patients undergoing RC for BC, the five-year RFS rate was 58% and CSS was 66% [394]. External validation of post-operative nomograms for BC-specific mortality showed similar results, with bladder-CSS of 62% [395].

Recurrence-free survival and OS in a large single-centre study of 1,054 patients was 68% and 66% at five years and 60% and 43%, at ten years, respectively [188]. However, the five-year RFS in node-positive patients who underwent cystectomy was considerably less at 34-43% [187, 396]. In a surgery-only study, the five-year RFS was 76% in patients with pT1 tumours, 74% for pT2, 52% for pT3, and 36% for pT4 [188].

A trend analysis according to the five-year survival and mortality rates of BC in the U.S. between 1973 and 2009 with a total of 148,315 BC patients, revealed increased stage-specific five-year survival rates for all stages, except for metastatic disease [397].

7.4.7 ***Impact of hospital and surgeon volume on treatment outcomes***

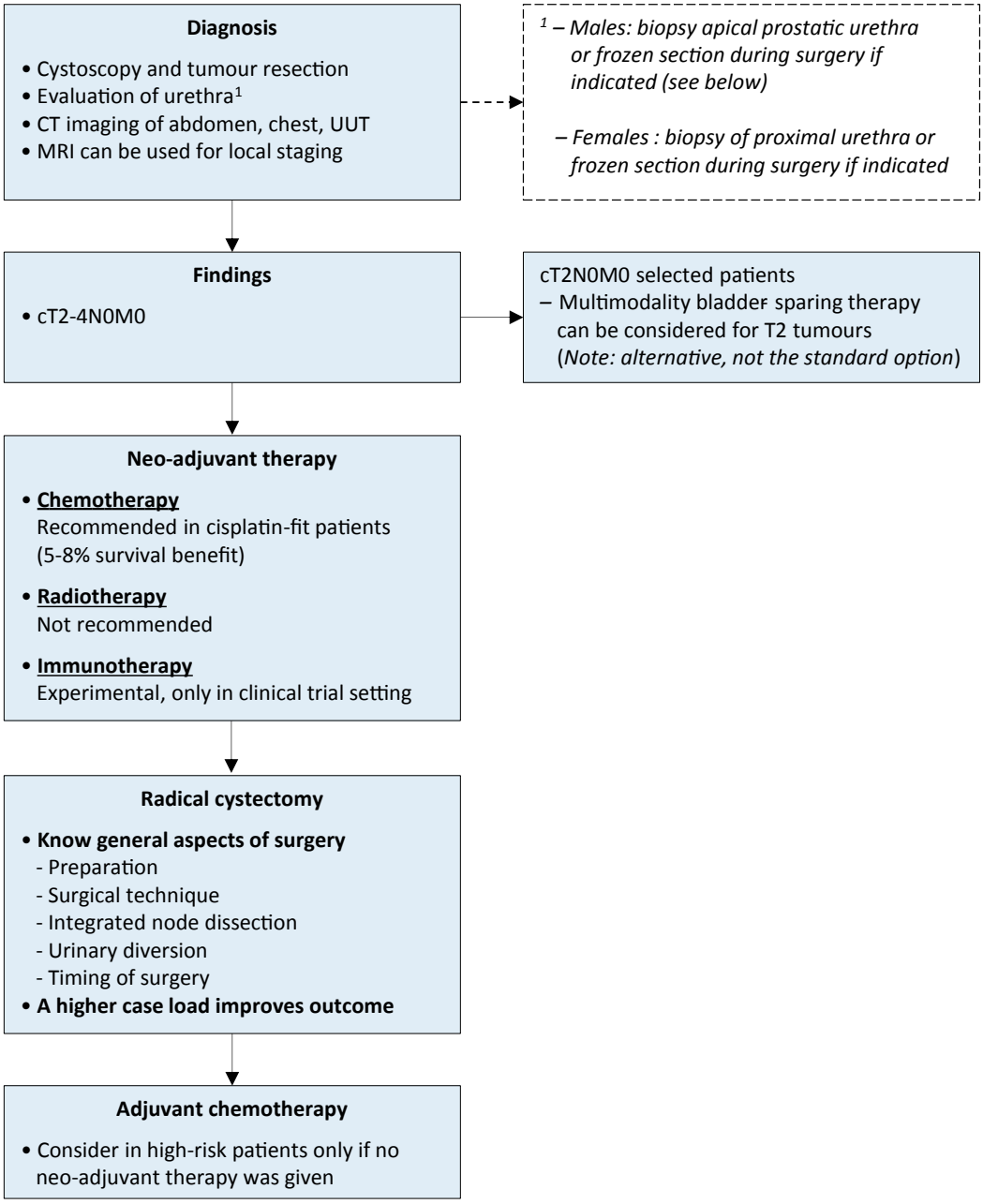
A SR was performed to assess the impact of hospital and/or surgeon volume on peri-operative mortality and morbidity of RC [10]. Out of 1,078 publications screened a total of 31 papers were included in the review. Fifteen studies reported on annual hospital volume only, five studies on surgeon volume only and eleven studies reported on both. Primary outcome of the SR was peri-operative mortality. Hospitals performing more RCs reported lower in-hospital, 30- and 90-day mortality in most publications. Also, the complication rate appeared to be lower in higher-volume hospitals. However, due to differences in baseline characteristics, subgroup definitions and statistical analyses among studies, a threshold hospital volume associated with improved outcomes could not be defined.

7.4.8 *Summary of evidence and guidelines for radical cystectomy and urinary diversion*

Summary of evidence	LE
For MIBC, offer radical cystectomy (RC) the curative treatment of choice.	3
A higher case load reduces morbidity and mortality of cystectomy.	3
Radical cystectomy includes removal of regional lymph nodes.	3
There are data to support that extended lymph node dissection (LND) (vs. standard or limited LND) improves survival after RC.	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 RC.	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 grading system for cystectomy is the Clavien grading system.	2
No conclusive evidence exists as to the optimal extent of LND.	2a

Recommendations	Strength rating
Do not delay radical cystectomy (RC) for > 3 months as it increases the risk of progression and cancer-specific mortality.	Strong
Before RC, fully inform the patient about the benefits and potential risks of all possible alternatives. The final decision should be based on a balanced discussion between the patient and the surgeon.	Strong
Do not offer an orthotopic bladder substitute diversion to patients who have a tumour in the urethra or at the level of urethral dissection.	Strong
Pre-operative bowel preparation is not mandatory. “Fast track” measurements may reduce the time to bowel recovery.	Strong
Offer RC in T2-T4a, N0M0, and high-risk non-MIBC.	Strong
Perform a lymph node dissection as an integral part of cystectomy.	Strong
Do not preserve the urethra if margins are positive.	Strong

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



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

7.5 Unresectable tumours

7.5.1 Palliative cystectomy for muscle-invasive bladder carcinoma

Locally advanced tumours (T4b, invading the pelvic or abdominal wall) may be accompanied by several debilitating symptoms, including bleeding, pain, dysuria and urinary obstruction. These patients are candidates for palliative treatments, such as palliative RT. Palliative cystectomy with urinary diversion carries the greatest morbidity and should be considered for symptom relief only if there are no other options [398-400].

Locally advanced MIBC can be associated with ureteral obstruction due to a combination of mechanical blockage by the tumour and invasion of ureteral orifices by tumour cells. In a series of 61 patients with obstructive uraemia, RC was not an option in 23 patients, and obstruction was relieved using permanent nephrostomy tubes [401]. Another ten patients underwent palliative cystectomy, but local pelvic recurrence occurred in all ten patients within the first year of follow-up. Another small study (n = 20) showed that primary cystectomy for T4 BC was technically feasible and associated with a very tolerable therapy-related morbidity and mortality [402].

7.5.1.1 *Guidelines for unresectable tumours*

Recommendations	Strength rating
Offer radical cystectomy as a palliative treatment to patients with inoperable locally advanced tumours (T4b).	Weak
Offer palliative cystectomy to patients with symptoms.	Weak

7.5.2 ***Supportive care***

7.5.2.1 *Obstruction of the upper urinary tract*

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

7.5.2.2 *Bleeding and pain*

In the case of bleeding, the patient must be screened first for coagulation disorders or the patient's use of anticoagulant drugs must be reviewed. Transurethral (laser) coagulation may be difficult in a bladder full of tumour or with a bleeding tumour. Intravesical rinsing of the bladder with 1% silver nitrate or 1-2% alum can be effective [403]. It can usually be done without any anaesthesia. The instillation of formalin (2.5-4% for 30 minutes) is a more aggressive and painful procedure, requiring anaesthesia. Formalin instillation has a higher risk of side-effects, e.g. bladder fibrosis, but is more likely to control the bleeding [403]. 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% [404]. 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% [403]. 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***

Transurethral resection of bladder tumour alone in patients with muscle-invasive bladder tumours is only possible as a therapeutic option if tumour growth is limited to the superficial muscle layer and if re-staging biopsies are negative for residual (invasive) tumour [405]. In general, approximately 50% of patients will still have to undergo RC for recurrent MIBC with a disease-specific mortality rate of up to 47% within this group [406]. A disease-free status at re-staging TURB appears to be crucial in making the decision not to perform RC [407, 408]. A prospective study by Solsona *et al.*, which included 133 patients with radical TURB and re-staging negative biopsies, reported a fifteen-year follow-up [408]. Thirty per cent had recurrent NMIBC and went on to intravesical therapy, and 30% (n = 40) progressed, of which 27 died of BC. After five, ten, and fifteen years, the results showed CSS rates of 81.9%, 79.5%, and 76.7%, respectively and PFS rates with an intact bladder of 75.5%, 64.9%, and 57.8%, respectively.

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

7.6.1.1 *Guideline for transurethral resection of bladder tumour*

Recommendation	Strength rating
Do not offer transurethral resection of bladder tumour alone as a curative treatment option as most patients will not benefit.	Strong

7.6.2 ***External beam radiotherapy***

Current RT techniques with soft-tissue matching result in superior bladder coverage and a reduced integral dose to the surrounding tissues. The target dose for curative EBRT in BC is 64-66 Gy [409], with a subsequent boost using external RT or interstitial RT. In a phase II study including 55 patients (median age 86) unfit for cystectomy or even daily RT, BC was treated with six-weekly doses of 6 Gy [410]. Forty-eight patients completed EBRT with acceptable toxicity and 17% had showed local progression after two years demonstrating good local control with this hypofractionated schedule.

The use of modern standard EBRT techniques results in major related late morbidity of the urinary bladder or bowel in less than 5% of tumour-free patients [411]. Acute diarrhoea is reduced even more with intensity-modulated RT [412]. Important prognostic factors for outcome include response to EBRT, tumour size, hydronephrosis and completeness of the initial TURB. Additional prognostic factors reported were age and stage [413].

With the use of modern EBRT techniques, efficacy and safely results seem to have improved over time. A 2002 Cochrane analysis demonstrated that RC has an OS benefit compared to RT [398], although this was not the case in a 2014 retrospective review using a propensity score analysis [399]. In a 2017 retrospective cohort study of U.S. National Cancer Data Base data, patients over 80 were identified with cT2-4, N0-3, M0 BC, who were treated with curative EBRT (60-70 Gy, n = 739) or concurrent chemoradiotherapy (n = 630) between 2004 and 2013 [414]. The two-year OS was 42% for EBRT vs. 56% for chemoradiotherapy ($p < 0.001$). For EBRT a higher RT dose and a low stage were associated with improved OS.

In conclusion, although EBRT results seem to improve over time, EBRT alone does not seem to be as effective as surgery or combination therapy (see Section 7.6.4). Factors that influence outcome should be considered. However, EBRT can be an alternative treatment in patients unfit for radical surgery, as it can be used to control bleeding.

7.6.2.1 Summary of evidence and guideline for external beam radiotherapy

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

Recommendation	Strength rating
Do not offer radiotherapy alone as primary therapy for localised bladder cancer.	Strong

*7.6.3 **Chemotherapy***

Chemotherapy alone rarely produces durable complete remissions. In general, a clinical complete response rate of up to 56% is reported in some series, which must be weighed against a staging error of > 60% [415, 416]. Response to chemotherapy is a prognostic factor for treatment outcome and eventual survival [417] although 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 [210, 225, 418, 419]. Neoadjuvant chemotherapy with two to three cycles of MVAC or CMV has led to a downstaging of the primary tumour in different prospective series [210, 225, 418].

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 [417]. However, this approach cannot be recommended for routine use.

7.6.3.1 Summary of evidence and guideline for chemotherapy

Summary of evidence	LE
Complete and partial local responses have been reported with cisplatin-based chemotherapy as primary therapy for locally advanced tumours in highly selected patients.	2b

Recommendation	Strength rating
Do not offer chemotherapy alone as primary therapy for localised bladder cancer.	Strong

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

Multimodality treatment (MMT) or trimodality treatment combines TURB, chemotherapy and radiation. The rationale to combine TURB with RT is to achieve local tumour control in the bladder and adjacent nodes. The addition of systemic chemotherapy or other radiosensitisers (mentioned below) is aimed at the potentiation of

RT. Micrometastases are targeted by platinum-based combination chemotherapy, for details see Section 7.2. The aim of MMT is to preserve the bladder and QoL without compromising oncological outcome. There are no completed RCTs comparing the outcome of MMT with RC, but MMT has been shown to be superior to RT alone [420, 421]. Many of the reported series have differing characteristics as compared to the larger surgical series, which typically have median ages in the mid to late 60s compared to mid-70s for some large RT series (reviewed by James, *et al.* [420]). In the case of MMT, two distinct patterns of care emerge: treatment aimed at patients fit for cystectomy and treatment aimed at older, less fit patients. For the former category, MMT presents selective bladder preservation. In that case, the initial step is a radical TURB, where as much tumour as possible should be resected. This implies that proper patient selection (T2 tumours, no CIS) is critical [422]. Even in the case of an initial presumed complete resection, a second TUR reveals tumour in > 50% of patients and subsequently improves five-year OS in case of MMT [423]. For patients who are not candidates for cystectomy, less stringent criteria can be applied, though extensive CIS and poor bladder function should both be regarded as strong contraindications.

A collaborative review has described the principles of MMT [424]. For radiation, two schedules are in common use worldwide: a split-dose format with interim cystoscopy is used in the U.S. [421], whilst single-phase treatment is more commonly used elsewhere [420]. A standard radiation schedule includes EBRT to the bladder and limited pelvic LNs with an initial dose of 40 Gy, with a boost to the whole bladder of 54 Gy and a further tumour boost, with a total dose of 64 Gy. In a small RCT, however, it was reported that leaving out elective pelvic nodal irradiation did not compromise pelvic control rate, but significantly decreased the acute radiation toxicity [425].

Different chemotherapy regimens have been used, but most evidence exists for cisplatin [426] and mitomycin C plus 5-FU [420]. In addition to these agents, other schedules have also been used, such as hypoxic cell sensitisation with nicotinamide, carbogen and gemcitabine. To detect non-responders, which should be offered salvage cystectomy, bladder biopsies should be performed after MMT.

Five-year CSS and OS rates vary between 50% to 82% and 36% to 74%, respectively, with salvage cystectomy rates of 10-30% [420, 424, 426, 427]. The Boston group reported on their experience in 66 patients with variant histology treated with MMT and found similar complete response, OS, DSS and salvage cystectomy rates as in UC [428]. The impact of MMT as compared to RC on long-term OS remains undefined. Two retrospective analyses of the National Cancer Database from 2004-2013, with propensity score matching, compared RC to MMT. Ritch *et al.* identified 6,606 RC and 1,773 MMT patients [429]. Worse survival was accompanied with higher age, comorbidity and tumour stage. After modelling, MMT resulted in a lower mortality at 1 year (HR: 0.84, 95% CI: 0.74-0.96, p = 0.01). However, in years 2 and onwards, there was a significant and persistent higher mortality after MMT (year 2: HR: 1.4, 95% CI: 1.2-1.6, p < 0.001; and year 3 onwards: HR: 1.5, 95% CI: 1.2-1.8, p < 0.001). The second analysis was based on a larger cohort, with 22,680 patients undergoing RC; 2,540 patients received definitive EBRT and 1,489 MMT [430]. Survival after modelling was significantly better for RC compared to any EBRT, definitive EBRT and MMT (HR: 1.4 [95% CI: 1.2-1.6]) at any point in time. On the other hand, a SR including 57 studies and over 30,000 patients comparing RC and MMT, found improved ten-year OS and DSS for MMT, but for the entire cohort OS and DSS between RC and MMT were not significantly different [431]. Complete response after MMT resulted in a significant better survival, as did downstaging after TUR or NAC in case of RC.

There are data that major complication rates are similar for salvage and primary cystectomy [432]. The majority of recurrences post-MMT are non invasive and can be managed conservatively [420]. A retrospective study showed QoL to be good after MMT and in most domains better than after cystectomy, although prospective validations are needed [433].

A collaborative review came to the conclusion that data are accumulating, suggesting that bladder preservation with MMT leads to acceptable outcomes and therefore MMT may be considered a reasonable treatment option in well-selected patients as compared to RC [424]. Multimodality bladder-preserving treatment should also be considered in all patients with a contraindication for surgery, either a relative or absolute contraindication since the factors that determine fitness for surgery and chemoradiotherapy differ.

There are no definitive data to support the benefit of using neoadjuvant or adjuvant chemotherapy. Patient selection is critical in achieving good outcomes [424].

A bladder-preserving multimodality strategy requires very close multidisciplinary cooperation, the importance of which was highlighted by a Canadian group [434]. In Ontario between 1994 and 2008 only 10% (370/3,759) of patients with cystectomy had a pre-operative radiation oncology consultation, with high geographical variations. Independent factors associated with this consultation included advanced age (p < 0.001), greater comorbidity (p < 0.001) and earlier year of diagnosis (p < 0.001). A bladder-preserving multimodality strategy also requires a high level of patient compliance. Even if a patient has shown a clinical response to a multimodality bladder-preserving strategy, the bladder remains a potential source of recurrence, hence long-

term bladder monitoring is essential and patients should be counselled that this will be required. A sub-analysis of two RTOG trials looked at complete response (T0) and near complete response (Ta or Tis) after MMT [435]. After a median follow-up of 5.9 years 41/119 (35%) of patients experienced a bladder recurrence, and fourteen required salvage cystectomy. There was no difference between complete and near-complete responders. Non-muscle-invasive BC recurrences after complete response to MMT were reported in 25% of patients by the Boston group, sometimes over a decade after initial treatment [436]. A NMIBC recurrence was associated with a lower DSS, although in properly selected patients, intravesical BCG could avoid immediate salvage cystectomy.

7.6.4.1 Summary of evidence and guidelines for multimodality treatment

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

Recommendations	Strength rating
Offer surgical intervention or multimodality treatments (MMT) as primary curative therapeutic approaches since they are more effective than radiotherapy alone.	Strong
Offer MMT as an alternative to selected, well-informed and compliant patients, especially for whom cystectomy is not an option.	Strong

7.7 Adjuvant therapy

*7.7.1 **Role of adjuvant platinum-based chemotherapy***

Adjuvant chemotherapy after RC for patients with pT3/4 and/or LN positive (N+) disease without clinically detectable metastases (M0) is still under debate [432, 437] and is infrequently used [206].

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 post-operative morbidity [438].

There is limited evidence from adequately conducted and accrued randomised phase III trials in favour of the routine use of adjuvant chemotherapy [437, 439-444]. An individual patient data meta-analysis [439] of survival data from six RCTs of adjuvant chemotherapy [427, 445-448] included 491 patients (unpublished data from Otto *et al.*, were included in the analysis). All included trials suffered from significant methodological flaws including small sample size (underpowered), incomplete accrual, use of inadequate statistical methods and design flaws (irrelevant endpoints and failing to address salvage chemotherapy in case of relapse or metastases) [437]. In these trials, three or four cycles of CMV, cisplatin, cyclophosphamide, and adriamycin (CISCA), methotrexate, vinblastine, adriamycin or epirubicin, and cisplatin (MVA(E)C) and cisplatin and methotrexate (CM) were used [449], and one trial used cisplatin monotherapy [447]. These data were not convincing enough to give an unequivocal recommendation for the use of adjuvant chemotherapy.

In 2014, this meta-analysis [440] was updated with an additional three studies [441-443] resulting in the inclusion of 945 patients from nine trials. None of the trials had fully accrued and individual patient data were not used in the analysis [440]. For one trial only an abstract was available at the time of the meta-analysis [442], and none of the included individual trials were significantly positive for OS in favour of adjuvant chemotherapy. In two of the trials more modern chemotherapy regimens were used (gemcitabine/cisplatin and paclitaxel/gemcitabine and cisplatin) [441, 442]. The HR for OS was 0.77 and there was a trend towards an OS benefit when including all nine trials. The effect was stronger for DFS (HR: 0.66; 95% CI: 0.48-0.92) and when stratified for the ratio of nodal positivity (HR: 0.64; 95% CI: 0.45-0.91), which is caused by the 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.

A retrospective cohort analysis including 3,974 patients after cystectomy and LND showed an

OS benefit in high-risk subgroups (extravesical extension and nodal involvement) (HR: 0.75; CI: 0.62-0.90) [450]. A 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 [451].

Furthermore, a large observational study including 5,653 patients with pathological T3-4 and/or pathological node-positive BC, treated between 2003 and 2006 compared the effectiveness of adjuvant chemotherapy vs. observation. Twenty-three percent of patients received adjuvant chemotherapy with a five-year OS of 37% for the adjuvant arm (HR: 0.70; 95% CI: 0.64-0.76), vs. 29.1% in the observation group [452].

From the currently available evidence it is still unclear whether immediate adjuvant chemotherapy or chemotherapy at the time of relapse is superior, or if the two approaches are equivalent with respect to the endpoint of OS. Cisplatin-based combination chemotherapy results in long-term DFS, even in metastatic disease, mainly in patients with LN metastases only, and with a good PS [453-455]. In the most recent meta-analysis, the positive role of adjuvant chemotherapy for BC has been strengthened; however, still with a poor level of evidence [440]. Patients should be informed about potential chemotherapy options before RC, including neoadjuvant and adjuvant chemotherapy, and the limited evidence for adjuvant chemotherapy.

*7.7.2 **Role of adjuvant immunotherapy***

To evaluate the benefit of PD1/PD-L1 checkpoint inhibitors, a number of clinical trials comparing checkpoint inhibitor monotherapy, including atezolizumab, nivolumab and pembrolizumab, and any of these inhibitors against placebo, are ongoing.

*7.7.3 **Guidelines for adjuvant therapy***

Recommendations	Strength rating
Offer adjuvant cisplatin-based combination chemotherapy to patients with pT3/4 and/or pN+ disease if no neoadjuvant chemotherapy has been given.	Strong
Offer immunotherapy with a checkpoint inhibitor only in a clinical trial setting.	Strong

7.8 Metastatic disease

*7.8.1 **Introduction***

Approximately 50% of patients with muscle-invasive UC relapse after RC, depending on the pathological stage of the primary tumour and the nodal status. Local recurrence accounts for 30% of relapses, whereas distant metastases are more common. Ten to fifteen percent of patients are already metastatic at diagnosis [456]. Before the development of effective chemotherapy, patients with metastatic UC had a median survival rarely exceeding three to six months [457].

7.8.1.1 Prognostic factors and treatment decisions

Prognostic factors are crucial for assessing phase II study results and stratifying phase III trials [458, 459]. In a multivariate analysis, Karnofsky PS of ≤ 80% and presence of visceral metastases were independent prognostic factors of poor survival after treatment with MVAC [459]. These prognostic factors have also been validated for newer combination chemotherapy regimens [460-462].

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 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 [463].

7.8.1.2 Comorbidity in metastatic disease

Comorbidity is defined as “the presence of one or more disease(s) in addition to an index disease” (see Section 6.2.1). Comorbidity increases with age. However, chronological age does not necessarily correlate with functional impairment. Different evaluation systems are being used to screen patients as potentially fit or unfit for chemotherapy, but age alone should not be used to base treatment selection on [464].

7.8.1.3 Definition - Not eligible for cisplatin (unfit)

The EORTC conducted the first randomised phase II/III trial for UC patients who were unfit for cisplatin chemotherapy [465]. The EORTC definitions were GFR < 60 mL/min and/or PS 2.

An international survey among BC experts [466] was the basis for a consensus statement on how to classify patients unfit for cisplatin-based chemotherapy. At least one of the following criteria has to be present: PS > 1; GFR ≤ 60 mL/min; grade ≥ 2 audiometric loss; peripheral neuropathy; and New York Heart Association (NYHA) class III heart failure [467].

More than 50% of patients with UC are not eligible for cisplatin-based chemotherapy [468-471]. Renal function assessment in UC is of utmost importance for treatment selection [468, 472]. In case of doubt, measuring GFR with radioisotopes (99mTc DTPA or 51Cr-EDTA) is recommended. Cisplatin has also been administered in patients with low GFR using different schedules. The respective studies were mostly small phase I and II trials [473-476]. In one phase III trial the GFR cut off for cisplatin eligibility was ≥ 50 mL/min [477].

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

Cisplatin-containing combination chemotherapy has been the standard of care since the late 1980s demonstrating an OS of twelve to fourteen months in different series (for a review see [478]). Methotrexate, vinblastine, adriamycin plus cisplatin (MVAC) and GC prolonged survival to up to 14.8 and 13.8 months, respectively, compared to monotherapy and older chemotherapy 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 efficacy of the two regimens [454]. The major difference between the above-mentioned combinations is toxicity. The lower toxicity of GC [160] has resulted in it becoming a new standard regimen [479]. Methotrexate, vinblastine, adriamycin plus cisplatin is better tolerated when combined with granulocyte colony-stimulating factor (G-CSF) [479, 480].

High-dose intensity MVAC (HD-MVAC) combined with G-CSF is less toxic and more efficacious than standard MVAC in terms of dose density, complete response (CR), and two-year survival rate. However, there is no significant difference in median survival between the two regimens [481, 482]. In general, all disease sites have been shown to respond to cisplatin-based combination chemotherapy. A response rate of 66% and 77% with MVAC and HD-MVAC, respectively, has been reported in retroperitoneal LNs vs. 29% and 33% at extranodal sites [481]. The disease sites also have an impact on long-term survival. In LN-only disease, 20.9% of patients were alive at five years compared to only 6.8% of patients with visceral metastases [454].

Further intensification of treatment using paclitaxel, cisplatin and gemcitabine (PCG) triple regimen did not result in a significant improvement in OS in the intent-to-treat (ITT) population of a large randomised phase III trial, comparing PCG triple regimen to GC [483]. 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 additional major side effects. Grade 4 neutropenia was more common (35.8% vs. 20% for GC), as was febrile neutropenia (13.2% vs. 4.3%), and the need for G-CSF was higher (17% vs. 11%). Gemcitabine/cisplatin alone caused more grade 4 thrombocytopenia and thrombocytopenia-induced bleeding (11.4% vs. 6.8%). Paclitaxel, cisplatin and gemcitabine is an additional option for first-line treatment of UC.

*7.8.3 **Carboplatin-containing chemotherapys for fit patients***

Carboplatin-containing chemotherapy is not equivalent to cisplatin combinations, and should not be considered interchangeable or standard. Several randomised phase II trials of carboplatin vs. cisplatin combination chemotherapy have produced lower CR rates and shorter OS for the carboplatin arms [484].

*7.8.4 **Chemotherapy in patients unfit for cisplatin***

Up to 50% of patients are ineligible for cisplatin-containing chemotherapy [467]. 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 was 13.6% in patients treated with GemCarbo vs. 23% with M-CAVI, while the ORR was 42% for GemCarbo and 30% for M-CAVI. Further analysis showed that in patients with PS 2 and impaired renal function, combination chemotherapy provided limited benefit [465]. The ORR and severe acute toxicity were both 26% for the former group, and 20% and 24%, respectively, for the latter group [465]. Phase III data have confirmed these results [462].

A recently published randomised, multinational phase II trial (JASINT1) assessed the efficacy and tolerability profile of two vinflunine-based regimens (vinflunine-gemcitabine vs. vinflunine-carboplatin). Both regimens showed equal ORR and OS with less haematologic toxicity for the combination vinflunine-gemcitabine [485].

*7.8.4.1 **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 RCTs; therefore, it is not recommended for first-line use in cisplatin-eligible patients [486-493].

7.8.4.2 *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 [494, 495]. Responses with single agents are usually short-lived, complete responses are rare and no long-term DFS has been reported. The median survival in such patients is only six to nine months.

7.8.5 *Second-line chemotherapy*

Second-line chemotherapy data are highly variable and prognostic factors have been established only recently (see Section 7.8.1.1) [463]. A reasonable strategy has been to re-challenge former cisplatin-sensitive patients if progression occurred, at least six to twelve months after first-line cisplatin-based combination chemotherapy. Second-line response rates of single agent treatment with paclitaxel (weekly), docetaxel, nab-paclitaxel [496] oxaliplatin, ifosfamide, topotecan, pemetrexed, lapatinib, gefitinib and bortezomib have ranged between 0% and 28% in small phase II trials [494, 497, 498]. Gemcitabine had also shown good response rates in second-line use but most patients receive this drug as part of their first-line treatment [493].

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 [457, 491, 499].

Vinflunine, a novel third-generation vinca alkaloid, provided promising results in phase II trials [500]. 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 [501]. The results showed a modest ORR (8.6%), a clinical benefit with a favourable safety profile and, most importantly, a survival benefit in favour of vinflunine, which was statistically significant in the eligible patient population (not in the ITT population). For second-line treatment of advanced or metastatic UC this trial reached the highest level of evidence. Based on these findings, vinflunine was approved in Europe (not in the U.S.) as the only second-line treatment option for this indication. As immunotherapy with checkpoint inhibitors has recently been approved for second-line treatment in metastatic UC, vinflunine should only be offered as second-line treatment if checkpoint inhibitors or combination chemotherapy are not feasible. However, vinflunine may be considered as third-line or subsequent treatment line option, although no randomised data exist for this indication.

7.8.6 *Low-volume disease and post-chemotherapy surgery*

With cisplatin-containing combination chemotherapy, excellent response rates may be obtained in patients with LN metastases only, good PS, and adequate renal function, including a high number of CRs, with up to 20% of patients achieving long-term DFS [454, 482, 502, 503]. The role of surgery of residual LNs after chemotherapy is still unclear. Although some studies suggest a survival benefit and QoL improvement, the level of evidence supporting this practice is mainly anecdotal [504-518]. Retrospective studies of post-chemotherapy surgery after partial or complete remission have indicated that surgery may contribute to long-term DFS in selected patients [519-522].

Surgery for limited pulmonary metastases may also be considered in highly selected cases. In the absence of data from RCTs, patients should be evaluated on an individual basis and discussed by an interdisciplinary tumour board [522].

7.8.7 *Treatment of patients with bone metastases*

The prevalence of metastatic bone disease (MBD) in patients with advanced/metastatic UC is 30-40% [523]. Skeletal complications due to MBD have a detrimental effect on pain and QoL and are also associated with increased mortality [524]. Bisphosphonates such as zoledronic acid (ZA) 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 [525]. Denosumab, a fully human monoclonal antibody that binds to and neutralises RANKL, was shown to be non-inferior to ZA in preventing or delaying SREs in patients with solid tumours and advanced MBD, including patients with UC [526]. Patients with MBD, irrespective of the cancer type, should be considered for bone-targeted treatment [524].

Patients treated with ZA or denosumab should be informed about possible side effects including osteonecrosis of the jaw and hypocalcaemia. Supplementation with calcium and vitamin D is mandatory. Dosing regimens of ZA should follow regulatory recommendations and have to be adjusted according to pre-existing medical conditions, especially renal function [527]. For denosumab, no dose adjustments are required for variations in renal function.

7.8.8 ***Role of immunotherapy***

Immunomodulatory therapies using checkpoint inhibition, particularly with antibodies directed against the programmed cell death-1 (PD-1) protein, its ligand (PD-L1) or the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)-pathway have shown significant anti-tumour activity with tolerable safety profiles and durable responses in patients with locally advanced and metastatic UC. Trials currently investigate different immunotherapeutic agents either as monotherapy or in combination with other immune-enhancing agents or chemotherapy in a range of different disease settings. Pembrolizumab, nivolumab, atezolizumab, avelumab, and durvalumab have demonstrated similar efficacy in patients progressing during, or after, standard platinum-based chemotherapy in phase I, II and III trials.

7.8.8.1 First-line immunotherapy for patients not eligible for standard cisplatin chemotherapy

A single arm phase II trial assessed the PD-1 inhibitor pembrolizumab in 370 patients with advanced or metastatic UC ineligible for cisplatin, showing an ORR of 29% and CR in 7% of patients [528]. The PD-L1 inhibitor atezolizumab, a second agent was also evaluated in this patient population in a two-cohort phase II trial (n = 119) including patients unfit for cisplatin (cohort 1). The ORR was 29%; 9% of patients presented with a CR and median OS was 15.9 months [529].

The toxicity profile was favourable for pembrolizumab as well as for atezolizumab. Since 2017 both drugs are U.S. Food and Drug Administration (FDA) and European Medicines Agency approved for first-line treatment in cisplatin-ineligible patients. Late 2018 the FDA issued a warning that patients with negative PD-L1 status (based on immunohistochemical staining) might have an impaired outcome when treated with first-line immunotherapy. This warning was based on preliminary results from ongoing phase III trials with pembrolizumab and atezolizumab. However, no data from these studies are, as yet, in the public domain.

7.8.8.2 Second-line immunotherapy for platinum-pre-treated patients

Pembrolizumab, a PD-1 inhibitor, was the first agent that showed significant OS benefit in patients progressing during, or after, platinum-based first-line chemotherapy. Based on the results of a phase III trial the agent was approved in 2017. In the trial, patients (n = 542) were randomised to receive either pembrolizumab monotherapy, or chemotherapy (either paclitaxel, docetaxel or vinflunine). The median OS in the pembrolizumab arm was 10.3 months (95% CI: 8.0-11.8) vs. 7.4 months (95% CI: 6.1-8.3) for the chemotherapy arm (HR for death, 0.73; 95% CI: 0.59-0.91, p = 0.002) independent of PD-L1 expression levels [530].

Atezolizumab was the first PD-L1 inhibitor approved by the FDA (May 2016) for patients progressing during, or after, previous platinum-based chemotherapy. In a phase II cohort study including 310 patients, the objective response rate was 15%, independent of the expression of PD-L1. Progression-free survival was 2.1 and OS was 7.9 months. According to the expression level of PD-L1 numbers for response rate, PFS and OS were greater in patients with high expression, but responses occurred also in patients with no expression of PD-L1. The toxicity profile of atezolizumab was favourable [531, 532]. The results of the phase III trial (IMvigor211) comparing atezolizumab with second-line chemotherapy were recently published [533]. The trial did not meet its first endpoint of improved OS for patients with high PD-L1 expression (IC score 2/3) but OS was significantly improved in the ITT population.

In 2017, nivolumab, another PD-1/PD-L1 inhibitor was approved based on the results of a single-arm phase II trial (CheckMate 275), enrolling 270 patients. The first endpoint was ORR. Patients were stratified by their PD-L1 expression (> 5% vs. < 5%). Objective response rate was 19.6%, and OS was 8.74 months for the entire group [534].

Based on results of phase I/II and phase Ib trials, two additional PD-1/PD-L1 inhibitors, durvalumab and avelumab are currently only approved for this indication in the United States [535-537].

Data show that in responders, PD-1/PD-L1 inhibitors not only produce durable responses but also offer a superior survival benefit as compared to standard chemotherapy regimens.

7.8.9 *Summary of evidence and guidelines for metastatic disease*

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

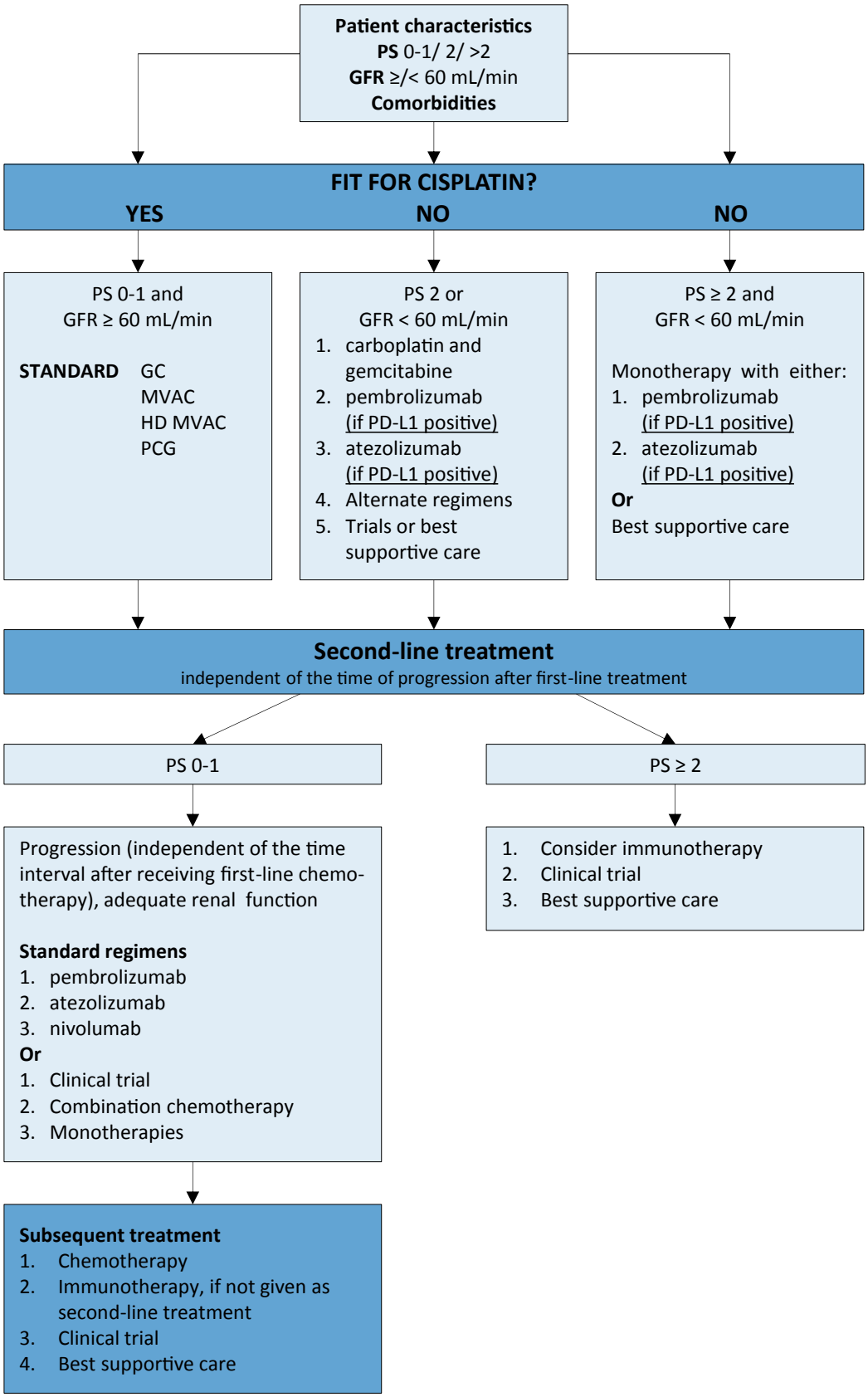
Recommendations	Strength rating
First-line treatment for cisplatin-eligible patients	
Use cisplatin-containing combination chemotherapy with GC, MVAC, preferably with G-CSF, HD-MVAC with G-CSF or PCG.	Strong
Do not offer carboplatin and non-platinum combination chemotherapy.	Strong
First-line treatment in patients ineligible (unfit) for cisplatin	
Offer checkpoint inhibitors pembrolizumab or atezolizumab depending on PDL-1 status.	Weak
Offer carboplatin combination chemotherapy if PD-L1 is negative.	Strong
Second-line treatment	
Offer checkpoint inhibitor (pembrolizumab) to patients progressing during or after platinum-based combination chemotherapy for metastatic disease. Alternatively, offer treatment within a clinical trial setting.	Strong
Offer zoledronic acid or denosumab for supportive treatment in case of bone metastases.	Weak
Only offer vinflunine to patients for metastatic disease as second-line treatment if immunotherapy or combination chemotherapy is not feasible. Alternatively, offer vinflunine as third- or subsequent treatment line.	Weak

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

7.8.10 ***Biomarkers***

Modest disease control rates with sporadic marked responses in some patients with UC have led to the investigation of biomarkers for assessment of post-operative prognosis and the potential value of peri-operative chemotherapy, and as predictors of response to chemotherapy or its monitoring. Most biomarkers are associated with tumour angiogenesis [538]. Small studies, usually retrospective, have investigated microvessel density, altered p53 tumour expression [538], serum vascular endothelial growth factor [539], urinary and tissue basic fibroblast growth factor [540], urinary (wild-type and mutant) and tissue fibroblast growth factor receptor-3 [541], and more recently, thrombospondin-1 [542], circulating tumour cells [543, 544], and multidrug resistance gene expression [545]. Although a few biomarkers have shown potential, as yet, there is insufficient evidence to support their routine clinical use (LE: 3).

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



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

7.9 Quality of life

7.9.1 Introduction

The evaluation of HRQoL considers physical, psychological, emotional and social functioning. The impact of BC on HRQoL was recently reported in a population-based study using the SEER registry, including a total of 535 BC patients (458 with non-invasive disease and 77 with invasive disease) older than 65 years and 2,770 matched non-cancer controls. The authors concluded that BC patients experienced statistically significant declined HRQoL in all domains. In invasive BC, particularly physical and social functioning were affected [546].

Several questionnaires have been validated for assessing HRQoL in patients with BC, including FACT (Functional Assessment of Cancer Therapy)-G [547], EORTC QLQ-C30 [548], EORTC QLQ-BLM (MIBC module) [549], and SF (Short Form)-36 [550, 551] and recently the BCI questionnaire specifically designed and validated for BC patients [552].

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 [553].

7.9.2 Radical cystectomy and urinary diversion

Two recent SRs focused on HRQoL after RC [554, 555] and one SR, based on 18 studies (n = 1,553), showed a slight, but not significant, improvement of QoL in patients with an orthotopic diversion [554]. However, analysing only the studies comparing exclusively ileal conduit vs. ileal orthotopic neobladder, the advantage in QoL of the latter group was significant. Another SR, based on 29 studies (n = 3,754), showed no difference in overall QoL between continent and incontinent diversion [555]. Subgroup analysis demonstrated greater improvement in physical health for incontinent compared to continent diversions (p = 0.002), but no differences in mental health (p = 0.35) or social health (p = 0.81). However, patients with a neobladder demonstrated superior emotional function and body image [555-557].

Clifford and co-workers prospectively evaluated continence outcomes in male patients undergoing orthotopic neobladder diversion [558]. Day-time continence increased from 59% at less than three months post-operatively to 92% after 12 to 18 months. Night-time continence increased from 28% at less than three months post-operatively to 51% after 18 to 36 months. Also of interest is the urinary bother in female neobladder. Bartsch and co-workers found in 56 female patients day-time and night-time continence rates of 70.4% and 64.8%, respectively. Thirty-five patients (62.5%) performed clean intermittent catheterisation, which is much worse when compared to male neobladder patients. Moreover, patients with non-organ-confined disease (p = 0.04) and patients with a college degree (p = 0.001) showed worse outcomes on HRQoL scores [559].

Altogether, HRQoL outcomes are most likely a result of good patient selection. An older, more isolated, patient is probably better served with an ileal conduit, whereas a younger patient with a likely higher level of interest in body image and sexuality is better off with an orthotopic diversion. The patient's choice is the key to the selection of reconstruction method [555].

7.9.3 Bladder sparing trimodality therapy

A cross-sectional bi-institutional study found in multivariable analysis that patients who received trimodality therapy (n = 64) had higher physical-, social-, emotional- and cognitive functioning, better general QoL, sexual function and body image than patients after RC (n = 109). However, urinary symptom scores were similar [433]. To draw valid conclusions, prospective studies are needed.

7.9.4 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 [560]. There is limited literature describing HRQoL in BC patients receiving palliative care [561], but there are reports of bladder-related symptoms relieved by palliative surgery [402], RT [562], and/or chemotherapy [563].

7.9.5 Summary of evidence and recommendations for health-related quality of life

Summary of evidence	LE
Compared to non-cancer controls, the diagnosis and treatment of bladder cancer has a negative impact on HRQoL.	2a
There is no difference in overall QoL between patients with continent or incontinent diversion.	1a
In most patient groups studied, the overall HRQoL after cystectomy remains good, irrespective of the type of urinary diversion used.	2b
Important determinants of (subjective) quality of life are a patient's personality, coping style and social support.	3

Recommendations	Strength rating
Use validated questionnaires to assess health-related quality of life in patients with MIBC.	Strong
Offer a continent urinary diversion unless a patient's comorbidities, tumour variables and coping abilities present clear contraindications.	Strong
Pre-operative patient information, patient selection, surgical techniques, and careful post-operative follow-up are the cornerstones for achieving good long-term results.	Strong
Provide clear and exhaustive information on all potential benefits and side-effects, allowing patients to make informed decisions. Encourage patients to actively participate in the decision-making process.	Strong

8. FOLLOW-UP

8.1 Follow-up in muscle invasive bladder cancer

An appropriate schedule for disease monitoring should be based on natural timing of recurrence; probability and site of recurrence; functional monitoring after urinary diversion and the potential available management options [564].

Nomograms on CSS following RC have been developed and externally validated, but their wider use cannot be recommended until further data become available [565, 566].

Current surveillance protocols are based on patterns of recurrence drawn from retrospective series only. Combining this data is not possible since most retrospective studies use different follow-up regimens and imaging techniques. Additionally, reports of asymptomatic recurrences diagnosed during routine oncological follow-up, and results from retrospective studies are contradictory [567-569]. From the Volkmer B, *et al.* series of 1,270 RC patients, no differences in OS were observed between asymptomatic and symptomatic recurrences [568]. Conversely, in the Giannarini, *et al.* series of 479 patients; those with recurrences detected during routine follow-up (especially in the lungs) and with secondary urothelial tumours as the site of recurrence, had a slightly higher survival probability [567]. Boorjian, *et al.* included 1,599 RC patients in their series, with 77% symptomatic recurrences. On multivariate analysis, patients who were symptomatic at recurrence had a 60% increased risk of death as compared to asymptomatic patients [569].

However, at this time, no data from prospective trials demonstrating the potential benefit of early detection of recurrent disease, and its impact on OS, are available [570]. For details see Section 7.6.4.

8.2 Site of recurrence

*8.2.1 **Local recurrence***

Local recurrence takes place in the soft tissues of the original surgical site or in LNs. Contemporary cystectomy has a 5-15% probability of pelvic recurrence which usually occurs during the first 24 months, most often within six to eighteen months after surgery. However, late recurrences can occur up to five years after RC. Risk factors described are pathological stage, LNs, positive margins, extent of LND and peri-operative chemotherapy [571].

Patients generally have a poor prognosis after pelvic recurrence. Even with treatment, median survival ranges from four to eight months following diagnosis. Definitive therapy can prolong survival, but mostly provides significant palliation of symptoms. Multimodality management generally involves a combination of chemotherapy, radiation and surgery [570].

*8.2.2 **Distant recurrence***

Distant recurrence is seen in up to 50% of patients treated with RC for MIBC. As with local recurrence, pathological stage and nodal involvement are risk factors [572]. Systemic recurrence is more common in locally advanced disease (pT3/4), ranging from 32 to 62%, and in patients with LN involvement (range 52–70%) [573].

The most likely sites for distant recurrence are LNs, lungs, liver and bone. Nearly 90% of distant recurrences appear within the first three years after RC, mainly in the first two years, although late recurrence has been described after more than 10 years. Median survival of patients with progressive disease treated with platinum-based chemotherapy is 9-26 months [574-576]. However, longer survival (28-33% at five years) has been reported in patients with minimal metastatic disease undergoing multimodality management, including metastasectomy [505, 513].

*8.2.3 **Urothelial recurrences***

After RC, the incidence of new urethral tumours was 4.4% (1.3-13.7%). Risk factors for secondary urethral tumours are urethral malignancy in the prostatic urethra/prostate and bladder neck (in women). Orthotopic neobladder was associated with a significant lower risk of urethral tumours after RC (OR: 0.44) [577].

There is limited data, and agreement, about urethral follow-up, with some authors recommending routine surveillance with urethral wash and urine cytology and others doubting the need for routine urethral surveillance. However, there is a significant survival advantage in men with urethral recurrence diagnosed asymptomatically vs. symptomatically, so follow-up of the male urethra is indicated in patients at risk of urethral recurrence [570]. Treatment is influenced by local stage and grade of urethral occurrence. In urethral CIS, BCG instillations have success rates of 83% [578]. In invasive disease, urethrectomy should be performed if the urethra is the only site of disease and in case of distant disease systemic chemotherapy is indicated [4].

Upper urinary tract urothelial carcinomas occur in 4-10% of cases and represent the most common sites of late recurrence (three-year DFS following RC) [579]. Median OS is 10-55 months, and 60-67% of patients die of metastatic disease [570]. A recent meta-analysis found that 38% of UTUC recurrence was diagnosed by follow-up investigations, whereas in the remaining 62%, diagnosis was based on symptoms. When urine cytology was used during surveillance, the rate of primary detection was 7% vs. 29.6% with UUT imaging. The meta-analysis concluded that patients with non-invasive cancer are twice as likely to have UTUC as patients with invasive disease [561]. Multifocality increases the risk of recurrence by threefold, while positive ureteral or urethral margins increase the risk by sevenfold. Radical nephro-ureterectomy can prolong survival [580].

8.3 Time schedule for surveillance

Although, based on low level of evidence, some follow-up schedules have been suggested, guided by the principle that recurrences tend to occur within the first years following initial treatment. A schedule suggested by the EAU Guidelines Panel includes a CT scan (every 6 months) until the third year, followed by annual imaging thereafter [4]. Patients with multifocal disease, NMIBC with CIS or positive ureteral margins are at higher risk of developing UTUC, which can develop late (> three years). In those cases, monitoring of the UUT is mandatory during follow-up. Computed tomography is to be used for imaging of the UUT [581].

The exact time to stop follow-up is not well known and recently a risk-adapted schedule has been proposed, based on the interaction between recurrence risk and competing health factors that could lead to individualised recommendations and may increase recurrence detection. Elderly and very low-risk patients (those with NMIBC or pT0 disease at final cystectomy report) showed a higher competing risk of non-BC mortality when compared with their level of BC recurrence risk. On the other hand, patients with locally advanced disease or LN involvement are at a higher risk of recurrence for more than 20 years [582]. However, this model has not been validated and does not incorporate several risk factors related to non-BC mortality. Furthermore, the prognostic implications of the different sites of recurrence should be considered. Local and systemic recurrences have a poor prognosis and early detection of the disease will not influence survival [583]. Despite this, the rationale for a risk-adapted schedule for BC surveillance appears to be promising and deserves further investigation.

8.4 Follow-up of functional outcomes and complications

Apart from oncological surveillance, patients with a urinary diversion need functional follow-up. Complications related to urinary diversion are detected in 45% of patients during the first five years of follow-up. This rate increases over time, and exceeds 54% after fifteen years follow-up. Therefore, long-term follow-up of functional outcomes is desirable [570].

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 [570]. Especially in women approximately two-thirds need to catheterise their neobladder, while almost 45% do not void spontaneously at all [559]. Recently a 21% increased risk of fractures was also described as compared to no RC, due to chronic metabolic acidosis and subsequent long-term bone loss [583].

8.5 Summary of evidence and recommendations for specific recurrence sites

Site of recurrence	Summary of evidence	LE	Recommendation	Strength rating
Local recurrence	Poor prognosis. Treatment should be individualised depending on the local extent of tumour.	2b	Offer radiotherapy, chemotherapy and possibly surgery as options for treatment, either alone or in combination.	Strong
Distant recurrence	Poor prognosis.	2b	Offer chemotherapy as the first option, and consider metastasectomy in case of unique metastasis site.	Strong
Upper urinary tract recurrence	Risk factors are multifocal disease (NMIBC/CIS or positive ureteral margins).		See EAU Guidelines on Upper Urinary Tract Urothelial Carcinomas.	Strong
Secondary urethral tumour	Staging and treatment should be done as for primary urethral tumour.	3	See EAU Guidelines on Primary Urethral Carcinoma.	Strong

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10. CONFLICT OF INTEREST

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

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11. CITATION INFORMATION

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