

EAU Guidelines on **Muscle-invasive and Metastatic Bladder Cancer**

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1. INTRODUCTION

1.1 Aims and scope

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

Separate EAU guidelines documents are available addressing upper urinary tract (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 bladder cancer (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 2020 document presents a limited update of the 2019 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 2020 EAU MIBC Guidelines.

Key changes in the 2020 print are:

- New section - 3.2.5 - Metabolic disorders – has been added, also providing a recommendation.

3.2.9 Summary of evidence and guidelines for epidemiology and risk factors

Recommendations	Strength rating
Do not prescribe pioglitazone to patients with active bladder cancer or a history of bladder cancer.	Strong

- Chapter 6 - Markers – this section has been completely revised.
- Section 7.1 - Treatment failure of non-muscle-invasive bladder cancer – this section has been updated to align with the 2020 NMIBC guidelines; in particular with respect to discussing unsuccessful treatment with intravesical BCG.

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

Recommendations	Strength rating
Offer patients with BCG-unresponsive tumours, who are not candidates for RC due to comorbidities, preservation strategies (intravesical chemotherapy, chemotherapy and microwave-induced hyperthermia, electromotive administration of chemotherapy, intravesical- or systemic immunotherapy; preferably within clinical trials).	Weak

- Section 7.4.3.2 - Radical cystectomy in women – this section has been revised.
- Section 7.4.6.1 - Patient selection and preparations for surgery – additional information on thromboprophylaxis has been included, as well as the final findings of the systematic review conducted to assess the impact of hospital and surgeon volume on treatment outcomes, resulting in two new recommendations.

7.4.10 Summary of evidence and guidelines for radical cystectomy and urinary diversion

Recommendations	Strength rating
Perform at least 10, and preferably > 20 radical cystectomies per hospital/per year	Strong
Offer pharmacological prophylaxis, such as low molecular weight heparin to RC patients, starting the first day post-surgery, for a period of 4 weeks.	Strong

- Section 7.8 – Metastatic disease – this section has been completely restructured, also incorporating updated information on novel programmed death ligand 1 (PD-1) and PD-L1 inhibitors.

7.8.6 Summary of evidence and guidelines for metastatic disease

Recommendations	Strength rating
First-line treatment in patients ineligible (unfit) for cisplatin	
Offer checkpoint inhibitors pembrolizumab or atezolizumab to PD-L1-positive patients.	Strong
Second-line treatment	
Only offer vinflunine to patients for metastatic disease as subsequent-line treatment if immunotherapy or combination chemotherapy or FGFR3-inhibitor therapy or inclusion in a clinical trial is not feasible.	Weak

- Section 7.9 – Quality of life – a new section 7.9.2 - Neoadjuvant chemotherapy has been included.

A number of text sections will include statements resulting from the EAU-ESMO consensus [5, 6], notably:

- Pathology – Section 3.3.4
- Diagnostic evaluation – Section 5.1.10
- Markers - Section 6.5.1
- Treatment failure of NMIBC – Section 7.1.3
- Pre- and post-operative radiotherapy in MIBC – Section 7.3.4
- Radical surgery and urinary diversion - Section 7.4.11
- Unresectable tumours - Section 7.5.1.2
- Bladder-sparing treatments for localised disease - Section 7.6.1.2
- External beam radiotherapy - Section 7.6.2.2
- Multimodality bladder-preserving treatment - Section 7.6.4.2
- Adjuvant therapy – Section 7.7.4
- Oligometastatic disease - Section 7.8.4.1
- Metastatic disease - Section 7.8.7
- Follow up - Section 8.6

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 1st, 2018 and May 10th, 2019. A total of 1,899 unique records were identified, retrieved and screened for relevance. Sixty-two new publications have been included in the 2020 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 [7, 8] 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 [9];
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' [8]. 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.

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.

The results of a collaborative multi-stakeholder consensus project on the management of advanced and variant bladder cancer have been incorporated in the 2020 MIBC Guidelines update [5, 6]. Only statements which reached the *a priori* defined level of agreement - $\geq 70\%$ agreement and $\leq 15\%$ disagreement - across all stakeholders involved in this consensus project are listed. The methodology is presented in detail in the scientific publications. Some of these statements may be replaced by higher levels of evidence, over time, even though for some areas it is unlikely that clinical trials and prospective comparative studies will be conducted.

2.2 Peer-review

The 2020 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 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:

- development of a diagnostic pathway for the assessment of visible and non-visible haematuria;
- 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 is the 7th most commonly diagnosed cancer in males, whilst it drops to 11th when both genders are considered [10]. The worldwide age-standardised incidence rate (per 100,000 person/years) is 9.0 for men and 2.2 for women [10]. In the European Union, the age-standardised incidence rate is 19.1 for men and 4.0 for women [11]. 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) [10, 12].

Worldwide, the BC age-standardised mortality rate (per 100,000 person/years) was 3.2 for men vs. 0.9 for women in 2012 [10]. 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 [11, 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 [10, 11].

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 [16]. 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 [17].

The incidence of BC is directly related to the duration of smoking and the number of cigarettes smoked per day [18]. 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 [19]. 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 [16]. 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 [18]. Encouraging people to stop smoking would result in the incidence of BC decreasing equally in men and women [16].

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 [20]. 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 [21, 22]. Population-based studies established the occupational attribution for BC in men to be 7.1%, while no such attribution was discernible for women [11, 23].

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 [24]. 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 [25].

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 [26]. 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 [26].

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 [27].

3.2.5 **Metabolic disorders**

In a large prospective study pooling six cohorts from Norway, Sweden, and Austria (The Metabolic syndrome and Cancer project, Me-Can 2.0), metabolic aberrations, especially elevated blood pressure and triglycerides, were associated with increased risks of BC among men, whereas high BMI was associated with decreased BC risk. The associations between body mass index (BMI), blood pressure and BC risk significantly differed between men and women [28].

The association of Diabetes Mellitus (DM) with the risk of BC has been evaluated in numerous meta-analyses with inconsistent results. When analysing specific subpopulations, DM was associated with BC or cancer mortality risk especially in men [29]. Thiazolidinediones (pioglitazone and rosiglitazone) are oral hypoglycaemic drugs used for the management of type 2 DM. Their use and the association with BC is still a matter of debate. In a recent meta-analysis of observational studies, the summary results indicated that pioglitazone use was significantly associated with an increased risk of BC which appears to be linked to higher dose and longer duration of treatment [30]. The U.S. Food and Drug Administration (FDA) recommend that healthcare professionals should not prescribe pioglitazone in patients with active BC. Several countries in Europe have removed this agent from the market or included warnings for prescription. Moreover, the benefits of glycaemic control vs. unknown risks for cancer recurrence with pioglitazone should be considered in patients with a prior history of BC.

3.2.6 **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 [31]. 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 [32, 33].

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 [34]. However, a recent meta-analysis found no statistical association when pooling data from the most recent and highest quality studies which highlights the need for higher quality data to be able to draw conclusions [35].

Similarly, urinary calculi and chronic irritation or inflammation of the urothelium have been described as possible risk factors for BC. A meta-analysis of case-control and cohort studies suggests a positive association between history of urinary calculi and BC [36].

3.2.7 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) [37]. 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 [38]. 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 [39]. The gender-specific difference in survival for patients with BC was also analysed in the Norway population. Survival was inferior for female patients but only within the first 2 years after diagnosis. This discrepancy was partly attributed to a more severe T-stage in female patients at initial diagnoses [40].

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 [41]. 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 [42-44].

3.2.8 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 [45]. Shared environmental exposure was recognised as a potentially confounding factor [46]. Recent studies detected genetic susceptibility with independent loci, which are associated with BC risk [47].

Genome-wide association studies (GWAS) of BC identified several susceptibility loci associated with BC risk [48, 49].

3.2.9 Summary of evidence and guidelines for epidemiology and risk factors

Summary of evidence	LE
Worldwide, bladder cancer is the 11 th 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
Counsel 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
Do not prescribe pioglitazone to patients with active bladder cancer or a history of bladder cancer.	Strong

3.3 Pathology

3.3.1 Handling of transurethral resection and cystectomy specimens

During transurethral resection (TUR), a 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 [50].

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 a female cystectomy specimen, the length of the urethral segment removed *en bloc* with the specimen should be checked, preferably by the urological surgeon [51].

Specimen handling should follow the general rules as published by a collaborative group of pathologists and urologists [52, 53]. 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 [54]. 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) have to be documented by the pathologist.

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 [55, 56]. 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+.

Potentially positive soft tissue margins should be inked by the pathologist for evaluation [57]. In rare cases, fresh frozen sections may be helpful to determine treatment strategy [58].

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 [59]. However, identification of morphological subtypes is important for prognostic reasons and treatment decisions [60-62].

An update of the World Health Organization (WHO) grading was published in 2016 [63], however, the data presented in these guidelines are based on the 2004 WHO classification [64].

Currently the following differentiations are used [60, 65]:

1. urothelial carcinoma (more than 90% of all cases);
2. urothelial carcinomas with partial squamous and/or glandular or trophoblastic differentiation;
3. micropapillary and microcystic UC;
4. nested variant (including large nested variant);
5. lymphoepithelioma-like;
6. plasmacytoid, signet ring, diffuse;
7. some UCs with small-cell carcinomas;
8. sarcomatoid carcinomas;
9. poorly differentiated.

Other, extremely rare, variants exist, which are not listed above.

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 pT4a and pT4b).	Strong
Record margins with special attention paid to the radial margin, prostate, ureter, urethra, peritoneal fat, 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.	
Record the presence of carcinoma <i>in situ</i> .	

3.3.4 **EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer** [5, 6]*

Consensus statement
Bladder urothelial carcinoma with small cell neuroendocrine variant should be treated with neoadjuvant chemotherapy followed by consolidating local therapy.
Muscle-invasive pure squamous cell carcinoma of the bladder should be treated with primary radical cystectomy and lymphadenectomy.
Muscle-invasive pure adenocarcinoma of the bladder should be treated with primary radical cystectomy and lymphadenectomy.
Muscle-invasive small cell neuroendocrine variant of bladder urothelial carcinoma should not receive preventive brain irradiation to avoid brain recurrence.
Differentiating between urachal and non-urachal subtypes of adenocarcinoma is essential when making treatment decisions.

*Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as $\geq 70\%$ agreement and $\leq 15\%$ disagreement, or vice versa).

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Pathological staging

For staging, the Tumour, Node, Metastasis (TNM) Classification (2017, 8th edition) is recommended [66]. Blood and lymphatic vessel invasion have an independent prognostic significance [67, 68].

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 [66] (Table 4.1).

Table 4.1: TNM Classification of urinary bladder cancer [66]

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

5. DIAGNOSTIC EVALUATION

5.1 Primary diagnosis

5.1.1 Symptoms

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

5.1.2 Physical examination

Physical examination should include rectal and vaginal bimanual palpation. A palpable pelvic mass can be found in patients with locally advanced tumours. In addition, bimanual examination under anaesthesia should be carried out before and after TUR of the bladder (TURB), to assess whether there is a palpable mass or if the tumour is fixed to the pelvic wall [69, 70]. 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 [71].

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% [72, 73] (LE: 2b). However, negative cytology does not exclude a tumour. There is no known urinary marker specific for the diagnosis of invasive BC [74].

A standardised reporting system, the 'Paris System' redefining urinary cytology diagnostic categories was published in 2016 [75]:

- 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 [76]. 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 [68, 77].

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 specimen.

In case MIBC is suspected tumours need to be resected separately in parts, which include the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle, and the edges of the resection area. At least the deeper part of the resection specimen must be referred to the pathologist in a separate labelled container to enable them to make a correct diagnosis. In cases in which RT is considered and CIS is to be excluded, PDD can be used [78].

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 [79-81] (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 [82-84].

5.1.7 **Second resection**

In the case of high-grade non-muscle-invasive tumour, residual disease is observed in 33-53% of patients [85-91]. In order to reduce the risk of understaging [86, 87], a second TURB resection is often required to determine subsequent treatment strategy.

Diagnosis of a urethral tumour before cystectomy will result in a urethrectomy which is a contraindication to a neobladder reconstruction.

In case the initial TUR did not include biopsies of the paracollicular (males) or bladder neck (females), frozen sections should be sent separately to the pathologist during the second resection.

5.1.8 **Concomitant prostate cancer**

Prostate cancer is found in 21-50% of male patients undergoing RC for BC [92-95]. Incidentally discovered clinically significant prostatic adenocarcinoma did not alter survival [94, 95]. Pathological reporting of the specimens should follow the recommendations as presented in the EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer [96].

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

Summary of evidence	LE
Cystoscopy is necessary for the diagnosis of bladder cancer.	1
Urinary cytology has high sensitivity in high-grade tumours including carcinoma <i>in situ</i> .	2b

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 <i>in situ</i> is present or suspected, when there is positive cytology without evidence of tumour in the bladder, or when abnormalities of the prostatic urethra are visible.	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
In the pathology report, specify the grade, depth of tumour invasion, and whether the lamina propria and muscle tissue are present in the specimen.	Strong

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

5.1.10 **EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer** [5, 6]*

Consensus statement
Differentiating between urachal and non-urachal subtypes of adenocarcinoma is essential when making treatment decisions.

*Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as $\geq 70\%$ agreement and $\leq 15\%$ disagreement, or vice versa).

5.2 **Imaging for staging of MIBC**

The treatment and prognosis of MIBC is determined by tumour stage and grade [97, 98]. 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) [99]. 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 17 studies showed a 91% sensitivity and 96% specificity for 3.0-T device MRI combined with diffusion-weighted imaging (DWI) to differentiate \leq T1 tumours from \geq T2 tumours before surgery [100]. These values were 10-33% (mean 19%) higher than those obtained with CT [101]. Dynamic contrast-enhanced-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 [101-103].

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 [104] (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% [105] and increases with more advanced disease [106].

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 [101, 107-111]. 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 [112, 113].

Positron emission tomography (PET) combined with CT is increasingly being used in clinical practice and its exact role continues to be evaluated [114].

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 [115]. The sensitivity of CT urography for UTUC is 0.67-1.0 and specificity is 0.93-0.99 [116].

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 [117, 118]. The presence of enlarged LNs is highly predictive of metastases in UTUC [119].

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 [120]. The sensitivity of MR urography is 0.75 after

contrast injection for tumours < 2 cm [120]. 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 [121] and liver metastases [122], 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 [123, 124]. Magnetic resonance imaging is more sensitive and specific for diagnosing bone metastases than bone scintigraphy [125, 126] (LE: 2b).

5.2.5 **Future developments**

Evidence is accruing in the literature suggesting that ¹⁸F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT might have potential clinical use for staging metastatic BC [127, 128], 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 [129]. 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

5.3 **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 [130-132]. 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 [133].

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 octogenarians compared to septuagenarians is higher (4.3% vs. 2.3%) [134]. 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 [135].

Sarcopenia has been shown to be an independent predictor for OS and CSS in a large multicentre study with patients undergoing RC for BC [136]. Other risk factors for morbidity include prior abdominal surgery, extravesical disease, and prior RT [137]. Female gender, an increased BMI and lower pre-operative albumin levels are associated with a higher rate of parastomal hernias [138]. Low pre-operative serum albumin is also associated with impaired wound healing, gastrointestinal complications and a decrease of recurrence-free and OS after RC [139, 140]. Therefore, it could be used as a prognostic biomarker for patients undergoing RC.

5.3.1 **Evaluation of comorbidity**

Rochon *et al.* have shown that evaluation of comorbidity provides a better indicator of life expectancy in MIBC than patient age [141]. 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 [142].

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 [143]. 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 [144]. Stratifying elderly patients according to their risk-benefit profile using a multidisciplinary approach will help selecting patients most likely to benefit from radical surgery and to optimise treatment outcomes [145]. Unfortunately, most published series evaluating RC do not include indices of comorbidity in their patient evaluation.

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

A range of comorbidity scales has been developed [146], six of which have been validated [147-152] (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 [153, 154], overall mortality [155], and CSM [133, 156-158]. Only the age-adjusted version of the CCI was correlated with both cancer-specific and other-cause mortality [159]. The age-adjusted CCI (Table 5.1) is the most widely used comorbidity index in cancer for estimating long-term survival and is easily calculated [160].

Table 5.1: 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 $z = 0.983^Y$ (where z is the 10-year survival)

Health assessment of oncology patients must be supplemented by measuring their activity level. Extermann *et al.* have shown that there is no correlation between morbidity and competitive activity level [161]. The Eastern Cooperative Oncology Group (ECOG) performance status (PS) scores and Karnofsky index have been validated to measure patient activity [162] (LE: 3). Performance score is correlated with patient OS after RC [157] and palliative chemotherapy [163-165].

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) [166] which is tailored to the care of cancer patients [167]. In BC, the CGA has been used to adapt gemcitabine chemotherapy in previously untreated elderly patients with advanced BC [168].

5.3.3 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/frail 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 5.3.2).	Strong

6. MARKERS

6.1 Introduction

Both patient and tumour characteristics guide treatment decisions and prognosis of patients with MIBC.

6.2 Prognostic markers

6.2.1 Histopathological and clinical markers

The most important histopathological prognostic variables after RC and LN dissection are tumour stage and LN status [169]. In addition, other histopathological parameters of the RC specimen have been associated with prognosis.

The value of lymphovascular invasion was reported in a systematic review and meta-analysis including 78,000 patients from 65 studies treated with RC for BC [170]. 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 [171].

In a systematic review 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) [171].

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 [97, 169, 172, 173].

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 5-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 5-year CSS of only 12% [174].

Recently neutrophil-to-lymphocyte ratio (NLR) has emerged as a prognostic factor in UUT tumours [1] and other non-urolological 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 disease-free survival (DFS) in both localised and metastatic disease [175]. In contrast, a secondary analysis of the SWOG 8710 trial, a randomised phase III trial assessing 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 [176].

In patients with LN-positive disease, the AJCC-TNM staging system provides 3 subcategories. In addition, several other prognostic LN-related parameters have been reported. These include, but are not limited to, the number of positive LNs, the number of LNs removed, LN density (the ratio of positive LNs to the number of LNs removed) and extranodal extension. In a systematic review and meta-analysis, it was reported that LN density was independently associated with OS (HR: 1.45; 95%, CI: 1.11-1.90) [177]. It has been suggested that LN density outperforms the AJCC-TNM staging system for LN-positive disease in terms of prognostic value [178]. 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 [179].

Two studies investigated whether any of the reported LN-related parameters may be superior to the routinely used AJCC-TNM staging system [179, 180]. Whilst conclusion was that the AJCC-TNM staging system for LN status did not perform well, none of the other tested variables outperformed the AJCC system.

6.2.2 **Molecular markers**

6.2.2.1 *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 subtypes have been described:

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

The basal group shows an over-expression of epidermal growth factor receptor 3 (EGFR3) and is chemosensitive. The luminal type can display an over-expression of fibroblast growth factor receptor 3 (FGFR3), epidermal growth factor receptors (*ERBB2*↑ and *ERBB3*), and is chemotherapy resistant [61, 62, 181].

Warrick *et al.* found that intratumoural molecular heterogeneity and great somatic mutation burden could also be related to therapeutic response [182].

Recently a consensus on molecular classification reported [183]. The authors analysed 1,750 MIBC transcriptomic profiles from 18 datasets and identified six MIBC molecular classes that reconcile all previously published classification schemes. The molecular subgroup classes include luminal papillary (LumP), luminal non-specified (LumNS), luminal unstable (LumU), stroma-rich, basal/squamous (Ba/Sq), and neuroendocrine-like (NE-like). Each class has distinct differentiation patterns, oncogenic mechanisms, tumour micro-environments and histological and clinical associations. However, the authors stressed that consensus was reached for biological rather than clinical classes. Therefore, at this moment in time, this classification should be considered as a research tool for retrospective and prospective studies until future studies will establish how these molecular subgroups can be used best in a clinical setting.

Molecular classification of MIBC is still evolving and treatment tailored to 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 **Predictive markers**

6.3.1 *Clinical and histopathological markers*

Based on retrospective data only, patients with secondary MIBC have a worse response to NAC compared to patients with primary MIBC [184]. Pietzak *et al.* retrospectively analysed clinicopathologic outcomes comparing

245 patients with clinical T2-4aN0M0 primary MIBC and 43 patients with secondary MIBC treated with NAC and RC. They found that patients with secondary MIBC had lower pathologic response rates following NAC than those with primary MIBC (univariable: 26% vs. 45%, multivariable: OR: 0.4 [95% CI: 0.18-0.84, $p = 0.02$]). They also found that MIBC patients progressing after NAC had worse CSS as compared to patients treated with cystectomy alone ($p = 0.002$).

Variant histologies and non-UC have also been linked to worse outcomes after NAC, but there is, as yet, insufficient data to conclude that they can be considered as predictive markers [185].

6.3.2 **Molecular markers**

Several predictive biomarkers have been investigated such as serum vascular endothelial growth factor [186], urinary (wild-type and mutant) and FGFR3, somatic genomic alterations (i.e. ERCC2); DDR and RB1 gene alterations and circulating tumour cells [184, 187-189]. Although promising, there are currently no predictive molecular markers that are routinely used in clinical practice. Further validation studies are awaited.

Recently, data of the PURE-01 study was published [190]. This study was designed to assess the efficacy and obtain biomarker results of single-agent, neoadjuvant pembrolizumab administration in patients with MIBC. The primary endpoint in the intention-to-treat (ITT) population was pathologic complete response (pT0). Biomarker analyses included programmed death-ligand 1 (PD-L1) expression using the combined positive score (CPS; Dako 22C3 pharmDx assay), genomic sequencing (FoundationONEassay), and an immune gene expression assay. Fifty patients were enrolled and pathological response was observed in 42% (95% CI: 28.2% to 56.8%). It was concluded that tumour mutational burden (TMB) and PDL-1-positive status was associated with a higher ratio of pT0 disease at RC [190].

An update of this PURE-01 study focusing on a subgroup of patients with variant histology reported that those patients presenting with SCC or a lymphoepithelioma-like variant feature had major pathological responses compared with those with other predominant variant histologies. And again, in this subset of patients, the expression of PDL-1 and TMB were predictive of pathological response to pembrolizumab [191]. Even though these data are promising, they are too preliminary for application in daily clinical practice.

6.4 **Conclusion**

Prospectively validated prognostic and predictive molecular biomarkers will present valuable adjuncts to clinical and pathological data, but large phase III randomised controlled trials (RCTs) with long-term follow-up will be needed to clarify the many questions currently still remaining. The increasing use of next-generation sequencing, in combination with predictive gene expression signatures and algorithms may also alter future treatment approaches.

6.5 **Summary of evidence for urothelial markers**

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

6.5.1 **EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer** [5, 6]*

Consensus statement
In patients with metastatic disease, genetic profiling should always be done.
Before prescribing a checkpoint inhibitor, tumour mutation burden does not need to be assessed.
In all fit metastatic patients receiving chemotherapy, established prognostic factors for first-line and second-line therapy must be considered when making treatment decisions (Bajorin for first-line and Bellmunt for second-line therapy).
In all fit metastatic patients receiving chemotherapy, established prognostic factors for first-line and second-line therapy should be considered when making treatment decisions (Bajorin for first-line and Bellmunt for second-line therapy).
Before prescribing checkpoint inhibitor therapy, ribonucleic acid subtypes need not be identified.
Before radical cystectomy or chemotherapy, the neutrophil-to-lymphocyte ratio does not need to be assessed.

*Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as $\geq 70\%$ agreement and $\leq 15\%$ disagreement, or vice versa).

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-Guerin (BCG), the risk for progression at 5 years was 19.3% for T1G3 tumours [192]. Meta-analyses have demonstrated that BCG therapy prevents the risk of tumour recurrence [193] and the risk of tumour progression [194, 195], but so far, no significant overall- or disease-specific survival advantages have been shown, as compared to no intravesical therapy [194-196]. The EAU NMIBC Guidelines present data supporting cystectomy in selected patients with NMIBC [2].

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 [197-199]. Second TURB identifies upstaging to > T2 tumours in 10-20% of patients [200, 201]. Residual T1 disease in second TURB is associated with higher recurrence and progression rates, as well as with a higher CSM [202].

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 progressing patients had a slightly better outcome [203].

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, 204]. Based on retrospective data only, so far patients with secondary MIBC have a worse response to NAC compared to patients with primary MIBC [184].

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 [205-209]. 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 10-year RFS rate is 80% and similar to that of TURB and BCG maintenance therapy [2, 198, 210, 211].

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 guidelines [2]:

BCG-refractory tumour	
1.	if T1G3/high-grade tumour is present at 3 months [212]. Further conservative treatment with BCG is associated with an increased risk of progression [213, 214];
2.	If TaG3/high-grade tumour is present after 3 months or at 6 months, after either re-induction or first course of maintenance [215];
3.	If CIS (without concomitant papillary tumour) is present at 3 months and persists at 6 months after either re-induction or first course of maintenance. If patients with CIS present at 3 months, an additional BCG course can achieve a complete response in > 50% of cases [215-217].
4.	If high-grade tumour appears during BCG maintenance therapy*.
BCG-relapsing tumour	
Recurrence of G3/high-grade (WHO 1973/2004) tumour after completion of BCG maintenance, despite an initial response) [204].	

BCG-unresponsive tumour
BCG-refractory or T1Ta/high-grade BCG recurrence within 6 months of completion of adequate BCG exposure** or development of CIS within 12 months of completion of adequate BCG exposure [218].
BCG intolerance
Severe side effects that prevent further BCG instillation before completing treatment [219].
*Patients with low-grade recurrence during or after BCG treatment are not considered to be a BCG failure.
** Adequate BCG is defined as the completion of at least 5 of 6 doses of an initial induction course plus at least 2 out of 6 doses of a second induction course or 2 out of 3 doses of maintenance therapy.

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 [220].

There are now several bladder-preservation strategies available; immunotherapy, chemotherapy, device-assisted therapy and combination therapy [221]. At the present time, treatments other than RC must, however, be considered oncologically inferior in such patients with BCG-unresponsive disease [212-214].

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

Recommendations	Strength rating
Discuss immediate radical treatment (radical cystectomy [RC]) with patients at the highest risk of tumour progression (i.e. high grade, multifocality, carcinoma <i>in situ</i> , and tumour size, as outlined in the EAU Guidelines for Non-muscle-invasive Bladder Cancer).	Strong
Offer RC to patients with BCG-unresponsive tumours.	Strong
Offer patients with BCG-unresponsive tumours, who are not candidates for RC due to comorbidities, preservation strategies (intravesical chemotherapy, chemotherapy and microwave-induced hyperthermia, electromotive administration of chemotherapy, intravesical- or systemic immunotherapy; preferably within clinical trials).	Weak

7.1.3 EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [5, 6]*

Consensus statement
T1 high-grade bladder urothelial cancer with micropapillary histology (established after complete TURBT and/or re-TURBT) should be treated with immediate radical cystectomy and lymphadenectomy.
An important determinant for patient eligibility in case of bladder preserving treatment is absence of carcinoma <i>in situ</i> .

*Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as $\geq 70\%$ agreement and $\leq 15\%$ disagreement, or vice versa).

TURBT = transurethral resection of bladder tumour.

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 5-year survival in about 50% of patients [199, 222-225]. To improve these results, cisplatin-based NAC has been used since the 1980s [199, 222-227].

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 [228, 229], 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 [230]. 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 [231].
- Clinical staging using bimanual palpation, CT or MRI may result in over- and understaging and have a staging accuracy of only 70% [71]. 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 [230, 232-240].

7.2.2.1 Summary of available data

Several randomised phase III trials addressed the potential survival benefit of NAC administration [230, 232-237, 241-245]. 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 [238-240]. In a meta-analysis, published in 2005 [240] with updated patient data from 11 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 [246]. Only cisplatin combination chemotherapy with at least one additional chemotherapeutic agent resulted in a meaningful therapeutic benefit [238, 240]; 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) [247].

The updated analysis of a large randomised phase III trial [232] with a median follow-up of eight years confirmed previous results and provided additional findings:

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

More modern chemotherapeutic regimens such as cisplatin/gemcitabine have shown similar pT0/pT1 rates as methotrexate, vinblastine, adriamycin plus cisplatin in retrospective series and pooled data analyses, but have not been assessed in RCTs [247-250]. Modified dose-dense MVAC (ddMVAC) was tested in two small single-arm phase II studies demonstrating high rates of pathologic complete remission [251, 252]. Moreover, a large cross-sectional analysis showed higher rates of down-staging and pathological complete response for ddMVAC [253]. Another dose-dense regimen using cisplatin/gemcitabine reported in two small phase II trials [254, 255]. While pathological response rates (< pT2) in the range of 45%-57% were achieved, one trial had to be closed prematurely due to high rates of severe vascular events [254]. This approach is therefore not recommended outside of clinical trials.

There seem to be differences in the outcomes of patients treated with NAC for primary or secondary MIBC. However, in the absence of prospective data, patients with secondary MIBC should be treated similarly to those presenting with primary MIBC [184].

It is unclear, if patients with non-UC histology will 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 [256].

A retrospective analysis assessed the use of NAC in MIBC based on data from the U.S. National Cancer Database [257]. Only 19% of all patients received NAC before RC (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 [230]. These results have to be interpreted with caution, especially since no information was available for the type of NAC applied. Such analyses emphasise the importance of pragmatically designed studies that reflect real-life practice.

As an alternative to the standard dose of cisplatin-based NAC with 70 mg/m² on day 1, split-dose modifications regimens are often used with 35 mg/m² on days 1+8 or days 1+2. In a retrospective analysis the standard schedule was compared to a split-dose schedule in terms of complete and partial pathological response. A lower number of complete and partial response rates was seen in the split-dose group, but these results were not statistically significant [258].

7.2.3 **The role of imaging and predictive biomarkers**

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, it is not ready yet for standard patient care. However, bladder mpMRI may be useful to inform on tumour stage after TURB and response to NAC [259]. So far neither PET-CT, conventional MRI nor DCE-MRI can accurately assess treatment response [260-263]. 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 [264]. Therefore, reliable predictive markers to identify patients most likely to benefit from chemotherapy are needed. Molecular tumour profiling might guide the use of NAC in the future but, as yet, this is not applicable in routine practice [265, 266] (see Section 6 - Prognosis).

7.2.4 **Role of neoadjuvant immunotherapy**

Inhibition of PD-1/PD-L1 checkpoint has demonstrated significant benefit in patients with unresectable and metastatic BC in the second-line setting and in platinum-ineligible PD-L1+ patients as first-line treatment using different agents. Checkpoint inhibitors are increasingly tested in the neoadjuvant setting, either as monotherapy or in combination with chemotherapy or CTLA-4 checkpoint inhibition. Preliminary data from several phase II trials has been presented with encouraging results. So far only the results of one phase II trial using the PD-1 inhibitor pembrolizumab has been published [190]. In this preliminary report complete pathological remission (pT0) was achieved in 42% and pathological response (< pT2) in 54% of patients. While immunotherapy is not yet approved in the neoadjuvant setting, enrolment of patients in clinical trials is encouraged.

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 as monotherapy, or in different combinations, is being 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**

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 [267]. An RCT, comparing pre-operative vs. post-operative RT and RC (n = 100), showed comparable OS, DFS and complication rates [268]. Approximately half of these patients had 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 [269].

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 systematic review [270]. A retrospective study from 2015 showed decreased cause-specific mortality and overall mortality for pre-operative RT in clinical T2b and T3 patients only [271]. Another retrospective study with pre-operative RT in clinical T1-3 tumours showed that down-staging to T0 tumours occurs in > 50% of the irradiated patients, as compared to < 10% of patients who did not receive pre-operative RT [272]. Additionally, down-staging resulted in a longer progression-free survival (PFS).

7.3.2.2 Randomised studies

To date, six RCTs 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 [273]. The OS data were difficult to interpret since chemotherapy was used in a subset of patients only and more than 50% of patients (241/475) did not receive the planned treatment and were excluded from the final analyses. Two smaller studies using a dose of 20 Gy showed only a small survival advantage in \geq T3 tumours [274, 275]. Two other small trials confirmed down-staging after pre-operative RT [276, 277].

A meta-analysis of the five RCTs showed a difference in 5-year survival (OR: 0.71; 95% CI: 0.48-1.06) in favour of pre-operative RT [278]. 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 down-staging after 4 to 6 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 down-staging, but will not improve survival.	Strong
Do not offer pre-operative RT when subsequent radical cystectomy with urinary diversion is planned.	Strong

7.3.4 EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [5, 6]*

Consensus statement
Candidates for curative treatment, such as cystectomy or bladder preservation, should be clinically assessed by at least an oncologist, a urologist and a neutral HCP such as a specialist nurse.
When assessing patient eligibility for bladder preservation, the likelihood of successful debulking surgery should be taken into consideration (optimal debulking).

*Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as \geq 70% agreement and \leq 15% disagreement, or vice versa).

HCP = healthcare professional.

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 [199, 279]. 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 [133]. The analysis found an association between comorbidity and adverse pathological- and survival outcomes following RC [133].

Performance status and comorbidity have a different impact on treatment outcomes and must be evaluated independently [161].

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 [280]. 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) [281]. A population-based study from the U.S. SEER database analysed patients who underwent a cystectomy between 1992 and 2001 and concluded that a delay of more than twelve weeks has a negative impact on outcome and should be avoided [282]. 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 [279]. 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 [283].

7.4.3 *Radical cystectomy: technique and extent*

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 Panel undertook two systematic reviews addressing sparing techniques in men and women [284, 285].

In men, standard RC includes removal of the bladder, prostate, seminal vesicles, distal ureters, and regional LNs. In women, standard RC includes removal of the bladder, entire urethra and adjacent vagina, uterus, distal ureters, and regional LNs [286].

7.4.3.1 *Radical cystectomy in men*

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 [287-297] and three single-arm case series [298-300]. 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 radical 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: <ul style="list-style-type: none"> organ-confined disease; absence of any kind of tumour at the level of the prostate, prostatic urethra or bladder neck. 	Strong

7.4.3.2 Radical cystectomy in women

Pelvic floor disorders, sexual and voiding dysfunction in female patients are prevalent after RC [301]. As part of the pre-operative evaluation a gynaecological history should be obtained and patients should be counselled on the potential negative impact of RC on sexual function and/or vaginal prolapse. Most importantly, a history of cervical cancer screening, abnormal vaginal bleeding and a family history of breast and/or ovarian cancer should be recorded, as well as ruling out possible pelvic organ prolapse. Equally important is screening for sexual and urinary function and prolapse post-operatively. 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.

Pelvic organ-preserving techniques involve preserving the neurovascular bundle, vagina, uterus, ovaries or variations of any of the stated techniques. From an oncological point of view, concomitant malignancy in gynaecological organs is rare and local recurrences reported after RC are infrequent [302, 303]. In premenopausal women, by preserving ovaries, hormonal homeostasis will be preserved, decreasing risk of cognitive impairment, cardiovascular diseases and loss of bone density. In case of an increased risk of hereditary breast or ovarian cancer (i.e. *BRCA1/2* mutation carriers, patients with Lynch syndrome), salpingo-oophorectomy should be advised after childbearing and to all women over 40 years of age [304]. On the other hand, preservation of the uterus and vagina will provide the necessary support for the neobladder thereby reducing the risk of urinary retention. It also helps to avoid post-operative prolapse. If there are no signs of tumour infiltration into the anterior vaginal wall, preservation should be considered, provided there is no

existing prolapse, in which case removing the uterus also treats the prolapse. It is noteworthy that by resecting the vaginal wall, the vagina shortens which could potentially impair sexual satisfaction and function.

Based on retrospective, low quality, data only, a systematic review evaluating the advantages and disadvantages of sexual-function preserving RC and orthotopic neobladder in female patients concluded that in well-selected patients, sparing female reproductive organs during RC appears to be oncologically safe and provides improved functional outcomes [285].

Pelvic organ-preserving RC could be considered also in elderly and fragile patients having abdominal diversions. By reducing excision range, it might be beneficial from the point of reduced operating time, estimated blood loss and quicker bowel recovery [305].

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: <ul style="list-style-type: none"> organ-confined disease; absence of tumour in bladder neck or urethra. 	Strong

7.4.4 **Lymphadenectomy: role and extent**

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 [306].

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 [307]. 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 [308-312]. Mapping studies also found that skipping lesions at locations above the bifurcation of the aorta, without more distally located LN metastases, is rare [312, 313].

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 [314]. 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 [314-318]. A super-extended lymphadenectomy extends cranially to the level of the inferior mesenteric artery [319, 320].

In order to assess how and if cancer outcome is influenced by the extent of lymphadenectomy in patients with clinical N0M0 MIBC, a systematic review of the literature was undertaken [321]. Out of 1,692 abstracts retrieved and assessed, nineteen studies fulfilled the review criteria [314-318, 320, 322-334]. 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 [335, 336]. No difference in outcome was reported between extended and super-extended LND in the two high-volume-centre studies identified [320, 332]. A prospective phase III RCT including 401 patients with

a median follow-up of 43 months recently reported [337]. Extended LND failed to show a significant advantage (the trial was designed to show an absolute improvement of 15% in 5-year RFS by extended LND) 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 [338]. 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 [339-341]. 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 [342]. 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 [139, 321].

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

Further publications on robotic-assisted laparoscopic RC (RARC) have become available, including a new RCT [343] with a separate publication of oncological results [344] and a Cochrane review summarising the five published RCTs [345].

Novara *et al.* published a systematic review including 105 studies on RARC in 2015 [346]. With the exception of three papers which had a higher level of evidence (2b) all other publications (n = 102) only presented expert opinion (LE: 4). For RARC with urinary diversion, the mean operative time was six to seven hours which seemed to decrease over time, although it remained longer than for open RC (ORC). The mean length of hospital stay for RARC also decreased with time and experience, and was 1 to 1.5 days shorter when compared to ORC. 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.

Although the low level of evidence of the included studies remains a major limitation of this review, most of the authors' findings are supported by a recent Cochrane review which includes data from all five published RCT's [345]. Time to recurrence, positive surgical margin rate, grade 3-5 complications and QoL was comparable for RARC and ORC, whilst transfusion rate was likely lower after RARC. For other endpoints outcomes were uncertain due to study limitations.

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 [347]. Additionally, they reported that RARC was associated with increased costs, although there are ergonomic advantages for the surgeon, as compared to laparoscopic RC (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. Safety after RT was confirmed by a small (n = 46) retrospective study [348]. In experienced hands the percentage of 90-day (major) complications after robotic cystectomy was independent of previous RT.

Oncological results of the first sufficiently powered RCT, comparing ORC (n = 58) vs. RARC (n = 60) and open diversion, were published in 2018 [344]. Overall recurrence rate, CSS and OS were comparable between the two procedures. For ORC an increase in metastatic sites at first recurrence was reported (HR 2.2, CI: 0.96-5.12) but more local/abdominal recurrences were associated with RARC (HR: 0.34, CI: 0.12-0.93). The Bochner *et al.* trial, however, was not powered to detect differences in recurrence. Jancke *et al.* reported on 8 patients with port-site metastasis (in addition to other metastatic sites) suggesting underreporting of metastatic sites after RARC, which is less common for open surgery [349].

The largest RCT to date is the RAZOR trial [343]. This study showed RARC to be non-inferior to ORC in terms of 2-year PFS (72.3% vs. 71.6%), adverse events (67% vs. 69%) and QoL. Most reviewed series, including the RAZOR trial, offer extracorporeal reconstruction. Hussein *et al.* retrospectively compared extracorporeal reconstruction (n = 1,031) to intracorporeal reconstruction (n = 1,094) and the latter was associated with a shorter operative time, fewer blood transfusions but more high-grade complications, which, again, decreased over time [350].

It is important to note that, although an intracorporeal neobladder is a very complex robotic procedure [351], the choice for neobladder or cutaneous diversion should not depend on the surgical approach.

For LRC, a review came to similar conclusions as described for RARC [351]. 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 a large LRC multicentre study [351].

The CORAL study was a small single-centre RCT comparing open (n = 20) vs. robotic (n = 20) vs. laparoscopic (n = 19) cystectomy [352]. 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 complication rates in the three study arms. Limitations of this study include the small sample size, three different, although experienced, surgeons, and cross over between arms.

7.4.5.1 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
Retrospective RARC series suffer from a significant stage selection bias as compared to ORC.	1
Grade 3, 90-day complication rate is lower with RARC.	2
Most endpoints, if reported, including intermediate-term oncological endpoint and quality of life, are not different between RARC and ORC.	2
Surgeons experience and institutional volume are considered the key factor for outcome of both RARC and ORC, not the technique.	2
Recommendations on how to define challenging patients and an experienced RARC surgeon are still under discussion.	3
The use of neobladder after RARC still seems under-utilised, and functional results of intracorporeally constructed neobladders should be studied.	4

Recommendations	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

7.4.6 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 [353]. Several studies have compared certain aspects of health-related quality of life (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.

7.4.6.1 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 [139, 354], particularly those related to the type of urinary diversion (Table 7.4) [355]. However, the ASA score is not a comorbidity scale and should not be used as such.

Table 7.4: ASA score [356, 357]

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 reconstructive surgery exposes the patient to excessive risk (as determined by comorbidity and age).

Diagnosis of an invasive urethral tumour prior to cystectomy leads to urethrectomy and therefore excludes neobladder reconstruction. If indicated; in males, in case of CIS and extension of the tumour in the prostatic urethra, in females, urethral frozen section has to be performed on the cystoprostatectomy specimen just under the verumontanum and on the inferior limits of the bladder neck. Non-muscle-invasive BC in prostatic urethra or bladder neck biopsies does not necessarily preclude orthotopic neobladder substitution, provided that patients undergo regular follow-up cystoscopy and urinary cytology [358].

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 [283].

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 [359].

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 [360]. Despite the necessary interruption and re-anastomosis of bowel, formal bowel preparation may not be necessary [361]. Bowel recovery time can be reduced by the use of early mobilisation and early oralisation, gastrointestinal stimulation with metoclopramide and chewing gum [362]. 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 [363].

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 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% ($p = 0.003$) [364].

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 [365]. However, this drug is, as yet, not approved in Europe.

Venous thromboembolism (VTE) prophylaxis may be implemented as part of an ERAS protocol. A single-centre non-RCT showed a significant lower 30-day VTE incidence rate in patients treated for 28 days with enoxaparin compared to patients without prophylaxis [366]. Data from the Ontario Cancer Registry including 4,205 cystectomy patients, of whom 1,084 received NAC, showed that VTE rates are higher in patients treated with NAC as compared to patients treated with cystectomy only (12% vs. 8%; $p = 0.002$) [367, 368].

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 [369].

7.4.6.2 *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 [370]. Age alone is not a criterion for offering continent diversion [369, 371]. 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 [372-375]. 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 m²) or 3a (eGFR 45-59 mL/min/1.73 m²) [376]. Only age and anastomotic strictures were found to be associated with a decline in eGFR.

7.4.6.2.1 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 ureterocutaneostomy as compared to ileal conduit [377]. Therefore, in older, or otherwise compromised, patients who need a supravescical diversion, uretero-cutaneostomy is the preferred procedure [378, 379]. 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 [377]. 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 [380].

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 [378].

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, $p < 0.001$) [381].

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 [382].

7.4.6.2.2 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 [382]. 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% [383-385]. 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) [386]; 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.

7.4.6.2.3 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 [387-389]. Different anti-reflux techniques can be used [390]. Most patients have a well-functioning reservoir with day-time and night-time continence approaching 93% [391]. 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 [391]. Stone formation in the pouch occurred in 10% of patients [390-392]. In a small series of previously irradiated female patients, incontinence and stomal stenosis was seen in 8/44 patients (18%) [393].

7.4.6.2.4 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) [394, 395]. 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 [359, 396]. 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 [397].

7.4.6.2.5 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 [222, 279, 369]. However, in elderly patients (> 80 years), it is rarely performed, even in high-volume expert centres [398, 399]. 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 [279]. 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 [400, 401]. In two studies with 1,054 and 1,300 patients [369, 402], 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 [403]. Urethral recurrence in neobladder patients seems rare (1.5-7% for both male and female patients) [369, 404]. 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 [405, 406].

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 [390, 401]. 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 [407]. In women undergoing RC the rate of concomitant urethral malignancy has been reported to range from 12-16% [408]. 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 [409].

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 [410, 411]. 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.

7.4.7 **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 [222, 370, 372, 412, 413]. In a large single-centre series, early complications (within three months of surgery) were seen in 58% of patients [370]. Late morbidity was usually linked to the type of urinary diversion (see also above) [373, 414]. 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 [415]. 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 [412, 416-420].

Table 7.6: Management of neobladder morbidity (30-64%) [421]

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 neobladder)
		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 systematic review 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 [422]. Buchner and co-workers showed similar results in a retrospective study. The 5-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 [423].

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 [424].

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 [425]. 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 [426].

7.4.8 **Survival**

According to a multi-institutional database of 888 consecutive patients undergoing RC for BC, the 5-year RFS rate was 58% and CSS was 66% [427]. External validation of post-operative nomograms for BC-specific mortality showed similar results, with bladder-CSS of 62% [428].

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 [199]. However, the 5-year RFS in node-positive patients who underwent cystectomy was considerably less at 34-43% [198, 429]. In a surgery-only study, the 5-year RFS was 76% in patients with pT1 tumours, 74% for pT2, 52% for pT3, and 36% for pT4 [199].

A trend analysis according to the 5-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 5-year survival rates for all stages, except for metastatic disease [430].

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

Recently, a systemic review was performed to assess the impact of hospital and/or surgeon volume on peri-operative outcomes of RC [431]. In total, 40 studies including over 560,000 patients were included. All studies were retrospective cohort studies. Twenty-two studies reported on hospital volume only, six studies on surgeon volume only and twelve studies reported on both. The results of the systematic review suggests that a higher hospital volume is likely associated with lower in-hospital, 30-day and 90-day mortality rates. Also, higher volume hospitals are likely to have lower positive surgical margins, higher LND and neobladder rates and lower complication rates. For surgeon volume, less evidence is available and it seems that outcome after RC is mainly hospital-driven. In spite of the lower quality, the available evidence suggests that performing more than 10 RCs per year per hospital reduces 30- and 90-day mortality. Performing more than 20 RCs per hospital per year might even further reduce these mortality rates.

7.4.10 Summary of evidence and guidelines for radical cystectomy and urinary diversion

Summary of evidence	LE
For MIBC, radical cystectomy (RC) is the curative treatment of choice.	3
Higher hospital volume likely improves quality of care and reduction in peri-operative mortality and morbidity.	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
The use of extended prophylaxis significantly decreases the incidence of venous thromboembolism after 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
Perform at least 10, and preferably > 20, RCs per hospital/per year.	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 pharmacological prophylaxis, such as low molecular weight heparin to RC patients, starting the first day post-surgery, for a period of 4 weeks.	Strong
Offer RC in T2-T4a, N0M0, and high-risk non-muscle-invasive BC.	Strong
Perform a lymph node dissection as an integral part of RC.	Strong
Do not preserve the urethra if margins are positive.	Strong

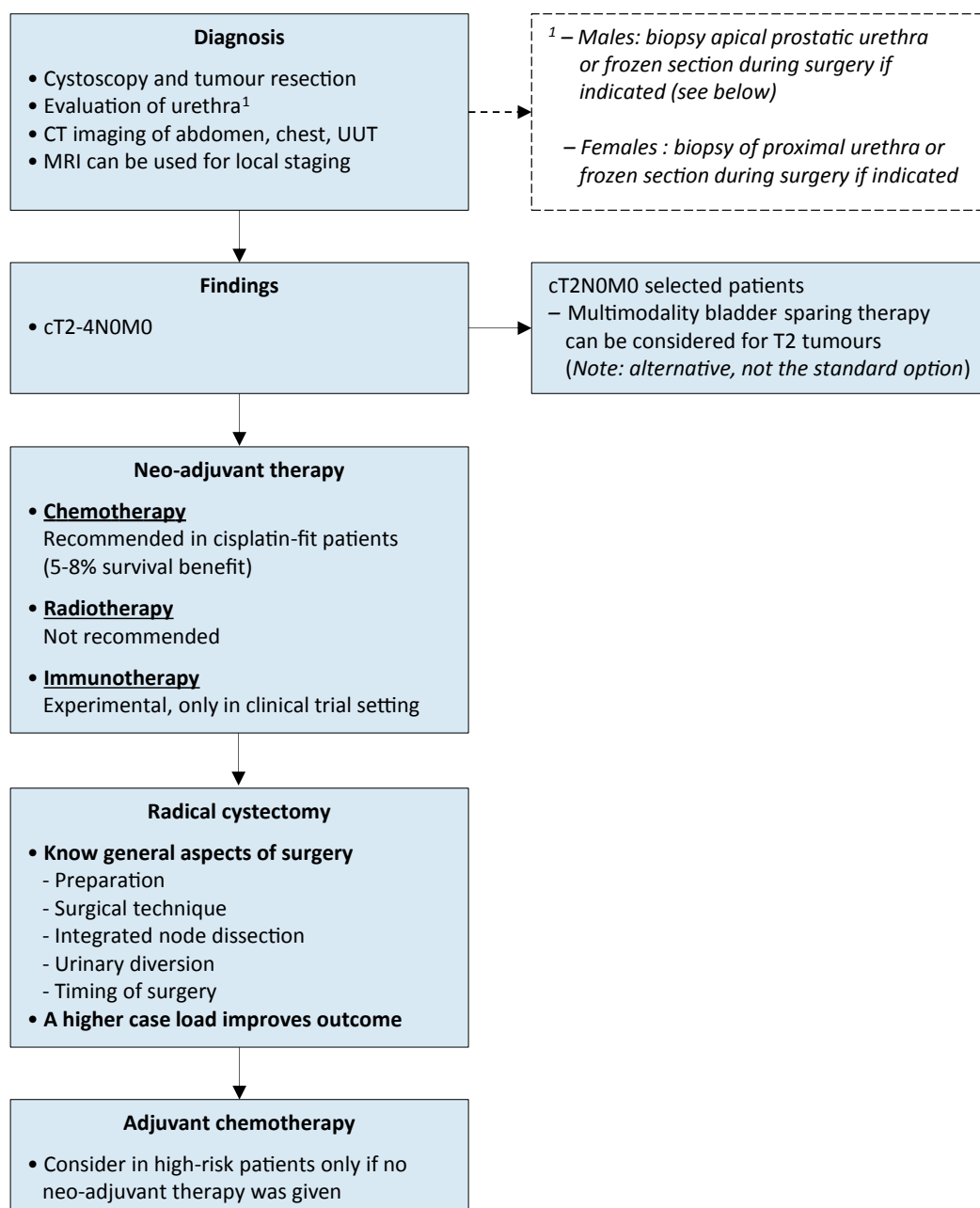
7.4.11 EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [5, 6]*

Consensus statement
Candidates for curative treatment, such as cystectomy or bladder preservation, should be clinically assessed by at least an oncologist, a urologist and a neutral healthcare professional such as a specialist nurse.
Muscle-invasive pure squamous cell carcinoma of the bladder should be treated with primary radical cystectomy and lymphadenectomy.
Muscle-invasive pure adenocarcinoma of the bladder should be treated with primary radical cystectomy and lymphadenectomy.
T1 high-grade bladder urothelial cancer with micropapillary histology (established after complete TURBT and/or re-TURBT) should be treated with immediate radical cystectomy and lymphadenectomy.

*Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as $\geq 70\%$ agreement and $\leq 15\%$ disagreement, or vice versa).

TURBT = transurethral resection of bladder tumour.

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 [432-434].

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 [435]. 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 [436].

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

7.5.1.2 EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [5, 6]*

Consensus statement
Chemoradiation should be given to improve local control in cases of inoperable locally advanced tumours.
In patients with clinical T4 or clinical N+ disease (regional), radical chemoradiation can be offered accepting that this may be palliative rather than curative in outcome.

*Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as $\geq 70\%$ agreement and $\leq 15\%$ disagreement, or vice versa).

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 [437]. 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 [437]. Vesicoureteral reflux should be excluded to prevent renal complications.

Radiation therapy is another common strategy to control bleeding and is also used to control pain. An older study reported control of haematuria in 59% of patients and pain control in 73% [438]. 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% [437]. 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 [439]. 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 [440]. A disease-free status at re-staging TURB appears to be crucial in making the decision not to perform RC [441, 442]. A prospective study by Solsona *et al.*, which included 133 patients with radical TURB and re-staging negative biopsies, reported a 15-year follow-up [442]. 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

7.6.1.2 EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [5, 6]*

Consensus statement
Candidates for curative treatment, such as cystectomy or bladder preservation, should be clinically assessed by at least an oncologist, a urologist and a neutral HCP such as a specialist nurse.
An important determinant for patient eligibility in case of bladder preserving treatment is absence of carcinoma <i>in situ</i> .
An important determinant for patient eligibility in case of bladder preserving treatment is absence or presence of hydronephrosis.
When assessing patient eligibility for bladder preservation, the likelihood of successful debulking surgery should be taken into consideration (optimal debulking).

*Only statements which met the *a priori* consensus threshold across all three stakeholder groups are listed (defined as $\geq 70\%$ agreement and $\leq 15\%$ disagreement, or vice versa).

HCP = healthcare professional.

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 [443], 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 6-weekly doses of 6 Gy [444]. 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 [445]. Acute diarrhoea is reduced even more with intensity-modulated RT [446]. 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 [447].

With the use of modern EBRT techniques, efficacy and safety results seem to have improved over time. A 2002 Cochrane analysis demonstrated that RC has an OS benefit compared to RT [432], although this was not the case in a 2014 retrospective review using a propensity score analysis [433]. 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 [448]. The 2-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

Consensus statement
Radiotherapy alone (single block) is not the preferred radiotherapeutic schedule.
Radiotherapy for bladder preservation should be performed with IMRT and IGRT to reduce side effects.
Dose escalation above standard radical doses to the primary site in case of bladder preservation, either by IMRT or brachytherapy, is not recommended.

*Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as $\geq 70\%$ agreement and $\leq 15\%$ disagreement, or vice versa).

IGRT = image-guided radiotherapy; IMRT = intensity-modulated radiotherapy.

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 $> 60\%$ [449, 450]. Response to chemotherapy is a prognostic factor for treatment outcome and eventual survival although it may be confounded by patient selection [451].

Several groups have reported the effect of chemotherapy on resectable tumours (neoadjuvant approach), as well as unresectable primary tumours [230, 245, 452, 453]. Neoadjuvant chemotherapy with two to three cycles of MVAC or CMV has led to a down-staging of the primary tumour in various prospective series [230, 245, 452].

A bladder-conserving strategy with TURB and systemic cisplatin-based chemotherapy has been reported several years ago and could lead to long-term survival with intact bladder in a highly selected patient population [451].

A recent large retrospective analysis of a National Cancer Database cohort reported on 1,538 patients treated with TURB and multi-agent chemotherapy [454]. The two and 5-year OS for all patients was 49% and 32.9% and for cT2 patients it was 52.6% and 36.2%, respectively. While these data show that long-term survival with intact bladder can be achieved in a subset of patients it is not 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 RT. 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 [455, 456]. 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.* [455]). 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 and in this case, the initial step is a radical TURB, where as much tumour as possible should be resected. In this case appropriate patient selection (T2 tumours, no CIS) is critical [457]. Even in case of an initial presumed complete resection, a second TUR reveals tumour in $> 50\%$ of patients and subsequently improves 5-year OS in case of MMT [458]. For patients who are not candidates for cystectomy, less stringent criteria can be applied, but extensive CIS and poor bladder function should both be regarded as strong contraindications.

A collaborative review has described the principles of MMT [459]. For radiation, two schedules are most commonly used: a split-dose format with interim cystoscopy is used in the U.S. [456], whilst single-phase treatment is more commonly used elsewhere [455]. 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 [460].

Different chemotherapy regimens have been used, but most evidence exists for cisplatin [357] and mitomycin C plus 5-FU [455]. In addition to these agents, other schedules have also been used, such as hypoxic cell sensitisation with nicotinamide, carbogen and gemcitabine, without clear preference for a specific radiosensitizer [5, 6]. In a recently published phase II RCT, twice-a-day radiation plus fluorouracil/cisplatin was compared to once-daily radiation plus gemcitabine [461]. Both arms were found to result in a >75% freedom of distant metastases at 3 years (78% and 84%, respectively). However, patients in the fluorouracil/cisplatin arm experienced more grade 4 bone marrow toxicity (7 vs. 2 respectively).

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% [357, 455, 459, 462]. The Boston group reported on their experience in 66 patients with variant histologies treated with MMT and found similar complete response, OS, DSS and salvage cystectomy rates as in UC [463]. Compared to RC, the impact of MMT 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 [464]. Worse survival was linked to higher age, comorbidity and tumour stage. After modelling, MMT resulted in a lower mortality at one 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 [465]. 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 time point. In older patients, potentially less ideal candidates for radical surgery, Williams *et al.* found a significantly lower OS (HR :1.49, 1.31-1.69) and CSS (1.55, 1.32-1.83) for MMT as compared to surgery as well as increased costs [466]. This was a retrospective SEER database study which, however, included 687 propensity-matched patients in each arm. On the other hand, a systematic review including 57 studies and over 30,000 patients comparing RC and MMT, found improved 10-year OS and DSS for MMT, but for the entire cohort OS and DSS did not significantly differ between RC and MMT [467]. Complete response after MMT resulted in significantly better survival, as did down-staging after TURB or NAC in case of RC.

Current data show that major complication rates are similar for salvage and primary cystectomy [468]. One option to reduce side effects after MMT is the use of IMRT and image-guided radiotherapy (IGRT) [5, 6]. The majority of recurrences post-MMT are non-invasive and can be managed conservatively [455]. A retrospective study showed QoL to be good after MMT and in most domains better than after cystectomy, although prospective validations are needed [469].

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 [459]. 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 supporting the benefit of using neoadjuvant or adjuvant chemotherapy. Patient selection is critical in achieving good outcomes [459]. Whether a node dissection should be performed before MMT, as in RC, remains unclear [5, 6].

A bladder-preserving multimodality strategy requires very close multidisciplinary cooperation [5, 6]. This was also highlighted by a Canadian group [470]. 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 [471]. 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 [472]. 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 radical cystectomy is not an option.	Strong

7.6.4.2 EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [5, 6]*

Consensus statement
Candidates for curative treatment, such as cystectomy or bladder preservation, should be clinically assessed by at least an oncologist, a urologist and a neutral HCP such as a specialist nurse.
An important determinant for patient eligibility in case of bladder preserving treatment is absence of carcinoma <i>in situ</i> .
An important determinant for patient eligibility in case of bladder preserving treatment is absence or presence of hydronephrosis.
When assessing patient eligibility for bladder preservation, the likelihood of successful debulking surgery should be taken into consideration (optimal debulking).
Bladder urothelial carcinoma with small cell neuroendocrine variant should be treated with neoadjuvant chemotherapy followed by consolidating local therapy.
In case of bladder preservation with radiotherapy, combination with a radiosensitiser is always recommended to improve clinical outcomes, such as cisplatin, 5FU/MMC, carbogen/nicotinamide or gemcitabine.
Radiotherapy for bladder preservation should be performed with IMRT and IGRT to reduce side effects.
Dose escalation above standard radical doses to the primary site in case of bladder preservation, either by IMRT or by brachytherapy, is not recommended.

*Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as $\geq 70\%$ agreement and $\leq 15\%$ disagreement, or vice versa).

HCP = healthcare professional; IGRT = image-guided radiotherapy; IMRT = intensity-modulated radiotherapy; 5FU = 5-fluorouracil; MMC = mitomycin-C.

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 [468, 473].

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 [474].

There is limited evidence from adequately conducted and accrued randomised phase III trials in favour of the routine use of adjuvant chemotherapy [473, 475-480]. An individual patient data meta-analysis [475] of survival data from six RCTs of adjuvant chemotherapy [462, 481-484] 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) [473]. 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 [485], and one trial used cisplatin monotherapy [483]. The data were not convincing to give an unequivocal recommendation for the use of adjuvant chemotherapy. In 2014, this meta-analysis was updated with an additional three studies [477-479] resulting in the inclusion of 945 patients from nine trials [476]. None of the trials had fully accrued and individual patient data were not used in the analysis [476]. For one trial only an abstract was available at the time of the meta-analysis [478], 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/cisplatin) [477, 478]. The HR for OS was 0.77 (95% CI: 0.59-0.99, $p = 0.049$) and for DFS 0.66 (95% CI: 0.45-0.91, $p = 0.014$) with a stronger impact on DFS in case of nodal positivity.

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) [486]. A recent publication of the largest RCT (EORTC 30994), although not fully accrued, showed a significant improvement of PFS for immediate, compared with deferred, cisplatin-based chemotherapy (HR: 0.54; 95% CI: 0.4-0.73, $p < 0.0001$), but there was no significant OS benefit [487].

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 5-year OS of 37% for the adjuvant arm vs. 29.1% (HR: 0.70; 95% CI: 0.64-0.76) in the observation group [488].

Another large retrospective analysis based on National Cancer Data Base including 15,397 patients with locally advanced (pT3/4) or LN-positive disease also demonstrated an OS benefit in patients with UC histology [489]. In patients with concomitant variant or pure variant histology, however, no benefit was found.

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. The most recent meta-analysis from 2014 showed a therapeutic benefit of adjuvant chemotherapy, but the level of evidence of this review is still very low, with significant heterogeneity and methodological flaws in the only nine included trials [476]. 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 PD-1/PD-L1 checkpoint inhibitors, a number of randomised phase III trials comparing checkpoint inhibitor monotherapy with atezolizumab, nivolumab or pembrolizumab have been performed but no data have been presented so far.

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
Only offer immunotherapy with a checkpoint inhibitor in a clinical trial setting.	Strong

7.7.4 **EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer** [5, 6]*

Consensus statement
When adjuvant chemotherapy is offered, patients should be selected based on the result of PLND (if done).

*Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as $\geq 70\%$ agreement and $\leq 15\%$ disagreement, or vice versa).

PLND = pelvic lymph node dissection.

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 [490]. Before the development of effective chemotherapy, patients with metastatic UC had a median survival rarely exceeding three to six months [491].

7.8.1.1 Prognostic factors and treatment decisions

Prognostic factors are crucial for assessing phase II study results and stratifying phase III trials [492, 493]. In a multivariate analysis, Karnofsky PS of $\leq 80\%$ and presence of visceral metastases were independent prognostic factors of poor survival after treatment with MVAC [493]. These prognostic factors have also been validated for newer combination chemotherapy regimens [494-496].

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 [497].

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 5.3). 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 [498].

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 [499]. The EORTC definitions were GFR < 60 mL/min and/or PS 2.

An international survey among BC experts [500] 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 [501]. More than 50% of patients with UC are not eligible for cisplatin-based chemotherapy [502-505]. Renal function assessment in UC is of utmost importance for treatment selection [502, 506]. In case of doubt, measuring GFR with radioisotopes (^{99m}Tc DTPA or ^{51}Cr -EDTA) is recommended. Cisplatin has also been administered in patients with lower GFR (40-60 mL/min) using different split-dose schedules. The respective studies were mostly small phase I and II trials in different settings (neoadjuvant and advanced disease) demonstrating that the use of split-dose cisplatin is feasible and appears to result in encouraging efficacy [507-510]. However, no prospective randomised trial has compared split-dose cisplatin with conventional dosing.

7.8.2 First line systemic therapy for metastatic disease

7.8.2.1 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 [511]). 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 [512]. The major difference between the above-mentioned combinations is toxicity. The lower toxicity of GC [164] has resulted in it becoming a new standard regimen [513]. Methotrexate, vinblastine, adriamycin plus cisplatin is better tolerated when combined with granulocyte colony-stimulating factor (G-CSF) [513, 514].

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 2-year survival rate. However, there is no significant difference in median survival between the two regimens [515, 516]. 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 [515]. 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 [512].

Further intensification of treatment using paclitaxel, cisplatin and gemcitabine (PCG) triple regimen did not result in a significant improvement in OS in the ITT population of a large randomised phase III trial, comparing PCG triple regimen to GC [517]. 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.

7.8.2.1.1 Carboplatin-containing chemotherapy

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 [518].

7.8.2.2 Chemotherapy in patients unfit for cisplatin

Up to 50% of patients are ineligible for cisplatin-containing chemotherapy [501]. 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 [499]. The ORR and severe acute toxicity were both 26% for the former group, and 20% and 24%, respectively, for the latter group [499]. Phase III data have confirmed these results [496].

A 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 [519].

7.8.2.2.1 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 [520-527].

7.8.2.2.2 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 [528, 529]. 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.

7.8.2.3 Immunotherapy in first-line treatment

Several randomised phase III trials are currently investigating the use of checkpoint inhibitors in the first-line setting for cisplatin-eligible and ineligible patients using combinations with chemotherapy or CTLA-4 inhibitors as well as monotherapy. At the moment published data from two single-arm phase II trials in cisplatin-ineligible patients are available to inform treatment decisions.

The PD-1 inhibitor pembrolizumab was tested in 370 patients with advanced or metastatic UC ineligible for cisplatin, showing an ORR of 29%, and complete remission in 7% of patients [530]. The PD-L1 inhibitor atezolizumab was also evaluated in the same patient population in a phase II trial including 119 patients. The ORR was 23%; 9% of patients presented with a complete remission and the median OS was 15.9 months [531]. The results are difficult to interpret due to the missing control arm and the heterogeneity of the study population with regards to PD-L1 status. The toxicity profile was favourable for pembrolizumab as well as for atezolizumab.

Both drugs are approved by the FDA and the EMA for first-line treatment in cisplatin-ineligible patients in case of positive PD-L1 status based on unpublished results from ongoing phase III trials only. Patients with negative PD-L1 should be treated with chemotherapy-based combinations.

7.8.3 Second-line systemic therapy for metastatic disease

7.8.3.1 Second-line chemotherapy

Second-line chemotherapy data are highly variable and mainly derive from small single-arm phase II trials apart from a single randomised phase III study which for the first time established prognostic factors (see Section 7.8.1.1) [497]. 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 [532] oxaliplatin,

ifosfamide, topotecan, pemetrexed, lapatinib, gefitinib and bortezomib have ranged between 0% and 28% in small phase II trials [528, 533, 534]. Gemcitabine has also shown good response rates in second-line use but most patients receive this drug as part of their first-line treatment [527].

The paclitaxel/gemcitabine combination has shown response rates of 38-60% in small single-arm studies. 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 [491, 525, 535].

Vinflunine, a novel third-generation vinca alkaloid, was tested in a randomised phase III trial and compared against best supportive care in patients progressing after first-line treatment with platinum-containing combination chemotherapy for metastatic disease [536]. The results showed a modest ORR (8.6%), a clinical benefit with a favourable safety profile and a survival benefit in favour of vinflunine, which was, however, only statistically significant in the eligible patient population (not in the ITT population).

Vinflunine was approved as second-line treatment in Europe (not in the U.S.). More recently, second-line therapy with PD-1/PD-L1 checkpoint inhibitors has been established as standard second-line therapy and vinflunine is reserved for patients with contraindications to immunotherapy and may be considered as third- or later-line treatment option although no randomised data for these indications exist.

A randomised phase III trial evaluated the addition of the angiogenesis inhibitor ramucirumab to docetaxel chemotherapy vs. docetaxel alone, which resulted in improved PFS (4.07 vs. 2.76 months) and higher response rates (24.5% vs. 14%), respectively [537]. While the primary endpoint of PFS prolongation was reached, the clinical benefit appears small and OS data have not yet been reported [537].

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

Trials investigated and still 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 and safety in patients progressing during, or after, standard platinum-based chemotherapy in phase I, II and III trials.

Pembrolizumab, a PD-1 inhibitor, has been tested in patients progressing during or after platinum-based first-line chemotherapy in a randomised phase III trial and demonstrated significant OS benefit leading to approval. In the trial, patients (n = 542) were randomised to receive either pembrolizumab monotherapy or chemotherapy (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 [538]. This trial was recently updated with a longer follow-up of 27.7 months with consistent improvement of OS [539]. In addition, HRQoL analysis showed that patients on pembrolizumab experience stable or improved HRQoL whereas it deteriorated on chemotherapy [540].

Atezolizumab, a PD-L1 inhibitor, tested in patients progressing during, or after, previous platinum-based chemotherapy in phase I, phase II and phase III trials, was the first checkpoint inhibitor approved for BC [541-543]. The phase III RCT (IMvigor211) included 931 patients comparing atezolizumab with second-line chemotherapy (either paclitaxel, docetaxel or vinflunine) did not meet its primary endpoint of improved OS for patients with high PD-L1 expression (IC score 2/3) with 11.1 months vs. 10.6 months (0.87, 95% CI: 0.63-1.21, p = 0.41) but OS was numerically improved in the ITT population in an exploratory analysis (8.6 months vs. 8.0 months, HR: 0.85, 95% CI: 0.73-0.99). A phase IV single-arm safety study was conducted with atezolizumab including 1,004 patients confirming the efficacy and tolerability profile [544].

The PD-1 inhibitor nivolumab was approved based on the results of a single-arm phase II trial (CheckMate 275), enrolling 270 platinum pre-treated patients. The first endpoint was ORR. Objective response rate was 19.6%, and OS was 8.74 months for the entire group [545]. Based on results of phase I/II and phase IB trials, two additional PD-L1 inhibitors, durvalumab and avelumab, are currently only approved for this indication in the U.S. [546-548].

7.8.3.3 Novel agents for second or later-line therapy

The results of a single-arm phase II trial using the FGFR inhibitor erdafitinib demonstrated encouraging response rates in patients with pre-specified FGFR alterations [549]. Moreover, a phase I trial investigated the FGFR inhibitor rogaratinib in patients with over-expression of FGFR mRNA including patients with UC resulting in clinical responses [550]. It is expected that both testing for molecular subtype, as well as identification of FGFR mutations and amplifications, will become an important basis for treatment decisions in localised and advanced UC [5, 6].

Another promising drug is enfortumab vedotin, an antibody-drug conjugate targeting Nectin-4, which is highly expressed in UC. A published phase-II single-arm study (n = 125) in patients previously treated with platinum

chemotherapy and checkpoint inhibition showed objective response rates of 44%, including 12% of complete responses with a tolerable safety profile. A phase III randomised trial comparing enfortumab vedotin with single-agent chemotherapy is ongoing [551].

7.8.4 **Post-chemotherapy surgery and oligometastatic disease**

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 [512, 516, 552, 553]. 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 [554-568]. Retrospective studies of post-chemotherapy surgery after partial or complete remission have indicated that surgery may contribute to long-term DFS in selected patients [569-572]. These findings have been confirmed in a recent systematic review including 28 studies [572].

In the absence of data from RCTs, patients should be evaluated on an individual basis and discussed by an interdisciplinary tumour board [572].

7.8.4.1 *EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [5, 6]**

Consensus statement
In a minority of patients with one metastatic lesion, cure is possible after radical treatment.
In patients with more than two metastatic sites, cure is not possible.
In metachronous OMD, time to relapse is an important prognostic indicator.
Liver is an unfavourable OMD site for curative therapy.
Bone is a unfavourable OMD site for curative therapy.
PET-CT scanning should be included in OMD staging when considering radical treatment.
Radical treatment of OMD should be accompanied by adjuvant or neoadjuvant systemic therapy.

**Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as $\geq 70\%$ agreement and $\leq 15\%$ disagreement, or vice versa).*

OMD = oligometastatic disease; PET-CT = positron emission tomography-computed tomography.

7.8.5 **Treatment of patients with bone metastases**

The prevalence of metastatic bone disease (MBD) in patients with advanced/metastatic UC is 30-40% [573]. Skeletal complications due to MBD have a detrimental effect on pain and QoL and are also associated with increased mortality [574]. Bisphosphonates such as zoledronic acid (ZA) reduce and delay skeletal-related events (SREs) due to bone metastases by inhibiting bone resorption, as shown in a small pilot study [575]. Denosumab, a fully human monoclonal antibody that binds to and neutralises RANKL (receptor activator of nuclear factor κ B ligand), 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 [576]. Patients with MBD, irrespective of the cancer type, should be considered for bone-targeted treatment [574].

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

7.8.6 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 (DFS) 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 DFS 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 to PD-L1-positive patients.	Strong
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 subsequent-line treatment if immunotherapy, or combination chemotherapy, or FGFR3-inhibitor therapy, or inclusion in a clinical trial is not feasible.	Weak

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

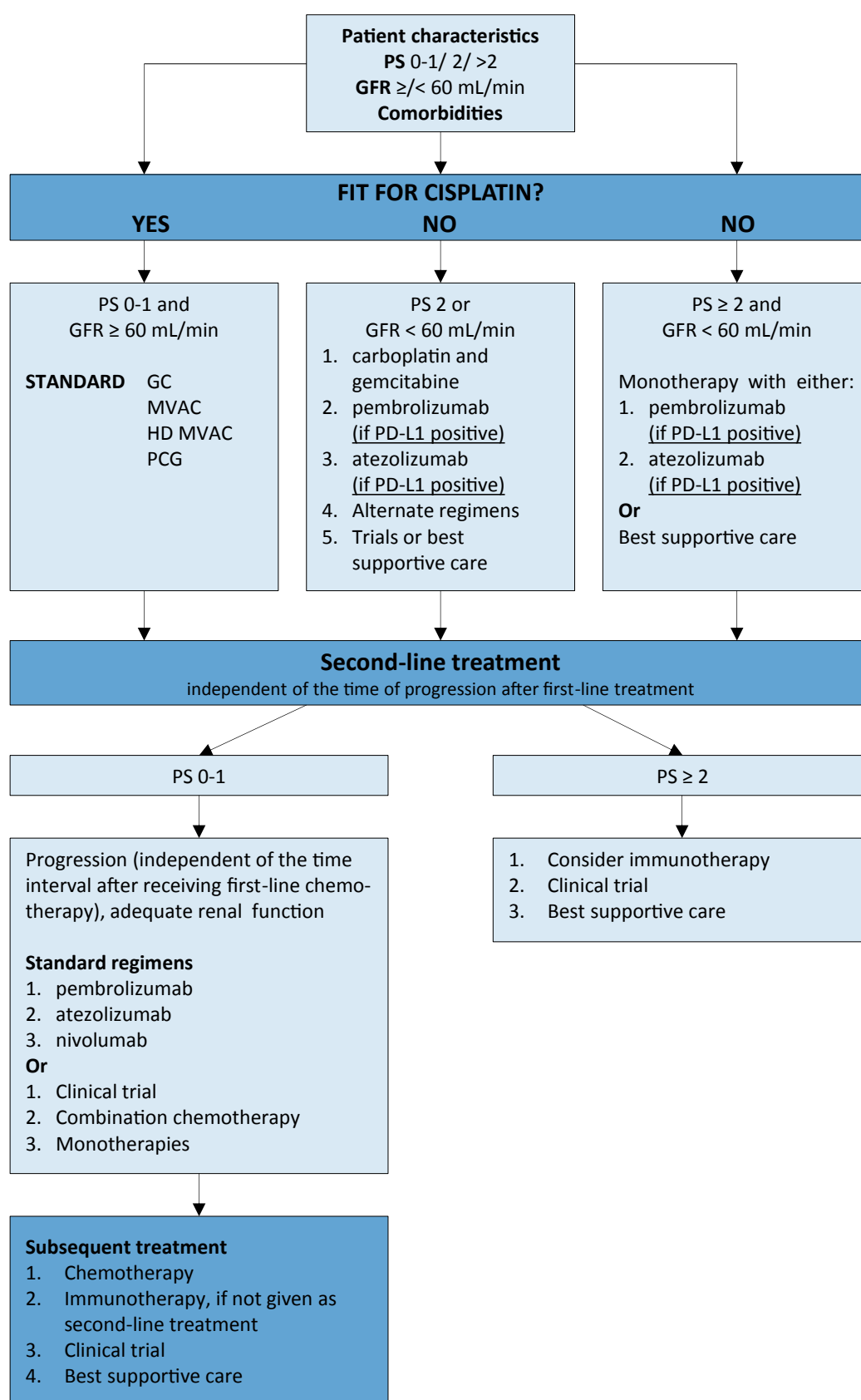
7.8.7 **EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer** [5, 6]*

Consensus statement
In patients with clinical T4 or clinical N+ disease (regional), radical chemoradiation can be offered accepting that this may be palliative rather than curative in outcome.
Pseudo-progression has not been demonstrated in urothelial cancer.
In patients with advanced/metastatic urothelial cancer who are ineligible for cisplatin-based therapy but with high PDL1 expression (as per approved drug specific methodology), both treatment with an ICI and chemotherapy can be offered.
Since no data exist for cisplatin-ineligible PDL1-positive patients in order to differentiate between different ICIs (atezolizumab and pembrolizumab), either agent can be administered.
Enrolment in a clinical trial remains the preferred option for patients with cisplatin-eligible advanced/metastatic urothelial cancer until ongoing randomised trials report in this population.
Treatment with an ICI should be offered to patients with advanced/metastatic urothelial cancer with progression after platinum-based chemotherapy. This includes tumours which have progressed within a year or following peri-operative (cystectomy) chemotherapy.
Once initiated, ICI therapy should be continued until progression of disease in patients with advanced/metastatic urothelial cancer.
In contrast to the first-line setting, the PD-L1 biomarker is not useful for selecting patients for immunotherapy in platinum-refractory metastatic urothelial cancer.
Carboplatin-based chemotherapy remains a viable first-line treatment option in cisplatin-ineligible, PD-L1-positive patients with metastatic urothelial carcinoma until data from randomised phase 3 trials of ICIs are available.
Cisplatin-ineligible, immunotherapy-refractory patients with metastatic urothelial carcinoma should be considered for chemotherapy instead of sequencing of immunotherapy.

**Only statements which met the a priori consensus threshold across all three stakeholder groups) are listed (defined as $\geq 70\%$ agreement and $\leq 15\%$ disagreement, or vice versa).*

ICI = immune checkpoint inhibitor; PD-L1 = programmed death-ligand 1.

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



GC = gemcitabine plus cisplatin; GFR = glomerular 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 [578].

Several questionnaires have been validated for assessing HRQoL in patients with BC, including FACT (Functional Assessment of Cancer Therapy)-G [579], EORTC QLQ-C30 [580], EORTC QLQ-BLM (MIBC module) [581], and SF (Short Form)-36 [582, 583] and recently the BCI questionnaire specifically designed and validated for BC patients [584].

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 [585].

7.9.2 Neoadjuvant chemotherapy

The impact of NAC on patient-reported outcomes (using EORTC QLQ questionnaires) was investigated by Feuerstein *et al.* [586]. A propensity-matched analysis of 101 patients who completed NAC and 54 patients who did not undergo NAC, did not demonstrate a negative effect of NAC on patient-reported outcomes.

7.9.3 Radical cystectomy and urinary diversion

Two recent systematic reviews focused on HRQoL after RC [587, 588] and one systematic review, based on 18 studies ($n = 1,553$), showed a slight, but not significant, improvement of QoL in patients with an orthotopic diversion [587]. However, analysing only the studies comparing exclusively ileal conduit vs. ileal orthotopic neobladder, the advantage in QoL of the latter group was significant. Another systematic review, based on 29 studies ($n = 3,754$), showed no difference in overall QoL between continent and incontinent diversion [588]. 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 [588-590].

Clifford and co-workers prospectively evaluated continence outcomes in male patients undergoing orthotopic neobladder diversion [591]. 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 [592].

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 [588].

7.9.4 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 [469]. To draw valid conclusions, prospective studies are needed.

7.9.5 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 [593]. There is limited literature describing HRQoL in BC patients receiving palliative care [594], but there are reports of bladder-related symptoms relieved by palliative surgery [436], RT [595], and/or chemotherapy [596]. Recently, a HRQoL analysis was performed in platinum-refractory patients who were randomised to pembrolizumab vs. another line of chemotherapy (KEYNOTE-45 trial) [540]. It was reported that patients treated with pembrolizumab had stable or improved global health status/QoL, whereas those treated with investigators' choice of chemotherapy experienced declines in global health [540].

7.9.6 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
In patients with platinum-refractory advanced urothelial carcinoma, pembrolizumab may be superior in terms of HRQoL compared to another line of chemotherapy.	1b

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 [597].

Nomograms on CSS following RC have been developed and externally validated, but their wider use cannot be recommended until further data become available [598, 599].

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 [600-602]. From the Volkmer B, *et al.* series of 1,270 RC patients, no differences in OS were observed between asymptomatic and symptomatic recurrences [601]. 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 [600]. 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 [602].

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 [603]. 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 6 to 18 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 [604].

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 [603].

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 [605]. 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%) [606].

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 [607-609]. However, longer survival (28-33% at 5 years) has been reported in patients with minimal metastatic disease undergoing multimodality management, including metastasectomy [555, 563].

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) [610].

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 asymptotically vs. symptomatically, so follow-up of the male urethra is indicated in patients at risk of urethral recurrence [603]. Treatment is influenced by local stage and grade of urethral occurrence. In urethral CIS, BCG instillations have success rates of 83% [611]. In invasive disease, urethrectomy should be performed if the urethra is the only site of disease; in case of distant disease, systemic chemotherapy is indicated [3].

Upper urinary tract UCs occur in 4-10% of cases and represent the most common sites of late recurrence (3-year DFS following RC) [612]. Median OS is 10-55 months, and 60-67% of patients die of metastatic disease [603]. A 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 [613]. Multifocality increases the risk of recurrence by three-fold, while positive ureteral or urethral margins increase the risk by seven-fold. Radical nephro-ureterectomy can prolong survival [614].

8.3 **Time schedule for surveillance**

Although, based on low level evidence only, 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. Patients with multifocal disease, NMIBC with CIS or positive ureteral margins are at higher risk of developing UTUC, which can develop late (> 3 years). In those cases, monitoring of the UUT is mandatory during follow-up. Computed tomography is to be used for imaging of the UUT [613].

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 [615]. 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 [616]. Despite this, the rationale for a risk-adapted schedule for BC surveillance appears to be promising and deserves further investigation.

Since data for follow-up strategies are sparse, a number of key questions were included in a recently held consensus project [5, 6]. Outcomes for all statements for which consensus was achieved are listed in Section 8.6.

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 15 years of follow-up. Therefore, long-term follow-up of functional outcomes is desirable [603].

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 [603]. Especially in women approximately two-thirds need to catheterise their neobladder, while almost 45% do not void spontaneously at all [592]. 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 [616].

Since low vitamin B12 levels have been reported in 17% of patients with bowel diversion, in case of cystectomy and bowel diversion, vitamin B12 levels should be measured annually [5, 6, 382].

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

8.6 EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [5, 6]*

Consensus statement
After radical cystectomy with curative intent, regular follow-up is needed.
After radical cystectomy with curative intent, follow-up for the detection of second cancers in the urothelium is recommended.
After radical cystectomy with curative intent, follow-up of the urethra with cytology and/or cystoscopy is recommended in selected patients (e.g. multifocality, carcinoma <i>in situ</i> and tumour in the prostatic urethra).
After trimodality treatment with curative intent, follow-up for the detection of relapse is recommended every 3–4 mos initially; then after 3 yrs, every 6 mos in the majority of patients.
After trimodality treatment with curative intent, regular follow-up for the detection of relapse is needed in the majority of patients.
After trimodality treatment with curative intent, follow-up imaging to assess distant recurrence or recurrence outside the bladder is needed.
After trimodality treatment with curative intent, assessment of the urothelium to detect recurrence is recommended every 6 mos in the majority of patients.
After trimodality treatment with curative intent, in addition to a CT scan, other investigations of the bladder are recommended.
In patients with a partial or complete response after chemotherapy for metastatic urothelial cancer, regular follow-up is needed. Imaging studies may be done according to signs/symptoms.
To detect relapse (outside the bladder) after trimodality treatment with curative intent, CT of the thorax and abdomen is recommended as the imaging method for follow-up in the majority of patients.
To detect relapse (outside the bladder) after trimodality treatment with curative intent, routine imaging with CT of the thorax and abdomen should be stopped after 5 yrs in the majority of patients.
In patients treated with radical cystectomy with curative intent and who have a neobladder, management of acid bases household includes regular measurements of pH and sodium bicarbonate substitution according to the measured value.
To detect relapse after radical cystectomy with curative intent, routine imaging with CT of the thorax and abdomen should be stopped after 5 yrs in the majority of patients.

To detect relapse after radical cystectomy with curative intent, a CT of the thorax and abdomen is recommended as the imaging method for follow-up in the majority of patients.
Levels of LDH and CEA are not essential in the follow-up of patients with urothelial cancer to detect recurrence.
Vitamin B12 levels have to be measured annually in the follow-up of patients treated with radical cystectomy and bowel diversion with curative intent.

**Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as $\geq 70\%$ agreement and $\leq 15\%$ disagreement, or vice versa).*

CEA = carcinoembryonic antigen; CT = computed tomography; LDH = lactate dehydrogenase; mos = months; yrs = years.

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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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