EAU Guidelines on

Muscle-invasive and Metastatic Bladder Cancer

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European Association of Urology

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1. INTRODUCTION

1.1 Aims and scope

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

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

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

1.2 Panel composition

The EAU Guidelines Panel consists of an international multidisciplinary group of clinicians, including urologists, oncologists, a pathologist, a radiologist and radiotherapists. In the course of 2021 two patient representatives formally joined the MIBC Guidelines Panel.

Section 5.3 -MIBC and health status, was developed with the assistance of Prof.Dr. S. O'Hanlon, consultant geriatrician, International Society of Geriatric Oncology (SIOG) representative and member of the EAU-EANM-ESTRO-ESUR-ISUP-SIOG Prostate Cancer Guidelines Panel. The MIBC Panel is most grateful for his support.

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: https://uroweb.org/guideline/bladder-cancer-muscle-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 2021 [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 2022 document presents a limited update of the 2021 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 2022 EAU MIBC Guidelines resulting in new sections and added and revised recommendations in:

- Section 5.2 Imaging for staging of MIBC, and in particular Section 5.2.1 Local staging of MIBC, with the provision of a revised recommendation.

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

Summary of evidence	LE
In local staging, MRI is superior to CT in terms of differentiating T1 from T2 disease.	2b

Recommendation	Strength rating
Use CT urography unless it is contraindicated for reasons related to contrast administration or radiation dose, in that case use MRI.	Strong

Considerable new data was added to:

- Section 7.1 Neoadjuvant therapy
- Section 7.1.2 Role of cisplatin-based chemotherapy; this section was revised with considerable new data added.
- Section 7.3.5 Laparoscopic/robotic-assisted laparoscopic cystectomy; a new section on stricture formation has been included.
- Section 7.3.6.2 Different types of urinary diversion, in particular Section 7.3.6.2.1 Uretero-cutaneostomy
- Section 7.6.2 Role of adjuvant immunotherapy has been completely revised including a new recommendation.

7.6.3 ***Summary of evidence and guidelines for adjuvant therapy***

Summary of evidence	**LE**
Adjuvant cisplatin-based chemotherapy for high-risk patients (pT3, 4 and/or or N+ M0) without neoadjuvant treatment can be associated with improvement in DFS and OS but trials are underpowered to adequately answer this question.	2a
To date, studies of immune checkpoint inhibitors in the adjuvant setting for patients with high-risk MIBC who have and have not received neoadjuvant chemotherapy have demonstrated conflicting results with the CheckMate 274 study demonstrating an improvement in DFS with adjuvant nivolumab and the IMvigor 010 study failing to show an improvement in DFS with adjuvant atezolizumab.	1b
Results for adjuvant treatment with immune-checkpoint inhibitors in high-risk MIBC are conflicting: nivolumab improved DFS (Checkmate 274) whereas atezolizumab did not (IMvigor 010).	1b
Circulating tumour DNA holds promise as both a prognostic and predictive biomarker to guide the use of adjuvant IO for UC in patients who are at a high risk of recurrence and positive for ctDNA treated with adjuvant atezolizumab demonstrating improved outcomes compared with observation.	2b

Recommendation	**Strength rating**
Discuss immunotherapy with nivolumab with selected patients with pT3/4 and/or pN+ disease not eligible for, or who declined, adjuvant cisplatin-based chemotherapy.	Weak

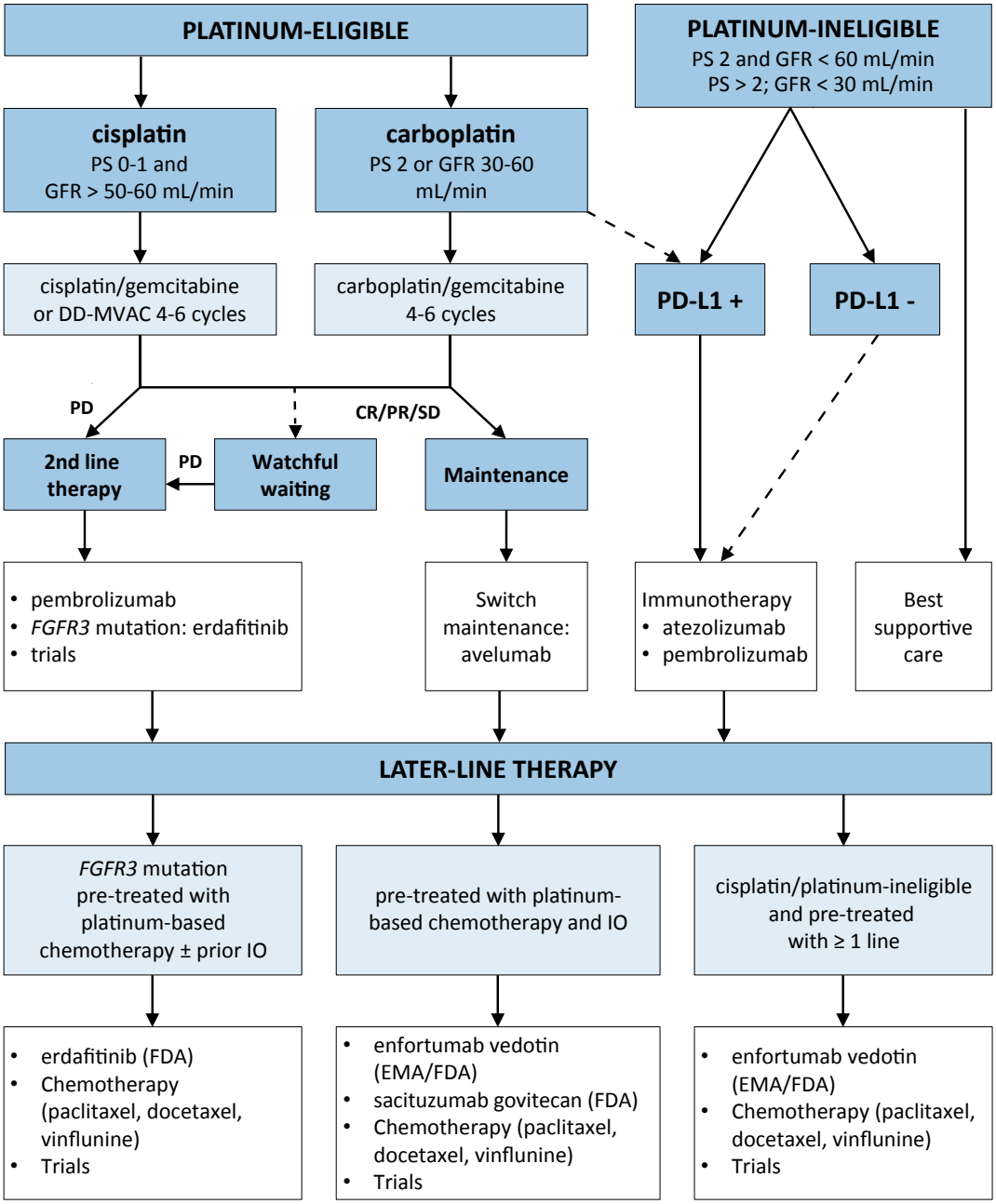
- Section 7.7 Metastatic disease was completely revised, resulting in the inclusion of new recommendation.

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

Summary of evidence	**LE**
Enfortumab vedotin after prior platinum chemotherapy and checkpoint inhibitor immunotherapy has demonstrated a significant survival benefit as compared to chemotherapy.	1b
PD-L1 inhibitor atezolizumab is approved for patients with advanced or metastatic UC unfit for cisplatin-based chemotherapy in case of high PD-1 expression defined as tumour-infiltrating immune cells covering ≥ 5% of the tumour area using the SP142 assay.	1b
PD-1 inhibitor pembrolizumab is approved for patients with advanced or metastatic UC unfit for any platinum-based chemotherapy in case of high PD-1 expression defined as CPS of ≥ 10 using the Dako 22C33 platform (EMA; FDA approval independent of PD-1 status).	1b

Recommendation	**Strength rating**
Evaluate for *FGFR2/3* genetic alterations for the potential use of erdafitinib in patients with locally advanced or metastatic urothelial carcinoma who have progressed following platinum-containing chemotherapy (including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy).	Weak

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



**Treatment within clinical trials is highly encouraged.*
BSC = best supportive care; CR = complete response; DD-MVAC = dose dense methotrexate vinblastine doxorubicin cisplatin; EMA = European Medicines Agency; EV = enfortumab vedotin; FDA = US Food and Drug Administration; FGFR = fibroblast growth factor receptor; GFR = glomerular filtration rate; IO = immunotherapy; PR = partial response; PS = performance status; SD = stable disease.

- Section 7.8 Quality of life, one recommendation was revised based on the new data added.

Summary of evidence	LE
HRQoL data are comparable for robotic radical cystectomy (with either intracorporeal or extracorporeal urinary diversion) and open radical cystectomy.	1b

- Chapter 8 Follow-up; a new section on variant histologies was added.

2. METHODS

2.1 Data identification

For the 2021 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 May 14th, 2020 and June 11th, 2021. A total of 2,290 unique records were identified, retrieved and screened for relevance resulting in 61 new publications having been included in the 2022 print. A detailed search strategy is available online: https://uroweb.org/guideline/bladder-cancer-muscle-invasive-and-metastatic/?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 [5, 6] 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 grade according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [7];
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' [6]. 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 BC have been incorporated in the 2020 MIBC Guidelines update [8, 9]. Only statements which reached the *a priori* defined level of agreement - ≥ 70% agreement and ≤ 15% disagreement – across all stakeholders involved in this consensus project are listed. The methodology is presented in detail in the scientific publications. Since the publication of these consensus papers, emerging evidence prompted a re-evaluation of these findings, resulting in the removal of a number of consensus statements.

2.2 Peer-review

The 2021 print of the MIBC Guidelines were peer reviewed prior to publication.

*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 2023 update of the MIBC Guidelines:

- a systematic review on the role of Positron Emission Tomography (PET) in the diagnosis and staging of patients presenting with suspected MIBC;
- 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 10th position when both genders are considered [10]. The worldwide age-standardised incidence rate (per 100,000 person/years) is 9.5 for men and 2.4 for women [10]. In the European Union, the age-standardised incidence rate is 20 for men and 4.6 for women [10]. 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].

Worldwide, the BC age-standardised mortality rate (per 100,000 person/years) was 3.3 for men vs. 0.86 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, 12]. 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, 17]. A causal relationship has been established between exposure to tobacco and cancer in studies in which chance, bias and confounding can be discounted with reasonable confidence [18].

The incidence of BC is directly related to the duration of smoking and the number of cigarettes smoked per day [19]. A meta-analysis looked at 216 observational studies on cigarette smoking and cancer published between 1961 and 2003, and the pooled risk estimates for BC demonstrated a significant association for both current and former smokers [20]. Recently, an increase in risk estimates for current smokers relative to never smokers has been described suggesting this could be due to changes in cigarette composition [16]. Starting to smoke at a younger age increased the risk of death from BC [21]. An immediate decrease in the risk of BC was observed in those who stopped smoking. The reduction was about 40% within one to four years of quitting smoking and 60% after 25 years of cessation [19]. Encouraging people to stop smoking would result in the incidence of BC decreasing equally in men and women [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 (with the exception of hair dyes [22]), rubbers, textiles, paints, leathers, and chemicals are used [23, 24]. 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 [25, 26]. Population-based studies established the occupational attribution for BC in men to be 7.1%, while no such attribution was discernible for women [11, 27].

3.2.3 *Radiotherapy*

Increased rates of secondary bladder malignancies have been reported after external-beam radiotherapy (EBRT) for gynaecological malignancies, with relative risks (RR) 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 [28].

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 [29]. 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 [29].

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 [30].

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 body mass index (BMI) was associated with decreased BC risk. The associations between BMI, blood pressure and BC risk significantly differed between men and women [31].

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 CSM risk especially in men [32]. 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 [33]. The U.S. Food and Drug Administration (FDA) recommend that healthcare professionals should not prescribe pioglitazone in patients with active BC [34]. 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 [35]. 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 [36, 37].

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 [38]. 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 [39].

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 [40].

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) [41]. This finding had already been presented in a descriptive nationwide 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 [42]. However, treatment patterns are unlikely to explain the differences in overall survival (OS) [43]. 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 OS, mortality and outcomes were found between males and females following radical therapy [44]. The gender-specific difference in survival for patients with BC was also analysed in the Norwegian 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 [45].

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 [46]. 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 finding 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 [47-49]. Moreover, a recent population study assessing impact of hormones on BC suggests that younger age at menopause (≤ 45 years) is associated with an increased risk of BC [50].

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 [51]. Shared environmental exposure was recognised as a potentially confounding factor [52]. Recent studies detected genetic susceptibility with independent loci, which are associated with BC risk [53].

Genome-wide association studies (GWAS) of BC identified several susceptibility loci associated with BC risk [54, 55].

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

Summary of evidence	**LE**
Worldwide, bladder cancer is the 10th most commonly diagnosed cancer.	2a
Several risk factors associated with BC diagnosis have been identified.	3
Active and passive tobacco smoking continues to be the main risk factor, while exposure-related incidence is decreasing.	2a
The increased risk of developing BC in patients undergoing EBRT, brachytherapy, or a combination of EBRT and brachytherapy, must be considered during patient follow-up. As BC requires time to develop, patients treated with radiation at a young age are at the greatest risk and should be followed-up closely.	3

Recommendations	**Strength rating**
Council patients to stop active and avoid passive smoking.	Strong
Inform workers in potentially hazardous workplaces of the potential carcinogenic effects of a number of recognised substances, including duration of exposure and latency periods. Protective measures are recommended.	Strong
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 [56]. The sampling sites must be recorded by the urologist; the pathologist report should include location of tumour tissue in the cystectomy specimen. Anatomical tumour location is relevant for staging and prognosis [57, 58].

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 [59].

Specimen handling should follow the general rules as published by a collaborative group of pathologists and urologists [60, 61]. 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 [62]. 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 vault (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 LNs, 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 [63, 64]. In 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 [65]. In rare cases, fresh frozen sections may be helpful to determine treatment strategy [66].

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 [67]. However, identification of morphological subtypes is important for prognostic reasons and treatment decisions [68-70].

The data presented in these guidelines are based on the 2004/2016 World Health Organization (WHO) classifications [71, 72].

Currently the following differentiations are used [68, 73]:

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

Outcomes may vary for divergent histologies, which need to be mentioned following international reporting standards [68, 74].

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 vault.	
Record the total number of lymph nodes (LNs), the number of positive LNs and extranodal spread.	
Record lymphovascular invasion.	
Record the presence of carcinoma *in situ*.	
Record the sampling sites as well as information on tumour size when providing specimens to the pathologist.	

3.3.4 *EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer* [8, 9]*

Consensus statement
Bladder UC 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 UC 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.
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 ≥ 70% agreement and ≤ 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 [75]. Blood and lymphatic vessel invasion have an independent prognostic significance [76, 77].

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 [75] (Table 4.1).

Table 4.1: TNM Classification of urinary bladder cancer [75]

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

Staging after neoadjuvant chemotherapy (NAC) and RC can be done, but must be mentioned as ypTNM (International Collaboration on Cancer Reporting) [74]. ypT0N0 after NAC and cystectomy is associated with good prognosis [78, 79].

5. DIAGNOSTIC EVALUATION

5.1 Primary diagnosis

*5.1.1 **Symptoms***

Painless visible haematuria is the most common presenting complaint. Other presenting symptoms and clinical signs include non-visible haematuria, 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 [80, 81]. 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 [82].

*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.

The high specificity of diagnostic imaging for detecting BC means that patients with imaging positive for BC may avoid diagnostic flexible cystoscopy and go directly to rigid cystoscopy and transurethral resection [83, 84].

5.1.4 *Urinary cytology*

Examination of voided urine or bladder washings for exfoliated cancer cells has high sensitivity in high-grade tumours 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% [85, 86]. However, negative cytology does not exclude a tumour. There is no known urinary marker specific for the diagnosis of invasive BC [87].

A standardised reporting system, the 'Paris System' redefining urinary cytology diagnostic categories was published in 2016 [88]:

- 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. An (outpatient) flexible cystoscopy is recommended to obtain a complete image of the bladder. However, in daily practice, 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. During the procedure, a thorough investigation of the bladder with rigid cystoscopy under anaesthesia is mandatory in order not to miss any tumours at the level of the bladder neck. 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 [89]. The use of a bladder diagram is recommended.

The use of PDD could be considered if a T1 high-grade tumour is present and to identify associated CIS. Presence of CIS may lead to a modified treatment plan (see EAU Guidelines on Non-muscle-invasive Bladder Cancer [2]). 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 [77, 90].

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 making a correct diagnosis. In cases in which RT is considered and CIS is to be excluded, PDD can be used [91].

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 [58, 92, 93]. 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 [94-96].

A negative urethral frozen section can reliably identify patients in whom urethrectomy should be avoided. However, a positive pre-operative biopsy seems to have limited utility as these findings are not reliably associated with final margin status [94, 97].

Diagnosis of a urethral tumour before cystectomy will result in a urethrectomy which could be a contraindication for an orthotopic diversion. However, an orthotopic diversion should not be denied based on positive pre-operative biopsy findings alone and frozen section should be part of the RC procedure, in particular in male patients [98, 99].

5.1.7 *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 *in situ*.	2b
In men, prostatic urethral biopsy includes resection from the bladder neck to the verumontanum (between the 5 and 7 o'clock position) using a resection loop. In case any abnormal-looking areas in the prostatic urethra are present at this time, these need to be biopsied as well.	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 *in situ* is present or suspected, when there is positive cytology without evidence of tumour in the bladder, or when abnormalities of the prostatic urethra are visible.	Strong
In men with a negative prostatic urethral biopsy undergoing subsequent orthotopic neobladder construction, an intra-operative frozen section can be omitted.	Strong
In men with a prior positive transurethral prostatic biopsy, subsequent orthotopic neobladder construction should not be denied a priori, unless an intra-operative frozen section of the distal urethral stump reveals malignancy at the level of urethral dissection.	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 cystectomy.	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])

5.1.8 *EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [8, 9]**

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 ≥ 70% agreement and ≤ 15% disagreement, or vice versa).*

5.2 Imaging for staging of MIBC

In clinical practice, tumour stage and histopathological grade are used to guide treatment and determine prognosis [73, 100, 101]. In symtomatic and high-risk patients imaging is used to assess bladder abnormalities. In addition, imaging is increasingly becoming an essential investigation for local- and distant staging of BC.

The goal of imaging patients with BC is to:

- detect lesions (US when applicable);
- differentiate T1 from T2 tumours as their treatment will differ (MRI using the Vesical Imaging Reporting and Data System [VI-RADS] score);
- Evaluate the extent of locally advanced tumour stage or tumour spread to LNs (CT scan and MRI for abdominal- and pelvic LNs or PET/CT scan);
- assess tumour spread to the upper UT or other distant organs (e.g., liver, lungs, bones, peritoneum, pleura, and adrenal glands) (CT urography for evaluating the UUT and PET/CT to detect distant organs metastasis).

Staging must be accurate to allow for the most optimal treatment choice.

5.2.1 ***Local staging of MIBC***

5.2.1.1 *Magnetic resonance imaging for local staging of MIBC*

Magnetic resonance imaging has superior soft tissue contrast resolution compared with CT and can evaluate post-biopsy reaction as enhancement of the tumour occurs earlier than that of the normal bladder wall due to neovascularisation [102, 103].

The accuracy of MRI for primary tumour staging varies from 73% to 96% (mean 85%). Huang *et al.*, in a systematic review, showed a pooled sensitivity and specificity of 0.90 and 0.88, respectively, with results going up to 0.92 and 0.96 when MRI was performed with a 3T scan, with diffusion-weighted magnetic resonance imaging (DWI) as part of the acquisition protocol [104]. A systematic review evaluating 20 studies (n = 1,724), showed a pooled sensitivity and specificity for differentiating between stages ≤ T1 and ≥ T2 of 0.92 (95% CI: 0.88–0.95) and 0.88 (95% CI: 0.78–0.94), respectively [105]. Considering the link established between the use of gadolinium-based contrast agents and nephrogenic systemic fibrosis (NSF), in patients with impaired renal function contrast medium should be managed according to the European Society of Urogenital Radiology (ESUR) Guidelines [106].

More recently, multiparametric (mp) MRI using the VI-RADS scoring system has been introduced which proved to be able to differentiate between muscle- and non-muscle-invasive primary BC (T1 vs. T2 tumours) with high diagnostic accuracy [107]. The VI-RADS offers a standardised approach to both acquisition and reporting of mpMRI for BC, however, the best use of mpMRI in this setting and which cut-off levels are to be used for VI-RADS scoring still need to be determined [103]. To date, the VI-RADS score has been validated by several research groups, showing good diagnostic performance in detecting MIBC [108, 109].

A meta-analysis found that the pooled sensitivity and specificity of mpMRI with VI-RADS acquisition and scoring for predicting MIBC were 0.83 and 0.90, respectively. The diagnostic performance of VI-RADS is similar to the diagnostic performance of bladder MRI in determining MIBC based on a previous meta-analysis of 24 studies in which the pooled sensitivity and specificity were 0.92 (95% CI: 0.88–0.95) and 0.87 (95% CI: 0.78–0.93), respectively [110]. The analysis found substantial inter-reader agreement, with kappa (κ) values ranging from 0.81 to 0.92 [110]. A systematic review and meta-analysis (n = 1,016) showed a pooled weighted mean κ estimate of 0.83 (95% CI: 0.78–0.88) [111].

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% [112] and increases with more advanced disease [113].

Both CT and MRI may be used for assessment of local invasion by T3b disease, or higher, but they are unable to accurately diagnose microscopic invasion of perivesical fat (T2 vs. T3a) [114]. Contrast-enhanced CT using iodinated contrast media can be considered as an alternative to MRI when MRI is contraindicated [115].

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 [116-120]. 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 [121, 122].

Positron emission tomography (PET) combined with CT is increasingly being used in clinical practice and its exact role continues to be evaluated [123].

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 [124]. The sensitivity of CT urography for UTUC is 0.67–1.0 and specificity is 0.93–0.99 [125].

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 [126, 127]. The presence of enlarged LNs is highly predictive of metastases in UTUC [128].

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 [129]. The sensitivity of MR urography is 0.75 after contrast injection for tumours < 2 cm [129]. 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 [130] and liver metastases [131], 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 [132, 133]. Magnetic resonance imaging is more sensitive and specific for diagnosing bone metastases than bone scintigraphy [134, 135].

5.2.5 ***Future developments***

Evidence is accruing in the literature suggesting that ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT might have potential clinical use for staging metastatic BC [136, 137], but results of further trials are awaited before a recommendation can be made. The potential role of mpMRI as first-line test for local staging of BC rather than TURB has been demonstrated in a recent clinical trial [138].

Future trends might include image analysis radiomic-based techniques in predicting MIBC. A meta-analysis (n = 860) provided summary estimates for sensitivity and specificity in predicting MIBC of 82% (95% CI: 77–86%) and 81% (95% CI: 76–85%), respectively [139].

A clinical trial assessed the role of PET/CT in evaluating LN involvement in patients receiving neoadjuvant pembrolizumab. The performance of PET/CT did not justify its routine use in cN0 MIBC patients, but proved useful in optimising selection of MIBC patients suited for neoadjuvant immunotherapy strategies in a clinical trial setting [140].

The first study evaluating the performance of MRI in assessing therapeutic response to induction chemotherapy showed superiority of DWI over T2-weighted and dynamic contrast-enhanced (DCE)-MRI [141]. 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. Pre-operative MRI in different settings may provide useful information regarding treatment response. Potential future application of the VI-RADS score may include prediction of therapy response as well as peri-operative outcomes [142].

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
The diagnosis of upper tract UC depends on CT urography and ureteroscopy.	2b
In local staging, MRI is superior to CT in terms of differentiating T1 from T2 disease.	2b

Recommendations	**Strength rating**
In patients with confirmed muscle-invasive bladder cancer, use computed tomography (CT) of the chest, abdomen and pelvis for staging, including some form of CT urography with designated phases for optimal urothelial evaluation.	Strong
Use CT urography, unless it is contraindicated for reasons related to contrast administration or radiation dose; in that case use magnetic resonance imaging.	Strong

5.3 MIBC and health status

Complications from 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 frailty [143-145]. Frailty is a syndrome of reduced ability to respond to stressors. Patients with frailty have a higher risk of mortality and

negative side effects of cancer treatment [146]. 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 [147].

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%) [148]. 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 older patients using a standardised geriatric assessment, as well as carrying out a standard medical evaluation [149].

Sarcopenia has been shown to be an independent predictor for OS and CSS in a large multicentre study with patients undergoing RC for BC [150]. In order to predict CSM after RC in patients receiving neoadjuvant chemotherapy (NAC), sarcopenia should be assessed after completing the chemotherapy [151]. Other risk factors for morbidity include prior abdominal surgery, extravesical disease, and prior RT [152]. Female gender, an increased BMI and lower pre-operative albumin levels are associated with a higher rate of parastomal hernias [153]. Low pre-operative serum albumin is also associated with impaired wound healing, gastrointestinal (GI) complications and a decrease of recurrence-free and OS after RC [154, 155]. Therefore, it could be used as a prognostic biomarker for patients undergoing RC.

*5.3.1 **Evaluation of comorbidity, frailty and cognition***

Rochon *et al.*, have shown that evaluation of comorbidity provides a better indicator of life expectancy in MIBC than patient age [156]. Evaluation of comorbidity helps to identify factors likely to interfere with, or have an impact on, treatment and the evolution and prognosis of MIBC [157].

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 [158]. 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 [159].

Stratifying older patients according to frailty using a multidisciplinary approach will help select patients most likely to benefit from radical surgery and to optimise treatment outcomes [160]. There are many different screening tools available for frailty and local approaches can be used. Examples include the G8 and the Clinical Frailty Scale (See Table 5.1 and Figure 5.1 below).

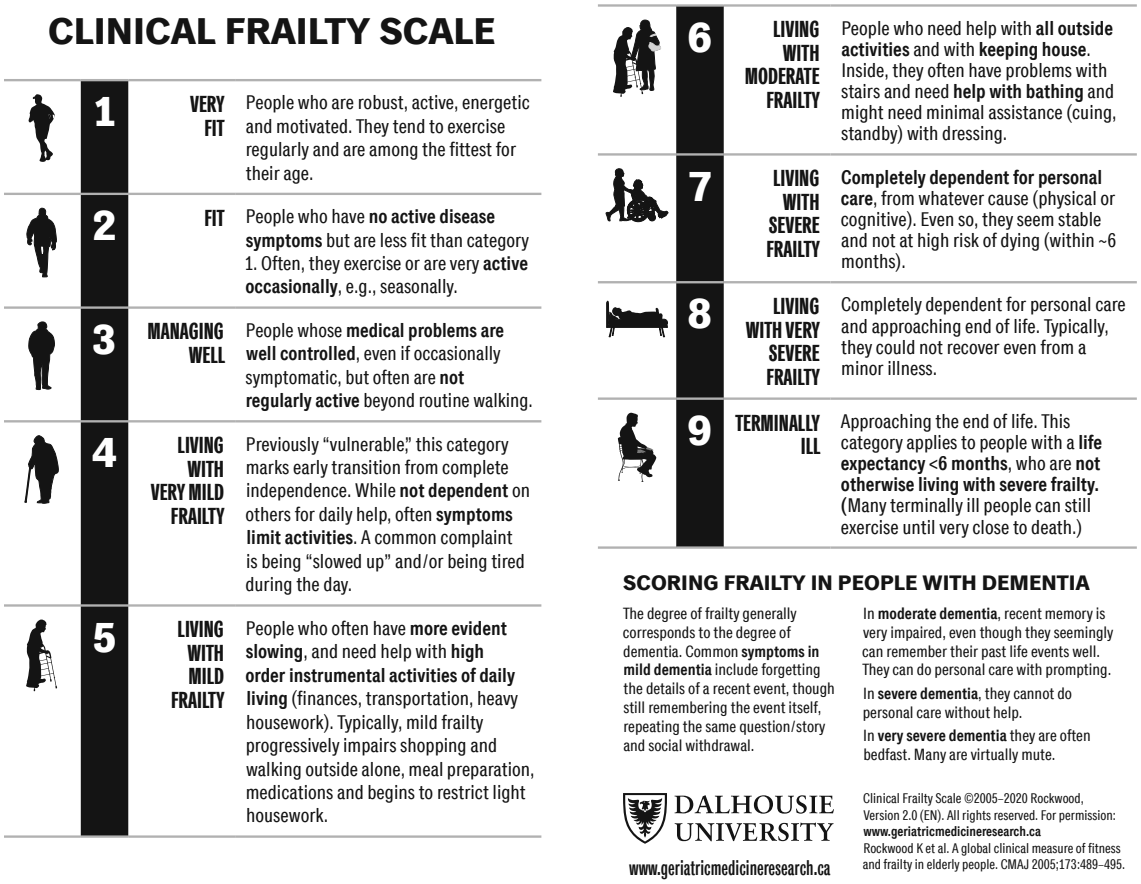
Cognitive impairment can be screened for using a tool such as the mini-COG (https://mini-cog.com/), which consists of three-word recall and a clock-drawing test, and can be completed within 5 minutes. A score of ≤ 3/5 indicates the need to refer the patient for full cognitive assessment. Patients with any form of cognitive impairment (e.g., Alzheimer's or vascular dementia) may need a capacity assessment of their ability to make an informed decision, which is an important factor in health status assessment. Cognitive impairment also predicts risk of delirium, which is important for patients undergoing surgery [161].

Table 5.1: G8 screening tool (adapted from [162])

	Items	Possible responses (score)
A	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing, or swallowing difficulties?	0 = severe decrease in food intake
		1 = moderate decrease in food intake
		2 = no decrease in food intake
B	Weight loss during the last 3 months?	0 = weight loss > 3 kg
		1 = does not know
		2 = weight loss between 1 and 3 kg
		3 = no weight loss
C	Mobility?	0 = bed or chair bound
		1 = able to get out of bed/chair but does not go out
		2 = goes out
D	Neuropsychological problems?	0 = severe dementia or depression
		1 = mild dementia
		2 = no psychological problems

E	BMI? (weight in kg)/(height in m^2)	0 = BMI < 19
		1 = BMI 19 to < 21
		2 = BMI 21 to < 23
		3 = BMI ≥ 23
F	Takes more than three prescription drugs per day?	0 = yes
		1 = no
G	In comparison with other people of the same age, how does the patient consider his/her health status?	0.0 = not as good
		0.5 = does not know
		1.0 = as good
		2.0 = better
H	Age	0 = ≥ 85
		1 = 80–85
		2 = < 80
	Total score	**0–17**

Figure 5.1: Clinical Frailty Scale©, Version 2.0* [163]



**Permission to reproduce the Clinical Frailty Scale© has been granted by the copyright holder.*

5.3.2 Comorbidity scales, anaesthetic risk classification and geriatric assessment

A range of comorbidity scales has been developed [164], seven of which have been validated [165-171]. 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 [172, 173], overall mortality [174], and CSM [147, 175-177]. Only the age-adjusted version of the CCI was correlated with both cancer-specific and other-cause mortality [178]. The age-adjusted CCI (Table 5.2) is the most widely used comorbidity index in cancer for estimating long-term survival and is easily calculated [179].

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 [180]. The Eastern Cooperative Oncology Group (ECOG) performance status (PS) scores and Karnofsky index have been

validated to measure patient activity [181]. Performance score is correlated with patient OS after RC [176] and palliative chemotherapy [182-184].

Patients who have screened positive for frailty or cognitive impairment benefit from an assessment by a geriatrician. This allows identification of geriatric syndromes and any scope for optimisation. The most complete protocol is the Comprehensive Geriatric Assessment (CGA) [185] which is useful in the care of cancer patients [186]. In BC, the CGA has been used to adapt gemcitabine chemotherapy in previously untreated older patients with advanced BC [187].

Table 5.2: 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–z 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 $\bar{Z} = 0.983^{Y}$ (where $\bar{Z}$ is the 10-year survival)

5.3.3 Summary of evidence and guidelines for comorbidity scales

Summary of evidence	LE
Chronological age is of limited relevance.	3
It is important to screen for frailty and cognitive impairment and provide a Comprehensive Geriatric Assessment (CGA) where optimisation is needed.	3

Recommendations	Strength rating
Base the decision on bladder-sparing treatment or radical cystectomy in older/frail patients with invasive bladder cancer on tumour stage and frailty.	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 [188]. 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 [189]. Lymphovascular invasion was present in 35% of the patients and correlated with a 1.5-fold higher risk of recurrence and CSM, independent of pathological stage and peri-operative chemotherapy. This correlation was even stronger in those patients with node-negative disease [190].

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 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) [190].

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 [188, 191-193].

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% [194].

Neutrophil-to-lymphocyte ratio (NLR) has emerged as a prognostic factor in UUT tumours [1] and other non-urological malignancies. In a pooled analysis of 21 studies analysing the prognostic role of NLR in BC, the authors correlated elevated pre-treatment NLR with OS, RFS and disease-free survival (DFS) in both localised and metastatic disease [195]. In contrast, a secondary analysis of the Southwest Oncology Group (SWOG) 8710 trial, a randomised phase III trial assessing cystectomy ± NAC in patients with MIBC, suggests that NLR is neither a prognostic nor a predictive biomarker for OS in MIBCs [196].

In patients with LN-positive disease, the American Joint Committee on Cancer (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) [197]. It has been suggested that LN density outperforms the AJCC-TNM staging system for LN-positive disease in terms of prognostic value [198, 199]. 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 [200].

Two studies investigated whether any of the reported LN-related parameters may be superior to the routinely used AJCC-TNM staging system [200, 201]. Whilst the 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 subtypes based on the Cancer Genome Atlas cohort

The updated Cancer Genome Atlas (TCGA) reported on 412 MIBCs and identified two main groups; luminal and basal-squamous - consisting of five mRNA expression-based molecular subtypes including luminal-papillary, luminal-infiltrated, luminal; basal-squamous; and neuronal, a subtype associated with poor survival in which the majority of tumours do not have small cell or neuroendocrine histology. Each subtype is associated with distinct mutational profiles, histopathological features and prognostic and treatment implications [202].

The basal-squamous subtype is characterised by expression of basal keratin markers, immune infiltrates and is felt to be chemosensitive. The different luminal subtypes are characterised by fibroblast growth factor receptor 3 (*FGFR3*) alterations (luminal-papillary [LumP]), epithelial-mesenchymal transition (EMT) markers (luminal-infiltrated) and may be associated with chemotherapy resistance [69, 70, 202, 203].

In 2019, a consensus on molecular subtype classification was reported [204]. 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 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 time, the classification should be considered as a research tool for retrospective and prospective studies until future studies 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. A novel 12-gene signature derived from patients in the TCGA utilising published gene signatures has been developed and externally validated to predict OS in MIBC [205]. Interestingly, a recently published analysis of molecular subtyping in MIBC demonstrated that although molecular subtypes reflect the heterogeneity of bladder tumours and are associated with tumour grade, clinical parameters outperformed subtypes for predicting outcome [206]. In the coming years, new insights into BC carcinogenesis may change our management of the disease and our ability to better predict outcomes [207]. Outside clinical trials, molecular subtyping, either by expression profiling or immunohistochemistry, is not yet part of routine clinical work-up awaiting more conclusive data.

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 [208]. Pietzak *et al.*, retrospectively analysed clinico-pathologic outcomes comparing 245 patients with clinical T2–4a N0M0 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 [209].

6.3.2 Molecular markers

Several predictive biomarkers have been investigated such as serum vascular endothelial growth factor [210], circulating tumour cells as well as defects in DNA damage repair (DDR) genes including *ERCC2, ATM, RB1* and *FANCC* that may predict response to cisplatin-based NAC [211, 212]. More recently, alterations in *FGFR3* including both mutations and gene fusions have been shown to be associated with response to *FGFR* inhibitors [213, 214].

More recent efforts have focused on markers for predicting response to immune checkpoint inhibition. Programmed death-ligand 1 (PD-L1) expression by immunohistochemistry has been evaluated in several studies with mixed results which may in part be related to the use of different antibodies and various scoring systems evaluating different compartments, i.e., tumour cells, immune cells, or both. The major limitation of PD-L1 staining relates to the significant proportion of PD-L1-negative patients that respond to immune checkpoint blockade. For example, in the IMvigor 210 phase II study of atezolizumab in patients with advanced/metastatic UC who progressed after platinum-based chemotherapy, responses were seen in 18% of patients with low/no PD-L1 expression [215]. At present, the only indication for PD-L1 testing relates to the use of immune checkpoint inhibitors as monotherapy in patients with locally advanced or metastatic UC unfit for cisplatin-containing chemotherapy who have not received prior therapy. In this setting, atezolizumab (approved by the FDA and EMA) or pembrolizumab (EMA approval only) should only be used in patients unfit for cisplatin-containing chemotherapy whose tumours overexpress PD-L1 (i.e., in case of atezolizumab; tumour-infiltrating immune cells [IC] covering ≥ 5% of the tumour area using the SP142 assay; in case of pembrolizumab, a combined positive score (CPS) of ≥ 10 using the Dako 22C33 platform) [216]. The FDA revised the label for pembrolizumab in patients with advanced UC with approval in first line only for patients not eligible for any platinum-based chemotherapy, however, irrespective of PD-L1 status.

Urothelial cancer is associated with a high tumour mutational burden (TMB) [217]. Both predicted neoantigen burden and TMB have been associated with response to immune checkpoint blockade in several malignancies. High TMB has been associated with response to immune checkpoint inhibitors in metastatic BC [215, 218]. Conflicting results have been seen in studies evaluating immune checkpoint inhibitors in the neoadjuvant setting with the Pembrolizumab as Neoadjuvant Therapy Before Radical Cystectomy in Patients With

Muscle-Invasive Urothelial Bladder Carcinoma (PURE)-01 study utilising pembrolizumab demonstrating an association of high TMB with response while there was no association with atezolizumab in the Phase II study investigating the safety and efficacy of neoadjuvant atezolizumab in MIBC (ABACUS) [219, 220].

Other markers that have been evaluated in predicting response to immune checkpoint inhibitors include molecular subtypes as discussed earlier, CD8 expression by immunohistochemistry and other immune gene cell signatures. Recent work has focused on the importance of stroma including the role of transforming growth factors (TGFs) in predicting response to immune checkpoint blockade [221, 222]. Most recently, Powles *et al.*, have reported on the potential for ctDNA to guide the use of adjuvant immunotherapy (IO) in UC [223]. In 581 patients from a phase III RCT of adjuvant atezolizumab vs. observation in UC, ctDNA testing at the start of therapy identified 214 (37%) patients who were positive for ctDNA and who had poor prognosis (observation arm HR = 6.3, 95% CI: 4.45–8.92; p < 0.0001). Patients who were positive for ctDNA had improved DFS and OS in the atezolizumab arm vs. the observation arm (DFS HR = 0.58 [95% CI: 0.43–0.79]; p = 0.0024, OS HR = 0.59 [95% CI: 0.41–0.86]). There was no difference in DFS or OS between treatment arms for patients who were negative for ctDNA. The rate of ctDNA clearance at week 6 was higher in the atezolizumab arm (18%) than in the observation arm (4%) (p = 0.0204). An ongoing clinical trial (IMvigor011) is evaluating atezolizumab as adjuvant therapy in patients with high-risk MIBC who are ctDNA positive following cystectomy [224]. Although promising, there are currently no validated predictive molecular markers that are routinely used in clinical practice. Further validation studies are awaited.

6.4 Conclusion

The updated TCGA and other efforts have refined our understanding of the molecular underpinnings of BC biology. Molecular subtypes, immune gene signatures as well as stromal signatures may ultimately have an important role in predicting response to IO. Although PD-L1 expression by immunohistochemistry and TMB have demonstrated predictive value in certain settings, additional studies are needed. Prospectively validated prognostic and predictive molecular biomarkers will present valuable adjuncts to clinical and pathological data, but large phase III RCTs with long-term follow-up will be needed to clarify the many questions remaining.

6.5 *Summary of evidence for urothelial markers*

Summary of evidence	LE
There is insufficient evidence to use TMB, molecular subtypes, immune or other gene expression signatures for the management of patients with urothelial cancer.	-

7. DISEASE MANAGEMENT

7.1 Neoadjuvant therapy

7.1.1 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 [225-229]. To improve these results in patients with cN0M0 disease, cisplatin-based NAC has been used since the 1980s [225-231].

7.1.2 Role of cisplatin-based chemotherapy

There are theoretical advantages and disadvantages of administering chemotherapy before planned definitive surgery to patients with resectable muscle-invasive cN0M0 UC of the bladder:

- 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 may respond to NAC and have a favourable pathological response as determined mainly by achieving ypT0, ≤ ypT1, ypN0 and negative surgical margins.
- Delayed cystectomy might compromise the outcome in patients not sensitive to chemotherapy [232-234]. A comparative survival analysis of patients treated with NAC and RC vs. RC alone based on data from the National Cancer Database showed that organ-confined disease (≤ pT2) after NAC was associated with decreased risk of death (HR: 0.85, 95% CI: 0.79–0.91) compared to RC alone, whereas > pT2 was associated with increased risk of death (HR: 1.46, 95% CI: 1.34–1.60) [235]. However, there are

no prospective trials indicating that delayed surgery due to NAC has a negative impact on survival. In the phase III VESPER trial, comparing gemcitabine/cisplatin (GC) vs. high-dose-intensity methotrexate, vinblastine, doxorubicine and cisplatin (HD-MVAC) in the peri-operative setting, approximately 90% of patients proceeded to surgery (with median delay of 48 days for GC and 51 days for ddMVAC) [236].

- 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 [237]. 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 [238].
- Clinical staging using bimanual palpation, CT or MRI may result in over- and understaging and have a staging accuracy of only 70% [78]. Overtreatment is a possible negative consequence.
- Gender may have an impact on chemotherapeutic response and oncologic outcomes [239, 240].
- 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 [237, 241-249].

7.1.2.1 Summary of available data

Several phase III RCTs addressed the potential survival benefit of NAC administration [237, 241-246, 250-254]. 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 [247-249]. In a meta-analysis including updated patient data from 11 randomised trials (n = 3,005), a significant survival benefit was shown in favour of NAC [249]. 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 including data from 427 new patients and updated information from 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 [255]. Only cisplatin-combination chemotherapy with at least one additional chemotherapeutic agent resulted in a meaningful therapeutic benefit [247, 249]; the regimens tested were methotrexate, vinblastine, adriamycin (epirubicin) plus cisplatin (MVA(E)C), cisplatin, methotrexate plus vinblastine (CMV), cisplatin plus methotrexate (CM), cisplatin plus adriamycin and cisplatin plus 5-fluorouracil (5-FU) [256].

The updated analysis of a large phase III RCT [241] 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;
- the addition of neoadjuvant CMV provided no benefit for locoregional control and locoregional DFS, independent of the definitive treatment.

More modern chemotherapeutic regimens such as GC have shown similar pT0/pT1 rates as methotrexate, vinblastine, adriamycin plus cisplatin in retrospective series and pooled data analyses [256-259]. Modified ddMVAC was tested in two small single-arm phase II studies demonstrating high rates of pathologic complete remission [260, 261]. Moreover, a large cross-sectional analysis showed higher rates of down-staging and pathological complete response for ddMVAC [262].

The recently reported results from the GETUG/AFU V05 VESPER RCT of perioperative chemotherapy with 6 cycles of ddMVAC vs. 4 cycles of GC in 493 patients (437 neoadjuvant and 56 adjuvant) demonstrated similar pathologic response rates (ypT0N0) in patients treated with ddMVAC 42% and GC 36% (p = 0.2). The < ypT2N0 rate was 63% and 50% in the ddMVAC and GC patients, respectively. Progression-free survival was significantly improved in the NAC receiving ddMVAC as compared to GC (HR = 0.70, 95% CI: 0.51–0.96; p = 0.025), however, the PFS endpoint was not significant in the entire perioperative chemotherapy population (HR: 0.77, 95% CI: 0.57–1.02; p = 0.077). Dose-dense MVAC was associated with more severe asthenia and GI side effects than GC [236]. Another dose-dense regimen using GC was reported in two small phase II trials [263, 264]. 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 [263]. This approach is therefore not recommended outside of clinical trials.

As an alternative to the standard dose of cisplatin-based NAC with 70 mg/m^2 on day 1, split-dose modifications regimens are often used with 35 mg/m^2 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 [265].

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 [208].

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 squamous cell carcinoma did not benefit from NAC [266]. A 2019 systematic review showed benefit of NAC for patients with micropapillary-, plasmacytoid-, sarcomatoid-, and mixed variants but especially for patients with neuroendocrine tumours [68].

7.1.3 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 predictive of outcome. Although mpMRI 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 [107]. So far PET/CT, MRI or DCE-MRI cannot accurately assess treatment response [267-270]. 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 [271, 272]. 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 [273-275] (see Chapter 6 - Markers).

7.1.4 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 also in the neoadjuvant setting; either as monotherapy or in combination with chemotherapy or CTLA-4 checkpoint inhibition. Data from two phase II trials have been presented with encouraging results [219, 220]. The results of the phase II trial using the PD-1 inhibitor pembrolizumab reported a complete pathological remission (pT0) in 42% and pathological response (< pT2) in 54% of patients, whereas in the single-arm phase II trial with atezolizumab a pathologic complete response rate of 31% was reported. In a recent study evaluating neoadjuvant GC plus pembrolizumab in MIBC, the primary endpoint was met with 56% of 46 evaluable patients downstaged to < ypT2N0 and 36% achieving ypT0N0 [276]. However, immunotherapy alone, or in combination, is not yet approved in the neoadjuvant setting.

7.1.5 Summary of evidence and guidelines for neoadjuvant therapy

Summary of evidence	LE
Neoadjuvant cisplatin-containing combination chemotherapy improves OS (5–8% at five years).	1a
Neoadjuvant treatment may have a major impact on OS in patients who achieve ypT0 or ≤ ypT2.	2a
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.	-

Recommendations	Strength rating
If eligible for cisplatin-based chemotherapy, offer neoadjuvant cisplatin-based combination chemotherapy to patients with muscle-invasive bladder cancer (T2-T4a, cN0 M0).	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

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

7.2.1 ***Post-operative radiotherapy***

Given the high rates of local-regional failure after RC in patients with locally advanced (pT3–4) BC, estimated at ~30%, as well as the high risk of distant failure and poor survival for these patients, there is an interest in adjuvant therapies that address both the risk of local and distant disease. Data on adjuvant RT after RC are limited and further prospective studies are needed, but a more recent phase II trial compared adjuvant sequential chemotherapy and radiation vs. adjuvant chemotherapy alone in 120 patients with locally advanced disease and negative margins after RC (with one or more risk factors: ≥ pT3b, grade 3, or node-positive), in a study population with 53% UC and 47% SCC. Addition of adjuvant RT to chemotherapy alone was associated with a statistically significant improvement in local relapse-free survival (at 2 years 96% vs. 69% favouring the addition of RT). Disease-free survival and OS also favoured the addition of RT, but those differences were not statistically significant and the study was not powered for those endpoints. Late-grade ≥ 3 GI toxicity in the chemoradiation arm was low (7% of patients) [277].

A 2019 systematic review evaluating the efficacy of adjuvant radiation for BC or UTUC found no clear benefit of adjuvant radiation following radical surgery (e.g., cystectomy), although the combination of adjuvant radiation with chemotherapy may be beneficial in locally advanced disease [278].

While there are no conclusive data demonstrating improvements in OS it is reasonable to consider adjuvant radiation in patients with pT3/pT4 pN0–2 urothelial BC following RC, although this approach has been evaluated in only a limited number of studies. Radiation fields should encompass areas at risk for harbouring residual microscopic disease based on pathologic findings at surgery and may include cystectomy bed and pelvic LNs. Doses in the range of 45 to 50.4 Gy may be considered. For patients who have not had prior NAC, it may be reasonable to sandwich adjuvant radiation between cycles of adjuvant chemotherapy. The safety and efficacy of concurrent radiosensitising chemotherapy in the adjuvant setting needs further study.

7.2.2 ***Pre-operative radiotherapy***

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 [279]. The OS data were difficult to interpret since chemotherapy was used in a subset of patients only and more than 50% of patients (241/475) did not receive the planned treatment and were excluded from the final analyses. Two smaller studies using a dose of 20 Gy showed only a small survival advantage in ≥ T3 tumours [280, 281]. Two other small trials confirmed downstaging after pre-operative RT [282, 283].

A meta-analysis of five RCTs showed a difference in 5-year survival (OR: 0.71, 95% CI: 0.48–1.06) in favour of pre-operative RT [284]. 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.

A more recent RCT, comparing pre-operative vs. post-operative RT and RC (n = 100), showed comparable OS, DFS and complication rates [285]. Approximately half of these patients had UC, while the other half had SCC.

In general, such older data is limited in being able to provide a robust evidence base for modern guideline recommendations.

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

Summary of evidence	**LE**
No contemporary data exists to support that pre-operative RT for operable 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 RC.	3
Addition of adjuvant RT to chemotherapy is associated with an improvement in local relapse-free survival following cystectomy for locally-advanced bladder cancer (pT3b–4, or node-positive).	2a

Recommendations	Strength rating
Do not offer pre-operative radiotherapy (RT) for operable muscle-invasive bladder cancer since it will only result in down-staging, but will not improve survival.	Strong
Do not offer pre-operative RT when subsequent radical cystectomy (RC) with urinary diversion is planned.	Strong
Consider offering adjuvant radiation in addition to chemotherapy following RC, based on pathologic risk (pT3b–4 or positive nodes or positive margins).	Weak

7.3 Radical surgery and urinary diversion

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

7.3.1.1 Introduction

Radical cystectomy is the standard treatment for localised MIBC in most Western countries [225, 286]. Increased recognition of the central patient role as a healthcare consumer and a greater focus on patients' QoL contributed to an increasing trend of utilising bladder-preserving treatment modalities, such as radio- and/or chemotherapy (see Section 7.5). Performance status and life expectancy influence the choice of primary management as well as the type of urinary diversion with RC being reserved for patients with a longer life expectancy without concomitant disease and a better PS. Frailty, nutritional status and decreased kidney function are conditions significantly related to an increased risk of post-operative adverse events (AEs) [287-289].

7.3.1.2 Radical cystectomy: timing

A 2020 meta-analysis including 19 studies concluded that a delay of > 3 months has a negative effect on OS (HR: 134, 95% CI: 1.18–1.53). Authors highlighted the lack of standardisation how delays were defined in the included studies which prohibited defining a clear cut-off time, although most studies used a cut-off of < 3 months [290]. Overall conclusion was that BC patients scheduled for RC should be treated without delays to maximise survival.

*7.3.2 **Radical cystectomy: indications***

Traditionally, RC was recommended in patients with T2–T4a, N0–Nx, M0 disease [286]. Other indications include BCG-refractory, BCG-relapsing and BCG-unresponsive NMIBC (see EAU Guidelines on Non-muscle-invasive Bladder Cancer [2]), as well as extensive papillary disease that cannot be controlled with TURB and intravesical chemotherapy alone.

Salvage cystectomy is indicated in non-responders to conservative therapy, recurrence after bladder-sparing treatment, and non-UC. It is also used as a purely palliative intervention, including for fistula formation, pain and recurrent visible haematuria (see Section 7.4.1 - Palliative cystectomy).

*7.3.3 **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 [291, 292].

7.3.3.1 Radical cystectomy in men

In men, standard RC includes removal of the bladder, prostate, seminal vesicles, distal ureters, and regional LNs.

7.3.3.1.1 Concomitant prostate cancer

Prostate cancer is found in 21–50% of male patients undergoing RC for BC [293-296]. Incidentally discovered clinically significant prostatic adenocarcinoma did not alter survival [295, 296]. Pathological reporting of the specimens should follow the recommendations as presented in the EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer [297].

7.3.3.1.2 Sexual-preserving techniques

Four main types 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 [298-308] and three single-arm case series [309-311]. In the majority of cases, an 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 RC 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.

7.3.3.1.3 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: • organ-confined disease; • absence of any kind of tumour at the level of the prostate, prostatic urethra or bladder neck.	Strong

7.3.3.2 Radical cystectomy in women

In women, standard RC includes removal of the bladder, the entire urethra and adjacent vagina, uterus, distal ureters, and regional LNs [312]. Pelvic floor disorders, sexual and voiding dysfunction in female patients are prevalent after RC [313]. 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 [314, 315]. 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 or patients with Lynch syndrome), salpingooophorectomy should be advised after childbearing and to all women over 40 years of age [316]. 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 as removal of the uterus predisposes to an anterior or posterior vaginal prolapse. In case of an already existing prolapse of the uterus, either isolated or combined with a vaginal prolapse, removing the uterus will be beneficial. 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 [292].

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 [317].

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

Summary of evidence	**LE**
Data regarding pelvic organ-preserving RC 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 organ-preserving techniques to women motivated to preserve their sexual function since the majority will benefit.	Weak
Select patients based on: • absence of tumour in the area to be preserved to avoid positive soft tissue margins; • absence of pT4 urothelial carcinoma.	Strong

*7.3.4 **Lymphadenectomy: role and extent***

Controversies in evaluating the clinical significance of lymphadenectomy (LND) are related to two main aspects of nodal dissection: therapeutic procedure and/or staging instrument.

Two important autopsy studies have been performed for RC 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 [318].

The second autopsy study focused on the nodal yield when super-extended pelvic LND was performed. Substantial inter-individual differences were found with counts ranging from 10 to 53 nodes [319]. 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 [320-324]. Mapping studies also found that skipping lesions at locations above the bifurcation of the aorta without more distally located LN metastases is rare [324, 325].

The optimal extent of LND has not been established to date. Standard LND 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 [326]. Extended LND 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 LND [326-330]. A super-extended LND extends cranially to the level of the inferior mesenteric artery [331, 332].

In order to assess how and if cancer outcome is influenced by the extent of LND in patients with clinical N0M0 MIBC, a systematic review of the literature was undertaken [333]. Out of 1,692 abstracts retrieved and assessed, nineteen studies fulfilled the review criteria [326-330, 332, 334-346]. 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 [347, 348]. No difference in outcome was reported between extended and super-extended LND in the two high-volume-centre studies identified [332, 344]. The LEA trial, a prospective phase III RCT, including 401 patients with a median follow-up of 43 months reported [349]. 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 LND 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 [350]. In retrospective studies removal of at least ten LNs has been postulated as sufficient for evaluation of LN status, as well as being beneficial for OS [351]. 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 [352]. 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 [333, 353].

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

A number of recent systematic reviews comparing open RC (ORC) and robot-assisted RC (RARC) reach similar conclusions; RARC has an approximately one-day shorter length of hospital stay (LOS) and less blood loss, but a longer operative time. Complication rates seem similar for both approaches but all published reviews suffer from low quality data.

In minimally-invasive cystectomy, with increasing age, LOS is markedly shorter; up to 2.56 days in patients over 80 years old [354].

Although the low level of evidence of the studies included in these reviews remains a major limitation, a recent Cochrane review incorporating data from all five published RCTs corroborates most findings [355]. Time to recurrence, positive surgical margin rates, grade 3–5 complications and QoL were 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, LND and urinary reconstruction) reached similar conclusions [356]. Additionally, they reported that RARC was associated with increased costs, although compared to laparoscopic RC (LRC) there are ergonomic advantages for the surgeon. For both techniques, surgeons' experience and institutional volume strongly predicted outcome. According to the literature, proficiency is reached after 20–250 cases. However, after statistical modelling, the Pasadena Consensus Panel suggested 30 cases but they also concluded that challenging patients (high BMI, post chemotherapy or RT, pelvic surgery, T4 or bulky tumours or positive nodes) should be performed by experienced robotic surgeons only. Safety of RC after RT was confirmed by a small retrospective study (n = 46) [357]. In experienced hands the percentage of 90-day (major) complications after robotic cystectomy was independent of previous RT [358].

Data on post-RC uretero-enteric stricture rates for both ORC and RARC remain inconclusive. Results are mainly reported by high-volume centres or derive from population-based studies with a large variety of endpoints and poor controlling of potential confounders, making comparison difficult [358-363]. From a surgical technique perspective, the main risk-factor for complications comparing ORC and RARC may be tissue handling; the same applies to different diversion techniques in RARC patients, as those managed by extracorporeal diversion (RARC-ECUD) tend to have more strictures compared to intracorporeal diversion (RARC-ICUD) [362]. This is explained by the need for more extensive dissection of ureter in RARC-ECUD, more tension, resulting in impaired blood supply [364, 365].

Positive surgical margins, as a surrogate for oncological outcome, are comparable between RARC and ORC, although with low certainty [355]. Recurrence-free survival, CSS and OS have been documented as similar

in all RCTs including the largest RAZOR (Robot-assisted radical cystectomy versus open radical cystectomy in patients with bladder cancer) trial (n = 302) [366]. Age over 70, poor PS and major complications were significant predictors of 36-month PFS whilst stage and positive margins were significant predictors of recurrence, PFS and OS. The surgical approach was not a significant predictor of any outcome. A larger (n = 595) single-centre study with a median follow-up of over five years also found comparable recurrence and survival data, including atypical recurrences (defined as one or a combination of the following: port-site metastasis or peritoneal carcinomatosis) [367]. However, recently, port-site metastases and atypical recurrences were reviewed by Mantica *et al.* [368]. Based on 31 studies and 6,720 evaluable patients, 105 patients (1.63%) were identified with an atypical recurrence, of which 63 (60%) were peritoneal carcinomatosis and 11 (10.5%) port-site metastases. The authors acknowledge, however, that these results may be linked to publication bias and retrospective study design of the included studies. Wei *et al.*, detected residual cancer cells in pelvic washing specimens during or after, but not before, RARC in approximately half of the patients (9/17), which was associated with aggressive variant histology and cancer recurrence. These findings need confirmation in larger studies [369].

The largest RCT to date, the RAZOR trial, supports all of the above findings showing RARC to be non-inferior to ORC in terms of 2-year PFS (72.3% vs. 71.6%), AEs (67% vs. 69%) and QoL [370]. A systematic review of five RCTs including the RAZOR trial supports all of the above findings showing RARC to be non-inferior to ORC with regard to time to recurrence, rates of major complications, QoL, and positive surgical margin rates (all low-certainty evidence) [371].

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); the latter was associated with a shorter operative time and fewer blood transfusions but more high-grade complications, which, again, decreased over time [372]. A retrospective report from a high-volume centre found less (major) complications after intracorporeal reconstruction (n = 301) as compared to extracorporeal reconstruction (n = 375) and open RC (n = 272) [373]. It is important to note that, although an intracorporeal neobladder is a very complex robotic procedure [374], the choice for neobladder or cutaneous diversion should not depend on the surgical approach.

An interim analysis of a small RCT of ORC (n = 27) vs. RARC with intracorporeal urinary diversion (n = 24), found comparable results at one year after surgery for most health-related quality of life (HRQoL) domains. Patients receiving ORC were more likely to experience a decline in role functioning and higher symptoms scale, while RARC-intracorporeal urinary diversion patients were more likely to report significant increases in urinary symptoms and problems [375]. A prospective, non-randomised, multicentre comparative effectiveness study showed no statistically significant differences after 12-months between ORC (n = 154) and RARC (n = 159) in terms of complications (67 vs. 64%) and HRQoL [376].

7.3.5.1 Laparoscopic radical cystectomy versus robot-assisted radical cystectomy

For LRC a review including sixteen studies came to similar conclusions as described for RARC [374]. As compared to ORC, LRC had a significantly longer operative time, fewer overall complications, less blood transfusions and analgesic use, less blood loss and a shorter LOS. 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 [377].

The CORAL study was a small single-centre RCT comparing open (n = 20) vs. robotic (n = 20) vs. laparoscopic (n = 19) RC [378, 379]. 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.

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

Summary of evidence	**LE**
Robot-assisted RC 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 ORC.	1
Robotic cystectomy and open cystectomy may result in similar rates of (major) complications.	2
Most endpoints, if reported, including intermediate-term oncological endpoint and QoL, 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	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

*7.3.6 **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 (infrequently used);
- urethral diversion, which includes various forms of GI pouches attached to the urethra as a continent orthotopic urinary diversion (neobladder, orthotopic bladder substitution);
- rectosigmoid diversions, such as uretero-(ileo-)rectostomy (infrequently used).

Different types of segments of the intestinal tract have been used to reconstruct the urinary tract, including the stomach, ileum, colon and appendix [380].

Several studies have compared certain aspects of HRQoL such as sexual function, urinary continence and body image in patient cohorts with different types of urinary diversion [381]. However, further research evaluating the impact of pre-operative tumour stage, functional- and socio-economic status, and time interval to primary surgery are needed.

7.3.6.1 Patient selection and preparations for 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).

Ensuring that patients make a well-informed decision about the type of urinary diversion is associated with less decision regret post-operatively, independent of the method selected [382].

Diagnosis of an invasive urethral tumour prior to cystectomy leads to urethrectomy which could be a contraindication for a neobladder reconstruction. If indicated; in males, in case of CIS and extension of tumour in the prostatic urethra, urethral frozen section has to be performed on the cystoprostatectomy specimen just under the verumontanum and on the inferior limits of the bladder neck; in females a urethral frozen section has to be taken just below 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 [383].

In the presence of positive LNs, orthotopic neobladder can nevertheless be considered in case of N1 involvement (metastasis in a single node in the true pelvis) but not in N2 or N3 tumours [384].

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 a neobladder compared to those with conduits or continent cutaneous diversions [385].

For cystectomy, general preparations are necessary as for any other major pelvic and abdominal surgery. If the urinary diversion is constructed from GI segments, the length or size of the respective segments and their pathophysiology when storing urine must be considered [386]. Despite the necessary interruption and re-anastomosis of the bowel, formal bowel preparation may not be necessary [387]. Bowel recovery time can be reduced by the use of early mobilisation and early oralisation, GI stimulation with metoclopramide and chewing gum [388]. 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 [389].

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% ($p = 0.003$) [390].

A multicentre randomised placebo-controlled trial showed that patients receiving alvimopan, a peripherally acting μ-opioid receptor antagonist, had quicker bowel recovery compared to patients receiving placebo [391]. 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-randomised study showed a significant lower 30-day VTE incidence rate in patients treated for 28 days with enoxaparin compared to patients without prophylaxis [392]. 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) [393, 394].

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;
- severe impaired liver or renal function;
- urothelial carcinoma positive 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 [395].

7.3.6.2 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 [396]. Age alone is not a criterion for offering continent diversion [395, 397]. 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 [398-401]. Nevertheless, no RCTs comparing conduit diversion with neobladder or continent cutaneous diversion have been performed.

A retrospective study including 1,383 patients showed that the risk of a decline in estimated glomerular filtration rate (eGFR) did not significantly differ after ileal conduit vs. neobladder in patients with pre-operative chronic kidney disease 2 (eGFR 60–89 mL/min/1.73 m^2) or 3a (eGFR 45–59 mL/min/1.73 m^2) [402]. Only age and anastomotic strictures were found to be associated with a decline in eGFR.

7.3.6.2.1 Uretero-cutaneostomy

Ureteral diversion to the abdominal wall is the simplest form of cutaneous diversion. Operating time, complication rate, blood loss, transfusion rate, stay at intensive care and length of hospital stay are lower in patients treated with ureterocutaneostomy as compared to ileal conduit [403, 404]. Therefore, in frail patients and/or in those with a solitary kidney who need a supravesical diversion, uretero-cutaneostomy is the preferred procedure [405, 406]. 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 [403]. However, maintaining a catheter for stoma patency might relate to an elevated incidence of urinary tract infections and therefore impair QoL [407, 408]. Nevertheless, in carefully selected elderly patients, all other forms of wet and dry urinary diversions, including orthotopic bladder substitutions, are possible [409].

Technically, in case patients have both kidneys; 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 abdominal wall creating a stoma. Due to the smaller diameter of the ureters, stoma stenosis has been observed more frequently for this technique as compared to using small or large bowel to create an intestinal stoma [405].

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) [410].

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 [411].

7.3.6.2.2 Ileal conduit

The ileal conduit is an established option with well-known/predictable results. However, up to 48% of patients develop early complications including UTIs, pyelonephritis, ureteroileal leakage and stenosis [411]. The main complications in long-term follow-up studies are stomal complications in up to 24% of patients and functional

and/or morphological changes of the UUT in up to 30% [411-413]. 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) [414]; 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.

7.3.6.2.3 Orthotopic neobladder

According to Dutch-, German- and Spanish bladder cancer registry data, an orthotopic bladder substitution to the urethra is used in approximately 10–20% of both male and female patients. 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 [226, 286, 395]. However, in elderly patients (> 80 years) it is rarely performed even in high-volume expert centres [415, 416].

The terminal ileum is the GI segment most often used for bladder substitution. There is less experience with the ascending colon, including the caecum, and the sigmoid [286]. 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 [417, 418]. In two studies of 1,054 and 1,300 patients [395, 419], long-term complications included diurnal (8–10%) and nocturnal (20–30%) incontinence, uretero-intestinal 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 [420]. Urethral recurrence in neobladder patients seems rare (1.5–7% in both male and female patients) [395, 421]. These results indicate that neobladder in male and female patients does not compromise the oncological outcome of cystectomy. It remains debatable whether patient's QoL for neobladder is better compared to non-continent urinary diversion [422, 423].

Continent cutaneous urinary diversion (a low-pressure detubularised ileal reservoir for self-catheterisation) and uretero-rectosigmoidostomy are rarely used techniques nowadays, due to their high complication rates, including stomal stenosis, incontinence in the continent cutaneous diversion, UUT infections and stone formation in case of uretero-rectosigmoidostomy [424].

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 [418, 425]. 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 [426]. In women undergoing RC the rate of concomitant urethral malignancy has been reported to range from 12–16% [427]. Localisation of the primary tumour at the bladder neck correlated strongly with concomitant urethral malignancy. In addition, tumour involving the bladder neck and urethra tended to be associated with a higher risk of advanced stage and nodal involvement [428].

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 [429, 430]. In selected patients, such as patients with a single kidney, uretero-cutaneostomy is surgically the least burdensome type of diversion. Recommendations related to RC and urinary diversions are listed in Section 7.3.10.

*7.3.7 **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 [226, 396, 398, 431, 432]. In a large single-centre series early complications (within three months of surgery) were seen in 58% of patients [396]. Late morbidity was usually linked to the type of urinary diversion (see also above) [399, 433]. 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 [434]. 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 [431, 435-439].

Table 7.1: Management of neobladder morbidity (30-64%) [440]

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 day 1) Chewing gum Avoid fluid excess and hypovolemia (provoke splanchnic hypoperfusion)
		Post-operative nausea and vomiting	Antiemetic agent (decrease opioids) Nasogastric intubation
		Urinary infection	Antibiotics, no ureteral catheter removal Check the 3 drainages (ureters and neobladdder)
		Ureteral catheter obstruction	Inject 5 cc saline in the ureteral catheter to resolve the obstruction Increase volume infusion to increase diuresis
		Intra-abdominal urine leakage (anastomosis leakage)	Check drainages and watchful waiting
		Anaemia well tolerated	Martial treatment (give iron supplement)
		Late complications:	
		Non compressive lymphocele	Watchful waiting
		Mucus cork	Cough Indwelling catheter to remove the obstruction
		Incontinence	Urine analysis (infection), echography (post-void residual) Physiotherapy
		Retention	Drainage and self-catheterisation education
Grade II	Requiring pharmacological treatment with drugs other than those allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.	Anaemia badly tolerated or if myocardial cardiopathy history	Transfusion[1,2]
		Pulmonary embolism	Heparinotherapy[3]
		Pyelonephritis	Antibiotics 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	Antibiotics 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 antibiotics
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 [441]. 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 [442].*

[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 VTE [443].*

[3] *Hammond and co-workers reviewed 20,762 cases of VTE after major surgery and found cystectomy patients to have the second highest rate of VTE among all cancers studied [444]. 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 [445].*

7.3.8 ***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% [413]. External validation of post-operative nomograms for BC-specific mortality showed similar results, with bladder-CSS of 62% [446].

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 [212]. However, the 5-year RFS in node-positive patients who underwent cystectomy was considerably less at 34–43% [447, 448]. 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 [225].

A trend analysis based on 148,315 BC patients identified in the SEER database between 1973 and 2009 showed increased stage-specific 5-year survival rates for all stages, except for metastatic disease [449].

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

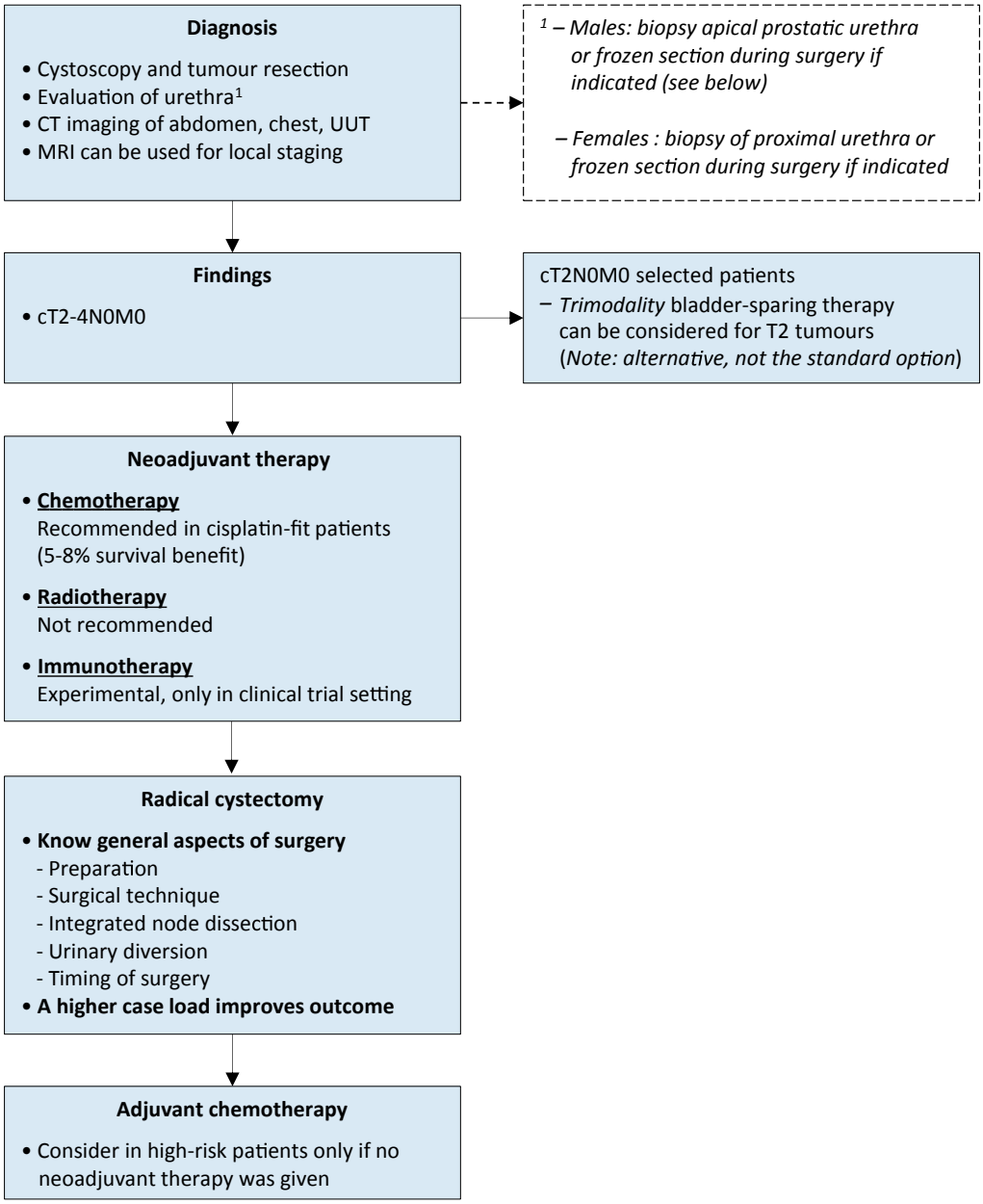
In a systematic review including 40 retrospective studies and 560,00 patients, the impact of hospital and/ or surgeon volume and peri-operative outcomes of RC was assessed [450]. A higher hospital volume was associated with lower in-hospital, 30-day and 90-day mortality. In addition, higher volume hospitals were more likely to have lower positive surgical margins, higher number of LNDs and neobladders and lower complication rates. For surgeon volume, less evidence was available. This study suggested performing at least 10 RCs per centre annually and preferably more than 20. Recently, a nationwide analysis of the Dutch Cancer Registry including almost 9,500 patients between 2008 and 2018 reported decreased 30- and 90-day mortality rates for annual hospital volumes of > 30 RCs. Furthermore, this study showed no true plateau curve for 30- and 90-day mortality beyond 30 RCs supporting the 'more is better' principle [451, 452].

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

Summary of evidence	LE
Ensuring that patients are well informed about the various urinary diversion options prior to making a decision may help prevent or reduce decision regret, independent of the method of diversion selected.	3
Higher RC hospital volume is associated with lower post-operative mortality rates and higher quality of care.	3
Radical cystectomy includes removal of regional LNs.	3
There are data to support that extended 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
The use of extended venous thromboembolism (VTE) prophylaxis significantly decreases the incidence of VTE 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, unless the patient receives neoadjuvant chemotherapy.	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 to patients with T2–T4a, N0M0 disease or high-risk non-muscle-invasive bladder cancer.	Strong
Perform a lymph node dissection as an integral part of RC.	Strong
Do not preserve the urethra if margins are positive.	Strong

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



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

7.4 Unresectable tumours

*7.4.1 **Palliative cystectomy***

Unresectable 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. If control of the symptoms is not possible by less invasive methods, patients may be offered a palliative cystectomy with urinary diversion or urinary diversion only. Palliative cystectomy carries the greatest morbidity, particularly in patients with a poor PS. In a series of 74 patients who underwent palliative cystectomy, severe complications (Clavien-Dindo grade ≥ 3) occurred in 30%. The 30-day mortality rate was 9% and at eight months follow-up, 70% had died [453].

7.4.1.1 Guidelines for unresectable tumours

Recommendations	Strength rating
Offer radical cystectomy as a palliative treatment to patients with locally advanced tumours (T4b).	Weak
Offer palliative cystectomy to patients with symptoms if control is not possible by less invasive methods.	Weak

*7.4.1.2 EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [8, 9]**

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.
Chemoradiation should be given to improve local control in cases of inoperable locally advanced tumours.

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

*7.4.2 **Supportive care***

7.4.2.1 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.

7.4.2.2 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 [454]. This 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 [454]. 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% [455]. 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% [454]. Radical surgery is a last resort and includes cystectomy and diversion (see above, Section 7.4.1).

7.5 Bladder-sparing treatments for localised disease

*7.5.1 **Transurethral resection of bladder tumour***

Transurethral resection of bladder tumour alone in MIBC patients 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 [456]. 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% in this group [457]. A disease-free status at re-staging TURB appears to be crucial in making the decision not to perform RC [458, 459]. A prospective study by Solsona *et al.*, including 133 patients with radical TURB and re-staging negative biopsies, reported a 15-year follow-up [459]. Thirty per cent of patients 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 trimodality (TMT) bladder-preserving approach.

7.5.1.1 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

*7.5.2 **External beam radiotherapy***

Current RT techniques with soft-tissue matching and image guidance result in superior bladder coverage and a reduced integral dose to the surrounding tissues. The target total dose (to bladder and/or bladder tumour) for curative EBRT in BC is 64–66 Gy [460, 461]. A reasonable alternative is moderately hypofractionated EBRT to 55 Gy in 20 fractions which has been suggested to be non-inferior to 64 Gy in 32 fractions in terms of invasive

locoregional control, OS, and late toxicity. In a phase II study, 55 patients (median age 86) with BC, unfit for cystectomy or even daily RT, were treated with 6-weekly doses of 6 Gy [462]. Forty-eight patients completed EBRT with acceptable toxicity and 17% showed local progression after two years demonstrating good local control with this more ultra-hypofractionated schedule.

Elective treatment to the LNs is optional and should take into account patient comorbidities and the risks of toxicity to adjacent critical structures. For node-positive disease, consider boosting grossly involved nodes to the highest achievable dose that does not violate normal tissue constraints based on the clinical scenario.

The use of modern standard EBRT techniques results in major related late morbidity of the urinary bladder or bowel in less than 5% of patients [463]. Acute diarrhoea is reduced even more with intensity-modulated RT [464]. Important prognostic factors for outcome include response to EBRT, tumour size, hydronephrosis, presence of CIS, and completeness of the initial TURB. Additional prognostic factors reported are age and stage [465].

With the use of modern EBRT techniques, efficacy and safely results seem to have improved over time. A 2002 Cochrane analysis demonstrated that RC has an OS benefit compared to RT [466], although this was not the case in a 2014 retrospective review using a propensity score analysis [467]. 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 [468]. 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 TMT therapy (see Section 7.5.4). Factors that influence outcome should be considered. However, EBRT can be an alternative treatment in patients unfit for radical surgery or concurrent chemotherapy, and it can also be quite effective in helping control bleeding.

7.5.2.1 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.	3
Radiotherapy can also be used to stop bleeding from the tumour when local control cannot be achieved by transurethral manipulation because of extensive local tumour growth.	3

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

*7.5.2.2 EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [8, 9]**

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 ≥ 70% agreement and ≤ 15% disagreement, or vice versa).*
IGRT = image-guided radiotherapy; IMRT = intensity-modulated radiotherapy.

*7.5.3 **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% [469, 470]. Response to chemotherapy is a prognostic factor for treatment outcome and eventual survival although it may be confounded by patient selection [471].

Several groups have reported the effect of chemotherapy on resectable tumours (neoadjuvant approach), as well as unresectable primary tumours [237, 254, 472, 473]. 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 [237, 254, 472].

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 [471].

A recent large retrospective analysis of a National Cancer Database cohort reported on 1,538 patients treated with TURB and multi-agent chemotherapy [474]. 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.

7.5.3.1 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

*7.5.4 **Trimodality bladder-preserving treatment***

Trimodality therapy combines TURB, chemotherapy and RT. The rationale to combine TURB with RT is to maximally achieve local tumour control in the bladder and adjacent nodes. The addition of radiosensitising 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 7.1). The aim of TMT is to preserve the bladder and QoL without compromising oncological outcome.

There are no successfully completed RCTs comparing the outcome of TMT with RC, but TMT using chemoradiation has been shown to be superior to RT alone [475-477]. 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.* [475]). Data from a retrospective series, with some methodological caveats, comparing RT (n = 66) and chemoradiation (n = 208) showed an improved complete response of chemoradiation vs. RT (OR: 2.32; 95% CI: 1.05–5.12; p = 0.037), with a 64% 5-year OS for chemoradiation vs. 45% for RT (HR: 0.7; 95% CI: 0.50–0.99; p = 0.045) [477].

In the case of TMT, two distinct patterns of care emerge; treatment aimed at patients fit for cystectomy who elect TMT or refuse cystectomy, and treatment aimed at older, less fit, patients. For the former category, TMT 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 (e.g., T2 tumours, no CIS) is critical [478, 479]. Even in case of an initial presumed complete resection, a second TUR has been suggested to reveal tumour in > 50% of patients and subsequently improves 5-year OS in case of TMT [480]. 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 relative contraindications.

A collaborative review has described the principles of TMT [481]. For radiation, two schedules are most commonly used; historically within the RTOG a split-course format with interval cystoscopy [476] and single-phase treatment which is now more commonly used [475]. A conventional radiation schedule includes EBRT to the bladder and limited pelvic LNs with an initial dose of 40-45 Gy, with a boost to the whole bladder of 50–54 Gy and a further tumour boost to a total dose of 60–66 Gy. If not boosting the tumour, it is also reasonable for the whole bladder to be treated to 59.4–66 Gy. For node-positive disease, consider boosting grossly involved nodes to the highest achievable dose that does not violate normal tissue constraints. Therefore, elective treatment to the LNs (when node negative) is optional and should take into account patient comorbidities and the risks of toxicity to adjacent critical structures.

In summary, reasonable radiation fields include pelvis (with bladder and/or bladder tumour boost), bladder only or partial bladder (tumour) only [475]. A reasonable radiation dosing alternative to conventional fractionation when treating the bladder-only fields is moderately hypofractionated EBRT to 55 Gy in 20 fractions which has been suggested to be non-inferior to 64 Gy in 32 fractions (fx) in terms of invasive loco-regional control, OS and late toxicity [460, 482].

Different chemotherapy regimens have been used, but most evidence exists for cisplatin [483] and mitomycin C plus 5-FU [475]. In addition to these agents, other regimens have also been used such as gemcitabine and hypoxic cell sensitisation with nicotinamide and carbogen, without clear preference for a specific radiosensitiser [8, 9]. In a recently published phase II RCT, twice-a-day radiation plus fluorouracil/cisplatin was compared to once-daily radiation plus gemcitabine [484]. Both arms were found to result in a > 75% freedom of distant metastases at 3 years (78% and 84%, respectively). Therefore, there are options for non-cisplatin candidates such as 5-FU/mitomycin C or low-dose gemcitabine.

To detect non-responders who should be offered salvage cystectomy, bladder biopsies should be performed after TMT [477].

Five-year CSS and OS rates vary between 50%–84% and 36%–74%, respectively, with salvage cystectomy rates of 10–30% [475, 478, 481, 483, 485, 486]. The Boston group reported on their experience in 66 patients with mixed variant histologies treated with TMT and found similar complete response, OS, DSS and salvage cystectomy rates as in UC [487]. The majority of recurrences post-TMT are non-invasive and can be managed conservatively [475]. In contemporary experiences, salvage cystectomy is required in about 10–15% of patients treated with TMT and can be curative [475, 478, 486]. Current data suggest that major late complication rates are slightly higher but remain acceptable for salvage- vs. primary cystectomy [488, 489].

A sub-analysis of two RTOG trials looked at complete response (T0) and near-complete response (Ta or Tis) after TMT [490]. 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 TMT were reported in 25% of patients by the Boston group, sometimes over a decade after initial treatment [491]. A NMIBC recurrence was associated with a lower DSS, although in properly selected patients, intravesical BCG could avoid immediate salvage cystectomy.

The differential impact of RC vs. TMT on long-term OS is lacking a randomised comparison and rigorous prospective data. A propensity score matched institutional analysis has suggested similar DSS and OS between TMT and RC [486]. Two retrospective analyses of the National Cancer Database from 2004–2013 with propensity score matching compared RC to TMT. Ritch *et al.*, identified 6,606 RC and 1,773 TMT patients [492]. Worse survival was linked to higher age, comorbidity and tumour stage. After modelling, TMT 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 TMT (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 TMT [493]. Survival after modelling was significantly better for RC compared to any EBRT, definitive EBRT and TMT (HR: 1.4, 95% CI: 1.2–1.6) at any time point. In older patients which are 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 TMT as compared to surgery as well as increased costs [494]. This was a retrospective SEER database study which included 687 propensity-matched patients in each arm, however, the median number of radiation fractions was well below what is considered adequate for definitive therapy and as such the radiation patients may have been treated inadequately or palliatively. In general, such population-based studies are limited by confounding, misclassification, and selection bias. A systematic review including 57 studies and over 30,000 patients comparing RC and TMT found improved 10-year OS and DSS for TMT, but for the entire cohort OS and DSS did not significantly differ between RC and TMT [495]. Complete response after TMT resulted in significantly better survival, as did down-staging after TURB or NAC in case of RC.

Overall significant late pelvic (GI/genitourinary [GU]) toxicity rates after TMT are low and QoL is good [475, 496, 497]. A combined analysis of survivors from four RTOG trials with a median follow-up of 5.4 years showed that combined-modality therapy was associated with low rates of late grade 3 toxicity (5.7% GU and 1.9% GI). No late grade 4 toxicities or treatment-related deaths were recorded [496]. A retrospective study showed QoL to be good after TMT and in most domains better than after cystectomy, although prospective validations are needed [498]. One option to reduce side effects after TMT is the use of IMRT and image-guided radiotherapy (IGRT) [8, 9, 499].

A collaborative review came to the conclusion that data are accumulating, suggesting that bladder preservation with TMT leads to acceptable outcomes and therefore TMT may be considered a reasonable treatment option in well-selected patients as compared to RC [481]. Bladder preservation as an alternative to RC is generally reserved for patients with smaller solitary tumours, negative nodes, no extensive or multifocal CIS, no tumour-

related hydronephrosis, and good pre-treatment bladder function. Trimodality 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 contemporary data supporting the benefit of using neoadjuvant or adjuvant chemotherapy combined with chemoradiation. Patient selection is critical in achieving good outcomes [481]. Whether a node dissection should be performed before TMT as in RC remains unclear [8, 9].

A bladder-preserving trimodality strategy requires very close multidisciplinary cooperation [8, 9]. This was also highlighted by a Canadian group [500]. 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 trimodality strategy also requires a high level of patient compliance. Even if a patient has shown a clinical response to a trimodality bladder-preserving strategy, the bladder remains a potential source of recurrence, hence long-term life-long bladder monitoring is essential and patients should be counselled that this will be required.

7.5.4.1 Summary of evidence and guidelines for trimodality bladder-preserving treatment

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

Recommendations	**Strength rating**
Offer surgical intervention or trimodality bladder-preserving treatments (TMT) to appropriate candidates as primary curative therapeutic approaches since they are more effective than radiotherapy alone.	Strong
Offer TMT as an alternative to selected, well-informed and compliant patients, especially for whom radical cystectomy is not an option or not acceptable.	Strong

*7.5.4.2 EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [8, 9]**

Consensus statement
Candidates for curative treatment, such as cystectomy or bladder preservation, should be clinically assessed by at least an oncologist, a urologist, a radiation oncologist (in case adjuvant radiotherapy or bladder preservation is considered) 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 *in situ*.
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).
In case of bladder preservation with radiotherapy, combination with a radiosensitiser is always recommended to improve clinical outcomes, such as cisplatin, 5FU/TMC, 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 ≥ 70% agreement and ≤ 15% disagreement, or vice versa).*
HCP = healthcare professional; IGRT = image-guided radiotherapy; IMRT = intensity-modulated radiotherapy; 5FU = 5-fluorouracil; MMC = mitomycin-C.

7.6 Adjuvant therapy

7.6.1 ***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 [488, 501]. 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 of or intolerability to chemotherapy, due to post-operative morbidity [502].

There is limited evidence from adequately conducted and accrued phase III RCTs in favour of the routine use of adjuvant chemotherapy [501, 503-508]. An individual patient data meta-analysis [503] of survival data from six RCTs of adjuvant chemotherapy [485, 509-512] 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) [501]. 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 [513], and one trial used cisplatin monotherapy [511]. The data were not convincing to support an unequivocal recommendation for the use of adjuvant chemotherapy. In 2014, this meta-analysis was updated with an additional three studies [505-507] resulting in the inclusion of 945 patients from nine trials [504]. None of the trials had fully accrued and individual patient data were not used in the analysis [504]. For one trial only an abstract was available at the time of the meta-analysis [506] 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) [505, 506]. 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) [514]. A recent publication of the largest RCT (European Organisation for Research and Treatment of Cancer [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 [515].

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 [516].

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 [517]. 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 [504]. Patients should be informed about potential chemotherapy options before RC, including neoadjuvant and adjuvant chemotherapy, and the limited evidence for adjuvant chemotherapy.

7.6.2 ***Role of adjuvant immunotherapy***

To determine the benefit of PD-1/PD-L1 checkpoint inhibitors, three phase III RCTs have evaluated checkpoint inhibitor monotherapy with atezolizumab, nivolumab or pembrolizumab in patients with muscle-invasive UC. The CheckMate 274 phase III multi-centre, double-blind, randomised, controlled trial of adjuvant nivolumab vs. placebo for up to 1 year in 709 patients with muscle-invasive UC (neoadjuvant cisplatin-based chemotherapy was allowed before trial entry) demonstrated a significant improvement in median DFS (20.8 months (95% CI:

16.5–27.6) with nivolumab and 10.8 months (95% CI: 8.3–13.9) with placebo). The percentage of patients who were alive and disease-free at 6 months was 74.9% with nivolumab and 60.3% with placebo (HR for disease recurrence or death, 0.70; 98.22% CI: 0.55–0.90; p < 0.001). Among patients with a PD-L1 expression level of ≥ 1%, the percentage of patients was 74.5% and 55.7%, respectively (HR: 0.55; 98.72% CI: 0.35–0.85; p < 0.001) [518]. The primary endpoint of DFS was not achieved in a multi-centre RCT of adjuvant atezolizumab vs. observation (IMvigor010) Median DFS was 19·4 months (95% CI: 15.9–24.8) with atezolizumab and 16.6 months (11.2–24.8) with observation (stratified HR: 0.89, 95% CI: 0.74–1.08, p = 0.24) [519]. A similarly designed trial of pembrolizumab in the adjuvant setting has completed accrual with results awaited. The FDA has approved nivolumab for adjuvant treatment of patients with UC who are at high risk of recurrence after undergoing surgery [520]. A promising report (see Marker section) has suggested for a potential role for ctDNA to guide the use of adjuvant IO for UC [223].

*7.6.3 **Summary of evidence and guidelines for adjuvant therapy***

Summary of evidence	LE
Adjuvant cisplatin-based chemotherapy for high-risk patients (pT3, 4 and/or or N+ M0) without neoadjuvant treatment can be associated with improvement in DFS and OS but trials are underpowered to adequately answer this question.	2a
To date, studies of immune checkpoint inhibitors in the adjuvant setting for patients with high-risk MIBC who have and have not received neoadjuvant chemotherapy have demonstrated conflicting results with the CheckMate 274 study demonstrating an improvement in DFS with adjuvant nivolumab and the IMvigor 010 study failing to show an improvement in DFS with adjuvant atezolizumab.	1b
Results for adjuvant treatment with immune-checkpoint inhibitors in high-risk MIBC are conflicting: nivolumab improved DFS (Checkmate 274) whereas atezolizumab did not (IMvigor 010).	1b
Circulating tumour DNA holds promise as both a prognostic and predictive biomarker to guide the use of adjuvant IO for UC in patients who are at a high risk of recurrence and positive for ctDNA treated with adjuvant atezolizumab demonstrating improved outcomes compared with observation.	2b

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
Discuss immunotherapy with nivolumab with selected patients with pT3/4 and/or pN+ disease not eligible for, or who declined, adjuvant cisplatin-based chemotherapy.	Weak

7.7 Metastatic disease

*7.7.1 **Introduction***

The treatment of metastatic UC had remained largely unchanged since pivotal trials published over 20 years ago set the standard of care for first-line treatment with cisplatin-based combinations demonstrating an OS benefit. In the past few years this longstanding paradigm has been challenged by several large studies investigating the benefit of immunotherapy using checkpoint inhibitors. Moreover, novel compounds including both targeted therapy and antibody-drug conjugates have been successfully tested and approved in later treatment lines.

*7.7.2 **First-line systemic therapy for metastatic disease***

In general, patients with untreated metastatic UC can be divided into three broad categories: fit for cisplatin-based chemotherapy, fit for carboplatin-based chemotherapy (but unfit for cisplatin) and unfit for any platinum-based chemotherapy.

Definitions: 'Fit for cisplatin, fit for carboplatin, unfit for any platinum-based chemotherapy'

An international survey among BC experts [521] was the basis for a consensus statement on how to classify patients unfit for cisplatin-based chemotherapy. At least one of the following criteria must be present: PS > 1; GFR ≤ 60 mL/min; grade ≥ 2 audiometric hearing loss; grade ≥ 2 peripheral neuropathy or New York Heart Association (NYHA) class III heart failure [522]. Around 50% of patients with BC are not eligible for cisplatin-based chemotherapy [522]. Renal function assessment is of utmost importance for treatment selection. Measuring GFR with radioisotopes (^{99}mTc DTPA or ^{51}Cr-EDTA) is recommended in equivocal cases.

Cisplatin has also been administered in patients with a 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 [523-525]. However, no prospective RCT has compared split-dose cisplatin with conventional dosing.

Most patients that are deemed unfit for cisplatin are able to receive carboplatin-based chemotherapy. However, some patients are deemed unfit for any platinum-based chemotherapy, i.e. both cisplatin and carboplatin. Patient are unfit for any platinum-based chemotherapy in case of PS > 2, GFR < 30 mL/min or the combination of PS 2 and GFR < 60 mL/min since the outcome in this patient population is poor regardless of platinum-based treatment or not [526]. Patients with multiple comorbidities may also be poor candidates for platinum-based chemotherapy. Definitions of platinum-eligibility for first-line treatment of metastatic UC are summarised in Table 7.2.

Table 7.2: Definitions of platinum-eligibility for first-line treatment of metastatic urothelial carcinoma

Platinum-eligible		Platinum-ineligible
Cisplatin-eligible	**Carboplatin-eligible**	
ECOG PS 0-1 *and*	ECOG PS 2 *or* GFR 30–60 mL/min	Any of the following:
GFR > 50–60 mL/min *and*	or not fulfilling other cisplatin-eligibility criteria	GFR < 30mL/min
Audiometric hearing loss grade < 2 *and*		ECOG PS > 2
Peripheral neuropathy grade < 2 *and*		ECOG PS 2 *and* GFR < 60 mL/min
Cardiac insufficiency NYHA class < III		Comorbidites > Grade 2

ECOG = Eastern Cooperative Oncology Group; GFR = glomerular filtration rate; NYHA = New York Heart Association; PS = performance status.

7.7.2.1 First-line chemotherapy in patients fit for cisplatin

Cisplatin-containing combination chemotherapy has been the standard of care since the late 1980s demonstrating an OS of 12 to 14 months in different series (for a review see [527]). Methotrexate, vinblastine, adriamycin plus cisplatin and GC achieved survival of 14.8 and 13.8 months, respectively [528]. Overall response rates were 46% for MVAC and 49% for GC. The lower toxicity of GC [183] compared to standard MVAC has resulted in GC becoming the standard regimen.

Dose-dense MVAC combined with granulocyte colony-stimulating factor (G-CSF) is less toxic and more efficacious than standard MVAC in terms of, complete response (CR), and 2-year OS. However, there is no significant difference in median survival between the two regimens [529, 530]. Further intensification of treatment using paclitaxel, cisplatin and gemcitabine (PCG) triple regimen did not result in a significant improvement in OS in the intention-to-treat (ITT) population of a phase III RCT, comparing PCG to GC [531]. Similarly, the addition of the angiogenesis inhibitor bevacizumab to GC did not result in OS improvement [532].

The disease sites 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 [528]. In the trials with long-term follow-up approximately 10-15% of patients with metastatic UC are alive at 5 years and longer, suggesting a sustained benefit from cisplatin-based chemotherapy in a minority of patients [528, 530].

Carboplatin-containing chemotherapy is not considered to be equivalent to cisplatin-based combinations, and should not be considered interchangeable or standard in patients fit for cisplatin. A comparative analysis of four randomised phase II trials of carboplatin vs. cisplatin combination chemotherapy demonstrated lower CR rates and shorter OS for the carboplatin arms [533]. Recently, a retrospective study highlighted the importance of applying cisplatin in cisplatin-eligible patients in order to maintain benefit [534].

7.7.2.2 First-line chemotherapy in patients fit for carboplatin (but unfit for cisplatin)

Up to 50% of patients are not fit for cisplatin-containing chemotherapy but most may be candidates for carboplatin [522]. The first randomised phase II/III trial in this setting was conducted by the EORTC and compared two carboplatin-containing regimens (methotrexate/carboplatin/vinblastine [M-CAVI] and gemcitabine/carboplatin [GemCarbo]) in patients unfit for cisplatin. The EORTC definitions for eligibility were GFR < 60 mL/min and/or PS 2. Severe acute toxicity was 13.6% with GemCarbo vs. 23% with M-CAVI, while the ORR was 42% for GemCarbo and 30% for M-CAVI, respectively [526]. Based on these results the combination of carboplatin and gemcitabine should be considered a standard of care in this patient group.

Combinations of gemcitabine and paclitaxel have been studied as first-line treatment and produced response rates between 38% and 60% but has never been tested in RCTs [535-537]. A randomised phase II trial 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 of vinflunine/gemcitabine [538]. Non-platinum combination chemotherapy is nevertheless not recommended for first-line use in platinum-eligible patients.

The use of single-agent chemotherapy has been associated with varying response rates. Responses with single agents are usually short, complete responses are rare, and no long-term DFS/OS has been reported. It is not recommended for first-line treatment of metastatic UC.

7.7.2.3 Integration of immunotherapy in the first-line chemotherapy treatment of patients fit for platinum (cisplatin or carboplatin)

7.7.2.3.1 Immunotherapy combination approaches

In 2020, the results of three phase III trials have been published investigating the use of immunotherapy in the first-line setting for platinum-eligible patients. The first trial to report was IMvigor130 investigating the combination of the PD-L1 inhibitor atezolizumab plus platinum-gemcitabine chemotherapy vs. chemotherapy plus placebo vs. atezolizumab alone [539]. The primary endpoint of PFS benefit for the combination vs. chemotherapy alone in the ITT group was reached (8.2 months vs. 6.3 months [HR: 0.82, 95% CI: 0.70–0.96; one-sided, p = 0.007]) while OS was not significant at the interim analysis after a median follow-up of 11.8 months. The small PFS benefit in the absence of an OS benefit has raised questions of its clinical significance. Due to the sequential testing design, the comparison of chemotherapy vs. atezolizumab alone has not yet been formally performed.

The KEYNOTE 361 study had a very similar design using the PD-1 inhibitor pembrolizumab plus platinum-gemcitabine vs. chemotherapy plus placebo vs. pembrolizumab alone. The results of the primary endpoints of PFS and OS for the comparison of pembrolizumab plus chemotherapy vs. chemotherapy plus placebo in the ITT population showed no benefit for the combination [540].

DANUBE compared the immunotherapy combination (IO-IO) of CTLA-4 inhibitor tremelimumab and PD-L1 inhibitor durvalumab with chemotherapy alone or durvalumab alone [541]. The co-primary endpoint of improved OS for the IO-IO combination vs. chemotherapy was not reached in the ITT group nor was the OS improved for durvalumab monotherapy vs. chemotherapy in the PD-L1-positive population.

In conclusion, these three trials do not support the use of combination of PD-1/L1 checkpoint inhibitors plus chemotherapy or the IO-IO combination as first-line treatment.

7.7.2.3.2 Use of first-line single-agent immunotherapy in patients unfit for cisplatinum-based chemotherapy

Based on the results of two single-arm phase II trials [542, 543] the checkpoint inhibitors pembrolizumab and atezolizumab have been approved by the U.S. FDA and the European Medicines Agency (EMA) for first-line treatment in cisplatin-unfit patients in case of positive PD-L1 status. PD-L1 positivity for use of pembrolizumab is defined by immunohistochemistry as a CPS of ≥ 10 using the Dako 22C33 platform and for atezolizumab as positivity of ≥ 5% tumour-infiltrating immune cells using Ventana SP142.

Pembrolizumab was tested in 370 patients with advanced or metastatic UC ineligible for cisplatin, showing an ORR of 29% and CR in 7% of patients [542]. Atezolizumab was evaluated in the same patient population in a phase II trial (n = 119) showing an ORR of 23% with 9% of patients achieving CR [543].

The trials IMvigor 130, Keynote 361 and DANUBE all included an experimental arm with immunotherapy alone using atezolizumab, pembrolizumab and durvalumab, respectively [539-541]. No benefit in terms of PFS or OS for the use of single-agent immunotherapy compared to platinum-based chemotherapy was found. The combination of carboplatin/gemcitabine therefore is considered the preferred first-line treatment choice for patients ineligible for cisplatin but eligible for carboplatin.

7.7.2.3.3 Switch maintenance with immunotherapy after platinum-based chemotherapy

A randomised phase II trial evaluated switch maintenance treatment with pembrolizumab in patients achieving at least stable disease on platinum-based first-line chemotherapy. The primary endpoint of PFS was met (5.4 months vs. 3.0 months, HR: 0.65, p = 0.04) but not the secondary endpoint of OS (22 months vs. 18.7 months, HR: 0.91, 95% CI: 0.52–1.59) [544].

The JAVELIN Bladder 100 study investigated the impact of switch maintenance with the PD-L1 inhibitor avelumab after initial treatment with platinum-gemcitabine chemotherapy. Patients achieving at least stable disease or better after 4–6 cycles of platinum-gemcitabine were randomised to avelumab or best supportive care (BSC). Overall survival was the primary endpoint which improved to 21.4 months with avelumab compared to 14.3 months with BSC (HR: 0.69, 95% CI: 0.56–0.86; p < 0.001). Of patients who

discontinued BSC and received subsequent treatment 53% received immunotherapy. Immune-related AEs occurred in 29% of all patients and 7% experienced grade 3 complications [545].

In conclusion, maintenance IO with avelumab is a standard of care for all patients with disease stabilisation on first-line platinum-based chemotherapy.

7.7.2.4 Treatment of patients unfit for any platinum-based chemotherapy

Very limited data exist regarding the optimal treatment for this patient population which is characterised by severely impaired PS (PS > 2) and/or severely impaired renal function (GFR < 30 mL/min). Historically, the outcome in this patient group has been poor. Best supportive care has often been chosen instead of systemic therapy. Most trials evaluating alternative treatment options to cisplatinum-based chemotherapy did not focus specifically on this patient population thereby making interpretation of data difficult. The FDA (but not EMA) has approved pembrolizumab and atezolizumab as first-line treatment for patients not fit to receive any platinum-based chemotherapy regardless of PD-L1 status based on the results of two single-arm phase II trials [542, 543]. These trials have not reported how many patients were unfit for any platinum-based chemotherapy.

*7.7.3 **Second-line systemic therapy for metastatic disease***

7.7.3.1 Second-line chemotherapy

Second-line chemotherapy data are highly variable and mainly derive from small single-arm phase II trials apart from a single phase III RCT. A reasonable strategy has been to re-challenge former platinum-sensitive patients if progression occurred at least six to twelve months after first-line platinum-based combination chemotherapy. Second-line response rates of single-agent treatment with paclitaxel (weekly), docetaxel, gemcitabine, nab-paclitaxel, oxaliplatin, ifosfamide, topotecan, pemetrexed, lapatinib, gefitinib and bortezomib have ranged between 0% and 28% in small phase II trials [546, 547].

The paclitaxel/gemcitabine combination has shown good response rates in small single-arm studies but no adequate phase III RCT has been conducted [548, 549].

Vinflunine was tested in a phase III RCT and compared against BSC in patients progressing after first-line treatment with platinum-based chemotherapy [550]. The results showed a very modest ORR (8.6%), a clinical benefit with a favourable safety profile and a survival benefit, which was however only statistically significant in the eligible patient population (not in the ITT population).

A randomised phase III trial evaluated the addition of the angiogenesis inhibitor ramucirumab to docetaxel chemotherapy vs. docetaxel alone, which resulted in improved PFS (4.1 vs. 2.8 months) and higher response rates (24.5% vs. 14%) but no OS benefit was achieved [551, 552].

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

The immune checkpoint inhibitors pembrolizumab, nivolumab, atezolizumab, avelumab, and durvalumab have demonstrated similar efficacy and safety in patients progressing during, or after, previous platinum-based chemotherapy in phase I, II and III trials.

Pembrolizumab demonstrated a significant OS Improvement as second-line treatment in a phase III RCT leading to EMA and FDA approval. Patients (n = 542) were randomised to receive either pembrolizumab monotherapy or chemotherapy (paclitaxel, docetaxel or vinflunine). The median OS with pembrolizumab was 10.3 months (95% CI: 8.0–11.8) vs. 7.4 months (95% CI: 6.1–8.3) with chemotherapy (HR 0.73, 95% CI: 0.59–0.91, p = 0.002) independent of PD-L1 expression levels [553].

Atezolizumab was the first checkpoint inhibitor approved by FDA for metastatic UC based on the results of phase I and II trials [215, 554] The phase III RCT (IMvigor211) included 931 patients comparing atezolizumab with second-line chemotherapy (paclitaxel, docetaxel or vinflunine) did not meet its primary endpoint of improved OS for patients with high PD-L1 expression with 11.1 months (atezolizumab) vs. 10.6 (chemotherapy) months (stratified HR: 0.87, 95% CI: 0.63–1.21, p = 0.41) [555].

The PD-1 inhibitor nivolumab was approved by the FDA based on the results of a single-arm phase II trial (CheckMate 275), enrolling 270 platinum pre-treated patients. The primary endpoint of ORR was 19.6%, and OS was 8.74 months for the entire group [556].

Based on level 1 evidence from a RCT, pembrolizumab has emerged in clinic as the preferred standard of care immunotherapy in the second-line setting.

7.7.3.3 Side-effect profile of immunotherapy

Checkpoint inhibitors including PD-1 or PD-L1 antibodies and CTLA-4 antibodies have a distinct side-effect profile associated with their mechanism of action leading to enhanced immune system activity. These AEs

can affect any organ in the body leading to mild, moderate or severe side effects. The most common organs affected are the skin, GI tract, liver, lung, thyroid, adrenal and pituitary gland. Other systems that may be affected include musculoskeletal, renal, nervous, haematologic, ocular and cardiovascular system. Any change during immunotherapy treatment should raise suspicion about a possible relation to the treatment. The nature of immune-related AEs has been very well characterised and published [557]. The timely and appropriate treatment of immune-related side effects is crucial to achieve optimal benefit from the treatment while maintaining safety. Clear guidelines for side-effect management have been published [558]. Immunotherapy treatment should be applied and supervised by trained clinicians only to ensure early side effect recognition and treatment. In case of interruption of immunotherapy, re-challenge will require close monitoring for AEs [559].

*7.7.4 **Integration of novel agents***

7.7.4.1 Antibody drug conjugates

The first antibody drug conjugate to report encouraging data was enfortumab vedotin, an antibody-drug conjugate targeting Nectin-4, a cell adhesion molecule which is highly expressed in UC conjugated to monomethyl auristatin E (MMAE). A phase-II single-arm study (EV-201) in 125 patients previously treated with platinum chemotherapy and checkpoint inhibition showed a confirmed objective response rate of 44%, including 12% complete responses [560]. This data led to accelerated FDA and EMA approval for enfortumab vedotin in locally advanced or metastatic UC patients who have previously received a PD-1 or PD-L1 inhibitor, and platinum-containing chemotherapy [561, 562]. Another cohort of the same EV-201 trial demonstrated similar promising results in a cohort of 91 patients that were cisplatin-ineligible and had received prior IO [563]. A phase III RCT (n = 608) comparing enfortumab vedotin with single-agent chemotherapy after prior platinum chemotherapy and checkpoint inhibitor immunotherapy demonstrated significant survival benefit of almost 4 months (12.88 months vs. 8.97 months; HR 0.7, 95% CI: 0.56–0.89) [564]. The most common treatment-related AEs included alopecia (45%), peripheral neuropathy (34%), fatigue (31%, 7.4% ≥ grade 3), decreased appetite (31%), diarrhoea (24%), nausea (23%). and skin rash (16%, 7.4% ≥ grade 3).

Preliminary results of the combination of enfortumab vedotin and pembrolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced/metastatic UC have been reported resulting in ORR of 73.3% with 15.6% complete responses [565]. Treatment-related AEs of interest included any rash (48% all grade, 11% ≥ grade 3) and any peripheral neuropathy (50% all grade, 3% ≥ grade 3). This combination is currently under investigation in a phase III trial in the first-line setting for platinum-eligible patients (EV-302).

Based on these results enfortumab vedotin has been FDA approved for patients who have received prior platinum-containing chemotherapy and prior IO with PD-1 or PD-L1 inhibitor as well as for cisplatin-ineligible patients who have received one or more prior lines of therapy.

Another new and also promising antibody drug conjugate is sacituzumab govitecan, consisting of a humanised monoclonal antibody targeting trophoblast cell surface antigen 2 (Trop-2) conjugated to SN-38, the active metabolite of irinotecan. Sacituzumab govitecan was tested in 113 platinum and IO pre-treated metastatic UC (mUC) patients [560] and achieved an ORR of 27% and a total of 77% had a decrease in measurable disease, median PFS was 5.4 months and median OS 10.9 months [566]. Side effects consisted of haematological toxicities (neutropenia 34% ≥ grade 3; febrile neutropenia 10% ≥ grade 3), fatigue (52%), alopecia (47%), nausea (60%), diarrhea (65%, 10% ≥ grade 3) and decreased appetite (36%) [566]. Sacituzumab govitecan has received accelerated FDA approval for metastatic UC with prior platinum and IO pre-treatment. Several trials using sacituzumab govitecan as monotherapy or in combinations are ongoing.

7.7.4.2 FGFR inhibition

Genomic profiling of UC has revealed common potentially actionable genomic alterations including alterations in *FGFR* [567]. Erdafitinib is a pan-*FGFR* tyrosine kinase inhibitor and the first FDA-approved targeted therapy for mUC with susceptible *FGFR2/3* alterations following platinum-containing chemotherapy. The phase II trial of erdafitinib included 99 patients whose tumour harboured an *FGFR3* mutation or *FGFR2/3* fusion and who had disease progression following chemotherapy [213]. The confirmed ORR was 40% and an additional 39% of patients had stable disease. A total of 22 patients had previously received immunotherapy with only one patient achieving a response, yet the response rate for erdafitinib for this subgroup was 59%. At a median follow-up of 24 months, the median PFS was 5.5 months (95% CI: 4.0–6.0) and the median OS was 11.3 months (95% CI: 9.7–15.2) [213]. Treatment-related AEs of ≥ grade 3 occurred in 46% of patients. Common AEs of ≥ grade 3 were hyponatraemia (11%), stomatitis (10%), and asthenia (7%) and 13 patients discontinued erdafitinib due to AEs, including retinal pigment epithelial detachment, hand-foot syndrome, dry mouth, and skin/nail events. In addition to erdafitinib, several other *FGFR* inhibitors are being evaluated including infigratinib which

has demonstrated promising activity [214]. The increased identification of *FGFR3* mutations/fusion has led to several ongoing trials with different agents and combination in different disease settings.

*7.7.5 **Current status of predictive biomarkers***

The most important advance in recent years has been the recognition of alterations in *FGFR3* including mutations and gene fusions as a predictive marker for response to *FGFR* inhibitors [213]. It is rrecommended to screen mUC patients ideally at diagnosis of metastatic disease for *FGFR3* alterations to plan optimal treatment including trials.

Many efforts have focused on markers for predicting response to immune checkpoint inhibition. Programmed death-ligand 1 expression by immunohistochemistry has been evaluated in many studies with mixed and, so far, inconclusive results. This may in part be related to the use of different antibodies and various scoring systems evaluating different compartments i.e., tumour cells, immune cells, or both. A major limitation of PD-L1 staining relates to the significant proportion of PD-L1-negative patients that respond to immune checkpoint blockade. The predictive value of PD-L1 was not confirmed in large phase III trials evaluating the integration of immunotherapy in the first-line setting for mUC [539-541]. At present, the only indication for PD-L1 testing in mUC is dictated by current the FDA and EMA approvals and relates to the potential use of immune checkpoint inhibitors as first-line monotherapy in patients unfit for cisplatin-containing chemotherapy.

Another biomarker that has been evaluated for predicting response to immunotherapy is high TMB [217]. Neoantigen burden and TMB have been associated with response to immune checkpoint blockade in several malignancies. High TMB has been associated with response to immune checkpoint inhibitors in metastatic UC in small single arm trials [215, 218] but was not confirmed so far in RCTs. Other markers that have been evaluated in predicting response to immune checkpoint inhibitors include molecular subtypes, CD8 expression by immunohistochemistry and other immune gene cell signatures. Recent work has focused on the importance of stroma including the role of TGFs in predicting response to immune checkpoint blockade [221, 222].

In conclusion, apart from *FGFR3* alterations, there are currently no further validated predictive molecular markers that are routinely used in clinical practice.

*7.7.6 **Special situations***

7.7.6.1 Impact of prior neoadjuvant/adjuvant therapy on treatment sequence

Peri-operative systemic treatment is increasingly used in UC including cisplatin-based chemotherapy in the neoadjuvant setting for BC and adjuvant platinum-based chemotherapy for upper tract UC [568]. Many ongoing phase III trials investigate the use of immunotherapy in this setting as well. So far, one trial has reported a significant DFS benefit for adjuvant treatment with nivolumab compared with placebo whereas one trial reported no significant benefit using atezolizumab vs. placebo in the same setting whilst another trial reported negative findings [518, 519]. It is expected that an increased number of patients with metastatic UC will have received pre-treatment with platinum and/or immunotherapy agents. No prospective trials have investigated the treatment of such patients. The choice of treatment in these patients depends on the applied peri-operative treatment and the time until relapse. If at least 12 months have passed since the end of peri-operative treatment the same systemic treatment as in treatment-naïve patients is recommended. To help prevent early relapse within 12 months the peri-operative systemic therapy has to be taken into account when planning further treatment.

7.7.6.2 Systemic treatment of metastatic disease with histology other than pure urothelial carcinoma

Pure urothelial carcinoma (PUC) represents the predominant histology in over 90% of patients with mUC. Variant histologies (e.g. micropapillary, nested, sarcomatoid) and divergent differentiation (e.g. SCC, adenocarcinoma) can be found in addition to PUC in up to 33% of patients. Such patients were often excluded from large phase II and phase III trials and therefore the knowledge about the best management of such patients is limited. The respective literature was reviewed recently [68] and an expert Delphi survey and consensus conference provided guidance [9]. In case of predominant PUC it is recommended to treat patients with mixed histology the same way as patients with PUC histology. Patients with predominant non-urothelial differentiation such as small cell neuroendocrine carcinoma, urachal adenocarcinoma, SCC and adenocarcinoma should be treated individually.

*7.7.7 **Treatment of patients with bone metastases***

The prevalence of metastatic bone disease (MBD) in patients with advanced/metastatic UC is 30–40% [569]. Skeletal complications due to MBD have a detrimental effect on pain and QoL and are also associated with increased mortality [570]. Bisphosphonates such as zoledronic acid reduce and delay skeletal-related events (SREs) due to bone metastases by inhibiting bone resorption, as shown in a small pilot study [571].

Denosumab, a fully human monoclonal antibody that binds to and neutralises RANKL (receptor activator of nuclear factor κB ligand), was shown to be non-inferior to zoledronic acid in preventing or delaying SREs in patients with solid tumours and advanced MBD, including patients with UC [572]. Patients with MBD, irrespective of the cancer type, should be considered for bone-targeted treatment [570].

Patients treated with zoledronic acid 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 zoledronic acid should follow regulatory recommendations and have to be adjusted according to pre-existing medical conditions, especially renal function [573]. For denosumab, no dose adjustments are required for variations in renal function.

*7.7.8 **Summary: treatment algorithm for metastatic urothelial cancer update 2021***

Figure 7.2 summarises the treatment algorithm for metastatic BC based on the evidence discussed in the text above.

Patients with treatment-naïve mUC are grouped according to platinum-eligibility based on clear definitions. In general, first-line treatment consists of platinum-based chemotherapy in which cisplatin is to be preferred to carboplatin. Patients who are cisplatin-ineligible but carboplatin-eligible should receive carboplatin-gemcitabine combination chemotherapy. In case of positive PD-L1 status, treatment with checkpoint inhibitors (atezolizumab or pembrolizumab) could be an alternative option.

Patients unfit for both cisplatin and carboplatin (platinum-unfit) can be considered for immunotherapy (FDA approved irrespective of PD-L1 status, EMA approved only for PD-L1 positive patients) or receive BSC.

In cases of disease stabilization on platinum-based chemotherapy switch, maintenance treatment with IO (avelumab) is recommended. Alternatively, patients can be followed closely and receive second-line immunotherapy at the time of progression (pembrolizumab).

It is recommended to determine *FGFR* mutation status before deciding about second-line treatment. Patients with *FGFR3* mutations are candidates for *FGFR* inhibitor treatment. Enfortumab vedotin therapy is the new standard in case of progression after platinum chemotherapy and IO but has not yet been approved in Europe. The optimal sequence of novel agents and potential combinations are the subject of many ongoing trials. It is generally recommended to treat patients within ongoing clinical trials.

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

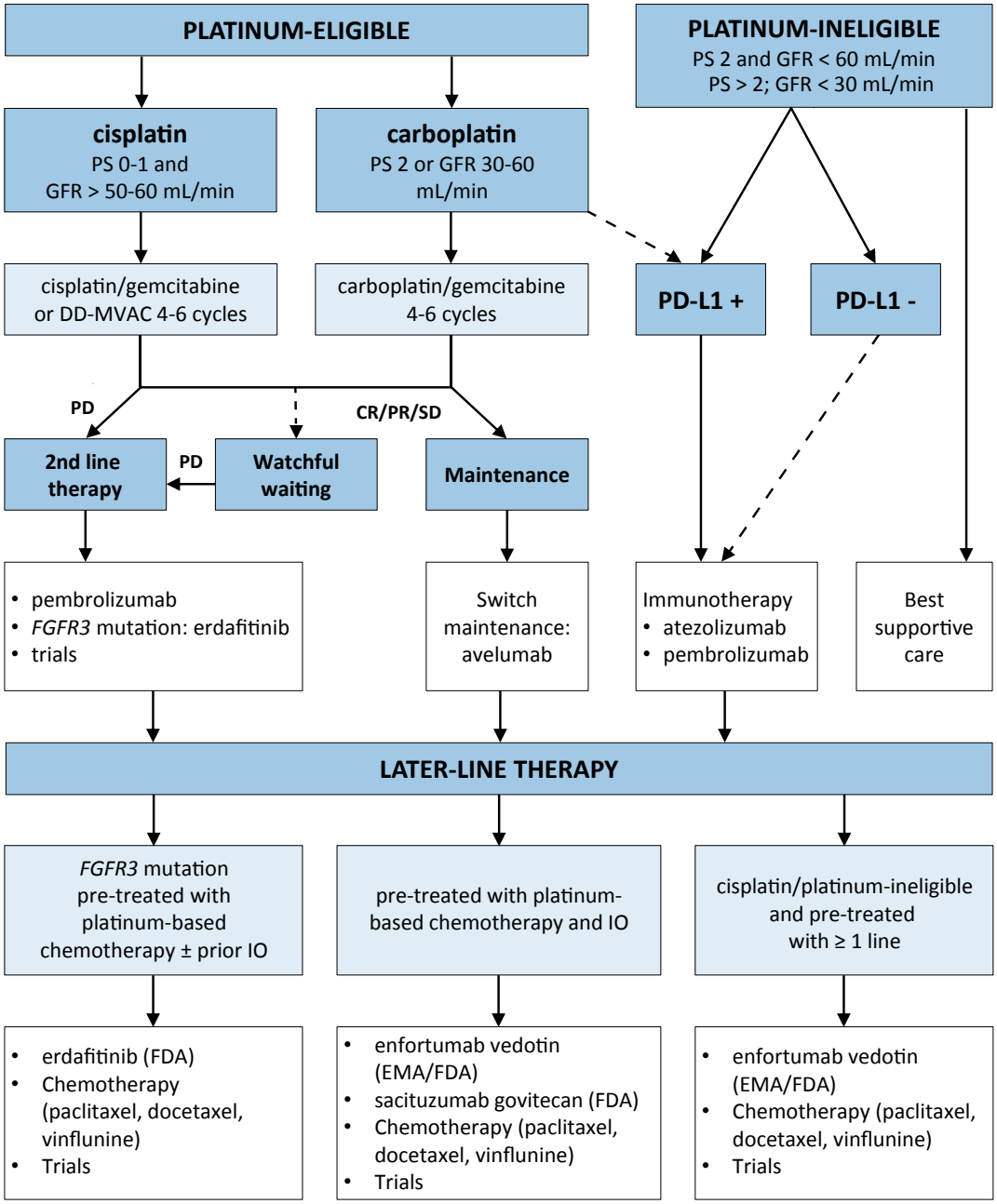
Summary of evidence	**LE**
In a first-line setting, PS and the presence or absence of visceral metastases are independent prognostic factors for survival.	1b
In a second-line setting, negative prognostic factors are: liver metastasis, PS ≥ 1 and low haemoglobin (< 10 g/dL).	1b
Cisplatin-containing combination chemotherapy can achieve median survival of up to 14 months, with long-term 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
There is no defined standard therapy for platinum chemotherapy-unfit patients with advanced or metastatic UC.	2b
Post-chemotherapy surgery after partial or complete response may contribute to long-term DFS in highly selected patients.	3
Zoledronic acid and denosumab have been approved for supportive treatment in case of bone metastases of all cancer types including UC, as 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
Enfortumab vedotin after prior platinum chemotherapy and checkpoint inhibitor immunotherapy has demonstrated a significant survival benefit as compared to chemotherapy.	1b
PD-L1 inhibitor atezolizumab is approved for patients with advanced or metastatic UC unfit for cisplatin-based chemotherapy in case of high PD-1 expression defined as tumour-infiltrating immune cells covering ≥ 5% of the tumour area using the SP142 assay.	1b

PD-1 inhibitor pembrolizumab is approved for patients with advanced or metastatic UC unfit for any platinum-based chemotherapy in case of high PD-1 expression defined as CPS of ≥ 10 using the Dako 22C33 platform (EMA; FDA approval independent of PD-1 status).	1b
The combination of chemotherapy plus pembrolizumab or atezolizumab and the combination of durvalumab and tremelimumab have not demonstrated OS survival benefit compared to platinum-based chemotherapy alone.	1b
Switch maintenance with the PD-L1 inhibitor avelumab has demonstrated significant OS benefit in patients achieving at least stable disease on first-line platinum-based chemotherapy.	1b

Recommendations	**Strength rating**
First-line treatment for platinum-fit patients	
Use cisplatin-containing combination chemotherapy with GC or HD-MVAC.	Strong
In patients unfit for cisplatin but fit for carboplatin, use the combination of carboplatin and gemcitabine.	Strong
In patients achieving stable disease, or better, after first-line platinum-based chemotherapy, use maintenance treatment with PD-L1 inhibitor avelumab.	Strong
First-line treatment in patients unfit for platinum-based chemotherapy	
Consider checkpoint inhibitors pembrolizumab or atezolizumab in case of high PD-1 expression (for definitions see text).	Weak
Second-line treatment	
Offer checkpoint inhibitor pembrolizumab to patients progressing during, or after, platinum-based combination chemotherapy for metastatic disease.	Strong
Further treatment after platinum- and immunotherapy	
Offer antibody drug conjugate enfortumab vedotin as monotherapy to patients with advanced or metastatic UC pre-treated with platinum and immunotherapy.	Strong
Offer treatment in clinical trials testing novel drugs (e.g. sacituzumab govitecan); or in case of patients with *FGFR3* alterations, *FGFR* tyrosine kinase inhibitors.	Strong
Evaluate for *FGFR2/3* genetic alterations for the potential use of erdafitinib in patients with locally advanced or metastatic urothelial carcinoma who have progressed following platinum-containing chemotherapy (including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy).	Weak

GC = gemcitabine plus cisplatin; FGFR = fibroblast growth factor receptor; HD-MVAC = high-dose intensity methotrexate, vinblastine, adriamycin plus cisplatin.

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



**Treatment within clinical trials is highly encouraged.*
BSC = best supportive care; CR = complete response; DD-MVAC = dose dense methotrexate vinblastine doxorubicin cisplatin; EMA = European Medicines Agency; EV = enfortumab vedotin; FDA = US Food and Drug Administration; FGFR = fibroblast growth factor receptor; GFR = glomerular filtration rate; IO = immunotherapy; PR = partial response; PS = performance status; SD = stable disease.

7.8 Quality of life

7.8.1 Introduction

The evaluation of HRQoL considers physical, psychological, emotional and social functioning. Several questionnaires have been validated for assessing HRQoL in patients with BC, including FACT-G [574], EORTC QLQ-C30 [575], EORTC QLQ-BLM30 [575], SF-36 [576] and recently the BCI questionnaire [577]. In spite of these validated questionnaires, there is heterogeneity in the measurements used to assess sexual health. A health questionnaire that covers the entire range of sexual health in bladder cancer patients is currently lacking [578]. In patients with bladder cancer, the overall HRQoL is lower compared to the general population and patients with other common pelvic cancers, independent of therapy received and disease stage [579].

In patients with MIBC, HRQoL appears to decline, particularly in the physical and social functioning domains [580]. Several questionnaires have been validated for assessing HRQoL in patients with BC, including

FACT (Functional Assessment of Cancer Therapy)-G [574], EORTC QLQ-C30 [575], EORTC QLQ-BLM (MIBC module) [575], and SF (Short Form)-36 [576, 581] and recently the BCI questionnaire specifically designed and validated for BC patients [577].

*7.8.2 **Neoadjuvant chemotherapy***

The impact of NAC on patient-reported outcomes (using EORTC QLQ questionnaires) was investigated by Feuerstein *et al.* [582]. A propensity-matched analysis of 101 patients who completed NAC and 54 patients who did not undergo NAC, showed no negative effect of NAC on patient-reported outcomes prior to RC. Recently, HRQoL data from two RCTs have been published [497, 583]. Huddart *et al.,* analysed the subset of patients within the BC2001 trial who underwent NAC prior to (chemo)radiation. Using the FACT-BL questionnaire, no detrimental impact of NAC on HRQoL was observed [497]. Kitamura *et al.*, reported on 64 patients included in the JCOG0209 study who underwent NAC (MVAC vs. MVAC and RC). An overall decline on HRQoL was reported directly following NAC using the FACT-BL questionnaire. However, no difference in HRQoL was observed after the consolidating RC.

*7.8.3 **Radical cystectomy and urinary diversion***

Two systematic reviews and meta-analyses focused on HRQoL after RC and urinary diversion [381, 584].

Yang *et al.*, compared HRQoL of incontinent and continent urinary diversions (all types) including 29 studies (n = 3,754) of which 9 had a prospective design (one of which was randomised) [381]. Only three studies reported HRQoL data both pre- and post-operatively. In these three studies, an initial deterioration in overall HRQoL was reported but general health, functional and emotional domains at 12 months post-surgery were equal or better than baseline. After 12 months, the HRQoL benefits diminished in all domains. Overall, no difference in HRQoL between continent and incontinent urinary diversion was reported although an ileal conduit may confer a small physical health benefit [584].

Cerruto *et al.*, reported HRQoL comparing ileal conduit with orthotopic neobladder reconstruction [584]. A pooled analysis was performed including 18 studies (n = 1,553) of which the vast majority were retrospective studies. The analysis showed no statistical significant difference in overall HRQoL, but methodological limitations need to be considered.

Clifford *et al.*, prospectively evaluated continence outcomes in male patients undergoing orthotopic neobladder diversion [585]. 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 females with an orthotopic neobladder. Bartsch and co-workers reported day-time and night-time continence rates of 70.4% and 64.8%, respectively, in 56 female neobladder patients. 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 [586].

Altogether, there is no superior type of urinary diversion in terms of overall HRQoL but it is rather a result of proper patient selection. An older and isolated patient is probably better served with an ileal conduit, whereas a younger patient with a 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 [381].

A number of RCTs comparing ORC with RARC (with either intra- or extracorporeal urinary diversion) have reported their HRQoL data [375, 376, 587, 588]. All studies reported no statistical significant difference in HRQoL outcomes between surgical techniques.

*7.8.4 **Bladder-sparing trimodality therapy***

The only HRQoL data in bladder sparing treatment collected in a RCT setting was published by Huddart *et al.* [497]. The primary endpoint was the change in the Bladder Cancer Subscale (BLCS), as part of the FACT-BL questionnaire, at one year post-treatment. Questionnaire return rate at one and five years was 70% and 60%, respectively. The remaining patients did mostly not respond as a result of recurrence or RC. A reduction in HRQoL was seen in the majority of the domains immediately following RT, however, in most patients the HRQoL scores returned to baseline 6 months after RT and maintained at this level for five years. Approximately 33% of patients reported persistent lower Bladder Cancer Subscale scores after five years. Addition of chemotherapy did not affect the HRQoL outcomes.

7.8.5 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 [589]. Beneficial impact of palliative surgery [590], RT [591], and/or chemotherapy on bladder-related symptoms have been described [592].

A HRQoL analysis was performed in platinum-refractory patients who were randomised to pembrolizumab vs. another line of chemotherapy (KEYNOTE-45 trial) [593]. 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 [593].

7.8.6 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 BC has a negative impact on HRQoL.	2a
There is no distinct difference in overall QoL between patients with continent or incontinent diversion.	2a
In patients with MIBC treated with RC, overall HRQoL declines immediately after treatment and recovers to baseline at 12 months post-operatively.	1a
HRQoL data are comparable for RARC (with either intracorporeal or extracorporeal urinary diversion) and ORC.	1b
In patients with MIBC treated with RT, overall HRQoL declines immediately after treatment. In most patients, overall HRQoL then recovers to baseline at 6 months and maintains at this level to 5 years.	1b
In patients with MIBC treated with radiotherapy, concomitant chemotherapy or neoadjuvant chemotherapy has no significant impact on HRQoL.	1b
In patients with platinum-refractory advanced UC, 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 muscle-invasive bladder cancer.	Strong
Discuss the type of urinary diversion taking into account a patient preference, existing comorbidities, tumour variables and coping abilities.	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 [594].

Nomograms on CSS following RC have been developed and externally validated, but their wider use cannot be recommended until further data become available [595, 596].

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 [597-599]. From the Volkmer B, *et al.*, series of 1,270 RC patients, no differences in OS were observed between asymptomatic and symptomatic recurrences [598]. 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 [597]. 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 [599].

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 [600].

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 [601].

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. Trimodality management generally involves a combination of chemotherapy, radiation and surgery [600].

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 [602]. 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%) [603].

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 [604-606]. However, longer survival (28–33% at 5 years) has been reported in patients with minimal metastatic disease undergoing trimodality management, including metastasectomy [607, 608].

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 (in men) and bladder neck (in women). Orthotopic neobladder was associated with a significant lower risk of urethral tumours after RC (OR: 0.44) [609].

There is limited data, and agreement, about urethral follow-up, with some authors recommending routine surveillance with urethral wash and urine cytology and others doubting the need for routine urethral surveillance. However, there is a significant survival advantage in men with urethral recurrence diagnosed asymptomatically vs. symptomatically, so follow-up of the male urethra is indicated in patients at risk of urethral recurrence [600]. Treatment is influenced by local stage and grade of urethral occurrence. In urethral CIS, BCG instillations have success rates of 83% [610]. 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) [611]. Median OS is 10–55 months, and 60–67% of patients die of metastatic disease [600]. 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 [612]. Multifocality increases the risk of recurrence by three-fold, while positive ureteral or urethral margins increase the risk by seven-fold. Radical nephroureterectomy can prolong survival [613].

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 [612].

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 [614]. However, this model has not been validated, does not differentiate between pure UC or variant histologies, and does not incorporate several risk factors related to non-BC mortality. Variant histology tumours (including urothelial variants,

non-urothelial variants, and mixed variants) might be associated with a greater recurrence risk than PUC. Recently, a different follow-up scheme for patients with variant histology tumours has been proposed [615]. In case of pT0 patients with previous variant histology in TURB or in those in the age range between 60 and 79 years, the follow-up should be longer than in PUC since the risk of recurrence persists over time. Similar to PUC, patients older than 80 years with variant histology tumours might not need oncologic surveillance given the higher risk of non-BC mortality compared to the risk of recurrence whereas patients younger than 60 years should be offered extended surveillance (> 10 years) since the risk of recurrence will exceed that of non-BC mortality [615]. Future prospective studies are needed to answer the question whether a more intense follow-up for variant histologies should be considered.

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 [8, 9]. 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. In a single-centre series of 259 male patients, long-term follow-up after orthotopic bladder substitution (median 121 months [range 60–267]), showed that excellent long-term functional outcomes can be achieved in high-volume centres with dedicated teams [617]. A smaller multi-centre series including women only (n = 102) showed complication rates between 5–12% after orthotopic neobladder (median follow-up of 24 months [range 1.5–100 months]). Both early (5%) and late (12%) complications related to the urinary diversion [618].

The functional complications are diverse and include: vitamin B12 deficiency, metabolic acidosis, worsening of renal function, urinary infections, urolithiasis, ureteroenteric stricture [619], stoma complications in patients with ileal conduit, neobladder continence problems, and emptying dysfunction [600]. Benign ureteroenteric strictures may occur in up to 20% of patients [619]. Functional complications are especially common in women: approximately two-thirds need to catheterise their neobladder, while almost 45% do not void spontaneously at all [586]. There seems to be a correlation between voiding patterns and nerve preservation; in 66 women bilateral preservation of autonomic nerves decreased the need for catheterisation to between 3.4–18.7% (CI: 95%) [618].

Based on SEER data, cystectomy was found to be associated with a 21% increased risk of fractures 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 [8, 9, 411].

8.5 Summary of evidence and recommendations for specific recurrence sites

Site of recurrence	Summary of evidence	Recommendation	Strength rating
Local recurrence	Poor prognosis. Treatment should be individualised depending on the local extent of tumour.	Offer radiotherapy, chemotherapy and possibly surgery as options for treatment, either alone or in combination.	Strong
Distant recurrence	Poor prognosis.	Offer chemotherapy as the first option, and consider metastasectomy or radiotherapy 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.	See EAU Guidelines on Primary Urethral Carcinoma.	Strong

8.6 EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [8, 9]*

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 *in situ* and tumour in the prostatic urethra).
After trimodality treatment with curative intent, follow-up for the detection of relapse is recommended every 3–4 months initially; then after 3 years, every 6 months 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 months 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 years 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 years 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 ≥ 70% agreement and ≤ 15% disagreement, or vice versa).*
CEA = carcinoembryonic antigen; CT = computed tomography; LDH = lactate dehydrogenase.

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10. CONFLICT OF INTEREST

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

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11. CITATION INFORMATION

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