EAU Guidelines on

Muscle-invasive and Metastatic Bladder Cancer

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1. INTRODUCTION

1.1 Aims and scope

This overview represents the updated European Association of Urology (EAU) Guidelines for Muscle-invasive and Metastatic Bladder Cancer (MIBC). The aim is to provide practical recommendations on the clinical management of MIBC. Separate EAU Guidelines are available addressing upper urinary tract tumours [1], non-muscle-invasive bladder cancer (TaT1 and carcinoma *in situ*) (NMIBC) [2] and primary urethral carcinomas (PUC) [3].

It must be emphasised that clinical guidelines present the best evidence available to the experts but following Guidelines 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 on MIBC is an international, multidisciplinary group of clinicians, including urologists, oncologists, a pathologist, a radiologist, a radiotherapist and two patient representatives. Section 6.2 on MIBC and health status was developed with the assistance of Prof. Dr. S. O'Hanlon, consultant geriatrician, International Society of Geriatric Oncology (SIOG) representative. 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/guidelines/muscle-invasive-and-metastatic-bladder-cancer/panel.

1.3 Available publications

A quick reference document (Pocket Guidelines) is available. This reference document is an abridged version that may require consultation together with the full text version. Several scientific publications are available, the latest dating to 2025 [4]. All documents are accessible through the EAU website Uroweb: https://uroweb.org/guidelines/muscle-invasive-and-metastatic-bladder-cancer. An EAU Guidelines App for iOS and Android devices is also available, containing the Pocket Guidelines, interactive algorithms and calculators, clinical decision support tools, Guidelines cheat sheets and links to the extended Guidelines.

1.4 Publication history and summary of changes

*1.4.1 **Publication history***

The EAU Guidelines on MIBC were first published in 2004. Standard procedure for EAU Guidelines includes an annual assessment of newly published literature in the field to guide future updates. These 2026 MIBC Guidelines present a comprehensive update of the 2025 publication.

*1.4.2 **Summary of changes***

For the 2026 MIBC Guidelines, new and relevant evidence was identified, collated and appraised through a structured assessment of the literature for all sections of the Guidelines. Key changes include:

- The Guidelines were restructured to follow the patient journey and illustrate real-world clinical pathways.
- Further data from the NIAGARA study was added, including that the perioperative regimen of cisplatin/gemcitabine and durvalumab has been approved by the European Medicines Agency (EMA) in July 2025, and it is also United States Food and Drug Administration (FDA) approved.
- The recently published results from the IMvigor011 trial evaluating the efficacy of atezolizumab as adjuvant therapy versus a placebo in patients with high-risk MIBC who are circulating tumour deoxyribonucleic acid (ctDNA) positive following cystectomy was added.
- The results from the phase III KEYNOTE-905/EV-303 study evaluating perioperative enfortumab vedotin plus pembrolizumab (EV + P) in patients with cisplatin-ineligible MIBC.
- Further data of extended follow-up from three phase III randomised controlled trials (RCTs) were included. The interim overall survival (OS) data reported a promising trend in favour of nivolumab.
- An RCT was included that reported on functional outcomes of robot-assisted radical cystectomy (RARC) with intracorporeal urinary diversion (ICUD) padua neobladder.
- A systematic review and meta-analysis was included that found that 90-day mortality was 11% in patients aged ≥ 80 years, compared to 2% for patients aged < 80 years.
- The withdrawal of the accelerated FDA approval indication for Sacituzumab govitecan was addressed, as the TROPiCS-04 trial reported that it did not significantly improve OS or progression-free survival (PFS) compared with physician's choice of chemotherapy.

- A systematic review and meta-analysis of metastasis-directed therapy was included, showing long-term survival after surgical metastasectomy in metastatic urothelial carcinoma.
- Statistics on mental health disorders after bladder cancer diagnosis have been included. Clinicians should monitor mental health post-MIBC surgery, refer to specialist support when needed, and inform patients of peer support options.
- The following new recommendations were included in Chapters 4, 6 and 10:
    - Determine immunohistochemical human epidermal growth factor receptor (HER) 2 expression to select patients for HER2-directed antibody-drug conjugate therapy.
    - Offer antibody-drug conjugate Trastuzumab deruxtecan in case of HER2 over expression (IHC 3+) and consider in case of HER2 (IHC 2+).
    - Offer perioperative chemo-immunotherapy with cisplatin/gemcitabine and durvalumab to patients with MIBC (T2-T4a, cN0 M0) who are eligible for cisplatin-based chemotherapy (GFR > 40mL/min. allowed) and immunotherapy.

2. METHODS

2.1 Data identification

For the 2026 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 Guidelines was performed. Databases searched included Medline, EMBASE and the Cochrane Libraries, covering a time frame between 1 May 2024 and 1 May 2025. After deduplication, a total of 922 unique records were identified, retrieved and screened for relevance. A detailed search strategy is available online: https://uroweb.org/guidelines/muscle-invasive-and-metastatic-bladder-cancer/publications-appendices.

Recommendations within the Guidelines are developed by the Panels to prioritise clinically important care decisions. 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 the nature and variability of patient values and preferences. This decision process, which can be reviewed in the strength rating forms that accompany each Guidelines recommendation, addresses a number of key elements:

1. the overall quality of the evidence that exists for the recommendation [5]
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 and certainty of patient values and preferences on the intervention.

Strong recommendations typically indicate a high degree of evidence quality and/or a favourable balance of benefit to harm and patient preference. Weak recommendations typically indicate availability of lower quality evidence and/or equivocal balance between benefit and harm, and uncertainty or variability of patient preference [6].

Additional methodology information and a list of associations endorsing the EAU Guidelines is available online: https://uroweb.org/eau-guidelines/methodology-policies.

2.2 Peer review

The MIBC Guidelines were peer reviewed in 2025. All systematic reviews and summary papers derived from the Guidelines have also been peer reviewed prior to publication.

2.3 Future goals

Topics considered for inclusion in the 2027 update of the MIBC Guidelines include:

- Development of a consensus-based strategy for functional- and oncological follow-up of patients treated for MIBC; and
- Participation in developing strategies to ensure meaningful participation of patients in the development and implementation of the MIBC Guidelines.

3. EPIDEMIOLOGY AND AETIOLOGY

3.1 Clinical presentation

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

3.2 Epidemiology

Bladder cancer (BC) is the sixth most commonly diagnosed cancer in males, and it is the ninth when both sexes are considered [7]. The worldwide age-standardised incidence rate (per 100,000 person/years) is 9.3 for males and 2.4 for females [7]. In the European Union, the age-standardised incidence rate is 23.2 for males and 5.9 for females [7]. In Europe, the highest age-standardised incidence rate has been reported in Spain (32.4 in males and 7.8 in females) and the lowest in Luxembourg (10.3 in males and 4.4 in females) [7].

Worldwide, the BC age-standardised mortality rate (per 100,000 person/years) in 2022 was 3.1 for males versus 0.80 for females [7]. Bladder cancer incidence and mortality rates vary across countries due to differences in risk factors, detection and diagnostic practices, and availability of treatments. The variations are, however, also partly caused by the various methodologies used in the studies and the quality of data collection [8]. The incidence and mortality of BC have decreased in some registries, possibly reflecting the decreased impact of causative agents [9-11].

Approximately 25% of patients with BC present with muscle invasive disease. In younger patients (< 40 years) this percentage is lower [12]. Patients with T2-4 tumours have a higher risk of cancer-specific mortality (CSM) compared with TaT1 and carcinoma *in situ* (CIS) [7, 8].

3.3 Aetiology

*3.3.1 **Tobacco smoking***

Tobacco smoking is the most well-established risk factor for BC, causing 50-65% of male cases and 20-30% of female cases [13]. A meta-analysis of 89 studies that comprised data from 57,145 BC cases calculated summary odds ratios (ORs). Dose-response meta-analyses were used to examine the relationships between smoking intensity, duration, pack-years and cessation with BC risk. The sources of heterogeneity were explored, and sensitivity analyses were conducted to test the robustness of findings. Former smokers (hazard ratio [HR]: 2.2) and current smokers (HR: 4.1) had higher risks of BC than never smokers [14]. In studies in which chance, bias and confounding can be discounted with reasonable confidence, a causal relationship has been established between exposure to tobacco and cancer [13, 15].

An increase in risk estimates for current smokers relative to never-smokers has been described, suggesting this could be due to changes in cigarette composition [13]. Starting to smoke at a younger age increased the risk of death from BC [16]. An immediate decrease in the risk of BC has been observed in those who stopped smoking. The reduction was approximately 40% within one to four years of quitting smoking, and 60% after 25 years of cessation [17]. Encouraging people to stop smoking would result in the incidence of BC decreasing equally in males and females [13].

*3.3.2 **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 (except hair dyes [18]), rubbers, textiles, paints, leathers and chemicals are used [19]. 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 [20]. Population-based studies established the occupational attribution for BC in males to be 7.1%, while no such attribution was discernible for females [21].

*3.3.3 **Radiotherapy***

Increased rates of secondary bladder malignancies have been reported after external-beam radiotherapy (EBRT) for gynaecological malignancies, with relative risks of 2 to 4 [22].

A recent study analysed 583 patients with prostate cancer who underwent brachytherapy, with or without EBRT, and assessed disease-free survival (DFS) for BC in this cohort. Of these patients, 2.4% developed BC after brachytherapy with or without EBRT. The percentage of high-grade urothelial carcinoma (UC) was 63.6%. A total of 85.7% of the patients had NMIBC, and 14.3% of patients had MIBC. Disease-free survival was longer in brachytherapy monotherapy than in combination therapy (brachytherapy + EBRT). The study showed that most

cases of BC after brachytherapy with or without EBRT are high grade and invasive. External-beam radiotherapy in combination might be a risk factor for BC in patients with prostate cancer who underwent brachytherapy [23].

It has been proposed that patients who have received EBRT for prostate cancer with modern modalities such as intensity-modulated radiotherapy (IMRT) may have lower rates of in-field bladder- and rectal secondary malignancies [24]. Nevertheless, since longer follow-up data are not yet available, and as BC requires a long period to develop, further studies are required [24].

*3.3.4 **Dietary factors***

It is biologically plausible for dietary factors to influence BC risk, considering that beneficial as well as harmful components of a diet are excreted through the urinary tract and in direct contact with the epithelium of the bladder. However, studies that investigated the association between dietary factors and BC risk have largely reported inconsistent results. Dietary carbohydrate intake does not appear to be directly associated with BC risk. Even though a large number of studies have investigated the association between fruit and vegetable consumption, their micronutrient content, and BC risk, these have yielded inconsistent results. No strong evidence is available to suggest that supplementation with any common micronutrient is effective in reducing BC risk. However, the limitations in published research do not totally eclipse the observation that a diet rich in fruits and vegetables and low in processed meat - especially along with smoking cessation - may convey some protective effects against BC risk [25].

*3.3.5 **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 males, whereas high body mass index (BMI) was associated with decreased BC risk. The associations between BMI, blood pressure and BC risk significantly differed between males and females [26].

The association of diabetes mellitus with the risk of BC has been evaluated in numerous meta-analyses with inconsistent results. When analysing specific subpopulations, diabetes mellitus was associated with BC or CSM risk, especially in males [27]. The FDA recommends that healthcare professionals should not prescribe pioglitazone in patients with active BC [28]. Several countries in Europe have removed this agent from the market or included warnings for prescription. However, a recent systematic review emphasised the importance of cautious interpretation regarding the safety profile of pioglitazone in relation to BC risk. Of the included studies, two suggested a potential association between pioglitazone use and an increased risk of BC, whereas four reported no statistically significant correlation [29]. Moreover, the benefits of glycaemic control versus unknown risks for cancer recurrence with pioglitazone should be considered in patients with a prior history of BC.

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

Bladder schistosomiasis (bilharzia) is the second most common parasitic infection after malaria, with approximately 250 million people infected annually [30]. There is a clear relationship between schistosomiasis and UC of the bladder, which can develop into BC and, if not treated, squamous cell carcinoma (SCC). Better control of the disease reduces the incidence of SCC of the bladder in endemic areas, such as Egypt [31].

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 twofold increased risk of BC in patients with recurrent UTIs in some series [31]. However, a meta-analysis found no statistical association when pooling data from the most recent and highest quality studies. This highlights the need for better quality data to be able to draw conclusions [32].

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 [33].

*3.3.7 **Sex***

Although males are more likely to develop BC than females, females present with more advanced disease and have worse survival rates. A meta-analysis including nearly 28,000 patients showed that female sex was associated with a worse survival outcome (HR: 1.20; 95% confidence interval [CI]: 1.09-1.32) compared to male sex after radical cystectomy (RC) [34]. This finding had already been presented in a descriptive nationwide analysis based on 27,773 Austrian patients. After analysis, it was found that cancer-specific survival (CSS) was

identical for pT1 tumours in both sexes, while females had a worse CSS in both age cohorts (< 70 years and ≥ 70 years) with higher tumour stages [35]. However, treatment patterns are unlikely to explain the differences in OS [36]. In a population-based study from the Ontario Cancer Registry analysing all patients with BC treated with cystectomy or radical radiotherapy (RT) between 1994 and 2008, no differences in OS, mortality and outcomes were found between males and females following radical therapy [37]. The sex-specific difference in survival for patients with BC was also analysed in the Norwegian population. Survival was inferior for females, but only within the first two years after diagnosis. This discrepancy was partly attributed to a more severe T-stage in female patients at initial diagnoses [38].

A population-based study from the MarketScan databases suggests that possible reasons for worse survival in the female population may include longer delays in diagnosis than males, as the differential diagnosis in females include diseases that are more prevalent than BC, such as UTIs [39]. Furthermore, differences in the sex prevalence of BC may be due to other factors besides tobacco and chemical exposure. In a large prospective cohort study, postmenopausal status was associated with an increased risk of BC, even after adjustment for smoking status. This finding suggests that the differences in oestrogen and androgen levels between males and females may be responsible for some of the difference in the sex prevalence of BC [40-42]. Moreover, a population study assessing impact of hormones on BC suggested that younger age at menopause (≤ 45 years) is associated with an increased risk of BC [43].

*3.3.8 **Genetic factors***

There is growing evidence that genetic susceptibility factors and family association may influence the incidence of BC. A 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 [44]. Shared environmental exposure was recognised as a potentially confounding factor [45]. Studies have detected genetic susceptibility with independent loci, which are associated with BC risk [46]. Genome-wide association studies of BC identified several susceptibility loci associated with BC risk [47].

3.4 Summary of evidence and recommendations for epidemiology and risk factors

Summary of evidence	LE
Worldwide, BC is the ninth most 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
Counsel patients to stop active and avoid passive smoking.	Strong
Inform workers in potentially hazardous workplaces of the potential carcinogenic effects of a number of recognised substances, including duration of exposure and latency periods. Protective measures are recommended.	Strong

4. PATHOLOGY AND CLASSIFICATION SYSTEMS

4.1 Cytology

Evaluation of cytology specimens can be hampered by low cellular yield, UTIs, stones or intravesical instillations, but for experienced readers, specificity exceeds 90% [48, 49]. However, negative cytology does not exclude a tumour.

A standardised reporting system, known as The Paris System, published in 2022 (2nd Edn.) redefined urinary cytology diagnostic categories and full category names should always be cited [50]:

- adequacy of urine specimens (Adequacy)
- negative for high-grade UC (Negative)
- atypical urothelial cells (AUC)
- suspicious for high-grade UC (SHGUC)
- high-grade UC (HGUC)

4.2 Histology

All muscle invasive UCs of the bladder are high grade. For this reason, no prognostic information can be provided by grading MIBC [51]. Identification of morphological subtypes is important for prognostic reasons and treatment decisions [52, 53].

The data presented in these Guidelines are based on the 2004/2016 World Health Organization (WHO) classifications. An update was presented in 2022 [51].
Currently, the following subtypes of UC are used [54]:

1. urothelial carcinoma (more than 90% of cases)
2. urothelial carcinomas with partial squamous and/or glandular or divergent differentiation
3. micropapillary UC
4. nested/microcystic
5. large nested UC
6. microtubular UC
7. plasmacytoid, signet ring
8. lymphoepithelioma-like
9. giant cell, diffuse, undifferentiated
10. sarcomatoid UC
11. some UCs with other rare differentiations
12. urothelial carcinomas with partial neuroendocrine (NE) differentiation (% to be given)
13. pure NE carcinoma (including small and large cell NE carcinomas [51]).

The percentage of subtype in the specimen must be reported, as it has been shown to be of prognostic value [55]. The majority of subtypes are MIBC, with no more than 15-30% being NMIBC [51, 55-61].

4.3 Pathological staging

For staging, the Tumour, Node, Metastasis (TNM) classification (2025, 9th edition) is recommended [62]. Blood and lymphatic vessel invasion have an independent prognostic significance [63].

4.4 Tumour, Node, Metastasis classification

The TNM Classification of malignant tumours is the method most widely used to classify the extent of cancer spread [62] (Table 4.1).

Table 4.1: Tumour, Node, Metastasis Classification of urinary bladder cancer [62]

T - Primary tumour	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma *in situ*: “flat tumour”
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
T2a	Tumour invades superficial muscle (inner half)

T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue:
T3a	microscopically
T3b	macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostate stroma, seminal vesicles, uterus or vagina
T4b	Tumour invades pelvic wall or abdominal wall
N - Regional lymph nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac or presacral)
N2	Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac or presacral)
N3	Metastasis in a common iliac lymph node(s)
M - Distant metastasis	
M0	No distant metastasis
M1a	Nonregional lymph nodes
M1b	Other distant metastasis

Staging after neoadjuvant chemotherapy (NAC) and RC can be done but must be reported as ypTNM (International Collaboration on Cancer Reporting) [64]. ypT0N0 after NAC and cystectomy is associated with better prognosis [51, 65, 66].

Photodynamic diagnosis (PDD) is highly sensitive for detecting CIS. In experienced hands, the false-positive rate may be similar to that of conventional white-light cystoscopy [67, 68].

4.5 Pathological markers

The most important histopathological prognostic variables after RC and lymph node dissection (LND) are tumour stage and lymph node (LN) status [69]. In addition, other histopathological parameters of the RC specimen have been associated with prognosis.

*4.5.1 **Lymphovascular invasion***

The value of lymphovascular invasion (LVI) was reported in a systematic review and meta-analysis including 78,000 patients from 65 studies treated with RC for BC [70]. In 35% of patients, LVI was present and correlated with a 1.5-fold higher risk of recurrence and CSM, independent of pathological stage and perioperative chemotherapy. This correlation was even stronger in those patients with node-negative disease [71].

*4.5.2 **Carcinoma in situ***

In a systematic review and meta-analysis that included 23 studies and over 20,000 patients, the presence of concomitant CIS in the RC specimen was associated with a higher 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 disease-specific survival (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) [71].

*4.5.3 **Tumour location***

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 [69, 72-74].

Prostatic urethral involvement at the time of RC was also found to be associated with worse survival outcomes. In a series of 995 patients, prostatic involvement was recorded in 31% of patients. The five-year CSS in patients with CIS of the prostatic urethra was 40%, whilst the prognosis of patients with UC invading the prostatic stroma was worse with a five-year CSS of only 12% [75].

The Southwest Oncology Group (SWOG) 8710 trial, a randomised phase III trial assessing cystectomy ± NAC in patients with MIBC, suggested that Neutrophil-to-lymphocyte ratio is neither a prognostic nor a predictive biomarker for OS in MIBC [76].

*4.5.4 **Lymph node-positive disease***

In patients with LN-positive disease, various prognostic parameters have been reported, such as the number of LNs removed, the number of positive LNs, LN density (the ratio of positive LNs to the number of LNs removed) and extranodal extension. LN density is subject to surgical and pathological factors. This makes it difficult to apply the concept of LN density uniformly [77].

To allow for pTNM staging, all LN specimens should be provided in their totality, separated in clearly labelled containers or *en bloc* on a board. In case of doubt or adipose differentiation of the LNs, the entire specimen must be included. Lymph nodes should be counted and measured on slides; capsular rupture and percentage of LN invasion should be reported as well as LVI [64, 78]. In case of metastatic spread in the perivesical fat without real LN structures (capsule, subcapsular sinus), this localisation should nevertheless be considered as N+.

4.6 Tissue handling

During transurethral resection, specimens should be taken from the superficial and deep areas of the tumour and sent to the pathology laboratory separately. If random biopsies of the normal-looking mucosa are taken, each biopsy specimen must be submitted separately [79]. 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 [80].

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.

Specimen handling should follow the rules of handing and sampling RC specimens [81]. 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 transurethral resection or NAC, and all retracted or ulcerated areas should be inked and included before fixation.

4.7 Recommendations for the assessment of tumour specimens

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

4.8 EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [82, 83]*

Consensus statements
Muscle-invasive pure SCC 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 preven-tive brain irradiation to avoid brain recurrence.
Differentiating between urachal and non-urachal subtypes of adenocarcinoma is essential when making treatment decisions.

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

The consensus statements were published in 2019 and 2020, respectively. Accordingly, not all consensus statements have been included.

4.9 Markers

4.9.1 Introduction

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

4.9.2 Clinical and histopathological markers

In a meta-analysis including 19 cohorts from 16 studies, inferior outcomes were seen in progressive versus *de novo* MIBC regardless of the use of NAC [84]. Subtypes and non-UC have also been linked to worse outcomes after NAC, but as yet, there is insufficient data to conclude that these can be considered as predictive markers [85].

4.9.3 Molecular variants

The updated Cancer Genome Atlas (TCGA) reported on 412 MIBCs and identified five messenger ribonucleic acid (mRNA) expression-based molecular variants, including luminal-papillary, luminal-infiltrated, luminal, basal-squamous and neuronal (a variant associated with poor survival in which some of the tumours did not have small cell or NE histology). Each variant is associated with distinct mutational profiles, sometimes with histopathological features and prognostic and treatment implications [86].

The basal-squamous variant is characterised by expression of basal keratin markers, immune infiltrates and is considered to be chemo-sensitive. The luminal papillary variant is characterised by fibroblast growth factor receptor 3 (*FGFR* 3) alterations (luminal-papillary [LumP]) [87]. In 2019, a consensus on molecular variant classification was reported [53]. An analysis of 1,750 MIBC transcriptomic profiles from 18 datasets identified six MIBC molecular classes that reconciled all previously published classification schemes. The molecular variant classes include LumP, luminal non-specified (LumNS), luminal unstable (LumU), stroma-rich, basal/squamous (Ba/Sq) and NE-like. Each class has distinct differentiation patterns, oncogenic mechanisms, tumour microenvironments and histological and clinical associations. However, it was stressed that consensus was reached for biological rather than clinical classes.

A study investigated how variants impact pathological response and survival in patients receiving preoperative cisplatin-based chemotherapy [88]. Patients with genomically unstable and urothelial-like tumours had higher proportions of pathologic complete response (16/31 [52%] and 17/54 [31%]), versus 5/24 (21%) for the Ba/Sq subtype following NAC and RC. Molecular subtype was independently associated with improved survival for patients with genomically unstable tumours (HR: 0.29; 95% CI: 0.11-0.79) and urothelial-like tumours (HR: 0.37; 95% CI: 0.14-0.94) compared with Ba/Sq tumours, adjusting for clinical stage. In a *post-hoc* analysis of the GETUG/AFU VESPER trial of NAC, Ba/Sq tumours had poor outcomes post-NAC compared to other consensus subtypes [89]. At this time, the classification should be considered as a research tool for retrospective and prospective studies until future studies establish how these molecular variants may best be used in a clinical setting.

4.9.4 *Molecular markers*

4.9.4.a DNA damage repair genes

Expression of, or defects in, DNA damage repair genes including *ERCC2*, ATM, *MRE11*, *RB1* and *FANCC* that may predict response to cisplatin-based NAC [90, 91] or chemoradiation [92-95]. The presence of a mutation in any of *ATM*, *RB1*, *ERCC2* and *FANCC* genes was found to be associated with a higher likelihood of achieving a pathologic complete response with NAC [96]. In a correlative analysis of the SWOG S1314 neoadjuvant trial of gemcitabine and cisplatin (GC) or dose-dense methotrexate, vinblastine, adriamycin, and cisplatin (DDMVAC), a mutation in any one of the four genes, *ATM*, *RB1*, *FANCC* or *ERCC2*, was predicted for pT0 at surgery [96].

4.9.4.b *FGFR* alterations

An important advance has been the recognition of alterations in *FGFR* 3, including mutations and gene fusions as a predictive marker for response to FGFR inhibitors [97, 98]. Alterations in *FGFR* 3 are used to select patients for treatment with the FGFR inhibitor erdafitinib (see Chapter 9, 'Metastatic disease') [99]. Screening metastatic UC (mUC) patients is recommended, ideally at diagnosis of metastatic disease, for *FGFR* 3 alterations to plan optimal treatment.

4.9.4.c Nectin-4

The membrane antigen receptor Nectin-4 is a target for the antibody-drug conjugate enfortumab vedotin (EV). Nectin-4 is believed to have ubiquitous expression on UC cells. Nectin-4 can be assessed either by immunohistochemistry or fluorescent *in situ* hybridisation (FISH). Reports from a German study group suggest that Nectin-4 expression is decreased on metastatic cells [100]. Nectin-4 amplification may represent a predictive factor for benefit from EV and merits further investigation [101].

4.9.4.d PD-L1 expression

Several 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. The predictive value of PD-L1 was, for example, not confirmed in large phase III trials evaluating the integration of immunotherapy (IO) in the first-line setting for mUC [102-104]. This may in part be related to the use of different antibodies and various scoring systems evaluating different compartments, that is, 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. At present, the indications for PD-L1 testing relate to the restricted EMA approval for nivolumab in the adjuvant setting (≥ 1% tumour cells PD-L1 positive) and pembrolizumab (combined positive score [CPS] of ≥ 10) and atezolizumab (immune cells ≥ 5%) as first-line monotherapy in patients with locally advanced or mUC unfit for cisplatin-containing chemotherapy.

4.9.4.e Circulating tumour DNA

Studies have reported on the potential for ctDNA to guide the use of adjuvant IO in UC [105-107]. In 581 patients from a phase III RCT of adjuvant atezolizumab versus observation in UC, ctDNA testing at the start of therapy identified 37% of patients who were positive for ctDNA and who had poor prognosis (observation arm HR: 6.3; 95% CI: 4.45-8.92; $p < 0.0001$) [105]. Patients who were positive for ctDNA had improved DFS and OS in the atezolizumab arm versus 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). For patients who were negative for ctDNA, there was no difference in DFS or OS between treatment arms. The rate of ctDNA clearance at week six was higher in the atezolizumab arm (18%) than in the observation arm (4%) ($p = 0.0204$) [105]. The results from the IMvigor011 trial evaluating the efficacy of atezolizumab as adjuvant therapy versus a placebo in patients with high-risk MIBC who are ctDNA positive were recently published (see Section 6.5.2.b) [108].

4.9.4.f Biomarkers for response to immune checkpoint inhibitors

Urothelial cancer is associated with a high tumour mutational burden (TMB) [109]. High TMB has been associated with response to immune checkpoint inhibitors (CPIs) in metastatic BC [110, 111]. However, the application of high TMB is limited by several factors, including inconsistent predictive power and the lack of a clear relationship with OS. The tumour microenvironment must also be considered.

Recent work has focused on the importance of stroma, including the role of transforming growth factors, in predicting response to immune checkpoint blockade [112, 113].

Recent findings suggest that neoadjuvant atezolizumab in MIBC is associated with clinical responses and high DFS. Expression of CD8+ cells and serial ctDNA levels can correlate with outcomes and may contribute to personalised therapy in the future [114].

An exploratory analysis in patients with mUC who received pembrolizumab in the first line (KEYNOTE-052 trial) and salvage (KEYNOTE-045 trial) settings demonstrated that TMB and T-cell inflamed gene expression profile were significantly associated with improved outcomes. However, PD-L1 was associated with improved outcomes and stromal signature with worse outcomes in KEYNOTE-052, but not in KEYNOTE-045, suggesting that these biomarkers may perform differently in different clinical disease states, such as first-line versus salvage settings [115]. In a second study, a scoring system (CPT) based on CD39, PD-L1 and TMB was shown to predict response to PD-L1 blockade and platinum-based chemotherapy in patients with MIBC [116].

4.9.4.g HER2 expression

Based on the FDA approval of transtuzumab deruxtecan for patients with pretreated, unresectable or metastatic HER2-positive (IHC3+) solid tumours, evaluation of HER2 immunohistochemistry may be performed [117].

4.9.5 Conclusion

The updated TCGA and other efforts have refined our understanding of the molecular underpinnings of BC biology. Variants, immune gene signatures, as well as stromal signatures may ultimately play 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.

4.9.6 Summary of evidence and recommendations for urothelial markers

Summary of evidence	LE
Defined alterations of *FGFR* 3 are predictive of response to therapy with the FGFR inhibitor erdafitinib.	1b
Circulating tumour DNA holds promise as both a prognostic and predictive biomarker to guide the use of adjuvant IO for UC in patients compared with observation.	2b

Recommendations	Strength rating
Use susceptible fibroblast growth factor receptor 3 alterations to select patients with unresectable or metastatic urothelial carcinoma for treatment with erdafitinib.	Strong
Determine immunohistochemical human epidermal growth factor receptor (HER) 2 expression to select patients for HER2-directed antibody-drug conjugate therapy.	Weak

5. DIAGNOSIS

5.1 History and physical examination

Physical examination should include rectal and vaginal bimanual palpation. A palpable pelvic mass can be found in patients with locally advanced tumours. In addition, bimanual examination under anaesthesia should be carried out before and after transurethral resection of the bladder tumour (TURBT) to assess whether there is a palpable mass or if the tumour is fixed to the pelvic wall [118, 119]. However, considering the discrepancy between bimanual examination and pT stage after cystectomy (11% clinical overstaging and 31% clinical understaging), bimanual examination findings must be interpreted with caution [120].

5.2 Urine 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.

5.3 Cystoscopy

The suspicion of BC is usually based on cystoscopy. An (outpatient) flexible cystoscopy is recommended to obtain a complete image of the bladder. However, the accuracy to predict muscle invasion by cystoscopy only is moderate [121].

If a bladder tumour is visualised on imaging studies such as computed tomography (CT), magnetic resonance imaging (MRI) or ultrasound (US), diagnostic cystoscopy can be omitted, and the patient can proceed directly to TURBT for resection and histological diagnosis.

Careful documentation of cystoscopy findings is necessary, including tumour location, size, number, and morphology (papillary or solid), as well as any mucosal abnormalities [122]. The use of a bladder diagram is recommended.

Photodynamic diagnosis can be considered in patients with multifocal tumours or when CIS is suspected, because the presence of CIS may lead to a modified treatment plan (see EAU Guidelines on NMIBC [2]).

5.4 Transurethral resection of invasive bladder tumours

The goal of TURBT is to provide histopathological diagnosis and staging, which requires inclusion of detrusor muscle in the resection specimen.

When MIBC is suspected, tumours should ideally be resected in separate parts: the exophytic part; the underlying bladder wall, including detrusor muscle; and the edges of the resection area. The deeper portion should be submitted in a clearly labelled, separate container to ensure accurate pathological assessment. If RT is being considered and CIS must be excluded, PDD can be used [123]. During TURBT, a thorough inspection of the bladder wall with rigid cystoscopy under anaesthesia is mandatory to ensure that no lesions are missed.

Involvement of the prostatic urethra and ducts has been reported in up to one-third of male patients with BC [124-126]. Involvement of the prostatic urethra can be determined during primary TURBT or by frozen section at cystoprostatectomy. A frozen section has a higher negative-predictive value and superior accuracy [127-129].

A negative urethral frozen section reliably identifies patients in whom urethrectomy can be avoided. By contrast, a positive preoperative biopsy has limited value, because it does not consistently predict final margin status. [127, 130]. Although the diagnosis of a urethral tumour before cystectomy generally leads to urethrectomy and may contra-indicate an orthotopic diversion, a positive preoperative biopsy alone should not prevent consideration of an orthotopic diversion.

5.5 Summary of evidence and recommendations for the primary assessment of presumably invasive bladder tumours*

Summary of evidence	LE
Cystoscopy is necessary for the diagnosis of BC.	1
Urinary cytology has high sensitivity in high-grade tumours including CIS.	2b
In males, prostatic urethral biopsy includes resection from the bladder neck to the verumontanum (between the five and seven 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 the following cases: 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 males with a negative prostatic urethral biopsy undergoing subsequent orthotopic neobladder construction, an intraoperative frozen section can be omitted.	Strong
In males with a prior positive transurethral prostatic biopsy, subsequent orthotopic neobladder construction should not be denied *a priori*, unless an intraoperative frozen section of the distal urethral stump reveals malignancy at the level of urethral dissection.	Strong
In females 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 the EAU Guidelines on NMIBC [2].*

5.6 Imaging for staging

In clinical practice, tumour stage and grade are used to guide treatment and determine prognosis [131-133]. Imaging is essential for both local and distant staging of BC.

*5.6.1 **Local staging***

5.6.1.a MRI with VI-RADS score

Differentiation between NMIBC and MIBC, as well as assessment of local tumour extent, is crucial for BC treatment. Compared with CT, MRI has superior soft tissue contrast resolution and can evaluate post-biopsy reaction, because tumour enhancement occurs earlier than in the normal bladder wall due to neovascularisation [134, 135]. At present, MRI is not ready to be implemented in standard patient care [136].

Multiparametric (mp)MRI using the Vesical Imaging-Reporting and Data System (VI-RADS) score provides a standardised approach to both acquisition and reporting. The VI-RADS has demonstrated high diagnostic accuracy in differentiating T1 from T2 bladder tumours [137]. The VI-RADS scoring has been shown to be an independent predictor of muscle invasion, supporting its potential role in risk stratification and guiding a more aggressive approach in patients at high risk of MIBC [138]. A meta-analysis reported pooled sensitivity and specificity of 83% and 90%, respectively, for mpMRI with VI-RADS in predicting MIBC, with substantial inter-reader agreement (κ = 0.81-0.92) [139]. Best practice for the routine use of MRI in clinical decision-making remains to be defined [135].

A modified Delphi process, including international experts and a patient representative, produced consensus-based recommendations for bladder MRI, particularly for preoperative staging and response assessment following systemic therapy. Among the agreed statements, experts recommended acquiring and interpreting MRI images according to VI-RADS and, if MRI is performed for primary staging purposes, it should be completed before TURBT [140].

To expedite diagnosis and initiation of definitive treatment for MIBC, increased attention has been given to imaging-guided pathways in which MRI is performed before TURBT. The BladderPath study demonstrated that such an approach can shorten time to definitive treatment for patients with MIBC [141]; however, the study has important limitations, and the clinical utility of this strategy requires confirmation in ongoing clinical trials.

Considering the link between oliniuolinium-based contrast agents and nephrogenic systemic fibrosis in patients with impaired renal function, contrast administration should follow the European Society of Urogenital Radiology (ESUR) Guidelines [142]. Interest is growing toward non-contrast MRI, with emerging evidence suggesting that non-contrast-enhanced VI-RADS scoring may achieve similar predictive accuracy to contrast-enhanced mpMRI. However, further evidence is required before any recommendation can be made [143].

5.6.1.b Computed tomography

General advantages of CT imaging include high spatial resolution, shorter acquisition time, wider coverage in a single breath hold, and lower susceptibility to variable patient factors. Despite its unreliability in differentiating between stages Ta and T3a tumours, CT is useful for detecting invasion into the perivesical fat (T3b) and adjacent organs. The accuracy of CT in determining extravesical tumour extension increases with more advanced disease [144].

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) [145]. When MRI is contraindicated or not available, contrast-enhanced CT using iodinated contrast media can be considered as an alternative [142].

*5.6.2 **Upper tract evaluation***

For local staging of the upper urinary tract, CT urography has the highest diagnostic accuracy of the available imaging techniques. The sensitivity of CT urography for upper urinary tract urothelial carcinoma (UTUC) is 0.67-1.0 and specificity is 0.93-0.99 [146].

Rapid acquisition of thin sections enables 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 [147]. The presence of enlarged LNs is highly predictive of metastases in UTUC [148].

Magnetic resonance urography (MR urography) is indicated in patients who cannot undergo CT urography, usually when radiation or iodinated contrast media are contraindicated [149]. The sensitivity of MR urography is 0.75 after contrast injection for tumours < 2cm [149]. For diagnosing and staging of UTUC, CT urography is generally preferred to MR urography.

*5.6.3 **Lymph node staging***

Assessment of LN metastases based on size alone is limited; both CT and MRI are unable to identify metastases in normal-sized or minimally enlarged nodes. Their sensitivity for LN metastases is low (48-87%), and specificity is limited, because enlargement may be due to benign disease. Both modalities show similar diagnostic performance across pelvic tumours [149-151]. Pelvic nodes > 8mm and abdominal nodes > 10mm in maximum short-axis diameter are considered pathologically enlarged [152]. In 1,104 patients, concordance between cN and pN stages on cross-sectional imaging was modest (65%: sensitivity: 30%; specificity: 84%) [153].

^{18}F-fluorodeoxy glucose-positron emission tomography (FDG-PET) with CT is increasingly used, but its role needs to be further evaluated [154, 155]. A meta-analysis including 785 patients showed a low sensitivity but high specificity for the detection of metastatic LNs in patients with newly diagnosed BC [156]. However, most studies comparing FDG-PET/CT with CT for LN assessment reported higher sensitivity with comparable specificity [157]. In a comparative analysis, PET/CT demonstrated superior diagnostic performance over contrast-enhanched CT. However, up to 20% of occult (micro-) metastases were still missed on final pathology [158].

Additional information to guide local treatment can also be provided by PET/CT in the presence of pelvic nodal metastases [159]. A study of 2,731 patients with MIBC showed that pretreatment staging with FDG-PET/CT led to clinical nodal upstaging in approximately one-fifth of cases, impacting treatment decisions [160]. However, both are retrospective studies.

In addition, the role of PET/CT in evaluating LN involvement in patients receiving neoadjuvant pembrolizumab has been investigated in a clinical trial. The performance of PET/CT did not justify its routine use in cN0 MIBC patients but proved useful in optimising the selection of MIBC patients suited for neoadjuvant IO strategies [161].

*5.6.4 **Distant staging***

Before any curative treatment, it is essential to evaluate the presence of distant metastases. The diagnostic techniques of choice are CT and MRI to detect, for example, lung [162] and liver metastases [163], respectively.

Evidence for the role of FDG-PET/CT for staging distant metastases of MIBC is still limited. In a recent series of 711 patients, FDG-PET/CT has been shown to provide important staging information through the detection of distant metastases, which may impact the clinical management of MIBC patients [159].

Bone and brain metastases are rare at the time of presentation of invasive BC. In a retrospective large sample study, a bone scan was shown to have an impact on patients' intended management in only 19 out of 1,148 (1.7%) patients, therefore, it should not be routinely used [164]. Whole-body MRI is more sensitive and specific for diagnosing bone metastases than bone scintigraphy [165]. Also, additional brain imaging is not routinely indicated unless the patient has specific symptoms or signs to suggest brain metastases.

Table 5.1: The role of imaging in treatment planning

Goal	Imaging modality
Detect bladder tumours	US, CT and MRI
Differentiate T1 from T2 tumours, as treatment will differ	MRI with the VI-RADS score
Assess upper urinary tract	CT or MRI urography
Evaluate locally advanced disease or LN staging	CT or MRI for abdominal- and pelvic LNs or PET/CT scan
Distant staging	CT, MRI or PET/CT to detect distant organ metasta-sis

CT = computed tomography; MRI = magnetic resonance imaging; LN = lymph node; PET = positron emission tomography; US = ultrasound; VI-RADS = vesical imaging-reporting and data system.

5.6.5 Future perspectives

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 [166].

Alternative molecular imaging tracers such as $^{64}CuCl_2$, [^{68}Ga]Ga-FAPI-46 and ^{68}Ga-FAP-2286 are being studied, and preliminary investigations of these agents have demonstrated promising results in nodal staging and restaging in MIBC [167, 168].

In patients who cannot receive intravenous iodinated contrast, PET/CT, combining the benefits of MRI with functional imaging, could be envisioned for the detection of metastatic BC lesions not seen on CT and may lead to improved treatment planning and monitoring for BC [169].

5.6.6 Summary of evidence and recommendations for staging in MIBC

Summary of evidence	LE
Imaging as part of staging in 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, if needed, ureteroscopy.	2b
In local staging, MRI is superior to CT in terms of differentiating T1 from T2 disease.	2b
Magnetic resonance imaging is accurate for the assessment of tumour response to systemic therapy.	3
^{18}F-fluorodeoxy glucose-positron emission tomography with CT can provide additional information to guide treatment.	2b

Recommendations	Strength rating
If magnetic resonance imaging (MRI) is performed for local staging of bladder cancer (BC), it should be carried out before transurethral resection of the bladder tumour.	Strong
In patients with confirmed muscle-invasive BC, 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
Offer MRI to assess the local response to systemic therapy.	Weak

6. DISEASE MANAGEMENT

6.1 Multidisciplinary team for patients with MIBC

All patients with MIBC should be discussed in a multidisciplinary team (MDT) before treatment initiation. For all suitable candidates, both bladder-preserving techniques and RC should be discussed to enable informed decision-making [82, 83]. This approach aligns with international consensus and policy recommendations, including the Lancet Oncology Policy Statement [170].

An MDT facilitates the integration of pathology, TURBT findings, molecular information (when available) and imaging results. Joint decision-making is essential to define the optimal treatment strategy, including RC, bladder-sparing strategies or systemic therapy. MIBC patients should be informed about the benefits and the risks of all possible treatment strategies.

6.1.1 Recommendations for a multidisciplinary team

Recommendations	Strength rating
Manage all patients who are candidates for trimodality therapy in a multidisciplinary team setting. The choice of treatment modality should be made through a shared decision-making process.	Strong
Fully inform the patient about the benefits and potential risks of all possible alternatives before radical cystectomy. The final decision should be based on a balanced discussion between the patient and the surgeon.	Strong

6.2 Health status assessment

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 [171-173]. 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 [174]. 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 [175].

A systematic review and meta-analysis including 58,504 older patients undergoing RC reported a 90-day mortality of 11% in patients aged ≥ 80 years, compared with 2% in those aged < 80 years. While the overall rate of major complications was not higher in older patients, they were significantly more likely to die as a result of these complications. Co-morbid status was predictive of post-RC mortality in both age groups, with a stronger association in the older patients [176].

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 [177].

In a large multicentre study with patients undergoing RC for BC, sarcopenia has been shown to be an independent predictor for OS and CSS [178]. To predict CSM after RC in patients receiving NAC, sarcopenia should be assessed after completing chemotherapy [179]. Other risk factors for morbidity include prior abdominal surgery, extravesical disease and prior RT [180]. Female sex, an increased BMI and lower preoperative albumin levels are associated with a higher rate of parastomal hernias [181]. Low preoperative serum albumin is also associated with impaired wound healing, gastrointestinal (GI) complications and a decrease of recurrence-free and OS after RC [182, 183]. Therefore, it could be used as a prognostic biomarker for patients undergoing RC.

Metformin has been suggested as having possibly anticancer activity in BC by inhibiting tumour growth as well as being synergistic with cisplatin. A systematic review and meta-analysis of 4,006 patients suggests that metformin use was associated with lower cancer specific and overall mortality in patients with MIBC [184].

6.3 Evaluation of comorbidity, frailty and cognition

Evaluation of comorbidity provides a better indicator of life expectancy in MIBC than patient age [185]. Evaluation of comorbidity helps to identify factors likely to interfere with, or have an impact on, treatment and the evolution and prognosis of MIBC [186].

The value of assessing overall health before recommending and proceeding with surgery was emphasised in a study that demonstrated an association between comorbidity and adverse pathological and survival outcomes following RC [187]. In a population-based competing risk analysis of > 11,260 patients from the Surveillance, Epidemiology, and End Results (SEER) registries, similar results were found for the impact of comorbidity on cancer-specific and other-cause mortality. 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 [188].

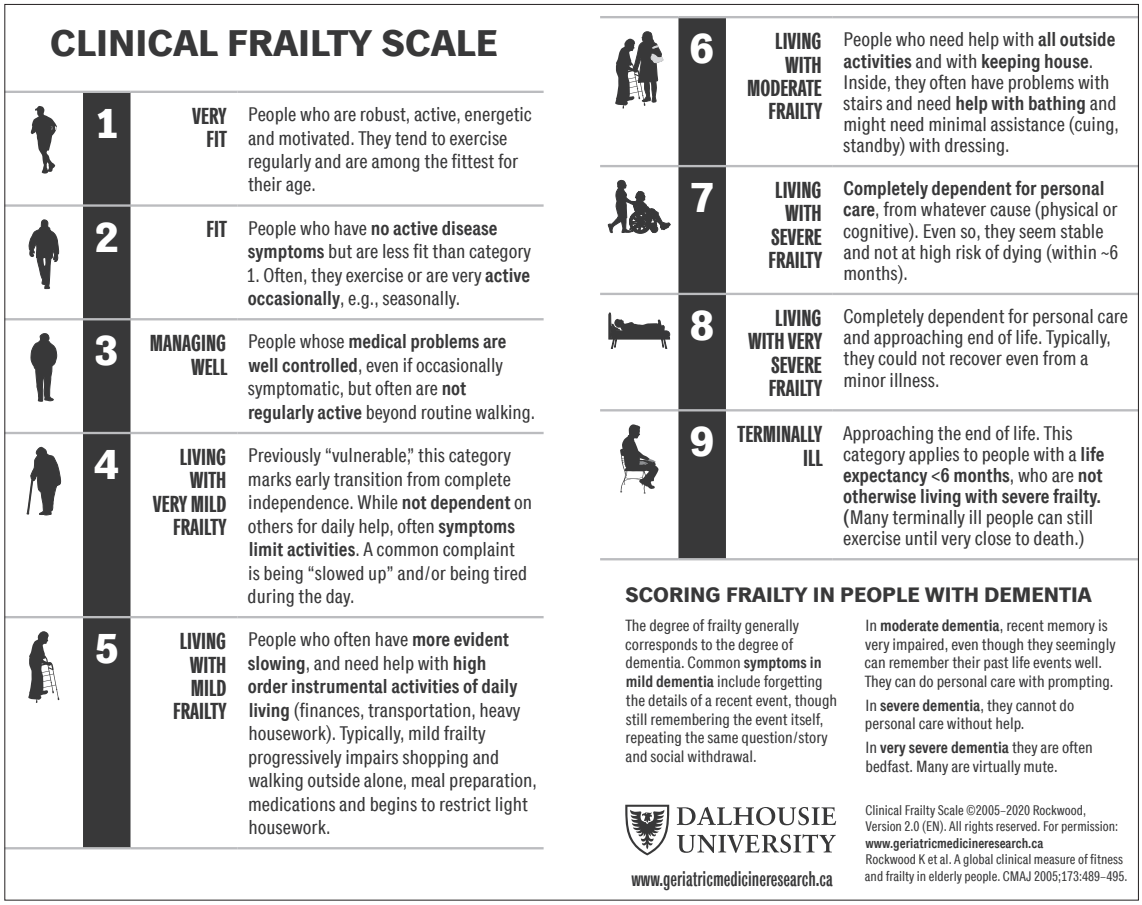
Stratifying older patients according to frailty using a multidisciplinary approach will help select patients most likely to benefit from radical surgery and to optimise treatment outcomes [189]. Many different screening tools are available to treat frailty, and local approaches can be used. Examples include the G8 screening tool and the Clinical Frailty Scale (See Table 6.1 and Figure 6.1 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 five 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 disease 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 [190].

Table 6.1: G8 screening tool (adapted from [191])

	Items	**Possible responses (score)**
A	Has food intake declined over the past three 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 three months?	0 = weight loss > 3kg
		1 = does not know
		2 = weight loss between 1 and 3kg
		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 their 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 6.1: Clinical Frailty Scale©, Version 2.0* [192]



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

6.4 Comorbidity scales, anaesthetic risk classification and geriatric assessment

A range of comorbidity scales has been developed [193], seven of which have been validated [194-200]. 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 a patient's medical records. The score has been widely studied in patients with BC and found to be an independent prognostic factor for perioperative mortality [201, 202], overall mortality [203] and CSM [175, 204-206]. Only the age-adjusted version of the CCI was correlated with both cancer-specific and other-cause mortality [207]. The age-adjusted CCI (Table 6.2) is the most widely used comorbidity index in cancer for estimating long-term survival and is easily calculated [208].

Health assessment of oncology patients must be supplemented by measuring their activity level. A prospective study has shown that there is no correlation between morbidity and competitive activity level [209]. The Eastern Cooperative Oncology Group (ECOG) performance status (PS) scores and Karnofsky index have been validated to measure patient activity [210]. Performance status score is correlated with patient OS after RC [205] and palliative chemotherapy [211-213].

Patients who have screened positive for frailty or cognitive impairment benefit from an assessment by a geriatrician. This enables identification of geriatric syndromes and any scope for optimisation. The most complete protocol is the Comprehensive Geriatric Assessment (CGA) [214], which is useful in the care of cancer patients [215]. In BC, the CGA has been used to adapt gemcitabine chemotherapy in previously untreated older patients with advanced BC [216].

Table 6.2: 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	81-90 years
5	> 90 years
6	Metastatic solid tumours
	AIDS

Interpretation:

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

6.4.1 Summary of evidence and recommendations 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 CGA where optimisation is needed.	3
In patients aged > 80 years with MIBC, cystectomy is an option.	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 6.4).	Strong

6.5 Perioperative systemic therapy

6.5.1 ***Neoadjuvant***

6.5.1.a Neoadjuvant chemotherapy

The standard surgical treatment for patients with urothelial MIBC and MIBC with subtypes is RC. However, RC only provides five-year survival in about 50% of patients [217-219]. To improve survival in patients with non-metastatic disease, cisplatin-based NAC has been used since the 1980s [217-221].

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 point in time, 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. An analysis to identify the optimal definition of pathological response reported a significantly higher risk of recurrence in patients with ypTaN0 or ypT1N0 disease (with or without Tis) at RC and thus proposed that optimal pathological response after NAC be defined as attainment of ypT0N0/ypTisN0 at RC [222]. However, the definition of pathological responses remains unclear.
- Delayed cystectomy might compromise the outcome in patients not sensitive to chemotherapy [223-225]. A comparative survival analysis of patients treated with NAC and RC versus RC alone based on data from the United States (U.S.) 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) [226]. However, there are no prospective trials indicating that delayed surgery due to NAC has a negative impact on survival.
- Neoadjuvant chemotherapy does not appear to affect the outcome of surgical morbidity. In a large multicentre retrospective analysis, NAC did not lead to an increased risk of postoperative complications after RC [227]. 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 [228].
- Sex may have an impact on chemotherapeutic response and oncologic outcomes [229, 230]. Female patients tend to have a better cancer-related response to NAC compared to male patients.
- Neoadjuvant chemotherapy should only be used in patients eligible for cisplatin-combination chemotherapy [231-238].

Several phase III RCTs addressed the potential survival benefit of NAC administration [231-235, 239-241]. As 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 [236-238]. In a meta-analysis including patient data from 11 randomised trials (n = 3,005), a significant survival benefit was shown in favour of NAC [238]. Another meta-analysis included four additional RCTs and used the results from the Nordic I, Nordic II and BA06 30894 trials, including data from 427 new patients and 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 needed-to-treat number of 12.5 [242].

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

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

Based on retrospective data alone, patients with secondary MIBC have a worse response to NAC compared to patients with primary MIBC [243]. A retrospective analysis of clinicopathologic outcomes comparing 245 patients with clinical T2-4a N0M0 primary MIBC and 43 patients with secondary MIBC treated with NAC and RC found that patients with secondary MIBC had lower pathologic response rates following NAC than those with primary MIBC (multivariable OR: 0.4; 95% CI: 0.18-0.84; p = 0.02). The results of the retrospective analysis

also showed that MIBC patients progressing after NAC had worse CSS as compared to patients treated with cystectomy alone (p = 0.002).

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 [244-247]. Modified dd-MVAC was tested in two small single-arm phase II studies. The studies demonstrated high rates of pathologic complete remission (CR) [248, 249]. Moreover, a large cross-sectional analysis showed higher rates of downstaging and pathological complete response for dd-MVAC [250].

In the GETUG/AFU V05 VESPER RCT of perioperative chemotherapy, 500 patients were randomised to either six cycles of dd-MVAC versus four cycles of GC before surgery (neoadjuvant group) or after surgery (adjuvant group) with a primary endpoint of PFS at three years. Eighty-nine percent of participants received neoadjuvant therapy, and similar pathologic response rates (ypT0N0) were observed in patients treated with dd-MVAC (42%) and GC (36%; p = 0.2). The < ypT2N0 rate was 63% in the dd-MVAC patients and 50% in the GC patients. Organ-confined response (< ypT3N0) was observed more frequently in the dd-MVAC arm (77% vs. 63%; p = 0.001). For all patients in the trial, intention-to-treat (ITT) included neoadjuvant and adjuvant therapy and three-year PFS was improved in the dd-MVAC arm, although the study did not meet its primary endpoint (three-year rate for ITT: 64% vs. 56%; HR: 0.77; 95% CI: 0.57-1.02; p = 0.066). At five-year follow-up, however, a significant benefit for the neoadjuvant group in favour of dd-MVAC with regards to PFS (HR: 0.74; 95% CI: 0.55-0.99) and OS (HR: 0.71; 95% CI: 0.52-0.97) was seen [251]. Dose-dense MVAC was associated with more severe asthenia and GI side effects than GC [89, 252]. In a single-centre retrospective analysis in patients with MIBC, neoadjuvant accelerated MVAC was safe and efficacious irrespective of age, provided that patients were fit and deemed suitable candidates for cisplatin [253]. Another dose-dense regimen using GC was reported in two small phase II trials [254, 255]. While pathological response rates (< pT2) in the range of 45-57% were achieved, one trial had to be closed prematurely due to high rates of severe vascular events [254]. This approach is therefore not recommended outside of clinical trials.

As an alternative to the standard dose of cisplatin-based NAC with 70mg/m^2 on day one, split-dose modification regimens are often used with 35mg/m^2 on days one and eight, or days one and two. In a retrospective analysis, the standard schedule was compared to a split-dose schedule to assess 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 [256].

For responders to NAC, especially in those with a complete response (ypT0N0), treatment has a major positive impact on OS [257, 258]. 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 [259-261].

It is unclear whether patients with non-UC histology will also benefit from NAC. A retrospective analysis demonstrated that patients with NE tumours had improved OS and lower rates of non-organ-confined disease when receiving neoadjuvant cisplatin/etoposide chemotherapy. In case of micropapillary differentiation, sarcomatoid differentiation and adenocarcinoma, lower rates of non-organ-confined disease were found, but no statistically significant impact on OS. Patients with SCC did not benefit from NAC [262]. A 2019 systematic review showed benefit of NAC for patients with micropapillary, plasmacytoid, sarcomatoid and mixed variants, but especially for patients with NE tumours [52]. A U.S. National Cancer Database study evaluating potential associations between receipt of NAC, pathological downstaging and OS for patients with histological subtype MIBC demonstrated that NAC was associated with pathological downstaging for all MIBC histological subtypes (UC, sarcomatoid UC, micropapillary UC, SCC, NE carcinoma and adenocarcinoma), with improved OS for patients with UC, sarcomatoid variant UC and NE carcinoma [263]. An analysis of the VESPER trial showed no impact of subtypes on the outcome of NAC, with the exception of SCC and micropapillary subtypes that appeared to have inferior outcome [264]. In a recent systematic review and meta-analysis of NAC prior to RC in MIBC subtypes, better survival outcomes and higher pathologic downstaging were associated with NAC when compared to surgery alone [265].

6.5.1.b Neoadjuvant combination therapies

Checkpoint inhibitors have been tested in the neoadjuvant setting, either as monotherapy or in combination with chemotherapy or CTLA-4 checkpoint inhibition. Data from two phase II trials using single-agent CPIs demonstrated encouraging results [112, 266]. The PURE-01 study, using the PD-1 inhibitor pembrolizumab, reported a complete pathological remission (pT0) in 42% and pathological response (< pT2) in 54% of patients [267], whereas in the ABACUS trial, with the PD-L1 inhibitor atezolizumab, the pathologic complete response

rate was 31% [114]. The combination of anti-CTLA4 and anti-PD1 therapy has also been investigated in the neoadjuvant setting. In the NABUCCO study using preoperative ipilimumab and nivolumab, the pathologic complete response was 46%, with 58% having no remaining invasive disease (< ypT2N0) [268]. In a study using preoperative tremelimumab and durvalumab in cisplatin-ineligible patients, the pathological complete response was 37.5% and downstaging to < ypT2N0 was seen in 58% of patients who completed surgery [269].

Three phase II studies have been published investigating the use of neoadjuvant chemoimmunotherapy in patients with MIBC. In a phase II study of gemcitabine plus split-dose cisplatin and pembrolizumab in patients with MIBC, 22 of 39 patients (56% [95% CI: 40-72]) achieved < ypT2N0 and 14 of 39 (36% [95% CI: 21-53]) achieved ypT0N0 [270]. In another phase II study evaluating neoadjuvant atezolizumab with gemcitabine and cisplatin, 27 of 39 patients (69%) were < ypT2N0 and 16 (41%) ypT0N0. [271]. A third phase II study evaluating NAC with GC plus durvalumab including adjuvant durvalumab with a primary endpoint of event-free survival (EFS) demonstrated EFS at three years of 73% (95% CI: 59-83). Complete pathologic response was achieved in 17 of 52 patients (33%), and 31 (60%) had pathologic response < ypTN0. A phase II trial demonstrated promising results using a stringent definition of clinical complete response rate for an organ-sparing treatment for MIBC with the combination of GC plus nivolumab [272].

The first randomised phase III trial (NIAGARA) testing perioperative addition of durvalumab to neoadjuvant cisplatin/gemcitabine chemotherapy has demonstrated significantly improved EFS and OS and higher pathological CR rate [273]. Patients with estimated glomerular filtration rate (eGFR) of 40mL/min. or higher were eligible, with cisplatin split-dose (day one and eight) given in case of eGFR 40-60mL/min. 1,063 patients underwent randomisation and received either four cycles of GC or the same chemotherapy plus durvalumab for four cycles every three weeks in the neoadjuvant part and durvalumab alone for eight cycles every four weeks in the adjuvant part. With a median follow-up of 42.3 months, the estimated EFS at two years was 67.8% with durvalumab compared to 59.8% without durvalumab (HR for progression, recurrence, not undergoing RC or death from any cause: 0.68; 95% CI: 0.56-0.82; p < 0.001) and the estimated OS at two years was 82.2% and 75.2% (HR: 0.75; 95% CI: 0.59-0.93; p = 0.01), respectively. There was no difference between groups in grade 3/4 treatment-related adverse events (AEs), RC rates or in the safety of surgery. The perioperative regimen of cisplatin/gemcitabine and durvalumab, as applied in the NIAGARA study, has been approved by the EMA in July 2025, and it is also FDA approved.

At the European Society of Medical Oncology (ESMO) 2025 Annual Meeting, the results from the phase III KEYNOTE-905/EV-303 study evaluating perioperative EV + P in patients with cisplatin-ineligible MIBC was presented [274]. In this, 344 patients with cisplatin-ineligible (or -declining) MIBC were randomised to perioperative EV + P versus RC with pelvic LND followed by observation. At a median follow-up of 25.6 months, perioperative EV + P was associated with a significant improvement in EFS (HR: 0.40; 95% CI: 0.28-0.57; P < 0.001) and OS (HR: 0.50; 95% CI: 0.33-0.74; P = 0.0002) as compared to surgery followed by observation. Pathologic complete response rate was 57.1% versus 8.6%, respectively. Perioperative EV + P did not impact the ability of participants to undergo surgery, and the safety profile was manageable [274]. The result of this trial supports a new standard of care with perioperative EV + P for patients with cisplatin-ineligible MIBC.

6.5.1.c Summary of evidence and recommendations for neoadjuvant therapy

Summary of evidence	LE
Neoadjuvant cisplatin-containing combination chemotherapy improves OS (8% at five years).	1a
Neoadjuvant treatment may have a major impact on OS in patients who achieve ypT0N0 or ≤ ypT2N0.	2a
Perioperative durvalumab plus neoadjuvant GC improves EFS and OS compared to neoadjuvant GC alone.	1b
Perioperative EV + P improves EFS and OS compared to surgery followed by observation in patients with cisplatin-ineligible MIBC.	1b
There are still no reliable tools available to select patients who have a higher probability of benefitting from NAC. In future, genomic markers in a personalised medicine setting might facilitate the selection of patients for NAC and differentiate responders from non-responders.	-

Recommendations	Strength rating
Offer perioperative chemoimmunotherapy with cisplatin/gemcitabine and durvalumab to patients with muscle-invasive bladder cancer (MIBC) (T2-T4a, cN0 M0) who are eligible for cisplatin-based chemotherapy (glomerular filtration rate > 40mL/min. allowed) and immunotherapy.	Strong
Offer perioperative enfortumab vedotin plus pembrolizumab to patients with MIBC who are ineligible for cisplatin-based chemotherapy.	Strong
Offer neoadjuvant cisplatin-based combination chemotherapy to patients with MIBC (T2-T4a, cN0 M0) who are eligible for cisplatin-based chemotherapy.	Strong
Do not offer neoadjuvant carboplatin-containing combination chemotherapy to patients who are ineligible for cisplatin-based combination chemotherapy.	Strong

6.5.2 Adjuvant therapy

6.5.2.a Adjuvant chemotherapy

Adjuvant chemotherapy after RC for patients with pT3/4 and/or LN positive (pN+) disease without clinically detectable metastases (M0) is still under debate. The general benefits of adjuvant chemotherapy include:

- chemotherapy is administered after accurate pathological staging, therefore treatment in patients at low risk for micro-metastases is avoided; and
- 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; and
- delay of or intolerability to chemotherapy, due to postoperative morbidity [275].

There is limited evidence from adequately conducted and accrued phase III RCTs in favour of the routine use of adjuvant chemotherapy [276-281]. An individual patient data meta-analysis [282] of survival data from six RCTs of adjuvant chemotherapy [283-285] included 491 patients. All included trials suffered from significant methodological flaws including small sample size (underpowered), incomplete accrual, use of inadequate statistical methods and design flaws [276]. The data were not convincing to support an unequivocal recommendation for the use of adjuvant chemotherapy. In 2014, this meta-analysis was updated with three additional studies [279-281] resulting in the inclusion of 945 patients from nine trials [278]. None of the trials had fully accrued and individual patient data were not used in the analysis. None of the included individual trials were significantly positive for OS in favour of adjuvant chemotherapy. The HR for OS was 0.77 (95% CI: 0.59-0.99; p = 0.049) and for DFS was 0.66 (95% CI: 0.45-0.91; p = 0.014). A systematic review and meta-analysis of individual patient data from RCTs in patients treated with adjuvant cisplatin-based chemotherapy for MIBC has more recently been conducted [286]. In an analysis of ten RCTs (n = 1,183), an OS benefit was demonstrated for cisplatin-based adjuvant chemotherapy (HR: 0.82; 95% CI: 0.70-0.96; p = 0.02). This translates into an absolute improvement in survival of 6% at five years, from 50% to 56%, and a 9% absolute benefit when adjusted for age, sex, pT stage, and pN category (HR: 0.77; 95% CI: 0.65-0.92; p = 0.004).

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) [287]. Although not fully accrued, a publication of the largest RCT (European Organisation for Research and Treatment of Cancer [EORTC] 30994) 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 [288]. 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 versus observation. Twenty-three percent of patients received adjuvant chemotherapy with a five-year OS of 37% for the adjuvant arm versus 29.1% (HR: 0.70; 95% CI: 0.64-0.76) in the observation group [289]. Another large retrospective analysis based on the U.S. National Cancer Database, including 15,397 patients with locally-advanced (pT3/4) or LN-positive disease, also demonstrated an OS benefit in patients with UC histology [290]. In patients with concomitant histological subtypes, however, no benefit was found.

Patients should be informed about potential chemotherapy options before RC and the limited evidence for adjuvant chemotherapy.

6.5.2.b Adjuvant immunotherapy

Four phase III RCTs have evaluated CPI monotherapy with atezolizumab, nivolumab or pembrolizumab in patients with muscle-invasive UC (MIUC). CheckMate 274, a phase III, double-blind RCT of adjuvant nivolumab versus placebo for up to one year in 709 patients with MIUC with a high risk of recurrence (≥ ypT2 or ypN+ after NAC or pT3, pT4a, or pN+ without neoadjuvant therapy), 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 six 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% (tumour cell [TC] score), the percentage of patients was 74.5% and 55.7%, respectively (HR: 0.55; 98.72% CI: 0.35-0.85; p < 0.001) [291]. In an analysis using both PD-L1 TC score and CPS, more patients had CPS ≥ 1 than TC ≥ 1% and patients with CPS ≥ 1 had improved DFS with nivolumab which may have contributed to the benefit seen with adjuvant nivolumab in patients with TC < 1% and CPS ≥ 1 [292]. There was no clinically meaningful deterioration in health-related QoL with adjuvant nivolumab compared to placebo [293]. With extended median follow-up of 36 months, interim OS data were reported demonstrating a promising trend (i.e. not meeting the prespecified boundary for statistical significance at the time of the analysis) in favour of nivolumab with an HR for OS with nivolumab versus placebo of 0.76 (95% CI: 0.61-0.96) in the ITT population and 0.56 (95% CI: 0.36-0.86) in the PD-L1 ≥ 1 population [294].

A second phase III trial evaluated adjuvant pembrolizumab for one year versus observation in patients with high-risk MIBC after radical surgery (Alliance A031501 AMBASSADOR). Adjuvant pembrolizumab demonstrated a significant improvement in median DFS compared to observation 29.6 months (95% CI: 20.0-40.7) with pembrolizumab and 14.2 months (95% CI: 11.0-20.2) with observation (HR for disease progression or death: 0.73; 95% CI: 0.59-0.90; two-sided p = 0.003) [295]. The primary endpoint of DFS was not achieved in a multicentre RCT of adjuvant atezolizumab versus 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) [296].

The FDA has approved nivolumab for adjuvant treatment of patients with MIUC who are at high risk of recurrence after undergoing surgery [297] whereas EMA has approved adjuvant nivolumab in the same population only if tumour cell PD-L1 expression is ≥ 1%. A promising report (see Section 4.9) has suggested a potential role for ctDNA to guide the use of adjuvant IO for UC [298].

The recently published phase III IMvigor011 trial evaluated a ctDNA-guided strategy for adjuvant treatment selection. Patients underwent serial ctDNA testing for one year following surgery [108]. Those who developed ctDNA positivity in the absence of radiographic recurrence were randomized to receive atezolizumab or placebo, whereas patients who remained ctDNA-negative received no adjuvant therapy. Among patients with ctDNA-positive status, adjuvant atezolizumab significantly improved both DFS and OS compared with placebo. Median DFS was 9.9 months with atezolizumab and 4.8 months with placebo, corresponding to a HR for recurrence or death of 0.64. Median OS was 32.8 months versus 21.1 months, respectively, with a HR for death of 0.59. Persistent ctDNA negative status was associated with excellent survival outcomes with a DFS of 95% at the end of the one-year monitoring period.

6.5.2.c Summary of evidence and recommendations for adjuvant therapy

Summary of evidence	**LE**
Adjuvant cisplatin-based chemotherapy for high-risk patients (pT3, 4 and/or or N+) without neoadjuvant treatment can be associated with improvement in DFS and OS but trials are underpowered to adequately answer this question.	2a
Two studies using immune CPI in the adjuvant setting for high-risk MIBC patients have demonstrated an improvement in DFS (CheckMate 274 with nivolumab, AMBASSADOR with pembrolizumab). In contrast, one study (IMvigor 010 with adjuvant atezolizumab) failed to show a DFS benefit.	1b
In patients with MIBC, ctDNA-guided adjuvant therapy with atezolizumab improves DFS and OS.	1b

Recommendations	Strength rating
Offer adjuvant cisplatin-based combination chemotherapy to patients with pT3/4 and/or pN+ disease if no neoadjuvant systemic therapy has been given.	Strong
Offer adjuvant nivolumab to patients with high-risk muscle-invasive urothelial carcinoma (≥ ypT2N0 after NAC or pT3/4 and/or pN+) who are not eligible for, or who declined, adjuvant cisplatin-based chemotherapy. Of note: FDA approval irrespective of PD-L1 status, EMA approval only for PD-L1 tumour cell expression ≥ 1%.	Strong

EMA = European Medicines Agency; FDA = United States Food and Drug Administration; PD-L1 = programmed death-ligand 1.

6.6 Perioperative radiotherapy

6.6.1 Preoperative radiotherapy

Historical data from six older RCTs assessing pre-operative RT before RC have shown improved pathologic downstaging but did not demonstrate a clear or consistent OS benefit. The largest trial, which used preoperative RT at a dose of 45 Gy, increased pathologic complete response (9% to 34%) but had major protocol deviations and/or non-adherence (> 50% excluded from final analysis) and selective chemotherapy use, limiting interpretation of survival outcomes [299]. Two small 20 Gy studies suggested only a modest survival signal in ≥ T3 disease [300, 301], and other smaller trials confirmed downstaging without survival gain [302, 303].

A meta-analysis of five RCTs showed a non-significant five-tear OS increase, which disappeared when the largest, non-adherent trial was excluded from the analysis [304]. A subsequent RCT (n = 100; mixed UC/SCC) found similar OS/DFS and complication rates for pre- versus postoperative RT [305].

Collectively, these older data do not support routine use of preoperative RT before RC. Interest has shifted to carefully selected adjuvant RT after cystectomy for high-risk pathology, with newer randomised data emerging for postoperative RT.

6.6.2 Postoperative radiotherapy

Locoregional recurrence after RC occurs in up to 30% of patients with pT3-4 disease, contributing to poor survival despite systemic therapy. Adjuvant RT aims to reduce this risk, particularly in patients with high-risk pathological features (pT3/pT4, pN+, positive margins or low nodal yield). Early evidence was limited, but several prospective and retrospective studies using modern radiation techniques have demonstrated improved locoregional control with acceptable toxicity [306]. In a phase II trial of patients with locally advanced disease and negative margins after RC (with one or more risk factors: ≥ pT3b, grade 3, or node-positive; n = 120; mixed UC/SCC), adjuvant sequential chemotherapy and RT significantly improved two-year locoregional relapse-free survival (96% vs. 69%) compared with chemotherapy alone, with low rates of late ≥ grade 3 GI toxicity (7%) [307].

An Egyptian randomised study (n = 122) using adjuvant IMRT (50Gy/25fx) reported three-year locoregional RFS 81% versus 71% (p = 0.046) favouring adjuvant RT, without significant OS or distant metastasis-free benefit and with similar late toxicity [308]. The BART phase III RCT (n = 153; urothelial MIBC with ≥ 1 high-risk feature after RC: pT3-4, pN1-3; nodal yield < 10; positive margin; or ≥ cT3 downstaged with NAC) compared observation with stoma-sparing image-guided IMRT (50.4Gy/28fx) prescribed to the cystectomy bed and pelvic nodes. Severe, acute and late toxicity were low and similar in both arms [309].

Adjuvant RT using modern conformal or IMRT techniques therefore appears safe and feasible, particularly for patients at high locoregional risk. Typical doses range 45-50.4Gy to the cystectomy bed and pelvic nodes, adapted to individual pathological findings [310]. Small studies have suggested that orthotopic neobladders can likely tolerate these doses with minimal morbidity [311]. Where adjuvant systemic therapy is indicated, sequential integration ('sandwich' approach) of RT between chemotherapy cycles may be considered. The role of concurrent radio-sensitising chemotherapy in the adjuvant setting remains investigational.

With the advent of adjuvant IO (e.g. nivolumab in CheckMate 274 showing improved DFS), the optimal sequencing or combination of RT with immune CPIs is not yet defined, and no prospective data currently guide their integration. Participation in ongoing clinical trials evaluating RT-IO combinations is encouraged for eligible high-risk patients.

In summary, adjuvant RT may be considered in selected high-risk patients (≥ pT3, pN+, positive margins) after RC to improve locoregional control, while routine use awaits confirmation of survival benefit and clarification of its role alongside modern systemic and immunotherapeutic strategies.

6.6.3 Summary of evidence and recommendations for pre- and postoperative radiotherapy

Summary of evidence	LE
No contemporary data exists to support that preoperative RT for operable MIBC increases survival.	2a
Preoperative RT for operable MIBC, using a dose of 45-50Gy in fractions of 1.8-2Gy, results in downstaging after four to six weeks.	2
Limited evidence supports the safe use of pre- and postoperative RT if a neobladder is planned or *in situ*.	3
Limited high-quality evidence supports the use of preoperative RT to decrease local recurrence of MIBC after RC.	3
Addition of adjuvant RT is associated with an improvement in local relapse-free survival following cystectomy for locally advanced BC (pT3b-4 or node-positive).	2a

Recommendations	Strength rating
Do not offer preoperative radiotherapy (RT) for operable muscle-invasive bladder cancer since it will not improve survival.	Strong
Adjuvant RT to the cystectomy bed and local pelvic nodes can be offered following radical cystectomy (pT3b-4 or positive nodes or positive margins) to improve locoregional relapse free survival, but not overall survival.	Weak

6.7 Radical cystectomy with pelvic lymph node dissection

6.7.1 Removal of the tumour-bearing bladder

6.7.1.a Introduction

For decades, the standard surgical treatment for patients with MIBC has been RC, pelvic LND, and urinary diversion, with or without NAC [312]. However, growing attention to QoL has led to an increasing use of bladder-sparing approaches, such as RT or trimodality therapy (TMT), in select patients. Performance status and life expectancy influence the choice of primary treatment and type of urinary diversion.

6.7.1.b Radical cystectomy: timing

A meta-analysis including 19 studies concluded that a delay of more than three months has a negative effect on OS (HR: 134; 95% CI: 1.18-1.53). The lack of standardisation regarding the definition of delays was highlighted, as this made it impossible to identify a clear cut-off time [313]. It was concluded that BC patients scheduled for RC should be treated without delays to maximise survival.

6.7.1.c Radical cystectomy: indications

Radical cystectomy is recommended in patients with T2-T4a, N0M0 disease, very high-risk NMIBC, bacillus Calmette-Guérin (BCG)-refractory, BCG-relapsing and BCG-unresponsive NMIBC (see the EAU Guidelines on NMIBC [2]), as well as extensive papillary disease that cannot be controlled with TURBT and intravesical chemotherapy/IO alone.

Salvage cystectomy is indicated in non-responders to bladder-sparing therapy, that is, non-metastatic muscle invasive recurrence after TMT. Rarely, RC can be used as a palliative intervention, for example, for fistula formation, pain and recurrent uncontrollable haematuria (see Section 6.7.10).

6.7.1.d Recommendation for radical cystectomy

Recommendation	Strength rating
Offer radical cystectomy to patients with T2-T4a N0M0 disease.	Strong

6.7.2 Radical cystectomy: technique and extent

Various techniques have been suggested to improve functional outcomes in patients undergoing RC for BC. However, concerns remain about their potential impact on cancer control, and there is no consensus on which method is most effective in preserving these functions.

6.7.2.a Radical cystectomy in male patients

In male patients, standard RC involves the removal of the bladder, prostate, seminal vesicles, distal ureters, and regional LNs.

6.7.2.a.1 Concomitant prostate cancer

A systematic review and meta-analysis of 13,140 patients showed an incidental prostate cancer rate of 24% in RC specimens [314]. Incidental prostate cancer was associated with higher age and lower five-year OS, likely due to the older age of affected patient. Pathological reporting of prostate cancer in the RC specimens should follow the recommendations outlined in the EAU-EANM-ESTRO-ESUR-ISUP-SIOG Prostate Cancer Guidelines [315].

6.7.2.a.2 Sexual-preserving techniques

Four main types of sexual-preserving RC techniques in male patients have been described:

- **Prostate-sparing cystectomy:** Preserves part or all of the prostate, including seminal vesicles, vas deferens and neurovascular bundles.
- **Prostate capsule sparing cystectomy:** Preserves the capsule or peripheral part of the prostate. Adenoma (including prostatic urethra) removed by transurethral resection of the prostate or *en bloc* with the bladder. Seminal vesicles, vas deferens and neurovascular bundles are preserved.
- **Seminal vesicle sparing cystectomy:** Preserves the seminal vesicles, vas deferens and neurovascular bundles.
- **Nerve-sparing cystectomy:** Only the neurovascular bundles are preserved.

A systematic review on oncological and functional outcomes of sexual function-preserving cystectomy in males identified 12 studies (n = 1,098) [316]. Most of these studies employed an open surgical approach, with orthotopic neobladder. Median follow-up exceeded three years in nine of the studies, and five years in three studies. Most of the studies included patients who were potent preoperatively with organ-confined disease and no bladder neck and/or prostatic urethra involvement. Prostate cancer was ruled out in all sexual-preserving cystectomy techniques, except for the nerve-sparing approach [315].

Oncological outcomes did not differ between groups in any of the comparative studies that measured local recurrence, metastatic recurrence, DSS and OS. Incidental prostate cancer rates in prostate- or capsule-sparing techniques ranged from 0 to 15%, with no cases of ISUP grade ≥ 4 reported.

Postoperative potency was significantly higher in patients who underwent any type of sexual-preserving cystectomy technique compared to conventional RC ($p < 0.05$), ranging from 80 to 90%, 50 to 100%, and 29 to 78% for prostate-, capsule- or nerve-sparing techniques, respectively. Urinary continence, defined as 'no pads', ranged from 88 to 100% (daytime continence) and from 31 to 96% (night-time continence) in the prostate-sparing cystectomy patients. No major differences were seen regarding continence rates between any of these 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 is moderate. Therefore, if a sexual-preserving cystectomy technique is offered, patients must be carefully selected, counselled and closely monitored.

6.7.2.a.3 Summary of evidence and recommendations for sexual-preserving techniques in males

Summary of evidence	LE
The majority of eligible 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
Only offer sexual-preserving techniques to eligible male patients who are highly motivated to preserve their sexual function.	Strong

Select patients based on: • organ-confined disease; and • absence of malignancy at the level of the prostate, prostatic urethra or bladder neck.	Strong

6.7.2.b Radical cystectomy in female patients

Historically, standard RC in female patients includes removal of the bladder, the entire urethra, adjacent vagina, uterus, distal ureters and regional LNs. Pelvic floor disorders, along with sexual and voiding dysfunction in female patients are prevalent after RC [317]. As part of the preoperative evaluation, a gynaecological history should be obtained, and patients should be counselled about the potential negative impact of RC on sexual function and/or vaginal prolapse. A history of cervical cancer screening, abnormal vaginal bleeding, and a family history of breast and/or ovarian cancer should be documented, along with an assessment for pelvic organ prolapse. Postoperatively, screening for sexual and urinary function and prolapse is mandatory.

6.7.2.b.1 Concomitant gynaecological malignancies and associated consequences

Pelvic organ-preserving techniques in female patients involve preserving the neurovascular bundle, vagina, uterus, ovaries or combinations thereof. In a retrospective multicentre study of 302 females with cTa-T4 BC, gynaecological organ involvement was seen in 6.6% of cases and was associated with higher clinical stages [318, 319]. Concomitant malignancy in gynaecological organs is rare and local recurrences following RC are infrequent [320, 321]. In premenopausal female patients, preserving the ovaries maintains hormonal homeostasis, which decreases the 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), salpingo-oophorectomy should be advised after childbearing and to all female patients over 40 years of age [322]. Preserving the uterus and vagina provides the necessary support for a neobladder, thereby reducing the risk of urinary retention or postoperative prolapse. In case of existing uterine prolapse, either isolated or combined with a vaginal prolapse, removing the uterus will be beneficial. Notably, resection of the vaginal wall shortens the vagina, which could impair sexual satisfaction and function. Patients should be informed about the potential consequences.

6.7.2.b.2 Sexual-preserving techniques

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 [323]. Patient selection has often been limited to cT2 disease, but recent encouraging reports support including female patients with more advanced T-stage and histological subtypes without compromising oncological outcomes [324]. Despite this, a non-sexual-preserving technique is most often used [325].

Pelvic organ-preserving RC could also be considered in elderly and fragile patients, as it may reduce blood loss and promote quicker bowel recovery [326].

A study demonstrated improved functional outcomes in female patients undergoing robotic cystectomy with neobladder formation when pelvic organ preservation was performed, without compromising safety [327].

6.7.2.b.3 Summary of evidence and recommendation for sexual-preserving techniques in females

Summary of evidence	**LE**
The risk of gynaecological organ involvement in female patients undergoing RC without clinical evidence of non-organ-confined disease is low.	3

Recommendation	**Strength rating**
Perform sexual organ-preserving techniques in eligible female patients. Select patients based on absence of tumour in the area to be preserved to avoid positive soft tissue margins.	Strong

6.7.3 Lymphadenectomy: role and extent

A number of LN templates have been described. Standard LND in MIBC 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, obturator fossa and external iliac nodes. The lateral borders are the genitofemoral nerves, caudally the circumflex iliac vein, the lacunar ligament and the LN of Cloquet [328]. Limited LND includes the nodes

from the true pelvis but excludes the deep obturator nodes. Extended LND includes the same boundaries as a standard LND, except for the cranial limit, which is the region of the aortic bifurcation [329]. A super-extended LND extends cranially to the level of the inferior mesenteric artery [330].

Controversies in the clinical importance of LND are related to the question of whether it should be considered a staging tool, a therapeutic procedure, or both.

The two RCTs investigating the anatomic extend of the LND are the German LEA trial and the U.S./Canadian SWOG S1011 trial [331, 332]. In the LEA trial, patients with MIBC (n = 346) or T1G3 disease (n = 55) were included. Patients underwent either a limited LND (n = 203) or extended LND (n = 198). Small survival differences between the groups were seen in favour of extended LND. However, extended LND failed to show a significant advantage (the trial was designed to show an absolute improvement of 15% in five-year RFS by extended LND) over limited LND for RFS, CSS and OS [331]. The results of the SWOG S1011 trial comparing standard versus extended LND showed no DFS (HR: 1.10; 95% CI: 0.86-1.40; p = 0.45) or OS (HR: 1.13; 95% CI: 0.88-1.45; p = 0.29) benefit for an extended LND in patients with clinically localised BC after a median six years follow-up [332]. Adverse events of grade 3 to 5 occurred in 157 patients (54%) in the extended LND group and in 132 (44%) in the standard LND group; death within 90 days after surgery occurred in 19 patients (7%) and seven patients (2%), respectively. Based on these studies, an extended LND is not associated with improved survival and increases the risk of morbidity.

6.7.3.a Summary of evidence and recommendations for lymphadenectomy

Summary of evidence	LE
An extended LND is not superior to a standard LND - it does not improve survival and increases the risk of morbidity.	1a
Radical cystectomy includes removal of regional LNs.	3

Recommendations	Strength rating
Perform a lymph node dissection (LND) as an integral part of radical cystectomy.	Strong
Perform a standard LND, because an extended LND does not improve survival and increases the risk of morbidity.	Strong

6.7.4 Robotic-assisted laparoscopic cystectomy

In 2023, a systematic review and meta-analysis compared open RC and RARC [333]. This study included eight RCTs, of which five studies performed extracorporeal urinary diversion (ECUD) and three studies intracorporeal urinary diversion (ICUD). The Early Recovery After Surgery (ERAS) pathway was adopted in one study with ECUD and in all three studies with ICUD [334-337]. The following outcomes were reported:

- Longer length of hospital stay for open RC (0.2 days), however, differences were seen depending on geographical location. In four U.S. and two United Kingdom trials, longer hospital stay for open RC was reported (0.6 and 1.5 days, respectively), whilst in two European-based trials, longer hospital stay for RARC was reported (0.9 days).
- Higher venous thromboembolic events (OR: 1.8) and transfusion rates (0.5 blood units) for open RC.
- Longer operative time for RARC (mean difference: 76 min.).
- No differences in 90-day complication rate and post-operative ileus rate.
- No differences in positive surgical margin rate.
- No differences in QoL, except for the domain of physical functioning favouring RARC.
- No differences in OS and RFS (median follow-up time: 36 months).

An RCT reported on functional outcomes of RARC with ICUD padua neobladder. Quantitative analysis of pad wetness revealed that 56% and 54% of patients were totally dry after RARC or open RC, respectively. However, there was no significant difference in the probability of night-time continence recovery at one year (RARC 36% vs. open RC 58%; HR: 0.6; 95% CI: 0.3-1.0; log rank p = 0.054). A quantitative analysis of pad use and wetness revealed a better night-time continence status in the open RC cohort [338].

Long-term oncological outcomes were also reported in a large (n = 595) single-centre study with a median follow-up of over five years. The study reported comparable recurrence and survival data, including atypical recurrences (defined as one or a combination of the following: port-site metastasis or peritoneal carcinomatosis) [339].

An economic evaluation (healthcare and societal perspective) of a Dutch prospective multicentre comparative effectiveness study assessing open RC (n = 168) versus RARC (n = 180) showed that both mean healthcare costs and societal costs per patient were significantly higher after RARC, resulting in an increase in quality-adjusted life years of 0.02 [340].

Data on post-RC ureteroenteric stricture rates for both open RC and RARC remain inconclusive. Results are mainly reported by high-volume centres or derived from population-based studies with a large variety of endpoints and poor controlling of potential confounders, making comparison difficult [341-345]. Those managed by extracorporeal diversion (RARC-ECUD) tend to have more strictures compared to intracorporeal diversion (RARC-ICUD) [345]. This is explained by the need for more extensive dissection of the ureter in RARC-ECUD and increased tension, resulting in impaired blood supply [346, 347].

6.7.4.a Summary of evidence and recommendations for robotic-assisted laparoscopic cystectomy

Summary of evidence	LE
Robot-assisted radical cystectomy and open RC provide similar 90-day complication rates, surgical margin rates, median-term oncological outcomes and QoL outcome.	1a
Operative time is longer for RARC compared to open RC (1 to 1.5 hours), but with less blood loss and possibly shorter length of hospital stay compared to open RC.	1a
Surgeon experience and institutional volume are considered the key factors for outcome of both RARC and open RC, not the technique.	4

Recommendations	Strength rating
Inform the patient of the advantages and disadvantages of open radical cystectomy (RC) and robotic assisted radical cystectomy (RARC) to allow selection of the proper procedure.	Strong
Select centres for both RARC and open RC based on experience, rather than the technique used.	Strong
Do not delay RC for more than three months, as this increases the risk of progression and cancer-specific mortality, unless the patient receives neoadjuvant chemotherapy.	Strong

6.7.5 Urinary diversion after radical cystectomy

Various types of segments of the intestinal tract can be used to reconstruct the urinary tract, including the ileum, colon and appendix, with ileum used in most cases. Several studies have compared advantages and disadvantages in terms of QoL, sexual function, urinary continence and body image between different urinary diversions [348], but further research evaluating the impact of tumour stage, functional and socioeconomic status are needed.

6.7.5.a Different types of urinary diversion

For the choice of urinary diversion, comorbidity, cardiac, pulmonary and cognitive function are important factors that should be considered, along with the patient's social support and preference (see Section 6.7.5.2). 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 [349]. Randomised controlled trials comparing conduit diversion with neobladder or continent cutaneous diversion have not been performed.

6.7.5.a.1 Ureterocutaneostomy

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 [350]. In frail patients and/or in those with a solitary kidney who need a supravesical diversion, ureterocutaneostomy is the preferred procedure. If patients have both kidneys and need a ureterocutaneostomy, 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 can be directly anastomosed to the abdominal wall to create a stoma.

Due to the smaller diameter of the ureters, stoma stenosis and ascending UTIs have been observed more frequently for this technique when compared to using small or large bowel to create an intestinal stoma [351].

6.7.5.a.2 *Ileal conduit*

The ileal conduit is an established option with well-known/predictable results. Early complications (30-day cut-off, used in most publications) include UTIs, pyelonephritis, ureteroileal leakage and stenosis, which occur in 48% of patients [352].

6.7.5.a.3 *Orthotopic neobladder*

According to Dutch, German and Spanish BC registry data, an orthotopic bladder substitution to the urethra is used in approximately 10-20% of both male and female patients. Emptying of the reservoir anastomosed to the urethra requires abdominal straining and sphincter relaxation. The terminal ileum is the GI segment most often used for orthotopic bladder substitution. Early and late morbidity in up to 22% of patients is reported [353].

Various forms of upper urinary tract 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 [354, 355]. According to the long-term results, the upper urinary tract is protected sufficiently by either method [353].

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 [356]. Urethral recurrence in neobladder patients seems rare (0.8-13.7% [pooled estimate of 4.6% in both male and female patients, also considering the significantly higher recurrence rates in male patients]) [357]. These results indicate that neobladder in male and female patients does not compromise the oncological outcome of cystectomy.

6.7.5.a.4 *Continent cutaneous urinary diversion*

Nowadays, continent cutaneous urinary diversion (a low-pressure detubularised ileal reservoir for self-catheterisation) and ureterorectosigmoidostomy are rarely used because of high complication rates, including stomal stenosis and incontinence with continent cutaneous diversion, and upper urinary tract infections and stone formation with ureterorectosigmoidostomy [358].

6.7.5.b Patient selection

Ensuring that patients make a well-informed decision about the type of urinary diversion is associated with less decision regret postoperatively, independent of the method selected [359]. Therefore, all applicable forms of urinary diversion should be discussed, taking into account patient preference, comorbidities, age and tumour characteristics.

Diagnosis of an invasive urethral tumour prior to cystectomy leads to urethrectomy, which is a contraindication for a neobladder reconstruction. 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 [360]. In females undergoing RC, the rate of concomitant urethral malignancy has been reported to range from 12 to 16% [361]. Localisation of the primary tumour at the bladder neck correlated strongly with concomitant urethral malignancy. Bladder neck biopsies prior to RC are important in females scheduled for an orthotopic bladder substitute [362].

In the presence of positive LNs, orthotopic neobladder can be considered in case of N1 disease, but not in N2 or N3 tumours [363].

Oncological results after orthotopic neobladder or ileal conduit 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 [364].

Patients undergoing continent urinary diversion must be motivated to learn about their diversion and be manually skilful and able to deal with their diversion. Contraindications to continent urinary diversions include:

- debilitating neurological and psychiatric illnesses;
- limited life expectancy; and
- severe impaired liver or renal function.

Relative contraindications for an orthotopic neobladder are high-dose preoperative RT, complex urethral strictures and severe urethral sphincter-related incontinence [365].

A retrospective study including 1,383 patients showed that the risk of a decline in eGFR did not significantly differ after ileal conduit versus neobladder in patients with preoperative chronic kidney disease 2 (eGFR 60-89mL/min./1.73m^2) or 3a (eGFR 45-59mL/min./1.73m^2) [366]. Only age and anastomotic strictures were found to be associated with a decline in eGFR.

Currently, it is not possible to recommend a particular type of urinary diversion. However, based on clinical experience, most institutions prefer ileal orthotopic neobladders and ileal conduits. In select patients, such as patients with a single kidney, ureterocutaneostomy is surgically the simplest.

6.7.5.c Perioperative care

Similar to other tumour types, such as colorectal cancer, a multimodal prehabilitation programme (i.e. physiotherapy, nutritional intervention, cessation of smoking) may improve patient health status before surgery and reduce subsequent postoperative complications [367]. However, evidence is limited and RCTs are missing.
Patients on 'Fast track'/ERAS protocols show better emotional and physical functioning, with fewer wound healing disorders, fever and thrombosis [368]. While there is no universal ERAS protocol for RC, preoperative recommendations include no bowel preparation or fasting, and may also include same-day admission, carbohydrate loading and a preoperative exercise programme.

Postoperatively, ERAS emphasises pain management with reduced opioid use, preferring high-dose acetaminophen and/or ketorolacs (only as breakthrough pain medication). Patients on ERAS experience more pain than those on traditional protocol (Visual Analogue Scale [VAS] 3.1 vs. 1.1; $p < 0.001$), but postoperative ileus decreased from 22% to 7.3% ($p = 0.003$) [369].

Venous thromboembolism (VTE) prophylaxis should be the standard of care for patients undergoing cystectomy [370]. A non-randomised study showed a lower 30-day VTE incidence rate in patients treated with enoxaparin for 28 days compared to those without prophylaxis [371]. 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%; $p = 0.002$) [372].

6.7.5.d Summary of evidence and recommendations for urinary diversion after radical cystectomy

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
The type of urinary diversion does not affect oncological outcome.	3

Recommendations	Strength rating
Do not offer an orthotopic bladder substitute diversion to patients who have an invasive tumour in the urethra or at the level of urethral dissection.	Strong
Do not offer preoperative bowel preparation.	Strong
Employ 'fast track' measurements to reduce the time to bowel recovery.	Strong

6.7.6 Morbidity and mortality

In four retrospective studies and one population-based cohort study, the perioperative mortality after RC was reported as 2.1-3.2% at 30 days and 3.4-8.0% at 90 days [373, 374]. Morbidity rates differ strongly according to the reporting system used. Using the Clavien-Dindo Classification system, complication rates ranged from 50 to 88% (I-IV) and severe complications from 30 to 42% (≥ III) [375-378].

In large national databases and institutional series, readmission rates are approximately 25% within 30 days of discharge [379]. An analysis of 4,638 RC patients in the Swedish national database showed that centralisation of RC services from 24 centres to ten resulted in significant reductions in 90-day mortality and reoperation rates [380]. In addition, the study revealed that the average age and comorbidity of patients being offered RC increased following centralisation. Late morbidity was usually linked to the type of urinary diversion (see also above). 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 [381, 382]. In general, lower morbidity and (perioperative) mortality have been observed by surgeons and in hospitals with a higher case load and therefore more experience [383-386]. A retrospective analysis of 1,303 patients managed in seven (non-academic) Dutch

hospitals revealed variation in treatment preferences between them. However, despite this, no significant difference was observed in OS [387].

Table 6.3: Management of neobladder morbidity (30-64%) [388]

CLAVIEN System		Morbidity	Management
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs such as antiemetics, antipyretics, analgesics, diuretics and electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.	**Immediate complications:**	
		Postoperative ileus	Nasogastric intubation (usually removed at day one) Chewing gum Avoid fluid excess and hypovolemia (provoke splanchnic hypoperfusion)
		Postoperative nausea and vomiting	Antiemetic agent (decrease opioids) Nasogastric intubation
		Urinary infection	Antibiotics, no ureteral catheter removal Check the three drainages (ureters and neobladder)
		Ureteral catheter obstruction	Inject 5cc saline in the ureteral catheter to resolve the obstruction Increase volume infusion to increase diuresis
		Intra-abdominal urine leakage (anastomosis leakage)	Check and reposition drainages, if required
		Anaemia well tolerated	Martial treatment (give iron supplement)
		Late complications:	
		Non-compressive lymphocele	Watchful waiting
		Mucus cork	Catheterise and rinse the bladder
		Incontinence	Urine analysis (infection) Echography (post-void residual) Physiotherapy
		Retention	Drainage and self-catheterisation education
		Ureteral reflux	No treatment if asymptomatic
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]
		Pulmonary embolism	Heparinotherapy[2]
		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	Reposition the ureteral catheter
		Anastomosis stenosis (7%)	Renal drainage (ureteral catheter or nephrostomy)

III-a	Intervention not under general anaesthesia	Compressive lymphocele	Transcutaneous drainage
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.	Neobladder rupture	Nephrostomy and indwelling catheter/surgery for draining the neobladder
		Severe sepsis	Antibiotics and check all the urinary drainages and CT scan in emergency
IV-a	Single organ dysfunction	Non-obstructive renal failure	Bicarbonate/aetiology treatment (including dialysis)
IV-b	Multi-organ dysfunction	Obstructive pyelonephritis and septicaemia	Treatment at intensive care unit, including urinary drainage 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 perioperative blood transfusion in patients who undergo RC correlates with increased overall mortality, CSM and cancer recurrence. It was hypothesised that this may be caused by the suggested immunosuppressive effect of a perioperative blood transfusion. In a retrospective study, a five-year decreased CSS was shown in cases in which intraoperative blood transfusion (CSS decreased from 67% to 48%) or postoperative blood transfusion (CSS decreased from 63% to 48%) were given [389].*

[2] *A review of 20,762 cases of VTE after major surgery found cystectomy patients to have the second-highest rate of VTE among all cancers studied [370]. 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 [372].*

*6.7.7 **Survival***

Of all cancers, BC ranks 13th in terms of mortality, with rates decreasing particularly in the most developed countries [390]. Disease-free survival and OS in a large population-based study were 35% and 58% at ten years, respectively [391]. However, the five-year OS in node-positive patients who underwent cystectomy was only 18% [392].

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

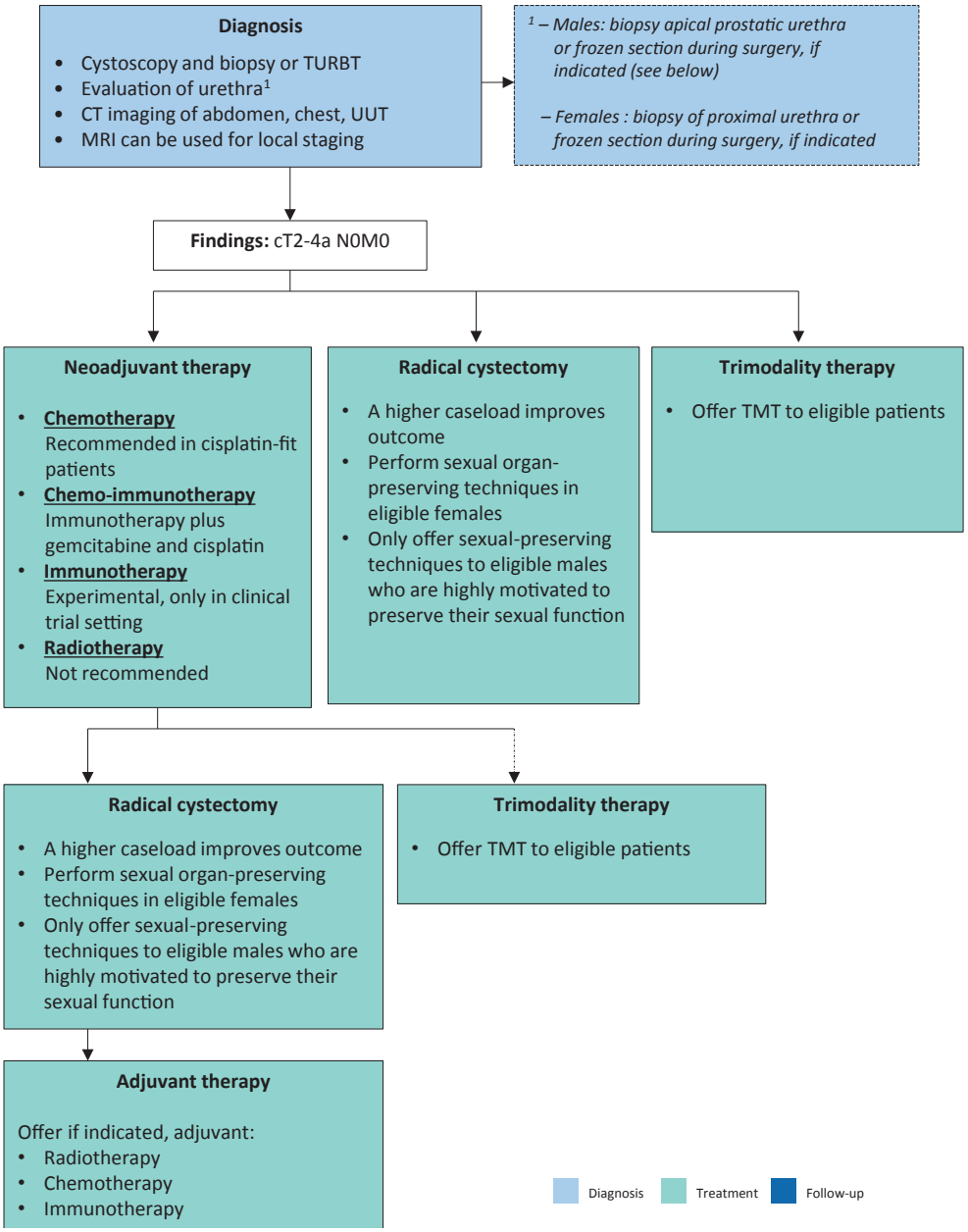
In a systematic review including 40 retrospective studies with 56,000 patients, the impact of hospital and/ or surgeon volume and perioperative outcomes of RC was assessed [393]. A higher hospital volume was associated with lower in-hospital, 30-day and 90-day mortality. In addition, higher volume hospitals 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. The study suggested performing at least ten RCs per centre annually and preferably more than 20. A nationwide analysis of the Dutch Cancer Registry including nearly 9,500 patients between 2008 and 2018 reported decreased 30- and 90-day mortality rates for annual hospital volumes of > 30 RCs. Moreover, this study showed no true plateau curve for 30- and 90-day mortality beyond 30 RCs, supporting the 'more is better' principle [394, 395]. An analysis of 4,638 RC patients in the Swedish national database showed that centralisation of RC services from 24 centres to ten resulted in significant reductions in 90-day mortality and reoperation rates. In addition, the study revealed that the average age and comorbidity of patients being offered RC increased following centralisation [380]. A German nationwide analysis found that hospitals performing over 50 RCs per year had lower in-patient mortality, shorter length of hospital stay, and fewer complications in comparison to the centres with 20-49 RCs per year [396].

6.7.9 *Summary of evidence and recommendations for quality indicators in radical cystectomy*

Summary of evidence	LE
Higher RC hospital volume is associated with lower post-operative mortality rates and higher quality of care.	3
The use of extended VTE prophylaxis significantly decreases the incidence of VTE after RC.	3
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 Dindo grading system.	2b

Recommendations	Strength rating
Perform at least 20 radical cystectomies (RCs) per hospital/per year.	Strong
Offer pharmacological venous thromboembolism prophylaxis, such as low-molecular-weight heparin, to RC patients, starting the first day post-surgery for a period of at least four weeks.	Strong

Figure 6.2: Flow chart for the management of T2-T4a N0M0 urothelial bladder cancer



CT = computed tomography; MRI = magnetic resonance imaging; TMT = trimodality therapy; TURBT = transurethral resection of bladder tumour; UUT = upper urinary tract.

*6.7.10 **Palliative cystectomy***

Locally advanced tumours may be accompanied by debilitating symptoms, including bleeding, pain, dysuria and urinary obstruction. These patients are candidates for palliative treatments, such as palliative RT [397]. 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 [398].

6.7.10.a Recommendations for palliative cystectomy

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

6.8 Trimodality therapy

*6.8.1 **Trimodality bladder-preserving treatment***

6.8.1.a Patient selection and treatment paradigm

Trimodality therapy combines TURBT, followed by concurrent chemo-RT. Trimodality therapy aims to achieve durable local control without compromising oncological outcome while also preserving bladder function and QoL. The addition of radio-sensitising chemotherapy or other radiosensitisers (as described below) is aimed at the potentiation of RT.

Trimodality therapy is best suited for patients with solitary, unifocal cT2-T3a tumours, absence of extensive or multifocal CIS, no or unilateral hydronephrosis, and good baseline bladder function. Patient selection is critical in achieving good outcomes [399-401]. In contemporary series, approximately 25-30% of cystectomy candidates may be appropriate for bladder preservation [402]. Trimodality therapy should also be considered for patients medically unfit or unwilling to undergo RC.

During TURBT, as much visible tumour as possible should be resected; a repeat transurethral resection may reveal residual disease in > 50% of cases [403]. Pelvic node dissection before TMT is not routinely performed [82, 83]. In higher-risk cases (e.g. more advanced stage T3-T4 or node positive disease), neoadjuvant or adjuvant platinum-based chemotherapy may be considered (for details, see Section 6.5), although robust evidence supporting its integration with chemoradiation is limited [404].

6.8.1.b Radiation therapy

A collaborative review has described the principles of TMT [399]. For radiation, the two most commonly used schedules have been the historically employed RTOG split-course regimen with mid-treatment cystoscopy, [405] and the continuous single-phase schedule, which is now considered standard [406]. A conventional radiation schedule includes EBRT to the bladder +/- limited pelvic LNs with an initial dose of 40-45Gy, with a boost to 60-66Gy to the entire bladder or tumour bed. Elective pelvic nodal irradiation (when node negative) remains optional and should take into account patient comorbidities and the risks of toxicity to adjacent critical structures. Retrospective data suggest that pelvic nodal radiation may be associated with better survival compared with bladder radiation alone after adjusted analysis [407]. For node-positive disease, consider boosting grossly involved nodes within normal tissue dose constraints.

An accepted radiation dosing alternative to conventional fractionation when treating the bladder-only fields is moderately hypofractionated EBRT to 55Gy in 20 fractions. In a meta-analysis of individual patient data from the BC2001 and BCON studies, this was shown to be non-inferior to 64Gy in 32 fractions in terms of invasive locoregional control, OS and late toxicity [408, 409].

6.8.1.c Concurrent radiosensitising chemotherapy

Various concurrent chemotherapy regimens have been used, but the most evidence is available for cisplatin [405, 410], mitomycin-C plus 5-FU [406] or gemcitabine [411, 412]. The BC2001 trial with ten-year follow-up showed that combined RT with mitomycin-C and fluorouracil significantly improved locoregional control and five-year cystectomy rates and non-significantly improved DFS, OS and DSS compared to RT alone [413]. Alternative regimens that have been evaluated include: capecitabine [414], paclitaxel [415] and hypoxia modification with carbogen/nicotinamide [82, 83, 414]. In a phase II RCT, twice-daily radiation plus 5-FU/cisplatin

was compared to once-daily radiation plus gemcitabine [412]. Both arms were found to result in a > 75% distant metastases-free rates at three years (78% and 84%, respectively). Therefore, good chemotherapy options are available for non-cisplatin candidates, such as 5-FU/mitomycin-C or low-dose gemcitabine.

The integration of IO with TMT is under investigation. Future studies may clarify sequencing of IO with bladder-preserving chemoradiation. Outside of trials, combined use remains investigational.

6.8.1.d Outcomes

Across modern TMT series, five-year CSS and OS rates vary between 50 and 84% and 36 and 74%, respectively, with salvage cystectomy rates of 10-30% [399, 400, 402, 406, 416, 417].

No successfully completed RCTs are available comparing the outcomes of TMT with RC. Many of the reported TMT series have differing baseline characteristics when compared to the larger surgical series. For example, in surgical series, typical median ages are in the mid-to-late 60s, as compared to mid-70s for RT series [406].

As there are no completed RCTs, RC and TMT have been compared in systematic reviews, meta-analyses, large population-based studies and multi-institutional propensity score matched and weighted analyses [391, 402, 418]. A systematic review including 57 studies (n = 30,293) assessed the long-term survival of patients treated with TMT and RC [391]. Ten-year OS was 30.9% and 35.1% for TMT and RC (p = 0.32), respectively, with a mean DSS of 50.9% for TMT and 57.8% for RC (p = 0.26). For T2 disease, ten-year DSS was 69% and 78.9% for TMT and RC, respectively, and for T3/T4 disease 43.5% and 43.1% for TMT and RC, respectively. A large multi-institutional propensity score matched and weighted analysis showed comparable oncological outcomes between RC and TMT for selected MIBC patients [402]. This retrospective analysis included 722 patients with clinical stage T2-T4N0M0 MIBC (440 underwent RC, 282 received TMT) who would have been eligible for both approaches, treated at three university centres in the U.S. and Canada between 2005 and 2017. All patients had solitary tumours less than seven centimetre, no or unilateral hydronephrosis, and no extensive or multifocal CIS. Five-year metastasis-free survival was 74% for RC and 75% for TMT with inverse probability treatment weighting and 74% for both cohorts with propensity score matching. Five-year CSS for RC and TMT was 81% versus 84% with inverse probability treatment weighting, and 83% versus 85% with propensity score matching, respectively. Salvage cystectomy was performed in 13% of TMT patients. A nationwide study in the Netherlands also found no statistically significant difference in OS and DFS between patients treated with TMT and RC [419]. Another study reported no difference in survival outcomes in cN+ patients treated with surgery versus radical RT [420].

6.8.1.e Histological subtypes

Most studies are limited by retrospective design, relatively small sample sizes, lack of central pathology review, and differing radiation protocols and chemotherapy regimens, and are unable to report on individual outcomes of specific histologic subtypes. That said, patients with MIUC squamous, glandular or micropapillary subtypes appear to have similar complete response, survival outcomes, and salvage cystectomy rates following TMT when compared to pure UC and may be considered for TMT-based approaches [421, 422].

Patients with pure SCC or adenocarcinoma may have worse survival outcomes following TMT compared to UC and should be counselled for upfront RC [423, 424].

6.8.1.f Toxicity

Overall significant late pelvic (GI/genitourinary [GU]) toxicity rates after TMT are low and QoL is good [406, 425, 426]. 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 [425].

Use of image-guided IMRT and adaptive planning may further reduce pelvic toxicity [82, 83, 427, 428]. A retrospective study showed QoL to be good after TMT and in most domains better than after cystectomy, although prospective validations are needed [429]. For further discussion of QoL after TMT, see Section 10.5.

In summary, TMT offers an effective, bladder-preserving alternative to RC for carefully selected patients with MIBC. Using modern RT techniques and concurrent radio-sensitising chemotherapy, oncologic outcomes are similar to RC, with durable bladder function and low toxicity. Trimodality therapy should be discussed within an MDT and considered a Guidelines-supported option for eligible, motivated, and appropriately selected patients.

6.8.1.g Summary of evidence and recommendations for trimodality bladder-preserving treatment

Summary of evidence	LE
Long-term survival rates of bladder-preserving TMT are comparable to those of early cystectomy. The contraindications for TMT or surgery have to be considered.	2
Combined chemotherapy and RT is more effective than RT alone in bladder sparing treatment.	1b

Recommendations	Strength rating
Offer radical cystectomy or bladder-preserving trimodality treatment (TMT) as primary curative option for eligible patients since they are more effective than radiotherapy alone.	Strong
Advise patients who are candidates for TMT that bladder monitoring post-treatment is essential.	Strong

6.9 External beam radiotherapy

6.9.1 Definitive external beam radiotherapy

Earlier studies suggested inferior OS with EBRT compared to RC [430], though more recent propensity-matched analyses have not confirmed a significant difference when accounting for patient and tumour factors [431]. A large U.S. National Cancer Database study (cT2-4N0-3M0) demonstrated superior two-year OS with chemoradiation (56%) versus EBRT alone (42%) [432], underscoring the benefit of concurrent radiosensitisation. Similar benefit was also demonstrated in the BC2001 RCT discussed above [413]. However, EBRT alone remains appropriate for patients unfit for cystectomy or concurrent radiosensitisation. Prognostic factors for outcome have included age, T-stage, response to EBRT, tumour size, hydronephrosis, presence of CIS and completeness of the initial TURBT [433].

6.9.1.a Radiation technique and dose

With advances in planning, image guidance and delivery, the efficacy and safety of EBRT for MIBC have improved substantially. Modern image-guided and intensity-modulated RT (IGRT/IMRT) allows accurate target coverage while sparing bowel and other normal tissues. Typical curative EBRT doses are 64-66Gy in 32-33 fractions (conventional fractionation) [408, 434] or 55Gy in 20 fractions (moderate hypofractionation), the latter of which showed non-inferior in terms of locoregional control, OS and late toxicity in pooled individual-patient analysis from BC2001 and BCON trials [408, 409].

In a phase II study, 55 patients (median age 86) with BC, unfit for cystectomy or even daily RT, were treated with six-weekly doses of 6Gy [435]. 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.

The RAIDER Phase II trial evaluated dose-escalated, image-guided adaptive radiotherapy (DART) to the tumour subvolume (60Gy in 20 fractions or 70Gy in 32 fraction) compared with standard whole-bladder RT (55Gy in 20 fractions or 64Gy in 32 fractions). The adaptive approach was feasible across multiple centres, achieved excellent target coverage, and showed low rates of ≥ grade 3 late toxicity with promising two-year OS (± 80%), though not statistically different to standard dosing [428].

Elective pelvic nodal irradiation remains optional and should take into account patient comorbidities and the risks of toxicity to adjacent critical structures. A retrospective study suggested that pelvic nodal radiation was associated with better survival compared with bladder radiation alone after adjusted analysis [407]. For node-positive disease, consider boosting grossly involved nodes to the maximum achievable safe dose within 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 [436]. Acute diarrhoea is reduced even more with intensity-modulated RT [437].

In conclusion, EBRT outcomes have improved with modern delivery, but EBRT alone remains less effective than TMT (chemoradiation) or surgery (see Section 6.8.1). However, ERBT provides a reasonable alternative for patients unfit or unsuitable for radical surgery or concurrent chemotherapy.

6.9.2 Palliative external beam radiotherapy

For symptomatic locally advanced/metastatic disease, hypofractionated bladder RT provides rapid relief, especially of haematuria, with high response rates and acceptable toxicity. The MRC BA09 RCT showed that 21Gy/3 fractions is as effective as 35Gy/10 fractions for palliation, supporting short schedules in frail patients [397]. Symptom control regimens commonly used include 30-35Gy/5-10 fractions, 36Gy/6 once-weekly [438], and even once only 8Gy. Haematuria control is achieved in ± 70-90% with durability often spanning most of a patient's remaining lifespan. Higher biological dose does not clearly improve initial response, though it may prolong haematuria control. Modern image-guided delivery further reduces acute GI toxicity.

6.9.3 Summary of evidence and recommendation for external beam radiotherapy

Summary of evidence	LE
External beam RT alone should only be considered as a therapeutic option when the patient is unfit for cystectomy or chemoradiation.	3
Radiotherapy can also be used to stop bleeding from the tumour when local control cannot be achieved by transurethral manipulation.	1b

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

6.10 Other approaches

6.10.1 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 restaging biopsies are negative for residual (invasive) tumour [439]. In general, approximately 50% of patients will still have to undergo RC for recurrent MIBC with a disease-specific mortality rate of up to 47% in this group [440]. A disease-free status at restaging TURBT appears to be crucial in making the decision not to perform RC [441, 442]. A prospective study including 133 patients after radical TURBT and restaging negative biopsies, reported a 15-year follow-up [442]. Thirty percent of patients had recurrent NMIBC and went on to intravesical therapy, and 30% (n = 40) progressed, of which 27 died of BC. After 5, 10 and 15 years, the results showed 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. It is essential to recognise that this is a highly selected population.

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

6.10.1.a Recommendation 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

6.10.2 Chemotherapy

Chemotherapy alone rarely produces durable CR. 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% [443, 444]. Response to chemotherapy is a prognostic factor for treatment outcome and eventual survival, although it may be confounded by patient selection [445].

Several groups have reported the effect of chemotherapy on resectable tumours (neoadjuvant approach), as well as unresectable primary tumours [231, 241, 446, 447]. Neoadjuvant chemotherapy with two to three cycles of MVAC or CMV has led to a downstaging of the primary tumour in various prospective series [231, 241, 446].

A bladder-conserving strategy with TURBT and systemic cisplatin-based chemotherapy has been reported several years ago and could lead to long-term survival with intact bladder in a highly select patient population [448].

A large retrospective analysis of a U.S. National Cancer Database cohort reported on 1,538 patients treated with TURBT and multiagent chemotherapy [449]. The two- and five-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.

6.10.2.a Summary of evidence and recommendation 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. FOLLOW-UP AND SURVEILLANCE

7.1 Response to neoadjuvant therapy

Restaging imaging exams after completion of neoadjuvant therapy are primarily performed to rule out the presence of local progression or metastatic disease before proceeding to definitive local therapy. Computed tomography of the thorax, abdomen or pelvis represents the standard of care, and the use of ^{18}F-FDG PET/CT is restricted to specific situations in which CT is inconclusive. No prospective trials have addressed this question.

Potential future application of bladder MRI and the VI-RADS score may include prediction of response to treatment as well as perioperative outcomes using its modified version, the NAC VI-RADS (nacVI-RADS) [450]. Recently, prospective evidence has been demonstrating the optimal diagnostic accuracy in defining response to therapy using MpMRI and nacVI-RADS after both NAC and IO [451].

In consensus-based recommendations, experts agreed that bladder MRI can be used to assess response to systemic therapy to support the selection of patients for radical treatment, surveillance or bladder-sparing surgery [140]. However, this is not standard care, and its clinical value requires validation.

A meta-analysis that investigated the predictive role of ^{18}F-FDG PET/CT for assessment of tumour response to NAC in a total of 278 patients showed a pooled sensitivity of 0.84 (95% CI: 0.72-0.91) and specificity of 0.75 (95% CI: 0.59-0.86). Among the five included studies, only three used both cR and pCR as a reference standard [452]. The use of ^{18}F-FDG PET/CT in this situation is not standard of care and requires further investigation.

7.1.1 Recommendation for response to neoadjuvant therapy

Recommendation	Strength rating
Perform restaging computed tomography after neoadjuvant therapy to rule out local progression and the presence of metastatic disease.	Strong

7.2 Follow-up after radical cystectomy

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 [453].

Current surveillance protocols are based on recurrence patterns from retrospective series that may vary in follow-up regimens and imaging techniques [454-456]. For example, in a series of 1,270 RC patients, no OS differences were found between asymptomatic and symptomatic recurrences [454, 455]. Another series found that symptomatic recurrences increased the risk of death by 60% compared to asymptomatic patients [456].

However, there are no prospective trials demonstrating the potential benefit of early detection of recurrent disease on OS [457].

There is no proven effective standardised follow-up regimen after RC for BC. Despite the lack of conclusive evidence on the benefits of early detection of recurrence, the Panel identified consistent general post-RC follow-up strategies amongst urologist members of the EAU Bladder Cancer Guidelines Panels and developed a practice-based framework guided by expert opinion (Table 7.1) [458].

A schedule suggested by the Panel includes a CT scan (every six 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 (> three years). In those cases, monitoring of the upper urinary tract is mandatory during follow-up. Computed tomography is to be used for imaging of the upper urinary tract [459].

The exact time to stop follow-up is not well known and a risk-adapted schedule has been proposed recently, 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 [460]. 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. Subtype tumours (including urothelial subtypes, non-urothelial subtypes and mixed subtypes) might be associated with a greater recurrence risk than pure UC.

A different follow-up scheme for patients with subtype tumours has been proposed [461]. In case of pT0 patients with previous subtype in TURBT or in those in the age range between 60 and 79 years, the follow-up should be longer than in pure UC, since the risk of recurrence persists over time. Similar to pure UC, patients older than 80 years with subtype 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 (> ten years) as the risk of recurrence will exceed that of non-BC mortality [461]. Future prospective studies are needed to answer the question of whether a more intense follow-up for subtypes should be considered.

Moreover, the prognostic implications of the various sites of recurrence should be considered. Local and systemic recurrences have a poor prognosis and early detection of the disease might not influence survival [462]. Despite this, the rationale for a risk-adapted schedule for BC surveillance appears to be promising and deserves further investigation.

Table 7.1: Framework for follow-up practice informed by a summary of non-risk-adapted data and supported by > 75% agreement for performing a specific follow-up intervention/test

	Day 0-90	Frequency in year 1					Frequency in year 2					Frequency in year 3					Frequency in year 4-5					Frequency in year 5-10			Frequency after year 10		
		0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	0	1	2
Patient assessment	According to individual patient's needs, depending on postoperative course and adjuvant therapies																										
Stoma care				x					x					x				x				x			No cons.		
Pain				x				x						x				x				No cons.			No cons.		
Sexuality			x					x					x				No cons.					No cons.			No cons.		
Mental health		x					No cons.						x				No cons.					No cons.			No cons.		
Urinary tract infections		x						x					x				No cons.					No cons.			No cons.		
Physical examination																											
General health					x				x				x				x					No cons.			x		
Abdomen					x			x					x				No cons.					No cons.			x		
Stoma (if applicable)					x			x					x				x					No cons.			x		
Genital region		No cons.					No cons.					No cons.					No cons.					x			x		
Laboratory tests - blood																											
Creatinine and GFR					x				x				x					x					x		No cons.		
Hemoglobine				x					x								No cons.					No cons.			No cons.		
Sodium and potassium				x				x					x					x				No cons.			No cons.		
Vit B12, chloride, bicarb, leuko		No cons.					No cons.					No cons.					No cons.					No cons.			x		
Laboratory tests - urine																											
Cytology		No cons.					No cons.					No cons.					No cons.					No cons.			No cons.		
Imaging																											
CT chest-abdomen-pelvis/IVU				x					x					x					x			No cons.			No cons.		
Ultrasound of abdomen		No cons.					x					No cons.					x					x			x		

CT = computed tomography; GFR = glomerular filtration rate; IVU = intravenous urography.

7.3 Follow-up after trimodality therapy

Following completion of TMT, patients require close surveillance to detect intravesical, upper-tract, urethral, nodal or distant recurrence, upper-tract or urethral disease, and treatment-related complications, as well as to identify candidates for timely salvage cystectomy.

Most recurrences occur within the first two to five years after treatment. Patients with muscle-invasive intravesical recurrence should be evaluated promptly for salvage cystectomy when feasible. There is general expert consensus that cystoscopy should be performed every three months during the first two years, every six months until year five, and annually thereafter. Urine cytology and cross-sectional imaging of the chest, abdomen, and pelvis (CT or MRI, including upper-tract imaging) is recommended every six to twelve months for the first three to five years, and then as clinically indicated.

These intervals are consistent with international Guideline recommendations and a 2024 systematic review of TMT follow-up [463]. Evidence is available indicating that close cystoscopic monitoring and early salvage cystectomy are critical to long-term bladder preservation and DSS [463]. Post-radiation cystoscopic and cytologic interpretation can be challenging due to post-RT mucosal changes. Surveillance should also include assessment of bladder function and late toxicity. Risk-adapted schedules personalised to the various risk factors for relapse and emerging biomarkers (e.g. ctDNA) are under study.

7.4 Follow-up of functional outcomes and complications

Apart from oncological surveillance, patients with a urinary diversion require functional follow-up. Complications related to urinary diversion are detected in 45% of patients during the first five years of follow-up. In a series of 131 patients, this rate increased to 94% in those surviving more than 15 years [464].

General functional complications are diverse and include vitamin B12 deficiency, metabolic acidosis, worsening of renal function, urinary infections, urolithiasis and ureteroenteric stricture [465]. Benign ureteroenteric strictures may occur in up to 20% of patients [465]. 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 [462]. In case of cystectomy and bowel diversion, vitamin B12 levels should be measured annually, because low vitamin B12 levels have been reported in 17% of patients with bowel diversion [82, 83, 466]. In a series of 3,360 patients who underwent RC for MIBC, 29% progressed to advanced chronic kidney disease within 12 months [467].

In a retrospective study comparing various forms of intestinal diversion, ileal conduits had fewer late complications than continent abdominal pouches or orthotopic neobladders [466]. The main long-term complications in ileal conduit patients are stomal complications in up to 24% and functional and/or morphological changes of the upper urinary tract in up to 30% of patients [466, 468, 469]. At 15 years of follow-up, 50% of patients developed upper urinary tract changes and 38% developed urolithiasis [470].

The main specific complications in patients with a neobladder are continence problems and emptying dysfunction [457]. A prospective evaluation of continence outcomes in male patients undergoing orthotopic neobladder diversion has been conducted [471]. Daytime continence increased from 59% at less than three months postoperatively to 92% after 12 to 18 months. Night-time continence increased from 28% at less than three months postoperatively to 51% after 18 to 36 months. Also of interest is the urinary bother in females with an orthotopic neobladder. Daytime and night-time continence rates of 70.4% and 64.8%, respectively, have been reported in 56 female neobladder patients. Emptying disfunction is especially common in females - approximately two-thirds need to catheterise their neobladder, while nearly 45% do not void spontaneously at all [472]. There appears to be a correlation between voiding patterns and nerve preservation. In 66 female patients, bilateral preservation of autonomic nerves decreased the need for catheterisation to between 3.4 and 18.7% (CI: 95%) [473].

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 [474].

8. RECURRENT DISEASE

8.1 Intravesical recurrence

8.1.1 Post-trimodality therapy bladder recurrences and salvage cystectomy

A bladder-preserving TMT strategy requires a high level of patient compliance. Even if a patient has shown a clinical response to a TMT 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.

The majority of recurrences post-TMT are non-invasive and can be treated with TURBT and bladder instillations with chemotherapy or BCG [2, 406]. Non-muscle-invasive BC recurrences after complete response to TMT were reported in 25% of patients by the Boston group, over a decade after initial treatment in some cases [475]. An NMIBC recurrence was associated with a lower DSS, although in properly selected patients, intravesical BCG could avoid immediate salvage cystectomy.

8.1.2 Salvage cystectomy post-trimodality therapy

A retrospective, single-centre analysis grouped 265 patients into salvage cystectomy post-TMT; primary cystectomy; primary cystectomy with a history of non-TMT abdominal; or pelvic RT. Post-TMT salvage cystectomy was associated with a higher incidence of any late (HR: 2.3; $p = 0.02$) and major late complications (HR: 2.1; $p < 0.05$), but there was no difference in intraoperative and early complications, DSS ($p = 0.8$) or OS ($p = 0.9$) between the groups [476].

In contemporary series, salvage cystectomy is required in approximately 10-15% of patients treated with TMT due to invasive in-bladder recurrences and can be curative [400, 402, 406, 417] (see Section 7.4). In fact, patients who required a salvage cystectomy for a recurrence had similar survival to those who did not require a salvage cystectomy [402].

Current data suggest that salvage cystectomy is feasible with acceptable morbidity. Major late complication rates were slightly higher but remain acceptable for salvage versus primary cystectomy, and there was no difference in intraoperative and early complications, DSS or OS [476, 477].

In a retrospective analysis of 1,846 evaluable patients, only 34 patients received RT prior to orthotopic neobladder reconstruction. It was concluded that, following pelvic RT, a neobladder is possible in highly selected patients with statistically similar perioperative complication rates compared to patients who did not receive prior RT. Patient selection, with oncologic factors (positive urethral margins, nodal involvement and extravascular disease) more commonly than technical factors (adhesions/difficult dissection, bleeding, urethral stricture) influence conversion from a planned neobladder reconstruction [478].

8.1.3 Recommendation for salvage cystectomy

Recommendation	Strength rating
Offer salvage cystectomy to patients with muscle-invasive bladder cancer recurrence after trimodality therapy.	Strong

8.2 Pelvic recurrence

Local recurrence takes place in the soft tissues of the original surgical site or in LNs. Contemporary cystectomy has a 5-15% probability of pelvic recurrence which usually occurs during the first 24 months, most often within six to 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 underutilisation of perioperative chemotherapy [479].

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 [457].

8.3 Upper tract recurrence

Upper urinary tract UCs occur in 4-10% of cases and represent the most common sites of late recurrence (three-year DFS following RC) [480]. Median OS is 10-55 months, and 60-67% of patients die of metastatic disease

[457]. 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% versus 29.6% with upper urinary tract imaging. The meta-analysis concluded that patients with non-invasive cancer are twice as likely to have UTUC as patients with invasive disease [459]. Multifocality increases the risk of recurrence threefold, while positive ureteral or urethral margins increase the risk sevenfold. Radical nephroureterectomy can prolong survival [481].

8.4 Urethral recurrence

Urethral recurrence-related death is rare, and prophylactic urethrectomy does not show a survival benefit. However, inappropriate urethra preserving surgery in patients at high-risk of urethral recurrence may increase local recurrence. This may be responsible for poor survival after urethra preserving surgery rather than disease progression derived from urethral recurrence. Robotic urethra-preserving surgery has the potential to reduce unnecessary urethral and local recurrence without compromising survival [482]. In a systematic review, the incidence of new urethral tumours after RC is 4.4% (1.3-13.7%). Risk factors for secondary urethral tumours are urethral malignancy in the prostatic urethra/prostate (in males) and bladder neck (in females). Orthotopic neobladder was associated with a significant lower risk of urethral tumours after RC (OR: 0.44) [483].

There is limited data, and agreement, regarding 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 males with urethral recurrence diagnosed asymptomatically versus symptomatically, therefore follow-up of the male urethra is indicated in patients at risk of urethral recurrence [457]. Treatment is influenced by local stage and grade of urethral occurrence. In urethral CIS, BCG instillations have success rates of 83% [484]. 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].

8.5 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 [485]. Systemic recurrence is more common in locally advanced disease (pT3/4), ranging from 32% to 62%, and in patients with LN involvement, ranging from 52 to 70% [486].

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 ten years. Median survival of patients with progressive disease treated with platinum-based chemotherapy is 9-26 months [487-489]. However, longer survival (28-33% at five years) has been reported in patients with minimal metastatic disease undergoing TMT management, including metastasectomy [490, 491].

8.6 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 (RT), chemotherapy and possibly surgery as options for treatment, either alone or in combination.	Strong
Distant recurrence	Poor prognosis.	Offer systemic therapy as the first option and consider metastasectomy or RT in case of unique metastasis site.	Strong
Upper urinary tract recurrence	Risk factors are multifocal disease, non-muscle-invasive bladder cancer / carcinoma *in situ* or positive ureteral margins.	See the EAU Guidelines on Upper Urinary Tract Urothelial Carcinomas [1].	Strong
Secondary urethral tumour	Staging and treatment should be done as for primary urethral tumour.	See the EAU Guidelines on Primary Urethral Carcinoma [3].	Strong

9. METASTATIC DISEASE

9.1 Introduction

The treatment of mUC 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. This longstanding paradigm has been challenged in the past years by the introduction of IO using CPIs and was upended in October 2023 with the presentation of the results of two practice-changing RCTs (EV-302/KEYNOTE A39 and CheckMate 901) demonstrating an OS benefit in the first-line setting against platinum-based chemotherapy [492, 493].

9.2 Management of oligometastatic bladder cancer

Oligometastatic cancer is defined as a situation with a limited number of metastatic sites. In a recent consensus, a maximum of three metastatic sites, all either resectable or amenable to stereotactic therapy, was proposed as the definition of oligometastatic BC [494]. Studies from other tumour types (e.g. prostate cancer, colorectal cancer and lung cancer) suggest possible survival benefit when adding local therapy. In BC, some retrospective studies suggest a potential survival benefit when incorporating local therapy to the bladder (including radiation therapy over chemotherapy alone) in metastatic disease [495, 496], and when employing metastasis-directed therapy [491, 497-499]. A favourable response to systemic treatment has been proposed as the criterion for selection of patients for any metastasis-directed therapy [494]. In a systematic review and meta-analysis of metastasis-directed therapy in the management of mUC, in which most patients were treated with surgical metastasectomy, many patients achieved long-term survival. The median OS was 46.2 months in patients treated for lung metastases (95% CI: 28.7-62.6), 31.2 months in those treated for LN metastases (95% CI: 16.1-51.8), and 29 months in those with mixed-location metastases (95% CI: 23.8-38.4) [500].

Another systematic review identified eight studies using SBRT for mUC with or without concomitant systemic therapies [501]. In metachronous patients, SBRT delivered with ablative doses (BED10 ≥ 78Gy) was associated with a two-year OS rate of 50.7% (95% CI: 35.1-64.4%). The use of subablative SBRT doses (BED10 = 43.2Gy) in combination with IO did not demonstrate significant clinical outcome improvement in two prospective studies. The overall tolerance was good, with only one study reporting toxicity of grade 3 in up to 18% of the patients treated with SBRT in combination with IO.

Overall, the data in oligometastatic disease are limited and it remains unclear how to best manage patients with oligometastatic disease. Further prospective studies in BC patients are needed.

9.3 First-line systemic therapy for metastatic disease: patient selection

In general, patients with untreated mUC can be divided into two broad categories: eligible or ineligible for combination therapies. The distinction between the two groups is currently based on the eligibility criteria for the pivotal EV-302/KEYNOTE 39A trial and is likely to undergo changes in the near future based on results from real-world evidence investigations. Major criteria include ECOG PS 0-2, GFR ≥ 30mL/min. and adequate organ functions based on eligibility for treatment with EV + P. With regards to platinum-based chemotherapy, the definitions to distinguish patients fit for cisplatin, fit for carboplatin and unfit for any platinum-based therapy remain valid, as outlined in Table 9.1.

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

An international survey among BC experts [443] 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 ≤ 60mL/min.; grade ≥ 2 audiometric hearing loss; grade ≥ 2 peripheral neuropathy or New York Heart Association (NYHA) class III heart failure [444]. Approximately 50% of patients with BC are not eligible for cisplatin-based chemotherapy [444]. Renal function assessment is of utmost importance for treatment selection. Measuring GFR with radioisotopes (99mTc DTPA or 51Cr-EDTA) is recommended in equivocal cases.

Cisplatin has also been administered in patients with a lower GFR (40-60mL/min.) using various split-dose schedules. The respective studies were mostly small phase I and II trials in various settings (neoadjuvant and advanced disease), demonstrating that the use of split-dose cisplatin is feasible and appears to result in encouraging efficacy [298, 502, 503]. 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, that is, both cisplatin and carboplatin. Patients are unfit for any platinum-based chemotherapy in case of PS > 2, GFR < 30mL/min. or the combination of PS 2 and GFR < 60mL/min. as the outcome in this patient population is poor regardless of whether or not platinum-based treatment is given [504]. Patients with multiple comorbidities may also be poor candidates for platinum-based chemotherapy.

Table 9.1: 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 30-60mL/min.	Any of the following:
GFR > 50-60mL/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 < 60mL/min.
Cardiac insufficiency NYHA class < III		Comorbidites > Grade 2

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

9.4 First-line therapy in patients fit for combination therapy

9.4.1 Enfortumab vedotin plus pembrolizumab

The combination of EV + P represents the new standard of care for patients who are deemed fit for combination therapies. This is based on EV-302/KEYNOTE 39A, a phase III trial that tested the antibody-drug conjugate EV directed against nectin-4 (EV: administered any number of times until progression) in combination with the immune CPI pembrolizumab (maximum of 35 cycles), against platinum-based chemotherapy (cisplatin or carboplatin permitted) in combination with gemcitabine (up to six cycles) in first-line advanced unresectable or metastatic UC. Thirty percent of the patients in the control arm received switch maintenance IO with avelumab. Both coprimary endpoints, PFS and OS, were clearly met with a significant improvement, with a median PFS of 12.5 versus 6.3 months (HR: 0.45; 95% CI: 0.38-0.54) and median OS of 31.5 versus 16.1 months (HR: 0.47; 95% CI: 0.38-0.58), respectively. The overall ORR was 67.7% (29.1% CR) compared to 44.4% (12.5% CR) with platinum-based chemotherapy (p < 0.001). All prespecified subgroups benefited equally from EV + P, regardless of cisplatin eligibility, PD-L1 expression or presence of liver metastases. Treatment-related toxicity grade ≥ 3 was reported in 56% for EV + P versus 70% in the chemotherapy arm. Specific and relevant EV toxicities include skin rash, peripheral neuropathy, ocular disorders and hyperglycaemia. Toxicity of EV + P must be managed proactively and attentively to avoid severe sequelae. The administration of EV + P requires adequate knowledge and care from a specialised MDT [493].

The combination of EV + P as first-line treatment in 45 cisplatin-ineligible patients with locally advanced mUC was also investigated in EV-103 - a phase Ib/II study. The results of the study demonstrated a confirmed objective response rate after a median of nine cycles of 73.3% with a complete response rate of 15.6% [505]. The median duration of response and median OS were 25.6 months and 26.1 months, respectively. The most common treatment-related AEs were peripheral sensory neuropathy (55.6%), fatigue (51.1%) and alopecia (48.9%) [505]. A second cohort within the same study randomly assigned previously untreated cisplatin-ineligible patients to EV alone or EV + P [506]. The ORR was 64.5% (95% CI: 52.7-75.1) and 45.2% (95% CI: 33.5-57.3) for patients treated with EV + P (n = 76) and EV monotherapy (n = 73), respectively. The median duration of response was not reached for the combination and was 13.2 months for monotherapy. Based on these results, EV + P has been granted FDA and EMA approval for patients with locally advanced UC or mUC.

9.4.2 Patients eligible for combination therapy but not eligible for enfortumab vedotin or enfortumab vedotin not available

Despite the results of the EV-302/KEYNOTE 39A study, EV is not available in all countries. Moreover, some patients might not be eligible for or refuse treatment with EV, including patients with uncontrolled diabetes, peripheral neuropathy grade ≥ 2 and pre-existing significant skin disorders. Platinum-based chemotherapy with integration of CPIs represents the preferred option in such patients. The general presumptions for cisplatin- and carboplatin-based therapy remain unchanged in this case and are outlined above.

9.4.2.a Patients fit for cisplatin

Cisplatin-containing combination chemotherapy was the standard of care since the late 1980s demonstrating an OS of 12 to 14 months in various series (for a review, see [507]). Methotrexate, vinblastine, adriamycin plus cisplatin and GC achieved survival of 14.8 and 13.8 months, respectively [508]. Overall response rates were 46% for MVAC and 49% for GC. The lower toxicity of GC [212] 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, and two-year OS. However, there is no significant difference in median survival between the two regimens [509, 510]. Further intensification of treatment using paclitaxel, cisplatin and gemcitabine (PCG) triplet regimen did not result in a significant improvement in OS in the ITT population of a phase III RCT comparing PCG to GC [511]. Similarly, the addition of the angiogenesis inhibitor bevacizumab to GC did not result in OS improvement [512].

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 [508]. In the trials with long-term follow-up, approximately 10-15% of patients with mUC were alive at five years and longer, suggesting a sustained benefit from cisplatin-based chemotherapy in a minority of patients [508, 510].

Carboplatin-containing chemotherapy, without the inclusion of IO, 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 versus cisplatin combination chemotherapy demonstrated lower complete response rates and shorter OS for the carboplatin arms [513]. A retrospective study highlighted the importance of applying cisplatin in cisplatin-eligible patients to maintain benefit [514].

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 [95% CI: 3.1-7.3 months] vs. 3.0 months [95% CI: 2.7-5.5 months]; HR: 0.65; $p = 0.04$) [515].

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 four to six 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 IO. Immune-related AEs occurred in 29% of all patients and 7% experienced grade 3 complications [516]. Patient-reported outcomes from JAVELIN Bladder 100 demonstrated no detrimental effect on QoL [517]. After ≥ two years of follow-up, OS remained significantly longer with avelumab plus BSC versus BSC alone (HR: 0.76; 95% CI: 0.63-0.91; $p = 0.0036$) [518].

Until recently, maintenance IO with avelumab was the standard of care for all patients with at least stable disease on first-line platinum-based chemotherapy.

In patients who are fit for cisplatin, the results of CheckMate 901 should be considered [492]. This trial tested the addition of nivolumab in combination with GC and followed by nivolumab maintenance (until progression or maximum of 24 months) compared to GC alone. Of note, only 9% in the control arm received switch maintenance therapy with avelumab. The coprimary endpoints, PFS and OS were reached with a median PFS of 7.9 versus 7.6 months (HR: 0.72; 95% CI: 0.59-0.88) and a median OS of 21.7 versus 18.9 months (HR: 0.78; 95% CI: 0.63-0.96). The response rate was improved with GC plus nivolumab (57.6% vs. 43.1.%). A CR was achieved in 21.7% of patients with nivolumab plus GC with a duration of 37.1 months. Nivolumab plus GC had higher treatment related grade ≥ 3 toxicity (62% vs. 52%). This combination represents an alternative to GC followed by maintenance therapy with avelumab in patients not eligible for EV or if EV is not available.

9.4.2.b 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 [444]. A 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 < 60mL/min.

and/or PS 2. Severe acute toxicity was 13.6% with GemCarbo versus 23% with M-CAVI, while the ORR was 42% for GemCarbo and 30% for M-CAVI [504]. Based on these results, the combination of carboplatin and gemcitabine should be considered a standard of care in this patient group. Importantly, both EV-302/KEYNOTE 39A and JAVELIN Bladder 100 included patients fit for carboplatin, while CheckMate 901 included patients fit for cisplatin only.

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. Single-agent chemotherapy is not recommended for first-line treatment of mUC.

9.5 First-line therapy in patients not eligible for combination therapy

Limited data exist regarding the optimal treatment for this patient population that is characterised by severely impaired PS (PS > 2) and/or severely impaired renal function (GFR < 30mL/min.) or inadequate organ function. 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 cisplatin-based chemotherapy did not focus specifically on this patient population, thus making interpretation of data difficult. The FDA (but not EMA) has approved pembrolizumab as first-line treatment for patients not fit to receive any platinum-based chemotherapy, regardless of PD-L1 status, based on the results of one single-arm phase II trial [519].

Based on the results of two single-arm phase II trials [519, 520], the CPIs pembrolizumab and atezolizumab have been approved by 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 UC or mUC ineligible for cisplatin, showing an ORR of 29% and CR in 7% of patients [519, 521]. 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 [520].

First-line avelumab was evaluated in patients with PD-L1 positive, metastatic or locally advanced disease and demonstrated a median OS of 10.0 months (95% CI: 5.5-14.5 months) with 43% of patients alive at one year.

A phase II randomised trial (BAYOU) evaluating durvalumab with olaparib or placebo in platinum-ineligible patients with mUC demonstrated no PFS or OS benefit for the addition of olaparib [522].

The IMvigor 130, Keynote 361 and DANUBE trials all included an experimental arm with IO alone using atezolizumab, pembrolizumab and durvalumab, respectively [102-104]. No benefit in terms of PFS or OS for the use of single-agent IO compared to platinum-based chemotherapy was found. Therefore, the combination of carboplatin/gemcitabine remains the preferred first-line treatment option for patients who are ineligible for cisplatin and are planned to receive chemotherapy.

9.6 Results of other trials integrating immunotherapy in the first-line setting without overall survival benefit

In 2020, the results of three phase III trials were published that investigated the use of IO in the first-line setting for platinum-eligible patients. The first trial, IMvigor130, investigated the combination of the PD-L1 inhibitor atezolizumab plus platinum-gemcitabine chemotherapy versus chemotherapy plus placebo versus atezolizumab alone [102]. The primary endpoint of PFS benefit for the combination versus 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]) after a median follow-up of 11.8 months. In the final OS analysis from IMvigor130, the PFS benefit did not translate into a significant OS benefit for combination therapy or atezolizumab versus chemotherapy alone [523].

The KEYNOTE 361 study had a very similar design using the PD-1 inhibitor pembrolizumab plus platinum-gemcitabine versus chemotherapy plus placebo versus pembrolizumab alone. The results of the primary endpoints of PFS and OS for the comparison of pembrolizumab plus chemotherapy versus chemotherapy plus placebo in the ITT population showed no benefit for the combination or pembrolizumab monotherapy versus chemotherapy alone [103].

DANUBE compared the IO combination (IO-IO) of CTLA-4 inhibitor tremelimumab and PD-L1 inhibitor durvalumab with chemotherapy alone or durvalumab alone [104]. The coprimary endpoint of improved OS for the IO-IO combination versus chemotherapy was not reached in the ITT group nor was the OS improved for durvalumab monotherapy versus chemotherapy in the PD-L1-positive population.

In conclusion, unlike CheckMate 901, these three trials do not support the use or combination of the PD-1/L1 CPIs plus platinum-based chemotherapy or the IO-IO combination as first-line treatment.

9.7 Further-line systemic therapy for metastatic disease

9.7.1 Introduction

Due to the results of the EV-302/KEYNOTE A39 trial and the expected paradigm shift in first-line therapy with establishment of the EV + P combination, as well as the CheckMate 901 trial with the combination of cisplatin, gemcitabine and nivolumab, selecting subsequent therapy lines in patients who fail during or progress after first-line treatment poses a significant challenge. Depending on the choice of first-line therapy, the below options exist.

9.7.2 Chemotherapy

In patients eligible for combination therapy that received EV + P, platinum-based chemotherapy with gemcitabine plus cisplatin or carboplatin may be considered. However, data is limited for this new post-EV + P clinical disease state and toxicities, for example, neuropathy from prior therapy, must be taken into consideration in determining a treatment plan. For patients that already received platinum-based chemotherapy with or without IO further-line chemotherapy, data are highly variable and mainly derive from small single-arm phase II trials, apart from one single phase III RCT. A reasonable strategy has been to rechallenge former platinum-sensitive patients if progression occurred at least six to 12 months after first-line platinum-based combination chemotherapy. A retrospective analysis of 296 patients within the Retrospective International Study of Cancers of the Urothelium (RISC) cohort revealed that subsequent platinum-based combination chemotherapy achieved a somewhat higher disease control rate (57.4% vs. 44.8%; p = 0.041) and OS (7.9 vs. 5.5 months; p = 0.035) compared to subsequent non-platinum-based chemotherapy [524]. 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 [525, 526].

The paclitaxel/gemcitabine combination has shown good response rates in small single-arm studies, but no adequate phase III RCT has been conducted [527, 528]. Vinflunine was tested in a phase III RCT and compared against BSC in patients progressing after first-line treatment with platinum-based chemotherapy [529]. 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 versus 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 [530, 531].

9.7.3 Immunotherapy for platinum-pretreated patients without previous immunotherapy

The immune CPIs 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) versus 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 [521, 532].

Atezolizumab was the first CPI approved by the FDA for mUC based on the results of phase I and II trials [110, 533], however, the indication has subsequently been withdrawn. The phase III RCT (IMvigor211) included 931 patients comparing atezolizumab with second-line chemotherapy (paclitaxel, docetaxel or vinflunine), but did not meet its primary endpoint of improved OS for patients with high PD-L1 expression with 11.1 months (atezolizumab) versus 10.6 (chemotherapy) months (stratified HR: 0.87; 95% CI: 0.63-1.21; p = 0.41) [282].

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 pretreated patients. The primary endpoint of ORR was 19.6%, and OS was 8.74 months for the entire group [534]. The TITAN-TCC study evaluated the safety and activity of nivolumab induction plus high-dose ipilumumab (3mg/kg) boosts in non-responders (stable or progressive disease) in the second-line treatment of 83 patients with mUC. Fifty patients (60%) received at least one boost with an investigator-assessed response rate of 33% (CR: 7%), demonstrating promising outcomes with this strategy compared to the rate reported in CheckMate 275 [535].

9.7.3.a 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 IO treatment should raise suspicion regarding a possible relation to the treatment. The nature of immune-related AEs has been very well characterised and published [536]. 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 [537]. Immunotherapy treatment should be applied and supervised by trained clinicians only to ensure early side effect recognition and treatment. In case of interruption of IO, rechallenge will require close monitoring for AEs [538].

9.8 Integration of other agents

9.8.1 Enfortumab vedotin monotherapy

The first antibody-drug conjugate to report encouraging data in patients previously treated with platinum-based chemotherapy and checkpoint inhibition was EV. The phase-II single-arm study EV-201 in 125 patients showed a confirmed objective response rate of 44%, including 12% complete responses [539]. This data led to accelerated FDA and EMA approval for EV in locally advanced or metastatic UC patients who previously received a PD-1 or PD-L1 inhibitor and platinum-containing chemotherapy, as well as for cisplatin-ineligible patients who received one or more prior lines of therapy [540, 541]. Another cohort of the same EV-201 trial demonstrated similar promising results in 91 patients that were cisplatin-ineligible and had received prior IO [542]. A phase III RCT (n = 608) comparing EV with single-agent chemotherapy after prior platinum chemotherapy and CPI IO demonstrated significant survival benefit of almost four months (12.88 months vs. 8.97 months; HR: 0.7; 95% CI: 0.56-0.89) [543]. 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). The reported 24-month findings from the EV-301 trial confirm the PFS, OS and overall response benefit for EV versus single-agent chemotherapy [544].

9.8.2 Sacituzumab govitecan

Another new and 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. In the TROPHY-U-01 study, sacituzumab govitecan was tested in 113 platinum and IO pretreated mUC patients [539]. It achieved an ORR of 27%, with a median PFS of 5.4 months and a median OS of 10.9 months [545]. Side effects consisted of haematological toxicities (neutropenia 34% ≥ grade 3; febrile neutropenia 10% ≥ grade 3), fatigue (52%), alopecia (47%), nausea (60%), diarrhoea (65%, 10% ≥ grade 3) and decreased appetite (36%) [545]. Sacituzumab govitecan received accelerated FDA approval for mUC with prior platinum and IO pretreatment. However, the indication was withdrawn after the TROPiCS-04 trial in patients with advanced UC whose disease had progressed on prior platinum-based chemotherapy and immune CPIs, because sacituzumab govitecan did not significantly improve OS or PFS compared with physician's choice of chemotherapy (paclitaxel, docetaxel or vinflunine). In addition, grade 3 treatment-related AEs (67% vs. 35%) and grade 5 treatment-emergent AEs 7% vs. 2%; majority were infections with neutropenia) were higher with sacituzumab govitecan versus chemotherapy [546].

9.8.3 FGFR inhibition

Genomic profiling of UC has revealed common potentially actionable genomic alterations, including alterations in *FGFR* [547]. Erdafitinib is a pan-FGFR tyrosine kinase inhibitor and the first FDA-approved targeted therapy for mUC with susceptible *FGFR* 2/3 alterations following platinum-containing chemotherapy. The phase II trial of erdafitinib included 99 patients whose tumour harboured an *FGFR* 3 mutation or *FGFR* 2/3 fusion and who had disease progression following chemotherapy [97]. The confirmed ORR was 40% and an additional 39% of patients had stable disease. A total of 22 patients had previously received IO 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) [97]. Treatment-related AEs of ≥ grade 3 occurred in 46% of patients. Common AEs of ≥ grade 3 were hyponatraemia (11%), stomatitis (10%) and asthenia (7%). Thirteen patients discontinued erdafitinib due to AEs, including retinal pigment epithelial detachment, hand-foot syndrome, dry mouth and skin/nail events. In a long-term follow-up, the efficacy and safety profile remained similar with no new safety signals with longer follow-up [548].

The THOR cohort 1 trial, a phase III trial of erdafitinib compared with chemotherapy (docetaxel or vinflunine) in patients with mUC with susceptible *FGFR* 2/3 alterations who had progression after one or two previous treatments that included an anti-PD-1 or anti-PD-L1, demonstrated an improvement in OS with erdafitinib compared to chemotherapy (12.1 months vs. 7.8 months; HR: 0.64; 95% CI: 0.47-0.88; p = 0.005). Median PFS was also longer with erdafitinib than with chemotherapy (5.6 vs. 2.7 months; HR: 0.58; 95% CI: 0.44-0.78) [99]. Treatment-related toxicity grade ≥ 3 was similar in the two groups. The most common treatment-related AEs of grade 3 or higher were palmar-plantar erythrodysesthesia syndrome (9.6%), stomatitis (8.1%), onycholysis (5.9%) and hyperphosphatemia (5.2%) in the erdafitinib group.

Data on cohort 2 with n = 351, anti-PD-L1 naïve and progressing after one prior treatment line compared erdafitinib with pembrolizumab. No difference in OS was detected (10.9 vs. 11.1 months; HR: 1.18; 95% CI: 0.92-1.51) [549]. The ORR was 40% and 21.6% and median duration of response was 4.3 and 14.4 months for erdafitinib and pembrolizumab, respectively. In addition, 64.7% and 50.9% of patients in the erdafitinib and pembrolizumab arms had ≥ 1 grade 3-4 AEs.

Based on the THOR cohorts 1 and 2, erdafitinib has received both FDA and EMA approval for the treatment of patients with advanced or mUC with susceptible *FGFR* 3 genetic alterations who have previously received at least one line of therapy containing a PD-1 or PD-L1 inhibitor.

In addition to erdafitinib, several other FGFR inhibitors are being evaluated, including infigratinib, which has demonstrated promising activity [98]. A phase II/III trial of the pan-FGFR inhibitor rogaratinib versus chemotherapy in patients with locally advanced or mUC with *FGFR* 1-3 mRNA overexpression demonstrated similar outcomes as compared to chemotherapy [550]. The increased identification of *FGFR* 3 mutations/fusion has led to several ongoing trials with different agents and combinations in various disease settings.

*9.8.4 **HER2 targeted agents***

For several years, HER2 has represented a potential target for the treatment of UC. The DESTINY-PanTumor02 phase II trial of the antibody-drug conjugate trastuzumab deruxtecan in patients with HER2-expressing solid tumours included a cohort of 41 patients with locally advanced or metastatic BC after ≥ 1 systemic treatment or without alternative treatment options [117]. The ORR for patients with BC, regardless of HER2 IHC status, was 39% with an ORR of 56.3% and 35% in HER2 IHC 3+ and 2+, respectively. The median PFS for all patients with BC was 7.0 months, and median OS was 12.8 months. For all patients in the study across seven tumour cohorts, grade ≥ 3 drug-related AEs were seen in 40.8% of patients with 10.5% experiencing drug-related interstitial lung disease, including three deaths.

Based on this study, the FDA has granted accelerated approval to transtuzumab deruxtecan for patients with unresectable or metastatic HER2-positive (IHC3+) solid tumours who have received prior systemic therapy and have no satisfactory alternative treatment options. Other HER2 targeted agents are being explored, including a recently reported combined analysis of two phase II trials evaluating the safety and efficacy of the antibody-drug conjugate Disitamab Vedotin in patients with HER2-positive locally advanced UC or mUC who have progressed on at least one line of systemic chemotherapy [551]. In 107 patients, the ORR was 50.5% with median PFS and OS of 5.9 months and 14.2 months, respectively. The most common treatment-related AEs were peripheral sensory neuropathy, leukopenia, AST increased and neutropenia. Ongoing studies are evaluating disitamab vedotin as monotherapy and in combinations.

*9.8.5 **Impact of prior neoadjuvant/adjuvant therapy on treatment sequence***

Perioperative 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 [552]. Many ongoing phase III trials are investigating the use of IO in this setting as well (see Section 7.6.2). So far, two trials have reported a significant DFS benefit for adjuvant immune CPIs (nivolumab compared with placebo and pembrolizumab compared with surveillance), whereas another trial reported no significant benefit using atezolizumab versus placebo in the same setting [291, 296]. A growing number of patients with mUC are expected to have undergone pretreatment with platinum and/or IO agents. However, no prospective trials have investigated the treatment of these patients. The choice of treatment depends on the applied perioperative

treatment and the time until relapse. If at least 12 months have passed since the end of perioperative treatment, the same systemic treatment as in treatment-naïve patients is recommended.

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

Pure UC represents the predominant histology in over 90% of patients with mUC. Subtypes (e.g. micropapillary, nested, sarcomatoid) and divergent differentiation (e.g. SCC, adenocarcinoma) can be found in addition to pure UC in up to 33% of patients. Such patients were often excluded from large phase II and phase III trials. Therefore, the knowledge about the best management of such patients is limited. The literature was reviewed [52] and an expert Delphi survey and consensus conference provided guidance [83]. In case of predominant pure UC, it is recommended to treat patients with mixed histology the same way as patients with a pure UC histology. Patients with predominant non-urothelial differentiation, such as small cell NE carcinoma, urachal adenocarcinoma, SCC and adenocarcinoma, should be treated individually.

9.9 Treatment of patients with bone metastases

The prevalence of metastatic bone disease (MBD) in patients with advanced or metastatic UC is 30-40% [553]. An interesting report described several observations concerning age- and sex-related differences in the distribution of metastases in patients with metastatic BC and demonstrated that bone was the most common metastatic site in males with other differences noted according to patient age and sex [554]. Skeletal complications due to MBD have a detrimental effect on pain and QoL and are also associated with increased mortality [555]. 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 [556]. 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 [557]. Patients with MBD, irrespective of the cancer type, should be considered for bone-targeted treatment [555].

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 must be adjusted according to pre-existing medical conditions, especially renal function [558]. For denosumab, no dose adjustments are required for variations in renal function.

9.10 Treatment algorithm for metastatic urothelial cancer

Figure 9.2 summarises the treatment algorithm for metastatic BC based on the evidence discussed in the text above. Patients with treatment-naïve mUC can be divided into two broad categories: eligible for combination therapies or ineligible for combination therapies (see Section 9.3).

The combination of EV + P represents the new standard of care for patients who are deemed fit for combination therapies. In patients that might not be eligible for or who refuse treatment with EV, including patients with uncontrolled diabetes, peripheral neuropathy grade ≥ 2 and pre-existing significant skin disorders, platinum-based chemotherapy with integration of immune CPIs represents the preferred options.

With regard to platinum-based chemotherapy, the definitions are grouped according to platinum eligibility based on clear definitions. In platinum-based chemotherapy, cisplatin is to be preferred to carboplatin. Patients who are cisplatin-ineligible but carboplatin-eligible should receive gemcitabine carboplatin combination chemotherapy. In case of positive PD-L1 status, treatment with CPIs (atezolizumab or pembrolizumab) could be an alternative option.

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

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

Determining *FGFR* mutation status is recommended before deciding about further-line treatment. Patients with *FGFR* 3 mutations are candidates for FGFR inhibitor treatment.

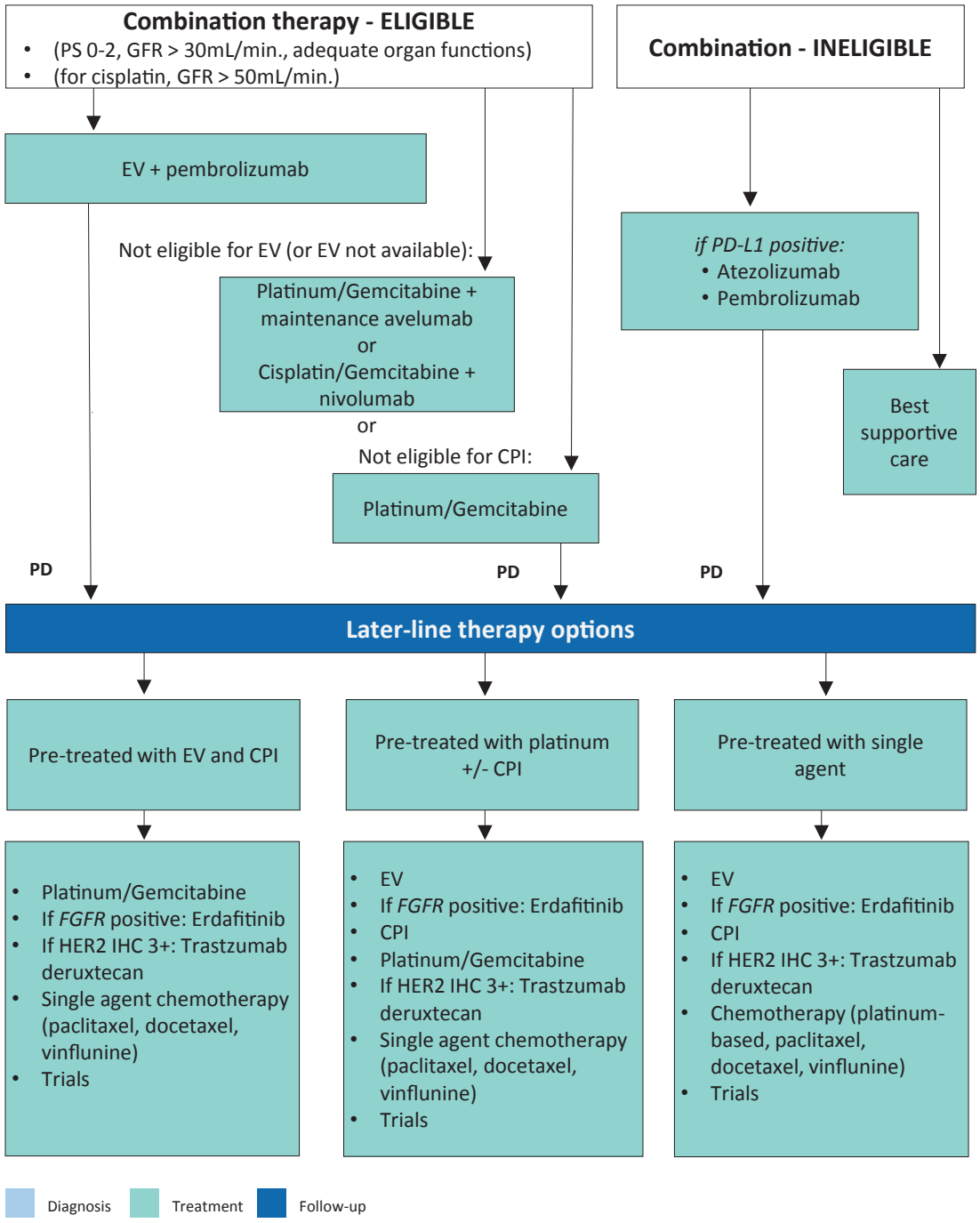
Enfortumab vedotin therapy is standard in case of progression after platinum chemotherapy and IO. However, based on EV-302/KEYNOTE 39A, the majority of patients will be candidates for EV + P in the first-line setting. The optimal sequence of novel agents and potential combinations are the subject of several ongoing trials. Treating patients within ongoing clinical trials is recommended whenever possible.

9.11 Summary of evidence and recommendations for metastatic disease

Summary of evidence	LE
Enfortumab vedotin in combination with pembrolizumab in the first-line setting demonstrated significant survival benefit as compared to chemotherapy.	1
The combination of cisplatin and gemcitabine plus nivolumab in the first-line setting demonstrated significant survival benefit as compared to 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
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
Enfortumab vedotin after platinum-containing chemotherapy and a CPI has demonstrated a significant survival benefit as compared to chemotherapy.	1b
Erdafitinib demonstrated a survival benefit compared to chemotherapy in patients with susceptible *FGFR* 3 genetic alterations who received one or two previous treatments that included at least a CPI.	1b
Pembrolizumab, a PD-1 inhibitor, 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
Atezolizumab, a PD-1 inhibitor, is approved for patients with advanced UC or mUC unfit for cisplatin-based chemotherapy in case of high PD-L1 expression defined as tumour-infiltrating immune cells covering ≥ 5% of the tumour area using the SP142 assay.	1b
Pembrolizumab, a PD-1 inhibitor, is approved for patients with advanced or mUC unfit for any platinum-based chemotherapy in case of high PD-L1 expression defined as CPS of ≥ 10 using the Dako 22C33 platform (EMA; FDA approval independent of PD-L1 status).	1b
Carboplatin combination chemotherapy is less effective than cisplatin-based chemotherapy in terms of complete response and survival.	2a
Single-agent chemotherapy provides low response rates of usually short duration.	2a
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, because they reduce and delay skeletal related events.	1b
Retrospective case series show some survival benefit for the additional of local therapy (to the primary and to sites of metastases) in oligometastatic BC.	3

Recommendations	Strength rating
First-line treatment if eligible for combination therapy	
Use antibody-drug conjugate enfortumab vedotin (EV) in combination with checkpoint inhibitor (CPI) pembrolizumab.	Strong
If contraindications for EV or EV not available: Offer platinum-containing combination chemotherapy (cisplatin or carboplatin plus gemcitabine) followed by maintenance treatment with CPI avelumab in patients with at least stable disease on chemotherapy.	Strong
If contraindications for EV (or EV not available) and cisplatin-eligible: Offer cisplatin/gemcitabine in combination with CPI nivolumab.	Strong
If contraindications for EV and CPI therapy: Use platinum-containing combination chemotherapy (cisplatin or carboplatin plus gemcitabine).	Strong
First-line treatment if not eligible for combination therapy	
Offer single agent CPI pembrolizumab or atezolizumab in case of high programmed death-ligand 1 (PDL-1) expression (for definitions see text).	Weak
Later-line treatment	
After prior EV + CPI	
Offer platinum-containing combination chemotherapy (cisplatin or carboplatin plus gemcitabine).	Weak
If actionable fibroblast growth factor receptor (*FGFR*) alterations: offer erdafitinib	Strong
Offer single agent chemotherapy (docetaxel, paclitaxel, vinflunine).	Weak
After prior platinum-based chemotherapy +/- CPI	
Offer antibody-drug conjugate enfortumab vedotin.	Strong
If actionable *FGFR* alterations and prior CPI: offer erdafitinib.	Strong
If no prior CPI: offer pembrolizumab.	Strong
Consider single agent chemotherapy (docetaxel, paclitaxel, vinflunine).	Weak
Further treatment after EV, CPI, platinum-based therapy	
Offer antibody-drug conjugate Trastuzumab deruxtecan in case of human epidermal growth factor receptor (HER) 2 over expression (IHC 3+) and consider in case of HER2 (IHC 2+).	Weak
Offer treatment in clinical trials. Consider best supportive care alone if patient is not a candidate for further cancer-specific systemic therapy.	Strong
If actionable *FGFR* alterations: offer erdafitinib.	Strong

Figure 9.2: Flow chart for the management of metastatic urothelial cancer



CPI = checkpoint inhibitor; EV = enfortumab vedotin; FGFR = fibroblast growth factor receptor; GFR = glomerular filtration rate; HER = human epidermal growth factor receptor; PD-L1 = programmed death-ligand 1; PD = programmed death; PS = performance status.

10. QUALITY OF LIFE AND PALLIATIVE CARE

10.1 Introduction

The evaluation of Health-Related Quality of Life (HRQoL) considers physical, psychological, emotional and social functioning. In patients with MIBC, HRQoL is affected, particularly in the physical and social functioning domains [559-561].

In fact, in a large population-based study of patients with MIBC and no prior psychiatric history, 31% of those patients were diagnosed with a new mental health disorder after their BC diagnosis [562]. The most common diagnoses were depression (13%), alcohol and drug abuse (12%) and anxiety (11%). Patients with a post-BC mental health diagnosis had a 57% higher hazard of overall mortality (HR 1.57; p = 0.048) and an 80% higher hazard of bladder CSM (HR 1.81; p = 0.037) [562]. Clinicians should remain attentive to the mental health of patients following surgery for MIBC and facilitate referral to specialist support when indicated, because validated postoperative mental health questionnaires are currently lacking. These patients should also be informed of peer support available through patient advocacy groups, which is intended to complement, not replace, professional mental health care when needed.

Several questionnaires have been validated for assessing HRQoL in patients with BC, including FACT-G [563], EORTC QLQ-C30/BLM30 [564], SF-36 [565] and the Bladder Cancer Index (BCI) [566]. Despite these validated questionnaires, there is no single questionnaire that covers all concerning domain. For patients undergoing RC and urinary diversion, a recent systematic review recommended both the EORTC QLQ-C30 and QLQ-BLM30 to identity the issues that impact patients most [561].

Regardless of the which questionnaire is used, assessment of the baseline and post-treatment HRQoL is important. Baseline assessment of HRQoL is not only important in clinical decision making but may also impact BC specific mortality [567].

10.2 Neoadjuvant therapy

Two RCTs including patients undergoing NAC have published their HRQoL data [426, 568]. One of these RCTs 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 [426]. Another reported on 64 patients included in the JCOG0209 study who underwent NAC (MVAC vs. MVAC and RC). An overall decline in HRQoL was reported directly following NAC using the FACT-BL questionnaire. However, no difference in HRQoL was observed after the consolidating RC.

10.3 Radical cystectomy and urinary diversion

Two systematic reviews and meta-analyses focused on HRQoL after RC and urinary diversion [348, 569].

One systematic review compared HRQoL of incontinent and continent urinary diversions (all types) including 29 studies (n = 3,754), of which nine had a prospective design (one of which was randomised) [348]. Only three studies reported HRQoL data both pre- and postoperatively. All three studies reported an initial deterioration in overall HRQoL, but general health, functional and emotional domains at 12 months post-surgery were equal or better than baseline. Overall, no difference in HRQoL between continent and incontinent urinary diversion was reported, although an ileal conduit may confer a small physical health benefit [569].

The other systematic review reported HRQoL comparing ileal conduit with orthotopic neobladder reconstruction [569]. A pooled analysis was performed including 18 studies (n = 1,553), of which the vast majority were retrospective studies. Although this study was hampered by methodological limitations, no statistically significant difference in overall HRQoL was found.

A number of RCTs comparing open RC with RARC (with either ECUD or ICUD) have reported their HRQoL data [340, 570-572]. All studies reported no statistically significant difference in HRQoL outcomes between surgical techniques.

Overall, no single type of urinary diversion appears to be superior in terms of general HRQoL. Rather, the patient's preference is important in the selection of a reconstruction method [348].

10.4 Adjuvant therapy

Health-related QoL data was reported in the phase III CheckMate 274 RCT in which patients were randomised for adjuvant nivolumab or placebo after radical surgery for BC or UTUC. Patients were not pretreated with NAC. No clinically meaningful deterioration in HRQoL was observed during nivolumab treatment (based on the EORTC QLQ-C30/VAS questionnaire) [293].

10.5 Bladder-sparing trimodality therapy

Health-related QoL data following bladder sparing treatment was collected in a RCT setting [426]. The primary endpoint was the change in the Bladder Cancer Subscale (BLCS), as part of the FACT-BL questionnaire, at one-year post-treatment. The questionnaire return rate at one and five years was 70% and 60%, respectively. 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 six months after RT and maintained at this level for five years. In a follow-up study using the same study population, potential differences between male and female participants were investigated [573]. An additional decline in HRQoL at two years post-treatment was observed for females compared to males. The exact reason was unclear but appeared to be related to worsening of urinary function. However, both females and males largely recovered to baseline levels of function at five years post-treatment. Approximately 33% of patients reported persistent lower BLCS scores after five years. Addition of chemotherapy did not affect HRQoL outcomes.

A systematic review and meta-analysis showed a trend in favour of higher mean reported values for global health score, physical functioning and role functioning for TMT compared to RC [574]. Another retrospective study showed QoL to be effective after TMT, and in most domains better than after cystectomy [429]. In a secondary analysis of this study, from six HRQoL instruments, two responses had a statistically significant difference between females and males - incidence of diarrhoea and degree of sexual activity [575]. Fifty percent of females compared to 86% of males reported no diarrhoea ($p = 0.02$). A greater percentage of females reported some degree of sexual activity in the four weeks prior to questionnaire completion ($p = 0.04$), and sexual interest following TMT declined significantly with age in males, but not in females.

An improved understanding of the effect of all these treatment modalities on HRQoL is essential to provide personalised patient care. Overall, data on HRQoL after TMT are scarce, and additional comparative studies including patients receiving RC (especially using ileal orthotopic neobladder) are needed [576]. See Section 7.5.4.5 for further discussion of toxicity after TMT.

10.6 Noncurative or metastatic bladder cancer

In patients with primary noncurative or metastatic disease, HRQoL is reduced due to associated micturition problems, bleeding and pain and therefore disturbance of social and sexual life [577]. Beneficial impact of palliative surgery [578], RT [579], and/or chemotherapy on bladder-related symptoms have been described [580].

An HRQoL analysis was performed in platinum-refractory patients who were randomised to pembrolizumab versus another line of chemotherapy (KEYNOTE-45 trial) [581]. Patients treated with pembrolizumab were reported to have stable or improved global health status/QoL, whereas those treated with investigators' choice of chemotherapy experienced declines in global health [581].

In the second-line situation, data are available from the EV-201 study, including 125 patients treated with EV after failing previous treatment with platinum chemotherapy and anti-PD-1/L1 therapy [582]. Patients who remained on EV treatment showed no deterioration in HRQoL. In patients with bone metastases at baseline, pain control and possibly pain reduction was observed.

10.7 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 have a negative impact on HRQoL.	2a
No distinct difference was seen in overall QoL between patients with continent or incontinent diversion.	1b
In patients with MIBC treated with RC, overall HRQoL declines immediately after treatment and recovers to baseline at 12 months postoperatively in most patients.	1b
In patients with MIBC treated with RC, HRQoL is not affected by the type of urinary diversion and operative technique (open or robotic) chosen.	1b

In patients with MIBC treated with RT, overall HRQoL declines immediately after treatment, and recovers near to baseline at six months post-treatment.	1b
In patients with MIBC treated with RT, concomitant chemotherapy or neoadjuvant chemotherapy has no significant impact on HRQoL.	1b
Adjuvant treatment with nivolumab does not result in a clinically meaningful decrease in HRQoL compared to placebo.	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, both at baseline and post-treatment.	Strong
Discuss the type of urinary diversion considering patient preference, existing comorbidities, tumour variables and coping abilities.	Strong

10.8 Supportive care

*10.8.1 **Obstruction of the upper urinary tract***

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

*10.8.2 **Bleeding and pain***

In case of bleeding, the patient must be screened first for coagulation disorders or the patient's use of anticoagulant drugs must be reviewed. Tumour debulking by TURBT, selective transurethral electrocoagulation or laser coagulation can be challenging in a bladder full of tumour or in case of gross haematuria. Intravesical rinsing of the bladder with 1% silver nitrate or 1-2% alum can be effective [583]. 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, for example, bladder fibrosis, but is more likely to control the bleeding [583]. 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% [584]. 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% [583]. Radical surgery is a last resort and includes cystectomy and diversion (see Sections 6.7.10.1 and 8.1.3).

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12. 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 EAU website: https://uroweb.org/guidelines/muscle-invasive-and-metastatic-bladder-cancer/panel.

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Disclosures: The EAU Guidelines Office certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/ affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following:

A.G. van der Heijden reported receiving company speaker honoraria fees from Merck Sharp & Dohme B.V.; and serving as a company consultant to Astellas Pharma International B.V., Johnson & Johnson Innovative Medicine, Merck Sharp & Dohme B.V. and Pfizer B.V. A. Carrión reported receiving company speaker honoraria, travel or consultation fees from Johnson & Johnson, Gebro, BMS and BC Platform; serving as a company consultant to BC Platforms; and participation in clinical trials by Janssen Research & Development, LLC. R. Cathomas reported receiving company speaker honoraria or consultation fees from Astellas, Astra Zeneca, Bayer, BMS, Johnson & Johnson, MSD, Pfizer, Roche, Merck Serono and Ipsen. E.M. Compérat reported serving as a company consultant to Daiitchi, Johnson and Astra. K. Dimitropoulos reported receiving company speaker honoraria fees from Astellas and Ipsen. J.A. Efstathiou reported receiving company speaker honoraria or consultation fees from Astellas; and serving as a company consultant for Boston Scientific and Blue Eagle Diagnostics.B. Kiss reported serving as a company consultant on the advisory board of Pfizer and Astra Zeneca. A. Lorch reported receiving company speaker honoraria or consultation fees from Astellas, Astra Zeneca, Bayer, BMS, Esai, Ipsen, Janssen, Merck, MSD, Novartis, Pfizer and Roche; receiving travel grants from Ipsen, Janssen and Bayer; participation in clinical trials as a principal investigator; and contributing as an author to the Onkopedia guidelines. P. Mariappan reported receiving company speaker honoraria fees from Bristol Myers Squibb, Janssen Cilag Ltd., Medac Pharma and Photocure; serving on the core committee of the International Bladder Cancer Group; receiving grants or research support from Nucleix; and participation in clinical trials by Nucleix. R.P. Meijer reported receiving grants or research support from Astellas Pharma International B.V., Gilead Sciences, Janssen Vaccines & Prevention B.V. and Merck Sharp & Dohme B.V. L.S. Mertens reported receiving company speaker honoraria fees from Johnson & Johnson Medical B.V and MSD (paid to hospital). M.I. Milowsky reported receiving grants or research support from Merck, Bristol-Myers Squibb, Alliance for Clinical Trials in Oncology, ALX Oncology, Novartis, Acrivon Therapeutics, PCCTC, OncoC4, Flare Therapeutics, Loxo/Lilly, Astellas Pharma, Pfizer, Amgen, Roche and G1 Therapeutics; being a stock shareholder in Pfizer and Gilead Sciences; presenting continuing medical education at Prime Education, Research to Practice and OncLive/MJH Life Sciences; and acting as uncompensated advisor to G1 Therapeutics and Loxo/Lilly. Y. Neuzillet reported receiving company speaker honoraria or consultation fees from AstraZeneca, Bristol-Myers Squibb, Merck, Astellas and MSD. M. Rink reported receiving company speaker honoraria fees from Johnson & Johnson,

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