

# EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer

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# TABLE OF CONTENTS

# PAGE

1.	INTRODUCTION	6
1.1	Aims and scope	6
1.2	Panel composition	6
1.3	Available publications	6
1.4	Publication history and summary of changes	6
1.4.1	Publication history	6
1.4.2	Summary of changes	6
2.	METHODS	7
2.1	Data identification	7
2.2	Peer-review	7
2.3	Future goals	7
3.	EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY	8
3.1	Epidemiology	8
3.2	Aetiology	8
3.2.1	Tobacco smoking	8
3.2.2	Occupational exposure to chemicals	8
3.2.3	Radiotherapy	8
3.2.4	Dietary factors	9
3.2.5	Metabolic disorders	9
3.2.6	Bladder schistosomiasis and chronic urinary tract infection	9
3.2.7	Gender	9
3.2.8	Genetic factors	10
3.2.9	Summary of evidence and recommendations for epidemiology and risk factors	10
3.3	Pathology	10
3.3.1	Handling of transurethral resection and cystectomy specimens	10
3.3.2	Pathology of muscle-invasive bladder cancer	11
3.3.3	Recommendations for the assessment of tumour specimens	11
3.3.4	EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer	11
4.	STAGING AND CLASSIFICATION SYSTEMS	12
4.1	Pathological staging	12
4.2	Tumour, node, metastasis classification	12
5.	DIAGNOSTIC EVALUATION	13
5.1	Primary diagnosis	13
5.1.1	Symptoms	13
5.1.2	Physical examination	13
5.1.3	Bladder imaging	13
5.1.4	Urinary cytology	13
5.1.5	Cystoscopy	13
5.1.6	Transurethral resection of invasive bladder tumours	14
5.1.7	Summary of evidence and recommendations for the primary assessment of presumably invasive bladder tumours	14
5.2	Imaging for staging of MIBC	15
5.2.1	Detection	15
5.2.2	Local staging of the bladder and upper tract	15
5.2.2.1	Magnetic resonance imaging for local staging of MIBC	15
5.2.2.2	CT imaging for local staging of MIBC	16
5.2.2.3	Computed tomography urography for local staging of the upper tract	16
5.2.2.4	Magnetic resonance urography for local staging of the upper tract	16
5.2.3	Distant staging of lymph nodes and other sites	16
5.2.3.1	Imaging of lymph nodes in MIBC	16
5.2.3.2	Distant metastases	17
5.2.4	Response to therapy	17

5.2.5	Future perspectives	17
5.2.6	Summary of evidence and guidelines for staging in muscle-invasive bladder cancer	18
5.3	Muscle-invasive and metastatic bladder cancer and health status	18
5.3.1	Evaluation of comorbidity, frailty and cognition	19
5.3.2	Comorbidity scales, anaesthetic risk classification and geriatric assessment	20
5.3.3	Summary of evidence and guidelines for comorbidity scales	21
6.	MARKERS	22
6.1	Introduction	22
6.2	Prognostic markers	22
6.2.1	Histopathological and clinical markers	22
6.2.2	Molecular markers	22
6.2.2.1	Molecular variants based on the Cancer Genome Atlas cohort	22
6.3	Predictive markers	23
6.3.1	Clinical and histopathological markers	23
6.3.2	Molecular markers	23
6.4	Conclusion	24
6.5	Summary of evidence and recommendation for urothelial markers	24
7.	DISEASE MANAGEMENT	25
7.1	Neoadjuvant therapy	25
7.1.1	Introduction	25
7.1.2	Role of cisplatin-based chemotherapy	25
7.1.2.1	Summary of available data	25
7.1.3	The role of imaging and predictive biomarkers	27
7.1.4	Role of neoadjuvant immunotherapy and chemo-immunotherapy	27
7.1.5	Summary of evidence and guidelines for neoadjuvant therapy	28
7.2	Pre- and post-operative radiotherapy in muscle-invasive bladder cancer	28
7.2.1	Post-operative radiotherapy	28
7.2.2	Pre-operative radiotherapy	29
7.2.3	Summary of evidence and recommendations for pre- and post-operative radiotherapy	29
7.3	Radical surgery and urinary diversion	29
7.3.1	Removal of the tumour-bearing bladder	29
7.3.1.1	Introduction	29
7.3.1.2	Radical cystectomy: timing	30
7.3.2	Radical cystectomy: indications	30
7.3.3	Radical cystectomy: technique and extent	30
7.3.3.1	Radical cystectomy in men	30
7.3.3.1.1	Concomitant prostate cancer	30
7.3.3.1.2	Sexual-preserving techniques	30
7.3.3.1.3	Summary of evidence and recommendations for sexual-preserving techniques in men	31
7.3.3.2	Radical cystectomy in women	31
7.3.3.2.1	Concomitant gynaecological malignancies and associated consequences	31
7.3.3.2.2	Sexual-preserving techniques	31
7.3.3.2.3	Summary of evidence and recommendation for sexual-preserving techniques in women	32
7.3.4	Lymphadenectomy: role and extent	32
7.3.5	Robotic-assisted laparoscopic cystectomy	32
7.3.5.1	Summary of evidence and recommendations for robotic-assisted laparoscopic cystectomy	33
7.3.6	Urinary diversion after radical cystectomy	33
7.3.6.1	Different types of urinary diversion	33
7.3.6.1.1	Uretero-cutaneostomy	33
7.3.6.1.2	Ileal conduit	34
7.3.6.1.3	Orthotopic neobladder	34
7.3.6.1.4	Continent cutaneous urinary diversion	34

	7.3.6.2	Patient selection	34
	7.3.6.3	Peri-operative care	35
	7.3.7	Morbidity and mortality	35
	7.3.8	Survival	37
	7.3.9	Impact of hospital and surgeon volume on treatment outcomes	37
	7.3.10	Summary of evidence and recommendations for radical cystectomy and urinary diversion	38
7.4		Palliative and salvage cystectomy	39
	7.4.1	Recommendations for palliative and salvage cystectomy	40
	7.4.1.1	EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer	40
	7.4.2	Supportive care	40
	7.4.2.1	Obstruction of the upper urinary tract	40
	7.4.2.2	Bleeding and pain	40
7.5		Bladder-sparing treatments for localised disease	40
	7.5.1	Transurethral resection of bladder tumour	40
	7.5.1.1	Recommendation for transurethral resection of bladder tumour	41
	7.5.2	External beam radiotherapy	41
	7.5.2.1	Definitive external beam radiotherapy	41
	7.5.2.2	Pallative external beam radiotherapy	41
	7.5.2.3	Summary of evidence and recommendation for external beam radiotherapy	42
	7.5.2.4	EAU-ESMO consensus statements on the management of advanced and variant bladder cancer	42
	7.5.3	Chemotherapy	42
	7.5.3.1	Summary of evidence and recommendation for chemotherapy	42
	7.5.4	Trimodality bladder-preserving treatment	42
	7.5.4.1	Patient selection and treatment paradigm	42
	7.5.4.1.1	Radiation therapy	43
	7.5.4.1.2	Concurrent radiosensitizing chemotherapy	43
	7.5.4.2	Outcomes	43
	7.5.4.3	Post-TMT bladder recurrences and salvage cystectomy	44
	7.5.4.4	Histological subtypes	44
	7.5.4.5	Toxicity	44
	7.5.4.6	Summary of evidence and recommendations for trimodality bladder-preserving treatment	45
	7.5.4.7	EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer	45
7.6		Adjuvant therapy	45
	7.6.1	Role of adjuvant platinum-based chemotherapy	45
	7.6.2	Role of adjuvant immunotherapy	46
	7.6.3	Summary of evidence and recommendations for adjuvant therapy	47
7.7		Metastatic disease	47
	7.7.1	Introduction	47
	7.7.2	First-line systemic therapy for metastatic disease	47
	7.7.2.1	First-line chemotherapy in patients fit for combination therapy	48
	7.7.2.1.1	Enfortumab vedotin plus Pembrolizumab	48
	7.7.2.1.2	Patients eligible for combination therapy but not eligible for EV or EV not available	49
	7.7.2.1.2.1	Patients fit for cisplatin	49
	7.7.2.1.2.2	Patients fit for carboplatin (but unfit for cisplatin)	50
	7.7.2.2	First line therapy in patients not eligible for combination therapy	50
	7.7.2.3	Results of other trials integrating immunotherapy in the first line setting without OS benefit	50
	7.7.3	Further-line systemic therapy for metastatic disease	51
	7.7.3.1	Introduction	51
	7.7.3.2	Chemotherapy	51
	7.7.3.3	Immunotherapy for platinum-pre-treated patients without previous immunotherapy	51

	7.7.3.4	Side-effect profile of immunotherapy	52
	7.7.4	Integration of other agents	52
	7.7.4.1	Antibody drug conjugates Enfortumab vedotin monotherapy	52
	7.7.4.2	Antibody drug conjugate Sacituzumab govectin	52
	7.7.4.3	FGFR inhibition	53
	7.7.4.4	HER2 targeted agents	53
	7.7.5	Current status of predictive biomarkers	54
	7.7.6	Special situations	54
	7.7.6.1	Impact of prior neoadjuvant/adjuvant therapy on treatment sequence	54
	7.7.6.2	Systemic treatment of metastatic disease with histology other than pure urothelial carcinoma	54
	7.7.6.3	Management of Oligometastatic Bladder Cancer	54
	7.7.7	Treatment of patients with bone metastases	55
	7.7.8	Summary: treatment algorithm for metastatic urothelial cancer update 2025	55
	7.7.9	Summary of evidence and recommendations for metastatic disease	56
7.8		Quality of life	58
	7.8.1	Introduction	58
	7.8.2	Neoadjuvant chemotherapy	59
	7.8.3	Radical cystectomy and urinary diversion	59
	7.8.4	Adjuvant therapy	59
	7.8.5	Bladder-sparing trimodality therapy	59
	7.8.6	Non-curative or metastatic bladder cancer	60
	7.8.7	Summary of evidence and recommendations for health-related quality of life	60
8.		FOLLOW-UP	61
	8.1	Follow-up in muscle invasive bladder cancer	61
	8.2	Site of recurrence	61
	8.2.1	Local recurrence	61
	8.2.2	Distant recurrence	61
	8.2.3	Urothelial recurrences	62
	8.3	Time schedule for surveillance	62
	8.4	Follow-up of functional outcomes and complications	62
	8.5	Summary of evidence and recommendations for specific recurrence sites	63
	8.6	EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer	64
9.		REFERENCES	65
10.		CONFLICT OF INTEREST	100
11.		CITATION INFORMATION	100
12.		COPYRIGHT AND TERMS OF USE	101

# 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 (UUT) tumours [1], non-muscle-invasive bladder cancer (TaT1 and carcinoma in situ) (NMIBC) [2], and primary urethral carcinomas [3].

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

## 1.2 Panel composition

The EAU Guidelines Panel consists of an international multidisciplinary group of clinicians, including urologists, oncologists, a pathologist, a radiologist, radiotherapists and a patient representative. Section 5.3 - MIBC and health status, was developed with the assistance of Prof. Dr. S. O'Hanlon, consultant geriatrician, International Society of Geriatric Oncology (SIOG) representative. 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 is an abridged version which may require consultation together with the full text version. Several scientific publications are available, the latest dating to 2023 [4]. All documents are accessible through the EAU website: <http://uroweb.org/guideline/bladder-cancer-muscle-invasive-and-metastatic/>. 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 Muscle Invasive Bladder Cancer 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. This 2025 MIBC Guidelines present a limited update of the 2024 publication.

### 1.4.2 Summary of changes

For the 2025 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:

- New summary of evidence and recommendation in section 6.5 for use of susceptible FGFR3 alterations to select patients with unresectable or metastatic urothelial carcinoma for treatment with erdafitinib.
- Significant adaptation and update to the recommendations for pre- and post-operative radiotherapy in section 7.2.3.
- Significant adaptation and update to the summary of evidence and recommendation in section 7.3.3.2.1 sexual-preserving techniques in women.
- New recommendation in section 7.3.10 related radical cystectomy and urinary diversion based on the results of the SWOG trial. In addition, the recommendation related to hospital volume in this section has been adapted.
- New recommendation in section 7.4.1 for salvage cystectomy after trimodality therapy.
- New recommendation in section 7.5.4.1 for management of all patients who are candidates for trimodality bladder-preserving treatment in a multidisciplinary team setting using a shared-decision making process.
- Significant adaptation and update to the recommendation for adjuvant nivolumab in selected patients with pT3/4 and/or pN+ disease not eligible for, or who declined, adjuvant cisplatin-based chemotherapy in section 7.6.3. Upgraded strength rating.
- Update of the summary of evidence in section 7.7.9 and addition of a new recommendation for metastatic disease regarding antibody drug conjugate Trastuzumab deruxtecan in case of HER2 overexpression. In addition, the recommendations on Sacituzumab govitecan have been removed as the manufacturer has withdrawn FDA approval for this product.
- Update of section 8.1 follow-up for MIBC.

- Update of figures 7.1 and 7.2.

## 2. METHODS

### 2.1 Data identification

For the 2025 MIBC Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the MIBC Guideline was performed. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between the 1<sup>st</sup> of May 2023 and 1<sup>st</sup> May 2024. A total of 1,102 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 which accompany each guideline statement, addresses a number of key elements:

1. the overall quality of the evidence which 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 can be found in the online: <https://uroweb.org/eau-guidelines/methodology-policies>.

### 2.2 Peer-review

The panel intends to submit the 2026 MIBC guidelines for peer review before publication. All systematic reviews and summary papers derived from the guidelines have been peer reviewed prior to publication.

### 2.3 Future goals

Topics considered for inclusion in the 2026 update of the MIBC Guidelines:

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

## 3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

### 3.1 Epidemiology

Bladder cancer is the 7<sup>th</sup> most commonly diagnosed cancer in males, whilst it drops to 10<sup>th</sup> position when both genders are considered [7]. The worldwide age-standardised incidence rate (per 100,000 person/years) is 9.5 for men and 2.4 for women [7]. In the European Union, the age-standardised incidence rate is 20 for men and 4.6 for women [7]. In Europe, the highest age-standardised incidence rate has been reported in Belgium (31 in men and 6.2 in women) and the lowest in Finland (18.1 in men and 4.3 in women) [7].

Worldwide, the BC age-standardised mortality rate (per 100,000 person/years) was 3.3 for men vs. 0.86 for women in 2012 [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 different methodologies used in the studies and the quality of data collection [8, 9]. The incidence and mortality of BC has decreased in some registries, possibly reflecting the decreased impact of causative agents [10-12].

Approximately 75% of patients with BC present with disease confined to the mucosa (stage Ta, carcinoma *in situ* [CIS]) or submucosa (stage T1). In younger patients (< 40 years) this percentage is even higher [13]. Patients with TaT1 and CIS have a high prevalence due to long-term survival in many cases and lower risk of cancer-specific mortality (CSM) compared to T2-4 tumours [7, 8].

### 3.2 Aetiology

#### 3.2.1 Tobacco smoking

Tobacco smoking is the most well-established risk factor for BC, causing 50–65% of male cases and 20–30% of female cases [14, 15]. A causal relationship has been established between exposure to tobacco and cancer in studies in which chance, bias and confounding can be discounted with reasonable confidence [16].

The incidence of BC is directly related to the duration of smoking and the number of cigarettes smoked per day [17]. A meta-analysis looked at 216 observational studies on cigarette smoking and cancer published between 1961 and 2003, and the pooled risk estimates for BC demonstrated a significant association for both current and former smokers [18]. 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 [14]. Starting to smoke at a younger age increased the risk of death from BC [19]. An immediate decrease in the risk of BC was observed in those who stopped smoking. The reduction was about 40% within one to four years of quitting smoking and 60% after 25 years of cessation [17]. A meta-analysis of nine studies, not distinguishing between MIBC and NMIBC, suggested that smokers who decide to quit during the diagnostic work-up or upon bladder cancer diagnosis do not have a better prognosis than those who continue to smoke [20]. Nevertheless, encouraging people to stop smoking would result in the incidence of BC decreasing equally in men and women [14].

#### 3.2.2 Occupational exposure to chemicals

Occupational exposure is the second-most important risk factor for BC. Work-related cases accounted for 20–25% of all BC cases in several series and it is likely to occur in occupations in which dyes (with the exception of hair dyes [21]), rubbers, textiles, paints, leathers, and chemicals are used [22]. 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 [23, 24]. Population-based studies established the occupational attribution for BC in men to be 7.1%, while no such attribution was discernible for women [8, 25].

#### 3.2.3 Radiotherapy

Increased rates of secondary bladder malignancies have been reported after external-beam radiotherapy (EBRT) for gynaecological malignancies, with relative risks (RR) of 2–4 [26]. In a population-based cohort study, the standardised incidence ratios for BC developing after radical prostatectomy (RP), EBRT, brachytherapy, and EBRT-brachytherapy were 0.99, 1.42, 1.10, and 1.39, respectively, in comparison with the general U.S. population [27].

It has been proposed that patients who have received radiotherapy (RT) for prostate cancer with modern modalities such as intensity-modulated RT (IMRT) may have lower rates of in-field bladder- and rectal secondary malignancies [28]. Nevertheless, since longer follow-up data are not yet available, and as BC requires a long period to develop, patients treated with radiation and with a long life expectancy are at a higher risk of developing BC [28].

### 3.2.4 **Dietary factors**

Several dietary factors have been related to BC; however, the links remain controversial. The European Prospective Investigation into Cancer and Nutrition (EPIC) study is an on-going multi-centre cohort study designed to examine the association between diet, lifestyle, environmental factors and cancer. They found no links between BC and fluid intake, red meat, vegetable and fruit consumption and only recently an inverse association between dietary intake of flavonoids and lignans and the risk of aggressive BC tumours has been described [29].

### 3.2.5 **Metabolic disorders**

In a large prospective study pooling six cohorts from Norway, Sweden, and Austria (The Metabolic syndrome and Cancer project, Me-Can 2.0), metabolic aberrations, especially elevated blood pressure and triglycerides, were associated with increased risks of BC among men, whereas high body mass index (BMI) was associated with decreased BC risk. The associations between BMI, blood pressure and BC risk significantly differed between men and women [30].

The association of diabetes mellitus (DM) with the risk of BC has been evaluated in numerous meta-analyses with inconsistent results. When analysing specific subpopulations, DM was associated with BC or CSM risk especially in men [31]. Thiazolidinediones (pioglitazone and rosiglitazone) are oral hypoglycaemic drugs used for the management of type 2 DM. Their use and the association with BC is still a matter of debate. In a meta-analysis of observational studies the summary results indicated that pioglitazone use was significantly associated with an increased risk of BC which appears to be linked to higher dose and longer duration of treatment [32]. The U.S. Food and Drug Administration (FDA) recommend that healthcare professionals should not prescribe pioglitazone in patients with active BC [33]. Several countries in Europe have removed this agent from the market or included warnings for prescription. Moreover, the benefits of glycaemic control vs. unknown risks for cancer recurrence with pioglitazone should be considered in patients with a prior history of BC.

### 3.2.6 **Bladder schistosomiasis and chronic urinary tract infection**

Bladder schistosomiasis (bilharzia) is the second most common parasitic infection after malaria, with about 600 million people exposed to infection in Africa, Asia, South America, and the Caribbean [34]. There is a clear relationship between schistosomiasis and urothelial carcinoma (UC) of the bladder, which can develop into squamous cell carcinoma (SCC). Better control of the disease reduces the incidence of SCC of the bladder in endemic areas such as Egypt [35, 36].

Similarly, invasive SCC has been linked to the presence of chronic urinary tract infection (UTI) distinct from schistosomiasis. A direct association between BC and UTIs has been observed in several case-control studies, which have reported a two-fold increased risk of BC in patients with recurrent UTIs in some series [37]. However, a meta-analysis found no statistical association when pooling data from the most recent and highest quality studies which highlights the need for better quality data to be able to draw conclusions [38].

Similarly, urinary calculi and chronic irritation or inflammation of the urothelium have been described as possible risk factors for BC. A meta-analysis of case-control and cohort studies suggests a positive association between history of urinary calculi and BC [39].

### 3.2.7 **Gender**

Although men are more likely to develop BC than women, women present with more advanced disease and have worse survival rates. A meta-analysis including nearly 28,000 patients shows that female gender was associated with a worse survival outcome (hazard ratio [HR]: 1.20, 95% CI: 1.09–1.32) compared to male gender after radical cystectomy (RC) [40]. This finding had already been presented in a descriptive nationwide analysis based on 27,773 Austrian patients. After their analysis the authors found that cancer-specific survival (CSS) was identical for pT1-tumours in both sexes, while women had a worse CSS in both age cohorts (< 70 years and ≥ 70 years) with higher tumour stages [41]. However, treatment patterns are unlikely to explain the differences in overall survival (OS) [42]. In a population-based study from the Ontario Cancer Registry analysing all patients with BC treated with cystectomy or radical RT between 1994 and 2008, no differences in OS, mortality and outcomes were found between males and females following radical therapy [43]. The gender-specific difference in survival for patients with BC was also analysed in the Norwegian population. Survival was inferior for female patients but only within the first two years after diagnosis. This discrepancy was partly attributed to a more severe T-stage in female patients at initial diagnoses [44].

A population-based study from the MarketScan Databases suggests that a possible reason for worse survival in the female population may be that women experienced longer delays in diagnosis than men, as the differential diagnosis in women includes diseases, such as UTIs, that are more prevalent than BC [45]. Furthermore, differences in the gender prevalence of BC may be due to other factors besides tobacco and chemical exposure. In a large prospective cohort study, post-menopausal status was associated with an increase in BC risk, even

after adjustment for smoking status. This finding suggests that the differences in oestrogen and androgen levels between men and women may be responsible for some of the difference in the gender prevalence of BC [46-48]. Moreover, a recent population study assessing impact of hormones on BC suggests that younger age at menopause ( $\leq 45$  years) is associated with an increased risk of BC [49].

### 3.2.8 Genetic factors

There is growing evidence that genetic susceptibility factors and family association may influence the incidence of BC. A recent population-based study of cancer risk in relatives and spouses of UC patients showed an increased risk for first- and second-degree relatives, and suggests genetic or environmental roots independent of smoking-related behaviour [50]. Shared environmental exposure was recognised as a potentially confounding factor [51]. Recent studies detected genetic susceptibility with independent loci, which are associated with BC risk [52]. Genome-wide association studies (GWAS) of BC identified several susceptibility loci associated with BC risk [53, 54].

### 3.2.9 Summary of evidence and recommendations for epidemiology and risk factors

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

Recommendations	Strength rating
Counsel patients to stop active and avoid passive smoking.	Strong
Inform workers in potentially hazardous workplaces of the potential carcinogenic effects of a number of recognised substances, including duration of exposure and latency periods. Protective measures are recommended.	Strong
Do not prescribe pioglitazone to patients with active bladder cancer or a history of bladder cancer.	Strong

## 3.3 Pathology

### 3.3.1 Handling of transurethral resection and cystectomy specimens

During transurethral resection (TUR), 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 flat mucosa are taken, each biopsy specimen of the flat mucosa should be submitted separately [55]. 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 [56, 57].

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 general rules as published by a collaborative group of pathologists and urologists [58, 59]. It must be stressed that it may be very difficult to confirm the presence of a neoplastic lesion using gross examination of the cystectomy specimen after TUR or chemotherapy, so the entire retracted or ulcerated area should be inked and included before fixation.

It is compulsory to study the urethra, the ureters, the prostate in men and the radial margins [60]. In urethra-sparing cystectomy; the level of urethral dissection, completeness of the prostate, specifically at the apex (in men), and the inclusion of the entire bladder neck and amount of adjacent urethra, uterus and vaginal vault (in women) have to be documented by the pathologist.

All lymph node (LN) specimens should be provided in their totality, separated in clearly labelled containers or *en bloc* on a board to allow for pTNM staging. In case of doubt or adipose differentiation of the LNs, the entire specimen is to be included. Lymph nodes should be counted and measured on slides; capsular rupture and percentage of LN invasion should be reported as well as vascular embols [61, 62]. In case of metastatic

spread in the perivesical fat without real LN structures (capsule, subcapsular sinus), this localisation should nevertheless be considered as N+.

Potentially positive soft tissue margins should be inked by the pathologist for evaluation [63]. In rare cases, fresh frozen sections may be helpful to determine treatment strategy [64].

### 3.3.2 Pathology of muscle-invasive bladder cancer

All muscle invasive UCs of the bladder are high grade. For this reason, no prognostic information can be provided by grading MIBC [65]. Identification of morphological subtypes is important for prognostic reasons and treatment decisions [66-68].

The data presented in these guidelines are based on the 2004/2016 World Health Organization (WHO) classifications [69, 70]. An update was presented in 2022 [71].

Currently the following subtypes of UC are used [71, 72]:

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;
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 - Chapter NE carcinomas in the genitourinary tract [71]).

The percentage of subtype in the specimen must be reported since it has been shown to be of prognostic value [73]. The majority of subtypes are MIBC, with no more than 15–30% being non-muscle invasive [73-80].

### 3.3.3 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.	
Record the total number of lymph nodes (LNs), the number of positive LNs and extranodal spread.	
Record lymphovascular invasion.	
Record the presence of carcinoma <i>in situ</i> .	
Record the sampling sites as well as information on tumour size when providing specimens to the pathologist.	

### 3.3.4 EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [81, 82]\*

Consensus statements
Bladder UC with small cell neuroendocrine variant should be treated with neoadjuvant chemotherapy followed by consolidating local therapy.
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 preventive brain irradiation to avoid brain recurrence.

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

T1 high-grade bladder urothelial cancer with micropapillary histology (established after complete TURBT and/or re-TURBT) should be treated with immediate radical cystectomy and lymphadenectomy.

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

## 4. STAGING AND CLASSIFICATION SYSTEMS

### 4.1 Pathological staging

For staging, the Tumour, Node, Metastasis (TNM) Classification (2017, 8<sup>th</sup> edition) is recommended [83]. Blood and lymphatic vessel invasion have an independent prognostic significance [84, 85].

### 4.2 Tumour, node, metastasis classification

The TNM classification of malignant tumours is the method most widely used to classify the extent of cancer spread [83] (Table 4.1).

Table 4.1: TNM Classification of urinary bladder cancer [83]

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

Staging after neoadjuvant chemotherapy (NAC) and RC can be done, but must be mentioned as ypTNM (International Collaboration on Cancer Reporting) [86]. ypT0N0 after NAC and cystectomy is associated with better prognosis [71, 87, 88].

## 5. DIAGNOSTIC EVALUATION

### 5.1 Primary diagnosis

#### 5.1.1 Symptoms

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

#### 5.1.2 Physical examination

Physical examination should include rectal and vaginal bimanual palpation. A palpable pelvic mass can be found in patients with locally-advanced tumours. In addition, bimanual examination under anaesthesia should be carried out before and after TUR of the bladder tumour (TURBT) to assess whether there is a palpable mass or if the tumour is fixed to the pelvic wall [89, 90]. However, considering the discrepancy between bimanual examination and pT stage after cystectomy (11% clinical overstaging and 31% clinical understaging), bimanual examination findings need to be interpreted with caution [91].

#### 5.1.3 Bladder imaging

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

Due to the high specificity of diagnostic imaging for detecting BC, patients with imaging positive for BC may avoid diagnostic flexible cystoscopy and go directly for TUR [92, 93].

#### 5.1.4 Urinary cytology

Examination of voided urine or bladder washings for exfoliated cancer cells has high sensitivity in high-grade tumours and is a useful indicator in cases of high-grade malignancy or CIS. However, positive urinary cytology may originate from an urothelial tumour located anywhere in the urinary tract.

Evaluation of cytology specimens can be hampered by low cellular yield, UTIs, stones or intravesical instillations, but for experienced readers, specificity exceeds 90% [94, 95]. However, negative cytology does not exclude a tumour. There is no known urinary marker specific for the diagnosis of invasive BC [96].

A standardised reporting system, the 'Paris System' redefining urinary cytology diagnostic categories has been updated in 2022 [97]:

- 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).

#### 5.1.5 Cystoscopy

Ultimately, the diagnosis of BC is made by cystoscopy and histological evaluation of resected tissue. An (outpatient) flexible cystoscopy is recommended to obtain a complete image of the bladder. However, in daily practice, if a bladder tumour has been visualised unequivocally by imaging studies such as computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound (US), diagnostic cystoscopy may be omitted and the patient can proceed directly to TURB for resection and histological diagnosis. During the procedure, a thorough inspection of the bladder wall with rigid cystoscopy under anaesthesia is mandatory in order not to miss any tumours.

A careful description of the cystoscopic findings is necessary. This should include documentation of the site, size, number, and appearance (papillary or solid) of the tumours, as well as a description of any mucosal abnormalities [98]. The use of a bladder diagram is recommended.

The use of photodynamic diagnosis (PDD) could be considered in multifocal tumours and in case CIS is suspected. Presence of CIS may lead to a modified treatment plan (see EAU Guidelines on Non-muscle-invasive Bladder Cancer [2]). Photodynamic diagnosis is highly sensitive for the detection of CIS and in experienced hands the rate of false-positive results may be similar to that with regular white-light cystoscopy [85, 99].

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

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

In case MIBC is suspected, tumours need to be (ideally) resected separately in parts, which include the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle, and the edges of the resection area. The deeper portion of the resection specimen should be sent to the pathologist in a separate clearly labelled container to ensure accurate diagnosis and staging. If RT is being considered and CIS needs to be excluded, PDD can be used [100].

The involvement of the prostatic urethra and ducts in men with bladder tumours has been reported in up to one in three patients [58, 101, 102]. Under-reporting possibly also means that the exact risk is not known, but it seems to be higher if the tumour is located on the trigone or bladder neck, with concomitant bladder CIS, and in the case of multiple tumours [57, 103, 104]. Involvement of the prostatic urethra can be determined either at the time of primary TURB or by frozen section during the cystoprostatectomy procedure. A frozen section has a higher negative-predictive value and is more accurate [105-107].

A negative urethral frozen section can reliably identify patients in whom urethrectomy should be avoided. However, a positive pre-operative biopsy seems to have limited utility as these findings are not reliably associated with final margin status [105, 108].

Diagnosis of a urethral tumour before cystectomy will result in a urethrectomy which could be a contraindication for an orthotopic diversion. However, an orthotopic diversion should not be denied based on positive pre-operative biopsy findings alone and frozen section should be part of the RC procedure, particularly in male patients [109, 110].

### 5.1.7 **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 bladder cancer.	1
Urinary cytology has high sensitivity in high-grade tumours including carcinoma <i>in situ</i> .	2b
In men, prostatic urethral biopsy includes resection from the bladder neck to the verumontanum (between the 5 and 7 o'clock position) using a resection loop. In case any abnormal-looking areas in the prostatic urethra are present at this time, these need to be biopsied as well.	2b

Recommendations	Strength rating
Describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities during cystoscopy. Use a bladder diagram.	Strong
Take a biopsy of the prostatic urethra in cases of bladder neck tumour, when bladder carcinoma <i>in situ</i> is present or suspected, when there is positive cytology without evidence of tumour in the bladder, or when abnormalities of the prostatic urethra are visible.	Strong
In men with a negative prostatic urethral biopsy undergoing subsequent orthotopic neobladder construction, an intra-operative frozen section can be omitted.	Strong
In men with a prior positive transurethral prostatic biopsy, subsequent orthotopic neobladder construction should not be denied <i>a priori</i> , unless an intra-operative frozen section of the distal urethral stump reveals malignancy at the level of urethral dissection.	Strong
In women undergoing subsequent orthotopic neobladder construction, obtain procedural information (including histological evaluation) of the bladder neck and urethral margin, either prior to, or at the time of cystectomy.	Strong
In the pathology report, specify the grade, depth of tumour invasion, and whether the lamina propria and muscle tissue are present in the specimen.	Strong

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

## 5.2 Imaging for staging of MIBC

In clinical practice, tumour stage and histopathological grade are used to guide treatment and determine prognosis [111-113]. Imaging is essential for local- and distant-staging of BC.

The goal of imaging patients with BC is to:

- Detect bladder tumours;
- Differentiate T1 from T2 tumours as their treatment will differ;
- Determine presence of any obstruction to the upper UT;
- Evaluate the extent of locally-advanced tumour stage or tumour spread to LNs;
- Assess synchronous tumour in the upper UT or other distant organs (e.g., liver, lungs, bones, peritoneum, pleura, and adrenal glands).

**Table 5.1: The role of imaging in treatment planning**

Goal	Imaging modality
Differentiate T1 from T2 tumours	MRI using the Vesical Imaging Reporting and Data System (VI-RADS) score
Evaluate locally-advanced stage or spread to LNs	CT scan and MRI for abdominal- and pelvic LNs or PET/CT scan
Assess UUT or other distant organs	CT urography for evaluating the UUT and PET/CT to detect distant organ metastasis

### 5.2.1 Detection

Imaging modalities used to detect bladder tumours are: US, CT and MRI-scan. Bladder tumours are often detected as part of the haematuria work-up (including cystoscopy) or as an incidental finding on imaging.

Ultrasound can visualise intraluminal masses in the bladder and additional signs such as hydronephrosis, but cannot rule out all possible causes of haematuria. According to the results of the DETECT I trial, CT urogram can be safely replaced by renal and bladder US in patients who have nonvisible haematuria [114].

### 5.2.2 Local staging of the bladder and upper tract

#### 5.2.2.1 Magnetic resonance imaging for local staging of MIBC

Differentiation between NMIBC and MIBC is crucial for BC treatment. Magnetic resonance imaging has superior soft tissue contrast resolution compared with CT and can evaluate post-biopsy reaction as enhancement of the tumour occurs earlier than that of the normal bladder wall due to neovascularisation [115, 116]. However, MR is not yet ready for standard patient care [117].

Multiparametric (mp)MRI using the Vesical Imaging – Reporting and Data System (VI-RADS) scoring system has been used to differentiate between T1 vs. T2 bladder tumours with a high diagnostic accuracy [118]. The VI-RADS offers a standardised approach to both acquisition and reporting of mpMRI for BC; however, the best practice of using mpMRI in this setting and the exact cut-off levels for VI-RADS scoring still need to be determined [116]. To date, the VI-RADS score has been validated by several research groups, showing good diagnostic performance in detecting MIBC [119, 120]. In addition, a high diagnostic performance for the detection of muscle invasion of UC subtypes was found [121].

VI-RADS assessment scoring proved to be an independent predictor of muscle-invasiveness, which might facilitate a shift toward a more aggressive approach for selection of patients at high risk of MIBC, according to a novel proposed predictive pathway [122].

A meta-analysis found that the pooled sensitivity and specificity of mpMRI with VI-RADS acquisition and scoring for predicting MIBC were 83% and 90%, respectively [123]. The diagnostic performance of using VI-RADS scoring is similar to the diagnostic performance of a conventional bladder MRI in determining MIBC based on a previous meta-analysis of 24 studies [123]. The analysis found substantial inter-reader agreement, with kappa ( $\kappa$ ) values ranging from 0.81 to 0.92 [123]. The potential role of mpMRI as first-line test for local staging of BC rather than TURB has been demonstrated in a recent clinical trial [124].

A modified Delphi methodology was developed by a panel of highly experienced, internationally recognised radiologists, urologists, oncologists, radiation oncologists and a representative from a patient advocacy group, to provide consensus-based recommendations for urinary bladder MRI to help formulate international guidelines, particularly for pre-operative cancer staging and the assessment of the response to systemic therapy. Among several statements that reached agreement, experts recommend acquiring and interpreting MR images according

to VI-RADS recommendations and if MRI is performed for primary staging purposes, it should be done before TURBT [125].

Considering the link established between the use of gadolinium-based contrast agents and nephrogenic systemic fibrosis (NSF) in patients with impaired renal function, contrast medium should be managed according to the European Society of Urogenital Radiology (ESUR) Guidelines [126]. Interest is growing in the role of non-contrast MRI for the assessment of MIBC using VI-RADS with studies demonstrating how non-contrast-enhanced VI-RADS scoring achieved similar predictive accuracy for diagnosis of MIBC to that of conventional VI-RADS; however, further additional evidence is required before any recommendations can be made [127].

#### 5.2.2.2 *CT imaging for local staging of MIBC*

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. Computed tomography is unreliable in differentiating between stages Ta to T3a tumours, but it is useful for detecting invasion into the perivesical fat (T3b) and adjacent organs. The accuracy of CT in determining extravesical tumour extension increases with more advanced disease [128].

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) [129]. Contrast-enhanced CT using iodinated contrast media can be considered as an alternative to MRI when MRI is contraindicated or not available [126].

#### 5.2.2.3 *Computed tomography urography for local staging of the upper tract*

For local staging of the UUT, computed tomography urography (CTU) has the highest diagnostic accuracy of the available imaging techniques. The sensitivity of CTU for upper urinary tract urothelial carcinoma (UTUC) is 0.67–1.0 and specificity is 0.93–0.99 [130].

Rapid acquisition of thin sections allows high-resolution isotropic images that can be viewed in multiple planes to assist with diagnosis without loss of resolution. Epithelial 'flat lesions' without mass effect or urothelial thickening are generally not visible with CT. The secondary sign of hydronephrosis is associated with advanced disease and poor oncological outcome [131]. The presence of enlarged LNs is highly predictive of metastases in UTUC [132].

#### 5.2.2.4 *Magnetic resonance urography for local staging of the upper tract*

Magnetic resonance urography is indicated in patients who cannot undergo CTU, usually when radiation or iodinated contrast media are contraindicated [133]. The sensitivity of MR-urography is 0.75 after contrast injection for tumours < 2 cm [133]. The use of MR-urography with gadolinium-based contrast media should be limited in patients with severe renal impairment (< 30 mL/min creatinine clearance), due to the risk of NSF. Computed tomography urography is generally preferred to MR-urography for diagnosing and staging UTUC.

### 5.2.3 *Distant staging of lymph nodes and other sites*

#### 5.2.3.1 *Imaging of lymph nodes in MIBC*

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. The sensitivity of these modalities for detection of LN metastases is low (48–87%). Specificity is also low because nodal enlargement may be due to benign disease. Overall, CT and MRI show similar results in the detection of LN metastases in a variety of primary pelvic tumours [133-135]. Pelvic nodes > 8 mm and abdominal nodes > 10 mm in maximum short-axis diameter, detected by CT or MRI, should be regarded as pathologically enlarged [136]. In a recent paper including 1,104 patients, conventional cross-sectional imaging showed slight concordance (64.9%) between cN and pN stages (sensitivity: 30%; specificity: 84%) [137].

<sup>18</sup>F-fluorodeoxy glucose-Positron emission tomography (FDG-PET) combined with CT is increasingly being used in clinical practice but its exact role needs to be further evaluated [138, 139]. According to a systematic review and meta-analysis including 785 patients, FDG-PET/CT showed a low sensitivity and high specificity for the detection of metastatic LNs in patients with newly diagnosed BC [140]. However, most studies comparing FDG-PET/CT with CT for LN assessment reported higher sensitivity, with comparable specificity [141]. In a comparative analysis PET/CT demonstrated superior diagnostic performance over contrast-enhanced CT; however, up to 20% of occult (micro-) metastases were still missed on final pathology [142].

Positron emission tomography/computed tomography can also provide additional information to guide local treatment in case of the presence of pelvic nodal metastases [143]. 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 [144]. However, both are retrospective studies. Additionally, determining the

definitive diagnostic accuracy is hampered due to variations in evaluation methods and the increasing use of neoadjuvant therapy.

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 immunotherapy (IO) strategies [145].

#### 5.2.3.2 *Distant metastases*

Before any curative treatment, it is essential to evaluate the presence of distant metastases. Computed tomography and MRI are the diagnostic techniques of choice to detect e.g., lung [146] and liver metastases [147], 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 [143].

Bone and brain metastases are rare at the time of presentation of invasive BC. In a recent retrospective, large sample, study bone scan has been 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 [148]. Whole-body MRI is more sensitive and specific for diagnosing bone metastases than bone scintigraphy [149]. Also, additional brain imaging is not routinely indicated unless the patient has specific symptoms or signs to suggest brain metastases.

#### 5.2.4 *Response to therapy*

Pre-operative MRI conducted in various clinical settings may provide useful information regarding treatment response. In the neoadjuvant setting, the first study evaluating the performance of MRI in assessing therapeutic response to chemotherapy showed superiority of DWI over T2-weighted and dynamic contrast-enhanced (DCE)-MRI [150]. The high specificity of DWI indicates its usefulness in accurately predicting a complete histopathological response, allowing for better patient selection for bladder-sparing protocols [151]. Dynamic contrast-enhanced MR imaging may also be useful for predicting a patient's response to chemotherapy. In addition, quantitative DWI/MRI analysis has shown to provide an accurate and non-invasive assessment of bladder RT response. However, multi-centre validation is required before prospective testing to inform MIBC follow-up schedules and decision making [152].

In the previously cited consensus-based recommendations, experts agreed upon the performance on MRI to assess response to systemic therapy to select patients for radical treatment, for surveillance, and for bladder-sparing surgery [125].

A meta-analysis investigated the predictive role of  $^{18}\text{F}$ -FDG PET/CT for assessment of tumour response to neoadjuvant chemotherapy 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 studies, only three used both cR and pCR as a reference standard [153].

The performance of PET/CT in evaluating LN involvement in patients receiving neoadjuvant pembrolizumab did not justify its routine use in cN0 MIBC patients [145].

#### 5.2.5 *Future perspectives*

Potential future application of the VI-RADS score may include prediction of response to treatment as well as peri-operative outcomes using its modified version: the NAC VI-RADS (nacVI-RADS); however, prospective evidence is warranted [154].

VI-RADS and nacVI-RADS have been proven to accurately predict pre- and post-pembrolizumab response in MIBC, being strongly associated with pathological downstaging and survival [117].

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 [155].

Alternative molecular imaging tracers are being studied such as  $^{64}\text{CuCl}_2$ ,  $^{68}\text{Ga}$ ]-Ga-FAPI-46 and  $^{68}\text{Ga}$ -FAP-2286 and preliminary investigations of these agents have demonstrated promising results in nodal staging and restaging in MIBC [156, 157].

Positron emission tomography/computed tomography combining the benefits of MRI with functional imaging could be envisioned for the detection of metastatic BC lesions not seen on CT in patients who cannot receive intravenous iodine contrast, and may lead to improved treatment planning and monitoring for BC [158].

Among the novel approaches and radiotracers, in a pilot study, Rietbergen *et al.*, showed that the sentinel node (SN) biopsy in bladder cancer using the hybrid tracer ICG- 99mTc-nanocolloid is feasible, and in patients with a successful pre-operative SN mapping using lymphoscintigraphy and SPECT/CT, the intra-operative SN guidance and detection are effective, even outside the extended pelvic lymph node dissection (ePLND) area [159].

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

Summary of evidence	LE
Imaging as part of staging in 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
MRI is accurate for the assessment of tumour response to systemic therapy.	3
Bone scintigraphy has limited value in the staging of invasive BC.	3
FDG-PET/CT can provide additional information to guide treatment.	2b

Recommendations	Strength rating
If an MRI is performed for local staging of bladder cancer it should be done before TURBT.	Strong
In patients with confirmed muscle-invasive bladder cancer, use computed tomography (CT) of the chest, abdomen and pelvis for staging, including some form of CT urography with designated phases for optimal urothelial evaluation.	Strong
Use CT urography, unless it is contraindicated for reasons related to contrast administration or radiation dose; in that case use MRI.	Strong
Offer MRI to assess the response to systemic therapy, which aids in the selection of patients for radical treatment, surveillance, and bladder-sparing surgery.	Weak

### 5.3 Muscle-invasive and metastatic bladder cancer and health status

Complications from RC may be directly related to pre-existing comorbidity as well as the surgical procedure, bowel anastomosis, or urinary diversion. A significant body of literature has evaluated the usefulness of age as a prognostic factor for RC, although chronological age is less important than frailty [160-162]. 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 [163]. 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 [164].

The largest retrospective study on RC in septuagenarians and octogenarians based on data from the National Surgical Quality Improvement Program database (n = 1,710) showed no significant difference for wound, cardiac, or pulmonary complications. However, the risk of mortality in octogenarians compared to septuagenarians is higher (4.3% vs. 2.3%) [165]. 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 [166].

Sarcopenia has been shown to be an independent predictor for OS and CSS in a large multi-centre study with patients undergoing RC for BC [167]. In order to predict CSM after RC in patients receiving NAC, sarcopenia should be assessed after completing chemotherapy [168]. Other risk factors for morbidity include prior abdominal surgery, extravesical disease, and prior RT [169]. Female gender, an increased BMI and lower pre-operative albumin levels are associated with a higher rate of parastomal hernias [170]. Low pre-operative serum albumin is also associated with impaired wound healing, gastrointestinal (GI) complications and a decrease of recurrence-free and OS after RC [171, 172]. Therefore, it could be used as a prognostic biomarker for patients undergoing RC.

Metformin has been suggested as having possibly anticancer activity in bladder cancer 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 [173].

### 5.3.1 Evaluation of comorbidity, frailty and cognition

Evaluation of comorbidity provides a better indicator of life expectancy in MIBC than patient age [174]. Evaluation of comorbidity helps to identify factors likely to interfere with, or have an impact on, treatment and the evolution and prognosis of MIBC [175].

The value of assessing overall health before recommending and proceeding with surgery was emphasised in another study which demonstrated an association between comorbidity and adverse pathological and survival outcomes following RC [176]. Similar results were found for the impact of comorbidity on cancer-specific and other-cause mortality in a population-based competing risk analysis of > 11,260 patients from the Surveillance, Epidemiology, and End Results (SEER) registries. Age carried the highest risk for other-cause mortality but not for increased cancer-specific death, while the stage of locally-advanced tumour was the strongest predictor for decreased CSS [177].

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 [178]. There are many different screening tools available for frailty and local approaches can be used. Examples include the G8 and the Clinical Frailty Scale (See Table 5.2 and Figure 5.1 below).

Cognitive impairment can be screened for by using a tool such as the mini-COG (<https://mini-cog.com/>), which consists of three-word recall and a clock-drawing test, and can be completed within 5 minutes. A score of  $\leq 3/5$  indicates the need to refer the patient for full cognitive assessment. Patients with any form of cognitive impairment (e.g., Alzheimer's or vascular dementia) may need a capacity assessment of their ability to make an informed decision, which is an important factor in health status assessment. Cognitive impairment also predicts risk of delirium, which is important for patients undergoing surgery [179].

**Table 5.2: G8 screening tool** (adapted from [180])

	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 > 3 kg
		1 = does not know
		2 = weight loss between 1 and 3 kg
		3 = no weight loss
C	Mobility?	0 = bed or chair bound
		1 = able to get out of bed/chair but does not go out
		2 = goes out
D	Neuropsychological problems?	0 = severe dementia or depression
		1 = mild dementia
		2 = no psychological problems
E	BMI? (weight in kg)/(height in m <sup>2</sup> )	0 = BMI < 19
		1 = BMI 19 to < 21
		2 = BMI 21 to < 23
		3 = BMI $\geq$ 23
F	Takes more than three prescription drugs per day?	0 = yes
		1 = no
G	In comparison with other people of the same age, how does the patient consider his/her health status?	0.0 = not as good
		0.5 = does not know
		1.0 = as good
		2.0 = better
H	Age	0 = $\geq$ 85
		1 = 80–85
		2 = < 80
	<b>Total score</b>	<b>0–17</b>

Figure 5.1: Clinical Frailty Scale®, Version 2.0\* [181]

CLINICAL FRAILTY SCALE		
	<b>1</b>	<b>VERY FIT</b> People who are robust, active, energetic and motivated. They tend to exercise regularly and are among the fittest for their age.
	<b>2</b>	<b>FIT</b> People who have <b>no active disease symptoms</b> but are less fit than category 1. Often, they exercise or are very active occasionally, e.g., seasonally.
	<b>3</b>	<b>MANAGING WELL</b> People whose <b>medical problems are well controlled</b> , even if occasionally symptomatic, but often are <b>not regularly active</b> beyond routine walking.
	<b>4</b>	<b>LIVING WITH VERY MILD FRAILITY</b> Previously "vulnerable," this category marks early transition from complete independence. While <b>not dependent</b> on others for daily help, often <b>symptoms limit activities</b> . A common complaint is being "slowed up" and/or being tired during the day.
	<b>5</b>	<b>LIVING WITH MILD FRAILITY</b> People who often have <b>more evident slowing</b> , and need help with <b>high order instrumental activities of daily living</b> (finances, transportation, heavy housework). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation, medications and begins to restrict light housework.
	<b>6</b>	<b>LIVING WITH MODERATE FRAILITY</b> People who need help with <b>all outside activities</b> and with <b>keeping house</b> . Inside, they often have problems with stairs and need <b>help with bathing</b> and might need minimal assistance (cuing, standby) with dressing.
	<b>7</b>	<b>LIVING WITH SEVERE FRAILITY</b> <b>Completely dependent for personal care</b> , from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~6 months).
	<b>8</b>	<b>LIVING WITH VERY SEVERE FRAILITY</b> Completely dependent for personal care and approaching end of life. Typically, they could not recover even from a minor illness.
	<b>9</b>	<b>TERMINALLY ILL</b> Approaching the end of life. This category applies to people with a <b>life expectancy &lt;6 months</b> , who are <b>not otherwise living with severe frailty</b> . (Many terminally ill people can still exercise until very close to death.)
<p><b>SCORING FRAILITY IN PEOPLE WITH DEMENTIA</b></p> <p>The degree of frailty generally corresponds to the degree of dementia. Common <b>symptoms in mild dementia</b> include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.</p> <p>In <b>moderate dementia</b>, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.</p> <p>In <b>severe dementia</b>, they cannot do personal care without help.</p> <p>In <b>very severe dementia</b> they are often bedfast. Many are virtually mute.</p>		
<p> <b>DALHOUSIE UNIVERSITY</b> www.geriatricmedicineresearch.ca</p> <p>Clinical Frailty Scale ©2005-2020 Rockwood, Version 2.0 (EN). All rights reserved. For permission: www.geriatricmedicineresearch.ca Rockwood K et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.</p>		

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

A range of comorbidity scales has been developed [182], seven of which have been validated [183-189]. The Charlson Comorbidity Index (CCI) ranges from 0 to 30 according to the importance of comorbidity described at four levels and is calculated by healthcare practitioners based on patients' medical records. The score has been widely studied in patients with BC and found to be an independent prognostic factor for peri-operative mortality [190, 191], overall mortality [192], and CSM [164, 193-195]. Only the age-adjusted version of the CCI was correlated with both cancer-specific and other-cause mortality [196]. The age-adjusted CCI (Table 5.3) is the most widely used comorbidity index in cancer for estimating long-term survival and is easily calculated [197].

Health assessment of oncology patients must be supplemented by measuring their activity level. Extermann *et al.*, have shown that there is no correlation between morbidity and competitive activity level [198]. The Eastern Cooperative Oncology Group (ECOG) performance status (PS) scores and Karnofsky index have been validated to measure patient activity [199]. Performance score is correlated with patient OS after RC [194] and palliative chemotherapy [200-202].

Patients who have screened positive for frailty or cognitive impairment benefit from an assessment by a geriatrician. This allows identification of geriatric syndromes and any scope for optimisation. The most complete protocol is the Comprehensive Geriatric Assessment (CGA) [203] which is useful in the care of cancer patients [204]. In BC, the CGA has been used to adapt gemcitabine chemotherapy in previously untreated older patients with advanced BC [205].

**Table 5.3: Calculation of the Charlson Comorbidity Index**

Number of points	Conditions
1	50–60 years
	Myocardial infarction
	Heart failure
	Peripheral vascular insufficiency
	Cerebrovascular disease
	Dementia
	Chronic lung disease
	Connective tissue disease
	Ulcer disease
	Mild liver disease
	Diabetes
2	61–70 years
	Hemiplegia
	Moderate to severe kidney disease
	Diabetes with organ damage
	Tumours of all origins
3	71–80 years
	Moderate to severe liver disease
4	81–90 years
5	> 90 years
6	Metastatic solid tumours
	AIDS

Interpretation:

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

### 5.3.3 Summary of evidence and guidelines for comorbidity scales

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

Recommendations	Strength rating
Base the decision on bladder-sparing treatment or radical cystectomy in older/frail patients with invasive bladder cancer on tumour stage and frailty.	Strong
Assess comorbidity by a validated score, such as the Charlson Comorbidity Index. The American Society of Anesthesiologists score should not be used in this setting (see section 5.3.2).	Strong

## 6. MARKERS

### 6.1 Introduction

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

### 6.2 Prognostic markers

#### 6.2.1 *Histopathological and clinical markers*

The most important histopathological prognostic variables after RC and LN dissection are tumour stage and LN status [206]. In addition, other histopathological parameters of the RC specimen have been associated with prognosis.

The value of lymphovascular invasion was reported in a systematic review and meta-analysis including 78,000 patients from 65 studies treated with RC for BC [207]. Lymphovascular invasion was present in 35% of the patients and correlated with a 1.5-fold higher risk of recurrence and CSM, independent of pathological stage and peri-operative chemotherapy. This correlation was even stronger in those patients with node-negative disease [208].

In a systematic review and meta-analysis including 23 studies and over 20,000 patients, the presence of concomitant CIS in the RC specimen was associated with a higher odds ratio (OR) of ureteral involvement (pooled OR: 4.51, 2.59–7.84). Concomitant CIS was not independently associated with OS, recurrence-free survival (RFS) and DSS in all patients, but in patients with organ-confined disease concomitant CIS was associated with worse RFS (pooled HR: 1.57, 1.12–2.21) and CSM (pooled HR: 1.51, 1.001–2.280) [208].

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 [206, 209-211].

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% [212].

Neutrophil-to-lymphocyte ratio (NLR) has emerged as a prognostic factor in UUT tumours [1] and other non-urolological malignancies. In a pooled analysis of 21 studies analysing the prognostic role of NLR in BC, the authors correlated elevated pre-treatment NLR with OS, RFS and disease-free survival (DFS) in both localised and metastatic disease [213]. In contrast, a secondary analysis of the Southwest Oncology Group (SWOG) 8710 trial, a randomised phase III trial assessing cystectomy ± NAC in patients with MIBC, suggests that NLR is neither a prognostic nor a predictive biomarker for OS in MIBC [214].

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. A systematic review and meta-analysis, reported that LN density was independently associated with OS (HR: 1.45, 95% CI: 1.11–1.90) [215]. It has been suggested that LN density outperforms the AJCC-TNM staging system for LN-positive disease (N1-N3) in terms of prognostic value [216, 217]. However, despite these studies supporting the use of LN density, LN density relies on the number of LNs removed which, in turn, is subject to surgical and pathological factors. This makes the concept of LN density difficult to apply uniformly [218].

Two studies investigated whether any of the reported LN-related parameters may be superior to the routinely used AJCC-TNM staging system [218, 219]. Whilst the conclusion was that the AJCC-TNM staging system for LN status did not perform well, none of the other tested variables outperformed the AJCC system.

#### 6.2.2 *Molecular markers*

##### 6.2.2.1 *Molecular variants based on the Cancer Genome Atlas cohort*

The updated Cancer Genome Atlas (TCGA) reported on 412 MIBCs and identified two main groups; luminal and basal-squamous - consisting of five mRNA expression-based molecular variants including luminal-papillary, luminal-infiltrated, luminal; basal-squamous; and neuronal; a variant associated with poor survival in which many of the tumours did not have small cell or neuroendocrine histology. Each variant is associated with distinct mutational profiles, histopathological features and prognostic and treatment implications [220].

The basal-squamous variant is characterised by expression of basal keratin markers, immune infiltrates and is considered to be chemosensitive. The different luminal variants are characterised by fibroblast growth factor receptor 3 (FGFR3) alterations (luminal-papillary [LumP]), epithelial-mesenchymal transition (EMT) markers (luminal-infiltrated) and may be associated with chemotherapy resistance [67, 68, 220, 221]. In 2019, a consensus on molecular variant classification was reported [222]. The authors analysed 1,750 MIBC transcriptomic profiles from eighteen datasets and identified six MIBC molecular classes that reconcile 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 neuroendocrine-like (NE-like). Each class has distinct differentiation patterns, oncogenic mechanisms, tumour micro-environments and histological and clinical associations. However, the authors stressed that consensus was reached for biological rather than clinical classes. Therefore, at this time, the classification should be considered as a research tool for retrospective and prospective studies until future studies establish how these molecular variants can be used best in a clinical setting.

Molecular classification of MIBC is still evolving and treatment tailored to molecular variant is not a standard yet. A novel 12-gene signature derived from patients in the TCGA utilising published gene signatures has been developed and externally validated to predict OS in MIBC [223]. Interestingly, an analysis of molecular typing in MIBC demonstrated that although molecular variants reflect the heterogeneity of bladder tumours and are associated with tumour grade, clinical parameters outperformed variants for predicting outcome [224]. In the coming years, new insights into BC carcinogenesis may change our management of the disease and our ability to better predict outcomes [225]. Outside clinical trials, molecular examination, either by expression profiling or immunohistochemistry, is not yet part of routine clinical work-up awaiting more conclusive data.

### **6.3 Predictive markers**

#### **6.3.1 Clinical and histopathological markers**

Based on retrospective data only, patients with secondary MIBC have a worse response to NAC compared to patients with primary MIBC [226]. Pietzak *et al.*, retrospectively analysed clinico-pathologic outcomes comparing 245 patients with clinical T2–4a N0M0 primary MIBC and 43 patients with secondary MIBC treated with NAC and RC. They found that patients with secondary MIBC had lower pathologic response rates following NAC than those with primary MIBC (univariable 26% vs. 45%, multivariable OR: 0.4 [95% CI: 0.18–0.84,  $p = 0.02$ ]). They also found that MIBC patients progressing after NAC had worse CSS as compared to patients treated with cystectomy alone ( $p = 0.002$ ). In a meta-analysis, including nineteen cohorts from sixteen studies, inferior outcomes were seen in progressive vs. *de novo* MIBC regardless of the use of neoadjuvant chemotherapy [227].

Subtypes and non-UC have also been linked to worse outcomes after NAC, but there is, as yet, insufficient data to conclude that they can be considered as predictive markers [228].

#### **6.3.2 Molecular markers**

Several predictive biomarkers have been investigated such as serum vascular endothelial growth factor (VEGF) [229], circulating tumour cells, immune and stromal signatures, as well as expression of or defects in DNA damage repair (DDR) genes including ERCC2, ATM, MRE11, RB1 and FANCC that may predict response to cisplatin-based NAC [230, 231] or chemoradiation [232–235]. 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 neoadjuvant chemotherapy [236]. Alterations in FGFR3 including both mutations and gene fusions have been shown to be associated with response to FGFR inhibitors [237, 238]. FGFR3 alterations are used to select for treatment with the FGFR inhibitor erdafitinib (see section 7.7 Metastatic disease) [239].

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 FISH. Reports from a German study group suggest that Nectin-4 expression is decreased on metastatic cells [240]. Nectin-4 amplification may represent a predictive factor for benefit from EV and merits further investigation [241]. Another potentially interesting predictive marker is HER2 expression on tumour cells. First results demonstrate promising response rates with HER2-directed antibody drug conjugates in patients with high expression of HER2 as assessed by immunohistochemistry (see section 7.7 Metastatic disease) [242].

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 which may in part be related to the use of different antibodies and various scoring systems evaluating different compartments, i.e., tumour cells, immune cells, or both. The major limitation of PD-L1 staining relates to the significant proportion of PD-L1-negative patients that respond to immune checkpoint blockade. For example, in the IMvigor 210 phase II study of atezolizumab in patients with advanced/metastatic UC who progressed after platinum-based chemotherapy, responses were seen in 18% of patients with low/no PD-L1 expression [243]. At present, the only indication for PD-L1 testing relates to the use of immune checkpoint inhibitors as monotherapy in patients with locally-advanced or metastatic UC unfit for cisplatin-containing chemotherapy who have not received prior therapy. In this setting, atezolizumab (the European Medicines Agency [EMA] approval) or pembrolizumab (EMA approval) should only be used in patients unfit for cisplatin-containing chemotherapy whose tumours overexpress PD-L1 (i.e., in case of atezolizumab; tumour-infiltrating

immune cells [IC] covering  $\geq 5\%$  of the tumour area using the SP142 assay; in case of pembrolizumab, a combined positive score [CPS] of  $\geq 10$  using the Dako 22C33 platform) [244]. The FDA revised the label for pembrolizumab in patients with advanced UC, approving it only for first-line treatment in patients not eligible for any platinum-based chemotherapy, irrespective of PD-L1 status.

Urothelial cancer is associated with a high tumour mutational burden (TMB) [245]. Both predicted neoantigen burden and TMB have been associated with response to immune checkpoint blockade in several malignancies. High TMB has been associated with response to immune checkpoint inhibitors in metastatic BC [243, 246]. Conflicting results have been seen in studies evaluating immune checkpoint inhibitors in the neoadjuvant setting with the Pembrolizumab as Neoadjuvant Therapy Before Radical Cystectomy in Patients With Muscle-Invasive Urothelial Bladder Carcinoma (PURE)-01 study demonstrating an association of high TMB with response while there was no association with atezolizumab in the Phase II study investigating the safety and efficacy of neoadjuvant atezolizumab in MIBC (ABACUS) [247, 248].

Other markers that have been evaluated in predicting response to immune checkpoint inhibitors include molecular variants as discussed earlier, CD8 expression by immunohistochemistry and other immune gene cell signatures. Recent work has focused on the importance of stroma including the role of transforming growth factors (TGFs) in predicting response to immune checkpoint blockade [249, 250]. Studies have reported on the potential for ctDNA to guide the use of adjuvant IO in UC [251-253]. In 581 patients from a phase III randomised controlled trial (RCT) of adjuvant atezolizumab vs. observation in UC, ctDNA testing at the start of therapy identified 214 (37%) patients who were positive for ctDNA and who had poor prognosis (observation arm HR = 6.3, 95% CI: 4.45–8.92;  $p < 0.0001$ ) [251]. Patients who were positive for ctDNA had improved DFS and OS in the atezolizumab arm vs. the observation arm (DFS: HR = 0.58 [95% CI: 0.43–0.79];  $p = 0.0024$ , OS: HR = 0.59 [95% CI: 0.41–0.86]). There was no difference in DFS or OS between treatment arms for patients who were negative for ctDNA. The rate of ctDNA clearance at week six was higher in the atezolizumab arm (18%) than in the observation arm (4%) ( $p = 0.0204$ ) [251]. An ongoing clinical trial (IMvigor011) is evaluating atezolizumab as adjuvant therapy in patients with high-risk MIBC who are ctDNA positive following cystectomy [254].

A exploratory analysis in patients with metastatic UC 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 KEYNOTE-045 suggesting that these biomarkers may perform differently in different clinical disease states i.e., first line versus salvage settings [255]. 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 [256].

#### 6.4 Conclusion

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

#### 6.5 Summary of evidence and recommendation for urothelial markers

Summary of evidence	LE
There is insufficient evidence to use TMB, molecular variants or immune-expression signatures for the management of patients with urothelial cancer.	NR
Defined alterations of FGFR3 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

Recommendation	Strength rating
Use susceptible FGFR3 alterations to select patients with unresectable or metastatic urothelial carcinoma for treatment with erdafitinib.	Strong

## 7. DISEASE MANAGEMENT

### 7.1 Neoadjuvant therapy

#### 7.1.1 Introduction

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 [257-259]. To improve survival in patients with cN0M0 disease, cisplatin-based NAC has been used since the 1980s [257-261].

#### 7.1.2 Role of cisplatin-based chemotherapy

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

- Chemotherapy is delivered at the earliest time-point, when the burden of micrometastatic disease is expected to be low.
- Potential reflection of in-vivo chemosensitivity.
- Tolerability of chemotherapy and patient compliance are expected to be better pre-cystectomy.
- Patients may respond to NAC and have a favourable pathological response as determined mainly by achieving ypT0,  $\leq$  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 [262].
- Delayed cystectomy might compromise the outcome in patients not sensitive to chemotherapy [263-265]. A comparative survival analysis of patients treated with NAC and RC vs. RC alone based on data from the U.S. National Cancer Database showed that organ-confined disease ( $\leq$  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) [266]. However, there are no prospective trials indicating that delayed surgery due to NAC has a negative impact on survival. In the phase III VESPER trial, comparing gemcitabine/cisplatin (GC) vs. high-dose-intensity methotrexate, vinblastine, doxorubicine and cisplatin (HD-MVAC) in the peri-operative setting, approximately 90% of patients proceeded to surgery (with median delay of 48 days for GC and 51 days for dd-MVAC) [267].
- Neoadjuvant chemotherapy does not seem to affect the outcome of surgical morbidity. In a recently reported large multicentre retrospective analysis, NAC did not lead to an increased risk of post-operative complications after RC [268]. 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 [269].
- Clinical staging using bimanual palpation, CT or MRI may result in over- and understaging and have a staging accuracy of only 70% [87]. Overtreatment is a possible negative consequence.
- Gender may have an impact on chemotherapeutic response and oncologic outcomes [270, 271]. Female patients tend to have a better cancer-related response to NAC as compared to male patients.
- Neoadjuvant chemotherapy should only be used in patients eligible for cisplatin-combination chemotherapy [272-279].

#### 7.1.2.1 Summary of available data

Several phase III RCTs addressed the potential survival benefit of NAC administration [272-276, 280-283]. The main differences in trial designs were the type of chemotherapy (i.e., single-agent cisplatin or combination chemotherapy) and the number of cycles provided. Patients had to be fit for cisplatin. Since these studies differed considerably for patient numbers, patient characteristics (e.g., clinical T-stages included) and the type of definitive treatment offered (cystectomy and/or RT), pooling of results was not possible.

Three meta-analyses were undertaken to establish if NAC prolongs survival [277-279]. In a meta-analysis including updated patient data from eleven randomised trials ( $n = 3,005$ ), a significant survival benefit was shown in favour of NAC [279]. The most recent meta-analysis included four additional RCTs, and used the updated results from the Nordic I, Nordic II, and BA06 30894 trials including data from 427 new patients and updated information from 1,596 patients. The results of this analysis confirmed the previously published data and showed an 8% absolute improvement in survival at five years with a number needed-to-treat of 12.5 [284]. Only cisplatin-combination chemotherapy with at least one additional chemotherapeutic agent resulted in a meaningful therapeutic benefit [277, 279]; the regimens tested were methotrexate, vinblastine, adriamycin (epirubicin) plus cisplatin (MVA(E)C), cisplatin, methotrexate plus vinblastine (CMV), cisplatin plus methotrexate (CM), cisplatin plus adriamycin and cisplatin plus 5-fluorouracil (5-FU) [285].

The updated analysis of a large phase III RCT [273] with a median follow-up of eight years confirmed previous results and provided additional findings:

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

More modern chemotherapeutic regimens such as GC have shown similar pT0/pT1 rates as methotrexate, vinblastine, adriamycin plus cisplatin in retrospective series and pooled data analyses [285-288]. Modified dd-MVAC was tested in two small single-arm phase II studies demonstrating high rates of pathologic complete remission (CR) [289, 290]. Moreover, a large cross-sectional analysis showed higher rates of down-staging and pathological complete response for dd-MVAC [291].

In the GETUG/AFU V05 VESPER RCT of peri-operative chemotherapy, 500 patients were randomised to either six cycles of dd-MVAC once every two weeks vs. four cycles of GC once every three weeks prior to surgery (neoadjuvant group) or after surgery (adjuvant group) with a primary endpoint of progression-free survival (PFS) at three years. Eighty-nine percent of participants received neoadjuvant therapy and a similar pathologic response rate (ypT0N0) in patients treated with dd-MVAC 42% and GC 36% ( $p = 0.2$ ) was seen. The  $< \text{ypT2N0}$  rate was 63% and 50% in the dd-MVAC and GC patients, respectively. Organ-confined response ( $< \text{ypT3N0}$ ) was observed more frequently in the dd-MVAC arm (77% vs. 63%,  $p = 0.001$ ). For all patients in the trial, ITT included neoadjuvant and adjuvant therapy three-year PFS was improved in the dd-MVAC arm, but 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],  $p = 0.066$ ). However, at five-years follow-up a significant benefit for the neoadjuvant group in favour of dd-MVAC with regards to PFS (0.74; 95% CI: 0.55-0.99) and OS (HR: 0.71; 95% CI: 0.52-0.97) was seen [292]. Dose-dense MVAC was associated with more severe asthenia and GI side effects than GC [267, 293]. In a single-center 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 [294]. Another dose-dense regimen using GC was reported in two small phase II trials [295, 296]. While pathological response rates ( $< \text{pT2}$ ) in the range of 45%–57% were achieved, one trial had to be closed prematurely due to high rates of severe vascular events [295]. This approach is therefore not recommended outside of clinical trials.

As an alternative to the standard dose of cisplatin-based NAC with 70 mg/m<sup>2</sup> on day one, split-dose modification regimens are often used with 35 mg/m<sup>2</sup> on days 1+8 or days 1+2. In a retrospective analysis the standard schedule was compared to a split-dose schedule in terms of complete and partial pathological response. A lower number of complete and partial response rates was seen in the split-dose group, but these results were not statistically significant [297].

There seem to be differences in the outcomes of patients treated with NAC for primary or secondary MIBC with retrospective data suggesting that patients with primary MIBC have better pathologic response rates to NAC in comparison to patients with secondary MIBC [298]. However, in the absence of prospective data, patients with secondary MIBC should be treated similarly to those presenting with primary MIBC [226].

It is unclear, if patients with non-UC histology will also benefit from NAC. A retrospective analysis demonstrated that patients with neuroendocrine tumours had improved OS and lower rates of non-organ-confined disease when receiving 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 [299]. A 2019 systematic review showed benefit of NAC for patients with micropapillary, plasmacytoid-, sarcomatoid-, and mixed variants but especially for patients with neuroendocrine tumours [66]. 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; neuroendocrine carcinoma; and adenocarcinoma), with improved OS for patients with UC, sarcomatoid variant UC and neuroendocrine carcinoma [300]. 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 [301].

### 7.1.3 **The role of imaging and predictive biomarkers (see also section 5.2 and 6)**

Data from small imaging studies aiming to identify responders in patients treated with NAC suggest that response after two cycles of treatment is predictive of outcome. Although mpMRI has the advantage of better resolution of the bladder wall tissue planes as compared to CT, it is not ready yet for standard patient care [117].

For responders to NAC, especially in those with a complete response (pT0 N0), treatment has a major positive impact on OS [302, 303]. Therefore, reliable predictive markers to identify patients most likely to benefit from chemotherapy are needed. A study investigated how molecular subtypes impact pathological response and survival in patients receiving pre-operative cisplatin-based chemotherapy [304]. Patients with genomically unstable (GU) and urothelial-like (Uro) tumours had higher proportions of complete pathological response (16/31 [52%] and 17/54 [31%]), vs. five out of 24 (21%) for the basal/squamous (Ba/Sq) subtype following NAC and RC. Molecular subtype was independently associated with improved survival for patients with GU tumours (HR: 0.29, 95% CI: 0.11–0.79) and UroC tumours (HR: 0.37, 95% CI: 0.14–0.94) compared with Ba/Sq tumours, adjusting for clinical stage. Molecular tumour profiling might guide the use of NAC in the future but, as yet, this is not applicable in routine practice [305-307] (see section 6 - Markers).

### 7.1.4 **Role of neoadjuvant immunotherapy and chemo-immunotherapy**

Inhibition of PD-1/PD-L1 checkpoint has demonstrated significant benefit in patients with unresectable and metastatic BC in the second-line setting and in platinum-ineligible PD-L1+ patients as first-line treatment using different agents. Checkpoint inhibitors are increasingly tested also in the neoadjuvant setting; either as monotherapy or in combination with chemotherapy or CTLA-4 checkpoint inhibition. Data from two phase II trials have been presented with encouraging results [248, 249]. The results of PURE-01, a phase II trial using the PD-1 inhibitor pembrolizumab reported a complete pathological remission (pT0) in 42% and pathological response (< pT2) in 54% of patients, whereas in the single-arm phase II trial with atezolizumab a pathologic complete response rate of 31% was reported. In an update to the ABACUS trial using single-agent atezolizumab, two-year DFS and OS were 68% (95% CI: 58–76) and 77% (95% CI: 68–85), respectively with two-year DFS in patients achieving a pathological complete response of 85% (95% CI: 65–94) [308]. In a update of PURE-01, after a median follow-up of 39 months, 36-month EFS and OS were 74% (95% CI: 68-82) and 84% (95% CI: 78-90), respectively with RFS in patients achieving a complete pathologic response of 96% (95% CI: 89-100) [309]. The combination of anti-CTLA4 and anti-PD1 therapy has also been investigated in the neoadjuvant setting. In the NABUCCO study using pre-operative ipilimumab and nivolumab, the pathologic complete response was 46% with 58% having no remaining invasive disease (pT0N0/pTisN0/pTaN0) [310]. In a second study using pre-operative tremelimumab and durvalumab in cisplatin-ineligible patients, the pathological complete response was 37.5% and downstaging to pT1 or less was seen in 58% of patients who completed surgery [311].

Three phase II studies have been published to date investigating the use of neoadjuvant chemo-immunotherapy 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 < pT2N0 and 14 of 39 (36% [95% CI: 21–53]) achieved pT0N0 [312]. In a second phase II study evaluating neoadjuvant atezolizumab with gemcitabine and cisplatin; 27 of 39 patients (69%) were < pT2N0 and 16 (41%) pT0N0. No patient with < pT2N0 relapsed and four (11%) with ≥ pT2N0 relapsed with a median follow-up of 16.5 months (range: 7.0–33.7 months) [313]. A third phase II study evaluating NAC with GC plus durvalumab including adjuvant durvalumab with a primary endpoint of 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 <ypT2 ypN0. Overall survival was 81% (95% CI: 67-89) at three years. A recently reported 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 gemcitabine and cisplatin plus nivolumab [314].

The first randomised phase III trial testing peri-operative addition of durvalumab to neoadjuvant cisplatin/gemcitabine chemotherapy has demonstrated significantly improved EFS and OS and higher pathological CR rate and OS [315], 1,066 patients were included and durvalumab was administered for four cycles every three weeks in the neoadjuvant part and 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 (HR 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.

At present, the results with immunotherapy alone, or in combination with chemotherapy, are promising but not yet approved in routine practice.

### 7.1.5 Summary of evidence and guidelines 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 ypT0 or ≤ ypT2.	2a
Peri-operative durvalumab plus neoadjuvant gemcitabine and cisplatin improves EFS and OS compared to neoadjuvant gemcitabine and cisplatin alone.	1b
Neoadjuvant immunotherapy with checkpoint inhibitors alone has demonstrated promising results.	-
There are still no reliable tools available to select patients who have a higher probability of benefitting from NAC. In the 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
If eligible for cisplatin-based chemotherapy, offer neoadjuvant cisplatin-based combination chemotherapy to patients with muscle-invasive bladder cancer (T2-T4a, cN0 M0).	Strong
Do not offer neoadjuvant cisplatin-containing combination chemotherapy to patients who are ineligible for cisplatin-based combination chemotherapy.	Strong
Only offer neoadjuvant immunotherapy with checkpoint inhibitors alone to patients within a clinical trial setting.	Strong

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

### 7.2.1 Post-operative radiotherapy

Given the high rates of local-regional failure after RC in patients with locally-advanced (pT3–4) BC, estimated at ~30%, as well as the high risk of distant failure and poor survival for these patients, there is an interest in adjuvant therapies that address both the risk of local and distant disease. Data on adjuvant RT (ART) after RC are limited. A systematic review evaluating the efficacy of ART for BC or UTUC found no clear benefit of adjuvant radiation following radical surgery (e.g., cystectomy), although the combination of adjuvant radiation with chemotherapy may be beneficial in locally-advanced disease [316]. In terms of prospective studies a more recent phase II trial compared adjuvant sequential chemotherapy and radiation vs. adjuvant chemotherapy alone in 120 patients with locally-advanced disease and negative margins after RC (with one or more risk factors: ≥ pT3b, grade 3, or node-positive), in a study population with 53% UC and 47% SCC. Addition of ART to chemotherapy alone was associated with a statistically significant improvement in local relapse-free survival (at two years 96% vs. 69% favouring the addition of RT). Disease-free survival and OS also favoured the addition of RT, but those differences were not statistically significant and the study was not powered for those endpoints. Late-grade ≥ 3 GI toxicity in the chemoradiation arm was low (7% of patients) [317].

Adjuvant RT appears to be safe and quite tolerable after RC when using precise radiation techniques. In another Egyptian trial of 122 patients randomised to adjuvant intensity modulated radiation therapy (IMRT) of 50 Gy/25 fractions four weeks after cystectomy or cystectomy alone, the three-year adjusted locoregional RFS rate was higher in the ART arm, measuring 81% compared with 71% ( $p = 0.0457$ ); however, overall and distant metastasis-free survival rates were not statistically different [318]. Even though the acute side effects were slightly higher in the ART arm, late toxicities were almost equal. In the BART phase III RCT of 153 patients with urothelial MIBC with ≥ 1 high-risk feature after RC (pT3-4, pN1-3, nodal yield < 10, positive margin, or ≥ cT3 downstaged with neoadjuvant chemotherapy) randomised to observation vs. ART using stoma-sparing image guided IMRT 50.4 Gy in 28 fractions prescribed to the cystectomy bed and pelvic nodes, severe acute and late toxicity were low and similar in both arms [319]. The oncological outcomes are awaited.

In summary, ART might be considered in patients with pT3/pT4 pN0–2 urothelial BC following RC, although this approach has been evaluated in only a limited number of studies without conclusive data demonstrating improvements in OS. Radiation fields should encompass areas at risk for harbouring residual microscopic disease based on pathologic findings at surgery and may include the cystectomy bed and pelvic LNs. Doses in the range of 45 to 50.4 Gy may be considered. A phase II trial with 72 patients showed that a dose of 50.4 Gy can be used with acceptable toxicity and a high rate of local control [320]. A small retrospective study of 25 patients (median age 64 years) evaluated acute and late toxicity of moderate doses of pelvic RT (range, 45–50.4 Gy). After a median follow-up of 10.4 months the authors concluded that orthotopic ileal neobladders can tolerate moderate radiation doses without significant induced morbidity. Most of the acute GI toxicity seen

was grade 1, four patients developed acute grade 2 toxicity; three of whom had been treated by NAC [321]. For patients not treated with NAC, it may be reasonable to sandwich adjuvant radiation between cycles of adjuvant chemotherapy. The safety and efficacy of concurrent radiosensitising chemotherapy in the adjuvant setting needs further study.

### 7.2.2 Pre-operative radiotherapy

To date, six RCTs have been published investigating pre-operative RT, although all are from several decades ago. In the largest trial, pre-operative RT at a dose of 45 Gy was used, resulting in a significant increase in pathological complete response (9% to 34%) in favour of pre-operative RT, which was also a prognostic factor for survival [322]. The OS data were difficult to interpret since chemotherapy was used in a subset of patients only and more than 50% of patients (241/475) did not receive the planned treatment and were excluded from the final analyses. Two smaller studies using a dose of 20 Gy showed only a small survival advantage in  $\geq$  T3 tumours [323, 324]. Two other small trials confirmed downstaging after pre-operative RT [325, 326]. In a retrospective analysis of 1,846 evaluable patients, only 34 patients received RT prior to orthotopic neobladder reconstruction. The authors conclude that following pelvic RT, a neobladder is possible in highly selected patients with statistically similar peri-operative 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 [327].

A meta-analysis of five RCTs showed a non-significant difference in five-year survival (OR: 0.71, 95% CI: 0.48–1.06) in favour of pre-operative RT [328]. However, the meta-analysis was potentially biased by data from the largest trial in which patients were not given the planned treatment. When the largest trial was excluded from the analysis, the OR became 0.94 (95% CI: 0.57–1.55), which was still not significant.

A more recent RCT, comparing pre-operative vs. post-operative RT and RC (n = 100), showed comparable OS, DFS and complication rates [329]. Approximately half of these patients had UC, while the other half had SCC. In general, such older data is limited in being able to provide a robust evidence base for modern guideline recommendations.

### 7.2.3 Summary of evidence and recommendations for pre- and post-operative radiotherapy

Summary of evidence	LE
No contemporary data exists to support that pre-operative RT for operable MIBC increases survival.	2a
Pre-operative RT for operable MIBC, using a dose of 45–50 Gy in fractions of 1.8–2 Gy, results in down-staging after four to six weeks.	2
Limited evidence supports the safe use of pre- and post-operative RT in case a neobladder is planned or <i>in situ</i> .	3
Limited high-quality evidence supports the use of pre-operative RT to decrease local recurrence of MIBC after RC.	3
Addition of adjuvant RT to chemotherapy is associated with an improvement in local relapse-free survival following cystectomy for locally-advanced bladder cancer (pT3b–4, or node-positive).	2a

Recommendations	Strength rating
Do not offer pre-operative radiotherapy (RT) for operable muscle-invasive bladder cancer since it will not improve survival.	Strong
Adjuvant RT can be offered following RC (pT3b–4 or positive nodes or positive margins) to improve loco-regional relapse free survival, but not overall survival.	Weak

## 7.3 Radical surgery and urinary diversion

### 7.3.1 Removal of the tumour-bearing bladder

#### 7.3.1.1 Introduction

For decades, the standard surgical treatment for patients with MIBC has been RC, pelvic LN dissection, and urinary diversion, with or without NAC [330]. However, growing attention to QoL has led to an increasing use of bladder-sparing approaches, such as RT or TMT, in selected patients (see section 7.5). Performance status and life expectancy influence the choice of primary treatment and type of urinary diversion.

### 7.3.1.2 *Radical cystectomy: timing*

A meta-analysis including nineteen studies concluded that a delay of > 3 months has a negative effect on OS (HR: 1.34, 95% CI: 1.18–1.53). Authors highlighted the lack of standardisation regarding the definition of delays which made it impossible to identify a clear cut-off time [331]. Overall conclusion was that BC patients scheduled for RC should be treated without delays to maximise survival.

### 7.3.2 *Radical cystectomy: indications*

Radical cystectomy is recommended in patients with T2–T4a, N0M0 disease, very high-risk NMIBC, BCG-refractory, BCG-relapsing and BCG-unresponsive NMIBC (see EAU Guidelines on Non-muscle-invasive Bladder Cancer [2]), as well as extensive papillary disease that cannot be controlled with TURBT and intravesical chemotherapy/immunotherapy alone.

Salvage cystectomy is indicated in non-responders to bladder-sparing therapy, i.e., recurrence after TMT. It is also used as a palliative intervention, e.g., for fistula formation, pain and recurrent uncontrollable haematuria (see section 7.4.1 Palliative cystectomy).

### 7.3.3 *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.

#### 7.3.3.1 *Radical cystectomy in men*

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

##### 7.3.3.1.1 Concomitant prostate cancer

A systematic review and meta-analysis of 13,140 patients showed an incidental prostate cancer rate of 24% in RC specimens [332]. 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 Guidelines on Prostate Cancer [333].

##### 7.3.3.1.2 Sexual-preserving techniques

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

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

A systematic review on oncological and functional outcomes of sexual function-preserving cystectomy in men identified twelve studies (n = 1,098) [334]. Most 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. The majority of the studies included patients who were potent pre-operatively with organ-confined disease and no bladder neck and/or prostatic urethra involvement. Prostate cancer was ruled out in all sexual-preserving cystectomy (SPC) techniques, except for the nerve-sparing approach [333].

Oncological outcomes did not differ between groups in any of the comparative studies that measured local recurrence, metastatic recurrence, DSS and OS, at a median follow-up of three to five years. Incidental prostate cancer rates in prostate- or capsule-sparing techniques ranged from 0–15%, with no cases of ISUP grade  $\geq 4$  reported.

Post-operative potency was significantly higher in patients who underwent any type of SPC technique compared to conventional RC ( $p < 0.05$ ), ranging from 80–90%, 50–100% and 29–78% for prostate-, capsule- or nerve-sparing techniques, respectively. Urinary continence, defined as ‘no pads’ ranged from 88–100% (day-time continence) and from 31–96% (night-time continence) in the prostate-sparing cystectomy patients. No major differences were seen with regard to 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 SPC technique is offered, patients must be carefully selected, counselled, and closely monitored.

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

Summary of evidence	LE
The majority of 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 men who are highly motivated to preserve their sexual function.	Strong
Select patients based on: <ul style="list-style-type: none"> <li>organ-confined disease;</li> <li>absence of any kind of tumour at the level of the prostate, prostatic urethra or bladder neck.</li> </ul>	Strong

### 7.3.3.2 Radical cystectomy in women

Historically, standard RC in women 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 [335]. As part of the pre-operative 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. Post-operatively, screening for sexual and urinary function and prolapse, is mandatory.

#### 7.3.3.2.1 Concomitant gynaecological malignancies and associated consequences

Pelvic organ-preserving techniques in women involve preserving the neurovascular bundle, vagina, uterus, ovaries or combinations thereof. In a retrospective multicenter study of 302 females with cTa-T4 bladder cancer, gynaecological organ involvement was seen in 6.6% of cases, and was associated with higher clinical stages [336, 337]. Concomitant malignancy in gynaecological organs is rare and local recurrences following RC are infrequent [338, 339]. In premenopausal women 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 women over 40 years of age [340]. Preserving the uterus and vagina provides the necessary support for a neobladder, thereby reducing the risk of urinary retention or post-operative 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.

#### 7.3.3.2.2 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 [341]. Patient selection has often been limited to cT2 disease, but there are recent encouraging reports that support including women with more advanced T-stage and histological subtypes without compromising oncological outcomes [342]. Despite this, a non-sexual preserving technique is most often used [343].

Pelvic organ-preserving RC could also be considered in elderly and fragile patients as it may reduce blood loss and promote quicker bowel recovery [344].

### 7.3.3.2.3 Summary of evidence and recommendation for sexual-preserving techniques in women

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

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

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

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 [345]. Limited LND includes the nodes from the true pelvis, but excluding 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 [346]. A super-extended LND extends cranially to the level of the inferior mesenteric artery [347].

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 US/Canadian SWOG S1011 trial [348, 349]. 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 [348]. The results of the SWOG S1011 trial comparing standard vs. 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 bladder cancer after a median six years follow-up [349]. Adverse events of grade 3 to 5 occurred in 157 patients (54%) in the extended-lymphadenectomy group and in 132 (44%) in the standard-lymphadenectomy group; death within 90 days after surgery occurred in nineteen 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.

### 7.3.5 **Robotic-assisted laparoscopic cystectomy**

A 2019 cochrane SR of five RCTs compared robotic radical cystectomy (RARC) with extracorporeal urinary diversion and open radical cystectomy (ORC) [350]. One study included an laparoscopic radical cystectomy arm (LRC) [351]. No differences were found in complications, time to recurrence, QoL and surgical margin rate for RARC and ORC. Robotic radical cystectomy was associated with lower transfusion rate and shorter length of hospital stay (median 0.7 days). The study had very-low to moderate certainty of evidence.

In 2023, an updated SR and meta-analysis was published including eight RCTs of which three studies performed intracorporeal urinary diversion [352]. The ERAS pathway was adopted in one study with extracorporeal urinary diversion and in three studies with intracorporeal urinary diversion [351, 353-355]. The following outcomes were reported:

- Longer length of hospital stay for ORC (0.2 days); however, differences were seen depending on geographical location. In four USA and two UK trials longer hospital stay for ORC was reported (0.6 and 1.5 days, respectively) whilst in two EU based trials longer hospital stay for RARC was reported (0.9 days).
- Higher venous trombo-events (OR: 1.8) and transfusion rates (0.5 blood units) for ORC.
- Longer operative time for RARC (mean difference: 76min).
- 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).

It should be noted that the meta-analysis did not distinguish between intracorporeal and extracorporeal approaches for urinary diversion in the RARC group.

Long-term oncological outcomes were also reported in a large (n = 595) single-centre study with a median follow-up of over five years. In this study comparable recurrence and survival data, including atypical recurrences (defined as one or a combination of the following: port site metastasis or peritoneal carcinomatosis) [356]. Interestingly, another study detected residual cancer cells in pelvic washing specimens during or after, but not before, RARC in approximately half of the patients (9/17), which was associated with aggressive histological subtypes and cancer recurrence; however, these findings require confirmation in larger studies [357].

An economic evaluation (healthcare and societal perspective) of a Dutch prospective multi-centre comparative effectiveness study assessing ORC (n = 168) vs. RARC (n = 180) showed that both mean healthcare costs and societal costs per patient were significantly higher after RARC, resulting in an increase in QALYs of 0.02 [358].

Data on post-RC uretero-enteric stricture rates for both ORC and RARC remain inconclusive. Results are mainly reported by high-volume centres or derive from population-based studies with a large variety of endpoints and poor controlling of potential confounders, making comparison difficult [359-363]. Especially those managed by extracorporeal diversion (RARC-ECUD) tend to have more strictures compared to intracorporeal diversion (RARC-ICUD) [363]. This is explained by the need for more extensive dissection of ureter in RARC-ECUD, more tension, resulting in impaired blood supply [364, 365].

#### 7.3.5.1 Summary of evidence and recommendations for robotic-assisted laparoscopic cystectomy

Summary of evidence	LE
Robot-assisted radical cystectomy and ORC 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 ORC (1 to 1.5 hours), but with less blood loss and possibly shorter length of hospital stay compared to ORC.	1a
Surgeon experience and institutional volume are considered the key factor for outcome of both RARC and ORC, not the technique.	4

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

#### 7.3.6 Urinary diversion after radical cystectomy

Different 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 [366], but further research evaluating the impact of tumour stage, functional- and socio-economic status are needed.

##### 7.3.6.1 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 7.3.6.2 patient selection/comorbidities). 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 [367]. Randomised controlled trials comparing conduit diversion with neobladder or continent cutaneous diversion have not been performed.

##### 7.3.6.1.1 Uretero-cutaneostomy

Ureteral diversion to the abdominal wall is the simplest form of cutaneous diversion. Operating time, complication rate, blood loss, transfusion rate, stay at intensive care, and length of hospital stay are lower in patients treated with ureterocutaneostomy as compared to ileal conduit [368]. In frail patients and/or in those with a solitary kidney who need a supravescical diversion, uretero-cutaneostomy is the preferred procedure. In case patients have both kidneys and need a uretero-cutaneostomy, 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 may be directly anastomosed to the abdominal wall creating a stoma.

Due to the smaller diameter of the ureters, stoma stenosis and ascending UTIs have been observed more frequently for this technique as compared to using small or large bowel to create an intestinal stoma [369].

#### 7.3.6.1.2 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 [370].

#### 7.3.6.1.3 Orthotopic neobladder

According to Dutch-, German- and Spanish bladder cancer registry data, an orthotopic bladder substitution to the urethra is used in approximately 10–20% of both male and female patients. 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 [371].

Various forms of UUT reflux protection, including a simple isoperistaltic tunnel, ileal intussusception, tapered ileal prolongation implanted subserosally, and direct (sub)mucosal or subserosal ureteral implantation, have been described [372, 373]. According to the long-term results, the UUT is protected sufficiently by either method [371].

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 [374]. 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]) [375]. These results indicate that neobladder in male and female patients does not compromise the oncological outcome of cystectomy.

#### 7.3.6.1.4 Continent cutaneous urinary diversion

Continent cutaneous urinary diversion (a low-pressure detubularised ileal reservoir for self-catheterisation) and uretero-rectosigmoidostomy are rarely used techniques nowadays, due to their high complication rates, including stomal stenosis, incontinence in the continent cutaneous diversion, UUT infections and stone formation in case of uretero-rectosigmoidostomy [376].

#### 7.3.6.2 Patient selection

Ensuring that patients make a well-informed decision about the type of urinary diversion is associated with less decision regret post-operatively, independent of the method selected [377]. 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 [378]. In women undergoing RC, the rate of concomitant urethral malignancy has been reported to range from 12–16% [379]. Localisation of the primary tumour at the bladder neck correlated strongly with concomitant urethral malignancy. Bladder neck biopsies prior to RC are important in women scheduled for an orthotopic bladder substitute [380].

In the presence of positive LNs, orthotopic neobladder can be considered in case of N1 disease, but not in N2 or N3 tumours [381].

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 [382].

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

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

Relative contraindications for an orthotopic neobladder are high-dose pre-operative RT, complex urethral strictures and severe urethral sphincter-related incontinence [383].

A retrospective study including 1,383 patients showed that the risk of a decline in estimated glomerular filtration rate (eGFR) did not significantly differ after ileal conduit vs. neobladder in patients with pre-operative chronic kidney disease 2 (eGFR 60–89 mL/min/1.73 m<sup>2</sup>) or 3a (eGFR 45–59 mL/min/1.73 m<sup>2</sup>) [384]. 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, most institutions prefer ileal orthotopic neobladders and ileal conduits based on clinical experience. In selected patients, such as patients with a single kidney, uretero-cutaneostomy is surgically the simplest.

#### 7.3.6.3 *Peri-operative 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 prior to surgery and subsequently post-operative complications [385]. However, evidence is limited and randomised controlled trials are missing.

Patients on 'Fast track'/ERAS (Early Recovery After Surgery) protocols show better emotional and physical functioning, with fewer wound healing disorders, fever and thrombosis [386]. While there is no universal ERAS protocol for RC, pre-operative recommendations include no bowel preparation or fasting, and may also include same day admission, carbohydrate loading and a pre-operative exercise programme.

Post-operatively, 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 post-operative ileus decreased from 22% to 7.3% ( $p = 0.003$ ) [387].

Venous thromboembolism (VTE) prophylaxis should be the standard of care for patients undergoing cystectomy [388]. 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 [389]. 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%,  $p = 0.002$ ) [390].

#### 7.3.7 **Morbidity and mortality**

In four retrospective studies and one population-based cohort study, the peri-operative mortality after RC was reported as 2.1–3.2% at 30 days and 3.4–8.0% at 90 days [391, 392]. Morbidity rates differ strongly according to the reporting system used. Using the Clavien-Dindo Classification system complication rates ranged from 50–88% (I–IV) and severe complications from 30–42% ( $\geq$  III) [393–396]. In large national databases and institutional series, readmission rates are approximately 25% within 30 days of discharge [397]. 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 re-operation rates [398]. In addition, the study revealed that the average age and co-morbidity 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 [399, 400]. In general, lower morbidity and (peri-operative) mortality have been observed by surgeons and in hospitals with a higher case load and therefore more experience [401–404]. A retrospective analysis of 1,303 patients managed in seven (non-academic) Dutch hospitals revealed variation in treatment preferences between them; however, despite this there was no significant difference in OS [405].

**Table 7.1: Management of neobladder morbidity (30-64%) [406]**

CLAVIEN System		Morbidity	Management
Grade I	<p>Any deviation from the normal post-operative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions.</p> <p>Allowed therapeutic regimens are: drugs such as antiemetics, antipyretics, analgesics, diuretics and electrolytes and physiotherapy.</p> <p>This grade also includes wound infections opened at the bedside.</p>	<b>Immediate complications:</b>	
		Post-operative ileus	Nasogastric intubation (usually removed at day 1) Chewing gum Avoid fluid excess and hypovolemia (provoke splanchnic hypoperfusion)
		Post-operative nausea and vomiting	Antiemetic agent (decrease opioids) Nasogastric intubation
		Urinary infection	Antibiotics, no ureteral catheter removal Check the 3 drainages (ureters and neobladder)
		Ureteral catheter obstruction	Inject 5 cc saline in the ureteral catheter to resolve the obstruction Increase volume infusion to increase diuresis
		Intra-abdominal urine leakage (anastomosis leakage)	Check and reposition drainages, if needed
		Anaemia well tolerated	Martial treatment (give iron supplement)
		<b>Late complications:</b>	
		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	<p>Requiring pharmacological treatment with drugs other than those allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included</p>
Pulmonary embolism	Heparinotherapy <sup>2</sup>		
Pyelonephritis	Antibiotics and check kidney drainage (nephrostomy if necessary)		
Confusion or neurological disorder	Neuroleptics and avoid opioids		
Grade III	<p>Requiring surgical, endoscopic or radiological intervention</p>	Ureteral catheter accidentally dislodged	Reposition the ureteral catheter
		Anastomosis stenosis (7%)	Renal drainage (ureteral catheter or nephrostomy)
III-a	<p>Intervention not under general anaesthesia</p>	Compressive lymphocele	Transcutaneous drainage

<b>III-b</b>	Intervention under general anaesthesia	Ileal anastomosis leakage	Ileostomy, as soon as possible
		Evisceration	Surgery in emergency
		Compressive lymphocele	Surgery (marsupialisation)
<b>Grade IV</b>	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
<b>IV-a</b>	Single organ dysfunction	Non-obstructive renal failure	Bicarbonate/aetiology treatment (including dialysis)
<b>IV-b</b>	Multi-organ dysfunction	Obstructive pyelonephritis and septicaemia	Treatment at intensive care unit, including urinary drainage and antibiotics
<b>Grade V</b>	Death of a patient		
<i>Suffix 'd'</i>	<i>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.</i>		

<sup>1</sup> A systematic review showed that peri-operative blood transfusion (PBT) in patients who undergo RC correlates with increased overall mortality, CSM and cancer recurrence. The authors hypothesised that this may be caused by the suggested immunosuppressive effect of PBT. In a retrospective study, Buchner and co-workers showed five-year decreased CSS in cases where intra-operative blood transfusion (CSS decreased from 67% to 48%) or post-operative blood transfusion (CSS decreased from 63% to 48%) were given [405].

<sup>2</sup> Hammond and co-workers reviewed 20,762 cases of VTE after major surgery and found cystectomy patients to have the second-highest rate of VTE among all cancers studied [406]. 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 [389].

### 7.3.8 **Survival**

Of all cancers, bladder cancer ranks 13<sup>th</sup> in terms of mortality, with rates decreasing particularly in the most developed countries [408].

Disease-free survival and OS in a large population-based study was 35% and 58% at ten years, respectively [409]. However, the five-year OS in node-positive patients who underwent cystectomy was only 18% [410].

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

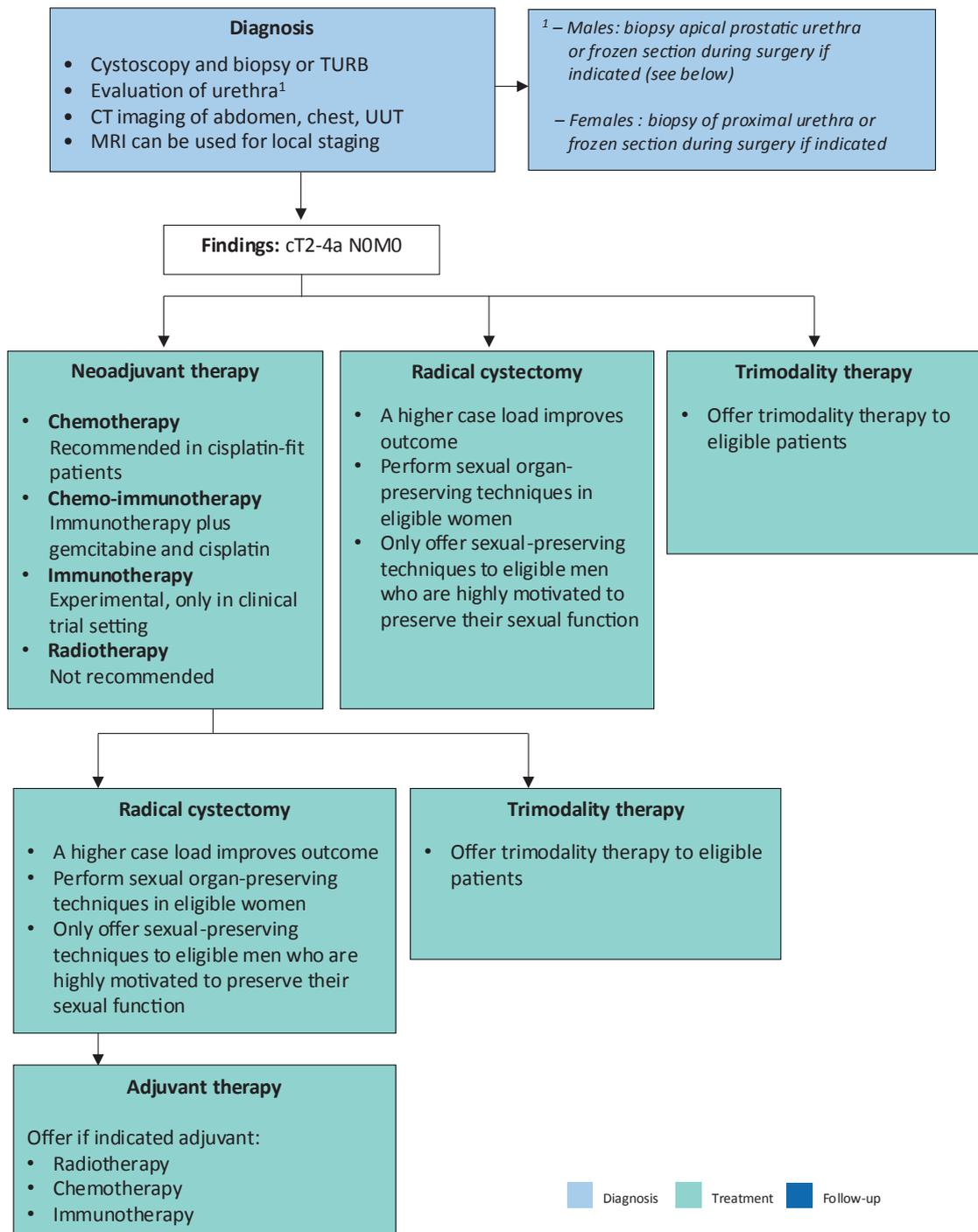
In a systematic review including 40 retrospective studies with 56,000 patients, the impact of hospital and/or surgeon volume and peri-operative outcomes of RC was assessed [411]. A higher hospital volume was associated with lower in-hospital, 30-day and 90-day mortality. In addition, higher volume hospitals were more likely to have lower positive surgical margins, higher number of LNDs and neobladders and lower complication rates. For surgeon volume, less evidence was available. This study suggested performing at least ten RCs per centre annually and preferably more than 20. A nationwide analysis of the Dutch Cancer Registry including almost 9,500 patients between 2008 and 2018 reported decreased 30- and 90-day mortality rates for annual hospital volumes of > 30 RCs. Furthermore, this study showed no true plateau curve for 30- and 90-day mortality beyond 30 RCs supporting the 'more is better' principle [412, 413]. 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 re-operation rates. In addition, the study revealed that the average age and co-morbidity of patients being offered RC increased following centralisation [398]. A German nationwide analysis found hospitals performing over 50 RCs per year had lower inpatient mortality, shorter length of hospital stay, and fewer complications in comparison to the centers with 20–49 RCs per year [414].

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

Summary of evidence	LE
Higher RC hospital volume is associated with lower post-operative mortality rates and higher quality of care.	3
Radical cystectomy includes removal of regional LNs.	3
An extended LND is not superior to a standard LND; it does not improve survival and increases the risk of morbidity.	1a
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
The use of extended VTE prophylaxis significantly decreases the incidence of VTE after RC.	3
In patients aged > 80 years with MIBC, cystectomy is an option.	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
Offer radical cystectomy (RC) to patients with T2–T4a, N0M0 disease or very high-risk non-muscle-invasive bladder cancer.	Strong
Do not delay RC for > 3 months as it increases the risk of progression and cancer-specific mortality, unless the patient receives neoadjuvant chemotherapy.	Strong
Perform a lymph node dissection as an integral part of RC.	Strong
Perform a standard LND, as an extended LND does not improve survival and increases the risk of morbidity.	Strong
Perform at least 20 RCs per hospital/per year.	Strong
Before RC, fully inform the patient about the benefits and potential risks of all possible alternatives. The final decision should be based on a balanced discussion between the patient and the surgeon.	Strong
Do not offer an orthotopic bladder substitute diversion to patients who have an invasive tumour in the urethra or at the level of urethral dissection.	Strong
Do not offer pre-operative bowel preparation.	Strong
Employ 'Fast track' measurements to reduce the time to bowel recovery.	Strong
Offer pharmacological VTE 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 7.1: Flow chart for the management of T2–T4a N0M0 urothelial bladder cancer



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

#### 7.4 Palliative and salvage cystectomy

Unresectable locally-advanced tumours (T4b, invading the pelvic or abdominal wall) may be accompanied by debilitating symptoms, including bleeding, pain, dysuria and urinary obstruction. These patients are candidates for palliative treatments, such as palliative RT [415]. 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  $\geq 3$ ) occurred in 30%. The 30-day mortality rate was 9% and at eight months follow-up, 70% had died [416].

A retrospective single-centre analysis grouped 265 patients into salvage cystectomy post-TMT, primary cystectomy or primary cystectomy with prior 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 intra-operative and early complications, DSS ( $p = 0.8$ ) or OS ( $p = 0.9$ ) between the groups [417]. In modern series, salvage cystectomy is required in 10-15% of cases due to invasive in-bladder recurrences post-TMT. Salvage cystectomy is feasible with acceptable morbidity and can be curative [327, 417-421].

#### 7.4.1 Recommendations for palliative and salvage cystectomy

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

##### 7.4.1.1 EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [81, 82]\*

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

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

#### 7.4.2 Supportive care

##### 7.4.2.1 Obstruction of the upper urinary tract

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

##### 7.4.2.2 Bleeding and pain

In the case of bleeding, the patient must be screened first for coagulation disorders or the patient's use of anticoagulant drugs must be reviewed. Tumour debulking by TURB, selective transurethral electrocoagulation, or laser coagulation can be challenging in a bladder full of tumor or in case of gross haematuria. Intravesical rinsing of the bladder with 1% silver nitrate or 1–2% alum can be effective [422]. This can usually be done without any anaesthesia. The instillation of formalin (2.5–4% for 30 minutes) is a more aggressive and painful procedure, requiring anaesthesia. Formalin instillation has a higher risk of side-effects, e.g., bladder fibrosis, but is more likely to control the bleeding [422]. 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% [423]. 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% [422]. Radical surgery is a last resort and includes cystectomy and diversion (see above, section 7.4.1).

## 7.5 Bladder-sparing treatments for localised disease

### 7.5.1 Transurethral resection of bladder tumour

Transurethral resection of bladder tumour alone in MIBC patients is only possible as a therapeutic option if tumour growth is limited to the superficial muscle layer and if re-staging biopsies are negative for residual (invasive) tumour [424]. 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 [425]. A disease-free status at re-staging TURB appears to be crucial in making the decision not to perform RC [426, 427]. A prospective study including 133 patients after radical TURB and re-staging negative biopsies, reported a fifteen-year follow-up [427]. Thirty

per cent of patients had recurrent NMIBC and went on to intravesical therapy, and 30% (n = 40) progressed, of which 27 died of BC. After five, ten, and fifteen years, the results showed CSS rates of 81.9%, 79.5%, and 76.7%, respectively and PFS rates with an intact bladder of 75.5%, 64.9%, and 57.8%, respectively. It is essential to recognise that this is a highly selected population.

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

#### 7.5.1.1 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

### 7.5.2 External beam radiotherapy

#### 7.5.2.1 Definitive external beam radiotherapy

With the use of modern EBRT techniques, efficacy and safety results seem to have improved over time. A 2002 Cochrane analysis demonstrated that RC has an OS benefit compared to RT [428], although this was not the case in a 2014 retrospective review using a propensity score analysis [429].

In a 2017 retrospective cohort study of U.S. National Cancer Database data, patients over 80 were identified with cT2–4, N0–3, M0 BC, who were treated with curative EBRT (60–70 Gy, n = 739) or concurrent chemoradiotherapy (n = 630) between 2004 and 2013 [430]. The two-year OS was 42% for EBRT vs. 56% for chemoradiotherapy (p < 0.001). For EBRT a higher RT dose and a low stage were associated with improved OS.

Current RT techniques with soft-tissue matching and image guidance result in superior bladder coverage and a reduced integral dose to the surrounding tissues. The target total dose (to bladder and/or bladder tumour) for curative EBRT in BC using conventional fractionation is 64–66 Gy [431, 432]. An accepted alternative is moderately hypofractionated EBRT to 55 Gy in 20 fractions which has been suggested to be non-inferior to 64 Gy in 32 fractions in terms of invasive locoregional control, OS, and late toxicity. In a phase II study, 55 patients (median age 86) with BC, unfit for cystectomy or even daily RT, were treated with six-weekly doses of 6 Gy [433]. Forty-eight patients completed EBRT with acceptable toxicity and 17% showed local progression after two years demonstrating good local control with this more ultra-hypofractionated schedule.

Elective treatment to the LNs is optional and should take into account patient comorbidities and the risks of toxicity to adjacent critical structures. A retrospective Canadian multicentre database study suggested that pelvic nodal radiation was associated with better survival compared with bladder radiation alone after adjusted analysis [434]. For node-positive disease, consider boosting grossly involved nodes to the highest achievable dose that does not violate normal tissue constraints based on the clinical scenario.

The use of modern standard EBRT techniques results in major related late morbidity of the urinary bladder or bowel in less than 5% of patients [435]. Acute diarrhoea is reduced even more with intensity-modulated RT [436]. Prognostic factors for outcome have included age, T-stage, response to EBRT, tumour size, hydronephrosis, presence of CIS, and completeness of the initial TURB [437].

In conclusion, although EBRT results seem to have improved over time, EBRT alone does not seem to be as effective as surgery or TMT therapy (see section 7.5.4). Factors that influence outcome should be considered. However, EBRT can be an alternative treatment in patients unfit for radical surgery or concurrent chemotherapy.

#### 7.5.2.2 Palliative external beam radiotherapy

The results of several studies show that RT delivered in a hypofractionated regime (such as 21 Gy in 3 fractions evaluated in the MRC BA09 randomised control trial [415]) can provide rapid relief of local bladder cancer symptoms, including in particular symptomatic hematuria. Other fractionation regimes include 35 Gy in 10 fractions, 30 Gy in 5 fractions, 36 Gy in 6 fractions given once weekly [438], and even a single 8 Gy fraction. In the palliative setting, symptom resolution typically lasts for the majority of the patients' remaining lifespan.

### 7.5.2.3 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

### 7.5.2.4 EAU-ESMO consensus statements on the management of advanced and variant bladder cancer [81, 82]\*

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

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

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

### 7.5.3 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  $> 60\%$  [439, 440]. Response to chemotherapy is a prognostic factor for treatment outcome and eventual survival although it may be confounded by patient selection [441].

Several groups have reported the effect of chemotherapy on resectable tumours (neoadjuvant approach), as well as unresectable primary tumours [272, 283, 442, 443]. Neoadjuvant chemotherapy with two to three cycles of MVAC or CMV has led to a down-staging of the primary tumour in various prospective series [272, 283, 442].

A bladder-conserving strategy with TURB and systemic cisplatin-based chemotherapy has been reported several years ago and could lead to long-term survival with intact bladder in a highly selected patient population [444].

A recent large retrospective analysis of a U.S. National Cancer Database cohort reported on 1,538 patients treated with TURB and multi-agent chemotherapy [445]. 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.

#### 7.5.3.1 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

### 7.5.4 Trimodality bladder-preserving treatment

#### 7.5.4.1 Patient selection and treatment paradigm

Bladder preservation as an alternative to RC is generally reserved for patients with smaller solitary tumours, no extensive or multifocal CIS, or only unilateral tumour-related hydronephrosis, and good pre-treatment bladder function. Patient selection is critical in achieving good outcomes [446]. Some studies have suggested that up to 30% of cystectomy patients may be eligible and good candidates for bladder preservation [418]. Trimodality bladder-preserving treatment should also be considered in all patients with a contraindication for

surgery, either a relative or absolute contraindication, since the factors that determine fitness for surgery and chemoradiotherapy differ.

Trimodality therapy (TMT) combines TURB, chemotherapy and RT. The rationale to combine TURB with RT is to achieve maximal local tumour control in the bladder and adjacent nodes. The addition of radiosensitising chemotherapy or other radiosensitisers (mentioned below) is aimed at the potentiation of RT. Micrometastases can be targeted by neoadjuvant or adjuvant platinum-based combination chemotherapy (see section 7.1). While there are no definitive contemporary data supporting the benefit of using neoadjuvant or adjuvant chemotherapy combined with chemoradiation, it is reasonable to consider especially in the setting of more advanced stage or node positive disease [447]. Whether a node dissection should be performed before TMT as in RC remains unclear and is not commonly done [81, 82]. The aim of TMT is to preserve the bladder and QoL without compromising oncological outcome.

In the case of TMT, two distinct patterns of care emerge; treatment aimed at patients fit for cystectomy who elect TMT or refuse cystectomy, and treatment aimed at older, less fit, patients. For the former category, TMT represents selective bladder preservation and in this case the initial step is a radical TURB where as much tumour as possible should be resected. In this case appropriate patient selection (e.g., cT2-T3a tumours, no CIS) is crucial [448, 449]. Even in case of an initial presumed complete resection, a second TUR has been suggested to reveal tumour in > 50% of patients [450]. For patients who are not candidates for cystectomy, less stringent criteria can be applied, but extensive CIS and poor bladder function should both be regarded as relative contraindications.

#### 7.5.4.1.1 Radiation therapy

A collaborative review has described the principles of TMT [446]. For radiation, the two schedules most commonly used have been: 1. historically within the RTOG a split-course format with interval cystoscopy [451]; and 2. single-phase treatment which is now more commonly used [419]. A conventional radiation schedule includes EBRT to the bladder +/- limited pelvic LNs with an initial dose of 40-45 Gy, with a boost to the whole bladder of 50–54 Gy and a further tumour boost to a total dose of 60–66 Gy. If not boosting the tumour, it is also reasonable for the whole bladder to be treated to 59.4–66 Gy. Elective treatment to the LNs (when node negative) is optional and should take into account patient comorbidities and the risks of toxicity to adjacent critical structures. While there is no definitive data indicating that nodal radiation is necessary, a recent retrospective Canadian multicentre database study suggested that pelvic nodal radiation was associated with better survival compared with bladder radiation alone after adjusted analysis [434]. For node-positive disease, consider boosting grossly involved nodes to the highest achievable dose that does not violate normal tissue constraints.

A radiation dosing alternative to conventional fractionation when treating the bladder-only fields is moderately hypofractionated EBRT to 55 Gy in 20 fractions which has been suggested to be non-inferior to 64 Gy in 32 fractions in terms of invasive loco-regional control, OS and late toxicity [431, 452] in a meta-analysis of individual patient data from the BC2001 and BCON studies.

#### 7.5.4.1.2 Concurrent radiosensitizing chemotherapy

Different concurrent chemotherapy regimens have been used, but most evidence exists for cisplatin [451, 453] and mitomycin-C plus 5-FU [419]. 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 [454]. Alternative regimens that have been evaluated include: single agent gemcitabine [455], capecitabine [456], paclitaxel [457] and hypoxia modification with carbogen/nicotinamide [81, 82, 456]. In a phase II RCT, twice-a-day radiation plus 5-FU/cisplatin was compared to once-daily radiation plus gemcitabine [455]. Both arms were found to result in a > 75% free from distant metastases rates at three years (78% and 84%, respectively). Therefore, there are good chemotherapy options for non-cisplatin candidates such as 5-FU/mitomycin-C or low-dose gemcitabine.

#### 7.5.4.2 Outcomes

Among TMT series, five-year CSS and OS rates vary between 50%–84% and 36%–74%, respectively, with salvage cystectomy rates of 10–30% [418-420, 446, 448, 458].

There are no successfully completed RCTs comparing the outcome of TMT with RC. Many of the reported TMT series have differing characteristics as compared to the larger surgical series. For example, in surgical series typical median ages are in the mid- to-late 60s compared to mid-70s for RT series (reviewed by James, *et al.*, [419]).

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 [409, 418, 459]. A systematic review including 57 studies (n = 30,293) assessed the long-term survival of patients treated with TMT and RC [409]. 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 [418]. 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 USA and Canada between 2005 and 2017. All patients had solitary tumours less than 7 cm, 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 (IPTW) and 74% for both cohorts with propensity score matching (PSM). Five-year CSS for RC and TMT was 81% vs. 84% with IPTW and 83% vs. 85% with PSM, respectively. Salvage cystectomy was done 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 [460]. Another study reported no difference in survival outcomes in cN+ patients treated with surgery vs. radical RT [461].

Overall, in balance, these studies show similar oncological outcomes between RC and TMT for select patients with MIBC. These results support that TMT, in the setting of multidisciplinary shared decision making, should be offered to all suitable candidates with MIBC and not only to patients with significant comorbidities for whom surgery is not an option [418].

#### 7.5.4.3 *Post-TMT 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 managed conservatively [419]. Non-muscle-invasive BC recurrences after complete response to TMT were reported in 25% of patients by the Boston group, sometimes over a decade after initial treatment [462]. A NMIBC recurrence was associated with a lower DSS, although in properly selected patients, intravesical BCG could avoid immediate salvage cystectomy.

In contemporary series, salvage cystectomy is required in about 10–15% of patients treated with TMT due to invasive in-bladder recurrences and can be curative [418-420, 448] (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 [418].

Current data suggest that salvage cystectomy is feasible with acceptable morbidity. Major late complication rates were slightly higher but remain acceptable for salvage- vs. primary cystectomy and there was no difference in intra-operative and early complications, DSS or OS [417, 421].

#### 7.5.4.4 *Histological subtypes*

Most studies are limited by retrospective design, relatively small sample sizes, lack of central pathology review, differing radiation protocols and chemotherapy regimens, and are limited in their ability to report on individual outcomes of specific histologic subtypes. That said, patients with muscle-invasive UC with divergent (squamous, glandular or micropapillary) differentiation 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 [463, 464].

Patients with predominant SCC or adenocarcinoma may have worse survival outcomes following TMT compared to UC and should be counselled for upfront RC [465, 466].

#### 7.5.4.5 *Toxicity*

Overall significant late pelvic (GI/genitourinary [GU]) toxicity rates after TMT are low and QoL is good [419, 467, 468]. 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 [467]. One option to reduce side effects after TMT is the use of IMRT and image-guided RT (IGRT) [81, 82, 469]. A retrospective study showed QoL to be good after TMT and in most domains better than after cystectomy, although prospective validations are needed [470]. For further discussion of QoL after TMT, see section 7.8.5.

A bladder-preserving TMT strategy requires very close multidisciplinary cooperation and MIBC patients should be seen in a multidisciplinary setting to allow for informed decision-making [81, 82].

#### 7.5.4.6 Summary of evidence and recommendations for trimodality bladder-preserving treatment

Summary of evidence	LE
Long-term survival rates of TMT bladder-preserving treatment 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 trimodality bladder-preserving treatments (TMT) as primary curative option for eligible patients since they are more effective than radiotherapy alone.	Strong
Manage all patients who are candidates for TMT in a multidisciplinary team setting. The choice of treatment modality should be made through a shared-decision making process.	Strong
Advise patients who are candidates for TMT that life-long bladder monitoring is essential.	Strong

#### 7.5.4.7 EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [81, 82]\*

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

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

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

## 7.6 Adjuvant therapy

### 7.6.1 Role of adjuvant platinum-based chemotherapy

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

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

The drawbacks of adjuvant chemotherapy are:

- assessment of *in vivo* chemosensitivity of the tumour is not possible and overtreatment is an unavoidable problem;
- delay of or intolerance to chemotherapy, due to post-operative morbidity [471].

There is limited evidence from adequately conducted and accrued phase III RCTs in favour of the routine use of adjuvant chemotherapy [472-477]. An individual patient data meta-analysis [478] of survival data from six RCTs of adjuvant chemotherapy [479-481] included 491 patients (unpublished data from Otto *et al.*, were included in the analysis). All included trials suffered from significant methodological flaws including small sample size (underpowered), incomplete accrual, use of inadequate statistical methods and design flaws (irrelevant endpoints and failing to address salvage chemotherapy in case of relapse or metastases) [472]. In these trials, three or four cycles of CMV, cisplatin, cyclophosphamide, and adriamycin (CISCA), methotrexate, vinblastine, adriamycin or epirubicin, and cisplatin (MVA(E)C) and cisplatin with methotrexate (CM) were used [482], and one trial used cisplatin monotherapy [483]. The data were not convincing to support an unequivocal recommendation for the use of adjuvant chemotherapy. In 2014, this meta-analysis was updated with an additional three studies [475-477] resulting in the inclusion of 945 patients from nine trials [474]. None of the trials had fully accrued and individual patient data were not used in the analysis [474]. For one trial only an abstract was available at the time of the meta-analysis [476] and none of the included individual trials were significantly positive for OS in favour of adjuvant chemotherapy. In two of the trials more modern chemotherapy regimens were used (gemcitabine/cisplatin and paclitaxel/gemcitabine/cisplatin) [475, 476]. The HR for OS was 0.77 (95% CI: 0.59–0.99,  $p = 0.049$ ) and for DFS 0.66 (95% CI: 0.45–0.91,  $p = 0.014$ ) with a stronger impact on DFS in case of nodal positivity. A systematic review and meta-analysis of individual patient data from RCTs in patients treated with adjuvant cisplatin-based chemotherapy for MIBC has been conducted [484]. 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,  $p = 0.004$ ). Adjuvant chemotherapy was also shown to improve RFS (HR: 0.71, 95% CI: 0.60–0.83,  $p < 0.001$ ), locoregional RFS (HR: 0.68, 95% CI: 0.55–0.85,  $p < 0.001$ ), and MFS (HR: 0.79, 95% CI: 0.65–0.95,  $p = 0.01$ ), with absolute benefits of 11%, 11%, and 8%, respectively.

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) [485]. A publication of the largest RCT (European Organisation for Research and Treatment of Cancer [EORTC] 30994), although not fully accrued, showed a significant improvement of PFS for immediate, compared with deferred, cisplatin-based chemotherapy (HR: 0.54, 95% CI: 0.4–0.73,  $p < 0.0001$ ), but there was no significant OS benefit [486]. Furthermore, a large observational study including 5,653 patients with pathological T3–4 and/or pathological node-positive BC, treated between 2003 and 2006 compared the effectiveness of adjuvant chemotherapy vs. observation. Twenty-three percent of patients received adjuvant chemotherapy with a five-year OS of 37% for the adjuvant arm vs. 29.1% (HR: 0.70, 95% CI: 0.64–0.76) in the observation group [487]. 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 [488]. 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.

#### 7.6.2 **Role of adjuvant immunotherapy**

To determine the benefit of PD-1/PD-L1 checkpoint inhibitors, three phase III RCTs have evaluated checkpoint inhibitor monotherapy with atezolizumab, nivolumab or pembrolizumab in patients with muscle-invasive UC (MIUC). The CheckMate 274 phase III multi-centre, double-blind, RCT of adjuvant nivolumab vs. placebo for up to 1 year in 709 patients with MIUC with a high risk of recurrence (pathological stage pT3, pT4a, or pN+) (neoadjuvant cisplatin-based chemotherapy was allowed before trial entry) demonstrated a significant improvement in median DFS (20.8 months [95% CI: 16.5–27.6] with nivolumab and 10.8 months [95% CI: 8.3–13.9] with placebo). The percentage of patients who were alive and disease-free at 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  $\geq 1\%$  (tumor cell [TC] score), the percentage of patients was 74.5% and 55.7%, respectively (HR: 0.55, 98.72% CI: 0.35–0.85,  $p < 0.001$ ) [489]. In an analysis using both PD-L1 TC score and CPS, more patients had CPS  $\geq 1$  than TC  $\geq 1\%$  and patients with CPS  $\geq 1$  had improved DFS with nivolumab which may have contributed to the benefit seen with adjuvant nivolumab in patients with TC  $< 1\%$  and CPS  $\geq 1$  [490]. There was no clinically meaningful deterioration in health-related QoL with adjuvant nivolumab compared to placebo [491].

A second phase III trial evaluated adjuvant pembrolizumab for one year vs. 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  $p = 0.003$ ) [492]. The primary endpoint of DFS was not achieved in a multi-centre RCT of adjuvant atezolizumab vs. observation (IMvigor010). Median DFS was 19.4 months (95% CI: 15.9–24.8) with atezolizumab and 16.6 months (11.2–24.8) with observation (stratified HR: 0.89, 95% CI: 0.74–1.08,  $p = 0.24$ ) [493].

The FDA has approved nivolumab for adjuvant treatment of patients with UC who are at high risk of recurrence after undergoing surgery [494] whereas the EMA has approved adjuvant nivolumab for the treatment of adults with MIUC with tumour cell PD-L1 expression  $\geq 1\%$ , who are at high risk of recurrence after undergoing radical resection of MIUC. A promising report (see Marker section) has suggested a potential role for ctDNA to guide the use of adjuvant IO for UC [495].

### 7.6.3 Summary of evidence and recommendations for adjuvant therapy

Summary of evidence	LE
Adjuvant cisplatin-based chemotherapy for high-risk patients (pT3, 4 and/or N+ M0) without neoadjuvant treatment can be associated with improvement in DFS and OS but trials are underpowered to adequately answer this question.	2a
To date, studies of immune checkpoint inhibitors in the adjuvant setting for high-risk MIBC patients, whether they have or have not received NAC, have yielded conflicting results. CheckMate 274 and the AMBASSADOR studies showed an improvement in DFS with adjuvant nivolumab and pembrolizumab, respectively, whereas the IMvigor 010 study failed to show a DFS benefit with adjuvant atezolizumab.	1b

Recommendations	Strength rating
Offer adjuvant cisplatin-based combination chemotherapy to patients with pT3/4 and/or pN+ disease if no neoadjuvant chemotherapy has been given.	Strong
Offer adjuvant nivolumab to selected patients with pT3/4 and/or pN+ disease not eligible for, or who declined, adjuvant cisplatin-based chemotherapy (FDA approval irrespective of PD-L1 status, EMA approval only for PD-L1 tumour cell expression $\geq 1\%$ ).	Strong

## 7.7 Metastatic disease

### 7.7.1 Introduction

The treatment of metastatic UC had remained largely unchanged since pivotal trials published over 20 years ago set the standard of care for first-line treatment with cisplatin-based combinations demonstrating an OS benefit. This longstanding paradigm was challenged in the past years by the introduction of immunotherapy using checkpoint inhibitors and it was finally upended in October 2023 with the presentation of the results of two practice changing RCTs demonstrating an OS benefit in the first line setting against platinum-based chemotherapy (EV-302/KEYNOTE A39 and Checkmate 901) [496, 497].

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

In general, patients with untreated metastatic UC 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 trial EV-302/KEYNOTE 39A and is likely to undergo changes in the near future based on results from real-world evidence investigations. Major criteria include ECOG performance status 0–2, GFR  $\geq 30$  ml/min and adequate organ functions based on eligibility for treatment with EV and Pembrolizumab. 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 7.2.

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

An international survey among BC experts [439] 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  $\leq 60$  mL/min; grade  $\geq 2$  audiometric hearing loss; grade  $\geq 2$  peripheral neuropathy or New York Heart Association (NYHA) class III heart failure [440]. Around 50% of patients with BC are not eligible for cisplatin-based chemotherapy [440]. Renal function assessment is of utmost importance for treatment selection. Measuring GFR with radioisotopes ( $^{99m}\text{Tc}$  DTPA or  $^{51}\text{Cr}$ -EDTA) is recommended in equivocal cases.

Cisplatin has also been administered in patients with a lower GFR (40–60 mL/min) using different split-dose schedules. The respective studies were mostly small phase I and II trials in different settings (neoadjuvant and advanced disease) demonstrating that the use of split-dose cisplatin is feasible and appears to result in encouraging efficacy [495, 498, 499]. However, no prospective RCT has compared split-dose cisplatin with conventional dosing.

Most patients that are deemed unfit for cisplatin are able to receive carboplatin-based chemotherapy. However, some patients are deemed unfit for any platinum-based chemotherapy, i.e., both cisplatin and carboplatin. Patients are unfit for any platinum-based chemotherapy in case of PS > 2, GFR < 30 mL/min or the combination of PS 2 and GFR < 60 mL/min since the outcome in this patient population is poor regardless of platinum-based treatment or not [500]. Patients with multiple comorbidities may also be poor candidates for platinum-based chemotherapy.

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

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

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

#### 7.7.2.1 First-line chemotherapy in patients fit for combination therapy

##### 7.7.2.1.1 Enfortumab vedotin plus Pembrolizumab

The combination of EV plus pembrolizumab 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 checkpoint inhibitor, 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 immunotherapy with avelumab. Both co-primary endpoints, PFS and OS were clearly met with a significant improvement in median PFS of 12.5 vs. 6.3 months (HR: 0.45 [0.38-0.54] and median OS of 31.5 vs. 16.1 months (HR: 0.47 [0.38-0.58], respectively. The overall ORR was 67.7% including 29.1% CR compared to 44.4% (12.5% CR) with platinum-based chemotherapy ( $p < 0.00001$ ). All prespecified subgroups benefited equally from EV+pembrolizumab regardless of cisplatin eligibility, PD-L1 expression or presence of liver metastases. Treatment-related toxicity grade  $\geq 3$  was reported in 56% for EV/Pembrolizumab versus 70% in the chemotherapy arm. Specific and relevant EV toxicities include skin rash, peripheral neuropathy, ocular disorders and hyperglycemia. Toxicity of EV/Pembrolizumab needs to be managed proactively and attentively to avoid severe sequelae. The administration of EV/Pembrolizumab requires adequate knowledge and care from a specialised interprofessional team [497].

The combination of EV and pembrolizumab as first-line treatment in 45 cisplatin-ineligible patients with locally-advanced/metastatic UC was also investigated in EV-103, phase 1b/2 study, and demonstrated a confirmed objective response rate after a median of nine cycles of 73.3% with a complete response rate of 15.6% [501]. 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%) [501]. A second cohort within the same study randomly assigned previously untreated cisplatin-ineligible patients to EV alone or EV with pembrolizumab [502]. The ORR was 64.5% (95% CI: 52.7 to 75.1) and 45.2% (95% CI: 33.5 to 57.3) for patients treated with EV+ pembrolizumab (N = 76) and EV monotherapy (n = 73), respectively. The median DOR was not reached for the combination and was 13.2 months for monotherapy. Based on these results enfortumab vedotin plus pembrolizumab has been granted FDA and EMA approval for patients with locally advanced or metastatic UC.

#### 7.7.2.1.2 Patients eligible for combination therapy but not eligible for EV or EV not available

In spite of the very recent results of EV-302/KEYNOTE 39A study, EV will not be 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  $\geq 2$  and pre-existing significant skin disorders. Platinum-based chemotherapy with integration of checkpoint inhibitors represents the preferred option in such patients. The general presumptions for cisplatin- and carboplatin-based therapy remain unchanged in this case and are outlined below.

##### 7.7.2.1.2.1 Patients fit for cisplatin

Cisplatin-containing combination chemotherapy was the standard of care since the late 1980s demonstrating an OS of twelve to fourteen months in different series (for a review see [503]). Methotrexate, vinblastine, adriamycin plus cisplatin and GC achieved survival of 14.8 and 13.8 months, respectively [504]. Overall response rates were 46% for MVAC and 49% for GC. The lower toxicity of GC [201] 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 CR, and two-year OS. However, there is no significant difference in median survival between the two regimens [505, 506]. Further intensification of treatment using paclitaxel, cisplatin and gemcitabine (PCG) triplet regimen did not result in a significant improvement in OS in the intention-to-treat (ITT) population of a phase III RCT, comparing PCG to GC [507]. Similarly, the addition of the angiogenesis inhibitor bevacizumab to GC did not result in OS improvement [508].

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 [504]. In the trials with long-term follow-up, approximately 10-15% of patients with metastatic UC were alive at five years and longer, suggesting a sustained benefit from cisplatin-based chemotherapy in a minority of patients [504, 506].

Carboplatin-containing chemotherapy, without the inclusion of immunotherapy, is not considered to be equivalent to cisplatin-based combinations, and should not be considered interchangeable or standard in patients fit for cisplatin. A comparative analysis of four randomised phase II trials of carboplatin vs. cisplatin combination chemotherapy demonstrated lower CR rates and shorter OS for the carboplatin arms [509]. A retrospective study highlighted the importance of applying cisplatin in cisplatin-eligible patients in order to maintain benefit [510].

##### *Switch maintenance with immunotherapy after platinum-based chemotherapy*

A randomised phase II trial evaluated switch maintenance treatment with pembrolizumab in patients achieving at least stable disease on platinum-based first-line chemotherapy. The primary endpoint of PFS was met (5.4 months vs. 3.0 months, HR: 0.65,  $p = 0.04$ ) [511].

The JAVELIN Bladder 100 study investigated the impact of switch maintenance with the PD-L1 inhibitor avelumab after initial treatment with platinum-gemcitabine chemotherapy. Patients achieving at least stable disease or better after 4–6 cycles of platinum-gemcitabine were randomised to avelumab or best supportive care (BSC). Overall survival was the primary endpoint which improved to 21.4 months with avelumab compared to 14.3 months with BSC (HR: 0.69, 95% CI: 0.56–0.86;  $p < 0.001$ ). Of patients who discontinued BSC and received subsequent treatment, 53% received immunotherapy. Immune-related AEs occurred in 29% of all patients and 7% experienced grade 3 complications [512]. Patient-reported outcomes from JAVELIN Bladder 100 demonstrated no detrimental effect on QoL [513]. After  $\geq 2$  years of follow-up, OS remained significantly longer with avelumab plus BSC vs. BSC alone (HR: 0.76, 95% CI: 0.63-0.91;  $p = 0.0036$ ) [514].

Maintenance IO with avelumab was until recently 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 [496]. This trial tested the addition of nivolumab in combination with gemcitabine/cisplatin (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 co-primary endpoints, PFS and OS were reached with a median PFS of 7.9 vs. 7.6 months (HR: 0.72, 95% CI: 0.59-0.88) and a median OS of 21.7 vs. 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  $\geq 3$  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.

#### 7.7.2.1.2.2 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 [440]. 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 < 60 mL/min and/or PS 2. Severe acute toxicity was 13.6% with GemCarbo vs. 23% with M-CAVI, while the ORR was 42% for GemCarbo and 30% for M-CAVI, respectively [500]. 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.

Combinations of gemcitabine and paclitaxel have been studied as first-line treatment and produced response rates between 38% and 60% but has never been tested in RCTs [515-517]. A randomised phase II trial assessed the efficacy and tolerability profile of two vinflunine-based regimens (vinflunine/gemcitabine vs. vinflunine/carboplatin). Both regimens showed equal ORR and OS with less haematologic toxicity for the combination of vinflunine/gemcitabine [518]. Non-platinum combination chemotherapy is nevertheless not recommended for first-line use in platinum-eligible patients.

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

#### 7.7.2.2 First line therapy in patients not eligible for combination therapy

Limited data exist regarding the optimal treatment for this patient population which is characterised by severely impaired PS (PS > 2) and/or severely impaired renal function (GFR < 30 mL/min) 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, thereby 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 checkpoint inhibitors 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  $\geq 10$  using the Dako 22C33 platform and for atezolizumab as positivity of  $\geq 5\%$  tumour-infiltrating immune cells using Ventana SP142.

Pembrolizumab was tested in 370 patients with advanced or metastatic UC ineligible for cisplatin, showing an ORR of 29% and CR in 7% of patients [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 complete response was achieved in 8.5% of patients, and 15.5% had a partial response [522].

A phase 2 randomised trial (BAYOU) evaluating durvalumab with olaparib or placebo in platinum-ineligible patients with metastatic UC demonstrated no PFS or OS benefit for the addition of olaparib; however, in a secondary analysis of patients with homologous recombination repair gene mutations, PFS was improved with the addition of olaparib as compared to placebo (median PFS was 5.6 months (95% CI: 1.9 to 8.1) versus 1.8 months (95% CI: 1.7 to 2.2), (HR: 0.18, 95% CI: 0.06 to 0.47) [523].

The trials IMvigor 130, Keynote 361 and DANUBE all included an experimental arm with immunotherapy alone using atezolizumab, pembrolizumab and durvalumab, respectively [524-526]. No benefit in terms of PFS or OS for the use of single-agent immunotherapy 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.

#### 7.7.2.3 Results of other trials integrating immunotherapy in the first line setting without OS benefit

In 2020, the results of three phase III trials were published investigating the use of immunotherapy in the first-line setting for platinum-eligible patients. The first trial to report was IMvigor130 investigating the combination of the PD-L1 inhibitor atezolizumab plus platinum-gemcitabine chemotherapy vs. chemotherapy plus placebo vs. atezolizumab alone [524]. The primary endpoint of PFS benefit for the combination vs. chemotherapy alone in the ITT group was reached (8.2 months vs. 6.3 months [HR: 0.82, 95% CI: 0.70–0.96; one-sided, p = 0.007])

while OS was not significant at the interim analysis after a median follow-up of 11.8 months. The small PFS benefit in the absence of an OS benefit has raised questions of its clinical significance. In the final OS analysis from IMvigor130, the PFS benefit did not translate into a significant OS benefit for combination therapy vs. chemotherapy alone [527]. Based on the trial design, the absence of an OS benefit for combination therapy vs. chemotherapy alone precluded formal statistical testing of the atezolizumab monotherapy vs. chemotherapy alone arms; however, a descriptive exploratory analysis did not show a significant improvement in OS with first-line atezolizumab monotherapy compared with platinum-based chemotherapy [528].

The KEYNOTE 361 study had a very similar design using the PD-1 inhibitor pembrolizumab plus platinum-gemcitabine vs. chemotherapy plus placebo vs. pembrolizumab alone. The results of the primary endpoints of PFS and OS for the comparison of pembrolizumab plus chemotherapy vs. chemotherapy plus placebo in the ITT population showed no benefit for the combination [525].

DANUBE compared the immunotherapy combination (IO-IO) of CTLA-4 inhibitor tremelimumab and PD-L1 inhibitor durvalumab with chemotherapy alone or durvalumab alone [526]. The co-primary endpoint of improved OS for the IO-IO combination vs. chemotherapy was not reached in the ITT group nor was the OS improved for durvalumab monotherapy vs. chemotherapy in the PD-L1-positive population.

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

### **7.7.3 Further-line systemic therapy for metastatic disease**

#### **7.7.3.1 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 plus Pembrolizumab 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 following options exist.

#### **7.7.3.2 Chemotherapy**

In patients eligible for combination therapy having received EV plus pembrolizumab, platinum-based chemotherapy with gemcitabine plus cisplatin or carboplatin may be considered; however, data is limited for this new post EV plus pembrolizumab clinical disease state and toxicities, e.g., neuropathy from prior therapy must be taken into consideration in determining a treatment plan. For patients already having received platinum-based chemotherapy with or without immunotherapy 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 re-challenge former platinum-sensitive patients if progression occurred at least six to twelve months after first-line platinum-based combination chemotherapy. A retrospective analysis of 296 patients within the RISC cohort (Retrospective International Study of Cancers of the Urothelium) 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 [529]. 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 [530, 531].

The paclitaxel/gemcitabine combination has shown good response rates in small single-arm studies but no adequate phase III RCT has been conducted [532, 533]. Vinflunine was tested in a phase III RCT and compared against BSC in patients progressing after first-line treatment with platinum-based chemotherapy [534]. The results showed a very modest ORR (8.6%), a clinical benefit with a favourable safety profile and a survival benefit, which was, however, only statistically significant in the eligible patient population (not in the ITT population). A randomised phase III trial evaluated the addition of the angiogenesis inhibitor ramucirumab to docetaxel chemotherapy vs. docetaxel alone, which resulted in improved PFS (4.1 vs. 2.8 months) and higher response rates (24.5% vs. 14%) but no OS benefit was achieved [535, 536].

#### **7.7.3.3 Immunotherapy for platinum-pre-treated patients without previous immunotherapy**

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

Pembrolizumab demonstrated a significant OS improvement as second-line treatment in a phase III RCT leading to EMA and FDA approval. Patients ( $n = 542$ ) were randomised to receive either pembrolizumab monotherapy or chemotherapy (paclitaxel, docetaxel or vinflunine). The median OS with pembrolizumab was

10.3 months (95% CI: 8.0–11.8) vs. 7.4 months (95% CI: 6.1–8.3) with chemotherapy (HR 0.73, 95% CI: 0.59–0.91,  $p = 0.002$ ) independent of PD-L1 expression levels [521, 537].

Atezolizumab was the first checkpoint inhibitor approved by the FDA for metastatic UC based on the results of phase I and II trials [243, 538], 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) did not meet its primary endpoint of improved OS for patients with high PD-L1 expression with 11.1 months (atezolizumab) vs. 10.6 (chemotherapy) months (stratified HR: 0.87, 95% CI: 0.63–1.21,  $p = 0.41$ ) [478].

The PD-1 inhibitor nivolumab was approved by the FDA based on the results of a single-arm phase II trial (CheckMate 275), enrolling 270 platinum pre-treated patients. The primary endpoint of ORR was 19.6%, and OS was 8.74 months for the entire group [539]. The TITAN-TCC study evaluated the safety and activity of nivolumab induction plus high-dose ipilimumab (3 mg/kg) boosts in non-responders (stable or progressive disease) in the second-line treatment of 83 patients with metastatic UC. Fifty (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 [540].

#### 7.7.3.4 *Side-effect profile of immunotherapy*

Checkpoint inhibitors including PD-1 or PD-L1 antibodies and CTLA-4 antibodies have a distinct side-effect profile associated with their mechanism of action leading to enhanced immune system activity. These AEs can affect any organ in the body leading to mild, moderate or severe side effects. The most common organs affected are the skin, GI tract, liver, lung, thyroid, adrenal and pituitary gland. Other systems that may be affected include musculoskeletal, renal, nervous, haematologic, ocular and cardiovascular system. Any change during immunotherapy treatment should raise suspicion about a possible relation to the treatment. The nature of immune-related AEs has been very well characterised and published [541]. 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 [542]. Immunotherapy treatment should be applied and supervised by trained clinicians only to ensure early side effect recognition and treatment. In case of interruption of immunotherapy, re-challenge will require close monitoring for AEs [543].

#### 7.7.4 *Integration of other agents*

##### 7.7.4.1 *Antibody drug conjugates 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 [544]. 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 [545, 546]. Another cohort of the same EV-201 trial demonstrated similar promising results in 91 patients that were cisplatin-ineligible and had received prior IO [547]. A phase III RCT ( $n = 608$ ) comparing EV with single-agent chemotherapy after prior platinum chemotherapy and checkpoint inhibitor immunotherapy demonstrated significant survival benefit of almost four months (12.88 months vs. 8.97 months; HR: 0.7, 95% CI: 0.56–0.89) [548]. The most common treatment-related AEs included alopecia (45%), peripheral neuropathy (34%), fatigue (31%, 7.4%  $\geq$  grade 3), decreased appetite (31%), diarrhoea (24%), nausea (23%) and skin rash (16%, 7.4%  $\geq$  grade 3). The reported 24-month findings from the EV-301 trial confirm the PFS, OS and overall response benefit for EV vs. single-agent chemotherapy [549].

##### 7.7.4.2 *Antibody drug conjugate 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 immunotherapy pre-treated metastatic UC (mUC) patients [544] and achieved an ORR of 27% and a total of 77% had a decrease in measurable disease, median PFS was 5.4 months and median OS 10.9 months [550]. Side effects consisted of haematological toxicities (neutropenia 34%  $\geq$  grade 3; febrile neutropenia 10%  $\geq$  grade 3), fatigue (52%), alopecia (47%), nausea (60%), diarrhea (65%, 10%  $\geq$  grade 3) and decreased appetite (36%) [550]. An updated safety and efficacy analysis for TROPHY-U-01 confirmed these findings [551]. Cohort 3 from TROPHY-U-01 has evaluated the combination of sacituzumab govitecan with pembrolizumab in 41 CPI-naïve patients with metastatic UC progression after platinum-based chemotherapy [552]. The ORR was

41% (20% CR) and median PFS and OS were 5.3 months and 12.7 months, respectively. Grade  $\geq 3$  TRAEs were seen in 61% of patients with neutropenia (37%), leukopenia (20%) and diarrhea (20%) seen most commonly. Sacituzumab govitecan received accelerated FDA approval for metastatic UC with prior platinum and IO pre-treatment; however, the indication has been withdrawn.

#### 7.7.4.3 FGFR inhibition

Genomic profiling of UC has revealed common potentially actionable genomic alterations including alterations in FGFR [553]. Erdafitinib is a pan-FGFR tyrosine kinase inhibitor and the first FDA-approved targeted therapy for mUC with susceptible FGFR2/3 alterations following platinum-containing chemotherapy. The phase II trial of erdafitinib included 99 patients whose tumour harboured an FGFR3 mutation or FGFR2/3 fusion and who had disease progression following chemotherapy [237]. The confirmed ORR was 40% and an additional 39% of patients had stable disease. A total of 22 patients had previously received immunotherapy with only one patient achieving a response, yet the response rate for erdafitinib for this subgroup was 59%. At a median follow-up of 24 months, the median PFS was 5.5 months (95% CI: 4.0–6.0) and the median OS was 11.3 months (95% CI: 9.7–15.2) [237]. Treatment-related AEs of  $\geq$  grade 3 occurred in 46% of patients. Common AEs of  $\geq$  grade 3 were hyponatraemia (11%), stomatitis (10%), and asthenia (7%) and 13 patients discontinued erdafitinib due to AEs, including retinal pigment epithelial detachment, hand-foot syndrome, dry mouth, and skin/nail events. In a long-term follow up, the efficacy and safety profile remained similar with no new safety signals with longer follow-up [554].

The THOR cohort 1 trial, a phase 3 trial of erdafitinib compared with chemotherapy (docetaxel or vinflunine) in patients with metastatic UC with susceptible FGFR3/2 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 [0.47 to 0.88];  $p = 0.005$ ). Median PFS was also longer with erdafitinib than with chemotherapy (5.6 vs. 2.7 months; (HR: 0.58 [0.44 -0.78]) [239]. Treatment-related toxicity grade  $\geq 3$  was similar in the two groups. The most common treatment-related adverse events 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 [0.92-1.51]) [555]. The ORR was 40.0% 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  $\geq 1$  grade 3-4 adverse events.

Based on the THOR cohorts 1 and 2, erdafitinib has received both FDA and EMA approval for the treatment of patients with advanced or metastatic UC with susceptible FGFR3 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 [238]. A phase 2/3 trial of the pan-FGFR inhibitor, rogaratinib vs. chemotherapy in patients with locally advanced or metastatic UC with *FGFR1-3* mRNA overexpression demonstrated similar outcomes as compared to chemotherapy [556]. The increased identification of *FGFR3* mutations/fusion has led to several ongoing trials with different agents and combinations in different disease settings.

#### 7.7.4.4 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 tumors included a cohort of 41 patients with locally advanced or metastatic bladder cancer after  $\geq 1$  systemic treatment or without alternative treatment options [242]. 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. For all patients with BC, the median PFS was 7.0 months and median OS was 12.8 months. For all patients on study across seven tumor cohorts, grade  $\geq 3$  drug-related adverse events 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 tumors 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 2 phase II trials evaluating the safety and efficacy of the antibody drug conjugate Disitamab Vedotin in patients with HER2-positive locally advanced or metastatic UC who have progressed on at least one line of systemic chemotherapy [557]. 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 TRAEs were peripheral sensory neuropathy, leukopenia, AST increased and neutropenia. Ongoing studies are evaluating Disitamab Vedotin as monotherapy and in combinations.

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

The most important advance in recent years has been the recognition of alterations in FGFR3 including mutations and gene fusions as a predictive marker for response to FGFR inhibitors [237]. It is recommended to screen mUC patients ideally at diagnosis of metastatic disease for FGFR3 alterations to plan optimal treatment including trials.

Many efforts have focused on markers for predicting response to immune checkpoint inhibition. Programmed death-ligand 1 expression by immunohistochemistry has been evaluated in many studies with mixed and, so far, inconclusive results. This may in part be related to the use of different antibodies and various scoring systems evaluating different compartments i.e., tumour cells, immune cells, or both. A major limitation of PD-L1 staining relates to the significant proportion of PD-L1-negative patients that respond to immune checkpoint blockade. The predictive value of PD-L1 was not confirmed in large phase III trials evaluating the integration of immunotherapy in the first-line setting for mUC [524-526]. At present, the only indication for PD-L1 testing in mUC is dictated by current EMA approvals and relates to the potential use of immune checkpoint inhibitors as first-line monotherapy in patients unfit for cisplatin-containing chemotherapy.

Another biomarker that has been evaluated for predicting response to immunotherapy is high TMB [245]. Neoantigen burden and TMB have been associated with response to immune checkpoint blockade in several malignancies. High TMB has been associated with response to immune checkpoint inhibitors in metastatic UC in small single-arm trials [243, 246] but was not confirmed so far in RCTs. Other markers that have been evaluated in predicting response to immune checkpoint inhibitors include molecular subtypes, CD8 expression by immunohistochemistry and other immune gene cell signatures. Recent work has focused on the importance of stroma including the role of TGFs in predicting response to immune checkpoint blockade [249, 250].

Based on the recent FDA approval for trastuzumab deruxtecan for patients with pretreated unresectable or metastatic HER2-positive (IHC3+) solid tumors, evaluation of HER2 immunohistochemistry may be performed.

### 7.7.6 **Special situations**

#### 7.7.6.1 *Impact of prior neoadjuvant/adjuvant therapy on treatment sequence*

Peri-operative systemic treatment is increasingly used in UC including cisplatin-based chemotherapy in the neoadjuvant setting for BC and adjuvant platinum-based chemotherapy for upper tract UC [558]. Many ongoing phase III trials investigate the use of immunotherapy in this setting as well (see section 7.6.2). So far, one trial has reported a significant DFS benefit for adjuvant treatment with nivolumab compared with placebo whereas one trial reported no significant benefit using atezolizumab vs. placebo in the same setting [489, 493]. It is expected that a growing number of patients with metastatic UC will have undergone pre-treatment with platinum and/or immunotherapy agents. However, no prospective trials have investigated the treatment of these patients. The choice of treatment depends on the applied peri-operative treatment and the time until relapse. If at least twelve months have passed since the end of peri-operative treatment the same systemic treatment as in treatment-naïve patients is recommended.

#### 7.7.6.2 *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 recently [66] and an expert Delphi survey and consensus conference provided guidance [82]. 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 neuroendocrine carcinoma, urachal adenocarcinoma, SCC and adenocarcinoma should be treated individually.

#### 7.7.6.3 *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 bladder cancer [559]. Studies from other tumour types (prostate cancer, colorectal cancer and lung cancer) suggest possible survival benefit when adding local therapy. In bladder cancer, some retrospective studies suggest a potential survival benefit when incorporating local therapy to the bladder (including radiation therapy over chemotherapy alone) in metastatic disease [560, 561], and when employing metastasis-directed therapy [562-565]. A favourable response to systemic treatment has been proposed as the criterion for selection of patients for any metastasis-directed therapy [559].

A systematic review identified eight studies using SBRT for oligometastatic UC with or without concomitant systemic therapies [566]. In metachronous patients, SBRT delivered with ablative doses (BED10  $\geq$  78 Gy) was associated with a two-year OS rate of 50.7% (95% CI: 35.1-64.4%). The use of sub-ablative SBRT doses (BED10 = 43.2 Gy) in combination with immunotherapy 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 immunotherapy.

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

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

The prevalence of metastatic bone disease (MBD) in patients with advanced/metastatic UC is 30–40% [567]. Interestingly, a recent report described several observations related to 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 men with other differences noted according to patient age and sex [568]. Skeletal complications due to MBD have a detrimental effect on pain and QoL and are also associated with increased mortality [569]. 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 [570]. Denosumab, a fully human monoclonal antibody that binds to and neutralises RANKL (receptor activator of nuclear factor  $\kappa$ B 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 [571]. Patients with MBD, irrespective of the cancer type, should be considered for bone-targeted treatment [569].

Patients treated with zoledronic acid or denosumab should be informed about possible side effects including osteonecrosis of the jaw and hypocalcaemia. Supplementation with calcium and vitamin D is mandatory. Dosing regimens of zoledronic acid should follow regulatory recommendations and have to be adjusted according to pre-existing medical conditions, especially renal function [572]. For denosumab, no dose adjustments are required for variations in renal function.

#### 7.7.8 **Summary: treatment algorithm for metastatic urothelial cancer update 2025**

Figure 7.2 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. The distinction between the two groups is currently based on the eligibility criteria for the pivotal trial EV-302/KEYNOTE 39A. Criteria include ECOG performance status 0-2, GFR  $\geq$  30mL/min and adequate organ functions with eligibility for treatment with EV and Pembrolizumab.

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

With regards 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 checkpoint inhibitors (atezolizumab or pembrolizumab) could be an alternative option.

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

In cases of disease 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 immunotherapy at the time of progression (pembrolizumab).

It is recommended to determine FGFR mutation status before deciding about further-line treatment. Patients with FGFR3 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 plus pembrolizumab in the first-line setting. The optimal sequence of novel agents and potential combinations are the subject of many ongoing trials. It is generally recommended to treat patients within ongoing clinical trials whenever possible.

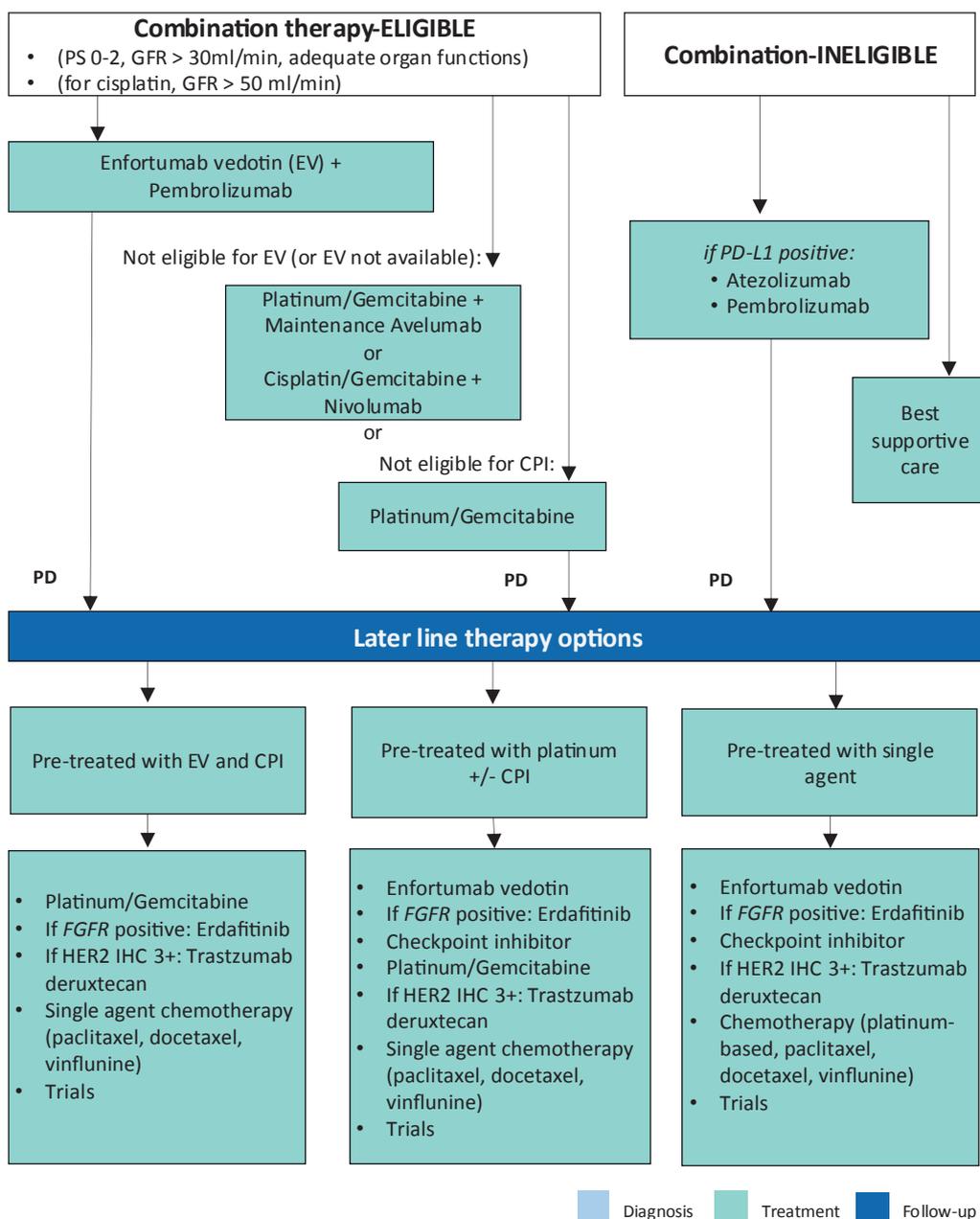
### 7.7.9 Summary of evidence and recommendations for metastatic disease

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 checkpoint inhibitor has demonstrated a significant survival benefit as compared to chemotherapy.	1b
Erdafitinib demonstrated a survival benefit compared to chemotherapy in patients with susceptible FGFR3 genetic alterations who received one or two previous treatments that included a checkpoint inhibitor.	1b
PD-1 inhibitor pembrolizumab has been approved for patients that have progressed during or after previous platinum-based chemotherapy based on the results of a phase III trial.	1b
PD-1 inhibitor atezolizumab is approved for patients with advanced or metastatic UC unfit for cisplatin-based chemotherapy in case of high PD-L1 expression defined as tumour-infiltrating immune cells covering $\geq 5\%$ of the tumour area using the SP142 assay.	1b
PD-1 inhibitor pembrolizumab is approved for patients with advanced or metastatic UC unfit for any platinum-based chemotherapy in case of high PD-L1 expression defined as CPS of $\geq 10$ 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
In a first-line setting, PS and the presence or absence of visceral metastases are independent prognostic factors for survival.	1b
In a second-line setting, negative prognostic factors are: liver metastasis, PS $\geq 1$ and low haemoglobin ( $< 10$ g/dL).	1b
Post-chemotherapy surgery after partial or complete response may contribute to long-term DFS in highly selected patients.	3
Zoledronic acid and denosumab have been approved for supportive treatment in case of bone metastases of all cancer types including UC, as they reduce and delay skeletal related events.	1b
Retrospective case series show some survival benefit for the additional of local therapy (to the primary and to sites of metastases) in oligometastatic bladder cancer.	3

Recommendations	Strength rating
<b>First-line treatment if eligible for combination therapy</b>	
Use antibody drug conjugate enfortumab vedotin (EV) in combination with checkpoint inhibitor (CPI) pembrolizumab.	Strong
<i>If contraindications for EV or EV not available:</i> 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

<i>If contraindications for EV (or EV not available) and cisplatin-eligible:</i> Consider cisplatin/gemcitabine in combination with CPI nivolumab.	Strong
<i>If contraindications for EV and checkpoint inhibitor therapy:</i> Use platinum-containing combination chemotherapy (cisplatin or carboplatin plus gemcitabine).	Strong
<b><i>First-line treatment if not eligible for combination therapy</i></b>	
Consider single agent CPI pembrolizumab or atezolizumab in case of high PD-1 expression (for definitions see text).	Weak
<b><i>Second-line treatment</i></b>	
<b><i>After prior EV + CPI</i></b>	
Offer platinum-containing combination chemotherapy (cisplatin or carboplatin plus gemcitabine).	Weak
If actionable fibroblast growth factor receptor (FGFR) alterations: offer erdafitinib.	Weak
Consider antibody drug conjugate Trastuzumab deruxtecan in case of HER2 over expression (IHC 3+).	Weak
Consider single agent chemotherapy (docetaxel, paclitaxel, vinflunine).	Weak
<b><i>After prior platinum-based chemotherapy +/- CPI</i></b>	
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
<b><i>Further treatment after EV, CPI, platinum-based therapy</i></b>	
General statement: 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 7.2: Flow chart for the management of metastatic urothelial cancer



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

## 7.8 Quality of life

### 7.8.1 Introduction

The evaluation of HRQoL considers physical, psychological, emotional and social functioning. In patients with MIBC, HRQoL is affected, particularly in the physical and social functioning domains [573, 574].

Several questionnaires have been validated for assessing HRQoL in patients with BC, including FACT-G [575], EORTC QLQ-C30/BLM30 [576], SF-36 [577] and the Bladder Cancer Index (BCI) [578]. In spite of these validated questionnaires, there is heterogeneity in the measurements used to assess sexual health. A health questionnaire that covers the entire range of sexual health in bladder cancer patients is currently lacking [579].

Regardless of the which questionnaire is used, assessment of the baseline and post-treatment HRQoL is important. Questionnaires are helpful tools in clinical decision making, but, in addition, data support the prognostic value of baseline HRQoL [580]. In a large population-based study of patients with MIBC and no prior psychiatric history, 31% of all patients with MIBC were diagnosed with a new mental health disorder after their bladder cancer diagnosis [581].

### 7.8.2 **Neoadjuvant chemotherapy**

Two RCTs including patients undergoing NAC have published their HRQoL data [468, 582]. Huddart *et al.*, analysed the subset of patients within the BC2001 trial who underwent NAC prior to (chemo)radiation. Using the FACT-BL questionnaire, no detrimental impact of NAC on HRQoL was observed [468]. Kitamura *et al.*, reported on 64 patients included in the JCOG0209 study who underwent NAC (MVAC vs. MVAC and RC). An overall decline on HRQoL was reported directly following NAC using the FACT-BL questionnaire. However, no difference in HRQoL was observed after the consolidating RC.

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

Two systematic reviews and meta-analyses focused on HRQoL after RC and urinary diversion [366, 583].

*Yang et al.*, 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) [366]. Only three studies reported HRQoL data both pre- and post-operatively. All three studies reported an initial deterioration in overall HRQoL but general health, functional and emotional domains at twelve 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 [583].

*Cerruto et al.*, reported HRQoL comparing ileal conduit with orthotopic neobladder reconstruction [583]. A pooled analysis was performed including eighteen studies (n = 1,553) of which the vast majority were retrospective studies. Although this study was hampered by methodological limitations, no statistical significant difference in overall HRQoL was found.

Overall, no single type of urinary diversion appears to be superior in terms of general HRQoL; rather, the outcome is largely determined by proper patient selection. An older and isolated patient is probably better served with an ileal conduit, whereas a younger patient with a higher level of interest in body image and sexuality is better off with an orthotopic diversion. The patient's choice is the key to the selection of reconstruction method [366].

A number of RCTs comparing ORC with RARC (with either intra- or extracorporeal urinary diversion) have reported their HRQoL data [358, 584-586]. All studies reported no statistical significant difference in HRQoL outcomes between surgical techniques.

### 7.8.4 **Adjuvant therapy**

HRQoL data was reported in the phase 3 Checkmate 274 RCT where patients were randomised for adjuvant nivolumab or placebo after radical surgery for bladder cancer or UTUC. Patients were not pre-treated with NAC. No clinically meaningful deterioration in HRQoL was observed during nivolumab treatment (based on the EORTC QLQ-C30/VAS questionnaire) [491].

### 7.8.5 **Bladder-sparing trimodality therapy**

Health-related QoL data following bladder sparing treatment was collected in a RCT setting [468]. The primary endpoint was the change in the Bladder Cancer Subscale (BLCS), as part of the FACT-BL questionnaire, at one year post-treatment. Questionnaire return rate at one and five years was 70% and 60%, respectively. 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 gender differences were investigated [587]. 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 Bladder Cancer Subscale scores after five years. Addition of chemotherapy did not affect the HRQoL outcomes.

A SR and MA showed a trend in favour of higher mean reported values for global health Score, physical functioning and role functioning for TMT compared to RC [588]. Another retrospective study showed QoL to be good after TMT and in most domains better than after cystectomy [470]. In a secondary analysis of this study, from six HRQoL instruments, there were two responses with a statistically significant difference between women and men - incidence of diarrhea and degree of sexual activity [589]. Fifty percent of women compared to 86% of men reported no diarrhea (p = 0.02). A greater percentage of women 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 men, but not in women.

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 [590]. See section 7.5.4.5 for further discussion of toxicity after TMT.

#### 7.8.6 **Non-curative or metastatic bladder cancer**

In patients with primary non-curative or metastatic disease HRQoL is reduced because of associated micturition problems, bleeding, pain and therefore disturbance of social and sexual life [591]. Beneficial impact of palliative surgery [592], RT [593], and/or chemotherapy on bladder-related symptoms have been described [594].

A HRQoL analysis was performed in platinum-refractory patients who were randomised to pembrolizumab vs. another line of chemotherapy (KEYNOTE-45 trial) [595]. It was reported that patients treated with pembrolizumab had stable or improved global health status/QoL, whereas those treated with investigators' choice of chemotherapy experienced declines in global health [595].

Recently, HRQoL data was presented from cohort 1 of the EV-201 study including 125 patients treated with enfortumab vedotin after failing previous treatment with platinum chemotherapy and anti-PD-1/L1 therapy [596]. Patients who remained on enfortumab vedotin treatment showed no deterioration in HRQoL. In patients with bone metastases at baseline, pain control and possibly pain reduction was observed.

#### 7.8.7 **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 has a negative impact on HRQoL.	2a
There is no distinct difference 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 twelve months post-operatively in most patients.	1b
In patients with MIBC treated with RT, overall HRQoL declines immediately after treatment, and recovers to baseline at six months post-treatment.	1b
Health-related quality of life data are comparable for RARC (with either intracorporeal or extracorporeal urinary diversion) and ORC.	1b
In patients with MIBC treated with RT, concomitant chemotherapy or neo-adjuvant 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 taking into account patient preference, existing comorbidities, tumour variables and coping abilities.	Strong



### 8.2.3 Urothelial recurrences

After RC, the incidence of new urethral tumours was 4.4% (1.3–13.7%). Risk factors for secondary urethral tumours are urethral malignancy in the prostatic urethra/prostate (in men) and bladder neck (in women). Orthotopic neobladder was associated with a significant lower risk of urethral tumours after RC (OR: 0.44) [610].

There is limited data, and agreement, about urethral follow-up, with some authors recommending routine surveillance with urethral wash and urine cytology and others doubting the need for routine urethral surveillance. However, there is a significant survival advantage in men with urethral recurrence diagnosed asymptotically vs. symptomatically, so follow-up of the male urethra is indicated in patients at risk of urethral recurrence [601]. Treatment is influenced by local stage and grade of urethral occurrence. In urethral CIS, BCG instillations have success rates of 83% [611]. In invasive disease, urethrectomy should be performed if the urethra is the only site of disease; in case of distant disease, systemic chemotherapy is indicated [3].

Upper urinary tract UCs occur in 4–10% of cases and represent the most common sites of late recurrence (three-year DFS following RC) [612]. Median OS is 10–55 months, and 60–67% of patients die of metastatic disease [601]. A meta-analysis found that 38% of UTUC recurrence was diagnosed by follow-up investigations, whereas in the remaining 62%, diagnosis was based on symptoms. When urine cytology was used during surveillance, the rate of primary detection was 7% vs. 29.6% with UUT imaging. The meta-analysis concluded that patients with non-invasive cancer are twice as likely to have UTUC as patients with invasive disease [613]. Multifocality increases the risk of recurrence by three-fold, while positive ureteral or urethral margins increase the risk by seven-fold. Radical nephroureterectomy can prolong survival [614].

### 8.3 Time schedule for surveillance

Although, based on low level evidence only, some follow-up schedules have been suggested, guided by the principle that recurrences tend to occur within the first years following initial treatment. A schedule suggested by the EAU Guidelines Panel includes a CT scan (every 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 (> 3 years). In those cases, monitoring of the UUT is mandatory during follow-up. Computed tomography is to be used for imaging of the UUT [613].

The exact time to stop follow-up is not well known and recently a risk-adapted schedule has been proposed, based on the interaction between recurrence risk and competing health factors that could lead to individualised recommendations and may increase recurrence detection. Elderly and very low-risk patients (those with NMIBC or pT0 disease at final cystectomy report) showed a higher competing risk of non-BC mortality when compared with their level of BC recurrence risk. On the other hand, patients with locally-advanced disease or LN involvement are at a higher risk of recurrence for more than twenty years [615]. 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. Recently, a different follow-up scheme for patients with subtype tumours has been proposed [616]. In case of pT0 patients with previous subtype in TURB 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 (> 10 years) since the risk of recurrence will exceed that of non-BC mortality [616]. Future prospective studies are needed to answer the question whether a more intense follow-up for subtypes should be considered.

Furthermore, the prognostic implications of the different sites of recurrence should be considered. Local and systemic recurrences have a poor prognosis and early detection of the disease might not influence survival [617]. Despite this, the rationale for a risk-adapted schedule for BC surveillance appears to be promising and deserves further investigation.

Since data for follow-up strategies are sparse, a number of key questions were included in a recently held consensus project [81, 82]. Outcomes for all statements for which consensus was achieved are listed in section 8.6.

### 8.4 Follow-up of functional outcomes and complications

Apart from oncological surveillance, patients with a urinary diversion need functional follow-up. Complications related to urinary diversion are detected in 45% of patients during the first five years of follow-up. In a series of 131 patients, this rate increased to 94% in those surviving > 15 years [618].

General functional complications are diverse and include: vitamin B12 deficiency, metabolic acidosis, worsening of renal function, urinary infections, urolithiasis and ureteroenteric stricture [619]. Benign ureteroenteric strictures may occur in up to 20% of patients [619]. 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 [617]. Since low vitamin B12 levels have been reported in 17% of patients with bowel diversion, in case of cystectomy and bowel diversion, vitamin B12 levels should be measured annually [81, 82, 620]. In a series of 3,360 patients who underwent RC for MIBC, 29% progressed to advanced chronic kidney disease within twelve months [621].

In a retrospective study comparing various forms of intestinal diversion, ileal conduits had fewer late complications than continent abdominal pouches or orthotopic neobladders [620]. The main long-term complications in ileal conduit patients are stomal complications in up to 24% and functional and/or morphological changes of the UUT in up to 30% of patients [620, 622, 623]. At fifteen years of follow-up, 50% of patients developed UUT changes and 38% developed urolithiasis [624].

The main specific complications in patients with a neobladder are continence problems and emptying dysfunction [601]. Clifford *et al.*, prospectively evaluated continence outcomes in male patients undergoing orthotopic neobladder diversion [625]. Day-time continence increased from 59% at less than three months post-operatively to 92% after twelve to eighteen months. Night-time continence increased from 28% at less than three months post-operatively to 51% after eighteen to 36 months. Also of interest is the urinary bother in females with an orthotopic neobladder. Bartsch and co-workers reported day-time and night-time continence rates of 70.4% and 64.8%, respectively, in 56 female neobladder patients. Emptying dysfunction is especially common in women: approximately two-thirds need to catheterise their neobladder, while almost 45% do not void spontaneously at all [626]. There seems to be a correlation between voiding patterns and nerve preservation; in 66 women bilateral preservation of autonomic nerves decreased the need for catheterisation to between 3.4–18.7% (CI: 95%) [627].

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 [628].

## 8.5 Summary of evidence and recommendations for specific recurrence sites

Site of recurrence	Summary of evidence	Recommendation	Strength rating
Local recurrence	Poor prognosis. Treatment should be individualised depending on the local extent of tumour.	Offer radiotherapy, chemotherapy and possibly surgery as options for treatment, either alone or in combination.	Strong
Distant recurrence	Poor prognosis.	Offer chemotherapy as the first option, and consider metastasectomy or radiotherapy in case of unique metastasis site.	Strong
Upper urinary tract recurrence	Risk factors are multifocal disease, NMIBC/CIS or positive ureteral margins.	See EAU Guidelines on Upper Urinary Tract Urothelial Carcinomas [1].	Strong
Secondary urethral tumour	Staging and treatment should be done as for primary urethral tumour.	See EAU Guidelines on Primary Urethral Carcinoma [3].	Strong

**8.6 EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [81, 82]\***

Consensus statement
After radical cystectomy with curative intent, regular follow-up is needed.
After radical cystectomy with curative intent, follow-up for the detection of second cancers in the urothelium is recommended.
After radical cystectomy with curative intent, follow-up of the urethra with cytology and/or cystoscopy is recommended in selected patients (e.g., multifocality, carcinoma <i>in situ</i> and tumour in the prostatic urethra).
After trimodality treatment with curative intent, follow-up for the detection of relapse is recommended every 3–4 months initially; then after 2-3 years, every six months in the majority of patients.
After trimodality treatment with curative intent, regular cystoscopic evaluation of the bladder wall is needed.
After trimodality treatment with curative intent, follow-up imaging with CT of thorax and abdomen to assess distant recurrence or recurrence outside the bladder is needed.
In patients with a partial or complete response after chemotherapy for metastatic urothelial cancer, regular follow-up is needed. Imaging studies may be done according to signs/symptoms.
In patients treated with radical cystectomy with curative intent and who have a neobladder, management of acid bases household includes regular measurements of pH and sodium bicarbonate substitution according to the measured value.
To detect relapse after radical cystectomy with curative intent, a CT of the thorax and abdomen is recommended up to five years post-operatively.
Vitamin B12 levels have to be measured annually in the follow-up of patients treated with radical cystectomy and bowel diversion with curative intent.

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

*CT = computed tomography.*

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## 10. CONFLICT OF INTEREST

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

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