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EAU Guidelines View

European Association of Urology Guidelines on Muscle-invasive and Metastatic Bladder Cancer: Summary of the 2025 Guidelines

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Abstract

Background and objective: This publication represents a summary of the updated 2025 European Association of Urology (EAU) guidelines for muscle-invasive and metastatic bladder cancer (MMIBC). The aim is to provide practical recommendations on the clinical management of MMIBC with a focus on diagnosis, treatment, and follow-up.

Methods: For the 2025 guidelines, new and relevant evidence was identified, collated, and appraised via a structured assessment of the literature. Databases searched included Medline, EMBASE, and the Cochrane Libraries. Recommendations within the guidelines were developed by the panel to prioritise clinically important care decisions. The strength of each recommendation was determined according to a balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including the certainty of estimates), and the nature and variability of patient values and preferences.

Key findings and limitations: The key recommendations emphasise the importance of thorough diagnosis, treatment, and follow-up for patients with MMIBC. The guidelines

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Transurethral resection
Urothelial carcinoma

stress the importance of a multidisciplinary approach to the treatment of MMIBC patients and the importance of shared decision-making with patients. The key changes in the 2025 muscle-invasive bladder cancer (MIBC) guidelines include the following: a new recommendation for the use of susceptible FGFR3 alterations to select patients with unresectable or metastatic urothelial carcinoma for treatment with erdafitinib; significant adaption and update of the recommendations for pre- and postoperative radiotherapy and sexual organ–preserving techniques in women; new recommendation related to radical cystectomy and extent of lymph node dissection based on the results of the SWOG trial; recommendation related to hospital volume; new recommendations for salvage cystectomy after trimodality therapy and for the management of all patients who are candidates for trimodality bladder-preserving treatment in a multidisciplinary team setting using a shared decision-making process; significant adaption 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; and addition of a new recommendation for metastatic disease regarding the antibody-drug conjugate trastuzumab deruxtecan in case of HER2 overexpression; in addition, removal of the recommendations on sacituzumab govitecan as the manufacturer has withdrawn the US Food and Drug Administration approval for this product; update of the follow-up of MIBC; and full update of the management algorithms of MIBC.

Conclusions and clinical implications: This overview of the 2025 EAU guidelines offers valuable insights into risk factors, diagnosis, classification, treatment, and follow-up of MIBC patients and is designed for effective integration into clinical practice.

1. Introduction

This summary represents the updated European Association of Urology (EAU) guidelines for muscle-invasive and metastatic bladder cancer (MMIBC). The aim is to provide practical recommendations for clinical management of MMIBC, in a multidisciplinary team, with a focus on diagnosis, treatment, and follow-up.

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 make decisions that also take the 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.

2. Methods

For the 2025 MMIBC guidelines, new and relevant evidence has been identified, collated, and appraised through a structured assessment of the literature. A broad and comprehensive scoping exercise covering all areas of the MMIBC guidelines was performed. 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 evidence (including certainty of estimates), and the nature and variability of patient values and preferences. 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 an equivocal balance between benefit and harm, and uncertainty or variability of patient preference [1].

3. Guidelines

3.1. *Epidemiology and aetiology*

Bladder cancer (BC) is the tenth most common cancer overall and seventh most common in men [2]. In the European Union (EU), the age-standardised incidence rate of BC per 100 000 is 20 for men and 4.6 for women. The incidence and mortality rates of BC vary across countries due to differences in risk factors, detection and diagnostic practices, and availability of treatments [3,4].

Smoking is the primary risk factor, while occupational exposure to chemicals in dyes, rubbers, textiles, paints, and leathers is the second risk factor, with a latency period of over 30 yr [5–9].

A link between BC and pelvic radiation exists, though modern techniques may lower secondary malignancy rates, with long-term data pending [10]. Dietary factors and metabolic conditions, such as high blood pressure and triglycerides, are associated with BC in men, while a high body mass index (BMI) appears to be protective. The diabetes-BC link remains unclear, but a meta-analysis found that thiazolidinediones increased the risk, prompting the U.S. Food and Drug Administration (FDA) to advise against prescribing pioglitazone for active BC (Table 1) [11].

Schistosomiasis is strongly linked to bladder urothelial carcinoma (UC) and can progress to squamous cell

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Table 1 – Recommendations for epidemiology and risk factors

Recommendations	Strength rating
Counsel patients to stop active smoking 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

carcinoma (SCC), though improved disease control has reduced SCC rates in endemic areas. The role of chronic urinary tract infections in SCC remains uncertain [12].

Despite BC being more common in men, women present with more advanced disease and have worse survival rates partly due to diagnostic delays rather than treatment differences. In Norway, female patients had worse survival, particularly in the first 2 yr after diagnosis, due to higher T stage at diagnosis [13,14]. Gender differences may also be explained by the differences in oestrogen and androgen levels between men and women [15–17]. A recent population study suggests that a younger age at menopause (≤45 yr) is associated with an increased risk of BC [18].

3.2. Pathology

During transurethral resection, specimens should be taken from the superficial and deep areas of the tumour and sent to the pathology laboratory separately [19]. If biopsies are taken, each biopsy specimen should be submitted separately. In radical cystectomy (RC), bladder fixation must be carried out as soon as possible. The pathologist should describe the location and size of the tumour(s), resection margins, ureters, and urethra, as well as the prostate in men.

All lymph node (LN) specimens should be provided in their totality, separated in clearly labelled containers or en bloc on a board. LNs should be counted and measured on slides; capsular rupture and percentage of LN invasion should be reported, as well as vascular emboli [20,21]. Identification of morphological subtypes is important for prognostic reasons and treatment decisions [22–24].

Subtypes are presented in Table 2 [25,26]. Pathology staging is performed according to the 2017 tumour, node, metastasis (TNM) classification (Table 3).

Table 2 – Urothelial carcinoma (UC) subtypes

1. Urothelial carcinoma (>90% of cases)
2. UC 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 differentiation
13. Pure neuroendocrine carcinoma (including small and large cell carcinomas)

Table 3 – TNM classification of urinary bladder cancer [194]

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

TNM = tumour, node, metastasis.

3.3. Diagnostic evaluation

3.3.1. Primary assessment

For haematuria or urinary symptoms, rectal and vaginal bimanual palpation should be assessed for the detection of masses, best done under anaesthesia. Discrepancies with pT stage after cystectomy (11% clinical overstaging and 31% clinical understaging) should be considered (Table 4) [27].

Patients with a bladder mass should undergo cystoscopy, biopsy, and/or resection for histopathological diagnosis and staging. Before transurethral resection of a bladder tumour (TURBT), a careful description of the cystoscopic findings is necessary (site, size, number, and tumour appearance), including any mucosal abnormalities. Involvement of the prostatic urethra and ducts has been reported in up to one in three male patients, and can be determined by TURBT or frozen section during cystoprostatectomy [28–30]. Diagnosis of a urethral tumour, which may affect the diversion

Table 4 – 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 in situ.	
Record the sampling sites as well as information on tumour size when providing specimens to the pathologist.	

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Table 5 – Recommendations for primary assessment of presumably MIBC[a]

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 tumours, when bladder carcinoma in situ is present or suspected, when there is positive cytology without evidence of a 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 intraoperative frozen section can be omitted.	Strong
In men with a prior positive transurethral prostatic biopsy, subsequent orthotopic neobladder construction should not be denied a priori, unless an intraoperative 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

EAU = European Association of Urology; MIBC = muscle-invasive bladder cancer.
[a] For general information on the assessment of bladder tumours, see EAU guidelines on non–muscle-invasive bladder [195].

choice, should not be based on positive preoperative biopsy findings alone; a frozen section analysis should be part of the RC procedure, particularly in male patients (Table 5) [31,32].

3.3.2. Imaging

The goal of imaging in patients with BC is to: (1) detect bladder tumours, (2) differentiate T1 from T2 tumours as their treatment will differ, (3) determine the presence of any obstruction to the upper urinary tract (UUT), (4) evaluate the extent of locally advanced tumours or spread to LNs, and (5) assess tumour spread to the UUT or other distant organs (Table 6).

3.3.2.1. Detection. Ultrasound can detect bladder tumours and hydronephrosis but cannot rule out all haematuria causes. The DETECT I trial suggests replacing computed tomography (CT) urography with renal and bladder ultrasound for nonvisible haematuria [33].

Table 6 – Role of imaging in treatment planning

Goal	Imaging modality
Differentiate T1 from T2 tumours	MRI using the Vesical Imaging Reporting and Data System 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

CT = computed tomography; LN = lymph node; MRI = magnetic resonance imaging; PET = positron emission tomography; UUT = upper urinary tract.

Table 7 – Recommendations for staging and urothelial markers in MIBC

Recommendations	Strength rating
Staging	
If 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 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
Urothelial markers	
Use susceptible FGFR3 alterations to select patients with unresectable or metastatic urothelial carcinoma for treatment with erdafitinib.	Strong

CT = computed tomography; MIBC = muscle-invasive bladder cancer; MRI = magnetic resonance imaging; TURBT = transurethral resection of a bladder tumour.

3.3.2.2. Local staging. Differentiation of non–muscle-invasive BC (NMIBC) from muscle-invasive BC (MIBC) is crucial for BC treatment. Magnetic resonance imaging (MRI) offers better soft tissue contrast than CT and detects tumour enhancement earlier due to neovascularisation, but it is not yet the standard practice [34–36].

Multiparametric MRI (mpMRI) with the Vesical Imaging Reporting and Data System (VI-RADS) differentiates T1 from T2 bladder tumours accurately [37]. Multiple studies have validated its performance in detecting MIBC [38,39]. A meta-analysis reported 83% sensitivity and 90% specificity, and a recent trial suggested mpMRI as a potential first-line tool for local BC staging over TURBT.

A Delphi consensus study recommends using VI-RADS for MRI interpretation and performing MRI before TURBT for primary staging (Table 7) [40]. For patients with impaired renal function, noncontrast MRI using VI-RADS shows promise, but more evidence is needed before recommendations can be made [41]. While CT offers high spatial resolution and fast acquisition, it cannot distinguish Ta-T3a tumours, but is useful for detecting T3b invasion into perivesical fat and adjacent organs, with accuracy improving in advanced disease [42].

For local UUT staging, CT urography has the highest diagnostic accuracy, with sensitivity of 0.67–1.0 and specificity of 0.93–0.99 [43]. MR urography is an alternative for patients unable to undergo CT urography, particularly when radiation or iodinated contrast is contraindicated, with sensitivity of 0.75 for tumours <2 cm after contrast injection [44].

3.3.2.3. LN staging. CT and MRI cannot detect metastases in normal-sized nodes. Pelvic nodes >8 mm and abdominal nodes >10 mm in short-axis diameter are considered pathologically enlarged [45]. A study found low concordance

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(64.9%) between cN and pN stages (sensitivity: 30%; specificity: 84%) [46]. Fludeoxyglucose-18 (FDG) positron emission tomography (PET)/CT is increasingly used but requires further evaluation [47,48].

3.3.2.4. Distant metastasis. CT and MRI are the preferred methods for detecting lung [49] and liver [50] metastases. The role of FDG-PET/CT in staging MIBC distant metastases remains limited, but a study of 711 patients showed that it provides valuable staging information that may influence clinical management [51].

3.3.2.5. Treatment response. Preoperative MRI can provide valuable insights into treatment response. The high specificity of diffusion-weighted imaging indicates its usefulness in predicting a complete histopathological response accurately, allowing for better patient selection for bladder-sparing protocols [52]. A meta-analysis on ^{18}F-FDG-PET/CT for assessing a tumour response to neoadjuvant chemotherapy (NAC) reported pooled sensitivity of 0.84 and specificity of 0.75. However, the role of PET/CT in evaluating LN involvement after neoadjuvant pembrolizumab did not justify its routine use in cN0 MIBC patients [53].

3.3.2.6. Future perspectives. Potential future application of the VI-RADS score may include the prediction of a response to treatment as well as perioperative outcomes using its modified version: the NAC VI-RADS (nacVI-RADS); however, prospective evidence is warranted [54]. VI-RADS and nacVI-RADS have been proved to accurately predict pre- and postpembrolizumab responses in MIBC, being strongly associated with pathological downstaging and survival [36]. Radiomic-based imaging techniques are emerging for MIBC prediction, with a meta-analysis reporting 82% sensitivity and 81% specificity [55]. Alternative molecular imaging tracers, such as $^{64}CuCl_2$, [^{68}Ga]Ga-FAPI-46, and ^{68}Ga-FAP-2286, show promising results in nodal staging and restaging [56,57].

3.4. BC and health status

Frailty increases mortality risk and treatment-related complications in cancer patients [58]. A retrospective study (n = 1710) found no significant differences in wound, cardiac, or pulmonary complications between septuagenarians and octogenarians undergoing RC, though mortality was higher in octogenarians (4.3% vs 2.3%) [59]. Sarcopenia is an independent predictor of overall (OS) and cancer-specific (CSS) survival in RC patients [60]. Additional morbidity risk factors include prior abdominal surgery, extravesical disease, prior radiotherapy (RT), female gender, high BMI, and low preoperative albumin [61–64].

Various screening tools assess frailty, including the G8 and Clinical Frailty Scale. Comorbidity evaluation is crucial, with the Charlson Comorbidity Index (CCI) being an independent prognostic factor for OS and cancer-specific mortality (CSM) in BC patients [65–70]. The age-adjusted CCI is used widely for estimating long-term survival in cancer [71]. Assessment of activity levels is essential, with Eastern Cooperative Oncology Group (ECOG) performance status and the Karnofsky index validated for this purpose [72]. Performance scores correlate with OS after RC [69] and palliative chemotherapy [73–75].

3.5. Markers

The most important histopathological prognostic variables after RC and LN dissection (LND) are tumour stage and LN status [76]. Lymphovascular invasion correlates with a 1.5-fold higher risk of recurrence and CSM, independent of pathological stage and perioperative chemotherapy [77]. In patients with organ-confined disease, concomitant carcinoma in situ (CIS) is associated with worse recurrence-free survival (RFS; pooled hazard ratio [HR]: 1.57, 1.12–2.21) and CSM (pooled HR: 1.51, 1.001–2.280) [77]. Tumours located at the prostatic urethra, bladder neck, or trigone have been associated with more nodal metastases and decreased survival [76,78–81].

Several predictive biomarkers have been investigated. Alterations in *FGFR3* have been shown to be associated with a response to fibroblast growth factor receptor (FGFR) inhibitors [82,83]. *FGFR3* alterations are used to select patients suitable for treatment with the FGRF inhibitor erdafitinib [84].

Several efforts have focused on markers for predicting a response to immune checkpoint inhibition. Results of the expression of programmed death-ligand 1 (PD-L1) in patients receiving immunotherapy are conflicting. 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.

Studies have reported on the potential of circulating tumour DNA (ctDNA) to guide the use of adjuvant immunotherapy in UC [85–87]. The on-going IMvigor011 trial is evaluating atezolizumab as adjuvant therapy for ctDNA-positive high-risk MIBC patients after cystectomy [88].

3.6. Disease management

3.6.1. Neoadjuvant therapy

The standard neoadjuvant treatment for patients with T2–4a cN0 M0 urothelial MIBC is cisplatin-based combination chemotherapy (Fig. 1 and Table 8) [89–93]. The advantages of NAC are the early delivery time and in vivo chemosensitivity assessment. A disadvantage is delayed local treatment in patients who do not respond [94–96]. Cisplatin-based NAC results in an 8% absolute improvement in survival at 5 yr [97].

In the GETUG/AFU V05 VESPER randomised controlled trial (RCT), dose-dense methotrexate, vinblastine, Adriamycin, and cisplatin (dd-MVAC) was compared with gemcitabine plus cisplatin (GC). Higher pathological complete responses (CRs) were reported after dd-MVAC, and at 5-yr follow-up, a significant benefit was seen in the neoadjuvant group in favour of dd-MVAC with regard to progression-free survival (PFS; 0.74; 95% confidence interval [CI] 0.55–0.99) and OS (HR 0.71; 95% CI 0.52–0.97) [98]. It is unclear whether patients with non-UC histology will also benefit from NAC. NAC is considered to be beneficial for patients

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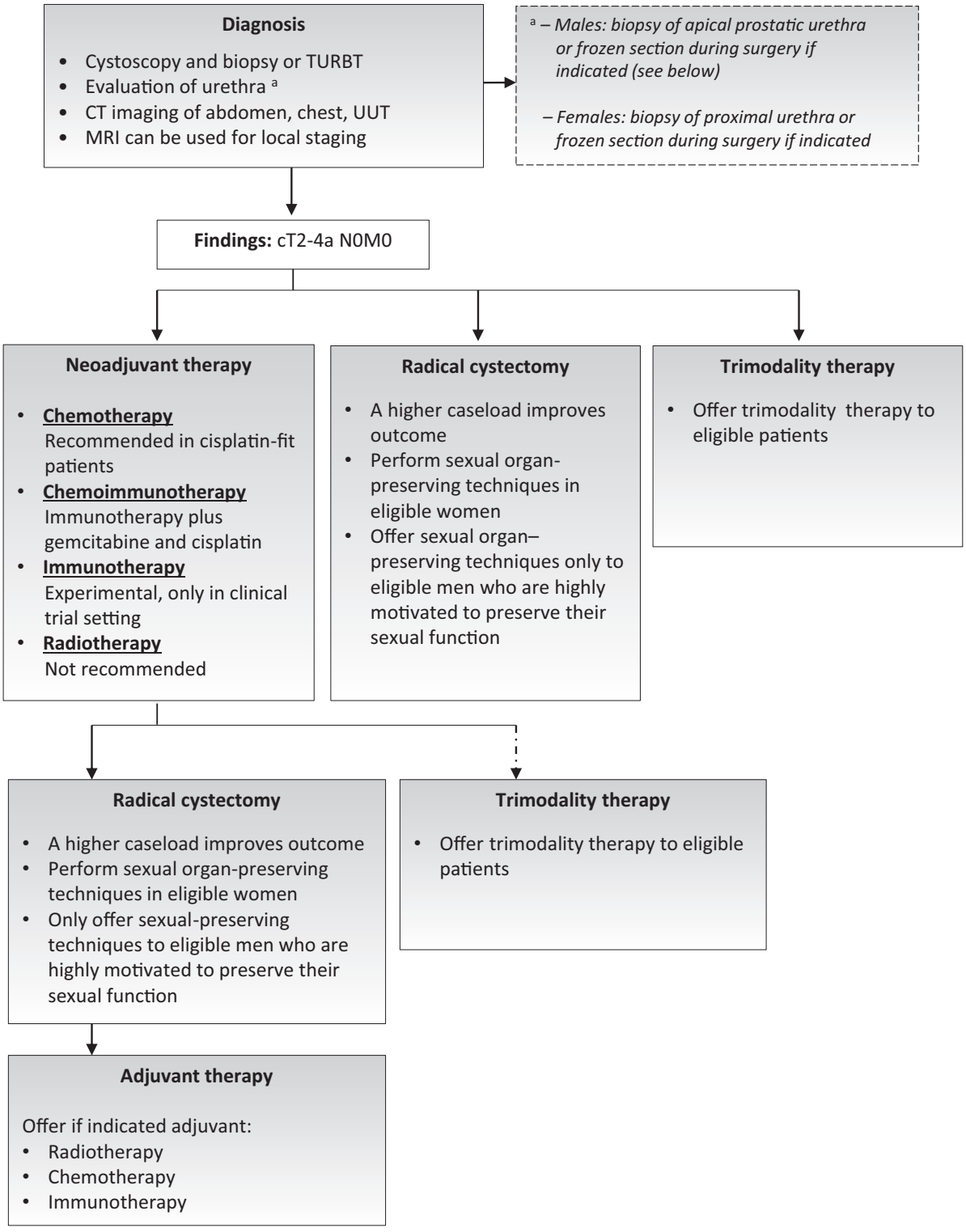

Fig. 1 – Flowchart for the management of T2-T4a N0M0 urothelial bladder cancer. CT = computed tomography; MRI = magnetic resonance imaging; TURBT = transurethral resection of a bladder tumour; UUT = upper urinary tract.

with micropapillary, plasmacytoid, sarcomatoid, and neuroendocrine tumours; however, pure squamous tumours seem to show a poor response [22,99].

Checkpoint inhibitors are increasingly being tested in the neoadjuvant setting, either as monotherapy or combined with chemotherapy or CTLA-4 inhibition. At present, the

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Table 8 – Recommendations for neoadjuvant therapy, perioperative radiotherapy, and sexual organ–preserving techniques in MIBC

Recommendations	Strength rating
Neoadjuvant therapy	
If eligible for cisplatin-based chemotherapy, offer neoadjuvant cisplatin-based combination chemotherapy to patients with muscle-invasive bladder cancer (T2-T4a, cN0 M0).	Strong
Do not offer NAC to patients who are ineligible for cisplatin-based combination chemotherapy.	Strong
Offer only neoadjuvant immunotherapy with checkpoint inhibitors alone to patients within a clinical trial setting.	Strong
Perioperative radiotherapy	
Do not offer preoperative RT for operable MIBC since it will not improve survival.	Strong
Adjuvant RT can be offered following radical cystectomy (pT3b–4 or positive nodes or positive margins) to improve locoregional relapse-free survival, but not overall survival.	Weak
Sexual organ–preserving techniques	
Only offer sexual organ–preserving techniques to eligible men who are highly motivated to preserve their sexual function.	Strong
Select patients based on: 1. Organ-confined disease 2. Absence of any kind of malignancy at the level of the prostate, prostatic urethra or bladder neck	Strong
Perform sexual organ–preserving techniques in eligible women. Select patients based on absence of a tumour in the area to be preserved to avoid positive soft tissue margins.	Strong

MIBC = muscle-invasive bladder cancer; NAC = neoadjuvant chemotherapy; RT = radiotherapy.

results with immunotherapy alone are promising but not yet approved in routine practice.

The NIAGRA randomised phase 3 trial including 1063 patients testing the perioperative addition of durvalumab to neoadjuvant cisplatin/gemcitabine chemotherapy (median follow-up 42.3 mo) has demonstrated significantly improved event-free survival (67.8% with durvalumab compared with 59.8% without; HR 0.68; 95% CI 0.56–0.82; $p < 0.001$) and OS (82.2% and 75.2%, respectively; HR 0.75; 95% CI 0.59–0.93; $p = 0.01$) at 2 yr [100]. Approval for this regimen is pending.

3.6.2. *Perioperative RT*

All RCTs investigating preoperative RT are from several decades ago. A meta-analysis of five RCTs showed a nonsignificant difference in 5-yr survival (odds ratio [OR] 0.71; 95% CI 0.48–1.06) in favour of preoperative RT [101].

Data on adjuvant RT (ART) after RC are also limited. A systematic review evaluating the efficacy of ART for BC or upper tract UC (UTUC) found no clear benefit of adjuvant radiation following radical surgery (eg, cystectomy), although the combination of adjuvant radiation with chemotherapy may be beneficial in locally advanced disease [102].

ART appears to be safe and tolerable after RC when using precise radiation techniques. In an Egyptian RCT, 122 patients were randomised to adjuvant intensity-modulated RT of 50 Gy in 25 fractions after cystectomy or cystectomy alone, the 3-yr adjusted locoregional RFS rate was higher in the ART arm, measuring 81% compared with 71% ($p = 0.0457$); however, OS and distant metastasis-free survival rates were not statistically different [103]. The results of the BART phase 3 trial 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.

3.6.3. *Radical surgery*

RC is recommended in patients with T2-T4a N0M0 disease; very-high-risk, BCG-refractory, BCG-relapsing, and BCG-unresponsive NMIBC; and extensive papillary disease that cannot be controlled with TURBT and intravesical chemotherapy/immunotherapy alone. A delay of >3 mo should be avoided due to the negative effect on OS (HR 134; 95% CI: 1.18–1.53).

For men, standard RC involves removal of the bladder, prostate, seminal vesicles, distal ureters, and regional LNs. Sexual organ–preserving cystectomy techniques can be offered to eligible men who are highly motivated to preserve their sexual function (Table 8). Postoperative potency ranges from 80% to 90%, 50% to 100%, and 29% to 78% for prostate-, capsule-, or nerve-sparing techniques, respectively [104].

In women, standard RC traditionally includes removal of the bladder, entire urethra, adjacent vagina, uterus, distal ureters, and regional LNs. However, the risk of gynaecological organ involvement in females without clinical evidence of non–organ-confined disease is low. Therefore, pelvic organ–preserving techniques, including preservation of the neurovascular bundle, vagina, uterus, ovaries, or combinations thereof, should be considered for eligible patients (Table 8). Preservation of the uterus and vagina also supports neobladder reconstruction, reducing the risk of urinary retention or postoperative prolapse. In patients with pre-existing uterine prolapse, whether isolated or combined with vaginal prolapse, removing the uterus may be beneficial.

3.6.4. *Lymphadenectomy*

The 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 [105].

Two RCTs, the German LEA trial and the US/Canadian SWOG S1011 trial, found that extended LND (including presacral, presciatic, and common iliac nodes up to the aortic bifurcation) does not improve survival compared with standard LND but increases morbidity risk [106,107].

3.6.5. *Robotic-assisted laparoscopic RC*

A systematic review and meta-analysis of eight RCTs reported a slightly longer hospital stay (0.2 d) for open RC (ORC), though regional differences were observed: in four US and two UK trials, ORC resulted in a longer hospital stay (0.6 and 1.5 d, respectively), whereas in two EU-based trials, robotic-assisted RC (RARC) had a longer hospital stay (0.9 d)

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Table 9 – Recommendations for radical cystectomy and urinary diversion

Recommendations	Strength rating
Inform the patient of the advantages and disadvantages of ORC and RARC to allow selection of the proper procedure.	Strong
Select experienced centres, not specific techniques, for both RARC and ORC.	Strong
Perform an LND 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 preoperative bowel preparation.	Strong
Employ "fast track" measurements to reduce the time to bowel recovery.	Strong
Offer pharmacological venous thromboembolism prophylaxis, such as low-molecular-weight heparin to RC patients, starting the 1st day after surgery, for a period of at least 4 wk.	Strong

LND = lymph node dissection; ORC = open radical cystectomy; RARC = robot-assisted radical cystectomy; RC = radical cystectomy.

[108]. ORC was also linked to higher rates of venous thromboembolism (OR 1.8) and transfusion (0.5 blood units). RARC had a longer operative time, with a mean difference of 76 min. However, no differences were found in the 90-d complication rate, postoperative ileus, positive surgical margins, or overall quality of life (QoL), except for improved physical functioning favouring RARC. Additionally, no differences were observed in OS and RFS, with a median follow-up of 36 mo (Table 9).

A Dutch prospective multicentre comparative effectiveness study assessing ORC versus RARC showed that both mean health care and societal costs per patient were significantly higher after RARC [109].

3.6.6. *Urinary diversion*

Ureterocutaneostomy is the simplest form of cutaneous diversion. The operating time, complication rate, blood loss, stay in intensive care, and overall hospital stay for this approach are all lower than in patients treated with an ileal conduit [110]. In frail patients with a solitary kidney who need a supravesical diversion, ureterocutaneostomy is the preferred procedure.

An ileal conduit is the most used urinary diversion method, offering well-known and predictable outcomes. Early complications, typically assessed within a 30-d period in most studies, occur in 48% of patients and include urinary tract infections, pyelonephritis, ureteroileal leakage, and stenosis [111].

According to BC registry data from the Netherlands, Germany, and Spain, orthotopic bladder substitution to the urethra is performed in approximately 10–20% of both male and female patients. Urethral recurrence in neobladder patients seems to be rare (0.8–13.7%) but significantly higher in male patients [112]. These results indicate that neobladders in male and female patients do not compromise the oncological outcome of cystectomy. An invasive urethral tumour prior to cystectomy is a contraindication for a neobladder reconstruction. However, NMIBC in prostatic urethra or bladder neck is not necessarily a contraindication if patients undergo regular follow-up cystoscopy and urinary cytology [113].

Well-informed urinary diversion decisions reduce postoperative regret, regardless of the method chosen [114]. All options should be discussed, considering patient preference, comorbidities, age, and tumour characteristics.

3.6.7. *Perioperative care, morbidity, and mortality*

Patients on Fast Track/Early Recovery After Surgery (ERAS) protocols experience better emotional and physical functioning, with fewer occurrences of wound healing disorders, fever, and thrombosis [115]. Patients on an ERAS protocol experience more pain than those on a traditional protocol because of decreased opioid use, but postoperative ileus decreases [116]. Venous thromboembolism prophylaxis should be part of the ERAS protocol [117]. The 30-d mortality rate is 2–3%, whereas the 90-d mortality rate is 3–8%. A Swedish national database study showed that centralisation of RC resulted in significant reductions in 90-d mortality and reoperation rates [118].

3.6.8. *Palliative cystectomy*

Unresectable T4b tumours may cause severe symptoms such as bleeding, pain, and urinary obstruction, requiring palliative treatments such as RT. If symptom control fails, cystectomy with urinary diversion or diversion alone may be considered. Palliative cystectomy carries a high morbidity (30% severe complications) and 30-d mortality rate of 9%, with 70% mortality at 8 mo [119,120].

3.6.9. *Bladder-sparing treatment*

Although a prospective study including 133 patients showed a 15-yr CSS rate of 76.7% after radical TURBT with negative restaging biopsies [121], TURBT alone should be considered only in patients unfit for or unwilling to undergo cystectomy.

Modern RT techniques with image guidance improve bladder coverage and reduce dose to surrounding tissues. Curative external beam RT (EBRT) for BC typically delivers 64–66 Gy, while a hypofractionated regimen of 55 Gy in 20 fractions is considered noninferior for locoregional control, OS, and late toxicity [122,123]. In a phase 2 study of 55 BC patients (median age 86 yr) unfit for cystectomy or daily RT, a 6-weekly 6 Gy regimen showed good local control, with 17% progressing after 2 yr and acceptable toxicity [124]. A Canadian multicentre study found that pelvic nodal radiation improved survival over bladder-only radiation [125]. In conclusion, although EBRT results seem to have improved over time, EBRT alone does not seem to be as effective as surgery or trimodality therapy (TMT).

Chemotherapy alone rarely produces durable complete remissions and should not be used as primary therapy in localised BC.

TMT combines TURBT, chemotherapy, and RT (Table 10). The addition of radiosensitising chemotherapy is aimed at

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Table 10 – Recommendations for TMT and adjuvant treatment

Recommendations	Strength rating
Trimodality therapy	
Offer radical cystectomy or trimodality bladder-preserving treatments (TMT) as primary curative option for eligible patients since these are more effective than radiotherapy alone.	Strong
Manage all patients who are candidates for TMT in a mutlidisciplinary 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
Adjuvant treatment	
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 and EMA approval only for PD-L1 tumour cell expression ≥1%).	Strong

EMA = European Medicines Agency; FDA = U.S. Food and Drug Administration; TMT = trimodality therapy.

increasing the effectiveness of RT. TMT is generally reserved for patients with smaller solitary tumours, no extensive or multifocal CIS, or only unilateral tumour-related hydronephrosis, and those with good pretreatment bladder function. There are no definitive contemporary data supporting the benefit of using NAC or adjuvant chemotherapy combined with chemoradiation. However, it is reasonable to consider it especially in the setting of more advanced stage or node-positive disease [126]. Radiation is typically delivered in two schedules: the historical RTOG split-course with interval cystoscopy [127] and the more common single-phase approach [128]. Conventional EBRT includes 40–45 Gy to the bladder ± pelvic LNs, with a whole bladder boost to 50–54 Gy and a tumour boost to 60–66 Gy. If no tumour boost is given, treating the whole bladder with a dose of 59.4–66 Gy is also reasonable. Different concurrent chemotherapy regimens, such as cisplatin, mitomycin-C plus 5-fluorouracil, gemcitabine, capecitabine, paclitaxel, and hypoxia modification with carbogen/nicotinamide have been used [127,129–131].

Among TMT series, 5-yr CSS and OS rates vary between 50% and 84% and between 36% and 74%, respectively, with salvage cystectomy rates of 10–30% [128,132–136]. Unfortunately, there are no successfully completed RCTs comparing the outcome of TMT with RC. A systematic review of 57 studies ($n = 30\ 293$) compared long-term survival of TMT and RC [137]. The 10-yr OS rate was 30.9% for TMT and 35.1% for RC ($p = 0.32$), with the mean disease-specific survival (DSS) rates of 50.9% and 57.8%, respectively ($p = 0.26$). For T2 disease, the 10-yr DSS rates were 69% for TMT and 78.9% for RC, and for T3/T4 disease, the rates were 43.5% and 43.1%, respectively. Another retrospective analysis included 722 patients with cT2-T4N0M0 MIBC (440 underwent RC and 282 received TMT). The 5-yr CSS rates for RC and TMT were 81% and 84%, respectively. Salvage cystectomy was performed in 13% of TMT patients [132]. A nationwide study in the Netherlands also found no difference in OS and DFS between patients treated with TMT and RC [138]. These findings support offering TMT to all eligible candidates with MIBC.

NMIBC recurred in 25% of patients after a CR to TMT [139]. Muscle-invasive recurrences occurred in 10–15%, requiring salvage cystectomy [128,132,133,135]. Patients with MIBC with divergent (squamous, glandular, or micropapillary) differentiation appear to have similar CRs, survival outcomes, and salvage cystectomy rates following TMT to those with pure UC and may be considered for TMT-based approaches [140,141]. Patients with predominant SCC or adenocarcinoma may have worse survival outcomes following TMT than those with UC and should be counselled for upfront RC [142,143].

3.6.10. *Adjuvant treatment*

Adjuvant chemotherapy after RC for patients with pT3/4 and/or LN-positive (N+) disease without clinically detectable metastases (M0) is still under debate. A systematic review and meta-analysis of ten RCTs ($n = 1183$) assessed adjuvant cisplatin-based chemotherapy for MIBC [144]. It showed an OS benefit (HR 0.82; 95% CI 0.70–0.96; $p = 0.02$), with a 6% absolute survival improvement at 5 yr (from 50% to 56%; Table 10). Patients should be informed about potential chemotherapy options before RC and the limited evidence for adjuvant chemotherapy.

Three phase 3 RCTs assessed PD-1 or PD-L1 checkpoint inhibitors as monotherapy in muscle-invasive UC. The CheckMate 274 trial ($n = 709$) evaluated adjuvant nivolumab versus placebo for 1 yr in high-risk patients without (pT3, pT4a, or pN+) or with prior cisplatin-based NAC (≥ypT2 or ypN+) [145]. Nivolumab significantly improved median DFS (20.8 months [95% CI 16.5–27.6]) versus placebo (10.8 mo [95% CI 8.3–13.9]; HR 0.70; 98.22% CI 0.55–0.90; $p < 0.001$). The phase 3 AMBASSADOR trial evaluated 1 yr of adjuvant pembrolizumab versus observation in the same patient population. Pembrolizumab significantly improved median DFS (29.6 mo [95% CI 20.0–40.7]) versus observation (14.2 mo [95% CI 11.0–20.2], HR 0.73, $p = 0.003$) [146]. In contrast, the IMvigor010 trial of adjuvant atezolizumab versus observation did not meet its primary DFS endpoint, with the median DFS of 19.4 mo (95% CI 15.9–24.8) versus 16.6 mo (95% CI 11.2–24.8; HR 0.89, $p = 0.24$) [147].

The FDA has approved nivolumab for adjuvant treatment in UC patients at a high risk of recurrence after surgery [148]. The European Medicines Agency (EMA) approval restricts its use in this population only to patients with PD-L1 expression of ≥1% in tumour cells.

3.7. *Metastatic disease*

3.7.1. *First-line systemic therapy for combination therapy–eligible patients*

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. The major criteria include ECOG performance status 0–2, glomerular filtration rate ≥30 ml/min, peripheral neuropathy of grade <2, and

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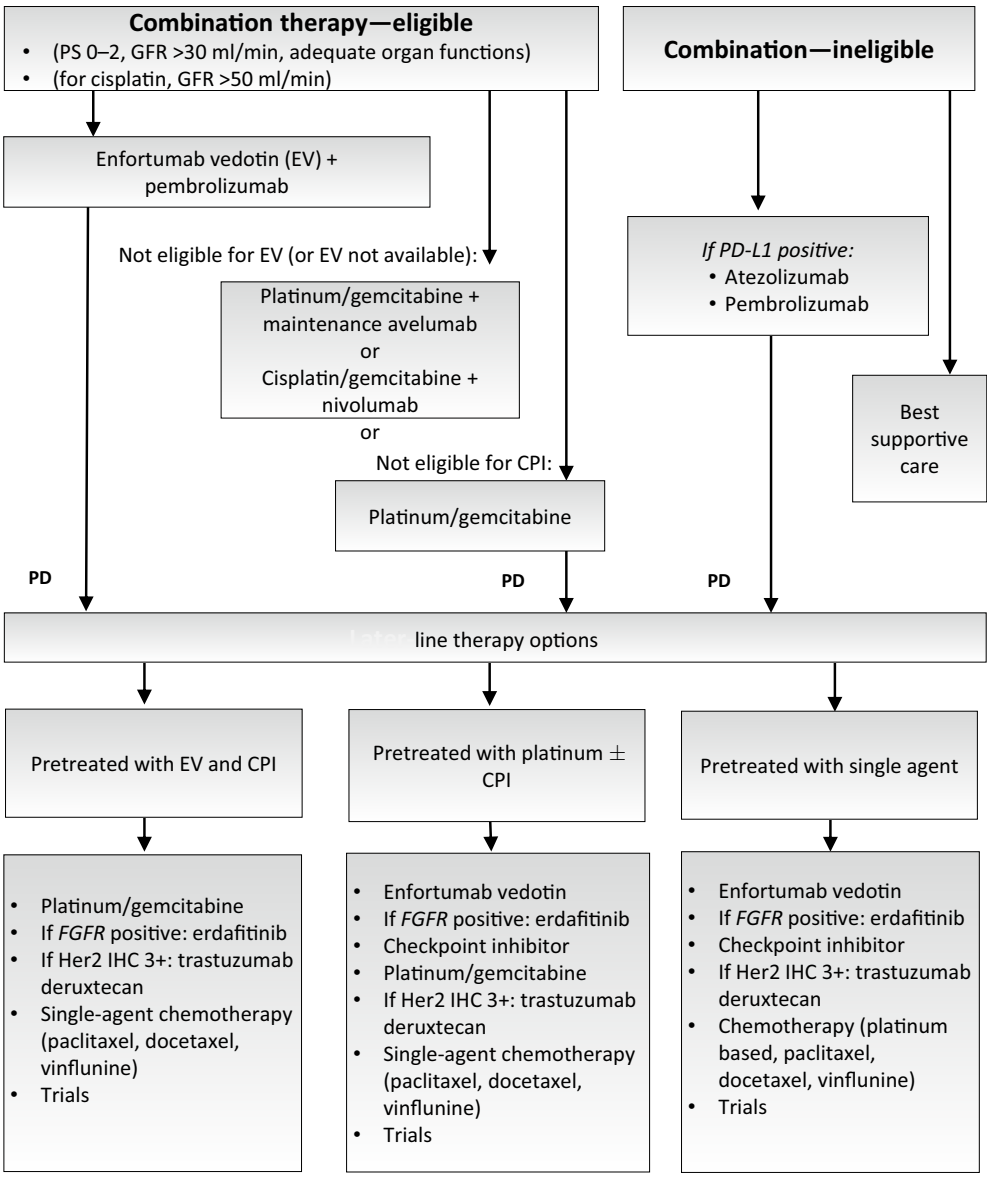

Fig. 2 – Flowchart for the management of metastatic urothelial cancer. CPI = checkpoint inhibitor; EV = enfortumab vedotin; FGFR = fibroblast growth factor receptor; GFR = glomerular filtration rate; PD = programmed death; PD-L1 = programmed death-ligand 1; PS = performance status.

adequate organ functions based on the eligibility for treatment with enfortumab vedotin (EV) and pembrolizumab (Fig. 2).

3.7.1.1. EV plus pembrolizumab. EV plus pembrolizumab is the new standard of care for patients eligible for combination therapy, based on the phase 3 EV-302/KEYNOTE-39A trial. This study compared EV, a nectin-4–targeted antibody-drug conjugate (administered until progression), plus pembrolizumab (up to 35 cycles) against platinum-based chemotherapy (cisplatin or carboplatin) with gemcitabine (up to six cycles) in first-line advanced unresectable or metastatic UC. The median PFS was 12.5 versus 6.3 mo (HR 0.45 [0.38–0.54]) and the median OS was 31.5 versus 16.1 mo (HR 0.47 [0.38–0.58]).

The objective response rate (ORR) was 67.7% (29.1% CR) versus 44.4% (12.5% CR) with platinum-based chemotherapy ($p < 0.00001$). Grade ≥3 treatment-related toxicity occurred in 56% with EV/pembrolizumab versus 70% with chemotherapy. The key EV toxicities include rash, neuropathy, ocular disorders, and hyperglycaemia.

The EV-103 phase 1b/2 study investigated EV plus pembrolizumab in 45 cisplatin-ineligible patients with locally advanced/metastatic UC. It showed a confirmed ORR of 73.3% (15.6% CR) after a median of nine cycles. The median duration of response and OS were 25.6 and 26.1 mo, respectively [149]. EV plus pembrolizumab is approved by the FDA but not yet approved by the EMA for locally advanced or metastatic UC.

3.7.1.2. EV unavailable or ineligible. EV is not available everywhere, and certain patients (eg, those with uncontrolled diabetes, grade ≥2 neuropathy, or significant skin disorders) may be ineligible or may decline treatment.

Table 11 – Definitions of platinum eligibility for first-line treatment of metastatic urothelial carcinoma

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

ECOG PS = Eastern Cooperative Oncology Group performance status; GFR = glomerular filtration rate.

In such cases, platinum-based chemotherapy with or followed by checkpoint inhibitors remains the preferred option, with the standard cisplatin- and carboplatin-eligibility criteria remaining unchanged (Table 11).

Cisplatin-containing combination chemotherapy was the standard of care since the late 1980s, demonstrating OS of 12–14 mo in different series. MVAC and GC achieved survival of 14.8 and 13.8 mo, respectively [150]. Overall response rates were 46% for MVAC and 49% for GC. The lower toxicity of GC than standard MVAC has resulted in GC becoming the standard regimen [74]. Intensification of treatment using the paclitaxel, cisplatin, and gemcitabine (PCG) triplet regimen showed no OS benefit in a phase 3 RCT comparing PCG with GC [151]. Likewise, addition of bevacizumab to GC did not improve OS [152].

Up to 50% of patients are unfit for cisplatin but may tolerate carboplatin [153].

Carboplatin-based chemotherapy is not equivalent to cisplatin-based regimens and should not replace these in cisplatin-eligible patients. A comparative analysis of four phase 2 RCTs showed lower CR rates and shorter OS with carboplatin combinations [154].

The JAVELIN Bladder 100 trial studied maintenance with avelumab after four to six cycles of platinum-gemcitabine chemotherapy. OS improved to 21.4 mo with avelumab versus 14.3 mo with best supportive care (BSC; HR 0.69; $p < 0.001$). Among those on BSC, 53% later received immunotherapy [155]. After $\geq$2 yr of follow-up, OS remained significantly longer with avelumab plus BSC than with BSC alone (HR 0.76; 95% CI 0.63–0.91; $p = 0.0036$) [156]. Platinum-gemcitabine chemotherapy followed by maintenance avelumab is one standard of care option in patients not eligible for EV or if EV is not available.

For cisplatin-eligible patients, the CheckMate 901 trial evaluated nivolumab plus GC followed by nivolumab maintenance versus GC alone [157]. The median PFS (7.9 vs 7.6 mo; HR 0.72) and OS (21.7 vs 18.9 mo; HR 0.78) improved with the addition of nivolumab. Response rates were higher (57.6% vs 43.1%), with 21.7% achieving a CR (duration: 37.1 mo). This regimen is an alternative to GC plus avelumab maintenance for patients ineligible for or without access to EV (Table 12).

Table 12 – Recommendations for metastatic disease

Recommendations	Strength rating
First-line treatment if eligible for combination therapy	
Use the antibody-drug conjugate EV in combination with the CPI pembrolizumab.	Strong
If contraindications for EV or EV not available: offer platinum-containing combination chemotherapy (cisplatin or carboplatin plus gemcitabine) followed by maintenance treatment with the CPI avelumab in patients with at least stable disease on chemotherapy.	Strong
If contraindications for EV (or EV is not available) and if cisplatin eligible: consider cisplatin/gemcitabine in combination with the CPI nivolumab.	Strong
If contraindications for checkpoint inhibitor therapy: use platinum-containing combination chemotherapy (cisplatin or carboplatin plus gemcitabine).	Strong
First-line treatment if not eligible for combination therapy	
Consider the single agent CPI pembrolizumab or atezolizumab in case of high PD-1 expression (for definitions see the text).	Weak
Second-line treatment	
After prior EV + CPI	
Offer platinum-containing combination chemotherapy (cisplatin or carboplatin plus gemcitabine).	Weak
If actionable FGFR alterations: offer erdafitinib.	Weak
Consider the antibody-drug conjugate trastuzumab deruxtecan in case of Her2 overexpression (IHC 3+).	Weak
Consider single agent chemotherapy (docetaxel, paclitaxel, or vinflunine)	Weak
After prior platinum-based chemotherapy ± CPI	
Offer the antibody-drug conjugate enfortumab vedotin.	Strong
If actionable FGFR alterations: offer erdafitinib.	Strong
If no prior CPI: offer pembrolizumab.	Strong
Consider the single agent chemotherapy (docetaxel, paclitaxel, vinflunine)	Weak
Further treatment after EV, CPI, and platinum-based therapy	
General statement: offer treatment in clinical trials. Consider BSC alone if patient is not a candidate for further cancer-specific systemic therapy.	Strong
If actionable FGFR alterations: offer erdafitinib.	Weak

BSC = best supportive care; CPI = checkpoint inhibitor; EV = enfortumab vedotin; FGFR = fibroblast growth factor receptor; GC = gemcitabine plus cisplatin.

3.7.2. *First-line systemic therapy for patients ineligible for combination therapy*

Based on two phase 2 trials [158,159], the EMA approved pembrolizumab and atezolizumab for first-line treatment in cisplatin-ineligible, PD-L1–positive patients. PD-L1 positivity is defined as a combined positive score of $\geq$10 for pembrolizumab (Dako 22C3) and $\geq$5% tumour-infiltrating immune cells for atezolizumab (Ventana SP142). Pembrolizumab ($n = 370$) showed an ORR of 29% with a CR rate of 7% [158,160], while atezolizumab ($n = 119$) had an ORR of 23% with a CR rate of 9% [159].

The RCTs IMvigor 130, Keynote 361, and DANUBE tested single-agent immunotherapy (atezolizumab, pembrolizumab, and durvalumab, respectively) but found no PFS or OS benefit over platinum-based chemotherapy [161–163]. Carboplatin/gemcitabine remains the preferred first-line treatment for chemotherapy-eligible, cisplatin-ineligible patients.

3.7.3. *Later-line systemic therapy options*

With the EV-302/KEYNOTE A39 trial establishing EV plus pembrolizumab as a new first-line standard and CheckMate 901 supporting cisplatin, gemcitabine, and

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nivolumab, selection of subsequent therapy for patients who fail or progress after first-line treatment is increasingly complex. Available options depend on the initial treatment choice.

3.7.3.1. Chemotherapy. Rechallenging platinum-sensitive patients is a reasonable strategy if progression occurs at least 6–12 mo after first-line platinum-based chemotherapy. A retrospective analysis (RISC cohort, $n = 296$) showed that subsequent platinum-based chemotherapy achieved a higher disease control rate (57.4% vs 44.8%, $p = 0.041$) and longer OS (7.9 vs 5.5 mo, $p = 0.035$) than non–platinum-based chemotherapy [164].

The paclitaxel/gemcitabine combination showed promising response rates in small studies but lacks phase 3 RCT validation [165,166]. Vinflunine, tested in a phase 3 RCT versus BSC, showed a modest ORR (8.6%) and survival benefit only in the per-protocol population [167]. A phase 3 trial adding ramucirumab to docetaxel improved PFS (4.1 vs 2.8 mo) and response rates (24.5% vs 14%) but did not extend OS [168,169].

3.7.3.2. Immunotherapy. The checkpoint inhibitors pembrolizumab, nivolumab, atezolizumab, avelumab, and durvalumab have shown similar efficacy and safety in platinum-pretreated patients in phase 1–3 trials.

Pembrolizumab improved OS significantly in a phase 3 RCT, leading to approval by the EMA and FDA. In 542 patients, the median OS was 10.3 mo with pembrolizumab versus 7.4 mo with chemotherapy (HR 0.73, $p = 0.002$), regardless of PD-L1 expression [160,170].

Atezolizumab, initially approved by the FDA, was later withdrawn after the phase 3 IMvigor211 trial ($n = 931$) failed to show OS improvement in PD-L1–positive patients (11.1 vs 10.6 mo, HR 0.87, $p = 0.41$) [171].

Nivolumab was approved by the FDA based on the phase 2 CheckMate 275 trial ($n = 270$), with an ORR of 19.6% and OS of 8.74 mo [172].

3.7.3.3. Monotherapy with antibody-drug conjugates. The randomised phase 3 EV-301 trial using single agent EV (n = 608) demonstrated a significant 4-mo OS benefit for EV over chemotherapy (12.88 vs 8.97 mo; HR 0.7) [173]. Common adverse events (AEs) included alopecia (45%), peripheral neuropathy (34%), fatigue (31%; 7.4% grade ≥3), decreased appetite (31%), diarrhoea (24%), nausea (23%), and skin rash (16%; 7.4% grade ≥3). The 24-mo EV-301 findings confirmed the PFS, OS, and OR benefit over chemotherapy [174].

In the TROPHY-U-01 trial ($n = 113$) sacituzumab govitecan, a Trop-2–targeting antibody-drug conjugate, achieved a 27% ORR, with 77% showing tumour reduction. The median PFS was 5.4 mo and OS was 10.9 mo [175]. Common AEs included neutropenia (34% grade ≥3), febrile neutropenia (10%), diarrhoea (65%; 10% grade ≥3), fatigue (52%), and alopecia (47%). The randomised phase 3 TROPICS-04 trial in patients pretreated with platinum and checkpoint inhibitors did not demonstrate a survival advantage compared with chemotherapy [176].

3.7.3.4. FGFR inhibition. Erdafitinib, a pan-FGFR tyrosine kinase inhibitor, is the first FDA-approved targeted therapy for metastatic UC with FGFR2/3 alterations after platinum chemotherapy. In a phase 2 trial ($n = 99$), the ORR was 40%, and at 24-mo median follow-up, the median PFS was 5.5 mo and OS was 11.3 mo [82]. Treatment-related grade ≥3 AEs occurred in 46% of patients, with hyponatraemia (11%), stomatitis (10%), and asthenia (7%) being most common.

The phase 3 THOR cohort 1 trial compared erdafitinib with chemotherapy (docetaxel or vinflunine) in metastatic UC patients with FGFR3/2 alterations who progressed after prior checkpoint inhibitor therapy. Erdafitinib significantly improved OS (12.1 vs 7.8 mo; HR 0.64; $p = 0.005$) and PFS (5.6 vs 2.7 mo; HR 0.58) over chemotherapy, with similar rates of grade ≥3 treatment-related toxicity. Based on these data, erdafitinib is approved by the FDA and EMA for advanced or metastatic UC with FGFR3 alterations in patients who have received at least one prior PD-1/PD-L1 inhibitor–containing therapy.

3.7.3.5. HER2 targeted agents. HER2 has been a potential target in UC for several years. The DESTINY-PanTumour02 phase 2 trial evaluated trastuzumab deruxtecan in 41 patients with HER2-expressing BC after one or more systemic treatments or without alternative options. The ORR was 39% overall, with 56.3% in HER2 IHC 3+ and 35% in HER2 IHC 2+. The median PFS was 7.0 mo and OS was 12.8 mo. Based on this study, the FDA granted accelerated approval for trastuzumab deruxtecan for treating unresectable or metastatic HER2-positive solid tumours lacking satisfactory treatment options.

3.8. Oligometastatic disease management

Oligometastatic BC is defined as up to three resectable or stereotactic therapy–amenable metastatic sites [177]. Retrospective data indicate potential survival benefits from bladder-directed therapy (eg, radiation) over chemotherapy alone and from metastasis-directed therapy [178–183]. A favourable systemic treatment response is proposed as a selection criterion for metastasis-directed therapy [177].

A systematic review of eight studies on stereotactic body RT (SBRT) for oligometastatic UC reported a 2-yr OS rate of 50.7% with ablative doses (BED10 ≥78 Gy). However, subablative SBRT (BED10 = 43.2 Gy) with immunotherapy showed no significant benefit. Tolerance was good, with only one study reporting grade 3 toxicity in up to 18% of patients [184]. Overall, data on oligometastatic BC remain limited, and optimal management is unclear.

Table 13 – Recommendations on health-related quality of life

Recommendations	Strength rating
Use validated questionnaires to assess health-related quality of life in patients with muscle-invasive bladder cancer, both at baseline and after treatment.	Strong
Discuss the type of urinary diversion taking into account patient preference, existing comorbidities, tumour variables, and coping abilities.	Strong

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Table 14 – Framework for follow-up practice informed by a summary of non–risk-adapted data and supported by >75% agreement for performing a specific follow-up intervention/test

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

According to individual patient's need, depending on post-operative course and adjuvant therapies

Bicarb = bicarbonate; cons. = consensus; CT = computed tomography; GFR = glomerular filtration rate; HB = haemoglobin; IVU = intravenous urography; leuko = leukocyte; Vit = vitamin.

Table 15 – 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 [196].	Strong

CIS = carcinoma in situ; EAU = European Association of Urology; NMIBC = non–muscle-invasive bladder cancer.

3.9. *Quality of life*

Treatment of (metastatic) BC has an impact on health-related QoL (HRQoL), which should be assessed at baseline and after treatment using a validated questionnaire for BC (Table 13). NAC has a temporary impact on HRQoL, as RC and multimodal treatment also seem to have. In the case of surgery, there appears to be no superior urinary diversion type in terms of overall HRQoL, which is rather a result of proper patient selection and the patient's choice [185]. No difference is reported in HRQoL between ORC and RARC (with either intracorporeal or extracorporeal urinary diversion), although data are limited.

A systematic review and meta-analysis suggested better global health, physical, and role functioning with TMT than with RC [186]. A retrospective study also found QoL to be better after TMT than after cystectomy [187]. However, data on HRQoL after TMT remain limited, and further comparative studies, including RC with ileal orthotopic neobladder, are needed [188].

3.10. *Follow-up*

An appropriate disease monitoring schedule should consider recurrence timing, likelihood, site, functional monitoring after urinary diversion, and available management options [189]. However, there is no standardised follow-up regimen after RC for BC. Although evidence on the benefits of early recurrence detection is inconclusive, the EAU Bladder Cancer Guideline Panel identified common post-RC follow-up strategies and developed an expert opinion–based framework (Table 14). The schedule includes a CT scan (every 6 mo) until the 3rd year, followed by annual imaging thereafter. Patients with multifocal disease, NMIBC with CIS, or positive ureteral margins are at a higher risk of developing UTUC, which can develop late (>3 yr). In these cases, monitoring of the UUT by CT urography is mandatory during follow-up [190].

There are limited data and consensus on urethral follow-up, with some recommending routine urethral wash and urine cytology, while others question its necessity. However, men with asymptomatic urethral recurrence have a significant survival advantage over those diagnosed symptomatically, supporting urethral follow-up in at-risk patients [191].

Distant recurrence occurs in up to 50% of MIBC patients after RC, with pathological stage and nodal involvement as key risk factors [192]. The most common recurrence sites are the LNs, lungs, liver, and bone. Nearly 90% of distant recurrences occur within 3 yr after RC, mostly in the first 2 yr, though late recurrences beyond 10 yr have also been reported (Table 15).

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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 5 yr of follow-up. In a series of 131 patients, this rate increased to 94% in those surviving >15 yr [193].

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