EAU GUIDELINES ON MUSCLE-INVASIVE AND METASTATIC BLADDER CANCER

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Introduction

Epidemiology and aetiology

Bladder cancer (BC) is the 7th most commonly diagnosed cancer in males, whilst it drops to 10th position when both genders are considered. Bladder cancer incidence and mortality rates vary across countries due to differences in risk factors, detection and diagnostic practices, and availability of treatments. Tobacco smoking is the most well-established risk factor for BC, causing 50–65% of male cases and 20–30% of female cases. Occupational exposure is the second-most important risk factor for BC.

Staging and classification systems

The 2017 Tumour, Node, Metastasis Classification (TNM) is used for staging (Table 1). For grading, the 1973 and 2004/2016 WHO grading classifications are used.

Table 1: TNM Classification 2017

T - Primary Tumour		
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
Ta	Non-invasive papillary carcinoma	
Tis	Carcinoma *in situ*: 'flat tumour'	
T1	Tumour invades subepithelial connective tissue	
T2	Tumour invades muscle	
	T2a	Tumour invades superficial muscle (inner half)
	T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue	
	T3a	Microscopically
	T3b	Microscopically (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 lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)	
N3	Metastasis in a common iliac lymph node(s)	

M - Distant Metastasis		
M0	No distant metastasis	
	M1a	Non-regional lymph nodes
	M1b	Other distant metastasis

Pathology of MIBC

All muscle invasive urothelial carcinomas (UC) of the bladder are high grade. For this reason, no prognostic information can be provided by grading muscle-invasive bladder cancer (MIBC). Identification of morphological subtypes is important for prognostic reasons and treatment decisions.

1. urothelial carcinoma (more than 90% of all cases);
2. urothelial carcinomas with partial squamous and/or glandular or divergent differentiation;
3. micropapillary UC;
4. nested/mycrocystic variant;
5. large nested variant;
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).

Recommendations for the assessment of tumour specimens	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.	

Diagnostic evaluation

Ultimately, the diagnosis of BC is made by cystoscopy and and transurethral resection of bladder tumours (TURBT). The goal of TURBT is to enable histopathological diagnosis and staging, which requires the inclusion of bladder muscle in the resection specimen.

Recommendations for the primary assessment of presumably invasive bladder tumours*	Strength rating
Describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities during cystoscopy. Use a bladder diagram.	Strong

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

* *For general information on the assessment of bladder tumours, see EAU Guidelines on NMIBC.*

Imaging for staging of MIBC

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

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

MIBC and health status

Complications from radical cystectomy may be directly related to pre-existing comorbidity as well as the surgical procedure, bowel anastomosis, or urinary diversion. Evaluation of comorbidity provides a better indicator of life expectancy in MIBC than patient age. In addition, it is important to screen for frailty and cognitive impairment and provide a Comprehensive Geriatric Assessment (CGA) when needed.

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.	Strong

Markers

There is insufficient evidence to use tumour mutational burden, molecular variants or immune-expression signatures for the management of patients with UC. However, defined alterations of FGFR3 are predictive of response to therapy with the FGFR inhibitor erdafitinib.

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

Disease Management

Neoadjuvant therapy

Neoadjuvant cisplatin-containing combination chemotherapy (NAC) improves overall survival (OS) (8% at five years), irrespective of the type of definitive treatment used. Neoadjuvant treatment may have a major impact on OS in patients who achieve ypT0 or ≤ ypT2.

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. Checkpoint inhibitors have shown significant benefit in patients with unresectable and metastatic BC in the salvage setting and in platinum-ineligible PD-L1+ patients as first-line treatment, but data are still immature.

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 chemotherapy to patients who are ineligible for cisplatin-based combination chemotherapy.	Strong
Only offer neoadjuvant immunotherapy to patients within a clinical trial setting.	Strong

Pre- and post-operative radiotherapy

No contemporary data exists to support that pre-operative radiotherapy (RT) for operable MIBC increases survival. Addition of adjuvant RT to chemotherapy is associated with an improvement in local relapse-free survival following cystectomy for locally-advanced BC (pT3b–4, or node-positive).

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

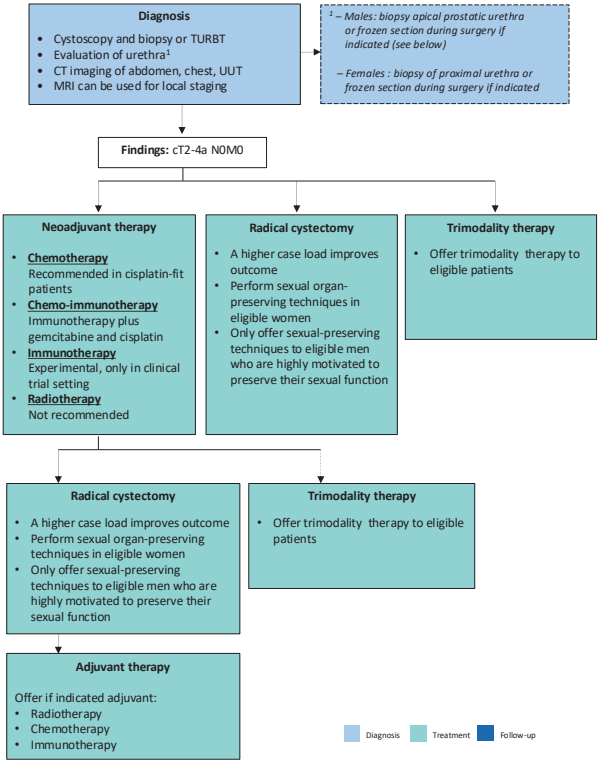
Radical cystectomy and urinary diversion

Radical cystectomy is recommended in patients with T2–T4a, N0M0 disease, very high-risk NMIBC, BCG-refractory, BCG-relapsing and BCG-unresponsive NMIBC, as well as extensive papillary disease that cannot be controlled with TURBT and intravesical chemotherapy/immunotherapy alone. Robot-assisted radical cystectomy (RARC) and open radical cystectomy (ORC) provide similar 90-day complication rates, surgical margin rates, median-term oncological outcomes and quality of life outcomes. Contraindications for orthotopic bladder substitution are positive margins at the level of urethral dissection, positive margins anywhere on the bladder specimen (in both sexes), if the primary tumour is located at the bladder neck or in the urethra (in women), or if tumour extensively infiltrates the prostate (in men).

Recommendations	Strength rating
Radical cystectomy and urinary diversion	
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
Sexual-preserving techniques	
Only offer sexual-preserving techniques to eligible men who are highly motivated to preserve their sexual function.	Strong
Select men for sexual-preserving techniques based on: • organ-confined disease; • 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 tumour in the area to be preserved to avoid positive soft tissue margins.	Strong
Laparoscopic/robotic-assisted laparoscopic cystectomy	
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

Figure 1: Flow chart for the management of T2-T4a N0M0 urothelial bladder cancer



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

Bladder-sparing treatments for localised disease

Transurethral resection of bladder tumour
Transurethral resection of bladder tumour alone is only possible in patients unfit for cystectomy, in whom tumour growth is limited to the superficial muscle layer and restaging biopsies are negative for residual tumour.

External beam radiotherapy
External beam radiotherapy alone should only be considered as a therapeutic option when the patient is unfit for cystectomy or as part of a trimodality bladder-preserving approach. Radiotherapy can also be used to stop bleeding from the tumour when local control cannot be achieved by transurethral manipulation due to extensive local tumour growth.

Chemotherapy
Complete and partial local responses have been reported with cisplatin-based chemotherapy as primary therapy for locally advanced tumours in highly-selected patients.

Trimodality (TMT) bladder-perserving treatment
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. Combined chemotherapy and RT is more effective than RT alone in bladder sparing treatment.

Recommendations	Strength rating
Do not offer transurethral resection of bladder tumour alone as a curative treatment option as most patients will not benefit.	Strong
Do not offer radiotherapy alone as primary therapy for localised bladder cancer.	Strong
Do not offer chemotherapy alone as primary therapy for localised bladder cancer.	Strong
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 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

Palliative and salvage radical cystectomy for metastatic disease

Primary RC in T4b BC is not a curative option. If there are symptoms, RC may be a therapeutic/palliative option. Intestinal or non-intestinal forms of urinary diversion can be used, with or without palliative 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

Adjuvant chemotherapy

Adjuvant cisplatin-based chemotherapy for high-risk patients (pT3, 4 and/or or N+ M0) without neoadjuvant treatment can be associated with improvement in DFS and OS but trials are underpowered to adequately answer this question. 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.

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 ≥ 1%).	Weak

Metastatic disease

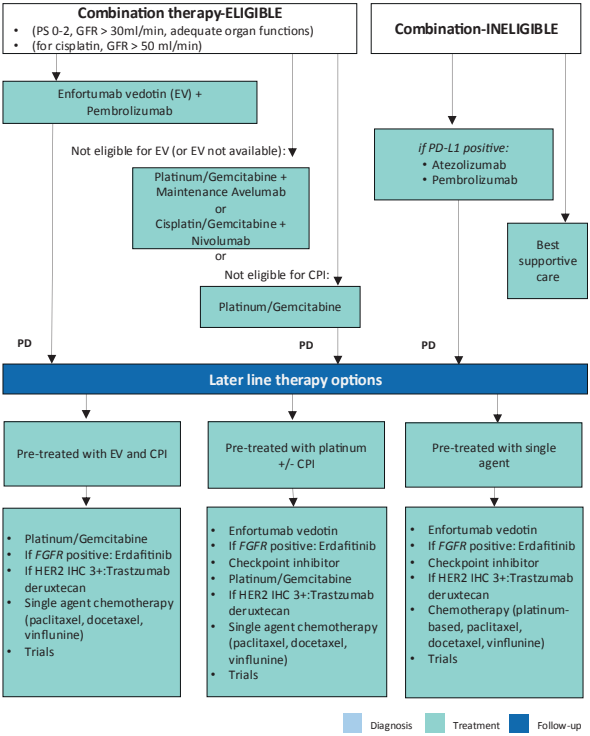
The treatment of metastatic disease has remained largely unchanged since pivotal trials published over 20 years ago set the standard of care for first-line treatment with cisplatin-based combinations. The introduction of immunotherapy using checkpoint inhibitors gradually challanged etablished practice, culminating in practice changing recommendations in 2023 based on the results of two practice changing randomised clinical trials (EV-302/KEYNOTE A39 and Checkmate 901) demonstrating an OS benefit in the first-line setting against platinum-based chemotherapy.

Recommendations	**Strength rating**
First-line treatment if eligible for combination therapy	
Use antibody drug conjugate enfortumab vedotin (EV) in combination with checkpoint inhibitor (CPI) pembrolizumab.	Strong

If contraindications for EV or EV not available: Offer platinum-containing combination chemotherapy (cisplatin or carboplatin plus gemcitabine) followed by maintenance treatment with CPI avelumab in patients with at least stable disease on chemotherapy.	Strong
If contraindications for EV (or EV not available) and cisplatin-eligible: Consider cisplatin/gemcitabine in combination with CPI nivolumab.	Strong
If contraindications for EV and checkpoint inhibitor therapy: Use platinum-containing combination chemotherapy (cisplatin or carboplatin plus gemcitabine).	Strong
First-line treatment if not eligible for combination therapy	
Consider single agent CPI pembrolizumab or atezolizumab in case of high PD-1 expression.	Weak
Second-line treatment	
After prior EV + CPI	
Offer platinum-containing combination chemotherapy (cisplatin or carboplatin plus gemcitabine).	Weak
If actionable fibroblast growth factor receptor (FGFR) alterations: offer erdafitinib.	Weak

Consider antibody drug conjugate Trastuzumab deruxtecan in case of HER2 over expression (IHC 3+).	Weak
Consider single agent chemotherapy (docetaxel, paclitaxel, vinflunine).	Weak
After prior platinum-based chemotherapy +/- CPI	
Offer antibody drug conjugate enfortumab vedotin.	Strong
If actionable FGFR alterations and prior CPI: offer erdafitinib.	Strong
If no prior CPI: offer pembrolizumab.	Strong
Consider single agent chemotherapy (docetaxel, paclitaxel, vinflunine).	Weak
Further treatment after EV, CPI, platinum-based therapy:	
General statement: Offer treatment in clinical trials. Consider best supportive care alone if a patient is not a candidate for further cancer-specific systemic therapy.	Strong
If actionable FGFR alterations: offer erdafitinib.	Weak

Figure 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.

Health-related quality-of-life

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. Several questionnaires have been validated for assessing HRQoL in patients with BC.

Recommendation	Strength rating
Use validated questionnaires to assess health-related quality of life in patients with MIBC, 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

Follow-up

An appropriate schedule for disease monitoring should be based on natural timing of recurrence; probability and site of recurrence; functional monitoring after urinary diversion and the potential available management options. Summary of evidence and recommenations for specific recurrence sites are summaried below.

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 chemo-therapy as the first option, and consider metastasectomy or radiotherapy in case of unique metastasis site.	Strong
Upper urinary tract recurrence	Risk factors are multifocal disease, NMIBC/ CIS or positive ureteral margins.	See EAU Guidelines on Upper Urinary Tract Urothelial Carcinomas.	Strong
Secondary urethral tumour	Staging and treatment should be done as for primary urethral tumour.	See EAU Guidelines on Primary Urethral Carcinoma.	Strong

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-29-5) available on the European Association of Urology website, http://www.uroweb.org/guidelines/.