EAU GUIDELINES ON MUSCLE-INVASIVE AND METASTATIC BLADDER CANCER

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Introduction

Optimal treatment strategies for Muscle-invasive Bladder Cancer (MIBC) require the involvement of a specialist multidisciplinary team and a model of integrated treatment strategies to avoid fragmentation of patient care.

Staging and grading systems

The 2017 TNM (Tumour, Node, Metastasis Classification) 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

Determination of morphological subtypes can be helpful in assessing the prognosis and treatment options of high-grade urothelial carcinomas (UCs) (grade II or grade III) as discussed in these guidelines. The following differentiations are used:

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

Recommendations for the assessment of tumour specimens	Strength rating
Record the depth of invasion (categories pT2a and pT2b, pT3a and pT3b or pT4a and pT4).	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.	

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 the EAU Guidelines on Non-MIBC.*

Recommendations for staging of MIBC	**Strength rating**
In patients with confirmed muscle-invasive bladder cancer, use computed tomography (CT) of the chest, abdomen and pelvis for staging, including some form of CT urography with designated phases for optimal urothelial evaluation.	Strong

Use CT urography, unless it is contraindicated for reasons related to contrast administration or radiation dose; in that case use magnetic resonance imaging.	Strong

Assess health status

Recommendations for the use of comorbidity scales	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

Prospectively validated prognostic and predictive molecular biomarkers will eventually present valuable adjuncts to clinical and pathological data, but until long-term follow-up data from phase III randomised controlled trials are available, many questions currently remain open.

Disease Management

Neoadjuvant therapy

Neoadjuvant cisplatin-containing combination chemotherapy (NAC) improves overall survival (OS) (5–8% at five years), irrespective of the type of definitive treatment used. Patients may respond to NAC and have a favourable pathological response as determined mainly by achieving ypT0, ≤ ypT1, ypN0 and negative surgical margins.

Currently, there are still no tools are available to select patients who have a higher probability of benefitting from NAC. Response after two cycles of treatment is related to outcome. In the future, genetic 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 bladder cancer in the salvage setting and in platinum-ineligible PD-L1+ patients as first-line treatment, but data are still immature.

Recommendations for neoadjuvant therapy	**Strength rating**
If eligible for cisplatin-based chemo-therapy, offer neoadjuvant cisplatin-based combination chemotherapy to patients with MIBC (T2–T4a, cN0 M0).	Strong
Do not offer NAC to patients who are ineligible for cisplatin-based combination chemotherapy.	Strong
Only offer neoadjuvant immunotherapy to patients within a clinical trial setting.	Strong

Recommendations for pre- and post-operative radiotherapy in MIBC	**Strength rating**
Do not offer pre-operative radiotherapy (RT) for operable MIBC since it will only result in down-staging, but will not improve survival.	Strong
Do not offer pre-operative RT when subsequent radical cystectomy (RC) with urinary diversion is planned.	Strong

Consider offering adjuvant radiation in addition to chemotherapy following RC, based on pathologic risk (pT3b–4 or positive nodes or positive margins).	Weak

Radical cystectomy and urinary diversion

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).

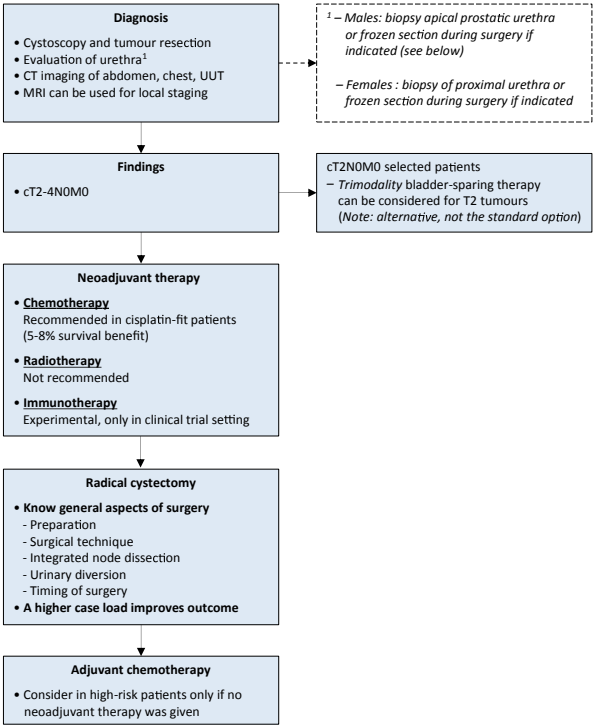
Recommendations for radical cystectomy and urinary diversion	**Strength rating**
Do not delay radical cystectomy (RC) for > 3 months as it increases the risk of progression and cancer-specific mortality, unless the patient receives neoadjuvant chemotherapy.	Strong
Perform at least 10, and preferably > 20, RCs per hospital/per year.	Strong
Before RC, fully inform the patient about the benefits and potential risks of all possible alternatives. The final decision should be based on a balanced discussion between the patient and the surgeon.	Strong
Do not offer an orthotopic bladder substitute diversion to patients who have a tumour in the urethra or at the level of urethral dissection.	Strong

Do not offer sexual-preserving RC to men as standard therapy for MIBC.	Strong
Offer sexual-preserving techniques to men motivated to preserve their sexual function since the majority will benefit.	Strong
Select men for sexual-preserving techniques based on: • organ-confined disease; • absence of any kind of tumour at the level of the prostate, prostatic urethra or bladder neck.	Strong
Do not offer pelvic organ-preserving RC to women as standard therapy for MIBC.	Strong
Offer sexual-preserving techniques to women motivated to preserve their sexual function since the majority will benefit.	Weak
Select women for sexual-preserving techniques based on: • absence of tumour in the area to be preserved to avoid positive soft tissue margins; • absence of pT4 urothelial carcinoma.	Strong
Pre-operative bowel preparation is not mandatory. 'Fast track' measurements may reduce the time to bowel recovery.	Strong
Offer pharmacological prophylaxis, such as low molecular weight heparin to RC patients, starting the first day post-surgery, for a period of 4 weeks.	Strong
Offer RC to patients with T2–T4a, N0M0 disease or high-risk non-MIBC.	Strong

Perform a lymph node dissection as an integral part of RC.	Strong
Do not preserve the urethra if margins are positive.	Strong

Recommendations for laparoscopic/ robotic-assisted laparoscopic cystectomy	**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

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 as a therapeutic option if tumour growth is limited to the superficial muscle layer and if 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 and best supportive care

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

Trimodality treatment

In a highly selected patient population, long-term survival rates of trimodality management of bladder tumours are comparable to those of early cystectomy. Delaying surgery can compromise survival rates.

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

Surgically non-curable tumours

Palliative radical cystectomy for metastatic disease

Primary radical cystectomy (RC) in T4b bladder cancer 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

Adjuvant chemotherapy

Recommendations	Strength rating
Offer adjuvant cisplatin-based combination chemotherapy to patients with pT3/4 and/or pN+ disease if no neoadjuvant chemotherapy has been given.	Strong
Discuss immunotherapy with nivolumab with selected patients with pT3/4 and/or pN+ disease not eligible for, or who declined, adjuvant cisplatin-based chemotherapy.	Strong

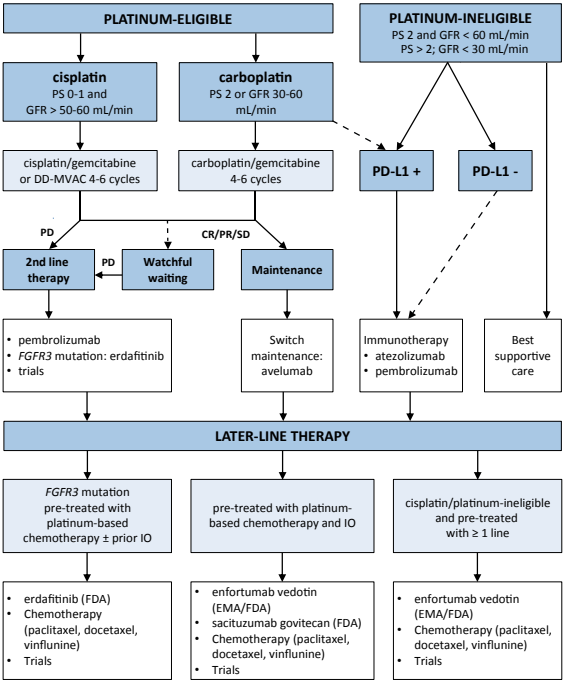
Metastatic disease

Recommendations	Strength rating
First-line treatment for platinum-fit patients	
Use cisplatin-containing combination chemotherapy with GC or HD-MVAC.	Strong
In patients unfit for cisplatin but fit for carboplatin, use the combination of carboplatin and gemcitabine.	Strong
In patients achieving stable disease, or better, after first-line platinum-based chemotherapy, use maintenance treatment with PD-L1 inhibitor avelumab.	Strong
First-line treatment in patients unfit for platinum-based chemotherapy	
Consider checkpoint inhibitors pembrolizumab or atezolizumab in case of high PD-1 expression.	Weak

Second-line treatment	
Offer checkpoint inhibitor pembrolizumab to patients progressing during, or after, platinum-based combination chemotherapy for metastatic disease.	Strong
Further treatment after platinum- and immunotherapy	
Offer antibody drug conjugate enfortumab vedotin as monotherapy to patients with advanced or metastatic UC pre-treated with platinum and immunotherapy.	Strong
Offer treatment in clinical trials testing novel drugs (e.g. sacituzumab govitecan); or in case of patients with *FGFR3* alterations, *FGFR* tyrosine kinase inhibitors.	Strong
Evaluate for *FGFR2/3* genetic alterations for the potential use of erdafitinib in patients with locally advanced or metastatic urothelial carcinoma who have progressed following platinum-containing chemotherapy (including within 12 months of neoadjuvant- or adjuvant platinum-containing chemotherapy).	Weak

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

Figure 2: Flow chart for the management of metastatic urothelial cancer*



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

Health-related quality-of-life

Important determinants of (subjective) quality of life are a patient's personality, coping style and social support.

Recommendation	Strength rating
Use validated questionnaires to assess health-related quality of life in patients with MIBC.	Strong
Discuss the type of urinary diversion taking into account a patient preference, existing comorbidities, tumour variables and coping abilities.	Strong

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-16-5) available to all members of the European Association of Urology at their website, http://www.uroweb.org/guidelines/.