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	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 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 or microcystic UC;
4. nested variant (including large nested variant);
5. lymphoepithelioma-like;
6. plasmocytoid, signet ring, diffuse,
7. some UCs with small-cell carcinomas;
9. sarcomatoid carcinomas;
10. poorly differentiated.

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 top.	
Record the total number of lymph nodes (LNs), the number of positive LNs and extranodal spread.	
Record lymphatic or blood vessel invasion.	
Record the presence of carcinoma *in situ*.	

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
Take a biopsy at the time of the second resection, if no biopsy was taken during the initial procedure.	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-muscle-invasive Bladder Cancer.*

Recommendations for staging of MIBC	**Strength rating**
In patients with confirmed MIBC, use computed tomography (CT) of the chest, abdomen and pelvis as the optimal form of staging.	Strong
Perform a CT urography for upper tract evaluation and for staging.	Strong
For upper tract evaluation, use diagnostic ureteroscopy and biopsy only in cases where additional information will impact treatment decisions.	Strong
Use magnetic resonance urography when CT urography is contraindicated for reasons related to contrast administration or radiation dose.	Strong
Use CT or magnetic resonance imaging (MRI) for staging locally advanced or metastatic disease in patients in whom radical treatment is considered.	Strong

Use CT to diagnose pulmonary metastases. Computed tomography and MRI are generally equivalent for diagnosing local disease and distant metastases in the abdomen.	Strong

Prognosis

Recommendations for the use of comorbidity scales	Strength rating
Base the decision on bladder-sparing treatment or radical cystectomy in elderly/frail patients with invasive bladder cancer on tumour stage and comorbidity.	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

Disease Management

Recommendations for treatment failure of non-muscle-invasive bladder cancer	Strength rating
Discuss immediate radical treatment (radical cystecomy [RC]) with patients at the highest risk of progression (i.e. high grade, multifocality, carcinoma *in situ*, and tumour size, as outlined in the EAU Guidelines for Non-muscle-invasive Bladder Cancer).	Strong
Offer RC to patients with BCG-unresponsive tumours.	Strong

Offer patients with BCG-unresponsive tumours, who are not candidates for RC due to comorbidities, preservation strategies (intravesical chemotherapy, chemotherapy and microwave-induced hyperthermia, electromotive administration of chemotherapy, intravesical- or systemic immunotherapy; preferably within clinical trials).	Weak

Neoadjuvant therapy

Neoadjuvant cisplatin-containing combination chemotherapy (NAC) improves overall survival (5-8% at five years), irrespective of the type of definitive treatment used. Currently, 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**
Offer neoadjuvant chemotherapy (NAC) for T2-T4a, cN0M0 bladder cancer. In this case, always use cisplatin-based combination therapy.	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 with urinary diversion is planned.	Strong

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).

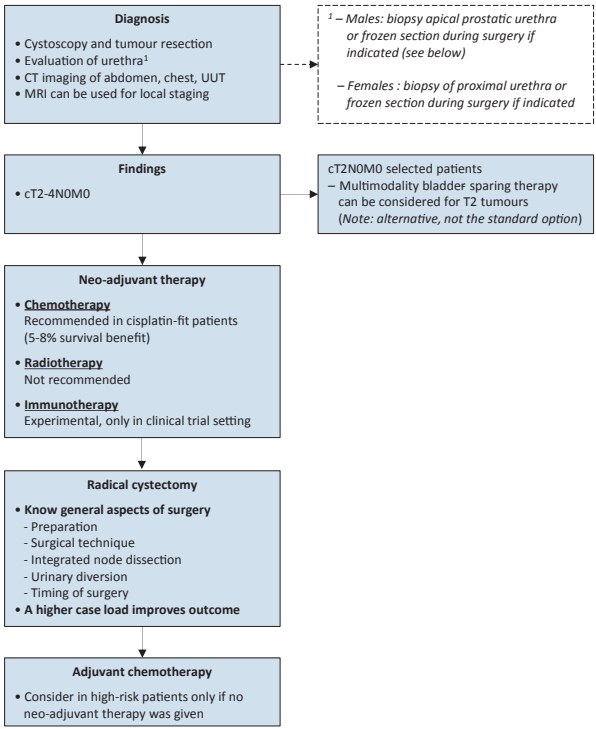
Recommendations for radical cystectomy and urinary diversion	Strength rating
Do not delay radical cystectomy (RC) for > 3 months as it increases the risk of progression and cancer-specific mortality.	Strong
Perform at least 10, and preferably > 20, RCs per hospital/per year.	Strong

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 radical cystectomy 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 radical cystectomy 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: • organ-confined disease; • absence of tumour in bladder neck or urethra.	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 in T2-T4a, N0M0, and high-risk non-muscle-invasive bladder cancer.	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 a multimodality 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.

Multimodality treatment

In a highly selected patient population, long-term survival rates of multimodality treatment 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 multi-modality treatments (MMT) as primary curative therapeutic approaches since they are more effective than radiotherapy alone.	Strong
Offer MMT as an alternative to selected, well-informed and compliant patients, especially for whom radical cystectomy is not an option.	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 inoperable locally advanced tumours (T4b).	Weak
Offer palliative cystectomy to patients with symptoms.	Weak

Adjuvant chemotherapy

Recommendation	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
Only offer immunotherapy with a check-point inhibitor in a clinical trial setting.	Strong

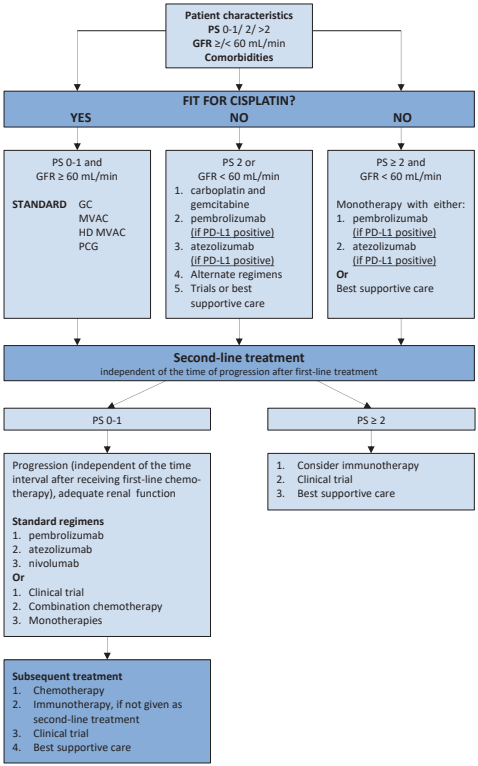
Metastatic disease

Recommendations	Strength rating
First-line treatment for cisplatin-eligible patients	
Use cisplatin-containing combination chemotherapy with GC, MVAC, preferably with G-CSF, HD-MVAC with G-CSF or PCG.	Strong
Do not offer carboplatin and non-platinum combination chemotherapy.	Strong
First-line treatment in patients ineligible (unfit) for cisplatin	
Offer checkpoint inhibitors pembrolizumab or atezolizumab to PD-L1-positive patients.	Strong

Offer carboplatin combination chemotherapy if PD-L1 is negative.	Strong
Second-line treatment	
Offer checkpoint inhibitor pembrolizumab to patients progressing during, or after, platinum-based combination chemo-therapy for metastatic disease. Alternatively, offer treatment within a clinical trial setting.	Strong
Offer zoledronic acid or denosumab for supportive treatment in case of bone metastases.	Weak
Only offer vinflunine to patients for metastatic disease as subsequent-line treatment if immunotherapy, or combination chemotherapy, or FGFR3-inhibitor therapy, or inclusion in a clinical trial is not feasible.	Weak

GC = gemcitabine plus cisplatin; G-CSF = granulocyte colony-stimulating factor; FGFR = fibroblast growth factor receptor; HD-MVAC = high-dose methotrexate, vinblastine, adriamycin plus cisplatin; PCG = paclitaxel, cisplatin, gemcitabine.

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



GC = gemcitabine plus cisplatin; GFR = glomerular filtration rate; HD MVAC = high-dose methotrexate, vinblastine, adriamycin plus cisplatin; MVAC = methotrexate, vinblastine, adriamycin plus cisplatin; PCG = paclitaxel, cisplatin, gemcitabine; PS = performance status.

Health-related quality-of-life (HRQoL)

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 HRQoL in patients with MIBC.	Strong
Offer a continent urinary diversion unless a patient's comorbidities, tumour variables and coping abilities present clear contraindications.	Strong
Pre-operative patient information, patient selection, surgical techniques, and careful post-operative follow-up are the cornerstones for achieving good long-term results.	Strong
Provide clear and exhaustive information on all potential benefits and side-effects, allowing patients to make informed decisions. Encourage patients to actively participate in the decision-making process.	Strong

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-07-3) available to all members of the European Association of Urology at their website, http://www.uroweb.org/guidelines/.