

MUSCLE-INVASIVE AND METASTATIC BLADDER CANCER

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J.A. Witjes (chair), E. Compérat, N.C. Cowan, G. Gakis,
M. De Santis, T. Le Bret, M.J. Ribal, A. Sherif

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Introduction

Optimal treatment strategies for MIBC require the involvement of a specialist multidisciplinary team and a model of integrated care to avoid fragmentation of patient care.

Staging system

The UICC 2009 TNM (Tumour, Node, Metastasis Classification) is used for staging.

Table 1: 2009 TNM classification of urinary bladder cancer**T - Primary tumour**

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma <i>in situ</i> : 'flat tumour'
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
T2a	Tumour invades superficial muscle (inner half)
T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue
T3a	Microscopically
T3b	Microscopically (extravesical mass)
T4	Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostate, uterus or vagina
T4b	Tumour invades pelvic wall or abdominal wall

N - 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
M1	Distant metastasis

Table 2: WHO grading 1973 and 2004

(Both classifications are used for the current guidelines since most of the retrospective studies were based on the old WHO 1973 grading system).

1973 WHO grading

Urothelial papilloma

Grade 1: well differentiated

Grade 2: moderately differentiated

Grade 3: poorly differentiated

2004 WHO grading

Urothelial papilloma

Papillary urothelial neoplasm of low malignant potential (PUNLMP)

Low-grade papillary urothelial carcinoma

High-grade papillary urothelial carcinoma

Morphological subtypes can be important for helping with prognosis and treatment decisions. Currently the following differentiation is used:

1. Urothelial carcinoma (more than 90% of all cases)
2. Urothelial carcinomas with squamous and/or glandular partial differentiation
3. Micropapillary urothelial carcinoma
4. Nested carcinoma
5. Some urothelial carcinomas with trophoblastic differentiation
6. Small cell carcinomas
7. Spindle cell carcinomas.

Recommendations for assessing tumour specimens*Mandatory evaluations*

- Histological subtype
- Depth of invasion
- Resection margins, including CIS

- Extensive lymph-node representation

Optional evaluation

- Bladder wall blood vessel invasion
- CIS, carcinoma *in situ*.

Specific recommendations for primary assessment of presumably invasive bladder tumours

(General information for assessment of bladder tumours, see EAU Guidelines on Non-muscle-invasive Bladder cancer)

Recommendations	GR
Cystoscopy should describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities. A bladder diagram is recommended.	C
Biopsy of the prostatic urethra is recommended for cases of bladder neck tumour, when bladder CIS 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. If biopsy is not performed during the initial procedure, it should be completed at the time of the second resection.	C
In women undergoing a subsequent orthotopic neobladder, procedure information is required (including a histological evaluation) of the bladder neck and urethral margin, either prior to, or at the time of cystoscopy.	C
The pathological report should specify the grade, the depth of tumour invasion and whether the lamina propria and muscle tissue are present in the specimen.	C

Recommendations for staging of MIBC	GR
In patients with confirmed muscle-invasive bladder cancer, CT of the chest, abdomen and pelvis is the optimal form of staging, including excretory-phase CT urography for complete examination of the upper urinary tracts.	B
Excretory-phase CT urography is preferred to MR urography for diagnosing UTUCs in terms of greater diagnostic accuracy, less cost, and greater patient acceptability. MR urography is used when CT urography is contra-indicated for reasons related to contrast administration or radiation dose.	C
Ureteroscopic-guided biopsy is recommended for histopathological confirmation of diagnosis in the preoperative assessment of UTUC.	C
CT or MRI is recommended for staging locally advanced or metastatic disease in patients in whom radical treatment is being considered.	C
CT and MRI are generally equivalent in diagnosing local and distant abdominal metastases but CT is preferred to diagnose pulmonary metastases.	C

Treatment failure of non-muscle invasive bladder tumours

Recommendations for treatment failure of non-muscle-invasive bladder cancer	GR
In all T1 tumours at high risk of progression (i.e. high grade, multifocality, carcinoma <i>in situ</i> , and tumour size, as outlined in the EAU guidelines for Non-muscle-invasive bladder cancer), immediate radical treatment is an option.	B
In all T1 patients failing intravesical therapy, radical treatment should be offered.	B

Muscle-invasive bladder cancer - Radical Surgery and Urinary Diversion

Conclusions	LE
For muscle-invasive bladder cancer radical cystectomy is the curative treatment of choice.	3
A higher case load reduces morbidity and mortality of cystectomy.	3
There is data to support that an extended LND (versus a standard or limited LND) improves survival after radical cystectomy.	3
Radical cystectomy in both sexes must not include the removal of the entire urethra in all cases, which may then serve as outlet for an orthotopic bladder substitution.	3
Terminal ileum and colon are the intestinal segments of choice for urinary diversion.	3
The type of urinary diversion does not affect oncological outcome.	3
Laparoscopic and robotic-assisted laparoscopic cystectomy is feasible but still investigational.	3
In patients with invasive bladder cancer older than 80 years cystectomy is an option.	3
Surgical outcome is influenced by comorbidity, age, previous treatment for bladder cancer or other pelvic diseases, surgeon and hospital volumes of cystectomy, and type of urinary diversion.	2
Surgical complications of cystectomy and urinary diversion should be reported in a uniform grading system. Currently, the best-adapted, graded system for cystectomy is the Clavien grading system.	2

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	GR
Radical cystectomy is recommended in T2-T4a, N0 M0, and high risk non-muscle-invasive BC.	A*
Do not delay cystectomy more than 3 months since it increases the risk of progression and cancer-specific death.	B
Pre-operative radiotherapy is not recommended in case of subsequent cystectomy with urinary diversion.	A
Lymph node dissection should be an integral part of cystectomy. An extended LND is recommended.	B
The urethra can be preserved if margins are negative. If no bladder substitution is attached, the urethra must be checked regularly.	B
Laparoscopic and robot-assisted laparoscopic cystectomy are both options. However, current data have not sufficiently proven the advantages or disadvantages for both oncological and functional outcomes of laparoscopic and robotic-assisted laparoscopic cystectomy.	C
Before cystectomy, the patient should be fully informed about the benefits and potential risks of all possible alternatives, and the final decision should be based on a balanced discussion between patient and surgeon.	B

The decision regarding bladder sparing or radical cystectomy in the elderly/geriatric patient with invasive bladder cancer should be based on tumour stage and comorbidity best quantified by a validated score, such as the Charlson score.	B
Pre-operative bowel preparation is not mandatory, 'fast track' measurements may reduce the time of bowel recovery.	C
An orthotopic bladder substitute should be offered to male and female patients lacking any contraindications and who have no tumour in the urethra and at the level of urethral dissection.	B

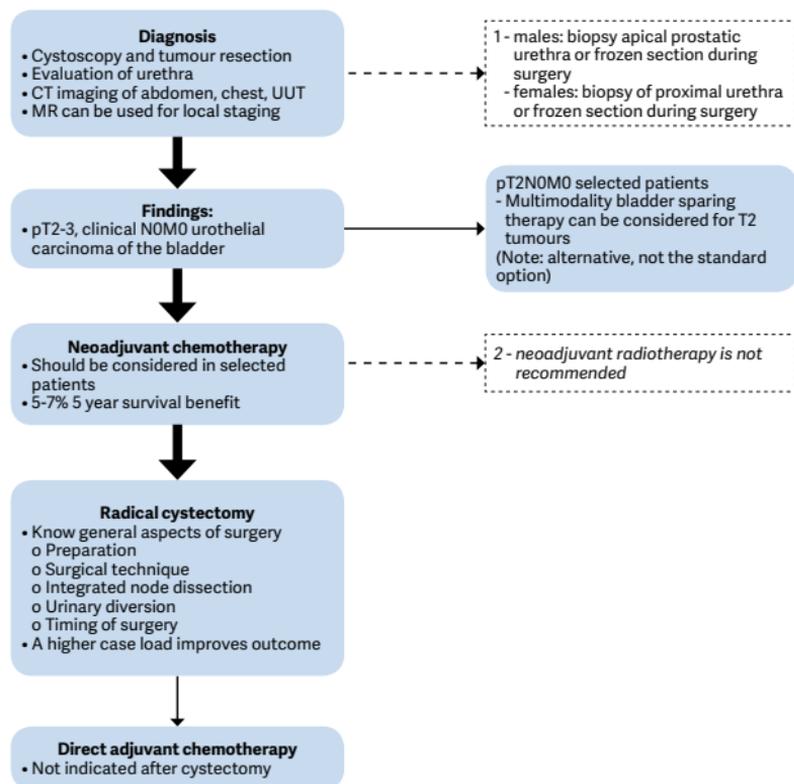
**Upgraded following panel consensus*

Neoadjuvant chemotherapy

Neoadjuvant cisplatin-containing combination chemotherapy improves overall survival, irrespective of the type of definitive treatment (LE: 1a). It has its limitations regarding patient selection, current development of surgical technique, and current chemotherapy combinations. In current routine clinical practice, it is difficult to select patients who will respond to neoadjuvant chemotherapy due to the lack of an applicable test. In the future, genetic markers, in a 'personalized medicine' setting, are expected to make it easier to select patients for treatment and to differentiate responders from non-responders.

Recommendations	GR
Neoadjuvant chemotherapy is recommended for T2-T4a, cN0M0 bladder cancer and should always be cisplatinum-based combination therapy.	A
Neoadjuvant chemotherapy is not recommended in patients with PS \geq 2 and/or impaired renal function.	B
In case of progression under neoadjuvant chemotherapy, this treatment should be discontinued.	

Fig. 1: Flowchart for the management for T2-T4a NOMO urothelial bladder cancer



Bladder-sparing treatments for localised disease

Transurethral resection of bladder tumour (TURB)

TURB alone is only possible as a therapeutic option if tumour growth is limited to the superficial muscle layer and if re-staging biopsies are negative for residual tumour.

External beam radiotherapy

External beam radiotherapy alone should only be consid-

ered 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 because of extensive local tumour growth (LE: 3).

Surgically non-curable tumours

Palliative cystectomy for metastatic disease

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

Recommendations	LE	GR
In patients with inoperable locally advanced tumours (T4b), primary radical cystectomy is a palliative option and cannot be offered as curative treatment.		B
In patients with symptoms palliative cystectomy may be offered.		
Prior to any further interventions, surgery-related morbidity and quality-of-life should be fully discussed with the patient.	3	B

Chemotherapy and best supportive care

With cisplatin-based chemotherapy as primary therapy for locally advanced tumours in highly selected patients, complete and partial local responses have been reported. (LE: 2b).

Recommendation	GR
Chemotherapy alone is not recommended as primary therapy for localised bladder cancer.	A

Adjuvant Chemotherapy

Neither randomized trials nor a meta-analysis have provided sufficient data to support the routine use of adjuvant chemotherapy (LE: 1a).

Recommendation	GR
Adjuvant chemotherapy is advised within clinical trials, but not as a routine therapeutic option.	A

Multimodality treatment

Conclusions	LE
In a highly selected patient population, long-term survival rates of multimodality treatment are comparable to those of early cystectomy.	3
Delay in surgical therapy can compromise survival rates.	2b

Recommendations	GR
Transurethral resection of bladder tumour (TURB) alone cannot be offered as a standard curative treatment option in most patients.	B
Radiotherapy alone is less effective than surgery and is only recommended as a therapeutic option when the patient is unfit for cystectomy or a multimodality bladder-preserving approach.	B
Chemotherapy alone is not recommended as primary therapy for muscle-invasive bladder cancer.	A
Surgical intervention or multimodality treatment are the preferred curative therapeutic approaches since they are more effective than radiotherapy alone.	B

Multimodality treatment could be offered as an alternative in selected, well-informed, well selected and compliant patients, especially for whom cystectomy is not an option.	B
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Metastatic disease

Conclusions for metastatic disease	LE
In a first-line setting, PS and the presence or absence of visceral metastases are independent prognostic factors for survival.	1b
In a second-line setting, prognostic factors are: liver metastasis, PS and haemoglobin (< 10 g/dL)	2
Cisplatin-containing combination chemotherapy can achieve median survival of up to 14 months, with long-term disease-free survival reported in ~15% of patients with nodal disease and good PS.	1b
Carboplatin combination chemotherapy is less effective than cisplatin-based chemotherapy in terms of complete response and survival.	2a
There is no defined standard chemotherapy for unfit patients with advanced or metastatic urothelial cancer.	2b
Vinflunine reached the highest level of evidence ever reported for second-line use.	1b
Post-chemotherapy surgery after partial or complete response may contribute to long-term disease-free survival.	3
Zoledronic acid and denosumab have been approved for all cancer types including urothelial cancer, because they reduce and delay SREs in metastatic bone disease.	1

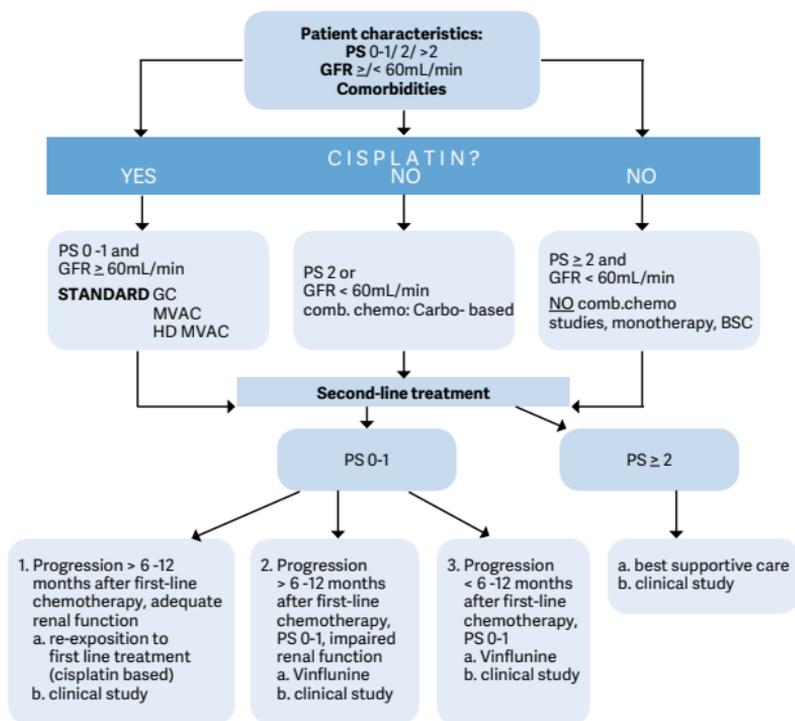
Recommendations for metastatic disease	GR
<i>First-line treatment for fit patients:</i>	
Use cisplatin-containing combination chemotherapy with GC, PCG, MVAC, preferably with G-CSF, or HD-MVAC with G-CSF.	A
Carboplatin and non-platinum combination chemotherapy is not recommended.	B
<i>First-line treatment in patients ineligible (unfit) for cisplatin:</i>	
For cisplatin-ineligible (unfit) patients, with PS2 or impaired renal function, as well as those with 0-1 poor Bajorin prognostic factors and impaired renal function, treatment with carboplatin-containing combination chemotherapy, preferably with gemcitabine/ carboplatin is indicated.	A
<i>Second-line treatment:</i>	
In patients progressing after platinum-based combination chemotherapy for metastatic disease, vinflunine should be offered. Alternatively, treatment within a clinical trial setting may be offered.	B*
Zoledronic acid or denosumab is recommended for treatment of bone metastases.	B

*Upgraded to Grade B recommendation; data not reaching statistical significance.

Recommendation for the use of biomarkers	GR
Currently, no biomarkers can be recommended in daily clinical practice since they have no impact on predicting outcome, treatment decisions or monitoring therapy in muscle-invasive bladder cancer.	A*

*Upgraded following panel consensus.

Fig. 2: Flowchart for the management of metastatic urothelial cancer



Health-related quality-of-life (HRQoL)

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

Recommendations for HRQoL	GR
The use of validated questionnaires is recommended to assess HRQoL in patients with muscle-invasive bladder cancer.	B
Unless a patient's co-morbidities, tumour variables and coping abilities present clear contra-indications, a continent urinary diversion should be offered.	C
Pre-operative patient information, patient selection, surgical techniques, and careful post-operative follow-up are the cornerstones for achieving good long-term results.	C
Patient should be encouraged to take active part in the decision-making process. Clear and exhaustive information on all potential benefits and side-effects should be provided, allowing them to make informed decisions.	C

This short booklet text is based on the more comprehensive EAU guidelines (ISBN 978-90-79754-71-7), available to all members of the European Association of Urology at their website, <http://www.uroweb.org>.