# 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 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 NE (neuroendocrine differentiation, % to be given);
13. pure neuroendocrine carcinoma (including small and large cell neuroendocrine carcinomas.

| Recommendations for epidemiology and risk factors | Strength rating |
|---|---|
| Council patients to stop active 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 |

| Recommendations for the assessment of tumour specimens | Strength rating |
|---|---|
| Record the depth of invasion for the entire speciment (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 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 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** |
|---|---|
| Always perform magnetic resonance imaging (MRI) before Transurethral resection of bladder tumour (TURB), if available. | Weak |
| 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 |
| 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 |

### 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 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 chemotherapy, offer neoadjuvant cisplatin-based combination chemotherapy to patients with MIBC (T2–T4a, cN0 M0). | Strong |
| Do not offer neoadjuvant chemotherapy (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 postoperative 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 RT in addition to chemotherapy following RC, based on pathologic risk (pT3b–4 or positive nodes or positive margins). | Weak |

| | |
|---|---|
| Inform patients with oligometastatic disease about treatment options. Patients should be carefully selected for treatment and fully informed of the potential benefits and harms of the different treatment modalities as well as the fact that there is no definitive evidence supporting local therapy in oligometastatic disease. | 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).

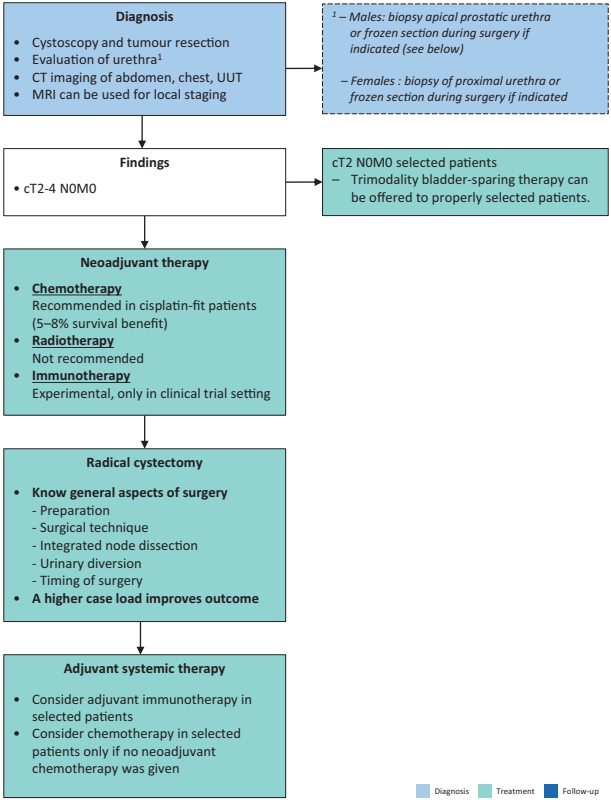
| **Recommendations for radical cystectomy and urinary diversion** | **Strength rating** |
|---|---|
| Do not delay radical cystectomy (RC) for > three months as it increases the risk of progression and cancer-specific mortality, unless the patient receives neoadjuvant chemotherapy. | Strong |
| Perform at least ten, and preferably > twenty, 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 |
| Only offer sexual-preserving techniques to eligible men very motivated to preserve their sexual function. | Strong |
| Select men for sexual-preserving techniques based on:<br>• organ-confined disease;<br>• absence of any kind of tumour at the level of the prostate, prostatic urethra or bladder neck. | Strong |
| Offer sexual-preserving techniques to eligible women to preserve their sexual function. | Strong |
| Select women for sexual-preserving techniques based on:<br>• absence of tumour in the area to be preserved to avoid positive soft tissue margins;<br>• absence of pT4 urothelial carcinoma. | Strong |
| Do not offer pre-operative 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 first day post-surgery, for a period of at least 4 weeks. | Strong |
| Offer RC to patients with T2–T4a, N0M0 disease or very high-risk non-MIBC. | Strong |

| | |
|---|---|
| Perform a lymph node dissection as an integral part of RC. | 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 |
| Advise patients who are candidates for TMT in a mutlidisciplinary setting including urologists, medical oncologists and radiation oncologists concerning the benfits and harms of TMT. | 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 |
| Advise patients who are candidates for TMT that life-long bladder monitoring is essential. | Strong |

### Surgically non-curable tumours

*Palliative- and salvage 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*

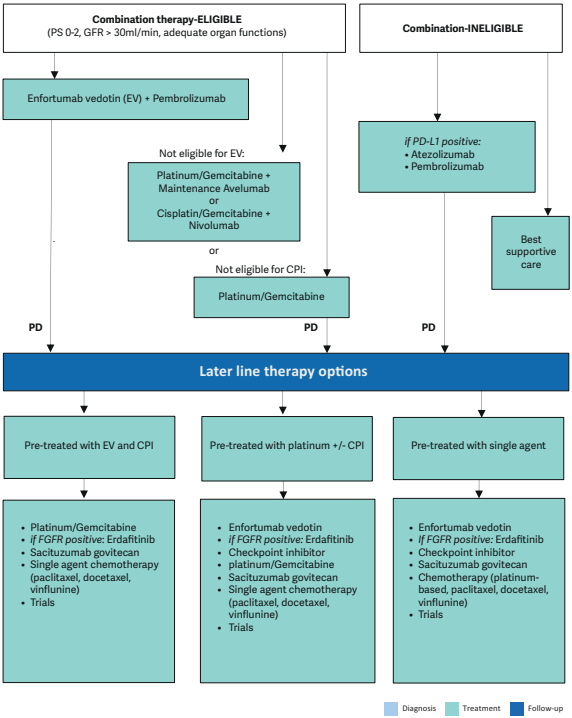
| Recommendations | Strength rating |
|---|---|
| Offer adjuvant cisplatin-based combination chemotherapy to patients with pT3/4 and/or pN+ disease if no neoadjuvant chemotherapy has been given. | Strong |
| Offer adjuvant nivolumab to selected patients with pT3/4 and/or pN+ disease not eligible for,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

## Metastatic disease

| 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:*<br>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:*<br>Consider cisplatin/gemcitabine in combination with CPI nivolumab. | Strong |
| *If contraindications for checkpoint inhibitor therapy:*<br>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. (for definitions see text). | 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 sacituzumab govitecan. | 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: offer erdafitinib. | Strong |
| If no prior CPI: offer pembrolizumab | Strong |
| Consider antibody drug conjugate sacituzumab govitecan. | Weak |
| 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 (BSC) alone if 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*




**EV = enfortumab vedotin; FGFR = fibroblast growth factor receptor; GFR = glomerular filtration rate; PS = performance status; CPI=checkpoint inhibitor; PD-L1= programmed death-ligand 1; PD= programmed death*

### 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, both at baseline and post-treatment. | 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 978-94-92671-23-3) available to all members of the European Association of Urology at their website, http://www.uroweb.org/guidelines/.*