EAU GUIDELINES ON MUSCLE-INVASIVE AND METASTATIC BLADDER CANCER

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Introduction

Epidemiology and aetiology

Bladder cancer (BC) is the sixth most commonly diagnosed cancer in males, and it is the ninth when both sexes 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.

Recommendations for epidemiology and risk factors	Strength rating
Counsel 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

Pathology and classification systems

The 2025 Tumour, Node, Metastasis (TNM) classification is used for staging (Table 1). For grading, the 1973 and 2004/2016 World Health Organization grading classifications are used.

Table 1: TNM classification 2025

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	Nonregional lymph nodes
	M1b	Other distant metastasis

All muscle invasive urothelial carcinomas (UCs) 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. Currently, the following subtypes of UC 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
5. large nested
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.	Strong
Record the total number of lymph nodes (LNs), the number of positive LNs and extranodal spread.	Strong
Record lymphovascular invasion.	Strong
Record the presence of carcinoma *in situ*.	Strong
Record the sampling sites, as well as information on tumour size, when providing specimens to the pathologist.	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 fibroblast growth factor receptor *(FGFR)* 3 are predictive of response to therapy with the *FGFR* inhibitor erdafitinib. Circulating tumour DNA (ctDNA) holds promise as

both a prognostic and predictive biomarker to guide the use of adjuvant immunotherapy (IO) for UC in patients compared with observation.

Recommendations for urothelial markers	Strength rating
Use susceptible fibroblast growth factor receptor *(FGFR)* 3 alterations to select patients with unresectable or metastatic urothelial carcinoma for treatment with erdafitinib.	Strong
Determine immunohistochemical human epidermal growth factor receptor *(HER)* 2 expression to select patients for *HER* 2-directed antibody-drug conjugate therapy.	Weak

Diagnosis

Ultimately, the diagnosis of BC is made by cystoscopy 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 the following cases: 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 males with a negative prostatic urethral biopsy undergoing subsequent orthotopic neobladder construction, an intraoperative frozen section can be omitted.	Strong
In males with a prior positive transurethral prostatic biopsy, subsequent orthotopic neobladder construction should not be denied *a priori*, unless an intraoperative frozen section of the distal urethral stump reveals malignancy at the level of urethral dissection.	Strong
In females 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 (NMIBC).*

Imaging for staging in MIBC

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

Recommendations for staging in muscle-invasive bladder cancer	Strength rating
If magnetic resonance imaging (MRI) is performed for local staging of bladder cancer (BC), it should be carried out before transurethral resection of the bladder tumour.	Strong
In patients with confirmed muscle-invasive BC, 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
Offer MRI to assess the local response to systemic therapy.	Weak

Disease management

Multidisciplinary team for patients with MIBC

All patients with MIBC should be discussed in a multidisciplinary team before treatment initiation. Joint decision-making is essential to define the optimal treatment strategy, including RC, bladder-sparing strategies or systemic therapy.

Recommendations for a multidisciplinary team	Strength rating
Manage all patients who are candidates for trimodality therapy in a multidisciplinary team setting. The choice of treatment modality should be made through a shared decision-making process.	Strong
Fully inform the patient about the benefits and potential risks of all possible alternatives before radical cystectomy. The final decision should be based on a balanced discussion between the patient and the surgeon.	Strong

Health status assessment

Complications from radical cystectomy (RC) 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 when needed.

Recommendations for 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

Perioperative systemic therapy

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. Perioperative durvalumab plus neoadjuvant gemcitabine and cisplatin (GC) improves event-free survival (EFS) and OS compared to neoadjuvant GC alone. In patients with cisplatin-ineligible MIBC, perioperative enfortumab vedotin plus pembrolizumab (EV + P) improves EFS and OS compared to surgery followed by observation. There are still no reliable tools available to select patients who have a higher probability of benefitting from NAC. In future, genomic markers in a personalised medicine setting might facilitate the selection of patients for NAC and differentiate responders from non-responders.

Recommendations for neoadjuvant therapy	Strength rating
Offer perioperative chemoimmunotherapy with cisplatin/gemcitabine and durvalumab to patients with muscle-invasive bladder cancer (MIBC) (T2-T4a, cN0-1 M0) who are eligible for cisplatin-based chemotherapy (glomerular filtration rate > 40mL/min. allowed) and immunotherapy.	Strong
Offer perioperative enfortumab vedotin plus pembrolizumab to patients with MIBC who are ineligible for cisplatin-based chemotherapy.	Strong

Offer neoadjuvant cisplatin-based combination chemotherapy to patients with MIBC (T2-T4a, cN0 M0) who are eligible for cisplatin-based chemotherapy.	Strong
Do not offer neoadjuvant carboplatin-containing combination chemotherapy to patients who are ineligible for cisplatin-based combination chemotherapy.	Strong

Adjuvant therapy

Adjuvant cisplatin-based chemotherapy for high-risk patients (pT3, pT4 and/or N+) without neoadjuvant treatment can be associated with improvement in disease-free survival (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. However, circulating tumour DNA-guided adjuvant therapy with atezolizumab improves DFS and OS in patients with MIBC.

Recommendations for adjuvant therapy	Strength rating
Offer adjuvant cisplatin-based combination chemotherapy to patients with pT3/4 and/or pN+ disease if no neoadjuvant systemic therapy has been given.	Strong
Offer adjuvant nivolumab to patients with high-risk muscle-invasive urothelial carcinoma (≥ ypT2N0 after NAC or pT3/4 and/or pN+) who are not eligible for, or who declined, adjuvant cisplatin-based chemotherapy. Of note: United States Food and Drug Administration approval irrespective of programmed death-ligand 1 (PD-L1) status, European Medicines Agency approval only for PD-L1 tumour cell expression ≥ 1%.	Strong

Perioperative radiotherapy

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

Recommendations for pre- and postoperative radiotherapy	Strength rating
Do not offer preoperative radiotherapy (RT) for operable muscle-invasive bladder cancer since it will not improve survival.	Strong

Adjuvant RT to the cystectomy bed and local pelvic nodes can be offered following radical cystectomy (pT3b–4 or positive nodes or positive margins) to improve locoregional relapse free survival, but not overall survival.	Weak

Radical cystectomy

Radical cystectomy is recommended in patients with T2–T4a, N0M0 disease, very high-risk NMIBC, bacillus Calmette-Guérin (BCG)-refractory, BCG-relapsing and BCG-unresponsive NMIBC, as well as extensive papillary disease that cannot be controlled with TURBT and intravesical chemotherapy/IO alone. Robot-assisted radical cystectomy (RARC) and open RC 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 females), or if tumour extensively infiltrates the prostate (in males).

Urinary diversion

Ensuring that patients are well informed about the various urinary diversion options prior to making a decision may help prevent or reduce decision regret, independent of the method of diversion selected. The type of urinary diversion does not affect oncological outcome.

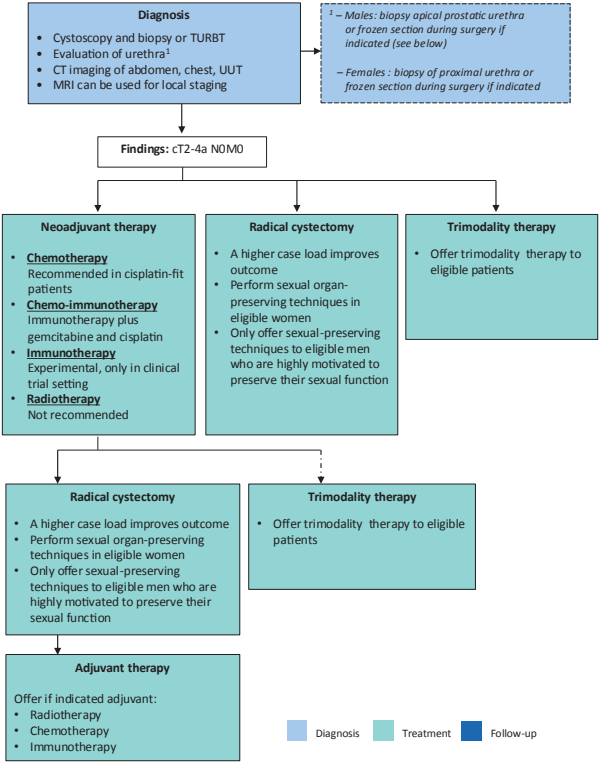
Quality indicators in radical cystectomy

Higher RC hospital volume is associated with lower postoperative mortality rates and higher quality of care. The use of extended venous thromboembolism (VTE) prophylaxis significantly decreases the incidence of VTE after RC.

Recommendations	Strength rating
Radical cystectomy	
Offer radical cystectomy (RC) to patients with T2-T4a N0M0 disease.	Strong
Sexual-preserving techniques in males	
Only offer sexual-preserving techniques to eligible male patients who are highly motivated to preserve their sexual function.	Strong
Select patients based on: • organ-confined disease; and • absence of malignancy at the level of the prostate, prostatic urethra or bladder neck.	Strong
Sexual-preserving techniques in females	
Perform sexual organ-preserving techniques in eligible female patients. Select patients based on absence of tumour in the area to be preserved to avoid positive soft tissue margins.	Strong
Lymphadenectomy	
Perform a lymph node dissection (LND) as an integral part of RC.	Strong
Perform a standard LND, because an extended LND does not improve survival and increases the risk of morbidity.	Strong

Robotic-assisted laparoscopic cystectomy	
Inform the patient of the advantages and disadvantages of open RC and robotic-assisted laparoscopic cystectomy (RARC) to allow selection of the proper procedure.	Strong
Select centres for both RARC and open RC based on experience, rather than the technique used.	Strong
Do not delay RC for more than three months, as this increases the risk of progression and cancer-specific mortality, unless the patient receives neoadjuvant chemotherapy.	Strong
Urinary diversion after radical cystectomy	
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 preoperative bowel preparation.	Strong
Employ 'fast track' measurements to reduce the time to bowel recovery.	Strong
Quality indicators in radical cystectomy	
Perform at least 20 RCs per hospital/per year.	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 four weeks.	Strong

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



CT = computed tomography; MRI = magnetic resonance imaging; TURBT = transurethral resection of bladder tumours; UUT = upper urinary tract.

Palliative cystectomy

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 for palliative cystectomy	Strength rating
Offer cystectomy as a palliative treatment to patients with locally advanced tumours.	Weak
Offer palliative cystectomy to patients with symptoms, if control is not possible by less invasive methods.	Weak

Trimodality bladder-preserving treatment

Long-term survival rates of trimodality therapy (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.

External beam radiotherapy

External beam RT alone should only be considered as a therapeutic option when the patient is unfit for cystectomy or chemoradiation. 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.

Other approaches

Transurethral resection of bladder tumour

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

Chemotherapy

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

Recommendations	Strength rating
Trimodality bladder-preserving treatment	
Offer radical cystectomy or trimodality bladder-preserving treatment (TMT) as primary curative option for eligible patients since they are more effective than radiotherapy (RT) alone.	Strong
Advise patients who are candidates for TMT that bladder monitoring post-treatment is essential.	Strong
External beam radiotherapy	
Do not offer RT alone as primary therapy for localised bladder cancer (BC).	Strong
Transurethral resection of bladder tumour	
Do not offer transurethral resection of bladder tumour alone as a curative treatment option as most patients will not benefit.	Strong

Chemotherapy	
Do not offer chemotherapy alone as primary therapy for localised BC.	Strong

Follow-up

Response to neoadjuvant therapy

Restaging imaging exams after completion of neoadjuvant therapy are primarily performed to rule out the presence of local progression or metastatic disease before proceeding to definitive local therapy. Computed tomography of the thorax, abdomen or pelvis represents the standard of care.

Recommendation for response to neoadjuvant therapy	Strength rating
Perform restaging computed tomography after neoadjuvant therapy to rule out local progression and the presence of metastatic disease.	Strong

Recurrent disease

Salvage cystectomy

Salvage cystectomy is required in approximately 10-15% of patients treated with TMT due to invasive in-bladder recurrences and can be curative.

Recommendation for salvage cystectomy	Strength rating
Offer salvage cystectomy to patients with muscle-invasive bladder cancer recurrence after trimodality therapy.	Strong

Specific recurrence sites

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.

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 (RT), chemotherapy and possibly surgery as options for treatment, either alone or in combination.	Strong
Distant recurrence	Poor prognosis.	Offer systemic therapy as the first option and consider metastasectomy or RT in case of unique metastasis site.	Strong
Upper urinary tract recurrence	Risk factors are multifocal disease, non-muscle-invasive bladder cancer / carcinoma *in situ* or positive ureteral margins.	See the EAU Guidelines on Upper Urinary Tract Urothelial Carcinomas.	Strong

Secondary urethral tumour	Staging and treatment should be done as for primary urethral tumour.	See the EAU Guidelines on Primary Urethral Carcinoma.	Strong

Metastatic disease

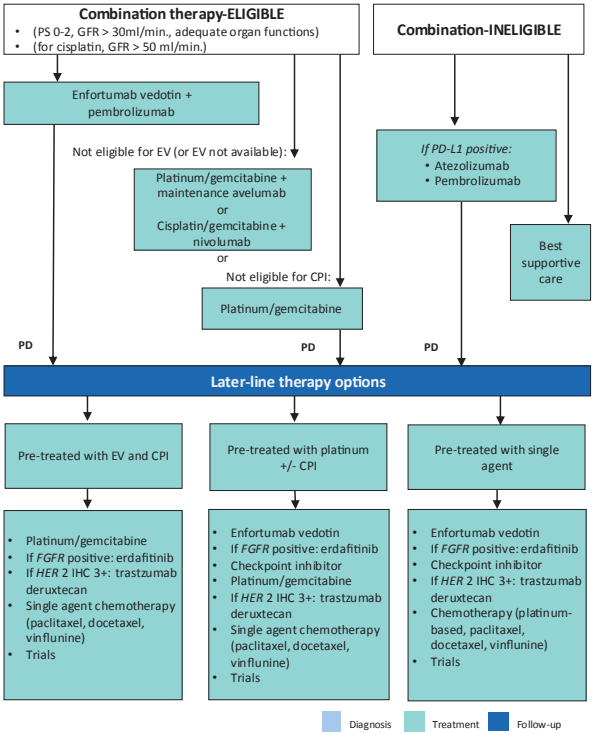
The treatment of metastatic disease remained largely unchanged since pivotal trials published over 20 years ago set the standard of care for first-line treatment with cisplatin-based combinations. The introduction of IO using checkpoint inhibitors gradually challenged established practice culminating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

Recommendations for metastatic disease	**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: Offer cisplatin/gemcitabine in combination with CPI nivolumab.	Strong
If contraindications for EV and CPI therapy: Use platinum-containing combination chemotherapy (cisplatin or carboplatin plus gemcitabine).	Strong
First-line treatment if not eligible for combination therapy	
Offer single agent CPI pembrolizumab or atezolizumab in case of high programmed death-ligand 1 (PD-L1) expression (for definitions see the extended full text Guidelines).	Weak
Later-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.	Strong
Offer single agent chemotherapy (docetaxel, paclitaxel, vinflunine).	Weak
After prior platinum-based chemotherapy +/- CPI	
Offer antibody drug conjugate EV.	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	
Offer antibody drug conjugate trastuzumab deruxtecan in case of human epidermal growth factor receptor *(HER)* 2 over expression (IHC 3+) and consider in case of *HER* 2 (IHC 2+).	Weak
Offer treatment in clinical trials. Consider best supportive care alone if patient is not a candidate for further cancer-specific systemic therapy.	Strong
If actionable *FGFR* alterations: offer erdafitinib.	Strong

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-L1 = programmed death-ligand 1; PD = programmed death; PS = performance status.

Quality of life and palliative care

The evaluation of health-related quality of life (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.

Recommendations for health-related quality of life	Strength rating
Use validated questionnaires to assess health-related quality of life in patients with muscle-invasive bladder cancer, both at baseline and post-treatment.	Strong
Discuss the type of urinary diversion considering patient preference, existing comorbidities, tumour variables and coping abilities.	Strong

This short booklet text is based on the more comprehensive EAU Guidelines accessible on the website: http://www.uroweb.org/guidelines/.