College of Oncology

NATIONAL EXPERT – BASED PRACTICE GUIDELINES

BLADDER CANCER

Guidelines V1.2021

BLADDER CANCER

EXPERT PANEL

These guidelines have been developed by a national multi-institutional and multidisciplinary expert working party, based on international guidelines.

COLLEGE OF ONCOLOGY

Prof. Dr. Marc Peeters – *Chairman College of Oncology*

Prof. Dr. Jacques De Grève – *Chair of the guidelines working party*

Ms. Isolde Van der Massen, MSc – *Scientific coordinator*

LEADER EXPERT PANEL

Prof. Dr. Thierry Roumeguère – Belgian Society of Urology *(SBU-BAU)*

EXPERT PANEL

Prof. Dr. Sylvie Rottey – *Belgian Society of Medical Oncology (BSMO)*

Dr. Daan De Maeseneer – *Belgian Society of Medical Oncology (BSMO)*

Prof. Dr. Raymond Oyen – *Belgian Society of Radiology (BSR)*

Prof. Dr. Olivier De Hertogh – *Belgian Society for Radiotherapy & Oncology (BeSTRO)*

Prof. Dr. Valérie Fonteyne – *Belgian Society for Radiotherapy & Oncology (BeSTRO)*

Prof. Dr. Sandrine Rorive – *Belgian Society of Pathology*

Prof. Dr. Sofie Verbeke – *Belgian Society of Pathology*

Prof. Dr. Karolien Goffin – *Belgian Society of Nuclear Medicine* (*BELNUC)*

Prof. Dr. Karel Decaestecker – *Belgian Association of Urology (BVU-BAU)*

Dr. Julien Van Damme – *Belgian Society of Urology (SBU-BAU)*

INTRODUCTION

This document provides an overview of the good clinical practice guidelines for **bladder cancer** and covers a broad range of topics such as screening, diagnosis, treatment and follow-up.

This guideline has been developed by a panel of experts comprising clinicians of different specialties and designated by their respective scientific societies.

The guidelines are based on the best evidence available at the time they are derived (2021).

The aim of this guideline is to assist all national care providers involved in the care of patients with bladder cancer and serve as a base and supporting tool for the local institutional guidelines and multidisciplinary oncological consult (MOC) discussions in Belgium.

SEARCH FOR EVIDENCE

This national guideline is derived from existing international guidelines and has been updated and adapted to the Belgian context by the expert panel. The following guidelines have mostly been used: EAU guidelines on non-muscle-invasive bladder cancer (TaT1 and CIS) 2019 and EAU guidelines on muscle-invasive and metastatic bladder cancer 2021 (Compérat et al. 2019; Witjes et al. 2021).

The expert panel consisted of experts in various settings and representatives of the relevant professional Belgian societies, implicated in the management of bladder cancer.

This national guideline will be regularly updated as new evidence with practice implications emerges.

The strength of each recommendation is represented by the words ‘strong’ or ‘weak’. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

This guideline consists of two main parts: guidelines on non-muscle invasive bladder cancer (first part) and guidelines on muscle invasive and metastatic bladder cancer (second part).

LIST OF ABBREVIATIONS

BCG: Bacillus Calmette-Guerin

CIS: carcinoma in situ

CT: computed tomography

CT-U: computed tomography urography

CUETO: Urological Club for Oncological Treatment

EAU: European Association of Urology

EORTC: European Organisation for Research and Treatment of Cancer

FDG-PET/CT: fluorodeoxyglucose positron emission tomography/computed tomography

ISUP: international society of urological pathology

LN: lymph node

MOC multidisciplinary oncological consult

MRI: Magnetic Resonance Imaging

MRU: Magnetic Resonance Urography

NAC: neoadjuvant chemotherapy

NCCN: National Comprehensive Cancer Network

ORC: open radical cystectomy

PDD: photodynamic diagnosis

PUNLMP: Papillary urothelial neoplasm of low malignant potential

RARC: robot-assisted radical cystectomy

RC: radical cystectomy

TNM: tumour, node, metastasis

TURB: transurethral resection of the bladder

TURBT: transurethral resection of bladder tumour

WG: working group

WHO: World Health Organization

1. NON-MUSCLE INVASIVE BLADDER CANCER

1.1 Staging and classification systems

- The depth of invasion (staging) is classified according to the tumour, node, metastasis classification (TNM; Table 1 in the Appendix) (Eight Edition, 2017). (EAU, strong recommendation)
- Papillary tumours confined to the mucosa and invading the lamina propria are classified as stage pTa and pT1, respectively. Flat, high-grade tumours that are confined to the mucosa are classified as carcinoma in situ (CIS). (EAU, strong recommendation)
- According to the last World Health Organization (WHO) Classification (2016), International Society of Urological Pathology (ISUP) and National Comprehensive Cancer Network (NCCN) guidelines, papillary urothelial are categorised as:
    - Papilloma
    - Papillary urothelial neoplasm of low malignant potential (PUNLMP)
    - Low-grade papillary urothelial carcinoma
    - High-grade papillary urothelial carcinoma
- Use both the 1973 and 2016 WHO classification system. (EAU, weak recommendation)
- As heterogeneity in grade is a characteristic of papillary carcinoma, the prevailing approach is to grade the tumour based on the highest-grade component. Some authors advocate 5% as a cut-off point for classifying a tumour (May et al. 2010). Low-grade non-invasive papillary urothelial carcinoma with < 5% of a high-grade component show a trend for more aggressive behaviour compared to pure low-grade cancers, but significantly better behaviour than cancer with a more extensive high-grade component (Reis et al. 2016). (Consensus working group (WG), strong recommendation)
- PUNLMP is stratified as low risk similarly to low-grade if: pTa staging, ≤ 3 cm and solitary lesion (Flaig and Philippe E. Spiess 2021). (NCCN, strong recommendation
- It is recommended to provide an assessment of the depth and/or extent of subepithelial (lamina propria) invasion in pT1 cases. Several substaging methods have been proposed to improve outcome prediction, but none have been routinely adopted regarding the lack of consensus on how to quantify this on transurethral resection of the bladder (TURB) (Eur. Urol. Supplements 2017). (Consensus WG, weak recommendation)

1.2 Diagnosis

- Take a patient history, focusing on urinary tract symptoms and haematuria. (EAU, strong recommendation)
- Use computed tomography urography (CT-U) during the initial work-up in patients with haematuria. (EAU + consensus WG, strong recommendation)
- If the diagnosis is obvious from the CT-U then cystoscopy can be omitted and immediate TURB can be performed. (Consensus WG, weak recommendation)
- Perform cystoscopy in patients with symptoms suggestive of bladder cancer or during surveillance. It cannot be replaced by cytology or by any other non-invasive test. (EAU, strong recommendation)
- In men, use a flexible cystoscope, if available. (EAU, strong recommendation)
- Describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities during cystoscopy. Use a bladder diagram (Figure 1). (EAU, strong recommendation)
- Use voided urine cytology as an adjunct to cystoscopy to detect high-

grade tumour. (EAU, strong recommendation)

- Perform cytology on at least 25 mL fresh urine with immediate, adequate fixation. Morning urine is not suitable because of the frequent presence of cytolysis. (EAU + consensus WG, strong recommendation)
- It is recommended to use the Paris system for cytology reporting (Consensus WG, strong recommendation). Alternatively, also the Bostwick system can be used.

1.2.1 Transurethral resection of the bladder, biopsy and pathology report

- In patients suspected of having bladder cancer, perform a TURB followed by pathology investigation of the obtained specimen(s) as a diagnostic procedure and initial treatment step. (EAU, strong recommendation)
- Outpatient fulguration or laser vaporisation of small papillary recurrences can be used in patients with a history of TaG1/LG tumours. (EAU, weak recommendation)
- Perform TURB systematically in individual steps (EAU, strong recommendation):
    - Bimanual palpation under anaesthesia. This step may be omitted in case non-invasive or early treatment for invasive disease is planned;
    - insertion of the resectoscope, under visual control with inspection of the whole urethra;
    - inspection of the whole urothelial lining of the bladder;
    - biopsy from the prostatic urethra (if indicated);
    - cold-cup bladder biopsies (if indicated);
    - resection of the tumour;
    - recording of findings in the surgery report/record;
    - precise description of the specimen for pathology evaluation
- Perform *en-bloc* resection or resection in fractions (exophytic part of the tumour, the underlying bladder wall and the edges of the resection area). (EAU, strong recommendation)
- Avoid cauterisation as much as possible during TURB to avoid tissue deterioration. (EAU, strong recommendation)
- Take biopsies from abnormal-looking urothelium. Biopsies from normal-looking mucosa (mapping biopsies from the trigone, bladder dome, right, left, anterior and posterior bladder wall) are recommended when cytology is positive, in case of a history of HG/G3 tumours and in tumours with non-papillary appearance. If equipment is available, perform fluorescence-guided (photodynamic diagnosis (PDD)) biopsies. (EAU, strong recommendation)
- Take a biopsy of the prostatic urethra in cases of bladder neck tumour, if bladder CIS is present or suspected, if there is positive cytology without evidence of tumour in the bladder, or if abnormalities of the prostatic urethra are visible. If a biopsy is not performed during the initial procedure, it should be completed at the time of the second resection. (EAU, strong recommendation)
- Take a prostatic urethral biopsy from the pre-collicular area (between the 5 and 7 o'clock position) using a resection loop. In case any abnormal-looking areas in the prostatic urethra are present at this time, these need to be biopsied as well. (EAU, weak recommendation)
- Use methods to improve tumour visualisation (fluorescence cystoscopy, narrow-band imaging) during TURB, if available. (EAU, weak recommendation)
- Refer the specimens from different biopsies and resection fractions to the pathologist in separately labelled containers. (EAU, weak recommendation)
- The TURB record must describe tumour location, appearance, size and multifocality, all steps of the procedure, as well as extent and

completeness of resection. (EAU, strong recommendation)

- In patients with positive cytology, but negative cystoscopy, exclude an upper tract urothelial carcinoma, CIS in the bladder (by mapping biopsies or PDD-guided biopsies) and tumour in the prostatic urethra (by prostatic urethra biopsy). (EAU, strong recommendation)
- Perform a second TURB in the following situations (EAU, strong recommendation):
    - After incomplete initial TURB, or in case of doubt about completeness of a TURB);
    - If there is no detrusor muscle in the specimen after initial resection, with the exception of Ta-LG/G1 tumours and primary CIS;
    - In T1 tumours.
- If indicated, perform a second TURB within two to six weeks after initial resection. This second TURB should include resection of the primary tumour site. (EAU, weak recommendation)
- Inform the pathologist of prior treatments (intra-vesical therapy, radiotherapy, etc.). (EAU, strong recommendation)
- The pathological report on biopsy/transurethral resection of bladder tumour (TURBT) should specify (Consensus WG, strong recommendation):
    - If muscularis propria (detrusor muscle) is present and if present whether it is invaded by tumour
    - Presence or absence of lamina propria invasion
    - Presence or absence of lymphovascular space invasion
    - Presence or absence of adjacent urothelial CIS
    - WHO tumour grade and TNM stage
    - Tumour location
    - Unusual (variant) histology

1.3 Predicting disease recurrence and progression

- Stratify patients into four risk groups according to Table 2 (Appendix). A patient's risk group can be determined using the European Association of Urology (EAU) risk group calculator available at www.nmibc.net. (EAU, strong recommendation)
- For information about the risk of disease progression in a patient with primary Ta-T1 tumours, use the data from Table 3 (Appendix). (EAU, strong recommendation)
- Use the 2006 European Organisation for Research and Treatment of Cancer (EORTC) scoring model to predict the risk of tumour recurrence in individual patients not treated with Bacillus Calmette-Guerin (BCG). (EAU, strong recommendation)
- Use the 2016 EORTC scoring model or the Urological Club for Oncological Treatment (CUETO) risk-scoring model to predict the risk of tumour recurrence in individual patients treated with BCG intravesical immunotherapy (the 2016 EORTC model is calculated for 1 to 3 years of maintenance, the CUETO model for 5 to 6 months of BCG). (EAU, strong recommendation)

1.4 Disease management

1.4.1 Adjuvant therapy in TaT1 tumours and for therapy of CIS

General recommendations

- Counsel smokers with confirmed non-muscle invasive bladder cancer to stop smoking. (EAU, strong recommendation)
- The type of further therapy after TURB should be based on the risk groups shown in Table 2 in the Appendix. For determination of a patient's risk group, use the 2021 EAU risk group calculator available at www.nmibc.net. (EAU, strong recommendation)
- In patients with intermediate-risk tumours (with or without immediate instillation), one-year full- dose BCG treatment (induction plus 3-weekly instillations at 3, 6 and 12 months), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of one year is recommended. The final choice should reflect the individual patient's risk of recurrence and progression as well as the efficacy and side effects of each treatment modality. (EAU, strong recommendation)
- In patients with high-risk tumours, full-dose intravesical BCG for one to three years (induction plus 3-weekly instillations at 3, 6, 12, 18, 24, 30 and 36 months), is indicated. The additional beneficial effect of the second and third years of maintenance should be weighed against its added costs, side effects and problems connected to BCG shortage. (EAU, strong recommendation)
- In patients with very high-risk tumours, discuss immediate radical cystectomy (RC). (EAU, strong recommendation)
- Offer transurethral resection of the prostate, followed by intravesical instillation of BCG to patients with CIS in the epithelial lining of the prostatic urethra. (EAU, weak recommendation)
- The definition of BCG unresponsive should be respected as it most precisely defines the patients who are unlikely to respond to further BCG instillations. (EAU, strong recommendation)
- Offer a RC to patients with BCG unresponsive tumours. (EAU, strong recommendation)
- Offer the opportunity to patients with BCG unresponsive tumours to have a second opinion regarding preservation strategies (intravesical chemotherapy, chemotherapy and microwave-induced hyperthermia, electromotive administration of chemotherapy, intravesical or systemic immunotherapy, radiotherapy) in an expert center* which performs clinical trials within this context. (Consensus WG, weak recommendation)
- For elderly patients who have a high-grade BCG unresponsive tumour, radiotherapy outside the context of a clinical trial is also an option. (Consensus WG, weak recommendation)

Intravesical chemotherapy

- If given, administer a single immediate instillation of chemotherapy within 24 hours (preferably within 6 - 8 hours) after resection. (EAU + consensus WG, weak recommendation)
- Omit a single immediate instillation of chemotherapy in any case of overt or suspected bladder perforation or bleeding requiring bladder irrigation. (EAU, strong recommendation)
- Give clear instructions to the nursing staff to control the free flow of the bladder catheter at the end of the immediate instillation. (EAU, strong recommendation)
- The optimal schedule and duration of further intravesical chemotherapy instillation is not defined. However, it should not exceed one year. (EAU, weak recommendation)
- If intravesical chemotherapy is given, use the drug at its optimal pH and maintain the concentration of the drug by reducing fluid intake before and during instillation. (EAU, strong recommendation)
- The length of individual instillation should be one to two hours. (EAU,

weak recommendation)

BCG intravesical immunotherapy

- Absolute contraindications of BCG intravesical instillation are (EAU, strong recommendation):
    - During the first two weeks after TURB;
    - In patients with visible haematuria;
    - After traumatic catheterisation;
    - In patients with symptomatic urinary tract infection.
- There is currently a BGC shortage in Belgium (https://www.fagg.be/nl/news/onbeschikbaarheid_van_geneesmiddelen_op_basis_van_bcg_oncotice_update_van_de_aanbevelingen (dd. 25-Mar-2021). Therefore, some recommendations regarding the rational use of the existing BCG stock were made by urologists: https://www.fagg.be/sites/default/files/Oncotice_aanbevelingen_DEF.pdf.

1.4.2 1.4.2 Treatment and TaT1 tumours and CIS according to risk stratification

EAU risk group low

- Offer one immediate instillation of intravesical chemotherapy after TURB. (EAU, strong recommendation)

EAU risk group intermediate

- In all patients either one-year full-dose BCG treatment (induction plus 3-weekly instillations at 3, 6 and 12 months), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of one year is recommended. The final choice should reflect the individual patient's risk of recurrence and progression as well as the efficacy and side effects of each treatment modality. Offer one immediate chemotherapy instillation to patients with small papillary recurrences detected more than one year after previous TURB. (EAU, strong recommendation)

EAU risk group high

- Offer intravesical full-dose BCG instillations for one to three years or RC. (EAU, strong recommendation)

EAU risk group very high

- Consider RC and offer intravesical full-dose BCG instillations for one to three years to those who refuse or are unfit for RC. (EAU, strong recommendation)

1.5 Follow-up

- Base follow-up of TaT1 tumours and CIS on regular cystoscopy. (EAU, strong recommendation)
- Patients with low-risk Ta tumours should undergo cystoscopy at three months. If negative, subsequent cystoscopy is advised nine months later, and then yearly for five years. (EAU, weak recommendation)
- It is not recommended to use cytology for local low-grade bladder tumour. (Consensus WG, weak recommendation)
- Patients with high-risk and those with very high-risk tumours treated conservatively should undergo cystoscopy and urinary cytology at three months. If negative, subsequent cystoscopy and cytology should be repeated every three months for a period of two years, and every six months thereafter until five years, and then yearly. (EAU, weak recommendation)
- Patients with intermediate-risk Ta tumours should have an in-between (individualised) follow-up scheme using cystoscopy. (EAU, weak recommendation)

- Regular (yearly) upper tract imaging (CT-U) is recommended for high-risk and very high-risk tumours. (EAU + consensus WG, weak recommendation)
- Endoscopy under anaesthesia and bladder biopsies should be performed when office cystoscopy shows suspicious findings or if urinary cytology is positive. (EAU, strong recommendation)
- During follow-up in patients with positive cytology and no visible tumour in the bladder, mapping biopsies or PDD-guided biopsies (if equipment is available) and investigation of extravesical locations (CT-U, prostatic urethra biopsy) are recommended. (EAU, strong recommendation)
- In patients initially diagnosed with TaLG/G1-2 bladder cancer, use (transvesical or transrectal) ultrasound of the bladder during surveillance in case cystoscopy is not possible or refused by the patient. (EAU + consensus WG, weak recommendation)

2 MUSCLE INVASIVE AND METASTATIC BLADDER CANCER

2.1 Epidemiology and pathology

2.1.1 Epidemiology and risk factors

- Council patients to stop active and avoid passive smoking. (EAU, strong recommendation)
- 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. (EAU, strong recommendation)
- Do not prescribe pioglitazone to patients with active bladder cancer or a history of bladder cancer. (EAU, strong recommendation)

2.1.2 Guidelines for the assessment of tumour specimens

- In the pathology report, specify the grade, depth of tumour invasion, and whether the lamina propria and muscle tissue are present in the specimen. (EAU, strong recommendation)
- Record margins with special attention paid to the radial margin, prostate, ureter, urethral peritoneal fat, uterus and vaginal vault. (EAU, strong recommendation)
- Record the total number of lymph nodes (LNs), the number of positive LNs and extranodal spread. (EAU, strong recommendation)
- Record lymphatic or blood vessel invasion. (EAU, strong recommendation)
- Record the presence of CIS. (EAU, strong recommendation)
- Record the sampling sites as well as information on tumour size when providing specimens to the pathologist. (EAU, strong recommendation)
- The pathologist needs to receive information regarding previous therapy from the physician. (Consensus WG, weak recommendation)
- Differentiating between urachal and non-urachal subtypes of adenocarcinoma is essential when making treatment decisions. (EAU, strong recommendation)

2.2 Staging and classification systems

- 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-U with designated phases for optimal urothelial evaluation. (EAU, strong recommendation)
- Use magnetic resonance urography (MRU) when CT-U is contraindicated for reasons related to contrast administration or radiation dose. (EAU, strong recommendation)
- Use CT or magnetic resonance imaging (MRI) for staging locally advanced or metastatic disease in patients in whom radical treatment is considered. (EAU, strong recommendation)
- Use CT to diagnose pulmonary metastases. CT and MRI are generally considered equivalent for diagnosing local disease and distant metastases in the abdomen. (EAU, strong recommendation)
- It is recommended to use FDG-PET/CT (fluorodeoxyglucose positron emission tomography/computed tomography) within a clinical trial. (Consensus WG, weak recommendation)

2.3 Diagnostic evaluation

- Describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities during cystoscopy. Use a bladder diagram (Figure 1) (Appendix). (EAU, strong recommendation)
- Take a biopsy of the prostatic urethra in 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. (EAU, strong recommendation)
- In men with a negative prostatic urethral biopsy undergoing subsequent orthotopic neobladder construction, an intra-operative frozen section can be omitted. (EAU, strong recommendation)
- 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. (EAU, strong recommendation)
- 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 cystectomy. (EAU, strong recommendation)

2.3.1 Co-morbidity scales

- Base the decision on radical therapy in patients with invasive bladder cancer on tumour stage and frailty. (Consensus WG, strong recommendation.
- 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. (EAU, strong recommendation)

2.4 Markers

- Evaluate PD-L1 expression (by immunohistochemistry) to determine the potential for use of pembrolizumab or atezolizumab in previously untreated patients with locally advanced or metastatic urothelial cancer who are unfit for cisplatin-based chemotherapy. (EAU, weak recommendation)
- 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). (EAU, weak recommendation)

2.5 Disease Management

- Treatment decision should be made during a MOC and patients should be properly informed by urology nurse specialist regarding treatment and follow-up. Patients should be put in contact with patient associations. (Consensus WG, strong recommendation)
- Patients with rare subtypes (pure squamous cell carcinomas) should be referred to an expert center*. Patients who should undergo partial cystectomy, should also be referred to an expert center* (Consensus WG, weak recommendation)
- Candidates for curative treatment, such as cystectomy or bladder preservation, should be clinically assessed by at least an oncologist, an urologist, a radiation oncologist (in case adjuvant radiotherapy or bladder preservation is considered) and a neutral healthcare professional such as an urology nurse specialist. (EAU, strong recommendation)

2.5.1 Neoadjuvant therapy (in the setting of radical cystectomy)

- Offer induction chemotherapy for cN+. (Consensus WG, weak recommendation)
- Offer neoadjuvant chemotherapy (NAC) for T2–T4a, cN0 M0 bladder cancer. In this case, always use cisplatin-based combination therapy. (EAU, strong recommendation)
- Do not offer NAC to patients who are ineligible for cisplatin-based combination chemotherapy. (EAU, strong recommendation)
- Only offer neoadjuvant immunotherapy to patients within a clinical trial setting. (EAU, strong recommendation)
- Bladder urothelial carcinoma with small cell neuroendocrine variant should be treated with NAC followed by consolidating local therapy (EAU, strong recommendation)

2.5.2 Pre-and postoperative radiotherapy in muscle invasive bladder cancer

- Do not offer pre-operative radiotherapy for operable muscle invasive bladder cancer since it will only result in down staging, but will not improve survival. (EAU, strong recommendation)
- Do not offer pre-operative radiotherapy when subsequent RC with urinary diversion is planned (EAU, strong recommendation)
- Consider offering adjuvant radiation in addition to chemotherapy following RC, based on pathologic risk (pT3b–4 or positive nodes or positive margins). (EAU, weak recommendation)
- Candidates for curative treatment, such as cystectomy or bladder preservation, should be clinically assessed by at least an (radiation) oncologist, an urologist and a neutral healthcare practitioner such as a specialist nurse. (EAU + consensus WG, strong recommendation)
- When assessing patient eligibility for bladder preservation, the likelihood of successful debulking surgery should be taken into consideration (optimal debulking). (EAU, strong recommendation)
- Do not perform partial cystectomy unless in a very specific indication. In case of urachal carcinoma or diverticula, it is recommended to be referred to an expert hospital. (consensus WG, weak recommendation)

2.5.3 Radical surgery and urinary diversion

Radical cystectomy

Recommendations for sexual-preserving techniques in men

- Do not offer sexual-preserving RC to men as standard therapy for muscle invasive bladder cancer. (EAU, strong recommendation)
- Offer sexual-preserving techniques to men motivated to preserve their sexual function since the majority will benefit. (EAU, strong recommendation)
- Select patients based on (EAU + consensus WG, strong recommendation):
  - Organ-confined disease;
  - Absence of any kind of tumour (urothelial or adenocarcinoma of the prostate).
- Squamous cell carcinoma and muscle-invasive pure adenocarcinoma of the bladder are no ideal candidates for bladder preserving therapies, but this is not the case for the other variants. In propensity score weighted sample, there was no statistical significant difference in OS for patients with BPCRT as compared to cystectomy (p = 0.387) and for neuroendocrine, micropapillary or not otherwise specified histology subgroups there was no significant difference. Patients with adenocarcinoma (HR 1.75) or squamous cell carcinoma (HR 1.49) had worse OS associated with BPCRT compared to surgery. (Janopaul-Naylor

et al. 2021).

Recommendations for sexual-preserving techniques in women

- Do not offer pelvic organ-preserving RC to women as standard therapy for muscle invasive bladder cancer. (EAU, strong recommendation)
- Offer sexual organ-preserving techniques to women motivated to preserve their sexual function since the majority will benefit. (EAU, weak recommendation)
- Select patients based on (EAU, strong recommendation):
    - Aabsence of tumour in the area to be preserved to avoid positive soft tissue margins
    - Absence of pT4 urothelial carcinoma

Laparoscopic/robotic-assisted laparoscopic cystectomy

- 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. (EAU, strong recommendation)
- Select experienced centres, not specific techniques, both for RARC and ORC. (EAU, strong recommendation).
- If RARC is chosen, an intracorporeal urinary diversion is preferred. (EAU + consensus WG, weak recommendation)
- Whatever technique is chosen, it should not compromise the chance of receiving a neobladder reconstruction. (EAU + consensus WG, strong recommendation)
- It is recommended to continue antiaggregant therapy (less than 100 mg/day). (Consensus WG, strong recommendation)

Radical cystectomy and urinary diversion

- Do not delay RC for > 3 months as it increases the risk of progression and cancer-specific mortality, unless the patient receives neo-adjuvant chemotherapy. (EAU, strong recommendation)
- Perform at least 20 RCs per hospital/per year. (Consensus WG, strong recommendation)
- 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 (EAU, strong recommendation). In Belgium, there are some patient groups:
    - Neobladder: Neovida (http://neovida.be/) and Association Cancer Vessie France (www.bellawear.fr)
    - Stoma: Stoma Ilco (www.stomailco.be)
- Do not offer an orthotopic bladder substitute diversion to patients who have a tumour in the urethra or at the level of urethral dissection. (EAU, strong recommendation)
- Pre-operative bowel preparation is not mandatory. “Fast track” measurements may reduce the time to bowel recovery. (EAU, strong recommendation)
- Offer pharmacological prophylaxis, such as low-molecular-weight heparin to RC patients, starting the first day post-surgery, for a period of 4 weeks. (EAU, strong recommendation)
- Offer RC to patients with T2–T4a, N0M0 disease or high-risk non-muscle-invasive bladder cancer. (EAU, strong recommendation)
- Perform a LN dissection as an integral part of RC. (EAU, strong recommendation)
- Do not preserve the urethra if margins are positive. (EAU, strong recommendation)

2.5.4 Unresectable tumours

- Offer RC as a palliative treatment to patients with inoperable locally advanced tumours. (EAU, weak recommendation)
- Offer palliative cystectomy to patients with symptoms. (EAU, weak recommendation)
- In patients with clinical T4 or clinical N+ disease (regional), radical chemoradiation can be offered accepting that this may be palliative rather than curative in outcome. (EAU, strong recommendation)
- Chemoradiation should be given to improve local control in cases of inoperable locally advanced tumours. (EAU, strong recommendation)
- Offer hypofractionated radiotherapy only to elderly patients or patients unfit for surgery or chemoradiotherapy (Huddart et al. 2021).

2.5.5 Bladder-sparing treatments for localised disease

- The ideal candidate for both surgery and radiotherapy is a patient with a single tumour, without massive multifocal CIS or severe hydronephrosis and a good bladder function. (Consensus WG, weak recommendation)
- Candidates for curative treatment, such as cystectomy or bladder preservation, should be clinically assessed by at least an oncologist, an urologist, a radiation oncologist (in case adjuvant radiotherapy or bladder preservation is considered) and a neutral HCP such as a specialist nurse. (EAU, strong recommendation)
- An important determinant (relative contra-indication) for patient eligibility in case of bladder-preserving treatment is absence of CIS, prior pelvic radiotherapy or hydronephrosis. (Consensus WG, strong recommendation)
- A contraindication for patient eligibility in case of bladder-preserving treatment is a very poor bladder capacity. (Consensus WG, strong recommendation)
- When assessing patient eligibility for bladder preservation, the likelihood of maximal TURBT should be taken into consideration (optimal debulking). (Consensus WG, strong recommendation)

Trimodality bladder-preserving treatment

- 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 TMT is maximal TURBT followed by chemoradiotherapy. (EAU + consensus WG, strong recommendation)
- Offer TMT as an alternative to selected, well-informed and compliant patients. TMT should not be the second option for patients who are not able to go for radical cystectomy. (EAU, strong recommendation)

Transurethral resection of bladder tumour

- Do not offer TURBT alone as a curative treatment option as most patients will not benefit. (EAU, strong recommendation)

External beam radiotherapy

- Do not offer radiotherapy alone as primary therapy for localised bladder cancer, although this might be an option for frail patients (who are too weak to be treated with concomitant systemic chemotherapy or radiochemotherapy. For them, a durable response can be obtained with 6x6 Gy (Huddart et al. 2021). (Consensus WG, strong recommendation)
- Radiotherapy for bladder preservation should be performed with IMRT and IGRT to reduce side effects. The preferred regimen is moderate hypofractionation until 50-55 Gy in 20 fractions to the bladder. The pelvic lymph nodes are not routinely involved. (EAU + consensus WG, strong recommendation)
- Dose escalation above standard radical doses to the primary site in case of bladder preservation, either by IMRT or brachytherapy, is not

recommended. This is currently being investigated in the RAIDER study (Hafeez et al. 2020). (Consensus WG, strong recommendation)

- In case of bladder preservation with radiotherapy, combination with a radiosensitiser is always (unless not fit for systemic therapy) recommended to improve clinical outcomes, such as cisplatin, 5FU, or gemcitabine. (EAU + consensus WG, strong recommendation)

Chemotherapy

- Do not offer chemotherapy alone as primary therapy for localised bladder cancer. (EAU, strong recommendation)

2.5.6 Adjuvant treatment

- Offer adjuvant cisplatin-based combination chemotherapy to patients with pT3/4 and/or pN+ disease if no neoadjuvant chemotherapy has been given (Zaghloul et al. 2018). (EAU, weak recommendation)
- Until further results from ongoing randomized trials are available, only offer immunotherapy within a clinical trial setting. (Consensus WG, strong recommendation)
- Addition of adjuvant radiotherapy to chemotherapy is associated with improved local relapse free survival. (EAU, weak recommendation)

2.5.7 Metastatic disease

First-line treatment for platinum-fit patients

- Use cisplatin-containing combination chemotherapy: gemcitabine plus cisplatin or high-dose intensity methotrexate, vincristine, Adriamycin and cisplatin. (EAU + consensus WG, strong recommendation)
- In patients unfit for cisplatin but fit for carboplatin use the combination of carboplatin and gemcitabine. (EAU, strong recommendation)
- In patients achieving stable disease, or better, after first-line platinum-based chemotherapy use maintenance treatment with PD-L1 inhibitor avelumab. (EAU, strong recommendation)

First-line treatment in patients unfit for platinum-based chemotherapy

- Consider checkpoint inhibitors pembrolizumab or atezolizumab in PD-L1 high patients. (EAU + consensus WG, weak recommendation)

Second line treatment

- Offer checkpoint inhibitor pembrolizumab to patients progressing during, or after, platinum-based combination chemotherapy for metastatic disease (phase 3 data). Alternative reimbursed regimens are atezolizumab and nivolumab. (Consensus WG, strong recommendation)

Further treatment after platinum- and immunotherapy

- Offer treatment in clinical trials testing (or in routine practice if available) novel antibody drug conjugates (enfortumab vedotin, sacituzumab govitecan); or in case of patients with FGFR3 alterations. (EAU, strong recommendation)
- Other chemotherapy regimens (taxanes, gemcitabine, etc.) could be used. (Consensus WG, weak recommendation)
- In case of relapse or in case of diagnosis of advanced cancer, it is mandatory to check for FGFR alterations. (Consensus WG, strong recommendation)

2.5.8 Quality of life

- Use validated questionnaires to assess health-related quality of life in patients with muscle invasive bladder cancer. (EAU, strong recommendation)
- Discuss the type of urinary diversion taking into account a patient preference, existing comorbidities, tumour variables and coping abilities.

(EAU, strong recommendation)

2.6 Follow-up

- In case of local recurrence: offer radiotherapy, chemotherapy and possibly surgery as options for treatment, either alone or in combination. (EAU, strong recommendation)
- In case of distant recurrence: offer chemotherapy as the first option, and consider metastectomy or radiotherapy in case of unique metastasis site. (EAU, strong recommendation)
- In case of upper urinary tract recurrence: see EAU Guidelines on Upper Urinary Tract Urothelial Carcinomas. (EAU, strong recommendation)
- In case of secondary urethral tumour: see EAU guidelines on primary urethral carcinoma. (EAU, strong recommendation)
- After radical cystectomy with curative intent, regular follow-up is needed, follow-up for the detection of second cancers in the urothelium is recommended and follow-up of the urethra with cytology and/or cystoscopy is recommended in selected patients (e.g., multifocality, CIS and tumour in the prostatic urethra). (EAU, strong recommendation)
- After trimodality treatment with curative intent, follow-up for the detection of relapse (including cytoscopic evaluation and cytology) is recommended every 3–4 months initially; then after 3 years, every 6 months in the majority of patients. (EAU + consensus WG, strong recommendation)
- In patients with a partial or complete response after chemotherapy for metastatic urothelial cancer, regular follow-up is needed. Imaging studies may be done according to signs/symptoms. (EAU, strong recommendation)
- To detect relapse after TMM or radical cystectomy, CT of the chest and abdomen is recommended as the imaging method for follow-up in the majority of patients. This should be done every 6 months at least during the first 3 years and then yearly thereafter, depending on the pathological risk factors. Routine imaging with CT of the chest and CT-IVU abdomen should be stopped after 5 years in the majority of patients. For those patients with multifocal CIS or positive ureteral margins, continued imaging of the upper urinary tract is mandatory. The follow-up frequency should be discussed with the patient. (Consensus WG, weak recommendation)
- Vitamin B12 levels have to be measured annually in the follow-up of patients treated with radical cystectomy and bowel diversion with curative intent. Besides oncological follow-up, also kidney function, stoma care and neobladder function should be followed up. In patients treated with radical cystectomy with curative intent and who have a neobladder, management of acid bases household includes regular measurements of pH and sodium bicarbonate substitution according to the measured value. (Consensus WG, strong recommendation)
- Local control is mandatory (even in a metastatic setting). (Consensus WG, strong recommendation)
- Local follow-up with cystoscopy is mandatory. (Consensus WG, weak recommendation)

Appendix

* Expert center: an expert center should at least measure their outcomes which should be comparable with literature. An expert center should have the capacity to provide all the potential therapeutics and should use a multidisciplinary approach.

Table 1 2017 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 *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 regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac or presacral)	
N3	Metastasis in common iliac lymph node(s)	
M - Distant metastasis		
M0	No distant metastasis	
	M1a	Non-regional lymph nodes
	M1b	Other distant metastases

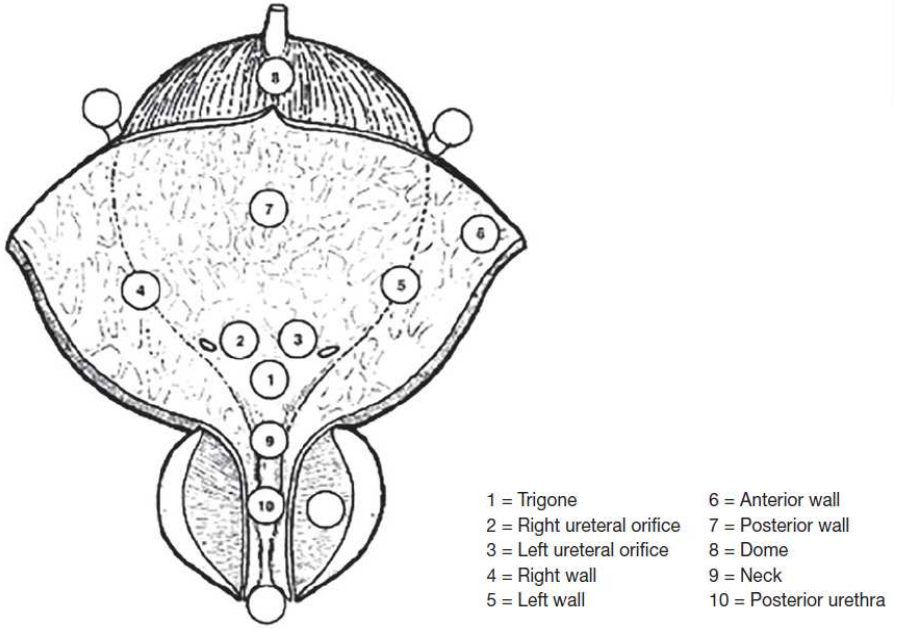

Figure 1 Bladder diagram (Compérat et al. 2019)

Table 2 Clinical composition of the new EAU NMIBC prognostic factor risk groups based on the WHO 2004/2016 or the WHO 1973 grading classification systems

Risk group	
Low Risk	• A primary, single, Ta/T1 LG/G1 tumour < 3 cm in diameter without CIS in a patient < 70 years
	• A primary Ta LG/G1 tumour without CIS with at most ONE of the additional clinical risk factors (see above*)
Intermediate Risk	Patients without CIS who are not included in either the low, high or very high-risk groups
High Risk	• All T1 HG/G3 without CIS, EXCEPT those included in the very high-risk group • All CIS patients, EXCEPT those included in the very high-risk group
	Stage, grade with additional clinical risk factors: • Ta LG/G2 or T1 G1, no CIS with all 3 risk factors • Ta HG/G3 or T1 LG, no CIS with at least 2 risk factors • T1 G2 no CIS with at least 1 risk factor
Very High Risk	**Stage, grade with additional clinical risk factors:** • Ta HG/G3 and CIS with all 3 risk factors • T1 G2 and CIS with at least 2 risk factors • T1 HG/G3 and CIS with at least 1 risk factor • T1 HG/G3 no CIS with all 3 risk factors

Table 3 Probabilities of disease progression in 1, 5 and 10 year(s) for the new EAU NMIBC risk groups

Risk group	Probability of Progression and 95% Confidence Interval (CI)		
	1 Year	5 Years	10 Years
New Risk Groups with WHO 2004/2016			
Low	0.06% (CI: 0.01%–0.43%)	0.93% (CI: 0.49%–1.7%)	3.7% (CI: 2.3%–5.9%)
Intermediate	1.0% (CI: 0.50%–2.0%)	4.9% (CI: 3.4%–7.0%)	8.5% (CI: 5.6%–13%)
High	3.5% (CI: 2.4%–5.2%)	9.6% (CI: 7.4%–12%)	14% (CI: 11%–18%)
Very High	16% (CI: 10%–26%)	40% (CI: 29%–54%)	53% (CI: 36%–73%)
New Risk Groups with WHO 1973			
Low	0.12% (CI: 0.02%–0.82%)	0.57% (CI: 0.21%–1.5%)	3.0% (CI: 1.5%–6.3%)
Intermediate	0.65% (CI: 0.36%–1.2%)	3.6% (CI: 2.7%–4.9%)	7.4% (CI: 5.5%–10%)
High	3.8% (CI: 2.6%–5.7%)	11% (CI: 8.1%–14%)	14% (CI: 10%–19%)
Very High	20% (CI: 12%–32%)	44% (CI: 30%–61%)	59% (CI: 39%–79%)

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