

Approved by the AUA
Board of Directors
March 2017

Authors' disclosure of potential conflicts of interest and author/staff contributions appear at the end of the article.

© 2017 by the American Urological Association

American Urological Association (AUA) / American Society of Clinical Oncology (ASCO) /
American Society for Radiation Oncology (ASTRO) / Society of Urologic Oncology (SUO)

TREATMENT OF NON-METASTATIC MUSCLE-INVASIVE BLADDER CANCER: AUA/ASCO/ASTRO/SUO GUIDELINE

Sam S. Chang, MD, MBA; Bernard H. Bochner, MD, FACS; Roger Chou, MD; Robert Dreicer, MD, MS, MACP, FASCO; Ashish M. Kamat, MD, MBBS, FACS; Seth P. Lerner, MD, FACS; Yair Lotan, MD; Joshua J. Meeks, MD, PhD; Jeff M. Michalski, MD, MBA; Todd M. Morgan, MD; Diane Z. Quale; Jonathan E. Rosenberg, MD; Anthony L. Zietman, MD; Jeffrey M. Holzbeierlein, MD, FACS

Purpose

Although representing approximately 25% of patients diagnosed with bladder cancer, muscle-invasive bladder cancer (MIBC) carries a significant risk of death that has not significantly changed in decades. Increasingly, clinicians and patients recognize the importance of multidisciplinary collaborative efforts that take into account survival and quality of life (QOL) concerns. For the first time for any type of malignancy, the American Urological Association (AUA), the American Society of Clinical Oncology (ASCO), the American Society for Radiation Oncology (ASTRO), and the Society of Urologic Oncology (SUO) have formulated an evidence-based guideline. This guideline provides a risk-stratified clinical framework for the management of muscle-invasive urothelial bladder cancer and is designed to be used in conjunction with the associated treatment algorithm.

Methodology

The systematic review utilized to inform this guideline was conducted by a methodology team at the Pacific Northwest Evidence-based Practice Center. The original review was funded by the Agency for Healthcare Research and Quality (AHRQ), and a subsequent supplemental report was funded by the AUA to address additional key questions and more recently published literature. A research librarian experienced in conducting literature searches for comparative effectiveness reviews searched in Ovid MEDLINE® (January 1990 to October 2014), the Cochrane Central Register of Controlled Trials (through September 2014), the Cochrane Database of Systematic Reviews (through September 2014), Health Technology Assessments (through Third Quarter 2014), the National Health Sciences Economic Evaluation Database (through Third Quarter 2014), and the Database of Abstracts of Reviews of Effects (through Third Quarter 2014) to capture published and gray literature. The methodology team searched for unpublished studies in clinical trial registries (ClinicalTrials.gov, Current Controlled Trials, ClinicalStudyResults.org and the World Health Organization International Clinical Trials Registry Platform) and regulatory documents (Drugs@FDA.gov and FDA Medical Devices Registration and Listing). A supplemental search of Ovid MEDLINE and Cochrane Central Register of Controlled Trials was conducted to capture additional published literature through February 2, 2016. When sufficient evidence existed, the body of evidence for a particular treatment was assigned a strength rating of A (high), B (moderate) or C (low) for support of Strong, Moderate, or Conditional Recommendations. In the absence of sufficient evidence, additional information is provided as Clinical Principles and Expert Opinions.

GUIDELINE STATEMENTS

INITIAL PATIENT EVALUATION AND COUNSELING

1. Prior to treatment consideration, a full history and physical exam should be

performed, including an exam under anesthesia, at the time of transurethral resection of bladder tumor for a suspected invasive cancer. (Clinical Principle)

2. Prior to muscle-invasive bladder cancer management, clinicians should perform a complete staging evaluation, including imaging of the chest and cross sectional imaging of the abdomen and pelvis with intravenous contrast if not contraindicated. Laboratory evaluation should include a comprehensive metabolic panel (complete blood count, liver function tests, alkaline phosphatase, and renal function). (Clinical Principle)
3. An experienced genitourinary pathologist should review the pathology of a patient when variant histology is suspected or if muscle invasion is equivocal (e.g., micropapillary, nested, plasmacytoid, neuroendocrine, sarcomatoid, extensive squamous or glandular differentiation). (Clinical Principle)
4. For patients with newly diagnosed muscle-invasive bladder cancer, curative treatment options should be discussed before determining a plan of therapy that is based on both patient comorbidity and tumor characteristics. Patient evaluation should be completed using a multidisciplinary approach. (Clinical Principle)
5. Prior to treatment, clinicians should counsel patients regarding complications and the implications of treatment on quality of life (e.g., impact on continence, sexual function, fertility, bowel dysfunction, metabolic problems). (Clinical Principle)

TREATMENT

NEOADJUVANT/ADJUVANT CHEMOTHERAPY

6. Utilizing a multidisciplinary approach, clinicians should offer cisplatin-based neoadjuvant chemotherapy to eligible radical cystectomy patients prior to cystectomy. (Strong Recommendation; Evidence Level: Grade B)
7. Clinicians should not prescribe carboplatin-based neoadjuvant chemotherapy for clinically resectable stage cT2-T4aN0 bladder cancer. Patients ineligible for cisplatin-based neoadjuvant chemotherapy should proceed to definitive locoregional therapy. (Expert Opinion)
8. Clinicians should perform radical cystectomy as soon as possible following a patient's completion of and recovery from neoadjuvant chemotherapy. (Expert Opinion)
9. Eligible patients who have not received cisplatin-based neoadjuvant chemotherapy and have non-organ confined (pT3/T4and/or N+) disease at cystectomy should be offered adjuvant cisplatin-based chemotherapy. (Moderate Recommendation; Evidence Level: Grade C)

RADICAL CYSTECTOMY

10. Clinicians should offer radical cystectomy with bilateral pelvic lymphadenectomy for surgically eligible patients with resectable non-metastatic (M0) muscle-invasive bladder cancer. (Strong Recommendation; Evidence Level: Grade B)
11. When performing a standard radical cystectomy, clinicians should remove the bladder, prostate, and seminal vesicles in males and should remove the bladder, uterus, fallopian tubes, ovaries, and anterior vaginal wall in females. (Clinical Principle)
12. Clinicians should discuss and consider sexual function preserving procedures for patients with organ-confined disease and absence of bladder neck, urethra, and prostate (male) involvement. (Moderate Recommendation; Evidence Level: Grade C)

URINARY DIVERSION

13. In patients undergoing radical cystectomy, ileal conduit, continent cutaneous, and orthotopic neobladder urinary diversions should all be discussed. (Clinical Principle)
14. In patients receiving an orthotopic urinary diversion, clinicians must verify a negative urethral margin. (Clinical Principle)

PERIOPERATIVE SURGICAL MANAGEMENT

15. Clinicians should attempt to optimize patient performance status in the perioperative setting. (Expert Opinion)

16. Perioperative pharmacologic thromboembolic prophylaxis should be given to patients undergoing radical cystectomy. (Strong Recommendation; Evidence Level: Grade B)
17. In patients undergoing radical cystectomy μ -opioid antagonist therapy should be used to accelerate gastrointestinal recovery, unless contraindicated. (Strong Recommendation; Evidence Level: Grade B)
18. Patients should receive detailed teaching regarding care of urinary diversion prior to discharge from the hospital. (Clinical Principle)

PELVIC LYMPHADENECTOMY

19. Clinicians must perform a bilateral pelvic lymphadenectomy at the time of any surgery with curative intent. (Strong Recommendation; Evidence Level: Grade B)
20. When performing bilateral pelvic lymphadenectomy, clinicians should remove, at a minimum, the external and internal iliac and obturator lymph nodes (standard lymphadenectomy). (Clinical Principle)

BLADDER PRESERVING APPROACHES

PATIENT SELECTION

21. For patients with newly diagnosed non-metastatic muscle-invasive bladder cancer who desire to retain their bladder, and for those with significant comorbidities for whom radical cystectomy is not a treatment option, clinicians should offer bladder preserving therapy when clinically appropriate. (Clinical Principle)
22. In patients under consideration for bladder preserving therapy, maximal debulking transurethral resection of bladder tumor and assessment of multifocal disease/carcinoma in situ should be performed. (Strong Recommendation; Evidence Level: Grade C)

MAXIMAL TURBT AND PARTIAL CYSTECTOMY

23. Patients with muscle-invasive bladder cancer who are medically fit and consent to radical cystectomy should not undergo partial cystectomy or maximal transurethral resection of bladder tumor as primary curative therapy. (Moderate Recommendation; Evidence Level: Grade C)

PRIMARY RADIATION THERAPY

24. For patients with muscle-invasive bladder cancer, clinicians should not offer radiation therapy alone as a curative treatment. (Strong Recommendation; Evidence Level: Grade C)

MULTI-MODAL BLADDER PRESERVING THERAPY

25. For patients with muscle-invasive bladder cancer who have elected multi-modal bladder preserving therapy, clinicians should offer maximal transurethral resection of bladder tumor, chemotherapy combined with external beam radiation therapy, and planned cystoscopic re-evaluation. (Strong Recommendation; Evidence Level: Grade B)
26. Radiation sensitizing chemotherapy regimens should include cisplatin or 5-fluorouracil and mitomycin C. (Strong Recommendation; Evidence Level: Grade B)
27. Following completion of bladder preserving therapy, clinicians should perform regular surveillance with CT scans, cystoscopy, and urine cytology. (Strong Recommendation; Evidence Level: Grade C)

BLADDER PRESERVING TREATMENT FAILURE

28. In patients who are medically fit and have residual or recurrent muscle-invasive disease following bladder preserving therapy, clinicians should offer radical cystectomy with bilateral pelvic lymphadenectomy. (Strong Recommendation; Evidence Level: Grade C)
29. In patients who have a non-muscle invasive recurrence after bladder preserving therapy, clinicians may offer either local measures, such as transurethral resection of bladder tumor with intravesical therapy, or radical cystectomy with bilateral pelvic lymphadenectomy. (Moderate Recommendation; Evidence Level: Grade C)

PATIENT SURVEILLANCE AND FOLLOW UP

IMAGING

30. Clinicians should obtain chest imaging and cross sectional imaging of the abdomen and pelvis with CT or MRI at 6-12 month intervals for 2-3 years and then may continue annually. (Expert Opinion)

LABORATORY VALUES AND URINE MARKERS

31. Following therapy for muscle-invasive bladder cancer, patients should undergo laboratory assessment at three to six month intervals for two to three years and then annually thereafter. (Expert Opinion)
32. Following radical cystectomy in patients with a retained urethra, clinicians should monitor the urethral remnant for recurrence. (Expert Opinion)

PATIENT SURVIVORSHIP

33. Clinicians should discuss with patients how they are coping with their bladder cancer diagnosis and treatment and should recommend that patients consider participating in cancer support groups or consider receiving individual counseling. (Expert Opinion)
34. Clinicians should encourage bladder cancer patients to adopt healthy lifestyle habits, including smoking cessation, exercise, and a healthy diet, to improve long-term health and quality of life. (Expert Opinion)

VARIANT HISTOLOGY

35. In patients diagnosed with variant histology, clinicians should consider unique clinical characteristics that may require divergence from standard evaluation and management for urothelial carcinoma. (Expert Opinion)

INTRODUCTION

PURPOSE

Although representing approximately 25% of patients diagnosed with bladder cancer, muscle-invasive bladder cancer (MIBC) carries a significant risk of death that has not significantly changed in decades. Increasingly, clinicians and patients recognize the importance of multidisciplinary collaborative efforts that take into account survival and quality of life (QOL) concerns. For the first time for any type of malignancy, the American Urological Association (AUA), the American Society of Clinical Oncology (ASCO), the American Society for Radiation Oncology (ASTRO), and the Society of Urologic Oncology (SUO) have formulated a consensus, evidence-based guideline. This guideline provides a risk-stratified, clinical framework for the management of muscle-invasive urothelial bladder cancer.

METHODOLOGY

Systematic Review. The systematic review utilized to inform this guideline was conducted by a methodology team at the Pacific Northwest Evidence-based Practice Center. The original review was funded by the Agency for Healthcare Research and Quality (AHRQ),¹ and a subsequent supplemental report was funded by the AUA to address additional key questions and more recently published literature. A research librarian experienced in conducting literature searches for comparative effectiveness reviews searched in Ovid MEDLINE® (January 1990 to October 2014), the Cochrane Central Register of Controlled Trials (through September 2014), the Cochrane Database of Systematic Reviews (through September 2014), Health Technology Assessments (through Third Quarter 2014), the National Health Sciences Economic Evaluation Database (through Third Quarter 2014), and the Database of Abstracts of Reviews of Effects (through Third Quarter 2014) to capture published and gray literature. The methodology team searched for unpublished studies in clinical trial registries (ClinicalTrials.gov, Current Controlled Trials, ClinicalStudyResults.org and the World Health Organization International Clinical Trials Registry Platform) and regulatory documents (Drugs@FDA.gov and FDA Medical Devices Registration and Listing). Reference lists of relevant studies and previous systematic reviews were hand-searched for additional studies. Scientific information packets were solicited from drug and device manufacturers and via a notice published in the Federal Register. Initial Database searches resulted in 3,921 potentially relevant articles. After dual review of abstracts and titles, 295 articles

were selected for full-text dual review, and 39 studies (in 41 publications) were determined to meet inclusion criteria and were included in this review. A supplemental search of Ovid MEDLINE and Cochrane Central Register of Controlled Trials was conducted to capture additional published literature through February 2, 2016.

Data Extraction and Data Management. The methodology team extracted the following information into evidence tables: study design; setting; inclusion and exclusion criteria; dose and duration of treatment for experimental and control groups; duration of follow up; number of subjects screened, eligible, and enrolled; population ES-5 characteristics (including age, race/ethnicity, sex, stage of disease, and functional status); results; adverse events; withdrawals due to adverse events; and sources of funding. Methodologists verified or calculated relative risks and associated 95% confidence intervals (CIs) based on the information provided (sample sizes and incidence of outcomes in each intervention group). Methodologists noted discrepancies between calculated and reported results when present. Data extraction for each study was completed by one investigator and independently reviewed for accuracy and completeness by a second investigator.

Assessment of the Risk of Bias of Individual Studies. The methodology team assessed the risk of bias for randomized controlled trials (RCTs) and observational studies using criteria adapted from those developed by the U.S. Preventive Services Task Force.² These criteria were applied in conjunction with the approach recommended in the AHRQ Methods Guide³ for medical interventions. Two investigators independently assessed the risk of bias of each study. Discrepancies were resolved through discussion and consensus. Each study was rated as low, medium, or high risk of bias. Methodologists rated the quality of each RCT based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; whether attrition was adequately reported and acceptable; similarity in use of co-interventions; compliance with allocated treatments; the use of intent-to-treat analysis; and avoidance of selective outcomes reporting.² Methodologists rated the quality of each cohort study based on whether it enrolled a consecutive or random sample of patients meeting inclusion criteria; whether it evaluated comparable groups; whether rates of loss to follow up were reported and acceptable; whether it used accurate methods for ascertaining exposures, potential confounders, and outcomes; and

whether it performed adjustment for important potential confounders (defined as a minimum of age, sex, tumor stage, and tumor grade).² Studies rated low risk of bias were considered to have no more than very minor methodological shortcomings with their results likely to be valid. Studies rated medium risk of bias have some methodological shortcomings, but no flaw or combination of flaws judged likely to cause major bias. In some cases, the article did not report important information, making it difficult to assess its methods or potential limitations. The category of medium risk of bias is broad, and studies with this rating vary in their strengths and weaknesses; the results of some studies assessed to have medium risk of bias are likely to be valid, while others may be only possibly valid. Studies rated high risk of bias have significant flaws that may invalidate the results. They have a serious or fatal flaw or combination of flaws in design, analysis, or reporting; large amounts of missing information (including publication of only preliminary results in a subgroup of patients randomized); or serious discrepancies in reporting. Methodologists did not exclude studies rated as having high risk of bias a priori, but they were considered the least reliable when synthesizing the evidence, particularly when discrepancies between studies were present.

Determination of Evidence Strength. The categorization of evidence strength is conceptually distinct from the quality of individual studies. Evidence strength refers to the body of evidence available for a particular question and includes not only individual study quality but consideration of study design, consistency of findings across studies, adequacy of sample sizes, and generalizability of samples, settings, and treatments for the purposes of the guideline. The AUA categorizes body of evidence strength as Grade A (well-conducted and highly-generalizable RCTs or exceptionally strong observational studies with consistent findings), Grade B (RCTs with some weaknesses of procedure or generalizability or moderately strong observational studies with consistent findings), or Grade C (RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes or observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data). By definition, Grade A evidence is evidence about which the Panel has a high level of certainty, Grade B evidence is evidence about which the Panel has a moderate level of certainty, and Grade C evidence is evidence about which the Panel has a low level of certainty.⁴

AUA Nomenclature: Linking Statement Type to Evidence Strength. The AUA nomenclature system explicitly links statement type to body of evidence strength, level of certainty, magnitude of benefit or risk/burdens, and the Panel's judgment regarding the balance between benefits and risks/burdens (Table 1). **Strong Recommendations** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is substantial. **Moderate Recommendations** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is moderate. **Conditional Recommendations** are non-directive statements used when the evidence indicates that there is no apparent net benefit or harm or when the balance between benefits and risks/burden is unclear. All three statement types may be supported by any body of evidence strength grade. Body of evidence strength Grade A in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances and that future research is *unlikely to change confidence*. Body of evidence strength Grade B in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances but that better evidence *could change confidence*. Body of evidence strength Grade C in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances but that better evidence *is likely to change confidence*. Body of evidence strength Grade C is only rarely used in support of a Strong Recommendation. Conditional Recommendations also can be supported by any evidence strength. When body of evidence strength is Grade A, the statement indicates that benefits and risks/burdens appear balanced, the best action depends on patient circumstances, and future research is *unlikely to change confidence*. When body of evidence strength Grade B is used, benefits and risks/burdens appear balanced, the best action also depends on individual patient circumstances and better evidence *could change confidence*. When body of evidence strength Grade C is used, there is uncertainty regarding the balance between benefits and risks/burdens, alternative strategies may be equally reasonable, and better evidence is *likely to change confidence*.

Where gaps in the evidence existed, the Panel provides guidance in the form of **Clinical Principles** or **Expert Opinion** with consensus achieved using a modified

Delphi technique if differences of opinion emerged.⁵ A *Clinical Principle* is a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature. *Expert Opinion* refers to a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there is no evidence.

Process. The Muscle-Invasive Bladder Cancer Panel was created in 2014 by the American Urological Association Education and Research, Inc. (AUA). The Practice Guidelines Committee (PGC) of the AUA selected the Panel Chair who in turn appointed the Vice Chair. In a collaborative process, additional Panel members, including additional members of the American Society for Radiation Oncology (ASTRO), the American Society of Clinical Oncology (ASCO), and Society of Urologic Oncology (SUO), with specific expertise in this area were then nominated and approved by the PGC. The AUA conducted a thorough peer review process. The draft guideline document was distributed to 128 peer reviewers, 67 of which submitted comments. The Panel reviewed and discussed all submitted comments and revised the draft as needed. Once finalized, the guideline was submitted for approval to the PGC and Science and Quality Council (S&Q). Then it was submitted to the AUA, ASTRO, ASCO, and SUO Board of Directors for final approval. Panel members received no remuneration for their work. This represents the first joint guidelines by these organizations.

BACKGROUND

EPIDEMIOLOGY

There are 79,030 new cases of bladder cancer and 16,870 bladder cancer deaths predicted for 2017 in the U.S.⁶ Approximately 25% of newly diagnosed patients have muscle-invasive disease,^{7,8} a rate that has not changed over the last 10 years based on data from the Surveillance, Epidemiology, and End Results (SEER) registry.⁹ In addition, up to 50% or more patients with high-risk non-muscle invasive bladder cancer (NMIBC) can progress to invasive disease. The male to female ratio is 3:1, and disease incidence increases with age. While rates of bladder cancer are higher in Caucasians than other ethnicities, disease specific survival is worse overall for African-Americans.^{6,8}

ETIOLOGY

All of the factors that contribute to the development of bladder cancer are not completely understood, but

exposure to carcinogens (e.g. tobacco smoke) is the primary cause with some impact from genetic susceptibility. Smoking tobacco is the most important and common risk factor and is estimated to contribute to the development of 50% of bladder tumors, with current smokers at higher risk than former smokers.^{10,11} Former smoking increases the risk of bladder cancer by a factor of 2.2 (95% CI 2.0-2.4), and current smoking by a factor of 4.1 (95% CI 3.7-4.5) compared to never having smoked.¹⁰ Second hand smoke can also increase the risk for the development of bladder cancer.¹² Following smoking, another risk factor that predisposes to bladder cancer is occupational exposure to carcinogens, namely aromatic amines (benzidine, 4-aminobiphenyl, 2-naphthylamine, 4-chloro-o-toluidine), polycyclic aromatic hydrocarbons, and chlorinated hydrocarbons, which contribute to approximately 20% of all bladder cancers.¹³⁻¹⁵ Occupational exposure accounts for 25% of bladder cancer diagnoses in men and 11% in women.¹⁶

There are several other well-documented risk factors. Pelvic radiation for other malignancies increases the likelihood of developing bladder cancer with a hazard ratio of 1.7.¹⁷ In addition, exposure to *S. haematobium* infection is predominantly associated with an increased risk of squamous cell carcinoma of the bladder and is a significant clinical problem in many developing nations. This disease process is a much less common entity in the United States and not the major focus of this report.

Genetic predisposition to bladder cancer has been linked to genes involved in metabolism of carcinogens such as N-acetyl transferase and *GSTM1*-null genotypes.¹⁸ Large genome-wide association studies have also found sequence variants that can increase the risk for bladder cancer, such as subjects with urea transporter gene *SLC14A* that is associated with renal urine concentration, and thus with variations in contact of carcinogens with urothelial surfaces.¹⁹⁻²³

Urothelial carcinoma is often multifocal with a high rate of recurrence; the exact etiology of this characteristic is currently unknown. Two of the most commonly held theories: 1) a genetic field defect exists with multiple new tumors spontaneously arising or, 2) the local reimplantation of tumor cells occurs with tumor resection. Evidence suggests that tumor reimplantation or submucosal migration may be early mechanisms for multifocality.²⁴ Multifocal tumors as well as upper tract and lower tract lesions arising in one individual may demonstrate clonality.²⁵

PROGNOSIS

TABLE 1: AUA Nomenclature Linking Statement Type to Level of Certainty, Magnitude of Benefit or Risk/Burden, and Body of Evidence Strength			
	Evidence Strength A (High Certainty)	Evidence Strength B (Moderate Certainty)	Evidence Strength C (Low Certainty)
<p>Strong Recommendation</p> <p>(Net benefit or harm substantial)</p>	<p>Benefits > Risks/Burdens (or vice versa)</p> <p>Net benefit (or net harm) is substantial</p> <p>Applies to most patients in most circumstances and future research is unlikely to change confidence</p>	<p>Benefits > Risks/Burdens (or vice versa)</p> <p>Net benefit (or net harm) is substantial</p> <p>Applies to most patients in most circumstances but better evidence could change confidence</p>	<p>Benefits > Risks/Burdens (or vice versa)</p> <p>Net benefit (or net harm) appears substantial</p> <p>Applies to most patients in most circumstances but better evidence is likely to change confidence</p> <p>(rarely used to support a Strong Recommendation)</p>
<p>Moderate Recommendation</p> <p>(Net benefit or harm moderate)</p>	<p>Benefits > Risks/Burdens (or vice versa)</p> <p>Net benefit (or net harm) is moderate</p> <p>Applies to most patients in most circumstances and future research is unlikely to change confidence</p>	<p>Benefits > Risks/Burdens (or vice versa)</p> <p>Net benefit (or net harm) is moderate</p> <p>Applies to most patients in most circumstances but better evidence could change confidence</p>	<p>Benefits > Risks/Burdens (or vice versa)</p> <p>Net benefit (or net harm) appears moderate</p> <p>Applies to most patients in most circumstances but better evidence is likely to change confidence</p>
<p>Conditional Recommendation</p> <p>(No apparent net benefit or harm)</p>	<p>Benefits = Risks/Burdens</p> <p>Best action depends on individual patient circumstances</p> <p>Future research unlikely to change confidence</p>	<p>Benefits = Risks/Burdens</p> <p>Best action appears to depend on individual patient circumstances</p> <p>Better evidence could change confidence</p>	<p>Balance between Benefits & Risks/Burdens unclear</p> <p>Alternative strategies may be equally reasonable</p> <p>Better evidence likely to change confidence</p>
<p>Clinical Principle</p>	<p>A statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature</p>		
<p>Expert Opinion</p>	<p>A statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there is no evidence</p>		

The overall prognosis of patients with MIBC has not changed in the last 30 years. In patients who undergo cystectomy, systemic recurrence rates vary by stage, but range from 20-30% for pathologic stage pT2, 40% for pT3, >50% for pT4 and approximately 70% for node-positive disease.^{26,27} Most recurrences will occur within the first two to three years after cystectomy, and at this time, most patients with recurrence after cystectomy are not cured with current systemic therapies.²⁸

A pooled analysis of multiple prospective Radiation Therapy Oncology Group (RTOG) protocols evaluating bladder preserving combined-modality therapy for MIBC with a median follow up of 4.3 years found the 5- and 10-year overall survival rates were 57% and 36%, respectively, and the 5- and 10-year disease specific survival rates were 71% and 65%, respectively.²⁹

The dominant pathologic predictors for recurrence and survival are tumor stage and nodal status. Other prognostic factors include gender, presence of hydronephrosis, lymphovascular invasion, soft tissue margin status, and molecular subtyping characteristics.³⁰⁻³⁵ Variant histology has become better described and recognized, and the treatment for these cancers may vary from conventional urothelial carcinoma. There is also a significant impact of treatment choices on outcome with the type and timing of therapy playing an important role.^{36,37}

SCOPE

This evidence-based guideline for clinically non-metastatic muscle-invasive urothelial bladder cancer (cT2-T4N0M0) focuses on the evaluation, treatment, and surveillance of MIBC and is guided toward curative intent. The treatment of patients with clinically evident metastatic bladder cancer is outside the context of this guideline and will not be discussed. Optimal initial evaluation of patients with MIBC, including imaging and proper staging, are discussed. The role of radical cystectomy and bilateral pelvic lymphadenectomy is defined. Bladder preserving regimens such as a multi-modal approach that combines maximal transurethral resection of bladder tumor (TURBT), chemotherapy and radiation therapy as well as partial cystectomy, radiation alone and maximal TURBT alone, are assessed.

In addition, this guideline will discuss QOL aspects of care and the importance of careful patient counseling. The guidelines will also address timing and mode of testing used in surveillance of disease. Finally, there will be a section devoted to variant histology and the

current unique aspects of care for certain non-urothelial cancers of the bladder.

INITIAL PATIENT EVALUATION AND COUNSELING

- 1. Prior to treatment consideration, a full history and physical exam should be performed, including an exam under anesthesia, at the time of transurethral resection of bladder tumor for a suspected invasive cancer. (Clinical Principle)**

A thorough history and physical exam is important in evaluating not only bladder cancer risk but also the overall health of the patient and his/her co-morbidities. This examination will help to determine optimal management and may impact both the readiness for surgery and the type of procedure or urinary diversion that is best suited for the patient.^{38,39} It will also identify potential risks of surgery and identify genitourinary abnormalities that may affect pre- or intra-operative decision-making. An exam under anesthesia (EUA) provides valuable information for the clinical staging and resectability of the primary tumor at surgery. This information contributes to the overall determination of clinical stage and assessment of potential benefit of neoadjuvant chemotherapy (NAC).^{40,41} Presence of a large/3-dimensional, residual mass after TURBT (cT3b), invasion of adjacent structures (cT4a), or fixation (cT4b) imply locally advanced clinical stage. If the patient has hydronephrosis on imaging or on retrograde pyelogram a ureteral stent should be placed if possible to maintain or improve renal function.

- 2. Prior to muscle-invasive bladder cancer management, clinicians should perform a complete staging evaluation, including imaging of the chest and cross sectional imaging of the abdomen and pelvis with intravenous contrast if not contraindicated. Laboratory evaluation should include a comprehensive metabolic panel (complete blood count, liver function tests, alkaline phosphatase, and renal function). (Clinical Principle)**

The goal of preoperative imaging is to identify, as accurately as possible, the clinical stage and to confirm that the bladder cancer is non-metastatic. The Panel recognizes the lack of both sensitivity and specificity for these imaging modalities to determine intra-abdominal and distant metastatic disease, and that no imaging modality has been proven to be superior to another. This imaging attempts to determine 1) feasibility and

safety of removing of the bladder 2) presence of pelvic or retroperitoneal lymph node metastases 3) the presence of hydronephrosis 4) the presence of upper tract disease 4) the local extent of the disease, and 5) possible visceral/distant metastatic sites.

The recommended preoperative imaging evaluation consists of cross-sectional imaging of the abdomen and pelvis in addition to chest imaging. The most common forms of imaging include CT or MRI of the abdomen and pelvis.^{42,43} Ideally, the patient should have intravenous contrast with delayed imaging that allows for evaluation of the renal pelvis and ureters for upper tract carcinomas. In patients who are not able to receive intravenous contrast, cross-sectional imaging with MRI (with gadolinium, if possible) or non-contrast imaging combined with retrograde pyelograms are acceptable alternatives.

In addition to abdominal and pelvic imaging, patients should have chest imaging. While realizing the possibility of false positive findings, there is a strong association of bladder cancer with smoking, therefore, prior smokers may benefit from a chest CT while non-smokers should have a minimum of a chest x-ray (with posterior-anterior and lateral images). Non-smokers also may benefit from CT imaging to evaluate for metastatic cancer.⁴⁴ In the absence of an elevated alkaline phosphatase, a bone scan need not be performed, but should be performed with bone pain symptoms.⁴⁵

The role of PET imaging is currently undefined in the staging of bladder cancer and is not routinely indicated for all initial staging evaluations.⁴⁶⁻⁴⁸ Although some studies have demonstrated increased sensitivity to identify abnormal pelvic lymph nodes and chest lesions in invasive bladder cancer patients, the Panel recommends that PET imaging should be reserved for patients with abnormal chest, abdominal, or pelvic imaging that require further evaluation, or if biopsy of a suspicious lymph node is not feasible. Laboratory evaluation should include a comprehensive metabolic panel as the choice of urinary diversion in patients undergoing cystectomy is greatly influenced by metabolic abnormalities, such as acidosis or renal or hepatic insufficiency, and abnormal laboratory values may impact the ability to administer chemotherapy. A complete blood count provides information regarding anemia and possible occult infection.

3. An experienced genitourinary pathologist should review the pathology of a patient when variant histology is suspected or if muscle invasion is equivocal (e.g.,

micropapillary, nested, plasmacytoid, neuroendocrine, sarcomatoid, extensive squamous or glandular differentiation).
(Clinical Principle)

The identification of variant bladder cancer histology can be challenging with high inter-observer variability among pathologists.⁴⁹ The Panel recommends that the TURBT pathology slides be evaluated by an experienced genitourinary pathologist if variant histology is suspected, and ideally the percentage of cancer that includes variant histology should be described. Pathologic re-review of cystectomy specimens by experienced genitourinary pathologists may identify variants that alter treatment in up to 33% of patients.^{50,51} Compared to carcinomas of pure urothelial origin, tumors with variant histology may be more locally advanced, and decisions about surgery, perioperative chemotherapy or bladder preservation may be influenced.⁵²⁻⁵⁴ The Panel recognizes that molecular biomarkers will likely assist in subtyping bladder cancer and may influence treatment choice in the future. Later in this document, the Panel outlines current differences in evaluation and treatment plans for patients with certain histologic variant pathology.

4. For patients with newly diagnosed muscle-invasive bladder cancer, curative treatment options should be discussed before determining a plan of therapy that is based on both patient comorbidity and tumor characteristics. Patient evaluation should be completed using a multidisciplinary approach. (Clinical Principle)

In order to provide the patient with all potential therapeutic options and to engage him or her in shared decision making, the Panel recommends a multidisciplinary discussion involving surgery, chemotherapy, and radiotherapy. In some practice locations, the patient is able to have consultation with multiple providers. Alternatively, at a minimum, this multidisciplinary approach would include discussing the potential risks and benefits of all accepted forms of therapy that takes into account patient preferences. For surgical intervention, this would include a discussion of the potential benefit of NAC and the risks and morbidity associated with radical cystectomy. Patients should be informed by the counseling clinician about all forms of urinary diversion and the life-style changes associated with each diversion. In patients who are candidates for (or desire) a continent diversion, a referral to a urologist trained in performing these diversions should be considered.⁵⁵ Consideration should be given to

geriatric or nutritional support to improve the status on patients who are frail, with advanced age or with poor cardiac and nutritional status, in whom surgery is planned but associated with a high risk of morbidity and mortality.^{56,57} For those patients considering bladder preservation, a multi-disciplinary team consultation and discussion is preferred. The urologist, radiation oncologist, and medical oncologist should determine if the patient's tumor and medical condition are favorable for such a regimen. These characteristics would include 1) unifocal tumor, 2) no carcinoma in situ (CIS), 3) no evidence of hydronephrosis, and 4) a tumor that can be completely transurethraly resected.

5. Prior to treatment, clinicians should counsel patients regarding complications and the implications of treatment on quality of life (e.g., impact on continence, sexual function, fertility, bowel dysfunction, metabolic problems). (Clinical Principle)

Patients with MIBC experience multiple issues with regard to QOL. The untreated disease can impact continence and result in bleeding from the primary tumor as well as pain and multiple lower urinary tract symptoms. Treatments such as radical cystectomy and urinary diversion can have a significant impact on continence, sexual function, fertility, bowel function, and metabolic parameters among others. Similarly, multi-modal approaches including chemotherapy and radiation therapy may have a significant impact on QOL. While cure is usually the primary goal, it is important to discuss the implications of different treatment options with patients prior to final decision making with regard to therapeutic approach as patients may ascribe different values to these issues from their clinicians.⁵⁸

There are considerable data regarding QOL for MIBC patients, focusing on cystectomy and urinary diversion to inform patient decision regarding surgical options. Several instruments are available to assess patient-reported outcomes (PROs) including five bladder cancer-specific PRO instruments (three of which have been validated) that focus on the experience of NMIBC patients,^{59,60} MIBC patients,⁶¹ and patients across the spectrum of NMIBC and MIBC.^{62,63} Prior to treatment, the acute and long-term impacts of therapy should be discussed. Patients should understand the possible impact of age and gender on the likelihood of complications after cystectomy, with older patients and women experiencing a higher rate of complications.^{64,65}

A review of cystectomy procedures in patients over 65 found that complication rates ranged extensively and

included ileus (2–32%), infections (mainly pyelonephritis, 5–39%), and urinary diversion-related complications (up to 33%).⁶⁵ Although a significant proportion of complications are less severe, high-grade complications have been observed in approximately 20% of patients after radical cystectomy.⁵⁴ Mortality rates are less than 3% in most series but can be as high as 4–6% in patients over 75 years of age.^{66–68} Readmission rates range from 10–30%,^{68–70} and a recent retrospective review reported that of those readmitted, 26% required readmission to an intensive care unit.⁷¹ A recent prospective RCT that compared open and robotic assisted radical cystectomy found similar 90-day grade 2–5 complications defined by a modified Clavien system and were observed in 62% and 66% of robotic assisted radical cystectomy and open radical cystectomy patients, with the majority being of lower grade.⁷²

Bladder preserving multi-modal therapy has also been associated with early and late (greater than 120 days post-therapy) toxicities. In a prospective study of 44 patients with localized bladder cancer who underwent maximal TURBT and concurrent platinum-based chemotherapy along with radiation therapy (64 Gy in 32 fractions to the whole bladder and 55 Gy to the pelvic nodes), 68% experienced reversible early gastrointestinal toxicity (all grade 1 and 2) and 84% experienced reversible early GU toxicity (Gr 1: 39%, Gr 2: 34%, Gr 3: 11%). Furthermore, late gastrointestinal and genitourinary toxicity were 27% and 29%, respectively.⁷³ Despite these late effects, the QOL reported by patients undergoing bladder preserving multi-modal therapy in one series reported that 85% of patients had only occasional or no urinary urgency, 25% moderate bowel control symptoms, and 50% normal erectile function.⁷⁴ Although not well-documented, a small increased chance of a secondary malignancy should be discussed. The patients also need to be informed that they will need continued evaluation of their bladder with cystoscopy and may require cystectomy in the future if their disease relapses within the bladder.

Other than early issues related to treatment, the long-term consequences of treatment are critical to discuss with patients. There are important consequences for urinary control and sexual function. Patients who undergo ileal conduit urinary diversion will have to contend with external appliances and potential issues with leakage or stomal complications.⁷⁵ Preoperative counseling with an enterostomal therapist provides valuable education and is recommended prior to surgery. Patients with continent cutaneous reservoirs

require self-catheterization for the rest of their lives and have the potential for incontinence via their stoma, stricture, pouchitis, pouch stones, and metabolic derangements. Patients with neobladders have a risk of incontinence (especially night-time), bladder neck contractures, voiding dysfunction with retention, fistula formation, as well as the risk of metabolic issues. The risk of urinary retention, described in the literature as hypercontinence (failure to empty), is higher in women.⁷⁶

Catheterization rates for men are up to 10% and vary between 30-50% for women.⁷⁷⁻⁸⁴ There are also significant risks of sexual dysfunction. Nerve-sparing cystectomy is not commonly utilized, and even with this approach the risk of impotence is 40% or greater.⁸⁵ Similarly, a review assessing female sexual function post radical cystectomy and urinary diversion found that loss of sexual desire and orgasmic disorders were frequently reported (49% and 39%, respectively). Dyspareunia and vaginal lubrication disorders were also reported in 25% and 9.5%, respectively. In female patients receiving gynecologic organ- or nerve-sparing cystectomy, the incidence of sexual dysfunction was reduced to 10% versus 59% for those receiving conventional cystectomy.⁸⁶ While most patients are not in the age group where fertility is an important factor, the impact on fertility needs to be discussed with younger patients as well. Furthermore, the preservation of uterus, anterior vaginal wall, and ovaries may be an option for women in highly select cases. Options for the preservation of the prostate and seminal vesicles (for men desiring fertility preservation) should be discussed with attention towards the impact on cancer control.

Bladder preserving multi-modal therapies for bladder cancer can also adversely impact long-term urinary and sexual function. Clinicians should inform patients about potential changes in sexual function resulting from bladder cancer treatment and should refer them to appropriate medical professionals for treatment of sexual dysfunction when indicated.

While the data is scant, there is a known harmful impact of pelvic radiation on sexual function in both men and women.⁸⁷ Furthermore, as noted above, there is a risk for late genitourinary and gastrointestinal toxicity.⁷³ Urinary symptoms can vary from obstructive symptoms, such as worsening stream, to irritative symptoms, such as frequency/urgency/nocturia, and bleeding. Bowel symptoms can include loose stools, diarrhea, hematochezia, or tenesmus.

Metabolic and nutritional issues can also result from urinary diversions.⁷⁵ Resection of an ileal or colonic

segment of bowel may result in malabsorption of bile salts, although this is uncommon for conduits. Use of the distal ileum may also lead to inadequate absorption of vitamin B12 intrinsic factor complex resulting in megaloblastic anemia or neurological symptoms. There is also a risk for electrolyte abnormalities due to reabsorption of excreted metabolites, with hyperchloremic hypokalemic metabolic acidosis representing the most common abnormality for ileal and colonic segments. Patients need to be informed that medications may be necessary to correct these abnormalities. Several studies have noted a risk of decline in long-term renal function in patients undergoing cystectomy.⁸⁸ A study of 1,631 patients who underwent radical cystectomy found that by 10 years after radical cystectomy, the risk of a renal function decrease was similar for incontinent and continent diversions (71% and 74%, respectively, $p = 0.13$).⁸⁸ There may also be a higher risk of fracture after cystectomy, possibly as a consequence of metabolic acidosis. A population-based study using SEER-Medicare-linked data including 50,520 patients, of whom 4,878 had cystectomy and urinary diversion, found that cystectomy was associated with a 21% greater risk of skeletal fracture (adjusted HR, 1.21; 95% CI, 1.10 to 1.32) compared with no cystectomy.⁸⁹

TREATMENT

NEOADJUVANT/ADJUVANT CHEMOTHERAPY

6. Utilizing a multidisciplinary approach, clinicians should offer cisplatin-based neoadjuvant chemotherapy to eligible radical cystectomy patients prior to cystectomy. (Strong Recommendation; Evidence Level: Grade B)

The Panel advocates cisplatin-based chemotherapy prior to radical cystectomy based predominantly on two large phase III randomized trials that evaluated the effects of NAC versus no NAC on mortality. The largest trial ($n=976$) tested neoadjuvant cisplatin, methotrexate and vinblastine (CMV) or no NAC prior to radical cystectomy, radiation therapy, or both.⁹⁰ This trial demonstrated a decreased risk of cancer-specific mortality for the combined approach (NAC followed by cystectomy) versus cystectomy or radiation therapy alone, or both without NAC. After an initial reported median follow up of four years, the difference was not statistically significant (HR 0.85, 95% CI 0.71 to 1.02), but longer follow up (median 8 years)⁹¹ of this study reported NAC led to a significantly decreased risk of cancer-specific mortality (HR 0.74, 95% CI 0.57 to 0.96) in the subgroup of patients who underwent

radical cystectomy (n=428). There was also a 16% reduction in cancer-specific mortality in those patients who received three cycles of CMV before radical cystectomy or radiation therapy. This led to an increase in 3-year cancer-specific survival from 50-56%, an increase in 10-year survival from 30-36%, and a median survival advantage of 7 months (from 37 to 44 months). Another trial⁹² (n=307) of neoadjuvant methotrexate, vinblastine, Adriamycin, and cisplatin (MVAC) plus radical cystectomy with regional lymphadenectomy was associated with a decreased risk of all-cause mortality (59% versus 65%, HR 0.75, 95% CI 0.57 to 1.00) and bladder cancer mortality (35% versus 50%, HR 0.60, 95% CI 0.41 to 0.82) versus cystectomy plus lymphadenectomy without NAC after a median of 8.7 years follow up. Neoadjuvant MVAC was also associated with longer median duration of survival (77 versus 46 months, p=0.05). Several other trials were unable to show significant differences in survival; however, many of them used regimens that are no longer used in clinical practice.⁹³⁻⁹⁶ Several non-randomized single arm phase II clinical trials have evaluated dose-intensified (dose-dense) regimens of MVAC and gemcitabine and cisplatin, and have reported significant clinical activity.^{97,98} These regimens have been evaluated in the metastatic setting and found to have similar activity with comparable or decreased toxicity.⁹⁹⁻¹⁰¹

There are no validated predictive factors or clinical characteristics (including age) associated with an increased or decreased probability of response and benefit using neoadjuvant cisplatin-based chemotherapy

Multiple retrospective studies have evaluated predictive biomarkers for response to NAC for MIBC, but none have been prospectively validated. One prospective trial testing MVAC prior to cystectomy in high-risk organ confined bladder cancer with p53 alterations by immunohistochemistry did not find any association with outcome.¹⁰² Several retrospective series have each suggested clinical and molecular parameters to identify patients who might benefit from NAC. However, these have not been prospectively tested and validated, and thus, the Panel does not recommend any at this time.^{36,41,103-105} One national prospective trial is examining this issue, but results are not available.

The best regimen and duration for cisplatin-based NAC remains undefined

No completed prospective randomized trials have compared gemcitabine and cisplatin (GC) to other regimens as NAC for MIBC. Several retrospective

cohort studies suggest that there may not be a significant difference in outcome between GC and MVAC, although these studies cannot be considered as conclusive evidence.¹⁰⁶⁻¹⁰⁹ As such, the current regimens with Level A evidence supports either CMV or MVAC in the neoadjuvant setting.

The optimal duration of NAC remains undefined. Most studies have evaluated three to four cycles of preoperative chemotherapy over about three months, although several smaller studies have tested shortened intensified regimens using six to eight weeks of chemotherapy.^{97,98} There have been no randomized trials comparing outcomes between different durations of therapy.

The decision regarding eligibility for cisplatin-based NAC should be based on comorbidities and performance status, including cardiac status and presence of peripheral neuropathy, hearing loss, and renal dysfunction

Cisplatin eligibility is a major determinant of candidacy for NAC. Toxicities of cisplatin, including nephrotoxicity, diminished cardiac function, neurotoxicity, and hearing loss, preclude 30-50% of MIBC patients from safe receipt of cisplatin-based chemotherapy.¹¹⁰ In addition, reduced performance status (WHO or ECOG PS ≥ 2 or Karnofsky performance status of $\leq 60-70\%$) is associated with increased toxic effects of cisplatin. Baseline renal dysfunction with an estimated or calculated creatinine clearance $< 60\text{ml/min}$ is generally felt to preclude patients from cisplatin-based chemotherapy, although selected patients may be treated by using split-dosing of cisplatin and aggressive hydration. New York Heart Association Class III-IV heart failure (marked or severe limitation in activity) is felt to be exclusionary due to the volume of intravenous fluid required for safe cisplatin administration. Hearing loss at baseline consisting of a decrease of $>25\text{ dB}$ in at least one ear at two contiguous frequencies (CTCAE v4.0 grade 2 hearing loss) is also considered a contraindication, as cisplatin may lead to an additional 20 dB loss in patients, resulting in severe hearing loss. Cisplatin-induced peripheral neuropathy is increased in patients with pre-existing sensory neuropathy and may preclude treatment.

7. Clinicians should not prescribe carboplatin-based neoadjuvant chemotherapy for clinically resectable stage cT2-T4aN0 bladder cancer. Patients ineligible for cisplatin-based neoadjuvant chemotherapy should proceed to definitive locoregional therapy. (Expert Opinion)

There is insufficient data to recommend non-cisplatin-based regimens as either NAC or adjuvant chemotherapy (AC) for MIBC. Although some suggestive cohort and clinical trial data exist,¹¹¹ there is no high level evidence that carboplatin-based regimens lead to increased survival in this setting for MIBC. Downstaging rates in these series appear lower than with cisplatin-based chemotherapy, and comparative data is lacking with either radical cystectomy alone or neoadjuvant cisplatin-based combinations. In the metastatic setting, carboplatin-based combinations are felt to be inferior based on the results of small randomized trials.^{112,113}

8. Clinicians should perform radical cystectomy as soon as possible following a patient's completion of and recovery from neoadjuvant chemotherapy. (Expert Opinion)

Although retrospective data exist in regards to a safe time from chemotherapy completion to cystectomy, there is no prospective data regarding the optimal timing of cystectomy after NAC and thus this remains undefined;¹¹⁴ however, the Panel recommends radical cystectomy preferably within six to eight weeks of completion of chemotherapy, and no more than four months following completion of chemotherapy, unless medically inadvisable. Frequent multidisciplinary collaboration between medical oncologists and urologists is critical for timely implementation of integrated therapy. Further delay may decrease the therapeutic benefit of systemic therapy.

9. Eligible patients who have not received cisplatin-based neoadjuvant chemotherapy and have non-organ confined (pT3/T4 and/or N+) disease at cystectomy should be offered adjuvant cisplatin-based chemotherapy. (Moderate Recommendation; Evidence Level: Grade C)

No single randomized clinical trial has demonstrated a significant improvement in overall survival with AC. Four trials reported AC with an associated decreased risk of mortality versus no AC, but no trial reported a statistically significant benefit.¹¹⁵⁻¹¹⁸ One trial (n=50) found no difference between adjuvant CMV versus no AC in 5-year survival (52% versus 32%, RR 0.71 95% CI 0.43 to 1.15).¹¹⁵ There was also no difference in the subgroup of patients (n=15) found to be node-negative (71% versus 25%, RR 0.38, 95% CI 0.11 to 1.31). Another trial (n=183) found no difference between adjuvant cisplatin and gemcitabine versus no AC in 5-

year survival among all patients (43% versus 54%, p=0.24) or in the subgroup of node-negative patients (65% versus 73%, p=0.65).¹¹⁶ One trial (n=83) found no difference between adjuvant cisplatin and methotrexate versus no AC in survival among node-negative patients after a median follow up of 69 months (49% versus 38%).¹¹⁸

The largest trial randomized 284 patients to either immediate adjuvant cisplatin-based combination chemotherapy with either MVAC, dose intensified MVAC, or gemcitabine and cisplatin versus treatment at relapse.¹¹⁹ This trial did not demonstrate a significant improvement in overall survival with immediate versus deferred treatment (adjusted HR 0.78, 95% CI 0.56-1.08; p=0.13). However, immediate treatment did prolong progression-free survival by an estimated 1.12 years (HR 0.54, 95% CI 0.4-0.73, p<0.0001).

All of the AC trials were terminated early, and therefore are underpowered to provide sufficient evidence to state definitively the benefit of AC in MIBC. However, meta-analyses have suggested a possible benefit, albeit based on data of variable quality.^{120,121} Thus, the Panel advocates that cisplatin-eligible patients with high-risk pathologic features who do not receive NAC be offered adjuvant therapy following radical cystectomy on the basis of a multi-disciplinary consultation with a thorough informed consent. In patients who are non-cisplatin-eligible, consideration of referral to clinical trials is reasonable.

RADICAL CYSTECTOMY

10. Clinicians should offer radical cystectomy with bilateral pelvic lymphadenectomy for surgically eligible patients with resectable non-metastatic (M0) muscle-invasive bladder cancer. (Strong Recommendation; Evidence Level: Grade B)

For non-metastatic MIBC, radical cystectomy combined with NAC is the standard of treatment.¹²² Radical cystectomy either alone or in combination with chemotherapy in patients with clinically non-metastatic MIBC has been compared to bladder sparing therapy in one RCT,¹²³ seven retrospective cohort studies¹²⁴⁻¹³⁰ and one non-randomized controlled clinical trial.¹³¹ Seven studies evaluated overall survival with bladder sparing therapies versus radical cystectomy.¹²³⁻¹²⁹ A population-based cohort study (n=1,843) found that bladder preserving therapy was associated with decreased 5-year survival compared to radical cystectomy (27.9% versus 46.5%).¹²⁴ The lower probability of mortality associated with cystectomy was

observed in the multivariable analysis adjusting for individual clinic-pathologic variables (HR for mortality 0.79, 95% CI 0.67 to 0.93) as well as in a propensity-adjusted analysis (HR 0.79, 95 CI 0.65 to 0.95). However, the AHRQ review found that these trials had methodological issues as well as bias in terms of survival comparisons; none evaluated QOL.¹

A retrospective cohort study (n =108) also found radical cystectomy associated with a higher likelihood of survival (50% versus 58% at 10 years) after adjustment for age, tumor stage, nodal status, grade, and tumor multiplicity, though the difference was not statistically significant (HR 0.62, 95% CI 0.28 to 1.43).¹²⁹ Four other cohort studies evaluated all-cause mortality but did not attempt to adjust for potential confounders.¹²⁵⁻¹²⁸ While differences in several studies were not statistically significant, one study (n=145) found radiotherapy associated with decreased likelihood of survival at 3 years versus radical cystectomy (39% versus 69%, p=0.03).¹²⁷ Another study (n=148) found bladder preserving radiation therapy or maximal TURBT each associated with increased risk of 5-year bladder cancer-specific mortality versus radical cystectomy in patients with T2 or T3 tumors (82% versus 75% versus 57%), though the difference was only statistically significant for radiation therapy (RR 1.44, 95% CI 1.02 to 2.05).¹²⁶

While both open and robotic approaches to cystectomy are currently employed, there is insufficient evidence to recommend for or against robotic cystectomy based on oncologic and/or functional outcomes. Based on three small randomized trials¹³²⁻¹³⁴ as well as observational data and systematic reviews, robotic cystectomy is associated with longer operative time, higher cost, decreased blood loss, similar lymph node yield, and no clear difference in major complication rates.¹³⁵

Patients considering a radical cystectomy should be counseled regarding the high rate of complications, both acute and chronic, as outlined previously in this guideline.^{136,137} This is particularly critical given that patients undergoing cystectomy are usually older and have multiple comorbid conditions. Coupled with the complexity of the procedure itself, the rate of perioperative complications is high, and readmission to the hospital is as high as 26% at 30 days.^{138,139} Therefore, an assessment of anesthetic and surgical fitness is a key component of the decision process in patients with MIBC. This is a multifactorial assessment and often requires a multidisciplinary team, including an anesthesiologist and primary care clinician and, when appropriate, geriatric specialists, pulmonologists,

and/or cardiologists.

11. When performing a standard radical cystectomy, clinicians should remove the bladder, prostate, and seminal vesicles in males and should remove the bladder, uterus, fallopian tubes, ovaries, and anterior vaginal wall in females. (Clinical Principle)

Radical cystectomy involves removal of the bladder (cystectomy) along with the organs at highest risk of harboring tumors that extend beyond the bladder. Thus, in males, this includes the prostate and seminal vesicles, and in females it includes the anterior vaginal wall, uterus, cervix, fallopian tubes, and ovaries. This is based on Clinical Principle and can be modified as specified below in selected patients (see statement 12). Preoperative counseling should be performed for patients who have cancer at the bladder neck (or prostatic urethra in men) in regards to its possible necessity.^{55,140} In men who have invasive cancer at the margin of resection at the apical urethra, a urethrectomy should be performed (immediate or delayed). This can be assessed with a frozen section or final pathology performed at the time of radical cystectomy.¹⁴¹ A urethrectomy should be performed for women not undergoing reconstruction with a neobladder in order to reduce the likelihood of a positive surgical margin or tumor recurrence.

12. Clinicians should discuss and consider sexual function preserving procedures for patients with organ-confined disease and absence of bladder neck, urethra, and prostate (male) involvement. (Moderate Recommendation; Evidence Level: Grade C)

Preservation of sexual function is safe and feasible in many patients undergoing radical cystectomy. In all patients who desire sexual function preservation and are sexually active, a nerve-sparing procedure should be discussed and offered as long as it will not compromise oncologic control.¹⁴² In women, vaginal sparing radical cystectomy can be performed when doing so will not compromise tumor control, such as in the absence of cancer in the trigone or bladder base.¹⁴³ Consideration may also be given to preserving the ovaries for hormonal homeostasis, and the anterior vaginal wall and/or uterus may be preserved in the absence of direct tumor extension. Preservation of the ovaries has not been associated with bladder cancer recurrence, and in patients with no known hereditary

risk of ovarian or breast cancer, oophorectomy may not be necessary.¹⁴⁴ In men, prostate-sparing and prostate-capsule sparing cystectomy may be offered to highly select individuals with negative prostatic urethral and transrectal prostate biopsies in whom fertility and sexual function are important considerations. Data on the safety of prostate preservation is based on limited observational data, indicating the need for improved data on oncologic outcomes and to guide its use and understand efficacy for preserving sexual function.^{85,145} It should be noted that nerve sparing procedures in men may offer similar rates of sexual function preservation when compared to prostate-sparing cystectomy.

URINARY DIVERSION

13. In patients undergoing radical cystectomy, ileal conduit, continent cutaneous, and orthotopic neobladder urinary diversions should all be discussed. (Clinical Principle)

The choice of urinary diversion has a significant impact on long-term QOL for patients who undergo radical cystectomy, and each type of diversion is associated with its own unique potential complications. Discussing the pros and cons of each approach is an important component of preoperative education. The Panel emphasized that clinicians should first determine whether or not a patient is a candidate for each of the diversion options, and patients should be counseled regarding all three categories of urinary diversion, if not contraindicated. The suitability of the appropriate bowel segments is a critical determining factor for creation of either a continent cutaneous reservoir or ileal neobladder. If there is limited available bowel or the patient is unwilling to perform self-catheterization, then an ileal conduit may be the most appropriate diversion. If ileum is not available, then a colon conduit or continent cutaneous diversion may be the preferred diversion choice.¹⁴⁶

Absolute contraindications to continent diversion include 1) Insufficient bowel segment length; 2) Inadequate motor function or psychological issues that limit the ability to perform self-catheterization; 3) Inadequate renal or hepatic function that increases the risk metabolic abnormalities as a consequence of reabsorption of urine from continent diversions (e.g. an eGFR < 45); 4) Cancer at the urethral margin (specifically for orthotopic neobladder); and 5) Significant urethral stricture disease that is not correctable.⁷⁵

Patients should understand that the ileal conduit is the

most commonly utilized urinary diversion type. It is an incontinent diversion using a short segment of distal ileum; preservation of the most distal 15 cm can reduce issues related to absorption of B12, fat soluble vitamins, and bile salts.¹⁴⁷ Orthotopic urinary diversions, or neobladders, represent the most common type of continent diversion. While there are several different techniques, the principle of connecting a segment of detubularized and folded bowel to the urethra is a common principle. The main rationale for this approach is to mimic as closely as possible the functional aspects and body image of a native bladder. Although studies have drawn different conclusions, and most show that well-counseled patients have equivalent levels of satisfaction regardless of diversion type, several studies have reported better or marginally better QOL outcomes with neobladders than other diversion types.^{148,149}

The last diversion type is the continent cutaneous reservoir. While there are many techniques for creating continent catheterizable reservoirs, the goal is to create a low-pressure reservoir from detubularized bowel with a continent catheterizable channel to the skin that will avoid involuntary efflux of urine. This type of reservoir is used in patients who want to avoid a stomal appliance and preserve continence but either are not candidates for or do not desire a neobladder. These diversions still require the same selection criteria as for patients with neobladders, including the ability/willingness to catheterize and adequate renal function.¹⁵⁰

14. In patients receiving an orthotopic urinary diversion, clinicians must verify a negative urethral margin. (Clinical Principle)

Pathologic assessment of urethral margin status at the time of surgery is a best practice to determine if a patient is eligible for an orthotopic diversion. The average risk of the development of cancer in the retained urethra is reported as between 1-17% overall in multiple contemporary cystectomy series, with the majority occurring within the first two years after surgery.^{151,152} Reported risk factors include tumor multiplicity, papillary pattern, CIS, tumor at the bladder neck, prostatic urethral involvement, and prostatic stromal invasion. Although prostate involvement is the most significant risk factor for cancer in the urethra, it should not preclude orthotopic diversion, provided that intraoperative frozen section analysis of the urethral margin is without evidence of tumor.^{153,154} Preoperative prostatic urethral biopsies have not proved to be as reliable as urethral frozen sections and should not

exclude patients from orthotopic diversion.¹⁵⁵

In women with MIBC, a comprehensive literature review found that urethral tumor involvement occurs in only approximately 12% of patients undergoing cystectomy.¹⁵⁶ Involvement of the bladder neck, posterior bladder base, or anterior vaginal wall with urothelial carcinoma is an important risk factor for urethral tumor involvement, and intraoperative frozen section analysis of the proximal urethra is a reliable approach to confirm the appropriateness of female candidates for orthotopic diversion. In patients with palpable masses (stage \geq T3b) on bimanual examination, intraoperative frozen sections of the urethral and vaginal margins should also be obtained if a neobladder is being considered.¹⁵⁷

PERIOPERATIVE SURGICAL MANAGEMENT

15. Clinicians should attempt to optimize patient performance status in the perioperative setting. (Expert Opinion)

Given the significant risk of morbidity and prolonged recovery time associated with radical cystectomy, the Panel recommends perioperative patient optimization in accordance with enhanced recovery pathway principles.¹⁵⁸ While a specific enhanced recovery after surgery (ERAS) protocol was not recommended, there are a number of important components that should be considered for any patient undergoing radical cystectomy. A substantial percentage of patients with MIBC are malnourished at the time of diagnosis, and preoperative malnutrition is associated with a significant increase in the risk of postoperative mortality.^{56,159,160} Cystectomy patients at high risk for malnutrition should undergo nutritional counseling in preparation for surgery with the goal of optimizing nutritional status prior to surgery. In addition, all patients undergoing treatment for bladder cancer should receive smoking cessation counseling. This is based on multiple studies supporting the importance of smoking cessation prior to cystectomy, both for reducing postoperative complications and improving long-term oncologic control.¹⁶¹⁻¹⁶³ In the immediate perioperative period, clinicians may consider not routinely prescribing a mechanical bowel preparation when only small bowel will be used for urinary tract reconstruction. While data from prospective RCTs supports not using a bowel preparation prior to colorectal surgery, there is also some data suggesting a potential benefit in the setting of colorectal resection.¹⁶⁴⁻¹⁶⁷ Additionally, limited data suggest that there is no increased risk of perioperative complications in the absence of a mechanical bowel

preparation prior to cystectomy.^{168,169} There are also data to support consideration of preoperative carbohydrate loading in order to diminish postoperative insulin resistance and shorten length of stay.^{170,171} Carbohydrate loading does not appear to lead to an increase in anesthetic risk, despite oral fluid intake within hours of surgery, and it may improve patient comfort and speed recovery of bowel function. During and immediately following surgery, a restrictive transfusion strategy should be utilized in the absence of coronary artery disease or other mitigating factors following American Association of Blood Bank guidelines.¹⁷² While there are no cystectomy-specific randomized trials evaluating disparate transfusion strategies, a restrictive strategy does not appear to increase the risk of adverse events or mortality compared to a liberal transfusion strategy.¹⁷³⁻¹⁷⁵ Other intraoperative considerations should include maintenance of normothermia and normal blood glucose during cystectomy in order to minimize postoperative infection risk. Additionally, fluid management during surgery should seek to avoid fluid excess, and hypovolemia may be utilized to reduce blood loss and expedite recovery of bowel function. Overall, utilization of clinical pathways is associated with decreased narcotic usage, lower incidence of postoperative ileus, and shorter hospital length of stay.¹⁷⁶

16. Perioperative pharmacologic thromboembolic prophylaxis should be given to patients undergoing radical cystectomy. (Strong Recommendation; Evidence Level: Grade B)

Thromboembolic risk following a major pelvic surgery such as radical cystectomy is significant and exposes patients to a potentially life-threatening postoperative complication. Many patients undergoing cystectomy possess several of the risk factors associated with the development of a thrombosis as described in the AUA Best Practice Statement for the Prevention of Deep Vein Thrombosis for patients undergoing a urologic surgery.¹⁷⁷ The use of intermittent pneumatic compression along with pharmacologic agents such as low-dose unfractionated heparin (LDUH) and low molecular weight heparin (LMWH) have been shown to reduce venous thromboembolic risk in patients undergoing a variety of general surgical, urological, and orthopedic procedures.¹⁷⁸⁻¹⁸¹ Thus, given the significant risk of morbidity and mortality, and the strong evidence to support the efficacy of prophylaxis, the Panel recommends the use of combined mechanical and pharmacologic prophylaxis in patients undergoing

radical cystectomy. Strong consideration should be given to initiating pharmacologic prophylaxis just prior to induction of anesthesia; however, the risks of bleeding need be weighed against the benefits of prophylaxis in determining the timing of heparin administration. The optimal timing and duration of chemoprophylaxis for venous thromboembolism prevention has yet to be defined for patients undergoing radical cystectomy. However, increasing evidence suggests that a preoperative dose may decrease venous thromboembolism risk. Perioperative coverage with up to four weeks of treatment following surgery may be beneficial.^{182,183}

17. In patients undergoing radical cystectomy μ -opioid antagonist therapy should be used to accelerate gastrointestinal recovery, unless contraindicated. (Strong Recommendation; Evidence Level: Grade B)

Delayed return of bowel function is a common event following radical cystectomy and a source of morbidity and prolonged hospital stay. The use of peripherally active μ -opioid receptor antagonists has been shown to enhance the recovery of bowel function and decrease hospital length of stay in patients undergoing radical cystectomy and other abdominal surgical procedures.¹⁸⁴⁻¹⁸⁶ Data supporting the use of μ -opioid receptor antagonists includes a prospective RCT of 277 patients that demonstrated a significant improvement in time to bowel function recovery after radical cystectomy (5.5 versus 6.8 days, $p < 0.001$), and shortened hospital length of stay (7.4 versus 10.1 days; $p = 0.005$). The first dose is given just prior to surgery and then continued until diet is tolerated or for a maximum of 15 doses. Other postoperative complications are similar in patients receiving μ -opioid receptor antagonists, although these therapies are contraindicated in patients who have taken opioids for one week or greater prior to surgery.

18. Patients should receive detailed teaching regarding care of urinary diversion prior to discharge from the hospital. (Clinical Principle)

Urinary diversion following radical cystectomy can have a significant impact on health-related QOL, and patient education, including preoperative stoma marking with an enterostomal therapist, has a critical role in preparing patients for the long-term care of their reconstructed urinary tract. Appropriate stoma education with nurse specialists can shorten the hospital length of stay and reduce subsequent stomal-

related complications.¹⁸⁷ Detailed teaching may also improve health-related QOL for patients undergoing stoma surgery.¹⁸⁸ In addition, patient-directed education for other diversion types, such as continent cutaneous diversions and orthotopic diversions, is essential in preparing patients for their post-cystectomy care.

PELVIC LYMPHADENECTOMY

19. Clinicians must perform a bilateral pelvic lymphadenectomy at the time of any surgery with curative intent. (Strong Recommendation; Evidence Level: Grade B)

Mapping studies from patients with invasive bladder cancer have documented the pathways of progression of invasive bladder cancer.^{189,190} Sequential dissemination from the lower pelvic to the more proximal lymph nodes in the pelvis and retroperitoneum is the general pattern of spread, and the risk of regional lymph node metastases is associated with the depth of invasion of the primary tumor. Data from a variety of studies have shown that a pelvic lymphadenectomy can improve disease specific survival and pelvic recurrence risk compared to no pelvic lymphadenectomy at the time of radical cystectomy.¹⁹¹⁻¹⁹⁴ Bilateral pelvic lymphadenectomy should be performed in all patients, including those with unilateral bladder wall involvement, due to documented crossover risk to the contralateral lymphatic chain. Complete bilateral pelvic lymphadenectomy may be difficult or not possible in subsets of patients who have undergone extensive prior pelvic surgery, prior pelvic radiation therapy, or those with extensive vascular disease.

Data on pelvic lymphadenectomy at the time of partial cystectomy are limited; however, complete bilateral pelvic lymphadenectomy should be performed in patients undergoing partial cystectomy for curative intent. A number of series have reported that lymphadenectomy is underutilized and often less extensive in patients undergoing partial cystectomy.^{195,196} Nevertheless, given the well documented role of a complete bilateral pelvic lymphadenectomy at the time of radical cystectomy, there is a strong rationale to extrapolate the same data to the partial cystectomy setting.

20. When performing bilateral pelvic lymphadenectomy, clinicians should remove, at a minimum, the external and internal iliac and obturator lymph nodes

(standard lymphadenectomy). (Clinical Principle)

The quality of the evidence does not currently support a uniform recommendation for the optimal extent of the pelvic lymphadenectomy to maximize therapeutic benefit. However, in order to facilitate adequate staging, a standard lymphadenectomy (bilateral external iliac, internal iliac and obturator lymph nodes), at a minimum, needs to be completed with >12 lymph nodes evaluated.¹⁹⁷ The number of lymph nodes identified by the pathologist is a surrogate for the adequacy of the lymphadenectomy. It reflects the quality and completeness of the surgical dissection as well as the quality of the pathologic examination.¹⁹⁸ Submission of separate nodal packets appears to facilitate identification of lymph nodes and is associated with an increased number of reported lymph nodes.

Eleven cohort studies found more extensive lymphadenectomy (with boundaries extending above the common iliac bifurcation up to or beyond the aortic bifurcation) to be associated with improved all-cause or bladder cancer-specific mortality versus less extensive lymphadenectomy, but studies had methodological limitations, including variability in the lymphadenectomy techniques evaluated, and inconsistency in results.^{191-194,199-206} Six cohort studies found that more extensive lymphadenectomy (above the bifurcation of the common iliac arteries) was associated with a lower risk of bladder cancer recurrence or progression, but again most studies had serious methodological limitations and inconsistent results.²⁰⁷⁻²¹²

BLADDER PRESERVING APPROACHES

PATIENT SELECTION

A multi-modal bladder preserving approach with its merits and disadvantages should be discussed in each individual case. The studies that support bladder preserving strategies, as a general rule, have highly select patient populations. There are currently no randomized trials comparing NAC and radical cystectomy versus multi-modality bladder preserving therapies. In reviewing the available studies regarding multi-modal bladder preserving protocols that employ TURBT, radiation therapy, and chemotherapy for carefully selected patients, the Panel found no strong evidence to determine whether or not immediate cystectomy improved survival when compared to initial bladder sparing protocols that employ salvage cystectomy as therapy for persistent bladder cancer.¹²³⁻

¹³¹ In addition, no high quality evidence directly

compares QOL between the different treatment options; instead a number of studies report on health-related QOL outcomes and draw comparisons to other therapies. The Panel also recognizes that other non-multi-modal bladder-preserving regimens, although having less oncologic efficacy as well as less data, do exist and may be a reasonable option for certain patients, especially those who have poorer performance status.

21. For patients with newly diagnosed non-metastatic muscle-invasive bladder cancer who desire to retain their bladder, and for those with significant comorbidities for whom radical cystectomy is not a treatment option, clinicians should offer bladder preserving therapy when clinically appropriate. (Clinical Principle)

Bladder preserving therapy should be considered for all patients with invasive cancer. Furthermore, it should be offered to all those for whom a cystectomy is medically contraindicated. The type and scope of bladder preserving therapy offered to such individuals will depend upon their age, their tumor, and co-morbidities. Choices include maximal TURBT, partial cystectomy with lymphadenectomy, primary radiation therapy, and multi-modal therapy. Each of these offers patients a treatment that attempts to avoid radical cystectomy, but the chance of success of local eradication of their invasive cancer varies. The Panel's preferred bladder preserving approach is a multi-modal plan that includes maximal TURBT, systemic chemotherapy, radiation therapy, and ongoing cystoscopy to evaluate response. For each of these approaches, cystectomy still needs to be strongly considered and discussed with patients.

22. In patients under consideration for bladder preserving therapy, maximal debulking transurethral resection of bladder tumor and assessment of multifocal disease/carcinoma in situ should be performed. (Strong Recommendation; Evidence Level: Grade C)

The Panel recommends maximal transurethral resection to remove all visible disease. In multiple prospective trials, the ability to resect all tumor predicted the best response to bladder preserving therapies. In prospective studies from the RTOG and from single institutions, the rates of local control are approximately 20% higher if a visibly complete resection was achieved at TURBT.²¹³⁻²¹⁵ In multivariable analyses this factor is independent of tumor size and stage.

Patients with large tumors unable to be resected by TURBT, multifocal CIS, T3/T4 tumors, and/or hydronephrosis are not ideal candidates for any type of bladder preserving therapy. Random biopsies may help ensure that there is no associated CIS. Although patients with these characteristics may be cured by a multi-modal treatment of maximal TURBT, systemic chemotherapy, and radiation, that likelihood is low, and the probability for the need of salvage cystectomy is significant.^{123-131,213-220}

For patients with newly diagnosed MIBC, it is unknown how variant histology affects outcomes associated with multi-modal bladder preserving therapy. Patients with adenocarcinomas, sarcomas, and squamous cell carcinomas have not been included in prospective studies of radiation-based bladder preservation and thus should not receive this therapy unless medically unfit for cystectomy.

MAXIMAL TURBT AND PARTIAL CYSTECTOMY

23. Patients with muscle-invasive bladder cancer who are medically fit and consent to radical cystectomy should not undergo partial cystectomy or maximal transurethral resection of bladder tumor as primary curative therapy. (Moderate Recommendation; Evidence Level: Grade C)

Although to date there are no randomized, head-to-head trials, radical cystectomy offers a significant therapeutic benefit for the vast majority of patients compared to partial cystectomy or maximal TURBT.²¹⁶ The few existing cohort studies comparing maximal TURBT alone to radical cystectomy to assess overall or bladder specific mortality or loco-regional recurrence do not provide absolute direction because of methodological shortcomings in the studies, inconsistent results, and imprecise estimates. Similarly, there was insufficient evidence from cohort studies on the outcomes of partial cystectomy compared with radical cystectomy on risk of overall or bladder specific mortality or loco-regional recurrence because of methodological shortcomings in the studies, inconsistent results, and imprecise estimates. With the exception of multi-modal bladder preserving chemotherapy and radiation therapy, therapies other than radical cystectomy (e.g., partial cystectomy, TURBT alone, chemotherapy alone, or radiation alone) are associated with increased risk of all-cause mortality in unadjusted analyses.^{216,218,219,221}

In a highly select group of patients, partial cystectomy or maximal TURBT may be considered. The selection

criteria include accessible tumor location, size <3cm, no multi-focal CIS, no hydronephrosis, adequate bladder function, and no residual T1 or higher stage disease. For these select patients, a maximal TURBT can be considered and may be achieved.^{131,220} Patients should be informed that approximately 40% of patients treated in this manner will ultimately require cystectomy and may have an increased risk of bladder cancer mortality.

Patients who are unfit either for cystectomy or multi-modal bladder preserving therapy may be offered radical, maximal TURBT alone if they have a tumor that can be macroscopically resected completely, and for which repeat TURBT is negative. Studies have demonstrated that a significant proportion of patients with small MIBC's who have a negative re-resection may be locally controlled by TURBT. One multi-center experience demonstrated cancer specific survival of 81.9% at 5 years with an intact bladder rate of 75.5% in patients treated in this manner.¹³¹ The proportion of cancer control varies according to the series and the selection criteria. It is unclear what small proportion of all patients with MIBC are in fact suitable for such an approach, and thus the Panel believes this indication is limited.

For patients who are medically unfit or decline cystectomy or multi-modal therapy with a solitary, small MIBC in a location that may be removed completely with an adequate negative margin and a functional residual bladder capacity, and without concomitant CIS, clinicians may offer partial cystectomy and bilateral pelvic lymphadenectomy. Clinicians should offer perioperative chemotherapy for cisplatin-eligible patients with MIBC who have chosen partial cystectomy and pelvic lymphadenectomy.

PRIMARY RADIATION THERAPY

24. For patients with muscle-invasive bladder cancer, clinicians should not offer radiation therapy alone as a curative treatment. (Strong Recommendation; Evidence Level: Grade C)

Radiation therapy alone in the form of external beam radiation therapy (EBRT) has resulted in inferior disease specific and overall survival outcomes to those reported with multi-modality therapy. Radiation therapy alone has been associated with high rates of pelvic failure; five-year local control rates of 31-50% have been reported, but these may be under-estimates as those who develop metastatic disease within this interval are less likely to undergo continued bladder surveillance.²²²⁻²²⁷

While a number of factors have been identified as more favorable for primary radiation therapy, primary, solitary radiation therapy demonstrates decreased efficacy compared to other multi-modal bladder preservation strategies.

For patients with a small MIBC at the dome of the bladder removed by partial cystectomy or TURBT, it has not been determined whether interstitial brachytherapy reduces local recurrence rates. Interstitial brachytherapy has been used in a number of specialized centers to treat small, solitary MIBCs. Although there are reports of high local control rates in the literature, the quality of this evidence is low, and the role of selection is paramount.²²⁸⁻²³⁰

MULTI-MODAL BLADDER PRESERVING THERAPY

25. For patients with muscle-invasive bladder cancer who have elected multi-modal bladder preserving therapy, clinicians should offer maximal transurethral resection of bladder tumor, chemotherapy combined with external beam radiation therapy, and planned cystoscopic re-evaluation. (Strong Recommendation; Evidence Level: Grade B)

The rationale for combining TURBT, concurrent chemotherapy, and EBRT is two-fold. Certain cytotoxic agents may sensitize tumor cells to radiation, thus increasing cell kill in a synergistic fashion. In addition, up to 50% of those with MIBC may harbor occult metastases. The addition of systemic chemotherapy has the potential to improve loco-regional control, and incorporating cisplatin-based multi-agent regimens in the neoadjuvant setting may provide additional benefit for control of occult metastatic disease at an early stage.

An important component of multi-modal therapy is the maximal resection of all visible tumor with TURBT prior to EBRT and chemotherapy. This has been shown in prospective series to improve local control by approximately 20%.²³¹

For medically operable patients receiving staged multi-modal therapy, clinicians should offer a mid-course evaluation to allow for the early selection of non-responders before consolidation radiotherapy is given. This may facilitate salvage cystectomy. Bladder preserving strategies all mandate close follow up and early salvage cystectomy if necessary.^{231,232} Pelvic surgery is more difficult after prior full-dose EBRT with a possible higher rate of complications, and radiation may limit the choice of urinary diversions and the

ability to perform nerve-sparing surgery.²³³ Ideally, patients would be assessed at an earlier point in their EBRT and those unlikely to be pathologic complete responders identified and offered cystectomy. Some of the multi-modal strategies halt the radiation at a dose of 40-45Gy (approximately 2/3 of the total dose), repeat a cystoscopy with re-biopsy, and, if muscle-invasive tumor still persists, recommend cystectomy at that time. While appealing to clinicians, there is no current evidence that this approach actually reduces the complication rate of salvage cystectomy. For patients who are medically unfit for surgery, this mid-course evaluation may be omitted, and these patients can be treated uninterrupted with a definitive dose of radiation along with concurrent chemotherapy.

Comparing multi-modal bladder preserving surgery with radical cystectomy is difficult. Much of the data, including one RCT and multiple cohort and registry series, have compared EBRT with and without chemotherapy versus radical cystectomy.¹²³⁻¹²⁹ The RCT found no difference in overall survival between the two approaches, although a higher risk of loco-regional failure was seen in the bladder preservation arm.¹²³ Unfortunately, none of these studies adequately corrected for age, comorbidities, nodal status, and pathologic versus clinical staging. Mak et al. have reported a 5-year survival of 57% for all study patients, of whom, 80% did have an intact bladder.²³¹ It is unclear what proportion of patients who, having initially chosen bladder preservation, ultimately require cystectomy in a non-study setting. The reported bladder preservation rates may be dependent upon the degree of initial patient evaluation and selection. Thus, currently the Panel believes that multi-modal bladder preserving therapy is the preferred treatment in those patients who desire bladder preservation and understand the unique risks associated with this approach or those who are medically unfit for surgery.

26. Radiation sensitizing chemotherapy regimens should include cisplatin or 5-fluorouracil and mitomycin C. (Strong Recommendation; Evidence Level: Grade B)

One randomized trial has directly addressed the value of adding chemotherapy to definitive EBRT.²³⁴ The Bladder Cancer 2001 trial of 360 patients demonstrated that concurrent chemo-radiation using 5-fluorouracil (5-FU) and mitomycin C significantly improved loco-regional disease-free survival when compared to radiation alone (67% versus 54% at two years; HR 0.68, $P = 0.03$ with median follow up of 70 months). Survival at 5 years was higher with chemo-radiotherapy

(48% versus 35%; HR 0.82; $P = 0.16$), but the study was not powered to determine a difference in overall survival. No increase in late bladder toxicity was observed.

Many prospective studies have reported high rates of local control (>70%) in patients selected for treatment on protocols that included cisplatin with or without 5-FU. One Canadian RCT compared patients receiving radiation with or without cisplatin and found that loco-regional control was enhanced with the use of cisplatin.²³⁵ However, the study was weakened by its small size (96 patients) and its inclusion of patients receiving both preoperative and definitive radiation. The precise regimen of chemotherapy combined with radiation remains undefined as various regimens of neoadjuvant, concurrent and adjuvant cisplatin-based regimens (e.g., cisplatin alone, CMV, cisplatin + paclitaxel or cisplatin + gemcitabine) have been studied.²³¹ In the neoadjuvant setting, chemotherapy with CMV reduced the risk of death regardless of definitive local therapy (either definitive radiation or cystectomy);^{90,91} however, concurrent chemoradiation was not used in this trial as definitive local therapy.

Alternative regimens to cisplatin or 5-FU and mitomycin C may include gemcitabine and taxanes as these may improve local control as well. A number of randomized phase II and prospective phase I-II studies suggested that gemcitabine and taxanes may be added to EBRT to produce similar local control rates as EBRT with cisplatin or 5-FU and mitomycin C.²³⁶⁻²³⁸ The studies, though large enough to assess toxicity, were too small and had insufficient power to make direct comparisons of efficacy or to advocate their routine use.

27. Following completion of bladder preserving therapy, clinicians should perform regular surveillance with CT scans, cystoscopy, and urine cytology. (Strong Recommendation; Evidence Level: Grade C)

Following bladder preserving treatment, clinicians should address any bladder and bowel issues that may result from treatment and consider referral of patients to experienced medical professionals to evaluate and treat. Those who are biopsy-proven complete responders to bladder preserving protocols remain at risk for both invasive and non-invasive recurrences as well as new tumors in the upper tracts. Recurrences may be successfully managed by prompt salvage therapy. Although there is no direct evidence to determine optimal frequency of surveillance, most bladder preserving protocols encourage careful follow

up. The overall survival rates achieved in bladder preserving series that appear comparable to those obtained with immediate cystectomy are likely, in part, due to the use of close surveillance with early salvage cystectomy in patients with residual/recurrent disease as well as careful patient selection. Published protocols recommend every 3 month cystoscopy during the first year, every 4-6 months in the second, and every 6-12 months thereafter.^{231,232} In addition, the Panel recommends cross-sectional imaging of the abdomen and pelvis and chest imaging every six months for the first two years, although, again, there is no published data showing that this improves survival.

BLADDER PRESERVING TREATMENT FAILURE

28. In patients who are medically fit and have residual or recurrent muscle-invasive disease following bladder preserving therapy, clinicians should offer radical cystectomy with bilateral pelvic lymphadenectomy. (Strong Recommendation; Evidence Level: Grade C)

Approximately 30% of those selected for treatment by multi-modal bladder preserving therapy will have an invasive recurrence.²³⁵ Cystectomy should, if the patient is medically fit, again be offered as a salvage procedure. While there is no direct evidence demonstrating the value of salvage cystectomy, the relatively high survival rates achieved in bladder preserving series are likely, in part, due to the use of close surveillance and the use of early salvage cystectomy for patients with invasive disease.

Patients offered radical cystectomy with bilateral pelvic lymphadenectomy after bladder preserving therapy must be made aware that the morbidity is likely to be higher than with initial cystectomy. This information should also be shared with and explained to patients prior to deciding on a multi-modal bladder preserving approach. In addition, the options for urinary diversion may be more limited.

29. In patients who have a non-muscle invasive recurrence after bladder preserving therapy, clinicians may offer either local measures, such as transurethral resection of bladder tumor with intravesical therapy, or radical cystectomy with bilateral pelvic lymphadenectomy. (Moderate Recommendation; Evidence Level: Grade C)

Case series show that NMIBC recurrences following bladder sparing therapy may still be managed by standard local measures similar to *de novo* NMIBC. The presence of an NMIBC relapse, however, predicts an increased likelihood for further future relapses, including both NMIBC and MIBC recurrences.²³⁹

PATIENT SURVEILLANCE AND FOLLOW UP

IMAGING

30. Clinicians should obtain chest imaging and cross sectional imaging of the abdomen and pelvis with CT or MRI at 6-12 month intervals for 2-3 years and then may continue annually. (Expert Opinion)

The Panel recommends chest imaging and cross sectional imaging preferably with intravenous contrast and delayed images to evaluate the collecting system and also other sites of disease. Radiographic evaluation of the abdomen and pelvis is important for 1) detection of upper tract cancer; 2) disease detection in the most common sites of recurrence, progression, and metastasis, including the pelvis and retroperitoneum, liver, lungs and bones; and 3) urinary diversion concerns like hydronephrosis.

In terms of upper tract cancers, a meta-analysis including 13,185 participants from 27 studies found that the overall prevalence of upper tract transitional cell cancer after cystectomy ranged from 0.75% to 6.4%.²⁴⁰ In 14 of the studies, 63 of 166 patients (38%) with upper urinary tract cancers were diagnosed by follow up investigation, whereas in the remaining 62%, diagnosis was based on symptoms such as hematuria. When upper tract imaging was used in surveillance, the rate of primary detection was 29.6%. Of 5,537 patients who underwent upper urinary tract imaging, ureter and/or renal pelvis cancer was diagnosed in 7.6/1,000. Symptoms many times may precede diagnosis of upper tract cancer despite surveillance, and these cancers may present even beyond the first two years after definitive treatment.^{241,242}

PET/CT may help resolve equivocal abnormal findings and potentially identify other sites of metastases but should not be used routinely for surveillance imaging as there is no current data supporting superiority over conventional imaging. Imaging beyond five years should be based on shared decision making between the patient and clinician. Long-term survivors remain at risk for the development of tumors of the upper urinary tract, especially in those who continue to smoke. In addition, imaging may detect diversion-related upper tract deterioration. Therefore, upper tract imaging,

including ultrasound, may be useful.

LABORATORY VALUES AND URINE MARKERS

31. Following therapy for muscle-invasive bladder cancer, patients should undergo laboratory assessment at three to six month intervals for two to three years and then annually thereafter. (Expert Opinion)

Following cystectomy and urinary diversion, all patients should undergo assessment of electrolytes and renal function as studies have demonstrated that a significant proportion of patients may experience declines in renal function over time associated with urinary diversion.²⁴³⁻²⁴⁶ In addition, depending upon the type, position, and length of bowel used, the potential for the development of hypokalemia, hyponatremia, and/or hypokalemic hyperchloremic metabolic acidosis is variable. In follow up, vitamin B 12 levels should be assessed as there is an increased risk of deficiency and consequent neurological damage in patients with resection of > 60 cm of ileum and in those patients in whom the terminal ileum is utilized.^{247,248} Routine frequent complete blood count and liver function testing for cancer surveillance has not been validated.

While urine cytology is non-invasive and easy to collect, the overall yield is low,^{249,250} and those patients with a positive cytology may not manifest tumors for several years. In a meta-analysis of post treatment surveillance, the authors estimated that it would require 2,000 urinary cytological examinations in order to find a single invasive upper tract cancer.²⁴⁰ Thus, the Panel concludes that urine cytology can be used to monitor for recurrence after cystectomy, but that its sensitivity is low for upper tract cancer, and there is difficulty with interpretation after urinary diversion. It should be noted that the urine collected from intestinal urinary diversion or previously irradiated bladders may contain desquamated intestinal epithelial cells or atypia due to therapy, which may lower the diagnostic specificity. When urine cytology was used in surveillance, the rate of primary detection was 7%, and with upper urinary tract imaging it was 29.6%.²⁴⁰ Thus, there is insufficient data to support the routine use of cytology or urine-based tumor markers in detection of upper tract urothelial cancers.

Several new urine biomarkers may show promise to detect recurrent cancer in the bladder or upper tract cancers following primary therapy.^{251,252} These tests are either protein-based or cell-based and have been evaluated extensively in non-muscle invasive disease.²⁵³ Nevertheless, the sensitivity and specificity

of these biomarkers does not support the routine use for MIBC post-therapy surveillance. In the setting of prior treatment for MIBC, these assays have not been thoroughly tested or validated for patients following prior cystectomy with urinary diversion or following bladder preserving therapy.

32. Following radical cystectomy in patients with a retained urethra, clinicians should monitor the urethral remnant for recurrence. (Expert Opinion)

The risk of urothelial cancers in the retained urethra has been reported to be approximately 4-17% in multiple contemporary cystectomy series.^{254,255} Risk factors for the development of a urethral cancer includes tumor multiplicity, papillary pattern, CIS, tumor at the bladder neck, prostatic urethral mucosal involvement, and prostatic stromal invasion. Some studies suggest orthotopic diversion may have a protective effect, although this may simply represent a selection bias since many of the aforementioned risk factors are also used to exclude patients from orthotopic diversion.²⁵⁴⁻²⁵⁶ Patients who are symptomatic (e.g., pain, urethral bleeding) at the time of diagnosis of urethral cancer tend have higher stage cancers compared to patients with asymptomatic urethral cancers. Urethral wash cytology is a specific method for detecting CIS of the retained urethra and can detect urethral cancer in the absence of symptoms.^{257,258} While data varies in regards to a survival benefit associated with urethral washes,^{259,260} it seems that a urethral wash cytology may be a valuable tool in higher risk patients with a retained urethra.¹⁵¹ This should be considered during follow up, and patients should undergo physical examination of the urethra and discussion of any urethral symptoms such as urethral discharge or spotting.

PATIENT SURVIVORSHIP

33. Clinicians should discuss with patients how they are coping with their bladder cancer diagnosis and treatment and should recommend that patients consider participating in a cancer support group or consider receiving individual counseling. (Expert Opinion)

Over the last 25 years there has been extensive research on the positive effects of support groups as a method of coping with cancer and improving QOL. Support groups help reduce the three most significant stressors associated with cancer: unwanted aloneness, loss of control, and loss of hope. There are a variety of

different types of support groups, including those that are disease specific, those that are professionally facilitated, and those facilitated by cancer survivors. There are community-based in-person cancer support groups (including bladder cancer specific support groups) as well as online bladder cancer specific support groups. Helpful websites include the Bladder Cancer Advocacy Network, www.bcan.org; Cancer Support Community, www.cancersupportcommunity.org; Cancer Care, www.cancer.org; the American Bladder Cancer Society, www.bladdercancersupport.org, the American Cancer Society, www.cancer.org, and the Urology Care Foundation, www.urologyhealth.org. For those patients who are not interested in a support group, individual counseling may be available through an oncology social worker, psychologist, or local religious organizations.

34. Clinicians should encourage bladder cancer patients to adopt healthy lifestyle habits, including smoking cessation, exercise, and a healthy diet, to improve long-term health and quality of life. (Expert Opinion)

Bladder cancer is the second most common tobacco-related malignancy.²⁶¹ Successful cancer treatment can be significantly compromised by continued tobacco use.²⁶² A bladder cancer diagnosis is an opportunity to promote smoking cessation. Clinicians can and should play an integral role in affecting patterns of tobacco use by patients with bladder cancer.

Most patients with smoking-related cancers appear motivated to quit smoking at the time of their diagnosis. A stepped-care approach to quitting is ideal, with strong clinician advice and brief counseling to quit. In addition, the provision of basic information to all patients at each contact during the first month of diagnosis, followed by more intensive treatment (pharmacologic and counseling by a smoking specialist) for those having difficulty quitting or remaining abstinent is critical.²⁶³ Patients can be carefully matched to specific smoking cessation strategies. Some smokers can quit with the help of counseling or psychological interventions, while others might need nicotine replacement therapies or medications to successfully quit smoking. Given the significant health benefits derived from smoking cessation, medications can be used in selected patients with appropriate monitoring.

Cancer survivors have special health needs, especially because of the risks of the late effects of cancer recurrence. Studies have shown that a healthy diet helps to prevent late effects, such as obesity, heart

disease, and metabolic syndrome. Researchers are also studying whether certain diet and exercise habits in cancer survivors can reduce cancer recurrence or keep new cancers from forming. A healthy diet includes consuming a variety of vegetables, fruit, whole grains, and legumes.²⁶⁴ This healthy diet is essential in achieving a healthy weight, as is engaging in physical activity.

VARIANT HISTOLOGY

35. In patients diagnosed with variant histology, clinicians should consider unique clinical characteristics that may require divergence from standard evaluation and management for urothelial carcinoma. (Expert Opinion)

As variant histologies become recognized, the most appropriate care and evaluation may also become better understood as well as increasingly defined. Importantly, treatment recommendations previously outlined may NOT apply to these patients who represent a small but significant number.

Multiple retrospective and small prospective single-arm studies support the use of systemic chemotherapy in patients with small cell/high-grade neuroendocrine MIBC, although the optimal regimen remains undefined.²⁶⁵⁻²⁶⁹ Regimens optimized for small cell lung carcinoma, such as cisplatin and etoposide, are preferred. Due to the early systemic spread of small cell carcinoma, some experts administer carboplatin-based regimens (e.g. carboplatin-etoposide) in patients not eligible for cisplatin. For this histologic subtype, NAC is preferred over AC.²⁷⁰ Platinum-based chemoradiation using chemotherapy regimens similar to small cell lung cancer may also be considered as there is no standard modality for local control of this rare entity.²⁷¹⁻²⁷⁴

The use of perioperative chemotherapy in other variant histology MIBC is unclear. The benefits of perioperative chemotherapy in micropapillary MIBC remain controversial, with the percentage of micropapillary component perhaps playing a role.²⁷⁵⁻²⁷⁷ For other pure histologic subtypes (squamous, adenocarcinoma, sarcomatoid), perioperative chemotherapy is not routinely recommended as they are perceived to generally be chemo-resistant.

FUTURE RESEARCH

Several key areas of future research need emphasis to improve clinical care and provide a path to better patient outcomes with invasive bladder cancer.

Detection and markers. Enhanced detection of

bladder cancer cells via imaging technology or other means is needed to identify patients with high-risk disease and advanced disease. This includes cystoscopic and radiographic imaging of local disease and more effective and accurate evaluation techniques of regional lymphatics and distant sites. Defining the role of PET imaging and the best PET imaging agent as well as the investigation and validation of other novel technologies are deemed high-priority.

Urine cytology can be used to monitor for recurrence after TURBT and cystectomy, but difficulties with interpretation after urinary diversion have limited its usefulness after bladder removal. Radiation therapy can alter the appearance of shed cells and oftentimes result in atypical results. Current urinary markers have a limited role in the routine monitoring for recurrence of urothelial carcinoma after radical cystectomy due to false positive rate. Future studies should focus on the development of urinary and serum based markers that can be used to identify early urothelial based and/or distant recurrences.

Increased knowledge gained from comprehensive genetic studies of invasive bladder cancer should be exploited to identify and validate markers that could be used to guide diagnosis and therapeutic decision making. This would include the identification of prognostic markers capable of stratifying patients at risk for advanced disease, predictive markers for the response to chemotherapeutic/immunotherapeutic agents as well as radiation-based therapies. In addition, further studies are needed to evaluate and validate the prognostic and predictive information obtained from novel molecular classifications of bladder cancer.

Therapy. The rapid introduction of novel immunotherapeutic agents into the therapeutic armamentarium for treatment of bladder cancer has begun to show promise. Phase II and III studies have now demonstrated significant antitumor activity of the anti-PD-1 and anti-PDL-1 antibodies in the metastatic setting. A myriad of studies are needed to further define the role of these agents alone or in combination with other therapies for all stages of bladder cancer.

In addition, further studies are needed to better integrate multi-modal therapy in patients with invasive bladder cancer. Specific examples include the role for AC or immunotherapy in patients who have previously received NAC followed by surgery but still possess high-risk pathology (residual invasive disease or regional lymph node involvement); and the role of radiation in patients undergoing radical cystectomy for T3 and T4

disease, including the use of intraoperative radiation therapy.

In terms of surgery, robotic technology has entered into the treatment of patients with invasive bladder cancer with the hope that it will improve the morbidity associated with radical cystectomy. Long-term data is needed to demonstrate the oncologic efficacy, potential for improved clinical outcomes, and QOL using this new technology compared to standard open techniques. RCTs currently underway may give additional information regarding the utility of robotic surgery in MIBC. (NCT01157676)

Pelvic lymphadenectomy is an important part of a radical cystectomy, improving control of local/regional disease and providing better long-term outcomes. The exact extent of the lymphadenectomy still has yet to be defined. Current properly powered long-term surgical trial results will help define the incremental benefit of an "extended" lymphadenectomy compared to a "standard" lymphadenectomy. (NCT01224665 and LEA AUO AB 25/02)

Tissue regenerative technology continues to advance, stimulating the hope that organ replacement may be available in the future. Support of basic and translational research is needed to move tissue regeneration forward into clinical use for patients who require bladder removal for invasive bladder cancer.

In addition, studies emphasizing PROs after treatment for invasive bladder cancer are needed. This information is necessary to help further support patient centered outcomes, and identify specific areas of treatment that require further attention to improve patient QOL.

Surveillance. Finally, the optimal strategies for surveillance after definitive treatment for invasive bladder cancer to identify pelvic, distant, and urothelial recurrences need to be defined. Specifically, the role of specific imaging tests and laboratory studies as well as their appropriate interval has yet to be established, and future studies are needed to define a patient specific approach.

REFERENCES

1. Chou R, Selph S, Buckley D, Gustafson K, Griffin J, Grusing S, Gore J. Treatment of Nonmetastatic Muscle-Invasive Bladder Cancer. Comparative Effectiveness Review No. 152. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2012-00014-1.) AHRQ Publication No. 15-EHC015-EF. Rockville, MD: Agency for Healthcare Research and Quality; June 2015.
2. U.S. Preventive Services Task Force. U.S. Preventive Services Task Force Procedure Manual. 2008. www.uspreventiveservicestaskforce.org/uspstf08/methods/proceduremanual.htm. Accessed April 4, 2014.
3. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10 (14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. January 2014. Chapters available at www.effectivehealthcare.ahrq.gov.
4. Faraday M, Hubbard H, Kosiak B et al: Staying at the cutting edge: a review and analysis of evidence reporting and grading; the recommendations of the American Urological Association. *BJU Int* 2009; **104**: 294.
5. Hsu C and Sandford BA: The Delphi technique: making sense of consensus. *Practical Assessment, Research & Evaluation* 2007; **12**: 1.
6. Siegel RL, Miller KD and Jemal A: Cancer statistics, 2017. *CA Cancer J Clin* 2016; **67**: 7.
7. Smith AB, Deal AM, Woods ME et al: Muscle-invasive bladder cancer: evaluating treatment and survival in the National Cancer Data Base. *BJU Int* 2014; **114**: 719.
8. Burger M, Catto JW, Dalbagni G et al: Epidemiology and risk factors of urothelial bladder cancer. *Eur Urol* 2013; **63**:234.
9. Charlton ME, Adamo MP, Sun L et al: Bladder cancer collaborative stage variables and their data quality, usage, and clinical implications: a review of SEER data, 2004-2010. *Cancer* 2014; **120** 3815.
10. Freedman ND, Silverman DT, Hollenbeck AR et al: Association between smoking and risk of bladder cancer among men and women. *JAMA* 2011; **306**:737.
11. Samanic C, Kogevinas M, Dosemeci M et al: Smoking and bladder cancer in Spain: effects of tobacco type, timing, environmental tobacco smoke, and gender. *Cancer Epidemiol Biomarkers Prev* 2006; **15**: 1348.
12. Jiang X, Yuan JM, Skipper PL et al: Environmental tobacco smoke and bladder cancer risk in never smokers of Los Angeles County. *Cancer Res* 2007; **67**: 7540.
13. Rushton L, Bagga S, Bevan R et al: Occupation and cancer in Britain. *Br J Cancer* 2010; **102**: 1428.
14. Samanic CM, Kogevinas M, Silverman DT et al: Occupation and bladder cancer in a hospital-based case-control study in Spain. *Occup Environ Med* 2008; **65**: 347.
15. Koutros S, Silverman DT, Baris D et al: Hair dye use and risk of bladder cancer in the New England bladder cancer study. *Int J Cancer* 2011; **129**: 2894.
16. Van der Poel HG, Mungan NA and Witjes JA: Bladder cancer in women. *Int Urogynecol J and pelvic floor dysfunction* 1999; **10**: 207.
17. Abern MR, Dude AM, Tsivian M et al: The characteristics of bladder cancer after radiotherapy for prostate cancer. *Urol Oncol* 2013; **31**:1628.
18. An Y, Li H, Wang KJ et al: Meta-analysis of the relationship between slow acetylation of N-acetyl transferase 2 and the risk of bladder cancer. *Genet Mol Res* 2015; **14**: 16896.
19. Guey LT, García-Closas M, Murta-Nascimento C et al: EPICURO/Spanish Bladder Cancer Study investigators. Genetic susceptibility to distinct bladder cancer subphenotypes. *Eur Urol* 2010; **57**: 283.
20. Kiemeny LA, Sulem P, Besenbacher S et al: A sequence variant at 4p16.3 confers susceptibility to urinary bladder cancer. *Nat Genet* 2010; **42**:415.
21. Kiemeny LA, Thorlacius S, Sulem P et al: Sequence variant on 8q24 confers susceptibility to urinary bladder cancer. *Nat Genet* 2008; **40**: 1307.
22. Wu X, Ye Y, Kiemeny LA et al: A multi-stage genome-wide association study of bladder cancer

- identifies multiple susceptibility loci. *Nat Genet* 2009; **41**: 991.
23. Rothman N, Garcia-Closas M, Chatterjee N et al: A multi-stage genome-wide association study of bladder cancer identifies multiple susceptibility loci. *Nat Genet* 2010; **42**:978.
 24. Bryan RT, Collins SI, Daykin MC et al: Mechanisms of recurrence of Ta/T1 bladder cancer. *Ann R Coll Surg Engl* 2010; **92**: 519.
 25. Lamy P, Nordentoft I, Birkenkamp-Demtröder K et al: Paired exome analysis reveals clonal evolution and potential therapeutic targets in urothelial carcinoma. *Cancer Res* 2016; **76**: 5894.
 26. Karakiewicz PI, Shariat SF, Palapattu GS et al: Nomogram for predicting disease recurrence after radical cystectomy for transitional cell carcinoma of the bladder. *J Urol* 2006; **176**: 1354.
 27. International Bladder Cancer Nomogram Consortium, Bochner BH, Kattan MW et al: Postoperative nomogram predicting risk of recurrence after radical cystectomy for bladder cancer. *J Clin Oncol* 2006; **24**: 3967.
 28. Seisen T, Sun M, Leow JJ et al: Efficacy of high-intensity local treatment for metastatic urothelial carcinoma of the bladder: a propensity score-weighted analysis from the National Cancer Data Base. *J Clin Oncol* 2016; [Epub ahead of print].
 29. Mak RH, Hunt D, Shipley WU et al: Long-term outcomes in patients with muscle-invasive bladder cancer after selective bladder-preserving combined-modality therapy: a pooled analysis of Radiation Therapy Oncology Group protocols 8802, 8903, 9506, 9706, 9906, and 0233 *J Clin Oncol* 2014; **32**:3801.
 30. Dobruch J, Daneshmand S, Fisch M et al: Gender and bladder cancer: a collaborative review of etiology, biology, and outcomes. *Eur Urol* 2016; **69**: 300.
 31. Lotan Y, Gupta A, Shariat SF et al: Lymphovascular invasion is independently associated with overall survival, cause-specific survival, and local and distant recurrence in patients with negative lymph nodes at radical cystectomy. *J Clin Oncol* 2005; **23**:6533.
 32. Choi W, Czerniak B, Ochoa A et al: Intrinsic basal and luminal subtypes of muscle-invasive bladder cancer. *Nat Rev Urol* 2014; **11**: 400.
 33. Xylinas E, Rink M, Novara G et al: Predictors of survival in patients with soft tissue surgical margin involvement at radical cystectomy. *Ann Surg Oncol* 2013; **20**:1027.
 34. Cancer Genome Atlas Research Network: Comprehensive molecular characterization of urothelial bladder carcinoma. *Nature* 2014; **507**: 315.
 35. Sjobahl G, Lauss M, Lovgren K et al: A molecular taxonomy for urothelial carcinoma. *Clin Cancer Res* 2012; **18**: 3377.
 36. Choi W, Porten S, Kim S et al: Identification of distinct basal and luminal subtypes of muscle-invasive bladder cancer with different sensitivities to frontline chemotherapy. *Cancer Cell* 2014; **25**: 152.
 37. Damrauer JS, Hoadley KA, Chism DD et al: Intrinsic subtypes of high-grade bladder cancer reflect the hallmarks of breast cancer biology. *Proc Natl Acad Sci USA* 2014; **111** 3110.
 38. Koppie TM, Serio AM, Vickers AJ et al: Age-adjusted Charlson comorbidity score is associated with treatment decisions and clinical outcomes for patients undergoing radical cystectomy for bladder cancer. *Cancer* 2008; **112**:2384.
 39. Lotan Y, Amiel G, Boorjian SA et al: Comprehensive handbook for developing a bladder cancer cystectomy database. Bladder Cancer Think Tank; Bladder Cancer Advocacy Network.
 40. Marshall, VF: The relation of the preoperative estimate to the pathologic demonstration of the extent of vesicle neoplasms. *J Urol* 1952; **68**:714.
 41. Culp SH, Dickstein RJ, Grossman HB et al:Refining patient selection for neoadjuvant chemotherapy before radical cystectomy. *J Urol* 2014; **191**:40.
 42. Husband JE, Olliff JF, Williams MP et al: Bladder cancer: staging with CT and MR imaging. *Radiology* 1989; **173**: 435.□
 43. Vargas HA, Akin O, Schoder H et al: Prospective evaluation of MRI, ¹¹C- acetate PET/CT and

- contrast-enhanced CT for staging of bladder cancer. *Eur J Radiol* 2012; **81**: 4131.
44. Moyer VA; U.S. Preventive Services Task Force: Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2014; **160**:330.
 45. Braendengen M, Winderen M and Fosså SD: Clinical significance of routine pre-cystectomy bone scans in patients with muscle-invasive bladder cancer. *Br J Urol* 1996; **77**: 36.
 46. Aljabery F, Lindblom G, Skoog S et al: PET/CT versus conventional CT for detection of lymph node metastases in patients with locally advanced bladder cancer. *BMC Urol* 2015; **15**: 87.
 47. Jeong IG, Hong S, You D et al: FDG PET-CT for lymph node staging of bladder cancer: a prospective study of patients with extended pelvic lymphadenectomy. *Ann Surg Oncol* 2015; **22**: 3150.
 48. Kibel AS, Dehdashti F, Katz MD et al: Prospective study of [18F]fluorodeoxyglucose positron emission tomography/computed tomography for staging of muscle-invasive bladder carcinoma. *J Clin Oncol* 2009; **27**: 4314.
 49. Sangoi AR, Beck AH, Amin MB et al: Interobserver reproducibility in the diagnosis of invasive micropapillary carcinoma of the urinary tract among urologic pathologists. *Am J Surg Pathol* 2010; **34**: 1367.
 50. Linder BJ, Boorjian SA, Cheville JC et al: The impact of histological reclassification during pathology re-review-- evidence of a Will Rogers effect in bladder cancer? *J Urol* 2013; **190**: 1692.
 51. Hansel DE, Amin MB, Comperat E et al: A contemporary update on pathology standards for bladder cancer: transurethral resection and radical cystectomy specimens. *Eur Urol* 2013; **63**: 321.
 52. Kim SP, Frank I, Cheville JC et al: The impact of squamous and glandular differentiation on survival after radical cystectomy for urothelial carcinoma. *J Urol* 2012; **188**: 405.
 53. Linder BJ, Frank I, Cheville JC et al: Outcomes following radical cystectomy for nested variant of urothelial carcinoma: a matched cohort analysis. *J Urol* 2013; **189**: 1670.
 54. Wang JK, Boorjian SA, Cheville JC et al: Outcomes following radical cystectomy for micropapillary bladder cancer versus pure urothelial carcinoma: a matched cohort analysis. *World J Urol* 2012; **30**: 801.
 55. Kassouf W, Spiess PE, et al: Prostatic urethral biopsy has limited usefulness in counseling patients regarding final urethral margin status during orthotopic neobladder reconstruction *J Urol* 2008; **180**: 164.
 56. Psutka SP, Carrasco A, Schmit GD et al: Sarcopenia in patients with bladder cancer undergoing radical cystectomy: impact on cancer-specific and all-cause mortality. *Cancer* 2014; **120**: 2910.
 57. Carli F, Awasthi R, Gillis C et al: Optimizing a frail elderly patient for radical cystectomy with a prehabilitation program. *Can Urol Assoc J* 2014; **8**:E884.
 58. Chhabra KR, Sacks GD and Dimick JB: Surgical decision making: challenging dogma and incorporating patient preferences. *JAMA* 2017; **317**: 357.
 59. Bladder Cancer: EORTC QLQ-NMIBC24, EORTC QLQBLM30 [Internet]. Available from: <http://groups.eortc.be/qol/bladder-cancer-eortc-qlq-nmibc24-eortc-qlq-blm30>.
 60. Blazeby JM, Hall E, Aaronson NK et al: Validation and reliability testing of the EORTC QLQ-NMIBC24 questionnaire module to assess patient-reported outcomes in nonmuscle invasive bladder cancer. *Eur Urol* 2014; **66**: 1148.
 61. Anderson CB, Feurer ID, Large MC et al: Psychometric characteristics of a condition-specific, health-related quality-of-life survey: the FACT-Vanderbilt Cystectomy Index. *Urology* 2012; **80**: 77.
 62. Gilbert SM, Dunn RL, Hollenbeck BK et al: Development and validation of the Bladder Cancer Index: a comprehensive, disease specific measure of health related quality of life in patients with localized bladder cancer. *J Urol* 2010; **183**: 1764.
 63. Danna BJ, Metcalfe MJ, Wood EL et al: Assessing symptom burden in bladder cancer: an overview of bladder cancer specific health-related quality of life instruments. *Bladder Cancer* 2016; **2**: 329.
 64. Siegrist T, Savage C, Shabsigh A et al: Analysis of gender differences in early

- perioperative complications following radical cystectomy at a tertiary cancer center using a standardized reporting methodology. *Urol Oncol* 2010; **28**: 112.
65. Froehner M, Brausi MA, Herr HW et al: Complications following radical cystectomy for bladder cancer in the elderly. *Eur Urol* 2009; **56**: 443.
 66. Quek ML, Stein JP, Daneshmand S et al: A critical analysis of perioperative mortality from radical cystectomy. *J Urol* 2006; **175**:886.
 67. Novara G, Catto JW, Wilson T et al: Systematic review and cumulative analysis of perioperative outcomes and complications after robot-assisted radical cystectomy. *Eur Urol* 2015; **67**: 376.
 68. Bream MJ, Maurice MJ, Altschuler J et al: Increased use of cystectomy in patients 75 and older: a contemporary analysis of survival and perioperative outcomes from the National Cancer Database. *Urology* 2017; **100**: 72.
 69. Djaladat H, Katebian B, Bazargani ST et al: 90-Day complication rate in patients undergoing radical cystectomy with enhanced recovery protocol: a prospective cohort study. *World J Urol* 2016; [Epub ahead of print].
 70. Chappidi MR, Kates M, Stimson CJ et al: Causes, timing, hospital costs and perioperative outcomes of index vs nonindex hospital readmissions after radical cystectomy: implications for regionalization of care. *J Urol* 2017; **197**: 296.
 71. Hu M, Jacobs BL, Montgomery JS et al: Sharpening the focus on causes and timing of readmission after radical cystectomy for bladder cancer. *Cancer* 2014; **120**: 1409.
 72. Bochner BH, Dalbagni G, Sjoberg DD et al: Comparing open radical cystectomy and robot-assisted laparoscopic radical cystectomy: a randomized clinical trial. *Eur Urol* 2015; **67**: 1042.
 73. Murthy V, Masodkar R, Kalyani N et al: Clinical outcomes with dose-escalated adaptive radiation therapy for urinary bladder cancer: a prospective study. *Int J Radiat Oncol Biol Phys* 2016; **94**:60.
 74. Zietman AL, Sacco D, Skowronski U et al: Organ conservation in invasive bladder cancer by transurethral resection, chemotherapy and radiation: results of a urodynamic and quality of life study on long-term survivors. *J Urol* 2003; **170**: 1772.
 75. Lee RK, Abol-Enein H, Artibani W et al: Urinary diversion after radical cystectomy for bladder cancer: options, patient selection, and outcomes. *BJU Int* 2014; **113**:11.
 76. Gross T, Meierhans Ruf SD, Meissner Cet al: Orthotopic ileal bladder substitution in women: factors influencing urinary incontinence and hypercontinence. *Eur Urol* 2015; **68**: 664.
 77. Hautmann RE, de Petriconi RC and Volkmer BG: Lessons learned from 1,000 neobladders: the 90-day complication rate. *J Urol* 2010; **184**: 990.
 78. Studer UE, Burkhard FC, Schumacher M et al: Twenty years experience with an ileal orthotopic low pressure bladder substitute--lessons to be learned. *J Urol* 2006; **176**: 161.
 79. Ali-el-Dein B, Shaaban AA, Abu-Eideh RH et al: Surgical complications following radical cystectomy and orthotopic neobladders in women. *J Urol* 2008; **180**: 206.
 80. Ahmadi H, Skinner EC, Simma-Chiang V et al: Urinary Functional Outcome Following Radical Cystoprostatectomy and Ileal Neobladder Reconstruction in Male Patients. *J Urol* 2013; **189**:1782.
 81. Hautmann RE, Paiss T and de Petriconi R: The ileal neobladder in women: 9 years of experience with 18 patients. *J Urol* 1996; **155**: 76.
 82. Hautmann RE, de Petriconi R, Kleinschmidt K et al: Orthotopic ileal neobladder in females: impact of the urethral resection line on functional results. *Int Urogynecol J Pelvic Floor Dysfunct* 2000; **11**:224.
 83. Stein JP, Ginsberg DA and Skinner DG: Indications and technique of the orthotopic neobladder in women. *Urol Clin North Am* 2002; **29**: 725.
 84. Bartsch G, Daneshmand S, Skinner EC et al: Urinary functional outcomes in female neobladder patients. *World J Urol* 2014; **32**: 221.
 85. Colombo R, Pellucchi F, Moschini M et al: Fifteen-year single-centre experience with three different surgical procedures of nerve-sparing cystectomy in selected organ-confined

- bladder cancer patients. *World J Urol* 2015; **33**:1389.
86. Zahran MH, Fahmy O, El-Hefnawy AS et al: Female sexual dysfunction post radical cystectomy and urinary diversion. *Climacteric* 2016; **20**:1.
 87. Feuerstein MA and Goenka A: Quality of life outcomes for bladder cancer patients undergoing bladder preservation with radiotherapy. *Curr Urol Rep* 2015; **16**:75.
 88. Eisenberg MS, Thompson RH, Frank I et al: Long-term renal function outcomes after radical cystectomy. *J Urol* 2014; **191**: 619.
 89. Gupta A, Atoria CL, Ehdaie B et al: Risk of fracture after radical cystectomy and urinary diversion for bladder cancer. *J Clin Oncol* 2014 ;**32**: 3291.
 90. International Collaboration of Trialists: Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. *Lancet* 1999; **354**:533.
 91. International Collaboration of Trialists, Medical Research Council Advanced Bladder Cancer Working Party, European Organisation for Research and Treatment of Cancer Genito-Urinary Tract Cancer Group et al: International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. *J Clin Oncol* 2011; **29**: 2171.
 92. Grossman HB, Natale RB, Tangen CM et al: Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med* 2003; **349**:859.
 93. Malmstrom PU, Rintala E, Wahlqvist R et al: Five-year follow-up of a prospective trial of radical cystectomy and neoadjuvant chemotherapy: Nordic Cystectomy Trial I. The Nordic Cooperative Bladder Cancer Study Group. *J Urol* 1996; **155**: 1903.
 94. Rintala E, Hannisdahl E, Fossa SD et al: Neoadjuvant chemotherapy in bladder cancer: a randomized study. *Nordic Cystectomy Trial I. Scand J Urol Nephrol* 1993; **27**:355.
 95. Sengelov L, von der Maase H, Lundbeck F et al: Neoadjuvant chemotherapy with cisplatin and methotrexate in patients with muscle-invasive bladder tumours. *Acta Oncologica*. 2002; **41**: 447.
 96. Sherif A, Rintala E, Mestad O et al: Neoadjuvant cisplatin-methotrexate chemotherapy for invasive bladder cancer -- Nordic cystectomy trial 2. *Scand J Urol Nephrol* 2002; **36**: 419.
 97. Plimack ER, Hoffman-Censits JH, Viterbo R et al: Accelerated methotrexate, vinblastine, doxorubicin, and cisplatin is safe, effective, and efficient neoadjuvant treatment for muscle-invasive bladder cancer: results of a multicenter phase II study with molecular correlates of response and toxicity. *J Clin Oncol* 2014; **32**: 1895.
 98. Choueiri TK, Jacobus S, Bellmunt J et al: Neoadjuvant dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin with pegfilgrastim support in muscle-invasive urothelial cancer: pathologic, radiologic, and biomarker correlates. *J Clin Oncol* 2014; **32**: 1889.
 99. Bamias A, Dafni U, Karadimou A et al: Prospective, open-label, randomized, phase III study of two dose-dense regimens MVAC versus gemcitabine/cisplatin in patients with inoperable, metastatic or relapsed urothelial cancer: a Hellenic Cooperative Oncology Group study (HE 16/03). *Ann Oncol* 2013; **24**: 1011.
 100. Sternberg CN, de Mulder P, Schornagel JH et al: Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours. *Eur J Cancer* 2006; **42**: 50.
 101. Sternberg CN, de Mulder P, Schornagel JH et al: Randomized phase III trial of high-dose intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MCAV) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. *J Clin Oncol* 2001; **19**: 2638.
 102. Stadler WM, Lerner SP, Groshen S et al: Phase III study of molecularly targeted adjuvant therapy in locally advanced urothelial cancer of the bladder

- based on p53 status. *J Clin Oncol* 2011; **29**: 3443.
103. Van Allen EM, Mouw KW, Kim P et al: Somatic ERCC2 mutations correlate with cisplatin sensitivity in muscle-invasive urothelial carcinoma. *Cancer Discov* 2014; **4**: 1140.
 104. Lee JK, Havaleshko DM, Cho H et al: A strategy for predicting the chemosensitivity of human cancers and its application to drug discover. *Proc Natl Acad Sci USA* 2007; **104**: 13086.
 105. Plimack ER, Dunbrack RL, Brennan TA et al: Defects in DNA repair predict response to neoadjuvant cisplatin-based chemotherapy in muscle-invasive bladder cancer. *Eur Urol* 2015; **68**: 959.
 106. Fairey AS, Daneshmand S, Quinn D et al: Neoadjuvant chemotherapy with gemcitabine/cisplatin vs. methotrexate/vinblastine/doxorubicin/cisplatin for muscle-invasive urothelial carcinoma of the bladder: a retrospective analysis from the University of Southern California. *Urol Oncol* 2013; **31**: 1737.
 107. Pal SK, Ruel NH, Wilson TG et al: Retrospective analysis of clinical outcomes with neoadjuvant cisplatin-based regimens for muscle-invasive bladder cancer. *Clin Genitourin Cancer* 2012; **10**: 246.
 108. Yeshchina O, Badalato GM, Wosnitzer MS et al: Relative efficacy of perioperative gemcitabine and cisplatin versus methotrexate, vinblastine, adriamycin, and cisplatin in the management of locally advanced urothelial carcinoma of the bladder. *Urology* 2012; **79**: 384.
 109. Galsky MD, Pal SK, Chowdhury S et al: Comparative effectiveness of gemcitabine plus cisplatin versus methotrexate, vinblastine, doxorubicin, plus cisplatin as neoadjuvant therapy for muscle-invasive bladder cancer. *Cancer* 2015; **121**: 2586.
 110. Galsky MD, Hahn NM, Rosenberg J et al: A consensus definition of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy. *Lancet Oncol* 2011; **12**: 211.
 111. Koie T, Ohyama C, Yamamoto H et al: Neoadjuvant gemcitabine and carboplatin followed by immediate cystectomy may be associated with a survival benefit in patients with clinical T2 bladder cancer. *Med Oncol* 2014; **31**: 949.
 112. Dogliotti L, Carteni G, Siena S et al: Gemcitabine plus cisplatin versus gemcitabine plus carboplatin as first-line chemotherapy in advanced transitional cell carcinoma of the urothelium: results of a randomized phase 2 trial. *Eur Urol* 2007; **52**: 134.
 113. Dreicer R, Manola J, Roth BJ et al: Phase III trial of methotrexate, vinblastine, doxorubicin, and cisplatin versus carboplatin and paclitaxel in patients with advanced carcinoma of the urothelium. *Cancer* 2004; **100**: 1639.
 114. Alva AS, Tallman CT, He C et al: Efficient delivery of radical cystectomy after neoadjuvant chemotherapy for muscle-invasive bladder cancer. *Cancer* 2012; **118**: 44.
 115. Freiha F, Reese J, Torti FM: A randomized trial of radical cystectomy versus radical cystectomy plus cisplatin, vinblastine and methotrexate chemotherapy for muscle invasive bladder cancer. *J Urol* 1996; **155**: 495.
 116. Cognetti F, Ruggeri EM, Felici A et al: Adjuvant chemotherapy with cisplatin and gemcitabine versus chemotherapy at relapse in patients with muscle-invasive bladder cancer submitted to radical cystectomy: an Italian, multicenter, randomized phase III trial. *Ann Oncol* 2012; **23**: 695.
 117. Skinner DG, Daniels JR, Russell CA et al: The role of adjuvant chemotherapy following cystectomy for invasive bladder cancer: a prospective comparative trial. *J Urol* 1991; **145**: 459.
 118. Bono AV, Benvenuti C, Gibba A et al: Adjuvant chemotherapy in locally advanced bladder cancer. Final analysis of a controlled multicentre study. *Acta Urologica Italica* 1997; **11**: 5.
 119. Sternberg CN, Skoneczna I, Kerst JM et al: Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4 or N+M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open-label, randomised phase 3 trial. *Lancet Oncol* 2015; **16**: 76.
 120. Leow JJ, Martin-Doyle W, Rajagopal PS et al: Adjuvant chemotherapy for invasive bladder cancer: a 2013 updated systematic review and meta-analysis of randomized trials. *Eur Urol* 2014; **66**: 42.

121. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration: Adjuvant chemotherapy for invasive bladder cancer (individual patient data). *Cochrane Database Syst Rev* 2006; **19**: CD06018.
122. Stenzl A, Witjes JA and Comperat E: Guidelines on bladder cancer muscle-invasive and metastatic. EAU 2012.
123. Sell A, Jakobsen A, Nerstrom, B et al: Treatment of advanced bladder cancer category T2 T3 and T4a. A randomized multicenter study of preoperative irradiation and cystectomy versus radical irradiation and early salvage cystectomy for residual tumor. DAVECA protocol 8201. Danish Vesical Cancer Group. *Scand J Urol Nephrol Suppl* 1991; **138**: 193.
124. Bekelman JE, Handorf EA, Guzzo T et al: Radical cystectomy versus bladder-preserving therapy for muscle-invasive urothelial carcinoma: examining confounding and misclassification bias in cancer observational comparative effectiveness research. *Value Health* 2013; **16**: 610.
125. Goossens-Laan CA, Leliveld AM, Verhoeven RHA et al: Effects of age and comorbidity on treatment and survival of patients with muscle-invasive bladder cancer. *Int J Cancer* 2014; **135**: 905.
126. Holmang S, Hedelin H, Anderstrom C et al: Long-term follow-up of all patients with muscle invasive (stages T2, T3 and T4) bladder carcinoma in a geographical region. *J Urol* 1997; **158**: 389.
127. Kalogeras D, Lampri E, Goussia A et al: Radical therapy for muscle-infiltrating bladder cancer (cystectomy or radiotherapy): does age affect the final therapeutic benefit for the patient? *J BUON* 2008; **13**: 353.
128. Kotwal S, Choudhury A, Johnston C et al: Similar treatment outcomes for radical cystectomy and radical radiotherapy in invasive bladder cancer treated at a United Kingdom specialist treatment center. *Int J Radiat Oncol Biol Phys* 2008; **70**: 456.
129. Nieuwenhuijzen JA, Pos F, Moonen LMF et al: Survival after bladder-preservation with brachytherapy versus radical cystectomy; a single institution experience. *Eur Urol*, 2005; **48**: 239.
130. Rincon Mayans A, Rosell Costa D, Zudaire Bergera JJ et al: Response and progression-free survival in T2 to T4 bladder tumors treated with trimodality therapy with bladder preservation. *Actas Urol Esp* 2010; **34**: 775.
131. Solsona E, Climent MA, Iborra I et al: Bladder preservation in selected patients with muscle-invasive bladder cancer by complete transurethral resection of the bladder plus systemic chemotherapy: long-term follow-up of a phase 2 nonrandomized comparative trial with radical cystectomy. *Eur Urol* 2009; **55**: 911.
132. Parekh DJ, Messer J, Fitzgerald J et al: Perioperative outcomes and oncologic efficacy from a pilot prospective randomized clinical trial of open versus robotic assisted radical cystectomy. *J Urol* 2013; **189**: 474.
133. Messer JC, Punnen S, Fitzgerald J et al: Health-related quality of life from a prospective randomised clinical trial of robot-assisted laparoscopic vs open radical cystectomy. *BJU Int* 2014; **114**: 896.
134. Nix J, Smith A, Kurpad R et al: Prospective randomized controlled trial of robotic versus open radical cystectomy for bladder cancer: perioperative and pathologic results. *Eur Urol* 2010; **57**: 196.
135. Yuh B, Wilson T, Bochner B et al: Systematic review and cumulative analysis of oncologic and functional outcomes after robot-assisted radical cystectomy. *Eur Urol* 2015; **67**: 402.
136. Shabsigh A, Korets R, Vora KC et al: Defining early morbidity of radical cystectomy for patients with bladder cancer using a standardized reporting methodology. *Eur Urol* 2009; **55**: 164.
137. Lowrance WT, Rumohr JA, Chang SS et al: Contemporary open radical cystectomy: analysis of perioperative outcomes. *J Urol* 2008; **179**: 1313.
138. Stimson CJ, Chang SS, Barocas DA et al: Early and late perioperative outcomes following radical cystectomy: 90-day readmissions, morbidity and mortality in a contemporary series. *J Urol* 2010; **184**: 1296.
139. Hu M, Jacobs BL, Montgomery JS et al: Sharpening the focus on causes and timing of readmission after radical cystectomy for bladder cancer. *Cancer* 2014; **120**: 1409.
140. Gaya JM, Matulay J, Badalato GM et al: The role of preoperative prostatic urethral biopsy in clinical decision-making at the time of radical

- cystectomy. *Can J Urol* 2014; **21**: 7228.
141. Kates M, Ball MW, Chappidi MR et al: Accuracy of urethral frozen section during radical cystectomy for bladder cancer. *Urol Oncol* 2016; **34**: 532.
 142. Schoenberg MP, Walsh PC, Breazeale DR et al: Local recurrence and survival following nerve sparing radical cystoprostatectomy for bladder cancer: 10-year follow-up. *J Urol* 1996; **155**: 490.
 143. Bhatta Dhar N, Kessler TM, Mills RD et al: Nerve-sparing radical cystectomy and orthotopic bladder replacement in female patients. *Eur Urol* 2007; **52**: 1006.
 144. Salem H and El-Mazny A: Primary and secondary malignant involvement of gynaecological organs at radical cystectomy for bladder cancer: review of literature and retrospective analysis of 360 cases. *J Obstet Gynaecol* 2012; **32**: 590.
 145. Jacobs BL, Daignault S, Lee CT et al: Prostate capsule sparing versus nerve sparing radical cystectomy for bladder cancer: results of a randomized, controlled trial. *J Urol* 2015; **193**: 64.
 146. Hautmann RE, Abol-Enein H, Davidsson T et al: ICUD-EAU International Consultation on Bladder Cancer 2012: Urinary Diversion 2013; **63**: 67.
 147. Madersbacher S, Schmidt J, Eberle J et al: Long-term outcome of ileal conduit diversion. *J Urol* 2003; **169**: 985.
 148. Ghosh A and Somani BK: Recent trends in postcystectomy health-related quality of life (qol) favors neobladder diversion: systematic review of the literature. *Urology* 2016; **93**: 22.
 149. Philip J, Manikandan R, Venugopal S et al: Orthotopic neobladder versus ileal conduit urinary diversion after cystectomy--a quality-of-life based comparison. *Ann R Coll Surg Engl* 2009; **91**: 565.
 150. Hussein Al Awamh Al B, Wang LC, Nguyen DP et al: Is continent cutaneous urinary diversion a suitable alternative to orthotopic bladder substitute and ileal conduit after cystectomy? *BJU Int* 2015; **116**: 805.
 151. Chan Y, Fisher P, Tilki D et al: Urethral recurrence after cystectomy: current preventative measures, diagnosis and management. *BJU Int* 2016; **117**: 563.
 152. Stein JP, Clark P, Miranda G et al: Urethral tumor recurrence following cystectomy and urinary diversion: clinical and pathological characteristics in 768 male patients. *J Urol* 2005; **173**: 1163.
 153. Kanaroglou A and Shayegan B: Management of the urethra in urothelial bladder cancer. *Can Urol Assoc J* 2009; **3**: S211.
 154. Wu SD, Simma-Chang V and Stein JP: Pathologic guidelines for orthotopic urinary diversion in women with bladder cancer: a review of the literature. *Rev Urol* 2006; **8**: 54.
 155. Leuret T, Hervé JM, Barré P et al: Urethral recurrence of transitional cell carcinoma of the bladder. Predictive value of preoperative latero-montanal biopsies and urethral frozen sections during prostatectomy. *Eur Urol* 1998; **33**: 170.
 156. Stein JP, Penson DF, Wu SD et al: Pathological guidelines for orthotopic urinary diversion in women with bladder cancer: a review of the literature. *J Urol* 2007; **178**: 756.
 157. Chen ME, Pisters LL, Malpica A et al: Risk of urethral, vaginal and cervical involvement in patients undergoing radical cystectomy for bladder cancer: results of a contemporary cystectomy series from M. D. Anderson Cancer Center. *J Urol* 1997; **157**: 2120.
 158. Collins JW, Patel H, Adding C et al: Enhanced recovery after robot-assisted radical cystectomy: EAU Robotic Urology Section Scientific Working Group consensus view. *Eur Urol* 2016. **70**: 649.
 159. Karl A, Staehler M, Bauer R et al: Malnutrition and clinical outcome in urological patients. *Eur J Med Res* 2011; **16**: 469.
 160. Gregg JR, Cookson MS, Phillips S et al: Effect of preoperative nutritional deficiency on mortality after radical cystectomy for bladder cancer. *J Urol* 2011; **185**: 90.
 161. Hemal S, Krane LS, Richards KA et al: Risk factors for infectious readmissions following radical cystectomy: results from a prospective multicenter dataset. *Therapeutic Advances in Urology* 2016; **8**: 167.
 162. Crivelli JJ, Xylinas E, Kluth LA et al: Effect of smoking on outcomes of urothelial carcinoma: a systematic review of the literature. *Eur Urol* 2014; **65**: 742.

163. Cumberbatch MG, Rota M, Catto JWF et al: The role of tobacco smoke in bladder and kidney carcinogenesis: a comparison of exposures and meta-analysis of incidence and mortality risks. *Eur Urol* 2016; **70**: 458.
164. Güenaga KF, Matos D and Wille-Jørgensen P: Mechanical bowel preparation for elective colorectal surgery. *Cochrane Database Syst Rev* 2011: CD001544.
165. Contant CME, Hop WCJ, van't Sant HP et al: Mechanical bowel preparation for elective colorectal surgery: a multicentre randomised trial. *Lancet* 2007; **370**: 2112.
166. Kiran RP, Murray AC, Chiuzan C et al: Combined preoperative mechanical bowel preparation with oral antibiotics significantly reduces surgical site infection, anastomotic leak, and ileus after colorectal surgery. *Ann Surg* 2015; **262**: 416.
167. Morris MS, Graham LA, Chu DI et al: Oral antibiotic bowel preparation significantly reduces surgical site infection rates and readmission rates in elective colorectal surgery. *Ann Surg* 2015; **261**: 1034.
168. Hashad MME, Atta M, Elabbady A et al: Safety of no bowel preparation before ileal urinary diversion. *BJU Int* 2012; **110**: E1109.
169. Large MC, Kiriluk KJ, DeCastro GJ et al: The impact of mechanical bowel preparation on postoperative complications for patients undergoing cystectomy and urinary diversion. *J Urol* 2012; **188**: 1801.
170. Gustafsson UO, Scott MJ, Schwenk W et al: Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations. *World J Surg* 2013; **37**: 259.
171. Bilku DK, Dennison AR, Hall TC et al: Role of preoperative carbohydrate loading: a systematic review. *Ann R Coll Surg Engl* 2014; **96**: 15.
172. Carson JL, Grossman BJ, Kleinman S et al: Red blood cell transfusion: a clinical practice guideline from the AABB*. *Ann Intern Med* 2012; **157**: 49.
173. Linder BJ, Frank I, Cheville JC et al: The impact of perioperative blood transfusion on cancer recurrence and survival following radical cystectomy. *Eur Urol* 2013; **63**: 839.
174. Morgan T, Barocas DA, Chang SS et al: The relationship between perioperative blood transfusion and overall mortality in patients undergoing radical cystectomy for bladder cancer. *Urol Oncol* 2013; **31**: 871.
175. Chalfin HJ, Liu JJ, Gandhi N et al: Blood transfusion is associated with increased perioperative morbidity and adverse oncologic outcomes in bladder cancer patients receiving neoadjuvant chemotherapy and radical cystectomy. *Ann Surg Oncol* 2016; **23**: 2715.
176. Xu W, Daneshmand S, Bazargani ST et al: Postoperative pain management after radical cystectomy: comparing traditional versus enhanced recovery protocol pathway. *J Urol* 2015; **194**: 1209.
177. Forrest JB, Clemens JQ, Finamore P et al: AUA Best Practice Statement for the prevention of deep vein thrombosis in patients undergoing urologic surgery. *J Urol* 2009; **181**: 1170.
178. Collins R, Scrimgeour A, Yusuf S et al: Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *N Engl J Med* 1988; **318**: 1162.
179. Bergqvist D: Low molecular weight heparin for the prevention of venous thromboembolism after abdominal surgery. *Br J Surg* 2004; **91**: 965.
180. Geerts WH, Bergqvist D, Pineo GF et al: Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; **133**: 381S.
181. Jacobs JJ, Mont MA, Bozic KJ et al: American Academy of Orthopaedic Surgeons clinical practice guideline on: preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty. *J Bone Joint Surg Am* 2012; **94**: 746.
182. Rasmussen MS, Jørgensen LN and Wille-Jørgensen P: Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery. *Cochrane Database Syst Rev* 2009: CD004318.
183. Forster R and Stewart M: Anticoagulants (extended duration) for prevention of venous thromboembolism following total hip or knee

- replacement or hip fracture repair. *Cochrane Database Syst Rev* 2016; **3**: CD004179.
184. Kauf TL, Svatek RS, Amiel G et al: Alvimopan, a peripherally acting μ -opioid receptor antagonist, is associated with reduced costs after radical cystectomy: economic analysis of a phase 4 randomized, controlled trial. *J Urol* 2014; **191**: 1721.
 185. Lee CT, Chang SS, Kamat AM et al: Alvimopan accelerates gastrointestinal recovery after radical cystectomy: a multicenter randomized placebo-controlled trial. *Eur Urol* 2014; **66**: 265.
 186. Vaughan-Shaw PG, Fecher IC, Harris S et al: A meta-analysis of the effectiveness of the opioid receptor antagonist alvimopan in reducing hospital length of stay and time to GI recovery in patients enrolled in a standardized accelerated recovery program after abdominal surgery. *Dis Colon Rectum* 2012; **55**: 611.
 187. Chaudhri S, Brown L, Hassan I et al: Preoperative intensive, community-based vs. traditional stoma education: a randomized, controlled trial. *Dis Colon Rectum* 2005; **48**: 504.
 188. Colwell JC and Gray M: Does preoperative teaching and stoma site marking affect surgical outcomes in patients undergoing ostomy surgery? *J Wound Ostomy Continence Nurs* 2007; **34**: 492.
 189. Leissner J, Ghoneim MA, Abol-Enein H et al: Extended radical lymphadenectomy in patients with urothelial bladder cancer: results of a prospective multicenter study. *J Urol* 2004; **171**: 139.
 190. Vazina A, Dugi D, Shariat SF et al: Stage specific lymph node metastasis mapping in radical cystectomy specimens. *J Urol* 2004; **171**: 1830.
 191. Abdollah F, Sun M, Schmitges J et al: Stage-specific impact of pelvic lymph node dissection on survival in patients with non-metastatic bladder cancer treated with radical cystectomy. *BJU Int* 2012; **109**: 1147.
 192. Herr HW, Bochner BH, Dalbagni G et al: Impact of the number of lymph nodes retrieved on outcome in patients with muscle invasive bladder cancer. *J Urol* 2012; **187**: 1295.
 193. Konety BR, Joslyn SA and O'Donnell MA: Extent of pelvic lymphadenectomy and its impact on outcome in patients diagnosed with bladder cancer: analysis of data from the Surveillance, Epidemiology and End Results Program data base. *J Urol* 2003; **169**: 946.
 194. Shirotake S, Kikuchi E, Matsumoto K et al: Role of pelvic lymph node dissection in lymph node-negative patients with invasive bladder cancer. *Jpn J Clin Oncol* 2010; **40**: 247.
 195. Fahmy N, Aprikian A, Tanguay S et al: Practice patterns and recurrence after partial cystectomy for bladder cancer. *World J Urol* 2010; **28**: 419.
 196. Capitanio U, Isbarn H, Shariat SF et al: Partial cystectomy does not undermine cancer control in appropriately selected patients with urothelial carcinoma of the bladder: a population-based matched analysis. *Urology* 2009; **74**: 858.
 197. Amin MB, Edge S, Greene F et al: *AJCC Cancer Staging Manual*. 8 ed: Springer International Publishing. 2017.
 198. Bochner BH, Cho D, Herr HW et al: Prospectively packaged lymph node dissections with radical cystectomy: evaluation of node count variability and node mapping. *J Urol* 2004; **172**: 1286.
 199. Herr HW, Faulkner JR, Grossman HB et al: Surgical factors influence bladder cancer outcomes: a cooperative group report. *J Clin Oncol* 2004; **22**: 2781.
 200. Brossner C, Pycha A, Toth A et al: Does extended lymphadenectomy increase the morbidity of radical cystectomy? *BJU Int* 2004; **93**: 64.
 201. Brunocilla E, Perneti R, Schiavina R et al: The number of nodes removed as well as the template of the dissection is independently correlated to cancer-specific survival after radical cystectomy for muscle-invasive bladder cancer. *Int Urol Nephrol* 2013; **45**: 711.
 202. Dhar NB, Klein EA, Reuther AM et al: Outcome after radical cystectomy with limited or extended pelvic lymph node dissection. *J Urol* 2008; **179**: 873.
 203. Leissner J, Hohenfellner R, Thuroff JW et al: Lymphadenectomy in patients with transitional cell carcinoma of the urinary bladder; significance for staging and prognosis. *BJU Int* 2000; **85**: 817.
 204. Poulsen AL, Horn T and Steven K: Radical cystectomy: extending the limits of pelvic lymph node dissection improves survival for patients

- with bladder cancer confined to the bladder wall. *J Urol* 1998; **160**: 2015.
205. Zehnder P, Studer UE, Skinner EC et al: Super extended versus extended pelvic lymph node dissection in patients undergoing radical cystectomy for bladder cancer: a comparative study. *J Urol* 2011; **186**: 1261.
 206. Simone G, Papalia R, Ferriero M et al: Stage-specific impact of extended versus standard pelvic lymph node dissection in radical cystectomy. *Int J Urol* 2013; **20**: 390.
 207. Morgan TM, Barocas DA, Penson DF et al: Lymph node yield at radical cystectomy predicts mortality in node-negative and not node-positive patients. *Urology* 2012; **80**: 632.
 208. Siemens DR, Mackillop WJ, Peng Y et al: Lymph node counts are valid indicators of the quality of surgical care in bladder cancer: a population-based study. *Urol Oncol* 2015; **33**: 425.e15.
 209. Koppie TM, Vickers AJ, Vora K et al: Standardization of pelvic lymphadenectomy performed at radical cystectomy: can we establish a minimum number of lymph nodes that should be removed? *Cancer* 2006; **107**: 2368.
 210. Stein JP, Cai J, Groshen S et al: Risk factors for patients with pelvic lymph node metastases following radical cystectomy with en bloc pelvic lymphadenectomy: concept of lymph node density. *J Urol* 2003; **170**: 35.
 211. Wright JL, Lin DW and Porter MP: The association between extent of lymphadenectomy and survival among patients with lymph node metastases undergoing radical cystectomy. *Cancer* 2008; **112**: 2401.
 212. Froehner M, Novotny V, Heberling U et al: Relationship of the number of removed lymph nodes to bladder cancer and competing mortality after radical cystectomy. *Eur Urol* 2014; **66**: 987.
 213. Kaufman DS, Winter KA, Shipley WU et al: The initial results in muscle-invasive bladder cancer of RTOG 95-06: a phase I/II trial of transurethral surgery plus radiation therapy with concurrent cisplatin and 5-fluorouracil followed by selective bladder preservation or cystectomy depending on initial response. *Oncologist* 2000; **5**:471.
 214. Hagan MP, Winter KA, Kaufman DS et al: RTOG 97-06: initial report of a phase I-II trial of selective bladder conservation using TURBT, twice-daily accelerated irradiation sensitized with cisplatin, and adjuvant MCV combination chemotherapy. *Int J Radiat Oncol Biol Phys* 2003; **57**:665.
 215. Kaufman DS, Winter KA, Shipley WU et al: Phase I-II RTOG study (99-06) of patients with muscle-invasive bladder cancer undergoing transurethral surgery, paclitaxel, cisplatin, and twice-daily radiotherapy followed by selective bladder preservation or radical cystectomy and adjuvant chemotherapy. *Urology* 2009; **73**:833.
 216. Herr HW: Outcome of patients who refuse cystectomy after receiving neoadjuvant chemotherapy for muscle-invasive bladder cancer. *Eur Urol* 2008; **54**: 126.
 217. Herr HW, Bajorin DF and Scher HI: Neoadjuvant chemotherapy and bladder-sparing surgery for invasive bladder cancer: ten-year outcome. *J Clin Oncol* 1998; **16**: 1298.
 218. Holzbeierlein JM, Lopez-Corona E, Bochner BH et al: Partial cystectomy: a contemporary review of the Memorial Sloan-Kettering Cancer Center experience and recommendations for patient selection. *J Urol* 2004; **172**: 878.
 219. Kassouf W, Swanson D, Kamat AM et al: Partial cystectomy for muscle invasive urothelial carcinoma of the bladder: a contemporary review of the M.D. Anderson Cancer Center experience. *J Urol* 2006; **175**: 2058.
 220. Herr HW. Transurethral resection of muscle-invasive bladder cancer: 10-year outcome. *J Clin Oncol* 2001; **19**:89.
 221. Herr HW, Bajorin DF and Scher HI: Neoadjuvant chemotherapy and bladder-sparing surgery for invasive bladder cancer: ten-year outcome. *J Clin Oncol* 1998; **16**: 1298.
 222. Duncan W and Quilty PM: The results of a series of 963 patients with transitional cell carcinoma of the urinary bladder primarily treated by radical megavoltage x-ray therapy. *Radiother Oncol* 1986; **7**: 299.
 223. Blandy JP, Jenkins BJ, Fowler CG et al: Radical radiotherapy and salvage cystectomy for T2/3 cancer of the bladder. *Prog Clin Biol Res* 1988; **260**: 447.
 224. Jenkins BJ, Caulfield MJ, Fowler CG et al: Reappraisal of the role of radical radiotherapy and

- salvage cystectomy in the treatment of invasive (T2/T3) bladder cancer. *Br J Urol* 1988; **62**: 342.
225. Gospodarowicz MK, Rider WD, Keen CW et al: Bladder cancer: long term follow-up results of patients treated with radical radiation. *Clin Oncol* 1991; **3**: 155.
226. Jahnsen S, Pedersen J and Westman G: Bladder carcinoma - a 20-year review of radical irradiation therapy. *Radiother Oncol* 1991; **22**: 111.
227. Fossa SD, Waehre H, Aass N et al: Bladder cancer definitive radiation therapy of muscle-invasive bladder cancer. A retrospective analysis of 317 patients. *Cancer* 1993; **72**: 3036.
228. Rozan R, Albuissou E, Donnarieix D et al: Interstitial iridium-192 for bladder cancer (a multicentric survey: 205 patients). *Int J Radiat Oncol Biol Phys* 1992; **24**:469.
229. Pernot M, Hubert J, Guillemain F et al: Combined surgery and brachytherapy in the treatment of some cancers of the bladder (partial cystectomy and interstitial iridium-192). *Radiother Oncol* 1996; **38**:115.
230. Pos F, Horenblas S, Dom P et al: Organ preservation in invasive bladder cancer: brachytherapy, an alternative to cystectomy and combined modality treatment? *Int J Radiat Oncol Biol Phys* 2005; **61**:678.
231. Mak R, Hunt D, Shipley W et al: Long-term outcomes in patients with muscle-invasive bladder cancer after selective bladder-preserving combined modality therapy: a pooled analysis of RTOG protocols 8802, 8903, 9506, 9706, 9906, and 0233. *J Clin Oncol* 2014; **32**:3801.
232. Efsthathiou JA, Spiegel DY, Shipley WU et al: Long-term outcomes of selective bladder preservation by combined-modality therapy for invasive bladder cancer: the MGH experience. *Eur Urol* 2012; **61**: 705.
233. Eswara JR, Efsthathiou JA, Heney NM et al: Complications and long-term results of salvage cystectomy after failed bladder sparing therapy for muscle invasive bladder cancer. *J Urol* 2012; **187**:463.
234. James ND, Hussain SA, Hall E et al: Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. *N Engl J Med* 2012; **366**:1477.
235. Coppin C, Gospodarowicz M, James K et al: Improved local control of invasive bladder cancer by concurrent cisplatin and preoperative or definitive radiation. The National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 1996; **14**: 2901.
236. Choudhury A, Swindell R, Logue JP et al: Phase II study of conformal hypofractionated radiotherapy with concurrent gemcitabine in muscle-invasive bladder cancer. *J Clin Oncol*. 2011; **29**:733.
237. Herman JM, Smith DC, Montie J et al: Prospective quality of life assessment in patients receiving concurrent gemcitabine and radiotherapy as a bladder preservation strategy. *Urology* 2004; **64**:69.
238. Mitin T, Hunt D, Shipley WU et al: Transurethral surgery and twice-daily radiation plus paclitaxel-cisplatin or fluorouracil-cisplatin with selective bladder preservation and adjuvant chemotherapy for patients with muscle invasive bladder cancer (RTOG 0233): a randomised multicentre phase 2 trial. *Lancet Oncol* 2013; **14**:863.
239. Zietman AL, Grocela J, Zehr E et al: Selective bladder conservation using transurethral resection, chemotherapy, and radiation: management and consequences of Ta, T1, and Tis recurrence within the retained bladder. *Urology* 2001; **58**:380.
240. Picozzi S, Ricci C, Gaeta M et al: Upper urinary tract recurrence following radical cystectomy for bladder cancer: a meta-analysis on 13,185 patients. *J Urol* 2012; **188**: 2046.
241. Sanderson KM, Cai J, Miranda G et al: Upper tract urothelial recurrence following radical cystectomy for transitional cell carcinoma of the bladder: an analysis of 1,069 patients with 10-year follow-up. *J Urol* 2007; **177**: 2088.
242. Tran W, Serio AM, Raj GV et al: Longitudinal risk of upper tract recurrence following radical cystectomy for urothelial cancer and the potential implications for long-term surveillance. *J Urol* 2008; **179**: 96.
243. Hall MC, Koch MO and McDougal WS: Metabolic consequences of urinary diversion through intestinal segments. *Urol Clin North Am* 1991; **18**:725.
244. Harraz AM, Mosbah A, El-Assmy A et al: Renal function evaluation in patients undergoing

- orthotopic bladder substitution: a systematic review of literature. *BJU Int* 2014; **114**: 484.
245. Amini E and Djaladat H: Long-term complications of urinary diversion. *Curr Opin Urol* 2015; **25**:570.
246. Krajewski W, Piszczek R, Krajewska M et al: Urinary diversion metabolic complications - underestimated problem. *Adv Clin Exp Med* 2014; **23**: 633.
247. Tan WS, Lamb BW, and Kelley D: Complications of radical cystectomy and orthotopic reconstruction. *Adv Urol* 2015; **2015**: 323157.
248. Van der Aa, F, Joniau S, Van Den Branden VD et al: Metabolic changes after urinary diversion. *Adv Urol* 2011; **2011**.
249. Volkmer BG, Schnoeller T, Kuefer R et al: Upper urinary tract recurrence after radical cystectomy for bladder cancer--who is at risk? *J Urol* 2009; **182**:2632.
250. Raj GV, Bochner BH, Serio AM et al: Natural history of positive urinary cytology after radical cystectomy. *J Urol* 2006; **176**:2000.
251. Sullivan PS, Nooraie F, Sanchez H et al: Comparison of Immuno-Cyt, UroVysion, and urine cytology in detection of recurrent urothelial carcinoma: a "split-sample" study. *Cancer (Cancer Cytopathol)* 2009;**117**:167.
252. Dimashkieh H, Wolff DJ, Smith TM et al: Evaluation of UroVysion and cytology for bladder cancer detection: a study of 1835 paired urine samples with clinical and histologic correlation. *Cancer (Cancer Cytopathol)*. 2013; **121**:591.
253. Chang SS, Boorjian SA, Chou R et al: Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO Guideline. *J Urol* 2016; **196**: 1021.
254. Sherwood JB and Sagalowsky AI: The diagnosis and treatment of urethral recurrence after radical cystectomy. *Urol Oncol* 2006; **24**: 356.
255. Clark PE and Hall MC: Contemporary management of the urethra in patients after radical cystectomy for bladder cancer. *Urol Clin North Am.*2005; **32**: 199.
256. Tobisu KI, Tanaka Y, Mizutani T et al: Transitional cell carcinoma of the urethra in men following cystectomy for bladder cancer: Multivariate analysis for risk factors. *J Urol* 1991; **146**:1551.
257. Nieder AM, Sved PD, Gomez P et al: Urethral recurrence after cystoprostatectomy: implications for urinary diversion and monitoring. *Urology* 2004; **64**:950.
258. Knapik JA and Murphy WM: Urethral wash cytopathology for monitoring patients after cystoprostatectomy with urinary diversion. *Cancer* 2003; **99**:352.
259. Lin DW, Herr HW and Dalbagni G: Value of urethral wash cytology in the retained male urethra after radical cystoprostatectomy. *J Urol* 2003;**169**:961.
260. Boorjian SA, Kim SP, Weight CJ et al: Risk factors and outcomes of urethral recurrence following radical cystectomy. *Eur Urol* 2011; **60**: 1266.
261. Bassett JC, Gore JL, Chi AC et al. Impact of a bladder cancer diagnosis on smoking behavior. *J Clin Oncol*, 2012; **30**:1871.
262. Karam-Hage M, Cinciripini P and Gritz E: Tobacco use and cessation for cancer survivors: an overview for clinicians. *CA Cancer J Clin* 2014; **64**: 272-90.
263. PDQ Supportive and Palliative Care Editorial Board. Smoking in Cancer Care (PDQ®): Health Professional Version. 2014 Jun 20. In: PDQ Cancer Information Summaries [Internet]. Bethesda (MD): National Cancer Institute (US); 2002.
264. PDQ Supportive and Palliative Care Editorial Board. Nutrition in Cancer Care (PDQ®): Health Professional Version. 2016 Jan 8. In: PDQ Cancer Information Summaries [Internet]. Bethesda (MD): National Cancer Institute (US); 2016.
265. Siefker-Radtke AO, Kamat AM, Grossman HB et al: Phase II clinical trial of neoadjuvant alternating doublet chemotherapy with ifosfamide/doxorubicin and etoposide/cisplatin in small-cell urothelial cancer. *J Clin Oncol* 2009; **27**: 2592.
266. Patel SG, Stimson CH, Zaid HB et al: Locoregional small cell carcinoma of the bladder: clinical characteristics and treatment patterns. *J Urol* 2014; **191**: 329.
267. Choong NW, Quevedo JF and Kaur JS: Small cell carcinoma of the urinary bladder. The Mayo Clinic experience. *Cancer* 2005; **103**: 1172.
268. Quek ML, Nichols PW, Yamzon J et al: Radical cystectomy for primary neuroendocrine tumors of

the bladder: the university of southern California experience. *J Urol* 2005; **174**: 93.

269. Kaushik D, Frank I, Boorjian SA et al: Long-term results of radical cystectomy and role of adjuvant chemotherapy for small cell carcinoma of the bladder. *Int J Urol* 2015; **22**: 549.
270. Siefker-Radtke AO, Dinney CP, Abrahams NA et al: Evidence supporting preoperative chemotherapy for small cell carcinoma of the bladder: a retrospective review of the M.D. Anderson cancer experience. *J Urol* 2004; **172**: 481.
271. Eswara JR, Heney JM, Wu CL et al: Long-term outcomes of organ preservation in patients with small cell carcinoma of the bladder. *Urol Int* 2015; **94**:401.
272. Mattes MD, Kan CC, Dalbagni G et al: External beam radiation therapy for small cell carcinoma of the urinary bladder. *Pract Radiat Oncol* 2015; **5**:e17.
273. Meijer RP, Meinhardt W, van der Poel HG et al: Local control rate and prognosis after sequential chemoradiation for small cell carcinoma of the bladder. *Int J Urol* 2013; **20**:778.
274. Bryant CM, Dang LH, Stechmiller BK et al: Treatment of small cell carcinoma of the bladder with chemotherapy and radiation after transurethral resection of a bladder tumor. *Am J Clin Oncol* 2016; **39**: 69.
275. Meeks JJ, Taylor JM, Matsushita K et al: Pathological response to neoadjuvant chemotherapy for muscle-invasive micropapillary bladder cancer. *BJU Int* 2013; **111**: E325.
276. Kamat AM, Dinney CP, Gee JR et al: Micropapillary bladder cancer: a review of the University of Texas M.D. Anderson Cancer Center experience with 100 consecutive patients. *Cancer* 2007; **110**: 62.
277. Ghoneim IA, Miocinovic R, Stephenson AJ et al: Neoadjuvant systemic therapy or early cystectomy? Single-center analysis of outcomes after therapy for patients with clinically localized micropapillary urothelial carcinoma of the bladder. *Urology* 2011; **77**: 867.

American Urological Association (AUA) / American Society of Clinical Oncology (ASCO) / American Society for Radiation Oncology (ASTRO) / Society of Urologic Oncology (SUO)

Muscle-Invasive Bladder Cancer

Muscle-Invasive Bladder Cancer Panel, Consultants and Staff

Sam S. Chang, MD, MBA, FACS (Chair)
Vanderbilt University Medical Center
Nashville, TN

Jeffrey M. Holzbeierlein, MD, FACS (Vice Chair)
Kansas University Medical Center
Kansas City, KS

Bernard H. Bochner, MD, FACS
Memorial Sloan Kettering Cancer Center
New York, NY

Robert Dreicer, MD, MS, MACP, FASCO
University of Virginia
Charlottesville, VA

Ashish M. Kamat, MD, MBBS, FACS
MD Anderson Cancer Center
Houston, TX

Seth P. Lerner, MD, FACS
Baylor College of Medicine
Houston, TX

Yair Lotan, MD
UT Southwestern
Dallas, TX

Joshua J. Meeks, MD, PhD
Northwestern University
Chicago, IL

Jeff M. Michalski, MD, MBA
Washington University School of Medicine
Saint Louis, MO

Todd M. Morgan, MD
University of Michigan
Ann Arbor, MI

Diane Z. Quale
Bladder Cancer Advocacy Network (BCAN)
Bethesda, MD

Jonathan E. Rosenberg, MD
Memorial Sloan Kettering Cancer Center
New York, NY

Anthony L. Zietman, MD
Massachusetts General Hospital
Salem, MA

Consultants

Roger Chou, MD
Jessica Griffin, MS

Staff

Heddy Hubbard, PhD, MPH, RN, FAAN
Abid Khan, MHS, MPP
Erin Kirkby, MS
Shalini Selvarajah, MD
Nenellia K. Bronson, MA
Leila Rahimi
Brooke Bixler, MPH

CONFLICT OF INTEREST DISCLOSURES

All panel members completed COI disclosures. Disclosures listed include both topic- and non-topic-related relationships.

Consultant/Advisor: **Sam S. Chang**, Astellas, GLG, Janssen; **Jeffrey M. Holzbeierlein**, Janssen; **Robert Dreicer**, Asana, Genentech, Churchill Pharma; **Ashish Kamat**, Photocure, Sanofi, Abbott, Theralase, Telecta, Heat Biologics, Merck, Spectrum Pharmaceuticals, Oncogenix; **Seth Paul Lerner**, Theracoat, Biocancell, Vaxxion, Sitka, Nucleix, OncoGeneX, Taris Biomedical; **Yair Lotan**, Danone, MDxHealth; **Todd M. Morgan**, Myriad Genetics, MDxHealth; **Jonathan E. Rosenberg**, Oncogenex, Eli Lilly, Genentech

Meeting Participant or Lecturer: **Jeffrey M. Holzbeierlein**, Janssen; **Ashish Kamat**, Photocure, Sanofi, Pacific Edge

Scientific Study or Trial: **Sam S. Chang**, NIH; **Bernard H. Bochner**, Genentech; **Ashish Kamat**, FKD, Photocure, Heat Biologics, Merck; **Seth Paul Lerner**, Endo, FKD, Dendreon, Viventia; **Yair Lotan**, Abbott, Danone, Cepheid, Pacific Edge, FKD, Biocancell, Genomic Health, GenomeDX Biosciences, Photocure; **Todd M. Morgan**, Myriad Genetics; **Jonathan E. Rosenberg**, Oncogenex, Genentech, Astellas, Mirati

Leadership Position: **Todd M. Morgan**, Visible Health; **Jonathan E. Rosenberg**, BCAN, NCI, Alliance for Clinical Trials in Oncology; **Anthony L. Zietman**, American Board of Radiology, NCI, ASTRO

Investment Interest: **Jonathan E. Rosenberg**, Merck, Illumina

Health Publishing: **Jonathan E. Rosenberg**, Uptodate.com

Other: **Joshua J. Meeks**, NCCN

Peer Reviewers

We are grateful to the persons listed below who contributed to the Guideline by providing comments during the peer review process. Their reviews do not necessarily imply endorsement of the Guideline.

Mehrdad Alemozaffar, MD
Christopher Anderson, MD
Jessie Au, MD
Trinity Bivalacqua, MD
Peter C. Black, MD
Stephen A. Boorjian, MD
Steven C. Campbell, MD
Karim Chamie, MD
Arnold Chin, MD
Rodney Davis, MD
Scott E. Delacroix, Jr., MD
John D. Denstedt, MD
Rian J. Dickstein, MD
James A. Eastham, MD
Pat Fox Fulgham, MD
Matthew Galsky, MD
David A. Ginsberg, MD
Mark Gonzalgo, MD
H. Barton Grossman, MD
Thomas J. Guzzo, MD
Donna E. Hansel, MD
Richard E. Hautmann, MD
Maha Hussain, MD
Andrew C. James, MD
Lawrence I. Karsh, MD
Wes Kassouf, MD
Louis R. Kavoussi, MD
Badrinath Konety, MD
Donald L. Lamm
Cheryl T. Lee, MD
Eugene K. Lee, MD
Stanley Liauw, MD
Deborah J. Lightner, MD
William T. Lowrance, MD
Edward M. Messing, MD
Kelvin A. Moses, MD
Katie S. Murray, MD
Matthew E. Nielsen, MD
Chong-Xian Pan, MD
Manish I. Patel, MD
Sanjay Patel, MD
Michael P. Porter, MD
Glenn M. Preminger, MD
Maniyur Raghavendran, MD
Matthew J. Resnick, MD
Stephen B. Riggs, MD
Arthur I. Sagalowsky, MD
Mark P. Schoenberg, MD
John D. Seigne, MD
Wade J. Sexton, MD
William U. Shipley, MD
Neal D. Shore, MD
Angela M. Smith, MD
Norm D. Smith, MD
Abhishek Solanki, MD
Gary D. Steinberg, MD
Kelly L. Stratton, MD
Thomas F. Stringer, MD
Seth A. Strobe, MD
Chandru P. Sundaram, MD
Dan Theodorescu, MD
J. Brantley Thrasher, MD
Alon Z. Wiezer, MD
J. Alfred Witjes, MD
J. Stuart Wolf, Jr., MD
Guo-Bing Xiong, MD
Alexandre R. Zlotta, MD

DISCLAIMER

This document was written by the Muscle Invasive Bladder Cancer Guideline Panel of the American Urological Association Education and Research, Inc., which was created in 2015. The Practice Guidelines Committee (PGC) of the AUA selected the committee chair. Panel members were selected by the chair. Membership of the Panel included specialists in urology/medical oncology/radiation oncology with specific expertise on this disorder. The mission of the Panel was to develop recommendations that are analysis-based or consensus-based, depending on Panel processes and available data, for optimal clinical practices in the treatment of non-muscle invasive bladder cancer.

Funding of the Panel was provided by the AUA. Panel members received no remuneration for their work. Each member of the Panel provides an ongoing conflict of interest disclosure to the AUA.

While these guidelines do not necessarily establish the standard of care, AUA seeks to recommend and to encourage compliance by practitioners with current best practices related to the condition being treated. As medical knowledge expands and technology advances, the guidelines will change. Today these evidence-based guidelines statements represent not absolute mandates but provisional proposals for treatment under the specific conditions described in each document. For all these reasons, the guidelines do not pre-empt physician judgment in individual cases.

Treating physicians must take into account variations in resources, and patient tolerances, needs, and preferences. Conformance with any clinical guideline does not guarantee a successful outcome. The guideline text may include information or recommendations about certain drug uses ('off label') that are not approved by the Food and Drug Administration (FDA), or about medications or substances not subject to the FDA approval process. AUA urges strict compliance with all government regulations and protocols for prescription and use of these substances. The physician is encouraged to carefully follow all available prescribing information about indications, contraindications, precautions and warnings. These guidelines and best practice statements are not in-tended to provide legal advice about use and misuse of these substances.

Although guidelines are intended to encourage best practices and potentially encompass available technologies with sufficient data as of close of the literature review, they are necessarily time-limited. Guidelines cannot include evaluation of all data on emerging technologies or management, including those that are FDA-approved, which may immediately come to represent accepted clinical practices.

For this reason, the AUA does not regard technologies or management which are too new to be addressed by this guideline as necessarily experimental or investigational.