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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 (AMENDED 2020)

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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 The methodology team searched for unpublished studies in clinical trial registries (ClinicalTrials.gov, Current Controlled Trials, ClinicalStudyResults.org and the World Health Organization International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. The guideline underwent review in 2020. The updated search (July 1, 2016 to May 18, 2020) identified 2,005 abstracts, of which 38 met inclusion criteria. 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 or clinical trial. (Expert Opinion)
8. Clinicians should perform radical cystectomy as soon as possible following a patient's completion of and recovery from neoadjuvant chemotherapy (ideally within 12 weeks unless medically inadvisable). (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 with curative intent, clinicians should remove the bladder, prostate, and seminal vesicles in males; clinicians should remove the bladder in females and should consider removal of adjacent reproductive organs based on individual disease characteristics and need to obtain negative margins. (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 should be included when using multimodal therapy with curative intent. (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.

In 2020, the MIBC guideline was updated through the AUA amendment process in which newly published literature is reviewed and integrated into previously published guidelines in an effort to maintain currency. The amendment allowed for the incorporation of additional literature released since the initial publication of this guideline in 2017. For this literature review the methodology team searched Ovid MEDLINE(R) ALL from July 1, 2016 to May 18, 2020 (overlapping with search dates for the 2016 review ending October 6, 2016), and eliminated duplicate abstracts reviewed for earlier reports. The literature search identified 2,005 abstracts, of which 38 met inclusion criteria. Two of these citations were from secondary publications of another study included in this update or a previous report. Seven abstracts reported RCTs, 29 observational studies, and 2 systematic reviews.

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 Guide[3] 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.

The 2020 amendment also underwent peer review. The draft amendment was distributed to 69 peer reviewers, 18 of whom submitted 38 comments. The Panel reviewed and discussed all submitted comments and revised the draft as needed. Once finalized, the amendment was submitted for approval in the same manner as with the full guideline.

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

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)**
Strong Recommendation (Net benefit or harm substantial)	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances and future research is unlikely to change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears substantial Applies to most patients in most circumstances but better evidence is likely to change confidence (rarely used to support a Strong Recommendation)
Moderate Recommendation (Net benefit or harm moderate)	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances and future research is unlikely to change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears moderate Applies to most patients in most circumstances but better evidence is likely to change confidence
Conditional Recommendation (No apparent net benefit or harm)	Benefits = Risks/Burdens Best action depends on individual patient circumstances Future research unlikely to change confidence	Benefits = Risks/Burdens Best action appears to depend on individual patient circumstances Better evidence could change confidence	Balance between Benefits & Risks/Burdens unclear Alternative strategies may be equally reasonable Better evidence likely to change confidence
Clinical Principle	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	A statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there may or may not be evidence in the medical literature		

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

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 multi-disciplinary 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) limited carcinoma in situ (CIS), 3) no evidence of hydronephrosis, and 4) a tumor that can be completely transurethrally 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 trial[92] (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

Although there are no prospective randomized trials comparing gemcitabine and cisplatin (GC) to MVAC, a number of retrospective studies have suggested that there is no difference between the regimens in terms of survival.[106-111] While controversy remains, trials are underway to look at this space.

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. A recent large retrospective study did demonstrate that those patients who did not receive cisplatin-based chemotherapy or fewer than 3 cycles of chemotherapy had worse outcomes.[112]

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.[113] In addition, reduced performance status (WHO or ECOG PS ≥2 or Karnofsky performance status of ≤60-70%) is associated with increased toxic effects of cisplatin. Baseline renal dysfunction with an estimated or calculated creatinine clearance < 60ml/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 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 or clinical trial. (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,[114] 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.[115,116]

8. Clinicians should perform radical cystectomy as soon as possible following a patient's completion of and recovery from neoadjuvant chemotherapy (ideally within 12 weeks unless medically inadvisable). (Expert Opinion)

Patients who receive neoadjuvant chemotherapy must be medically fit to undergo cystectomy. The exact time frame when it is optimal to proceed with cystectomy after chemotherapy has not been defined. However, there are observational studies that suggest that if cystectomy is delayed more than 12 weeks after the completion of chemotherapy, outcomes may be worse.[117,118]

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)

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.[119-122] 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).[119] 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).[120] 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%).[122]

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.[123] 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.[124,125] 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.[126] 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,[127] seven retrospective cohort studies[128-134] and one non-randomized controlled clinical trial.[135] Seven studies evaluated overall survival with bladder sparing therapies versus radical cystectomy.[127-133] 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%).[128] 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).[133] Four other cohort studies evaluated all-cause mortality but did not attempt to adjust for potential confounders.[129-132] 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).[131] 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).[130]

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 trials[136-138] 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.[139]

Patients considering a radical cystectomy should be counseled regarding the high rate of complications, both acute and chronic, as outlined previously in this guideline.[140,141] 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.[142,143] 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 with curative intent, clinicians should remove the bladder, prostate, and seminal vesicles in males; clinicians should remove the bladder in females and should consider removal of adjacent reproductive organs based on individual disease characteristics and need to obtain negative margins. (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. In males, this includes the prostate and seminal vesicles. In females this may include the anterior vaginal wall, uterus, cervix, fallopian tubes, and ovaries. In select women with early stage disease and a desire to preserve fertility and/or sexual function, organ preservation may be considered as long as complete tumor resection can be achieved. 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.[55,144] 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.[145] 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.[146] 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.[147] 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.[148] 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.[85,149] 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.[150]

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.[151] 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.[152,153]

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.[154]

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 urethral is reported as between 1-17% overall in multiple contemporary cystectomy series, with the majority occurring within the first two years after surgery.[155,156] 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.[157,158] Preoperative prostatic urethral biopsies have not proved to be as reliable as urethral frozen sections and should not exclude patients from orthotopic diversion.[159]

In women with MIBC, a comprehensive literature review found that urethral tumor involvement occurs in only approximately 12% of patients undergoing cystectomy.[160] 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 ≥T3b) on bimanual examination, intraoperative frozen sections of the urethral and vaginal margins should also be obtained if a neobladder is being considered.[161]

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.[162] 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.[56,163,164] 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.[165-167] 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.[168-171] Additionally, limited data suggest that there is no increased risk of perioperative complications in the absence of a mechanical bowel preparation prior to cystectomy.[172,173] There are also data to support consideration of preoperative carbohydrate loading in order to diminish postoperative insulin resistance and shorten length of stay.[174,175] 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.[176] 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.[177-179] 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.[180]

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.[181] 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.[182-185] 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.[186,187]

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.[188-190] 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.[191] Detailed teaching may also improve health-related QOL for patients undergoing stoma surgery.[192] 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.[193,194] 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.[195-198] 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.[199,200] 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.[201] 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.[202] 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.[195-198,203-210] 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.[211-216]

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 generally 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.[127-135] 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.[217-219] 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.[127-135,217-224]

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.[220] 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.[220,222,223,225]

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.[135,224] 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.[135] 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.[226-231]

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.[232-234]

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%.[235]

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.[235,236] 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.[237] 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.[127-133] 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.[127] 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.[235] 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 should be included when using multimodal therapy with curative intent. (Strong Recommendation; Evidence Level: Grade B)

Several radiosensitizing chemotherapeutic agents have been shown safe and effective for trimodal bladder cancer therapy. While there are many agents to choose from, it is clear that radiation with concurrent chemotherapy is superior to radiation alone.[238] 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.[239] 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.[235,240] In the noeadjuvant 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.

Radiosensitizing gemcitabine has been shown safe and well-tolerated, and, along with 5-FU and mitomycin C, is another alternative for cisplatin-ineligible patients.[241-243] A recent phase II trial randomized 70 patients with invasive bladder cancer to 5-FU plus cisplatin with twice daily radiation or gemcitabine with once daily radiation.[244] Both regimens met the study's endpoint of distant metastasis free survival of >75% at 3 years with no statistically significant difference between the two arms (78% versus 84%, p=0.73), and no statistically significant difference in grade 3 and 4 toxicity. While carboplatin has been used as a radiosensitizer, there is little evidence to support its effectiveness, and it has been found to be inferior to cisplatin in this setting.[245-247] Carboplatin should not be used as a radiosensitizer unless there are contraindications to cisplatin, 5-FU, and gemcitabine.

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.[235,236] 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.[239] 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.[248]

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%.[249] 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.[250,251]

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.[252-

[255] 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.[256,257] 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,[258,259] 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.[249] 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%.[249] 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.[260,251] These tests are either protein-based or cell-based and have been evaluated extensively in non-muscle invasive disease.[262] 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.[263,264] 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.[263-265] 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.[266,267] While data varies in regards to a survival benefit associated with urethral washes,[268,269] it seems that a urethral wash cytology may be a valuable tool in higher risk patients with a retained urethra.[155] 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.cancercare.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.[270] Successful cancer treatment can be significantly compromised by continued tobacco use.[271] 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.[272] 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.[273] 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.[274-278] 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.[279] 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.[280-283]

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.[284-286] 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 cystocopic 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.

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DISCLAIMER

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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.

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