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DIAGNOSIS AND TREATMENT OF NON-MUSCLE INVASIVE BLADDER CANCER: AUA/SUO GUIDELINE

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Guideline Panel

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SUMMARY

Purpose

The survival rate for the majority of patients with non-muscle invasive bladder cancer (NMIBC) is favorable; however, the rates of recurrence and progression to muscle-invasive bladder cancer (MIBC) are important surrogate endpoints for overall prognosis, as these are major determinants of long-term outcome. The recurrence and progression probability rates depend on several clinical and pathologic factors. Therefore, the ability to predict risk of recurrence and progression and treat the disease appropriately is important. This guideline provides a risk-stratified clinical framework for the management of NMIBC. Please also refer to the associated NMIBC Treatment Algorithm.

Methodology

The systematic review utilized in the creation of this guideline was completed in part through the Agency for Healthcare Research and Quality (AHRQ) and through additional supplementation that further addressed 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 – October 2014), Cochrane Central Register of Controlled Trials (through September 2014), Cochrane Database of Systematic Reviews (through September 2014), Health Technology Assessment (through 3rd Quarter, 2014), National Health Sciences Economic Evaluation Database (through 3rd Quarter, 2014), and Database of Abstracts of Reviews of Effects (through 3rd Quarter, 2014) to capture both published and grey literature. Database searches resulted in 3,740 potentially relevant articles. After dual review of abstracts and titles, 643 articles were selected for full-text dual review, and 149 studies (in 192 publications) were determined to meet inclusion criteria and were included in this review. The AHRQ review was then updated by a consultant methodologist though September 2, 2015. Reference lists and previous systematic reviews were also reviewed for additional studies. This supplementation added 29 studies to the completed systematic review used in the creation of guideline statements. The guideline underwent review in 2019. The updated search (June 1, 2015 to November 22, 2019) identified 1,626 abstracts, of which 76 met inclusion criteria. An additional review was performed in 2023. The updated search (July 2019 to May 2023) identified 1918 abstracts, of which 75 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

DIAGNOSIS

1. At the time of resection of suspected bladder cancer, a clinician should perform a thorough cystoscopic examination of a patient's entire urethra and bladder that evaluates and documents tumor size, location, configuration, number, and mucosal abnormalities. (*Clinical Principle*)

2. At initial diagnosis of a patient with bladder cancer, a clinician should perform complete visual resection of the bladder tumor(s), when technically feasible. (*Clinical Principle*)

3. A clinician should perform upper urinary tract imaging as a component of the initial evaluation of a patient with bladder cancer. (*Clinical Principle*)

4. In a patient with a history of NMIBC with normal cystoscopy and positive cytology, a clinician should consider prostatic urethral biopsies and upper tract imaging, as well as enhanced cystoscopic techniques (blue light cystoscopy [BLC], when available), ureteroscopy, or random bladder biopsies. (*Expert Opinion*)

RISK STRATIFICATION

5. At the time of each occurrence/recurrence, a clinician should assign a clinical stage and classify a patient accordingly as "low-," "intermediate-," or "high-risk." (*Moderate Recommendation; Evidence Strength: Grade C*)

VARIANT HISTOLOGIES

6. An experienced genitourinary pathologist should review the pathology of a patient with any doubt in regard to variant or suspected variant histology (e.g., micropapillary, nested, plasmacytoid, neuroendocrine, sarcomatoid), extensive

squamous or glandular differentiation, or the presence/absence of lymphovascular invasion (LVI). (*Moderate Recommendation; Evidence Strength: Grade C*)

7. If a bladder sparing approach is being considered in a patient with variant histology, then a clinician should perform a restaging transurethral resection of bladder tumor (TURBT) within four to six weeks of the initial TURBT. (*Expert Opinion*)

8. Due to the high rate of upstaging associated with variant histology, a clinician should consider offering initial radical cystectomy. (*Expert Opinion*)

URINE MARKERS AFTER DIAGNOSIS OF BLADDER CANCER

9. In surveillance of NMIBC, a clinician should not use urinary biomarkers in place of cystoscopic evaluation. (*Strong Recommendation; Evidence Strength: Grade B*)

10. In a patient with a history of low-risk cancer and a normal cystoscopy, a clinician should not routinely use a urinary biomarker or cytology during surveillance. (*Expert Opinion*)

11. In a patient with NMIBC, a clinician may use biomarkers to assess response to intravesical BCG (UroVysion® FISH) and adjudicate equivocal cytology (UroVysion® FISH and ImmunoCyt™). (*Expert Opinion*)

TURBT/REPEAT RESECTION: TIMING, TECHNIQUE, GOAL, INDICATION

12. In a patient with non-muscle invasive disease who underwent an incomplete initial resection (not all visible tumor treated), a clinician should perform repeat transurethral resection or endoscopic treatment of all remaining tumor if technically feasible. (*Strong Recommendation; Evidence Strength: Grade B*)

13. In a patient with high-risk, high-grade Ta tumors, a clinician should consider performing repeat transurethral resection of the primary tumor site within six weeks of the initial TURBT. (*Moderate Recommendation; Evidence Strength: Grade C)*

14. In a patient with T1 disease, a clinician should perform repeat transurethral resection of the primary tumor site to include muscularis propria within six weeks of the initial TURBT. (*Strong Recommendation; Evidence Strength: Grade B*)

INTRAVESICAL THERAPY; BCG/MAINTENANCE; CHEMOTHERAPY/BCG COMBINATIONS

15. In a patient with suspected or known low- or intermediate-risk bladder cancer, a clinician should consider administration of a single postoperative instillation of intravesical chemotherapy (e.g., gemcitabine, mitomycin C) within 24 hours of TURBT. In a patient with a suspected perforation or extensive resection, a clinician should not use postoperative intravesical chemotherapy. (*Moderate Recommendation; Evidence Strength: Grade B*)

16. In a low-risk patient, a clinician should not administer induction intravesical therapy. (*Moderate Recommendation; Evidence Strength: Grade C*)

17. In an intermediate-risk patient a clinician should consider administration of a six-week course of induction intravesical chemotherapy or immunotherapy. (*Moderate Recommendation; Evidence Strength: Grade B*)

18. In a high-risk patient with newly diagnosed carcinoma *in situ* (CIS), high-grade T1, or high-risk Ta urothelial carcinoma, a clinician should administer a six-week induction course of BCG. (*Strong Recommendation; Evidence Strength: Grade B*)

19. In an intermediate-risk patient who completely responds to an induction course of intravesical chemotherapy, a clinician may utilize maintenance therapy. (*Conditional Recommendation; Evidence Strength: Grade C*)

20. In an intermediate-risk patient who completely responds to induction BCG, a clinician should consider maintenance BCG for one year, as tolerated. (*Moderate Recommendation; Evidence Strength: Grade C*)

21. In a high-risk patient who completely responds to induction BCG, a clinician should continue maintenance BCG, based on availability, for three years, as tolerated. (*Moderate Recommendation; Evidence Strength: Grade B*)

BCG RELAPSE AND SALVAGE REGIMENS

22. In an intermediate- or high-risk patient with persistent or recurrent disease or positive cytology following intravesical therapy, a clinician should consider performing prostatic urethral biopsy and an upper tract evaluation prior to administration of additional intravesical therapy. (*Conditional Recommendation; Evidence Strength: Grade C*)

23. In an intermediate- or high-risk patient with persistent or recurrent Ta or CIS disease after a single course of induction intravesical BCG, a clinician should offer a second course of BCG. (*Moderate Recommendation; Evidence Strength: Grade C*)

24. In a patient fit for surgery with high-grade T1 disease after a single course of induction intravesical BCG, a clinician should offer radical cystectomy. (*Moderate Recommendation; Evidence Strength: Grade C*)

25. A clinician should not prescribe additional BCG to a patient who is intolerant of BCG or has documented recurrence on TURBT of high-grade, non-muscle-invasive disease and/or CIS within six months of two induction courses of BCG or induction BCG plus maintenance. (*Moderate Recommendation; Evidence Strength: Grade C*)

26. In a patient with persistent or recurrent high-grade NMIBC within 12 months of completion of adequate BCG therapy (two induction courses or one induction course plus one maintenance cycle) who is unwilling or unfit for cystectomy, a clinician may recommend clinical trial enrollment, an alternative intravesical therapy (i.e., nadofaragene [firadenovec-vncg]) or alternative intravesical chemotherapies (gemcitabine/docetaxel). A clinician may also offer systemic immunotherapy with pembrolizumab to a patient with CIS within 12 months of completion of adequate BCG therapy. (*Conditional Recommendation; Evidence Strength: Grade C*)

ROLE OF CYSTECTOMY IN NMIBC

27. In a patient with Ta low- or intermediate-risk disease, a clinician should not perform radical cystectomy until bladder-sparing modalities (staged TURBT, intravesical therapies) have failed. (*Clinical Principle*)

28. In a high-risk patient who is fit for surgery with persistent high-grade T1 disease on repeat resection, or T1 tumors with associated CIS, LVI, or variant histologies, a clinician should consider offering initial radical cystectomy. (*Moderate Recommendation; Evidence Strength: Grade C*)

29. In a high-risk patient with persistent or recurrent disease within one year following treatment with two induction cycles of BCG or BCG maintenance, a clinician should offer radical cystectomy. (*Moderate Recommendation; Evidence Strength: Grade C*)

ENHANCED CYSTOSCOPY

30. In a patient with NMIBC, a clinician should offer BLC at the time of TURBT, if available, to increase detection and decrease recurrence. (*Moderate Recommendation; Evidence Strength: Grade B*)
31. In a patient with NMIBC, a clinician may consider use of narrow-band imaging (NBI) to increase detection and decrease recurrence. (*Conditional Recommendation; Evidence Strength: Grade C*)

RISK ADJUSTED SURVEILLANCE AND FOLLOW-UP STRATEGIES

32. After completion of the initial evaluation and treatment of a patient with NMIBC, a clinician should perform the first surveillance cystoscopy within three to four months. (*Expert Opinion*)
33. For a low-risk patient whose first surveillance cystoscopy is negative for tumor, a clinician should perform subsequent surveillance cystoscopy six to nine months later, and then annually thereafter; surveillance after five years in the absence of recurrence should be based on shared-decision making between the patient and clinician. (*Moderate Recommendation; Evidence Strength: Grade C*)
34. In an asymptomatic patient with a history of low-risk NMIBC, a clinician should not perform routine surveillance upper tract imaging. (*Expert Opinion*)
35. In a patient with a history of low-grade Ta disease and a noted sub-centimeter papillary tumor(s), a clinician may consider in-office fulguration as an alternative to resection under anesthesia. (*Expert Opinion*)
36. For an intermediate-risk patient whose first surveillance cystoscopy is negative for tumor, a clinician should perform subsequent cystoscopy with cytology every 3-6 months for 2 years, then 6-12 months for years 3 and 4, and then annually thereafter. (*Expert Opinion*)
37. For a high-risk patient whose first surveillance cystoscopy is negative for tumor, a clinician should perform subsequent cystoscopy with cytology every three to four months for two years, then six months for years three and four, and then annually thereafter. (*Expert Opinion*)
38. For an intermediate- or high-risk patient, a clinician should consider performing surveillance upper tract imaging at one- to two-year intervals. (*Expert Opinion*)

INTRODUCTION

PURPOSE

The survival rate for the majority of patients with NMIBC is favorable; however, the rates of recurrence and progression to muscle-invasive bladder cancer (MIBC) are important surrogate endpoints for overall prognosis, as these are major determinants of long-term outcome. The recurrence and progression probability rates depend on several clinical and pathologic factors. Therefore, the ability to predict risk of recurrence and progression and treat the disease appropriately is important. This guideline provides a risk-stratified clinical framework for the management of NMIBC.

METHODOLOGY

Systematic Review

The systematic review utilized in the creation of this guideline was completed in part through AHRQ and through additional supplementation that further addressed 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 – October 2014), Cochrane Central Register of Controlled Trials (through September 2014), Cochrane Database of Systematic Reviews (through September 2014), Health Technology Assessment (through 3rd Quarter, 2014), National Health Sciences Economic Evaluation Database (through 3rd Quarter, 2014), and Database of Abstracts of Reviews of Effects (through 3rd Quarter, 2014) to capture both published and grey literature. Database searches resulted in 3,740 potentially relevant articles. After dual review of abstracts and titles, 643 articles were selected for full-text dual review, and 149 studies (in 192 publications) were determined to meet inclusion criteria and were included in this review. The AHRQ review was then updated by a consultant methodologist though September 2, 2015. Reference lists and previous systematic reviews were also reviewed for additional studies. This supplementation added 29 studies to the completed systematic review used in the creation of guideline statements.

In 2020, the NMIBC 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 2016. For this updated literature review the methodology team searched Ovid MEDLINEI ALL from June 1, 2015 to November 22, 2019, and eliminated duplicate abstracts reviewed for earlier reports. Following initial report review, the Panel suggested additional abstracts that were assessed for inclusion as well. In total, the updated literature search identified 1,626 abstracts, of which 76 met inclusion criteria.

An additional update was performed in 2023. The updated search gathered literature from July 2019 to May 2023. This review identified 1,918 abstracts, of which 75 met inclusion criteria.

Data Extraction and Data Management

For treatment studies, the following information was extracted 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 characteristics (including age, race, sex, stage of disease, and functional status), results, adverse events, withdrawals due to adverse events, and sources of funding. Relative risks and associated 95 percent confidence intervals (CI) were calculated based on the information provided (sample sizes and incidence of outcomes in each intervention group). Discrepancies between calculated and reported results were noted when present.

For diagnostic accuracy studies, the following information was abstracted: setting, screening test or tests, method of data collection, reference standard, inclusion criteria, population characteristics (including age, sex, race, smoking status, signs or symptoms, and prior bladder cancer stage or grade), proportion of individuals with bladder cancer, bladder cancer stage and grade, definition of a positive screening exam, proportion of individuals unexaminable by the screening test, proportion who did not undergo reference standard, results, and sources of funding. When possible, two-by-two tables were created from information provided (sample size, prevalence, sensitivity, and specificity) and

compared to calculated measures of diagnostic accuracy based on the two-by-two tables with reported results. Discrepancies between calculated and reported results were noted 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

Risk of bias was assessed for randomized trials and observational studies using criteria adapted from those developed by the U.S. Preventive Services Task Force.[1] Studies of diagnostic accuracy were rated using criteria adapted from QUADAS-2.[2] These criteria were applied in conjunction with the approaches recommended in the AHRQ Methods Guide[3] for medical interventions and the AHRQ Methods Guide for Medical Test Reviews.[4] 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.[3]

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 (**Table 1**).[5] The 38 statements created vary in level of evidence, but none include Level A evidence, and a majority are Level C evidence.

TABLE 1: Strength of Evidence Definitions

AUA Strength of Evidence Category	GRADE Certainty Rating	Definition
A	High	• Very confident that the true effect lies close to that of the estimate of the effect
B	Moderate	• Moderately confident in the effect estimate • The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
C	Low	• Confidence in the effect estimate is limited • The true effect may be substantially different from the estimate of the effect
	Very Low	• Very little confidence in the effect estimate • The true effect is likely to be substantially different from the estimate of effect

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 2)**. ***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.[6] 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, which is based on members' clinical training, experience, knowledge, and judgment for which there is no evidence.

Process

The NMIBC 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 Society of Urologic Oncology (SUO) with specific expertise in this area, where then nominated and approved by the PGC. The AUA conducted a thorough peer review process. The draft guidelines document was distributed to 128 peer reviewers, 66 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 Board of Directors for final approval.

The 2020 amendment also underwent peer review. The draft amendment was distributed to 77 peer reviewers, 21 of whom submitted 57 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.

Additionally, the 2024 amendment underwent peer review. The draft amendment was distributed to 83 peer reviewers, 18 of whom submitted 80 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.

Funding of the Panel was provided by the AUA; Panel members received no remuneration for their work.

TABLE 2: AUA Nomenclature Linking Statement Type to Level of Certainty, Magnitude of Benefit or Risk/Burden, and Body of Evidence Strength

Evidence Grade	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 (Net benefit or harm comparable to other options)	-Benefits = Risks/Burdens -Best action depends on individual patient circumstances -Future Research is 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 -Net benefit (or net harm) comparable to other options -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		

BACKGROUND

Epidemiology

NMIBC represents approximately 75% of the 74,000 estimated new bladder cancer cases diagnosed in the United States in 2015.[7, 8] Bladder cancer is more common in males than females with a ratio of approximately 3:1, and it is the fourth most common solid malignancy in men. There are 16,000 estimated deaths for 2015, predominantly affecting males.[7, 9] Bladder cancer primarily affects Caucasian Americans and those older than 65 years with relatively stable mortality rates since 1975.[9]

National registry data from the U.S. Surveillance Epidemiology and End Results program demonstrates that the incidence of all stages of NMIBC has been relatively stable from 1988-2006; however, the adjusted incidence of stage Ta has significantly increased, while stages Tis and T1 have slightly decreased.[10]

Etiology

Risk factors

Multiple factors are associated with bladder carcinogenesis; however, tobacco smoking is the most significant and most common risk factor.[11] Although smoking cessation may somewhat decrease carcinogenesis risk, former smokers still have a higher risk of bladder cancer than those who never smoked.[11] With respect to NMIBC, current tobacco use and cumulative lifetime exposure may be associated with recurrence and progression.[12, 13] Although an incomplete list, the Panel has identified other more common risk factors. Occupational exposure to chemical carcinogens, such as aromatic amines, polycyclic aromatic hydrocarbons, and arsenic, is another reported risk factor.[14, 15] Patients with other malignancies, such as lymphomas and leukemias, who receive treatment with cyclophosphamide may be at increased risk for bladder cancer.[16, 17] Patients with Lynch Syndrome may also be at increased risk of urothelial carcinoma of the bladder, as well as, the upper urinary tract.[18, 19] Infection also increases the risk of bladder cancer; in particular, *Schistosoma hematobium*, the pathogen responsible for schistosomiasis, is a risk factor for squamous cell carcinoma of the bladder in certain regions of the world.[20] In looking at squamous cell carcinoma of the bladder, chronic catheter use also serves as a risk factor. Additionally, aristolochic acid, a natural compound found in a number of plants of the *Aristolochia* genus, has been linked to upper-tract urothelial carcinoma.[21] Another known risk factor includes external beam radiation to the pelvis.[22]

Molecular Mechanism and Genetics

There is no currently accepted genetic or inheritable cause of bladder cancer; however, studies suggest that genomic instability and genetic pathway mutations/alterations may play a role in bladder carcinogenesis. Studies suggest that polymorphisms in two carcinogen-detoxifying genes GSTM-1 and NAT-2 may be responsible for increased susceptibility to developing bladder cancer in certain patients.[23] Chromosome 9 deletion is a common genetic alteration found in NMIBC, with loss of heterozygosity (LOH) of 9p, homozygous deletion of CDKN2A, and loss of expression of p16 in NMIBC predicting recurrence free survival.[24-26] Mutations in tumor suppressor genes can lead to disruption of cell cycle regulation and predispose to carcinogenesis. CIS frequently demonstrates mutations in the tumor suppressor genes TP53, RB1 (retinoblastoma), and PTEN.[27] Oncogenes that promote tumor cell development and alterations in FGFR3, PIK3CA, and RAS are common in NMIBC.[27, 28]

Presentation and Diagnosis

The most common presenting symptom is painless hematuria (gross or microscopic). According to the AUA Guideline on the diagnosis, evaluation, and follow-up of patients with asymptomatic microhematuria (AMH), the rate of urinary tract malignancy in AMH is approximately 2.6%.[29] Irritative voiding symptoms (e.g., frequency, urgency, dysuria) may also be associated with CIS in patients with no sign of urinary tract infection (UTI). Physical exam rarely reveals significant findings in patients with NMIBC. However, a bimanual exam may be performed under anesthesia at the time of TURBT and should be performed at that time if the tumor appears invasive. Although not indicated for routine screening and evaluation of AMH, urinary cytology (voided or barbotage) may be used in the surveillance of bladder cancer for certain patients as it possesses a high sensitivity and positive predictive value for high-grade tumors and CIS.[30, 31] Contrast-based axial imaging, such as computed tomography (CT) or magnetic resonance imaging (MRI) is

the recommended imaging modality during the work-up for bladder cancer. Retrograde pyelogram and intravenous urography may also be used when CT or MRI are unavailable. Abdomino-pelvic sonography alone may not provide sufficient anatomic detail for upper urinary tract imaging during the work-up of bladder cancer.[32]

The diagnosis of bladder cancer is confirmed by direct visualization of the tumor and other mucosal abnormalities with endoscopic excision using cystoscopy and TURBT. An adequate TURBT requires complete resection of all visible tumor with adequate sampling of the bladder to assess the depth of invasion.

Staging and Grading

Staging for bladder cancer is separated into clinical and pathologic stage, as outlined by the American Joint Committee on Cancer (AJCC), also known as the Tumor-Node-Metastases (TNM) classification.[33] Clinical stage reflects the histologic findings at TURBT; the clinician's physical exam, including bimanual exam under anesthesia; and findings on radiologic imaging. The pathologic report of the TURBT should indicate whether lamina propria and muscularis propria are present as well as the degree of involvement, if present. In addition, effort should be made by the pathologist to examine the specimen for lymphovascular invasion (LVI), when applicable, as this is associated with worse prognosis.[34-37] Pathological staging, also known as surgical staging, is based on the extent of disease following surgical resection of the bladder (partial versus radical cystectomy) and of the adjacent pelvic lymph nodes. Under the AJCC staging system, NMIBC includes the following: (1) papillary tumors confined to the epithelial mucosa (stage Ta), (2) tumors invading the subepithelial tissue (i.e., lamina propria; T1), and (3) Tis. (**Table 3**)

TABLE 3: Staging of primary tumors (T) in bladder cancer[33]

TX	Primary tumor cannot be assessed
Ta	Noninvasive papillary carcinoma
Tis	Carcinoma in situ (CIS)
T1	Tumor invades lamina propria
T2	Tumor invades muscularis propria
T2a	Tumor invades superficial muscularis propria (inner half)
T2b	Tumor invades deep muscularis propria (outer half)
T3	Tumor invades perivesical tissue/fat
T3a	Tumor invades perivesical tissue/fat microscopically
T3b	Tumor invades perivesical tissue fat macroscopically (extravesical mass)
T4	Tumor invades prostate, uterus, vagina, pelvic wall, or abdominal wall
T4a	Tumor invades adjacent organs (uterus, ovaries, prostate stoma)
T4b	Tumor invades pelvic wall and/or abdominal wall

Tumor grade is an important prognostic factor for determining risk of recurrence and progression in bladder cancer. Prior to the 2004 revised classification, the 1973 World Health Organization (WHO) classification was the widely accepted format for grading bladder neoplasia.[38, 39] The 1973 version designated tumors as either

papilloma, grade 1, 2, or 3, whereas the 2004 revision designated tumors as 'low' or 'high' grade. The 1973 grade 2 or 'intermediate' grade tumors are now re-classified as either 'low' or 'high' grade depending on cellular morphology.[38, 39] In addition, the 2004 classification introduced the new category of papillary urothelial neoplasm of low malignant potential to describe lesions with an increased number of urothelial layers when compared with papilloma but without cytologic features of malignancy. The WHO/International Society of Urological Pathology 2004 grading system is now the most widely accepted and utilized system in the United States. (**Table 4**)

TABLE 4: 2004 WHO/ International Society of Urologic Pathologists: Classification of Non-muscle Invasive Urothelial Neoplasia[38]
Hyperplasia (flat and papillary)
Reactive atypia
Atypia of unknown significance
Urothelial dysplasia
Urothelial CIS
Urothelial papilloma
Papillary urothelial neoplasm of low malignant potential
Non-muscle invasive low-grade papillary urothelial carcinoma
Non-muscle invasive high-grade papillary urothelial carcinoma

Prognosis

The survival prognosis for patients with NMIBC is relatively favorable, with the cancer-specific survival (CSS) in high-grade disease ranging from approximately 70-85% at 10 years and a much higher rate for low-grade disease.[40, 41] The rates of recurrence and progression to MIBC are important surrogate endpoints for prognosis in NMIBC, as these are major determinants of long-term outcome. However, NMIBC is a clinically heterogeneous group of cancers with a wide range of recurrence and progression probabilities that depend on several clinical and pathologic factors. For example, long-term follow up of low-grade Ta lesions demonstrates a recurrence rate of approximately 55%, but with a much lower percentage (6%) experiencing stage progression.[42] In contrast, high-grade T1 lesions have both a significant risk of recurrence (45%) and increased chance of progression (17%) in single institution series.[40] Therefore, the ability to predict recurrence and progression risk in NMIBC, based on patient-specific disease characteristics, holds prognostic significance. Risk stratification in NMIBC aids personalized treatment decisions and surveillance strategies as opposed to a generalized 'one-size fits all' approach.

Risk Stratification

Significant effort has been put forth to develop tools for risk stratification and prognostication. A widely published system is the European Organization for Research and Treatment of Cancer (EORTC) risk calculator, based on the combined data from seven trials involving patients with NMIBC.[43] Using clinical and pathologic variables in a scoring system, the EORTC calculator provides a probability of recurrence and progression at one and five years. Important factors for recurrence identified by the EORTC study include prior recurrence rate, number of tumors, and tumor size.[43] With respect to progression, important factors include T-stage, presence of CIS, and grade. A second risk stratification tool is that developed by the Spanish Urological Club for Oncological Treatment/Club Urologico Espanol de Tratamiento Oncologico (CUETO).[44] These models are examples of carefully constructed risk stratification systems; however, they have limitations. Both tools are limited by lack of applicability to current patient populations because few patients from the development cohort received BCG maintenance, underwent re-staging transurethral-resection, or received single-dose post-operative mitomycin C. A recent update of the EORTC nomogram for risk stratification attempted to address the lack of BCG maintenance in prior studies, by analyzing a cohort of patients treated with one to three years of BCG. This updated study cohort lacked patients with CIS and again was limited by absence of routine re-resection.[45] Additionally, the EORTC risk calculator utilizes the 1973 WHO grading system to generate risk probabilities as opposed to the 2004 version. As previously mentioned, the 2004 revision is the currently accepted classification for tumor grade; therefore, the EORTC risk tables are commonly not considered in the U.S.

Risk groupings are evaluated by their ability to predict the outcome of patients who are felt to be similar to one another. The most commonly used tool to assess the accuracy of risk groupings is the concordance index (C-index). The C-index is a measure of the ability of a risk assessment tool to separate those patients with the outcome of interest from those without the outcome of interest (e.g., recurrence or progression).[46] A C-index of 0.5 implies that the ability to predict outcome is no better than random chance. For the original EORTC study, the C-indices for recurrence and progression were 0.66 and 0.75, respectively and 0.64 and 0.7, respectively, for the CUETO study.[43, 44] A further important limitation of the existing risk stratification models is that neither reported formal measures of calibration (the degree to which predicted and observed risk estimates agree). Several studies have retrospectively evaluated the ability of the EORTC and CUETO models to predict the risk of recurrence and progression in other patient populations.[47-52] These attempts at external validation using other patient populations have yielded variable C-index results and underscore the fact that both instruments are limited by suboptimal calibration and inherent biases based on their designs. Evaluation of these studies investigating the utility of risk stratification in multiple populations demonstrate that they have a poor to fair ability to discriminate risk of recurrence (C-index 0.52 to 0.66) and good to fair (C-index 0.62 to 0.81) ability to discriminate risk of progression.

The Panel acknowledges that Level A evidence does not support stratification as affecting disease recurrence, progression, or survival. However, despite the lack of evidence confirming a positive influence on clinical outcome, the Panel agrees that there is value to creating fundamental categories that broadly estimate the likelihood of recurrence and progression. The Panel set out to create such a system, with categories summarized as 'low,' 'intermediate,' and 'high' risk for recurrence and/or progression. (**Table 5**) This risk grouping system is a simple tool, intended for use in clinical practice as a general framework for guiding patient counseling and aiding in treatment and surveillance decisions based on prognosis. While there are similarities between the current risk categories outlined in the Guideline and the EORTC stratification, it should be noted that they are not based on a meta-analysis or original studies and represent the Panel's consensus regarding the likelihood of recurrence and progression. To develop the current risk groupings, the Panel set forth defining first those at lowest and highest risk for recurrence and/or progression. Numerous clinical scenarios based on disease characteristics were then incorporated into the grouping system, and each one was placed into a category based on unanimous expert consensus and available published data. The Panel also recognizes that the intermediate group is somewhat heterogeneous, and the outcome of patients within this group may still exhibit some variation along the spectrum of risk of recurrence and progression.

Unique to the AUA/SUO Guideline Risk Stratification System is the incorporation of prior BCG intravesical therapy on prognosis. There are limited data that demonstrate that patients who have persistent or recurrent disease at six months following BCG therapy are at increased risk of disease progression.[53, 54] As such, the Panel reasons that patients who are intermediate risk and demonstrate BCG failure should be re-stratified to the high-risk group. The rationale for this approach is that those patients who do not respond to standard intravesical therapy likely harbor more aggressive disease than implied by clinical or pathologic features; therefore, a lack of response serves as a surrogate marker for increased risk of recurrence and/or progression. The Panel also understands and appreciates that within each of these risk strata that an individual patient may have more or less concerning features that can influence care.

The Panel acknowledges the need for validation of these risk groups in large, contemporary patient cohorts in order to assess the model's performance for predicting disease recurrence and progression.

Relevance of the International BCG Shortage to the AUA Guidelines

The global shortages in TICE BCG that occurred in 2014 and 2019 led the AUA to recommend several management strategies to maintain high quality care for patients with NMIBC. These recommendations may supersede the guideline statements below. In particular, the BCG shortage impacts guideline statements 17, 20, and 21. The AUA Statement on the BCG Shortage is available at https://www.auanet.org/about-us/bcg-shortage-info.

TABLE 5: AUA Risk Stratification for NMIBC		
Low Risk	**Intermediate Risk**	**High Risk**
LG[a] solitary Ta ≤ 3cm	Recurrence within 1 year, LG Ta	HG T1
PUNLMP[b]	Solitary LG Ta > 3cm	Any recurrent, HG Ta
	LG Ta, multifocal	HG Ta, >3cm (or multifocal)
	HG[c] Ta, ≤ 3cm	Any CIS[d]
	LG T1	Any BCG failure in HG patient
		Any variant histology
		Any LVI[e]
		Any HG prostatic urethral involvement
[a]LG = low grade; [b]PUNLMP = papillary urothelial neoplasm of low malignant potential; [c]HG = high grade; [d]CIS=carcinoma *in situ*; [e]LVI = lymphovascular invasion		

GUIDELINE STATEMENTS

Diagnosis

1. **At the time of resection of suspected bladder cancer, a clinician should perform a thorough cystoscopic examination of a patient's entire urethra and bladder that evaluates and documents tumor size, location, configuration, number, and mucosal abnormalities. (Clinical Principle)**

The diagnosis of NMIBC relies upon cystoscopy and tissue sampling. Initial cystoscopic evaluation is often performed in the office setting with or without biopsies of visualized tumor(s). Flexible cystoscopy in conjunction with topical intraurethral anesthetic lubricant decreases patient discomfort during the procedure, particularly in men.[55] Most cases of NMIBC are initially treated with transurethral resection, but careful cystoscopic examination of the entire urethra and bladder should precede resection.[56] However, surgeons may proceed directly to TURBT should CT or MRI reveal a bladder lesion during the evaluation of hematuria. During resection, tumors of significant size should be resected and labeled. The anatomic location of tumors with respect to the bladder neck and ureteral orifices, tumor configuration (papillary or sessile), as well as both the size and number of tumors should be documented in some consistent manner (e.g., diagram, text description) to inform future follow-up and evaluate treatment response.

2. **At initial diagnosis of a patient with bladder cancer, a clinician should perform complete visual resection of the bladder tumor(s), when technically feasible. (Clinical Principle)**

Incomplete TURBT is likely a significant contributing factor to early bladder cancer recurrences, as tumors are seen at first surveillance cystoscopy in up to 45% of patients.[57] Thus, complete TURBT is critical in management of NMIBC for accurate tumor type, staging, grading, and optimization of patient outcomes.[57-59] A lack of detrusor muscle in the resection specimens is associated with increased risk of understaging, residual disease on repeat TURBT, and early tumor recurrence.[59, 60] In addition to complete resection, bimanual examination under anesthesia after TURBT can also assist with clinical staging. Enhanced cystoscopy methods and newer resection techniques, such as bipolar electrocautery, may serve to enhance complete resection and reduce complications from TURBT.[61-63] For patients with a history of small, low-grade Ta tumors, however, office-based cystoscopy and fulguration of small recurrences or even cystoscopic surveillance are treatment options and may reduce overall therapeutic burden.[64-67] Emerging larger clinical experiences and confirmatory trials are needed to validate these conservative approaches.

3. **A clinician should perform upper urinary tract imaging as a component of the initial evaluation of a patient with bladder cancer. (Clinical Principle)**

In patients with a known history of bladder cancer, upper tract tumors occur in less than 5% of patients and can be evaluated with common imaging techniques, including retrograde pyelography, CT, MRI, as well as transabdominal ultrasonography (US), in select cases. CT urogram or MR urogram have advantages over US, showing not only potential hydronephrosis, but also filling defects, as well as regional lymph nodes and adjacent organs. US and retrograde pyelography are typically reserved for patients with renal function non-supportive of contrast-enhanced CT or MRI. The overall incidence of significant findings with imaging of the upper tracts in patients with newly diagnosed bladder cancer is low but increases with tumors of the trigone, CIS, and high-risk disease.[68, 69] The timing of initial upper tract imaging for bladder cancer is not clear, but it should likely be risk stratified and generally within six months of initial diagnosis. Repeat upper tract imaging should occur every one to two years in a high-risk patient.

4. **In a patient with a history of NMIBC with normal cystoscopy and positive cytology, a clinician should consider prostatic urethral biopsies and upper tract imaging, as well as enhanced cystoscopic techniques (blue light cystoscopy [BLC], when available), ureteroscopy, or random bladder biopsies. (Expert Opinion)**

The likelihood of detecting CIS on random bladder biopsies in patients with low-risk disease is exceedingly small but increases significantly in patients with high-risk disease or positive cytology.[70, 71] Similarly, involvement of the prostatic urethra is very uncommon in men with low-risk disease but increases substantially in the presence of CIS, multifocal disease, and tumors of the bladder neck and trigone.[40, 72] Furthermore, enhanced cystoscopic techniques, including BLC and NBI, seem particularly valuable for diagnosis of urothelial carcinoma in the setting of positive cytology but negative white light cystoscopy (WLC).[73, 74]

Risk Stratification

5. **At the time of each occurrence/recurrence, a clinician should assign a clinical stage and classify a patient accordingly as "low-," "intermediate-," or "high-risk." (Moderate Recommendation; Evidence Strength: Grade C)**

In creating the AUA/SUO Guideline Risk Stratification System (see Table 5), the Panel chose to adhere to the general principles of the EORTC and CUETO models by including factors that have been found to have a significant impact on risk of recurrence and progression, such as tumor size, tumor focality, grade, and stage. In addition, however, the Panel incorporated evidence from other studies that has demonstrated that LVI, prostatic urethral involvement, variant histology, and poor response to BCG also confer high-risk for progression to muscle invasion.[53, 54, 75-77]

Risk stratification for each patient is a dynamic and iterative process. Patients may recur multiple times during the continuum of their care and may face repetitive therapeutic interventions, such as intravesical therapy. Those patients who recur following optimal standard intravesical therapy likely harbor more aggressive disease than implied by clinical or pathologic features; as such, continued risk evaluation and classification is

necessary for the optimal care of patients prior to each treatment decision.

Variant Histologies

6. **An experienced genitourinary pathologist should review the pathology of a patient with any doubt in regard to variant or suspected variant histology (e.g., micropapillary, nested, plasmacytoid, neuroendocrine, sarcomatoid), extensive squamous or glandular differentiation, or the presence/absence of lymphovascular invasion (LVI). (Moderate Recommendation; Evidence Strength: Grade C)**

The pathology report should specify the presence and percentage of variant histology (e.g., squamous and/or glandular differentiation, micropapillary, nested, plasmacytoid, neuroendocrine, sarcomatoid) as well as the presence or absence of LVI. These currently recognized histologic variants are less common and can influence disease prognosis and treatment choices. The Panel recognizes that future pathologic and molecular subtypes will continue to be elucidated and that these may require secondary review. In cases of non-muscle invasive disease, re-resection is mandatory to rule out muscle-invasive disease given the high rate of upstaging with variant histology. Several studies suggest that variant differentiation may affect survival; however, there is a paucity of data due to the rarity of most variants. Some of the variants, such as micropapillary, have been described fairly recently (1994), and others are under-recognized or understaged.[78] In one study from the Mayo Clinic, pathological re-review of cystectomy specimens identified variant histologies in up to one third of patients initially classified with pure urothelial carcinoma.[79] Compared to patients with pure urothelial carcinoma, those with variant histology have a greater incidence of locally advanced disease and worse survival.[80-82]

The diagnosis of LVI is defined by the presence of tumor within endothelium-lined spaces. Numerous studies have documented the clinical importance of LVI as an important prognostic marker of upstaging, lymph node involvement, recurrence, and decreased overall survival.[34-37] Thus, the committee believes that the reporting of the presence or absence of LVI is important.

7. **If a bladder sparing approach is being considered in a patient with variant histology, then a clinician should perform a restaging transurethral resection of bladder tumor (TURBT) within four to six weeks of the initial TURBT. (Expert Opinion)**

Historically, the variant histologies have been under-appreciated and under-reported, but data is accumulating in regard to their aggressiveness. With their potential risk, the committee believes that if a clinician is considering any treatment that would preserve the bladder, that at a minimum, a repeat TURBT should be done to evaluate clinical stage for these tumor types.

The presence of variant histology within the TURBT specimen is uniformly associated with high-grade disease and almost always invasive. In one study, 86% of patients with variant histology presented with muscle-invasive disease at TURBT compared with 53% of those with high-grade pure urothelial carcinoma. At cystectomy, 64% of the patients with variant histology were found to have T3-T4 disease compared to 34% of those with pure high-grade urothelial carcinoma.[83] In 2021, Iida and colleagues reported on a cohort of 94 patients with BCG-unresponsive NMIBC treated without radical cystectomy. They found that the presence of variant histology was an independent predictor of poor overall survival. Although this study did not evaluate the role of re-TURBT in this population, it does support the high-risk nature of variant histology.[84] As such, patients with mixed histologic features are generally not ideal candidates for bladder sparing protocols and are best served with an aggressive treatment modality.[85]

8. **Due to the high rate of upstaging associated with variant histology, a clinician should consider offering initial radical cystectomy. (Expert Opinion)**

There is a lack of evidence regarding the efficacy of intravesical therapy for patients with non-muscle invasive urothelial carcinoma with variant histology. Given the high rate of upstaging associated with variant histology and the presence of LVI, surgeons should consider offering patients early cystectomy.[83, 85, 86] The Iida and colleagues study cited previously supports the rationale for radical cystectomy when variant histology is present in patients with NMIBC unresponsive to BCG.[84]

Urine Markers after Diagnosis of Bladder Cancer

9. In surveillance of NMIBC, a clinician should not use urinary biomarkers in place of cystoscopic evaluation. (Strong Recommendation; Evidence Strength: Grade B)

For many years, researchers have attempted to identify and utilize urinary markers for bladder cancer detection. Voided urine cytology has been the mainstay of urine-based diagnosis of bladder cancer since the original description by Papanicolou and Marshall.[87] Urine cytology, however, has several drawbacks, including a poor sensitivity for low-grade/stage tumors, a lack of interobserver consistency, a range of readings (e.g., atypical, atypical-suspicious, non-diagnostic), a need to send the specimen to an external laboratory, and a delay in obtaining results.[88] These shortcomings have inspired the search for a more sensitive urinary bladder cancer marker.

Several markers have been investigated and developed over the past three decades, with five of these markers approved by the FDA and/or are commercially available in the US.[89, 90] The NMP22® and BTA® tests are protein-based, while UroVysion® FISH, ImmunoCyt™ and CxBladder™ are cell-based. The pooled sensitivity, specificity, positive and negative likelihood ratios are shown in **Table 6**.[91]

The NMP22® test is available as a point of care test (NMP22BladderChek®) or in a more quantitative format. This test identifies a nuclear matrix protein that is involved in the mitotic apparatus. The BTA® test identifies a basement membrane antigen that is related to complement factor H and is present within urine at higher levels in patients with bladder cancer. Like NMP22®, the BTA® test is also available in qualitative and quantitative formats. Both tests are FDA-approved for initial evaluation and surveillance of bladder cancer; however, these protein-based urine markers have a tendency to be falsely positive in the presence of inflammation, resulting in lower specificity than urine cytology. This can result in subjecting patients to unnecessary diagnostic evaluations.

The UroVysion® (FISH) test identifies altered copy numbers of four specific chromosomes or loss of regions of chromosome 9p using fluorescent probes. The ImmunoCyt™ test identifies three cell surface glycoproteins that are present on the membrane of cancer cells and can be used in conjunction with cytology to enhance the sensitivity of cytology. The Cxbladder™ test identifies the presence of five mRNA fragments in the urine that are expressed at high levels in patients with bladder cancer.[90] One such fragment, CXCR2, is an inflammatory marker that helps discriminate false positive cases. This test appears to be able to distinguish between low- and high-grade tumors and may perform better than protein-based markers, such as NMP22® and BTA®. Although not a complete listing, given the lower specificity of all of the other currently available urinary markers to urine cytology as well as other concerns, the use of these markers has not been widely adopted.

Direct comparisons of protein markers, such as NMP22® and BTA®, suggest that there is little difference in sensitivity or specificity between them.[92] Comparing ImmunoCyt™ to UroVysion® FISH suggests that ImmunoCyt™ has a higher sensitivity but a lower specificity than UroVysion® FISH. Most of the studies evaluating these markers utilized cystoscopy as a gold standard for detecting tumors, while some utilized a pathologic evaluation of the biopsy specimen as the final reference. Direct comparisons between markers are difficult, and given the uncertainty in sensitivity, these tests **cannot** be used to replace cystoscopy.

The update review identified six new observational studies (in seven publications) including 1,604 participants and one systematic review relevant to this guideline statement. Since the guideline's initial publication in 2016, several new urinary biomarkers have been developed to detect recurrent bladder cancer in NMIBC patients on surveillance.[93-95] One such marker is CxBladder Monitor. It was designed as a high sensitivity rule-out test such that a negative result can be used to defer cystoscopy or confirm negative cystoscopy. In a cohort of 763 NMIBC patients on surveillance, CxBladder Monitor had a 93% sensitivity and 97% negative predictive value for recurrent NMIBC; however, the test specificity was not reported. Approximately one-third of patients had a negative test and could potentially avoid cystoscopy. The test performed well for both low- and high-grade recurrences[93] and outperformed urine cytology, NMP22, and UroVysion® FISH.[96] While a patient with a negative test is unlikely to have recurrent NMIBC, a non-negative test requires continued

cystoscopic surveillance and is not necessarily diagnostic of a recurrence. Although the early data on CxBladder Monitor are promising, further validation studies are needed to determine if a negative test is sufficient to defer surveillance cystoscopy and what the clinical implications are of a non-negative test.

TABLE 6: Performance Characteristics of Commonly Used and FDA Approved Urinary Markers[91]

Marker	Sensitivity	Specificity	Pos. likelihood ratio (95% CI)	Neg. likelihood ratio (95% CI)
NMP22® quantitative Overall Diagnosis Surveillance	 69% 67% 61%	 77% 84% 71%	3.05 (2.28-4.10)	0.40 (0.32-0.50)
NMP22® qualitative Overall Diagnosis Surveillance	 58% 47% 70%	 88% 93% 83%	4.89 (3.23-7.40)	0.48 (0.33-0.71)
BTA® quantitative Overall Diagnosis Surveillance	 65% 76% 58%	 74% 53% 79%	2.52 (1.86-3.41)	0.47 (0.37-0.61)
BTA® qualitative Overall Diagnosis Surveillance	 64% 76% 60%	 77% 78% 76%	2.80 (2.31-3.39)	0.47 (0.30-0.55)
UroVysion® FISH Overall Diagnosis Surveillance	 63% 73% 55%	 87% 95% 80%	5.02 (2.93-8.60)	0.42 (0.30-0.59)
ImmunoCyt™ Overall Diagnosis Surveillance	 78% 85% 75%	 78% 83% 76%	3.49 (2.82-4.32)	0.29 (0.20-0.41)
CxBladder™	82%	85%	5.53 (4.28-7.15)	0.21 (0.13-0.36)
CxBladder Monitor™*[93]	93%			

*Additional data outside sensitivity not reported

The role of markers as adjuncts to cystoscopy in select instances along with urine cytology continues to be evaluated. Comprehensive literature analysis showed that urinary markers have an increased sensitivity and specificity as tumor grade and stage increase. Urinary marker sensitivity is improved in patients with larger tumors. Several studies have examined markers for bladder cancer screening in high-risk populations.[97, 98] Utilization of urine markers could potentially reduce the frequency of cystoscopy in screening.[99] While this is an intriguing idea, the prevalence of bladder cancer even in high-risk individuals is *not* high enough to justify routine screening at this time. Further, the point of care protein markers used in screening do not appear helpful in identifying the screen-detectable cancers;[99, 100] therefore, this approach cannot be endorsed.

10. In a patient with a history of low-risk cancer and a normal cystoscopy, a clinician should not routinely use a urinary biomarker or cytology during surveillance. (Expert Opinion)

Many urine markers have been evaluated and even FDA-approved in the context of surveillance for recurrent bladder cancer. However, while they exhibit excellent sensitivity, particularly for lower-grade tumors, their specificity is still lower than that of urine cytology, and although cytology's sensitivity for intermediate and high-risk cancer may approach 80%, its level is low in detecting low-risk cancer (approximately 20%).[88, 101] Thus, this low sensitivity renders cytology as little use in this context.[102] While ImmunoCyt™ appears to have the highest sensitivity and specificity in the context of surveillance, the specificity still falls short of urine cytology. Since recurrent bladder tumors detected during surveillance tend to be smaller than primary tumors, the amount of protein expressed by these small tumors is also less. This has led to the suggestion that lower cutoff levels need to be utilized for protein-based markers, such as NMP22®, in order to enhance sensitivity for detecting small recurrent bladder tumors. Although at least one prospective randomized study reported that when a clinician knows the marker result, he/she detects and biopsies more tumors,[103] it remains unknown if this results in any clinical benefit or harm. Among other things, the new urine markers were aimed at specifically overcoming the low detection rate of urine cytology for low-grade tumors, but this came at the expense of specificity. The previously discussed CxBladder Monitor was designed to detect recurrent bladder cancer in NMIBC patients on surveillance. Although this biomarker performed well for intermediate- and high-risk NMIBC patients in a large cohort study, its sensitivity was only 53% in a small subset of patients with an EORTC risk score of 0, which is equivalent to AUA low-risk.[93] As such, there is currently insufficient evidence to recommend CxBladder Monitor during surveillance for low-risk patients. With the overall lack of combined effective specificity and sensitivity for low-risk patients, the Panel believes that current urinary biomarkers and cytology should not be routinely used for surveillance in these patients.

11. In a patient with NMIBC, a clinician may use biomarkers to assess response to intravesical BCG (UroVysion® FISH) and adjudicate equivocal cytology (UroVysion® FISH and ImmunoCyt™). (Expert Opinion)

The presence of significant inflammation immediately post BCG instillation can affect the accuracy of urine cytology. Urinary markers may be used to assess response to intravesical BCG therapy. In examining the change in UroVysion® FISH results before and after an induction or induction + maintenance course of BCG, several studies have noted a correlation between response to BCG and likelihood of disease progression.[104-108] Based on these studies, it appears that the presence of a persistently positive UroVysion® FISH following completion of induction BCG predicts a poor response to BCG therapy with a higher likelihood of recurrence and progression. Additionally an observational study utilizing a novel scoring system based upon UroVysion® (FISH) in patients who had a history of NMIBC identified an association between a positive FISH and the development of MIBC.[109] Based on these data, clinicians can use UroVysion® FISH as an early guide to predict response to intravesical BCG therapy. The utility of protein-based markers in this setting has not been well tested, but as with cytology, inflammation may also negatively impact their ability to predict response.

Equivocal urine cytology can occur in as high as 21% of patients being evaluated for hematuria.[110] Performance of a complete diagnostic workup to rule out cancer is typically the default approach in many of these patients with atypical cytology readings and is one reason why its routine use is no longer advocated for hematuria evaluations. Even in patients with high-grade cancers, cytology may be read as suspicious or atypical.[111, 112]

Thus, utilization of another test to arbitrate an atypical or equivocal cytology reading may be helpful in reducing the need for unnecessary diagnostic evaluations in intermediate- and high-risk bladder cancer patients. While a smaller observational study suggests diagnostic accuracy of UroVysion® FISH to be inferior to urine cytology, studies have used UroVysion® FISH in this context, and found that these urine markers may help distinguish between patients with recurrence versus no recurrence.[109] In more recent observational studies, Bladder Epicheck had improved sensitivity but decreased specificity as compared to urine cytology, indicating potential utility in conjunction with cystoscopy for surveillance of recurrent disease.[113-115]

Some patients may present with a positive urinary marker while the bladder appears cystoscopically tumor-free. A proportion but not all of such patients subsequently develop cystoscopically-identifiable tumors. In these instances, the urinary marker is able to identify a tumor before it manifests, resulting in an "anticipatory positive" test. Among the newer markers, UroVysion® FISH has been found to yield an "anticipatory positive" test in approximately 30-40% of patients.[116, 117] A recent study suggests that patients with atypical cytology and positive UroVysion® FISH may develop recurrent identifiable tumors earlier than a patients with a negative UroVysion® FISH.[118] In light of these data, these patients should continue close surveillance but do not all develop identifiable tumors.

TURBT/ Repeat Resection: Timing, Technique, Goal, Indication

12. In a patient with non-muscle invasive disease who underwent an incomplete initial resection (not all visible tumor treated), a clinician should perform repeat transurethral resection or endoscopic treatment of all remaining tumor if technically feasible. (Strong Recommendation; Evidence Strength: Grade B)

Incomplete resection is likely a significant contributing factor to what have been described and diagnosed as early recurrences, as tumors have been noted at the first follow-up cystoscopic evaluation in up to 45% of patients.[57] The Panel recognizes specific, albeit rare, circumstances in which transurethral resection is not likely to impact clinical management and may be omitted for patients with incompletely resected non-muscle invasive disease. Examples of such patients include those with large-volume, high-grade tumors not amenable to complete endoscopic resection for whom immediate radical cystectomy is planned. An additional example includes those patients with a tumor diagnosed within a bladder diverticulum and for whom subsequent surgical resection (e.g., partial or radical cystectomy) is planned. However, for the majority of patients, complete resection is essential for adequate staging and optimal clinical management.

Although surgeons may utilize BLC for this situation, of note, there is insufficient evidence in this repeat transurethral resection setting to support the routine use of enhanced or BLC versus standard WLC, particularly in light of the noted increase in false positive diagnosis with BLC following recent TURBT.[119-121]

13. In a patient with high-risk, high-grade Ta tumors, a clinician should consider performing repeat transurethral resection of the primary tumor site within six weeks of the initial TURBT. (Moderate Recommendation; Evidence Strength: Grade C)

Residual tumor can be found at the time of repeat resection in up to 50% of patients with high-grade Ta disease, with up to 15% of such tumors being upstaged.[122-125] Larger and multifocal tumors (i.e., high-risk tumors) are at a particularly increased risk for incomplete initial resection, and it this incomplete resection that is likely a significant contributing factor to inadequately treated tumors that are then diagnosed as early recurrences.[126] Nevertheless, the Panel acknowledges the paucity of data demonstrating an absolute therapeutic benefit to repeat resection for high-grade Ta tumors, and recognizes that in select cases, for example small high-grade Ta lesions in which a visually complete initial resection was performed, repeat resection may not be necessary. Thus, the Panel advocates careful consideration for repeat resection for these patients.

14. In a patient with T1 disease, a clinician should perform repeat transurethral resection of the primary tumor site to include muscularis propria within six weeks of the initial TURBT. (Strong Recommendation; Evidence Strength: Grade B)

Repeat transurethral resection for patients with T1 tumors achieves diagnostic, prognostic, and therapeutic benefit. From a diagnostic standpoint, disease understaging is

common for these patients; therefore, a second resection provides a more thorough interrogation for the presence of muscle-invasive disease. Upstaging at repeat resection to muscle-invasive disease has been reported in approximately 30% of patients with T1 tumors.[122] The risk of upstaging is related to the presence or absence of muscularis propria on the initial resection specimen, with rates of upstaging varying from 40-50% among patients without muscle present on the first TURBT specimen to 15-20% in patients with muscle present at the first TURBT.[122] Repeat resection is recommended even when the initial TURBT demonstrates the presence of muscularis propria given the noted risk of upstaging in that setting. Additionally, the pathology at repeat resection contains prognostic value that may guide subsequent clinical management. Patients found to have muscle-invasive disease may be offered neoadjuvant chemotherapy and radical cystectomy as well as tri-modality definitive local treatment. The presence of residual T1 disease at the time of repeat resection is associated with subsequent progression risk approaching 80%. As such, these patients should be counseled regarding the potential benefit of early cystectomy.[127] Alternatively, patients with non-invasive disease at repeat resection may be considered for initial bladder preservation with intravesical therapy.

In terms of a therapeutic benefit, approximately 50-70% of patients with T1 tumors have been reported from prior white-light cystoscopy series to have residual disease at the time of repeat TURBT.[122-125] In addition, repeat resection is associated with improved response rates to intravesical BCG therapy, specifically with a decreased risk of subsequent tumor recurrence and progression.[128-130] Moreover, a prospective, randomized trial of patients with T1 tumors treated with intravesical mitomycin C demonstrated that repeat TURBT significantly decreased recurrence and progression rates.[131]

The Panel recognizes that for select patients, repeat transurethral resection is not likely to impact clinical management and may, therefore, be omitted. Such patients include those with high-risk non-muscle invasive disease who would not be eligible to receive neoadjuvant chemotherapy even if muscle-invasive disease is documented and for whom immediate radical cystectomy is planned. In addition, the role of repeat transurethral resection for patients with pure non-urothelial histology is not well defined; therefore, management of these patients should be individualized, with consideration given to the specific tumor histology as well as patient comorbidity and renal function status.

Intravesical Therapy; BCG/Maintenance; Chemotherapy/BCG Combinations

15. In a patient with suspected or known low- or intermediate-risk bladder cancer, a clinician should consider administration of a single postoperative instillation of intravesical chemotherapy (e.g., gemcitabine, mitomycin C) within 24 hours of TURBT. In a patient with a suspected perforation or extensive resection, a clinician should not use postoperative intravesical chemotherapy. (Moderate Recommendation; Evidence Strength: Grade B)

The rationale for postoperative instillation of intravesical chemotherapy includes both destruction of residual microscopic tumor at the site of TURBT and of tumor cells dispersed within the bladder.[132-134] A single postoperative instillation of intravesical chemotherapy after TURBT has been demonstrated in multiple studies to decrease tumor recurrence without effects on progression or survival. SWOG 0337, which was a randomized, controlled double-blind trial of a single dose of intravesical gemcitabine (2g in 100mL of saline) versus normal saline reduced recurrences of low-grade Ta bladder cancer with a relative risk reduction of 35% and an absolute risk reduction of 10-15% at 4 years.[135] In addition, there were no Grade 4-5 adverse events in any patient in the trial, and the incidence of Grade 3 adverse events between gemcitabine and saline were equal, emphasizing the safety of gemcitabine. Three separate meta-analyses have reported that a single postoperative instillation of chemotherapy significantly decreases tumor recurrence between 10-15% compared to TURBT, although a recent randomized 3-arm trial in 82 patients of a single dose of mitomycin C, gemcitabine or saline failed to demonstrate an improvement in recurrence.[135-138] Intravesical mitomycin C and epirubicin are additional agents that have been studied as a single perioperative dose of chemotherapy.[139] In the trials, the agents had a dwell time of one to two hours and both decrease recurrence in this setting, but there have been no direct head to head comparison trials between these two agents to date. Recently, a trial demonstrating the efficacy of using these

two agents (epirubicin and mitomycin C) together was published showing a 31% relative-risk reduction.[140] Single instillation postoperative intravesical chemotherapy seems to have the greatest effect in patients with single, small, low-grade tumors[141, 142] and may decrease recurrences even when additional adjuvant intravesical therapy is given.[143-146] However, in patients with quickly recurrent tumors and multiple, larger tumors, this postoperative instillation may not be as helpful.[146] Single instillation studies have given the drug within 24 hours, and physiologic rationale exists for this early treatment, as tumor cells implant and are covered by extracellular matrix within a few hours in various *in vitro* and murine studies.[147-149] The most common side effects of single instillation postoperative chemotherapy are irritative lower urinary tract symptoms, but severe complications have been reported in patients with drug extravasation.[150, 151] Thus, immediate intravesical chemotherapy should be avoided when TURBT is extensive, perforation is suspected, significant bleeding requires bladder irrigations, or the tumor appears invasive.

Given the low toxicity of gemcitabine and case reports of adverse events with mitomycin C, careful consideration should be given to the selection of the best agent for perioperative single dose chemotherapy.

16. In a low-risk patient, a clinician should not administer induction intravesical therapy. (Moderate Recommendation; Evidence Strength: Grade C)

Patients with low-risk NMIBC have a risk of recurrence of approximately 30-40% at 5 years.[43] As noted previously, a single post-operative dose of intravesical chemotherapy has been shown in multiple studies and meta-analyses to decrease the risk of recurrence, with a number needed to treat of approximately 8.5.[146] Subsequent studies have found that the patients most likely to benefit from a single post-operative dose are those with low-risk NMIBC.[146] A number of trials have examined the addition of various combinations of intravesical chemotherapy following the single post-operative dose with a goal of further decreasing the risk of recurrence. Trials of additional mitomycin C[152] and epirubicin[153-155] have demonstrated no benefit of additional chemotherapy courses as compared to a single post-operative dose and in most cases demonstrate an increased risk of side effects.

17. In an intermediate-risk patient a clinician should consider administration of a six-week course of induction intravesical chemotherapy or immunotherapy. (Moderate Recommendation; Evidence Strength: Grade B)

The patient group with intermediate-risk bladder cancer is heterogeneous and primarily at risk of recurrence rather than progression. As discussed previously, there are tools that a clinician can use, albeit with uncertain accuracy, to estimate if a patient in this group has a higher or lower recurrence risk.[43] Therefore, the decision to administer or not administer additional intravesical therapy (distinct from the immediate postoperative dose) and the type of additional intravesical therapy can be based on a clinician's assessment of recurrence risk, morbidity of subsequent TURBT's, patient symptomatology and history, and toxicity of therapy.

Meta-analyses have demonstrated that BCG (3 trials, RR: 0.56; 95% CI: 0.43 to 0.71: I^2=0%), mitomycin C (8 trials, RR: 0.71; 95% CI: 0.57 to 0.89: I^2=72%), doxorubicin (10 trials, RR: 0.80; 95% CI: 0.72 to 0.88; I^2=46%) and epirubicin (9 trials, RR: 0.63; 95% CI: 0.53 to 0.75; I^2=64%) all decrease the risk of recurrence as compared to no intravesical therapy.[91] As previously noted, BCG has been shown to be superior to doxorubicin or epirubicin and similar to mitomycin with regard to preventing recurrence.[91] However, BCG does have a greater risk of adverse events, both local (granulomatous cystitis, dysuria, hematuria) and systemic (fever), as compared to most intravesical chemotherapies.[91] Thus, when the recurrence risk is moderate and intravesical therapy is felt appropriate, a better-tolerated intravesical chemotherapy may have a better risk to benefit ratio than BCG when the primary goal is to prevent recurrence.

If mitomycin C is the chosen agent, there is evidence from one randomized trial that treatment efficacy can be enhanced by using an optimized administration program that consists of a period of dehydration (no fluids for 8 hours prior to treatment), urinary alkalinization (1.3 g $NaHCO_3$ by mouth, the night prior, the morning of, and 30 minutes prior to the intravesical therapy), confirmed complete bladder drainage prior to intravesical therapy (post-void residual <10 mL by US bladder scanner), and a higher mitomycin C concentration (40 mg in 20 mL of sterile water).[156]

18. In a high-risk patient with newly diagnosed carcinoma *in situ* (CIS), high-grade T1, or high-risk Ta urothelial carcinoma, a clinician should administer a six-week induction course of BCG. (Strong Recommendation; Evidence Strength: Grade B)

Patients with newly diagnosed high-risk NMIBC have a 60-70% chance of recurrence and a 10-45% chance of progression to muscle-invasive or metastatic bladder cancer within 5 years.[43] Multiple studies and meta-analyses have shown that a six-week induction course of BCG decreases the risk of recurrence.[157-160] In further analysis performed for this systematic review, BCG was shown to be superior in the prevention of recurrence (3 trials, RR: 0.56; 95% CI: 0.43 to 0.71; I^2=0%) and progression (4 trials, RR: 0.39; 95% CI: 0.24 to 0.64; I^2=40%) compared to no intravesical therapy.[91] BCG was superior to doxorubicin (2 trials RR: 0.31; 95% CI: 0.16 to 0.61; and RR: 0.75; 95% CI: 0.64 to 0.88), epirubicin (5 trials, RR: 0.54; 95% CI: 0.40 to 0.74; I^2=76%) and mitomycin (when BCG maintenance is added to induction [5 trials, RR: 0.79; 95% CI: 0.71 to 0.87; I^2=0%]) in the prevention of recurrence.[91]

There is insufficient evidence to recommend one particular strain of BCG: Bacillus Calmette-Guerin is a heterogeneous organism with at least eight different strains being used for intravesical therapy worldwide.[161] Although there is insufficient evidence to recommend one strain over another, several small studies suggest that different strains may have different efficacies. For instance, one study of patients with NMIBC comparing the two most commonly used strains in the US (BCG Tice versus BCG Connaught) reported that a 6-week course of BCG Connaught resulted in a significantly better recurrence free survival (74.0%; 95% CI: 62.8 to 87.2) compared to BCG Tice (48.0%; 95% CI: 35.5 to 65.1; p = 0.0108). However, there was no difference in progression free survival.[162]

There is insufficient evidence to prescribe a particular strength of BCG: Seven trials have compared standard dose BCG to reduced dose BCG given as a variety of different strains, in various combinations and permutations. Most trials found no clear difference between standard dose and reduced dose BCG in terms of recurrence and other outcomes.[91] In favor of standard dose BCG, a meta-analysis by Zhu et al. demonstrated improved recurrence free survival with standard dose as compared to a reduced dose (HR=1.162; 95% CI: 1.051-1.285; P=0.003), but no difference in progression free survival (HR: 1.151; 95% CI: 0.853 to 1.554; P=0.356).[163] The largest individual study of 1,355 patients (EORTC 30962) compared different BCG strengths (full dose versus 1/3 dose) and different BCG maintenance schedules (1 year versus 3 years) and found no difference in recurrence free survival between 1/3 dose and full dose administered for either 1 year or 3 years. However, in high-risk patients (patients with high-grade, T1 tumors), the 3-year full dose schedule had an improved recurrence free survival (HR: 1.61; 95% CI: 1.13 to 2.30; p = 0.009) as compared to the 1-year 1/3 dose schedule, leading the authors to recommend full dose BCG in this patient subgroup (although EORTC 30962 was not formally powered to test this hypothesis).[164] In most studies, dose reduction was associated with a decreased risk of local and systemic side effects.[91] However, in this study there was no difference in the risk of local or systemic side effects or in the discontinuation rate between full dose and 1/3 dose BCG.[164] Importantly, it should be noted, EORTC 30962 did not include patients with CIS.

There is insufficient evidence to recommend using BCG in combination with other intravesical agents: There is significant interest in developing synergistic combinations that enhance the efficacy of BCG in preventing recurrence and progression of bladder cancer. BCG has been combined with intravesical chemotherapy to test the concept that the inflammatory reaction caused by chemotherapy increases exposure of fibronectin. As BCG binds to the urothelium and tumor cells through fibronectin, enhanced exposure of fibronectin should improve the immunological response. Unfortunately, trials to date have not consistently demonstrated a decreased recurrence or progression with such combinations. A meta-analysis performed in 2013 found that adjuvant BCG followed by maintenance therapy is the appropriate standard of care when compared with combination therapy.[165] More recently CUETO 93009, a randomized trial of sequential mitomycin followed by BCG versus BCG alone in patients with intermediate- or high-risk bladder cancer found an improved 5-year disease free interval (HR: 0.57; 95% CI: 0.39 to 0.83; p = 0.003) at the cost of increased toxicity in the sequential arm. The clinical relevance of the decrease in recurrence is uncertain as no maintenance therapy was used.[166]

An alternative strategy to enhance the immune response is to add cytokines or other agents to BCG. In a 670-patient study Nepple compared BCG + maintenance to BCG with Interferon α2B + maintenance +/- megadose vitamins. No difference was found in two-year disease free survival for any of these combination therapies.[167]

Despite these disappointing results of combination therapy to date, there remains considerable interest in developing new synergistic combinations with several ongoing clinical trials examining different drug combinations as well as surgical techniques not currently available in the U.S. One such therapy includes chemo-hyperthermia, which may be an effective treatment but requires additional study and is not currently available in the U.S.[168]

Patients with higher-risk features, such as persistent high-grade T1 disease on repeat resection, T1 tumors with associated CIS, LVI presence, or variant histologies, should be offered radical cystectomy as an alternative to BCG.

19. In an intermediate-risk patient who completely responds to an induction course of intravesical chemotherapy, a clinician may utilize maintenance therapy. (Conditional Recommendation; Evidence Strength: Grade C)

As discussed previously, the available data supports the use of mitomycin C, doxorubicin, and epirubicin as choices for induction intravesical therapy in patients with intermediate-risk NMIBC. Relatively few studies directly test the benefit of maintenance therapy for those patients who completely respond (defined as a normal cystoscopy and cytology, with no evidence of cancer on pathology if a bladder biopsy is performed) to an induction course of intravesical chemotherapy.[145] If a bladder biopsy or TURBT is performed, to meet a complete response definition, no evidence of cancer is detected. Although the specific best maintenance regimen is unknown, common maintenance regimens include full dose chemotherapy given at monthly intervals for a 6–12-month time period. Available studies are difficult to generalize due to variability of the tumor characteristics in the populations treated and the dosing regimens chosen for each trial. For mitomycin C there is a single trial that focused on patients with higher-risk disease (T1, higher-grade, multifocality, or recurrent) that reported that the addition of three years of maintenance therapy compared to a 6-week induction only course of mitomycin C (20 mg) reduced the recurrence rate in half (RR: 2.5; 95% CI: 1.5 to 4.2) without any clear difference in adverse events.[169] Conversely, for epirubicin two studies that compared induction therapy with and without a maintenance regimen failed to find any significant improvement in recurrence rates.[170, 171] A study of 395 patients by Serretta et al. found no significant difference in the four year recurrence rate when they compared an induction course of six weekly instillations of epirubicin (80 mg) to the same induction course plus monthly maintenance for one year (recurrence rate of 46% versus 50%, p=0.26).[171] Similarly, a study of 148 patients by Okamura et al. compared a six week induction course of epirubicin (40 mg) to the same induction course plus once monthly maintenance for one year and reported no difference in recurrence free survival at three years (75% versus 77%, p=0.62).[170] In both trials, there was no significant difference in the rate of adverse events between the two study arms. Importantly, however, there are five trials that compared differing induction plus maintenance regimens and demonstrated a benefit of increased dosing intensity of epirubicin on disease recurrence.[172-176] While these trials varied considerably in their patient inclusion criteria and dosing regimens, the analysis conducted for this review[91] found that, in general, more intensive exposure to intravesical epirubicin was associated with decreased risk of recurrence. For doxorubicin, two trials that compared induction intravesical therapy to induction plus maintenance therapy for either one year[177] or two years[178] demonstrated that maintenance was not associated with any significant improvement in recurrence rates. For all three of these agents, there was no evidence to suggest that, where it was analyzed, maintenance therapy decreased disease progression or cancer related mortality in NMIBC. Therefore, the Panel felt that, although there was some evidence to support the use of maintenance intravesical chemotherapy in those with a complete response after induction therapy, its routine use could not be supported, and more trials are needed to assess this question.

20. In an intermediate-risk patient who completely responds to induction BCG, a clinician should consider maintenance BCG for one year, as tolerated. (Moderate Recommendation; Evidence Strength: Grade C)

Approximately 70% of patients receiving BCG complain of side effects with 8% of these being severe enough to

discontinue treatment.[179] The toxicity of long term maintenance and the lack of high-quality studies to support the value of more prolonged maintenance over a re-induction course at the time of relapse have led some to question the routine use of a three-year maintenance program,[180] especially in lower risk patients. In a sub-group analyses of EORTC 30962, three years of full dose maintenance was not superior to one year of full dose maintenance (HR: 0.88; 95% CI: 0.64 to 1.21; p = 0.4380)[164] in an intermediate-risk group (as defined by a progression risk score of ≤6 and a recurrence score of ≤9 using the EORTC risk calculator).[43] Given the data from meta-analyses supporting the need for maintenance therapy with the data from EORTC 30962 suggesting that a more prolonged maintenance is not necessary, the Panel supports one year of maintenance therapy in the patient with intermediate-risk NMIBC who has responded to an induction course of BCG.

21. In a high-risk patient who completely responds to induction BCG, a clinician should continue maintenance BCG, based on availability, for three years, as tolerated. (Moderate Recommendation; Evidence Strength: Grade B)

Several meta-analyses have reported that the superiority of BCG compared to intravesical chemotherapy to prevent recurrence and progression of high-risk NMIBC is restricted to those patients who receive maintenance therapy.[145, 181, 182] The optimal schedule and duration of maintenance therapy is unknown. A three-year maintenance schedule for those who can tolerate maintenance is supported by data from SWOG 8507[183] and EORTC 30962.[164] SWOG 8507 showed that maintenance BCG given as a weekly instillation for 3 weeks at months 3,6,12,18,24,30, and 36 as compared to induction BCG alone increased the 5-year recurrence free survival from 41% to 60% (P<0.0001).[183] EORTC 30692, using a similar regimen, showed that high-risk patients (high-grade, T1) receiving three years of full dose maintenance had an increased likelihood of remaining disease free at five years compared to those receiving one year of maintenance (HR: 1.61; 95%CI: 1.13 to 2.30; P=0.009).[164]

BCG Relapse and Salvage Regimens

22. In an intermediate- or high-risk patient with persistent or recurrent disease or positive cytology following intravesical therapy, a clinician should consider performing prostatic urethral biopsy and an upper tract evaluation prior to administration of additional intravesical therapy. (Conditional Recommendation; Evidence Strength: Grade C)

Urothelial carcinoma, particularly CIS, is considered a field-change disease with the entire urothelium at risk in affected individuals. Clinicians should remain aware of sites outside the bladder as potential sources for metachronous tumors. While the initial diagnostic evaluation includes radiographic/endoscopic visualization of the entire urinary tract, the extra-vesical urothelium remains at long-term risk for subsequent tumor development. Moreover, these sites may harbor disease and contribute to cancer recurrence within the bladder.

Indeed, tumor recurrence involves the prostatic urethra in 24-39% of patients with NMIBC.[184, 185] In addition, approximately 20% of patients with a positive cytology but no visible bladder tumors after a complete BCG response have urethral recurrence.[186] Meanwhile, metachronous upper tract tumors are discovered in up to 25% of patients with NMIBC,[185] and patients with more frequent bladder recurrences have an increased risk for upper tract tumor diagnosis.[187] Further, a recent study of patients with high-risk non-muscle invasive disease failing two or more courses of BCG demonstrated upper tract and/or urethral carcinoma in over half of the cases during follow-up.[188] Important to note, however, is that the overall risk for patients with bladder cancer to develop upper tract carcinoma is low (0.8% to 10%).[189-191]

Upper urinary tract imaging and prostatic urethral biopsy are warranted to assess potential tumor sites that may serve as a source for bladder recurrence in patients with persistent or recurrent disease after intravesical therapy. The technique for prostate urethra evaluation is at the discretion of the surgeon, with acceptable approaches including transurethral loop resection and cold-cup biopsy of the prostatic urethra at the 5- and 7-O'clock positions.[186, 192] It is the Panel's consensus that upper tract evaluation be performed with contrast-based imaging (i.e., CT or MR urography, intravenous pyelogram [IVP], or retrograde pyelogram). In addition, at

the time of cystoscopic evaluation, bilateral selective ureteral cytology via washing may be obtained. Further diagnostic evaluation may then be undertaken pending the findings of these initial studies.

Although bladder cancer represents the most common source for a positive voided urine cytology,[193] both the upper urinary tract and the prostatic urethra should be evaluated for tumor recurrence in patients with a persistently positive cytology after intravesical therapy in the absence of demonstrated disease in the bladder. In particular, the Panel supports investigation of the upper tract and urethra prior to further bladder-directed therapies for patients with a positive cytology and no evidence of concurrent disease in the bladder. For such patients with a positive cytology and negative cystoscopy, surgeons should consider use of fluorescence-guided cystoscopy to evaluate the bladder. Indeed, BLC has been demonstrated to increase the detection of CIS by 20-40%[61, 121, 194] and has been demonstrated to be of benefit in additional tumor detection, specifically among patients with a positive cytology and negative white-light cystoscopy.[195, 196] Nevertheless, the Panel acknowledges that the value of BLC has not been directly tested to date versus random bladder biopsies in this setting and that the false positive rate of BLC may be increased in patients recently treated with BCG.[121, 194, 197]

Of note, the Panel recognizes that evaluation of the upper urinary tract and urethra may be withheld in select patients who have received a single induction course of intravesical BCG and subsequently have persistent evidence of disease and are to undergo a second course of BCG.

23. In an intermediate- or high-risk patient with persistent or recurrent Ta or CIS disease after a single course of induction intravesical BCG, a clinician should offer a second course of BCG. (Moderate Recommendation; Evidence Strength: Grade C)

Approximately 50% of patients who have persistent or recurrent NMIBC following a single induction course of BCG respond to a second induction course of BCG.[198-201] Patients, particularly those with Ta or CIS after a single induction course of BCG, should be offered re-treatment with BCG, provided that the patient tolerated the initial induction course of BCG. Retreatment may consist of a second six-week induction course or, particularly for patients with CIS, three weekly treatments, which would effectively represent the first of the patient's maintenance therapy.[202, 203]

While the use of interferon alpha 2b (IFN-α2B) in combination with BCG has been reported in patients previously treated with BCG,[204-207] this regimen has not been directly compared with a second course of BCG alone, and, therefore, the incremental additive value of BCG with IFN-α2B over BCG alone in this setting remains unknown. In addition, when compared to BCG induction and maintenance in a BCG-naïve population, the group that received combination BCG and IFN-α2B had no improvement in tumor recurrence rates and had more side effects.[167] The Panel believes that this combination should not be used as a primary initial therapy. In addition, one phase II randomized trial demonstrated that intravesical gemcitabine was associated with a superior 2-year recurrence-free survival compared to BCG (19% versus 3%; p<0.008) among patients with high-risk non-muscle invasive recurrence after a single course of BCG, albeit with no significant difference in progression.[208] However, the small sample size of the study (n=80), the high rate of disease recurrence noted in the BCG arm, and lack of robust subsequent validation raise questions about the study's generalizability.

24. In a patient fit for surgery with high-grade T1 disease after a single course of induction intravesical BCG, a clinician should offer radical cystectomy. (Moderate Recommendation; Evidence Strength: Grade C)

The Panel recognizes the adverse prognostic significance of high-grade T1 disease in patients treated with induction BCG.[209] Data have demonstrated adverse cancer-specific survival among patients with NMIBC recurrence after BCG who undergo delayed versus early cystectomy.[210] Patients initially with NMIBC who progress to muscle invasion have been found to have a worse prognosis than patients initially presenting with muscle-invasive disease.[211-213] Further, in a retrospective comparative analysis, patients with T1 recurrence after BCG treated with radical cystectomy were noted to have a decreased 5-year cumulative incidence of death from disease (31%) compared to patients with T1 recurrence after BCG treated with repeat resection and BCG (48%).[214] Thus, the Panel recommends that patients with high-grade T1 disease after a single course of induction BCG who are fit for surgery be offered radical cystectomy. The timing of tumor recurrence following BCG may be incorporated into

the decision process for treatment as well as the time between BCG treatment and tumor detection has been identified as an additional prognostic feature.[53, 207, 215]

25. **A clinician should not prescribe additional BCG to a patient who is intolerant of BCG or has documented recurrence on TURBT of high-grade, non-muscle-invasive disease and/or CIS within six months of two induction courses of BCG or induction BCG plus maintenance. (Moderate Recommendation; Evidence Strength: Grade C)**

Clinicians should avoid prescribing additional BCG instillations to patients who are not likely to benefit from further BCG therapy. Various definitions have been put forth to more specifically classify patients in which disease continues or recurs quickly after BCG.[202, 215-217] Historical evidence has demonstrated the lack of clinical benefit of additional BCG in patients who have continued disease after two prior BCG induction courses,[200, 204] while a short time interval between completion of BCG treatment and subsequent tumor detection has been identified as an adverse prognostic feature.[53, 207, 215] Recently, separate consensus panels have put forth similar defining characteristics of patients not likely to benefit from additional BCG; specifically, patients with high-grade non-muscle invasive disease who have received two induction courses of BCG or induction plus maintenance within six months, as well as those who are intolerant of BCG.[218, 219] The intention of such a definition as put forth in the statement here is to avoid patients receiving treatments from which they are unlikely to benefit, as well as to aid in future clinical trial design by establishing appropriate eligibility criteria for studies of novel therapies for patients with persistent or recurrent tumor despite BCG treatment.

26. **In a patient with persistent or recurrent high-grade NMIBC within 12 months of completion of adequate BCG therapy (two induction courses or one induction course plus one maintenance cycle) who is unwilling or unfit for cystectomy following two courses of BCG, a clinician may recommend clinical trial enrollment, an alternative intravesical therapy (i.e., nadofaragene [firadenovec-vncg]) or alternative intravesical chemotherapies (gemcitabine/docetaxel). A clinician may also offer systemic immunotherapy with pembrolizumab to a patient with CIS within 12 months of completion of adequate BCG therapy. (Conditional Recommendation; Evidence Strength: Grade C)**

The optimal management for patients with persistent or recurrent high-grade NMIBC after two courses of BCG (e.g., two induction six-week courses or an induction six-week course and maintenance three-week course) who are unwilling to undergo or unfit for cystectomy remains to be established.

Continued investigation through clinical trials of novel therapeutic approaches for such patients remains paramount, and clinicians should seek trials and enroll patients.

The Panel recognizes that clinical trials may not be available in all such cases, and certain patients might not meet trial eligibility criteria. When clinical trial enrollment is not available for such patients, several options for intravesical chemotherapy exist and may be offered,[215] but the existing supportive data is limited. As such, the Panel cannot advocate a single preferred therapy.

Possible therapies include intravesical valrubicin, administered weekly for six weeks. This regimen is an FDA-approved intravesical treatment for BCG-refractory CIS in patients who are unfit or unwilling to undergo cystectomy. The complete response rate after valrubicin treatment is only 18%, and only 10% of patients have been found to be disease-free at one year following therapy.[220]

In December 2022, the FDA approved nadofaragene (firadenovec-vncg) for patients with high-risk BCG-unresponsive NMIBC with CIS with or without papillary tumors.[221] This intravesical medication instilled every 3 months is a suspension of adenoviral-vector based gene therapy for intravesical instillation. The active ingredient is recombinant, non-replicating adenovirus serotype 5 (Ad5) vector containing a transgene encoding the human interferon alfa-2b (IFNα2b). Phase III data reported a 53.4% complete response rate at 3 months after the first dose and 45.5% of the complete responders continue to have a complete response at 12 months.[222]

Gemcitabine, frequently used as a component of systemic chemotherapy for advanced bladder cancer, has also been given intravesically for patients with recurrent non-muscle invasive disease. A Phase II trial of 30 patients noted a 1-year recurrence free survival of 21%, with 37% of patients subsequently undergoing cystectomy.[223]

Furthermore, a randomized Phase III trial inclusive of 109 patients with recurrent NMIBC, of whom 83% had received prior BCG, demonstrated that intravesical gemcitabine was associated with a greater disease-free survival and a lower rate of chemical cystitis than intravesical mitomycin.[224] Sequential intravesical gemcitabine and mitomycin C for recurrent non-muscle invasive disease has been studied.[225] In a retrospective study of 27 patients, the median disease-free survival was 15.2 months, with 37% of patients without evidence of disease at last follow-up.[225] Also, docetaxel, a microtubule depolymerization inhibitor, has been evaluated as an intravesical therapy for patients with recurrent non-muscle invasive disease. A Phase I study of 18 patients treated with 6 weekly instillations demonstrated that the agent was well-tolerated and that 56% of patients had no evidence of disease at posttreatment evaluation.[226] A subsequent report from the same group of investigators, including 33 treated patients, noted a 2-year recurrence-free survival of 32%.[227]

Currently being examined in the BCG-naïve patient group, sequential intravesical gemcitabine and docetaxel has demonstrated efficacy. A multi-institutional review of 276 patients with NMIBC who received at least an induction course (once weekly for 6 weeks) reported 1-year recurrence-free rates of 65% and a 2-year recurrence-free rate of 52%.[228] Sequential intravesical gemcitabine and docetaxel are currently being examined in the BCG-naïve patient group.

Meanwhile, intravesical nanoparticle albumin-bound paclitaxel represents another taxane-based intravesical treatment option that attempts.[229] In a Phase II trial of 28 patients treated with induction plus maintenance, 35% were found to have no evidence of disease at one year.

As of January 2020, intravenous pembrolizumab became FDA approved for the treatment of patients with BCG-unresponsive, high-risk, NMIBC with CIS with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy. The approval is based on findings from the multicenter, open-label, single-arm, multicohort, phase II KEYNOTE-057 trial. The study enrolled 148 patients with high-risk NMIBC, 96 of whom had BCG-unresponsive, high-risk NMIBC with CIS with or without papillary tumors. Of those 96 patients, the initial response rate was 41%; however, the durable response rate at data cutoff was 21%.[230]

The number of clinical trials for patients who continue to have disease or have disease-recurrence soon after any exposure to BCG continue to increase. These include novel intravesical agents as well systemic therapies. The avoidance of radical cystectomy, the oncologic standard, has become a secondary endpoint for many of these trials.

Role of Cystectomy in NMIBC

27. In a patient with Ta low- or intermediate-risk disease, a clinician should not perform radical cystectomy until bladder-sparing modalities (staged TURBT, intravesical therapies) have failed. (Clinical Principle)

Low-grade, noninvasive tumors very rarely metastasize, and even large-volume, multifocal cancers can usually be managed with techniques such as staged resection. Patients with low-grade recurrences can be successfully managed with intravesical chemotherapy[231] or BCG.[181, 232, 233] In addition, small, multifocal recurrences despite intravesical therapy can usually be treated effectively with office fulguration, repeat TURBT or even surveillance, in select cases.[64-67]

28. In a high-risk patient who is fit for surgery with persistent high-grade T1 disease on repeat resection, or T1 tumors with associated CIS, LVI, or variant histologies, a clinician should consider offering initial radical cystectomy. (Moderate Recommendation; Evidence Strength: Grade C)

Although randomized trials comparing initial radical cystectomy versus intravesical therapy for high-grade T1 bladder cancer are lacking, numerous studies demonstrate poor oncological outcomes with intravesical therapy in patients with the aforementioned “highest-risk” features. The potential benefits of timely, upfront radical cystectomy need to be weighed against the risks associated with cystectomy, such as complications, morbidity, and decreased quality of life for any given patient. Several factors support early radical cystectomy in patients with highest risk NMIBC, including significant understaging of high-grade T1 tumors and increased risk of progression to muscle-invasive disease despite appropriate intravesical therapy. Up to 50% of T1 tumors are upstaged to T2 or greater at time of radical cystectomy.[76, 234-237] Factors associated with high risk of

progression to muscle-invasion are high-grade T1 tumors with large tumor size, multifocality, associated CIS, LVI or prostatic urethral involvement, as well as presence of variant histologies, diffuse disease or tumor location in a site not amenable to complete resection.[40, 43, 44, 86, 238-240] It is not clear if intravesical therapy alters the risk of progression in these highest-risk patients with NMIBC, and excellent oncological outcomes are reported with immediate radical cystectomy.[241, 242] Thus, despite the recognized morbidity of radical cystectomy, the Panel supports considering timely, initial radical cystectomy in this patient population.

However, radical cystectomy with urinary diversion has considerable morbidity, including gastrointestinal, genitourinary, infectious and wound-related complications totaling over 60% within 90 days of surgery, even in high-volume centers of excellence and regardless of open versus robotic approaches.[243, 244] Mortality after radical cystectomy is typically < 5%,[243] but may increase substantially in the elderly with 90-day mortality rates over 10% in patients > 75 years of age and almost 20% in octagenarians.[245] Thus, the risks of radical cystectomy and urinary diversion must be weighed and balanced carefully against the risks of disease progression and potential loss of the opportunity for cure in high-risk patients.

29. In a high-risk patient with persistent or recurrent disease within one year following treatment with two induction cycles of BCG or BCG maintenance, a clinician should offer radical cystectomy. (Moderate Recommendation; Evidence Strength: Grade C)

All guidelines and substantial literature recommend radical cystectomy for patients who are fit for surgery with high-risk urothelial cancer that persists or recurs despite adequate intravesical BCG therapy. Patients with early, high-risk recurrences after BCG therapy are at significant risk of progression, and salvage intravesical therapies have poor success rates. These patients should be offered radical cystectomy. In addition, a recent study demonstrated that patients with a low GFR, variant histology, and tumor size greater than 3 cm may have particularly poor outcomes if they do not respond to BCG and should be prioritized for consideration of cystectomy.[84]

Limited studies support that select patients will respond to second induction regimens, particularly with BCG, and repeat intravesical therapy seems most appropriate in patients with late recurrences (> 1 year) after previous complete response to intravesical therapy.[183, 200, 201] Recurrent, high-grade T1 tumors in patients after adjuvant induction BCG carry a poor prognosis.[209] When radical cystectomy is performed for pathologic NMIBC, 5-year cancer-specific survival is greater than 80%.[246-249] However, there is substantial risk of progression to muscle-invasion in these patients with reported adverse consequences of further intravesical therapy and delayed cystectomy.[210] Similarly, patients with T1 recurrence after BCG treated with radical cystectomy had improved five-year cancer-specific survival compared to patients with T1 recurrence after BCG managed with second-look TUR and further intravesical therapy.[214] Interestingly, radical cystectomy patients who progress to muscle-invasive disease after initial management of NMIBC have decreased cancer-specific survival compared to patients with *de novo* muscle-invasive disease.[211-213] Only minimal data examines chemoradiation in management of high-risk NMIBC,[250] but current trials are underway evaluating the role of radiation therapy in patients with recurrent, high-grade T1 disease after intravesical BCG.

Enhanced Cystoscopy

30. In a patient with NMIBC, a clinician should offer BLC at the time of TURBT, if available, to increase detection and decrease recurrence. (Moderate Recommendation; Evidence Strength: Grade B)

Standard bladder cancer surveillance utilizes WLC; however, bladder tumors can display various gross morphological features, and CIS in particular can appear as normal urothelium under WLC. Use of fluorescent cystoscopy improves the detection of urothelial carcinoma, especially CIS.[194, 251] A recent meta-analysis of 13 trials concluded that the risk of bladder cancer recurrence is decreased with fluorescent cystoscopy versus WLC at short-term (<3 months, 9 trials, RR: 0.58; 95% CI: 0.36 to 0.94; I^2=75%), intermediate-term (3 months to <1 year, six trials, RR: 0.70; 95% CI: 0.56 to 0.88, I^2=19%), and long-term follow-up (≥1 year, 12 trials, RR: 0.81; 95% CI: 0.70 to 0.93; I^2=49%).[91] Although 5-aminolevulinic acid (5-ALA) was used in some of the aforementioned clinical studies, it is not approved by the FDA, and Hexaminolevulinate (HAL) is currently the only agent approved in the US and Europe for use with BLC.

Focusing on studies that used HAL only, fluorescent cystoscopy was associated with a decreased risk in bladder cancer recurrence at long-term follow-up (≥1 year, 7 trials, RR: 0.75; 95% CI: 0.62 to 0.92; I^2=41%). In a large RCT of HAL–BLC performed in patients with NMIBC, there was a statistically significant reduction in recurrence rates at 9 months (47% for patients who received HAL–BLC and WLC compared with 56% for those who underwent WLC alone; p = 0.026), and a non-significant reduction in the rate of recurrent 'worrisome' tumors (defined as CIS, recurrent T1 or muscle-invasive disease; 16% versus 24%; p = 0.17).[252] With a median follow-up of 53 months for patients who underwent WLC alone and 55 months for those who received HAL–BLC in addition to WLC, a large international RCT reported that the HAL–BLC group experienced a significant delay in median time to recurrence (16.4 months) compared with the WLC group (9.4 months; p = 0.04). A meta-analysis using pooled data from nine prospective trials that included only HAL using actual raw data demonstrated that HAL–BLC was associated with lower recurrence rates at 12 months compared with WLC (35% versus 45%; RR: 0.761; p = 0.006). The benefits were independent of the baseline risk of recurrence and were demonstrated in patients with primary or recurrent Ta, T1 or CIS lesions.[253]

In contrast, the PHOTO trial, a randomized prospective trial, did not find a difference in recurrence or progression rates over 44 months in intermediate and high-risk NMIBC patients undergoing initial TURBT with BLC versus WLC.[254] 538 patients with an initial clinical diagnosis of intermediate-/high-risk NMIBC were randomized to undergo either white light or blue light resection at several UK centers. At 44 months, the HR for recurrence was 0.94 (95% CI: 0.69 to 1.28; P=0.70). There was no difference in progression detected between groups (HR: 1.41; 95% CI: 0.67 to 2.96). CIS was present in only 13% of the resection specimens of patients enrolled in the trial; thus, a key group in which blue light detects the most "missed" tumors was under-represented in the study. Additionally, the trial was published prior to enrolling the full number of patients for adequate power to detect a difference between groups and is also underpowered in the efficacy of high-risk patients. Five other systematic reviews have shown decreased recurrence rates with the use of BLC compared to WLC.[255-259]

Importantly, however, researchers have reported higher false-positive results for HAL–BLC compared to WLC, particularly in patients who have undergone recent TURBT, who have concurrent UTI or inflammation, or who have recently received intravesical BCG or chemotherapy. This over-detection may be improved if BLC is delayed for greater than or equal to three months after intravesical therapy.[252] The reported false-positive rates of BLC also seem decrease over time with experience.[74]

31. In a patient with NMIBC, a clinician may consider use of narrow-band imaging (NBI) to increase detection and decrease recurrence. (Conditional Recommendation; Evidence Strength: Grade C)

One trial evaluating outcomes following use of NBI versus WLC found that NBI was associated with a lower risk of bladder cancer recurrence at 3 months (3.9% versus 17%; OR: 0.62; 95% CI: 0.41 to 0.92) and at 12 months (OR: 0.24; 95% CI: 0.07 to 0.81).[260] Another trial (n=179) found NBI plus WLC to be associated with a non-statistically significant decreased risk of recurrence at 1 year versus WLC in patients with multiple tumors >3 cm in diameter (7.9% versus 18%; RR: 0.44; 95% CI: 0.19 to 1.02).[261] Another randomized trial of 600 patients undergoing either white light/white light or white light/ NBI cystoscopy for previously diagnosed high-risk NMIBC showed no benefit with regards to recurrence for patients undergoing second look with NBI (26% [78/300] versus 23% [70/300]; p = 0.507) There was also no difference in time to recurrence between groups.[262] Four recent systematic reviews have examined WLC versus white light + NBI.[256, 263-265] In a combined analysis of six RCT's, one systematic review found improved recurrence for NBI plus white light versus white light alone in patients with suspected or confirmed NMIBC (6 RCTs, 1244 patients, HR: 0.63; 95% CI: 0.45 to 0.89; I^2=53%).[264] The other three systematic reviews found no difference in recurrence with white light versus white light +NBI cystoscopy.[256, 257, 266]

The Panel acknowledges that NBI technology is readily available to many clinicians whereas blue-light might not be. While not proven to decrease recurrence, there is no evidence of additional risk incurred by patients with its use.

Risk Adjusted Surveillance and Follow-up Strategies

32. After completion of the initial evaluation and treatment of a patient with NMIBC, a clinician should perform the first surveillance cystoscopy within three to four months. (Expert Opinion)

The natural history of NMIBC is often characterized by recurrence, even for solitary, small, low-grade papillary tumors. At the time of first evaluation and treatment, none of the existent risk stratification tools or urinary biomarkers is sufficiently sensitive and specific to predict which patient will have an early tumor recurrence. Therefore, the only reliable way to know in a particular patient whether they are at risk for early recurrence is by cystoscopic visualization of the urothelium at a relatively early interval after the first treatment/resection. In addition, visualization at a relatively early interval allows the treating urologist to verify that the initial resection was complete. The Panel, therefore, felt that the first repeat cystoscopic evaluation should occur three to four months after the initial treatment and evaluation, regardless of the patient's overall risk.

33. For a low-risk patient whose first surveillance cystoscopy is negative for tumor, a clinician should perform subsequent surveillance cystoscopy six to nine months later, and then annually thereafter; surveillance after five years in the absence of recurrence should be based on shared-decision making between the patient and clinician. (Moderate Recommendation; Evidence Strength: Grade C)

The data comparing different surveillance regimens for NMIBC and associated oncologic outcomes are very limited. One study by Olsen and Genster randomized 97 patients with papillary grade 1-2 tumors who remained tumor free three months after the first TURBT between two follow up regimens.[267] A more frequent follow up regimen (every three months for two years, every six months in year three, then annually thereafter) was compared to a less frequent regimen (every six months for year one, then annually thereafter). While the study is small and likely underpowered, there was no difference in the risk of recurrence (RR: 1.2; 95% CI: 0.87 to 1.8) or progression (RR: 3.5; 95% CI: 0.37 to 32.0) with a median follow up of 27 to 31 months. This suggests that those patients who are low-risk can be surveyed at a less stringent interval while maintaining a similar risk of recurrence and/or progression. Less stringent endoscopic surveillance may reduce a patient's exposure to the anxiety, discomfort, and modest infection risks associated with cystoscopy without unduly compromising a patient's risk.

There is relatively little data on the ongoing rates of recurrence for patients with NMIBC who remain disease free for a prolonged period of time. Two retrospective studies reported a recurrence rate of 10-15% in patients who had been free of disease for 5 or more years, with about 3% of patients having muscle invasive disease.[268, 269] The initial stage and grade of tumor did not appear to determine the risk of recurrence[268] and it is unclear if routine annual cystoscopic as opposed to symptom based evaluation would have resulted in a significant change in clinical outcome. Life-long surveillance in the absence of documented recurrence subjects a patient to repeated anxiety, discomfort, and the small risk of infection or bleeding associated with cystoscopic surveillance of the bladder. Given these competing risks and a relative paucity of data to drive decision-making, the Panel feels that ongoing surveillance after five years in the absence of recurrence should be based on shared-decision making between the patient and their clinician.

34. In an asymptomatic patient with a history of low-risk NMIBC, a clinician should not perform routine surveillance upper tract imaging. (Expert Opinion)

There are no studies that directly test whether differing follow up regimens for upper tract imaging impact oncologic outcomes among NMIBC patients. However, there are several retrospective single cohort series that suggest that patients with "lower-risk" bladder cancer have a low incidence of subsequent upper tract urothelial carcinoma on the order of 0.6-0.9%.[69, 190] Furthermore, a more recent cohort study suggests that even among those patients who do develop upper tract recurrence after a diagnosis of NMIBC, only 29% are incidentally found on routine surveillance imaging.[270] The remaining recurrences were found only after the patient developed symptoms prompting an evaluation. Optimal upper tract imaging currently utilizes CT with the administration of intravenous contrast. Therefore, the Panel felt that in asymptomatic, low-risk patients, routine use of upper tract imaging for surveillance unnecessarily subjects patients

to the risks associated with intravenous contrast reagents, including nephrotoxicity, anaphylaxis, and repeated radiation exposure, with only a small chance of detecting upper tract urothelial carcinoma.

35. In a patient with a history of low-grade Ta disease and a noted sub-centimeter papillary tumor(s), a clinician may consider in-office fulguration as an alternative to resection under anesthesia. (Expert Opinion)

Prospective, randomized trials comparing office-based fulguration to operating room-based resection for small, papillary bladder tumors in low-risk NMIBC patients have not been completed. Several centers have reported on retrospective cohort series of office-based endoscopic fulguration of small bladder masses with acceptable oncologic outcomes.[66, 271-273] While these cohort series varied in their inclusion criteria, in general office-based fulguration was restricted to patients with known low-grade Ta disease in which the size of the tumor was small (typically defined at less than 0.5 to 1.0 cm). This suggests that selected patients with low-risk NMIBC and isolated, small, papillary recurrences may be effectively managed with office-based, endoscopic fulguration with local anesthesia and sedation. This has the potential to spare a patient the risks associated with anesthesia required for a more invasive resection in an operating room setting. For highly selected patients, clinicians may opt for watchful waiting or conservative management in those patients for whom the risks of fulguration may outweigh the risks of disease progression. This might include those cases where in-office fulguration is not readily available or patients who required ongoing anti-coagulation. This should include careful shared decision making with the patient.

However, the Panel felt several important caveats should be kept in mind. A fulguration approach that does not obtain tissue for pathologic evaluation should not be utilized unless a diagnosis of low-grade Ta disease or PUNLMP has been previously established. A fulguration approach should be restricted to those patients in whom the lesion is papillary in appearance, rather than sessile or flat, and is no more than 1 cm in size. Furthermore, patients in whom a urinary cytology is suspicious for urothelial carcinoma are at higher risk for harboring occult high-grade disease and warrant pathologic evaluation of any visible lesion. Upper tract imaging to assess occult disease also may be considered in patients who develop repeated recurrences of small papillary lesions in the bladder.

36. For an intermediate-risk patient whose first surveillance cystoscopy is negative for tumor, a clinician should perform subsequent cystoscopy with cytology every 3-6 months for 2 years, then 6-12 months for years 3 and 4, and then annually thereafter. (Expert Opinion)

Unlike the case for low-risk patients, there are no prospective studies that compare outcomes among differing cystoscopic surveillance regimens for intermediate-risk NMIBC patients. The risk of progression, however, among these patients is higher, and in the absence of data to demonstrate otherwise, the Panel felt a slightly more intensive cystoscopic surveillance regimen was warranted. Panel consensus and historic precedence support surveillance cystoscopy and urinary cytology every three to six months for two years, then every six to twelve months for years three and four, and then annually thereafter. The Panel felt that the gaps in the literature should permit clinicians more flexibility and clinical judgement in determining the surveillance cystoscopic regimen in the intermediate- compared to the high-risk group (see below). Future research is needed to determine if less stringent follow up regimens can be employed without significantly affecting oncologic outcomes in both intermediate-and higher-risk patients, especially as the time to recurrences increases beyond five years. As with low-risk tumors, shared decision-making is imperative beyond five years if the patient remains disease-free.

37. For a high-risk patient whose first surveillance cystoscopy is negative for tumor, a clinician should perform subsequent cystoscopy with cytology every three to four months for two years, then six months for years three and four, and then annually thereafter. (Expert Opinion)

As with intermediate-risk patients, there are no prospective studies that compare outcomes among differing cystoscopic surveillance regimens for high-risk NMIBC patients. Given the risk of progression among high-risk patients is higher than any other group, the Panel felt a more intensive cystoscopic surveillance regimen was warranted. Panel consensus and historic precedence support surveillance cystoscopy and urinary cytology every three months for two years, then every six months for years three and four, and then annually

thereafter. As with intermediate-risk disease, there is an urgent need for studies to determine if less stringent follow up regimens can be employed without significantly affecting oncologic outcomes in these patients. As the risk of recurrence decreases and the time to recurrences increases beyond five years, a decision to decrease the frequency of cystoscopy or stop routine follow up cystoscopy after five years should only be made after a shared decision-making conversation with the patient.

38. For an intermediate- or high-risk patient, a clinician should consider performing surveillance upper tract imaging at one- to two- year intervals. (Expert Opinion)

As is the case with low-risk patients, there are no studies that directly compare varying upper tract imaging surveillance regimens on oncologic outcomes in NMIBC patients. Retrospective cohort studies have suggested, however, that in a "higher-" risk cohort of patients, including those with higher-grade, multiple recurrences, or stage T1 disease, the subsequent rate of upper tract recurrence is as high as 10%[69, 190] of which almost half will have at least stage T1 disease. As such, these recurrences, which are often high-stage and/or high-grade, are potentially life threatening. Whether routine imaging in asymptomatic patients is likely to diagnose such recurrences in a manner that actually improves oncologic outcomes or therapeutic options is controversial.[270] Nevertheless, the Panel believes that periodic upper tract surveillance imaging offers potential benefit in this patient population. While optimally upper tract surveillance would be through the use of CT-Urography, the Panel acknowledges that not all patients can undergo this study. Alternative options can include MR urography, retrograde pyelography, renal ultrasound, or foregoing upper tract imaging depending on the patient's co-morbidities and shared decision-making regarding the risks of alternative imaging approaches.

FUTURE DIRECTIONS

The future of NMIBC will likely be driven forward by basic science, novel technologies, new therapeutics and clinical trials. The bladder cancer genome atlas project provided analysis of 131 muscle-invasive urothelial carcinomas in an effort to describe molecular alterations and, ideally, provide insight into use of molecularly targeted agents for both muscle-invasive and NMIBC. The NMIBC community is fortunate to have a multitude of clinical trials currently in this disease space, the vast majority of which are studying novel agents to improve outcomes of BCG or treat BCG failures with both intravesical and systemic agents. There are also several trials investigating new technology, surgical techniques, radiation therapy, and variable surveillance schedules.

As new treatment alternatives for NMIBC are being examined, research should continue in optimizing the dosing, scheduling, and administration of currently used medications that have already shown efficacy.

Novel urinary biomarkers. Although the current consensus of the guideline panel describes a limited role for urinary biomarkers to replace cystoscopic surveillance in NMIBC, the future directions in this field hold promise. Advances in sensitivity for detection of high-grade disease in a surveillance population of high-grade NMIBC patients using the CX Bladder platform have been significant. In addition the recent review article by Rose and colleagues has outlined the future applications of urinary cell free DNA in both detection and molecular risk stratification of patients with NMIBC and the Panel believes that this technology holds promise for future clinical application.[274]

Novel agents to improve BCG efficacy or manage BCG failures. Management of patients with intermediate- or high-risk bladder cancer recurrences after two induction courses of BCG unwilling or unfit for radical cystectomy remains uncertain. Although many different salvage intravesical therapies have been evaluated, these studies are generally limited by small patient numbers, modest improvements in recurrence-free survival with respective intravesical agent(s), and no significant effects on progression or survival. These limitations highlight the dire need for novel agents in this disease setting. For instance, immune checkpoint inhibitors have been a resounding success in metastatic bladder cancer with trials already underway moving these agents into earlier stages of bladder cancer, including adjuvant, neoadjuvant and NMIBC settings.[275] There are multiple current open clinical trials evaluating novel agents for BCG failures, including an oncolytic virus regimen (BOND 2), recombinant fusion proteins (Vicinium), immune modulation (ALT-801, HS-410, ALT-803, PANVAC), cytotoxic therapies (cabazitaxel, gemcitabine, cisplatin,) and targeted small molecule kinase inhibitors (sunitinib, dovitinib, erlotinib). In an open-

label, multicenter, parallel-arm, phase II study, 43 patients with HG BCG-unresponsive or relapsed NMIBC received intravesical nadofaragene (firadenovec-vncg).[276] Fourteen patients remained free of HG recurrence 12 months after initial treatment. These results lead to the FDA approval of this agent in 2022. More recently in the Quilt -3.0-32 trial, Suderman and colleagues reported their results using a combination of BCG and nogapendekin alfa inbakicept, an IL-15 superagonist.[277] This combination therapy achieved a one-year disease free survival of 45% in BCG-unresponsive CIS and papillary bladder cancer with limited toxicity.

As research continues in this space, we are likely to see an increase in the number of available treatment options for such patients.

New technologies. Enhanced cystoscopy, including BLC at time of TURBT, has been demonstrated in multiple studies to decrease bladder tumor recurrence and seems particularly valuable in evaluation of positive urinary cytology in the setting of negative WLC.[73] Further studies of new technologies in management of patients with NMIBC include a current phase IV trial (NCT01567462) underway to evaluate TURBT using a PK button vaporization electrode compared to standard monopolar loop electrocautery. Investigators hypothesize TURBT using PK button vaporization may be less invasive with fewer side effects and improved patient recovery.

Therapeutic Trials in Surgery/Radiation. There are minimal data to support chemoradiation in the management of high-risk NMIBC,[250] but current trials are underway evaluating the role of radiation therapy in patients with recurrent high-grade T1 disease after intravesical BCG. RTOG 0926 (NCT00981656) is a Phase II trial evaluating chemoradiation (cisplatin or mitomycin/fluorouracil with three-dimensional conformal radiation therapy) with a primary endpoint of three-year freedom from radical cystectomy and several secondary endpoints, including progression-free, disease-specific and overall survival.

Imaging. The advent of multiparametric MRI imaging has led to advances in the accuracy of staging both NMIBC and MIBC. In centers of expertise, the use of the vesical imaging reporting and data system (VI-RADS) coupled with state of the art 3 Tesla MR systems, has reported outstanding sensitivity and specificity for detection of MIBC in the setting of high-risk NMIBC.[278] If reproducible, this form of imaging may lead to a decrease in the burden of re-TURBT and improved selection of patients with MIBC for more appropriate therapy.[278]

Surveillance. Finally, a randomized pilot clinical trial (NCT02298998) evaluating common surveillance schedules could significantly impact follow-up in patients with NMIBC. Patients will be randomized to either cystoscopy at 3 months, 12 months and then annually for 5 years versus cystoscopy every 3 months for 2 years, every 6 months for 2 years and annually thereafter. The primary objectives of this study include development of methodology to assess both patient satisfaction and costs associated with cystoscopy for bladder cancer surveillance with secondary objectives of cost, number of overall procedures and proportion of patients with disease recurrence and progression at two years. Monitoring patients with NMIBC less frequently may potentially decrease costs and improve patient satisfaction without increased risk of progression to muscle-invasive disease.

Abbreviations

AHRQ	Agency for Healthcare Research and Quality
AJCC	American Joint Committee on Cancer
AMH	Asymptomatic Microhematuria
BLC	Blue light cystoscopy
CSS	Cancer-specific survival
CIS	Carcinoma in situ
CT	Computed tomography
CUETO	Club Urologico Español de Tratamiento Oncologico
EORTC	European Organization for Research and Treatment of Cancer
LVI	Lymphovascular invasion
MRI	Magnetic resonance imaging
NBI	Narrow band imaging
NMIBC	Non-muscle invasive bladder cancer
US	Ultrasonography
TURBT	Transurethral resection of bladder tumor
UTI	Urinary tract infection
WHO	World Health Organization
WLC	White light cystoscopy

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This document was written by the NMIBC Panel of the American Urological Association Education and Research, Inc., which was created in 2016. The Practice Guidelines Committee (PGC) of the AUA selected the Panel Chair. Panel members were selected by the Panel and PGC Chair.

Membership of the panel included specialists with specific expertise on this disorder. The mission of the panel was to develop recommendations that are analysis-based or consensus-based, depending on panel processes and available data, for optimal clinical practices in the early detection of prostate cancer setting.

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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 intended to provide legal advice about use and misuse of these substances.

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

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

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