Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline

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Purpose: Although associated with an overall favorable survival rate, the heterogeneity of non-muscle invasive bladder cancer (NMIBC) affects patients' rates of recurrence and progression. Risk stratification should influence evaluation, treatment and surveillance. This guideline attempts to provide a clinical framework for the management of NMIBC.

Materials and Methods: A systematic review utilized research from the Agency for Healthcare Research and Quality (AHRQ) and additional supplementation by the authors and consultant methodologists. Evidence-based statements were based on body of evidence strength Grade A, B, or C and were designated as Strong, Moderate, and Conditional Recommendations with additional statements presented in the form of Clinical Principles or Expert Opinions.[1]

Results: A risk-stratified approach categorizes patients into broad groups of low-, intermediate-, and high-risk. Importantly, the evaluation and treatment algorithm takes into account tumor characteristics and uniquely considers a patient's response to therapy. The 38 statements vary in level of evidence, but none include Grade A evidence, and many were Grade C.

Conclusion: The intensity and scope of care for NMIBC should focus on patient, disease, and treatment response characteristics. This guideline attempts to improve a clinician's ability to evaluate and treat each patient, but higher quality evidence in future trials will be essential to improve level of care for these patients.

Key Words: urinary bladder neoplasms, cystectomy, drug therapy, immunotherapy

Abbreviations and Acronyms

AUA = American Urological Association

BCG = bacillus Calmette-Guérin

CIS = carcinoma *in situ*

EORTC = European Organization for Research and Treatment of Cancer

FDA = Food and Drug Administration

LVI = lymphovascular invasion

NMIBC = non-muscle invasive bladder cancer

SUO = Society of Urologic Oncology

TURBT = transurethral resection of bladder tumor

WLC = white light cystoscopy

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For another article on a related topic see page 1270.

BACKGROUND

Epidemiology

NMIBC represents approximately 80% of the 74,000 estimated new bladder cancer cases diagnosed in the United States in 2015 and primarily affects Caucasian Americans and those older than 65 years.[2–5] 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.[5] Multiple factors are associated with bladder carcinogenesis; however, tobacco smoking is the most significant and common risk factor.[6]

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Staging and Grading

Staging for bladder cancer is separated into clinical and pathologic stage, as outlined by the American Joint Committee on Cancer.[7] Pathological staging is based on the extent of disease following surgical resection of the bladder and adjacent pelvic lymph nodes.

Tumor grade is an important prognostic factor for determining risk of recurrence and progression. The World Health Organization/International Society of Urological Pathology 2004 classification, which designates tumors as "low-" or "high-grade," is currently the most widely utilized system in the U.S.[8,9]

Prognosis

The cancer-specific survival in high-grade NMIBC is approximately 70-85% at 10 years.[10,11] Long-term follow-up of low-grade Ta lesions demonstrates a progression rate of approximately 6%, whereas high-grade T1 lesions have an increased chance of progression of approximately 17%.[10,12] Therefore, the ability to predict recurrence and progression risk based on patient-specific disease characteristics holds prognostic significance.

METHODOLOGY

The AUA categorizes body of evidence strength as Grade A, B, or C based on both individual study quality and 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.

Evidence-based statements are provided as *Strong, Moderate,* and *Conditional Recommendations* with additional statements provided in the form of *Clinical Principles* or *Expert Opinion* (table 1).

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)**

Table 1. *AUA nomenclature linking statement type to level of certainty, magnitude of benefit or risk/burden, and body of evidence strength*

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

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, when available), ureteroscopy, or random bladder biopsies. (Expert Opinion)**

The most common presenting symptom is painless hematuria (gross or microscopic). Irritative voiding symptoms may also be associated with carcinoma *in situ* in patients with no sign of urinary tract infection. A bimanual exam may be performed under anesthesia at the time of transurethral resection of bladder tumor and should be performed if the tumor appears invasive. Although not indicated for routine screening and evaluation of hematuria, urinary cytology may be used in the diagnosis and surveillance of bladder cancer. Contrast-based axial imaging, such as computerized tomography or magnetic resonance imaging is the recommended imaging modality during the work-up for bladder cancer. Retrograde pyelogram and intravenous urography may be used when computerized tomography or magnetic resonance imaging is unavailable.

Bladder cancer is confirmed by direct visualization of the tumor and other mucosal abnormalities with endoscopic excision using cystoscopy and TURBT.

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)**

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 risk calculator, based on the combined data from seven trials involving patients with NMIBC.[13] 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. With respect to progression, important factors include T-stage, presence of CIS, and grade. A second risk stratification tool is that developed by the Club Urologico Español de Tratamiento Oncologico.[14] 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, but the updated study cohort lacked patients with CIS and again was limited by absence of routine re-resection.[15]

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 2). This risk grouping system is intended for use in clinical practice as a general framework for guiding patient counseling and aiding in treatment and surveillance decisions (see figure). It should be noted that these risk categories are not based on a meta-analysis or original studies and represent the Panel's consensus regarding the likelihood of recurrence and progression.

Unique to the AUA/SUO System is the incorporation of prior bacillus Calmette-Guérin intravesical therapy on prognosis. Limited data demonstrate that patients who have persistent or recurrent disease at six months following BCG therapy are at increased risk of disease progression.[16,17] The Panel understands that within each of these risk strata, an individual patient may have more or less concerning features that 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.

Variant Histologies. 6. **An experienced genitourinary pathologist should review the pathology of a patient with any doubt in regards to variant or suspected variant histology (e.g., micropapillary, nested, plasmacytoid,**

Table 2. *AUA risk stratification for non-muscle invasive bladder cancer*

Low Risk	Intermediate Risk	High Risk
Low grade solitary Ta $\leq$ 3 cm Papillary urothelial neoplasm of low malignant potential	Recurrence within 1 year, low grade Ta Solitary low grade Ta >3 cm Low grade Ta, multifocal High grade Ta, $\leq$3 cm Low grade T1	High grade T1 Any recurrent, high grade Ta High grade Ta, >3 cm (or multifocal) Any CIS Any BCG failure in high grade case Any variant histology Any LVI Any high grade prostatic urethral involvement

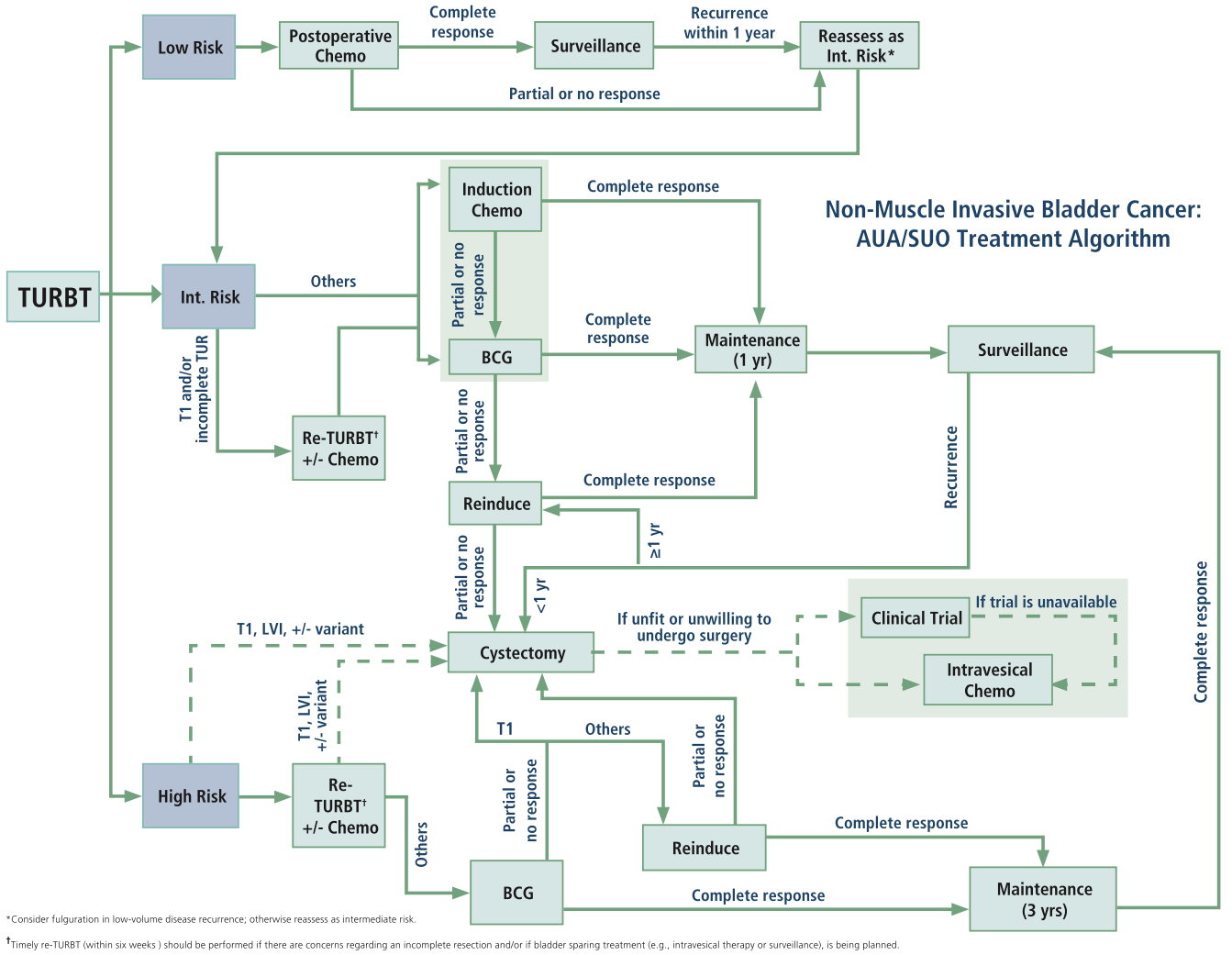

Figure. AUA/SUO treatment algorithm for non-muscle invasive bladder cancer

neuroendocrine, sarcomatoid), extensive squamous or glandular differentiation, or the presence/absence of 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 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)**

Historically, variant histologies have been underappreciated and under-reported, but data are accumulating in regards to their aggressiveness. Studies suggest that variant differentiation may affect survival; however, there is a paucity of data due to the rarity of most variants. The pathology report should specify the presence and percentage of variant histology as well as the presence or absence of lymphovascular invasion.

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.[18] As such, patients with mixed histologic features are generally not good candidates for bladder sparing protocols and are best served with an aggressive treatment modality.[19]

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)**

Researchers have long attempted to identify and utilize urinary markers for bladder cancer detection. Five markers are currently approved by the FDA and/or commercially available in the U.S. (table 3).[20–22] At present, urinary biomarkers are insufficiently accurate to replace cystoscopy for diagnosis/surveillance, though some appear to have predictive utility for assessing response to intravesical BCG and may help interpret indeterminate cytology.

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)**

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.[23] Larger and multifocal tumors are at a particularly increased risk for incomplete initial resection. Moreover, repeat resection for patients with T1 tumors achieves diagnostic, prognostic, and therapeutic benefit.

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., mitomycin C or epirubicin) within 24 hours of TURBT. In a patient with a suspected perforation or extensive resection, a clinician should not use postoperative chemotherapy. (Moderate Recommendation; Evidence Strength: Grade B)**

16. **In a low-risk patient, a clinician should not administer induction intravesical**

Table 3. *Performance characteristics of commonly used and FDA approved urinary markers*

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

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 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 for three years, as tolerated. (Moderate Recommendation; Evidence Strength: Grade B)**

BCG is a heterogeneous organism with at least eight different strains being used for intravesical therapy worldwide.[24] 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.[25] Meta-analysis performed for this guideline found that single dose intravesical chemotherapy is more effective than no intravesical therapy for prevention of recurrence. This benefit is reduced in low-risk patients who have a lower risk of recurrence/progression.[22] Additionally, while BCG and certain other intravesical therapies were associated with a lower risk of recurrence, BCG was the only therapy associated with a decreased risk of progression.

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 intermediate- or high-risk NMIBC who is unwilling or unfit for cystectomy following two courses of BCG, a clinician may recommend clinical trial enrollment. A clinician may offer this patient intravesical chemotherapy when clinical trials are unavailable. (Expert Opinion)**

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.[26–29] Evidence on treatment of patients who relapse following BCG treatment is very limited. However, data have demonstrated adverse cancer-specific survival among patients with NMIBC recurrence after BCG who undergo delayed versus early cystectomy.[30]

The timing of tumor recurrence following BCG may be incorporated into the decision process for treatment as this has been identified as an additional prognostic feature.[16]

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)**

Low-grade, noninvasive tumors very rarely metastasize, and even large-volume, multifocal cancers can usually be managed with techniques such as staged resection. Many patients with low-grade recurrences can be successfully managed with intravesical chemotherapy or BCG.[31–34] However, 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.

Enhanced Cystoscopy. 30. **In a patient with NMIBC, a clinician should offer blue light cystoscopy 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)**

Standard bladder cancer surveillance utilizes white light cystoscopy (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, and can decrease progression/recurrence rates.[35] Importantly, however, researchers have reported higher false-positive results for HAL—blue light cystoscopy (BLC) compared to WLC, particularly in patients who have undergone recent TURBT, who have concurrent urinary tract infection or inflammation, or who have recently received intravesical BCG or chemotherapy.

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)**

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 are sufficiently sensitive and specific to predict which patient will have an early tumor recurrence. Therefore, the most reliable way to know whether patients are at risk for early recurrence is by cystoscopic visualization.

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 the use of molecularly targeted agents.[36] 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, but there are also several trials investigating new technology, surgical techniques, radiation, and surveillance schedules.

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DISCLAIMER

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

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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 which are too new to be addressed by this guideline as necessarily experimental or investigational.

CONFLICT OF INTEREST DISCLOSURES

All panel members completed COI disclosures. Those marked with (C) indicate that compensation was received. Disclosures listed include both topic– and non-topic-related relationships.

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