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Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline: 2024 Amendment

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Purpose: The purpose of this American Urological Association (AUA)/Society of Urologic Oncology (SUO) guideline amendment is to provide a useful reference on the effective evidence-based treatment strategies for non-muscle invasive bladder cancer (NMIBC).

Materials and Methods: In 2023, 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 previous 2020 amendment. The updated search gathered literature from July 2019 to May 2023. This review identified 1918 abstracts, of which 75 met inclusion criteria.When sufficient evidence existed, the body of evidence was assigned a strength rating of A (high), B (moderate), or C (low) in support of Strong, Moderate, or Conditional Recommendations. In the absence of sufficient evidence, additional information is provided as Clinical Principles and Expert Opinions.

Results: Updates were made to statements on variant histologies, urine markers after diagnosis of bladder cancer, intravesical therapy, BCG maintenance, enhanced cystoscopy, and future directions. Further revisions were made to the methodology and reference sections as appropriate.

Conclusions: This guideline seeks to improve clinicians' ability to evaluate and treat patients with NMIBC based on currently available evidence. Future studies will be essential to further support or refine these statements to improve patient care.

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

Abbreviations and Acronyms:

AJCC = American Joint Committee on Cancer
BLC = Blue light cystoscopy
CIS = Carcinoma in situ
LVI = Lymphovascular invasion
MRI = Magnetic resonance imaging
NBI = Narrow band imaging
NMIBC = Non-muscle invasive bladder cancer
RCT = Randomized Control Trial
SUO = Society of Urologic Oncology
TURBT = Transurethral resection of bladder tumor
WLC = White light cystoscopy

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EPIDEMIOLOGY

NMIBC represents approximately 75% of the 82,000 estimated new bladder cancer cases diagnosed in the United States in 2023.[1] 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 16,700 estimated deaths for 2023 predominantly affecting males.[1]

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-

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Metastases (TNM) classification.[2] Clinical stage reflects the histologic findings at transurethral resection of bladder tumor (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.[3-6] 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 (ie, lamina propria; T1), and (3) Tis (Table).

PROGNOSIS

The survival prognosis for patients with NMIBC is relatively favorable, with the cancer-specific survival in high-grade disease ranging from approximately 70 to 85% at 10 years and a much higher rate for low-grade disease.[7,8] 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.[9] In contrast, high-grade T1 lesions have both a significant risk of recurrence (45%) and increased chance of progression (17%) in single institution series.[7] 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.

GUIDELINE STATEMENTS

Variant Histologies

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)

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.[10] 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.[11]

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.[11] The Iida et al study cited previously supports the rationale for radical cystectomy when variant histology is present in patients with NMIBC unresponsive to BCG.[10]

Urine Markers after Diagnosis of Bladder Cancer

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.[12-16] 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

Table. *Staging of Primary Tumors (T) in Bladder cancer*[2]

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

based upon UroVysion® (FISH) in patients who had a history of NMIBC identified an association between a positive FISH and the development of MIBC.[17] 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 many as 21% of patients being evaluated for hematuria.[18] 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.[19,20] 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.[17] 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.[21-23]

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 (eg, 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.[24] 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 (2 g in 100 mL 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 to 15% at 4 years.[25] In addition, there were no Grade 4 to 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 to 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.[25-28] Intravesical mitomycin C and epirubicin are additional agents that have been studied as a single perioperative dose of chemotherapy.[29] In the trials, the agents had a dwell time of one to 2 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.[30]

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 (ie, nadofaragene [firadenovec-vncg]) or alternative intravesical chemotherapies (ie, gemcitabine/docetaxel). A clinician may also offer systemic immunotherapy with pembrolizumab to a patient with carcinoma in situ (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 (eg, two induction 6-week courses or an induction 6-week course and maintenance 3-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.

In December 2022, the FDA approved nadofaragene (firadenovec-vncg) for patients with high-risk BCG-unresponsive NMIBC with CIS with or without papillary tumors.[31] 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.[32]

Sequential intravesical gemcitabine and docetaxel has shown efficacy in a BCG-naïve patient group currently under examination. 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%.[33] Sequential intravesical gemcitabine and docetaxel are currently being examined in the BCG-naïve patient group.

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 as systemic therapies. Safely avoiding radical cystectomy, which has been considered the oncologically safest treatment while associated with morbidity and risks, has become a secondary endpoint for many of these trials.

Role of Cystectomy in NMIBC

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)

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; as such, these patients should be prioritized for consideration of cystectomy.[10]

Enhanced Cystoscopy

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

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 white light cystoscopy (WLC).[34] A group of 538 patients with 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% confidence interval [95% CI]: 0.69 to 1.28; $P = .70$). 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. Five other systematic reviews have shown decreased recurrence rates with the use of BLC compared to WLC.[35-39]

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)

A 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), $P = .507$). There was also no difference in time to recurrence between groups.[40] Four recent systematic reviews examined WLC versus white light + NBI.[36,37,41,42] In a combined analysis of six randomized control trials (RCT's), one systematic review found improved recurrence for NBI plus white light versus white light alone in patients with suspected or confirmed NMIBC (HR: 0.63; 95% CI: 0.45 to 0.89; $I^2 = 53\%$; 6 RCTs, 1244 patients).[41] The other three systematic reviews found no difference in recurrence with white light versus white light + NBI cystoscopy.[36,37,42]

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

FUTURE DIRECTIONS

Novel Urinary Biomarkers

Although the current consensus of the 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 et al 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 this technology holds promise for future clinical application.[43]

Novel Agents to Improve BCG Efficacy or Manage BCG Failures

Fourteen patients remained free of high-grade recurrence 12 months after initial treatment. These results lead to the FDA approval of nadofaragene (firadenovec-vncg) in 2022. More recently in the Quilt -3.0-32 trial, Chamie et al reported their results using a combination of BCG and nogapendekin alfa inbakicept, an IL-15 superagonist.[44] This combination therapy achieved a 1-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.

Imaging

The advent of mpMRI 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.[45] 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.[45]

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