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Guideline of Guidelines – Non-Muscle Invasive Bladder Cancer

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Abstract

Non-muscle invasive bladder cancer (NMIBC) represents the vast majority of bladder cancer diagnoses, however this definition represents a spectrum of disease with a variable clinical course notable for significant risk of recurrence and potential for progression. Management involves risk-adapted strategies of cystoscopic surveillance and intravesical therapy with a goal of bladder preservation when safe to do so. Multiple organizational guidelines exist to help practitioners manage this complicated disease process, however adherence to management principles amongst practicing urologists is reportedly low. We review four major organizational guidelines on NMIBC: American Urological Association (AUA)/Society of Urologic Oncology (SUO), European Association of Urology (EAU), National Comprehensive Cancer Network (NCCN), and National Institute for Health and Care Excellence (NICE).

Keywords

non-muscle invasive bladder cancer; bladder cancer; guidelines; management

INTRODUCTION

Bladder cancer represents the 11th most common malignancy worldwide, and 7th most common in men.[1] Smoking is the most established risk factor for bladder cancer, while other risk factors include occupation exposes to aromatic amines and hydrocarbons. The vast majority of bladder cancers are of urothelial histology, and localized urothelial carcinoma of the bladder (UCB) is broadly categorized into non-muscle invasive bladder cancer (NMIBC) and muscle-invasive disease. About 75% of bladder tumors present at NMIBC and this disease entity will be the focus of this review.[2]

There is considerable debate regarding management of this complicated disease process that exhibits a variable clinical course punctuated by risk of recurrence and progression to invasive disease. Adherence to guidelines is reportedly low, reasons for this are speculative, but perhaps confusion about the different guidelines plays a role in poor adoption of fundamental aspects of NMIBC management.[3–5] We sought to summarize the findings of

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CONFLICT OF INTEREST

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four major organizational guidelines, with an emphasis on differences and areas of unanimity.

METHODS

We performed a MEDLINE/PubMed search from 2010-present of guidelines on NMIBC and manually searched the websites of urological or oncological societies and journals to identify relevant guidelines. The American Urological Association (AUA), Society of Urologic Oncology (SUO), European Association of Urology (EAU), National Comprehensive Cancer Network (NCCN), National Institute for Health and Care Excellence (NICE), International Consultation on Urologic Diseases (ICUD), International Bladder Cancer Network (IBCN), International Bladder Cancer Group (IBCG), Canadian Urological Association (CUA), and European Society for Medical Oncology (ESMO) guidelines were reviewed. We narrow our review of guidelines to those that are most commonly used in practice, most recently updated, and with the most detail, namely AUA/SUO, EAU, NCCN, and NICE guidelines. Each guidelines is based on systematic literature reviews by expert panels, however they differ in terms of topics addressed, detail, and methodology.

AUA/SUO Guidelines [6]

The AUA/SUO guidelines panel consists of 13 panel members and 128 peer reviewers; evidence strength is grade as A, B, or C and statements are provided as ‘strong’, ‘moderate’, or ‘conditional recommendations’, in addition to ‘clinical principles’ and ‘expert opinion.’ The recently updated 2016 AUA/SUO guidelines adopt a risk-stratified approach in contrast to the ‘index patient’ approach that was employed in the 2007 iteration. The guidelines are available via PubMed search through the Journal of Urology and online via the AUA website: <https://www.auanet.org/education/guidelines/non-muscle-invasive-bladder-cancer.cfm>.

EAU Guidelines [7]

The EAU guidelines panel consists of 15 medical professions and has continually updated NMIBC guidelines every 2–3 years since 2008 and most recently in 2016. Recommendations are classified according to their level of evidence (I–IV) and are given a grade of recommendation (A–D) according to a modification of the 2009 Oxford Center for Evidence-Based Medicine Levels of Medicine.[8] The EAU guidelines are available via PubMed search through the European Urology journal and online via the EAU website: <https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/>.

NCCN Guidelines [9]

The NCCN guidelines (United States) includes both NMIBC and muscle-invasive disease, and represents the work of 33 medical professionals, technical experts and patient advocates. The guidelines are based on treatment algorithm and flow charts according to pathologic stage and grade. Categories of evidence and consensus range from 1 (uniform consensus based on high-level evidence), 2A (uniform consensus based on lower-level evidence), 2B (consensus based on lower-level evidence), and 3 (major disagreement). Originally published in 1998, the NCCN guidelines on NMIBC are updated regularly with the most

recent update in February 2016, and are available, free of cost, to registered users through the NCCN website: https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf.

NICE Guidelines [10]

The NICE guidelines (United Kingdom) represent the work of 15 members that include medical professionals, technical experts, and patients meant to represent the lay public. Both NMIBC and muscle-invasive disease are combined into one document. Recommendations vary from ‘must’ (or ‘must not’) to represent a legal duty, ‘should’ (or ‘should not’) to imply a strong recommendation, to ‘consider’ to imply an option that is felt to do more good than harm and be cost-effective. The guidelines were most recently published in February 2015, will next be reviewed in 2019, and are available on-line: <https://www.nice.org.uk/guidance/ng2>.

RESULTS

Lifestyle Modification

Both the EAU and NICE guidelines recommend smoking cessation counseling based on studies suggesting active smoking increases risk of tumor recurrence progression, and impairs response to immunotherapy.[11, 12].

Classification of Tumors

All guidelines statements adopt the 2009 American Joint Committee on Cancer/Union Internationale Contre le Cancer (AJCC/UICC) TNM staging system and define NMIBC as noninvasive papillary UCB (Ta), *carcinoma in situ* (CIS) (Tis), or with invasion limited to the lamina propria (T1).[13, 14]

While the grading system was just recently updated,[15, 16] two older grading systems are commonly used for urothelial malignancy; the World Health Organization (WHO) 1973 with papillary histology graded from 1–3 and the WHO/International Society of Urological Pathology (ISUP) 2004 system which simplifies grading as low-grade (LG) or high-grade (HG).[17, 18] The AUA and NCCN guidelines rely on the WHO 2004 classification scheme, the NICE guidelines rely on the WHO/ISUP 1973 classification, while the EAU guidelines allow for simultaneous use of both grading systems, which may be useful as the European Organization for Research and Treatment of Cancer (EORTC) and Club Urológico Español De Tratamiento Oncológico (CUETO) risk scoring systems to predict recurrence and progression in NMIBC are based on the older grading system.[19]

There is consensus about describing mandatory pathologic features including depth of invasion, presence of muscularis propria (detrusor muscle) in the specimen, presence of CIS, and variant histology.

Evaluation and Resection

Comprehensive history, physical exam, followed by cystourethroscopy is required for initial evaluation of suspected bladder cancer, making note of macroscopic features (i.e. tumor size, site, number, configuration, and any mucosal abnormalities).

Initial Transurethral Resection (TUR)—Proper initial transurethral resection (TUR) of bladder tumor is a critical step in initial management and staging of disease. Early recurrence and improper staging can result from inadequate resection of the initial tumor, inadequate sampling of muscularis propria or missing tumors such as CIS.[20–22]

There is consensus that all visible papillary tumors should be resected. The EAU offers specifics about TUR technique, including *en bloc* resection of small papillary tumors including the underlying bladder wall, while larger tumors should be resected in fractions and include the underlying detrusor muscle, and edges of the resection area. Although AUA and NCCN guidelines do not require sampling of underlying detrusor muscle at initial TUR, this is recommended on re-TUR for T1 disease (AUA) or HG or T1 disease (NCCN).

Re-TUR—Repeating TUR in select cases is associated with discovering persistent tumor [22–24], more accurate staging (especially if no detrusor muscle in the initial TUR) [20, 25], improved recurrence free survival [23], and response to bacillus-Calmette-Guerin (BCG). [26] All guidelines recommend re-TUR, for similar indications which should optimally should be performed within 1–6 weeks (Table 2).

Evaluation of the Upper Tract—The AUA and NCCN recommend that all patients with confirmed NMIBC should have upper tract imaging performed. The EAU concludes that the need to perform routine upper tract imaging studies is questionable [27], but does recommend upper tract imaging in select cases; tumors near the trigone, multiple tumors, or high-risk tumors. NICE guidelines recommend upper tract evaluation only in new or recurrent high-risk NMIBC. It should be noted that many patients with newly-diagnosed bladder cancer have had upper tract imaging as part of their hematuria evaluation.

Staging—The NCCN does not recommend routine chest, bone, or brain imaging in the initial staging of NMIBC, but does recommend consideration of pelvic MRI (magnetic resonance imaging) for local staging of sessile or high-grade tumors. NICE recommends CT (computed tomography) or MRI of abdomen and pelvis if muscle-invasive disease is suspected or in patients being considered for radical treatment, and consideration of fluorodeoxyglucose positron emission tomography (FDG PET)-CT when there are indeterminate findings. EAU and AUA do not make staging recommendations.

Prostatic Urethra Sampling—The involvement of urothelial carcinoma at the prostatic urethra (PU) is a negative prognostic factor for recurrence and progression. EAU recommends PU biopsy in cases of visible PU or bladder neck tumors, when bladder CIS is present/suspected, or in the case of positive cytology. The AUA classifies any patient with documented high-grade PU involvement as ‘high-risk’ and recommends that PU biopsy be considered in intermediate or high-risk patients with persistent or recurrent disease or positive cytology following intravesical therapy and in patients with a history of NMIBC with a normal cystoscopy but positive cytology. NCCN recommends consideration of PU sampling in the setting of sessile tumors suspicious for HG or Tis disease. NICE does not make specific recommendations about PU sampling.

Random Bladder Biopsies—Some urothelial carcinomas, in particular CIS, may not be visible cystoscopically and may only be detected by random or ‘mapping’ biopsies.[28–30] Given the low-yield in all-comers, no organization advocates random bladder biopsy routinely. Except for NICE, each organization suggests indications in which this strategy might be appropriate: AUA - positive cytology; EAU - CIS treated with intravesical BCG, positive cytology, exophytic tumor with a non-papillary appearance; and NCCN – sessile tumor or suspicion of HG/CIS. Additionally, the EAU suggests that photodynamic diagnosis (PDD) guided biopsies may substitute for random biopsies, although strong evidence is lacking to support this approach.

Urine Cytology and Biomarkers—Urine cytology is the most widely accepted urinary biomarker, but is limited with respect to sensitivity and has issues related to inter- and intra-observer variability.[31, 32] The AUA makes no recommendation regarding urine cytology in the primary assessment but advocates for its use in the surveillance of intermediate- and high-risk patients. Conversely, EAU and NCCN guidelines recommend the use of urine cytology as an adjunct to cystoscopy at primary assessment and in the surveillance of high-risk tumors. NICE guidelines are the least specific, stating that it should be offered at the time of TURBT (or alternatively, enhanced cystoscopic visualization or other urinary biomarkers).

A number of commercially-available urinary biomarkers (e.g. UroVysion, ImmuoCyt, NMP22, Bladder Tumor Antigen) for detection of UCB are not routinely recommended due to inadequate performance characteristics.[32–35] The AUA suggests that urinary biomarkers may be used to assess BCG-response or ‘adjudicate equivocal cytology’ and NCCN recommends consideration of urinary biomarkers in the surveillance setting, acknowledging unclear benefits.

Enhanced Cystoscopy—New technologies in the form of fluorescence cystoscopy (PDD) or narrow-band imaging (NBI) focus on improving detection of small or flat lesions. NBI is less well studied, thus guidelines statements focus on PDD.[36] PDD does appear to improve detection, reduce residual disease after TUR, decrease recurrences, and possibly decrease progression.[37–39] Both AUA and NICE recommend enhanced cystoscopy be offered at the time of TUR. EAU recommends PDD-guided biopsies in the setting of positive cytology but negative cystoscopy. NCCN does not recommend routine use of PDD-enhanced cystoscopy citing lack of evidence regarding reduced progression.

Risk Stratification

With the exception of the NCCN, guidelines classify NMIBC according to risk groupings based on combined pathologic and clinical features reflecting likelihood of recurrence and progression (Table 3). These risk groupings provide the framework for surveillance protocols, adjuvant intravesical therapies, and guidance on when to continue or abandon conservative management and proceed with radical cystectomy (RC).

The EAU guidelines employs the EORTC risk tables based on the results of 2596 patients with TaT1 tumors randomized into 7 trials for determining individual risks of recurrence and progression.[19] Importantly, these patients did not receive a re-TUR or maintenance BCG,

limiting applicability. Recently, the EORTC published an updated model which included patients treated with 1–3 years of maintenance BCG, however excluded patients with CIS and repeat TUR was not performed in high-risk patients.[40] The updated AUA guidelines adopts a similar system of risk grouping but incorporates prior intravesical BCG therapy on prognosis.[41, 42]

Variant Histologies—One controversial area in NMIBC is management of UCB with divergent differentiation (e.g. squamous or glandular) or variant histologies (e.g. micropapillary, nested, plasmacytoid, neuroendocrine, sarcomatoid). A number of studies report these to be adverse prognostic factors with limited response to intravesical BCG, thus advocating early RC. However these studies are generally small cohorts and for some subtypes it is not clear that their prognosis or response to intravesical therapy truly differs from HG, high-stage UCB of the usual type.[43] Nonetheless, all guidelines consider variant histologies to be high-risk and advocate for consideration of aggressive management, including early RC.

Surveillance

Periodic cystoscopy is the mainstay of NMIBC management, as HG tumors have progression rates reported from 15–40% and even LG tumors have a mean recurrence rate of 50%.[43, 44] Most guidelines recommend early initial cystoscopy and risk-stratified surveillance schedules (Table 4), with no high-level evidence to support a specific schedule. Uniquely, the NICE guidelines recommend that patients with low-risk NMIBC who are free from recurrence at 12 months may be discharged from routine urologic follow-up. Additionally, all guidelines (except NCCN which makes no comment) suggest that it is appropriate to consider office-based fulguration *in lieu* of TUR under anesthesia for small solitary, papillary in patients with an established history of LG Ta disease.[45, 46]

Intravesical Therapy

Immediate Intravesical Chemotherapy Instillation—Immediate instillation of intravesical chemotherapy following TUR has been shown to reduce recurrence in lower-risk NMIBC [47–51]. All guidelines recommend immediate instillation of chemotherapy following TUR in certain settings: NICE – after initial TUR (with no distinction by risk stratification); AUA – suspected/known low- or intermediate-risk NMIBC; EAU – presumed low-risk or intermediate-risk with previous low recurrence and expected EORTC recurrence score < 5; and NCCN – LG Ta tumors (Table 5). Although considerable variation exists based on region, training, physician’s patient volume, etc., compliance with these recommendations is low.[52, 53] Among reasons for non-compliance with recommendations are concerns for side effects and logistical difficulty with immediate postoperative intravesical chemotherapy instillation. Additionally, with the exception of the NICE guidelines, recommendations for immediate intravesical chemotherapy instillation are based on presumed pathology – not a clearly defined criterion.

Induction and Maintenance Intravesical Therapy—The optimal dosing, schedule, and indications for further intravesical treatment are not well-defined, however there is evidence that further adjuvant chemotherapy instillations are associated with a reduction in

recurrence in patients with intermediate-risk disease.[54, 55] Additionally, several studies have confirmed the superiority of intravesical BCG over chemotherapy for prevention of NMIBC recurrence and progression [56–62] and level 1 evidence supports the use of maintenance BCG therapy over induction alone.[63] These studies represent heterogeneous inclusion criteria, maintenance schedules, and alternative treatments at recurrence therefore guidelines on this subject reflect disparate conclusions at lower strength recommendations (Table 5).

NICE guidelines are specific in recommending only an induction course of intravesical MMC for intermediate-risk NMIBC with no mention of maintenance, while high-risk patients should be offered induction and maintenance BCG. AUA recommends against the use of induction intravesical therapy in low-risk NMIBC but for intermediate-risk patients does recommend consideration of either 6 weeks of induction intravesical chemotherapy (with maintenance for an unspecified duration) or BCG (with 1 year of maintenance therapy). High-risk patients with CIS, HG T1, or high-risk Ta NMIBC should be offered 6 weeks of BCG followed by maintenance BCG for 3 years. EAU recommends induction and 1 year of maintenance intravesical chemotherapy or BCG as options for intermediate-risk NMIBC, and induction plus 1–3 years of maintenance BCG for high-risk patients. NCCN guidelines are less specific, with options including observation, intravesical MMC or BCG based on pathology. In patients responding to induction BCG, NCCN recommends maintenance BCG with no defined schedule, although most NCCN members follow the SWOG protocol.[63]

Management of Recurrence after Intravesical BCG—EAU offers definitions of BCG failure, which include progression to muscle-invasive disease, HG recurrence after completion of BCG maintenance, and BCG-refractory disease which includes HG Ta/T1 present at 3 months, Tis present at both 3 and 6 months, and HG tumor appearance during BCG therapy.[64–66] All these BCG failures are recommended to have early RC as a preferred option [67], while non-HG/G3 recurrence after BCG for primary intermediate-risk tumors are recommended to have repeat intravesical BCG or chemotherapy. NICE does not offer many specifics for tumors which recur despite intravesical therapy; patients whose tumors recur after induction BCG should be assessed for suitability of RC or further intravesical therapy if RC is unsuitable. Low- or intermediate-risk recurrences after BCG induction should be assessed for further intravesical therapy. AUA recommends that patients with persistent or recurrent Ta or CIS should be offered a second induction course of BCG, while patients with HG T1 disease should be offered RC. Patients with HG recurrence within 6 months of two BCG induction courses or BCG plus maintenance should not be offered additional BCG, instead this is an indication for RC. Patients unwilling or unfit for RC, may be offered enrollment in a clinical trial or intravesical chemotherapy. NCCN recommends that persistent or recurrent tumors in patients that respond to induction intravesical therapy can be given a second induction course, but no more than two induction courses should be given. Patients with residual or recurrent Tis or Ta disease may be treated with a different intravesical agent [68, 69], as an alternative to RC, however RC is main option for these patients, as it is for persistent or recurrent T1 disease.

Indication for Radical Cystectomy

While NMIBC is usually managed with bladder preservation in mind, a number of instances should prompt early RC, as ‘delayed cystectomy’ has been implicated to have worse cancer-specific survival [70] and a number of clinical scenarios have been demonstrated to be associated with compromised outcomes with continued attempts at intravesical management. [19, 40, 71]

AUA recommends offering initial RC in patients with variant histologies, T1 tumors associated with CIS or lymphovascular invasion (LVI), and in high-risk patients with persistent HG T1 disease on repeat resection. Additionally, high-risk patients with persistent or recurrent disease within 1 year following two induction cycles of BCG or BCG plus maintenance should be offered RC. EAU recommends that initial RC should be considered in patients with the highest risk of progression, which they define as those with T1G3/HG associated with concurrent bladder CIS, multifocal, large, or recurrent T1G3/GH, T1G3/HG with CIS in the PU, variant histologies, and LVI. RC is also recommended for BCG unresponsive tumors. NCCN recommends early RC may be preferred for patients with T1 tumors which are multifocal, associated with LVI, or recur after BCG. NICE recommends offering RC to patients with high-risk NMIBC, variant histologies, based on presence of CIS, PU involvement, bladder neck involvement, tumor multifocality, and in whom BCG induction fails either due to intolerance or persistent/recurrent disease.

CONCLUSION

Despite some variations in guidelines for NMIBC, significant consensus exists in the majority of areas. All guidelines generally apply a risk-stratified approach to sub-classifying NMIBC (Table 3), and this stratification informs subsequent management including surveillance (Table 4) and intravesical therapy protocols (Table 5). In areas of unanimity, these recommendations are based on high-quality evidence or expert opinions that should provide guidance to patient management. In areas of discrepancy, physicians should take into account individual patient characteristics and adopt the most reasonable management strategy for the particular clinical scenario.

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KEY POINTS

1. Properly performed and complete initial transurethral resection of all visible bladder tumor is essential, and an early repeat resection should be performed when indicated
2. Patients should be risk stratified according to pathology, clinical history, and response to intravesical therapy
3. According to risk stratification, patients should be offered expectant management, intravesical therapy, or radical cystectomy, as appropriate
4. The follow-up of non-muscle invasive bladder cancer is based on the principle of regular cystoscopic surveillance due to risk of recurrence and progression
5. Non-invasive tests (i.e. urinary biomarkers, imaging) should not replace cystoscopy in the surveillance of non-muscle invasive bladder cancer

Table 1

Pathologic Classification of Non-Muscle Invasive Bladder Cancer

TNM Staging System [13, 14]	
T: Primary Tumor	Description
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Noninvasive papillary tumor
Tis	Carcinoma in situ, “flat tumor”
T1	Invades subepithelial connective tissue
Histologic Classification of Urothelial Carcinoma	
WHO/ISUP 2004 [17]	
Flat lesions with atypia	
In situ carcinoma	
Papillary lesions	
Papilloma	
UNLMP	
Papillary carcinoma, low grade	
Papillary carcinoma, high grade	
WHO 1973 [18]	
In situ carcinoma	
Papillary lesions	
Papilloma	
Grade 1, well differentiated	
Grade 2, intermediate differentiation	
Grade 3, poorly differentiated	

WHO - World Health Organization; ISUP - International Society of Urological Pathology; UNLMP - urothelial neoplasm of low malignant potential

Table 2

Recommendations for Performance of Re-TUR (If Pursuing Bladder-Sparing Approach)

AUA	Incomplete initial resection (<i>strong recommendation</i>) High-risk (recurrent, multifocal, >3cm) HG/Ta tumors (<i>moderate recommendation</i>) Any T1 tumor – resection to include detrusor muscle (<i>strong recommendation</i>) Variant histology (<i>expert opinion</i>)
EAU	Incomplete initial resection (<i>grade of recommendation A</i>) Any T1 tumor (<i>grade of recommendation A</i>) HG/G3 tumor - except primary CIS (<i>grade of recommendation A</i>) Detrusor muscle not sampled in the initial specimen - except TaG1 and primary CIS (<i>grade of recommendation A</i>)
NCCN	Incomplete resection (<i>recommend</i>) HG/Ta with detrusor muscle not sampled in the initial specimen (<i>strongly consider</i>) Any T1 tumor, especially if detrusor muscle not sampled in initial specimen or there is presence of LVI (<i>strongly advise</i>)
NICE	Incomplete initial resection Detrusor muscle not sampled in the initial specimen (<i>consider</i>) High-risk cancer

AUA – American Urological Association; EAU – European Association of Urology; NCCN – National Comprehensive Cancer Network; NICE – National Institute for Health and Care Excellence; TUR – transurethral resection (of bladder tumor); HG – high grade; CIS – *carcinoma in situ*; LVI – lymphovascular invasion

Table 3**Risk Stratification for Non-Muscle Invasive Bladder Cancer**

AUA		
Low Risk	Intermediate Risk	High Risk
Low Grade Solitary Ta $\leq$ 3cm	Recurrence within 1 year of low grade Ta	High grade T1
PUNLMP	Solitary low grade Ta > 3cm	Recurrent high-grade Ta
	Multifocal low grade Ta	High grade Ta > 3cm
	High grade Ta $\leq$ 3cm	Multifocal high grade Ta
	Low grade T1	Any CIS
		Any BCG failure in high grade cases
		Any variant histology
		Any LVI
		Any high grade prostatic urethral involvement
EAU		
Low Risk	Intermediate Risk	High Risk
Primary, solitary, LG/G1 <3cm, no CIS	All tumors not defined in the two adjacent categories	T1 tumor
		HG/G3 tumor
		CIS
		Multiple, recurrent, and large (>3cm) Ta G1G2 tumors (all conditions must be present)
NICE		
Low Risk	Intermediate Risk	High Risk
Solitary pTaG1 <3cm	Solitary pTaG1 > 3cm	pTaG3
Solitary pTaG2 (low grade) <3cm	Multifocal pTaG1	pT1G2
PUNLMP	Solitary pTaG2 (low grade) > 3cm	pT1G3
	Multifocal pTaG2 (low grade)	pTis (CIS)
	pTaG2 (high grade)	Aggressive variant histology of urothelial carcinoma
	Any pTaG2 (grade no further specified)	
	Any low-risk NMIBC recurring within 12 month	

AUA – American Urological Association; EAU – European Association of Urology; NICE – National Institute for Health and Care Excellence
 PUNLMP – papillary neoplasm of low malignant potential; CIS – *carcinoma in situ*; BCG – bacillus Calmette-Guerin; LVI – lymphovascular invasion; LG – low grade; HG – high grade

Table 4**Surveillance Recommendations for Bladder Recurrence in Non-Muscle Invasive Bladder Cancer**

AUA	All patients: initial cystoscopy within 3–4 months of completion of treatment Low-risk: cystoscopy 6–9 months later, and then annually for at least 5 years Intermediate-risk: cystoscopy + cytology every 3–6 months for 2 years, then every 6–12 months for years 3–4, and then annually thereafter High-risk: cystoscopy + cytology every 3–4 months for 2 years, then every 6 months for years 3–4, and then annually thereafter Upper tract evaluation: every 1–2 years in intermediate- or high-risk NMIBC, not routinely recommended for low-risk NMIBC
EAU	All patients: initial cystoscopy at 3 months Low-risk: another cystoscopy at 9 months later, then annually for 5-years. Consider stopping after 5 years without recurrence. Intermediate-risk: surveillance scheme between low and high-risk High-risk: cystoscopy and cytology every 3 months for 2 years, then every 6 months until 5 years, and then annually thereafter Upper tract evaluation: yearly for high-risk NMIBC, no specific recommendations for low- or intermediate-risk NMIBC
NCCN	LG Ta: cystoscopy at 3 months, and then at “increasing intervals” (no specifics about when safe to stop surveillance) HG Ta, T1, Tis: cystoscopy + cytology at every 3–6 months for first 2 years, and then at “increasing intervals” thereafter Upper tract evaluation: every 1–2 years in high-grade NMIBC
NICE	All patients: cystoscopy at 3 months Low-risk: cystoscopy at 12 months, patients without recurrence may be discharged to PCP, do not offer routine cystoscopic follow-up after 12 months Intermediate-risk: cystoscopy at 9 and 18 months, then annually thereafter. Consider discharging to PCP after 5 years of disease free follow-up High-risk: cystoscopy every 3 months for 2 years, every 6 months for years 3–4, then annually thereafter. Upper tract evaluation: no recommendations

AUA – American Urological Association; EAU – European Association of Urology; NCCN – National Comprehensive Cancer Network; NICE – National Institute for Health and Care Excellence

Table 5**Recommendations for Intravesical Therapy in Non-Muscle Invasive Bladder Cancer**

AUA	Low-Intermediate-risk: single instillation of intravesical chemotherapy post-TUR Low-risk: do not offer induction chemotherapy Intermediate-risk: consider induction chemotherapy or immunotherapy Maintenance may be utilized in those that respond to induction chemotherapy Maintenance should be considered for 1 year in those that respond to induction BCG High-risk: administer induction BCG and continue maintenance BCG for 3 years, as tolerated
EAU	Low-intermediate risk: single instillation of intravesical chemotherapy post-TUR Intermediate-risk: induction BCG or chemotherapy Maintenance for maximum of 1 year recommended in those that respond to induction chemotherapy Maintenance for 1 year recommended in those that respond to induction BCG High-risk: induction BCG with maintenance BCG for 1–3 years
NCCN	All patients: Single-instillation of intravesical chemotherapy within 24 hours of TUR LGTa: observation or induction chemotherapy HGTa: observation, or induction chemotherapy, or BCG (preferred). Maintenance BCG in those that respond to BCG. T1: BCG or cystectomy if residual disease on re-TUR, BCG (preferred), chemotherapy, or observation in select cases with limited lamina propria invasion and no CIS. Maintenance preferred in those that respond to BCG Tis: BCG induction with maintenance
NICE	All patients: single-dose of intravesical chemotherapy at time of initial TUR Intermediate-risk: 6 doses of intravesical mitomycin C High-risk: Radical cystectomy or intravesical BCG (no defined schedule)

AUA – American Urological Association; EAU – European Association of Urology; NCCN – National Comprehensive Cancer Network; NICE – National Institute for Health and Care Excellence; TUR – transurethral resection; BCG - bacillus Calmette-Guerin; LG – low grade; HG – high grade