Prior to publication, this guideline underwent review by the CUA Guidelines Committee, CUA members, and the CUA Executive Board.

Canadian Urological Association guideline on the management of non-muscle-invasive bladder cancer – Full-text

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3. Urine cytology (voided or collected by bladder washing) is recommended as an adjunct to cystoscopy in patients suspected to have bladder cancer *(LE 2, strong recommendation)*.
4. Upper urinary tract imaging is recommended in the initial workup of patients suspected to have bladder cancer *(LE 3, strong recommendation)*.

Prognostic factors for recurrence and progression

5. The most important prognostic factors for recurrence and progression of non-muscle-invasive bladder cancer (NMIBC) are stage and grade *(LE 2)*. All patients with bladder cancer should be properly staged and, specifically for NMIBC, reporting grade is paramount for further management decisions *(LE 2, strong recommendation)*.
6. Other prognostic factors are age >70 years, large tumor size (≥3 cm), multiple tumors, the presence of concomitant carcinoma in situ (CIS), extensive invasion of the lamina propria, prior recurrence rates >1 per year, and status at first assessment after transurethral resection of the bladder tumor (TURBT) *(LE 2),* as well as lymphovascular invasion (LVI*) (LE 3)*.
7. Aggressive histological variants, such as micropapillary, plasmacytoid, and sarcomatoid, are associated with increased risk of under-staging and progression *(LE 3)*. Pathological review, preferably by a dedicated uro-pathologist, should be considered in settings where variant histology is suspected or atypical tumors are seen during TURBT (e.g., sessile mass) *(LE 3, weak recommendation)*.

Risk stratification

8. All patients with NMIBC should be stratified according to the risk of both recurrence and progression for adequate patient counselling and treatment planning *(LE 2, strong recommendation)*. The modified Canadian Urological Association (CUA) risk stratification system is a suitable tool for this purpose.

Transurethral resection

9. Patients presenting with a bladder tumor should undergo initial TURBT for diagnostic confirmation and pathological evaluation *(LE 2, strong recommendation)*.
10. Initial TURBT aims for complete tumor resection with sampling of the underlying detrusor muscle as the first step of curative-intent treatment of *NMIBC (LE 2, strong recommendation)*. Patients with presumed low-grade (LG) Ta or CIS might be spared from muscle sampling at initial TURBT *(LE 3, weak recommendation)*.
11. When available, blue light cystoscopy (BLC) *(LE 1, weak recommendation)* or narrow band imaging *(LE 2, weak recommendation)* can increase tumor detection at first TURBT and reduce recurrence risk.

12. A re-staging TURBT should be performed in patients with T1 NMIBC, or when a complete resection was not achieved with the first TURBT *(LE 2, strong recommendation)*. Re-staging TURBT is not required in patients who will proceed to radical cystectomy (RC) based on the findings of the first TURBT.
13. In select cases of high-grade (HG) Ta tumors (e.g., large and/or multiple tumors), a re-staging TURBT can be considered *(LE 3, weak recommendation)*.
14. The suggested window for a restaging TURBT is within six weeks of the first resection *(LE 3, weak recommendation)*.
15. Patients presenting with a positive urine cytology, but normal-appearing bladder at WLC and normal upper urinary tract imaging are at higher risk of harboring occult CIS and should undergo random bladder biopsies (or use of BLC with directed biopsies) *(LE 2, strong recommendation)*.
16. Biopsies or transurethral resection of the prostatic urethra should be included with random bladder biopsies in the presence of a positive bladder urine cytology, but normal-appearing bladder at WLC and normal upper tract imaging *(LE 3, strong recommendation)*.
17. Prostatic urethral biopsies (or a transurethral resection) can also be considered in the presence of extensive bladder CIS or tumor at the bladder neck or trigone *(LE 3, weak recommendation)*.
18. Patients with prostatic urethral involvement (PUI) with CIS restricted to the urethral mucosa can be managed conservatively with transurethral resection of the prostate (TURP) plus intravesical bacillus Calmette-Guérin (BCG) *(LE 3, weak recommendation)*. Repeat prostatic urethral biopsies after induction BCG should be considered *(LE 3, weak recommendation)*. RC can be discussed as an alternative option *(LE 4, weak recommendation)*.
19. In patients with HG T1 or CIS extending into the prostatic ducts, RC should be considered *(LE 3, weak recommendation)*. TURP followed by intravesical BCG is an alternative option. In this instance, close followup with repeat prostatic urethral biopsies after induction BCG should be considered *(LE 3, weak recommendation)*.
20. In patients with prostatic stromal invasion, neoadjuvant cisplatin-based chemotherapy followed by RC is recommended *(LE 3, strong recommendation; refer to CUA guideline on MIBC)*.

Single instillation of chemotherapy (SIC) post-TURBT

21. SIC (with mitomycin-C, epirubicin, doxorubicin, pirarubicin, or gemcitabine) should be offered to all patients with presumed low-risk NMIBC at TURBT and should be administered within 24 hours after endoscopic resection *(LE 1, strong recommendation)*.
22. SIC is recommended for intermediate-risk NMIBC and for patients with ≤1 recurrence/year and European Organization for Research and Treatment of Cancer (EORTC) recurrence score <5 *(LE 1, strong recommendation)*. SIC should be discussed even when further adjuvant intravesical chemotherapy is planned *(LE 2, weak recommendation)*.
23. The benefit of SIC in patients with high-risk NMIBC is unclear when intravesical BCG is planned as adjuvant treatment *(LE 3)*.
24. SIC should not be administered after extensive resection or when bladder perforation is suspected *(LE 3, strong recommendation)*.

Adjuvant intravesical chemotherapy

25. Patients with intermediate-risk NMIBC should be considered for adjuvant induction intravesical chemotherapy *(LE 1, strong recommendation)* with subsequent maintenance for up to one year *(LE 3, weak recommendation)*, or induction BCG with maintenance therapy (refer to statement #30).
26. Substratification of intermediate-risk patients with recurrent LG Ta NMIBC can be used to guide adjuvant treatment decisions *(LE 3, weak recommendation)*. For this purpose, four

factors should be considered: number of tumors, size (≥3 cm), time to recurrence (<1 year), and frequency of recurrence (>1/year).
   - Patients with low-intermediate-risk NMIBC (0 factors) may be treated similarly to low-risk patients, with SIC alone *(LE 3, weak recommendation)*.
   - Patients with high-intermediate-risk NMIBC (≥3 factors) may be treated as high-risk patients with induction and maintenance BCG *(LE 3, weak recommendation)*.

27. Patients who develop recurrence during intravesical chemotherapy may be offered induction followed by maintenance BCG *(LE 3, weak recommendation)*.
28. Although intravesical chemotherapy through device-assisted therapy has shown promising results in small, randomized controlled trials, further studies are needed to validate its routine clinical use.

Adjuvant intravesical BCG

29. In patients with high-risk NMIBC, BCG therapy with induction (weekly instillations for six weeks) followed by three-year maintenance (weekly instillations for three weeks at three, six, 12, 18, 24, 30, and 36 months) is the standard of care for reducing disease recurrence and progression rates *(LE 1, strong recommendation)*.
30. When BCG is administered for intermediate-risk NMIBC, induction (weekly instillations for six weeks) followed by one-year maintenance (weekly instillations for three weeks at three, six, and 12 months) is recommended *(LE 1, strong recommendation)*.
31. RC with pelvic lymph node dissection is the standard of care for BCG-unresponsive bladder cancer in surgically fit patients *(LE 3, strong recommendation)*. For patients with BCG-unresponsive CIS or HG Ta, a second-line bladder-preserving therapy can be considered before RC *(LE 3, weak recommendation)*.
32. Promising efficacy has been reported with intravenous pembrolizumab, intravesical oportuzumab monatox, nadofaragene firadenovec, and BCG plus N-803. These should be considered as potential options in patients with BCG-unresponsive CIS who are unfit for or refuse to undergo RC *(LE 2, weak recommendation)*.
33. Alternative options, such as sequential intravesical gemcitabine/docetaxel (induction plus maintenance), may be considered for patients with BCG-unresponsive disease who are unfit for or refuse to undergo RC *(LE 3, weak recommendation)*. Additional alternatives may also include other combination intravesical therapy (e.g., sequential gemcitabine/mitomycin-C, BCG + interferon if available) or single-agent intravesical therapy (mitomycin-C, epirubicin, docetaxel, gemcitabine) *(LE 3, weak recommendation)*.
34. Clinical trials may be considered for BCG-unresponsive patients who are unfit for or refuse to undergo RC.

Treatment adjustments only if BCG shortage

35. For patients with intermediate-risk NMIBC during BCG shortage, intravesical chemotherapy is recommended as the first-line option. If BCG is planned as a second-line therapy for this population, induction might be administered with reduced dosing (one-half or one-third dose) and maintenance can be omitted (*LE 3, weak recommendation)*.
36. For patients with high-risk NMIBC, full BCG schedule (induction followed by maintenance) is recommended *(LE 1, strong recommendation)*. Only during BCG shortage, when full dose is not possible due to limited supply, dose reduction to one-half or one-third might be considered, while maintenance can be reduced to one year *(LE 3, weak recommendation)*.
37. When BCG is unavailable, single-agent chemotherapy (e.g., mitomycin-C, gemcitabine) or sequential combination of intravesical chemotherapy (e.g., gemcitabine/docetaxel) is recommended with induction followed by monthly maintenance for up to one year *(LE 3, weak recommendation)*.

Timely cystectomy

38. Upfront RC should be considered for patients with large-volume, diffuse, endoscopically unresectable NMIBC *(LE 3, strong recommendation)*.
39. Upfront RC should be offered to patients with HG T1 disease with additional adverse tumor pathological features, including: variant histology (e.g., micropapillary, plasmacytoid, sarcomatoid), extensive invasion of the lamina propria or invasion into or beyond the muscularis mucosa (T1b/c), presence of LVI, concomitant CIS in the bladder or prostatic urethra, multiple and large (≥3 cm) tumors, or persistent HG T1 upon re-staging TURBT *(LE 3, strong recommendation)*.

Followup

40. The first surveillance cystoscopy is recommended for all patients at three months after TURBT *(LE 2, strong recommendation)*.
41. A risk-based surveillance strategy should be used in patients with no evidence of recurrence at the three-month cystoscopy:
    - Low-risk patients might be followed with cystoscopy at one year and then yearly for five years *(LE 3, weak recommendation)*. Urine cytology is not necessary in the followup of low-risk patients (*LE 4, weak recommendation)*.
    - Intermediate-risk patients should be followed with cystoscopies and urine cytology every 3–6 months in the first two years, every 6–12 months in the third year, and annually thereafter *(LE 3, weak recommendation)*.
    - High-risk patients should be followed with cystoscopies and urine cytology every 3–4 months during the first two years, every six months during years three and four, and annually thereafter *(LE 3, weak recommendation)*.
42. Upper tract imaging is recommended with random bladder/prostatic urethral biopsies (or use of BLC with directed biopsies) if positive urine cytology with normal WLC is found during surveillance *(LE 3, weak recommendation)*.
43. Upper tract imaging is recommended in the first year and every two years thereafter for high-risk patients *(LE 3, weak recommendation)*.
44. Fulguration under local anesthesia might be considered for small (<5 mm) papillary tumors and negative cytology in patients with a prior history of papillary urothelial neoplasm of low malignant potential or LG Ta NMIBC *(LE 3, weak recommendation)*.

Introduction

Bladder cancer is the fifth most common cancer worldwide.[1] In Canada, the estimated incidence for 2020 was of 12 200 new cases, with 2600 disease-related deaths during that same year.[2] Canadian population-based studies suggest that incidence was stable from 2010 until 2015.[3] More recent estimates, however, have shown an increase in incidence rates from 21.8 to 25.0 cases per 100 000 from 2018 to 2020.[2] Bladder cancer is the fourth most common cancer among men, accounting for 8.1% of all cancer diagnoses and the male to female ratio is 3:1. It is considered a disease of the elderly, with an average age at diagnosis of 73 years. It is more prevalent in resourced and industrialized countries with the highest incidence rates in North America, Europe, and Western Asia.[4]Approximately 75% of all bladder tumors are diagnosed at early stages, classified as non-muscle-invasive bladder cancer (NMIBC). NMIBC corresponds to clinical tumor stages Tis (carcinoma in situ [CIS]), Ta, and T1 according to the eight edition of the American Joint Committee on Cancer and the Union for International Cancer Control classification (Table 1).[5] These tumors are either confined to the mucosal layer or invade the submucosal layer (lamina propria) of the bladder wall without invading the underlying detrusor muscle (muscularis propria). Despite having a good prognosis, NMIBC is associated with high recurrence rates and some patients will progress to muscle-invasive disease (T2 or higher). The remaining 25% of bladder tumors are muscle-invasive (MIBC) upfront at diagnosis (cT2–T4) and/or metastatic (cM1) and are associated with higher mortality rates. The management of MIBC and metastatic bladder cancer is addressed in separate CUA guidelines.[6,7] In addition, estimated life cost of bladder cancer is one of the highest among all malignancies because of the need for close surveillance and the high recurrence and progression rates, which often necessitate multiple lines of therapy.[8,9]

Table 1. Bladder TNM classification – AJCC UICC, 8th edition

T – primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Non-invasive papillary carcinoma
Tis	Urothelial carcinoma in situ: 'flat tumor'
T1	Tumor invades lamina propria (subepithelial connective tissue)
T2	Tumor invades muscularis propria (detrusor muscle)
T3	Tumor invades perivesical soft tissue
T3a	Microscopic invasion
T3b	Macroscopic invasion (extravesical mass)
T4	Extravesical tumor invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumor invades prostatic stroma, seminal vesicles, uterus or vagina
T4b	Tumor invades pelvic wall or abdominal wall
N – regional lymph nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No lymph node metastasis
N1	Single regional lymph node metastasis in the true pelvis (perivesical, obturator, external iliac, or sacral)
N2	Multiple regional lymph node metastasis in the true pelvis (perivesical, obturator, external iliac, or sacral)
N3	Lymph node metastasis to common iliac lymph node(s)
M – distant metastasis	
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph nodes (beyond the common iliac vessels)
M1b	Other distant metastasis

Methods

For this updated guideline, a non-systematic literature review was performed in Medline and PubMed using keywords and MESH terms. Previously published sections of the 2015 version[10] were reorganized and updated, adding recent literature from October 14, 2015 until February 13, 2021.

Statements for interventions and prognosis provided here were assigned a level of evidence (LE) based on a modified version of the 2009 Oxford Center for Evidence-based Medicine classification, which has been used by the Joint Consultation of the Société Internationale d'Urologie and International Consultation on Urological Disease (SIU-ICUD) on Bladder Cancer, published in 2017 (Table 2).[11] Moreover, recommendation statements were classified as strong vs. weak using a modified GRADE approach.[12] The strength of each recommendation was judged based on the quality of evidence, the estimated magnitude, precision and consistency of the effect, and the balance between potential benefits and harms, resource use, value judgments, and patient preferences. Other society NMIBC guidelines published by the European Association of Urology (EAU), the American Urological Association (AUA), the National Institute for Health and Care Excellence (NICE), and the National Comprehensive Cancer Network (NCCN) were used for comparison.[13-16]

1. Risk factors

– **Former or current tobacco smoking is the most common risk factor associated with bladder cancer and smoking cessation should be encouraged in all patients** *(LE 3, strong recommendation)*.

Table 2. Levels of evidence

Level of evidence	Studies on intervention	Studies on prognosis
1	Meta-analysis of randomized controlled trials Good-quality randomized controlled trial	Meta-analysis of inception cohort studies
2	Low-quality randomized controlled trial Good-quality prospective cohort study	Inception cohort study
3	Good-quality retrospective case-control or cohort study	Cohort study or control arm of randomized controlled trial
4	Expert opinion	Case series, case-control study, or poor-quality prognostic cohort study

1.1. Smoking

Among several well-established risk factors, tobacco use is the most remarkable one, being the attributable cause of bladder cancer in 50% of the cases.[17,18] In 2016, Cumberbatch et al conducted a meta-analysis including 83 studies and found a relative risk for bladder cancer of 3.47 and 2.04 for current and ex-smokers, respectively, compared to those who have never smoked.[19] Smoking history is associated with a three-fold increase in the risk of developing bladder cancer, and the risk is linearly associated with both the quantity and duration of exposure, in pack-years.[20,21] The benefit of smoking cessation is based on weak evidence and prospective evaluation is lacking.[19,22,23] Nevertheless, smoking cessation should be highly encouraged after a bladder cancer diagnosis, with potential additional benefits of reducing the risk of developing other malignancies (e.g., lung cancer) and cardiovascular disease *(LE 3, strong recommendation)*.[23,24]

Electronic cigarette (e-cigarette) use may also be associated with a risk of developing bladder cancer, as similar carcinogens have been detected in the urine of both regular and e-cigarette users (e.g., o-toluidine and 2-naphthylamine).[25] A recent systematic review on 22 studies showed that a total of 40 compounds linked to potential development of bladder cancer were identified in the urine of e-cigarette smokers, of which 12 are classified as group 1 (carcinogenic to humans) according to the International Agency for Research on Cancer (IARC).[26] To date, however, defining a direct causal link between e-cigarettes and bladder cancer has been challenging due to current study limitations, such as dual exposure (patients exposed to multiple tobacco products) and need for longer followup. Patients should be counselled regarding a potential risk of e-cigarettes and bladder cancer.

The role of cannabis use and bladder cancer was investigated in a small study that suggested a potential risk increase, based on a higher proportion of users among bladder cancer patients compared to controls.[27] This study, however, was limited by small sample size and selection bias.[27] More recently, a large cohort study with more than 84 000 men investigated the incidence of bladder cancer among tobacco and cannabis users.[28] Cannabis use was associated with bladder cancer risk reduction of 45% (hazard ratio [HR] 0.55, 95% confidence interval [CI] 0.31–1.00) when adjusting for other confounders.[28] Although a potential antiproliferative role of cannabinoids in urological cancers has been proposed, further prospective studies are needed to validate this hypothesis.[29]

1.2. Occupational risk

Occupational exposure is the second most common cause of bladder cancer and was reported as being the attributable cause of approximately 8–10% of cases during the 1980s. With workplace legislation, this estimate has recently decreased to approximately 5%.[30-32] The most important carcinogens are those associated with the rubber (2-napthylamine), plastic (1,1-dichloroethane, 4,4′-methylenebis(2-chloroaniline) – MBOCA – and 4,4′-methylenedianiline), and dye (aromatic amines and polycyclic aromatic hydrocarbons) industries.[33,34] In a meta-analysis with 263 studies and more than 30 million people, 42 occupations were associated with increased risk of bladder cancer, with the greatest risk among patients working in factories (relative risk [RR] 16.6, 95% CI 2.1–131.3]) and in the dye industry (RR 13.4, 95% CI 1.5–48.2]).[32]

1.3. Other

Advanced age is an independent risk factor for developing bladder cancer and incidence increases remarkably after the age of 65, reaching its peak at the age of 84.[35] Median age at bladder cancer diagnosis is 73 years.[36] Additionally, over 80% of bladder cancer-related deaths occur in patients over 65 years old.[37] Sex is a well-recognized risk factor, as male to female bladder cancer incidence ratio is 3:1. Gender and sex disparities are multifactorial and have been related in the past to unequal exposure to carcinogens (e.g., tobacco, occupational exposure), hormonal factors, and delays in diagnosis.[38-41] Moreover, women also tend to present with more aggressive disease at diagnosis (e.g., a higher proportion of MIBC) and a higher proportion of certain variant histologies (e.g., squamous cell carcinoma), which results in worse oncological outcomes.[42,43] Particularly for NMIBC, woman seem to harbor a higher risk of disease recurrence when treated with intravesical bacillus Calmette-Guérin (BCG), according to a meta-analyses with 23 754 patients.[44] Currently, other biological factors are being studied, with the aim to understand additional reasons for sex disparities in bladder cancer, and ultimately to optimize healthcare

delivery and encourage earlier diagnosis and adequate treatment to mitigate this discrepancy.[45-48]

Previous pelvic irradiation for other cancers has been associated with second malignancies, including bladder cancer. For example, after radiation for prostate cancer, the HR for developing bladder cancer is 1.67 (95% CI 1.55–1.80), with median time from exposure to bladder cancer diagnosis of 58 months (interquartile range [IQR] 31–93).[49,50] Bladder cancer risk is increased in patients exposed to arsenic (e.g., in drinking water).[18] The association between other dietary factors and bladder cancer is controversial and requires further investigation.[18,51] Cyclophosphamide, phenacetin, and chlornaphazine are listed carcinogens that can cause bladder cancer, according to the IARC.[52] Other medications, such as pioglitazone, may be associated with bladder cancer risk, although evidence to date remains controversial.[53-56]

Genetic susceptibility to bladder cancer has been demonstrated. Inherited mutations in carcinogen-detoxification genes, such as NAT2 and GSTM1, can lead to higher exposure to carcinogens (e.g., cigarette components) and higher risk of bladder cancer.[57] Lynch syndrome (LS), also known as hereditary non-polyposis colorectal cancer, is caused by an autosomal-dominant germline mutation in mismatch repair genes.[58] LS is related to both colonic and extracolonic cancers, including upper tract urothelial carcinoma (UTUC). A study by Skeldon et al suggested that LS is also associated with bladder cancer, as more than 6% of patients carrying a specific mutation in the MSH2 gene were diagnosed with the disease.[59] Therefore, awareness of LS among urologists is important for appropriate screening and counselling of bladder cancer patients.[60]

Chronic inflammation to the bladder mucosa (e.g., recurrent urinary tract infections and indwelling catheters) is also associated with higher bladder cancer risk.[18] Additionally, infection with *Schistosoma haematobium* is a well-recognized cause of chronic bladder inflammation and is associated with increased risk of squamous cell carcinoma (SCC) of the bladder.[18,61] Schistosomiasis-induced bladder cancer is more common in developing countries, such as Egypt, but its incidence has been decreasing in the last 20 years such that urothelial carcinoma (UC) has replaced SCC as the most common histology of bladder cancer in these countries as well.[62]

2. Symptoms and diagnosis

- **White-light cystoscopy (WLC) is recommended in the initial evaluation of patients suspected to have bladder cancer. Cystoscopy should be performed with a flexible cystoscope whenever available** *(LE 1, strong recommendation)*.
- **Urine cytology (voided or collected by bladder washing) is recommended as an adjunct to cystoscopy in patients suspected to have bladder cancer** *(LE 2, strong recommendation)*.
- **Upper urinary tract imaging is recommended in the initial workup of patients suspected to have bladder cancer** *(LE 3, strong recommendation)*.

Workup for suspected bladder cancer includes a complete history and a focused physical exam, followed by cystoscopy and imaging. Ultrasound is operator-dependent, and historically, its sensitivity and specificity for detecting bladder cancer is 91% and 79.3%, respectively, with overall accuracy of 88%.[63] Accuracy, however, dramatically decreases for defining lesions <5 mm and its utility for staging bladder cancer and ruling out UTUC is limited.[64] Cross-sectional imaging is, therefore, recommended in the initial workup of bladder cancer, especially in patients presenting with gross hematuria where contrast-enhanced computerized tomography (CT) with delayed images is the first-line option, showing high sensitivity (85%) and specificity (94%) in detecting bladder tumors with a diagnostic accuracy of 90%.[65] Despite its limitation in determining depth of invasion (NMIBC vs. MIBC tumors), CT is important to assess for concurrent UTUC (present in approximately 2% of patients with bladder cancer), hydroureteronephrosis (associated with higher T-stage bladder cancer), and to rule out metastatic disease *(LE 3, strong recommendation)*.[66,67]

Recently, a standardized evaluation of local bladder tumor staging through multiparametric magnetic resonance (MRI) was proposed – the Vesical Imaging-Reporting and Data System (VI-RADS).[68] The objective was to mitigate staging errors and optimize treatment of bladder cancer by improving the accuracy in predicting muscularis propria invasion at the time of diagnosis.[68] In a meta-analysis of six studies, VI-RADS was able to predict muscle invasion with 83% sensitivity and 90% specificity in patients undergoing transurethral resection (TUR) and/or radical cystectomy (RC).[69] Despite promising results, VI-RADS still needs validation in larger, prospective studies to determine the added value compared to TUR alone and the ideal timing for the MRI (before vs. after initial TUR).

WLC is the cornerstone for establishing bladder cancer diagnosis. According to randomized controlled trials (RCTs), flexible cystoscopy in males has been shown to reduce pain and improve patients' acceptance of this procedure *(LE 1)*.[70,71] Likewise, a recent RCT demonstrated lower pain levels during flexible, compared to rigid cystoscopy, in female patients.[72] Therefore, initial WLC should be done using gel lubrication and a flexible cystoscope when available *(LE 1, strong recommendation)*. On the other hand, the benefit of using an anesthetic lubricant for pain relief during flexible cystoscopy, in comparison to plain lubricant, is currently not consistent in the literature.[73,74] A recent randomized study also showed that the "bag squeeze" technique (applying

pressure to the saline bag during cystoscopy at the level of the membranous/prostatic urethra) was significantly associated with a lower mean pain score during the procedure when compared to controls (1.91 vs. 3.39, respectively, p<0.001).[71]

Either voided or bladder washing urine cytology should be performed as an adjunct to cystoscopy in the initial diagnosis of NMIBC *(LE 2, strong recommendation)*.[75,76] Overall, the sensitivity of a positive urine cytology in detecting bladder cancer is low, ranging from 40–60%, but is as high as 70–90% for high-grade (HG) tumors and CIS.[77-80] Specificity, however, is high (around >95%), leading to a very low rate of false-positive results.[81] Novel biomarkers for detecting bladder cancer at initial diagnosis or surveillance are being studied. To date, however, biomarkers are not yet able to outperform or replace cystoscopy.

3. Prognostic factors for recurrence and progression

- **The most important prognostic factors for recurrence and progression of NMIBC are stage and grade** *(LE 2)*. **All patients with bladder cancer should be properly staged and, specifically for NMIBC, reporting grade is paramount for further management decision** *(LE 2, strong recommendation)*.
- **Other prognostic factors are age >70 years, large tumor size (≥3 cm), multiple tumors, the presence of concomitant CIS, extensive invasion of the lamina propria, prior recurrence rates >1 per year, and status at first assessment after TUR of the bladder tumor (TURBT)** *(LE 2)***, as well as lymphovascular invasion (LVI)** *(LE 3)*.
- **Aggressive histological variants, such as micropapillary, plasmacytoid, and sarcomatoid, are associated with increased risk of understaging and progression** *(LE 3)*. **Pathological review, preferably by a dedicated uro-pathologist, should be considered in settings where variant histology is suspected or atypical tumors are seen during TURBT (e.g., sessile mass)** *(LE 3, weak recommendation)*.

3.1. Stage and grade

Stage and grade are the most important predictors of recurrence and progression of NMIBC.[82,83] A large, retrospective study by Millan-Rodriguez et al with 1529 patients treated for primary NMIBC showed that, when adjusted for other confounders in a multivariate model (including stage), grade was the most important factor associated with both progression (odds ratio [OR] 19.9, 95% CI 2.6–150.0) and disease-specific mortality (OR 14.0, 95% CI 1.8–109.0).[84] Regarding time to progression, the presence of HG disease was associated with a higher HR compared to stage (2.67, 95% CI 1.99–3.59 vs. 2.19, 95% CI 1.67–2.86, respectively), resulting a higher weight for grade in the European Organisation for Research and Treatment of Cancer (EORTC) risk calculation tables for recurrence and progression *(LE 2)*.[83] Therefore, all bladder cancer patients should be properly staged and, specifically for NMIBC, reporting grade is considered paramount for further management decision *(LE 2, strong recommendation)*.

In 1973 the World Health Organization (WHO) defined a grading system for pathologists to report, dividing NMIBC into three categories according to levels of cell differentiation: grades 1, 2, and 3. Despite well-established criteria, difficulties in distinguishing grade 2 from grades 1 and 3 resulted in the middle category being overreported.[85] To address this issue, the WHO and the International Society of Urologic Pathologists (ISUP) updated this classification in 2004, which is, to date, the most widely adopted grading system in North America. It classifies tumors into three categories: papillary urothelial neoplasm of low malignant potential (PUNLMP), low-grade (LG), and HG. The same grading system was reviewed without major changes in 2016. With the 2004/2016 WHO/ISUP system, 30–40% of the former grade 2 lesions with bland cytological features were re-classified as LG, while the other 60–70% were re-classified as HG.[86]

In a recent systematic review including 20 studies, the interobserver reproducibility of the 2004/2016 WHO/ISUP system by pathologists was low (43–66%), although higher when compared to the previous 1973 version.[86] Moreover, when PUNLMP and LG tumors were considered together, reproducibility increased from 71–82% to 86–90%. In that same study, recurrence rates among 624 patients with PUNLMP was 12%. Importantly, a comparable recurrence rate (9%) was reported among 1303 patients with G1 tumors.[86] Progression of PUNLMP is rare (1.7%), and this entity should be followed similarly to LG tumors *(LE 3, weak recommendation)*.[86]

Approximately 70% of newly diagnosed NMIBC is detected at stage Ta.[87] Among Ta tumors, the vast majority are LG, with HG Ta tumors being diagnosed in only 7% of cases, while 5–10% of Ta tumors harbor concomitant CIS.[88] Patients with single papillary LG Ta tumors measuring <3 cm have the most favorable prognosis, with five-year recurrence and progression risks of 21–31% and 0.8–3.8%, respectively.[89] On the other hand, HG Ta tumors have a 43.5% risk of recurrence (28.8% within the first year), and a risk of progressing to ≥pT1 and ≥pT2 of 7.4% and 3.2%, respectively, at a median followup of 44.5 months.[90,91] Stage T1 tumors represent 20% of NMIBC.[87] In addition to a recurrence rate of 41.8% (95% CI 398.5–44.9), 20.2% (95% CI 17.6–22.7) of HG T1 tumors progress to muscle invasion at five years, according to a meta-analysis.[92] Stage T1 tumors are almost always HG, and only 2% have been classified as LG. Additionally, retrospective studies have shown that patients with these rare LG T1 tumors experienced similar

oncological outcomes when compared to HG T1 patients, suggesting that the impact of grade within the spectrum of T1 disease remains questionable.[93-95]

3.2. Carcinoma in situ

Concomitant CIS is diagnosed in up to 19% of NMIBC cases.[96] This entity is described as a flat lesion confined to the bladder mucosa and is HG by definition.[97] If treated only with TURBT, CIS recurrence can be as high as 90%, while progression to muscle-invasive disease can occur in 54–80% of patients.[98,99] CIS is rarely found in isolation, with the majority of cases (90%) being found in association with papillary or nodular bladder tumors.[87,100] CIS can be classified as primary (no previous history of bladder cancer), which carries the best prognosis, concomitant (with a papillary or nodular tumor), or secondary (new lesion diagnosed during followup).[101,102] CIS is also considered a field disease, as it can affect multiple areas in the bladder, the upper urinary tract, and the urethra.[103] Concomitant CIS has prognostic importance; it is significantly associated with risk of progression (OR 2.1, 95% CI 1.1–4.0) and disease-specific mortality (OR 3.0, 95% CI 1.4–6.6) *(LE 2)*.[84] Therefore, erythematous areas suspicious for CIS should be biopsied during cystoscopy/TURBT *(LE 2, strong recommendation)*.

3.3. Lymphovascular invasion

Initial series evaluating LVI for NMIBC have shown inconsistent results regarding its association with oncological outcomes.[104-106] A prospective study by Cho et al showed LVI was a significant predictor for recurrence and progression, and was negatively associated with metastasis-free survival, but these results were limited by potential selection bias and short followup.[107] A meta-analysis by Kim et al in 2014 with 3905 patients taken from 16 retrospective studies showed the association of LVI with upstaging in RC specimens (OR 2.21, 95% CI 1.44–3.39), recurrence-free survival (RFS) (HR 1.47, 95% CI 1.24–1.74), and progression-free survival (PFS) (HR 2.28, 95% CI 1.45–3.58) when detected in TURBT specimens of patients with NMIBC.[108] In a meta-analysis with 15 215 patients designed to identify prognostic factors for HG T1 disease, Martin-Doyle et al showed that LVI was significantly associated with RFS, PFS, and disease-specific survival (DSS) when including studies with at least 75% of patients with HG T1 tumors *(LE 3)*.[92] When analysis was performed on studies with 100% of HG T1 tumors, statistical significance was not maintained. Importantly, LVI was associated with deep invasion into the lamina propria, which was the most important adverse prognostic factor. Based on these findings, the authors questioned the independent role of LVI in the prognosis of HG T1 disease, suggesting it could ultimately reflect the extent of invasion into the lamina propria.[92] More recently, however, another meta-analysis with 33 retrospective studies and 6194 patients showed that LVI was present in 15% of TURBT NMIBC specimens *(LE 3)*.[109] In this study, LVI was a significant factor for recurrence (HR 1.97, 95% CI 1.47–2.62), progression (HR 2.95, 95% CI 2.11–4.13), and upstaging after RC, particularly for cT1 *(LE 3)*.[109]

Pathological evaluation of LVI may be limited if only hematoxylin & eosin staining is used and the use of immunohistochemistry is encouraged in challenging cases in order to differentiate LVI from retraction artifact *(LE 3, weak recommendation)*.[110] Although it has not yet been integrated in the major risk stratification tools for NMIBC, LVI may be considered as an independent marker of worse prognosis in patients with high-risk NMIBC *(LE 3, weak recommendation)*.

3.4. Extent of invasion

The extent of invasion of T1 tumors is also associated with prognosis. It has been evaluated using two different criteria: 1) micrometric, which evaluates the millimetric extent of invasion into the lamina propria, either in depth, or as a linear measurement of the invasive cancer focus (single largest focus or in aggregate); and 2) microanatomic, which evaluates the level of invasion in relation to the muscularis mucosa (T1a – no muscularis mucosa invasion, T1b – invasion at the level of the muscularis mucosa, and T1c – invasion beyond the muscularis mucosa).[111-113] Although no single approach has been universally adopted, the micrometric method has the advantage of not being limited by the anatomical variability of muscularis mucosa (which may be discontinuous or absent, limiting the applicability of the microanatomic approach in daily practice). On the other hand, no single cutoff of either depth or length of invasive focus has been consistently demonstrated to be prognostic yet. A study by van Rhijn et al with 134 patients with newly diagnosed bladder cancer identified a significant association between extensive T1 invasion of the lamina propria and progression (HR 3.0, 95% CI 1.5–5.90, p=0.001] and DSS (HR 2.7, 95% CI 1.1–6.8, p=0.032). Importantly, assessment of microscopic vs. extensive T1 invasion was possible in 100% of the cases.[112] This was later confirmed in a multicentric study with 601 patients with primary pT1 bladder tumors in which extensive lamina propria invasion (but not muscularis mucosa level of invasion) was independently associated with PFS (HR 3.8, 95% CI 2.3–6.0, p<0.001) and DSS (HR 2.7, 95% CI 1.6–4.8, p<0.001).[113] Notably, the meta-analysis by Martin-Doyle showed that extensive invasion of the lamina propria was considered the most significant prognostic factor for HG T1 patients (HR 3.34, 95% CI 2.04–5.49, p<0.001).[92] More recently, a systematic review and meta-analysis with 36 studies and 6781 patients confirmed both deep invasion into the lamina propria and invasion to the muscularis mucosa to be associated with disease

recurrence and progression in NMIBC when adjusted for other potential confounders, such as tumor grade, CIS, and multifocality.[114] This meta-analysis included four prospective studies, of which three showed a significant prognostic role of deep lamina propria invasion in both recurrence and progression during followup *(LE 2)*.[115-117]

3.5. Tumor burden (size and multifocality)

The number and size of tumors are also important prognostic factors for recurrence in NMIBC.[118-121] Recurrence rates are significantly higher for NMIBC patients with multiple (OR 1.9, 95% CI 1.1–3.2) and large (≥3 cm) tumors (OR 1.7, 95% CI 1.0–3.0) *(LE 2)*.[84] Both variables were included in the European Organization for Research and Treatment of Cancer (EORTC) and the Spanish Urological Club for Oncological Treatment (CUETO) risk stratification tools.[83,122] More recently, diameter ≥3 cm and the presence of multiple tumors were confirmed as significant predictors of NMIBC progression.[123]

3.6. Early cystoscopic findings

In a study by Sylvester et al, persistent disease diagnosed at the first surveillance cystoscopy after induction intravesical treatment was a risk factor associated with progression, which occurred in 25.3% vs. 8.7% of patients with or without pathologically confirmed malignancy, respectively.[83] Early RCTs in the 1980s by the EORTC group showed that the number of tumors, as well as a recurrence rate higher than one per year, were associated with future intravesical recurrence *(LE 2)*.[124] Later, secondary analyses of RCTs also confirmed the association of previous recurrence rates (more than one per year) and multifocality with early tumor recurrence (or persistent disease) at the first surveillance cystoscopy after treatment, potentially reflecting not only small, missed tumors at first TURBT, but also resistance to first-line intravesical therapy.[118,125,126]

3.7. Histology

Approximately 90% of bladder cancers are pathologically classified as UCs (previously named "transitional cell carcinomas"), arising from the bladder urothelium. Pure squamous cell carcinoma and pure adenocarcinoma are less commonly diagnosed (2–5% and 2% of cases, respectively).[127] Among UCs, 75% are classified as pure, while 25% harbor a secondary histological variant, the most common being squamous (20–40%) and glandular differentiation (18%).[127] Particularly for NMIBC, variant histologies have been under-reported by pathologists in up to 44% of cases.[128] Furthermore, initial diagnosis through biopsies or TURBT specimens have shown low sensitivity (35% and 43%, respectively) to predict variant histologies after RC, according to retrospective data.[129] Variant histologies have implications for management and prognosis, due to their higher risk for under-staging, higher risk of progression, and possibly differential response to treatment. Therefore, a pathological review, preferably by a dedicated uro-pathologist, should be considered in settings where variant histology is suspected by the pathologist or atypical tumors are seen by the urologist during TURBT (e.g., sessile mass) *(LE 3, weak recommendation)*.[129]

Not all variant histologies have the same prognostic implications. For example, controlling for stage, oncological outcomes are similar between pure UC vs. UC with squamous or glandular differentiation.[130,131] Therefore, NMIBC with squamous or glandular differentiation can be managed similarly to pure UC *(LE 3, weak recommendation)*. The presence of nested variant of UC has been associated with higher stage and nodal invasion, but main oncological outcomes were comparable to patients with pure UC when matched by stage in both the NMIBC and MIBC settings.[132,133] Other variant histologies, such as micropapillary, plasmacytoid, and sarcomatoid differentiation are associated with higher rates of progression and worse prognosis, prompting consideration for aggressive treatment with upfront RC in the majority of cases *(LE 3)*.[127,134,135] Small cell (or neuroendocrine) bladder cancer is rarely diagnosed at an early stage and requires individualized approach with multidisciplinary tumor board review. Neoadjuvant chemotherapy followed by consolidation with either RC or radiation-based therapy should be considered.[135]

4. Risk stratification

– **All patients with NMIBC should be stratified according to the risk of both recurrence and progression for adequate patient counselling and treatment planning** *(LE 2, strong recommendation)*. **The modified CUA risk stratification system is a suitable tool for this purpose.**

After diagnosis, clinical and pathological factors must be considered to allow for risk stratification of NMIBC. In order to estimate risks for recurrence and progression and to plan additional treatments after TURBT, the EORTC developed a comprehensive scoring system based on 2596 patients from seven clinical trials.[83] A score is calculated to estimate the risks of recurrence and progression at one and five years, based on six prognostic factors: number of tumors (single vs. 2–7 vs. ≥8), tumor size (<3 cm vs. ≥3 cm), number of previous recurrences (≤1 per year vs. >1 per year), pT stage (pTa vs. pT1), presence of concurrent CIS, and grade (available at *http://www.eortc.be/tools/bladdercalculator/*).[83]

The EORTC risk calculator, however, likely overestimates recurrence (15–61%) and progression (1–17%) at one year when compared to high-risk NMIBC patients receiving BCG, since the majority of the patients in the included RCTs were

treated with intravesical chemotherapy, which is associated with inferior outcomes compared to BCG. Additionally, all 171 patients treated with BCG in this analysis underwent only an induction course, which is today considered suboptimal for high-risk patients.[83] To address that, the CUETO developed a similar calculator, also to predict recurrence and progression, but including 1062 patients treated with induction (six weekly instillations for six weeks) and maintenance (six two-weekly doses for up to 12 doses) of BCG.[122]

A recent multicenter study by Sylvester et al using individual patient data for 3401 NMIBC patients sought to stratify patients into risk groups for progression, incorporating the grade categories of the WHO 2004/2016 grading system, since it was not considered in previous systems by the EORTC.[123] In a multivariable analysis, age >70 years was significantly associated with disease progression (HR 1.72, 95% CI 1.24–2.40, p=0.001), together with T1 stage (HR 2.20, 95% CI 1.53–3.16, p<0.001), high-grade disease (HR 2.33, 95% CI 1.58–3.42), multiple tumors (HR 1.64, 95% CI 1.17–2.29), tumor diameter ≥3 cm (HR 1.97, 95% CI 1.41–2.77), and concomitant CIS (HR 2.76, 95% CI 1.62–4.70).[123]

Table 3. Modified Canadian Urological Association risk stratification system†

Risk group	Tumor characteristics
Low	1. PUNLMP 2. Primary, solitary, and small (<3 cm) LG Ta
Intermediate	*Patients without CIS who are not included in the other risk categories:* 1. Recurrent, multifocal, and/or large (>3 cm) LG Ta – Consider sub-stratification: a) Low-intermediate-risk: 0 factors* – consider treating as low-risk patients b) Intermediate-risk: 1–2 factors c) High-intermediate-risk: ≥3 factors – consider treating as high-risk patients *Multiple tumors, >3 cm, time to recurrence (<1 year), and frequency of recurrence (>1/year) 2. Primary, solitary, and small (<3 cm) HG Ta – Consider treating as high-risk patients
High	Any: 1. T1§ 2. Recurrent, or multiple, or ≥3 cm HG Ta 3. Presence of CIS (primary or concomitant) §Very high-risk: HG T1 with any of the following: a) Multiple and ≥3 cm b) Presence of concurrent CIS (in the bladder or prostatic urethra) c) Presence of LVI d) Variant histology (e.g., micropapillary, plasmacytoid, sarcomatoid, neuroendocrine)

†Modified from EORTC and CUETO stratification tools, Sylvester et al,[123] and other major guidelines. CIS: carcinoma in situ; HG: high-grade; LG: low-grade; LVI: lymphovascular invasion; PUNLMP: papillary urothelial neoplasm of low malignant potential.

As a result, age >70 years was included as an additional factor to be considered when stratifying patients based on progression risk *(LE 2, strong recommendation)*. Importantly, patients with initial recurrent disease, primary CIS with no associated papillary tumors, CIS in the prostatic urethra, LVI, variant histologies, and those treated with intravesical BCG were not included in the analysis, as these factors could potentially affect progression rates.[123]

The modified CUA risk stratification method is proposed here (Table 3). Although validation in larger populations is required, this classification can be easily implemented in daily practice. It stratifies patients individually in low-, intermediate- and high-risk NMIBC.

5. Transurethral resection of bladder tumor (TURBT)

– **Patients presenting with a bladder tumor should undergo initial TURBT for diagnostic confirmation and pathological evaluation** *(LE 2, strong recommendation)*.
– **Initial TURBT aims for complete tumor resection with sampling of the underlying detrusor muscle as the first step of curative-intent treatment of NMIBC** *(LE 2, strong recommendation)*. **Patients with presumed LG Ta or CIS might be spared from muscle sampling at initial TURBT** *(LE 3, weak recommendation)*.

Initial TURBT is a key step in the management of bladder cancer. It has a diagnostic, prognostic, and therapeutic role, and its quality can impact oncological outcomes. Sampling of detrusor muscle is an important quality indicator (in tumors other than PUNLMP, LG Ta, and CIS), and its absence is associated with risk of under-staging, residual disease, and recurrence.[136]

Steps for a standardized TURBT are presented here (Table 4).[137-139] Systematic characterization and mapping of all lesions should be performed. All visible tumors should be completely resected, and ideal depth should include the detrusor muscle (muscularis propria) to allow for optimal staging. Multiple tumors should be sent as separate specimens. For large tumors, consider sending the tumor base and deep resection separately. Bimanual examination should be performed.

Anesthetic technique, whether general with neuromuscular blockade (associated with reduction of the obturator reflex and lower risk of bladder perforation)[140] or spinal anesthesia, should be recommended based on the patient's risk factors, comorbidities, and tumor location.[141] Bipolar energy was shown to reduce the obturator nerve reflex and rates of bladder perforation when compared to resection with monopolar energy, according to a meta-analysis on eight studies (six RCTs).[142] Another meta-analysis of eight RCTs with 1147 patients reinforced the association of bipolar resection and shorter hospital stay, resection time, and lower

Table 4. Stepwise checklist for high-quality TURBT MIBC objective: Provide enough information for adequate risk stratification

MIBC objective: Provide enough information for adequate risk stratification
Cystoscopy: 1. Provide detailed description of urethra, bladder walls, and lesions (number, size, appearance, suspicion for concurrent/primary CIS) 2. Report visual impression of clinical stage and grade 3. Collect washing or voided urine cytology if not previously obtained
TURBT: 1. Completely resect all visible tumors and suspicious areas 2. Send labeled tumor specimens separately 3. Avoid excessive fulguration 4. Use enhanced visualization techniques when available 5. Use bipolar energy when indicated and available 6. Deep resection of the detrusor muscle – send deep specimens separately 7. Random biopsies (bladder and prostatic urethra) if indicated 8. Ensure adequate hemostasis 9. Assess bladder wall integrity after resection (evaluate for perforation) 10. Perform bimanual exam under anesthesia

CIS: carcinoma in situ; NMIBC: non-muscle-invasive bladder cancer; TURBT: transurethral resection of bladder tumor.

rates of bladder perforation and hemoglobin fall, although no difference was seen with respect to the obturator reflex when compared to monopolar resection.[143]

5.1 TURBT optimization

– **When available, blue light cystoscopy** (BLC) *(LE 1, weak recommendation)* **or narrow band imaging (NBI)** *(LE 2, weak recommendation)* **can increase tumor detection at first TURBT and reduce recurrence risk.**

Several clinical trials have evaluated enhanced imaging methods, such as BLC and NBI, with the intent of improving tumor detection rates and reducing disease recurrence. BLC and NBI are potential useful tools in the initial management and surveillance of NMIBC.

5.1.1. Blue light cystoscopy (BLC)

Fluorescent cystoscopy or BLC uses a photosensitizing agent, such as 5-aminolevulinic acid (ALA) or hexyl aminolevulinic acid (HAL). Instilled in the bladder before the procedure for 1–4 hours,[144] these substances are metabolized to protoporphyrin IX by tumor cells, showing a red fluorescence under blue light (380–470 nm), which provides contrast between tumors and the normal urothelium.[145] Currently, the only available agent is HAL.

Clinical trials have shown a consistent positive impact of BLC on NMIBC recurrence.[146-149] A large meta-analysis of 2212 patients with primary and recurrent NMIBC from nine prospective studies showed that adding BLC-HAL to WLC increased detection rates by 14.7% for Ta tumors and by 40.8% for CIS lesions *(LE 1)*.[150] Furthermore, at least one additional lesion was detected in 24.9% of patients and there was a significant reduction in recurrence rates at 12 months for all risk subgroups, including patients treated with BCG *(LE 1)*.[150] The recurrence benefit of BLC-HAL was also confirmed in studies with longer followup.[151] Geavlete et al showed two-year recurrence rates of 31.2% vs. 45.6% (p=0.001), while Gallagher et al showed three-year recurrence rates of 39.0% vs. 53.3% (p=0.02) for BLC-HAL vs. WLC, respectively.[152,153] Despite a trend for BLC in decreasing progression rates and prolonging time to progression, current data is inconclusive, and its impact on oncological outcomes other than recurrence remains unclear.[154]

Most clinical trials testing BLC have not used single-dose chemotherapy at the time of TURBT, so the impact of combining both interventions remains uncertain. All patients in the trial by Geavlete et al received single-dose chemotherapy.[152] However, in another prospective randomized trial by O'Brien et al, there was no significant difference in recurrence rates between WLC and BLC in 249 patients undergoing TURBT with single-dose mitomycin-C (MMC).[155] The lack of difference could be explained by an ablative effect of MMC on potentially missed lesions at WLC.[155]

Especially when proposing new technologies associated with bladder cancer care, cost-effectiveness needs to be evaluated, as bladder cancer has the highest lifetime treatment cost per patient among all cancers.[156,157] Regarding implementation of BLC at initial TURBT, a cost-effectiveness analysis was performed and found that BLC-HAL at initial TURBT was associated with better quality-adjusted life-years and overall cost over time than WLC by reducing NMIBC recurrences.[158] Meanwhile a study by Klaassen et al suggested that, despite high initial costs associated with the implementation of BLC, this approach could result in 87–338 fewer bladder recurrences annually in Canada.[159]

5.1.2. Narrow-band imaging

NBI enhances visualization of bladder tumors by using filters to narrow the bandwidth of light into wavelengths of 415 nm (blue) and 540 nm (green). Since these wavelengths correspond to the peak absorption of hemoglobin, NBI provides enhanced contrast between benign and hypervascular malignant lesions.[160] NBI is activated by pressing a switch in cystoscopes equipped with this technology and does not require bladder instillation of any kind before the procedure.

Several articles compared NBI with WLC, focusing on recurrence rate reduction.[161,162] In 2012, Naselli et al randomized 223 patients to receive TUR with NBI or WLC. With a median followup of 11 months, recurrence rates were found to be 3.9% vs. 16.7% (p=0.008) at three months and 31.6% vs. 51.4% (p=0.014) at one year for NBI vs. WLC,

respectively.[163] Another RCT by Geavlete et al showed a higher specificity for detecting CIS using NBI in comparison with WLC (53.8% vs. 15.4%, respectively).[164] Finally, a multicenter trial by the Clinical Research Office of the Endourological Society (CROES) randomized 965 patients to undergo NBI vs. WLC-assisted TURBT. Their results showed similar overall recurrence rates of 27.1% for WLC vs. 25.4% for NBI at one year (p=0.585), although subgroup analysis showed that the one-year recurrence rate for low-risk patients was significantly lower for NBI over WLC (5.6% vs. 27.3%, respectively, p=0.002) *(LE 2)*.[165] The authors stated that the effectiveness of NBI for low-risk patients can be explained by the fact that most recurrences might be caused by small, overlooked lesions at WLC that were identified through NBI. Finally, in a meta-analysis, Kang et al compared 1084 patients from six studies (out of which four were RCTs) and found lower RFS rates at three months (RR 0.39, p<0.0001)), one year (RR 0.52, p<0.00001), and two years (RR 0.60, p=0.004) for NBI when compared to WLC.[166]

5.1.3. En-bloc TURBT

En-bloc resection aims for complete removal of the bladder tumor with the adjacent bladder tissue and muscularis propria in one single specimen, being first described in the late 1990s.[167,168] Based on historical oncological principles for other malignancies, it claims to be a "no-touch" technique and is advocated by some urologists under the rationale that it provides for better-quality specimens (less fulguration), improved accuracy of pathology diagnosis, reduced number of floating tumor cells, and lower risk of bladder perforation during TURBT.[169] In a randomized study by Hashem et al, the detrusor muscle was present in 98% of specimens of patients undergoing holmium laser en-bloc resection vs. 62% undergoing conventional TURBT (p<0.001).[170] On the contrary, the multicentric, randomized study by Gakis et al showed no statistical difference regarding the presence of detrusor muscle in en-bloc vs. conventional TURBT specimens (77.4% vs. 66.7%, respectively, p=0.28), although a higher proportion of negative surgical margins was observed with en-bloc technique (57% vs. 9%, respectively, p<0.001).[171] Regarding T1 substaging, the concordance among pathologists when assessing depth of T1 invasion is higher when specimens are obtained by en-bloc TURBT in comparison to conventional TURBT.[1] A large, systematic review with meta-analysis by Teoh et al included 32 studies for qualitative and 10 RCTs for quantitative analysis on the effectiveness of en-bloc resection vs. standard TURBT.[173] According to this study, en-bloc resection was associated with longer operative time (mean difference 9.07 minutes, 95% CI 3.36–14.8, p=0.002), shorter postoperative irrigation time (mean difference -7.2 hours, 95% CI -9.3 to -5.2, p<0.001), and lower rate of bladder perforation (RR 0.30, 95% CI 0.11–0.83, p=0.02) when compared to TURBT. On the other hand, there was no statistical difference regarding the presence of muscularis propria in the final specimen, nor recurrence rates at one, two, and three years.[173] Larger, randomized studies are needed to define the role of en-bloc TURBT in clinical practice, including its learning curve, impact in recurrence rates, and whether it could potentially spare a subset of patients from re-staging TURBT or additional adjuvant instillations.[174] In conclusion, en-bloc TURBT is considered an emerging resection technique that may improve detrusor sampling and provide for better-quality specimens for pathological evaluation *(LE 3, weak recommendation)*. Its benefit on disease recurrence has not been established and further studies are needed prior to recommending its routine use.

5.2. Re-staging TURBT

- **A re-staging TURBT should be performed in patients with T1 NMIBC or when a complete resection was not achieved with the first TURBT** (*LE 2, strong recommendation*). **Re-staging TURBT is not required in patients who will proceed to RC based on the findings of the first TURBT.**
- **In select cases of HG Ta tumors (e.g., large and/or multiple tumors), a re-staging TURBT might be considered** *(LE 3, weak recommendation)*.
- **The suggested window for a re-staging TURBT is within six weeks of the first resection** *(LE 3, weak recommendation)*.

Re-staging TURBT (re-TURBT) changes NMIBC management in many patients.[175] It not only improves staging but also has therapeutic benefit and should be performed in all patients with T1 disease, aiming for the identification of occult muscle-invasive disease and resection of initially unresected lesions.[125]

In 1998, Herr published a series of 150 patients who underwent a re-TURBT for newly diagnosed and recurrent bladder cancer, showing that 76% (114) had residual tumor at re-TURBT, while 29% of those with NMIBC at initial TURBT were upstaged to MIBC (≥T2) after a second-look resection.[175] Other studies reported up to 9.5% upstaging for HG Ta tumors (to ≥T1) and 28% for T1 tumors (to ≥T2).[176,177] Divrik et al analyzed 210 patients with newly diagnosed T1 who were randomized to undergo re-TURBT or not, and were followed until death or a minimum time of 54 months.[178] They reported five-year RFS of 59% vs. 32% (p=0.0001) and PFS of 93% vs. 79% (p=0.0001) favoring re-TURBT. Additionally, re-TURBT was an independent predictor for both lower recurrence and progression rates in multivariate analysis *(LE 2)*.[178] This study, however, likely overestimated the effect of re-TURBT on long-term recurrence and progression and was criticized by lack of predefined endpoints, sample size power, method of randomization, and potential impacts of further intravesical therapy on oncological outcomes of both arms.[178]

Cumberbatch et al recently published a systematic review including 31 studies (only one RCT) and 8409 patients with HG tumors.[179] Re-TURBT resulted in upstaging rates of 0.4% (0–8%) and 8% (0–32%) of initial pTa vs. initial pT1 tumors, respectively *(LE 3)*. In pTa patients, a re-TURBT was associated with lower rates of recurrence, but not progression, while for pT1 patients, it resulted in lower rates of progression and overall mortality, with an additional trend for lower cancer-specific mortality. Most residual lesions were identified in the original tumor resection bed.[179] Another meta-analysis on 29 studies confirmed the presence of residual disease in 56% of pT1 patients, with 10% of patients experiencing upstaging to pT2 at re-TURBT.[180]

Smaller studies have focused on the value of re-TURBT in patients who subsequently receive BCG therapy. A retrospective study on 347 patients presenting with HG Ta or T1 tumors, who were treated with a six-weekly induction course of BCG, demonstrated a risk of recurrence at first followup evaluation in 57% of patients who did not undergo re-TURBT before BCG vs. 29% when a re-TURBT was performed (p=0.001).[181] The rate of progression in this study was reduced from 34% without TURBT to 7% (p=0.001) with re-TURBT.[181] Another retrospective study with 427 patients with a median followup of 63 months showed that patients with high-risk NMIBC benefited from induction and maintenance BCG even when re-TURBT confirmed absence of any tumor (pT0).[182] These results suggest that a complete resection before BCG therapy is important for obtaining optimal results from this approach *(LE 3, weak recommendation)*.

Timing of re-TURBT is also important. A multicenter, retrospective study was performed on 242 patients with high-risk NMIBC and treated with induction and at least one year of maintenance BCG.[183] With a followup of 29.4 months, multivariable analysis showed that a re-TURBT beyond 42 days was an adverse independent predictor for both recurrence (OR 3.60, p=0.001) and progression (OR 2.14, p=0.003).[183] Another retrospective analysis on 491 patients with high-risk NMIBC treated with BCG therapy found no recurrence or progression benefit for patients re-staged beyond eight weeks and suggested the optimal window for re-TURBT would be from 2–6 weeks.[184] Therefore, a re-staging TURBT should be performed within six weeks of the first resection *(LE 3, weak recommendation)*.

The presence of benign muscularis propria confirmed in the first TURBT has been identified as the most significant predictor of having no tumor (pT0) at re-staging TURBT (OR 3.05, p=0.03) *(LE 3)*.[185] More recent studies reinforced the indication of a re-TURBT when detrusor muscle is not reported at the first resection and questioned the role of a repeat TURBT in patients with single and small T1 or HG Ta disease with benign muscularis propria at first resection.[186-189] For T1 tumors, Cumberbatch et al showed that when the detrusor muscle was absent or not reported in the first resection, a re-staging TURBT resulted in upstaging to MIBC in up to 45% of the cases.[179] Although the absence of muscularis propria in the first TURBT specimen is a clear indication for a re-staging TURBT in T1 tumors, a similar benefit for Ta tumors is less clear. Therefore, in select cases of HG Ta (e.g., multiple and/or ≥3 cm tumors), a re-staging TURBT might be considered (*LE 3, weak recommendation)*.[190,191]

5.3. Random bladder biopsies

– **Patients presenting with a positive urine cytology but normal-appearing bladder at WLC and normal upper urinary tract imaging are at a higher risk of harboring occult CIS and should undergo random bladder biopsies (or use of BLC with directed biopsies)** *(LE 2, strong recommendation)*.

A secondary analysis of two EORTC trials including low-risk (EORTC 30863) vs. intermediate- and high-risk (EORCTC 30911) patients showed little benefit of routine random bladder biopsies in detecting CIS *(LE 2)*.[192] In this study, 90% of patients had negative random biopsies, although concurrent CIS was found in 1.5% vs. 3.5% of patients with low- vs. intermediate/high-risk NMIBC, respectively.[192] In another study by Hara et al including 173 patients, up to 59% of high-risk patients with normal-appearing cystoscopy had confirmed CIS in biopsy specimen and a significant association between a positive urine cytology and detection of CIS through random bladder biopsies was demonstrated.[193] Urine cytology had a sensitivity of 87.1% and specificity of 63% for detecting CIS in a recent meta-analysis by Subiella et al *(LE 2)*, meaning that 37% of patients with negative urine cytology samples might, in fact, harbor CIS.[96] In this same study, the overall detection rate of CIS through random bladder biopsies of normal-appearing mucosa was 17.4%, which increased to 57.3% when urine cytology was positive.[96] In a setting of normal cystoscopy and normal upper urinary tract imaging, random bladder biopsies should be performed if urine cytology is positive *(LE 2, strong recommendation)*. In this scenario, enhanced imaging methods may play a role in identifying targets for directed biopsy when cystoscopy is normal, also aiming for higher detection of CIS in those cases *(LE 3, strong recommendation)*.[158]

5.4. Prostatic urethral involvement (PUI)

– **Biopsies or transurethral resection of the prostatic urethra should be included with random bladder biopsies in the presence of a positive urine cytology but normal-appearing bladder at WLC and normal upper urinary tract imaging** *(LE 3, strong recommendation)*.
– **Prostatic urethral biopsies (or a transurethral resection) can also be considered in the presence of extensive**

bladder CIS or tumor at the bladder neck or trigone *(LE 3, weak recommendation)*.

- **Patients with PUI with CIS restricted to the urethral mucosa can be managed conservatively with transurethral resection of prostate (TURP) plus intravesical BCG** *(LE 3, weak recommendation)*. **Repeat prostatic urethral biopsies after induction BCG should be considered** *(LE 3, weak recommendation)*. **RC can be discussed as an alternative option** *(LE 4, weak recommendation)*.
- **In patients with HG T1 or CIS extending into the prostatic ducts, RC should be considered** *(LE 3, weak recommendation)*. **TURP followed by intravesical BCG is an alternative option. In this instance, close followup with repeat prostatic urethral biopsies after induction BCG should be considered** *(LE 3, weak recommendation)*.
- **In patients with prostatic stromal invasion, neoadjuvant cisplatin-based chemotherapy followed by RC is recommended** *(LE 3, strong recommendation;* **refer to CUA MIBC guideline available at** *cua.org* and *cuaj.ca)*.

Incidence of primary prostatic urethral UC is rare (1–4%), but contiguous PUI by bladder cancer can range from 12–48% according to retrospective series *(LE 3)*.[194,195] The prostatic urethra is less exposed to intravesical therapy, allowing CIS and high-risk papillary disease to advance through the prostatic ducts into the prostatic stroma.[196] A clear association between CIS detected in the prostatic urethra and worse oncological outcomes has been demonstrated.[197,198] Palou et al retrospectively analyzed 146 NMIBC patients with HG T1 tumors treated with TURBT followed by BCG and showed that CIS was present in the prostatic urethra of 11.7% of the cases and associated with worse rates of recurrence (HR 2.53, p=0.0003), progression (HR 3.59, p=0.001), and disease-specific mortality (HR 3.53, p=0.004).[199]

A retrospective study by Mungan et al including 340 patients treated with TURBT for primary NMIBC showed that the only significant predictive factor for PUI was the presence of multiple tumors in multivariable analysis *(LE 3)*.[200] Similarly, a study by Brant et al evaluated 177 patients with NMIBC who underwent RC, and had no upstaging in final pathology.[201] It revealed that PUI was significantly associated with worse RFS (p=0.01), DSS (p=0.03), and overall survival (OS) (p<0.01) on log-rank test. In a logistic regression model, significant predictors for having PUI in final RC specimen were previous intravesical therapy (OR 2.90, p<0.02), positive urethral/ureteral margins (OR 4.01, p=0.01), and multifocal tumors (OR 7.56, p<0.001) *(LE 3)*, while PUI was an independent predictor of overall mortality in multivariable analysis (HR 2.08, p<0.01).[201]

The depth of invasion of PUI is associated with oncological outcomes. Solsona et al evaluated 96 patients with PUI and classified tumors in three groups: limited to the prostatic urethral mucosa (group 1), prostatic ductal invasion (group 2), and prostatic stromal invasion (group 3).[202] They found a statistically significant better prognosis for groups 1 and 2 when compared to group 3 (p<0.001) *(LE 3)*. Multivariable analysis showed that stromal (but not mucosal or ductal) invasion, bladder CIS, and pan-urothelial involvement were independent predictors for worse OS.[202] The prognostic association of the depth of PUI was later reinforced by other series, where stromal involvement was associated with five-year OS of 40–50% vs. 100% for PUI restricted to the urethral mucosa.[195]

Prostatic urethral biopsies can be considered in patients with tumors located at the bladder neck and trigone, those with associated bladder CIS, and whenever bladder urine cytology is positive in the setting of a negative cystoscopy and normal upper tract imaging *(LE 3, weak recommendation)*.[203]. Moreover, for highest accuracy, any suspicious areas in the prostatic urethra should be biopsied along with 5 and 7 o'clock (precollicular area) at the level of the verumontanum, where the highest concentration of prostatic ducts is located *(LE 3, weak recommendation)*.[203]
Patients with PUI limited to the mucosa have better prognosis and can be managed with TURP, followed by intravesical BCG.[199,204] TURP aims for accurate staging, surgical resection of the disease, and bladder neck opening, which allows for better exposure of the prostatic urethra to BCG instillations.[205] On the other hand, RC should be considered in patients with ductal invasion *(LE 3, weak recommendation)*, although bladder preservation with TURP followed by BCG has been described in small, retrospective series.[206] If managed conservatively, PUI with associated CIS needs close followup with early assessment after BCG induction therapy, including early prostatic urethral re-biopsy, due to higher risk of local recurrences and distant metastasis *(LE 3, weak recommendation)*.[207] Finally, invasion of the prostatic stroma requires aggressive treatment with neoadjuvant chemotherapy followed by RC ± urethrectomy (refer to CUA MIBC guideline; available at *cua.org* and *cuaj.ca*).[204]

6. Intravesical therapy

First-line adjuvant intravesical therapy options consist mainly of chemotherapy and immunotherapy (including BCG). It is administered with therapeutic (treatment of CIS or residual non-visible tumor) and prophylactic (prevention of recurrence and progression of disease) intents.

6.1. Intravesical chemotherapy

6.1.1. Single instillation of chemotherapy (SIC) post-TURBT

- **SIC (with MMC, epirubicin, doxorubicin, pirarubicin, or gemcitabine) should be offered to all patients with presumed low-risk NMIBC at TURBT and should be administered within 24 hours after endoscopic resection** (*LE 1, strong recommendation*).

- **SIC is recommended for intermediate-risk NMIBC and for patients with ≤1 recurrence/year and EORTC recurrence score <5** *(LE 1, strong recommendation)*. **SIC should be discussed even when further adjuvant intravesical chemotherapy is planned** *(LE 2, weak recommendation)*.
- **The benefit of SIC in patients with high-risk NMIBC is unclear when BCG is planned as adjuvant treatment** *(LE 3)*.
- **SIC should not be administered after extensive resection or when bladder perforation is suspected** *(LE 3, strong recommendation)*.

Injury to the bladder wall and fulguration during TURBT can facilitate tumor cell re-implantation. When TURBT is performed alone without SIC, persistent NMIBC at the first three-month cystoscopy can be as high as 21%.[208] SIC was initially proposed with the intent of reducing the number of floating malignant cells in the bladder after a TURBT, preventing cancer cell re-implantation and reducing early recurrence rates after resection. In addition, this approach might have an ablative effect on small occult tumors.[209]

Several RCTs have identified a role of SIC after TURBT in reducing NMIBC recurrence. At least five RCTs performed from 1984–2011 showed a relative risk reduction in early recurrence rates of about 50% with a SIC with MMC.[210-214] Epirubicin was also associated with a decrease in recurrence risk of up to 50% in two years.[215-218] Additionally, comparable results were reported with thiothepa, doxorubicin, and pirarubicin.[219-221] More recently, gemcitabine was tested in an RCT by Messing et al.[222] In comparison with saline irrigation, SIC with gemcitabine given within three hours of TURBT was associated with a 12% absolute risk reduction in four-year recurrence rates, conferring a relative risk reduction of 34% (HR 0.66, 95% CI 0.48–0.90, p<0.01).[222] Intravesical gemcitabine was associated with minimal adverse effects and low cost.[222] The most used protocols for SIC are presented in Table 5.

For intermediate- and high-risk patients, however, results are controversial and heterogeneous regarding different drugs and protocols.[223] In 2004, Sylvester et al published a meta-analysis including seven RCTs and 1476 patients, mostly low-risk, where one immediate instillation of chemotherapy with either MMC, epirubicin, or pirarubicin after TURBT was associated with recurrence rate of 36.7%, vs. 48.4% for the TURBT alone, resulting in a 39% decrease in the odds of recurrence favoring SIC *(LE 1, strong recommendation)*. The benefit, however, was not statistically significant for patients with multiple tumors when adjusted for stage.[224] With similar results, two additional meta-analyses endorsed the use of immediate intravesical instillation after a TURBT, although highlighting concerns on heterogeneity and publication bias among trials.[225,226]

Table 5. Regimens of single instillation of chemotherapy

Chemotherapy	Dose	Protocol
Gemcitabine	2 g	Dilution in 100 ml of saline (60 min)
Mitomycin-C	40 mg	Dilution in 20–40 ml of water (60 min)
Doxorubicin	30 mg	Dilution in 30 ml of saline (60 min)
Epirubicin	50–80 mg	Dilution in 50 ml of saline (60 min)
Pirarubicin	30 mg	Dilution in 30 ml (60 min)

The most recent meta-analysis revisiting the topic in 2016 was published again by Sylvester et al, this time including individual data analysis of 2278 randomized patients.[227] A reduction of 35% in the relative risk of recurrence was reported favoring SIC (HR 0.65, p<0.001), with five-year recurrence of 44.8% vs. 58.8% for TURBT alone *(LE 1)*. This study showed no benefit of SIC for patients with more than one recurrence per year and those with an EORTC recurrence score ≥5. Interestingly, OS was significantly lower in patients meeting these higher-risk criteria when treated with SIC. The authors stated that this was possibly influenced by the number of high-risk patients with intrinsic poor performance status and prognosis who would ultimately not be the ideal candidates for SIC.[227]

A large, multicenter trial by Bosschieter et al randomized 2243 patients to receive intravesical instillation of MMC within the first 24 hours after TURBT (immediate) or two weeks after the procedure (delayed), followed in both scenarios by adjuvant instillations of chemotherapy for intermediate (nine doses) and high-risk (15 doses) patients.[228] Recurrence rates at three years were of 27% in the immediate vs. 36% in the delayed instillation group (p<0.001), reflecting a 34% reduction in the relative risk favoring immediate instillation *(LE 1)*. Despite possible selection bias and unique risk stratification (primary and solitary LG Ta and LG T1 tumors were classified as low-risk; multiple tumors were classified as high-risk), this was the first study suggesting lower rates of recurrence even in patients with intermediate- and high-risk disease who received further adjuvant intravesical instillations.[228] Moreover, lower recurrence rates were reported for intermediate- and high-risk patients when compared to low-risk, possibly as a result of further adjuvant intravesical chemotherapy administered in these patients.[228] Later, a re-analysis of patients included in this trial was conducted.[229] Using updated risk definition, the authors concluded that the benefit of SIC was significant regardless of risk group and suggested that SIC should not be withheld from intermediate- and high-risk patients.[229]

Discussion regarding conflicting data taken from the largest meta-analysis and the largest RCT conducted so far were published,[230-232] recommending SIC for all low-risk patients *(LE 1, strong recommendation)* and intermediate-risk patients regardless of whether further adjuvant intravesical chemotherapy is given *(LE 2, weak recommendation)*. Patients who fall in the high-risk category but meet the criteria of EORTC score for recurrence <5 may be considered for SIC (available

at http://www.eortc.be/tools/bladdercalculator/) *(LE 3, weak recommendation)*. The benefit of SIC for high-risk patients with multiple and large tumors who are planned for further BCG treatment is unclear, as patients with intermediate- and high-risk disease in the study by Bosschieter et al were treated with adjuvant chemotherapy rather than BCG *(LE 3)*.[228]

Although heterogeneous, studies on SIC seem to agree that the timing of postoperative instillation is important. The majority suggests that the benefit is more obvious when SIC is done within the first 24 hours after the TURBT, with a trend for lower recurrence rates when instillation is delivered even earlier *(LE 1, strong recommendation)*.[233,234] Non-randomized comparisons taken from the same study by Sylvester et al in 2016 suggested that an instillation within two hours after TURBT was more effective than beyond this timepoint, supporting the rationale that the earlier the SIC is given post-TURBT, the more effective a SIC will be in reducing re-implantation and early recurrences.[227] Recently, Onishi et al randomized 227 patients with low- and intermediate-risk NMIBC (mainly single LG Ta tumors <3 cm) to receive post-TURBT continuous instillation of normal saline (2000 mL/h in the first hour and then 500 mL/h for the following 15 hours) vs. a single instillation of MMC (30 mg in 30 mL of saline for one hour).[235] With a median followup of 37 months, RFS at three years was comparable (p=0.53) and no difference in PFS was observed between groups.[235] This was further explored by two meta-analyses that showed no significant difference in RFS for immediate bladder irrigation with saline vs. chemotherapy, although limited by a low number of studies.[236,237] Therefore, saline irrigation might be a consideration for patients with low- and intermediate-risk NMIBC post-TURBT when intravesical chemotherapy is contraindicated (e.g., extensive bladder resection) or unavailable *(LE 2, weak recommendation)*.

6.1.2. Adjuvant intravesical chemotherapy

- **Patients with intermediate-risk NMIBC should be considered for adjuvant induction intravesical chemotherapy** *(LE 1, strong recommendation)* **with subsequent monthly maintenance for up to one year** *(LE 3, weak recommendation)*, **or induction BCG with maintenance therapy (refer to section 6.2).**
- **Substratification of intermediate-risk patients with recurrent LG Ta NMIBC can be used to guide adjuvant treatment decisions** *(LE 3, weak recommendation)*. **For this purpose, four factors should be considered: number of tumors, size (≥3 cm), time to recurrence (<1 year), and frequency of recurrence (>1/year).**
  - **Patients with low-intermediate-risk NMIBC (0 factors) may be treated similarly to low-risk patients with SIC alone** *(LE 3, weak recommendation)*.
  - **Patients with high-intermediate-risk NMIBC (≥3 factors) may be treated as high-risk patients with induction and maintenance BCG** *(LE 3, weak recommendation)*.
- **Patients who develop recurrence during intravesical chemotherapy may be offered induction followed by maintenance BCG** *(LE 3, weak recommendation)*.

No further treatment is needed other than SIC following TURBT for low-risk patients, while intermediate- and high-risk patients should be considered for additional intravesical therapy. Several RCTs have shown lower rates of recurrence for patients undergoing induction intravesical chemotherapy, with or without maintenance therapy, using either MMC, epirubicin, doxorubicin, or pirarubicin, compared to TUR alone *(LE 1)*.[238-241]

Nevertheless, RCTs comparing induction only vs. induction intravesical chemotherapy followed by maintenance have shown conflicting results.[221,240,242-245] A meta-analysis by Huncharek included 3703 patients from 11 RCTs designed to study a benefit of adjuvant intravesical chemotherapy with followup duration of at least one year following TURBT.[246] This study suggested a reduction in recurrence rates of 31% at two years and 73% at three years for patients undergoing maintenance for a duration of one and two years, respectively.[246]

Conversely, two more recent meta-analyses revisited this topic and showed a more modest effect of maintenance intravesical chemotherapy in recurrence rates. The schedule and duration of intravesical chemotherapy was studied by Sylvester et al.[247] They highlighted significant heterogeneity across studies regarding different regimens, schedules, and duration of maintenance intravesical chemotherapy, concluding that no high-level recommendations were possible due to conflicting data.[247]

The most recent meta-analysis sought to evaluate the added benefit of maintenance intravesical chemotherapy (most commonly for 7–12 months; range 3–36 months) vs. induction intravesical chemotherapy alone for intermediate- and high-risk patients.[248] This study showed that epirubicin, doxorubicin, and MMC were the most commonly studied agents for maintenance intravesical chemotherapy but results among RCTs were inconsistent (out of 16 RCTs, only three showed significant benefit). The authors concluded that high heterogeneity resulted in insufficient statistical power to show a significant benefit of maintenance intravesical chemotherapy compared to induction alone regarding recurrence, progression, and survival rates.[248] Although further studies are needed to confirm the effect, ideal dose, schedule, and recommended duration of maintenance intravesical chemotherapy, the approach of a single monthly instillation for up to one year might be considered for intermediate- and high-risk patients in which an initial response to induction therapy was achieved after TURBT *(LE 3, weak recommendation)*.

When adjuvant intravesical chemotherapy was compared to BCG, data from RCTs and meta-analyses suggested a reduced risk of recurrence (but not progression) with BCG for intermediate- and high-risk patients *(LE 1)* at the cost of higher toxicity.[249-251] In an individual patient data meta-analysis of 2820 patients with primarily papillary disease, where 74% were intermediate-risk, Malmstrom et al found a 32% reduction in recurrence rates with BCG induction plus maintenance when compared to induction MMC, while BCG without maintenance was inferior to induction MMC *(LE 1)*.[252] Moreover, progression and long-term survival rates were available for 1880 patients but not statistically different across groups. A Cochrane review reached similar conclusions regarding likely reduced recurrence rates but greater serious adverse events with BCG vs. MMC, with no significant difference in progression risk, although this meta-analysis highlighted that the certainty of the evidence was low.[253]

Intermediate-risk disease accounts for 35% of all cases of NMIBC and represents a heterogeneous subgroup of patients. In 2010, a substratification of intermediate-risk patients with recurrent LG Ta disease was proposed by Lamm et al and further adopted by the International Bladder Cancer Group (IBCG).[254] Four factors were considered: number of tumors (multiplicity), tumor size (>3 cm), early recurrence (<1 year), and recurrence frequency (>1 per year). Patients with none of the factors are classified as having "low-intermediate-risk" disease and can be managed similarly to low-risk patients with SIC. Those with 1–2 factors are considered true "intermediate-risk" patients and should be managed with adjuvant intravesical chemotherapy (induction followed by monthly maintenance for one year) or BCG (induction followed by maintenance for one year with weekly instillations for three weeks at three, six, and 12 months). Finally, patients with ≥3 factors are classified as "high-intermediate-risk," which are at higher risk for recurrence and progression and should be treated as high-risk patients, with full BCG schedule (induction followed by maintenance for three years with weekly instillations for three weeks at three, six, 12, 18, 24, 30, and 36 months).[255] Similarly, intermediate-risk patients with primary, small, and solitary HG Ta should be treated as high-risk patients with induction BCG followed by maintenance therapy. In the previously cited meta-analysis by Malmstrom et al, BCG was effective even in patients receiving prior chemotherapy instillations.[252] Failure of adjuvant intravesical chemotherapy in intermediate-risk patients warrants consideration for BCG induction plus maintenance.

6.1.3. Device-assisted therapy

– **Although intravesical chemotherapy through device-assisted therapy has shown promising results in small RCTs, further studies are needed to validate its routine clinical use.**

Electromotive drug administration (EMDA) is capable of increasing the uptake of drugs by cancer cells through electric current. It was tested with MMC, either in monotherapy or in association with BCG, for high-risk NMIBC with promising results.[256-258] Di Stasi et al randomized 212 patients with BCG-naive T1 NMIBC to undergo six weeks BCG induction vs. nine weeks of sequential weekly BCG (weeks 1, 2, 4, 5, 7, 8) and EMDA-MMC (weeks 3, 6, and 9).[257] Monthly maintenance therapy was given in each arm to complete responders. With a median followup of 88 months, BCG + EMDA-MMC was associated with longer disease-free interval (69 vs. 21 months, p=0.0012), lower rates of progression (9.3% vs. 21.9%, p=0.005), and lower overall mortality (21.5% vs. 32.4%, p=0.045) compared to BCG alone. Side effects were acceptable in both treatment groups.[257] These results have not been validated in a second trial and, although approved by Health Canada, EMDA has not been widely adopted. Of note, EMDA catheters are no longer available in Canada.

Chemohyperthermia (CHT) with intravesical MMC has been studied for NMIBC. Radiofrequency elevates the temperature of the urothelium to 41–44ºC while intravesical chemotherapy is delivered. Colombo et al enrolled 75 patients with primary or recurrent NMIBC and compared MMC alone to CHT-MMC, with both induction and maintenance schedules. Recurrence rates at 24-month followup were lower for the CHT-MMC group when compared to MMC alone (17.1% vs. 57.5%, respectively, p=0.002).[259] The authors also published a long-term update with median followup of 91 months and a sustained effect was seen in recurrence rates (15% vs. 53%, p<0.001).[260] A multicenter, randomized trial by Arends et al with 190 intermediate- and high-risk NMIBC patients compared one-year CHT (induction + maintenance) vs. one-year BCG (induction + maintenance). In this study, intention-to-treat analysis was unable to prove any benefit of CHT-MMC over BCG on RFS at 24 months of followup (78.1% vs. 64.8%, respectively, p=0.08), highlighting the need for larger studies on device-assisted therapies in the first-line setting.[261] Although promising, especially in the context of chronic BCG shortage, CHT with MMC is not Health Canada-approved and needs validation in larger studies before being integrated into routine clinical practice for high-risk NMIBC.

6.2. BCG

– **In patients with high-risk NMIBC, BCG therapy with induction (weekly instillations for six weeks) followed by three-year maintenance (weekly instillations for three weeks at three, six, 12, 18, 24, 30, and 36 months) is the standard of care for reducing disease recurrence and progression rates** *(LE 1, strong recommendation)*.
– **When BCG is administered for intermediate-risk**

NMIBC, induction (weekly instillations for six weeks) followed by one-year maintenance (weekly instillations for three weeks at three, six, and 12 months) is recommended *(LE 1, strong recommendation)*.

6.2.1. Oncological outcomes and BCG

When administered intravesically, BCG was proven to reduce recurrence rates of bladder cancer for the first time in 1976 by Morales et al.[262] During the mid 1980s and 1990s, six controlled trials confirmed a significant decrease in recurrence rates of up to 67% when tumor resection was followed by adjuvant intravesical BCG in comparison with TURBT alone *(LE 1)*.[263-268] Meta-analyses including these studies confirmed a clear benefit of BCG in decreasing rates of recurrence compared to either TURBT alone or TURBT followed by different regimens of intravesical chemotherapy, with the greatest benefit reported among patients with high-risk NMIBC *(LE 1, strong recommendation)*.[249,251,269-272]

BCG has been the standard of care for decreasing not only recurrence, but also progression rates for high-risk disease. Initial studies by Herr and colleagues demonstrated a reduction in progression rates, from 35% to 28% in patients treated with TURBT alone vs. TURBT plus BCG induction, and also better OS outcomes (mortality rates of 32% vs. 14%) favoring BCG.[273] Later, Sylvester et al, in a meta-analysis including 4863 patients from 24 RCTs, showed that 9.8% of patients progressed in the BCG group vs. 13.8% in controls, reflecting a 27% relative reduction in the odds of progression (OR 0.73, p=0.001) in favor of BCG.[270] Notably, the benefit of BCG over other intravesical regimens was seen only in patients treated with BCG maintenance, rather than induction only *(LE 1)*.[270]

For concurrent or primary CIS, BCG is also the standard of care, as it eradicates CIS and reduces risk of both recurrence and progression. Subgroup analysis of an early RCT in 1983 on patients with CIS demonstrated complete disease remission in 65% of patients undergoing TURBT plus BCG (median 18 months) vs. 8% for TURBT alone (median three months).[274] The meta-analysis by Sylvester et al in 2002 highlighted that the benefit of BCG in progression was seen for both papillary tumors and CIS.[270] In 2005, another meta-analysis by the same group compared patients with CIS treated with intravesical chemotherapy (MMC, epirubicin, doxorubicin, or sequential MMC/doxorubicin) vs. BCG.[272] They found that treatment failure and progression rates were higher with intravesical chemotherapy regimens compared with BCG *(LE 1)*.[272]

6.2.2. BCG schedule, dose, and strains

Two-hour intravesical instillation of weekly induction therapy with BCG is usually administered over six weeks starting 2–4 weeks after TURBT to avoid systemic symptoms.[262] In the SWOG 8507 trial, 550 patients with recurrent NMIBC were randomized to BCG induction therapy with or without maintenance.[275] BCG maintenance was administered weekly over three weeks at three, six, 12, 18, 24, 30, and 36 months, counting from the beginning of induction therapy. Median RFS was 76.8 months for maintenance BCG vs. 35.7 months for induction BCG only (p<0.0001).[275] In this study, 278 patients had CIS. Although the study was not designed to assess BCG response for CIS patients, six-month overall response rates were significantly improved for those treated with maintenance therapy when compared to induction only (83.8% vs. 68.1%, respectively, p=0.004) *(LE 3)*.[275] EORTC 30911 was a multicenter RCT with 957 intermediate- and high-risk patients (Ta/T1 only), designed to compare BCG vs. epirubicin using induction and maintenance therapy in both arms. BCG was superior to epirubicin with respect to time to first recurrence (p<0.001), distant metastasis (p=0.046), OS (p=0.023), and DSS (p=0.026). Moreover, the relative benefit of BCG over epirubicin was at least as great in intermediate-risk as in high-risk patients.[275] The EORTC 30962 was a non-inferiority trial that sought to evaluate if duration and dose of BCG maintenance could be reduced to one year (vs. three years) and one-third dose (vs. full dose), respectively.[276] The study found that one-third dose plus one year maintenance was inferior to full-dose plus three years of maintenance BCG. However, there was no evidence that patients with intermediate-risk disease receiving full-dose derived any benefit with three-year compared to one-year maintenance BCG. In contrast, for high-risk patients receiving full-dose, three years of maintenance was superior to one year.[276] Meanwhile, an RCT by the CUETO group with 500 patients showed no difference in RFS, DFS, and OS among patients treated with full-dose BCG (81 mg) vs. one-third dose (27 mg).[277] However, for multifocal disease, the full-dose was associated with lower recurrence and progression rates. Nevertheless, the results of the CUETO trial should be analyzed with caution, as this study was considered statistically underpowered to prove equivalence or non-inferiority with clinically meaningful margins *(LE 2)*.[277]

The NIMBUS trial was a phase 3, randomized study with HG, recurrent, or primary NMIBC in the BCG-naive setting, including CIS patients.[278] The study compared standard induction plus maintenance (SWOG protocol) vs. reduced-frequency BCG therapy, in which induction was delivered with once-weekly BCG instillations at one, two, and six weeks, while maintenance was delivered with single instillations at weeks one and three of months three, six, and 12. This study was halted early as a result of an inferior efficacy of the reduced schedule. Median followup was 12 months and a relative risk reduction for recurrence of 60% was reported for the standard vs. reduced BCG schedule. Early separation of the Kaplan-Meier curves suggests that the reduced dose during induction therapy might have resulted in the significant impact on the efficacy of BCG for

high-risk patients rather than duration of maintenance.[278] Taking into account all data, for intermediate-risk patients treated with BCG, the recommended schedule is induction followed by one-year maintenance, while the three-year schedule is recommended for high-risk patients *(LE 1, strong recommendation)*.

Lastly, there are currently several strains of BCG available. Although differences in efficacy between strains have been proposed, a recent network meta-analysis was unable to confirm the association of different BCG strains with oncological outcomes.[279-284]

6.2.3. BCG toxicity

Although BCG is associated with more adverse effects than intravesical chemotherapy, serious toxicity occurs in only 5% of patients.[270,285] The most common local side effect of BCG instillation is the development of cystitis-like symptoms (urgency, dysuria, and increased urinary frequency) that can be present in up to 71% of patients.[253] In such instances, a urine culture should be performed to rule out urinary tract infection.[286] Hematuria can occur and delay BCG instillations. If hematuria persists, cystoscopy to rule out early tumor recurrence or tumor persistence may be warranted. Epididymitis and prostatitis are less frequent effects, occurring in 10% and 3% of cases, respectively.[287,288]

The most common systemic effect is fever, usually mild (<38.5ºC), lasting for less than 48 hours and accompanied by malaise and nausea. Persistent (>48 hours) and high fever (≥38.5ºC) should prompt a complete workup for infection. Allergic reactions develop in less than 1% of patients undergoing intravesical BCG and are treated with antituberculous drugs.[288] BCG sepsis requires hospitalization and active treatment *(LE 3, strong recommendation)*.[287] Adverse effects of BCG and their suggested management are described in Table 6.

One study has evaluated whether toxicity is reduced if prophylactic antibiotics (ofloxacin) are administered following intravesical BCG therapy.[289] Although adverse local and systemic effects were reduced from 83.3% to 61.1% (p=0.017) and from 75.9% to 54.4% (p=0.019), respectively, further studies are needed to validate the systematic use of antibiotics for this purpose.[289] Furthermore, a study comparing BCG vs. epirubicin was unable to show a role of prophylactic isoniazid in reducing side effects during BCG schedule.[290] Other maneuvers that may be used in patients who poorly tolerate BCG include decreasing BCG dose and/or intravesical dwell time.

6.2.4. BCG failure

Despite adequate BCG administration, up to 40% of high-risk patients will experience long-term recurrence within five years.[295] Three different categories of BCG failure have been defined in the past:

Table 6. BCG adverse events and recommendations

	Management
Local side effects	
Visible hematuria	Suspend BCG until resolved; laboratory workup (urine, blood, cultures); culture-directed antibiotics for urinary tract infection, if present; if hematuria persists, then perform cystoscopy to rule out bladder cancer recurrence
Epididymitis/ prostatitis	Suspend BCG; laboratory workup (urine, blood, cultures); add antibiotics (e.g., quinolones); consider INZ 300 mg/day or RFP 600 mg/day; consider infectious disease consultation; consider orchiectomy
Systemic side effects	
Malaise/ nausea (usually <48h)	Symptomatic treatment (e.g., antiemetics)
Allergic reactions	Mild and <48h: Antihistamines; NSAID – delay BCG until resolved. Persistent: Suspend BCG and consider discontinue treatment; consider INZ 300 mg/day or RFP 600 mg/day
Fever	<38.5ºC and/or <48h: Symptomatic treatment (e.g., antipyretics). ≥38.5 ºC for ≥48h: Suspend BCG until resolved/ consider dose reduction; laboratory workup (urine, blood, cultures); start with at least 2 empiric antimicrobials (e.g., quinolones, INZ 300 mg/day, RFP 600 mg/day); consider infectious disease consultation
BCG sepsis	Suspend BCG definitively; hospitalization; laboratory workup (urine, blood, cultures); start empiric antibiotics (e.g., high-dose quinolones); initiate INZ 300 mg/day + RFP 600 mg/day + ethambutol 1200 mg/day, for 6 months); high-dose corticosteroids if persistent (e.g., prednisolone 40 mg/day); infectious disease consult

*Modified from references 87, 291–294. BCG: bacillus Calmette-Guérin; INZ: isoniazide; LUTS: lower urinary tract symptoms; NSAID: non-steroidal anti-inflammatory drug; RFP: rifampicin; UTI: urinary tract infection.

1. BCG-refractory includes any HG T1 after one induction course at three-month followup or any HG Ta or CIS after induction plus one round of maintenance or a second course of induction BCG at six-month followup.[296] Patients with BCG refractory disease are at increased risk of progression and worse five-year survival rates when compared to patients with a complete response to induction therapy (LE 3).[297,298]
2. BCG-relapsing disease is defined based on achieving a complete response to BCG treatment at six months but then experiencing any HG recurrence during followup thereafter. The prognosis of these patients improves with duration of the disease-free period after the last dose of BCG, and their prognosis is better than patients

with BCG-refractory NMIBC. Therefore, patients with relapses before vs. beyond 12 months of completing BCG are classified as early vs. late relapse, respectively.

3. BCG-intolerant patients are those who experience recurrences after an inadequate course of BCG due to severe adverse effects. These patients have the best prognosis among BCG failure subcategories.

In order to standardize BCG failure and increase homogeneity among patients who are unlikely to respond to further intravesical BCG therapy, the term "BCG-unresponsive" NMIBC was developed by a consensus panel representing experts from the American Urological Association and the U.S. Food and Drug Administration (www.fda.gov/media/101468/download) (Table 7). Additionally, BCG-unresponsive disease implies patients being previously treated with adequate BCG schedule, defined as: at least 5–6 weekly instillations of an induction course followed by at least one maintenance cycle (consisting of at least two out of three weekly BCG instillations) or a second induction cycle (whereby at least two of six weekly instillations were received).

BCG-unresponsive bladder cancer includes patients meeting any one of the following criteria:

- HG T1 at the first evaluation following induction BCG (at three months).
- Recurrent HG Ta/T1 within six months of completion of adequate BCG treatment.
- Recurrent CIS (± Ta/T1) within 12 months of completing adequate BCG treatment.

Table 7. BCG failure classification

BCG failure stratification	Definition†
BCG-unresponsive	HG T1 at the first evaluation following induction BCG (3 months) Recurrent HG Ta/T1 within 6 months of adequate BCG treatment* Recurrent CIS within 12 months of last adequate BCG treatment*
BCG refractory	HG T1 at the first evaluation following induction BCG (3 months) Persistent/recurrent HG Ta/CIS following adequate BCG (6 months)*
BCG relapsing	HG recurrence after reaching a disease-free state within 6 months of receiving adequate BCG*
BCG intolerant	Disease recurrence/persistence after failure to receive adequate BCG therapy due to severe adverse effects

†By definition, low-grade recurrences during or after BCG are not considered BCG failure. *Adequate BCG — at least 5–6 weekly induction courses followed by at least one maintenance cycle (consisting of at least 2 out of 3 weekly BCG treatments) or a second induction cycle (whereby at least 2 of 6 weekly instillations were received). BCG: bacillus Calmete-Guérin; CIS: carcinoma in situ; HG: high-grade.

6.2.5. Management of BCG-unresponsive NMIBC

- **RC with pelvic lymph node dissection is the standard of care for BCG-unresponsive bladder cancer in surgically fit patients** *(LE 3, strong recommendation)*. **For patients with BCG-unresponsive CIS or HG Ta, a second-line intravesical therapy might be considered before RC** *(LE 3, weak recommendation)*.
- **Promising efficacy has been reported with intravenous pembrolizumab, intravesical oportuzumab monatox, nadofaragene firadenovec, and BCG plus N-803. These should be considered as potential options in patients with BCG-unresponsive CIS who are unfit for or refuse to undergo RC** *(LE 2, weak recommendation)*.
- **Alternative options, such as sequential intravesical gemcitabine/docetaxel (induction plus maintenance) may be considered for patients with BCG-unresponsive disease who are unfit for or refuse to undergo RC** *(LE 3, weak recommendation)*. **Additional alternatives may also include other combination intravesical therapy (e.g., sequential gemcitabine/MMC, BCG + interferon if available) or single-agent intravesical therapy (MMC, epirubicin, docetaxel, gemcitabine**) *(LE 3, weak recommendation)*.
- **Clinical trials may be considered for BCG-unresponsive patients who are unfit for or refuse to undergo RC.**

6.2.5.1. Radical cystectomy with pelvic lymphadenectomy

RC is the standard for patients with BCG-unresponsive NMIBC, and studies have shown that patients with recurrent disease benefit from early radical surgery *(LE 3, strong recommendation)*. A study by Herr et al evaluated a subset of 90 patients that underwent cystectomy after failing BCG therapy.[299] With a followup of 96 months, survival rates among patients undergoing RC within two years of the initial BCG therapy was of 92% vs. 56% for patients having surgery after two years of the initial BCG therapy. Early RC was also confirmed as an independent predictor of survival in multivariable analysis *(LE 3)*.[299] Patients considered surgically unfit and those unwilling to undergo RC should be counselled regarding higher risks of recurrence and progression associated with bladder-preserving alternatives. Whenever available, enrolment in a clinical trial should also be considered *(LE 3, weak recommendation)*.

Although patients with BCG-unresponsive HG T1 are recommended for RC *(LE 3, strong recommendation)*, those with BCG-unresponsive CIS or HG Ta may be offered an attempt for second-line bladder-sparing therapy prior to RC, as retrospective studies and recent single-arm trials suggest that such patients can be managed conservatively for up to one year after initial TURBT without an impact on cancer-specific mortality *(LE 3, weak recommendation)*.[300-302]

6.2.5.2. Single-agent adjuvant therapies – chemotherapy

a) Valrubicin

Steinberg et al enrolled 90 patients with recurrent CIS after multiple courses of intravesical therapy (including at least one BCG course), to receive weekly 800 mg of intravesical valrubicin for six weeks.[303] Median followup was 30 months and complete response at three and six months was seen in 19 (21%). Complete responders had a median time to recurrence of 18 months and recurrences were registered in 88% of patients at the end of this study's followup.[303] Similar initial responses for valrubicin were found in another study with CIS patients failing BCG, but the long-term disease-free rate was 10% and 4% at 12 and 24 months, respectively.[304] Although valrubicin was the only approved agent in the U.S. (until recently) for patients with BCG-refractory CIS, it has rarely been used in clinical practice).

Other

Laudano et al published on long-term outcomes of a phase 1 trial with induction docetaxel in 18 patients with recurrent NMIBC with no toxicities reported.[305] More recently, a study by Barlow et al included 54 patients with BCG-refractory NMIBC who received induction intravesical docetaxel (weekly dose for six weeks) followed by maintenance (monthly dose for up to nine months) if an initial complete response was achieved. With a median followup of 39 months, complete response was reported in 59% of patients. RFS rates at one and three years were 40% and 25%, respectively.[306] Similarly, intravesical gemcitabine was studied in a phase 1 trial with 18 patients with BCG-refractory disease also showing a favorable toxicity profile.[307] SWOG S0353 was a multicentric, phase 2 trial assessing intravesical gemcitabine in recurrent NMIBC (where 89% were high-risk) after at least two courses of BCG. Fifty-eight patients were enrolled and treated with induction (2000 mg of gemcitabine in six-weekly instillations) followed by monthly dose maintenance for up to 12 months. Complete response was seen in 47% of patients at the first three-month assessment. RFS at one and two years were of 28% and 21%, respectively *(LE 2)*.[308]

As other single-agent therapies also demonstrated only modest efficacy for BCG-unresponsive disease,[309,310] combinations of drugs have been evaluated to increase response rates (see below).

6.2.5.3. Device-assisted therapy

Device-assisted therapy was also tested in the setting of BCG-unresponsive disease. Racioppi et al recently published the results of a phase 2, single-arm study on 26 patients using EMDA-MMC (induction and maintenance) for high-risk NMIBC who failed BCG therapy.[311] Median followup was 36 months and HG disease-free rate was 61.5%.[311] In this study, a total of 10 patients underwent RC; of those, six (23.1%) had recurrent HG NMIBC and four (15.4%) had disease progression (three patients with pT2 and one with pT4a).[311] Moreover, a retrospective study by Juvet et al evaluated 26 patients who failed BCG (all, except four were classified as BCG-unresponsive) and were treated with sequential BCG and EMDA-MMC.[312] Complete response rates at six, 12, and 18 months were 62%, 44%, and 30%, respectively, while PFS at two years was of 48%. Importantly, 15% of patients died of bladder cancer after two years of followup, highlighting the potential risks of conservative management in this patient population.[312] Of note, EMDA catheters are no longer available in Canada.

A phase 3 RCT by Tan et al (HYMN) evaluated radiofrequency-induced CHT in patients with intermediate- or high-risk NMIBC recurrences who failed initial BCG therapy.[313] This trial was closed prematurely due to higher than expected CIS recurrence rates in patients treated with CHT and, overall, there was no benefit in 24-month DFS rates among the two groups: 35% vs. 41% for CHT vs. control (HR 1.33, 95% CI 0.84–2.10, p=0.23).[313] Therefore, until further studies evaluate the role of CHT in BCG-unresponsive disease, this option should only be offered to patients in the setting of a clinical trial.

6.2.5.4. Combination intravesical therapies

For BCG-unresponsive patients undergoing intravesical chemotherapy, sequential combination of drugs is favored instead of single-agent regimens *(LE 3, weak recommendation)*.[314,315]

a) Sequential gemcitabine + docetaxel

Due to worldwide shortages of MMC during the late 1990s, sequential instillation of gemcitabine followed by docetaxel after TURBT has been studied. Steinberg et al reported the first experience of this combination in 45 patients mainly with BCG-refractory and -relapsing disease.[315] Treatment was generally well-tolerated and side effects were mild, although five patients were unable to undergo the full induction course with six weekly instillations. Response was achieved in 66% of patients at first assessment, while one-year and two-year RFS rates were 54% and 34%, respectively *(LE 3)*.[315] Another study with 33 patients confirmed similar results with sequential gemcitabine-docetaxel; RFS at one and two years was 56% and 42%, respectively.[316]

More recently, a multicentric, retrospective study reported on 275 patients, of whom 38% had BCG-unresponsive disease.[317] Induction consisted of weekly instillation of gemcitabine (1000 mg in 50 ml of normal saline instilled for 60–90 minutes), followed by docetaxel (37.5 mg in 50 mL of normal saline for 60–120 minutes) for six weeks. The majority (78%) of patients with a complete response at three months were treated with monthly maintenance for 12–24 months. With a median followup of 22.9 months, RFS was

77%, 60%, and 46% at six, 12, and 24 months, respectively. HG-RFS for BCG-unresponsive patients was 50% at 24 months. In multivariable analysis, the only variable associated with increased RFS was the use of gemcitabine-docetaxel maintenance schedule. Overall, gemcitabine-docetaxel was well-tolerated and considered effective by the authors as a rescue therapy in patients previously treated with BCG for NMIBC *(LE 3, weak recommendation)*.[317]

b) Sequential gemcitabine + MMC

The sequential combination of intravesical gemcitabine and MMC was prospectively investigated but studies were limited by a low number of patients and single-arm design. In a phase 1 trial including 10 BCG-refractory/intolerant patients, toxicity was acceptable and six were recurrence-free after median followup of 14 months.[318] Later, Lightfoot et al reviewed 45 patients treated with induction of six-weekly gemcitabine (1000 mg in 50 mL of sterile water instilled for 90 minutes) followed by MMC (40 mg in 20 mL of sterile water for 90 min) for six weeks, followed by monthly maintenance for up to 12 months. Treatment was overall well-tolerated; a complete response was achieved in 68% of patients and RFS at one and two years was 48% and 38%, respectively.[314] A recent series on 27 patients have shown similar results, with 37% (10) of patients with no evidence of disease at a median followup of 22 months.[319]

c) BCG + interferon-alpha

Joudi et al studied the combination of BCG and interferon-alpha in a phase 2 trial. A total of 536 patients were

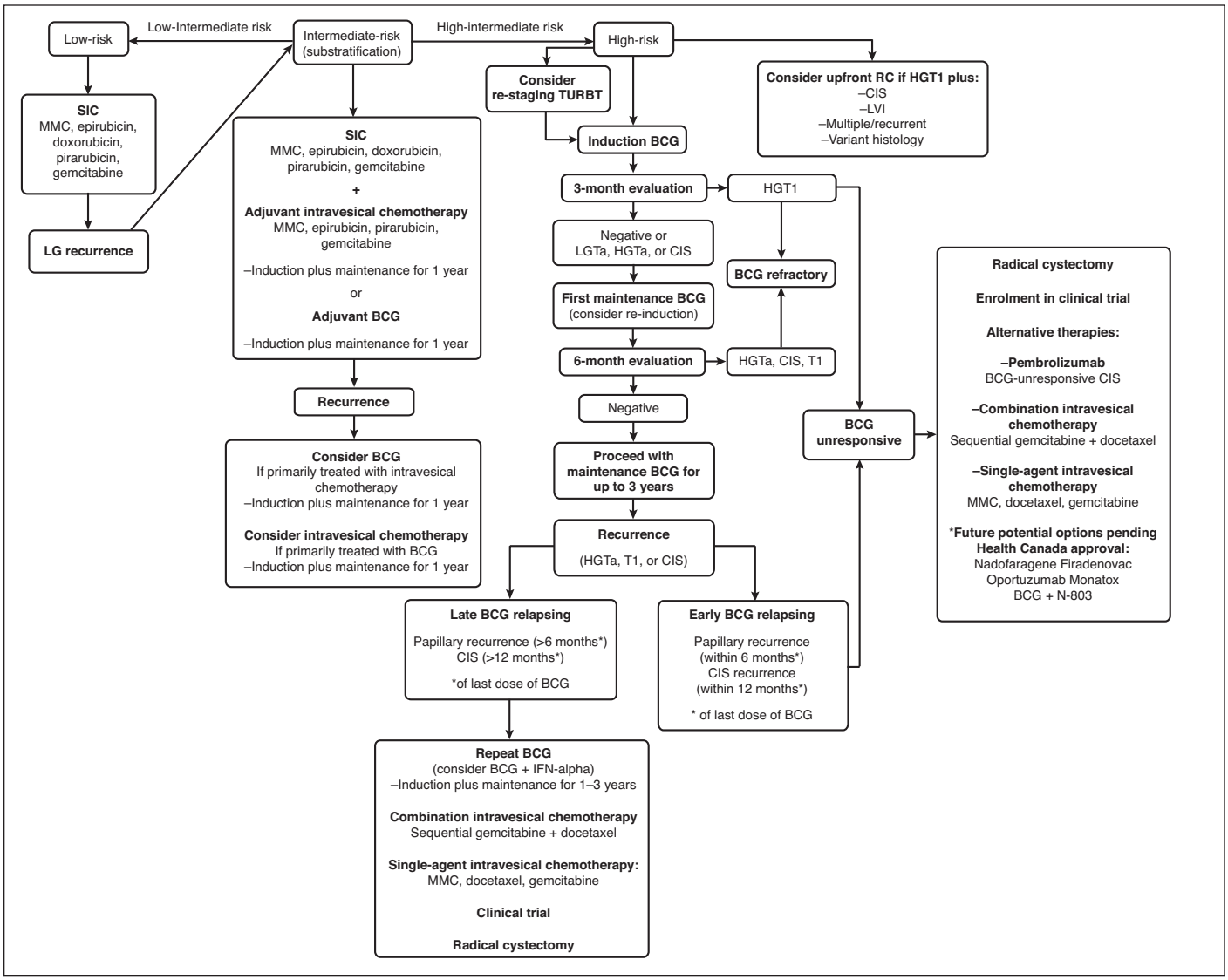

Fig. 1. Flow chart for the management of patients with non-muscle-invasive bladder cancer. *Modified from Chehroudi et al.[330] BCG: bacillus Calmette-Guérin; CIS: carcinoma in situ; GEM: gemcitabine; HG: high-grade; Ind: induction; LG: low-grade; LVI: lymphovascular invasion; MMC: mitomycin-C; RC: radical cystectomy; SIC: single instillation of chemotherapy; TURBT: transurethral resection of bladder tumor.

BCG-naive, while 467 were in the BCG-failure group (39% previously treated with two or more BCG courses). Recurrence-free rates at median followup of 24 months were 45% and 59% for the BCG-failure and BCG-naive subgroups, respectively.[320] Further analysis of this study suggested the combination of BCG + interferon-alpha might be a reasonable choice, especially for patients relapsing more than one year after initial BCG treatment, but seems to not be effective in patients with BCG-refractory disease.[321] Therefore, BCG + interferon-alpha is not recommended for BCG-refractory patients who are at higher risk of recurrence, while it might be considered in patients with BCG relapse if available *(LE 3, weak recommendation)*. Of note, interferon-alpha will no longer be available in 2021, as Merck has announced that it will soon discontinue its production.

6.3.5.5 Novel agents

a) Pembrolizumab

Pembrolizumab (Keytruda®) is a PD-1 checkpoint inhibitor approved for metastatic bladder cancer patients in the second-line or first-line when cisplatin-ineligible.[322] It was also recently approved for BCG-unresponsive CIS in 2020 in the U.S. (by the FDA) and in Canada by Health Canada, based on results from the Keynote-057 study.[301] In this single-arm study, 200 mg of pembrolizumab was administered intravenously every three weeks for 24 months or until recurrence, progression, or limiting toxicity. Out of 96 patients with BCG-unresponsive CIS, a complete response was achieved in 39 patients (40.6%, 95% CI 30.7–51.1%) at three months and median duration of response was 16.2 months. Median followup was 36.4 months. Out of 39 responders, 18 (46.2%) were recurrence-free at 12 months with no progression events; this translates to an overall 12-month complete response rate of 19% in the CIS cohort (LE 2). Treatment was well-tolerated and adverse effects were reported in 67 patients (65.7%), of which, 13 (12.7%) were grade 3 or 4.[301]

b) Nadofaragene firadenovec

rAd-INFa/Syn3 is a non-replicating adenovirus vector together with recombinant IFN-alpha2b, also known as nadofaragene firadenovec (Adstiladrin®). When given intravesically, the virus is transduced into bladder cells and the IFN-alpha2b gene is incorporated by the DNA. IFN-alpha2b protein, which has anti-tumor activity, is then produced. The first phase 2, multicenter, open-label study including 43 patients with HG BCG-refractory or relapsed disease showed a RFS rate of 35% at 12 months.[323] Recently, a phase 3 study was published by Boorjian et al and reported on 151 patients with BCG-unresponsive disease.[302] After one initial instillation of nadofaragene firadenovec, patients with no high-grade recurrence received additional doses every three months up to a maximum of four years. Of 103 patients with CIS (with or without HG Ta/T1), complete response at three and 12 months was reported in 53.4% and 24.3%, respectively. A durable response within responders was seen in 45.5% at 12 months. For papillary HG Ta/T1 disease with no CIS, 12-month complete response rate was 43.8%. Nadofaragene firadenovec was well-tolerated, with only 4% of patients experiencing drug-related grade 3 or 4 adverse effects.[302]

c) Oportuzumab monatox

Oportuzumab monatox (Vicineum®) is a specific antibody to epithelial cell adhesion molecule (EpCAM) fused to a *Pseudomonas* toxin that binds specifically to bladder cancer cells. A single-arm, phase 3 trial (VISTA) was conducted in patients with BCG-unresponsive NMIBC.[324] Intravesical treatment was given with an induction course (two times/week for six weeks then weekly for six weeks) followed by a maintenance regimen (once every weeks for up to two years). Complete response rates for patients with CIS were 40% and 17% at three and 12 months, respectively. For papillary HG Ta/T1 disease with no CIS, 12-month disease-free rate was 50%. Severe adverse effects were reported in three patients, but overall, the drug was well-tolerated.[324]

d) BCG plus N-803

N-803 is an IL-15 superagonist antibody cytokine fusion protein that can be co-administered intravesically with BCG to induce activation and proliferation of endogenous natural killer (NK) cells and CD8+ T-cells without inducing a T-reg response.[325] Interim analysis of the pivotal phase 2/3 QUILT 3.032 single-arm trial was recently presented in the 2021 ASCO Genitourinary Cancers Symposium. In that trial, 80 patients with BCG-unresponsive CIS ± Ta/T1 NMIBC received 50 mg BCG plus 400 μg of N-803 intravesically, with induction and maintenance courses. Re-induction was allowed for persistent disease. At a median followup of 10.7 months, 71% of patients achieved a complete response, with a 56% probability of duration of complete response >12 months, and an 87.5% probability of not undergoing RC. The most common treatment-related adverse events were dysuria, hematuria, and pollakiuria (mostly grade 1–2). Final peer-review publication and regulatory review were still pending at the time of writing of this guideline.

6.3.5.6. Future perspectives for BCG-unresponsive disease

Other novel agents are being developed and tested in the BCG-unresponsive setting. Ongoing trials include FGFR 3 inhibitors, gene therapy, viral gene therapy, IDO1 inhibitors, interleukin antagonists, and vaccines.[326] A summary of the management of NMIBC is presented in Fig. 1. Patients with HG NMIBC that recurs after some BCG therapy, but does not

fulfill the FDA-AUA criteria of BCG-unresponsive disease were recently termed "BCG-experienced" or "BCG-exposed." BCG in combination with immunotherapy is being evaluated in such patients with persistent or recurrent HG disease or CIS after one single BCG induction course without maintenance.[327]

a) Radiation therapy

In the NMIBC setting, evidence for radiation-based therapy is scarce. Weiss et al published their retrospective series on 141 patients with primary or recurrent high-risk NMIBC who underwent radiotherapy (median dose 55.8 Gy) and concurrent platinum-based chemotherapy (either cisplatin or carboplatin).[328] Complete response was achieved in 88% of patients. Median followup was 62 months and failure rates, defined as any recurrence or progression, at five and 10 years were 49% and 64%, respectively *(LE 3)*. Among survivors, 80% were able to preserve their bladders, with acceptable toxicity and no treatment-related deaths.[328] Currently, the RTOG-0926 study (NCT00981656) has completed accrual and awaits readout on the role of trimodal therapy for patients with recurrent papillary HG Ta/T1 who fail BCG. Notably, data extrapolated from studies with chemoradiation for MIBC suggest that patients with concomitant CIS experience worse outcomes.[329] As a result, chemoradiation for NMIBC should not be recommended for patients with BCG-unresponsive CIS.

6.2.6. Treatment adjustments only if BCG shortage

- **For patients with intermediate-risk NMIBC during BCG shortage, intravesical chemotherapy is recommended as the first-line option. If BCG is planned as a second-line therapy for this population, induction might be administered with reduced dose (one-half or on-third dose) and maintenance can be omitted** *(LE 3, weak recommendation)*.
- **For patients with high-risk NMIBC, full BCG schedule (induction followed by three-year maintenance) is recommended** *(LE 1, strong recommendation)*. **Only during BCG shortage, when full-dose is not possible due to limited supply, dose reduction to one-half or one-third might be considered, while maintenance can be reduced to one year** *(LE 3, weak recommendation)*.
- **When BCG is unavailable, single-agent chemotherapy (e.g., MMC, gemcitabine) or sequential combination of intravesical chemotherapy (e.g., gemcitabine/docetaxel) is recommended with induction followed by monthly maintenance for up to one year** *(LE 3, weak recommendation)*.

Between 2013 and 2016, global production of BCG decreased dramatically. A study conducted in France suggested that recurrence rates increased during that period when compared to previous years (46.9% vs. 16.2%, respectively, p<0.001) *(LE 3)*.[331] Costs also increase during a BCG shortage because alternative treatments are currently more expensive than BCG.[331,332] Therefore, this worldwide shortage remains a challenge. The shortage applies to different BCG strains and is mainly caused by slow production process, manufacturing issues, and limited supplies, negatively affecting the ideal treatment of NMIBC. Urologists should be aware that alternatives in this scenario are continuously being studied and discussed by the scientific community.

In June 2019, the medical advisory board of Bladder Cancer Canada, together with the Canadian Urological Association Guidelines Committee, released a document in response to continuous limited supply of the Tice strain of BCG in Canada (https://bladdercancercanada.org/wp-content/uploads/2019/06/Approach-to-Address-BCG-Shortage-updated-June-2019.pdf).

Strategies to overcome a BCG shortage are presented here and stratified in two scenarios: BCG-restricted and BCG-unavailable.

6.2.6.1. BCG-restricted supply

Although optimized BCG schedules were studied with the purpose of keeping production sustainable and available for a higher number of patients, in the recently published NIMBUS trial, a reduced schedule of BCG was inferior to the standard schedule in patients with high-risk NMIBC.[278] Moreover, the EORTC study by Oddens et al showed that, although for intermediate-risk the one-year BCG maintenance schedule was not inferior to a three-year schedule, high-risk patients benefited from the three-year full schedule.[276] However, no difference in progression rates were noted across the treatment arms. Hence, during a shortage period with reduced BCG supplies, high-risk patients may receive a reduced induction BCG dose of one-half or one-third, while maintenance therapy can also be reduced to one year instead of three years *(LE 3, weak recommendation)*.

For intermediate-risk patients, intravesical chemotherapy in the first-line setting would be the preferred choice. Moreover, if BCG is used in the second-line for intermediate-risk patients, a reduced dose can be administered during BCG shortage, and maintenance therapy omitted *(LE 3, weak recommendation)*.

6.2.6.2. BCG-unavailable

For high-risk patients, when BCG is not available, intravesical chemotherapy with MMC is an alternative, as its efficacy in patients with papillary disease may be similar to BCG with respect to progression and DSS according to some studies.[252,333] Other alternatives presented in this manuscript should also be considered, namely, hyperthermic or electromotive MMC, or single-agent chemotherapy (gemcitabine, doxorubicin, pirarubicin, epirubicin).[219,241,251,271,334] Some alternatives tested in the BCG-failure setting, such

as sequential gemcitabine-docetaxel or gemcitabine-MMC, might also be explored during a BCG shortage in high-risk NMIBC, although further studies are needed to confirm their efficacy in the first-line BCG-naive setting *(LE 3, weak recommendation)*.[315,316,319] Importantly, patients with high-risk disease and additional higher-risk features, such as CIS, LVI, PUI, or variant histology (micropapillary, plasmacytoid, and sarcomatoid), should be counselled for upfront RC *(LE 3, strong recommendation)* or enrollment in clinical trials *(weak recommendation)*.

7. Timely cystectomy

- **Upfront RC should be considered for patients with large-volume, diffuse, endoscopically unresectable NMIBC** *(LE 3, strong recommendation)*.
- **Upfront RC should be offered to patients with HG T1 disease with additional adverse tumor pathological features, including variant histology (e.g., micropapillary, plasmacytoid, sarcomatoid), extensive invasion of the lamina propria or invasion into or beyond the muscularis mucosa (T1b/c), presence of LVI, concomitant CIS in the bladder or prostatic urethra, multiple or large (≥3 cm) tumors, and persistent HG T1 upon re-staging TURBT** *(LE 3, strong recommendation)*.

Timely RC is an important consideration for patients with NMIBC considered at higher-risk of progression.[299,300] Although the terms "upfront" and "early" RC have been used indistinctively in the literature, upfront refers to surgery offered at the time of NMIBC diagnosis, while early RC refers to patients with persistent or recurrent disease after initial intravesical treatment, but who were not yet diagnosed with MIBC.[335] Upfront RC is associated with higher cancer-specific survival at 10 years when compared to early RC (79% vs. 65%, respectively) according to a retrospective study by Hautmann et al (LE 3).[336] The term "timely cystectomy" includes both scenarios when the attempt at bladder-sparing therapies is unsuccessful or inappropriate in high-risk patients.[335] Therefore, defining patients at the higher risk of progression is key not only to refine the indication for timely RC, but also to avoid overtreatment in this population, since perioperative complications, morbidity, mortality, and long-term quality of life are major concerns with RC.[337,33]Several risk factors discussed in this guideline are known to be associated with higher rates of recurrence and, more importantly, progression (refer to section 3). For HG recurrent NMIBC despite adequate BCG therapy, any further attempt at bladder preservation is not ideal and early RC should be offered whenever feasible *(strong recommendation)*. Furthermore, patients with de novo high-risk disease and additional high-risk features discussed in this guideline should also be offered timely RC *(LE 3, strong recommendation)*, particularly those with variant histology (micropapillary, plasmacytoid, and sarcomatoid) or the following risk factors: extensive or deep T1 invasion, multiple/large tumors, CIS (bladder and/or prostate), LVI, persistent T1 disease at re-staging TURBT, and pT1 recurrence *(LE 4)*.[339] Shared decision-making should take place with the patient, weighing the risk of cancer progression if treated without RC against the risk of overtreatment with RC.

A recent multicenter pilot feasibility study by Catto et al (BRAVO) evaluated the possibility of recruiting patients with high-risk NMIBC to undergo either upfront RC or BCG induction + maintenance.[340] Of 407 screened patients, 215 were eligible and 50 were ultimately randomized during a pre-set period of 18 months. For this reason, recruitment was stopped due to failure to accrue a minimum 60 patients in 18 months as initially planned. Despite advanced age (>70 years in 66% of patients) and smoking history (in 75% of patients), 80% of screened patients were deemed fit for RC and considered eligible. Quality of life was comparable among groups. Finally, this study showed that 25% of patients in the cystectomy arm were pT0 after final specimen pathology evaluation, possibly suggesting overtreatment. On the other hand, although NMIBC is considered a non-lethal disease by many urologists, up to 10% of patients in the RC group had MIBC in the final specimen of that study, highlighting the need for radical surgery in a minor subset of high-risk patients.[340]

8. Followup

- **The first surveillance cystoscopy is recommended for all patients at three months after TURBT** *(LE 2, strong recommendation)*.
- **After the three-month cystoscopy, a risk-based surveillance strategy should be used in patients with no evidence of recurrence:**
  - **Low-risk patients might be followed with cystoscopy at one year and then yearly for five years** *(LE 3, weak recommendation)*. **Urinary cytology is not necessary in the followup of low-risk patients** *(LE 4, weak recommendation)*.
  - **Intermediate-risk patients should be followed with cystoscopies and urine cytology every 3–6 months in the first two years, every 6–12 months in the third year, and annually thereafter** *(LE 3, weak recommendation)*.
  - **High-risk patients should be followed with cystoscopies and urine cytology every 3–4 months during the first two years, every six months during years three and four, and annually thereafter** *(LE 3, weak recommendation)*.
- **Upper tract imaging is recommended with random bladder/prostatic urethral biopsies (or use of BLC with**

directed biopsies) if positive urine cytology with normal cystoscopy is found during surveillance (*LE 3, weak recommendation*).

- **Upper tract imaging surveillance is recommended in the first year and every two years thereafter for high-risk patients** *(LE 3, weak recommendation)*.
- **Fulguration under local anesthesia might be considered for small (<5 mm) papillary tumors and negative cytology in patients with a prior history of PUNLMP or LG Ta tumors** *(LE 3, weak recommendation)*.

There is currently no high-level evidence on specific surveillance protocols for the different stages of NMIBC. Due to high rates of recurrences for low-risk and progression for high-risk patients, surveillance for NMIBC should be diligent and ideal followup consists of adapting strategies based on individual risk *(LE 3)*.[83,122] General recommendations are that all newly diagnosed patients treated with initial TURBT should undergo a first assessment at three months with voided urine cytology (cytology not required for patients with low-risk NMIBC) and cystoscopy. Cystoscopic and pathological findings at first three-month assessment post-TURBT are associated with oncological outcomes (recurrence and progression), particularly for high-risk patients.[83,84,298] Additionally, urine cytology is a useful tool during surveillance for high-risk patients, with sensitivity as high as 70–90%.[77-80] For pTa disease, urine cytology yields sensitivity of 47%, while for grades 1 and 2, rates of 27% and 54% were reported, respectively *(LE 3)*.[341]

Importantly, followup schedule should restart if recurrent disease is identified during surveillance. Studies with long-term followup have shown that there is a significant decrease in recurrence rates after five years, particularly for LG Ta tumors.[342] Mariappan et al reported significantly lower recurrence rates after five years (14.1%) compared to the first five years of surveillance (29.1%, p=0.009) in 115 patients with LG Ta tumors followed for a mean time period 19.4 years.[343] Therefore, surveillance can be stopped after five years for patients with low-risk NMIBC, if there is no evidence of recurrence, while long-term surveillance is recommended for patients with intermediate- and high-risk disease *(LE 3, weak recommendation)*. PUNLMP is associated with recurrence rates comparable to LG Ta tumors and progression is rare. Therefore, these patients should be followed up similarly to LG tumors *(LE 3, weak recommendation)*.[86]

A study by Millan-Rodriguez et al evaluated the incidence of UTUC after bladder cancer diagnosis in 1529 patients. Overall, incidence was 2.6% but varied according to risk stratification from 1.6% (low-risk) to 4.1% (high-risk).[344] Upper tract imaging is recommended in cases of gross hematuria or positive urine cytology with a normal-appearing bladder at cystoscopy *(LE 3, weak recommendation)*. Furthermore, population-based studies have suggested that patients with T1, multifocal, and/or HG tumors are at 2.5-fold higher risk of recurrence in the upper tract *(LE 3)*.[345] Additionally, the presence of CIS/T1 tumors invading the intramural portion of the ureteral orifices confers higher risk of UTUC (HR 6.85, p=0.005 and HR 7.25, p=0.001, respectively).[346] Therefore, high-risk NMIBC patients should undergo CT and intravenous urography every 1–2 years *(LE 3, weak recommendation)*, while high-level evidence is lacking regarding on how long upper tract surveillance should be continued.

Fulguration under local anesthesia is a suitable alternative to TURBT for patients with prior LG Ta tumors who have a small (<5 mm) recurrent papillary tumor found on surveillance cystoscopy. It is associated with similar recurrence rates when compared to TURBT but with lower rates of complications and at a lower cost.[347-349] This procedure might be considered in the surveillance of previously low-risk and select intermediate-risk patients (*LE 3, weak recommendation)*.[350,351]

More recently, active surveillance has been proposed for asymptomatic, few (≤3) and small (≤10 mm) papillary tumors with negative urine cytology and a known history of LG Ta tumors. Although considered potentially safe in initial studies, additional prospective studies are needed to identify ideal candidates and define surveillance protocols for this approach.[352]

Based on the current literature, a risk-stratified surveillance schedule is proposed (Table 8).

Competing interests: Dr. Bhindi has been an advisory board member for Bayer and Janssen; and has received speaker honoraria from Merck. Dr. Kulkarni has been an advisory board member for Astellas, Ferring, Janssen, Merck, Roche, and Theralase; has received grants and/or honoraria from Abbvie, Ferring, Sanofi, and TerSera; and has participated in clinical trials supported by Merck, Astra

Table 8. Risk-stratified schedule for NMIBC followup

Risk stratification	Surveillance schedule
Low-risk NMIBC	– Assessment with cystoscopy at 3 months – Cystoscopy at 1 year, then yearly until 5 years – Consider fulguration under local anesthesia for small (<5 mm), LG Ta tumors with negative cytology.
Intermediate-risk NMIBC	– Assessment with cystoscopy and urine cytology at 3 months – Cystoscopy + urine cytology every 3–6 months for 2 years, every 6–12 months until 4th year and yearly thereafter
High-risk patients	– Assessment with cystoscopy and urine cytology at 3 months – Cystoscopy + urine cytology every 3–4 months for 2 years, every 6 months until 5th year and yearly thereafter – Upper tract evaluation within 12 months, then every 2 years thereafter

Modified and adapted from Kassouf et al.[351] LG: low-grade; NMIBC: non-muscle-invasive bladder cancer.

Zeneca, Bristol Myers Squibb, Janssen, and Theralase. Dr. Siemens has participated in clinical trials supported by Astellas, Merck, and Pfizer. Dr. Aprikian has been an advisory board member for Abbvie, Astellas, and Bayer; and has received grants and/or honoraria from Abbvie, Astellas, Bayer, Sanofi, and TerSera. Dr. Hanna has received honoraria from Astellas and Bayer; and has participated in clinical trials supported by Merck. Dr. Izawa has received honoraria from Abbvie. Dr. McPherson has been an advisory board member for Abbvie and TerSera; has received travel funding from TerSera; and has participated in clinical trials supported by Bristol-Myers Squibb and Pfizer. Dr. Rendon has been an advisory board member for Abbvie, Amgen, Astellas, AstraZeneca, Bayer, Ferring, Janssen, Pfizer, Roche, and Sanofi; a speakers' bureau member for Abbvie, Amgen, Astellas, AstraZeneca, Bayer, Ferring, Janssen, Pfizer, Roche , and Sanofi; has received grants and/or honoraria from Abbvie, Astellas, Bayer, Ferring, Janssen, and Sanofi; holds investments in Myovant; and has participated in clinical trials supported by Abbvie, Astellas, Bayer, Bavarian Nordic, Ferring, Janssen, Myovant, and Sanofi. Dr. Shayegan has been an advisory board member for AbbVie, Astellas, Bayer, Ferring Janssen, Knight, Merck, Pfizer, Sanofi, and TerSera; and has participated in clinical trials supported by Ipsen, Janssen, Merck, Myovant, and Pfizer. Dr. So has been an advisory board member for Abbvie, Amgen, Astellas, Bayer, Janssen, Ferring, and TerSera; and has participated in clinical trials supported by Astellas, Ferring, and Janssen. Dr. Zlotta has been an advisory board member for AstraZeneca, Ferring, Janssen, Merck, Sanofi, and Verity. Dr. Black has been an advisory board member for AbbVie, Asieris, Astellas, AstraZeneca, Bayer, Biosyent, BMS, EMD-Serono, Ferring, Fergene, H3-Biomedicine, Janssen, Merck, Protara Therapeutics, Roche, Sanofi, and Urogen; a speakers' bureau member for AbbVie, Biosyent, Ferring, Janssen, Pfizer, and TerSera; has received payment from Bayer and Sanofi; has received grants and/or honoraria from iProgen; holds a patent marketed by Decipher Biosciences; and has participated in clinical trials supported by Astellas, AstraZeneca, BMS, Genentech, Janssen, MDx Health, Pacific Edge, and Therelase. Dr. Kassouf has been an advisory board member for EMD Serono and Pfizer; has received grants and/or honoraria from Abbvie, Astellas, BMS, Ferring, Janssen, Merck, Roche, and Sesen Bio; and has participated in clinical trials supported by Astra Zeneca, BMS, Janssen, Pfizer, Roche, Sesen Bio, and Theralase

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