



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 – Abridged version

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### Introduction and objectives

Approximately 75% of all bladder tumors are diagnosed at early stages and classified as non-muscle-invasive bladder cancer (NMIBC), which corresponds to clinical tumor stages Tis (carcinoma in situ [CIS]), Ta, and T1 according to the eighth edition of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) classification.<sup>1</sup> For this updated version of the Canadian Urological Association (CUA) guideline on the management of NMIBC, a non-systematic literature review was performed in Medline and PubMed using keywords and MESH terms. Statements were assigned a level of evidence (LE) and recommendations were classified as strong vs. weak (Table 1).<sup>2</sup> Previously published sections of the 2015 version<sup>3</sup> were reorganized and updated.

A summary of the main statements and recommendations regarding the management of NMIBC are presented here. A review of the epidemiology and risk factors associated

with NMIBC, as well a detailed discussion on the current literature for the topics highlighted in this manuscript are available online ([cuaj.ca](http://cuaj.ca) or [cua.org/guidelines](http://cua.org/guidelines)).

### 1. 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.

The main risk factors for NMIBC recurrence and progression include pT stage (pTa vs. pT1), grade (high vs. low), presence of concurrent CIS, number of tumors (single vs. multiple), size (<3 cm vs. ≥3), and frequency of previous recurrences (≤1 per year vs. >1 per year).<sup>4-6</sup> The modified CUA risk stratification method is proposed here (Table 2). Although further validation is required, this classification can be easily implemented in daily practice. It stratifies patients individually into low-, intermediate- and high-risk NMIBC.



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

Risk group	Tumor characteristics
Low	1. PUNLMP 2. Primary, solitary, and small (<3 cm) LG Ta
Intermediate	<i>Patients without CIS who are not included in the other risk categories:</i> 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 <sup>§</sup> 2. Recurrent, or multiple, or ≥3 cm HG Ta 3. Presence of CIS (primary or concomitant) <sup>§</sup> 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)

<sup>†</sup>Modified from EORTC and CUETO stratification tools, Sylvester et al,<sup>8</sup> 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.

## 2. Transurethral resection of bladder tumor (TURBT)

- 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).
- 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.
- 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.
- In select cases of high-grade (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).
- Patients presenting with a positive urine cytology, but normal-appearing bladder at white light cystoscopy (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).
- 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 biopsy (or 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 prostatic urethra involvement (PUI) with CIS restricted to the urethral mucosa can be managed conservatively with transurethral resection of 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).
- 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 muscle-invasive bladder cancer guideline).

A high-quality TURBT is of utmost importance for diagnosis, staging, and further management of NMIBC (Table 3). Several clinical trials have evaluated enhanced imaging methods, such as BLC and NBI, with the intent of improving tumor detection rates at cystoscopy/TURBT and reducing disease recurrence.<sup>7,8</sup> BLC and NBI are potential useful tools in the initial management and surveillance of NMIBC. Despite a trend for BLC in decreasing progression rates and prolonging time to progression, current data is inconclusive, and impact on oncological outcomes other than recurrence with either BLC or NBI remains unclear.<sup>9</sup>

A re-staging TURBT within six weeks of the initial procedure aims for identification and resection of residual or previously missed lesions and the identification of occult muscle-invasive disease.<sup>10</sup> It results in upstaging rates of 0.4% (0–8%) and 8% (0–32%) of initial pTa vs. initial pT1 tumors, respectively, according to a recent systematic review.<sup>11</sup> In pTa patients, a re-staging TURBT is associated with lower rates of recurrence but not progression, while for pT1 patients, a re-staging TURBT resulted in lower rates of progression and overall mortality, with additional trend for lower cancer-specific mortality.<sup>11</sup>

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, however, is less clear.<sup>12,13</sup> Therefore, in select cases of HG Ta (e.g., multiple and/or  $\geq 3$  cm tumors), a re-staging TURBT might be considered (*LE 3, weak recommendation*).

The overall detection rate of CIS through random bladder biopsies of normal-appearing mucosa is 17.4% but

increases to 57.3% when urine cytology is positive.<sup>14</sup> 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*).<sup>15</sup>

Incidence of primary prostatic urethral urothelial carcinoma is rare (1–4%), but contiguous PUI by bladder cancer can range from 12–48% according to retrospective series (*LE 3*).<sup>16,17</sup> A clear association between CIS detected in the prostatic urethra and worse oncological outcomes has been demonstrated.<sup>18,19</sup> 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*).<sup>20</sup>

Moreover, the depth of invasion of PUI is associated with oncological outcomes.<sup>21</sup> Patients with PUI limited to the mucosa have better prognosis and can be managed with TURP, followed by intravesical BCG.<sup>22,23</sup> 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.<sup>24</sup> Finally, invasion of the prostatic stroma requires aggressive treatment with neoadjuvant chemotherapy followed by RC  $\pm$  urethrectomy (refer to muscle-invasive bladder cancer guideline).<sup>23</sup>

**Table 3. Stepwise checklist for high-quality TURBT**  
MIBC objective: Provide enough information for adequate risk stratification

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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.

### 3. 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.

#### 3.1. Single instillation of chemotherapy (SIC) post-TURBT

- **SIC (with mitomycin C [MMC], epirubicin, doxorubicin, pirarubicin, or gemcitabine) should be offered to all patients with presumed low-risk NMIBC at TURBT and administered within 24 hours after endoscopic resection (*LE 1, strong recommendation*).**
- **SIC is recommended for intermediate-risk NMIBC and patients with  $\leq 1$  recurrence/year and European Organisation 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*).**

- **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).**

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 and is recommended in patients with presumed low-risk NMIBC.<sup>25</sup>

In 2004, Sylvester et al published a meta-analysis including 1476 patients, mostly low-risk, where one immediate instillation of chemotherapy with either MMC, epirubicin, or pirarubicin after TURBT was associated with 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.<sup>26</sup> 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.<sup>27</sup> A reduction of 35% in the relative risk of recurrence was reported favoring SIC (hazard ratio [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  $\geq 5$ .<sup>27</sup>

A large, multicenter trial by Bosschietter 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).<sup>28</sup> Recurrence rates at three years were 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 (LG T1 tumors were classified as low-risk; multiple tumors 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.<sup>28</sup> Furthermore, in a re-analysis of this same trial 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.<sup>29</sup>

For intermediate- and high-risk patients, current data is conflicting regarding the benefit of SIC post-TURBT. Patients who fall into the high-risk category but meet the criteria of EORTC score for recurrence  $< 5$  (<http://www.eortc.be/tools/bladdercalculator/>) may be considered for SIC (*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 from the study by Bosschietter et al treated with adjuvant therapy received intravesical chemotherapy rather than BCG (*LE 3*).<sup>30-32</sup>

### 3.2. 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 3.3).**
- **Sub-stratification 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 ( $\geq 3$  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 ( $\geq 3$  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 tumor resection for low-risk patients, while intermediate- and high-risk patients should be considered for additional intravesical therapy. Several randomized controlled trials (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*).<sup>33-36</sup>

Although RCTs comparing induction only vs. induction intravesical chemotherapy followed by maintenance have shown conflicting results, this approach might be considered monthly for up to one year for intermediate- and high-risk patients in which an initial response to induction therapy was achieved after TURBT (*LE 3, weak recommendation*).<sup>34,35,37-42</sup>

In 2010, a sub-stratification of intermediate-risk patients with recurrent LG Ta disease was proposed considering four factors: number of tumors (multiplicity), tumor size ( $> 3$  cm), early recurrence ( $< 1$  year), and recurrence frequency ( $> 1$  per year).<sup>43</sup> As presented in Table 2, 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 one-year maintenance) or BCG (induction followed by that maintenance for one year with three weekly instillations at three, six, and 12 months). Finally, patients with  $\geq 3$  factors are the “high-intermediate-risk” group and should be treated as high-risk patients, with full BCG schedule (induction followed by maintenance for three years with three weekly instillations at three, six, 12, 18, 24, 30, and 36 months).<sup>44</sup> 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.

### 3.3. BCG

- **In patients with high-risk NMIBC, BCG therapy with weekly induction (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 for reducing disease recurrence and progression rates (LE 1, strong recommendation).**
- **When BCG is administered for intermediate-risk NMIBC, induction followed by one-year maintenance is recommended (LE 1, strong recommendation).**

#### 3.3.1. Oncological outcomes and BCG

BCG has been the standard of care for decreasing not only recurrence, but also progression rates for high-risk NMIBC (LE 1, strong recommendation).<sup>45-50</sup> 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 (odds ratio [OR] 0.73,  $p=0.001$ ) in favor of BCG.<sup>46</sup> Notably, the benefit of BCG over other intravesical regimens was seen only in patients treated with BCG maintenance, rather than induction only (LE 1).<sup>46</sup>

For concurrent or primary CIS, BCG is the standard of care, as it eradicates CIS and reduces risk of both recurrence and progression. 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.<sup>46</sup> In 2005, another meta-analysis compared patients with CIS treated with intravesical chemotherapy (MMC, epirubicin, doxorubicin, or sequential MMC/doxorubicin) vs. BCG.<sup>50</sup> They found that treatment failure and progression rates were higher with intravesical chemotherapy regimens compared with BCG (LE 1).<sup>50</sup>

Although BCG is associated with more adverse effects than intravesical chemotherapy, serious toxicity occurs in only 5% of patients.<sup>46,51</sup> 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.<sup>52</sup> The management of BCG-related adverse effects is presented in Table 4.

**Table 4. BCG adverse events and recommendations**

Management	
<b>Local side effects</b>	
Visible hematuria	Suspend BCG until resolved; laboratory workup (urine, blood, cultures); culture-directed antibiotics for UTI, if present; if hematuria is persistent, 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
<b>Systemic side effects</b>	
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 discontinuation; consider INZ 300 mg/day or RFP 600 mg/day
Fever	<38.5°C and/or <48h: Symptomatic treatment (e.g., antipyretics) $\geq 38.5$ °C for $\geq 48$ h: 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 73–77. BCG: bacillus Calmette-Guérin; INZ: isoniazide; NSAID: non-steroidal anti-inflammatory drug; RFP: rifampicin; UTI: urinary tract infection.

#### 3.3.2. BCG failure

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 US Food and Drug Administration (FDA) ([www.fda.gov/media/101468/download](http://www.fda.gov/media/101468/download)). Current BCG failure classification is presented in Table 5.

#### 3.3.3. 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 still be considered for BCG-unresponsive patients who are unfit for or refuse to undergo RC.

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*).<sup>53</sup> Patients considered surgically unfit and those unwilling to undergo RC should be counselled regarding higher risks of recurrence and progression associated with bladder preservation. Whenever available, enrolment in a clinical trial should also be considered (*LE 3, weak recommendation*).

**Table 5. BCG failure classification**

BCG failure stratification	Definition <sup>†</sup>
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

<sup>†</sup>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 Calmette-Guérin; CIS: carcinoma in situ; HG: high-grade.

Single-agent therapies demonstrated only modest efficacy for BCG-unresponsive disease.<sup>54–58</sup> Therefore, patients undergoing intravesical chemotherapy might be considered for sequential combination of drugs, such as gemcitabine followed by MMC or gemcitabine followed by docetaxel (*LE 3, weak recommendation*).<sup>59,60</sup> Novel agents, such as pembrolizumab, nadofaragene firadenovec, oportuzumab monatox, and BCG + N-803 were tested in patients with BCG-unresponsive CIS with promising results.<sup>61–64</sup> Complete response rates at three months reported in these trials ranged from 40.0–53.4% (71% at any time for BCG + N-803), with durable response rates at 12 years of 45.5–56.0%. A summary of the management of NMIBC is presented in Fig. 1.

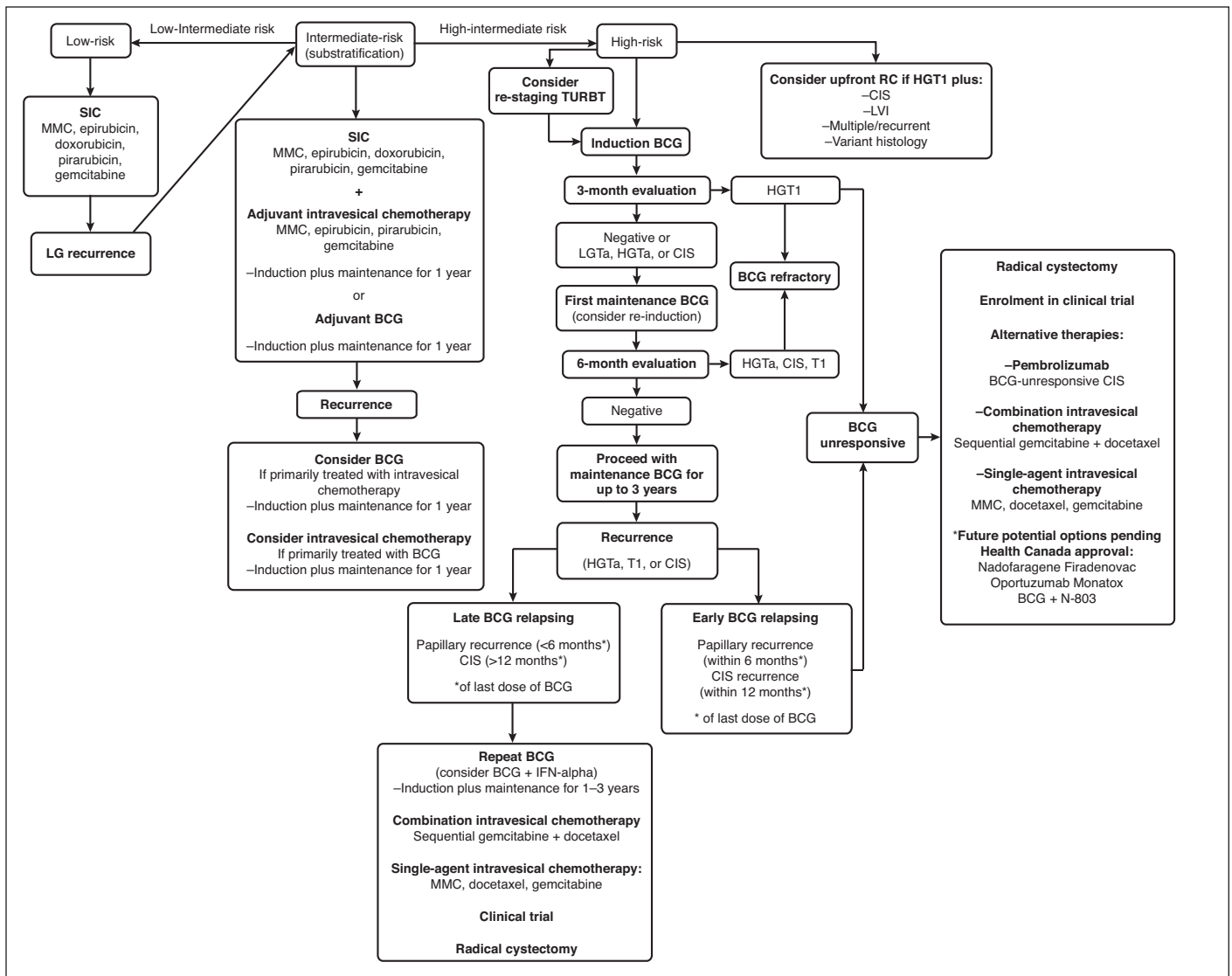
#### 3.3.4. Treatment adjustments only if BCG shortage

- 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, it might be administered with reduced dose (1/2 or 1/3 dose) and maintenance can be omitted (*LE 3, weak recommendation*).
- For patients with high-risk NMIBC, full BCG schedule is recommended (*LE 1, strong recommendation*). Only during BCG shortage, when full dose is not possible due to limited supply, dose reduction to 1/2 or 1/3 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*).

The worldwide BCG shortage remains a challenge and urologists should be aware that alternatives in this scenario are continuously being studied and discussed by the scientific community. Moreover, in June 2019, the medical advisory board of Bladder Cancer Canada, together with the CUA 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>).

## 4. 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: variant histology (e.g., micropapillary, plasmacytoid, sar-



**Fig. 1.** Flow chart. \*Modified from Chehroudi et al.<sup>79</sup> BCG: bacillus de 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.

comatoid), extensive invasion of the lamina propria or invasion into or beyond the muscularis mucosa (T1b/c), presence of lymphovascular invasion (LVI), concomitant CIS in the bladder or prostatic urethra, multiple and large ( $\geq 3$  cm) tumors, or 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.<sup>53,65</sup> 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 recommenda-

tion), 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, tumor found at initial three-month cystoscopy, and pT1 recurrence (LE 4).<sup>66</sup>

### 5. 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:

**Table 6. Risk-stratified schedule for NMIBC followup**

Risk stratification	Surveillance schedule
Low-risk NMIBC	<ul style="list-style-type: none"> <li>– Assessment with cystoscopy at 3 months</li> <li>– Cystoscopy at 1 year, then yearly until 5 years</li> <li>– Consider fulguration under local anesthesia for small (&lt;5 mm), LG Ta tumors with negative cytology</li> </ul>
Intermediate-risk NMIBC	<ul style="list-style-type: none"> <li>– Assessment with cystoscopy and urine cytology at 3 months</li> <li>– Cystoscopy + urine cytology every 3–6 months for 2 years, every 6–12 months until 4th year and yearly thereafter</li> </ul>
High-risk patients	<ul style="list-style-type: none"> <li>– Assessment with cystoscopy and urine cytology at 3 months</li> <li>– Cystoscopy + urine cytology every 3–4 months for 2 years, every 6 months until 5th year and yearly thereafter</li> <li>– Upper tract evaluation within 12 months, then every 2 years thereafter</li> </ul>

Modified and adapted from Kassouf et al.<sup>78</sup> LG: low-grade; NMIBC: non-muscle-invasive bladder cancer.

- **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 3 and 4, 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 papillary urothelial neoplasm of low malignant potential (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).<sup>4,5</sup> General recommendations are that all newly diagnosed patients treated with initial TURBT should undergo a first assessment at three months with voided urine cytology (except 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.<sup>4,67,68</sup> Additionally, urine cytology is a useful tool during surveillance for high-risk patients, with sensitivity as high as 70–90%.<sup>69-72</sup> A risk-stratified schedule for NMIBC followup is presented in Table 6.

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