CUA guidelines on the management of non-muscle invasive bladder cancer

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Introduction

According to the Canadian Cancer Society, bladder cancer is the fifth most common cancer overall, accounting for 7800 cases/year.[1] The most common type of histology is urothelial carcinoma (greater than 90%), followed by adenocarcinoma, squamous cell, and small cell carcinoma. Risk factors associated with bladder cancer include smoking, chronic inflammatory changes in the bladder (due to persistent bladder stones, recurrent urinary tract infections, chronic indwelling catheters or schistosomiasis), and chemotherapeutic exposure, such as cyclophosphamide.[2-7] Other risk factors include pelvic irradiation, occupational exposure to chemicals from the aromatic amine family, and chronic phenacetin use.[8-11] Lynch syndrome (hereditary nonpolyposis colon cancer) is associated with extracolonic cancers, including bladder cancer in 6% to 7% of cases.[12-14] Non-muscle invasive bladder cancer (NMIBC) accounts for about 75% to 80% of all incident bladder cancer cases;[15] Ta accounts for most NMIBC (60%), whereas T1 and Tis (carcinoma in situ [CIS]) account for 30% and 10%, respectively. The associated long-term survival and recurring nature of NMIBC create a major economic burden on healthcare systems.[16] As measured on the basis of cumulative per patient cost from diagnosis until death, bladder cancer is the most expensive human cancer to treat.[17] The management of NMIBC has changed over the last decade.

Methods

We update the previously published 2009 Canadian guidelines on the management of NMIBC, emphasizing intravesical therapy.[18] We conducted a comprehensive literature search using Medline and Pubmed. Pre-existing sections were updated after the literature review from January 2009 to September 2014. A search from January 1998 to September 2014 was completed for newly added sections in these guidelines. A keyword search and MeSH search, or a combination of both, was used to retrieve high-quality studies, emphasizing randomized controlled trials. In addition, the guidelines from the European Association of Urology, the American Urological Association, and the National Comprehensive Cancer Network were considered for comparison.[19-21] References have been assigned a level of evidence, and recommendations have been graded using the Oxford Centre for Evidence-based Medicine. Figure 1 summarizes the management in an algorithm.

Prognostic factors for recurrence and progression of NMIBC

- **Prognostic factors for recurrence and progression include stage, grade, presence of concomitant CIS, tumour size, prior recurrence rate, and number of tumours (Level of Evidence 2a)**
- **Other factors include variant histology, and presence of lymphovascular invasion (Level of Evidence 3)**

Stage and grade

The overall rate of recurrence for NMIBC is 60% to 70%, and the overall rate of progression to a higher stage or grade is

20% to 30%.[22,23] The two most important prognostic factors in NMIBC are stage and grade. Grade can either be reported using the 1973 World Health Organization (WHO) grading system (Grade 1, 2, and 3) or more commonly with the 2004 WHO grading system (papillary urothelial neoplasm of low malignant potential [PUNLMP], low grade, high grade). Ta tumours (which are usually low grade) rarely progress to a higher stage, but tend to recur frequently. On the other hand, T1 tumours (which are usually high grade) have a higher potential for progression to muscle invasion and metastasis. Studies have shown that the risk of progression to muscle invasion is strongly associated with tumour grade.[15,24] The risk of progression for Ta tumours is 2%, 11% and 45% for grades 1, 2, and 3, respectively. Controlling for stage, grade still correlates with progression and cancer-specific mortality. Many studies have demonstrated that grade is a

better prognostic indicator of progression and mortality than is tumour recurrence.[25-28]

However, recurrence is still a significant problem in the management of NMIBC. As many as 60% to 90% of NMIBC will recur if treated by transurethral resection (TUR) alone.[29] Using 6 clinico-pathologic parameters (grade, stage, tumour size, prior recurrence rate, presence of concomitant CIS and number of tumours), the probability of recurrence and progression of NMIBC can be calculated with European Organization for Research and Treatment of Cancer (EORTC) risk tables. These risk tables were developed and based on individual patient data from 2596 patients diagnosed with Ta/T1 tumours who were randomized in 7 EORTC trials (www.eortc.be/tools/bladdercalculator). In general, patients with NMIBC can be stratified into low-risk (solitary and low-grade Ta [TaLG] lesion and <3 cm), intermediate-risk (>3 cm, multiple, or multi-recurrent low-intermediate grade tumours), and high-risk (high-grade Ta, T1 tumours or CIS) disease. Patients with low-grade non-invasive disease are also classified and treated as high-risk NMIBC if they possess all of the following: large size (>3 cm), and multifocal and multi-recurrent low-grade Ta lesions.[24] It is important to note that the EORTC risk calculator likely overestimates the risk of tumour recurrence and disease progression, as very few of the patients in these 7 prospective trials received intravesical bacillus Calmette-Guerin (BCG).

Other factors

Retrospective studies demonstrate that the presence of lymphovascular invasion (LVI) is an independent factor for progression in patients with high-risk NMIBC. It has also been associated with worse survival in patients with organ-confined disease. However, the use of LVI as a prognostic variable on transurethral resection (TUR) specimen requires prospective validation.[30-32] The presence of concomitant CIS has been reported as a prognostic factor for recurrence and progression.[33-35] Furthermore, CIS of the prostatic urethra is strongly associated with recurrence and progression.[36] The presence of mixed histology, such as micropapillary variants, is under-reported by
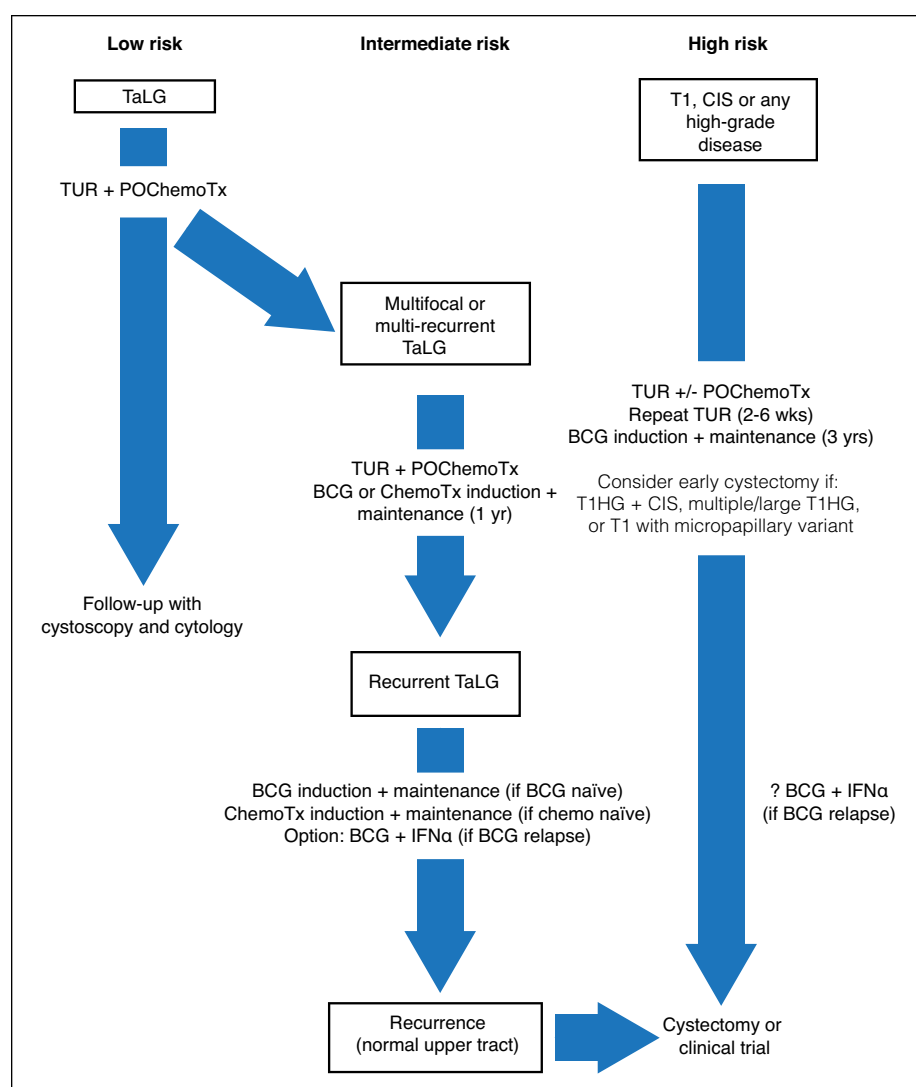
Fig. 1. Management algorithm for non-muscle invasive bladder cancer. POChemoTx: postoperative intravesical chemotherapy; TaLG: Ta low-grade disease; TUR: transurethral resection; BCG: bacillus Calmette-Guerin.

pathologists and associated with early progression to muscle invasive disease.[37-39]

TURBT

- **The quality of the initial transurethral resection of bladder tumour (TURBT) is of utmost importance. Complete resection of all visible tumours with adequate depth to include muscularis propria should be performed (Grade A recommendation).**

TURBT is the first and gold standard treatment option for NMIBC. The quality of the initial TURBT is of utmost importance. Complete resection of the tumour, including focal areas of suspected CIS and abnormal areas in the prostatic urethra and bladder neck, should be performed. Bimanual examination under anesthesia is a valuable staging component of the TURBT procedure (Level of Evidence 3). TURBT should include detrusor muscle (muscularis propria) in the specimen to rule out T2 disease and minimize the risk of under staging (Grade A recommendation).[40,41] It not only eradicates all visible tumours, it also provides tissue for pathological analysis and determination of histological type and grade together with detecting the presence, depth and type of invasion.[42]

Methods for enhanced visualization

- **Enhanced visualization methods (hexyl-aminolevulinate [HAL]- photodynamic diagnosis [PDD] or narrow band imaging [NBI]) may improve tumour detection and early recurrences (Level of Evidence 1b); whether the benefit persists in the context of immediate instillation of mitomycin C (MMC) post-TURBT requires further evaluation.**
- **The clinical impact of HAL-PDD or NBI on long-term recurrence or progression is unknown.**

Fluorescent cystoscopy

When using fluorescent cystoscopy, either 5-aminolevulenic acid (5-ALA) or HAL, a derivative of 5-ALA, is instilled in the bladder. Use of HAL is more practical as it requires instillation for only 1 hour before cystoscopy compared with 2 to 4 hours for 5-ALA. The 2 compounds have similar efficacy in PDD-guided transurethral resection (TUR).[43,44] Integration of fluorescent cystoscopy during TURBT improves tumour detection (and quality of resection) and reduces recurrence rates (Level of Evidence 1b).[45,46] The detection rate for CIS is about 25% to 30% higher under PDD guidance compared with white light cystoscopy (WLC) alone.[47,48] PDD also reduces the rate of residual tumour by 20% compared to WLC.[49]

Two randomized studies with long-term follow-up using PDD reported a lower risk of recurrence and longer recurrence-free survival compared to WLC (Level of Evidence 1b).[46,50] In a follow-up of 551 randomized patients, Grossman and colleagues found that recurrence-free survival was higher for patients who received HAL PDD (38% vs. 31.8%).[51] A recent meta-analysis by Burger and colleagues on 2212 patients from 9 studies showed that a single application of blue light cystoscopy with HAL, as an adjunct WLC, detects more tumours and reduces recurrences up to 1 year. This applies to most subgroups, including primary and recurrent Ta, primary T1, primary and recurrent CIS, and high- and intermediate-risk Ta patients. The analysis also showed that HAL maintains its superior detection rates and beneficial effect even in the subgroup of patients who have received intravesical BCG.[52] Ray and colleagues evaluated the potential of HAL to improve diagnosis when performed on patients treated with BCG at a median of 59 days (range: 29–226). The false positive rates were high (63%), but seem to be similar to standard WLC after BCG in this study.[53] However, a prospective randomized trial by O'Brien and colleagues compared HAL photodynamic-assisted TURBT plus 1 postoperative intravesical instillation of MMC to standard WLC plus 1 postoperative intravesical instillation of MMC; the authors found no significant difference in recurrence rates at 3 months and 1 year. In their discussion, the authors attributed the lack of significant difference in the 2 arms to MMC that could have successfully treated any small volume disease possibly missed by conventional WLC.[54]

In summary, although some studies have demonstrated an impact on short-term recurrences, the impact of PDD on long-term recurrences and progression is unknown. Most studies did not evaluate the impact of PDD in the context of immediate instillation of MMC post-TURBT. False positives with fluorescent cystoscopy can be increasingly induced by inflammation, recent TUR or recent intravesical instillations (especially if within 2 months). HAL is approved for use both in Europe and the United States, but currently does not have Health Canada approval.

Narrow band imaging (NBI)

NBI is an optical image enhancement technology that filters white light into wavelengths of 415 nm (blue) and 540 nm (green). The light penetrates the superficial bladder tissues and is strongly absorbed by hemoglobin, enhancing the contrast between normal urothelium and the highly vascular cancerous tumours. Higher cancer detection rates have been shown in the initial studies of NBI-guided resection.[55] In a randomized trial, Naselli and colleagues found that NBI reduces the recurrence risk of NMIBC by at least 10% at 1 year. The trial compared traditional white light TURBT versus NBI-TURBT in patients with NMIBC to assess the impact of NBI on recurrence risk. The 1-year recurrence was 32.9% (25 of 76 patients) in the NBI and 51.4% (37

of 72 patients) in the WLC group (odds ratio [OR] 0.62; $p = 0.0141$).[56]

A more recent trial by Herr evaluated patients already diagnosed with high-risk NMIBC (high grade pTa, T1 and CIS) by standard white light resection. In his randomized prospective trial, patients were assigned to a second look TURBT and follow-up either by WLC or NBI. Patients undergoing NBI-TURBT were found to have more CIS compared to WLC-TURBT suggesting increased detection by NBI cystoscopy. Moreover at first follow-up cystoscopy after BCG induction, patients in the NBI-TURBT group had 13% lower tumour recurrence. The recurrence rate at 2 years was 11% less in the NBI-TURBT group. Recurrence-free duration and progression-free survival was 22 months versus 19 months and 94% versus 87% for NBI and WLC, respectively. However, the number of patients who remained disease free at 2 years did not achieve the ambitious targeted 20% difference.[57] Two meta-analyses showed the superiority of NBI in detecting NMIBC compared to WLC, especially for CIS.[58,59] These findings require validation in large multi-institutional studies. NBI may improve tumour detection, but the prognostic impact on patients is poorly defined due to limited data.

Prostatic urethra involvement

- **When indicated, biopsy of prostatic urethra should include all suspicious areas, as well as the precollicular area (Level of Evidence 3).**
- **In cases of conservative management, a transurethral resection of the prostate (TURP) is recommended prior to BCG for more accurate staging and to potentially increase efficacy of BCG by opening the bladder neck to allow more contact of the prostatic urethra with BCG (Grade B recommendation). Consider re-biopsy of prostatic urethra post-BCG induction to detect recurrences early (Grade C recommendation).**
- **Radical cystectomy plus urethrectomy is recommended with any high-grade prostatic urethral recurrence following BCG (Grade C recommendation).**

The incidence of primary prostatic urethral urothelial carcinoma is low (1%–4%).[60] However, prostatic urethra involvement is more prevalent with high-risk NMIBC, tumours at the trigone or bladder neck, multifocal disease, and in the presence of bladder CIS.[61,62] Prostatic urethral biopsies are advised in the presence of extensive bladder CIS, presence of bladder neck tumour, positive cytology without bladder tumour, or suspicious areas in the prostatic urethra. For highest yield, prostatic urethral biopsies should include any suspicious area, as well as at 5 and 7 o'clock (precollicular area) especially at the level of the verumontanum, as this area contains the highest concentration of prostatic ducts (Level of Evidence 3).[63] The sample should contain both intact mucosa and deeper sections to provide the pathologist with sufficient amount of stroma.[64]

Treatment of prostatic urethra involvement depends on the degree or depth of involvement. The 5-year survival varies greatly among the different stages: up to 100% for those with urethral mucosal involvement; 50% with ductal/acinar involvement; and 40% with stromal invasion.[65,66]

An initial attempt of conservative management by TURP plus BCG is a reasonable option for isolated CIS of the prostatic urethra and for visible prostatic urethra tumour concomitant with NMIBC of the bladder. A TURP is recommended prior to BCG to obtain more accurate staging and to potentially increase the efficacy of BCG by opening the bladder neck to allow more contact of the prostatic urethra with BCG (Level of Evidence 3, Grade B recommendation).[67]

The management of CIS involving the prostatic ducts is more controversial. Despite good response to BCG, prostatic ductal involvement has potential for invasion, and if invasion occurs there is a high risk of metastasis.[68]

Re-biopsy of the prostatic urethra post-BCG induction is recommended to detect recurrences early (Level of Evidence 4, Grade C recommendation). Counselling towards a radical cystectomy plus urethrectomy should be considered with any high-grade prostatic urethral recurrence following BCG.[69] In patients diagnosed with prostatic stromal invasion, conservative therapy with BCG should not be attempted; extirpative surgery with radical cystectomy ± urethrectomy should be considered (Level of Evidence 2).[66,70,71]

Restaging TURBT

- **Restaging TUR should always be performed after the initial resection when the initial TUR is incomplete or a T1 tumour is detected in the absence of muscularis propria in the specimen (Grade A recommendation).**
- **Restaging TUR is also recommended for any high-grade or T1 tumours with benign muscularis propria in the specimen (Grade C recommendation).**

Restaging TUR provides more tissue for pathologic examination and better staging, as well as insight into the biology of the disease (Level of Evidence 2). In patients with T1HG, re-TUR upstaged tumours to T2 disease in 49% of patients if muscularis propria was not present in the initial specimen compared to 14% if the initial TURBT specimen contained benign muscularis propria.[72] Restaging TUR is also associated with better local control of tumour (Level of Evidence 3). Among patients who underwent repeat TURBT in 2 to 6 weeks after initial resection, 75% had residual tumours, and 44% had T1 or muscle invasive tumour. Furthermore, Schips and colleagues found that 17% of patients actually had histological evidence of cancer at their previous resection site despite a normal cystoscopic examination.[73] After a 5-year

follow-up in 124 patients, Grimm and colleagues found that 63% of those who underwent a repeat TURBT had tumour-free bladders compared with 40% of those who did not.[74] A more recent study from Memorial Sloan-Kettering Cancer Center confirmed the need for restaging TURBT, especially in high-risk NMIBC. In a retrospective analysis of 1021 patients with high-risk NMIBC, Sfakianos and colleagues found that viable tumour was found in 55% of patients with high-grade NMIBC when undergoing a restaging TURBT. A follow-up of these patients by TUR at 3 months showed that patients who had a restaging TURBT had significantly fewer recurrences compared with those with a single resection (9.6% vs. 44.3%). Restaging TUR was associated with less recurrence (62% vs. 77%) and prolonged progression-free survival (82% vs. 67%, $p < 0.001$) at 5-year follow-up.[75]

Divrik and colleagues prospectively evaluated 142 patients who were randomized into 2 groups. The first group received MMC after a restaging TURBT and the second group had MMC directly after an initial TURBT. All patients received 8 weekly MMC instillations. Patients with incomplete resection, CIS or muscle-invasive disease were excluded from study. The mean follow-up was 31.5 months. Restaging TUR significantly decreased recurrences regardless of tumour grade. The study also showed that intravesical chemotherapy does not compensate for inadequate resection. Restaging TUR was not associated with lower progression, although there was a trend favouring the repeat TURBT group (4% vs. 11.8%, $p = 0.097$).[76] The major flaw of this study, however, was due to a lack of intention-to-treat analysis.

Herr and colleagues demonstrated that a restaging TUR improved initial response to intravesical immunotherapy.[42] The results were also corroborated by another study by Guevara and colleagues that showed that patients who were tumour-free at repeat TUR have a better response to maintenance BCG in terms of tumour recurrence compared to patients with residual disease on repeat TUR (11.4% vs. 27.7%). During follow-up, tumour-free patients on repeat TUR were more likely to recur with low-grade lesions compared to patients who had residual disease on repeat TUR.[77]

We recommend that a second TUR always be performed 2 to 6 weeks after the initial resection when the initial TUR is incomplete or a T1 tumour is detected in the absence of muscularis propria in the specimen (Grade A recommendation). A second TUR is also recommended for any high-grade or T1 tumours with benign muscularis propria in the specimen (Grade C recommendation). Larger studies evaluating the role of re-TUR stratified by the extent of invasion of the initial tumour (T1a, T1b, T1c) are needed. Collectively, removing all residual tumours in a second therapeutic TURBT allows for more accurate staging, improves patient selection (and thus response) to BCG therapy, reduces the frequency of recurrence, and potentially delays tumour progression (Level of Evidence 2).[74]

Follow-up

- **Cystoscopy at 3 months following TURBT is recommended for all patients (Grade A recommendation).**
- **Generally, cystoscopy with urine cytology (or other urine marker) is recommended every 3 to 4 months for 2 years, then every 6 months for years 3 and 4, then yearly thereafter (Grade B recommendation). Patients with low-risk Ta tumours may undergo cystoscopy at 3 and 12 months, then annually (Level of Evidence 3).**
- **Upper tract imaging every 1 to 2 years is recommended for patients with high-risk NMIBC (Grade C recommendation).**

All patients are recommended to undergo a cystoscopy at 3 months following TURBT, as cystoscopic findings at 3 months have been shown to be a prognostic factor of recurrence and progression of disease (Grade A recommendation).[24,78-82] Prospective studies to better refine the surveillance schedule are sorely needed. Although there is no consensus for surveillance strategies, our general recommendation is to perform a follow-up cystoscopy with urine cytology (or other urine marker) every 3 to 4 months for 2 years, then every 6 months for years 3 and 4, then yearly thereafter (Grade B recommendation).

Patients with a primary, solitary, low-grade Ta tumour may have less frequent cystoscopic examination (3 and 12 months, then annually thereafter) (Level of Evidence 3). Mariappan and colleagues followed 115 low-risk patients over 20 years, and showed that the recurrence rate of low-risk NMIBC dropped significantly after 5 years of follow-up. In patients who did not recur after 5 years, 98.3% remained tumour-free after 20 years.[83] This study had many patients that were excluded from long-term follow-up and the data are contrary to other retrospective data suggesting that long-term follow-up is necessary in patients with low-grade NMIBC.[84] For patients with low-grade disease and no recurrence for 10 years, discontinuation of routine cystoscopic surveillance or replacement with urinary markers and/or ultrasonography may be considered (Level of Evidence 3). However, patients with high-risk NMIBC require lifelong cystoscopic surveillance. Any recurrence resets the clock in the follow-up schedule.

Upper tract surveillance

Although the sensitivity and specificity of computed tomography (CT) urography is high for detecting upper tract tumours, the probability of discovering a new upper tract lesion is low on routine imaging. In a retrospective study of 935 patients

with papillary T1 or Ta NMIBC, Sternberg and colleagues found that a total of 3074 routine CT urographies had to be done to detect 15 patients, showing an efficacy of only 0.49%. All the patients with tumours detected by CT scan had at least positive cytology or hydronephrosis and could have been potentially discovered by other means.[85-87] In light of this evidence, upper tract imaging should also be considered every 1 to 2 years for patients with high-risk NMIBC (Grade C recommendation). Recent evidence suggests that BCG failure in patients with non-muscle-invasive urothelial carcinoma of the bladder may be due to the failure to detect urothelial carcinoma of the upper urinary tract and urethra.[88]

Intravesical therapy

Intravesical therapy can be either chemotherapy or immunotherapy, and is either therapeutic (treatment of CIS or residual non-visible tumour), prophylactic (prevention of recurrence and progression of disease), or adjuvant in the immediate postoperative setting.

Chemotherapy

Single immediate postoperative instillation

- **Immediate postoperative instillation of a chemotherapeutic agent is recommended for all patients with NMIBC after TURBT (Grade B recommendation).**
- **The efficacy of the immediate postoperative instillation is optimal when administered within 6 hours from the time of TUR and significantly decreases if given beyond 24 hours (Level of Evidence 2).**
- **Patients with suspected bladder perforation or deep/extensive resection should not receive an immediate instillation (Grade C recommendation).**
- **For patients in whom treatment with BCG is planned, the benefit of an immediate postoperative instillation of chemotherapy is less clear (Grade D recommendation).**

A high proportion of patients with NMIBC will develop recurrences with a significant number recurring 3 months following TURBT. Incomplete TUR or tumour cell implantation post-TUR is the postulated mechanisms for the high proportion of these recurrences at 3 months. As such, several studies have evaluated the role of a single postoperative intravesical instillation of chemotherapy. The commonly used intravesical chemotherapeutic agents are doxorubicin, epirubicin and MMC.

Sylvester and colleagues performed a meta-analysis of 7 randomized trials (n = 1476) on the outcome of TUR alone versus TUR plus one immediate postoperative instillation of intravesical chemotherapy.[89] Over a median follow-up of 3.4 years, patients who received one immediate instilla-

tion had a recurrence rate of 37% compared with 48% for patients who had TUR alone. The benefit was more pronounced for those with single, low-grade papillary tumours compared with patients with multiple tumours. A more recent meta-analysis confirmed that intravesical chemotherapy prolonged recurrence-free interval by 38% (hazard ratio 0.62; 95% confidence interval [CI] 0.50–0.77; $p < 0.001$) and decreased early recurrences by 12% (absolute risk reduction 0.12; 95% CI, -0.18--0.06; $p < 0.001$). However, there was a high risk of bias in 12 out of 13 randomized control trials and thus the quality of evidence was low for recurrence-free interval and early recurrence.[90] Tumour recurrences are often small, non-invasive, low-grade papillary tumours that can often be managed by office fulguration.[91] Therefore, the potential risks of a single postoperative dose should be weighed against the cost and benefit of reducing recurrences of these small, low-grade tumours.[92]

The efficacy of the immediate postoperative instillation is optimal when administered within 6 hours from the time of TUR and significantly decreases if given beyond 24 hours (Level of Evidence 2).[93] Immediate postoperative instillation of the chemotherapeutic agent is recommended for all patients with NMIBC after TURBT (Grade B recommendation). Any trial concerns would be mitigated by further research on the impact of chemotherapy. For patients in whom treatment with BCG is planned, the benefit of an immediate postoperative instillation of chemotherapy is less clear (Grade D recommendation). Overall, long-term recurrence reduction is similar between the different chemotherapeutic agents (about 15%). The most commonly used intravesical chemotherapeutic agents in Canada are MMC and epirubicin. Patients with suspected bladder perforation or deep/extensive resection should not receive an immediate instillation, as severe complications have been reported in this setting.[94-96] Efficacy of MMC is dependent on the concentration at which the drug is administered. Recently, Au and colleagues published a phase III, randomized trial that showed superiority and prolonged median time to recurrence with an "optimized" MMC administration. This optimization included a period of pre-treatment dehydration (no fluids for 8 hours prior to treatment), urinary alkalinization, confirmation of complete bladder drainage prior to instillation, and a higher MMC concentration (40 mg in 20 mL).[97]

Multiple adjuvant instillations

- **Induction followed by 1-year maintenance of intravesical chemotherapy in intermediate-risk disease is recommended to prevent or delay recurrence (Grade B recommendation).**
- **An optimized MMC administration, which includes a period of pre-treatment dehydration, urinary alkalini-**

zation, and a higher MMC concentration, yields lower recurrences (Grade B recommendation).

In addition to the single postoperative instillation, patients with intermediate-risk low-grade Ta disease (TaLG) will benefit from induction chemotherapy followed by maintenance therapy. There are no published trials that directly compare an induction course of MMC to MMC induction with maintenance therapy; however a meta-analysis suggests that long-term maintenance therapy enhances the effectiveness of MMC induction in preventing recurrences.[21] Two meta-analyses assessing the impact of intravesical chemotherapy in primary and recurrent NMIBC demonstrated reduction in recurrences with the use of chemotherapy; the benefit appeared to be more significant when 1 year of maintenance therapy was used.[98] Although monthly instillations are commonly used, the optimal maintenance dose, schedule and duration remain unclear.

Importantly, none of the studies incorporated the "optimized" administration of MMC, which has been shown to significantly influence the drug's efficacy in a phase III trial. Furthermore, none of the trials directly compared MMC maintenance therapy to a single, immediate postoperative instillation. Patients who develop recurrent or multifocal low-grade Ta lesions (intermediate-risk disease) should be counselled to receive an induction followed by a 1 year maintenance course of intravesical chemotherapy to prevent or delay recurrence (Grade B recommendation). A meta-analysis of 22 randomized, prospective studies evaluating the role of intravesical chemotherapy for NMIBC did not show any benefit in reducing progression rates compared to TURBT alone (Level of Evidence 1).[99]

Immunotherapy

BCG

- **BCG induction with maintenance therapy is the standard of care for high-risk NMIBC (Grade A recommendation).**
- **Although we recommend intravesical chemotherapy, patients with intermediate-risk NMIBC may also be treated with intravesical induction course of BCG followed by maintenance as an alternative option (Grade B recommendation).**
- **Patients with intermediate-risk NMIBC who fail intravesical chemotherapy may benefit from BCG therapy (Grade B recommendation); similarly, patients with intermediate-risk NMIBC who fail BCG may benefit from intravesical chemotherapy.**

The US Food and Drug Administration approved BCG for the treatment of CIS of the bladder in 1990. Since then, BCG immunotherapy has emerged as the standard against which all new therapies are compared. Six controlled trials from 1985 to 1996 showed that BCG decreases recurrence rates from 67% to 29%.[100-105] Six meta-analyses compared BCG with intravesical chemotherapy; all of them except one[106] showed superiority of BCG over chemotherapy in terms of decreasing recurrence.[106-111] BCG following TUR is superior to TUR alone or TUR plus intravesical chemotherapy in decreasing recurrences, particularly in patients with high-risk disease (Level of Evidence 1).

BCG is the only intravesical agent that has been shown to delay tumour progression in randomized trials (Level of Evidence 1).[102,103] Herr and colleagues evaluated 86 patients with high-risk NMIBC and showed that the disease progression and mortality rates in patients treated with induction BCG decreased from 35% to 28% and 32% to 14%, respectively.[103] This apparent advantage is less significant over long-term follow-up at 15 years.[112] Among several series, BCG induced a complete response in patients with CIS in over 70% of cases.[113] In a meta-analysis involving 24 randomized trials of 4863 patients treated with TUR plus intravesical BCG, TUR alone or TUR plus treatment other than BCG, Sylvester and colleagues demonstrated a statistically significant decrease in progression rates (27% reduction) for patients who received BCG compared with the TURBT only group (9.8% vs. 13.8%, respectively).[107] A subset analysis demonstrated that the reduction in progression rate was significant only when BCG maintenance was administered. In 2005, Sylvester and colleagues reported their analysis on 12 different randomized trials that included patients with CIS. BCG was compared with different intravesical chemotherapy regimens. A complete response rate for BCG was 68% versus 48% for intravesical chemotherapy.[114] The overall disease-free rates over a median follow-up of 3.75 years were 51% and 27% for BCG and chemotherapy, respectively. Similarly, another meta-analysis of 9 randomized trials showed similar results.[111] Takenaka and colleagues found that the overall response rate to BCG in patients with primary, concomitant or secondary CIS was 86.6%, with a 5-year progression-free survival rate of 78.5%.[115] Most recurrence or progression events occur within the first 5 years.[116] BCG is the standard of care following TUR for high-risk NMIBC (Grade A recommendation). Although we recommend intravesical chemotherapy, patients with intermediate-risk NMIBC may be treated with intravesical induction course of BCG followed by maintenance as an alternative option (Grade B recommendation). Patients with intermediate-risk NMIBC who fail intravesical chemotherapy may benefit from BCG induction and maintenance (Grade B recommendation).

Treatment schedule

- **Full dose of induction BCG and 3-year maintenance is recommended for patients with high-risk NMIBC who can tolerate intravesical therapy with dose reduction reserved for cases of BCG intolerance (Grade B recommendation).**

BCG is given 2 to 4 weeks following TURBT to avoid systemic side effects. Optimal treatment schedules have not been established, but there is an agreement that only 6 weekly inductions are not sufficient.[117] In patients who received BCG induction only, a second induction course has an additional benefit of about 25% when used for prophylaxis and 30% when used for CIS (Level of Evidence 3).[117,118] There is sufficient evidence that BCG maintenance in addition to induction confers reductions in both recurrence and progression (Level of Evidence 1). Lamm and colleagues randomized patients with intermediate and high-risk NMIBC to receive 6 weekly inductions with BCG versus 6 weekly inductions followed by maintenance (3 weekly cycles at 3 months and 6 months, then every 6 months up to 36 months).[119] Patients receiving maintenance showed improved median recurrence-free and worsening-free survival. In a meta-analysis of 24 trials with 4863 patients, Sylvester and colleagues showed a demonstrated superiority of BCG over intravesical chemotherapy.[107] Progression-free survival was improved only in patients who received maintenance BCG. Similarly, Bohle and colleagues had similar conclusions in their meta-analysis of 9 trials, in which 1328 patients with NMIBC treated with adjuvant MMC were compared with 1421 patients treated with adjuvant BCG.[108,109] With a median follow-up of 26 months, recurrence rates were 46.4% for patients treated with adjuvant MMC versus 38.6% for those treated with adjuvant BCG; progression rates were 9.4% for patients treated with adjuvant MMC versus 7.7% for those treated with adjuvant BCG ($p = 0.08$, OR 0.77). When only trials using maintenance were included (5 trials), the difference was significant ($p = 0.02$, OR 0.66). The authors concluded that at least 1 year of maintenance BCG was required to show superiority of BCG over chemotherapy in decreasing recurrence or progression.

The optimal BCG dose and maintenance schedule has not been clearly identified. Several European studies have demonstrated that the BCG dose can be reduced to one-third or one-quarter with a reduction in toxicity but comparable efficacy.[120-122] However, Morales and colleagues have shown that dose reduction is associated with decreased efficacy in North American patients; they hypothesize that a lower immune response may be induced in patients with no previous exposure or inoculation with tuberculosis. Recently, a randomized trial of 1355 patients with intermediate and high-risk NMIBC compared full-dose and one-third dose

BCG and 1-year and 3-year maintenance. Oddens and colleagues showed that a 3-year maintenance of full-dose BCG had superior recurrence-free rates without increased toxicity. No differences in progression or overall survival were demonstrated. Risk stratification demonstrated that patients with high-risk NMIBC achieved maximal benefit when treated with full-dose BCG induction followed by 3-year maintenance. However, patients with intermediate-risk did not achieve further improvement beyond the full dose BCG induction and 1-year maintenance.[123] Based on the above data, we recommend the Lamm protocol with full-dose induction BCG and 3-year maintenance be given to patients with high-risk NMIBC who can tolerate intravesical therapy, with dose reduction reserved for cases of BCG intolerance (Grade B recommendation).

The addition of interferon to BCG in the treatment of BCG-naïve patients in a large multicentre prospective randomized study yielded no benefit compared to BCG alone.[124] However, in a recent randomized prospective trial from Singapore (unpublished) that was presented at the AUA meeting in 2014, superiority of BCG plus interferon when compared to BCG alone was demonstrated.[125] At the present time, it remains controversial as to whether adding interferon to BCG improves efficacy in BCG naïve patients.

BCG toxicity

BCG toxicity most commonly occurs in the first year of therapy.[126] The effect of BCG dose on toxicity is unclear. According to the CUETO (Club Urológico Español de Tratamiento Oncológico) study, a reduction in dose was associated with a decrease in the side effects of the drug; however, in the EORTC study, this association was not observed when comparing full-dose to one-third-dose instillations.[127-129]

Some studies suggest that prophylactic antibiotics given after intravesical BCG instillation may decrease the rate or severity of adverse events without a significant decrease in efficacy.[130,131] However further clinical research is needed to assess whether antibiotics usage with BCG can affect tumour progression by impairing the efficacy of BCG. Common and uncommon side effects of BCG and their management are summarized in Table 1.[132,133]

BCG failure

- **In patients with BCG-refractory high-risk NMIBC, radical cystectomy is recommended (Grade B recommendation).**
- **In patients with BCG relapse, BCG plus interferon, gemcitabine, or re-induction with BCG are valid options when patients are not suitable for or refuse radical cystectomy (Level of Evidence 3).**

Table 1. BCG side effects and treatment[132-133]

Common side effects			
Grade 1 (mild to moderate)	Grade 2 (moderate to severe)	Grade 3 (regional and systemic)	Grade 4 (generalized BCGitis or BCG sepsis)
- Mild to moderate and <48 hours (Grade 1) - Irritative lower urinary tract symptoms (frequency, dysuria and urgency) - Fever 38.5°C or less	- Symptoms severe or lasting >48 hours	- Allergic reactions: Skin rashes, migratory polyarthritis and rheumatoid arthritis-like symptoms with possible eye involvement - Epididymitis and symptomatic granulomatous prostatitis - Caseous abscesses, granulomatous masses of the kidney, hepatitis, pneumonitis and osteomyelitis	- Multi-organ failure and septic shock
Treatment			
- Symptomatic treatment with phenazopyridine (pyridium), anticholinergics and analgesics	- Symptomatic treatment with pyridium, analgesics and anticholinergics - Antibiotics as necessary and consider INH 300 mg once daily; suspend BCG instillations until resolution of symptoms - Consider dose reduction to 1/3 dose	- Antihistamines: If symptoms persist for more than 7 to 10 days, consider INH and RFP for 3 months. Resumption of BCG after resolution of symptoms only if benefits outweigh risks and dose reduction should be considered - Treat with INH and RFP for 3 months with or without fluoroquinolones - Treat with INH, RFP and ethambutol for 6 months	- Emergency hospital admission and treatment, possible intensive care management. - INH 300 mg daily - RFP 600 mg daily - Ethambutol 1200 mg daily - Prednisolone 40 mg daily

BCG: bacillus Calmette-Guerin; INH: isoniazid; RFP: rifampicin.

BCG failure is defined as the presence of high-grade NMIBC at 6 months from time of TURBT (or at 3 months if the initial tumour is T1G3/T1HG) or any worsening of the disease (higher grade, stage or appearance of CIS) while on BCG therapy despite initial response to BCG.[134] In fact, any tumour recurrence after BCG therapy can be defined as BCG failure. However, not all failures under this definition have a similar prognosis. Unfortunately, most of the literature did not differentiate the type of BCG failure when evaluating various salvage intravesical regimens. BCG failure can be stratified into several categories: BCG intolerance; BCG resistance; BCG relapse; and BCG refractory (Table 2). Among patients with BCG failure, BCG intolerance has the best prognosis, whereas BCG refractory disease portrays the worst prognosis.[134,135]

For patients with high-risk NMIBC who fail BCG, the option of radical cystectomy should be recommended and discussed with the patient (Grade B recommendation). Herr and colleagues compared the outcome of 2 groups of patients with NMIBC who received a radical cystectomy due to recurrence of disease within 2 years from initial BCG therapy, with patients who received radical surgery after 2 years. Early radical cystectomy was associated with significantly improved survival in patients with non-muscle invasive recurrence as well as muscle-invasive recurrence.[136] In patients with NMIBC treated with an induction course of BCG (without maintenance) who later develop recurrence of disease (BCG relapse), a second induction course may achieve up to 30 to 50% response rates.[118,137] Beyond 2 induction courses with BCG, further courses are not recommended, as there is a 7% actuarial risk of progression with each additional course.[138] The impact of re-induction on patients receiving maintenance is unknown.

After BCG failure, second-line intravesical therapy with combined low-dose BCG and interferon alpha 2b (induction followed by maintenance therapy) is a viable option with lower toxicity, but may be associated with significant oncologic risk (Level of Evidence 3). In a recent large multicentre phase II trial, 467 BCG failure patients receiving low-dose BCG and interferon alpha 2b were followed in parallel with 536 BCG-naïve patients receiving standard dose BCG with interferon alpha 2b.[139] After a median follow-up of 24 months, 45% of the BCG failure patients and 59% of BCG-naïve patients were disease-free.[140] Response was only seen in patients with BCG relapse. Patients with BCG refractory disease demonstrated no benefit from BCG with interferon.

Dalbagni's phase II trial evaluated the efficacy of gemcitabine on 30 patients with NMIBC refractory or intolerant to intravesical BCG. Patients received 2 courses, each course consisting of 2000 mg/100 mL of gemcitabine twice weekly for 3 consecutive weeks, with each course separated by 1 week. In total, 50% of patients achieved a complete response at 8 weeks, and among those with a complete response, the 1-year recurrence-free survival was only 21%. At 2 years, 2 patients maintained complete response.[141] The same group from Memorial Sloan-Kettering Cancer Center retrospectively analyzed 69 patients who received gemcitabine after BCG failure. Of those, 37 patients had BCG refractory disease. The median follow-up in progression-free patients was 3.3 years. Overall, 27 patients had a complete response. There were no serious adverse events and only a minority of patients discontinued the treatment due to

Table 2. Categories of BCG failure

BCG refractory
- Persistent high-grade disease at 6 months despite BCG therapy (or at 3 months if initial tumour is T1HG).
- Progression in stage, grade, or disease extent by 3 months after first cycle of BCG

BCG resistant
- Recurrence or persistence of disease at 3 months after induction cycle but of lesser stage or grade which subsequently is no longer present at 6 months

BCG relapsing
- Recurrence of tumour after being disease-free at the 6-month evaluation:
  o Early relapse (<1 year), intermediate (1–2 years), and late (>2 years)

BCG intolerant
- Tumour recurs due to inadequate course of BCG owing to adverse effects

BCG: bacillus Calmette-Guerin.

adverse events.[142] A recent multi-institutional phase II study from the Southwest Oncology Group (SWOG) showed that intravesical gemcitabine induction plus maintenance therapy for patients with recurrent NMIBC (CIS, T1, high-grade Ta or multifocal Ta low grade), after at least 2 prior courses of BCG, has activity in those high-risk patients not fit for cystectomy. However at the 1- and 2-year follow-up, the recurrence-free rate was only 28% and 21%, respectively.[143] Addeo and colleagues compared intravesical mitomycin with intravesical gemcitabine in patients with proven Ta and T1 disease of any grade after failure of BCG or epirubicin. A total of 109 patients (55 in the MMC arm and 54 in the gemcitabine arm) received induction consisting of a 4-week course of 40 mg/50 cc MMC in 55 patients and a 6-week course of 2000 mg/50 cc gemcitabine. The initial responders in both arms, who remained recurrence free, were given a 10 maintenance doses during the first year. After a median follow-up of 36 months, the gemcitabine arm had better efficacy (72% vs. 61% recurrence free) and less toxicity than the MMC arm.[144]

In a multicentre prospective randomized trial, Di Lorenzo and colleagues compared gemcitabine to another course of BCG in patients with high-risk NMIBC who failed a first course of BCG. Recurrence-free survival at 2 years was prolonged in the gemcitabine arm (19% vs. 3%; $p < 0.008$). However, many patients who recurred in the gemcitabine and BCG arms developed disease progression requiring either cystectomy or radiation therapy and systemic chemotherapy (76% and 77%, respectively).[145] A phase I trial assessing the use of intravesical docetaxel in patients with NMIBC refractory to intravesical chemotherapy found that docetaxel is safe and well-tolerated, with dysuria being the most common side effect.[146] Preliminary results are promising; however, further evaluation is needed to assess efficacy of docetaxel in patients who fail BCG.[147,148] In conclusion, gemcitabine in the setting of BCG failure shows modest early responses. It remains an option for patients who failed BCG or are BCG intolerant and are either not suitable for radical cystectomy or refuse surgery (Level of Evidence 3).

BCG strain

One prospective comparative study showed no significant differences between the Tokyo and Connaught strains in terms of complete response, recurrence-free survival or adverse event rate.[149] Over the last 2 decades, the literature has portrayed similar efficacy across varying BCG strains. However, a recent prospective randomized single institution trial showed that the BCG Connaught strain was superior in preventing recurrences compared with the OncoTice (Organon Laboratories Limited) strain.[150] The trial did not reach statistical significance for progression; however, these findings are provocative and require validation.

Device-assisted therapy

• **Device-assisted therapies have shown promising results; however multicentre studies are needed to further validate their efficacy as first- and second-line treatments in the North American population.**

Several studies have evaluated the efficacy of device-assisted therapy in the treatment of patients with NMIBC to improve the penetration of chemotherapeutic drugs into the bladder wall thus potentially improving outcomes. Several small studies have demonstrated that patients with intermediate/high-risk NMIBC treated with MMC combined with hyperthermia (thermochemotherapy using the Synergo system [Medical Enterprises Group]) had significantly prolonged recurrence-free survival compared to those treated with MMC alone.[28,151,152] Witjes and colleagues retrospectively collected data from patients with CIS and treated with intravesical MMC combined with hyperthermia. The initial complete response rate was 92%, half of whom remained complete responders at 2 years.[153]

A randomized controlled trial evaluated the benefits of a single preoperative electromotive drug administration (EMDA) of MMC and demonstrated reduced recurrence rates, and longer disease-free intervals compared to passive

diffusion MMC after TURBT or TURBT alone. Over a median follow-up of 86 months, patients who received EMDA MMC prior to TURBT had a lower rate of recurrence (38% vs. 59% and 64%) and a longer disease-free interval (52 vs. 16 and 12 months) compared to passive diffusion MMC after TURBT or TURBT alone, respectively. Importantly, whether passive diffusion MMC prior to TURBT would achieve a similar benefit as EMDA MMC prior to TURBT has not been evaluated.[154]

Another phase III study demonstrated improved recurrence and progression rates in 108 patients with T1 disease treated with sequential BCG and EMDA MMC compared with BCG alone.[155] After a median follow-up of 88 months, EMDA MMC used sequentially with intravesical BCG demonstrated decreased recurrence (41.9% vs. 57.9%, $p = 0.0012$), progression (9.3% vs. 21.9%, $p = 0.004$), cancer-specific mortality (5.6% vs. 16.2%, $p = 0.01$), and overall mortality (21.5% vs. 32.4%, $p = 0.045$) compared to BCG alone (Level of Evidence 2b). A study on the cost-effectiveness of EMDA, MMC used sequentially with BCG in high-risk NMIBC showed that the use of EMDA MMC is cost-effective in the Canadian healthcare system.[156] Multicentre studies are needed to further validate the efficacy of device-assisted therapies as first- and second-line treatment in the North American population.

Indications for early radical cystectomy

- **Early radical cystectomy may be advised for very high-risk patients: T1HG with variant features; T1HG with LVI; multiple and/or large T1HG; T1HG with concomitant bladder/prostatic CIS; persistent T1HG on restaging TUR; early high-grade recurrence at 3 months; and invasive tumours involving bladder diverticula (Grade C recommendation).**

Radical cystectomy remains the standard treatment in surgically fit patients with MIBC. Although intravesical therapy is the most widely used treatment for NMIBC, there is a subgroup of high-risk NMIBC patients in which early cystectomy may be advised due to the high potential for progression and even metastasis (Grade C recommendation). One of the most important causes of decreased disease-specific survival was upstaging of T1 tumours at cystectomy in up to 50% of cases.[157-160] Clinical and pathological features that characterize a very high-risk subgroup where a trigger for early cystectomy may be indicated include: T1HG with variant features (micropapillary, sarcomatoid, plasmacytoid, or small cell); T1HG with LVI, multiple and/or large T1HG tumours; T1HG with concomitant bladder/prostatic CIS; persistent T1HG on restaging TUR; early high-grade recurrence at 3 months, and invasive tumours involving bladder diverticula due to the absence of a muscularis propria layer (Level of Evidence 3).[19,26,31,33,36,80,161-163]

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