Introduction

According to the Canadian Cancer Society, bladder cancer is the fifth most common cancer overall, accounting for 7800 cases/year. The most common type of histology is urothelial carcinoma (greater than 90%), followed by adenocarcinoma, squamous cell and small cell carcinoma. Risk factors that have been 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. Other risk factors include pelvic irradiation, occupational exposure to chemicals from the aromatic amine family and chronic phenacetin use. Lynch syndrome (hereditary nonpolyposis colon cancer) is associated with extracolonic cancers including bladder cancer in 6-7%. Non-muscle invasive bladder cancer (NMIBC) accounts for about 75% to 80% of all incident bladder cancer cases; 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 creates a major economic burden on health-care systems.\textsuperscript{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.\textsuperscript{17} The management of NMIBC has changed over the last decade.

**Methods**

Here we update the previously published Canadian guidelines on the management of NMIBC from 2009, with an emphasis on intravesical therapy.\textsuperscript{18} A comprehensive search of the literature was done using Medline and Pubmed. Pre-existing sections were updated after review of the literature 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, with emphasis on 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.\textsuperscript{19-21} References have been assigned a level of evidence (LE), 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 (LE 2a)
- Other factors include variant histology, and presence of lymphovascular invasion (LE 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\%,\textsuperscript{22,23} The two most important prognostic factors in NMIBC are stage and grade. Grade can either be reported using the 1973 WHO grading system (Grade 1, 2, and 3) or more commonly with the 2004 WHO grading system (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 \textsuperscript{[HG]}\) 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.\textsuperscript{15,24} The risk of progression for Ta tumours was 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.\textsuperscript{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.\textsuperscript{29} Using six 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 that 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 \textit{[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) disease. Patients with low-grade non-invasive disease can also be classified as having high-risk NMIBC if they possess all of the following: large size (>3 cm), multifocal, and multi-recurrent low-grade Ta lesions.\textsuperscript{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 seven prospective trials received intravesical bacillus Calmette-Guerin (BCG).

\textit{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.\textsuperscript{30-32} Presence of concomitant CIS has been reported to be a prognostic factor for recurrence and progression.\textsuperscript{33-35} Furthermore, CIS of the prostatic urethra is strongly associated with recurrence and progression.\textsuperscript{36} The presence of mixed histology such as micropapillary variants is underreported by pathologists and associated with early progression to muscle invasive disease.\textsuperscript{37-39}

**TURBT**

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

Transurethral resection of bladder tumour (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 should be performed including focal areas of suspected CIS and abnormal areas in the prostatic urethra
and bladder neck. Bimanual examination under anesthesia is a valuable staging component of the TURBT procedure (LE 3). Transurethral resection of bladder tumour should include detrusor muscle (muscularis propria) in the specimen in an attempt to rule out T2 disease and minimize the risk of under staging (Grade A recommendation).\textsuperscript{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.\textsuperscript{42}

**Methods for enhanced visualization**

- Enhanced visualization methods (HAL-PDD or NBI) may improve tumor detection and early recurrences (LE 1b); whether the benefit persists in the context of immediate instillation of 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 hexyl-aminolevulinate (HAL), a derivative of 5-ALA, is instilled in the bladder. Use of HAL is more practical as it requires instillation for only one hour before cystoscopy compared with 2 to 4 hours for 5-ALA. The two compounds have similar efficacy in photodynamic diagnosis (PDD) guided transurethral resection\textsuperscript{43,44}. Integration of fluorescent cystoscopy during TURBT has been shown to improve tumour detection (and quality of resection) and reduce recurrence rates (LE 1b).\textsuperscript{35,46} The detection rate for CIS is approximately 25–30% higher under PDD guidance compared with white light cystoscopy (WLC) alone.\textsuperscript{47,48} PDD also reduces the rate of residual tumour by 20% compared to WLC.\textsuperscript{49}

Two randomized studies with long-term follow-up using PDD reported a lower risk of recurrence and longer recurrence-free survival compared to white light cystoscopy (LE 1b).\textsuperscript{46,50} Grossman et al. also showed in a follow-up of 551 randomized patients that recurrence free survival was higher for patients who have received HAL PDD (38% vs. 31.8%).\textsuperscript{51} A recent meta-analysis by Burger et al. on 2212 patients from nine studies showed that a single application of blue light cystoscopy with HAL, as an adjunct WLC, detects more tumours and thus reduces recurrences up to one 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 shows that HAL maintains its superior detection rates and benefit effect even in the subgroup of patients who have received intravesical BCG.\textsuperscript{52} Ray et al. 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. However, a prospective randomized trial by O’Brien et al. compared HAL photodynamic-assisted TURBT plus one shot post-operative mitomycin C (MMC) to standard WLC plus one shot post-operative MMC and found no significant difference in recurrence rates at three months and one year. In their discussion, the authors attributed the lack of significant difference in the two arms to MMC that could have successfully treated any small volume disease that could have been missed on conventional white light cystoscopy.

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 two months). HAL is approved for use both in Europe and the U.S.A., but does not currently have Health Canada approval.

**Narrow band imaging:** Narrow band imaging (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 highly vascular cancer. Higher cancer detection rates have been shown in the initial studies of NBI-guided resection. In a randomized trial, Naselli et al. found that NBI modality reduces the recurrence risk of NMIBC by at least 10% at one year. The trial compared traditional white light TURBT vs. NBI-TURBT in patients with NMIBC to assess the impact of NBI on recurrence risk. The one-year recurrence risk was 32.9% (25 of 76 patients) in the NBI and 51.4% (37 of 72 patients) in the WLC group (OR=0.62; p=0.0141).

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 relook 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% less tumour recurrence. The recurrence rate at two years was 11% less in the NBI-TURBT group. Recurrence-free survival time and progression-free survival was 22 months vs. 19 months and 94% and 87% respectively for NBI vs. WLC. However, the number of patients who remained disease free at two years did not achieve the ambitious targeted 20% difference. Two meta-analyses showed the superiority of NBI in detecting NMIBC compared to WLC, especially for CIS. These findings require validation in large multi-institutional studies. NBI may improve tumour detection, but the impact on patients is poorly defined due to limited
Prostatic urethra involvement:

- When indicated, biopsy of prostatic urethra should include all suspicious areas as well as the precollicular area (LE 3).
- In cases of conservative management, a TURP is recommended prior to BCG to obtain 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%). 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. 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 five and seven o’clock (precollicular area) especially at the level of the verumontanum, as this area contains the highest concentration of prostatic ducts (LE 3). The sample should contain both intact mucosa and deeper sections to provide the pathologist with sufficient amount of stroma.

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.

An initial attempt of conservative management by transurethral resection of the prostate (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 (LE 3, Grade B recommendation).

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.

Re-biopsy of the prostatic urethra post BCG induction is recommended to detect
recurrences early (LE 4, Grade C recommendation). Counseling towards a radical cystectomy plus urethrectomy should be considered with any high-grade prostatic urethral recurrence following BCG. In patients diagnosed with prostatic stromal invasion, conservative therapy with BCG should not be attempted; rather extirpative surgery with radical cystectomy +/- urethrectomy should be considered (LE 2).

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 (LE 2). In patients with T1HG, re-TUR upstaged tumours to T2 disease in 49% of patients if muscularis propria was not present in the specimen compared to 14% if the initial TUR contained benign muscularis propria. Restaging TUR is also associated with better local control of tumour (LE 3). Herr previously reported that 75% of patients who underwent repeat TURBT in two to six weeks after initial resection had residual tumour. Forty-four percent of them were found to have T1 or muscle invasive tumour. Furthermore, 17% of patients actually had histological evidence of cancer at their previous resection site despite a normal cystoscopic examination. After five years of follow-up in 124 patients, Grimm et al. found that 63% of those who underwent a repeat TURBT had tumour-free bladders compared with 40% of those who did not. A more recent study from Memorial Sloan-Kettering confirmed the need for restaging TURBT, especially in high-risk NMIBC. In a retrospective analysis of 1021 patients with high-risk NMIBC, Sfakianos et al. 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 three 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 five-year follow-up.

Divrik et al. prospectively evaluated 142 patients who were randomized into 2 groups. The 1st 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 progression although there was a trend favouring the repeat TURBT group (4% vs. 11.8%, p=0.097). However, the major flaw of this study was due a lack of intention-to-treat analysis.

Herr et al. demonstrated that a restaging TUR improved initial response to intravesical immunotherapy. The results were also corroborated by another study by Guevara et al. 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.

We recommend that a second TUR should always be performed two to six 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,b,c) 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 (LE 2). 

Follow-up

- Cystoscopy at three months following TURBT is recommended for all patients (Grade A recommendation)
- Generally, cystoscopy with urine cytology (or other urine marker) is recommended every three to four months for two years, then every six months for years three and four, then yearly thereafter (Grade B recommendation). Patients with low-risk Ta tumours may undergo cystoscopy at three and twelve months, then annually (LE 3)
- Upper tract imaging every one to two years for patients with high-risk NMIBC (Grade C recommendation)

All patients are recommended to undergo a cystoscopy at three months following
TURBT, as cystoscopic findings at three 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 three to four months for two years, then every six months for years three and four, then yearly thereafter (Grade B recommendation).

Patients with a primary, solitary, low-grade Ta tumour may have less frequent cystoscopic examination (three and twelve months, then annually thereafter) (LE 3). Mariappan et al. followed 115 low-risk patients over 20 years, and showed that the recurrence rate of low-risk NMIBC dropped significantly after five years of follow-up. In patients who did not recur after five 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 is 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 (LE 3). However, patients with high-risk NMIBC require life-long cystoscopic surveillance. Any recurrence resets the clock in the follow-up schedule.

*Upper tract surveillance:* Although the sensitivity and specificity of 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 et al. found that a total of 3074 routine CT urographies had to be done in order to detect 15 patients, showing an efficacy of only 0.49%. All the patients who were 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 one to two 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 six hours from the time of TUR and significantly decreases if given beyond 24 hours (LE 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 three months following TURBT. Incomplete TUR or tumour cell implantation post-TUR is the postulated mechanisms for the high proportion of recurrences at three 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 et al. performed a meta-analysis of seven randomized trials (n = 1476) on the outcome of TUR alone vs. TUR plus one immediate postoperative instillation of intravesical chemotherapy. Over a median follow-up of 3.4 years, patients who received one immediate instillation had a recurrence rate of 37% compared with 48% of patients who had TUR alone. The benefit was more pronounced for those with single, low-grade papillary tumour compared with patients with multiple tumours. A more recent meta-analysis confirmed that intravesical chemotherapy prolonged recurrence-free interval by 38% (HR: 0.62; 95% CI 0.50–0.77; p < 0.001) and decreased early recurrences by 12% (ARR: 0.12; 95% CI, -0.18 to -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. Tumour recurrences are often small, non-invasive, low-grade papillary tumours that can be managed by office fulguration. Therefore, the potential risks of a single post-operative dose should be weighed against the cost and benefit of reducing recurrences of these small, low-grade tumours.

The efficacy of the immediate postoperative instillation is optimal when administered within six hours from the time of TUR and significantly decreases if given beyond 24 hours (LE 2). Immediate postoperative instillation of the
chemotherapeutic agent is recommended for all patients with NMIBC after TURBT (Grade B recommendation). Concerns with the quality of the trials would suggest that further research is likely to have an impact on the confidence in the estimate of effect. 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, being in the range of 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. Efficacy of MMC is dependent on the concentration at which the drug is administered. Recently, Au et al. published a phase III, randomized trial that showed superiority and prolonged median time to recurrence with an “optimized” MMC administration which consists of a period of pre-treatment dehydration (no fluids for eight hours prior to treatment), urinary alkalinization, confirmation of complete bladder drainage prior to instillation and a higher MMC concentration (40 mg in 20 ml).

**Multiple adjuvant instillations**

- Induction followed by one-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 alkalinization, 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 compared 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. 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 one year of maintenance therapy was used. 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 counseled to receive an induction followed by a one year maintenance course of intravesical chemotherapy to prevent or delay recurrence (Grade B recommendation). Meta-analysis of 22 randomized, prospective studies evaluating the role of intravesical chemotherapy for NMIBC did not show any benefit in the reduction of progression rates compared to TURBT alone (LE 1).  

**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 with 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 carried out from 1985 to 1996 showed that BCG decreases recurrence rates from 67% to 29%. Six meta-analyses compared BCG with intravesical chemotherapy; all of them except one showed superiority of BCG over chemotherapy in terms of decreasing recurrence. BCG following TUR is superior to TUR alone or TUR plus intravesical chemotherapy in decreasing recurrences, particularly in patients with high-risk disease (LE 1).

BCG is the only intravesical agent that has been shown to delay tumour progression in randomized trials (LE 1). Herr et al 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. This apparent advantage is less significant over long-term follow-up at 15 years. Among several series, BCG induced a complete response rate to CIS in over 70%. 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 et al. demonstrated a statistically significant decrease in progression rates (27% reduction) for patients who received BCG compared with the TUR only group
A subset analysis demonstrated that the reduction in progression rate was significant only when BCG maintenance was administered. In 2005, Sylvester et al. reported their analysis on 12 different randomized trials that included patients with CIS. They compared BCG with different intravesical chemotherapy regimens. They found a 68% complete response rate with BCG vs. a 48% complete response rate with chemotherapy. The overall disease-free rates over a median follow-up of 3.75 years were 51% vs. 27% for BCG vs. chemotherapy, respectively. Similarly, another meta-analysis of nine randomized trials showed similar results. Takenaka et al. found that the overall response rate to BCG in patients with primary, concomitant or secondary CIS was 86.6%, with a five-year progression-free survival rate of 78.5%. Most recurrence or progression events occur within the first five years. 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 with 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 three-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 two to four weeks following TURBT to avoid systemic side effects. Optimal treatment schedules have not been established, but there is an agreement that only six weekly inductions are not enough. In patients who received BCG induction only, a second induction course has been shown to have an additional benefit of about 25% when used for prophylaxis and 30% when used for CIS (LE 3). There is sufficient evidence that BCG maintenance in addition to induction confers reductions in both recurrence and progression (LE 1). Lamm et al. randomized patients with intermediate and high-risk NMIBC to receive six weekly inductions with BCG vs. six weekly inductions followed by maintenance (three weekly cycles at three months and six months, then every six months up to 36 months). Patients receiving maintenance showed improved median recurrence-free and worsening-free survival. In a meta-analysis of 24 trials with 4863 patients, Sylvester et al. showed a proven superiority of BCG over intravesical chemotherapy. Progression-free survival was improved only in the patients that received maintenance BCG. Similarly, Bohle et al. had similar conclusions in their meta-analysis of nine trials where 1328 patients with NMIBC treated with adjuvant MMC were compared with 1421 patients treated with adjuvant BCG. With a median follow-up of 26 months, recurrence
rates were 46.4% for patients treated with adjuvant MMC vs. 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 ($p = 0.08$, Odds ratio = 0.77). When only trials using maintenance were included (five trials), the difference was significant ($p = 0.02$, Odds ratio = 0.66). The authors concluded that at least one 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 definitively identified. Several European studies have demonstrated that BCG can be reduced to one-third to one-quarter with a reduction in toxicity but comparable efficacy. However, Morales et al. 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 who do not have previous exposure or inoculation with tuberculosis. Recently, a randomized trial of 1355 patients with intermediate and high-risk NMIBC compared full-dose vs. one-third dose BCG and one-year vs. three-year maintenance. Oddens et al. showed that a three-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 three-year maintenance. However, patients with intermediate-risk did not achieve further improvement beyond the full dose BCG induction and one-year maintenance. Based on the above data, we recommend the Lamm protocol with full-dose induction BCG and three-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 multicenter prospective randomized study yielded no benefit compared to BCG alone. 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. 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. The effect of BCG dose on toxicity is unclear. According to the CUETO study, a reduction in dose was associated with a decrease in the side effects of the drug, but in the
EORTC study, this association was not observed when comparing full-dose to one-third dose instillations.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 (LE 3)

BCG failure is defined as the presence of high-grade NMIBC at six months from time of TURBT (or at three 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.\textsuperscript{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.\textsuperscript{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 et al. compared the outcome of patients with NMIBC who received a radical cystectomy due to recurrence of disease within two years from initial BCG therapy with patients who received radical surgery after two years; early radical cystectomy was associated with significantly improved survival in patients with non-muscle invasive recurrence as well as muscle-invasive recurrence.\textsuperscript{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.\textsuperscript{118,137} Beyond two induction courses with BCG, further courses are not recommended, as there is a 7% actuarial risk of progression with each additional course.\textsuperscript{138} The impact of ‘reinduction’ on patients receiving maintenance is unknown.
After BCG failure, second-line intravesical therapy with combined low-dose BCG and interferon alpha 2b (induction followed maintenance therapy) is a viable option with lower toxicity but may be associated with significant oncologic risk (LE 3). In a recent large multi-centre 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. After a median follow-up of 24 months, 45% of the BCG failure patients and 59% of BCG naïve patients were disease-free. 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 two courses, each course consisting of 2000 mg/100 ml of gemcitabine twice weekly for three consecutive weeks, with each course separated by one week of rest. Fifty percent of patients achieved a complete response rate at eight weeks, and among those with a complete response, the one-year recurrence free survival was only 21%. At two years, two patients maintained complete response. The same group from MSKCC 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 year. Overall, 27 patients had a complete response. There were no serious adverse events and only a minority of patients discontinued the treatment due to adverse events. A recent multi-institutional phase II study within the SWOG cooperative group 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 two prior courses of BCG, has activity in those high-risk category patients not fit for cystectomy. However at one and two year follow-up the recurrence free rate was only 28% and 21% respectively. Addeo et al. 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 GEM arm) received induction consisting of a four-week course of 40 mg/50cc MMC in 55 patients and a six-week course of 2000mg/50cc gemcitabine. The initial responders in both arms, who remained recurrence free, were given a 10 monthly maintenance doses during the first year. After a median follow-up of 36 months, gemcitabine arm had better efficacy (72% vs. 61% recurrence free) and less toxicity than the MMC arm.

In a multicenter prospective randomized trial, Di Lorenzo et al. compared gemcitabine to another course of BCG in patients with high-risk NMIBC who failed a first course of BCG. Recurrence-free survival at two 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). 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. Preliminary results are promising; however, further evaluation is needed to assess efficacy of docetaxel in patients who fail BCG. 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 (LE 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. Over the last 2 decades, the literature have portrayed similar efficacy across varying BCG strains. However, a recent prospective randomized single institution trial showed that BCG Connaught strain was superior in preventing recurrences compared with the OncoTice® strain. The trial did not reach statistical significance for progression. These findings are provocative and require validation.

**Device-assisted therapy**

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

Several studies have evaluated the efficacy of device-assisted therapy in the treatment of patients with NMIBC in order to improve the penetration of the 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) had significantly prolonged recurrence-free survival compared to those treated with MMC alone. Witjes et al. 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 two years.

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 interval 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.\textsuperscript{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.\textsuperscript{155} After a median follow-up of 88 months, EMDA MMC used sequentially with intravesical BCG demonstrated decreased recurrence (41.9% vs. 57.9%, \textit{p}=0.0012), progression (9.3% vs. 21.9%, \textit{p}=0.004), cancer-specific mortality (5.6% vs. 16.2%, \textit{p}=0.01), and overall mortality (21.5% vs. 32.4%, \textit{p} =0.045) compared to BCG alone (LE 2b). A study on the cost-effectiveness of EMDA MMC used sequentially with BCG in high-risk NMIBC was done and showed that the use of EMDA MMC is cost-effective in the Canadian health care system.\textsuperscript{156} Multicenter 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 the following 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 three months; and invasive tumours involving bladder diverticula (Grade C recommendation)

Radical cystectomy remains the standard treatment in surgically fit patients with muscle-invasive bladder cancer. 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%.\textsuperscript{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 three months, and invasive
tumours involving bladder diverticula due to its lack a muscle layer.19,26,31,33,36,80,161-163 (LE 3)

References:

32. Streeper NM, Simons CM, Konety BR, et al. The significance of lymphovascular invasion in transurethral resection of bladder tumour and
cystectomy specimens on the survival of patients with urothelial bladder cancer. BJU Int 2009;103:475-9.


76. Divrik RT, Yildirim U, Zorlu F, et al. The effect of repeat transurethral resection on recurrence and progression rates in patients with T1 tumors of the


Figure 1: Management algorithm for non-muscle invasive bladder cancer

**Low-Risk**

- TaLG

  - TUR + POChemoTx

  - Multifocal or multi-recurrent TaLG

  - TUR + POChemoTx
    - BCG or ChemoTx induction + maintenance (1 yr)

  - Recurrent TaLG

    - BCG induction + maintenance (if BCG naïve)
    - ChemoTx induction + maintenance (if chemo naïve)
    - Option: BCG + IFNα (if BCG relapse)

**Intermediate-Risk**

**High-Risk**

- T1, CIS or any high-grade

  - TUR +/- POChemoTx
    - Repeat TUR (2-6 wks)
    - BCG induction + maintenance (3 yrs)

    - Consider early cystectomy if:
      - T1HG + CIS, multiple/large T1HG, or T1 with micropapillary variant

**Legend:**
- POChemoTx: Postoperative intravesical chemotherapy
- TaLG: Ta low-grade disease
- TUR: Transurethral resection

**Recurrence (normal upper tract)**

**Cystectomy or clinical trial**
Table 1: **BCG SIDE EFFECTS AND TREATMENT**

<table>
<thead>
<tr>
<th>Common side effects</th>
<th>Uncommon side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1 (mild to moderate)</strong></td>
<td><strong>Grade 2 (moderate to severe)</strong></td>
</tr>
<tr>
<td>Mild to moderate and less than 48 hours (Grade 1)</td>
<td>Symptoms severe or lasting greater than 48 hours</td>
</tr>
<tr>
<td>Irritative lower urinary tract symptoms (frequency, dysuria and urgency)</td>
<td>2. Epididymitis and symptomatic granulomatous prostatitis</td>
</tr>
<tr>
<td>Fever 38.5°C or less</td>
<td>3. Caseous abscesses, granulomatous masses of the kidney, hepatitis, pneumonitis and osteomyelitis</td>
</tr>
</tbody>
</table>

**Treatment**
| Symptomatic treatment with phenazopyridine (pyridium), anticholinergics and analgesics | Symptomatic treatment with pyridium, analgesics and anticholinergics | 1. 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  
2. Treat with INH and RFP for 3 months with or without fluoroquinolones  
3. 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 1,200 mg daily Prednisolone 40 mg daily |

|  |  |  |  |
Table 2. Categories of BCG failure

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG refractory:</td>
<td>Persistent high-grade disease at 6 months despite BCG therapy (or 3 month if initial tumor is T1HG). Disease progression in stage, grade, or disease extent by 3 months after first cycle of BCG</td>
</tr>
<tr>
<td>BCG resistant:</td>
<td>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</td>
</tr>
<tr>
<td>BCG relapsing:</td>
<td>Recurrence of tumor after being disease-free at the 6-month evaluation: early relapse (&lt;1 year), intermediate (1-2 years), and late (&gt; 2 years)</td>
</tr>
<tr>
<td>BCG intolerant:</td>
<td>Tumor recurs due to inadequate course of BCG owing to adverse effects</td>
</tr>
</tbody>
</table>