



# Intravesical Therapies in Non-muscle Invasive Bladder Tumors

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## Abstract

In the European Association of Urology (EAU) 2015 Guidelines for non-muscle invasive bladder tumors, maintenance Bacillus Calmette-Guérin (BCG) therapy is a grade A recommendation. In the intermediate-risk group, re-evaluation is recommended after 1-year full-dose treatment; in the high-risk group, full-dose BCG is recommended for 1-3 years. Intravesical BCG therapy fails in 40% patients in an average of 2 years. In these cases, there is no alternative treatment that is considered effective. In patients with failed BCG, comparison of BCG and gemcitabine showed less recurrence in the long term with gemcitabine while progression and toxicity were similar. Early radical cystectomy should be considered in non-muscle invasive bladder cancer patients with BCG-refractory T1G3 who have good performance status and low comorbidity. In T1 tumors, invade deeper than 3 mm and/or larger than 6 mm in diameter has been associated with a 100% progression rate. BCG decreased recurrence more significantly in high-risk Ta and T1 tumors. In terms of progression of high-risk superficial bladder cancer, comparison of mitomycin C and BCG showed that BCG is superior if maintenance therapy is given. EAU guidelines recommend early bladder chemotherapy instillation (EBCI), in the low-to-intermediate risk group. There was no clear effect of EBCI in the intermediate- and high-risk group. EBCI alone reduces recurrence only in the low-risk group. However, adjuvant intravesical chemotherapy (AIVC) is recommended in the intermediate- and high-risk groups because it improves relapse-free survival. BCG and maintenance BCG therapy were found to be more effective than AIVC in reducing progression and preventing recurrence.

**Keywords:** Intravesical BCG, intravesical chemotherapy, early bladder chemotherapy instillation, non-muscle invasive bladder tumors

## Introduction

Urothelial tumors are the fourth most common of all tumors (1). Bladder tumors account for 90-95% of the cases, while 5-10% originate in the upper urinary tract (2). At initial diagnosis, most cases (75-85%) are non-muscle invasive bladder cancer (NMIBC). According to pathological T staging, 70% are classified as Ta, 20% as T1, and 10% as carcinoma *in situ* (CIS) (3). CIS is prone to muscle invasion (54%) if not treated effectively. Recurrence, progression, and prognosis in NMIBC are predicted using nomograms and European Organization for Research and Treatment of Cancer (EORTC) and Spanish Urological Club for Oncological Treatment (CUETO) classification based on pathological examination of transurethral resection of the bladder (TUR-B) specimens. Adjuvant therapy decisions during follow-up of patients with NMIBC are made based on risk group stratification (low, intermediate, high) according to the clinical and pathological data. The EORTC classification is believed to require strengthening with new parameters due to several reasons such as the absence of additional pathological variants,

lack of prognostic factors in the T1 tumor invasion subgroups, and lack of lymphovascular invasion criteria in histopathology (4). Muscle invasion occurs in about 30% of high-risk NMIBCs during follow-up. For high-grade T1 tumors, survival is as low as 34%. This may be attributable to lower grade in initial pathology or the tumor having invasive characteristics (5). A study performed in 2011 showed that patients with invasive progression had worse prognosis than patients whose initial pathology was muscle invasive (3-year survival rate, 37% vs 67%) (6). Previous studies suggested the need to define a "very-high-risk" subgroup within the high-risk NMIBC group in order to avoid the delay of correct treatment (7). As a result, the 2014 European Association of Urology (EAU) NMIBC guidelines included a highest-risk subgroup in addition to the low-, intermediate-, and high-risk groups and recommend early radical cystectomy (Table 1).

In cases with persistent T1 disease after secondary TUR-B, the progression rate for T1G3 patients with 3 poor prognostic factors (age over 70 years, presence of CIS, tumor larger than 3 cm) was reported as 52%. Progression rates of 40% were reported

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for female patients with T1G3 or in the presence of prostatic CIS. Strikingly, invasion deeper than 3 mm and/or greater than 6 mm in diameter was associated with 100% progression in T1 patients (8). The standard follow-up and treatment of NMIBC is cystoscopy. In low-grade Ta disease, 3-year progression is rare (5%), while recurrence rates are high (50-70%). High-grade T1 disease shows substantially high rates of both progression (50%) and recurrence (80%) (9) (Table 2). In this study, we evaluated the clinical role and efficacy of intravesical treatments in NMIBC in light of the studies and reviews conducted to date.

### Bacillus Calmette-Guérin Therapy and Prognosis in Bladder Cancer

Bacillus Calmette-Guérin (BCG) vaccine contains attenuated bacteria and its use within the bladder was first described by Morales in 1976 (10). It remains the most effective treatment method for the prevention of recurrence and progression in high-risk NMIBC. Application 2-4 weeks after TUR is recommended to prevent adverse effects. Urinary tract infections must be either excluded or treated before BCG therapy. The procedure should be postponed in cases of traumatic catheterization or other causes of disrupted tissue integrity. After BCG instillation, it should remain in the bladder for 1-2 hours (dwell time). Although this therapy has been used for more four decades, the mechanism of action is thought to be related to the immune response that develops due to local T-cell activation in the bladder mucosa. The local immune response induced by BCG involves both cellular and humoral immune mechanisms. Long-term follow-up of treated patients has revealed predominant increase in T cells and Th1-type cytokines. Local inflammation induced by BCG is called granuloma and is known to play an important role in reducing tumor recurrence (11). The amount of bacteria in standard dose BCG solution should be 108 colony-forming units (CFU)/mL or higher. In their 2013 meta-analysis, Zhu et al. (12) determined that a below-standard BCG dose was associated with higher recurrence rate. However, CUETO previously showed that treatment with a one-third dose reduced recurrence and

progression in selected intermediate-risk patients. Although the authors emphasized that full-dose BCG may not be necessary for effective treatment based on their results, their selection of moderate-risk patients for the study makes it difficult to draw a definitive conclusion on this issue (13). Treatment of ureteral and bladder cancer depends on cancer stage and grade. Considering that three-quarters of cases are NMIBC at diagnosis and that one-quarter exhibit progression, there is an undeniable need for additional treatment to prevent both recurrence and progression. BCG is still considered the most effective treatment in the prevention of recurrence and progression. However, careful patient selection is important due to its toxic effects. While intravesical BCG treatment is regarded as unnecessary in the low-risk group, it is strongly recommended for the high-risk group (Table 3). In the intermediate-risk group, the decision to administer intravesical BCG therapy is made based on an evaluation of the likelihood of recurrence and progression. In particular, CIS in addition to superficial bladder cancer should be managed as an invasive tumor. BCG therapy is regarded as first-line treatment for NMIBC patients with CIS (14). In another study it was determined that BCG with maintenance therapy should be the treatment of choice for intermediate- and high-risk patients with CIS (15). Among the recent studies in the literature, a retrospective 2018 study by Yorozuya et al. (16) including 53 patients with variant histology (squamous or glandular differentiation) stands out. Their results support that in NMIBC, intravesical BCG therapy for variant histology has better prognosis in terms of progression and cancer-specific survival than other intravesical treatments (mitomycin C and thiotepa) with no need for additional treatment.

### Bacillus Calmette-Guérin Therapy Doses (Induction and Maintenance)

The currently accepted BCG induction protocol is that described by Morales et al. (10), in which BCG is instilled once a week for six weeks. Intravesical BCG therapy prevents not only recurrence, but also progression. Therefore, it is especially recommended for the high-risk group. Unlike induction, there are no optimal treatment protocols for maintenance therapy. An EORTC study demonstrated the superiority of 3-year full-dose maintenance therapy to 1-year maintenance therapy in high-risk patients. In the same study, this effect was not observed in intermediate-risk patients; therefore, 1-year full-dose maintenance therapy is recommended for the intermediate-risk group. The use of different doses in that study showed no difference between one-third and full-dose maintenance BCG therapy in terms of toxicity (17). Maintenance therapy is a grade A recommendation in the 2015 EAU guidelines. Reevaluation after 1-year full-dose in the intermediate-risk group and continuation of full-dose maintenance BCG for 1-3 years in the high-risk group is recommended (18). Lamm et al.

T1G3 with concurrent bladder CIS
T1G3 with concurrent prostatic urethral CIS
Multiple and/or large (>3 cm) T1G3 tumors and/or recurrent T1G3
Presence of variant histology (especially micropapillary variant)
Lymphovascular invasion
CIS: Carcinoma <i>in situ</i>

Tm pathology	Recurrence (3-year follow-up)	Progression (3-year follow-up)
Low-grade Ta	50-70%	5%
High-grade T1	80%	50%

Low-risk group	Primary, Ta, solitary, Tm <3 cm, G1, no CIS
High-risk group	T1, G3, presence of CIS
CIS: Carcinoma <i>in situ</i>	

(19) analyzed the outcomes of a 6-week induction followed by 3-week treatment cycles performed at 3, 6, 12, 18, 24, 30, and 36 months. Particularly in CIS and selected Ta-T1 patients, maintenance intravesical BCG therapy was shown to approximately double the recurrence-free period.

#### Adverse Effects of Bacillus Calmette-Guérin Therapy

Local and systemic infections are adverse events that occur after BCG therapy. Hypersensitivity reactions (20) and adverse effects secondary to active infection (21) have been reported. The absolute and relative contraindications to BCG therapy must be known prior to treatment (Table 4) (22). The local adverse effects of intravesical BCG have been investigated in six different randomized studies. The main factors associated with adverse events were age over 70 years, immunosuppression, and urothelial damage. The most common local adverse effects included pollakiuria (71%), cystitis (67%), fever (25%), and hematuria (23%) (23). Lamm (24) reported the rate of severe complications as below 5% in their retrospective study. The most common adverse effect is fever (2.9%), and anti-tuberculosis treatment should be considered if it exceeds 39 °C for more than 48 hours. Severe hematuria (1%), granulomatous prostatitis (0.9%), pneumonia, hepatitis, arthralgia (<0.8%), and more rarely, epididymitis, ureteral obstruction, bladder contracture, and renal abscess have also been reported in the literature. The most common complication is BCG cystitis. It develops within 2-4 hours of treatment and usually resolves within 48 hours. The most feared adverse effect is systemic disease and sepsis. The development of systemic disease has been reported in the first 8-12 weeks. Diagnosis can only be made in the presence of granuloma in tissue biopsies. Infections secondary to BCG therapy may not always manifest with leukocytosis (25). Classical sepsis is very rare (26).

#### Non-response to Bacillus Calmette-Guérin

Intravesical BCG therapy fails in 40% of NMIBCs in an average of 2 years. In such cases, there is no alternative intravesical therapeutic agent considered completely effective. Progression is rare in patients with initial low-grade pathologic diagnosis. For NMIBC patients classified as high-risk, the probability of muscle invasion and progression must not be overlooked. The main factors in treatment failure are previous exposure to mycobacteria, inappropriate BCG dose, lack of expected cellular immune response in the individual, and therapies initiated based on missing or inaccurate staging (27). Early cystectomy is recommended after failed BCG therapy in T1G3 patients with good performance status and low comorbidity. Promising studies on the development of bladder-sparing intravesical therapies for patients with treatment failure are ongoing.

Absolute contraindications for BCG	Relative contraindications for BCG
<ul style="list-style-type: none"> <li>- Immunosuppression</li> <li>- History of BCG sepsis</li> <li>- Macroscopic hematuria</li> <li>- Total incontinence</li> <li>- Early post-TUR</li> <li>- Traumatic catheterization</li> </ul>	<ul style="list-style-type: none"> <li>- Urinary tract infection</li> <li>- Liver disease</li> <li>- History of tuberculosis</li> <li>- Advanced age</li> <li>- Poor performance status</li> </ul>
BCG: Bacillus Calmette–Guérin, TUR: Transurethral resection	

#### Intravesical Chemotherapy in Non-muscle Invasive Bladder Cancer

The addition of IVCT to TUR-B aims to eliminate residual tumor and prevent progression and recurrence (28). The superiority of any of the IVCT agents (mitomycin C, epirubicin, pirarubicin, and thiotepa) to one another has yet to be demonstrated (29). Choice of drug is based on cost, adverse effects, and practitioner experience. Mitomycin C is the most frequently used agent. Its mechanism of action is the inhibition of DNA synthesis. It is an antimicrobial and anticancer agent obtained from *Streptomyces* species. In normal conditions, systemic absorption is limited due to its molecular weight (334 kD). However, it is not recommended for patients with mucosal damage, widespread resection, and radiotherapy (7). Although an optimum protocol has not been established, urine alkalinization followed by instillation of 40 mg/20 mL mitomycin C and dwell time of 1 hour was recommended (30). When applied as 20 mg/50 mL dose, recurrence was reported to decrease from 57% to 17%, and when used for 6-8 weeks at higher doses (40-80 mg), the proportion of high-grade bladder cancers that were recurrence-free at 2 years was reported as 75% (31). Applying mitomycin C with hyperthermia (41-44 °C) was reported to increase treatment efficacy and survival. However, the use of this technique is limited due to increased cost associated with the special catheter necessary for hyperthermia, increased adverse effects of mitomycin C due to hyperthermia, and patient compliance problems (32). The most common effects associated with mitomycin C toxicity are chemical cystitis (40%) (33) and allergic skin reactions (5-12%) (34). In intravesical applications performed after TUR-B, normal epithelialization of healing areas may be disrupted and replaced by dystrophic calcification, or extravasation from the bladder may cause necrosis, peritonitis, and pelvic pain (35). A 2003 review by Shelley et al. (36) including 6 studies compared BCG and mitomycin C treatments in Ta and T1 tumors. BCG resulted in a more pronounced reduction in the recurrence of high-risk Ta and T1 tumors. Local adverse effects (dysuria, pollakiuria, cystitis, hematuria) and systemic adverse effects (fever, fatigue) were in favor of BCG. A total of 108 patients were divided into passive mitomycin C, electromotive mitomycin C, and BCG groups. Complete response rates at 6 months were 31-58% for passive and electromotive mitomycin C, respectively, and 64% with BCG. Adverse effects were most frequent in the electromotive mitomycin C group and least frequent in the group administered BCG only (37). Five studies with an average follow-up of 26 months compared BCG with and without maintenance therapy to mitomycin C in terms of progression of high-risk superficial bladder cancer. As a result, it was emphasized that BCG treatment is superior if maintenance therapy is provided (38). In another study, 212 T1 patients were divided into two groups, BCG only or sequential BCG and electromotive mitomycin C. Both groups underwent maintenance therapy. At the end of 88 months of follow-up, all parameters (recurrence, progression, and survival) were better in the group that received sequential treatment. Disease-free interval was 69 vs 21 months, recurrence rate was 42% vs 58%, and disease-specific mortality rate was 6% vs 16%. In terms of preventing progression, the difference in progression rates was

noteworthy (16.2% with BCG, 9.3% with sequential treatment) (39). In their meta-analysis of the long-term outcomes of a total of 2820 patients in 9 studies, Malmström et al. (40) compared mitomycin C and BCG therapy. Over 4.4 years of follow-up, the recurrence rate was 43%. There was no difference between BCG and mitomycin C in terms of time to first recurrence. If maintenance BCG was administered, recurrence was 32% lower compared to mitomycin C. A notable recent publication is a 2018 review by Chantada-Abal et al. (41) which evaluated the safety and efficacy of sequential intravesical BCG and mitomycin C in NMIBC. Their analysis revealed that sequential treatment does not cause more toxicity and leads to prolonged disease-free survival by reducing tumor progression more than BCG or mitomycin C monotherapy. They emphasized the need for further clinical research to enable the adoption of combination therapy into routine practice. Anthracyclines (valrubicin, epirubicin, doxorubicin): drugs in this group have lower systemic absorption and cause fewer systemic adverse effects due to their higher molecular weight. They exert their effects by inhibiting DNA topoisomerase 2 and protein synthesis, and via free radical formation and direct cytotoxicity on the cell membrane (42). Valrubicin is FDA-approved for BCG-refractory CIS patients who are ineligible for cystectomy. A complete response rate of 21% was reported in 90 BCG-refractory CIS patients. Adverse effects are local (symptoms of bladder irritation such as cystitis and hematuria) (43). Epirubicin has fewer adverse effects than doxorubicin but similar efficacy (31). Epirubicin is used at various doses between 20-100 mg, but is most frequently used at 50 mg/50 mL once a week for a total of 8 weeks. In a study by EORTC, comparison of single-dose 80 mg epirubicin with TUR-B alone showed that epirubicin reduced recurrence by 12-15% (44). More recently, intravesical BCG and epirubicin therapies in patients with Ta and T1 bladder cancer were analyzed in terms of recurrence, progression by stage, mortality, distant metastases, and adverse effects. Five studies (549 patients treated with BCG and 562 with epirubicin) were included in the analysis. Recurrence rate was 51.4% in the epirubicin group and 35.5% in the BCG group. Differences between the two groups in terms of distant metastases and progression were not statistically significant. In 2 of the 5 studies analyzed, mortality and morbidity were equal in both groups. Local (cystitis, hematuria) and systemic toxicity (fever, fatigue) were more common in the BCG group (45). Gemcitabine acts by inhibiting cellular growth and inducing apoptosis. It has proven systemic efficacy in metastatic bladder cancer. While the results of its intravesical use are promising, more phase 3 studies are required to determine dosing and efficacy. In primary Ta-T1, patients who did not have CIS and did not receive additional treatment had comparable recurrence and progression rates while adverse effects were less common than with BCG (10% vs 45%). In the high-risk NMIBC group, compared to BCG alone, gemcitabine therapy was associated with shorter time to recurrence (25.5 months vs 39.4 months) and higher recurrence rate (53% vs 28%). In BCG-refractory patients, comparison of BCG and gemcitabine showed that recurrence occurred later and less frequently (52% to 87%) with gemcitabine therapy. Progression and toxicity were similar (46). Doxatrel is an antineoplastic agent that acts by disrupting the microtubular network during cell division. In

2013, 54 BCG non-responders were followed for an average of 39.1 months. Complete response was achieved in 59% of the patients. Recurrence-free survival was 40% in at 1 year and 25% at 3 years. Cystectomy was performed on 24% of the patients. The 5-year disease-free survival rate was reported as 85% (47). Thiotepa is an FDA-approved agent and was the first to be used intravesically in NMIBC. However, it caused severe adverse effects because it is readily absorbed through the bladder mucosa and passes into the systemic circulation due to its low molecular weight. It is hardly ever used today due to its systemic (myelosuppression and secondary leukemia in up to 54%) and local (irritative urinary symptoms up to 70%) adverse effects (48). Interferon alpha is an immunomodulatory and antiproliferative agent. In terms of recurrence, it is less effective compared with BCG and mitomycin C (49).

### Early Single-dose Intravesical Chemotherapy

One of the mechanisms regarded as most important in tumor recurrence is the implantation of residual tumor cells in the bladder after TUR on the mucosal surface. The purpose of early single-dose IVCT is the chemoresection of free tumoral tissues. Technically, it is recommended within the first 24 hours (preferably within the first hours) after TUR-B (50). It is listed as a recommendation in the EAU guidelines for the treatment of low-to-intermediate risk bladder cancers. In a meta-analysis of 1476 patients by Sylvester et al. (51), it was shown that recurrence decreased by 11.7% with early single-dose IVCT. Independent of agent used, recurrence rates are reported as 65% in patients with multiple tumors and 36% in patients with solitary tumors. In a study evaluated based on the EORTC bladder cancer risk classification, it was shown that epirubicin treatment reduced recurrence by 28% in the low-risk group (score 0-2) but had no effect on recurrence in the high-risk group (score 3 or higher). It was emphasized that the best response to treatment was in cases with solitary tumors, and that the same response was not achieved in recurrent multifocal cases (52). Solsona et al. (53) reported that early single-dose IVCT only prevents recurrences occurring within 2 years after TUR-B, but did not prevent recurrences in the longer term. No clear effect of early single-dose IVCT could be demonstrated on progression, recurrence, and time to recurrence in the intermediate- and high-risk group. As a result, the EAU guidelines recommend early single-dose IVCT for low- to intermediate-risk patients with a single tumor focus (54). Choice of drug is based on past experience, accessibility, low cost, and fewer adverse effects. There are no drugs with definitively proven superiority. It is not recommended for wide and very deep resections due to the possibility of extravasation from the bladder and associated risk of systemic toxicity. Secondly, the most important hidden factor in treatment success may be a good pathological examination and obtaining a second confirmation from a different pathology department. Based on these analyses, intravesical approaches to NMIBC can be summarized as follows: early single-dose IVCT alone decreases recurrence only in the low-risk group, and adjuvant IVCT is recommended in the intermediate- and high-risk groups because it increases recurrence-free survival (55). Although the duration of adjuvant IVCT is controversial, less than a year is recommended (56). When TUR-B + IVCT



was compared with TUR-B alone, the recurrence rate decreased by 13-14% with the addition of IVCT (57). BCG and BCG maintenance therapy were found to be more effective than IVCT in reducing progression and preventing recurrence (58).

## Ethics

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