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Factors predicting local or systemic side effects related to intravesical BCG (Bacillus Calmette-Guérin) therapy: a retrospective observational study

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Abstract

Objective Intravesical BCG treatment is the most frequently preferred adjuvant treatment option with its effective results in non-muscle invasive bladder tumors. Despite effective results, systemic and local side effects can be observed and can be one of the main reasons for treatment discontinuation. In this study we aimed to identify clinical factors predicting BCG-related side effects during intravesical BCG therapy in patients with non-muscle invasive bladder cancer.

Methods Demographic and clinical data of patients who received intravesical adjuvant BCG therapy for non-muscle invasive bladder tumor were obtained from patient records. Data on side effects following intravesical BCG therapy and clinical approaches were collected. After creating the patient sample, binary logistic regression analysis was performed to identify parameters and independent risk factors predicting BCG-related side effects, and to evaluate data related to the clinical management of BCG-related side effects.

Results Among the 276 patients included in the study, 23(8.3%) developed BCG-related local and systemic side effects. The mean IPSS(13.5 ± 2.9 vs. 17.6 ± 1.7) and mean tumor size(2.5 ± 0.9 vs. 3.6 ± 1.0 cm)were significantly higher in the group with BCG-related side effects($p < 0.001$). The rate of CIS was significantly higher in the group with BCG-related side effects(21.7% vs. 3.9%,$p = 0.004$). Local side effects included cystitis symptoms in 18(78.2%) patients and epididymo-orchitis in 2(8.6%) patients. Systemic side effects included malaise and fever below 38.5 °C in 4(17.3%) patients, and fever above 38.5 °C lasting longer than 48 h in 2(8.6%) patients. Logistic regression analysis identified IPSS, tumor size, and the presence of CIS as independent risk factors.

Conclusion High IPSS, large tumor size, and the presence of CIS were significant predictors of side effects during intravesical BCG therapy. Clinicians can ensure more effective use of BCG by preventing treatment discontinuation through approaches such as the use of quinolones and dose reduction in patients with these factors.

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Keywords Intravesical BCG therapy, Non-Muscle invasive bladder Cancer, BCG-Related side effects, Independent risk factors

Introduction

Intravesical BCG (Bacillus Calmette-Guérin) therapy is an effective method used as adjuvant treatment for intermediate and high-risk non-muscle invasive bladder cancer (NMIBC) and is recommended in current guidelines [1]. While other adjuvant treatment options, such as intravesical chemotherapeutics like epirubicin and mitomycin C, as well as combined use with interferon, are available for NMIBC, meta-analyses have shown that recurrence and progression is lower in patients who have taken intravesical BCG therapy [2–4].

Intravesical BCG therapy's prominent effect mechanism involves the interaction of the attenuated Mycobacterium bovis strain with the urothelium and fibronectin, leading to humoral immunity that stimulates cytotoxic T cells, thereby targeting tumor cells by the immune system [5]. Typically, intravesical BCG therapy is administered with an induction phase of 1 dose weekly for 6 weeks, followed by a maintenance phase of 1 dose weekly for 3 weeks at the 3rd, 6th, and 12th months over a period of 1 or 3 years [6]. BCG-related side effects are generally observed in less than 5% of cases, with infectious complications being the most common [7]. Infectious complications can be successfully managed with antibiotic therapy and supportive treatment; however, this process can rarely lead to systemic responses such as sepsis [8].

Another risk posed by side effects related to intravesical BCG is the potential discontinuation or incompletion of treatment [9]. Consequently, the inability to provide adjuvant therapy poses a potential risk for tumor recurrence and progression. Patients generally experience symptoms within the first year of treatment, leading to discontinuation [9]. Additionally, findings suggest that elderly patients are able to continue intravesical BCG therapy with fewer side effects [10].

Based on these frequently observed clinical complications that can lead to treatment discontinuation, our study aims to evaluate the associated risk factors in patients who develop side effects following intravesical BCG therapy.

Materials and methods

Patients

The study commenced after obtaining approval from the local ethics committee (Approval No: BAEK 2024/04–90). After receiving approval from the ethics committee, patients diagnosed with NMIBC and treated with intravesical BCG instillation in our urology clinic from January 1, 2014, to December 30, 2023, were included in the study. Patients diagnosed with muscle-invasive bladder tumor, upper urinary tract urothelial cancer, those in the EAU NMIBC low-risk group, those with a history of intravesical chemotherapy, those with positive urine culture before BCG, and those whose medical records were inaccessible were excluded from the study. IPSS, total PSA and prostate volume were obtained from all male patients and 17 patients without these data were excluded from the study.

Clinical management

Patients diagnosed with primary bladder tumors undergo TUR-B, and intravesical BCG therapy is initiated for intermediate and high-risk NMIBC cases based on EAU NMIBC risk classification following pathology results [11]. Intravesical BCG therapy is planned with a 6-week induction BCG treatment, followed by 3-week intravesical BCG treatments at 3, 6, 12, 18, 24, 30, and 36 months. First intravesical BCG administratition was started at least two weeks after last TUR-B. An urine culture is taken before each BCG dose, and appropriate antibiotic therapy is administered in case of infection. Before intravesical BCG treatment, patients are informed about BCG-related side effects according to the EAU guideline and if occurs hospital admission is recommended. Patients who develop cystitis related to intravesical BCG are recorded in the hospital's record system upon the relevant application and hospitalized if necessary. Patients who didn't develop BCG-related side effects or didn't apply to the hospital are questioned about side effects when they came for the next BCG dose and are recorded in the hospital record system. BCG-related side effects were classified as local and systemic, according to EAU 2024 guidelines. Patients with lower urinary tract symptoms such as dysuria, urgency, hematuria, and pollakiuria without bacterial growth in urine culture, as well as those developing epididymo-orchitis and granulomatous prostatitis, were identified as having local side effects, whereas fever above > 38.5 °C and over 48 h, malaise accompanied by arthralgia, allergic rashes, and sepsis were considered systemic side effects [1].

Data collection

After applying the inclusion and exclusion criteria, demographic and clinical data obtained prior to TUR-B were recorded from the hospital management system. These data included age, gender, BMI, smoking status, preoperative complete blood count, serum creatinine levels, total PSA (for male patients), International Prostate Symptom Score (IPSS) (for male patients), and prostate volume (for male patients). Data on tumor location, size (of the

largest lesion), and operation duration were obtained from operation notes. Tumor diameter was measured intraoperatively using the tip of the TUR loop. Pathological data, including tumor T stage, grade, and accompanying carcinoma in situ (CIS), were collected. Additionally, BCG-related side effects, the time of side effects, treatment and follow-up period, and data of patients whose treatment had to be terminated were recorded.

Statistical analysis

Data were analyzed using SPSS, version 22.0. Categorical variables were reported as numbers and percentages, while continuous variables were expressed as means and standard deviations. The normality of continuous variable distributions was assessed with the Kolmogorov-Smirnov test. For comparing the means of two independent groups with normal distributions, the Student's t-test was used. For groups that did not follow a normal distribution, the Mann-Whitney U test was applied. The percentages of categorical variables were compared using Pearson's chi-square test and Fisher's exact test. Univariable and multivariable logistic regression analyses were performed to identify factors predictive of BCG-related side effects. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 276 patients who received intravesical BCG therapy were included in the study. Among these, 23 patients (8.3%) developed BCG-related local and systemic side effects. The mean age for the groups with and without BCG-related side effects was 59.8 ± 6.5 years and 57.5 ± 6.3 years ($p > 0.05$). When comparing demographic and clinical parameters, gender, BMI, smoking history, WBC count, HGB level, PLT count, creatinine, PSA levels, and prostate volume were similar between the groups ($p > 0.05$). The mean IPSS was significantly higher in the group with BCG-related side effects (13.5 ± 2.9 vs. 17.6 ± 1.7, $p < 0.001$). Timing of first BCG dose were similar for each groups (17.4 ± 2.1 vs. 18.0 ± 1.9, $p > 0.05$).

When comparing intraoperative findings and pathological results between the groups, tumor size and operation time were significantly higher in the group with BCG-related side effects ($p < 0.001$). Tumor localization and tumor T classification were similar for both groups ($p > 0.05$). The rate of CIS in the group with BCG-related side effects was significantly higher at 21.7% compared to 3.9% ($p = 0.004$), and the rate of low-grade tumors was 56.5% compared to 30.4% ($p = 0.011$). The clinical characteristics and their comparison between groups are presented in Table 1.

BCG-related side effects included cystitis symptoms in 18 (78.2%) patients, epididymo-orchitis in 2 (8.6%) patients as local side effects, malaise and fever below 38.5 °C in 4 (17.3%) patients, and fever above 38.5 °C lasting longer than 48 h in 2 (8.6%) patients as systemic side effects. Twelve patients with local side effects had positive urine cultures. Two of the patients with systemic side effects had positive urine cultures. Side effects were observed during the induction phase of BCG therapy in 15 patients, within the first year in 5 patients, and after the first year in 6 patients. One patient discontinued treatment due to BCG-related cystitis symptoms, 2 patients due to epididymo-orchitis, and 2 patients due to fever lasting longer than 48 h. One of these patients developed a contracted bladder despite treatment, and radical cystectomy was planned. The clinical characteristics, treatment protocols, and follow-up data of patients with BCG-related side effects are summarized in Table 2.

Univariate binary logistic regression analysis was conducted to assess the parameters predicting BCG-related side effects. In the univariate analysis, IPSS, tumor size, the presence of CIS, and WHO bladder tumor grade (LG, HG) were identified as significant predictive factors. Due to the small number of female patients, they were excluded from the multivariate analysis, which identified IPSS, tumor size, and the existence of CIS as independent risk factors for predicting BCG-related side effects ($p < 0.05$). Table 3 shows the results of binary logistic regression analysis.

Discussion

Intravesical BCG therapy is a treatment modality recommended in the EAU 2024 guidelines, having been shown to be most effective treatment option in reducing both recurrence and progression in intermediate- and high-risk NMIBC [12]. However, this treatment modality carries the risk of local inflammatory reactions and even severe systemic infections, which can be life-threatening [13]. While the precise rate of side effects from intravesical BCG therapy is not thoroughly documented, the EAU 2024 guidelines suggest that severe adverse effects are reported in less than 5% of patients. In a cohort study conducted by Larsen et al., involving 15 years of patient data, the incidence of BCG-related side effects was reported to be 1%, with 78.4% of these being local genitourinary system-related [8]. Brausi et al. reported cystitis symptoms as the most common side effect, observed in 35% of cases following intravesical BCG therapy [9]. In our sample, the incidence of BCG-related side effects was 8.3%, with cystitis symptoms being the most frequently observed side effect, similar to other studies. Larsen et al.'s retrospective cohort study only screened patients with ICD (International Statistical Classification of Diseases and Related Health Problems) codes, while Brausi et al. conducted a prospective multicenter study. The different designs of these studies and the varying rates of

Table 1 Comparison of demographic and clinic variables between BCG related side effects observed and non-observed group

Variables	None BCG side effects	BCG side effects	*P* value
Number of patients, n(%)	253 (91.7)	23 (8.3)	
Gender, n(%)			1.000&
Male	232 (91.6)	22 (95.7)	
Female	21 (8.4)	1 (4.3)	
Mean age ± SD, (yrs)	57.5 ± 6.3	59.8 ± 6.5	0.822**
Smoking, n(%)			0.274#
Yes	140 (55.3)	10 (43.5)	
No	113 (44.7)	13 (56.5)	
Mean BMI ± SD, kg/m^2	22.9 ± 2.09	23.7 ± 2.92	0.100**
Mean WBC count ± SD, µ/L	8.47 ± 2.11	8.35 ± 2.04	0.753**
Mean HGB level ± SD, g/dl	15.3 ± 1.7	15.5 ± 1.0	0.784**
Mean PLT count ± SD, 10^3 µ/L	281.9 ± 65.4	278.9 ± 67.9	0.831*
Mean creatinine value ± SD, mg/dL	0.89 ± 0.31	0.90 ± 0.20	0.793*
Mean PSA ± SD, ng/ml	1.3 ± 0.9	1.3 ± 0.6	0.286**
Mean prostat volume ± SD, ml	63.9 ± 17.3	69.4 ± 25.6	0.413**
Mean IPSS ± SD	13.5 ± 2.9	17.6 ± 1.7	**< 0.001****
Mean tumor diameter ± SD, cm	2.5 ± 0.9	3.6 ± 1.0	**< 0.001****
Tumor localization, n(%)			0.251&
Trigon (1)	66 (26.1)	11 (47.8)	1 vs. 2 0.266
Right bladder wall (2)	65 (25.7)	6 (26.1)	1 vs. 3 0.155
Left bladder wall (3)	46 (18.2)	3 (13.0)	1 vs. 4 0.130
Upper wall (4)	38 (15.0)	2 (8.7)	1 vs. 5 0.058
Posterior wall (5)	38 (15.0)	1 (4.3)	2 vs. 3 0.736
			2 vs. 4 0.709
			2 vs. 5
			0.418
			3 vs. 4
			1.000
			3 vs. 5
			0.626
			4 vs. 5
			1.000
T stage, n(%)			0.584#
Ta	114 (45.1)	9 (39.1)	
T1	139 (54.9)	14 (60.9)	
Second TUR-B			0.852#
Yes	154 (60.8)	15 (65.2)	
No	99 (39.2)	8 (34.8)	
Carcinoma in situ, n(%)			**0.004&**
Yes	10 (3.9)	5 (21.7)	
With T1	8 (80.0)	5 (100.0)	
With Ta	2 (20.0)	0 (0.0)	
No	243 (96.1)	18 (78.3)	
Tumors' WHO grade, n(%)			**0.011#**
Low grade	77 (30.4)	13 (56.5)	
High grade	176 (69.6)	10 (43.5)	
Mean operation time ± SD, min.	34.9 ± 18.6	45.5 ± 12.2	**0.003****
Timing of first BCG ± SD, days	17.4 ± 2.1	18.0 ± 1.9	0.153*

*Independent sample t test

**Mann whitney U test

#Pearson chisquare test

&Fisher's exact test

SD, standart deviation; BCG, Bacillus calmette guerin; SD, standart deviation; BMI, body mass index; WBC, white blood cell; HGB, Hemoglobine; PLT, platelet; PSA, Prostate specific antigen; IPSS, International prostatic symptom score

Statistically significant values shown as bold

Table 2 BCG-related side effects, clinical management and follow-up characteristics

BCG-related side effects	*N* (%)	Time of symptoms	Clinical management and treatment	Follow-up
Local	20 (86.9)			
Symptoms of cystitis	18 (78.2)	Induction period: 12 (66.6) Induction-1 year: 5 (27.7) Over 1 year: 1 (5.5)	BCG treatment postponed. Urine culture performed. 11 patients' urine cultures were positive. Quinolon and NSAİD were started.	17 patient continues ıntravesical BCG treatment. 1 patient developed contracted bladder and underwent radical cystectomy.
Epididimo-orchitis	2 (8.6)	Over 1 year: 2 (100.0)	BCG treatment stopped. Urine culture performed. 1 patient's urine culture was positive. Quinolon and NSAİD were started.	Intravesical therapy was stopped.
Systemic	6 (26.0)			
Fever > 38.5 °C for > 48 h	2 (8.6)	Induction period: 2 (100)	BCG treatment stopped. Urine culture, Chest X-ray and blood tests performed. 2 patients' urine culture were positive. Meropenem was started with the recommendation of the infectious diseases specialist.	Intravesical therapy was stopped.
Malasia with fever < 38.5 °C for < 48 h	4 (17.3)	Induction period:1 (25.0) Over 1 year: 3 (75.0)	BCG treatment postponed. Urine culture performed. NSAİD started.	Intravesical therapy continues.

Table 3 To predict BCG related side effects, univariable and multivariable binary logistic regression analysis were performed

Variable	Univariate			Multivariate		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Age(yr)	1.006	0.724-1.104	0.683			
Gender	0.581	0.072-4.383	0.581			
BMI(kg/m^2)	1.005	0.374-2.702	0.992			
Smoking(mm)	0.484	0.193-1.216	0.123			
WBC count(µ/L)	1.003	0.796-1.263	0.981			
HGB level(g/dl)	1.083	0.812-1.445	0.586			
PLT count(10^3 µ/L)	1.000	0.993-1.006	0.903			
Creatinine value(mg/dL)	1.064	0.099-5.047	0.730			
PSA value(ng/ml)	0.700	0.518-1.554	0.898			
Prostate volume(ml)	1.018	0.995-1.042	0.119			
IPSS	1.359	1.197–1.542	**< 0.001**	1.269	1.110–1.451	< 0.001
Tumor diameter(cm)	2.708	1.709–4.291	**< 0.001**	2.666	1.561–4.553	< 0.001
TNM classification(Ta-T1)	1.377	0.544-3.476	0.495			
Carcinoma in situ	6.500	1.982–21.320	**0.002**	5.271	1.165–23.839	0.031
WHO grade (LG-HG)	0.337	0.141–0.801	0.014	1.667	0.181-1.442	0.205
Operation time(min.)	1.023	0.994-1.047	0.057			
Timing of first BCG (days)	1.012	0.802-1.119	0.672			

OR, odds ratio; CI, confidence interval; BMI, body mass index; WBC, white blood cell; HGB, hemoglobine level; PLT, platelet count; PSA, prostate specific antigen; IPSS, International prostatic symptom score; LG, Low grade; HG, High grade; WHO, world health organization

Statistically significant values shown as bold

BCG-related side effects observed in our sample can be attributed to the differences in study designs.

Deterioration in bladder function following TUR-B, may be confused with BCG toxicity. Lower urinary tract symptoms are frequently observed after TUR-B, particularly following deep resections involving large areas. Reduced bladder capacity and impaired contractility are expected outcomes in such cases. Although this raises the question of whether lower urinary tract symptoms in symptomatic patients are related to BCG or TUR-B, the absence of large-based tumor resections in our sample that could have caused bladder dysfunction, along with symptom improvement after treatment, supported the evaluation of patients in terms of BCG toxicity. The lack of standardized definitions based on duration and symptoms in evaluating BCG toxicity highlights the necessity of further investigation and underscores the need for a classification system in this regard.

The most significant factor that puts clinicians in a dilemma regarding the application of intravesical BCG is the potential for serious systemic side effects. Systemic side effects can manifest in various clinical presentations, including malaise, fever, arthralgia, allergic reactions, and BCG sepsis, requiring long-term treatment [14].

Although the incidence of BCG-related sepsis is less than 1%, its potential to cause mortality has driven clinicians to seek preventive approaches [15]. The most commonly implemented protocol is to complete the treatment regimen with a one-third dose, which has been shown in literature studies to reduce BCG toxicity while preventing recurrence and progression similarly to the full-dose regimen [16–18]. However, the EORTC study suggests that dose reduction does not decrease toxicity and increases the risk of recurrence, particularly in the one-year treatment group [19]. Another approach involves the use of quinolone antibiotics in conjunction with intravesical BCG, which has been reported to reduce side effects, although it is not yet a standardized routine clinical prophylaxis [20]. Therefore, dose reduction or the addition of quinolones in patients at high risk for BCG-related side effects could be alternative approaches for clinicians.

Although there are limited studies investigating risk factors for BCG toxicity, age has been examined in a study by Oddens et al., which reported that 16.4% of patients over 75 years of age discontinued treatment due to BCG toxicity compared to 21.9% of those aged 60 and below [10]. In a study by Brausi et al. comparing BCG administration regimens, no significant findings were detected regarding BCG toxicity among groups based on dose and timing of administration [9]. In this study, side effects leading to discontinuation of treatment were predominantly observed in the first year. Similarly, in our study, intravesical BCG-related side effects were most frequently observed during the induction period of BCG therapy. Supporting the literature, fewer side effects were encountered after the first year of intravesical BCG therapy [21].

In the cohort analysis by Larsen et al., male gender was identified as a risk factor for BCG-related side effects, while age and comorbidity burden were not [8]. In our sample, gender was not a statistically significant factor for BCG-related side effects, which could be due to the limited number of female bladder cancer cases.

The IPSS, a widely used tool for evaluating benign prostatic hyperplasia (BPH), helps assess the severity of lower urinary tract symptoms and the effectiveness of BPH management [22]. Given that advanced age and male gender are risk factors for bladder cancer, BPH and LUTS are often encountered comorbidities in this patient group. Consequently, IPSS, which had not been previously evaluated as a parameter according to our literature review, emerged as an independent risk factor for the development of BCG-related side effects in male patients in our study.

Tumor diameter and the existence of CIS are crucial parameters for classifying patients with non-muscle invasive bladder cancer (NMIBC) into intermediate- and high-risk categories, as they indicate the extent and aggressiveness of the disease within the bladder and significantly influence treatment decisions [1]. We hypothesize that in patients with larger tumor sizes and CIS, the larger resected bladder mucosa area may increase the contact of intravesical BCG with the systemic circulation, potentially leading to more frequent side effects.

Despite the findings presented in our study, there are limitations. The small number of female cases limited the ability to evaluate gender as a significant factor. Due to the retrospective design, the timing of the first BCG dose was not available for all patients, and the small sample size is a primary limitation. Despite these limitations, our study contributes to current research on BCG toxicity, suggesting that parameters such as IPSS, tumor size, and the presence of CIS, which we identified as risk factors, should be considered by clinicians. In patients at high risk for BCG-related side effects, dose reduction or the addition of quinolone prophylaxis may help reduce the risk of BCG toxicity and provide valuable guidance to clinicians.

Conclusions

Intravesical BCG therapy, especially during the first year of treatment, is associated with BCG-related side effects. Independent risk factors for predicting these side effects include a high IPSS, larger tumor size, and accompanying CIS. Evaluating these factors in high-risk patients can help clinicians take preventive measures, such as the use of quinolones or dose reduction, without compromising the effectiveness of BCG therapy. Additional researches with larger sample sizes is necessary to validate these findings and develop more detailed guidelines for managing BCG toxicity.

Abbreviations

BCG	Bacillus Calmette Guerin
NMIBC	Non-muscle invasive bladder cancer
EAU	European Association of Urology
TUR-B	Transurethral resection-bladder
BMI	Body mass index
PSA	Prostate specific antigen
IPSS	International prostatic symptom score
CIS	Carcinoma in situ
SPSS	Statistical Package for the Social Sciences
WBC	White Blood Cell
HGB	Hemoglobine
PLT	Platelet
LG	Low grade
HG	High grade
ICD	International Statistical Classification of Diseases and Related Health Problems
EORTC	European Organisation For Research And Treatment Of Cancer
LUTS	Lower Urinary Tract Symptoms

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Author contributions
TA, FC and AEC designed the study protocol. SOD and MA collected the data and did the statystical analysis. IK and AU revised the manuscript. All authors wrote and revised the main text.

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Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the University of Health Sciences, Erzurum Medicine Faculty Scientific Research Ethics Committee. This study was conducted in accordance with the Declaration of Helsinki.

Consent for publication
Written informed consent was taken from all participants to participate in the study.

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Conflict of interest
All authors declare no potential conflict of interest with this publication.

Competing interests
The authors declare no competing interests.

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