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Acute Adverse Events of Intravesical Bacillus Calmette-Guérin Induction in Non-Muscle-Invasive Bladder Cancer: A Prospective Observational Study From a Tertiary Care Centre in South India

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Abstract

Introduction

Intravesical bacillus Calmette-Guérin (BCG) is the standard adjuvant treatment for intermediate- and high-risk non-muscle-invasive bladder cancer (NMIBC), but its adverse events can limit tolerability. Prospective data on the acute adverse events of BCG induction in Indian practice are limited. We describe the acute adverse events of BCG induction at a tertiary care centre in South India.

Methods

In this prospective observational study, 29 consecutive patients with histologically confirmed NMIBC received a six-week induction course of intravesical BCG (120 mg weekly) after complete transurethral resection between December 2023 and February 2025. Patients were assessed at each weekly instillation and for one month after the last instillation. Adverse events were classified as local or systemic, and proportions are reported with exact 95% confidence intervals (CIs).

Results

The median age was 67 years (interquartile range 52-73), and 25 patients (86.2%) were male. Adverse events occurred in 17/29 (58.6%) patients (95% CI 38.9-76.5). Local events occurred in 12 patients (41.4%): cystitis in 10 (34.5%), hematuria in one (3.4%), and epididymo-orchitis in one (3.4%). Systemic events occurred in five patients (17.2%), all of which were fever below 38.5°C. In 16 of the 17 affected patients (94.1%), the adverse event began within 48 hours of an instillation. No patient required hospital admission or interruption of BCG therapy (0/29, 0%; 95% CI 0-11.9), and no baseline characteristic was significantly associated with adverse events.

Conclusions

In this small cohort treated with 120-mg Russia (Moscow) strain BCG, acute adverse events during induction were common, predominantly local and began early after instillation, and none led to hospital admission or interruption of treatment. These findings support outpatient induction with early symptom review after each instillation, but this sample cannot exclude uncommon serious complications; larger studies with standardised grading and follow-up through maintenance are needed.

Categories: Urology, Oncology
Keywords: adverse events, bcg immunotherapy, bladder cancer, intravesical therapy, non-muscle-invasive bladder cancer

Introduction

Bladder cancer is one of the most common urological cancers worldwide [1], and most patients present with non-muscle-invasive bladder cancer (NMIBC) [2]. After complete transurethral resection of bladder tumour (TURBT), intravesical bacillus Calmette-Guérin (BCG) immunotherapy is recommended for intermediate- and high-risk disease [2], and a meta-analysis of randomised trials showed that BCG reduces the risk of progression [3].

The benefit of BCG comes at the cost of frequent adverse events. In the European Organisation for Research

and Treatment of Cancer (EORTC) 30962 trial, 69.5% of 1,316 patients had local or systemic side effects, and 7.8% stopped treatment because of them [4]. Most events are irritative bladder symptoms and low-grade fever, but serious complications, such as BCG sepsis and disseminated BCG infection, are rare and potentially life-threatening [5,6]. Older age has not been associated with toxicity leading to treatment discontinuation [7].

Bacillus Calmette-Guérin strain and dose differ between countries. Moscow-strain BCG is used in Indian practice, and its optimal intravesical dose has been debated [8,9]. In an Indian series comparing two strains, moderate-to-severe adverse events were more frequent with Moscow-I than with Danish 1331 BCG (67.4% vs. 48.5%) [10]. Prospective data collected systematically at each instillation during induction remain limited, particularly for the 120-mg dose of the Russia (Moscow) strain used in Indian practice.

We therefore prospectively recorded the type, timing, and consequences of acute adverse events during BCG induction in patients with NMIBC at a tertiary care centre in South India, and we explored whether baseline patient and tumour characteristics were associated with these events.

Materials And Methods

Study design, setting, and ethics

This prospective observational study was conducted in the Department of Urology, Sri Venkateswara Institute of Medical Sciences (SVIMS), Tirupati, India. The study was approved by the Institutional Ethics Committee (IEC) of SVIMS (IEC No. 1587; approval dated December 23, 2023). Consecutive eligible patients who started BCG induction after ethics approval were enrolled from December 25, 2023, until February 2025, and written informed consent was obtained from all participants. The study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [11].

Participants

Patients with histologically confirmed NMIBC who were scheduled for intravesical BCG after complete TURBT were eligible, including patients whose TURBT preceded ethics approval, provided that all instillations were given after approval. All patients had intermediate- or high-risk disease according to the European Association of Urology (EAU) criteria, as assessed by the treating surgeon; patients with Ta low-grade tumours received BCG because of intermediate-risk features, such as multiple, large (>3 cm) or recurrent tumours [2]. Detrusor muscle was present in the resection specimens of patients with T1 tumours, and a second TURBT was not routinely performed when the initial resection was macroscopically complete and the detrusor muscle was present and uninvolved. A single immediate postoperative instillation of mitomycin C was given routinely after TURBT, except in patients with incomplete resection, suspected perforation, gross hematuria or other contraindications. Tumours were staged according to the tumour, node, and metastasis classification [2] and graded as low- or high-grade according to the 2016 World Health Organization classification [12]. Performance status was recorded with the Eastern Cooperative Oncology Group (ECOG) scale [13]. Patients who declined participation, had known hypersensitivity to BCG, were immunocompromised, or had urinary incontinence that would prevent retention of the instillation were excluded. The minimum sample size of 29 patients was calculated with the single-proportion formula $n = \frac{z^2 p(1-p)}{d^2}$, using z = 1.96, an anticipated proportion (p) of 5% and an absolute precision (d) of 8%. All consecutive eligible patients during the study period were enrolled, and no power calculation was performed for comparisons between subgroups.

BCG administration

Induction of BCG was started two to three weeks after TURBT. Each instillation consisted of 120 mg of BCG (Onco-BCG, Serum Institute of India, Pune, India; BCG strain Russia, also known as the Moscow strain [14]; three 40-mg vials) reconstituted in 50 mL of normal saline and was given once weekly for six weeks. Instillations were performed under aseptic conditions through an atraumatic urethral catheter after complete bladder drainage. Patients retained the instillation for two hours, changing position every 30 minutes, and then voided.

Assessment of adverse events

Patients were reviewed at each weekly instillation, and symptoms and clinical findings were recorded on a structured proforma that included irritative and obstructive lower urinary tract symptoms, hematuria, dysuria, fever, allergic reactions, and loin pain. Instillations were given only in the absence of symptomatic urinary infection or gross hematuria, and no scheduled instillation had to be postponed. Follow-up continued for one month after the sixth instillation. As in previous reports [4,15], adverse events were classified as local (cystitis, hematuria, and epididymo-orchitis) or systemic (fever and other systemic manifestations); fever was categorised as below or at least 38.5°C. Cystitis was defined as new or worsening lower urinary tract symptoms or dysuria persisting for more than 48 hours after an instillation [16], hematuria as macroscopic hematuria, fever as an axillary temperature of 38.0°C (100.4°F) or higher, and

epididymo-orchitis as scrotal pain and swelling confirmed by ultrasonography. The time of onset was recorded as within or after 48 hours of the preceding instillation; these operational thresholds follow published descriptions of BCG-related adverse events, in which irritative symptoms and fever below 38.5°C usually resolve within 48 hours [16], and hospital admission and any interruption of BCG therapy were documented. Adverse events were not graded with a standardised system, such as the Common Terminology Criteria for Adverse Events (CTCAE). One adverse-event category was recorded for each affected patient; when a patient had more than one type of event, such as cystitis with fever, the predominant event, as judged by the treating clinician, was recorded. Urine culture was obtained only when symptoms suggested urinary infection, and no routine prophylactic antibiotics, anticholinergics or anti-inflammatory drugs were given. The primary outcome was any adverse event during induction or the one-month follow-up.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range, IQR), and categorical variables as numbers and percentages. Proportions of adverse events are reported with exact (Clopper-Pearson) 95% confidence intervals (CIs) [17]. Associations between baseline characteristics and any adverse event were explored with Fisher's exact test, with conditional maximum likelihood odds ratios (ORs) and exact 95% CIs reported as the measure of association, because Fisher's exact test does not produce a t, χ^2, or F statistic; age was compared with the Mann-Whitney U test, and the U statistic is reported. Because the sample was small and these comparisons were exploratory, no adjustment was made for multiple testing and no multivariable model was fitted. All tests were two-sided, and $P<0.05$ was considered statistically significant. The data were analysed in Python version 3.11 (Python Software Foundation, Wilmington, Delaware, United States) with the pandas (version 3.0.2) and SciPy (version 1.17.1) libraries [18].

Results

Patient and tumour characteristics

Twenty-nine patients were enrolled, and all 29 (100%) completed the six-week induction course. The mean age was 62.1 ± 18.3 years (median 67, IQR 52-73; range 21-85), and 14 patients (48.3%) were aged 70 years or older. Twenty-five patients (86.2%) were male, 19 (65.5%) had a history of smoking, and 19 (65.5%) had at least one comorbidity, most commonly hypertension (12, 41.4%) and diabetes mellitus (nine, 31.0%). High-grade tumours were present in 17 patients (58.6%), stage T1 tumours in 13 (44.8%), and multiple tumours in eight (27.6%); no patient had carcinoma in situ (0/29, 0%) (Table *1*).

Characteristic	Value
Age, years, mean ± SD	62.1 ± 18.3
Age, years, median (IQR); range	67 (52–73); 21–85
Age ≥70 years	14 (48.3)
Male sex	25 (86.2)
History of smoking	19 (65.5)
Any comorbidity	19 (65.5)
Hypertension	12 (41.4)
Diabetes mellitus	9 (31.0)
Coronary artery disease	3 (10.3)
Chronic obstructive pulmonary disease	1 (3.4)
Chronic kidney disease	1 (3.4)
ECOG performance status 0	8 (27.6)
ECOG performance status 1	11 (37.9)
ECOG performance status 2	9 (31.0)
ECOG performance status 3	1 (3.4)
High-grade tumor	17 (58.6)
Stage Ta	16 (55.2)
Stage T1	13 (44.8)
Ta low-grade tumour	8 (27.6)
Ta high-grade tumour	8 (27.6)
T1 low-grade tumour	4 (13.8)
T1 high-grade tumour	9 (31.0)
Carcinoma in situ	0 (0)
Multiple tumors	8 (27.6)

TABLE 1: Baseline patient and tumor characteristics (n=29)

Values are n (%) unless otherwise indicated. Comorbidities are not mutually exclusive. ECOG: Eastern Cooperative Oncology Group; IQR: interquartile range; SD: standard deviation.

Adverse events

Adverse events occurred in 17 of 29 patients (58.6%; 95% CI 38.9-76.5; Table *2*, Figure *1*). Local events occurred in 12 patients (41.4%; 95% CI 23.5-61.1): cystitis in 10 (34.5%), hematuria in one (3.4%), and epididymo-orchitis in one (3.4%). Systemic events occurred in five patients (17.2%; 95% CI 5.8-35.8), and all had fever below 38.5°C; no patient had fever of 38.5°C or higher (0/29, 0%).

Outcome	n/N	% (95% CI)
Any adverse event	17/29	58.6 (38.9–76.5)
Local adverse event	12/29	41.4 (23.5–61.1)
Cystitis	10/29	34.5 (17.9–54.3)
Hematuria	1/29	3.4 (0.1–17.8)
Epididymo-orchitis	1/29	3.4 (0.1–17.8)
Systemic adverse event	5/29	17.2 (5.8–35.8)
Fever <38.5°C	5/29	17.2 (5.8–35.8)
Fever ≥38.5°C	0/29	0 (0–11.9)
Onset within 48 hours of instillation	16/17	94.1 (71.3–99.9)
Onset after 48 hours	1/17	5.9 (0.1–28.7)
Hospital admission	0/29	0 (0–11.9)
Interruption of BCG therapy	0/29	0 (0–11.9)

TABLE 2: Acute adverse events during BCG induction and one-month follow-up (n=29)

One adverse-event category was recorded for each affected patient. Onset percentages use the 17 patients with an adverse event as the denominator. 95% CIs are exact (Clopper-Pearson). BCG: Bacillus Calmette-Guérin; CI: confidence interval.

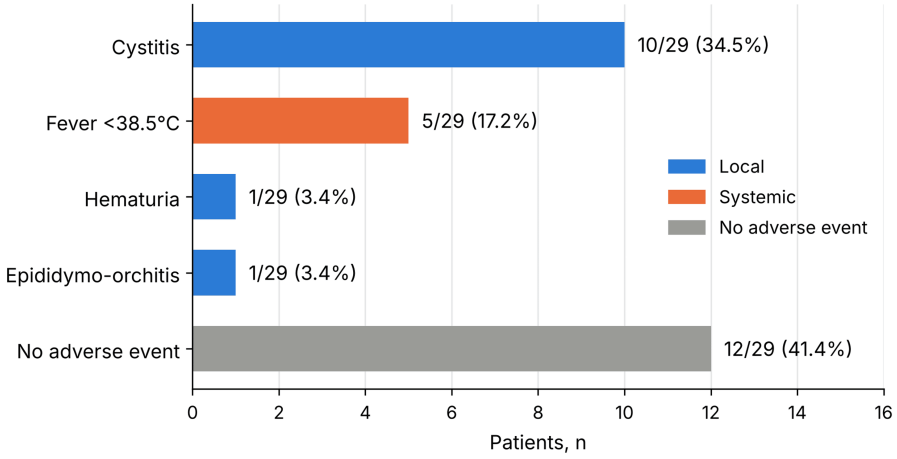


FIGURE 1: Acute adverse events during BCG induction (n=29)

Number and percentage of patients with each recorded outcome during BCG induction and one-month follow-up. One adverse-event category was recorded for each affected patient. BCG: Bacillus Calmette-Guérin.

The patient with epididymo-orchitis developed scrotal tenderness and mild swelling three to four days after the sixth and final induction instillation, and ultrasonography confirmed the diagnosis. The episode was mild, and he improved with oral antibiotics and analgesics, so anti-tubercular therapy was not given; the symptoms resolved gradually. Because the event occurred after induction was complete, no change in BCG therapy was required, and he later received maintenance BCG as planned. This was the only adverse event that began more than 48 hours after an instillation.

Factors associated with adverse events

No baseline characteristic was significantly associated with adverse events (Table 3). Adverse events were numerically less frequent in patients aged 70 years or older (6/14, 42.9%, vs. 11/15, 73.3%; OR 0.29, 95% CI 0.04-1.63; P=0.139) and in patients with a history of smoking (9/19, 47.4%, vs. 8/10, 80.0%; OR 0.24, 95% CI

0.02-1.65; P=0.126), but these differences were not statistically significant. The median age was 66 years in patients with an adverse event and 73 years in those without (Mann-Whitney U=76.5; P=0.267; Table 3).

Characteristic	Characteristic present: adverse event, n/N (%)	Characteristic absent: adverse event, n/N (%)	OR (95% CI) or U statistic	P
Age, years, median (IQR): with vs without an adverse event	66 (49–73)	73 (58–76)	U=76.5	0.267
Age ≥70 years	6/14 (42.9)	11/15 (73.3)	0.29 (0.04–1.63)	0.139
Male sex	15/25 (60.0)	2/4 (50.0)	1.48 (0.09–23.59)	1.000
History of smoking	9/19 (47.4)	8/10 (80.0)	0.24 (0.02–1.65)	0.126
Any comorbidity	11/19 (57.9)	6/10 (60.0)	0.92 (0.14–5.54)	1.000
ECOG performance status ≥2	6/10 (60.0)	11/19 (57.9)	1.09 (0.18–7.12)	1.000
High-grade tumor	10/17 (58.8)	7/12 (58.3)	1.02 (0.17–5.78)	1.000
Stage T1	6/13 (46.2)	11/16 (68.8)	0.40 (0.07–2.25)	0.274
Multiple tumors	5/8 (62.5)	12/21 (57.1)	1.24 (0.18–10.16)	1.000

TABLE 3: Exploratory associations between baseline characteristics and any adverse event

For age (first row), values are median (IQR) in patients with and without an adverse event, compared with the two-sided Mann-Whitney U test; the U statistic is shown. For the other rows, P values are from two-sided Fisher's exact tests, which do not produce a t, χ^2, or F statistic; conditional maximum likelihood odds ratios with exact 95% CIs are shown as the measure of association. P values are not adjusted for multiple comparisons. CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; IQR: interquartile range; OR: odds ratio; U: Mann-Whitney U statistic.

Discussion

In this prospective cohort, 17 of 29 patients (58.6%) had an acute adverse event during BCG induction. Most events were local (12/17, 70.6%), chiefly cystitis (10/17, 58.8%), and all systemic events (5/5, 100%) were low-grade fever. In almost all affected patients (16/17, 94.1%), the adverse event began within 48 hours of an instillation, and no patient (0/29, 0%) needed hospital admission or interruption of therapy.

The overall frequency of adverse events is consistent with that in larger series. In the EORTC 30962 trial, 69.5% of patients had local or systemic side effects, and 7.8% stopped treatment [4]. In retrospective series, BCG was interrupted in 35.6% of 149 Indian patients treated with Moscow-strain BCG, in 15.4% because of adverse effects, and cystitis occurred in 26.2% [19]; treatment was terminated in 8% of 101 Indian patients with high-risk disease [20]; and, in 239 patients from Türkiye, cystitis occurred in 27.6% and fever in 23.8% [21]. The proportions of cystitis and fever in our cohort are broadly comparable with these reports. The EORTC trial followed patients through up to three years of maintenance, whereas our observation was limited to induction and one month of follow-up, which may partly explain the lower proportion and the absence of treatment discontinuation in our cohort.

Published data on Moscow-strain BCG are limited and heterogeneous. In an Indian two-strain comparison, moderate-to-severe adverse events, defined to include treatment dropout, were more frequent with Moscow-I than with Danish 1331 BCG (67.4% vs. 48.5%) [10], whereas a retrospective series of 60 patients treated with Onco-BCG reported only grade 1 and grade 2 adverse reactions [9]. In a Swiss prospective registry of the same product at the same 120-mg dose, adverse events occurred in 72.3% of 101 patients over induction and maintenance, and 3% discontinued treatment during induction [14]. Our findings are closer to the latter: events were frequent, but none led to admission or interruption. Because the optimal dose of Moscow-strain BCG has been debated [8], prospective studies that compare doses with standardised toxicity grading would be useful.

The timing of events has practical implications. In 16 of 17 affected patients (94.1%), the adverse event began within 48 hours of instillation, which supports counselling patients before each instillation and reviewing symptoms during the first two days, either in person or by telephone. Persistent fever or symptoms lasting beyond this period should prompt evaluation for BCG infection, which, although uncommon, can be serious [5,6], and practical recommendations for the prevention and management of BCG-related adverse events have been published [15,16].

No serious adverse events occurred, but our sample cannot exclude them. With no events among 29

patients, the upper limit of the 95% CI for hospital admission or treatment interruption is 11.9%, so this study can only rule out such events occurring more often than about one in eight patients. Rare complications, such as BCG sepsis, require much larger cohorts or registries to estimate [6]. Our findings also apply specifically to acute toxicity during induction with the 120-mg Russia (Moscow) strain product used in this study and may not apply to other strains, doses or maintenance schedules.

We found no significant association between adverse events and age, sex, smoking, comorbidity, performance status, tumour grade, stage, or multiplicity. This is consistent with the EORTC finding that older age was not associated with discontinuation because of toxicity [7]. However, because the subgroups were small and the comparisons were not powered, the absence of statistically significant associations does not show that these factors are unrelated to toxicity, and the numerically lower frequency of adverse events in older patients and in smokers should not be over-interpreted.

This study has several limitations. It was a small, single-centre study, and the results may not apply to other BCG products, doses, or populations; immunocompromised patients were excluded. Follow-up covered induction only, so adverse events during maintenance therapy were not captured. Adverse events were not graded with a standardised system, such as the CTCAE, and only one adverse-event category was recorded for each affected patient, so patients with more than one type of event could not be identified. Onset was recorded only as within or after 48 hours, and urine culture was obtained only in symptomatic patients, so BCG cystitis could not be systematically distinguished from bacterial infection. Individual risk factors, such as tumour size and prior recurrence, were not recorded in the study data set, so each patient's EAU risk group could not be verified retrospectively, and a routine second TURBT, recommended by current guidelines for T1 tumours, was not performed. Oncological outcomes were not assessed.

Conclusions

In this prospective cohort of patients receiving induction with 120-mg Russia (Moscow) strain BCG for NMIBC, acute adverse events were common but predominantly local; fevers were low-grade, almost all events began early after an instillation, and none led to hospital admission or interruption of treatment. No patient or tumour characteristic was significantly associated with adverse events, although the study was too small to exclude such associations. These findings support outpatient BCG induction with structured counselling and symptom review in the days after each instillation, but they do not establish the overall safety of the regimen or exclude uncommon serious complications. Larger studies that use standardised toxicity grading, record multiple events per patient, and extend follow-up through maintenance therapy are needed to define the tolerability of BCG in this setting more precisely.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Institutional Ethics Committee, Sri Venkateswara Institute of Medical Sciences issued approval IEC No. 1587. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **AI use statement:** The authors used ChatGPT (OpenAI, San Francisco, CA, USA; version used October–November 2026) and Claude (Anthropic, San Francisco, CA, USA; Claude Opus 5.5) as follows: language polishing, structure or formatting, literature comparison, drafting summaries, data cleaning or exploratory analysis, extensive copy editing or writing support, methodological or statistical suggestions in Introduction, Materials & Methods (statistical analysis), Results (Tables 1–3, Figure 1, confidence intervals and P values), Discussion, Conclusions, and reference formatting. The authors reviewed and verified all AI-assisted outputs. Statistical analysis code was written and run with AI assistance; the

authors checked the code and verified every reported value against the original study dataset. The authors independently reviewed the statistical methods, interpreted the results, and confirmed that all reported values corresponded to the study data. All references were checked against the original publications. The manuscript was critically reviewed and edited by the authors, who take full responsibility for its accuracy, originality, and integrity. AI tools were not used to generate, fabricate, or alter clinical data. The authors confirm that they have reviewed and verified all AI-assisted content and take full responsibility for the work. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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