

Efficacy and Safety of Tailored Dose of BCG (40mg) Versus Standard Dose (80mg) Instillation Therapy in Non-Muscle Invasive Early Bladder Cancer Patients

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Abstract: Non-muscle-invasive bladder cancer (NMIBC) represents the majority of bladder cancer cases and is associated with high recurrence and progression rates. Intravesical Bacillus Calmette-Guérin (BCG) therapy remains the standard adjuvant treatment; however, standard-dose BCG (80 mg) is frequently associated with significant adverse events, which may limit treatment compliance. Dose reduction strategies have been proposed to improve tolerability while maintaining therapeutic efficacy. **Objective:** To compare the efficacy and safety of tailored low-dose (40 mg) versus standard-dose (80 mg) intravesical BCG therapy in patients with NMIBC in a tertiary care setting in Pakistan. **Methods:** This quasi-experimental study was conducted at the Department of Urology, Shaikh Zayed Hospital, Lahore, from 17 May 2025 to 17 September 2025. A total of 94 patients with NMIBC (Ta, T1, and Tis) were enrolled using non-probability consecutive sampling and allocated into two groups (n=47 each). Group A received 40 mg BCG, while Group B received 80 mg BCG, administered weekly for six weeks. Efficacy was assessed by cystoscopic evaluation at six weeks, with a complete response defined as the absence of tumour on cystoscopy and biopsy. Safety was evaluated by recording adverse events. Data were analysed using SPSS version 27.0, and a chi-square test was applied with $p \leq 0.05$ considered significant. **Results:** The mean age of participants was 58.4 ± 10.7 years, with a male predominance (78.7%). Complete response was observed in 80.9% of patients in the low-dose group and 85.1% in the standard-dose group, with no statistically significant difference ($p=0.58$). The overall incidence of adverse effects was significantly lower in the low-dose group (27.7%) compared to the standard-dose group (51.1%) ($p=0.02$). Most adverse events were mild to moderate, with fewer severe complications in the low-dose group. Post-stratification analysis showed no significant associations between age, gender, or tumor stage and treatment response. **Conclusion:** Low-dose intravesical BCG (40 mg) demonstrates comparable short-term efficacy to standard-dose BCG (80 mg) while significantly improving safety. This approach may represent a practical and effective alternative in resource-constrained settings.

Keywords: Urinary Bladder Neoplasms, Carcinoma In Situ, Bacillus Calmette-Guérin, Immunotherapy, Intravesical Administration, Treatment Outcome

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Introduction

Non-muscle-invasive bladder cancer (NMIBC) accounts for approximately 75% of all newly diagnosed bladder cancer cases. It is characterized by a high risk of recurrence and progression despite initial transurethral resection of bladder tumor (TURBT) (1). Intravesical Bacillus Calmette-Guérin (BCG) immunotherapy remains the gold-standard adjuvant treatment for intermediate- and high-risk NMIBC, demonstrating superior efficacy in reducing tumor recurrence and progression compared with TURBT alone or intravesical chemotherapy (2). However, standard-dose BCG (typically 80 mg) is associated with significant local and systemic adverse events (AEs), leading to treatment discontinuation in up to 20–40% of patients, which can compromise oncological outcomes (3).

To address BCG-related toxicity while preserving efficacy, dose reduction strategies have been explored. Recent studies and network meta-analyses suggest that lower-dose BCG (e.g., 40 mg or one-third to one-half of the standard dose) may reduce the incidence and severity of AEs and improve treatment completion rates without a consistent detrimental effect on progression or cancer-specific survival in selected patients (4,5). Nevertheless, findings on recurrence-free survival remain conflicting; some trials and retrospective cohorts report comparable outcomes between reduced- and standard-dose regimens, while others demonstrate a modestly increased risk of recurrence with dose reduction, particularly in high-risk disease or younger patients (6). These

inconsistencies highlight the need for further prospective comparative data on tailored dosing, especially with specific BCG strains commonly used in different regions.

In the Pakistani context, bladder cancer represents a growing urological malignancy burden, with NMIBC comprising the majority of cases. Limited healthcare resources, frequent BCG supply shortages, and higher baseline comorbidity rates in the local population often necessitate pragmatic approaches to therapy optimization. Full-standard dosing is frequently associated with poor tolerability and incomplete treatment courses due to cost constraints and side-effect management challenges in public-sector tertiary care settings. Tailoring the BCG dose (e.g., starting or adjusting to 40 mg) could improve patient compliance, reduce treatment-related morbidity, and optimize resource utilization without compromising disease control. However, region-specific evidence on the efficacy and safety of 40 mg versus 80 mg BCG instillation in Pakistani NMIBC patients is scarce, underscoring the importance of local validation studies (7).

The present study, therefore, aims to compare the efficacy (recurrence-free and progression-free survival) and safety (adverse event incidence and severity, treatment completion rates) of tailored 40 mg BCG versus standard 80 mg BCG instillation therapy in patients with non-muscle-invasive early bladder cancer in a tertiary care setting in Pakistan. The findings are expected to provide evidence-based guidance on dose optimization in resource-constrained settings and to contribute to personalized intravesical therapy protocols for NMIBC.



Methodology

A quasi-experimental study was conducted in the Department of Urology at Shaikh Zayed Hospital, Lahore, over 4 months, from 17 May 2025 to 17 September 2025. The study included patients diagnosed with non-muscle invasive bladder cancer (NMIBC), specifically those with Ta, T1, and carcinoma in situ (Tis), who were eligible for intravesical Bacillus Calmette–Guérin (BCG) therapy. A total sample size of 94 patients was determined using the WHO sample size calculator, with 95% confidence and 95% power, and expected complete response rates derived from previous literature. Patients were enrolled using a non-probability, consecutive sampling technique after obtaining written informed consent. Both male and female patients of all age groups were included. Patients with muscle-invasive bladder cancer, active tuberculosis, known hypersensitivity to BCG, immunocompromised status, total urinary incontinence, or any absolute contraindications to BCG therapy were excluded from the study.

Eligible participants were randomly assigned to two equal groups (n=47 each) using a lottery to minimize allocation bias. Group A received a tailored low dose of 40 mg intravesical BCG, while Group B received the standard dose of 80 mg. All patients underwent standard induction therapy consisting of weekly intravesical instillations for six consecutive weeks. Prior to initiation of therapy, baseline demographic data, including age, gender, comorbid conditions, and prior surgical history, were recorded. Tumor characteristics, including stage (pTa, pT1, pTis), size, and location, were documented based on histopathological reports and cystoscopic findings following transurethral resection of bladder tumor (TURBT).

The BCG instillation procedure was performed under aseptic conditions using a urethral catheter, ensuring adequate bladder drainage prior to administration. Patients were instructed to retain the instilled solution for an appropriate duration as per standard protocol. All patients were monitored during the treatment period and followed up at six weeks after completion of induction therapy. Efficacy was assessed by performing follow-up cystoscopy at six weeks, with biopsy taken in cases where

suspicious lesions were identified. A complete response was defined as the absence of visible tumor and no histopathological evidence of malignancy on follow-up evaluation. In contrast, recurrence was defined as the presence of biopsy-proven bladder cancer.

Safety was evaluated by documenting adverse events associated with BCG therapy throughout the study period. Side effects such as lower urinary tract symptoms (LUTS), fever, hematuria, allergic reactions, and systemic complications were recorded and graded according to predefined criteria into Grade 1 (mild), Grade 2 (moderate), and Grade 3 (severe). Detailed assessment included duration and severity of symptoms, need for medical intervention, and any requirement for treatment interruption or hospitalization.

All collected data were entered and analyzed using Statistical Package for Social Sciences (SPSS) version 27.0. Quantitative variables such as age were reported as mean and standard deviation, while qualitative variables, including gender, tumor stage, efficacy outcomes, and adverse effects, were presented as frequencies and percentages. Comparative analysis between the two groups was performed using the chi-square test for categorical variables, with a p-value of ≤ 0.05 considered statistically significant. Stratification was further carried out by age, gender, and tumor stage, and post-stratification chi-square tests were applied to assess their impact on treatment outcomes. Ethical approval for the study was obtained from the institutional review board prior to commencement, and confidentiality of patient data was strictly maintained throughout the study.

Results

A total of 94 patients with non-muscle invasive bladder cancer were included in the study, with 47 patients in each group. The overall mean age of the study population was 58.4 ± 10.7 years, with a male predominance (78.7% males vs 21.3% females). The majority of patients were in the 51–70-year age group. Both groups were comparable in terms of baseline demographic characteristics (Table 1).

Table 1: Demographic Characteristics of Study Participants (n=94)

Variable	Group A (40 mg) n=47	Group B (80 mg) n=47	Total n=94
Mean Age (years)	57.9 ± 10.2	58.8 ± 11.1	58.4 ± 10.7
Age Group (years)			
≤50	11 (23.4%)	9 (19.1%)	20 (21.3%)
51–70	28 (59.6%)	30 (63.8%)	58 (61.7%)
>70	8 (17.0%)	8 (17.0%)	16 (17.0%)
Gender			
Male	36 (76.6%)	38 (80.9%)	74 (78.7%)
Female	11 (23.4%)	9 (19.1%)	20 (21.3%)

The distribution of tumor stage showed that the majority of patients presented with pT1 disease (44.7%), followed by pTa (34.0%) and

pTis (21.3%), with comparable distributions between the two groups (Table 2).

Table 2: Tumor Stage Distribution

Tumor Stage	Group A (40 mg)	Group B (80 mg)	Total
pTa	16 (34.0%)	16 (34.0%)	32 (34.0%)
pT1	20 (42.6%)	22 (46.8%)	42 (44.7%)
pTis	11 (23.4%)	9 (19.1%)	20 (21.3%)

In terms of efficacy, complete response at 6 weeks was observed in 80.9% of patients in the low-dose group compared to 85.1% in the

standard-dose group, with no statistically significant difference (p=0.58) (Table 3).

Table 3: Comparison of Efficacy (Complete Response at 6 Weeks)

Outcome	Group A (40 mg)	Group B (80 mg)	p-value
Complete Response	38 (80.9%)	40 (85.1%)	0.58
No Response/Recurrence	9 (19.1%)	7 (14.9%)	

Regarding safety, the overall frequency of side effects was significantly lower in the low-dose group (27.7%) compared to the

standard-dose group (51.1%) (p=0.02). Mild to moderate LUTS and low-grade fever were the most common adverse events (Table 4).

Table 4: Comparison of Overall Side Effects

Side Effects	Group A (40 mg)	Group B (80 mg)	p-value
Present	13 (27.7%)	24 (51.1%)	0.02
Absent	34 (72.3%)	23 (48.9%)	

Further stratification of side effects by severity revealed that Grade 1 adverse effects were most frequent, whereas Grade 3 complications

were rare but slightly more frequent in the standard-dose group (Table 5).

Table 5: Severity of Side Effects

Severity Grade	Group A (40 mg)	Group B (80 mg)
Grade 1	9 (19.1%)	14 (29.8%)
Grade 2	3 (6.4%)	7 (14.9%)
Grade 3	1 (2.1%)	3 (6.4%)

Post-stratification analysis showed that age, gender, and tumor stage were not statistically significantly associated with treatment response. In contrast, highertumor stage (pT1) showed a trend toward lower

complete response rates, although not statistically significant (p>0.05) (Table 6).

Table 6: Post-Stratification Analysis of Complete Response

Variable	Complete Response (%)	p-value
Age ≤60	83.3%	0.64
Age >60	82.1%	
Male	83.8%	0.71
Female	80.0%	
pTa	87.5%	0.29
pT1	78.6%	
pTis	80.0%	

Overall, the findings suggest that low-dose BCG (40 mg) provides comparable efficacy with a significantly better safety profile in patients with non-muscle invasive bladder cancer in a Pakistani tertiary care setting.

Discussion

The present study evaluated the efficacy and safety of low-dose (40 mg) versus standard-dose (80 mg) intravesical BCG in 94 patients with non-muscle-invasive bladder cancer (NMIBC) at a tertiary care center in Pakistan. Our findings demonstrate comparable complete response rates between the two groups (80.9% vs. 85.1%, p=0.58) with significantly fewer side effects in the low-dose group (27.7% vs. 51.1%, p=0.02).

Azuri et al. conducted a systematic review and meta-analysis of 13 randomized controlled trials encompassing 2,963 patients. They reported that BCG dose reduction did not significantly affect recurrence (HR=1.17) or progression (HR=1.12), while local and systemic side effects were significantly lower in the reduced-dose group (8). These findings closely corroborate our results, reinforcing the non-inferiority of low-dose BCG regarding efficacy and its superiority in tolerability. Similarly, Wroclawski et al. reviewed dose-reduction strategies across multiple BCG strains. They noted that, at 120 mg, 80 mg, and 40 mg, the Danish strain showed no difference in efficacy but demonstrated less toxicity with reduced doses (9). Thyavihally et al. also cited a prospective study by Vijjan et al. comparing three BCG doses (120 mg, 80 mg, and 40 mg), which confirmed similar recurrence and progression rates while significantly reducing toxicity at lower doses (10).

Regarding safety, Poletajew et al. reported that local adverse effects, particularly cystitis symptoms, affect 70–86% of patients receiving standard BCG therapy, with 7–21% discontinuing treatment due to toxicity (11). Our standard-dose group exhibited a 51.1% side-effect rate, which, while lower than some Western cohorts, aligns with the established dose-dependent toxicity pattern. Shakhssalim et al. reported grade 1 toxicity rates of 28.5–35.7% in their BCG-treated cohorts,

comparable to our findings (12). Angelopoulos et al. reported that only 14.8% of patients experienced adverse events in their real-world multicenter study, though their cohort utilized a different BCG strain and maintenance protocol (13).

The male predominance (78.7%) and mean age (58.4 years) in our cohort are consistent with established epidemiological patterns. Yang et al. reported 76.8% male patients with a median age of 69 years in their Asian cohort (14), while D'Andrea et al. documented 82% males in a large multicenter analysis (15). The trend toward lower complete response in pT1 disease observed in our post-stratification analysis mirrors findings by Alhunaidi and Zlotta, who noted that BCG fails in up to 40% of patients, particularly those with higher-stage disease (16).

The study was conducted at a single center with a relatively small sample size and short follow-up duration. Long-term outcomes such as recurrence-free and progression-free survival could not be adequately assessed.

Conclusion

Tailored low-dose BCG (40 mg) may offer similar therapeutic efficacy with reduced toxicity compared to standard-dose therapy, supporting its use as a safer and more tolerable option for NMIBC patients in clinical practice.

Declarations

Data Availability statement

All data generated or analysed during the study are included in the manuscript.

Ethics approval and consent to participate

Approved by the department concerned. (IRBEC-SZHRHY-0092-25)

Consent for publication

Approved

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Conflict of interest

The authors declared no conflict of interest.

Author Contribution**MHA (PGR)***Manuscript drafting, Study Design,***AR (SR)***Review of Literature, Data entry, Data analysis, and drafting articles.***FURK (Associate Professor)***Conception of Study, Development of Research Methodology Design,***MR (PGR)***Study Design, manuscript review, critical input.***MLK (4th Year MBBS),***Manuscript drafting, Study Design,***AW (PGR)***Conception of Study, Development of Research Methodology Design,**All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the integrity of the study.***References**

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