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Research Article

EFFECT OF BACILLUS CALMETTE GUERIN INDUCTION IMMUNOTHERAPY ON NONMUSCLE INVASIVE BLADDER CANCER: FIRST CHECK CYSTOSCOPY FINDINGS

Dr Ulaspreet Singh Bhangu[1], Dr Gurpreet Singh Bhangu[2], Dr Rachhpal Singh[3]

[1] Junior Resident, Department of General Surgery, Sri Guru Ram Das Institute of Medical Sciences & Research, Vallah, Sri Amritsar Sri Guru Ram Das University of Health Sciences, Amritsar EMAIL- ulassingh@gmail.com

[2]Professor, Department of General Surgery, Sri Guru Ram Das Institute of Medical Sciences & Research, Vallah, Sri Amritsar Sri Guru Ram Das University of Health Sciences, Amritsar.

[3]Assistant Professor, Department of General Surgery, Sri Guru Ram Das Institute of Medical Sciences & Research, Vallah, Sri Amritsar Sri Guru Ram Das University of Health Sciences, Amritsar.

*Corresponding Author
Dr. Gurpreet singh Bhangu
drgurpreetsinghbhangu@gmail.com

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Abstract: ***Introduction:*** **Objective:** To evaluate the effectiveness of intravesical Bacillus Calmette-Guérin (BCG) induction therapy in patients with non-muscle invasive bladder cancer (NMIBC) by assessing tumor recurrence and post-treatment tumor characteristics.**Methods:** A hospital-based observational study was conducted at Sri Guru Ram Das Institute of Medical Sciences & Research, Amritsar, involving 40 patients with histopathologically confirmed NMIBC. All patients underwent transurethral resection of bladder tumor (TURBT) followed by a standard six-week course of intravesical BCG induction therapy. Baseline demographic, clinical, and tumor characteristics were recorded. Treatment response was evaluated by first check cystoscopy performed six weeks after completion of BCG induction, with recurrence assessed based on cystoscopic and histopathological findings.**Results:** The mean age of the study population was 59.80 ± 13.23 years, with males comprising 70% of the cohort. At first follow-up, the recurrence-free rate was 72.5%, while tumor recurrence was observed in 27.5% of patients. Among patients with recurrence, the mean tumor size was reduced by 43.2% compared with baseline. No patient demonstrated progression to muscle-invasive bladder cancer during the study period. Treatment compliance was excellent, with 92.5% of patients completing the full six-dose induction regimen. Adverse events were infrequent, mild, and predominantly limited to local urinary symptoms. **Conclusion:** Intravesical BCG induction therapy was effective in reducing early tumor recurrence and preventing progression to muscle-invasive disease in patients with NMIBC during short-term follow-up. The high treatment completion rate and favorable safety profile further support its role as the standard adjuvant therapy for high-risk NMIBC. Larger prospective studies with longer follow-up are warranted to evaluate long-term oncological outcomes.

Keywords: Non-muscle invasive bladder cancer, intravesical Bacillus Calmette-Guérin, BCG induction therapy, transurethral resection of bladder tumor, recurrence-free survival, bladder cancer recurrence, cystoscopy.

INTRODUCTION

Bladder cancer (BC) is a prevalent malignancy of the urinary tract, ranking as the ninth most common cancer worldwide with approximately 390,000 new cases annually. It predominantly affects older adults, with a strong male predominance, and is strongly associated with environmental factors like tobacco smoking and chronic bladder irritation [1]. BC is classified into two major categories: non-muscle invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC). NMIBC constitutes about 75% of all newly diagnosed cases, with tumors confined to the mucosa (Ta), carcinoma in situ (CIS), or lamina propria (T1) [2].

Although NMIBC is generally associated with a favorable short-term prognosis, it is characterized by a high recurrence rate of up to 50%, and nearly 9% of cases may progress to MIBC, which is associated with a significantly poorer prognosis [3]. The management of NMIBC faces challenges due to recurrence and progression, emphasizing the need for effective adjuvant therapies and vigilant surveillance.

The primary treatment for NMIBC involves transurethral resection of bladder tumor (TURBT), but recurrence and microscopic tumor persistence often occur, necessitating the use of adjuvant intravesical therapies to reduce recurrence and progression. Bacillus Calmette-Guérin (BCG) immunotherapy, introduced in the 1970s and FDA-approved in 1990, has emerged as the gold standard intravesical therapy for high-risk NMIBC and CIS [4]. Numerous clinical trials and meta-analyses have shown that BCG significantly reduces tumor recurrence and progression compared to intravesical chemotherapy [5]. BCG therapy has demonstrated long-term survival

benefits, particularly in high-risk patients, and is crucial for preventing the progression from NMIBC to MIBC.

Despite its efficacy, BCG therapy is associated with adverse effects, which can impact patient compliance. Up to 70% of patients experience side effects ranging from mild local symptoms, such as dysuria and hematuria, to severe systemic reactions, including fever, sepsis, pneumonitis, and disseminated BCG infection [6]. These side effects may necessitate treatment adjustments, such as dose reduction or discontinuation, potentially compromising therapeutic outcomes. The mechanisms underlying the therapeutic efficacy and adverse effects of BCG remain incompletely understood.

It is believed that BCG exerts its antitumor effects through immune-mediated mechanisms rather than direct cytotoxicity [5]. Upon intravesical instillation, BCG adheres to the urothelial lining, triggering an immune response that involves the activation of macrophages, neutrophils, T lymphocytes, and the release of pro-inflammatory cytokines and chemokines [7]. The magnitude of this immune response plays a critical role in treatment success and the severity of adverse effects.

The long-term outcomes of BCG therapy, including recurrence patterns, progression to muscle invasion, and changes in tumor grade, necessitate continued evaluation. Although BCG significantly reduces recurrence and progression rates, failures still occur, and a subset of patients experience persistent or recurrent disease. Cystoscopic surveillance after BCG induction therapy is critical to monitor treatment response, identify recurrence, and assess for progression to MIBC [8]. The first follow-up cystoscopy is particularly crucial for assessing treatment efficacy and informing further management decisions. Early identification of unfavorable outcomes, such as recurrence or upstaging, allows timely intervention, improving long-term prognosis.

This study aims to evaluate the post-intravesical BCG induction outcomes in NMIBC, focusing on the first follow-up cystoscopy findings. The primary objectives are to determine recurrence rates, assess tumor staging changes, and identify the incidence of muscle invasion after BCG therapy. The results of this study will contribute to refining clinical decision-making in NMIBC management, providing insights into early treatment response and identifying predictors of long-term outcomes. Furthermore, this research will help optimize BCG therapy usage and enhance patient counseling, particularly in the context of global BCG shortages and rising healthcare costs [9].

MATERIALS AND METHODS

Study Design

This study was conducted as a hospital-based observational study aimed at evaluating the outcomes of intravesical Bacillus Calmette-Guérin (BCG) therapy in patients with non-muscle invasive bladder cancer (NMIBC).

Study Setting

The study was carried out in the Department of General Surgery, Sri Guru Ram Das Institute of Medical Sciences & Research, Amritsar.

Study Population

The study included all eligible patients diagnosed with non-muscle invasive bladder cancer (NMIBC) and admitted to the Department of General Surgery during the study period. After obtaining approval from the Institutional Ethics Committee and Research Committee, patients meeting the inclusion criteria were enrolled. Written informed consent was obtained from all participants prior to inclusion in the study.

Inclusion Criteria

1. Patients with histopathologically confirmed high-grade non-muscle invasive bladder cancer (NMIBC).
2. Patients with histopathologically confirmed low-grade NMIBC involving the lamina propria.

Exclusion Criteria

1. Patients who were not mentally competent to provide informed consent.
2. Patients who were unable to tolerate or complete intravesical BCG therapy.

Methodology

A detailed and systematic methodology was adopted to ensure comprehensive data collection and analysis. Upon enrollment, all eligible patients underwent a thorough clinical evaluation. Demographic data, including age, gender, occupation, marital status, educational status, socioeconomic status, and body mass index (BMI), were recorded. Clinical details, such as presenting complaints, comorbidities, and risk factors, were also documented.

Baseline tumor characteristics were assessed based on cystoscopic findings and histopathological reports obtained from transurethral resection of bladder tumor (TURBT). These characteristics included tumor size, number, location, and stage.

BCG Induction Immunotherapy Protocol

All enrolled patients received intravesical BCG induction immunotherapy according to the institutional protocol. A dose of 80 mg of BCG (BCG Onco) was instilled intravesically once a week for six consecutive weeks. The instilled solution was retained in the bladder for approximately two hours during each session. Patients were monitored for tolerance and adverse effects throughout the treatment period.

Follow-up and Assessment

After the completion of the induction therapy, all patients were followed up systematically. The first check cystoscopy was performed six weeks after the completion of the last cycle of BCG therapy. During the follow-up cystoscopy, detailed findings were recorded, including the presence or absence of tumor recurrence, suspicious lesions, and any visible progression. In cases where abnormalities were detected, cystoscopy-guided biopsy or repeat TURBT was performed.

Histopathological Evaluation

All biopsy and resection specimens obtained during follow-up were subjected to histopathological examination. These reports were used to confirm tumor recurrence, evaluate tumor grade, and assess any changes in tumor staging, including upstaging or downstaging, and evidence of muscle invasion.

Outcome Measures

The primary outcomes assessed in this study were tumor recurrence and changes in tumor staging following BCG induction therapy.

- Tumor Recurrence: Defined as the presence of new tumor growth detected during follow-up cystoscopy and confirmed by histopathology.
- Tumor Staging Changes: Defined as any change in tumor stage (upstaging or downstaging), including progression to muscle-invasive disease following BCG therapy.

Independent Variables

The independent variables considered in this study included age, gender, occupation, marital status, educational qualification, socioeconomic status, and BMI.

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using SPSS version 27. Descriptive statistics, including mean and standard deviation, were used for continuous variables, while frequencies and percentages were used for categorical variables. Inferential statistical tests, including the Chi-square test and independent t-test, were applied to determine associations and compare variables where appropriate. A non-probability consecutive sampling technique was used to include all eligible patients during the study period. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The study enrolled 40 patients diagnosed with non-muscle invasive bladder cancer (NMIBC) who underwent transurethral resection of bladder tumor (TURBT) followed by intravesical BCG induction immunotherapy. The mean age of the study population was 59.80 ± 13.23 years, ranging from 34 to 84 years. The majority of patients (40.0%) were in the 51–65 years age group, followed by those aged over 65 years (37.5%). The male to female ratio was 2.3:1, with 28 males (70.0%) and 12 females (30.0%). Regarding risk factors, 95.0% of the patients were non-smokers, and 60.0% had no comorbidities, with hypertension being the most common comorbidity. Most patients (77.5%) had a single tumor, with 82.5% of tumors being 2–3 cm in size. The majority (32.5%) had tumors located on the posterior wall, with all patients presenting with T1 stage disease at baseline. Histopathological analysis showed that 82.5% of tumors were high-grade, and 17.5% were low-grade, with no prior recurrence in any of the patients.

In terms of BCG therapy, 92.5% of patients completed all six doses, with an overall treatment compliance rate of 92.5%. Adverse events were minimal, with 95.0% of patients reporting no adverse effects, and only 5.0% experiencing local adverse events. At the first follow-up cystoscopy, 72.5% of patients remained recurrence-free, while 27.5% experienced tumor recurrence. Among the 11 patients with recurrence, most had a single recurrent tumor (72.7%), with the mean recurrent tumor size being 1.55 ± 0.69 cm, representing a 43.2% reduction compared to baseline. Despite the recurrence, all patients remained at T1 stage, with no progression to muscle-invasive bladder cancer. Histopathologically, the grading of recurrent tumors did not differ significantly from baseline, with 81.8% remaining high-grade.

The study also assessed various clinicopathological factors to identify associations with recurrence. No significant associations were found between recurrence and demographic, tumor, or treatment variables, including gender, smoking history, tumor grade, number of tumors, tumor size, or BCG therapy compliance. Follow-up duration ranged from 3 to 6 months, with the majority of patients (65.0%) having a follow-up of 4 months. Overall, the study demonstrated a recurrence-free survival rate of 72.5%, with no progression to muscle-invasive disease, highlighting the protective effect of BCG therapy during the follow-up period. The mean follow-up duration was 4.33 ± 0.69 months.

Table 1: Demographic Characteristics of Study Population (n=40)

Parameter	Category	Frequency (n)	Percentage (%)
Age Distribution	≤ 40 years	4	10.0
	41 – 50 years	5	12.5
	51 – 65 years	16	40.0

	> 65 years	15	37.5
Mean ± SD		59.80 ± 13.23	
Range		34 – 84 years	
Gender	Male	28	70.0
	Female	12	30.0
Male : Female Ratio		2.3:1	

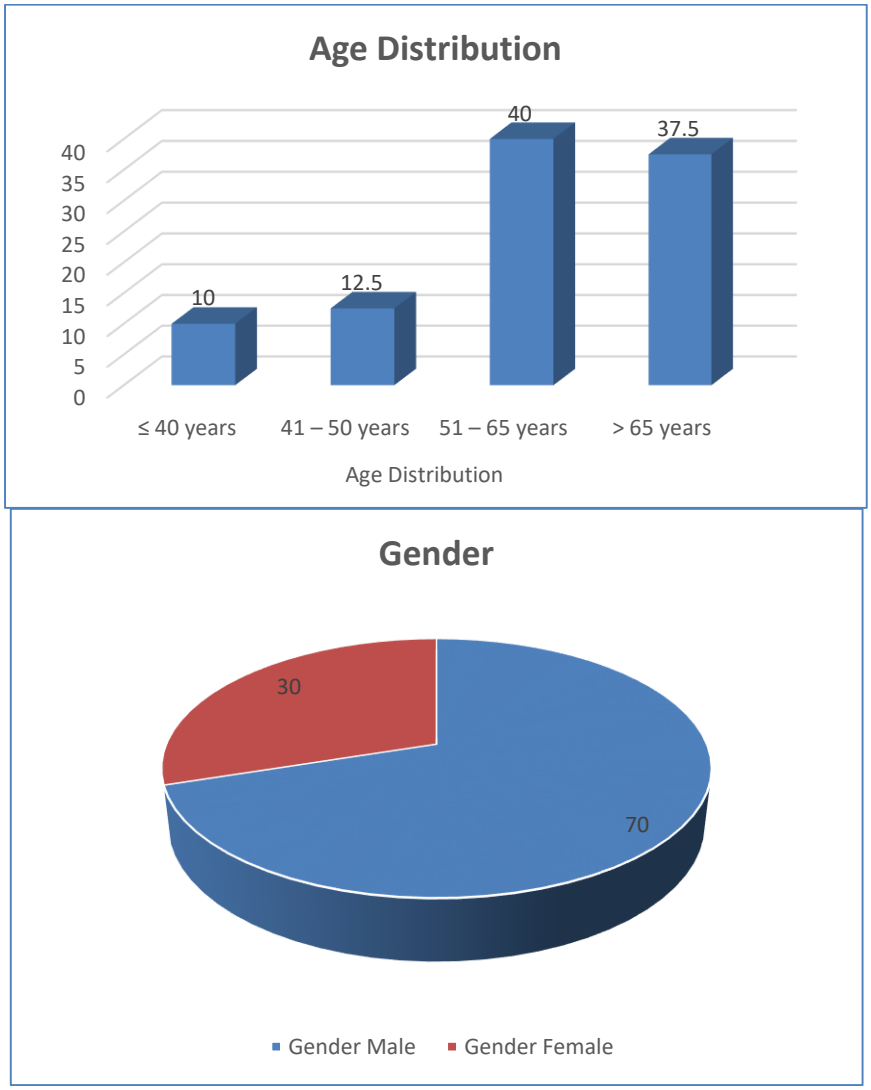

Figure 1 Demographic Characteristics of Study Population (n=40)

Table 2: Risk Factors and Comorbidity Profile (n=40)

Parameter	**Category**	**Frequency (n)**	**Percentage (%)**
Smoking History	Non-smoker	38	95.0
	Smoker	2	5.0
Comorbidities	None	24	60.0
	Hypertension (alone)	6	15.0
	Diabetes Mellitus (alone)	2	5.0
	Hypertension + Diabetes	3	7.5
	Others (BA, CAD, CVA, DM/Hypothyroidism, HTN/Hypothyroidism)	5	12.5

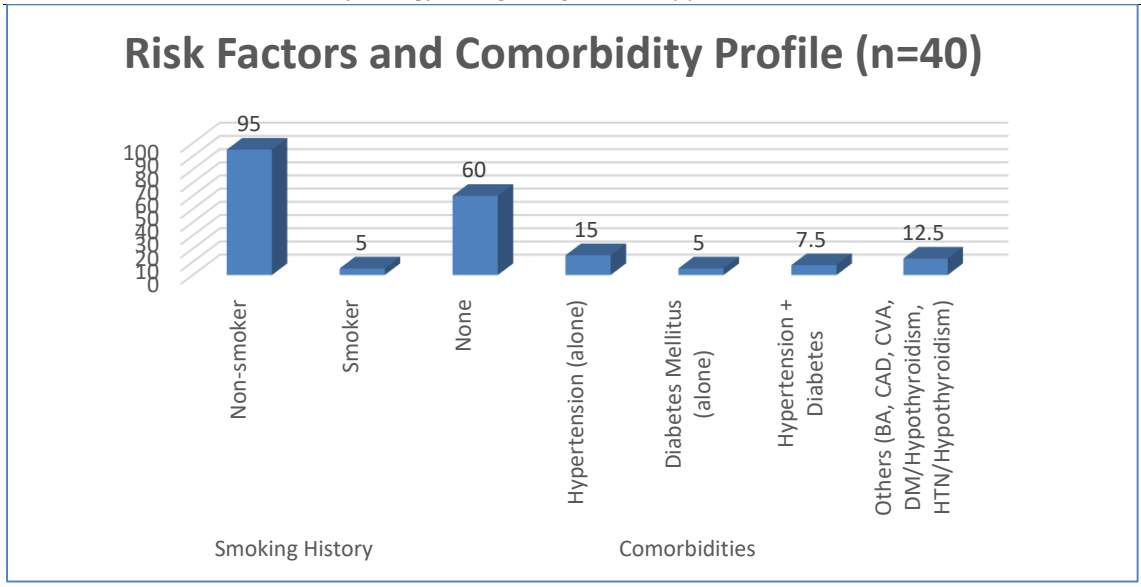

Figure 2 Risk Factors and Comorbidity Profile (n=40)

Table 3: Baseline Tumor Characteristics – Number and Size (n=40)

Parameter	Category	Frequency (n)	Percentage (%)
Number of Tumors	Single	31	77.5
	Multiple (>1)	9	22.5
Maximum Tumor Size	≤ 1 cm	2	5.0
	2 cm	16	40.0
	3 cm	17	42.5
	4 cm	1	2.5
	5 cm	4	10.0
Mean ± SD		2.73 ± 0.99	

Table 4: Recurrence Status at First Check Cystoscopy (n=40)

Recurrence Status	Frequency (n)	Percentage (%)
No Recurrence	29	72.5
Recurrence Present	11	27.5
Total	40	100.0

DISCUSSION

This study investigates the effect of intravesical Bacillus Calmette-Guérin (BCG) induction immunotherapy on non-muscle invasive bladder cancer (NMIBC) in a cohort of 40 patients. The findings show a promising recurrence-free rate of 72.5% at the first check cystoscopy following the standard six-week BCG induction protocol, which is consistent with previous literature. Notably, none of the patients progressed to muscle-invasive bladder cancer (MIBC) during the follow-up period, and recurrent tumors showed a significant reduction in mean size compared to baseline. These results reinforce the effectiveness and safety of BCG induction therapy, especially for high-risk T1 disease patients.The mean age of patients in this study was 59.8 years, with a significant proportion (77.5%) aged above 50 years, aligning with the typical age distribution of bladder cancer. The male-to-female ratio was 2.3:1, in line with the male preponderance in bladder cancer reported worldwide. Notably, only 5% of patients had a history of smoking, which is considerably lower than what is typically seen in Western populations. This could indicate regional differences in risk factors, suggesting that occupational or environmental exposures in the Indian subcontinent might play a larger role in the etiology of bladder cancer.In line with previous studies, such as those by Patel et al. (2024)[10], hypertension emerged as the most common comorbidity, observed in 15% of patients. The relative low prevalence of comorbidities in this cohort could suggest better treatment tolerability. This is particularly relevant, as comorbid conditions such as hypertension have been shown to increase the risk of BCG treatment intolerance (Patel et al., 2024)[10].The study predominantly included patients with single, high-grade T1 tumors (82.5%), a characteristic that is widely recognized as high-risk in NMIBC. The baseline tumor size averaged

2.73 cm, consistent with other studies like those by Novotny et al. (2016)[11] that emphasize the significance of high-grade T1 disease in determining prognosis and treatment strategies. Novotny et al. demonstrated that BCG therapy significantly improved survival in high-grade T1 disease patients, supporting the critical role of BCG induction in this cohort.The most common sites of tumor involvement were the posterior and posterolateral regions of the bladder, which comprised 32.5% and 37.5% of cases, respectively. However, tumor location did not correlate with recurrence in this cohort, suggesting that other factors, such as tumor grade and size, may be more influential in determining treatment outcomes.The completion rate for the six-dose BCG induction protocol was impressively high at 92.5%, with minimal adverse events (5%) reported. This mirrors findings from studies such as those by Pillippu Hewa et al. (2024)[12], who also found high compliance and low rates of severe toxicity in BCG-treated NMIBC patients. The study population in the present cohort experienced no systemic adverse events, which highlights the relative safety of BCG induction therapy when administered to patients with minimal comorbidity.Patel et al. (2024)[10] also reported that treatment interruptions were common, but they did not significantly affect recurrence rates, suggesting that minor deviations from the standard protocol may not compromise the oncological efficacy of BCG therapy. The absence of severe systemic side effects in this study further emphasizes the favorable safety profile of BCG monotherapy, particularly in patients with fewer comorbid conditions.The recurrence-free survival rate of 72.5% in the present cohort is comparable to other studies evaluating the role of BCG in high-risk NMIBC. For instance, Matulay et al. (2021)[13] reported one-year recurrence-free survival rates of 81%, and Pillippu Hewa et al. (2024)[12] noted a recurrence rate of 55% at a median follow-up of 37 months. These findings suggest that while BCG induction is effective in the short term, long-term recurrence rates may vary depending on follow-up duration and patient characteristics.

The study found that tumor size had a non-significant association with recurrence ($p = 0.106$), but the significant reduction in tumor size (43.2%) in recurrent tumors suggests that BCG induces an immune response that may partially shrink tumors, even in cases where complete remission is not achieved. This partial response could have clinical implications in terms of reducing tumor burden and the risk of progression.Histopathological analysis of recurrent tumors showed a similar high-grade profile to baseline tumors, indicating that BCG treatment does not induce histological changes that would suggest a shift towards more aggressive tumor subtypes. These findings are consistent with those of Matulay et al. (2021)[13], who noted a low incidence of progression to muscle-invasive disease in high-risk NMIBC patients treated with BCG. The stability in tumor grade observed in the present study suggests that BCG induction does not necessarily select for more aggressive clones.Although this study focused on BCG induction monotherapy, the literature also suggests potential benefits from combination therapies. Huang et al. (2019)[14] reported that adding chemotherapy to BCG therapy improved recurrence-free survival without significantly increasing toxicity, making combination therapy a promising strategy in the treatment of NMIBC. Similarly, Shepherd et al. (2017)[15] found that adding interferon-α (IFN-α) to BCG therapy did not significantly reduce recurrence rates, highlighting that not all combinations of adjunctive therapies are beneficial.The emergence of alternative strategies, including new immunotherapies and intravesical chemotherapy agents, offers additional options for patients with BCG-unresponsive disease. However, as Li et al. (2020)[16] pointed out, salvage therapies currently offer limited benefit, underscoring the importance of optimizing initial BCG responses to prevent progression to more difficult-to-treat disease stages.

CONCLUSION

Overall findings from this study underscore the effectiveness and safety of BCG induction therapy in high-risk NMIBC, particularly in patients with high-grade T1 disease. The study demonstrates favorable recurrence-free survival rates, minimal adverse events, and no progression to muscle-invasive disease, highlighting the clinical value of BCG in this patient cohort. Further studies with larger sample sizes and longer follow-up periods are needed to confirm these findings and to explore the potential benefits of combination therapies in enhancing BCG treatment efficacy.

LIMITATIONS OF THE STUDY

The study's limitations include a small sample size (n=40) and a short follow-up duration (3–6 months), which may limit the statistical power and long-term insight into recurrence and progression. Additionally, the study was conducted at a single tertiary care center and only evaluated BCG induction therapy, excluding maintenance therapy and advanced prognostic markers.

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