A retrospective analysis of patients treated with intravesical BCG for high-risk nonmuscle invasive bladder cancer

Julie Mariam Joshua iD, Meenu Vijayan* and Ginil Kumar Pooleri*

Abstract

Background: Adjuvant intravesical immunotherapy with Bacillus Calmette–Guerin (BCG) is considered as the first-line agent in patients with high-risk nonmuscle invasive bladder cancer (NMIBC) after surgery. There are no data in India where there is a high prevalence of tubercle bacillus and inherent immunity against *Bacillus* sp. The present study aims to evaluate the outcomes of intravesical BCG in the Indian population.

Methods: A retrospective study of 101 patients who underwent intravesical BCG for high-risk NMIBC between January 2006 and December 2015 was carried out in a single centre. We compared the recurrence-free rate and progression rate of patients who received induction alone and induction with maintenance BCG therapy. The safety profile of intravesical BCG therapy was also assessed in the study.

Results: After a median follow up of 2 years, the disease-free survival (DFS) rates of the induction group and maintenance group were 82% and 88% respectively ($p = 0.233$). There was no difference in progression-free survival (PFS) rates at 2 years in those who receive maintenance BCG (95%) and those with induction BCG (94.7%; $p = 0.721$). A total of 69.36% of our patients had local adverse events.

Conclusion: Our results suggest that maintenance therapy does not enhance the therapeutic effects of BCG in patients who respond favourably to 6 weeks of induction. Additional prospective studies are warranted in those countries where tuberculosis exposure is prevalent.

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Introduction

Bladder cancer ranks ninth in international cancer incidence and is the second most common genitourinary malignancy after prostate cancer.[1,2] Around 75% of patients with bladder tumours are initially diagnosed with nonmuscle invasive bladder cancer (NMIBC).[3–5] According to the European Organisation for Research and Treatment of Cancer risk stratification tables, high-risk NMIBC exists as a challenging group with an increased 5 year risk of recurrence (up to 80%) and progression (up to 50%) after transurethral resection of bladder tumour (TURBT) which necessitates additional therapy with intravesical agents.[6] According to the American Urological Association and European Association of Urology guidelines, Bacillus Calmette–Guerin (BCG) is considered as the first-line agent for high-risk NMIBC.[7–9] It is considered as the most successful intravesical therapy for the management of patients with carcinoma *in situ* (CIS) and with Ta/T1HG.[10] For optimal effectiveness, a 6 week induction course followed by maintenance BCG is usually recommended.[11–13]

However, all the evidence on maintenance BCG is from western populations where exposure to tuberculosis (TB) is very low. There is still a paucity of Indian studies which compare the effectiveness of induction BCG and maintenance BCG in NMIBC. As compared with western countries, south Asian countries like India are more exposed to TB, so BCG is widely used as a vaccine for neonates.[14,15] To our knowledge, there are no published data on the effect of intravesical BCG in India, where there is high prevalence of TB bacilli. We therefore hypothesized that the effect of intravesical BCG in the Indian population might be quite different because of the pre-existing immunity to the BCG vaccine.

Materials and methods

A retrospective, single-centre study was performed at our institution after Institutional Review Board approval. A total of 101 patients who received intravesical BCG between January 2006 and December 2015 were identified through our institutional database. Patients were considered eligible if they met the following criteria: patients with histologically confirmed NMIBC (Ta, T1, or Tis stage), patients under all age groups, patients who were treated with intravesical BCG after transurethral resection of bladder, adequate haematologic, hepatic, and renal function, (absolute neutrophil count >1500/mm³, haemoglobin >9.0 g/dl, platelet count >100,000/mm³, serum total bilirubin: ≤1.5 × upper limit of normal (ULN), alanine transaminase (ALT) and aspartate transaminase (AST) ≤ 2.5 × ULN, and adequate renal function with serum creatinine ≤2.5 mg/dl).

The exclusion criteria were as follows: history of muscle invasive bladder cancer, previous systemic or radiation therapy for bladder cancer, and those who could not tolerate the first induction course of BCG. The medical data of BCG-treated patients were collected by chart review. After BCG instillations, all patients underwent urinalysis, urinary cytology and cystoscopy. The presence of recurrence and progression were observed by repeating these examinations every 3 months for the first 3 years and thereafter, every 6 months.

Disease-free survival (DFS) and progression-free survival (PFS) of both induction and maintenance groups were estimated and compared. DFS was calculated from the date of initiation of therapy till recurrence; PFS was calculated from the date of initiation of therapy till recurrence with a higher stage and overall survival was calculated from the date of initiation of therapy till death. The tolerability and safety of BCG instillations were determined from the reported adverse effects (AEs) and severity was assessed by Hartwig's severity assessment scale.

All statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). To obtain the association of categorical variables, a Chi-square test was applied. The Kaplan–Meier method was used to calculate DFS, PFS and differences were evaluated with the log rank test.

Results

The study group included 101 patients with a mean age of 68 years and a median age of 69 years. The present study shows a male predominance (92.1%) with a male to female ratio of 12:1.

Treatment compliance

All patients received an induction course of BCG with a median of 6-weekly instillations and only 61 (60.3%) patients received a maintenance dose. Among the maintenance groups, 34 patients underwent maintenance BCG using the SWOG protocol, while 27 patients received a monthly protocol. A total of 93 out of 101 patients (92%) completed the intravesical BCG treatment protocol as planned, while BCG termination was needed in 8 patients (8%).

Effectiveness

Over a median follow up of 2 years, 86 patients were disease free, including 32 (80%) in the induction group and 54 in the maintenance group (88.5%). The 2-year DFS of the induction group was 82% and 88% in the maintenance group ($p = 0.233$; Figure 1). Out of 101 patients, 95 patients (94.05%) remained free of progression during the entire follow-up period, while 6 patients (5.94%) had tumour progression ($p = 0.721$; Figure 2). Table 1 shows the characteristics of the patients with induction therapy alone and those with maintenance therapy. Overall, four patients progressed from low grade to high grade and the remaining two patients progressed from T1G3 to T2 disease. For the induction group, the PFS at 2 years was 94.7%, while the value for the maintenance group was 95%, showing the fact that maintenance therapy does not provide a therapeutic benefit over the
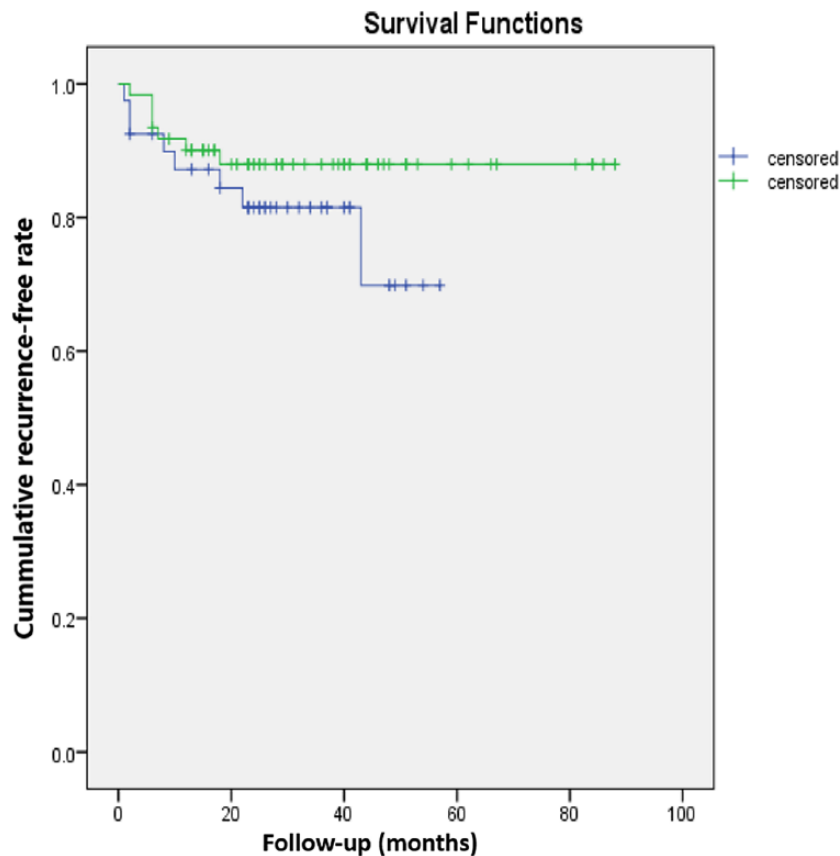
Figure 1. Kaplan–Meier curves showing DFS of induction BCG (blue curve) compared with maintenance BCG (green curve).
Log rank test: $p = 0.233$.
BCG, Bacillus Calmette–Guerin vaccine; DFS, disease-free survival.

standard 6-week induction regimen with respect to delaying recurrence. Among the maintenance schedule, a recurrence rate of 16.2% and 4.16% was observed with the monthly and SWOG protocol ($p = 0.217$). Moreover, compared with the SWOG protocol (4.16%), the monthly protocol had a progression rate of 8.10% ($p = 0.775$). A univariate and multivariate analysis showed a high-grade tumour and prior recurrence rate as the significant factors for disease recurrence and progression (Tables 2–4). At the last follow up, 94 patients (93.1%) were still alive and only 7 patients succumbed. There were no cancer-specific deaths at a median follow up of 2 years and the overall survival at 2 years was 97.6% (Figure 3). Radical cystectomy was performed in six (5.94%) patients.

Safety profile
AEs were seen in 49.5% of patients in which local AEs were found to be more prevalent than systemic. The most commonly reported local AEs

were: dysuria (31.9%), haematuria (19.4%), lower urinary tract symptoms (LUTS) (12.5%), cystitis (4.16%) and epididymo-orchitis (21.38%). For systemic adverse drug reactions (ADRs), fever (12.5%), allergy (12.5%) and urinary tract infection (UTI; 5.5%) were most common. The majority of the AEs occurred during the first 6 months of treatment in which 27 (54%) of patients experience AEs in the first month of therapy. In eight patients, BCG terminations were related to multiple AEs. The one patient who developed epididymo-orchitis was treated by orchidectomy and two patients with BCG cystitis required anti-tubercular therapy. According to Hartwig's severity assessment scale, 54% AEs were rated as moderate and the remaining were mild (46%).

Discussion
BCG is an attenuated strain isolated from *Mycobacterium bovis*, developed as a vaccine for TB. Over the past 40 years, it has been considered
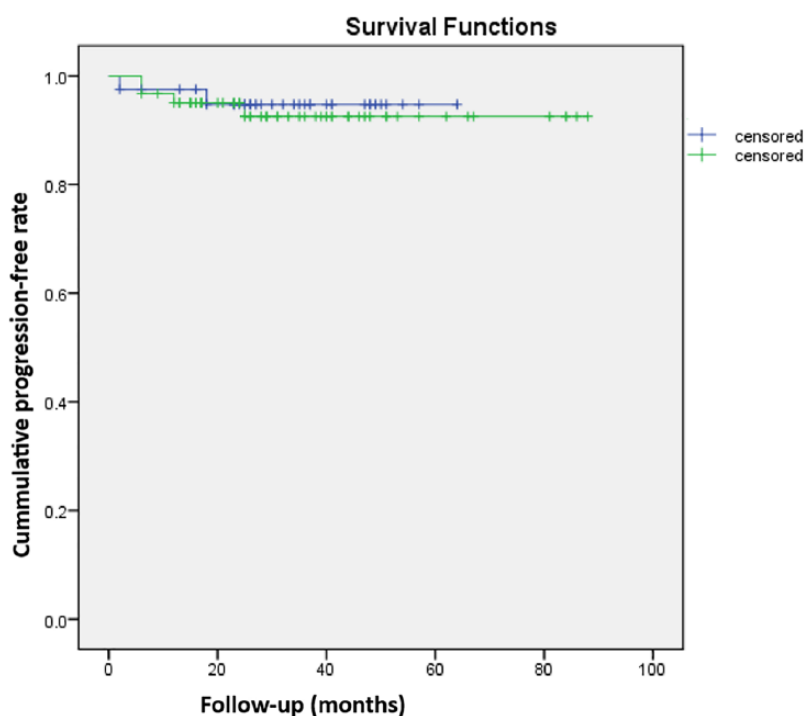
Survival Functions

Figure 2. Kaplan–Meier curves showing PFS of induction BCG (blue curve) compared with maintenance BCG (green curve).
Log rank test: $p = 0.721$.
BCG, Bacillus Calmette–Guerin vaccine; PFS, progression-free survival

Table 1. Comparison of BCG induction therapy and maintenance therapy.

Parameter	BCG induction (*n* = 40)	BCG maintenance (*n* = 61)	*p* value
Age, years	68 ± 12.58	68 ± 9.11	0.211
Sex			
Male	36 (90)	57 (93.4)	0.531
Female	4 (10)	4 (6.5)	
High-risk group			
Ta (low grade)	13 (32.5)	33 (54.0)	0.033
T1, CIS (high grade)	27 (67.5)	28 (45.9)	
Tumour size			
<3 cm	36 (90)	51 (83.6)	0.363
>3 cm	4 (10)	10 (16.3)	
Tumour extent			
Single	7 (17.5)	14 (22.9)	0.509
Multiple	33 (82.5)	47 (77.1)	
Prior recurrence rate			
Yes	9 (22.5)	12 (19.6)	0.732
No	31 (77.5)	49 (80.3)	

BCG, Bacillus Calmette–Guerin vaccine.

Table 2. Univariate analysis of factors affecting recurrence and progression of tumour.

Factors	Recurrence		Progression	
	No of patients (*n* = 15)	*p* value	No of patients (*n* = 6)	*p* value
Age (years)				
<70	7	0.56	4	0.50
>70	8		2	
Tumour size				
<3 cm	12	0.45	4	0.15
>3 cm	3		2	
Tumour extent				
Single	1	0.144	1	0.79
Multiple	14		5	
High-risk group				
Low grade	3	0.031	0	0.021
High grade	12		6	
Prior recurrence rate				
Yes	8	0.007	3	0.06
No	7		3	

Table 3. Multivariate analysis of factors affecting recurrence of tumour.

| Factors	B	Wald	*p* value	Exp (B)	95% CI for Exp (B)	
					Lower	Upper
Tumour extent	1.137	1.026	0.311	3.118	0.345	28.155
High-risk group	1.834	5.749	0.016	6.256	1.398	28.006
Prior recurrence rate	1.832	7.232	0.007	6.246	1.643	23.737

CI, confidence interval.

as the most successful immunotherapy for the management of NMIBC.[15] The effect of BCG in the prevention of tumour recurrence and progression has already been proven by several investigators. Most studies on intravesical BCG have been reported from western countries (United States, Australia etc.), where the prevalence of TB is low. In these countries, the incidence is fewer than 10 cases per 100,000 populations per year. Despite these, there remains a paucity of data on BCG in TB burden countries like India, Indonesia, and China. India has the world's highest incidence of TB with 2.8 million cases annually and BCG is widely used as a vaccine for neonates.[16] Indian patients are culturally and ethnically different from their western counterparts. Because of the pre-existing immunity to BCG, the course of disease and response to intravesical BCG may be different in an Indian scenario. Due to the paucity of data in India, we followed the treatment schedules

Table 4. Multivariate analysis of factors affecting progression of tumour.

Factors	B	Wald	*p* value	Exp (B)	95% CI for Exp (B)	
					Lower	Upper
Tumour size	1.790	2.947	0.086	5.989	0.776	46.228
Prior recurrence rate	1.871	3.780	0.050	6.493	0.985	42.804
CI, confidence interval.						
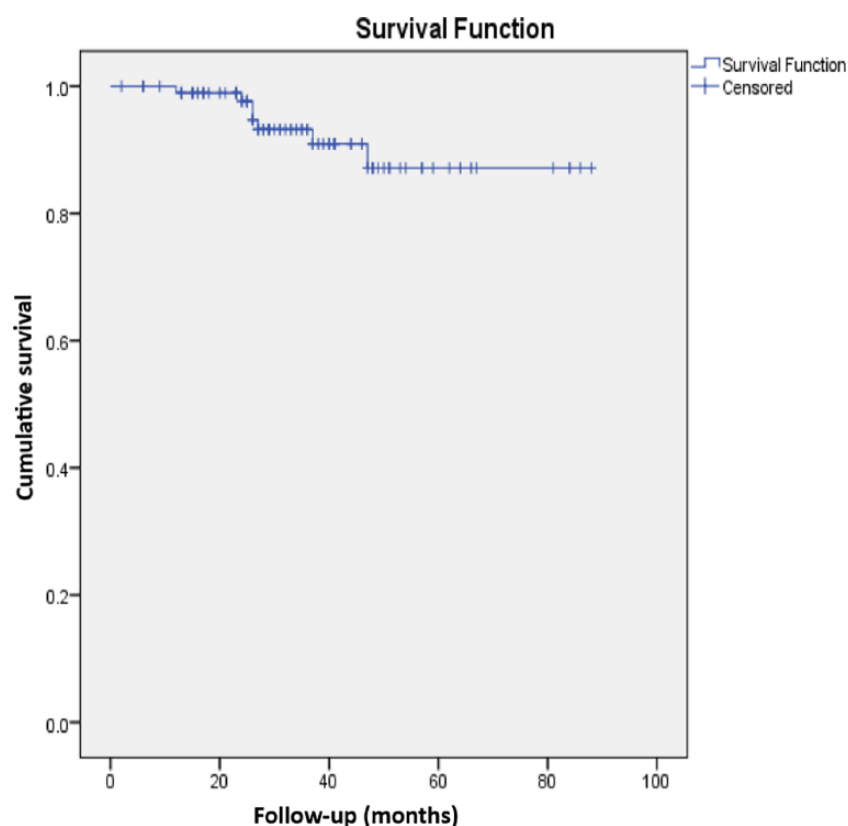
Figure 3. OS after BCG treatment.
BCG, Bacillus Calmette–Guerin vaccine; OS, overall survival.

of BCG which were reported in western literature. The effect of prior BCG vaccination was observed in a trial conducted by Biot and colleagues in 2012. They carried out studies in an orthotropic tumour model of bladder cancer (C57BL/6 mice implanted with MB49 tumour cells) to investigate the phenomenon of pre-existing immunity to BCG. The investigators made the striking observation that immunizing mice 3 weeks before starting intravesical BCG therapy resulted in 100% survival up to 70 days, compared with 80% survival up to 50 days in mice treated with intravesical therapy alone.[17] Since

this, the effect of previous vaccination has not been explored previously. Even though these initial findings were reported, no further studies were conducted in prior vaccinated patients to support these observations.

Several studies have discussed and reported the outcomes of induction and maintenance BCG in high-risk NMIBC. Hudson and colleagues conducted a prospective randomized trial which showed no significant difference between the induction and maintenance groups (recurrence rate was 71% in the induction group *versus* 67%

in the maintenance group).[18] Out of major maintenance BCG trials, the SWOG trial was the only one that showed a significant benefit of maintenance BCG over induction BCG alone.[19–22] Despite this, several meta-analyses have confirmed superior results with maintenance BCG in the prevention of both tumour recurrence and progression.[23,24] But all these studies were conducted in western populations.

In our study, we did not find any significant difference in the DFS and PFS rate between the induction and maintenance groups within 2 years of treatment. So, our results provide convincing evidence that induction BCG alone is adequate for high-risk NMIBC and maintenance BCG does not improve therapeutic outcomes over the standard 6-week induction regimen. The pre-existing immunity to BCG might be the reason behind the unique success of induction BCG in our population. Another possible reason behind the negative results with maintenance BCG is that after initiating intravesical BCG, immune stimulation commonly peaks at 6 weeks. However, with subsequent instillations (as for the maintenance therapy) the immune stimulation peaks at 3 weeks and is suppressed at weeks 4 and 5.[25] In fact, we observed a recurrence rate of 22.2% and 2.94% in patients treated with monthly and SWOG maintenance protocols ($p = 0.217$). Additionally, patients treated with the SWOG protocol had a progression rate of 2.94% and the monthly protocol had 11.1% ($p = 0.775$). Although our results are in line with SWOG-treated patients, a statistically significant difference was not achieved.

The identification of risk factors that affect recurrence and progression of the tumour is essential for making treatment decisions. However, only a few studies reported the prognostic factors in patients treated with intravesical BCG. In the present analysis, a high-grade tumour and prior recurrence rates were found to be the independent factors of tumour recurrence. For tumour progression, a high-grade tumour was found to be the independent predictor. In multivariate analysis, the factors that maintained significance for disease recurrence were prior recurrence rate and high-grade tumour. For disease progression, the prior recurrence rate was the only significant predictor. The possible reason behind the progression of the high-grade tumour is that since the lamina propria in the trigone and bladder neck regions is very thin and the muscularis propria is

very close to the surface, the tumour can easily spread to the muscle region.[26]

BCG intolerance and the development of complications are important factors in further determining treatment modification or cessation. As expected, due its direct local mechanism of action, local AEs were found to be higher than systemic AEs. BCG was generally well tolerated and increasing age was not associated with toxicity ($p = 0.91$). On the basis of cytokine studies on interleukin (IL)-2 and IL-10 in urine samples, immunosenescence in elderly patients resulted in the decreased production of cytokines (responsible for BCG toxicity) and subsequently fewer side effects.[27]

Treatment during the induction phase of BCG is associated with more AEs (54%) than the maintenance phase. It has been hypothesized that the release of more inflammatory cytokines during the first 6 weeks of therapy (as in induction) is responsible for this.[28] Safety data from a retrospective study conducted in NMIBC patients have indicated that 70% of BCG-induced AEs occurred during the induction phase of BCG therapy.[29]

Restaging or second transurethral resection (re-TUR) is an important step in prognostication. The presence of residual tumour on re-TUR for T1 HG/G3 was associated with a 63% increased risk of disease recurrence and a 56% increased risk of disease progression.[30] But the effect of re-TUR on the outcome of BCG needs to be assessed; this was not evaluated in our study group.

The discovery of reliable tools for the prediction of recurrence and progression are necessary for urologists to stratify patients for individualized follow up or to perform early radical cystectomy. Inflammation and obesity play a key role in various malignancies especially in urothelial tumours. The neutrophil-to-lymphocyte ratio seems to be a strong predictor of disease recurrence, progression, as well as cancer-specific survival in patients with primary T1 HG/G3 NMIBC treated with intravesical BCG therapy.[31] An increased body mass index is also associated with a worse prognosis in patients treated with intravesical BCG.[32]

While promising, our study does have its disadvantages. The major limitations of our study were the retrospective nature and the lack of randomization. We provided only a single-centre experience with a shorter follow up, and the

sample size was too small to provide statistical significance to the study.

Conclusion

In conclusion, our data are limited to support any change in the contemporary treatment with BCG for NMIBC. The effect of intravesical BCG in pre-immunized patients and those who had prior TB needs to be evaluated. The present study shows that the effect of intravesical BCG in an Indian population is different from western populations. Our results encourage future studies with maintenance BCG to assess its role in countries where there is high prevalence of TB and inherent immunity against tubercle bacillus.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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