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Original Article

EVALUATION OF RISK FACTORS AFFECTING RECURRENCE AND PROGRESSION AFTER BCG THERAPY IN NON-MUSCLE INVASIVE BLADDER CANCER

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ABSTRACT

Objective: The study was conducted to evaluate the risk factors associated with recurrence and progression in high-risk non muscle-invasive bladder cancer (NMIBC) patients treated with intravesical Bacillus Calmette Guerin (BCG).

Methods: We retrospectively analysed 101 patients who underwent intravesical BCG for high-risk NMIBC from 2006-2015. Multiple factors such as age, sex, smoking status, prior recurrence rate, high-risk group, tumour size and tumour extent were tested as risk factors for recurrence and progression. We also assessed the probabilities of recurrence and progression after BCG therapy using CUETO (Spanish Urological Club for Oncological Treatment) Scoring model.

Results: Total of 93 males (92.1%) and 8 females (7.9%) were enrolled in our study. Over a median follow up of 24 mo, fifteen patients had a recurrence and six patients had progression after BCG therapy. Both univariate and multivariate analysis shows prior recurrence rate and high-grade tumour as a significant factor for tumour recurrence (p=<0.05). For disease progression, univariate analysis revealed high-grade tumour as the significant factor, whereas multivariate analysis showed prior recurrence rate as the dependent factor (p=<0.05). In our study population, probabilities of recurrence and progression were not comparable with the score described in CUETO.

Conclusion: Intravesical BCG remains as a valuable therapeutic option for high-risk NMIBC. However, our data revealed that patients with high-grade tumour and prior recurrence rate might be considered having the highest risk of recurrence and progression even after the BCG therapy. CUETO scoring system overestimates the rate of recurrence and progression in our population. So, in the future, another scoring model must be developed which should include smoking as one of the risk factors for tumour recurrence and progression.

Keywords: High-risk NMIBC, Intravesical BCG, Recurrence, Progression, Risk factors, CUETO scoring model

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INTRODUCTION

Urinary bladder cancer is considered as one of the most commonly diagnosed cancers, with the incidence being four times higher in men than in women [1]. According to the recent reports of National Cancer Registry Programme in India, the overall incidence rate of the urinary bladder cancer is 2.25% (per 10,000 annually) [2]. Two-thirds of all patients with bladder cancer are initially diagnosed with non-muscle invasive bladder cancer (NMIBC) [3, 4]. High-risk NMIBC (Ta, T1G3, carcinoma *in situ* (CIS)) represents as the challenging group with increased risk of recurrence and progression as compared to low risk and intermediate-risk group [5]. There are a number of immunological agents and several chemotherapeutics that have been administered intravesically for the management of NMIBC. Intravesical instillations with bacillus Calmette-Guerin (BCG) is considered as the standard therapy for patients with intermediate or high-risk NMIBC. The intravesical BCG is administered via catheter directly into the bladder where it remains for two hours [6].

Presently, there are no specific biological or pathological markers capable of predicting the response to intravesical BCG [7]. Several prognostic factors have been described, and scoring system has been developed to predict the risk of recurrence and progression after the BCG therapy. In order to predict the short term and long term risks of recurrence and progression after BCG therapy, Spanish urological association published a scoring model called CUETO scoring model. Diagnosis of BC depends on cystoscopy and histological evaluation of the tissue obtained by transurethral resection (TURB) in papillary tumours or by multiple bladder biopsies in CIS. Along with cystoscopy, urine cytology is currently the standard method for the diagnosis and surveillance of bladder cancer [8].

The present study aims to analyse the risk factors of recurrence and progression in patients with high-risk NMIBC who received intravesical BCG as the first-line therapy after the surgery.

MATERIALS AND METHODS

After the approval from the Institutional Review Board, a retrospective study was carried out in 101 patients who received intravesical BCG as an adjunctive treatment of NMIBC between January 2006 and December 2013. Patients were considered as eligible if they met the following criteria: those under all age groups histologically confirmed high-risk NMIBC and patients who have treated with intravesical BCG after TURBT. The exclusion criteria were patients who cannot tolerate the first induction course of BCG.

Medical data were collected by chart review. Data collected included age, gender, smoking, T1 category, grade, size, prior recurrence, and the number of bladder tumours. Data on therapy including date of first and last intravesical BCG instillations, recurrence, progression and survival were also assimilated. After BCG installations, all patients underwent urinalysis, urinary cytology and cystoscopy. Over a median follow up of two years, the presence of recurrence and progression were observed by repeating these examinations every 3 mo for the first 3 y and thereafter every 6 mo.

Statistical analysis

The significant variables associated with recurrence and progression after BCG therapy was assessed using the Cox proportional hazards regression model, including age, gender, smoking, grade, tumour size, prior recurrence and number of bladder tumours. Recurrence Free Survival (RFS) and Progression free survival (PFS) was analysed by Kaplan–Meier method. All statistical analyses were conducted using IBM SPSS 20.0 (SPSS Inc, Chicago, USA).

RESULTS

A total of 101 patients who met the inclusion criteria were identified retrospectively through our institutional database. The median age

(SD) of the study group was 69±10.485 y. 59 (58.4%) were<70 y of age and 42 (41.5%) were>70 y of age. Present study shows a male predominance (92.1%) with a male to the female ratio of 12:1. Characteristics of the study population are summarized in [table 1].

Forty patients (39.6%) received an induction course of BCG and the remaining sixty-one patients had maintenance dose (60.3%). Over a median follow up of two years, 15/101 (14.8%) patients experienced recurrence, 6/101 (5.94%) patients had progression and 7 (6.93%) patients succumbed due to other causes. Using Kaplan-Meier analysis, two-year disease-free survival (DFS) of BCG treated patients was 85% and progression-free survival (PFS) was 94% respectively [fig.1, fig. 2].

Results of univariate and multivariate analysis are shown in [table 2, 3 and 4] respectively. With respect to recurrence, univariate analysis showed a high-grade tumour and prior recurrence rate as the significant factors. In multivariate analysis, same factors showed a significant correlation. With respect to progression (muscle-invasive disease), the high-grade tumour showed a significant correlation on univariate analysis. In multivariate analyses, prior recurrence rate showed a significant correlation to the risk of progression.

Recurrence rates, as well as progression rates for all categories in our study population, were significantly lower than those described by CUETO, i. e the probability of recurrence and progression after BCG therapy in our patient population is low.

Table 1: Patient characteristics (n=101)

Age (years)	69±10.485
Sex	
Male	93 (92.1)
Female	8 (7.9)
Smoking status	
Former/Current	66 (65.3)
Never	35 (34.7)
Tumour size	
<3 cm	87 (86)
>3 cm	14 (14)
Tumour extent	
Single	21 (20.79)
Multiple	80 (79.21)
Prior recurrence rate	
Yes	21 (20.79)
No	80 (79.21)
High-risk group	
Ta (low grade)	46 (45.5)
T1, CIS (high grade)	55 (54.5)
BCG Treatment	
Induction	40 (39.6)
Maintenance	61 (60.3)

BCG, Bacillus Calmette-Guerin

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	>0.05	4	>0.05
>70	8		2	
Sex				
Male	13	>0.05	5	>0.05
Female	2		1	
Smoking				
Former/Current	8	>0.05	4	>0.05
Never	7		2	
Tumour size		>0.05		>0.05
<3 cm	12		4	
>3 cm	3		2	
Tumour extent		>0.05		>0.05
Single	1		1	
Multiple	14		5	
High risk group				
Low grade	3	<0.05	0	<0.05
High grade	12		6	
Prior recurrence rate				
Yes	8	<0.05	3	>0.05
No	7		3	

Table 3: Multivariate analysis of factors affecting the progression of tumour

Factors	**HR**	**95% C. I.**	**p-value**
Tumour size	1.790	0.776-46.228	>0.05
Prior recurrence rate	1.871	0.985-42.804	<0.05

HR, hazard ratio; C. I, Confidence Interval

Table 4: Multivariate analysis of factors affecting recurrence of tumour

Factors	HR	95% C. I.	p value
Tumour extent	1.137	0.345-28.155	>0.05
High risk group	1.834	1.398-28.006	<0.05
Prior recurrence rate	1.832	1.643-23.737	<0.05

HR, hazard ratio; C. I, Confidence Interval

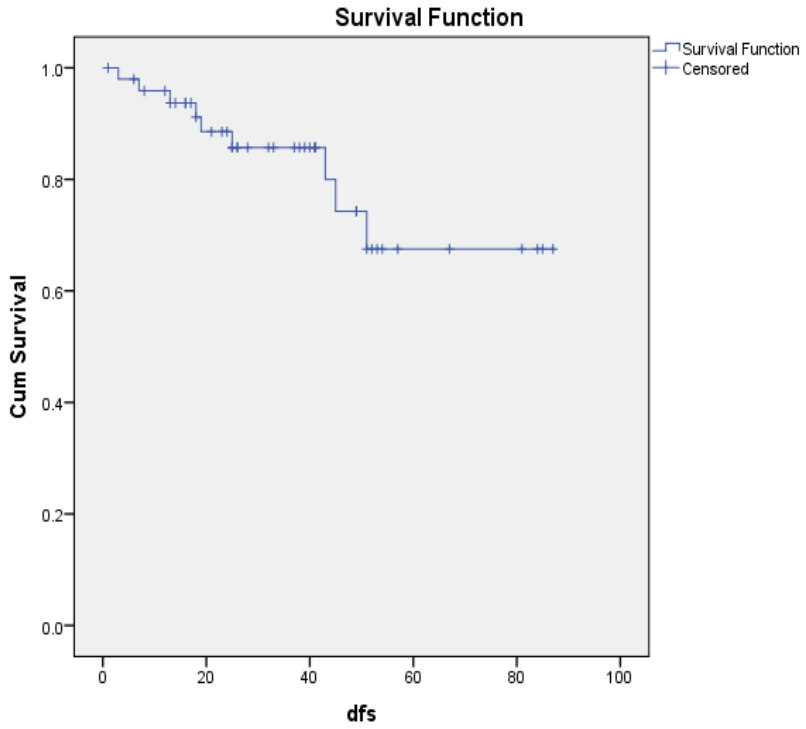

Fig. 1: Kaplan-meier estimates of disease-free survival after BCG treatment

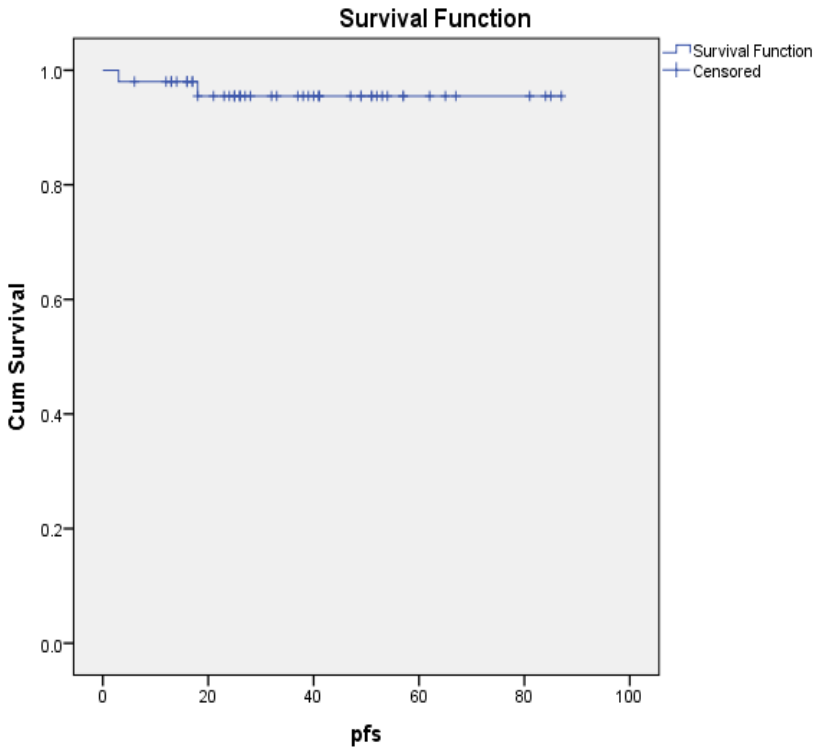

Fig. 2: Kaplan-meier estimates of progression-free survival after BCG treatment

Table 5: Probabilities of recurrence and progression at 1, 2 and 5 y after BCG therapy using CUETO scoring model

CUETO score	Recurrence (%)	Progression (%)
1 y		
1-3	46 (8.24)	23 (1.17)
4-6	38 (12.07	13 (3)
7-9	16 (25.36)	33 (5.55)
10-13	1 (41.79)	32 (13.97)
2 y		
1-3	46 (12.60)	23 (2.16)
4-6	38 (22.28)	13 (4.97)
7-9	16 (39.61)	33 (11.95)
10-13	1 (52.55)	32 (24.81)
5 y		
1-3	46 (20.98)	23 (3.76)
4-6	38 (35.57)	13 (11.69)
7-9	16 (47.61)	33 (21.26)
10-13	1 (67.61)	32 (33.57)

CUETO, (Spanish Urological Club for Oncological Treatment)

DISCUSSION

Non-muscle invasive bladder cancer (NMIBC) represents a heterogeneous group of tumours with different rates of recurrence, progression, and disease-related mortality. Intravesical immunotherapy with BCG is considered as the most effective therapy which can prevent both tumour recurrence and progression after TURB [9]. According to EORTC (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 %) [10]. Thus, it is very important to recognise the patients with increased risk of recurrence and progression, so that more frequent follow-up or early radical cystectomy can be suggested. Therefore, our study aims to find out the risk factors associated with tumour recurrence and progression after BCG therapy.

Her HW, reported age>70 y as a significant factor with regard to recurrence [11]. In our retrospective study, age>70 y was found to be a negative factor affecting recurrence and progression. Gontero *et al.*, in a large retrospective multicentre study observed that patients with tumour size>3 cm had a higher risk of progression [12]. But, in our population, it was found as a negative factor. Only high-grade tumour and prior recurrence rates were found as the significant factors associated with tumour recurrence in univariate and multivariate analysis. In univariate analysis, the high-grade tumour was the only significant factor of progression, whereas in multivariate analysis prior recurrence rate was found to be a significant factor for progression. The possible reason behind the progression of the high-grade tumour is that since the lamina propria in trigone and bladder neck regions is very thin and the muscularis propria is very close to the surface, tumour can easily spread to the muscle region [13]. The current study shows that patients with high-grade tumour remained at a significant risk of recurrence and progression after BCG therapy, so additional or alternative treatments are urgently required in these cases.

CUETO scoring model was published by Spanish Urological Association for BCG treated patients to discriminate patients at risk of recurrence and progression. It is based on seven factors such as age, sex, prior recurrence, number of tumours, tumour category, associated CIS and tumour size. Recurrence and progression rate in our study was not comparable with the score described in CUETO. This model failed to discriminate our BCG treated patients. The plausible reason behind this is: first, our patient population differed significantly from the population analysed by the CUETO scoring in terms of geographic location, ethnic background, treatment algorithm and malignant potential. Second, maybe due to the pre-existing immunity of BCG in our population. Since this scoring model is based on the western population, other predictive tools must be developed for Indians. The discovery of reliable tools will be helpful for the urologists to discuss treatment options with patients after finding probabilities of tumour recurrence and progression [14].

In order to improve the prediction, we analysed other variables such as smoking which is not included in CUETO scoring model. However, we found smoking as a negative factor for the prognosis of BCG treated patients with respect to recurrence and progression. Whereas, Serge Holz *et al.*, in his retrospective study reported smoking as a significant predictor for progression [15].

CONCLUSION

To conclude, patients with high-grade tumour and prior recurrence rates might be considered having the highest risk of recurrence and progression after two years of BCG therapy. CUETO scoring system overestimates rates of recurrence and progression in our population. So, in the future, another scoring model must be developed which should include smoking as one of the risk factors for tumour recurrence and progression.

While promising, our study does have its disadvantages such as its retrospective design and the small sample size.

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AUTHORS CONTRIBUTIONS

Julie Mariam Joshua collected the case profiles, compiled the collected information and involved in writing. Santhosh M Mathews was involved in correction, scientific editing, and communicating the manuscript to the journal. All authors reviewed and approved the final manuscript.

CONFLICT OF INTERESTS

The data and research results are honest and the author reports no conflicts of interest in this work.

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