

# Recurrence and progression in nonmuscle invasive transitional cell carcinoma of urinary bladder treated with intravesical *Bacillus Calmette–Guerin*: A single center experience and analysis of prognostic factors

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## Abstract

**Background:** Intravesical *Bacillus Calmette–Guerin* (BCG) has been the standard of care for the prevention of nonmuscle invasive bladder cancer (NMIBC) recurrence following resection. Attempts to improve on the result by combining it with other agents have largely failed. This study addresses the result of BCG therapy in our patient population and compares the result with our combination BCG and interferon therapy published earlier.

**Materials and Methods:** The medical records of patients diagnosed with NMIBC and treated with transurethral resection and intravesical BCG were reviewed. Univariate analysis was performed on most known prognostic factors. Results were compared to published data on the use of BCG and interferon from the same institution.

**Results:** Thirty-one patients were identified. Median age was 66 (range 33–109), 80.6% were males. Fourteen patients (45%) had  $\leq 3$  tumors and 18 (58.1%) had T1 lesions. Four patients (12.9%) had Grade 3 tumors and 25 (80.6%) had Grade 2 tumors. One patient (3.2) had concurrent carcinoma *in situ* and 11 (35.5%) were treated upon initial diagnosis. At 5 years, the relapse-free survival was 61.3% (95% confidence interval (CI) 44.2–78.4%), progression-free survival was 85.6% (95% CI 73.3–97.9%), and overall survival was 93% (95% CI 84.1–100%). Comparison with the BCG and interferon data showed no significant difference.

**Conclusion:** The result of BCG therapy in our patient population is similar to western reported data. Efficacy of BCG alone is equal to BCG and interferon within our institution.

**Key Words:** *Bacillus Calmette–Guerin*, interferon, nonmuscle invasive bladder cancer, prognostic factors

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## INTRODUCTION

Bladder cancer is the 7<sup>th</sup> most common cancer in men

and the 17<sup>th</sup> most common cancer in women worldwide with an age-standardized incidence of 17 and 6/100,000,

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respectively.<sup>[1]</sup> More than 70% of all bladder cancers are nonmuscle invasive involving only the mucosa and the submucosa.<sup>[2]</sup> Mortality of bladder cancer has decreased reflecting an advancing development of new therapeutic approaches.<sup>[3]</sup> Standard of care for the treatment of nonmuscle invasive bladder cancer (NMIBC) is transurethral resection (TUR). However, unfortunately, a large percentage of patients do relapse, and many of them progress to muscle invasive disease necessitating radical cystectomy.<sup>[4]</sup> The high recurrence and progression rate prompted investigators to use intravesical therapy in an attempt to prevent recurrences. Intravesical *Bacillus Calmette–Guerin* (BCG) has been the standard adjuvant therapy for NMIBC following TUR, showing superiority to many chemotherapeutic agents (doxorubicin and mitomycin-C).<sup>[5,6]</sup> Despite this, around 30–45% of patients receiving adjuvant intravesical BCG therapy develop recurrence of their cancer.<sup>[7]</sup> Several attempts have been made to reduce the recurrence rate after intravesical BCG therapy. This includes maintenance BCG therapy, combining BCG with other agents such as interferon and the use of other chemotherapeutic agents instead of BCG. We have previously published the result of two investigational approaches to reduce NMIBC recurrence after BCG therapy by either alternating intravesical BCG with interferon on a weekly basis<sup>[8]</sup> or combining BCG and Interferon.<sup>[9]</sup> Compared to published literature, our results were similar to the results obtained with BCG alone. In this study, we review the result of BCG therapy alone in our institution and compare it to our previously published data of BCG and interferon. In addition, we combine the data of the two groups and evaluate several factors that might affect recurrence.

## MATERIALS AND METHODS

The medical records of patients who were treated with intravesical BCG for NMIBC between July 1998 and June 2002 were reviewed. The above period was selected since later on patients were enrolled on multiple prospective investigational trials. Demographic data including age, gender, date of histological diagnosis, recurrent versus de novo tumor, the number of bladder tumors, the size of the largest tumor, concomitant carcinoma *in situ* (Tis), prostatic urethral involvement, and urine cytology were recorded. Data on therapy including baseline blood count, renal and liver function tests, date of TUR, date of the first and last BCG intravesical instillations, number of weekly induction BCG instillations, and reason for stopping short of six instillations if any were recorded. Data on maintenance therapy if given were recorded including the number of courses given (all patients were planned for six maintenance courses per the Southwest Oncology Group [SWOG] protocol), reason

for stopping maintenance, recurrence rate, and survival. The project was conducted in accordance with the ethical principles contained in the declaration of Helsinki 2013 version,<sup>[10]</sup> good clinical practice guidelines and the policies and guidelines of the research advisory council at our institution. Patients identifying data were kept confidential during the study. Tabulation and statistics were done using SPSS statistical program (IBM corporation, Armonk, NY, USA). Survival was calculated using Kaplan–Meier method. Disease-free survival (DFS) was calculated from the date of initiation of therapy till recurrence or death. Progression-free survival was calculated from the date of initiation of therapy till recurrence with a higher stage or death. Overall survival was calculated from the date of initiation of therapy till death. P value for survival was calculated using the log-rank method.

Individual patient's data were then pooled with our previously reported Phase II trial of concurrent BCG and interferon.<sup>[9]</sup> Recurrence and survival were then analyzed for the whole group and according to the treatment cohort (BCG alone and combined BCG and interferon), in addition to factors of possible prognostic importance: Age, gender, number of recurrences, urine cytology, tumor size and number, concurrent Tis, T-stage, T-grade, and maintenance therapy when available.

## RESULTS

Thirty-one patients were identified with a male to female ratio of 25:6. Median age was 66 years (range: 33–109). Patient's characteristics are shown in Table 1.

**Table 1: Patients characteristics-retrospective cohort**

Item	n=31 (%)
Median age (range)	66 (33-109)
Gender	
Male	25 (80.6)
Female	6 (19.4)
Number of tumors	
≤3	14 (45.2)
>3	14 (45.2)
Unknown	3 (9.7)
T stage	
Ta	13 (41.9)
T1	18 (58.1)
Concurrent Tis	
Yes	1 (3.2)
No	25 (80.6)
Unknown	5 (16.1)
Tumor grade	
Grade 1	1 (3.2)
Grade 2	25 (80.6)
Grade 3	4 (12.9)
Unknown	1 (3.2)
Prior recurrences	
None	11 (35.5)
One	8 (25.6)
Two	5 (16.1)
Three	7 (22.6)

### Treatment compliance

All patients received induction course of BCG with a median of 6 weekly instillation (range 4–6). All patients received the treatment on time except for three who had treatment delays (two for patients request and one because of gross hematuria). Eleven patients underwent maintenance BCG using the SWOG protocol,<sup>[11]</sup> with a median of three courses given (3 weekly instillation per course, range 1–6). Eight patients did not complete the maintenance course, three because of patient request, and three because of toxicity, one lost to follow-up and one unknown.

### Efficacy

A total of 12 patients (38.7%) relapsed over the follow-up period (median 103.5 months, range 46–138.9). Seven of them relapsed at the 3-month evaluation. Stage at the time of relapse was Ta in six patients, T1 in three, and three patients with metastatic disease, two of them were at 3-month evaluation. Five years relapse-free survival for the whole group was 61.3% (95% confidence interval (CI) 44.2–78.4%), progression-free survival was 85.6% (95% CI 73.3–97.9%) (five patients developed metastasis), and overall survival was 93% (95% CI 84.1–100%). Univariate analysis of factors that are known to affect recurrence and progression was performed and showed no significant difference in any subgroup as shown in Table 2. However, it is worth noting that patients with Ta tumors had much lower chance of being disease free at 5 years than patients with T1 lesions (38.5 vs. 77.8%) and similarly those who were treated upon recurrence as compared to those who were treated on first presentation (50.0 vs. 72.7%). In addition, none of the patients who had three or less tumors progressed at 5 years.

Twenty-four patients were disease free at 3 months evaluation and are eligible for analysis of the benefit of maintenance therapy. Out of those, 11 had maintenance therapy. Median relapse-free survival for both groups was not reached, and the difference was not significant with  $P = 0.3$ . Reasons for stopping maintenance varied from failure to follow-up in two patients, patient refusal in three, and severe toxicity in three.

Pooled data of our retrospective analysis and prospective Phase II trial comprised a total of 81 patients (31 retrospective and fifty prospective). Univariate analysis of DFS was performed according to the treatment received number of tumors ( $\leq 3$  or  $>3$ ), single or multiple tumors, T-stage (Ta vs. T1), and tumor grade (Grade 1 vs. 2 vs. 3). No significant difference was found in any of the above factors [Table 3].

### DISCUSSION

We have previously reported the result of post-TUR therapy for NMIBC with the combination of BCG and interferon

**Table 2: Univariate analysis of factors that affect disease-free and progression-free survival for the retrospective cohort and the combined cohort**

Factor	Retrospective cohort		Combined cohort			
	DFS <sup>†</sup> at 5 years (%)	P	PFS <sup>†</sup> at 5 years (%)	P	DFS <sup>†</sup> at 5 years (%)	P
Prior recurrence						
<i>De novo</i>	72.7	0.3	90.9	0.5	NA	NA
recurrence	55.0		83.35		NA	NA
T stage						
Ta	38.5	0.08	84.6	0.6	52	0.1
T1	77.8		87.4		55	
Number to tumors						
$\leq 3$	78.6	0.1	100	0.08	60	0.8
$>3$	50.0		85.1		57	
Maintenance therapy*						
Yes	81.8	0.3			NA	NA
No	76.9				NA	NA
Type of therapy						
BCG alone	NA	NA	NA	NA	57	0.9
BCG + IFN <sup>†</sup>	NA		NA		59	

<sup>†</sup>DFS: Disease-free survival, PFS: Progression free survival, IFN: Interferon, NA: Not applicable, \*Based on 24 disease free patients after 3 months evaluation

**Table 3: Univariate analysis of factors that affect recurrence in pooled patients' data**

Factor	DFS <sup>†</sup> at 5 years (%)	P	PFS at 5 years (%)	P
Prior recurrence				
<i>De novo</i>	72.7	0.3	90.9	0.5
Recurrence	55.0		83.35	
T stage				
Ta	38.5	0.08	84.6	0.6
T1	77.8		87.4	
Number to tumors				
$\leq 3$	78.6	0.1	100	0.08
$>3$	50.0		85.1	
Maintenance therapy*				
Yes	81.8	0.3		
No	76.9			

\*Based on 24 disease free patients after 3 months evaluation, <sup>†</sup>DFS: Disease-free survival, PFS: Progression free survival

given in a context of Phase II trial and compared it with international historical control.<sup>[9]</sup> This study is the first and only one from Saudi Arabia to report the result of BCG prophylaxis in the prevention of recurrence of superficial bladder cancer.

Our study confirms similar efficacy of BCG in the prophylaxis of recurrence of NMIBC in a retrospectively studied cohort compared to published literature. Our 5-year relapse-free survival of 61.8% was similar to the results seen with different Phase III trials using BCG alone and meta-analysis of BCG therapy.<sup>[12-14]</sup> This is seen despite that 58.1% of the patient has T1 tumors, 45% have more than three tumors, and the majority (64.3%) were recurrent rather than primary presenting tumors.

We have looked at several factors that affect the result of therapy with BCG. Of these, the issue of maintenance therapy remains controversial. Out of five maintenance trials,<sup>[15-18]</sup> the SWOG trial was the only one which showed a significant benefit over no maintenance therapy.<sup>[11]</sup> Despite this, several meta-analysis has confirmed the improved results with maintenance therapy.<sup>[5,19-21]</sup> In our study, there was no difference in DFS at 5 years between maintenance versus no maintenance groups (81.8 vs. 76.9, respectively,  $P = 0.3$ ). This is likely secondary to the small number of patients in the study and the retrospective nature of it. Three of the II maintenance patients in our study (27%) completed the full course compared to 18% reported in the SWOG trial, confirming the difficulty in finishing maintenance therapy. This is mainly secondary to toxicity. Other factors previously identified that affect recurrence or progression include treatment on the first presentation versus recurrence, number of tumors on presentation, tumor stage (Ta vs. T1), tumor grade, positive urine cytology, and maximum tumor size.<sup>[22,23]</sup> Our data showed no significant difference in recurrence and progression-free survival among patients with primary presentation versus recurrence, patients with more than three tumors versus less, likely secondary to small number. Although not significant, it is interesting to know that our study showed a superior 5 year DFS (77.8% vs. 38.5%) but equal 5-year PFS (87.4% vs. 84.6%) for patients with T1 compared to those with Ta lesions, respectively. It is important to note that in view of the retrospective nature of the study, data like urine cytology and tumor size were not consistently available and accordingly were not included in the analysis.

Finally, the combined analysis confirms the equal efficacy of BCG alone versus combined BCG and Interferon as has been concluded and reported in our previously published Phase II trial.<sup>[9]</sup>

## CONCLUSION

Our study shows similar results for the use of BCG in the prevention of recurrence of NMIBC, compared to published literature. In addition, it confirms that combining BCG with interferon does not add to its efficacy in first-line management.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

## REFERENCES

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 10. International Agency for Research on Cancer; 2010. Available from: <http://globocan.iarc.fr/>. [Last accessed on 2016 Mar 16].
2. Babjuk M, Burger M, Zigeuner R, Shariat SF, van Rhijn BW, Compérat E, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: Update 2013. *Eur Urol* 2013;64:639-53.
3. Ferlay J, Randi G, Bosetti C, Levi F, Negri E, Boyle P, et al. Declining mortality from bladder cancer in Europe. *BJU Int* 2008;101:11-9.
4. Nargund VH, Tanabalan CK, Kabir MN. Management of non-muscle-invasive (superficial) bladder cancer. *Semin Oncol* 2012;39:559-72.
5. Böhle A, Bock PR. Intravesical bacille Calmette-Guérin versus mitomycin C in superficial bladder cancer: Formal meta-analysis of comparative studies on tumor progression. *Urology* 2004;63:682-6.
6. Shelley MD, Mason MD, Kynaston H. Intravesical therapy for superficial bladder cancer: A systematic review of randomised trials and meta-analyses. *Cancer Treat Rev* 2010;36:195-205.
7. Fuge O, Vasdev N, Allchorne P, Green JS. Immunotherapy for bladder cancer. *Res Rep Urol* 2015;7:65-79.
8. Bazarbashi S, Raja MA, El Sayed A, Ezzat A, Ibrahim E, Kattan S, et al. Prospective phase II trial of alternating intravesical *Bacillus Calmette-Guérin* (BCG) and interferon alpha IIB in the treatment and prevention of superficial transitional cell carcinoma of the urinary bladder: Preliminary results. *J Surg Oncol* 2000;74:181-4.
9. Bazarbashi S, Soudy H, Abdelsalam M, Al-Jubran A, Akhtar S, Memon M, et al. Co-administration of intravesical *Bacillus Calmette-Guérin* and interferon a-2B as first line in treating superficial transitional cell carcinoma of the urinary bladder. *BJU Int* 2011;108:1115-8.
10. World Medical Association. World medical association declaration of Helsinki: Ethical principles for medical research involving human subjects. *JAMA* 2013;310:2191-4.
11. Lamm DL, Blumenstein BA, Crissman JD, Montie JE, Gottesman JE, Lowe BA, et al. Maintenance *Bacillus Calmette-Guérin* immunotherapy for recurrent TA, T1 and carcinoma *in situ* transitional cell carcinoma of the bladder: A randomized Southwest Oncology Group Study. *J Urol* 2000;163:1124-9.
12. Shang PF, Kwong J, Wang ZP, Tian J, Jiang L, Yang K, et al. Intravesical *Bacillus Calmette-Guérin* versus epirubicin for Ta and T1 bladder cancer. *Cochrane Database Syst Rev* 2011;(5):CD006885.
13. Pan J, Liu M, Zhou X. Can intravesical *Bacillus Calmette-Guérin* reduce recurrence in patients with non-muscle invasive bladder cancer? An update and cumulative meta-analysis. *Front Med* 2014;8:241-9.
14. Gandhi NM, Morales A, Lamm DL. *Bacillus Calmette-Guérin* immunotherapy for genitourinary cancer. *BJU Int* 2013;112:288-97.
15. Hudson MA, Ratliff TL, Gillen DP, Haaff EO, Dresner SM, Catalona WJ. Single course versus maintenance *Bacillus Calmette-Guérin* therapy for superficial bladder tumors: A prospective, randomized trial. *J Urol* 1987;138:295-8.
16. Palou J, Laguna P, Millán-Rodríguez F, Hall RR, Salvador-Bayarri J, Vicente-Rodríguez J. Control group and maintenance treatment with *Bacillus Calmette-Guérin* for carcinoma *in situ* and/or high grade bladder tumors. *J Urol* 2001;165:1488-91.
17. Badalament RA, Herr HW, Wong GY, Gnecco C, Pinsky CM, Whitmore WF Jr., et al. A prospective randomized trial of maintenance versus nonmaintenance intravesical *Bacillus Calmette-Guérin* therapy of superficial bladder cancer. *J Clin Oncol* 1987;5:441-9.
18. Akaza H, Hinotsu S, Aso Y, Kakizoe T, Koiso K. *Bacillus Calmette-Guérin* treatment of existing papillary bladder cancer and carcinoma *in situ* of the bladder. Four-year results. The Bladder Cancer BCG Study Group. *Cancer* 1995;75:552-9.
19. Sylvester RJ, van der Meijden AP, Lamm DL. Intravesical *Bacillus Calmette-Guérin* reduces the risk of progression in patients with superficial bladder cancer: A meta-analysis of the published results of randomized clinical trials. *J Urol* 2002;168:1964-70.
20. Sylvester RJ, van der Meijden AP, Witjes JA, Kurth K. *Bacillus Calmette-Guérin* versus chemotherapy for the intravesical treatment of

- patients with carcinoma *in situ* of the bladder: A meta-analysis of the published results of randomized clinical trials. *J Urol* 2005;174:86-91.
21. Böhle A, Jocham D, Bock PR. Intravesical *Bacillus Calmette-Guerin* versus mitomycin C for superficial bladder cancer: A formal meta-analysis of comparative studies on recurrence and toxicity. *J Urol* 2003;169:90-5.
  22. Ali-El-Dein B, Sarhan O, Hinev A, Ibrahim el-HI, Nabeeh A, Ghoneim MA. Superficial bladder tumours: Analysis of prognostic factors and construction of a predictive index. *BJU Int* 2003;92:393-9.
  23. Millán-Rodríguez F, Chéchile-Toniolo G, Salvador-Bayarri J, Palou J, Algaba F, Vicente-Rodríguez J. Primary superficial bladder cancer risk groups according to progression, mortality and recurrence. *J Urol* 2000;164 (3 Pt 1):680-4.