

Original Article

Failure of Bacillus Calmette Guerin (BCG) Therapy for the Treatment of Bladder Cancer: Al-Azhar Experience

E. S. M. Elmallah

Urology Department, Al-Azhar University, Cairo, Egypt

ABSTRACT

Objective: To determine the failure rate of intravesical Bacillus Calmette Guerin (BCG) instillation following complete transurethral resection of superficial transitional cell carcinoma (TCC) of the urinary bladder at the Urology Department, Al-Azhar University, Cairo, Egypt.

Patients and Methods: A prospective analysis of 160 patients with superficial TCC of the urinary bladder treated by transurethral resection of the bladder tumor (TUR) and adjuvant intravesical BCG instillation was performed at the Urology Department, Al-Azhar University, Cairo, between 2002 and 2008. The mean follow-up was 37 ± 4 (range 3 to 64) months.

Results: After the initiation of BCG treatment 12 patients (7.5%) were lost to follow-up, 6 (3.8%) stopped BCG due to side-effects and were subsequently treated with intravesical chemotherapy, while another 5 (3.1%) died during BCG therapy due to tumor-unrelated causes. The overall survival rate at 3 years was 90.4%. At a mean follow-up period of 37 ± 4 months, 70.4% of the patients showed no tumor recurrence and 82% no tumor progression. BCG failure was significantly observed in cases with stage T1, or grade-3 tumors or in cases associated with carcinoma in situ.

Conclusion: TUR with adjuvant intravesical BCG therapy is considered the first treatment option in high and intermediate risk patients with superficial TCC. Failure of BCG treatment is mainly observed in stage T1 or grade-3 tumors. Different treatment modalities can be used after a second tumor recurrence or progression according to the tumor aggressiveness and the patient's preference.

Keywords : Superficial bladder cancer, Bacillus Calmette Guerin (BCG), tumor recurrence, progression

Corresponding Author: Ehab Elmallah, M.D., Dept. of Urology, Sayed Galal University Hospital, 540 Port Said St., Eldaher, Cairo, E-mail: ehabelmalah@yahoo.com, ehalmallah@hotmail.com

Article Info: Date received : 23/6/2009

Date accepted (after revision): 15/10/2009

INTRODUCTION

Transurethral resection of a superficial bladder tumor (TUR) is used to remove the tumor for histological diagnosis of tumor cell type, grade and stage¹. About 70% of these tumors recur as superficial tumors, but some progress. Stage T1, high grade, multiplicity and carcinoma in situ are risk factors and increase the possibility of tumor progression^{2,3}. To minimize tumor recurrence,

adjuvant intravesical immunotherapy or chemotherapy is usually used after TUR. Several studies have confirmed the efficacy of Bacillus Calmette Guerin (BCG) in reducing tumor recurrence and delaying its progression⁴. In the European Association of Urology (EAU) guidelines for the treatment of bladder cancer BCG is considered more effective than intravesical chemotherapy and

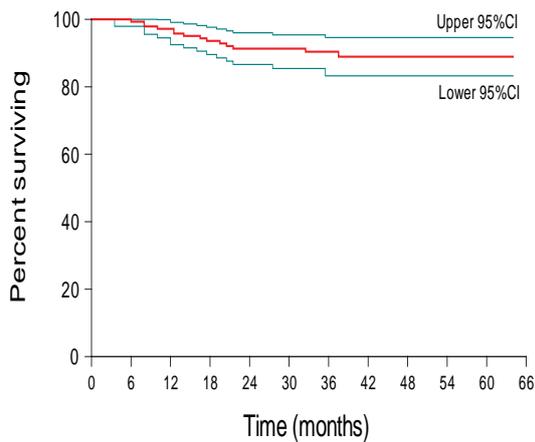


Fig. 1: Overall survival at a mean follow-up of 3 years

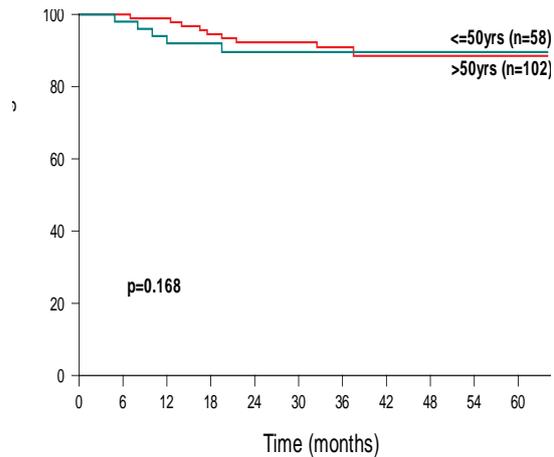


Fig. 2: Survival according to age groups (<50 and > 50 years)

is advocated as the first treatment option in high-risk patients and in the intermediate-risk patients after failure of intravesical chemotherapy¹.

Intravesical BCG instillation protocols with various doses of BCG, intervals of instillation and periods of BCG maintenance have been used. The objective of this study is to report on the Al-Azhar experience with special emphasis on the failure rate and factors affecting the results of intravesical BCG instillation after complete transurethral resection of superficial transitional cell carcinoma (TCC) of the urinary bladder.

PATIENTS AND METHODS

This prospective study conducted between 2002 and 2008 included 160 patients (113 men and 47 women) with superficial TCC of the bladder treated by TURT followed by intravesical BCG instillation. The mean follow-up was 37 ± 4 (range 3 to 64) months. The mean age of the patients was 62.2 ± 9.5 (range: 27 to 83) years. Informed consent was routinely taken from all patients.

All patients were evaluated by clinical assessment, routine laboratory tests, abdomino-pelvic ultrasound and excretory urography. Pelvic CT scan was performed in 109 patients, while non-contrast CT scan of

the abdomen and pelvis was indicated in 13 patients with impaired renal function.

Hematuria was the most common clinical presentation as shown in Table 1. Mean serum creatinine was 1.1 ± 0.2 (range: 0.4 to 1.5) mg/dL in 147 and 2.6 ± 0.5 (range: 1.9 to 4.9) mg/dL in the remaining 13 patients.

All patients underwent complete TURT in a single session (113 cases) or in two sessions (47 patients). To assess the tumor stage and grade all resected tumor tissue, as well as a biopsy from the tumor base, random mucosal biopsies from the remaining bladder and a biopsy specimen of the prostatic urethra were sent for histopathologic analysis. Repeated TURT was indicated in 26 patients due to the absence of muscle tissue in the first specimen. Staged resection of multiple or large-volume tumors was done 2 weeks after the first session in 21 patients. The histopathologic features of the tumor cell type, stage, grade, multiplicity and association of carcinoma in situ were documented in all cases.

All low-risk patients with stage-Ta, grade-1 TCC who received no adjuvant therapy were excluded from this study, while cases of Ta with a higher tumor grade (2-3) or cases with T1, grade-1 TCC were considered high or intermediate-risk patients and were included in the study.

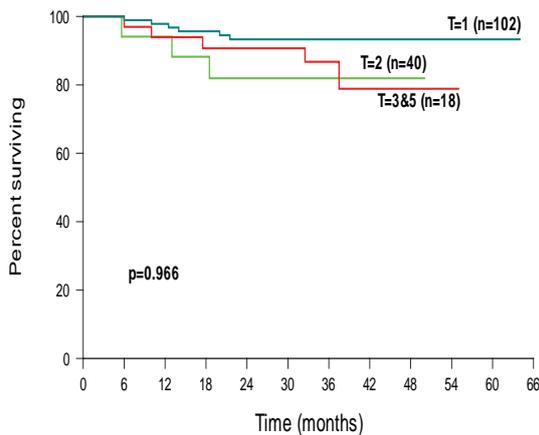


Fig. 3: Survival according to the number of tumors

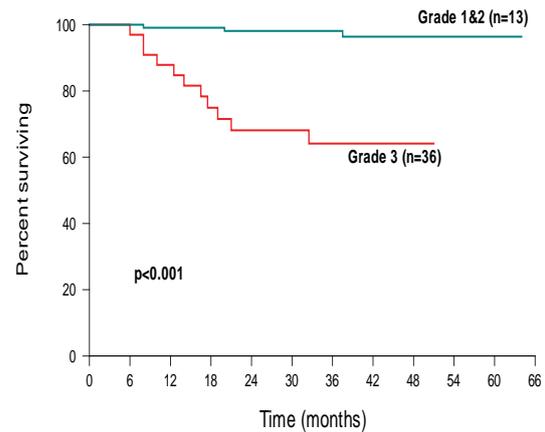


Fig. 5: Survival according to tumor grade.

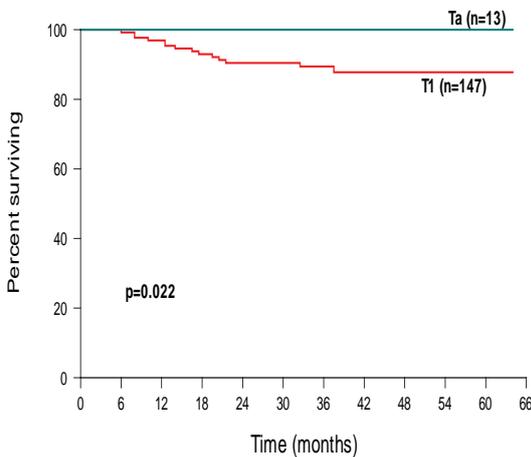


Fig. 4: Survival according to tumor stage.

Two weeks after TURT, a 6-week induction course of intravesical BCG instillations was started. It consisted of a weekly administration of 80 mg BCG dissolved in 50 ml of normal saline instilled through a urethral catheter into an empty bladder and held for at least 2 hours. This BCG induction course was followed after 2 weeks by clinical assessment, urine cytology (34 cases) and pelvic ultrasound to determine the presence of any bladder tumor.

If no recurrence was present, a maintenance course of monthly 80 mg BCG was given

in the first year, then every 3 months for the next 2 years. In patients with recurrence of superficial TCC after the induction course of BCG, a second session of TURT and BCG instillation was performed

Failure of BCG was considered in cases with tumor progression or recurrence after the second BCG course. These cases were managed by either repeated TURT with intravesical chemotherapy or salvage cystectomy.

For post-operative assessment, clinical evaluation and pelvic ultrasound were done for all patients before the induction course of BCG and every 3 months during the maintenance course. Urine cytology was done in 34 patients with high-grade TCC and in cases with associated carcinoma in situ. Abdomino-pelvic CT scan was done in cases with tumor recurrence or tumor progression. Furthermore, evaluation of the upper urinary tract was performed after 3, 12 and 24 months with assessment of serum creatinine and abdominal ultrasound. Cystoscopy was performed 6 weeks after the induction BCG course, then annually with mucosal biopsy of the site of the resected primary tumor and randomly from the remaining bladder in high-risk patients.

Statistical analysis was performed with Student's t-test and Chi-square test and

Table 1: Presenting symptoms*

Clinical presentation	Patient No.	%
Hematuria	135	84.4%
Burning micturition	77	48.1%
Increased urinary frequency	45	28.1%
Urgency	41	25.6%
Urge incontinence	12	7.5%

*Some patients had more than one presenting symptom

Table 2: Tumor characteristics

		No.	%
No. of tumors	1	102	63.8%
	2	40	25.0%
	3	10	6.2%
	4	5	3.1%
	5	3	1.9%
Tumor stage	T1	138	86.3%
	T1 + Tis	9	5.6%
	Ta	9	5.6%
	Ta + Tis	1	0.6%
	Tis	3	1.9%
Tumor grade		24	15.0%
	G1		
	G2	100	62.5%
	G3	36	22.5%

statistical significance was defined as $p < 0.05$. Factors affecting tumor recurrence, progression and survival were subjected to univariate analysis. Factors that appeared significant in univariate analysis were subjected to multivariate analysis..

RESULTS

Pelvic CT scan diagnosed the presence of superficial bladder tumors in 98 out of 109 patients (89.9%), while it overestimated the

tumor stage in 11 cases. The tumor features including multiplicity, stage, grade and association with carcinoma in situ are shown in Table 2.

After the induction BCG course 12 patients (7.5%) were lost to follow-up, 6 (3.8%) stopped BCG treatment due to side-effects and were further treated with intravesical chemotherapy, and 5 (3.1%) died during the maintenance BCG course due to tumor-unrelated causes.

Table 3: Correlation between age, tumor features and outcome

Factors	Number of cases	Recurrence-free rate (%)		Progression-free rate (%)		Overall survival rate (%)	
		3 years	p-value*	3 years	p-value*	3 years	P-value*
Overall	160	70.4		82.0		90.4	
Age							
≤50 yrs	58	64.0		79.6		89.6	
>50 yrs	102	73.9	0.168	83.6	0.555	90.4	0.855
No. of tumors							
1	102	70.9		83.5		93.3	
2	40	61.3		84.6		86.8	
3-5	18	70.6	0.966	79.7	0.385	81.9	0.178
Tumor stage							
Ta	13	100		91.7		100.0	
T1	147	68.4	0.022	81.1	0.295	89.4	0.219
Tumor grade							
1 and 2	124	79.1		92.6		98.1	
3	36	41.4	<0.001	45.9	<0.001	64.1	<0.001

* A p-value ≤ 0.05 is considered significant.

Age had no impact on the outcome of the used treatment modality in our patients ($p>0.855$). The overall survival rate at 3 years follow-up was 90.4% (Fig.1). There were no significant differences in overall survival between patients aged <50 and >50 years ($p=0.168$) or numbering those with single versus multiple tumors ($p=0.966$) (Figs. 2 and 3). On the other hand, overall survival was significantly determined by tumor stage ($p=0.022$) and tumor grade ($p=0.001$) (Figs. 4 and 5). Out of 160 patients, 70.4% were considered tumor-free after a mean follow-up period of 37 ± 4 months, while tumor progression was noted in 16%.

Recurrence- and progression-free rates at 3 years did not differ significantly between patient groups with single versus multiple tumors (Table 3). A significant association between tumor stage and tumor recurrence was confirmed ($p<0.022$), but there was no statistically significant association between tumor stage and overall survival rate ($p>0.219$) or tumor progression ($p>0.295$) (Table 3). Tumor grade had the most important impact

on tumor recurrence, progression and overall survival rates (Table 3).

BCG failure was experienced in 29.6% due to recurrence and in 18% due to progression after the second BCG induction course. Of the patients with tumor recurrence after a second TURT and a second BCG induction course, 11 underwent radical cystectomy due to aggressive tumor behavior with an increased tumor number (4 cases) or grade (7 patients). The remaining patients received a third TURT session followed by intravesical chemotherapy instillation. Radical cystectomy was done in 13 patients with tumor progression, and combined radiotherapy and chemotherapy was administered in 4, while palliative treatment was chosen for 3 patients.

DISCUSSION

The European Association of Urology (EAU) recommends intravesical BCG instillation as the first treatment option in

high-risk and intermediate-risk patients after failure of intravesical chemotherapy¹. However, BCG intolerance and tumor recurrence or progression following adjuvant BCG therapy have been reported by various authors⁵⁻⁹. At Al-Azhar Urology Department the treatment policy for superficial bladder TCC consists of TURBT followed by long-term adjuvant intravesical BCG therapy after exclusion of cases with single, stage Ta, grade-1 (low-risk group) bladder carcinoma. In accordance with the EAU guidelines check-up cystoscopy is routinely done for all patients with high-grade Ta and T1 papillary tumors¹⁰.

In the present study 3.8% of the patients stopped BCG therapy due to side-effects and were treated with adjuvant intravesical chemotherapy; this incidence is comparable to other reports^{5,11}.

In a randomized study carried out by the European Organization for Research and Treatment of Cancer (EORTC) 957 patients with intermediate or high-risk TCC who had received adjuvant BCG were evaluated. The tumor-free rate was 65% at 3 years follow-up¹². Comparable results were obtained in this study with a 70.4% tumor recurrence-free rate at a mean follow-up of 3 years. In contrast, Lockyer et al. reported a tumor-free rate of 51% after TURBT and adjuvant BCG therapy for one year⁷; this lower rate may be attributed to the short term of the maintenance BCG adjuvant therapy.

In the present study, BCG failure was experienced in 29.6% of the patients due to tumor recurrence and in 18% due to tumor progression. Relatively similar results were described by Bohle et al. with 38.6% post-BCG tumor recurrence in a meta-analysis of 1421 patients⁴. Furthermore, Mungan et al. reported BCG failure in 0% to 42% in a review of several studies with a minimal one-year follow-up¹³.

Both tumor recurrence and progression depend on the tumor risk category and the use of long-term intravesical adjuvant BCG therapy. In the present study, long-term BCG maintenance therapy was associated with 29.6% tumor recurrence and 18% tumor progression, which is significantly less than the 51% recurrence rate found by Lockyer et al. after short-term BCG therapy⁷. In another study the recurrence rate ranged between 20% and 40% depending on the tumor-risk factors and the period of follow-up after long-term BCG therapy⁵.

Tumor multiplicity, stage T1, high grade and presence of carcinoma in situ are risk factors and enhance the possibility of tumor recurrence and progression^{2,3}. Similarly in this study, tumor recurrence and progression were statistically significant in cases with stage T1 and high-grade TCC.

In the present study BCG failure was significantly determined by tumor grade, with recurrence in 41.4% versus 79.1% ($p=0.001$) and progression in 45.9% versus 92.6% ($p=0.001$) of patients with grade-3 compared to grades 1-2 TCC. Orsola et al. reported a 42% recurrence and progression rate in cases with deep invasion (stage T1) superficial bladder cancer¹⁴. Lockyer et al. reported tumor recurrence in 24% and 29% with grade-3 and stage-T1 bladder TCC, respectively⁷. Moreover, the progression rate of 12% to 54% in T1 bladder TCC depends on the degree of tumor aggressiveness as defined in many studies¹⁵⁻¹⁷.

In conclusion, standard TURBT followed by long-term adjuvant BCG therapy is the advocated treatment modality for all cases of superficial bladder cancer at the Urology Department, Al-Azhar University, except in cases with Ta, grade-1 tumors. This treatment regimen yields a higher tumor-free rate in low-grade than in high-grade tumors. BCG

failure was significantly noted in cases with stage T1, or grade-3 tumors and in those associated with carcinoma in situ. The high number of cases lost to follow-up in this study indicates the importance of educating patients about the necessity for repeat assessment to improve long-term survival. Different treatment modalities can be used after second tumor recurrence or progression according to the tumor aggressiveness and the patient's preference.

REFERENCES

- Oosterlinck W, Lobel B, Jakse G, Malmstrom PU, Stockle M, Sternberg C. Guidelines on bladder cancer. *Eur.Urol.* 2002; Feb;41(2):105-12.
- Parmar MK, Freedman LS, Hargreave TB, Tolley DA. Prognostic factors for recurrence and follow-up policies in the treatment of superficial bladder cancer: Report from the British Medical Research Council Subgroup on superficial bladder cancer (Urological Cancer Working Party). *J.Urol.* 1989; Aug;142(2 Pt 1):284-8.
- Pagano F, Garbeglio A, Milani C, Bassi P, Pegoraro V. Prognosis of bladder cancer. I. Risk factors in superficial transitional cell carcinoma. *Eur.Urol.* 1987;13(3):145-9.
- Bohle 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; Jan;169(1):90-5.
- Witjes JA. Management of BCG failures in superficial bladder cancer: A review. *Eur.Urol.* 2006; May;49(5):790-7.
- Pansadoro V, Emiliozzi P, de Paula F, Scarpone P, Pansadoro A, Sternberg CN. Long-term follow-up of G3T1 transitional cell carcinoma of the bladder treated with intravesical bacille Calmette-Guerin: 18-year experience. *Urology.* 2002; Feb;59(2):227-31.
- Lockyer CR, Sedgwick JE, Gillatt DA. Beware the BCG failures: A review of one institution's results. *Eur.Urol.* 2002; Dec;42(6):542-6.
- Friedrich MG, Pichlmeier U, Schwaibold H, Conrad S, Huland H. Long-term intravesical adjuvant chemotherapy further reduces recurrence rate compared with short-term intravesical chemotherapy and short-term therapy with Bacillus Calmette-Guérin (BCG) in patients with non-muscle-invasive bladder carcinoma. *Eur.Urol.* 2007;52(4):1123-30.
- Lamm DL, Riggs DR, Traynelis CL, Nseyo UO. Apparent failure of current intravesical chemotherapy prophylaxis to influence the long-term course of superficial transitional cell carcinoma of the bladder. *J.Urol.* 1995; May;153(5):1444-50.
- Van der Meijden AP, Sylvester R, Oosterlinck W, Solsona E, Boehle A, Lobel B, et al. EAU guidelines on the diagnosis and treatment of urothelial carcinoma in situ. *Eur.Urol.* 2005; Sep;48(3):363-71.
- Ojea A, Nogueira JL, Solsona E, Flores N, Gómez JMF, Molina JR, et al. A multicentre, randomised prospective trial comparing three intravesical adjuvant therapies for intermediate-risk superficial bladder cancer: Low-dose Bacillus Calmette-Guerin (27 mg) versus very low-dose Bacillus Calmette-Guerin (13.5 mg) versus Mitomycin C {A figure is presented}. *Eur.Urol.* 2007;52(5):1398-406.
- Van der Meijden AP, Sylvester RJ, Oosterlinck W, Hoeltl W, Bono AV. Maintenance Bacillus Calmette-Guerin for Ta T1 bladder tumors is not associated with increased toxicity: Results from a European Organisation for Research and Treatment of Cancer Genito-Urinary Group Phase III Trial. *Eur.Urol.* 2003; Oct;44(4):429-34.
- Mungan NA, Witjes JA. Bacille Calmette-Guerin in superficial transitional cell carcinoma. *Br.J.Urol.* 1998; Aug;82(2):213-23.
- Orsola A, Trias I, Raventos CX, Espanol I, Cecchini L, Bucar S, et al. Initial high-grade T1 urothelial cell carcinoma: Feasibility and prognostic significance of lamina propria invasion microstaging (T1a/b/c) in BCG-treated and BCG-non-treated patients. *Eur.Urol.* 2005; Aug;48(2):231,8; discussion 238.
- Pansadoro V, Emiliozzi P, Defidio L, Donadio D, Florio A, Maurelli S, et al. Bacillus Calmette-Guerin in the treatment of stage T1 grade 3 transitional cell carcinoma of the bladder: Long-term results. *J.Urol.* 1995; Dec;154(6):2054-8.
- Herr HW. Progression of stage T1 bladder tumors after intravesical Bacillus Calmette-Guerin. *J.Urol.* 1991; Jan;145(1):40,3; discussion 43-4.
- Pham HT, Soloway MS. High-risk superficial bladder cancer: Intravesical therapy for T1 G3 transitional cell carcinoma of the urinary bladder. *Semin.Urol.Oncol.* 1997; Aug;15(3):147-53.