



Pan African Urological Surgeons' Association

African Journal of Urology

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Evaluating the need for transurethral bladder biopsy at first follow up after intravesical BCG therapy for superficial bladder cancer: Preliminary data

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Received 27 April 2011; received in revised form 19 September 2011; accepted 7 February 2012

KEYWORDS

BCG;
Tumor;
Superficial;
Bladder

Abstract

Introduction: Patients with high-risk superficial transitional cell carcinoma (TCC) of the bladder have a lifelong risk of progression and require particular attention. Intravesical Bacillus Calmette-Guerin (BCG) is recommended as a first-choice adjuvant treatment to reduce the risk of progression of high-grade tumors and carcinoma in situ (CIS).

Objectives: To evaluate the need for routine transurethral bladder biopsy from the site of previously resected tumor three months following intravesical BCG therapy, even if the urine cytology and cystoscopy were both negative.

Subjects and methods: A prospective study was carried out on 45 patients of both genders presenting with superficial bladder cancer. All patients received a six-week course of intravesical BCG. The mean age of the patients was 59 (range 33–80) years. Three months following resection, urine cytology was negative in all patients. Cystoscopy was then performed and although it was negative for any suspicious lesions, a routine biopsy from the previous resection site was taken.

Results: The indication for BCG instillation was T1G1 in 20 patients (44%), T1G2 in 12 patients (27%) and TaG2 in eight patients (18%). Three patients (7%) had a positive bladder biopsy for malignancy at follow-up

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Peer review under responsibility of Pan African Urological Surgeons' Association.



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<http://dx.doi.org/10.1016/j.afju.2012.04.003>

despite the negative cystoscopy and cytology. There were no statistically significant differences between patients with positive and those with negative biopsies with regard to the stage and grade of the tumor before resection or the number of resected lesions. The original pathology of the three positive patients was T1G1 (two patients) and T1G2 (one patient). The pathology after BCG treatment was the same as before instillation, T1G1 (two patients) and T1G2 (one patient).

Conclusion: Until more studies on larger numbers of patients are done, a routine biopsy from the site of previously resected tumor at the time of check cystoscopy may improve the detection of tumor recurrence.

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Introduction

Patients with high-risk non-muscle invasive transitional cell carcinoma (TCC) of the bladder have a lifelong risk of progression and require particular attention [1,2]. Intravesical Bacillus Calmette-Guerin (BCG) instillation is recommended as a first-choice treatment to reduce the risk of progression of high-grade tumors as well as carcinoma in situ (CIS) [3].

Although one-third of patients are cured after intravesical BCG treatment, one-third of patients progress to infiltrating disease and the remaining one-third show recurrence [4–6].

Diagnosis of recurrence of a high-grade tumor is very important because it indicates a worse prognosis which may change the decision to perform cystectomy [7].

The effect of BCG therapy following the resection of superficial bladder cancer can be evaluated by urine cytology, cystoscopy and a bladder biopsy. Because of the invasiveness of bladder biopsy and its cost, some urologists do not perform it routinely, although others support the concept of a routine biopsy regardless of the findings on cystoscopy and cytology [6].

In the literature, the sensitivity of urine cytology in diagnosing recurrence of high-risk tumors varies from 44% to 97% [8,9]. Studies have reported that following treatment with intravesical BCG, performing a routine biopsy can be avoided if both the urine cytology and cystoscopy were negative [10,11].

The aim of our study was to evaluate the need for routine biopsy from the site of previously resected superficial bladder tumor three months following resection and intravesical BCG therapy in the presence of negative urine cytology and cystoscopy.

Patients and methods

This is a prospective study carried out in the period between December 2008 and February 2010 on 45 patients with superficial bladder cancer of both genders presenting to both Nasser Institute and the urology department of Cairo University.

All patients presented with hematuria and irritative voiding symptoms. The patients were investigated by urine analysis, serum creatinine, abdominal and pelvic ultrasound (US) and intravenous urography (IVU). The diagnosis was then made by cystoscopy and complete transurethral resection of the lesion. Under completely aseptic conditions, all patients received intravesical BCG in a dose of 90 mg diluted in 50 ml normal saline that was instilled intravesi-

cally using a transurethral Foley catheter. The patients were asked to retain the BCG solution in the bladder for 1 h. This instillation was then repeated weekly for six successive weeks. Three months after initial resection, urine cytology was performed on all patients and they were scheduled for check cystoscopy. At the time of cystoscopy, a routine biopsy was taken from the site of previously resected tumor. All patients included in the study had negative urine cytology and cystoscopy at the time of biopsy.

Results

The mean age of the 45 patients was 59.3 years (range 33–80 years).

Routine biopsy from the previously resected site was positive in three patients (7%) despite having negative urine cytology and the cystoscopy being clear of any suspicious lesions.

Concerning these three patients with positive bladder biopsy, the pathology of the originally resected tumor was T1G1 in two patients and T1G2 in the third patient. Table 1 shows the pathology of the original tumors before BCG instillation.

The pathology result of the biopsies taken from the site of the previously resected tumor is shown in Table 2.

There were no statistically significant differences between patients with positive and negative biopsies with regard to the stage and grade of the tumor before resection, or the number of resected lesions (Tables 3–5).

Regarding the three patients with positive biopsies, another six-week course of intravesical BCG therapy was given. Three months later, they were re-evaluated by urine cytology and cystoscopy. None of them showed recurrence.

Table 1 Initial pathology before BCG therapy (stage and grade).

	Number	Percentage (%)
CIS	1	2
TaG2	8	18
TaG3	1	2
T1G1	20	44
Rec. TaG1	1	2
T1G3	2	5
T1G2	12	27
Total	45	100

Table 2 Pathology after resection and 6 weekly intravesical BCG instillations.

Frequency	Number	Percentage (%)
Cystitis	19	42
Cystitis with dysplasia	12	27
Cystitis cystica and cystitis glandularis	3	7
Granuloma	1	2
Non-specific fibrosis	2	4
Polypoid cystitis	5	11
TCC	3	7
Total	45	100

Table 3 T stage of the studied sample in relation to biopsy result.

T stage × group			
T stage	Group		
	Negative	Positive	Total
CIS			
Count	1	0	1
% within group	2%	0%	2%
T1			
Count	31	3	34
% within group	74%	100%	76%
Ta			
Count	10	0	10
% within group	24%	0%	22%
Total			
Count	42	3	45
% within group	100%	100%	100%

Table 4 Grading of the studied sample in relation to biopsy result.

Grade × group			
Grade	Group		
	Negative	Positive	Total
G1			
Count	19	2	21
% within group	46%	67%	48%
G2			
Count	19	1	20
% within group	46%	33%	45%
G3			
Count	3	0	3
% within group	7%	0%	7%
Total			
Count	41	3	44
% within group	100%	100%	100%

Discussion

The management of patients with superficial papillary TCC of the bladder has recently become controversial regarding whether to perform a routine transurethral bladder biopsy at the time of the

Table 5 Number of lesions of the studied sample in relation to biopsy results.

No. of lesion × group			
No. of lesions	Group		
	Negative	Positive	Total
1			
Count	37	3	40
% within group	88%	100%	89%
2			
Count	4	0	4
% within group	10%	0%	9%
3			
Count	1	0	1
% within group	2%	0%	2%
Total			
Count	42	3	45
% within group	100%	100%	100%

Table 6 Comparison between our study and other studies.

	Total number of cases	No. of +ve bladder biopsies	
Dalbagni et al. [13]	81	1	(1%)
Skemp and Fernandes [14]	41	1	(2%)
Guy et al. [16]	76	0	(0%)
Murakami et al. [15]	48	1	(2%)
Hara et al. [12]	63	10	(15.9%)
Our study, 2012	45	3	(7%)

first follow-up cystoscopy, in order to increase the sensitivity of cystoscopy.

In our study, three patients (7%) out of 45 patients with negative urine cytology and cystoscopy demonstrated a positive bladder biopsy from the site of the previously resected tumor (Table 6).

Although urine cytology in the patients with positive biopsies was negative, the pathology revealed a high-risk superficial urothelial tumor. According to Hara and his colleagues, this false-negative result may be attributed to the effect of intravesical BCG therapy which decreases the sensitivity of urine cytology [12].

In 1999, Dalbagni et al. [13] investigated the need for doing a routine bladder biopsy three months following resection and BCG instillation. They concluded that there is no need to perform a biopsy if cystoscopy was normal and the urine cytology was negative. In our study no biopsies were positive in 37 patients with cystoscopy showing mucosal erythema and negative cytology. Only one patient out of 13 with negative cystoscopy had a positive biopsy.

Although Highshaw et al. [10] did not perform a cytological examination, they recommended performing a biopsy only in those patients with suspicious findings on cystoscopy.

Skemp and Fernandes [14] had only one patient (2%) with a positive biopsy out of 41 patients with negative cystoscopy and cytology. They concluded that at three-month post-BCG therapy, bladder biopsy can be avoided in those patients with a negative cystoscopy and urine cytology, thus avoiding more cost and morbidity.

In a study by Guy et al. [16], the sensitivity of cytology and cystoscopy for detecting recurrence after intravesical BCG instillation, was 56% and 87.5% respectively, while the specificity of cytology and cystoscopy was 56% and 81.6% respectively. By combining the two examinations, sensitivity reached 100% and specificity reached 76%. Seventy-six patients had a negative cytology and cystoscopy and none of them had tumor recurrence on biopsy. They concluded that there is no need to perform a bladder biopsy when cystoscopy and cytology are both negative.

Murakami et al. [15] reported no necessity to perform a routine bladder biopsy in patients who do not have a visible tumor on cystoscopy and negative urine cytology. Of 48 patients with negative cystoscopy and urine cytology, only one patient (2%) had a positive bladder biopsy.

Hara et al. [12] reported that performing routine bladder biopsy and urine cytology helped in the early detection of BCG-resistant cancer in ten (16%) out of 63 patients who had a normal appearing bladder mucosa on cystoscopy and negative cytology.

Conclusion

Due to the relatively small number of patients in this study and in similar published studies, more research is required to answer the question whether to perform a routine biopsy at the site of a previously resected tumor at the time of the first follow-up cystoscopy after BCG treatment. Until then, we recommend combining routine biopsy with cytology and cystoscopy to increase the sensitivity of early detection of BCG failures and tumor recurrence.

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