

Efficacy of Bacillus Calmette-Guerin (BCG) Therapy and Cauterization of the Tumor Versus BCG Therapy Without Cauterization for Superficial Bladder Cancer

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ABSTRACT

INTRODUCTION: Bladder cancer recurrence occurs in 30-80% of cases after resection depending upon the grade, stage and number of tumors. The rate of recurrence for superficial bladder cancer is 70%. Cauterization is known to destroy malignant cells. Therefore, the authors studied the efficacy and tumor recurrence rate of bacillus Calmette-Guerin (BCG) therapy with cauterization of 10 mm of the tumor margin versus BCG therapy without cauterization.

METHODS: The authors reviewed files of 60 patients, including 30 patients with cauterization (group 1) and 30 patients without cauterization (group 2). Patients were referred from March 2006 to June 2008 with primary stage Ta, T1, and T2a, grade G1 to G3 transitional cell carcinoma (TCC) of the bladder. All patients were treated by transurethral resection of the tumor (TUR-BT). The 2 groups did not differ significantly in age and sex or in tumor grade, location, and size. Grade, stage, location and size of tumors with recurrence were compared.

RESULTS: There were no significant differences between the two groups in stage, location, and size of tumors. Tumors returned in 25 of the 60 patients (9 from group 1; 16 from group 2). The group difference in recurrence rate was not statistically significant ($P = .06$). The mean time of tumor recurrence was 21 months and 13 months in groups 1 and 2, respectively. Group 1 had a significant delay in tumor recurrence when compared with group 2 ($P = .01$). Most of the tumors that recurred were from patients with grade 1 and grade 2 tumors (5 patients in group 1; 15 in group 2). Four out of 5 patients with grade 3 tumors in group 1 and the only patient with a grade 3 tumor in group 2 had recurrence. The recurrence rate for low-grade tumors in group 1 was significantly less than in group 2 ($P = .02$).

CONCLUSIONS: Cauterization of the tumor margins combined with BCG therapy appears to be useful for reducing recurrence in patients with grade 1 and grade 2 bladder tumors. Cauterization also resulted in a longer period of time before recurrence.

KEYWORDS: Bladder tumor; Cauterization; BCG therapy, Bladder cancer recurrence

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INTRODUCTION

Bladder cancer is the fourth most common cancer in men and the ninth most common cancer in women [1]. Seventy percent of bladder cancers are superficial (ie, stage Ta and stage T1) at initial presentation [2]. Unfortunately, these superficial bladder cancers can recur in as many as 70% of patients and a substantial number (10% to 15%) progress to muscle-invasive disease [3].

Udai et al [4] reported multiple, solid, high-grade tumors that were larger than 3 cm with three or more previous resections. These characteristics were predictors of the presence of residual tumor in Relook transurethral resection of bladder tumor (TUR-BT). The presence of residual growth is a significant risk factor for recurrence.

Hyperthermia causes an inhibition of cellular respiration and synthesis of DNA, RNA, and proteins, blocking the cells in the S phase. These injuries may be lethal to the cell if repair mechanisms are not effective [5]. Local hyperthermia resulted in a synergistic cell killing effect when used in combination with chemotherapy for the treatment of many solid tumors, including transitional cell carcinoma of the bladder [6, 7].

The aim of the present investigation was to study the efficacy of bacillus Calmette-Guerin (BCG) therapy and cauterization of 10 mm of tumor margin versus BCG therapy without cauterization in superficial bladder cancer.

METHODS

Participants

The authors conducted a retrospective study of 60 patient files. The patients were referred from March 2006 to June 2008. To participate in the study, patients were required to have a single, primary, superficial transitional cell carcinoma (TCC) of the bladder. The tumors were primary stage Ta, T1, and T2a, grade 1 to grade 3, based on pathology reports.

Exclusion criteria included a tumor stage higher than T2a, multiple tumors, residual tumor after complete transurethral resection of the tumor (TUR-BT), transitional tumor of the bladder involving the prostatic urethra, carcinoma in situ (CIS), and distant or lymph node metastases. Patients with grade 3 BCG toxicity were also excluded.

Clinical pretreatment assessment included ultrasound evaluation of the abdomen and pelvis and intravenous urography (IVU) or abdominal CT scan. Laboratory tests including CBC, liver

function tests (LFT), FBS, BUN, creatinine, and coagulation profiles were performed.

Surgery

All patients underwent complete TUR-BT. The surgery was performed by 2 of the authors who are expert surgeons (SF; AR). Patients who needed additional resection were excluded. All patients received a single dose of mitomycin.

Treatment

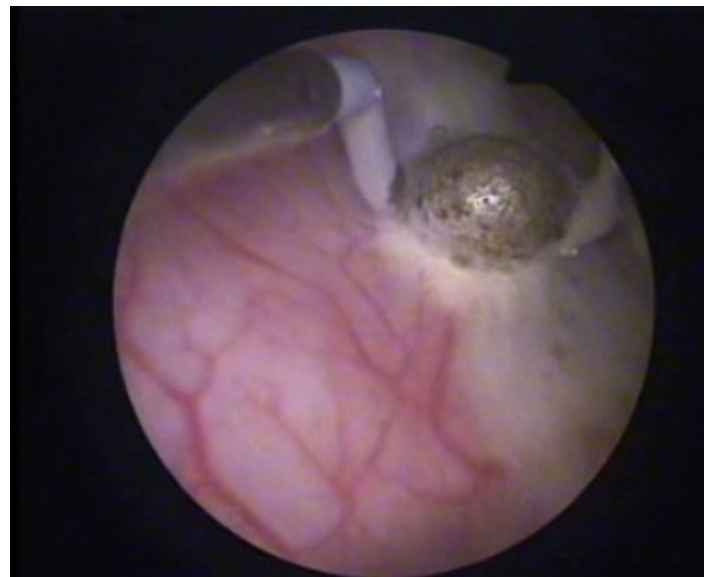
Patients were divided into 2 groups. Group 1 (n = 30) received BCG therapy and cauterization of 10 mm of the tumor margin. Group 2 (n = 30) received BCG therapy without cauterization.

For both groups of patients, BCG therapy included an induction cycle of 6 weekly sessions. The duration of each session was 120 minutes and all sessions were performed on an outpatient basis.

In group 1, 10 mm of the tumor margin was cauterized (Figure 1). Cauterization was performed by rolling ball in 80°, with an estimated diameter of about 10 mm. Cauterization was not performed on the ureteral orifice for prevention of ureteral stricture.

Figure 1. Cauterization of 10 mm of the Tumor Margin.

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Outcome

Recurrence was evaluated by cystoscopic findings for all patients. Cytology and cystoscopy were performed every 3 months for 2 years following resection. The authors performed cytology before and after surgery for all patients, but they did not evaluate the correlation between cytologic and cystoscopic findings.

Chi-square and *t* tests were used to compare differences between groups 1 and 2 for categorical and continuous variables, respectively. Statistical significance was defined as $P < .05$. SPSS software was used for all statistical analyses.

RESULTS

Demographic Data and Tumor Characteristics

There were 30 patients in each of 2 groups ($N = 60$). The patient data and probability of between-group differences for each of the characteristics are contained in Table 1. There were more males than females in each group and the patients averaged 66-years and 65-years-old for groups 1 and 2, respectively. There were no statistically significant differences between groups for sex or age.

Information about the tumor size, grade, stage, and location for patients in groups 1 and 2 are also contained in Table 1. The tumor sizes averaged 24.7 and 21.4 for groups 1 and 2, respectively. Most of the tumors in both groups were grade 1 or grade 2; most involved the mucosa or submucosa; and most were located in the trigone region or on the bladder walls. There were no statistically significant differences between groups for tumor size, grade, stage, or location of tumor.

Tumor Recurrence

Of the 60 patients in the investigation, 25 patients (9 from group 1; 16 from group 2) had tumor recurrence that was observed during a follow-up cystoscopic examination. There was no statistically significant difference in recurrence rate between the two groups ($P = .06$). However, this P value approaches significance and further studies with a larger number of patients may show a significant difference between treatments.

The characteristics of the tumors and probability of between-group differences for each characteristic are contained in Table 2. The mean time of tumor recurrence was 21 months and 13 months in groups 1 and 2, respectively. There was a statistically significant group difference in time of recurrence ($P = .01$).

Most of the tumors that recurred were from patients with

Table 1. Patient Demographic Data, Tumor Characteristics, and Probability of Differences Between Group 1 (With Cauterization) and Group 2 (Without Cauterization) ($N = 60$). doi: 10.3834/uij.1944-5784.2009.08.01t1

Characteristic	Group 1		Group 2		P
	Mean	SD	Mean	SD	
Age	66.36	13.12	65	10.38	.65
Tumor Size (mm)	24.7	15.07	21.4	17.92	.43
	n	% n	n	% n	
Sex					
Male	23	76.6	27	90	.16
Female	7	23.3	3	10	
Grade					
1	14	46.7	17	56.7	.22
2	11	36.7	12	40	
3	5	16.6	1	3.3	
Stage					
Mucosa	11	36.6	9	30	.36
Submucosa	13	43.4	18	60	
Superficial Muscle	6	20	3	10	
Location					
Trigone	15	50	7	23.4	.17
Lateral Walls	11	36.6	18	60	
Bladder Neck	3	10	3	10	
Bladder Dome	1	3.3	2	6.6	

grade 1 and grade 2 tumors (5 patients in group 1; 15 in group 2). Four out of 5 patients with grade 3 tumors in group 1 and the only patient with a grade 3 tumor in group 2 had recurrence. The recurrence rate for low-grade tumors in group 1 was significantly less than in group 2 ($P = .02$).

In group 1, there was an approximately even distribution of mucosal, submucosal, and superficial muscle involvement. In group 2, the majority of patients had submucosal involvement. The tumor location for the majority of patients in both groups was the lateral walls. Group differences in the tumor stage and location were not statistically significant. It should be noted that this study did not include patients with major complications such as perforation of bladder and BCG complications.

Table 2. Tumor Characteristics for Patients with Recurrence and Probability of Differences Between Group 1 (With Cauterization) and Group 2 (Without Cauterization) (N = 25). doi: 10.3834/uj.1944-5784.2009.08.01t2

Characteristic	Group 1		Group 2		P
	Mean	SD	Mean	SD	
Tumor Recurrence Time (months)	20.88	12.2	13.06	11.9	.01
	n	% n	n	% n	
Grade					
1, 2	5	55.5	15	93.8	.02
3	4	44.5	1	6.2	
Stage					
Mucosa	3	33.3	4	25	.34
Submucosa	2	22.2	11	68.8	
Superficial Muscle	4	44.5	1	6.2	
Location					
Trigone	1	11.1	3	18.8	.46
Lateral Walls	6	66.7	10	62.5	
Bladder Neck	2	22.2	1	6.2	
Bladder Dome	0	0	2	12.5	

DISCUSSION

Bladder cancer is more than 2.5 times more common in men than in women [9]. Bladder cancer can occur at any age, with the median ages at diagnosis being 69 years in males and 71 years in females [10]. There was no statistically significant difference in patient age and sex between the 2 groups in the present study.

The vast majority of patients with newly diagnosed bladder cancers have superficial, low-grade neoplasms that are associated with an excellent prognosis. However, these tumors have a 30% to 70% recurrence rate and may progress to invasive cancers in 10% to 30% of patients [4]. Progression greatly increases the risk of metastasis and subsequent mortality. For this reason, the early detection of bladder tumors is essential for improved patient prognosis and long-term survival [1]. The patients in both groups of the current investigation had single, low-stage tumors with similar grades because the authors believe that cauterization in high-grade tumors does not reduce recurrence rate.

European guidelines state that intravesical instillation of BCG is the best intravesical adjuvant therapeutic agent in reducing tumor recurrences and disease progression in the intermediate-risk (Ta/T1, G 1 or G2, multifocal, size > 3 cm) and high-risk (T1, G3, CIS) groups. Although BCG is currently considered the most effective agent in reducing the recurrence and disease progression rates in superficial bladder cancer (SBC), its real efficacy remains controversial [11]. All of the patients in both groups of the present study underwent intravesical instillation of BCG. The authors showed that recurrence was not related to tumor size in the cauterization group ($P = .73$).

It is well known from scientific literature that malignant cells are more sensitive than normal cells to heat [5]. Hyperthermia causes inhibition of DNA, RNA, and protein synthesis. These changes may be lethal for the cell if repair mechanisms are not effective [12].

Homogeneous heating of the tumor depends on its volume, the temperature applied, and the thermal dissipation via the blood supply. When used as a monotherapy approach, local hyperthermia obtained only limited results in clinical trials [12,13]. However, local hyperthermia has been proven to develop a synergistic antitumor cell killing effect when used in combination with selected cytostatic agents for the treatment of many solid tumors, including transitional cell carcinoma. Superficial bladder tumors, due to their endocavitary location, have represented a model for the simultaneous administration of local hyperthermia and chemotherapy for a long time. However, the lack of suitable technology has so far strongly limited the clinical application of this regimen. After intensive laboratory and animal investigations, a novel system (based on a transurethral radiofrequency applicator) was developed and clinically tested in patients with superficial TCC of the bladder. During the last decade, this system was mainly used as an alternative to TUR-BT and was shown to be effective and safe. In a randomized trial study, the system was more effective than intravesical chemotherapy alone [5].

The authors of the present study investigated the efficacy and safety of cauterization of the tumor margin, compared with intravesical chemotherapy alone, as adjuvant treatment for superficial bladder cancer after a complete transurethral resection. The heating effect of this study may mimic local hyperthermia. The results showed that the recurrence rate in low-grade bladder tumors treated with cauterization of the tumor margin was significantly lower than with standard therapy. In addition, cauterization resulted in a longer period of time before recurrence.

CONCLUSIONS

Cauterization of the tumor margins combined with BCG therapy appears to be useful for reducing recurrence in patients with grade 1 and grade 2 bladder tumors. Additionally, there was a significantly longer period of time before recurrence for tumors treated with cauterization. Therefore, the authors suggest that in low-stage and low-grade bladder tumors (after TUR-BT), the surgeon should cauterize 10 mm of tumor margin to prevent tumor recurrence or delay recurrence time.

Conflict of Interest: None declared

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