Kaohsiung Journal of Medical Sciences (2016) 32, 147–151

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journal homepage: http://www.kjms-online.com

ORIGINAL ARTICLE

Can immediate second resection be an alternative to standardized second transurethral resection of bladder tumors?

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Received 5 October 2015; accepted 6 January 2016
Available online 21 March 2016

KEYWORDS
Bladder tumor;
Immediate;
Transurethral resection

Abstract This study analyzed the impact of an immediate second transurethral resection of bladder tumor (TURBT) protocol on residual tumor status at the initial TURBT session and the recurrence rate in the primary resection area. We prospectively evaluated and randomized 47 consecutive patients who underwent TURBT sessions for bladder cancer. In accordance with the inclusion criteria, of the 47 consecutive patients, 19 (Group I) underwent immediate second resection of the tumor bed after complete TUR and 28 (Group II) did not. After standard TURBT, Group I underwent a second cystoscopy and resection of the bed of the tumor or an ignored tumor, which was performed by a different urologist. After 4–6 weeks, delayed second TURB was performed, and all pathological results were evaluated. Tumors were detected in two patients during the immediate second resection. Of these, one was a misdiagnosed tumor, whereas the other was diagnosed at the bed of the tumor by pathological examination. Tumors were detected in nine patients at the delayed second TURB, of which only one was part of Group I, while the others were part of Group II ($p = 0.04$). The results of this study demonstrated that residual tumors may remain after initial TURB, either in the tumor bed or in a different location within the bladder. Although this was a pilot study enrolling only a small number of patients, our initial results supported the assertion that immediate second resection can be an alternative to standard second TURBT.

Conflicts of interest: All authors declare no conflicts of interest.

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http://dx.doi.org/10.1016/j.kjms.2016.02.002

Introduction

At the time of diagnosis, ~75% of patients with a bladder tumor (BT) present with a disease confined to the mucosa (stage Ta, CIS) or submucosa (stage T1) [1]. Guidelines recommend a transurethral resection of bladder tumor (TURBT) to treat and provide an exact diagnosis (grading, staging, residual tumor) for further follow-up and treatment, if necessary [2]. However, a significant risk of residual tumor after the initial TURBT for Ta and T1 lesions has been demonstrated [3,4]. Furthermore, persistent disease after the resection of T1 tumors has been observed in 33–53% of patients and after the resection of TaG3 tumors in 41.4% [4,5]. Additionally, although muscularis propria (MP) in the TURBT specimen is essential for adequate staging, it can be missing in as many as 36–51% of initial TUR specimens [6–8].

Keeping in mind that understaging or residual tumors remain after the initial TURBT, a delayed second TURBT that increases recurrence-free survival (RFS) rates [9,10] may be necessary. Guidelines recommend a delayed second TURBT after an incomplete initial TURBT if there was no muscle in the specimen after the initial resection, with the exception of TaG1 tumors and primary CIS and in all T1 tumors and G3 tumors, with the exception of primary CIS [2]. However, most urologists recommend resection at 2–6 weeks after the initial TURBT, and there is no current consensus regarding strategies and timing of a delayed second TURBT.

Because there is a lack of standards regarding how to perform the initial TURBT, a standardized extended TURBT protocol was developed by Richterstetter et al. [11] in 2001. The study was designed to analyze the impact of this protocol on the determination of the residual tumor status at the initial TURBT session and the recurrence rate in the primary resection area [11]. By contrast, Kim et al. [12] investigated whether an immediate second resection during the initial TURBT could confirm the presence of MP in the specimen, provide a more accurate pathological diagnosis, and improve the RFS rate in patients with non-muscle-invasive bladder cancers (NMIBC).

This study aims to assess the impact of an immediate second TURBT protocol on residual tumor status at the initial session and the recurrence rate in the primary resection area.

Methods

Between February 2009 and November 2013, 87 consecutive primary patients who underwent TURBT sessions for bladder cancer were prospectively evaluated and included in the study. Written approval was obtained from the local medical ethics committee, and all patients provided written informed consent prior to the study. The study was conducted in accordance with good clinical practices and the 1964 Declaration of Helsinki. Exclusion criteria included solid tumors, high-risk patients (e.g., those $>$ 70 years), American Society of Anesthesiologists scores $<$ 3, unavailable for follow-up, invasive tumors ($\geq$ T2 stage), and unresectable tumors; 40 patients were excluded.

Patients with primary BT who were judged by the surgeon to have had a complete first resection were randomized into two groups. First, all patients underwent a complete TURBT that was performed by a single surgeon. After the operation was completed, a random chance method was used to determine which patients were to undergo an immediate second TURBT that would be performed by a different surgeon. Second, an urologist conducted a second cystoscopy and resected the bed of the tumor or an ignored tumor. In all cases, a standardized delayed second TURBT was conducted after 4–6 weeks, and all pathological results were evaluated. All immediate second resections were extended by taking additional deep and marginal specimens. Furthermore, patient records and follow-up information were recorded.

All patients received one immediate chemotherapy instillation (mitomycin C) for tumors presumed to be NMIBC, except in cases of suspected bladder perforation. In patients with low-risk tumors, one immediate chemotherapy instillation was considered as a complete adjuvant treatment. In patients with intermediate-risk Ta tumors, the chemotherapy protocol was either one immediate chemotherapy instillation, followed by 1-year full-dose bacillus Calmette-Guérin (BCG) treatment or by further chemotherapy instillation for a maximum of 1 year. For patients with high-risk tumors, the protocol was full-dose intravesical BCG for 1–3 years. Our follow-up protocol after TURBT included urinalysis, ultrasonography of the urinary system, cystoscopy, and voided urine cytology every 3 months for the 1st year, biannually for the next 2 years, and then annually. In the case of high-risk disease, the 1st year protocol was extended to the 1st 2 years.

All statistical analyses were conducted using SPSS 15.0 statistical software (SPSS Inc., Chicago, IL, USA). After the distribution of all parameters was tested using the Pearson Chi-square test, independent samples tests, Fisher's exact tests, and Mann–Whitney *U* tests were employed. The threshold for statistical significance was set at $p < 0.05$.

Results

On the basis of the study inclusion criteria, 19 patients (Group I) underwent an immediate second resection of the tumor bed after complete TURBT, while 28 (Group II) did not. The remaining 40 patients were excluded from the study according to the exclusion criteria. The mean age of the 47 patients was 63.1 $\pm$ 11.4 years, and the mean follow-up period was 25.9 $\pm$ 17.7 months. Seventeen patients had multiple tumors, while the others (n = 30) had a single tumor. The mean tumor diameter was 3.8 $\pm$ 1.4 cm. The pathological T stages at the first TURBT were Ta (n = 20) and T1 (n = 27). Of these, 18 patients had TaG2, 16 had T1G2, seven had T1G3, four had T1G1, and one patient had TaG1. The remaining patient had TaG3. Patient age, sex distribution, number of tumors, and pathological T stage and grade were similar in both groups (Table 1). There were no perioperative or postoperative complications that required additional treatment or surgical procedures.

Tumors were detected in two patients during the immediate second resection. Of these, one was a misdiagnosed tumor and the other was diagnosed in the bed of

Table 1 Demographic features and initial TURBT pathologies of the study group.

	Group I	Group II	*p*
No. of patients	19	28	
Gender (male/female)	16/3	23/5	0.853
Mean age (y)	63.11 ± 14.1	63.18 ± 9.4	0.983
Mean tumor size (cm)	3.47 ± 1.5	3.29 ± 1.1	0.919
<3	5	7	
>3	14	21	
Number of tumors			0.485
Single	11	19	
Multiple	8	9	
T stage			0.582
Ta	9	11	
T1	10	17	
Grade			0.83
1	2	3	
2	13	21	
3	4	4	
Mean follow-up (mo)	19.53	22.04	0.507

TURBT = transurethral resection of bladder tumor.

the tumor by pathological examination. Tumors were detected in nine patients at the standardized delayed second TURBT after 4–6 weeks. Only one of them was in Group I, while the others were in Group II ($p = 0.04$). Tumors were detected in five patients during follow-up cystoscopies, which were considered as recurrence. The median time to recurrence was 12 months. Of these, two patients were in Group I and the others were in Group II ($p = 0.130$). Pathological results of all procedures are listed in Table 2. Only one patient in Group II revealed a tumor that had progressed from T1G2 to T2G3 at Month 12. Study design, number of tumor-positive patients, and recurrences are shown in Figure 1.

Table 2 Pathologic results of patients.

	Group I	Group II
Initial TURBT pathologies		
Ta	9	11
T1	10	17
CIS	0	0
Immediate 2nd TURBT pathologies		
Ta	2	—
T1	0	—
CIS	0	—
Delayed 2nd TURBT pathologies (after 4–6 wks)		
Ta	1	4
T1	0	2
CIS	0	2
Recurrence pathologies		
Ta	2	1
T1	0	1
T2	0	1

TURBT = transurethral resection of bladder tumor.

There was no statistically significant difference between the two groups regarding immediate mitomycin C treatment ($p = 0.086$). Although 10 patients in Group I did not receive additional treatment, two patients received BCG and seven received mitomycin C as adjuvant chemotherapy. In Group II, 14 patients did not receive additional treatment, 10 received BCG, and four received mitomycin C as adjuvant chemotherapy.

Discussion

A sufficient and effective TURBT has two essential roles in the treatment of BTs. First, it is important for the correct diagnosis and staging of high-risk tumors and particularly muscle-invasive lesions, which require additional therapy. Second, it has the potential to cure selected BTs. The question facing urologists is whether or not this goal can be achieved after the initial TURBT. There have been numerous published studies with results demonstrating that NMIBC has high recurrence (35–70%) and progression rates (10–50%) after the initial TURBT [3,13]. Moreover, the results of several studies reported that there was at least a 15–40% chance of finding residual tumors during standardized delayed second TUR surrounding the initial tumor bed after the initial TURBT [14–16].

There are two common theories used to explain the etiology of residual tumors after the initial TURBT. One posits that early recurrences are, in fact, residual or overlooked tumors present during the initial TUR, strongly emphasizing the importance of TUR quality. The other proposes that tumor cell implantation immediately after resection is responsible for many early recurrences, which has been used to explain the observation that initial tumors are most commonly found on the floor and lower side walls of the bladder, whereas recurrences are often located near the dome [17]. Thus, intravesical chemotherapy has been used to kill such cells before implantation [13,18].

The results of this study lend support to the first theory by demonstrating that tumors were detected in 28.5% of patients in Group II at the second TURBT at ~4–6 weeks after the initial TURBT, while only 5.2% of patients in Group I had tumors ($p = 0.04$). Because there was no difference between the groups in terms of immediate chemotherapy treatment use, our results were not indicative of tumor cell implantation immediately after resection. Most likely, intravesical chemotherapeutic agents killed tumor cells, which were in the tumor bed and were insufficiently resected. Additionally, recent studies focused on modified techniques designed to enhance the performance of TURBT. These include transurethral en bloc resection, en bloc holmium laser resection, and transurethral Tru-Cut biopsy [19–21].

Richterstetter et al. [11] described a standardized extended delayed second TURBT protocol to investigate the best method of TURBT in 2001 and analyzed the impact of the protocol on the residual tumor status at the initial TURBT session and the recurrence rate in the primary resection area in 2012. After completing tumor resection, they obtained additional deep specimens from the center and from endoscopically "normal"-appearing margin sites of the resection area. According to the study results, the

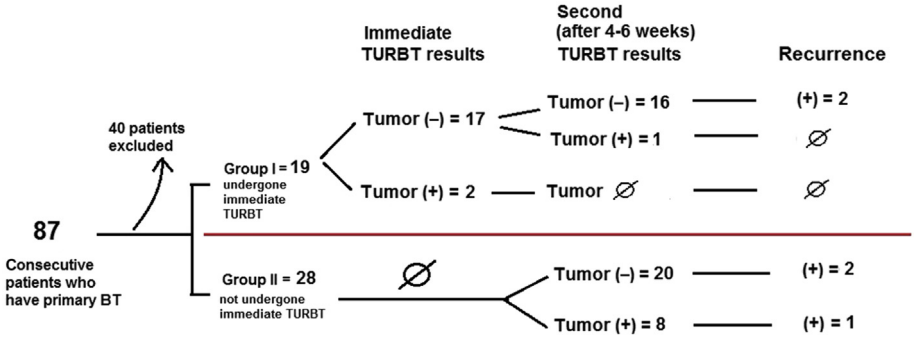

Figure 1. Study design and number of tumor-positive patients.

authors reported that extended delayed second TURBT provided detailed information regarding the horizontal and vertical extent of the BT lesion [11].

Recently, Kim et al. [12] reported the results of a prospective randomized trial to investigate the value of immediate second resection of the tumor bed in order to determine if it improved the effectiveness of TURBT. A total of 126 consecutive patients undergoing TURBT were randomized into two groups: those undergoing immediate second resection or those not. In the Immediate second resection group, after complete TURBT, additional TUR of the tumor bed was performed, and the result was confirmed by the frozen biopsy results during TUR. TUR was repeated until MP was included in the specimen, and the depth of tumor invasion was also determined. Eleven (17.5%) patients required a further resection due to the absence of MP in the first frozen specimen. In conclusion, the study authors stated that immediate second resection of the tumor bed after complete TURBT improved the effectiveness of the resection by immediately confirming the presence of MP in the specimen and accurately differentiating muscle-invasive diseases. The advantages of the immediate second resection were precise prediction of final pathology results and reduced early recurrence. However, the authors did not compare their initial and immediate TURBT pathologies with a standardized delayed second TURBT. Had they done so, they may have been able to determine whether an immediate second resection could be considered as an alternative to the standardized delayed second TURBT.

Another important result from this study was the finding that if the pathological report of immediate TURBT is negative, the pathological result of the standardized delayed second TURBT should be ~95% negative. If an immediate TURBT determined an additional or insufficient resected tumor, the delayed second TURBT should also be negative. Thus, our results demonstrated that an immediate TURBT can act as a standardized delayed second TURBT. Because there were no differences between the immediate and non-immediate groups, avoiding a second surgical procedure should be considered as the main advantage of this protocol. This is significant, because it may reduce costs and complications associated with related additional surgeries and anesthesia.

Finally, our Immediate second TURBT procedure was conducted by a urologist who was not the main surgeon. At present, it is unclear whether confirmation of the resected area by another surgeon is necessary. Because insufficient resections have real clinical and economic implications, it is likely that the urologists conducting TURBT believe that they have performed well at the time of the surgery. Therefore, devising an extended TURBT or other different protocols may not contribute to more accurate resections. It is our view that the addition of another surgeon may improve the accuracy, effectiveness, and sufficiency of the resection procedure.

The results of this prospective, randomized study revealed that residual tumors may remain after an initial TURB, either in the tumor bed or in a different location within the bladder. Although our study enrolled and examined data from a relatively small number of patients, our initial results suggested that an immediate second resection may be an alternative to standardized delayed second TURBT. If confirmed, the costs and complications associated with related additional surgeries and the use of anesthesia can be reduced.

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