OncoTargets and Therapy

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ORIGINAL RESEARCH

The value of extensive transurethral resection in the diagnosis and treatment of nonmuscle invasive bladder cancer with respect to recurrence at the first follow-up cystoscopy

This article was published in the following Dove Press journal:
OncoTargets and Therapy
5 April 2016
Number of times this article has been viewed

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Objective: To evaluate the value of extensive transurethral resection (TUR) in the diagnosis and treatment of nonmuscle invasive bladder cancer (NMIBC) and its further impact on the recurrence rate at the first follow-up cystoscopy (RR-FFC).

Patients and methods: A retrospective review of consecutive series of 523 patients with NMIBCs who underwent TUR from June 2009 to July 2015 at the Second Hospital of Tianjin Medical University was conducted. Extensive TURs were performed by taking additional tumor base and marginal specimens for 317 patients (group 1). Extensive TURs were not done in the other 206 patients (group 2). Urine cytology and follow-up cystoscopy were performed at 3 months after the initial TUR. The positive findings of additional specimens were noted and it was found whether or not the diagnosis and treatment plan had changed in group 1. Also, a comparison was made of the RR-FFC between group 1 and 2.

Results: There were 51/317 (16.1%) patients whose additional specimens revealed pathological findings such as Ta, T1, and carcinoma in situ diseases. Of these positive findings, 6/51 (11.8%) were Ta stage, 16/51 (31.4%) were T1 stage, 18/51 (35.3%) were T2 stage, and 11/51 (21.5%) were carcinoma in situ. Due to the positive findings, 29/317 (9.1%) patients had their final diagnosis changed and 45/317 (14.2%) had their post-TUR treatment plans adjusted. The RR-FFC of group 1 and 2 were 4.7% (14/297) and 13.1% (27/206), respectively (P=0.001).

Conclusion: Routine extensive TUR is helpful for the pathological diagnosis and the post-TUR treatment of NMIBC. Furthermore, it can significantly reduce the RR-FFC of NMIBC, especially in patients with T1 stage or high-grade disease.

Keywords: bladder cancer, urothelial carcinoma, transurethral resection, specimens, recurrence

Introduction

Bladder cancer (BC) is one of the most commonly diagnosed cancer, with an estimated 429,800 new cases and 165,100 deaths occurring in 2012 worldwide.[1] In 75%–85% of the patients with bladder tumor, the disease is confined to the mucosa (Ta, carcinoma in situ [Tis]) or submucosa (T1); this is what we call nonmuscle invasive bladder cancer (NMIBC).[2] Transurethral resection (TUR) of bladder tumor remains the gold standard for management of NMIBC.[3] The initial TUR of bladder tumors has three main goals: 1) to provide pathological material to determine the histological type and grade of bladder tumors; 2) to determine the presence, depth, and type of tumor invasion; and 3) to remove all visible tumors. The quality of TUR directly affects the diagnosis, post-TUR treatment, and even the prognosis of NMIBC.

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http://dx.doi.org/10.2147/OTT.S103703

In order to perform a thorough and complete resection, an extensive TUR had been recommend in clinical practice. The resection range of extensive TUR should include the exophytic part of the tumor, the underlying bladder wall with the detrusor muscle, and the edges of the resection area.[4] These additional specimens from different areas should be sent to the pathologist in separate containers. The current guidelines of the European Association of Urology (2013) had brought this practice into a systematically performed TUR.[5] But few data are available regarding its value in the diagnosis and treatment of NMIBC, even less about its impact on the prognosis.

A standardized extensive TUR protocol was developed at our institution in 2009. Here, we report the results of our study, including the rate of positive findings of additional specimens, and the frequency of final diagnosis and post-TUR treatment plan being changed due to these additional specimens in patients with NMIBCs who underwent an extensive TUR. It is well established that the 3-month recurrence rate is one of the main prognostic factors for Ta/T1 BC[6] and the 3-month recurrence rate reflects the quality of TUR directly. So, we observed the recurrence rate at the first follow-up cystoscopy (RR-FFC) in this retrospective clinical trial.

Patients and methods

Clinical data

This study was approved by the Institutional Review Board of Tianjin Medical University and written informed consent was obtained from each patient. All data were anonymized and de-identified before being used in this study. A consecutive series of 536 patients with NMIBCs underwent TUR from June 2009 to July 2015 at the Second Hospital of Tianjin Medical University, Tianjin, People's Republic of China. Except for the incomplete and missing clinical data in 13 cases, 523 routine TURs were included in this research. An extensive TUR procedure was performed by taking additional tumor base and margin specimens in 317 patients (group 1). Extensive TURs were not done in the other 206 patients (group 2). Except for the patients found to have residual disease by extensive TUR, patients of both the groups did not routinely undergo second TUR. The mean age of these 523 patients was 66.5 (39–91) years and they consisted of 377 males and 146 females. All features of tumor (tumor size, number, and localization) were collected from a "bladder map" described by the operating surgeon in operation notes. We estimated the size of the tumor by comparing it with the resection loop of a known diameter (6 mm); tumor with a diameter ≤3 cm was considered a small tumor and tumors >3 cm were considered large tumors. According to the number of tumors, cases were divided into single tumor and multiple tumors (≥2 tumors). Among the patients, 359 patients had small tumors and 164 cases had large tumors; 336 cases had a single tumor and multiple tumors were present in 187 cases.

Treatments

All TURs were performed by two experienced urologists with an Olympus active resectoscope UES 40, SurgMaster (Olympus Medical Systems Corp., Tokyo, Japan), using monopolar cutting energy of 100 W. According to a standardized protocol (Figure 1), an extensive TUR was performed

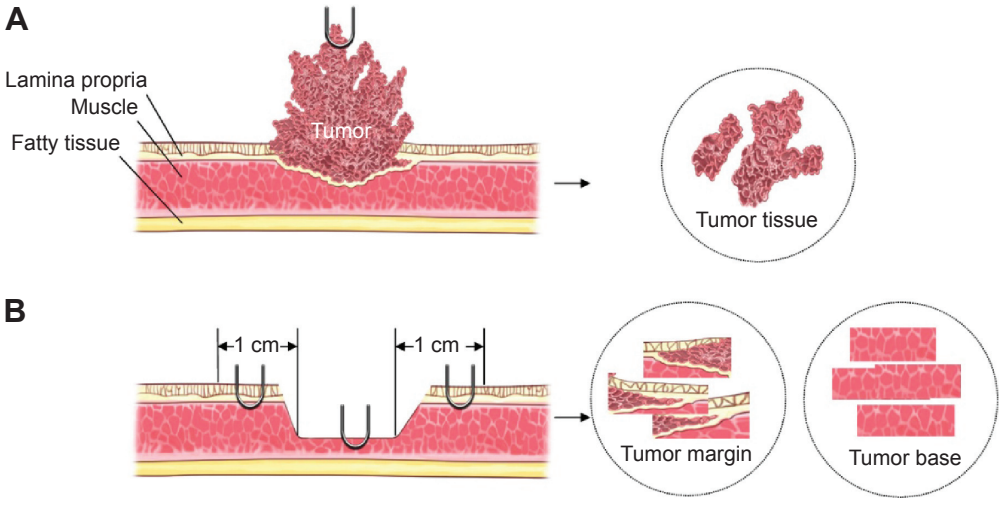

Figure 1 A flow chart of the extensive transurethral resection procedure.
Notes: (**A**) Remove the entire visible tumor and then collect all the tumor tissue specimens. (**B**) Get additional specimens of tumor base and margin (tumor margin means at least 1 cm around bladder tumor).

by taking additional tumor base and marginal specimens in the extensive TUR group. To avoid bladder perforation, it is necessary to appropriately reduce intra-vesical pressure by decreasing normal saline poured into the bladder when taking additional specimens from the resection bed. Several additional specimens from the resection margin and bottom were taken, depending on the size of the tumor. These specimens were sent to the urological pathologist separately for evaluation of the residual tumor status. After taking additional specimens, hemostasis was performed carefully in the resection bed. The video data of the operation process was reserved for further treatment.

According to the findings of all the specimens (gross specimens and additional specimens), a final diagnosis was made and post-TUR treatment strategy was followed. Tumors were classified according to the 2009 Tumor Node Metastasis (TNM) system of International Union Against Cancer and were graded according to the World Health Organization classification.[7] Considering that papillary urothelial neoplasm of low malignant potential and low-grade carcinoma have similar risks of progression when compared with high-grade carcinoma, we classified patients with papillary urothelial neoplasm of low malignant potential under low-grade carcinoma group.[8]

A second TUR was performed only in those patients in whom residual tumors were found in additional specimens, such as Ta, T1, and single Tis disease, according to the operation video. Patients with Tis disease also received instillation of Bacillus Calmette–Guerin (BCG 60 mg once a week for 6 weeks as one course). Radical cystectomy (RC) was performed in patients with multiple Tis or T2 disease. Partial cystectomy (PC) was carried out when single or localized T2 disease was detected in additional specimens.

Urine cytology and follow-up cystoscopy were performed at 3 months after the initial TUR. Recurrence was defined as histologically confirmed presence of tumor within the bladder detected at first follow-up cystoscopy after the initial TUR. If no lesions were seen at cystoscopy but cytology was positive, multiple biopsies had to be taken. Patients with positive biopsies of tumor tissue were also defined as recurrence.

Statistical analysis

All statistical tests were performed by software package used for statistical analysis 20.0 (IBM Corporation, Armonk, NY, USA). The positive rate of these additional surgical specimens was determined, and it was found whether or not the diagnosis and treatment plan had changed in group 1. We described the frequency and stage distribution of the residual tumor in different localization of additional specimens. We also used chi-squared test to compare the RR-FFC between the two groups. Subgroup analysis was performed between the two groups, separated by the number, size, stage, and grade of tumors. Patients' age was compared by the independent sample *t*-test. The chi-squared test was also used in the comparison of gender distribution, characteristics of the tumor, and the early recurrence rate between the two groups.

Results

In the extensive TUR group, additional specimens were taken from a total of 324 patients successfully by two experienced urologists at our institution from June 2009 to July 2015. These additional specimens were finally confirmed by two urological pathologists. Seven cases were excluded due to incomplete clinical data, and thus, 317 patients were enrolled in group 1. Of these patients, 51/317 (16.1%) had histopathologically detected residual tumors. Analysis of the frequency and stage distribution of the residual tumors in different localization of additional specimens showed that residual tumors were detected from the tumor base in 25/317 (7.9%) cases, from the tumor margin in 22/317 (6.9%) cases, and from both of them in 4/317 (1.3%) cases (Table 1). The positive tumor base specimens were composed of eight T1 stage diseases, 13 T2 stage diseases, and four Tis diseases. Six Ta stage, seven T1 stage, four T2 stage, and five Tis diseases constituted the positive tumor margin specimens (Table 1). Also, in 29/317 patients (9.1%), the final diagnosis changed due to the specimens' results and 45/317 (14.2%) patients had their post-TUR treatment plans changed. Of these 29 patients with staging error, five patients were upstaged from Ta to T1 stage, 13 and five patients were upstaged from T1 and Ta stage, respectively, to T2 stage, and there were also four T1 and two Ta stage patients detected with residual Tis disease.

Table 1 Frequency and stage distribution of the residual tumor correlated to the localization of additional specimens

Additional specimens	Ta, n	Single or concomitant carcinoma in situ, n	T1, n	T2, n	Overall n (%)
Positive tumor base	0	4	8	13	25 (7.9)
Positive tumor margin	6	5	7	4	22 (6.9)
Positive tumor base and tumor margin	0	2	1	1	4 (1.3)
Total	6	11	16	18	51 (16.1)

Of the 45 patients who had their further therapeutic plans adjusted after extensive TUR, 25 patients underwent second TUR, three patients also received instillation of BCG after second TUR, seven patients had to proceed with PC followed by chemoradiotherapy, four patients just underwent PC only (for reasons of poor health and serious side effect to chemoradiotherapy), and nine patients underwent RC finally.

In the nonextensive TUR group, a total of 212 patients had undergone normal TURs by the same two experienced urologists at our institution. Six cases were excluded due to incomplete and missing clinical data, and thus, 206 patients were included in group 2. As a control group, we compared it with group 1 and found that there were no significant differences with regard to demographics and tumor characteristics in the two groups (Table 2).

Considering that there were 20 patients who had undergone PC or RC for having been detected with T2 diseases (18 patients) or multiple Tis diseases (two patients) after extensive TUR, these 20 patients were excluded from the comparison of RR-FFC between the two groups. Of the remaining patients, 14/297 (4.7%) were observed to have recurrence at the first follow-up cystoscopy in group 1. Among the patients who had their final diagnosis changed due to the additional specimens' results, 2/9 patients (except for the 20 patients who underwent PC or RC) were observed to have recurrence at the first follow-up cystoscopy. Of the patients who had their post-TUR treatment plans adjusted, 3/25 patients (except for the 20 patients who underwent PC or RC) were observed to have recurrence at the first follow-up cystoscopy. For the remaining patients with no changes in their post-TUR treatments, the RR-FFC was 3.3% (9/272). Compared with group 1, 27/206 (13.1%) patients were observed to have recurrence at the first follow-up cystoscopy in group 2 (P=0.001). The number, size, stage, and grade of tumors did correlate with the impact of extensive resection at RR-FFC. The incidences of RR-FFC between the two groups were significantly different in multiple tumors (9.0% vs 22.2%, P=0.010), large tumors (11.1% vs 30.9%, P=0.015), T1 stage tumors (3.5% vs 13.4%, $P<0.001$), and high-grade tumors (5.0% vs 18.4%, $P<0.001$) (Table 3).

Discussion

The overall rate of recurrence following TUR in patients with NMIBCs can be as high as 70%.[9] A study reported that residual tumors were found in 33% of 124 cases; in 81% of these cases, the tumor was present at the original TUR site.[10] It shows that besides the biological characteristics of bladder tumor (multiple tumors, large tumor bulk, or high-grade tumor), incomplete resection may also be a compelling prognostic factor for tumor recurrence.

Nowadays, many different resection techniques, such as taking random biopsies, performing second or extensive resection appear to optimize the operation of TUR. However, most studies have focused mainly or exclusively on random biopsies or second TUR.[11–14] Data on the extensive TUR are sparse, as reported by Bressel et al[15] as early as 1969, who suggested lower tumor persistence with resection of tumor base and tumor surroundings. Considering that the tumor tissue left behind will lead to new cancer growth, extensive TUR serves the same purpose as other techniques to improve the results.

Table 2 Distribution of patient and tumor characteristics

	Extensive TUR	Nonextensive TUR	*P*-value
Mean age, years (range)	66.8 (39–89)	65.9 (41–91)	0.340
Sex, n (%)			0.319
Male	223 (70.3)	154 (74.8)	
Female	94 (29.7)	52 (25.2)	
N of tumors, n (%)			0.780
Single	202 (63.7)	134 (65.0)	
Multiple	115 (36.3)	72 (35.0)	
Size, n (%)			0.563
≤3 cm	221 (69.8)	138 (67.0)	
>3 cm	96 (30.2)	68 (33.0)	
Stage, n (%)			0.293
Ta	61 (19.2)	50 (24.3)	
T1	240 (75.7)	149 (72.3)	
Tis (single or concomitant)	16 (5.0)	7 (3.4)	
Grade, n (%)			0.123
Low	120 (37.9)	92 (44.7)	
High	197 (62.1)	114 (55.3)	

Abbreviation: TUR, transurethral resection.

Table 3 Comparison of the two groups according to the RR-FFC

	Extensive TUR	Nonextensive TUR	*P*-value
RR-FFC, n (%)	14/297 (4.7)	27/206 (13.1)	0.001
RR-FFC according to the number of tumors, n (%)			
Single	5/197 (2.5)	10/134 (8.2)	0.056
Multiple	9/100 (9.0)	17/72 (22.2)	0.010
RR-FFC according to tumor size, n (%)			
≤3 cm	4/216 (1.9)	6/138 (4.3)	0.320
>3 cm	10/71 (14.1)	21/68 (30.9)	0.015
RR-FFC according to tumor stage, n (%)			
Ta	0/56 (0)	3/50 (6.0)	0.102
T1	8/227 (3.5)	20/149 (13.4)	<0.001
Tis (single or concomitant)	6/14 (42.9)	4/7 (57.1)	0.659
RR-FFC according to tumor grade, n (%)			
Low	5/118 (4.2)	6/92 (6.5)	0.540
High	9/179 (5.0)	21/114 (18.4)	<0.001

Note: Eighteen patients detected with T2 diseases and two patients detected with multiple Tis diseases after extensive TUR were excluded from this comparison.
Abbreviations: RR-FFC, recurrence at the first follow-up cystoscopy; TUR, transurethral resection.

The current European Association of Urology NMIBC guidelines panel recommended an extensive resection during a systematically performed TUR, but few data exist regarding its impact on the outcome of treating NMIBC. Due to lack of these data, urologists may not be able to know the effect and importance of extensive TUR, and some of them do not even know how to implement it properly.

It is well understood that an extensive TUR practice is useful for finding residual tumors and provides detailed information about the stage of bladder tumor during initial TUR. An extensive TUR was developed by Richterstetter et al[16] in 2001, according to a standardized protocol of taking additional specimens from endoscopically "normal"-appearing areas from the bottom and margin of the tumors. In their long-term study, residual tumor was detected histopathologically in 50/227 NMIBCs (22.0%). They concluded that extensive TUR provides detailed information about the horizontal and vertical extent of the bladder tumor lesion. Thomas et al[17] pointed out that the practice of resecting the base and sending the material separately reduces the risk of a staging error. In our study, there were 16.1% of patients (51/317) whose additional specimens revealed residual tumor lesion. Of these positive specimens, staging error was detected in 56.9% (29/51), with 35.3% (18/51) cases upstaged to T2 and new found Tis present in 11.8% (6/51).

TUR is the initial step in treating NMIBCs, and more important than that is the treatment that follows such as second TUR, BCG intravesical instillation, or even turning to PC or RC. A routine second TUR for an NMIBC after initial TUR was recommended by the European Association of Urology guidelines in 2011, especially in patients with high-grade T1 tumors.[18] After the second TUR, the rate of residual tumor diagnosis varies between 27% and 78%.[19] As reported in the literature, a second TUR appears to improve the oncological outcomes obviously.[20] Although residual tumors are found in approximately one-third of the patients who undergo a second TUR for high-grade T1 BCs, a second anesthesia and operation may be unnecessary for the remaining two-thirds.[21] We hold the opinion that extensive TUR can help in making a decision on whether a second TUR is needed or not. But there were not enough patients who routinely underwent second TUR in our retrospective study. This may be one of the limitations of our research. Of course, a rigorous prospective randomized controlled trial should be performed to evaluate the value of both extensive and second TUR in the diagnosis and treatment of NMIBC, which will be more meaningful. The effect of BCG against residual small tumors such as Tis is well known, but how to find Tis is the key point. An extensive TUR not only avoids diagnostic errors, but also provides advanced information for post-TUR treatment changes. In our study, 14.2% (45/317) patients had their postoperative treatment plans changed due to the positive findings of additional specimens, including second TUR, PC, RC, and intravesical treatment.

Whether or not an extensive TUR really influenced the recurrence and progression rates of NMIBC is still under debate.[22,23] The prognosis of NMIBC was associated with many factors such as tumor number, size, grade, stage, and the following treatment. In addition, incomplete resection is an important risk factor, which can be avoided. The RR-FFC has been attributed to incomplete resection of the tumors.[24] The European Organization for Research and Treatment of Cancer Genitourinary Group and the UK Medical Research Council have shown that recurrence at

any site in the bladder at the first follow-up cystoscopy after TUR is one of the most important prognostic factors for time to progression.[6,25,26]

In our study, recurrence at the first follow-up cystoscopy was observed in 4.7% of patients in group 1 compared to 13.1% of patients in group 2. It is important to note that 20 patients upstaged to T2 stage or had multiple Tis diseases detected in group 1 and were excluded from the comparison of RR-FFC. Based on a balance of tumor distribution between the two groups, their counterparts contributed greatly to the higher recurrence rate in group 2 versus group 1. We also observed the RR-FFC in several subgroups according to different tumor stages, grades, size, and number. For patients with multiple tumors (9.0% vs 22.2%, P=0.010), large tumors (11.1% vs 30.9%, P=0.015), T1 stage tumors (3.5% vs 13.4%, $P<0.001$), or high-grade tumors (5.0% vs 18.4%, $P<0.001$), extensive TURs were mostly recommended. Patients with single, Ta stage, and low-grade tumors can choose an en bloc resection or single TUR first. Considering Tis as a special stage of NMIBC and that only a few cases were included in our study, a better strategy toward the same still needs further discussion.

Conclusion

Based on the present study, it can be clearly concluded that routine extensive TUR is helpful for the pathological diagnosis and post-TUR treatment of NMIBC. Also, we have further found that it can significantly reduce the RR-FFC of NMIBC, especially in patients with T1 stage and high-grade disease. Yet, a large series of prospective trials are needed for more comprehensive details about its impact on prognosis.

Acknowledgments

This work was funded by grants from the Natural Science Foundation of Tianjin (No 14JCYBJC26300) and National Key Specialty Construction of Clinical Projects, the Natural Science Foundation of Tianjin (No 15JCYBJC24600), and Tianjin Major Scientific and Technological Special Project (No 12ZCDZSY16900). We thank all the study participants, urologists, and study coordinators for participating in the study. No competing financial interests exist.

Disclosure

The authors report no conflicts of interest in this work.

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