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For which non-muscle invasive bladder cancer is Re-Transurethral Resection more valuable?

Which bladder cancer deserves Re-TUR?

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Abstract
Aim: In this study, we aimed to evaluate the re-transurethral resection (re-TUR) pathologies and to compare the pathology results between transurethral resection of the bladder (TUR-B) and re-TUR for non-muscle invasive bladder cancer (NMIBC). Additionally, we aimed to assess the factors affecting the re-TUR pathology and try to define more valuable re-TUR patient groups. We also aimed to evaluate the effect of re-TUR on recurrence and progression.
Material and Method: We performed re-TUR in intermediate/high-risk NMIBC patients, 4-6 weeks after the index TUR-B. Both TUR-B and re-TUR pathology characteristics, including tumor stage, grade, size, number, lymphovascular invasion (LVI), carcinoma in situ (CIS), variant pathology, and intermediate/high-risk status were analyzed retrospectively. The recurrence and progression rates were also evaluated according to re-TUR.
Results: A total of 78 patients with NMIBC were included in the study. The index TUR-B pathologies were Ta-Low: 6 (7,7%), Ta-High: 5 (6,4%), T1-Low: 14 (17,9%), T1-High: 53 (67,9%). Re-TUR positivity was n: 40 (51 %), and upstaging/upgrading at re-TUR was n: 11 (14 %) in all groups. Re-TUR positivity was significantly higher in high-risk compared to intermediate-risk NMIBC (p:0,026). Re-TUR positivity was higher in patients with hydronephrosis, CIS, LVI, differentiation, size (>3 cm), and multiple tumor presence (p<0,05). There was no significant relationship between recurrence/progression and re-TUR (p>0,05).
Discussion: Residual tumor was common after the index TUR-B, and upstaging after re-TUR was very important. Re-TUR is critically important in high-risk NMIBC, presence of hydronephrosis, CIS, LVI, variant pathology, size (>3 cm), and multiple number of tumors.

Keywords
Bladder Cancer, TUR-B, Re-TUR, Pathology

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Introduction

Bladder cancer (BC) is 7th most common cancer in males and 13th most mortal cancer in both males and females [1]. Smoking, genetic factors, chemical agents, and many other factors are risk factors for the etiology of BC [2-4]. Approximately 75% of BC is non-muscle invasive bladder cancers (NMIBC) and 25% are muscle-invasive bladder cancers (MIBC) at the time of diagnosis [5]. Differentiating the NMIBC from MIBC is so important because the treatment protocol is totally different. If patients were misdiagnosed with NMIBC instead of MIBC, it would be catastrophic for the treatment strategy. To prevent this situation, re-TUR (re-transurethral resection) is performed 2-6 weeks after the index TUR-B (transurethral resection of the bladder) operation [6]. Complementary TUR-B should be performed if there is no muscle tissue at the pathology specimen or the index TUR-B is incomplete. However, re-TUR is a totally different procedure from complementary TUR-B. Re-TUR is performed after complete TUR-B to prevent misclassification or to resect undetected tumors after the index TUR-B [7].

The European Urology Association (EAU) guidelines defined Ta_Low grade tumors as low-risk NMIBC category, which means that the risk of progression is low for this group. On the other hand, T1 tumors, high-grade tumors, carcinoma in situ (CIS) pathologies, and all features, including multiple, recurrent, and large (>3 cm) tumors are in the high-risk NMIBC group. The rate of progression in this group is significantly higher than low-risk group [8,9]. Pathologies between these two groups are considered intermediate-risk groups for NMIBC. Re-TUR is proposed to be unnecessary in low-risk NMIBC. On the other hand, in high-risk NMIBC, re-TUR is routinely recommended. However, there is no exact recommendation about the feasibility of re-TUR for intermediate-risk NMIBC [9].

In this study, we aimed to evaluate the re-TUR pathologies and to compare pathology results between TUR-B and re-TUR for intermediate and high-risk NMIBC. In addition, we aimed to evaluate the most valuable patient groups for re-TUR and factors affecting re-TUR pathology. We also aimed to assess the influence of re-TUR on recurrence and progression for intermediate and high-risk NMIBC patients.

Material and Methods

Study population and protocol

With the permission of the local ethics committee, the patients who underwent the re-TUR between 2013-2020 in our clinic were retrospectively included in the study. The patients underwent TUR-B operation under general or spinal anesthesia using a continuous flow 27 French 30° optical resectoscope instrument and a video camera system (Karl StorzTM, Tuttlingen, Germany).

The study included patients who were at intermediate and high-risk classification. Patients with Ta_Low grade pathology who present one of following parameters: multiple, recurrent, or >3 cm tumors, were considered intermediate risk NMIBC. Therefore, re-TUR was also applied for these Ta_Low grade patients who were classified as intermediate-risk group. On the other hand, patients who had low-risk NMIBC, patients with MIBC, patients with in-complete TUR-B, and patients who had no muscle tissue in the pathologic specimen, were excluded from the study.

The re-TUR operation was performed approximately 4-6 weeks after the index TUR-B for intermediate and high-risk NMIBC patients. During re-TUR operation, resection was performed from the same area of the primary tumor including the deep muscle layer, regardless of residual or recurrent tumor. The re-TUR specimen was checked for any residual tumor and for changes in tumor stage or grade. All patients who were not upstaged to MIBC received standard BCG immunotherapy.

Both TUR-B and re-TUR pathology characteristics, including tumor stage, tumor grade, tumor size, tumor number, presence of lymphovascular invasion (LVI), presence of CIS, presence of variant pathology, and tumor risk status were analyzed. The Re-TUR positivity (residual tumor) of the patients was evaluated and analyzed according to these variables.

Statistical Analysis

In descriptive statistics of the data, frequency, ratio, mean, and standard deviation values were used. Continuous data were reported as means ± standard deviations (SD) or median values, as appropriate. Statistical analyses were performed using the SPSS 21.0 package program. The chi-square/Fisher's Exact test in cross tables was used in statistical analyses. P <0.05 was considered statistically significant.

Results

A total of 78 patients with intermediate and high-risk NMIBC were included in the study. The mean age of the patients was 63.9±9.0 (38- 85 years). There were 72 (92,3 %) males and 6 (7,7 %) female patients. The mean follow-up time was 42,1±29,6 (min 10 - max 142) months. According to the EAU risk classification, 6 (7,7 %) patients were in the intermediate-risk group and 72 (92,3 %) patients were in the high-risk group. The index TUR-B and re-TUR pathologies of the patients were shown in Table 1.

Most of the re-TUR positivity was seen in high-grade patients. Three of (60 %) Ta_High grade patients (n:5) had re-TUR positivity and 1 of them upstaged to MIBC. T1_High grade patients (n:53) had the highest number of re-TUR positivity (n:31) (58,5 %). Eight of the T1_High grade patients upstaged to MIBC (15 %). The patients who were upstaged to T2 were treated with 'radical cystectomy' or 'radiotherapy + chemotherapy'. On the other hand, none of the Ta_Low grade patients (n:6) had re-TUR positivity (Table 1).

Re-TUR positivity and up-stage/grade were demonstrated according to tumor stage, tumor grade, and intermediate/high-risk NMIBC in Table 2. Re-TUR positivity was n: 40 (51 %), and upstaging/upgrading at re-TUR was n: 11 (14 %) in all groups. There was a statistically significant difference between Re-TUR positivity and T stage/grade (p:0.031). In addition, re-TUR positivity was significantly higher in high-risk compared to intermediate-risk NMIBC (p:0.026). Although the recurrence (n:18) and progression (n:11) were higher in the high-risk group (n:72), statistical analysis did not show any significant difference. The odds ratio of re-TUR positivity was 5,57 for recurrence (95% CI: 1,7-18,5) and 6,52 for progression (95% CI: 1,3-33,5).

Re-TUR positivity was significantly higher in patients with hydronephrosis, CIS, LVI, variant pathology, size (3 cm>), and

Table 1. TUR-B pathologies (T stage and grade) of the patients and Re-TUR pathologies according to index TUR-B

TUR_B pathology	n (%)
Ta_Low	6 (7,7 %)
Ta_High	5 (6,4 %)
T1_Low	14 (17,9%)
T1_High	53 (67,9 %)
Re_TUR pathology	**n (%)**
T0	6 (100 %)
Ta Low	0
Ta High	0
T1 Low	0
T1 High	0
T2	0
T0	2 (40 %)
Ta Low	1 (20 %)
Ta High	0
T1 Low	0
T1 High	1 (20 %)
T2	1 (20 %)
T0	8 (57,1 %)
Ta Low	3 (21,4 %)
Ta High	0
T1 Low	2 (14,3 %)
T1 High	1 (7,1 %)
T2	0
T0	22 (41,5 %)
Ta Low	4 (7,5 %)
Ta High	1 (1,9 %)
T1 Low	2 (3,8 %)
T1 High	16 (30,2 %)
T2	8 (15,1 %)

(TUR-B: Transurethral resection of bladder, Re-TUR: Re-transurethral resection)

Table 2. Re_TUR Positivity, Up-stage/grade at Re_TUR, Recurrence and Progression status according to T stage/grade, Intermediate and High-risk NMIBC patients

	Re_TUR positivity n (%)	Up-stage/ grade at re_TUR n (%)	Recurrence n (%)	Progression n (%)
Ta_Low (n:6)	0 (0 %)	0 (0 %)	2 (33 %)	0 (0 %)
Ta_High (n:5)	3 (60 %)	2 (40 %)	2(40 %)	1 (20 %)
T1_Low (n:14)	6 (43 %)	1 (7 %)	2 (14 %)	2 (14 %)
T1_High (n:53)	31 (58 %)	8 (15 %)	14 (26 %),	8 (15 %)
p value	p:0.031	p:0.29	p:0.69	p: 0.80
Intermediate Risk (n:6)	0 (0 %)	0 (0 %)	2 (33 %)	0 (0 %)
High Risk (n:72)	40 (56 %)	11 (15 %)	18 (25 %)	11 (15 %)
p value	p:0.026	p:0.646	p:0.66	p:0.581

(Re-TUR: Re-transurethral resection, NMIBC: Non-muscle invasive bladder cancer)

multiple tumor presence (Table 3). In addition, different tumor variants such as sarcomatoid, neuroendocrine, micropapillary, plasmacytoid differentiation had a worse prognosis than others. In our study, there were 4 patients with different variants and 3 of them (75 %) had re-TUR positivity.

Discussion

Bladder cancer is an aggressive tumor with high morbidity and mortality rate. It is really important to choose the best treatment option for BC. The EAU guidelines recommend re-TUR for possible upstaging of NMIBC to invasive cancer and clearance of residual tumor after index TUR-B [9]. It was demonstrated that the presence of residue and tumor upstaging was high in the re-TUR series. Therefore, re-TUR is critically important for complete resection and re-staging after index TUR. Disease management and mortality of the patients may totally change with the help of re-TUR pathology. Although there are different recommendations on the timing of re-TUR, the most accepted time for the procedure is from 2 to 6 weeks after the index TUR-B [10].

The upstaging rates of T1 patients were found to be high in the literature. Fritsche et al analyzed the data of 1136 patients treated with radical cystectomy for the clinical T1 high stage group and demonstrated that nearly half of the pT1 patients (49,7 %) had MIBC pathology [11]. These rates supported the inadequacy of clinical decision-making based on current treatment paradigms and staging tools for T1_high stage tumors. Herr et al also stated that re-TUR revealed up to 43 % upstaging and up to 85 % of re-TUR positivity [12]. The re-TUR positivity was 51 %, and the upstaging rate was 14 % in our study. In recently published reviews, the residual tumor rates were approximately 51-58 % and T2 upstaging rates were 8-11 %, which were similar to our study results [13,14]. Subgroup analysis in the literature documented that re-TUR positivity was 17-67 % in Ta patients and 20-71% in T1 patients. Most residual tumors (36-86 %) were found at the original resection site [14]. In our study, the re-TUR positivity was found 27 % for Ta and 55 % for T1 patients, which was similar to the literature. The necessity of re-TUR was not uniformly accepted. Some authors did not recommend re-TUR due to the low percentage of upstaging, possible complications, and the cost of the surgery [15]. Gaya et al claimed that re-TUR is mandatory only if there was no muscle tissue in the initial resection specimen. They thought that the absence of muscle is the only risk factor for understaging [16]. However, their patient population was low, and the lack of muscle tissue is the reason for complementary TUR-B not for re-TUR. In our study, the re-TUR positivity of T1_high grade patients was 58 %, and the upstaging rate was 15 %. T1 high grade is the highest stage for NMIBC and these patients are at the edge of the border for MIBC. Therefore, it

Table 3. Re_TUR Positivity according to Hydronephrosis, CIS, LVI, Differentiation, Size and Number of tumors

	Hydronephrosis (n:7)	CIS (n:5)	LVI (n:49)	Differentiation (n:4)	Size>3cm (n:32)	Multiple (n:26)
Re_TUR positivity n (%)	6 (86 %)	5 (100 %)	32 (65 %)	3 (75 %)	21 (66 %)	17(65 %)
p value	0,008	0,028	0,022	0,025	0,014	0,005

(Re-TUR: Re-transurethral resection, CIS: Carcinoma in situ, LVI: Lymphovascular invasion)

would be proper to undertake re-TUR for these patients. On the other hand, re-TUR is an invasive operation; the pros and cons of the procedure also should be considered. There are also questions about the necessity of re-TUR, especially in the COVID-19 pandemic period. Clinicians need to be more careful to make the surgical indications for their patients in terms of both patient and public health [17]. Any surgical procedure that does not have significant indication must be questioned. Shared decision-making would be the solution for this situation. In this way, clinicians should discuss the decision of re-TUR requirement collectively with patients in light of the evidence-based literature.

The impact of re-TUR on long-term outcomes for T1 patients was discussed in several studies in the literature [16-20]. Divrik et al revealed in their prospective randomized clinical trial that re-TUR had significantly decreased the recurrence and progression rates in patients with newly diagnosed T1 stage [18]. In addition to this Sfakianos et al claimed that the absence of re-TUR before initiating intravesical BCG therapy for high-risk NMIBC significantly increased the risk of recurrence [19]. On the other hand, some studies claimed that the recurrence and progression of T1_high grade patients treated with BCG without re-TUR were not as bad as previously thought [20]. They reported that oncological results and the rate of recurrence/progression would not be affected after re-TUR for T1_high-grade. Moreover, re-TUR can cause patient distress and higher re-operation-related healthcare costs [21]. In our study, we could not find any statically significant relation between re-TUR and recurrence/progression. It might be due to appropriate intravesical BCG and other curative treatments plus close follow-up.

The presence of hydronephrosis, CIS, LVI, variant pathology, and tumor size >3cm in index TUR are generally associated with a poor prognosis of BC. Bishr et al reported that the adverse prognostic features related to re-TUR were as follows: the number of tumors (>3 lesions), tumor size (>3 cm), hydronephrosis, invasion of the lamina propria (T1), high-grade, concomitant CIS, different tumor variants and T1 stage [22]. We also analyzed these variables in terms of re-TUR positivity. We examined that the re-TUR positivity rate was significantly higher in patients with these variables. When these factors are present, it will no doubt be critically important to perform re-TUR.

Limitations

The retrospective study design was one of our limitations. However, according to our clinical policy, we performed a strict follow-up protocol for BC patients. The strict follow-up protocol of the patients might reduce potential bias associated with the retrospective nature of the study. The relatively low number of patients was another limitation of our study. This might be related to the exclusion criteria from our study population. To standardize our study population, patients with incomplete index TUR-B and patients with no muscle tissue at index TUR-B specimens were excluded from the study. Another limitation of our study was the absence of a control group to whom we did not perform re-TUR. However, the presence of a control group in the high-risk group is an ethical problem for this study design. In our clinical practice, we routinely perform re-TUR in high-risk NMIBC patients.

Conclusion

The residual tumor is common after index TUR-B. The re-TUR is definitely required to detect this residual tumor and to reveal cancer upstaging. It should be noted that re-TUR is critically important in high-risk NMIBC, presence of hydronephrosis, CIS, LVI, variant pathology, size (>3 cm), and multiple tumors. However, collaborative decision-making would be useful in determining the re-TUR indication for selected patients. The effect of re-TUR on recurrence and progression in NMIBC is still a dilemma.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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