

Time between First and Second Transurethral Resection of Bladder Tumors in Patients with High-Grade T1 Tumors: Is It a Risk Factor for Residual Tumor Detection?

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Key Words

Bladder tumor · Transurethral resection · Second transurethral resection · Residual tumor

Abstract

Purpose: We evaluated the risk factors for residual tumor detection after transurethral resection of bladder tumors (TURBT) in patients with newly diagnosed high-grade T1 transitional cell carcinoma of the bladder. **Patients and Methods:** Overall 132 patients underwent TURBT for primary bladder tumors and were diagnosed as high-grade T1 bladder cancer. Patients with incomplete resections were excluded from the study. Clinical and pathologic characteristics of the patients were compared and multivariate analysis was performed to determine independent prognostic factors. **Results:** Residual tumor was demonstrated in 57 (43.1%) of the patients. The residual tumor rate was significantly lower in patients with solitary tumors, tumors <3 cm in diameter, muscle presence in the initial TURBT pathologic sample and treated by an expert surgeon. In patients with solitary bladder tumors, tumors at the dome and posterior wall of the bladder exhibited higher rates of residual tumor ($p < 0.0001$). The time elapsed between first and second TURBT was significantly shorter in patients without residual tumor compared to patients with residual tumor at second TURBT (32.6

± 9.1 vs. 39.3 ± 10.9 days, respectively, $p = 0.001$). Multivariate analysis demonstrated that time elapsed between first and second TURBT is the most important parameter for residual tumor detection. **Conclusion:** Our study revealed that multiple tumors, tumors >3 cm in size, absence of detrusor muscle in the initial TURBT specimen, TURBT performed by trainees and finally, as a new finding, prolonged interval between first and second TURBT are independent predictors for residual tumor detection in patients with high-grade T1 tumors.

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Introduction

Transurethral resection of bladder tumors (TURBT) is the first stage in the diagnosis and treatment of bladder tumors. The major objectives of TURBT are to remove all visible tumor and provide the necessary information to accurately stage the patients. However, there are significant problems in the initial transurethral resection of non-muscle-invasive bladder cancer (NMIBC) concerning correct staging and complete resection of the tumor [1]. A high number of recurrences and the requirement of adjuvant therapy indicate incomplete tumor resection in most of the patients [2–4]. Moreover understaging due

to inadequate resection may influence the progression rate in NMIBC.

Especially in high-grade tumors, good and complete TURBT is the essential part of initial management. Early recurrence is an unfavorable prognostic factor for these tumors and is mostly attributed to incomplete resection at the initial TURBT [5]. Although the quality of TURBT is accepted as the mainstay feature in the management of NMIBC, experienced surgeons reported considerable residual tumor rates and understaging even after resection of all visible tumors [6, 7]. Furthermore there are increasing data which demonstrate the favorable effects of second TURBT on the recurrence-free survival of these patients [8]. Due to these findings, a second transurethral resection is recommended when a high-grade or T1 tumor has been detected at initial transurethral resection [9]. There is no established timing for the second TURBT, however 2–6 weeks after the initial resection is mostly accepted.

Many clinical and pathologic factors may alter the outcomes of second TURBT [10, 11]. In this study our aim was to investigate the risk factors and their impact on residual tumor detection by second TURBT in high-grade T1 bladder cancer.

Patients and Methods

We reviewed our bladder tumor database and selected patients with bladder tumor who were diagnosed between 2005 and 2011. The resections were performed by 4 experienced urooncologists and trainees in years 3–5 (urology training is 5 years in our country). The trainees performed these operations under the supervision of senior urologists. White light cystoscopy and conventional resection equipments were utilized during TURBT. Fluorescence cystoscopy was not performed in the initial TURBT. All visible tumors, the tumor bed and the margins were resected separately. Results of these resections were reported in the pathology report. We implemented intravesical 40 mg mitomycin C within 24 h of resection except for patients with serious hematuria and suspicion of bladder perforation. We performed second TURBT in patients with incomplete initial resection, multiple and/or large tumors, high-grade or T1 tumors and tumor specimens without detrusor muscle samples. Tumors were classified according to the TNM staging system [12] and were graded according to the WHO grading system [13]. The inclusion criteria were (1) primarily diagnosed urothelial bladder cancer, (2) macroscopically complete initial TURBT without any visible residual tumor, (3) T1 or high-grade tumors, and (4) no extravesical urothelial cancer.

The recorded clinicopathologic parameters in these patients were age, gender, medical history, tumor size, tumor grade, tumor stage, multifocality, tumor localization for solitary tumors, operating surgeon, timing of the second TURBT and presence of detrusor muscle in the pathologic specimen.

Table 1. Clinical and pathologic characteristics of patients who underwent initial TURBT for primary bladder tumors

	Number of patients
Total	132 (100%)
Male	100 (75.75%)
Female	32 (18.9%)
Solitary	76 (57.5%)
Multifocal	56 (42.4%)
Tumor size, cm	
<3 cm	73 (55.3%)
≥3 cm	59 (44.7%)
Residual tumor	57 (43.1%)
Progression	12 (9.1%)
Detrusor muscle presence in initial TURBT specimen	89 (67.4%)
Operator	
Trainee	60 (45.5%)
Expert	72 (54.5%)
Carcinoma in situ	7 (5.3%)

The aforementioned parameters were compared between patients with and without residual tumors detected by second TURBT after the initial resection. We investigated the impact of localization in solitary bladder tumors by dividing tumor localization according to the accessibility of the tumors. We excluded multifocal tumors from this analysis as these tumors are generally located in different sites of the bladder. Solitary tumors at the dome or posterior wall and tumors at the lateral or inferior bladder wall were accepted as tumors difficult and easy to access with the resectoscope, respectively. The interval between initial and second TURBT was recorded using days as the time unit. All statistical evaluations were performed using SPSS. Pearson χ^2 and Mann-Whitney U tests were used for standard statistical procedures. To determine independent prognostic factors, multivariate survival analysis was performed by a Cox regression model with respect to potential influencing factors. Statistical significance in this study was defined as $p < 0.05$.

Results

Overall 132 patients underwent TURBT for primary bladder cancer and were diagnosed as T1 or high-grade urothelial cancer. Mean age was 63.35 ± 10.51 years. Second TURBT was performed at a mean of 35.7 ± 8.03 years (20–69). Residual cancer and progression was demonstrated in 57 (43.1%) and 12 (9.09%) of all patients, respectively. Associated carcinoma in situ was reported in 7 patients at initial TURBT pathologic report. The clinical and pathologic characteristics of the study population are demonstrated in table 1.

Table 2. Comparison of patients with and without residual tumor after initial TURBT

	With residual tumor (57 patients)	Without residual tumor (75 patients)	p value
Mean age, years	62.84±11.406	64.13±9.834	0.435
Gender			
Male	42 (42.00%)	58 (58.00%)	0.530
Female	15 (46.87%)	17 (53.12%)	
Tumor number			
Solitary	27 (35.52%)	49 (64.47%)	0.013
Multifocal	30 (53.57%)	26 (46.42%)	
Tumor size			
<3 cm	23 (32.85%)	47 (67.14%)	0.021
≥3 cm	34 (54.83%)	28 (45.16%)	
Detrusor muscle			
Present	26 (29.30%)	63 (70.70%)	0.012
Absent	31 (72.09%)	12 (27.90%)	
Surgeon			0.038
Trainee	33 (55.00%)	27 (45.00%)	
Expert	24 (33.33%)	48 (66.66%)	

Table 3. Cox proportional model according to residual tumor detection

	HR	95% CI	p value
Age	0.943	0.896–0.993	0.56
Tumor size	3.737	1.280–10.878	0.016
<3 cm			
≥3 cm			
Tumor number	5.283	1.657–16.841	0.005
Solitary			
Multifocal			
Detrusor muscle	2.981	1.007–10.046	0.049
Present			
Absent			
Surgeon	3.128	1.317–10.931	0.014
Expert			
Trainee			
Time elapsed between first and second TURBT	8.010	2.718–23.602	0.000

The comparison of patients with and without residual tumor after the initial TURBT is shown in table 2. Residual tumor rate did not display any significant difference according to age and gender ($p > 0.05$). Residual tumor rate was significantly lower in patients with solitary tumors, tumors <3 cm, muscle presence in the initial TURBT pathologic sample and treated by an expert surgeon (all $p < 0.05$) (table 2). In accordance with the demonstrated

difference of residual tumor rates between TURBT performed by trainees and experts, detrusor muscle presence was reported to be significantly higher in TURBT performed by the experts (61.1 vs. 80.7%, $p = 0.032$). The time elapsed between first and second TURBT was significantly shorter in patients without residual tumor compared to patients with residual tumor at second TURBT (32.6 ± 9.1 vs. 39.3 ± 10.9 days, respectively, $p = 0.001$).

The impact of bladder cancer localization on the residual tumor rate was evaluated in solitary bladder cancer patients. Of the 76 patients with solitary bladder cancer, residual tumor was found in 27 (35.5%). A total of 24 (31.57%) had tumors at the dome or posterior wall of the bladder (group I) and 52 (68.42%) had tumors at the lateral or inferior wall of the bladder (group II). The residual tumor rate was 58.3 and 25.0% for patients in group I and II, respectively. This difference was demonstrated to be significant ($p < 0.0001$).

Cox proportional model was formed according to residual tumor rate (table 3). According to this analysis, multiple tumors, tumor size >3 cm, prolonged interval between first and second TURBT, absence of detrusor muscle and trainees were independent predictors of residual tumor detection. Upon these parameters timing for the second TURBT was the most important factor (odds ratio 8.1, 95% confidence interval 2.7–23.6, $p < 0.0001$).

Discussion

Complete resection is the irrefutable section for the treatment of NMIBC. To achieve high success rates further resections are performed in selected patients. The European Association of Urology guidelines recommend a second TURBT when a high-grade NMIBC or a T1 tumor has been detected at the initial transurethral resection [1]. Herr [7] demonstrated a 76% residual tumor rate even in experienced hands and recommended routine repeat TURBT. Divrik et al. [14] assessed second TURBT for primary bladder cancer and demonstrated a residual tumor rate of 33.3%. They showed a high correlation between grade and residual tumor rate. In their prospective study, Grimm et al. [6] reported a residual tumor rate of 51% in grade 2–3 T1 bladder cancer patients. In our study, the residual tumor rate was 43.1%. As all of our patients had high-grade T1 cancers, this rate is acceptable.

Many clinical and pathologic factors may affect the outcomes of second TURBT. However, to our knowledge, no study evaluated the risk factors for residual tu-

mors after initial TURBT in a specific group of patients, namely patients with high-grade T1 tumors. Our study revealed that multiple tumors, tumors >3 cm in size, absence of detrusor muscle in the initial TURBT specimen, TURBT performed by trainees and finally prolonged interval between first and second TURBT are independent predictors for residual tumor detection in patients with high-grade T1 tumors.

Divrik et al. [8] classified further resections after initial TURBT according to their indication. They defined second TURBT as transurethral resection after complete resection and pathologic specimen with detrusor muscle. It is not possible to make an accurate staging without detrusor resection. In our study only 71.2% of the patients had detrusor muscle in their initial TURBT specimen. The rates of absence of detrusor muscle in previous series are also not negligible and were reported in a range between 15 and 50% [7, 15, 16]. In a recent study Mariappan et al. [11] demonstrated the presence of detrusor muscle in the pathologic sample of initial TURBT as a favorable predictive factor for recurrence after first cystoscopy. They specified detrusor presence as a surrogate marker for the quality of initial TURBT. Surgeon experience was also linked with obtaining detrusor muscle. In their study, detrusor muscle presence was 56 and 72% for junior and senior surgeons, respectively. This outcome was in accordance with our results (61.1 and 80.7% for trainees and expert surgeons, respectively).

High-grade T1 patients stand at the border of muscle-invasive disease status, and second TURBT is strongly advocated for better staging and long-term outcomes in these patients. Brausi et al. [10] in many cases attributed early recurrences to incomplete resection. Many surgeons are aware of incomplete resection because of large, multiple tumors and tumors which are difficult to access by resectoscope. However residual tumors may be detected even after the impression of an adequate resection. Tumor grade, tumor size and multifocality of tumors are the most recognized risk factors for residual tumors [8, 10, 17]. In our study tumor size >3 cm and multifocal tumors were also independent risk factors for residual tumor detection.

Learning curve and experience are other crucial factors which affect the residual tumor rate. Initially Zurkirchen et al. [18] demonstrated the residual tumor rate as 37% for beginners and 26% for experts. Brausi et al. [10] emphasized the importance of surgeon experience and attributed the heterogeneity of various centers' recurrence rate following first cystoscopy to the quality of the surgery. Although all TURBT are performed under the

supervision of an experienced surgeon, the residual tumor rate was significantly higher in our patients who were operated by trainees. The stress of possible bladder perforation during the procedure and difficulty of determining borders of the tumor for the beginner may contribute to these outcomes.

Tumor localization is another potential risk factor for residual tumor detection after initial TURBT. Tumors located at the upper hemisphere of the bladder are more difficult to approach and resect. In our study we evaluated the impact of tumor localization on patients with solitary tumors. We detected significantly higher rates of residual tumor in patients with tumor at the upper hemisphere of the bladder. The shortcomings of resectoscope manipulations and access difficulties seem to be the major reasons for this outcome.

Although most authors recommend resection at 2–6 weeks after initial TURBT, there is no consensus about the timing of a second TURBT [1]. To our knowledge, this is the first study which evaluates the effect of the elapsed time between first and second TURBT as a factor for tumor detection at the time of second TURBT. We found significantly shorter elapsed time in patients without residual tumor compared to patients with residual tumor at second TURBT. This finding may be a factor in explaining the different rates of residual tumor at second TURBT in different series. Prolonging the period between two TURBT procedures may give a chance to small undetected or inadequately resected tumors to grow and become detectable. However, considering a mean difference of 7 days, this explanation does not make sense from a biological point of view. Rather, residual inflammatory conditions may have impaired surgery or some other kind of bias may be responsible for this observation. Nevertheless, we think that this finding should be looked at in prospective randomized studies with a larger number of patients.

Conclusion

A significant number of patients has persistent disease after resection of high-grade T1 tumors. Our study revealed that multiple tumors, tumors >3 cm in size, absence of detrusor muscle in the initial TURBT specimen, TURBT performed by trainees and finally, as a new finding, prolonged interval between first and second TURBT are independent predictors for residual tumor detection in patients with high-grade T1 tumors.

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