# Second Transurethral Resection of Bladder Tumor: Is it Necessary in All T1 and/or High-Grade Tumors?

Mohsen Ayati[1], Erfan Amini[1], Reza Shahrokhi Damavand[1]*, Mohammad Reza Nowroozi[1], Mohammad Soleimani[2] , Ehsan Ranjbar[1], Ali Nowroozi[1]

**Purpose:** To evaluate the role of second transurethral resection of bladder tumor (TURBT) in patients with T1 and/or high-grade bladder tumor regarding tumor size, multiplicity, and presence or absence of muscle in specimens of initial resection.

**Materials and Methods:** A total of 107 patients with either primary T1 or high-grade urothelial bladder cancer underwent second TURBT within 6 weeks after initial surgery and prior to starting intravesical immunotherapy. We assessed the incidence of residual disease and upstaging in second TURBT.

**Results:** Upstaging was noted in 11 (10.3%) patients and residual tumor was evident in 29 (27%) patients. Disease upstaging had a statistically significant association with tumor size, multifocality, and absence of muscle at initial resection in univariate analysis. Presence of residual tumor in second resection also showed significant association with tumor size and absence of muscle at initial resection but not multifocality. Multivariate logistic regression analysis revealed that absence of muscle at initial resection independently predicts disease upstaging during second TURBT (OR = 8.123, 95% CI: 1.478-44.632). Furthermore, both tumor size (OR = 13.573, 95% CI: 3.104-59.359) and absence of muscle (OR = 21.214, 95% CI: 6.062-74.244) were independent predictors of residual disease in second TURBT.

**Conclusion:** We showed that second TURBT in a subset of patients with single, small T1 and/or high-grade tumor who underwent complete initial resection might be of limited value.

**Keywords:** residual tumor; second-look surgery; transurethral resection; upstaging; urinary bladder neoplasms

## INTRODUCTION

Bladder cancer is the most common malignancy involving the urinary system and the ninth most common cancer throughout the world[1]. Based on Globocan data, about 430,000 new cases diagnosed in 2012 with mortality rate of 3.2 and 0.9 per 100,000 men and women respectively[2].

Approximately 70% of urothelial bladder cancers are non-muscle-invasive at presentation. Of these 70% present as stage Ta, 20% as T1 and 10% as carcinoma in situ[3]. Transurethral resection of bladder tumor (TURBT) is the initial procedure in the diagnosis and treatment of these tumors.

Different studies have reported presence of residual disease in about 40% of high-grade Ta and up to 55% of patients with T1 tumors, after initial resection [4-7]. Moreover, there is significant potential for risk of understaging in patients with high-grade non-muscle-invasive tumors in the initial resection especially those with T1 tumors[8,9]. So, many investigators recommended that patients with Ta high-grade and or T1 tumors should undergo second TURBT.

However, despite the fact that many retrospective studies showed a high rate of residual tumor and understaging after repeat TURBT, several factors including surgeon experience and quality of initial resection in addition to tumor characteristics might affect the results of these reports[10-12]. Some of these studies included patients with even macroscopic residual tumor. Presence of macroscopic residual tumor may lead to erroneous conclusions in such studies and overestimate the significance of second TURBT. Furthermore, only few investigators have evaluated the role of second TURBT in a subgroup of patients with single and small T1 and/or high-grade tumors and those who underwent initial complete TURBT.[6,11,13]

Because of ongoing debate concerning the indications of second TURBT and to identify groups of patients who may benefit most from a second TURBT, we evaluated the role of second TURBT in a series of 107 patients with high-grade non-muscle-invasive bladder tumor who had a second TURBT regarding tumor size, multiplicity and presence or absence of muscle in specimens of initial resection.

## PATIENTS AND METHODS

### *Study population*

Using our institutional review board-approved bladder

[1] Department of Urology, Uro-Oncology Research Center, Tehran University of Medical Sciences, Tehran, Iran.
[2] Department of Urology, Shahid Modarres Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
*Correspondence: Department of Urology, Uro-Oncology Research Center, Tehran University of Medical Sciences, Tehran, Iran.
Tel: +98 21 66903063. Fax: +98 21 66903063. E-mail: rshahrokhi@razi.tums.ac.ir.
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**Table 1.** Pathologic findings at second TURBT stratified according to tumor characteristics during initial resection.

| First TURBT Tumor characteristics | | Distribution no. (%) | Tumor stage at second TURBT T0, no. (%) | Ta, no. (%) | T1, no. (%) | T2, no. (%) |
|---|---|---|---|---|---|---|
| Size | ≤ 3 cm | 87(81.3) | 73(84) | 10(11.5) | 3(3.4) | 1(1.1) |
| | >3 cm | 20(18.6) | 5(25) | 8(40) | 1(5) | 6(30) |
| Multifocality | Single | 92(86) | 69(75) | 16(17.3) | 3(3.2) | 4(4.3) |
| | Multiple | 15(14) | 9(60) | 2(13.3) | 1(6.6) | 3(20) |
| Muscle in the specimen | Present | 73(68.2) | 67(91.8) | 4(5.4) | 1(1.4) | 1(1.4) |
| | Absent | 34(31.7) | 11(32.3) | 14(41.1) | 3(8.8) | 6(17.6) |
| Overall | | 107(100) | 78(72.9) | 18(16.8) | 4(3.7) | 7(6.5) |

cancer database, we retrospectively evaluated all patients who underwent second TURBT between 2011 and 2015. Definition of second TURBT was based on undergoing second resection within 6 weeks from initial surgery. Tumor size was determined based on the ultrasonography findings. In this retrospective analysis of prospectively collected data, patients with macroscopic residual disease after initial TURBT according to the surgeon's subjective observation were excluded from enrollment. In addition, patients with muscle invasive disease after initial resection who underwent second TURBT (i.e. as a part of bladder preservation protocol) were excluded from enrollment. Receiving intravesical immunotherapy after initial TURBT and prior to second resection was also an additional exclusion criterion. Administration of intravesical mitomycin after TURBT was done based on the decision of treating urologist. A total of 107 patients met inclusion criteria and were enrolled in the analysis.

### *Surgical technique*

Initial TURBTs were performed by a limited number of expert urologists and visible tumors with adequate margin were resected separately in fractions. During the second TURBT, all visible tumors and scars from previous surgery were resected. All TURBTs were performed using monopolar loop electrocautery employing distilled water as solution. Staging was performed according to the TNM 2009 system of the American Joint Committee on Cancer (AJCC) and tumors were graded based on 2004 WHO grading classification.

### *Outcome assessment*

The incidence of residual disease, tumor upstaging, and upstaging to muscle-invasive disease were the outcome measures of the study. The collected data were analyzed using SPSS software (version 16, SPSS Inc, Chicago, IL, USA). Categorical data were compared using chi-square or fisher's exact test and quantitative variables were compared using *T*-Test. Multivariate logistic regression analysis was used to determine variables that independently predict risk of upstaging/residual disease.

## RESULTS

Among 107 patients, 90 (84%) were male and 17 (16%) female. The mean age was 59±12 years (range from 24 to 80). Ninety-two patients had a single tumor and the remaining (14%) had multifocal tumors. Histopathological evaluation after initial TURBT revealed 4 high-grade Ta and 103 T1 tumors.

Residual tumor was detected in 29 (27%) patients after second resection and upstaging occurred in 11 (10.3%) cases. Upstaging to muscle-invasive disease occurred in 7 patients of whom 6 patients did not have muscle in the initial specimen. **Table 1** shows pathologic findings in second TURBT stratified according to various tumor characteristics in initial surgery. The association of tumor size, multifocality, and absence of muscle in initial resection with the risk of residual disease and upstaging has been shown in **Table 2**. Disease upstaging had a statistically significant association with tumor size, multifocality, and absence of muscle at initial resection in univariate analysis. Presence of residual tumor in second resection also showed significant association with tumor size and absence of muscle at initial resection but not multifocality. Multivariate logistic regression analysis (**Table 3**) revealed that absence of muscle at initial resection can independently predict disease upstaging during second TURBT. Furthermore, both tumor size and absence of muscle were independent predictors of residual disease in second TURBT.

Among 59 patients with single, small (≤ 3cm) tumors who underwent adequate initial resection, identified by the presence of muscularis properia in the specimen, upstaging was not found and only 3 patients showed residual disease in second TURBT.

## DISCUSSION

Approximately 70% of patients who present with blad-

**Table 2.** Association between baseline tumor characteristics and disease upstaging/residual disease.

| Tumor characteristics in first TURBT | | Residual tumor (%) | *P*-value | Upstaging to muscle- invasive disease (%) | P-value | Upstaging (%) | *P*-value |
|---|---|---|---|---|---|---|---|
| Tumor size | ≤3 cm | 14 (16.1) | < 0.001 | 1 (1.1) | < 0.001 | 4 (4.6) | < 0.001 |
| | >3 cm | 15 (75.0) | | 6 (30) | | 7 (35.0) | |
| Tumor multifocality | Single | 23 (25.0) | 0.226 | 4 (4.3) | 0.023 | 7 (7.6) | 0.024 |
| | Multifocal | 6 (40.0) | | 3 (20) | | 4 (26.7) | |
| Presence of muscle in the specimen | Present | 6 (8.2) | < 0.001 | 1 (1.4) | 0.002 | 2 (2.7) | < 0.001 |
| | Absent | 23 (67.6) | | 6 (17.6) | | 9 (26.5) | |

**Table 3.** Multivariate Regression analysis to predict risk of residual tumor and disease upstaging.

| Tumor characteristics in first TURBT | Risk of residual tumor, OR [95% CI] | *P*-value | Risk of upstaging to muscle-invasive disease, OR [95% CI] | *P*-value | Risk of upstaging, OR [95% CI] | *P*-value |
|---|---|---|---|---|---|---|
| Tumor size (>3 cm vs. ≤3 cm) | 13.573 [3.104-59.359] | 0.001 | 17.069 [1.632-178.482] | 0.018 | 4.707 [0.990-22.379] | 0.052 |
| Tumor multifocality (Multifocal vs. Single) | - | - | 2.048 [0.285-14.736] | 0.476 | 2.508 [0.443-14.203] | 0.299 |
| muscle in the specimen (Absent vs. present) | 21.214 [6.062-74.244] | <0.001 | 6.517 [0.641-66.206] | 0.113 | 8.123 [1.478-44.632] | 0.016 |

der cancer have non-muscle-invasive disease and TURBT remains the treatment of choice in these patients. Adequate resection of bladder tumor during TURBT is of utmost importance. All macroscopic tumors with underlying muscle as well as edge of the resection area, preferably in fractions, should be removed. This allows the histopathologist to accurately stage the disease and decreases risk of understaging and inadequate treatment. Klan et al demonstrated that patients who initially had a fractionated TURBT had a reduced rate of residual tumor (36.7%) compared to patients who did not undergo resection of the tumor bed (56%)[14].

The results of the second TURBT mainly reflect the quality of initial resection. However, because of factors such as anatomic inaccessibility, tumor multiplicity, excessive tumor volume or medical instability requiring premature cessation, complete tumor removal is not always possible. Recent studies have suggested that initial TURBT may be incomplete in a significant number of cases[4,12,14,15]. Therefore, presence of residual tumor or upstaging during second TURBT could be a consequence of incomplete initial resection. Furthermore, several prognostic factors i.e. multifocality, tumor size and absence of muscle in the first resection might also impact the outcome of second TURBT. Most data on second TURBT come from studies, which did not specifically analyze aforementioned prognostic factors in the first resection which are also important.

Risk of residual disease and upstaging in second TURBT vary from 26 to 83% and 1.3 to 64% in different studies, respectively[13,16-20]. Although the term second TURBT should not be used for the repeat resection after incomplete TURBT with macroscopic residual disease, several studies addressing significance of second TURBT are retrospective with the potential of including patients with incomplete initial resection. In a series of 58 patients with G2-3 pT1 bladder cancer a rate of 74% of residual tumors in second TURBT has been reported. However, information regarding the quality of first resection was not available. In addition, muscle was not present at initial resection in about 40% of patients, questioning the quality of resection[18]. To evaluate the value of second TURBT for T1 bladder cancer, Schwaibold et al reported 52% residual disease in 136 patients who underwent second TURBT because of T1 urothelial cancer in initial resection. However, the study population consisted of relatively high-risk patients as more than 25% of patients had recurrent disease[21].

As mentioned before, Multifocality and tumor size may influence the risk of residual tumor and/or upstaging in second TURBT. In a randomized prospective study investigators performed complete and correct resection during the first TURBT and showed a rate of 33.3% of residual tumor in 105 patients who underwent re-TURBT, 2-6 weeks following primary diagnosis of T1 disease[11]. Patients with no muscle tissue in the specimen were excluded from the study. In patients with solitary tumor, they reported 22.6% and 5.7% residual mass and upstaging respectively. Also in tumors less than 3cm, the rate of residual disease and upstaging in second TURBT was 18.9% and 2.7% respectively. These results are similar to our findings and corroborate with our observations (**Table 2**). Similarly, in a prospective study, the authors reported a rate of 36.8% of residual tumor in 38 patients with single tumor versus 64.3% in patients with multifocal disease[22]. In the present study, we also noted that 25% of patients with single tumor had residual cancer in second TURBT, whereas risk of residual disease was 40% in patients with multiple tumors; however the difference was not statistically significant.

Several investigators showed that absence of detrusor muscle in initial specimen significantly increases the risk of residual disease and upstaging in second resection[17,18]. Our findings in this study support this notion. Of 73 patients with muscle in the initial resection, 6 (8.2%) had residual tumor. Of these, only 2 patients had upstaging. On the other hand, 23 of 34 patients (67.6%) without muscle at first resection had residual tumor, and upstaging occurred in 26.5% of them.

A major problem associated with TURBT is undersatging. In a retrospective study 27% of T1 tumors were upstaged after radical cystectomy (RC)[23]. Similarly, Stein reported that one-third of patients believed to have non-muscle-invasive cancer at the time of cystectomy were found to have muscle-invasive disease[24]. The risk increased to 50% in some RC series[25]. However, these findings are not attributable to all high-grade or T1 tumors in second TURBT as the majority of patients with non-muscle-invasive disease in RC cohorts may harbor poor prognostic clinical and radiological features including multiple large tumors or refractory to intravesical therapy[17].

Performing TURBT according to a "well-standardized strategy" decreases the likelihood of residual tumor and upstaging in patients with superficial disease. This issue has been confirmed in recent studies with report of 26-43% and 1.3-8.2% residual tumor and upstaging respectively [13,15,19,20,26,27]. In our study, residual tumor was also detected in 27% of patients and upstaging occurred in 10.3%. Nevertheless, present study questioned the importance of second TURBT in a subset of patients with single and small tumors (≤ 3cm), especially when muscle is present in first specimen. It should be considered that omitting second TURBT in this subgroup of patients is not equal to overlooking follow up evaluations. Actually these patients will undergo cystoscopy within 3 months after TURBT and all potential residual tumors can be detected at that time.

Limitation of this study is mainly related to the retrospective nature of the study. It comprised patients with relatively low-risk disease as 81.3% and 86% of

patients had small (≤ 3 cm) and single tumors respectively. Low incidence of disease upstaging could also be a result of clinical characteristics of the study cohort. In addition, in this multi-institutional study specimens were assessed in different pathology departments and slides were not re-reviewed for the purpose of the study. Another limitation of this cohort is the very low sample size of high-grade Ta. However, it should be considered that our finding for T1 tumors (majority of them were also high grade) can be generalized to Ta tumors. Ta tumors are probably associated with even lower risk of residual disease and upstaging in second TURBT. Finally, we couldn't assess the site of initial tumors in bladder, because it is not recorded in our data registry. Nevertheless, our study showed that Subjecting all patients with T1 and/or high-grade urothelial cancer to repeat TURBT has the potential to impose unnecessary risk and additional financial burden. Further studies are needed to identify subgroups of patients that may benefit most from second TURBT.

## CONCLUSIONS

We showed that absence of muscle in first resection can independently predict risk of upstaging and residual disease in second TURBT. According to our findings, second TURBT might be overtreatment in a significant proportion of patients with high-grade and/or T1 disease and in contrast to prior reports it does not seem to be necessary in all patients with T1 and/or high-grade tumors. We noted that second TURBT in patients with single, small T1 and/or high-grade tumors who underwent adequate initial resection is not associated with upstaging or residual disease.

## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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