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# Importance of Restaging Transurethral Resection of Bladder Tumor in High-Grade Non-Muscle Invasive Urothelial Bladder Tumor

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**Abstract** **Original Research Article**

***Objective:*** To study the importance of Restaging transurethral resection of bladder tumor (Re-TURBT) in detecting additional disease in patients with non-muscle invasive bladder tumors. ***Methods:*** A prospective study was conducted between January 2017 and March 2019 in patients diagnosed with Ta/T1 high-grade bladder cancer. Patients with non-muscle invasive high-grade bladder tumor were included. TUR of visible tumors was conducted to evaluate the bladder cancer invasion into muscular layer. Patients underwent Re-TURBT process within 6-8 weeks followed by first operation. Further, Bacillus-Calmette-Guerin (BCG) vaccination was given. ***Results:*** Among 32 patients, 19 had solitary tumors or tumors ≤3 cm in diameter and 13 had multifocal tumors or tumors >3 cm in diameter. Post cystoscopy 15 patients had visible papillary tumors, five patients had erythematous lesions/ mucosal changes suspicious of malignant lesion without visible tumors, and 12 patients had no macroscopic abnormalities. On Re-TURBT, 20 patients were detected with residual tumors and 12 with non-residual tumors. Post BCG vaccination, ten patients had recurrence with higher number of patients in residual tumor group (n=7, 70%). Four patients progressed from T1 high-grade to pT2 disease and two had multiple metastases within 24 months after BCG injection post Re-TURBT. The two-year progression-free survival rate was slightly lower for the residual tumor group than non-residual tumor group (80% vs. 100%). ***Conclusion:*** Transurethral resection is a standard treatment approach to manage non-muscle invasive bladder cancer (NMIBC) with essential repeat -TUR to attain adequate tumor resection and to identify patients requiring prompt radical cystectomy.

**Keywords:** BCG vaccination, Progression-free survival, Recurrence, Residual tumors, Re-TURBT.



## INTRODUCTION

Bladder is the most prevalent site for cancer manifestation in the genitourinary system causing an extensive morbidity and mortality. According to the International Agency for Research on Cancer, an estimated number of new cases of urinary bladder cancer in the year 2018 for Asian countries is 198,753 [1]. Males are three to four times more prone to bladder cancer due to smoking and exposure to external toxins [2]. The symptoms of bladder tumor often consist of haematuria, altered urinary symptoms and infections. The diagnostic modalities include imaging techniques, computed tomography (CT) scan, magnetic resonance imaging (MRI)), cystoscopy and biopsy.

Various advancements are taking place for management of bladder cancer with an aim to decrease mortality and improve quality of life. Majority of newly diagnosed bladder tumor patients have non-muscle invasive bladder cancer (NMIBC) of different stages; Ta, T1 and carcinoma in situ (CIS) [3, 4]. Transurethral resection of bladder tumor (TURBT) is the most preferred treatment modality by urologist over chemotherapy or immunotherapy as it aims at proper diagnosis and staging of tumor with lesion clearence [5,6]. Repeat transurethral resection (Re-TUR) is often indicated in case of stage T1 tumors within the first 4 to 6 weeks of initial resection or if high-grade tumor is identified [7]. Repeat transurethral resection of bladder tumor (Re-TURBT) includes the verification of complete tumor resection, an assessment of existence of multifocality or associated CIS and an attempt to reduce the rate of understaging. The previous literature suggests necessity of the second endoscopic procedure to ensure the absence of residual tumor before starting conservative treatment for T1 bladder tumors [8, 9].

The data from literature supports the role of Re-TUR among patients with high-risk non-invasive urothelial carcinoma. It is recommended that, Re-TUR

should be performed within 6 weeks of the initial resection, and that the strategy includes resection of the initial tumor bed as well as random or directed biopsies to assess for multifocality or CIS [10]. Although TURBT is a gold standard in treating bladder tumor, it is associated with few risks like bleeding that hinders endoscopic visualization, increased operating time, it's an intricate process hence difficult to grasp by the urologist. There is reported evidence that the TUR is often not performed to adequate standards. This has influenced some to recommend a Re-TUR, aimed at eradicating residual cancers and improving the staging of bladder cancers. Furthermore, making patients aware of Re-TURBT procedure by the urologist beforehand will be supportive and helpful to the patients. The current study aimed to demonstrate the rationale for use of Re-TUR for management of non-muscle invasive high-risk bladder tumors.

## METHODS

This was a prospective study conducted by Department of Urology, at S.C.B Medical College, Cuttack between January 2017 and March 2019 in patients with high-grade bladder cancer.

The study was conducted in accordance with the S.C.B Medical College Institutional Ethical Board guidelines and appropriate Institutional Ethical Board's approval was obtained prior to conduct of this study. Written informed consent was obtained from each patient for participation in accordance with Declaration of Helsinki.

Inclusion criteria included patients with non-muscle invasive high-grade bladder tumor. Exclusion criteria involved patients with low-grade tumors, carcinoma in situ and muscle invasive bladder tumor.

All the patients were operated by experienced surgeons. The bladder observations were made with 30° lens 17 French Cystoscope for number, location and size of bladder tumors. TUR of visible tumors was conducted to evaluate the bladder cancer invasion into muscular layer. All patients were initially diagnosed with Ta/T1 high-grade bladder cancer and underwent TURBT. Patients were further examined for presence of remnant lesions, advancement in the disease with respect to initial pathologic investigation of tissue samples. Majority of patients underwent Re-TURBT process within 6-8 weeks followed by first operation. During Re-TURBT process, formerly resected sites and area around them with inclusion of deep muscle as well as any suspicious erythematous lesion on bladder mucosa in high grade carcinoma were resected. This procedure was followed by Bacillus Calmette Guerin (BCG) vaccination. Formation and recognition of urothelial carcinoma with Ta or T1 stage was observed as relapse.

## STATISTICAL ANALYSIS

The data was statistically analysed using descriptive statistics by SPSS version 16. Qualitative data was reported as number (percentages) and quantitative data as mean (standard deviation [SD]). A p-values $< 0.05$ was considered as statistically significant.

## RESULTS

Out of 35 patients included in the study, total 32 patients underwent Re-TURBT. The mean (SD) age of the study patients was 62 (6) years with 27 men and five women. Table 1 presents the baseline characteristics and clinicopathological properties of all the patients. Among 32 patients, 19 (59.37 %) showed the presence of solitary tumors or tumors ≤3 cm in diameter and 13 (40.63 %) had multifocal tumors or tumors >3 cm in diameter.

Cystoscopy carried out at 3 to 8 weeks after the initial TURBT revealed that 15 (46%) patients had visible papillary tumors, five (16%) patients had erythematous lesions/ mucosal changes suspicious of malignant lesion without visible tumors, and 12 (38%) patients had no macroscopic abnormalities (Table 2).

On Re-TURBT, a total of 20 patients were detected with residual tumor pathologically, of which 15 patients were with visible tumor, two patients with suspicious lesions and three patients had no macroscopic abnormality respectively. Twelve patients showed presence of non-residual tumors (Table 3).

All the complications during initial TURBT and Re-TURBT were classified according to Clavein-Dindo classification (Table 4). Among 20 patients with residual tumor, five patients had upstaging of tumor, three patients were subjected to radical cystoprostatectomy, one patient lost to follow up, and one patient was subjected to chemo-radiotherapy and followed up. One patient had Tis in conjunction with T1, four patients had Ta in conjunction with primary tumor and ten patients had complete resection of their residual disease with non-muscle invasive T1 tumor. All the patients with non-muscle invasive T1 tumors and tumors with conjunction of other histological types were followed up regularly.

Patients from residual group (n=15; non-muscle invasive T1, T1 + Tis and T1 with Ta) as well as non-residual group (n=12) on Re-TURBT were treated with BCG intravesical immunotherapy according to Southwest Oncology Group (SWOG) protocol (a single 6-week induction course of BCG followed by maintenance BCG cycles [administered as 3 weeks of therapy at 3 months, 6 months, and then every 6 months for 3 years]) [11, 12]. Out of these 27 patients, 17 remained disease free during the course of study period and ten had recurrence at different time intervals during follow up (seven patients: within the

first year and three patients: at 14 to 17 months). Median time to recurrence was 10 months (range: 6-17 months). Proportion of patients with recurrence was higher in residual tumor group (70%, n=7) than non-residual tumor group (30%, n=3). The recurrence rate was also higher in residual tumor group than non-residual group (75% vs. 65%, respectively). Among 10 patients with recurrence, 40% progressed from T1 high-grade to pT2 with recurrence within 24 months after BCG injection post Re-TURBT. The progression-free survival rate at 24 months for the residual tumor group was 80%, whereas for the non-residual tumor group, it was 100%.

**Table-1: Baseline characteristics**

| Characteristics | Number of patients (n=32) |
|---|---|
| **Age (years), mean (SD)** | 62 (6) |
| **Gender** | |
| Men | 27 (84.37) |
| Women | 5 (15.62) |
| **Macroscopic appearance** | |
| **Solitary (≤3 cm diameter)** | 19 (59.37) |
| Residual | 7 (36.84) |
| Non-residual | 12 (63.15) |
| **Multifocal (>3 cm diameter)** | 13 (40.63) |
| Residual | 10 (76.92) |
| Non- residual | 3 (23.07) |
| Data shown as n (%), unless otherwise specified. | |

**Table-2: Cystoscopy performed after 3-8 weeks of initial TURBT**

| Pathological conditions | Number of patients (n=32) |
|---|---|
| Visible papillary tumors | 15 (46) |
| Erythematous lesions | 5 (16) |
| No macroscopic abnormalities | 12 (38) |
| Data shown as n (%). | |

**Table -3: Number of cases with residual disease at second stage TURBT**

| Pathological conditions | Residual tumor (n=20) | Non residual tumor (n=12) |
|---|---|---|
| Macroscopic lesions | 3 (15) | 9 (75) |
| Mucosal changes | 2 (10) | 3 (25) |
| Visible tumors | 15 (75) | 0 (0) |
| Data shown as n (%). | | |

**Table-4: Clavein-Dindo classification system**

| Parameters | Number of patients (n=32) |
|---|---|
| **CCS grade with pathology** | |
| Grade 1 | |
| Fever | 6 (18.75) |
| Transient haematuria | 12 (37.5) |
| Grade 2 | |
| EP bladder rupture | 1 (3.13) |
| Grade 3 | |
| Clot retention | 4 (12.5) |
| Grade 5 | |
| Death | 0 (0) |
| Data shown as n (%).<br>CCS, Clavien–Dindo classification system; EP, extraperitoneal. | |

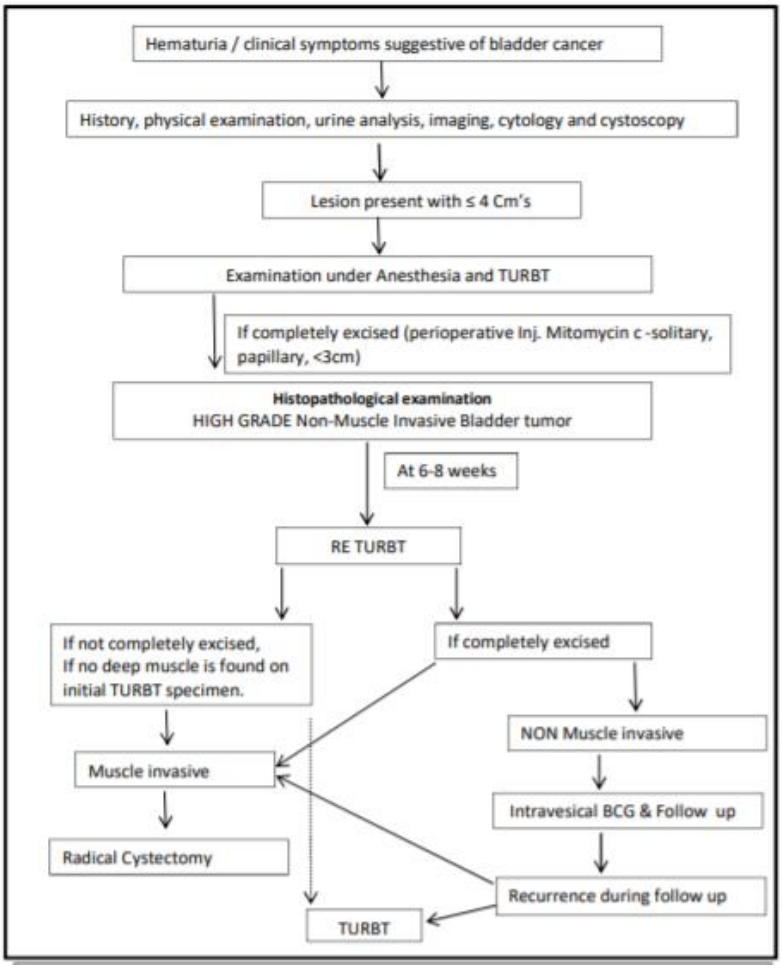


**Fig-1: Methodology followed in management of Non muscle invasive bladder tumors**

BCG, Bacillus Calmette Guerin; RE TURBT, restaging transurethral resection of bladder tumor

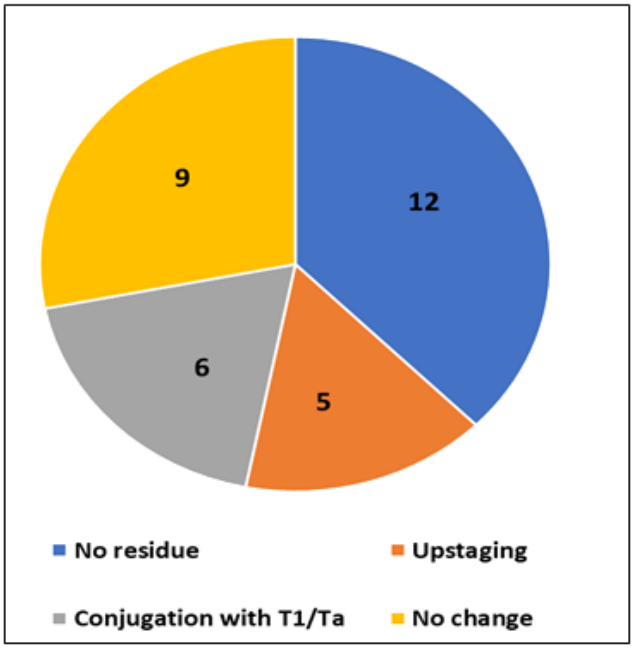


**Fig-2: Number of Patients with upstaging and conjunction with T1/Ta**

## DISCUSSION

In circumstances where high-grade tumors like T1 are involved having greater risk of progression and death, TUR alone is inefficient whereas Ta tumors are less prone to progression, around 5% reported [13, 14]. TURBT that is performed under local or general anaesthesia is the first line of treatment to eliminate all visible tumors and determine precisely the stage and grade of tumors. TUR is indicated in circumstances such as excessive tumor volume, anatomic unapproachability, and medical instability necessitating premature termination or perforation. Albeit, absence of these circumstances may also require repeat TUR if high-grade tumor is recognized. A previous study by Vasdev *et al*. reported that in almost 40% of patients with pT1 high-grade NMIBC, recurrence of tumor was identified after several days or weeks at site of initial resection [15]. Previous studies have also demonstrated necessity of thorough TUR and Re-TURBT in Ta high-grade tumor, as proper histopathologic staging is crucial for therapy planning and corresponding instillation therapy is more effective [16, 17].

In this study, residual tumor was detected in 62% patients and 25% patients displayed absence of macroscopically visible tumors by endoscopic examination but exhibited residual tumor on the second TURBT. These observations support the evidence that cystoscopy is not sufficient to find remnant lesions. Previous studies have reported presence of residual tumors after second TURBT in 33.8-61% of patients [14, 15, 18]. Another finding from this study revealed that 33% of patients with stage T1 disease containing muscularis propria in the specimen were upstaged to T2.

Whereas, a study by Herr *et al*. reported 25% of patients who were upstaged to T2 if no muscular layer existed in the resected tissue [19]. Furthermore, Dutta et al. reported a higher rate of under staging in T1 tumors in absence of muscularis propria than in their presence (64% vs. 30%) [21]. The present study could not find a definite relationship depending upon muscle inclusion, which may have been due to that large portion of specimens containing muscular layer after the first TURBT.

Consensus does not exist regarding the technique for the repeat resection. However, it is conceded that the repeat TURBT procedure should be performed at the original site involving the muscularis propria. Rotating the resection loop, can easily control the tissue depth of resection by using the lateral resecting portion of the conventional right-angle loop electrode [3]. Random biopsy was not performed since it rarely results in the identification of additional neoplasms and may result in tumor seeding [21, 22].

Second resection is rather tough to perform or accept since it is unknown beforehand, whether residual disease exists in the bladder. However, recent data support the necessity of a second TURBT for bladder cancer, especially in T1 high-grade disease, and several guidelines reflect these findings [7, 14, 23-26]. The risk of residual tumors is higher with high-grade lesions and multiple sites and appears to be elevated with the pathologic stage of the initial lesion. A clinical trial performed by the Nordic Association of Urology in which about 40% of patients with T1 bladder tumors had remnant disease after an initial resection confirmed this fact [25]. However, in the present study 63% of patients had remnant disease.

In this study, 37% patients exhibited recurrence under regular follow up. The median time for recurrence was 10 months. Recurrences appeared predominantly higher in residual cancer than in non-residual cancer group (70% vs. 30%). Previous studies also reported recurrence rates between 34 to 40% in patients with high-grade T1 bladder cancer [27-29]. These observations concord with the present study. Progression was observed in 15% of patients under regular follow up within 24 months after injection of BCG treatment after Re-TURBT. Four patients progressed from T1 high-grade to pT2 disease and there were multiple metastases in two patients; all of these patients had residual cancer after their initial TURBT. The past literature demonstrated progression rates in the range of 4% to 25% post Re-TURBT [16, 27-29].

To enhance residual tumor detection, a second TURBT was performed after 3 to 8 weeks in accordance with the clinical guidelines [30, 31]. The latest version of the European Association of Urology guidelines recommends a second TUR if the initial resection was incomplete (multiple lesions or large tumors or no muscularis propria in the sample) [32]. Also, a repeat TUR should be recommended when a high-grade, non–muscle invasive tumor or a T1 tumor is detected in the first TUR [25, 33, 34]. However, existing data suggests failure of second TURBT procedure for detecting infiltrative tumors for most cases because they undergo radical cystectomy [34, 35].

Despite the preceding arguments, the value of a second TURBT procedure is considerable. The remnant tumor, which might be the source of the recurrent lesion, can be respected by a second TURBT. Additionally, the tumor burden will be decreased, and this could reduce the frequency of tumor recurrence and delay early progression. In many cases, the second TURBT may be the only method to reveal the “real” tumor burden, the existence of muscle invasive lesions, or extensive T1 high-grade tumor, all of which could lead to a change in the eventual treatment strategy. In our analysis, muscularis propria invasion was established at the second TURBT in 15.6% of cases diagnosed with T1 bladder cancer at the initial operation, in accordance with the results of previous trials [25, 26, 33].

Limitations of the present study include small sample size and short follow up period. However, study population included patients with T1 high-grade bladder cancer, incidence of which is known to be very low i.e. 3% to 4%. Moreover, the second TURBT procedure was performed prospectively by the same operator in this study. This makes it clear that a second TURBT is necessary, especially for patients with T1 high-grade bladder cancer.

## CONCLUSION

In the current study, recurrence rate was significantly higher in residual tumor patients than non-residual tumor patients post Re-TURBT. Two-year progression-free survival rates were slightly higher in non-residual patients. Therefore, Re-TURBT is a suitable means of detecting and staging of residual tumors that can help to manage high-grade NMIBC efficiently.

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