

## Clinical Assessment of the Utility of Restage Transurethral Resection of Bladder Tumor (reTURBT)

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### Abstract

Transurethral resection of bladder tumors (TURBT) is the first step in the initial management of bladder cancer. A TURBT is both diagnostic and therapeutic, and the procedure provides critical staging information. In a TURBT, the configuration (flat, sessile, or papillary), location (trigone, base, dome, or lateral walls), size (cm), and the number of tumors should be recorded. Tumors should be completely resected if they are small, solitary, and available for resection, and also other than superficial appearing low-grade tumors, muscularis propria must be included in the specimen to ensure adequate resection. Management might include directed bladder biopsies of abnormal-appearing urothelium or biopsies of the prostatic urethra. Biopsy or resection of the prostatic urethra should also be considered if the patient has tumor at the bladder neck or if the tumor is within the prostatic urethra. Based on above findings the present study was planned to evaluate the clinical assessment of the utility of restage transurethral resection of bladder tumor (rTURBT). The present study was planned in the Department of Urology Hanuman Hospital, Bhavnagar, Gujarat and Kurji Holy Family Hospital, Patna, Bihar, India. The study was performed from the May 2016 to Dec 2019. Total 30 cases of the proven histological diagnosis of nonmuscle invasive urothelial cancer with either high grade or T1 cancers on histopathology were enrolled in the present study. The data generated from the present study concludes that TURBT is necessary in patients with solid bladder tumors. The presence of tumor at restage confers a higher risk of recurrence and progression. Poor patient compliance for a restage TURBT remains a matter of concern.

**Keywords:** Turbt, reTURBT, Restage Transurethral Resection of Bladder Tumor, Bihar region, etc.

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### Introduction

Transurethral resection of bladder tumor (TURBT), performed endoscopically, is the first-line procedure for diagnosis, staging, and treatment of visible tumors. In select patients, office-based fulguration of small tumors allows control of low-risk bladder lesions without incurring the cost and inefficiencies of the operating room. [1] More than 70% of bladder tumors are non-muscle-invasive bladder cancer (NMIBC). TURBT is the main procedure for the diagnosis and treatment of NMIBC, yielding 62% long-term overall survival in patients with well-differentiated (G1) and moderately well differentiated (G2) grade Ta tumors. [2] TURBT is not effective

for carcinoma in situ (CIS) because the disease is often so diffuse and difficult to visualize that surgical removal is not feasible. Therefore, the role of cystoscopy in these cases is to establish the diagnosis so that therapy can be instituted. Obvious areas of CIS may also be fulgurated, but the benefits of this have not been proven. When a combination of papillary tumor and CIS is present, the papillary tumor is removed before treatment of the CIS is initiated.

Patients scheduled for cystoscopy or anesthetic cystoscopy with transurethral resection of bladder tumor (TURBT) must have sterile urine documented prior to instrumentation. Sterility is usually presumed on the basis of a microscopic urinalysis showing no bacteria or white blood cells (WBCs). A urine culture is ideal but not always feasible for surveillance cystoscopy. The risk of urinary tract infection with instrumentation is approximately 1%. In the past, a single prophylactic dose of fluoroquinolone was given to patients undergoing cystoscopy. However, American Urological Association guidelines recommend

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considering an antibiotic from a different class, on a case-by-case basis, in view of the 2016 US Food & Drug Administration (FDA) black box warning on safety issues with fluoroquinolones. In addition, the guidelines suggest considering whether low-risk patients require any antibiotics prior to routine cystoscopy. [3]

A review of a zero antimicrobial prophylaxis protocol for outpatient cystoscopy concluded that it is safe and can be effective. The incidence of UTI after cystoscopy rose slightly when the protocol was implemented (from 2.9% to 3.7%), but the difference was not statistically significant. Catheter use (indwelling, suprapubic, or intermittent) was the only risk factor identified for post-cystoscopy infection. [4] Some patients may need additional antibiotics based on a history of valvular heart disease. The American Heart Association guidelines recommend prophylaxis in these patients to prevent endocarditis. In moderate-risk patients, administer 2 g of ampicillin intravenously or intramuscularly at least 30 minutes before the procedure (or 2 g of amoxicillin orally at least 1 h before the procedure). In patients allergic to penicillin, vancomycin at a dosage of 1 g intravenously over 1-2 hours, completed at least 30 minutes before the procedure, may be substituted. High-risk patients also receive 120 mg of gentamicin parenterally 30 minutes before the procedure, then a second dose of ampicillin or amoxicillin 6 hours later. Patients with prosthetics may merit additional antibiotics based on the clinical scenario.

General or regional anesthesia can be used. Complete eradication of tumor is the first step of transurethral resection of bladder tumor (TURBT). Most tumors are papillary and are easily removed by endoscopically transecting their narrow stalk or base. Following this, biopsy of the base is performed to ensure complete removal and the absence of invasion. Muscle tissue (or fat) must be present in the base biopsy specimen to ensure accurate staging. Medium and large tumors are resected piecemeal prior to transection of the stalk. This ensures that large segments do not remain that might be too large to evacuate through the resectoscope.

Smaller and more friable tumors may be removed at least partially by knocking off fragments with the cutting loop of the resectoscope without the electricity turned on. This sometimes allows partial removal with less risk of bladder perforation. Pulling the cutting loop away from the tumor is generally much safer than pushing it toward the tumor. Lifting the tumor away from the surrounding normal bladder tissue using the cutting loop is also advisable. Continuous-irrigation

resectoscopes concern some surgeons regarding fluid absorption. However, continuous infusion lessens the bladder wall movement that occurs during filling and emptying and thereby may decrease the risk of bladder perforation. Overfilling also stretches and thins the detrusor, which is another risk factor.

Transurethral resection (TUR) syndrome due to fluid absorption is uncommon unless the tumor being resected is particularly large. If this is a concern, glycine prevents hemolysis, but not hyponatremia. Overuse of cautery at the base of the tumor increases cautery artifact, which can complicate pathological determination of muscle invasion status.

Traditionally, TURBT was performed using monopolar electrocautery to provide the necessary energy for resecting the tumor and cauterizing blood vessels. More recently, as bipolar technology has emerged and improved, its application has extended to TURBT, with a potential benefit of decreased risk of bladder perforation from obturator reflex and decreased risk of TUR syndrome. With bipolar technology, the active and return electrodes are very close together on the loop so that the current does not travel through the patient's body to an external pad, as is the case with monopolar cautery. This also allows for the use of nonconductive isotonic irrigation fluid, mitigating the aforementioned risks of TUR syndrome. [5]

Wang and colleagues were the first to report on bipolar TURBT and compared the pathologic specimens from 11 patients who underwent bipolar TURBT with a matched historic cohort of 11 patients who underwent standard monopolar TURBT. [6] No differences in the degree of cautery artifact were noted between the 2 groups, and a full and proper diagnosis was achieved in all cases when assessed by a single pathologist who was blinded to the form of electrocautery used.

Yang and associates retrospectively compared clinical and pathologic results in 115 patients who underwent bipolar (n=64) versus monopolar (n=51) TURBT. [7] Postoperative change in hemoglobin (-0.58±0.91 g/dL vs -0.95±1.28 g/dL, P =.038) and mean duration of catheterization (2.20±0.96 d vs 2.65±1.45 d, P =.026) favored the bipolar TURBT group. No difference in the grade of thermal damage was noted between the 2 groups as well. Furthermore, reducing the power settings to 50-W cutting and 40-W coagulation may reduce the incidence of obturator nerve reflex and bladder perforation to close to zero while still maintaining diagnostic and therapeutic efficacy. [8]

Photodynamic diagnosis (PDD) has emerged as a viable adjunct to white-light (WL) cystoscopy to assist in the performance of a complete TURBT. [9] Lesions can be missed using WL cystoscopy, and PDD has

been developed to assist in the detection of these lesions, reduce the rate of recurrence, and improve the completeness of resection. PDD exploits the photodynamic properties of several compounds, including hexaminolevulinate (HAL) (Hexvix, Cysview, Photocure; Oslo, Norway) and 5-aminolevulinic acid (5-ALA).

Approximately 1 hour prior to planned TURBT, 50 mL of reconstituted solution of HAL is instilled into the emptied bladder via an intravesical catheter. Following instillation, protoporphyrin IX accumulates preferentially in neoplastic tissue, producing a clearly demarcated red fluorescence with illumination with blue-violet light (380-440 nm). Cysview (HAL hydrochloride) was approved by the United States Food and Drug Administration in 2010 for use with the Karl Storz D-Light C PDD system with the blue-light (BL) setting as an adjunct to the WL setting in the detection of nonmuscle invasive papillary cancer of the bladder in patients suspected or known to have lesions on the basis of a prior cystoscopy.

A recent meta-analysis reviewed the raw data from prospective studies on 1,345 patients with known or suspected nonmuscle invasive bladder cancer on whom HAL and BL as an adjunct to WL cystoscopy. [10] HAL BL cystoscopy detected significantly more Ta tumors (14.7%;  $P < .001$ ) and CIS lesions (40.8%;  $P < .001$ ) than WL cystoscopy. Furthermore, recurrence rates up to 12 months were significantly lower overall with BL HAL versus WL cystoscopy (34.5% vs 45.4%;  $P = .006$ ).

The European Association of Urology 2013 guidelines on nonmuscle invasive bladder cancer recommend PDD in patients who are suspected of harboring a high-grade tumor for guidance of TURBT. It is possible that BL HAL-assisted TURBT improves completeness and quality of resection and might obviate the need for perioperative intravesical instillation of chemotherapy or a second TURBT, but further study is needed in this area to test this hypothesis.

While 5-ALA is not currently approved for routine clinical use for the detection of bladder cancer in Europe or the United States, it has been extensively studied in numerous clinical trials. Furthermore, orally applied 5-ALA has been approved in Europe to enhance intraoperative detection of malignant glioma. Inoue et al evaluated the clinical value of PDD with intravesical ( $n=75$ ) and oral ( $n=135$ ) instillation of 5-ALA and PDD-guided TURBT for nonmuscle invasive bladder cancer in a multi-institutional retrospective study in 210 patients. [11] Rates of recurrence were compared with historical controls subjects who underwent TURBT with WL cystoscopy. 5-ALA-

guided TURBT improved detection of CIS, as 72.1% of flat lesions (including dysplasia and CIS) could only be detected with BL 5-ALA-assisted TURBT. The route of administration of 5-ALA (oral vs intravesical) did not affect diagnostic accuracy or recurrence-free survival.

The management of nonmuscle invasive bladder cancer is expensive, stemming from high recurrence rates necessitating repeat TURBT and frequent surveillance cystoscopies. As HAL and 5-ALA have been shown to help increase the detection and reduce the recurrence of nonmuscle invasive bladder cancer, this technology may reduce the cost of bladder cancer management. Garfield et al assessed the cost effectiveness of BL HAL-assisted cystoscopy as an adjunct to WL cystoscopy versus WL cystoscopy alone at the time of initial TURBT and noted a cost savings of nearly \$5,000 in the PDD group in their model over a 5-year projected period. [12-13]

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#### Methodology:

The present study was planned in the Department of Urology, Hanumant Hospital, Bhavnagar, Gujarat and Kurji Holy Family Hospital, Patna, Bihar, India. The study was performed from the May 2016 to Dec 2019. Total 30 cases of the proven histological diagnosis of nonmuscle invasive urothelial cancer with either high grade or T1 cancers on histopathology were enrolled in the present study.

During initial cystoscopy, the operative details such as the number of lesions, solid or papillary configuration of lesions and the site of lesions were mapped and recorded. TURBT at our center was performed using a

26 Fr resectoscope and monopolar cautery (settings 70 for pure cutting and 30 for coagulation on fulguration mode). After complete TURBT, a deep biopsy from the base of the tumor was taken. The TURBT chips and the deep biopsy were sent separately. The data of patients in which TURBT was performed at a peripheral center was retrieved from the operative notes and those with incomplete data were excluded. Restage TURBT was advised at 4–6 weeks from initial TURBT as per the EAU guidelines. The cystoscopic findings were recorded during the restage TURBT similar to that at the initial TURBT. In patients with no obvious tumors, resection of the tumor bed was performed and sent for analysis. The histopathology reports of all patients were recorded. Post restage, the patients were then managed by a standard treatment protocol and follow-up.

All the patients were informed and consents taken. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

### Results & Discussion

TURBT is performed to confirm the diagnosis and determine the extent of disease within the bladder. The standard treatment for Ta, T1, and Tis disease is TURBT, and NCCN guidelines strongly suggest second-look TURBT for T1 tumor during the initial TURBT.[15]

As there are controversies regarding indications for reTURBT, we intended to compare significance of particular indications and evaluate them as the predictors of residual disease. Moreover, little is known about the safety of reTURBT, which we intended to analyze as a secondary study aim. Considerably high rate (40.2%) of residual tumor was found in reTURBT, which is consistent with the findings from some previously published studies [16-18].

The strategy of reTURBT remains under the debate. Kamat directly calls it a failure of urological technique, which by definition assumes the risk of incompleteness [19]. Also, the indications for reTURBT are not clear and vary between institutions and authorities. Expert panel of the European Association of Urology recommends reTURBT in patients with T1 tumors, high-grade cancer, if there is no muscle layer in the specimen and after incomplete initial TURBT [20]. However, the evidence behind this recommendation is not consistent. In the recent update of EAU guidelines, lack of muscle in specimen without evidence of T1 or HG has been questioned as indication to restaging resection in recurrent tumors. Since this retrospective study was based on patients treated before this update, we decided not to remove pTx(a)LG patients from analysis. Noteworthy, although no restaging to MIBC was recorded in this group, residual disease was found in 2 patients. These findings emphasize that even in low-risk tumors, surveillance on resection completeness is of primary importance.

**Table 1: Characteristics of Patients Undergone restage Transurethral resection of bladder tumor (TURBT)**

Characteristic Value	No. of Cases
Total number of patients	30
Age (year)	34 – 67
Gender (%)	
Male	22
Female	08
Interval between TURBT (weeks),	4 – 10
Muscle layer presence in initial TURBT specimen (%)	
Included	24
Not included	4
Not mentioned	2
Grade:	
High grade	19
Low grade	11
Morphology of tumor:	
Papillary	26
Solid	4
Number of tumors:	

Single	18
Multiple	12
Size of tumor (cm) :	
<3	21
>3	9
Place of initial TURBT:	
Operated parent hospital	22
Operated in a different hospital	8

Herr et al. published the largest repeat TURBT series, summarizing unpublished data on routine repeat TUR and including 1,312 patients with NMIBC [21]. They found residual disease in 51%–78% of patients, with the highest rate in the group with T1 disease at initial TUR. The natural history of the residual tumors after TURBT is not yet clear. However, a few studies have reported that the presence of residual tumors is a potential risk factor for disease recurrence and poor prognosis [22-23].

Grims et al. demonstrated that tumor stage and grade at initial TURBT predicted residual tumor after re-TUR in their univariate analysis, but our multivariate analysis results differ somewhat. Tumor multiplicity and grade and concomitant CIS were revealed as risk factors for residual tumors after re-TURBT in our study, but initial T stage was not a significant predictor of these residual tumors. This difference may be because most of the patients who underwent re-TURBT in this study were at the initial T1 stage.

It was notable that the presence of residual tumors on re-TURBT was associated with higher risks of tumor recurrence compared with patients who had no tumors on re-TURBT. Similar results were reported in a previous study in which tumor-free status at re-TURBT was associated with fewer tumor recurrences and longer times to recurrence [24]. A retrospective study also reported that 83% of patients with residual tumors on re-TURBT developed recurrence compared with 39% of patients at stage T0 [25].

Few studies have analyzed re-TURBT pathology findings as prognosis risk factors; as mentioned above, most studies on re-TURBT in bladder cancer have focused on the stage migration and presence of the residual tumors. In this study, both the tumor pathology and the residual tumor status after re-TURBT were also associated with recurrence; in univariate analysis, stage T1 and high tumor grade in re-TURBT were significantly associated with residual tumor recurrence, and stage T1 in re-TURBT was still statistically significant in multivariate analysis

There were some limitations in our study. First, the fact that this was a retrospective study with a small sample

population is the most important limitation that could have introduced bias. Second, in our study, the indication for second-look TURBT depended on the surgeons' intraoperative finding and experience. Therefore, the association between the interval from initial to second-look TURBT and tumor outcomes, such as recurrence, progression, or survival, should be investigated in the future. Third, the percentage of patients that accepted second-look TURBT in the group of patients diagnosed with T1 urothelial carcinoma increased year by year.

### Conclusion

The data generated from the present study concludes that TURBT is necessary in patients with solid bladder tumors. The presence of tumor at restage confers a higher risk of recurrence and progression. Poor patient compliance for a restage TURBT remains a matter of concern.

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