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Original research article

A prospective observational study to evaluate the utility of restages transurethral resection of bladder tumor

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Abstract

Aim: The aim of the present study to evaluate the utility of restages transurethral resection of bladder tumor.

Methods: This was a prospective observational study conducted in the Department of urology, IGIMS Patna, Bihar, India, for 1 year.

All patients with proven histological diagnosis of non-muscle invasive urothelial cancer with either high grade or T1 cancers on histopathology were enrolled. 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. After complete TURBT, a deep biopsy from the base of the tumor was taken. The TURBT chips and the deep biopsy were sent separately. 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.

Results: 100 patients satisfied the inclusion criteria as per EAU guidelines for restage (T1 or high grade). 52 had T1 high grade, 48 patients had T1 low grade. A total of 100 patients underwent restage TURBT, 70 patients within 4–6 weeks, and 30 patients between 6 to 12 weeks of the initial TURBT. The mean age of the 100 patients was 54 years (range 18–79 years) and 20(20%) of them were females. Tumor was detected in 30 patients (30%) during restage TURBT, of which 25 patients had non invasive disease. The stage distribution after restage TURBT. Of these 25 patients, tumor was present at the same site in 22 patients (88%) and at different site in 3 patients (12%). All the tumors were <3 cm in size, 19 (76%) had single lesion and 6 patients (24%) had multiple growths. In 18 patients (72%) the recurrence was of same stage (T1), in 7 (28%) it was of lower stage (Ta) and stage up-migration to muscle invasive disease (T2) was found in 6 cases (24%).

Conclusion: The restage 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: bladder tumors, resection, risk

Introduction

Bladder cancer, the seventh most common cancer in the world[1], is highly prevalent in the United States, Europe, and Egypt. More than 400,000 people are diagnosed every year worldwide.[2] Approximately 75–85% of bladder cancer patients have non muscle invasive bladder cancer, for which transurethral resection of bladder tumor (TURBT) is the standard

treatment.[3] As with any cancer, staging accuracy is important because treatment can vary depending on pathology results. Stage is determined by histology, grade, and invasion depth. Depending on stage, treatment methods such as TURBT, intravesical Bacillus Calmette–Guerin vaccine, ´ chemo agent instillation, and radical cystectomy are used.[4] Staging can be determined through TURBT; however, the accuracy is not always precise since tumors might not be immediately visible under the mucosa.[5] In cases of such invisible tumors, exact extent and depth cannot be precisely determined. Therefore, there is a risk of upstaging and residual cancer when repeat TURBT is performed. Many previous studies have discussed the importance of repeat TURBT for this reason. In cases of incomplete initial TURBT, no muscle in the specimen afer the initial resection (with the exception of TaG1 tumors and primary carcinoma in situ [CIS]), all T1 tumors, and all HG/G3 tumors (except primary CIS), Te European Association of Urology (EAU) guideline recommends repeat TURBT.[4] Most previous studies were the results of repeat TURBT afer initial TURB in the same hospital.[6-8] 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.

Material and methods

This was a prospective observational study conducted in the Department of urology, IGIMS Patna, Bihar, India, India for 1 year, after taking the approval of the protocol review committee and institutional ethics committee. The technique, risks, benefits, results and associated complications of the procedure were discussed with all patients.

Methodology

All patients with proven histological diagnosis of nonmuscle invasive urothelial cancer with either high grade or T1 cancers on histopathology were enrolled. 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 . 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. The complications of restage TURBT and recurrences and progression were recorded in the follow-up. The follow-up data of patients who could not undergo restage was maintained and analyzed separately.

Statistical analysis

The analysis was conducted using IBM SPSS STATISTICS (version 21.0,). Continuous data was evaluated in mean, median, standard deviation, and categorical data in percentages. Paired *t*-test and unpaired *t*-test were applied for dependent and independent data variables of parametric data, respectively, and Wilcoxon signed rank test was applied to compare the nonparametric data. Statistical significance was defined as $P < 0.05$.

Results

100 patients satisfied the inclusion criteria as per EAU guidelines for restage (T1 or high grade). 52 had T1 high grade, 48 patients had T1 low grade. A total of 100 patients underwent restage TURBT, 70 patients within 4–6 weeks, and 30 patients between 6 to 12 weeks of the initial TURBT. The mean age of the 100 patients was 54 years (range 18–79 years) and 20(20%) of them were females. The findings of initial TURBT and patient characteristics were shown in table 1.

Table 1: Primary characteristics of patients who underwent restage transurethral resection of bladder tumor

Characteristic	**Number**	**Percentage**
Total number of patients	100	100
Age	54(18-79)	
Gender		
Male	80	80
Female	20	20
Interval between TURBT(weeks), mean (range)	4.75(2-13)	
Muscle layer presence in initial TURBT specimen		
Included	60	60
Non included	36	36
Not mentioned	4	4
Grade		
high grade	52	52
low grade	48	48
Morphology of tumor		
Papillary	83	83
Solid	17	17
Number of tumors		
Single	45	45
Multiple	55	55

Size of tumor (cm)		
>3 cm	60	60
> 3 cm	40	40
Place of initial TURBT		
Operated parent hospital	70	70
Operated in a different hospital	30	30

Primary outcomes

Tumor was detected in 30 patients (30%) during restage TURBT, of which 25 patients had non-invasive disease. The stage distribution after restage TURBT. Of these 25 patients, tumor was present at the same site in 22 patients (88%) and at different site in 3 patients (12%). All the tumors were <3 cm in size, 19 (76%) had single lesion and 6 patients (24%) had multiple growths. In 18 patients (72%) the recurrence was of same stage (T1), in 7 (28%) it was of lower stage (Ta) and stage up-migration to muscle invasive disease (T2) was found in 6 cases (24%). In these five who had muscle invasive disease, deep muscle was not seen at the initial TURBT specimen in only 1 case.

Secondary outcomes

We assessed various tumor characteristics of the primary TURBT which could preict presence of tumor at restage. Patients with solid growths at the initial TURBT had a significant chance of the presence of tumor at restage TURBT (P = 0.01) as compared to those with papillary growths. Other features such as presence of multiple growths versus single growth, size less than versus > 3 cm, TURBT performed at peripheral center versus in the institute were comparable. Histopathological features of the primary TURBT, such as grade and presence or absence of deep muscle at the initial TURBT did not have any significant association with presence of tumor at restage [Table 2].

Table 2: Analysis of factors affecting tumor positivity in restage transurethral resection of bladder tumor

Characteristic	**Tumor positivity in restage TURBT**	p-value
Size of tumor (cm)		
>3 cm	20/65(30.77%)	0.502
> 3 cm	13/35 (37.14%)	
Type of growth		
Papillary	21/80 (26.25%)	0.029
Solid	12/20 (60%)	
Number of growth		
Single	12/45 (26.67%)	0.288
Multiple	24/55 (43.64%)	
Grade		
high grade	15/47 (31.91%)	0.423
low grade	16/53 (30.19%)	
Muscle status		

Included	21/63 (33.33%)	0.359
Non included	10/27 (37.04%)	
Place of initial TURBT		
Parent hospital	20/70 (28.57 %)	0.287
outside hospital	13/30 (43.33%)	
Recurrence rate		
Tumor present on restage	8/31 (25.81%)	0.026
No tumor on restage	7/69 (10.14%)	
Progression rate		
Tumor present on restage	6/31 (19.35%)	0.08
No tumor on restage	2/69 (2.89%)	
Recurrence rate		
Restage TURBT Performed	14/84 (16.67 %)	0.033
Restage TURBT not Performed	7/16 (43.75%)	
Progression rate		
Restage TURBT Performed	8/84 (9.52 %)	0.89
Restage TURBT not Performed	2/16 (12.5%)	

Of these 100 patients, 31 patients had tumor at restage and 69 did not. 14 out of 100 patients (16.67%) had tumor recurrence during the follow-up and he mean recurrence period was 3.4 months (range 1–6 months). Of these 14 recurrences, 8 patients had tumor at restage and 7 did not. 8 out of 100 patients (8%) had progression of the disease (4 had the grade up-migration and four had upstaging). Out of 8 progressions, 6 patients had tumor on restage and 2 did not. The recurrence and progression rates of those who had tumor at restage TURBT were 14/31 (45.16%) and 8/31 (25.81%) respectively, whereas they were 7/69 (10.14%) and 2/69 (2.89%) respectively for those who did not have tumor. There was statistically significant difference in recurrence and progression between two groups [$P = 0.026$ and 0.08 respectively table 2. There was a significant difference in the recurrence rate (P value = 0.033) but not in the progression rate (P value = 0.89) between those who had undergone restage TURBT and those who did not.

Overall 12% of patients had one or more complications. None of the patients had major complications such as bladder perforation or severe bleeding requiring re-interventions. Few patients had minor complications related to spinal anesthesia in the form of postspinal headache.

Discussion

Managing T1 lesions and high-grade lesions by a single TURBT is challenging. Guidelines state that restage TURBT is essential because of high risk of recurrence and progression. Restage TURBT has shown to be effective in staging the disease appropriately and thereby prognosticating it better. It also has shown that by early detection and resection of residual tumor restage TURBT reduces the risk of recurrence and progression. In an Indian setup, where the resources are limited compared to the patient population, there is always a dilemma regarding this second surgery. At times, it is very difficult to convince a patient to undergo second surgery when he is symptom free. It is an economic burden to him as well as adds to

the health care costs of the nation. Hence, the question is whether restaging is necessary or is beneficial? And which patients will benefit from such an intervention the most.
The oncological benefit has been clearly shown in our study. Tumor was detected in 30 patients (30%) during restage TURBT, of which 25 patients had noninvasive disease. The stage distribution after restage TURBT. Of these 25 patients, tumor was present at the same site in 22 patients (88%) and at different site in 3 patients (12%). All the tumors were <3 cm in size, 19 (76%) had single lesion and 6 patients (24%) had multiple growths. In 18 patients (72%) the recurrence was of same stage (T1), in 7 (28%) it was of lower stage (Ta) and stage upmigration to muscle invasive disease (T2) was found in 6 cases (24%). In these five who had muscle invasive disease, deep muscle was not seen at the initial TURBT specimen in only 1 case.

This is in accordance to already published literature wherein about one-third of patients would have residual disease detected on restage. The presence of muscle in the specimen of initial TURBT decreases the residual tumor rate at the second TUR.[11] In a study by Herr et al,[12] patients who did not have muscle in the initial TURBT had higher chances of having a residual tumor at restage sa compared to those who had muscle layer (49% vs. 14%). In our study, the presence of muscle specimen in the initial TURBT did not significantly affect the tumor presence on restage TURBT (33.33% vs. 37.4%, $P = 0.359$). These findings defy the common notion that restage TURBT has no value if muscle was included in the specimen. None of the patients had major complications such as bladder perforation or severe bleeding. Thus, restaging seems essential and safe. We can extrapolate these findings to all kinds of population and conclude that restaging is beneficial even in the developing countries.
The second question is what features at the initial TURBT predict the presence of tumor at restage thus making restage TURBT mandatory. Only the presence of a solid tumor growth at initial TURBT was associated with higher chances of finding a tumor at restage (60% vs. 26.25%, $P = 0.029$). Characteristics such as grade of the tumor and the size of the tumor did not significantly affect the outcomes of restage surgery. Similar observations about the number of tumors was made in another study performed at CMC Vellore,[13] where they identified solitary papillary lesions as a subgroup where second TUR is avoidable. We believe that restage could be specifically targeted to patients with these findings on initial CPE, thereby avoiding unnecessary surgeries and reducing health care costs.
Logically, the quality of initial TURBT should affect the residual tumor rates. Ark *et al*.[14] compared the incidence of under-staging when the initial TURBT was performed at their institute versus at an outside hospital. However, there was no statistically significant difference in under-staging based on the place of initial TURBT (28.57% vs. 43.33%). We also did not find significant difference between those who had undergone initial TURBT in our institute or elsewhere. Thus, even when the initial TURBT is performed in other hospitals, the incidence of tumor at restage may be low when a careful complete resection is performed.

Third to addresses the question that does restaging TURBT helps in reducing the disease progression? We followed up these patients for recurrence and progression. The mean followup period was 11.2 months. The standard treatment protocol for managing nonmuscle invasive bladder cancer (NMIBC) as per risk stratification of EAU was followed. The recurrence and progression rates were 16.67% and 9.52%, respectively. The recurrence rate for those who had tumor at the restage was significantly higher than the recurrence rate in those who did not (43.75% vs. 16.67%, $P = 0.033$). Thus, the presence of tumor at the restage implies high chances of recurrence at follow-up. This may be due to aggressive tumor biology. In a similar study by Shim *et al*.[15] 29 patients with T1 high grade disease underwent restage TURBT and 22 of these were found to have residual tumor. There were total of 9 recurrences during

followup after restage TURBT, 7 of which were in the group that had residual tumor at restage. Progression occurred in four patients within 2 years, all of whom had residual cancers at restage. The recurrence free survival at 3 years in residual tumor group was 68.6% as compared to 50% in the group without residual tumor ($P = 0.5$), Progression occurred in 4 patients, all in the residual tumor group. Thus authors recommended routine restage TURBT in T1 high grade tumors. In the current study, the recurrence rates when compared between those who had residual tumor at restage and those who did not were 43.75% vs 16.67% and the progression rates were 22.58% vs 5.79% ($P = 0.08$). Hence, the presence of tumor at restage is a risk factor for disease recurrence and progression.

Conclusion

The present study concluded that restage 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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