



RECURRENCE RATE AFTER REPEAT TRANSURETHRAL RESECTION AMONG PATIENTS WITH NEWLY DIAGNOSED T1 BLADDER CANCER

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ABSTRACT **Background:** Transurethral resection of the bladder tumor (TURBT) is the cornerstone of diagnosis and TURBT followed by selective adjuvant intravesical chemotherapy or immunotherapy is the gold standard of treatment for the patients with non-muscle invasive bladder cancer (NMIBC). Even after complete resection of the tumor there is high risk of residual tumor and subsequent recurrence and progression of the disease. The recurrence of T1 tumor is found to be around 71 % within 5 years and High grade T1 lesions recur in more than 80% of the cases and progress in 50% of the patients within 3 years. Disease status at 3 months after initial resection is an important predictor of subsequent recurrence and progression. **Objective:** To assess the tumor recurrence rate among patients with newly diagnosed T1 bladder cancer between repeat transurethral resection group and single TURBT group. **Type of study:** Randomized controlled trial. Place of study: Department of urology, BSMMU, Dhaka, Bangladesh. **Materials And Methods:** This Randomized Controlled Trial was conducted in urology department of BSMMU, Dhaka, Bangladesh from February 2017 till September 2018. A total of 50 patients, diagnosed as a case of T1 bladder cancer and who fulfill the selection criteria were randomly divided in two groups consisting of 25 patients in each group. After informed consent, repeat TUR was done after 4 weeks of the initial TURBT for only 22 patients in group I since 3 of the patients did not show up on the scheduled date of surgery. Whereas, repeat TUR was not done for other 25 patients in group II. All the patients in both the groups were further treated with intravesical therapy according to the histopathological report. The patients in both the groups were followed up at 3 months and 6 months of the initial intervention where detailed history was taken, relevant investigations were done and check cystoscopy was done. TURBT was done for recurrent tumors. Out of 22 patients in group I, 2 patients were excluded for follow up on the basis of repeat TUR findings. Whereas in group II, 2 patients missed the follow up and one of them missed the normal scheduled dose of intravesical therapy. Hence, 22 patients completed the study in group II. **Results:** The baseline variables like age and sex were similar in both the groups with higher male predominance. There was no statistical significant difference in tumor characteristics such as size, number and grade of the tumor between the two groups. Out of 22 patients in group I who underwent repeat TUR at 4 weeks of initial TUR, residual disease was found in 8 (36.36%) patients. One of the patient was found to have T2 disease and 1 patient had CIS during repeat TUR. These 2 patients were not followed up since the treatment strategy changed after the results of repeat TUR. After 6 months of follow up of all the patients, 2 (10%) out of 20 patients in group I were found to have tumor recurrence however, in group II, 9 (40.9%) patients had tumor recurrence. The tumor recurrence rate between the two groups was found to be statistically significant ($p=0.023$). **Conclusion:** In the light of findings of this study, it can be concluded that performing repeat transurethral resection in patients with newly diagnosed T1 bladder cancer at 4 weeks of initial TURBT, helps to detect significant number of residual tumor and reduce early recurrence rate of the tumor.

KEYWORDS : Repeat TURBT, Bladder Cancer, Transurethral resection.

INTRODUCTION

Bladder cancer is the second most common malignancy of genitourinary tract after prostate and accounts for 7 % of all cancers [1]. Males are 3 to 4 times more likely to develop bladder cancer than females, presumably because of increased prevalence of smoking and exposure to environmental toxins [1]. Incidence of bladder cancer is assumed to be increasing in Bangladesh, though there is no epidemiological study. Gross, painless hematuria is the primary symptom in 85% of patients with a newly diagnosed bladder tumor and microscopic hematuria occurs in virtually all patients [2]. In a smaller percentage of the patients it is accompanied by symptoms of vesical irritability such as frequency, urgency and dysuria. Histologically, 90% of bladder cancers are of urothelial origin, 5% are squamous cell carcinomas and less than 2% are adenocarcinoma and other variants [3]. Currently, the most commonly used staging system is TNM (American joint committee on cancer, 1977). In this system superficial bladder cancer includes Tis (carcinoma in situ), Ta (noninvasive papillary carcinoma) and T1 (lamina propria invasion). The natural history of the bladder cancer is defined by two separate but related processes: tumor recurrence and progression. The risks for both recurrence and progression are related to various factors such as

histological grade, stage, depth of invasion, tumor size, multiplicity, presence or absence of carcinoma in situ [4]. At initial presentation 74% of the bladder tumors are superficial or non-muscle invasive [5]. Transurethral resection of the bladder tumor followed by adjuvant intravesical chemotherapy or immunotherapy is the treatment of choice in patients with superficial carcinoma of urinary bladder to delay or prevent tumor recurrence, and possibly to prevent tumor progression [6]. Even after complete resection and intravesical therapy, T1 tumors recur in around 71% of the cases Divirik et al. [7], whereas, high grade T1 lesions recur in more than 80% of the cases and progress to higher stages in 53% of the cases [12]. Maximum recurrence occurs within the first 6 months Divirik et al. [6], and disease status at 3 months after initial resection is an important predictor of subsequent recurrence and progression [8]. Several studies have showed that, for T1 tumors clinician should perform repeat transurethral resection of the primary tumor site to include muscularis propria within 6 weeks of the initial TURBT since there is significant risk of residual tumor and high chance of recurrence and progression. Complete removal of the tumor and correct staging are of paramount importance in primary diagnosis and subsequent management of the bladder cancer. However, even in the experienced

hands, there exists significant percentage of residual disease and risks of under staging the tumor n [9]. The rate of residual disease during re-TUR ranges from 21 to 78% Zukirchen et al. [10], for T1 tumors and the rate of upstaging on repeat transurethral resection ranges from 0 to 28% when muscle is present in the specimen but is higher, up to 49% when muscle is not present in the initial specimen [11]. In a patient with T1 disease, a clinician should perform repeat transurethral resection of the primary tumor site to include muscularis propria within six weeks of the initial TURBT [6]. Repeat transurethral resection for patients with T1 tumors may achieve diagnostic, prognostic, and therapeutic benefit for the patients. Hence the aim of this study was to assess the effectiveness of repeat transurethral resection in detecting the residual tumor and preventing the early tumor recurrence in patients with newly diagnosed T1 bladder carcinoma.

MATERIAL AND METHODS

It was a randomized controlled trial. The study was conducted in the department of urology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh between the periods of Feb 2017- Sep 2019. Random sampling was followed as per inclusion and exclusion criteria to include a total of 50 patients with T1 bladder cancer, they were divided in two group, Group I re-TUR at 4 wks. of initial TURBT. Group II only underwent single TURBT, were not subject to do repeat TUR. For group I patients, repeat TUR was performed at 4 weeks of initial TURBT. At first the bladder was assessed by cystoscopy for detection of any visible residual tumor and previous resection site. Biopsy was taken from the scar of the first resection site including the deep muscle and sample sent for histopathology. For group II re-TUR was not done and treated as per guideline.

All patients in both group were advised to follow up at 3 and 6 months of initial resection following the standard follow up protocol. TURBT was done for recurrent tumor and subsequent guideline. After compilation of data was presented as table, figure and graph as per required. Statistical analysis of result was done by computer based statistical software SPSS 23.0.0 forward operating system, Result was expressed as mean(±SD) and compared by independent simple t- test for continuous and for categorical variable either Chi- square test or by Fisher's exact test was used. A p-value of <0.05 was considered as significant.

RESULTS

Total 42 patients were available for study, of them 20 were in group I and 22 were in Group II. Mean age of the patients in group I was found to be (mean±SD, yrs) 61.68±8.10 and 60.45±8.36 in group II respectively. There was no statistical significant difference in age between the two groups (p=0.624). Male female ratio is; 2.6:1 in group I in group II and it was not statistically significant (p=1.000) (Table-I).

Table-I: Demographic And Tumor Characteristics Of Both Groups.

	Group I Study (n=22)	Group II Control (n=22)	p-value
Age (mean±SD)	61.68±8.10	60.45±8.36	0.624
Sex n, (%)			
Male	16 (72.7)	17 (77.3)	1.000
Female	6 (27.3)	5(22.7)	
Size of the tumor n, (%)			
<3 cm	10(45.5)	9(40.9)	0.761
>3 cm	12(54.5)	13 (59.1)	
Number of the tumor n, (%)			
Single	12 (54.5)	13 (59.1)	0.761
Multiple	10 (45.5)	9(40.9)	
Grade of the tumor n, (%)			
Low grade	8 (36.4)	10 (45.5)	0.540
High grade	14(63.6)	12 (54.5)	

Quantitative data was analyzed by using Independent Sample T-test Qualitative data was analyzed by using Chi-square test p-value <0.05 was considered significant.

Majority of the tumors are of >3cm, multiple and high grade. The difference in tumor characteristics between the two groups were not found to be statistically significant in terms of size, number and grade of the tumor (Shows in table-I). Frequency and stage distribution of the residual tumor after repeat TUR in relation to tumor characteristics at first TUR in group I. Only 1 (12.5%) patient having low grade tumor

during the initial TUR had residual disease during second TUR however, 7 (50%) out of 14 patients having high grade tumor initially were found to have residual disease during repeat TUR. Out of 10 patients with multiple tumor during first TUR, 7 (70%) patients were found to have residual disease. 3 (30%) out of 10 patients having <3 cm tumor during first TUR were found to have residual disease and 5 (41.66%) patients with >3 cm tumor at first TUR were found to have residual disease. The patient who upstaged to T2 disease had initial large size, multiple and high grade of the tumor. The patient who upstaged to muscle invasive had initial large size, multiple and high grade type. The incidence of residual disease during the repeat TUR was directly associated with the large size, multiple and high grade of the tumor but only multiplicity of the tumor had statistical significant value (p=0.006) (Shown in table II & fig-1).

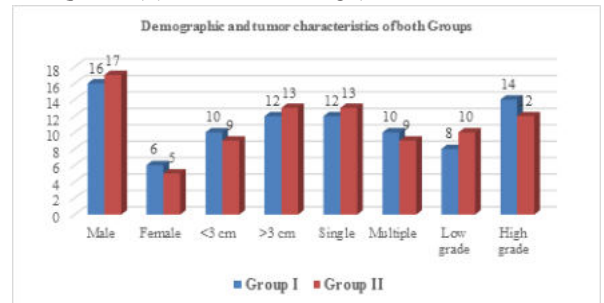


Fig-1: Demographic And Tumor Characteristics Of Both Groups.

Table-II: Frequency And Stage Distribution Of The Residual Tumor After Repeat TUR In Relation To Tumor Characteristics At First TUR In Group I (n=22).

At first TUR	Results of repeat TUR						p-value
	Distribution n (%)	Stage of the tumor after repeat TUR					
		T0 N (%)	Ta N (%)	Tis	T1 N (%)	T2 N (%)	
Grade of tumor							
Low	8 (36.4)	7 (87.5)	0	0	1 (12.5)	0	0.167
High	14 (63.6)	7 (50.0)	0	1 (7.14)	5 (35.71)	1 (7.14)	
Number of tumor							
Single	12(54.5)	11 (91.66)	0	0	1 (8.33)	0	0.006
Multiple	10(45.5)	3 (30.0)	0	1 (10.0)	5 (50.0)	1 (10.0)	
Size of tumor							
<3 cm	10 (45.5)	7 (70.0)	0	1 (10.0)	2 (20.0)	0	0.675
>3 cm	12 (54.5)	7 (58.33)	0	0	4 (33.33)	1 (8.33)	

Fisher's Exact Test was done for analysis and p<0.05 was considered significant.

Out of 22 patients who routinely underwent re-TUR after 4 weeks of initial TUR, residual disease was found in 8 (36.36%) patients. Out of 22 patients in group II, 9 (40.9%) patients had tumor recurrence during the subsequent follow up. The difference in the tumor recurrence within the first 6 months between the two groups was statistically significant (p=0.023) (Shows in table III).

Table-III: Comparison Of Two Groups Regarding Tumor Recurrence At 3 And 6 Months Of First TUR.

Recurrence at 3 month			
	Group I (n=20)	Group II (n=22)	P value
Yes	1 (5.0)	6 (27)	0.023
No	19 (95)	16 (73)	
Recurrence at 6 month			
Yes	2 (10.0)	18 (90.0)	0.023
No	9 (40.9)	13 (59.1)	

Data was expressed as number and percentage Chi-square test was done for analysis and A (p-value<0.05 was considered significant.

DISCUSSION

This Randomized Controlled Trial had been designed to observe the outcome of repeat transurethral resection among patients with newly diagnosed T1 bladder carcinoma and compare the early recurrence rate with the patients undergoing single TURBT. In present study, age of the patients ranged from 45 years to 75 years. Majority of the patients were between 50 to 70 years of age in both the groups, 90.9% in group I and 86.36% in group II. The mean age of this study was comparable with the study conducted by Divirik et al. [6], where the mean age of the patients in re-TUR group was 62.7 years and 61.5 years in the other group. According to the study conducted by David et al. [13], the majority of the patients with bladder cancer were older than 60 years of age which was comparable with this study. Male population are 3 to 4 times more likely to develop bladder carcinoma than females, most likely because of increased prevalence of smoking and exposure to environmental toxins [14, 1]. Similarly, in this present study for patients with bladder carcinoma male to female ratio was found to be 2.66:1 in group I and 3.4:1 in group II. 72.27% of the patients in group I were male and 27.27% were female. In group II 68.18% of the patients were male and 22.72% of them were female. The sex distribution in this study was also comparable with the study conducted by Vasdev et al. [15]. The recurrence rate and progression of the disease depends upon several factors such as stage, tumor size and number of lesions and grade of the tumor [16]. In this study, the different prognostic factors such as size, number and grade of the tumor were compared between the two groups prior to re-TUR and, none of them were statistically significant. Similar results were found in a study conducted by Divirik et al. [6]. Several studies have documented the presence of residual tumors after second TUR with few of them being upstaged. In this study, repeat TUR was routinely done at 4 weeks of initial TURBT for all the patients in group I and the histopathology report was analyzed. A total of 8 patients out of 22 were found to have residual disease which accounted for 36.36%. According to the study conducted by Cao et al. [17], where 134 patients with T1 bladder cancer routinely underwent re-TUR, the rate of residual disease was found to be 38.81% which was comparable to this study. Similar studies were conducted by Zukirchen et al. [10], where the rate of residual tumor after re-TUR were found to be 37%, 33% and 34% respectively. However, in a study conducted by Herr et al. [18], the rate of residual tumor was found to be significantly higher (78%) in comparison to this study since they performed repeat TUR in all the patients with T1 tumors irrespective of whether the initial TURBT was complete or incomplete. One (4.54%) of the patient was upstaged to T2 disease in this study who subsequently underwent radical cystectomy with urinary diversion and one (4.54%) patient was found to have carcinoma in situ during re-TUR. Hence re-TUR definitely changed the management for these two patients.

Upstaging of the tumor observed by Divirik et al. [6], was 3% and Vasdev et al. [15]. Was 7% which were similar to this study hence, highlighting the necessity of re-TUR in patients with newly diagnosed T1 bladder cancer. Dwivedi et al. [19], devaluated various prognostic factors predicting the residual growth in re-TUR in superficial bladder cancer patients and they found that residual malignant T0 tissue had a statistically significant correlation with size of the tumor (> 3cm), number of the tumor (multiple) and grade of the tumor (high). In this study, the rate of residual tumor during re-TUR for patients with single tumor was found to be 8.3% whereas 70% of the patients with multiple tumor had residual disease which was statistically significant (p=0.006). In a similar study conducted by Divirik et al. [6], they found higher incidence of residual disease in patients with multiple tumor than patients with solitary tumor (p=0.023) which was comparable to this study. Regarding the grade of the tumor at initial TUR and findings of residual tumor during re-TUR, present study showed incidence of 12.5% for patients with low grade tumor and 50% for patients with high grade tumor. The rate of residual disease was much higher in patients with high grade tumor in comparison to the patients with low grade tumor. In the study of Divirik et al. [6], there was statistically significant difference in the rate of residual tumor when low vs high grade tumor was compared (p=0.038). They found residual tumor in 42.85% of the patients with high grade tumor at initial TUR and 22.44% in patients with low grade tumor. The findings were similar to our study but the data was not found to be statistically significant in our study which might be due to relatively small sample size of the present study. Similarly regarding the size of the tumor (<3cm vs >3 cm) at initial TUR, there was no statistically significant difference in

incidence of the residual disease at re-TUR. However, in a study conducted by Yucel et al. [20], the risk of having a residual tumor was found to be directly correlated with the size of the tumor (p=0.007). The statistically insignificant finding in present study might be explained by the fact that, all 3 patients with less than 3 cm tumor having residual disease at re-TUR had high grade disease with 2 of them having multiple tumors, which might be the major factor for presence of residual tumor. In a study conducted by Gendy et al. [11], supported the role of re-TUR as evident by significant difference in 3-6 months recurrence rates when re-TUR was performed. For T1 tumors, the patients who did not routinely undergo re-TUR, recurrence rate was found to be 84% which was significantly higher in comparison to the patients who underwent re-TUR (39.6%). In this study all the patients were followed up at 3 and 6 months of initial resection as per follow up protocol for non-muscle invasive bladder cancer. There was significant reduction in recurrence rate in patients who routinely underwent re-TUR (p=0.023). We found a recurrence rate of 10% in patients who routinely underwent re-TUR whereas the recurrence rate was found to be 40.9% in patients who did not, at the end of 6 month follow up. The findings of present study were comparable with the study conducted by Gendy et al. [11]. In a randomized study conducted by Divirik et al. [6], they found a significantly lower recurrence rate of 6.45% in patients who underwent re-TUR compared to 31.6% in those who did not, at the end of 6 month follow up and the findings were similar to this study. Similar results were obtained in other randomized studies conducted by Vasdev et al. [15], and Divirik et al. [6]. Patients with T1 disease at first TUR have a 2-fold increased risk of recurrence and 4-fold increased risk of progression when re-TUR is not done Audenet et al. [21]. The rate of tumor recurrence depends upon the several factors such as tumor grade, size, and number of lesions and use of adjuvant therapy [16]. In present study we compared the recurrence rate between low and high grade tumor, single vs multiple tumor and <3 cm vs >3 cm tumors. High grade NMIBC has a recurrence rate of 70% with 15-40% risk of progression as compared to less than 5% for low grade tumors at 5 years [22]. In this study at the end of 6 months follow up, there were 9 patients with tumor recurrence in group II and 8 (66.7%) out of them had high grade tumor after first TURBT. The recurrence rate was significantly higher in patients with initial high grade tumor (p = 0.011). Similar results were obtained by Divirik et al. [6], and Khan et al. [23]. The rate of recurrence in terms of size of the tumor was compared in this study and majority of the tumors that recurred had >3 cm tumor during initial TURBT (p=0.031). Similar results were found in a study conducted by Khan et al. [23], where a significant number of patients with large tumor size had recurrence (p=0.04). In patients with tumor recurrence in group II, 6 (66.7%) had multiple tumor and 3 (23.1%) had single tumor during initial TUR signifying multiple tumor as a risk factor for subsequent recurrence. However, when the recurrence rate was compared between them, the data was not sufficient to be statistically significant in this study most probably due to relatively small sample size of the study. Divirik et al. [6], however, found statistically significant rate of tumor recurrence in patients with large size of tumor (>3 cm). Hence, as evident by our study and multiple other studies, recurrence rate of the T1 bladder cancer seems to be directly related with the grade, size and multiplicity of the lesions. In conclusion, the present study found that most of the patients with T1 bladder cancer have a higher tumor load than initially suspected on the basis of single transurethral resection and a routine second transurethral resection helps to identify and resect the residual tumor, corrects under tagging which leads to the change in treatment strategy and most importantly prevents the early recurrence of the tumor which is the most important prognostic factor for subsequent recurrence and disease progression.

CONCLUSION

Comparing the findings of this present study, it can be concluded that performing repeat transurethral resection in patients with newly diagnosed T1 bladder cancer can detect significant number of residual tumor and reduce early recurrence of the tumor.

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