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Impact of Routine Second Transurethral Resection on the Long-Term Outcome of Patients with Newly Diagnosed pT1 Urothelial Carcinoma

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Abstract

Background: Transurethral resection (TUR) of bladder tumours is not only mandatory for adequate staging but also crucial in delaying or preventing tumour recurrence and progression. Objective: To evaluate the impact of routine second TUR on the long-term outcome of patients with newly diagnosed pT1 urothelial carcinoma. **Methods:** This prospectively randomized Trial was conducted in urology department of BSMMU, Dhaka, Bangladesh from January 2017 and January 2020. Two hundred ten newly diagnosed T1 bladder cancer patients were prospectively randomized to two groups between January 2017 and January 2020. Second TUR was performed within 2–6 wk. after the initial resection for the patients of group 1. Second TUR was not done in group 2. All patients (groups 1 and 2) received the first instillation of intravesical chemotherapy within 24 h after the initial resection. Urine cytology and follow-up cystoscopy were performed at 3-mo intervals for the first year, biannually for the second year, and annually thereafter. All patients were followed until death or a minimum of 54 months. **Results:** The mean follow-up period was 66.1 months without a significant difference between the groups. Residual tumour was detected histopathologically in 35 of 105 patients in group 1. Of these patients, eight had upper-stage (pT2) disease. Recurrence was observed in 37 of the 93 patients in group 1 and 70 of the 98 patients in group 2. Median recurrence-free survival was 47 months for group 1 compared with 12 months for group 2. Progression was observed in 6.5% of patients for group 1 compared to 23.5% of patients for group 2 (p = 0.001). Median progress-free survival was 73 months for group 1 compared to 53.5 months for group 2. The overall survival rate was 67.7% and 64.3% in groups 1 and 2, respectively (log rank test result: 0.363). Only 5 of the 30 patients in group 1 died of cancer compared to 11 of the 35 patients in group 2 (p=0.038). **Conclusion:** We have clearly shown that second TUR, which is performed only after complete first TUR, has significantlydecreasedtherecurrenceandprogressionratesinpatientswithnewly diagnosed T1 disease compared to patients with T1 disease but with no second TUR. This study once more underscores the effect of TUR, which is usually underappreciated.

Keywords: Urothelial carcinoma, Bladder cancer, Superficial transitional cell carcinoma, Second TUR, Recurrence Progression.

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INTRODUCTION

Transurethral resection (TUR) of bladder tumours is the mainstay in the diagnosis and treatment of bladder cancer (BCa). The first and most important rule is the complete resection of the superficial BCa. This procedure is not only mandatory for adequate staging but also crucial in delaying or preventing tumour recurrence and progression. The definition of complete and correct resection is to eradicate all macroscopic tumours, preferably in fractions, which includes the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle, and the edges of the resection area. The specimens from different fractions must be sent to the pathologist in separate containers. Cauterisation has to be avoided as much as possible during the resection to prevent tissue destruction. The pathologic report should specify the grade of the lesion and the depth of tumour invasion into the bladder wall and provide information on whether the lamina propria and muscle are present in the specimen.[1] Second TUR refers only to those procedures performed 2-6 wk. following the complete TUR of the bladder (TURB) defined above. Of course, nobody can guarantee that a complete TURB has been performed for the nonvisualising microscopic tumours on the base or margins of the tumours. Nevertheless, the surgeon has to report that all visible tumours have been resected, and the pathologist has to reveal that lamina propria and muscularispropria were obtained. Moreover, the term second TUR should not be used for the repeat resection after incomplete resection having left behind residual tumour tissue because of factors such as multiplicity, size, and location. Restaging TUR is another term referring to TUR that provides additional pathologic information for the lamina propria or muscularispropria. Both the rate of the residual tumour and understaging after second TUR were reported, with a range of 28% to 74% and 1.7% to 64%, respectively, because of the complexities of definitions.[2–7] According to the strict definitions, we have reported the results of our previous data, including the rate of residual tumours, the rate of understaging, and the recurrence and progression rate in patients with newly diagnosed pT1 BCa who underwent second TUR in a prospective, randomized clinical trial.[8] This is the first study to show the positive impact of routine second TUR on the long-term outcome of patients with newly diagnosed pT1 BCa with respect to the recurrence rate, time to recurrence, progression rate, and disease-specific mortality in a prospective, randomised trial.

MATERIALS AND METHODS

This prospectively randomized Trial was conducted in urology department of BSMMU, Dhaka, Bangladesh from January 2017 and January 2020. A total of 210 patients with newly diagnosed pT1 tumours considered to have been resected correctly and completely during the first TUR as described,[2] were prospectively randomised to two

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groups. All of the resections were performed by experienced urologists in our department. After the first resection, the surgeon documented the location, size, and number of the tumours on a designed bladder map. Second TUR was performed for any residual tumour that is unexpected and/or scar of the first resection within 2–6 wk. after the initial resection for the patients of group 1. If tumour was detected macroscopically and/or histologically during the second TUR, a third TUR was recommended. Second TUR was not done for the other 105 patients in group 2. The final treatment strategy was decided according to the findings of the second or third TUR in group 1.

All patients (groups 1 and 2) received the first instillation of 40 mg mitomycin C (MMC) within 24 h after the initial resection. The strategy of instillation was described in the initial paper.[8] Urine cytology and follow-up cystoscopy were performed at 3-mo intervals for the first year, biannually for the second year, and annually thereafter. All cohorts were followed until death or a minimum of 54 mo. Event-free survival was defined as the time from the surgery (the last for group 1) to the earlier event (recurrence or progression). The end points used to assess the efficacy of the treatment of the groups were the time to histologically confirmed BCa recurrence and to progression to muscle-invasive disease. Multivariate analysis using the Cox proportional hazards model determined independent variables predictive of tumour recurrence and progression. Recurrence-free survival (RFS), progression-free survival (PFS), and overall survival (OS) curves were calculated by the Kaplan-Meier method and compared using the logrank test. Tumours were classified according to the TNM system of the Union Internationale Contre le Cancer and were graded according to the World Health Organization classification.[9] Informed consent for the treatment strategy was obtained from each patient, and local ethics committee approval was obtained.

RESULTS

Group 1: In all 105 patients, no tumour was visible at the end of the initial TUR; therefore, complete resection was reported. However, residual tumour was detected histopathologically in 35 of 105 (33.3%) patients at the second TUR. In eight of these patients (7.6%), disease was upstaged to pT2, and an additional four patients had Tis in conjunction with residual pT1 disease. Therefore, second TURB definitely resulted in a major change in the treatment strategy of eight (7.6%) patients. Intravesical bacillus Calmette-Guerin (BCG) treatment became almost mandatory in an additional four patients in whom Tis was discovered in the second TURB. These 12 patients were excluded from this study. The number, size, and grade of tumours did correlate with the incidence of residual tumour at second resection. The risk of having carcinoma in situ (CIS) or pT2 tumour at the second TUR directly correlated with the grade (2.0% vs

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19.6%), size (5.4% vs 14.7%), and number (5.7% vs 17.3%) of the initial tumour (Table 2). Tumour-free status was histologically confirmed at the second resection in 70 cases (66.7%) and in an additional 18 cases (17.1%) at the third resection. Second TURB was performed without a major morbidity on 105 patients with primary T1 transitional cell carcinoma. Minor complications included prolonged bleeding managed conservatively in four patients and epididymitis and transient urinary retention in two patients each. Group 2: Of the 105 patients, 7 were excluded from this study (4 patients were lost to follow-up within the first year after TURB, and 3 patients could not complete the 8-wkintravesical treatment because of skin reaction or severe irritative urinary symptoms).

Table-1: Distribution of patient and tumour characteristics.

	Second TUR	No second TUR	Overall	p
Mean age, yr (range)	62.7 (37–87)	61.5 (37–82)	62.1 (37–87)	0.407
Mean follow-up, mo (range) Sex, no. (%)	66.4 (13–102)	65.7 (12–102)	66.1 (12–102)	0.852
Male	82 (88.2)	89 (90.8)	171 (89.5)	0.639
Female	11 (11.8)	9 (9.2)	20 (10.5)	
Single tumour				0.833
<3 cm, no. (%)	20 (40.0)	16 (37.2)	36 (38.7)	
≥3 cm, no. (%)	30 (60.0)	27 (62.8)	57 (61.3)	
Multiple tumours				0.879
<3 cm, no. (%)	15 (34.9)	20 (36.4)	35 (35.7)	
≥3 cm, no. (%)	28 (65.1)	35 (63.6)	63 (64.3)	
Multiple tumour or ≥3 cm, no. (%)	73 (78.5)	82 (83.6)	155 (81.2)	0.459
Grade, no. (%)				0.629
Low	48 (51.6)	54 (55.1)	102 (53.4)	
High	45 (48.4)	44 (44.9)	89 (46.6)	

Table-2: Frequency and stage distribution of the residual tumour at second transurethral resection (TUR) as a result of tumour characteristics at first TUR.

Tumour characteristics	Distribution No. (%)	T0, No. (%)	Ta, no. (%)	Tumour and/or CIS, No. (%)	T1, no. (%)	T2, no. (%)	p*
Grade							0.038
Low	49-46.1	38-77.6	7-14.3	0	3-6.1	1-2.0	
High	59-53.3	32-57.1	7-12.5	4-7.1	6-10.7	7-12.5	
No. Of Tumours							
1	53-50.5	41-77.4	5-9.4	0	4-7.1	3-5.7	0.023
>1	52-49.5	29-55.8	9-17.3	1-7.7	5-8.1	5-9.6	
Size							

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<3 cm	37-35.2	30-81.1	2-5.4	1-2.7	3-8.1	1-2.7	0.030
≥3 cm	68-64.8	40-58.8	12-17.6	3-4.4	6-8.8	7-10.3	
Overall	105-100.0	70-66.7	14-13.5	4-3.8	9-8.5	8-7.6	
* The p value refers to a comparison of subgroups of tumour characteristics according to second TUR results (low vs high; single vs multiple; <3 cm vs ≥3 cm).							

Table 3: Comparison of the two groups according to recurrence, progression, cystectomy, and mortality.

	Second TUR	**No second TUR**	**p**
RFS rate, overall, %	52	21	0.0001
1 yr, %	82	57	
3 yr, %	65	37	
5 yr, %	59	32	
Recurrences, no. (%)	37 (39.8)	70 (71.4)	0.0001
Recurrences within the first year, no. (%)	19 (51.4)	51 (72.9)	0.023
Mean RFS, mo (range)	64.6 (3–102)	40.1 (3–102)	0.0001
Recurrence rate as a result of tumour grade			
Low, %	28.0	53.8	0.55
High, %	41.1	77.8	0.001
Recurrence rate as a result of the number of tumours			
Single, %	33.3	51.2	0.070
Multiple, %	45.8	87.3	0.001
Recurrence rate as a result of tumour size			-
<3 cm, %	37.5	69.4	0.005
≥ 3 cm, %	41.5	72.6	0.001
PFS rate, overall, %	93	76	0.0001
1 yr, %	96	94	-
3 yr, %	93	83	-
5 yr, %	93	79	-
Progression, no. (%)	6 (6.5)	23 (23.5)	0.001
Mean PFS, months (range)	92.5 (7–102)	80.6 (3–102)	0.002
Cystectomy (overall), no. (%)	6 + 8* (13.3)	23 (23.5)	0.031
Deaths, no. (%)	30 (32)	35 (36)	0.363
Cancer-specific mortality, no. (%)	5 (16.7)	11 (31.4)	0.038
* Eight patients with pT2 after second TUR excluded from the study were also included in the comparison of cystectomy numbers.			

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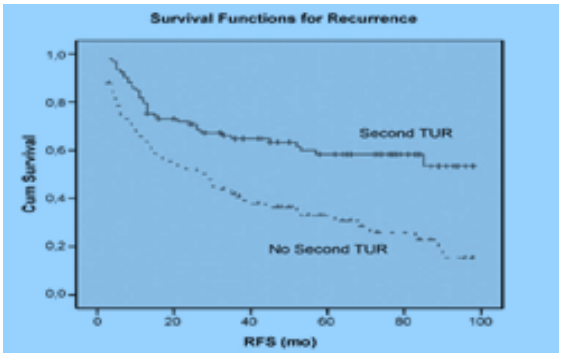

Figure 1: Kaplan-Meier curve of the recurrence-free survival rates for the two groups (log-rank test result: 0.0001).

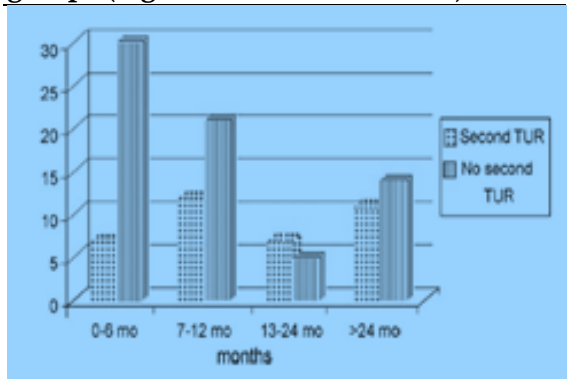

Figure 2: Distribution of the recurrent patients for each group.

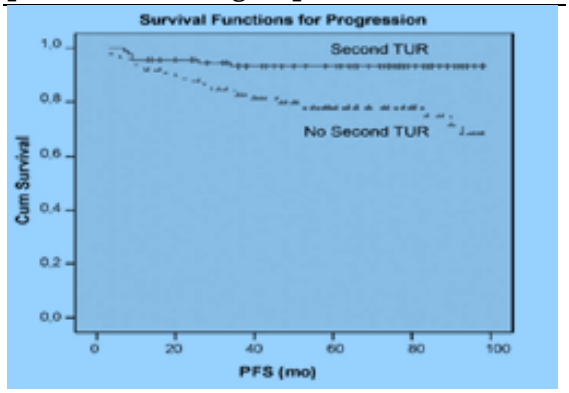

Figure 3: Kaplan-Meier curve of the progression-free survival rates for the two groups (log-rank test result: 0.0001).

Comparison of the groups: The mean follow-up period was 66.1 months (range: 12–102) without a significant difference between the groups. There were no significant imbalances in regard to demographics and tumour characteristics in the two groups (Table 1). Recurrence: The rate of RFS was 82%, 65%, and 59% in group 1 and 57%, 37%, and 32% in group 2 for the first, third, and fifth year, respectively (overall: 52 vs 21%; log-rank test result: 0.0001). The recurrence-free curves for the two groups are shown in Fig. 1. Recurrence was observed in 37 of the 93 patients in group 1 and in 70 of the 98 patients in group 2. Nineteen of the 37 patients in group 1 and 51 of the 70 patients in group 2 recurred within 12 months [Figure 2]. Median RFS was 47 months (range: 3–102; estimated mean: 64.6) for group 1 compared with 12 months (range: 3–102; estimated mean: 40.1) for group 2 [Table 3]. To separately predict the prognostic factors of recurrence, multivariate analysis was performed, and the second TUR was the most powerful prognostic factor for RFS (p = 0.001; [Table 4]). Progression: The rate of PFSwas96%, 93%, and93%ingroup1and94%, 83%, and 79% in group 2 for the first, third, and fifth year, respectively (overall: 93% vs 76%; log-rank test result: 0.0001). Progression was observed in 6 of the 93 patients in group 1 compared to 23 of the 98 patients in group 2(p = 0.001; [Figure 3]).

Table4: Multivariate analysis according to recurrence and progression.

Variables	Recurrence			Progression
	HR	P	HR	P
Age	0.990	0.363	0.985	0.451
Sex	0.821	0.582	0.365	0.620
No. of	1.77	0.00	1.38	0.395

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tumours(single vs multiple)	2	7	9	
Tumour size(<3 cm vs ≥3 cm)	1.328	0.161	2.649	0.035
Grade (low vs high)	1.799	0.023	0000	0000
Second TUR (yes vs no)	2.482	0.001	3.487	0.007
* HR according to Cox regression analysis.				

Of these six patients, four had cancer, while the remaining two had no tumour on second TUR. All of those patients who had progression to muscle-invasive disease during follow-up underwent radical cystectomy (RC)-6 fromgroup1 and23 from group2. Median PFS was 73 months (range: 7–102; estimated mean: 92.5) for group 1 compared to 53.5 months (range: 3–102; estimated mean: 80.6) for group 2 (Table 3). Survival: The OS rate was 67.7% and 64.3% in groups 1 and 2, respectively (log-rank test result: 0.363). Only 5 of the 30 (16.7%) patients in group 1 died of cancer as compared to 11 of the 35 (31.4%) in group 2 (p = 0.038).

DISCUSSION

Because of the complexities of definitions, both the rate of the residual tumour and understating after the second TUR were reported with a range of 28% to 74% and 1.7% to 64%, respectively, in different studies.[2–7] The TUR after incomplete resection resulting from factors such as multiplicity, size, and location has to be called repeat resection. If second intervention was done to provide additional pathologic information for the muscular is propria, it has to be called restaging TUR. The term second TUR has to be used only if the procedure was done after complete and correct TUR. In light of these new definitions, the rate of residual tumour in the patients with pT1 BCa detected by second TUR is 33–43%, and the rate of understaging is 1.7–7.9% in the literature.[2,3,7,10-12]We also determined these rates to be 33.3% and 7.6%, respectively. In our prospective, randomized study, 5-yr RFS was 59% in the second TUR group and 32% in the TUR-only group (log-rank test result: 0.0001). Only one prospective, nonrandomized study was performed— by Grimm et al.[13] —that resembles the current study in terms of the impact of second TUR on the recurrence and progression of superficial carcinoma of the bladder. However, in the aforementioned study, 78% of patients had pTatumours and 62% of cases with newly diagnosed BCa. Furthermore, patient characteristics in the group designated TURB only were similar but not balanced compared with the second TUR group. They have found that the estimated risk of recurrence at 3 yr was 32% in patients treated with second TUR and 61% in patients treated with TUR only. Although most of the patients had pTatumours and low grade disease, Jarvinen et al.[14] reported that the probability of recurrence in patients treated with TUR and adjuvant MMC was 77% at 5 yr. The probability of recurrence at 5 yr. in patients with intermediate- and high risk superficial BCa was calculated as

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62% and 78%, respectively, by using European Organization for Research and Treatment of Cancer risk tables.[15] Recurrence was observed in 28% of patients with low grade tumours and 44.1% of patients with high-grade tumours for the second TUR group in our study, showing a superiority of the approach suggested in this study. Bono et al reported a recurrence rate of 56% following 1-yr intravesical prophylaxis with doxorubicin in 128 patients with pT1G3 tumours.[16] Clinical studies on adjuvant BCG prophylaxis of stage pT1G3 carcinoma have shown recurrence rates between 39% and 44%; median follow-up ranged from 59 to 78 months.[17–19] Herr,[20] reported a recurrence rate of 45% in 67 patients who underwent restaging/second TUR before BCG treatment and 80% in 30 patients who received BCG treatment after initial TUR for the 12-mo follow-up. In this study, all patients had multiple high-grade pT1 tumours, and the majority of the patients (74%) had CIS. It was concluded that second TUR of high-risk superficial BCa improved the initial response rate to BCG therapy and reduced the frequency of subsequent tumour recurrence. When we compare the recurrence rate of the patients who underwent second TUR before MMC with the result of patients not undergoing second TUR in the literature at 5 yr, we have definitely showed that the patients who underwent second TUR have perfect results for RFS. In addition, all patients had pT1 disease; nearly half of these patients had high-grade tumours, and 79% of these patients had multiple tumours or tumours 3 cm in our series.

In a study reported by Grimm et al.[13] progression to muscle-invasive disease was observed in only 2 of all 78 pTa and pT1 patients after a mean observation of 61 mo. But they did not give any information about whether progression was seen in 2 of 17 pT1 patients. In the retrospective study of Brauers et al.[4] upstaging to pT2 was observed in 2 of 42 primary pT1G2–3 superficial BCa cases with or without CIS in the second resection (the number of patients with CIS after the initial resection was unknown). None of the 15 patients without residual tumour in the second resection had progression to muscle-invasive disease at amean follow-up of 60 mo. During the follow-up, cystectomy was performed in 9 out of 40 patients, but there was no information about preoperative staging. Another study compared the progression rate of patients who underwent restaging/second TUR before BCG with BCG after initial TUR. Five out of 67 patients who underwent restaging TUR had progression within 3 yr. of follow-up compared to 13 of 30 patients who underwent single TUR [20]. In our study, progression was observed in 6.5% of patients for group 1 compared to 23.5% of patients for group 2. Of these six patients, four had cancer, while the remaining two had no tumour on second TUR. All of those patients who had progression to muscle-invasive disease during follow-up underwent RC-6 from group 1 and 23 from group 2. The median PFS was 73 months for group 1 compared to 53.5 months for group 2. The OS rate was 67.7% and 64.3% in group 1 and 2, respectively. Only 5 of the 30 patients

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in group 1 died of cancer, as compared to 11 of the 35 patients in group 2.

CONCLUSION

Although repeat TUR has been shown to affect favorably recurrence and progression rates, several times before, these studies included patients with all stages and grades and even patients with macroscopic residual tumours. In the present study, we have clearly shown that second TUR, which is performed only after complete first TUR, has significantly decreased the recurrence and progression rates in patients with newly diagnosed T1 disease compared to patients with T1 disease who have not undergone second TUR. This study once more underscores the effect of TUR, which is usually underappreciated. Although second TUR proved effective in decreasing both recurrence and progression overall in pT1 patients, the study could not definitively document the role of second TUR in the subgroup of single, low-grade, and small pT1 tumours because of the limited amount of patients with these characteristics.

Abbreviation:

1. TUR= transurethral resection
2. CIS = carcinoma in situ
3. Cum = cumulative
4. RFS = recurrence-free survival
5. HR = hazard ratio
6. TUR = transurethral resection.
7. PFS =progression-free survival

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