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ROLE OF EARLY SECOND TURBT IN DETECTION OF RECURRENCE AND DISEASE PROGRESSION IN T1 TCC BLADDER

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ABSTRACT

INTRODUCTION: Majority of the Bladder cancers are non-muscle invasive T1 tumours which have a high propensity of recurrence and at times may be under staged during the initial trans-urethral resection. This study aims to evaluate the role of early second transurethral resection of the bladder tumour (TURBT) in timely diagnosing disease recurrence and progression in T1 staged tumours.

MATERIALS AND METHODS: It was a prospective study done at the Department of Urology, Army Hospital (Research & Referral), New Delhi over a period of two years from June 2013 to May 2015. The study included 32 patients diagnosed to have T1 Transitional Cell Carcinoma of bladder on histopathology following the initial TURBT.

RESULTS: In this study, 23 (71.86%) of the 32 specimen on initial TURBT were deep enough to include the muscularis propria for histopathological staging. In the early second TURBT, 12 (37.55%) patients had residual disease with 7 of them having gross residual disease. On histopathology 5 (15.6%) patients were found to have disease progression to muscle invasion (T2)

CONCLUSION: Early second TURBT (within 6 weeks of first TURBT) has a definitive role in detecting residual disease, early recurrence or progression in patients diagnosed to have T1 tumour on initial resection.

KEYWORDS : T1 Bladder Cancer, Early Relook Turbt, Early Restaging Turbt

INTRODUCTION

Approximately 356,000 new bladder cancer cases (274,000 males and 83,000 females) occur worldwide every year.[1] When diagnosed, urothelial carcinoma of the bladder presents as non-muscle invasive papillary tumour in 70–85% of the cases.[2] Recurrence is common within this group ranging from 0 to 80%, and more importantly, 10% of pTa tumours and 35% of pT1 tumours will eventually progress to muscle invasive disease.[3,4] Disease progression has been demonstrated to correlate with tumour size, multi-focality, tumour stage, grade, and early recurrence.[2] The incidence of residual tumour following initial TURBT in patients with high-grade non-muscle invasive (T1G3) bladder cancers can be as high as 33–53%.[2,4] Additionally, 10% of initial resections are deemed to be under-staged.[4,5] Such information may change the definitive management options in these individuals. Many studies also suggest that early re-resection may improve recurrence-free survival.[1,5,6]

Because of the complexities of the definitions, both the rate of the residual tumour and under-staging after the second TUR were reported with a range of 28% to 74% and 1.7% to 64% respectively in different studies.[7,8,9] 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 muscularis propria, it is called restaging TUR. The term second TUR has to be used only if the procedure was done after a complete and correct TUR.

The current version of the European Association of Urology (EAU) guidelines recommends considering a second TUR if there is a suspicion that the initial resection was incomplete (example, when multiple or large tumours are present or when the pathologist reported no muscle tissue in the specimen). Furthermore, it should be performed when a high-grade non–muscle-invasive tumour or a T1 tumour was detected at the initial TURBT.[10]

AIM AND OBJECTIVES

To determine the role of repeat early (within 6 weeks) TURBT in evaluating and managing T1 TCC Bladder.

METHODOLOGY

After approval from the institutional ethical committee and obtaining informed written consent from all the patients the study was conducted in a tertiary care hospital with the aim of determining the role of early TURBT in patients of T1 TCC bladder.

DURATION OF STUDY :

Study was conducted over a period of two years from June 2013 to May 2015.

SAMPLE SIZE :

The study recruited 32 patients with the histopathology report of T1 TCC bladder on initial TURBT

INCLUSION CRITERIA :

1. Patients of TCC bladder with T1 disease during initial TURBT were included in this study.

EXCLUSION CRITERIA :

1. Patients with upper tract Transitional cell carcinoma.
2. Patient with associated carcinoma in situ during initial biopsy.
3. Patients with recurrent high grade (T1) disease.
4. Patients who have undergone intra-vesical therapy.

STUDY DESIGN :

This was a prospective study in which 32 patients of (T1) TCC bladder were included after duly taking an informed and written consent. Their epidemiological data was collected which included age, sex and occupation. A detailed history which incorporated analysis of risk factors such as smoking, oral tobacco chewing and exposure to chemical carcinogens was recorded. General physical examination of all the patients was done.

All the above 32 patients with (T1) TCC bladder underwent relook CPE and biopsy within two to six weeks of prior surgery. All the surgeries were performed under spinal anaesthesia. During surgery cystopanendoscopy was performed using 17 Fr cystoscope. The scar of previous surgery was identified and findings were correlated with the initial surgery. Resection was performed using 24 Fr resectoscope

with passive bipolar cutting loop and continuous irrigation out-flow system. Biopsy from the base of scarred area including deep muscle tissue was taken. In patients with residual/ recurrent disease, resection followed by deep muscle biopsy was performed. The resected tissue was sent in 40% Formalin saline for histopathology examination. Post operatively patients were maintained on bladder irrigation for 6 to 12 hours depending on the return fluid.

Per-operative findings of both the surgeries were analysed. Depending on the findings of first TURBT, tumours were divided into three groups:-
(a) Single papillary
(b) Multiple papillary
(c) Sessile

These three groups were further analysed separately for presence or absence of same, lower or higher stage disease on second TUR. Further course of treatment of patients was done depending on the HPE report of repeat TURBT.

STATISTICALANALYSIS:
Mean and median were calculated using descriptive statistical analysis. Odds ratio about recurrent/residual disease on second TURBT was calculated using 'Chi-square' test at 95% confidence interval.

RESULTS
Total 32 patients were evaluated in the study period. Mean age of the patients was 63.02 years. Among the study group, 71.4% (n=25) of the patients were smokers 15.6% (n=5) were oral tobacco chewers and 6.25% (n=2) did not have any history of tobacco abuse in any form [Table 1; Figure1]. Mean Duration between the time of onset of disease and tobacco abuse was approximately 26 years. All the smokers in the study group were Bidi smokers with most of them smoking more than 20 bidi's a day.

TABLE 1: Demographic data

Male : Female ratio	31:1
Average age in years	63.02

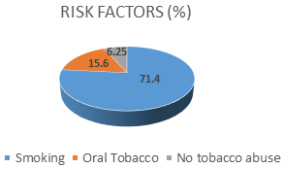

FIGURE 1 : Risk Factors

Twenty two (68.75%) of the patients studied were agriculturists with history of exposure to various pesticides. Nine (28 %) of the patients were retired/ serving army personnel. Two (6.25%) of the army personnel were drivers by profession. The only lady patient in our group was a house wife.

Twenty four patients (75%) had presented with hematuria before first TURBT. Six (18.75%) of them presented with irritative lower urinary tract symptoms. Two (6.25%) patients were incidentally detected to have a bladder mass while undergoing routine ultrasonography for some other indication [Figure2].

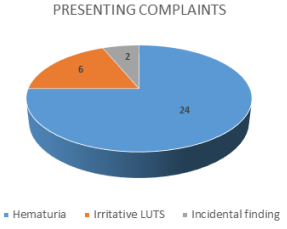

FIGURE 2: Presenting symptoms

All the patients were taken up for Transurethral resection(TUR) of bladder tumor using 24 French bipolar resectoscope in saline. The surgeries were performed by either urologists or by residents under their supervision. Histopathological examination (HPE) was done by two uropathologists posted at our centre.

The primary lesions were grouped as solitary papillary, multiple papillary and sessile lesions according to their cystoscopic appearance. Thirteen (40.6%) of the lesions were solitary papillary, Fifteen (46.8%) were multiple papillary and four (12.6%) of them sessile [Figure3].

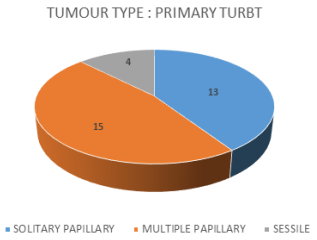

FIGURE 3 :Tumour characteristics on primary TUR

All the tumors were lamina invasive (pT1). Muscle was seen in first TUR specimen in 23 (71.8%) patients.

Second resection was done within 6 weeks of the first TUR. Histopathology examination of 12(37.5%) patients was suggestive of residual disease. Of these twelve patients, seven (21.8%) had gross residual disease and 5 (15.6%) were found to be harbouring disease only on histopathology. So even in the absence of gross residual tumour a second resection identified 5 patients (15.6 %) with positive histopathology. All the patients with solitary papillary lesions did not have any gross disease on second TUR. Six of the seven cases of gross residual disease was seen in patients with primary multiple papillary lesions and one patient from the sessile group had a gross residual disease as depicted in Table 2.

TABLE 2 : Gross residual tumour and primary lesions

	Solitary papillary	Multiple papillary	Sessile lesions
Gross residual lesion (n=7)	0(0)	6(85.7%)	1(14.3%)

The characteristics of the primary lesion with the pathology found in the second resection were compared. Histopathologically, these were categorized as no residual disease, same stage tumours, lower stage tumours and higher staged lesions. Of the 13 patients with solitary papillary lesions, twelve (92.3%) did not have any residual disease in the second TUR and one had a lower stage disease. Seven (46.6%) of the patients with primary multiple papillary lesions were free of tumor at the second resection. Five (33.3%) of the patients had the same stage tumor and Three (20%) had upstaging of the disease. In the sessile group with residual disease, the same stage was seen in one (25%) of the patients and upstaging seen in two (50%) patients [Figure 4].

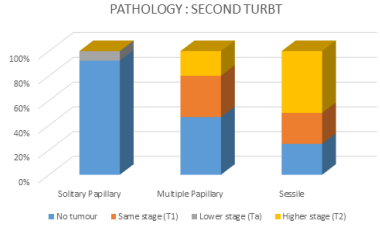

FIGURE 4 : Pathology of second resection

Sessile tumours had 9.75 times greater risk of residual disease as compared to solitary papillary lesions (RR 9.75, 95% CI 1.11 – 142.52) and 1.40 times greater risk of residual disease as compared to multiple papillary tumours (RR 1.40, 95% CI 0.36 – 2.09). When multiple papillary lesions were compared to solitary papillary lesions, there was almost 7-fold increase in risk of residual disease (RR 6.93, 95% CI 1.13 – 146.32). The residual disease in the sessile tumours and multiple papillary lesions was statistically significant when compared to the solitary papillary lesions, while no significant difference in residual disease was seen between sessile tumours and multiple papillary lesions [Table 3].

TABLE 3:Comparative analysis of residual disease in different tumour types

Comparative group	Relative Risk	95% CI	p values*
Sessile vs Solitary papillary	9.75	1.11 – 142.52	0.006

Sessile vs Multiple papillary	1.40	0.36 – 2.09	0.435
Multiple vs Solitary Papillary	6.93	1.13 – 146.32	0.011

* p value < 0.05 : significant

Out of the five patients who were upgraded to muscle invasive T2 disease, muscle was seen in the original specimen in only 2 patients, therefore, if the muscle was present in the original specimen, only 8.7% (2 out of 23 patients) were upstaged to muscle-invasive disease, but if there was no muscle in the specimen, 33.3%(3 out of 9) were upstaged to T2 disease. This suggests that in spite of muscle being present in the initial specimen, an additional transurethral resection detected muscle-invasion in up to 8.7% of cases [Table 4].

TABLE 4 : Rate of recurrence and stage upgradation

	n (%)	Tumour	
		Recurrence	Stage upgradation
Total patients	32	12 (37.55%)	05 (15.6%)
Muscle seen in original specimen	23	07 (30.4%)	02 (8.7%)
Muscle not seen	09	05 (55.5%)	03 (33.3%)

DISCUSSION

The criteria of quality of TURBT have never been clearly defined.[11] It is generally accepted that the procedure is successful if the resection is complete and there are no missed lesions. Mariappan *et al.* assessed patients who supposedly underwent TURBT by experienced surgeons to determine whether the presence or absence of detrusor muscle in the first resection specimen is a suitable surrogate marker of the quality of resection.[12] Experienced surgeons were more likely to resect detrusor muscle with a lower risk of early recurrence, and the absence of muscle independently predicted a higher risk of early recurrence. However, even if TURBT was performed by an experienced surgeon and muscle was present in the specimen, the risk of residual disease in T1 tumours reached 30%. This report clearly demonstrates that even optimally performed TURBT using modern equipment is also weighed down by a high risk of tumour persistence. The frequent failure and absence of clear quality criteria of initial resection strongly underlines the role of early second TURBT in T1 lesions.

In patients with T1 tumours, the risk of tumour persistence detected by the second TUR ranged between 33% and 78%.[9,13,14,15] Presence of the uninvolved muscularis propria in the resected specimen is the only identification for a complete resection.[16] Retrospective studies have shown that residual disease can be seen in up to 68% cases.[17] These high rates may also have been due to the fact that no muscle was present in many of the primary TUR specimens. 49% of T1 lesions without muscle in the resected specimen were under-staged when compared to only 14% with muscle in the resected specimen.[18] Under-staging was reported in 64% of T1 tumours when muscle was absent in the specimen versus 30% when it was present.[19]

In our patients all the TURBT were done by urologists or by residents under supervision. Muscle was present in first TUR specimen in 23 (71.8%) patients. At second TUR twelve (37.5%) patients had residual disease. Recurrent disease was found in 21.8% of our cases who had muscle present during initial TUR and 55.5% of cases in whom muscle was not seen. The recurrence rates seen in our study group corroborated with other studies [Table 5].

TABLE 5 : Recurrence rate

	n (%)	Tumour recurrence
Total patients	32	12 (37.55%)
Muscle seen in original specimen	23 (71.8%)	07 (21.8%)
Muscle not seen	09 (28.2%)	05 (55.5%)

The optimal interval to perform re-resection remains controversial. While Klan *et al*.[20], reporting a rate of residual tumour of 43%, did not find any advantage in waiting more than two weeks from initial TUR, many studies have advocated a delay of two to six weeks to allow post-resection inflammatory change to settle facilitating better visualization and demarcation of tissues. In our series, all patients were subjected to repeat TUR within six weeks from initial TUR, with the mean interval of 34 days between two procedures, demonstrating the presence of residual tumour in 37.4% of cases. This rate of residual disease emphasises the importance of re-resection and is comparable to the other published series employing shorter re-resection intervals of four to six weeks and reporting residual tumour rates ranging from 33% to 62%.[9,16] It therefore appears that delaying second TUR for up to six weeks does not impact negatively on the quality of the re-resection.

Gross residual tumours were seen in 21.8% of our study population. 90% of the gross residual lesions were seen in those with primary multiple papillary lesions. Divrik *et al.* studied the short and long term effects of second TUR on recurrence in high grade T1 tumours. Second TUR reduces recurrence rate in T1 tumours from 63 to 26%.[6] At the end of the first, third and fifth year, the recurrence free survival was 82%, 65% and 59% respectively, in the patients who underwent a second TUR when compared to 57%, 37% and 32% respectively, in the patients who did not undergo the second resection.[21]

Primary tumour architecture, papillary or sessile, and multifocality of these lesions are important prognostic factors for recurrence and progression of the disease. A solitary papillary lesion is considered to be a good prognostic factor as against multiple papillary and sessile lesions.[22] In our series, among those with solitary papillary lesions, one had a lower stage residual disease and 92.3% did not have any residual disease in the second resection. Perhaps this is the subgroup that is least likely to benefit from a second resection. Multiple papillary lesions and the sessile lesions had significant residual disease in the second resection. 53% of the multiple papillary lesions and nearly 75% of the sessile lesions had residual disease. 20% of the patients with multiple papillary pathology and 50% with sessile tumours had disease upgradation on second TUR as depicted in Table 4.

Persistence of T1 disease on second TUR can also provide important prognostic information. Herr presented the outcome of 352 (T1) tumours treated with second TUR. Of the 92 patients with residual T1 cancer detected by second TUR, 82% progressed to muscle invasion within 5 years compared to 19% of 260 without tumour or with Ta disease only. Moreover, in another study, the tumour-free status at the time of second TUR significantly improved the response rate to BCG intravesical immunotherapy and delayed tumour recurrence.[23] During our study period none of our patients having persistent T1 disease on repeat resection were seen to be having progression of disease.

Another factor is the invasion of lamina propria superficial to the muscularis mucosa (T1a) which is considered a good prognostic factor as against the lamina propria deeper to muscularis mucosa.[24] Questions have been raised whether a second resection is really necessary in a well-performed initial resection of high-grade T1 solitary papillary lesions with only superficial invasion of lamina propria (T1a) with negative deep muscle biopsy, especially when intravesical therapy is planned.[25] However our pathologists did not specifically mention the depth of lesion as regards to muscularis mucosa, so we were unable to compare our study group with these studies.

A comparison of similar studies is shown in the Table 6. In many studies stress was not given on complete resection as presence of muscle in initial resection was not specified. One series had muscle in only 40% of the primary TURBT specimens but the recurrence rate was well above 90%.[26] In another series, though the presence of muscularis propria was not mentioned in the primary TURBT, 55% of the lesions were tumour free at re-resection.[14] The primary characteristic of the lesion, which is an important prognostic factor, was also not considered in many of these studies.[15,18,20]

TABLE 6 : Comparison of our study with various other studies.

Study	N	Primary Lesion			Muscle in HPE Primary TURBT	HPE of second TUR			
		Solitary	Multiple	Sessile		No Tumor	Same Stage	Lower Stage	Upstage
Our study	32	13(40.6)	15(46.8)	04(1 2.6)	23(71.8)	20(62.5)	6(18.75)	1(3.12)	5(15.62)
Klan et al	46	NS	NS	NS	NS	20(44)	11(26)	7(15)	8(16)

Schweboid et al	136	NS	NS	NS	NS	64(47)	32(24)	11(8)	27(21)
Herr et al	58	NS	NS	NS	35(63)	13(22)	14(24)	15(26)	16(27)
Schips et al	52	25(48)	14(27)	13(25)	NS	29(55)	9(17)	5(9)	9(17)
Dalbagni et al.	15	NS	9(60)	NS	6(40)	1(6.66)	14(93.4)	0	0
N=number of cells , percentage in parentheses, NS=Not specified									

Maurizio A. *et al.* [27] have challenged the EAU guidelines regarding early repeat transurethral resection. Early re-TUR should be considered mandatory only in selected cases like when muscle tissue is not present in the first TUR specimen, when the surgeon is uncertain of the first TUR, when pathologists are uncertain about the correct staging/grading, in patients referred from other specialists or institutions (30% discrepancy in staging/grading) and when a bladder-sparing approach is planned. In all other cases, re-TUR is optional and depends on the accuracy of the first TUR.

We recognize the limitations of our study, viz., a small study group and also not considering factors like the size of the lesion and depth of lamina propria involved.

CONCLUSION

Our study established that second TUR confirmed the presence of residual cancer and tumour under staging in a significant number of [pT1] tumours. The pathologic findings of second TUR further modified treatment strategy in a very high number of cases. These arguments strongly support the recommendation of second TUR in patients with T1 disease.

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