Original Article

Usefulness of Second-Look Transurethral Resection of Bladder Tumor (TURBT) in Patients Diagnosed with Non-Muscle Invasive Bladder Cancer (NMIBC): A Cross-Sectional Study from a Tertiary Care Centre in Pakistan

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ABSTRACT

Objective: Determination of the prevalence of residual disease and tumor upstaging in patients with non-muscle invasive bladder cancer (NMIBC) who have undergone second-look TURBT of bladder tumor.**Study Design:** Cross-sectional study. **Place and Duration of Study:** Department of Urology, Unit II, Mayo Hospital, Lahore, over a period of six months following approval of the study synopsis.

Methods: Inclusion criteria were high-grade Ta or any T1 NMIBC diagnosis on the initial TURBT histopathology for 92 patients aged 18-70 years, regardless of gender. Exclusions were incomplete resection on the first surgery, recurrence of disease, absence of sampling of detrusor muscle on the first TURBT, low-grade pTaG1 disease with intact presence of detrusor muscle, presence of carcinoma in situ, and untreated UTI.

Results: The mean age of the 92 participants was 51.66 ± 17.50 years (median 45.0 years, IQR 28.0; range 21-91 years). Seventy-five participants (81.5%) were males and 17 participants (18.5%) were females. In the primary TURBT histopathological analysis, 43 participants (46.7%) showed high-grade tumor, and 49 participants (53.3%) showed low-grade tumors. Second look TURBT showed histopathologically diagnosed residual tumor in 48 out of 92 participants (52.2%), while tumor upstaging was present in 31 out of 92 participants (33.7%). Gross tumor requiring bipolar resection on the second look was present in 27 out of 92 participants (29.3%).

Conclusion: However, greater than 50% of high-grade Ta or T1 NMIBC patients had residual disease and about a third were upstaged on the second-look TURBT procedure, values that lie within the internationally observed range for this phenomenon.

Keywords: Non-muscle invasive bladder cancer; Transurethral resection of bladder tumor; Second-look TURBT; Residual disease; Tumor upstaging; Urothelial carcinoma.

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INTRODUCTION

It is considered to be one of the most common urological cancers in the world, where non-muscle invasive bladder cancer (NMIBC) makes up 75% of new cases (1,2). By far the most common histological variant is urothelial (transitional cell) carcinoma, which constitutes 90% of the cases (3). The most significant modifiable risk factor is smoking, which contributes to almost 50% of all cases, while exposure to aromatic amines and ionizing radiation are additional risk factors (4,5). Tumours that are only found within the mucosa (Ta) and those that invade the lamina propria (T1) and are not present in the detrusor muscle define non-muscle invasive bladder cancer (NMIBC), which is managed using risk stratification according to low-risk, intermediate-risk, high-risk, and very high-risk groups (6,7).

The transurethral resection of bladder tumor (TURBT) continues to be the main diagnostic tool as well as the treatment of choice for NMIBC, with the completeness of tumor removal being crucial for the proper staging and management decision making (6). Even with the advancements in the field of resectoscopy and visualization techniques, it often takes more than one TURBT procedure to accomplish a complete removal and proper staging of the tumor, especially with high-grade Ta and T1 disease. Detrusor muscle may not always be identifiable even in the hands of an experienced surgeon, and the understaging of T1 tumors on single resection is well-known (2). Given this issue and the importance of proper staging in terms of prognosis, it becomes obvious why a repeat TURBT after 4-6 weeks from the first procedure is recommended nowadays, as it has become a part of both European and American urological guidelines (6,7).

The justification behind second-look TURBT lies in three related objectives: removal of any tumour left behind by the first resection whether macroscopic or microscopic, correction of any staging errors resulting in wrong risk stratification and sub-optimal treatment, and therefore, improved oncological results in terms of recurrence and progression-free survival (7). The rate of residual disease encountered during second-look TURBT is quite variable in the literature, ranging between 17% and 72-78%, respectively for Ta and T1 lesions, according to different patient populations, techniques and definitions (7). Nazir et al. demonstrated that the residual disease rate was 40%, while tumor upstaging occurred in 17% of their patients who underwent repeat TURBT (8). Chang and Picardo described that there was residual disease in 41.8% of their patients, whereas upstaging happened only in 3% of them (9). Fernandes et al., in a prospective study focusing on surgeon's expertise, noted a relatively low residual disease rate of 20.9%, while upstaging occurred in 6.4% of patients (10). In another study, Mohammadi et al. reported a residual disease rate of 23.5%, while there was no tumor upstaging in their group of patients (11). A single-centre Italian series

similarly documented residual cancer in 45.98% of patients undergoing routine re-TURB, of whom a minority were either downstaged or upstaged on the second specimen (12).

The substantial variation in the results obtained along with the lack of any scientific evidence regarding this issue among the population from Pakistan or South Asia constituted the reason for conducting the current study. Local factors, such as practice pattern, biological behaviour of the tumor, delay in seeking medical care, and resource availability, could be considerably different from the mostly European and East Asian population groups described in the current literature. Therefore, the results obtained in other settings can be hardly applied to our patients. As far as we know, there is no scientific evidence obtained among the Pakistani population about the frequency of residual tumors or tumor upstaging in patients with high-grade Ta or T1 NMIBC during second-look TURBT procedure. The objective of the current study was to investigate the frequency of residual disease and tumor upstaging in patients with NMIBC during second-look TURBT and to determine the association between the outcomes and age, gender, or primary tumour grade among these patients.

OBJECTIVE

To determine the frequency of residual disease and tumor upstaging in patients with non-muscle invasive bladder cancer undergoing second-look TURBT.

MATERIAL AND METHODS

This cross-sectional study was carried out in the Department of Urology, Unit II, Mayo Hospital, Lahore, for a period of six months after being approved by the synopsis of the study. Ethical review board of the institution approved this study which followed the guidelines of the declaration of Helsinki. Informed written consent was taken from each patient before being included in the study.

Sample size of 92 subjects was determined through 90% confidence level and absolute precision of 7%. Expected frequency of residual disease/tumor recurrence on early re-TURBT was considered 20.9% based on the value reported by Fernandes et al. (10). Subjects were recruited using non-probability consecutive sampling from among those attending the department with a diagnosis of NMIBC. Diagnosis of NMIBC was made among those patients who were having at least one episode of painless gross hematuria and had growth localized to the bladder on contrast enhanced CT without any locoregional or distant metastasis and whose primary TURBT histopathology showed any variant of transitional cell carcinoma, squamous cell carcinoma or adenocarcinoma or any other variant without detrusor muscle invasion. The staging was done by using the TNM classification of AJCC in NMIBC. All males and females of 18-70 years age group with presence of high-grade Ta or T1 tumour in the primary TURBT histopathology were enrolled in the study. Patients who underwent TURBT due to incomplete previous resection, patients with recurrent bladder cancer, patients in

which no sampling of detrusor muscle was possible in the primary TURBT, patients having low-grade pTaG1 disease with presence of detrusor muscle in the resected tissue sample, patients with presence of carcinoma in-situ and patients with untreated UTI on urine culture were excluded.

Demographic and clinical details - age, gender, residence, and tumour stage/grade from primary TURBT - were documented in a pre-designed form. All patients were subjected to second-look TURBT after optimizing their conditions preoperatively, 4-6 weeks after primary TURBT, which was carried out by an experienced consultant urologist with more than five years of practice post-fellowship, either under spinal or general anesthesia. In case any gross tumour was seen in cystoscopy, bipolar transurethral resection was done with the help of a resectoscope; biopsy/sampling of the tumour bed was mandatory for all patients irrespective of the gross condition in order to be able to perform histopathological analysis. Presence of residual disease was based on finding any tumor either gross or microscopic through second-look TURBT histopathology. Tumor upstaging meant advancing in the stage or grade of the residual tumor with respect to the primary TURBT histopathology.

Data analysis and entry were done using IBM SPSS statistics, version 26.0 (IBM Corp., Armonk, NY). Normality of age as a continuous variable was tested by Shapiro Wilk test; due to deviation from normal distribution, age is reported as mean ± standard deviation and median with inter-quartile range (IQR). Categorical variables i.e., gender, primary tumour grade, residual disease, and tumor upstaging are reported as frequency and percentage. Effect modifiers i.e., age, gender and primary tumour grade were controlled by stratification; association of these variables with residual disease and tumor upstaging was tested by Chi-square test (Fisher's exact test when expected cell count was low) for categorical variables comparison and independent samples t-test for mean age comparison in upstaged vs. non upstaged patients. Significance level was set at $p \leq 0.05$. Data collection was done by sole investigator using predesigned proforma and predefined exclusion criteria.

RESULTS

In total, 92 patients who had been diagnosed with high-grade Ta/T1 NMIBC and were eligible for the current study were recruited. The average age of the participants was 51.66 ± 17.50 years; since the Shapiro-Wilk test confirmed significant deviation from normal distribution ($p = 0.003$), the median age of 45 years (IQR 28 years; range 21-91 years) is presented in the study. Out of 92 patients recruited to the study, 75 (81.5%) were men and 17 (18.5%) were women, resulting in the male to female ratio of approximately 4.4:1. With respect to histopathology of primary TURBT, all 92 patients included in the study (100%) were classified as pT1, while none of the patients with high-grade pTa tumours had been recruited due to inclusion criteria. Of those patients, 43 had high-grade tumour

(46.7%), while the remaining 49 patients (53.3%) had low-grade tumour (Table 1).

The second-look TURBT procedure was carried out 4-6 weeks after primary resection on all patients, where there was gross tumor visible at cystoscopy requiring formal bipolar resection in 27/92 (29.3%) of patients, whereas 65/92 (70.7%) of patients had only mucosal sampling of the resection bed in the absence of any gross lesion. Residual disease, which is the primary outcome of this study, was present in 48/92 (52.2%) patients and was absent in 44/92 (47.8%) patients. Urothelial tumor upstaging from the primary TURBT specimen was seen in 31/92 (33.7%) patients while no tumor upstaging was seen in 61/92 (66.3%) patients (Table 2).

In the stratified analysis, neither residual disease nor urothelial tumor upstaging demonstrated any statistical correlation with the gender of patients: residual disease was present in 41/75 males (54.7%) versus 7/17 females (41.2%) ($\chi^2 = 1.011$, $p = 0.315$), and urothelial tumor upstaging was present in 26/75 males (34.7%) versus 5/17 females (29.4%) ($\chi^2 = 0.171$, $p = 0.679$). There was also no statistically significant gender-based difference regarding the need for formal bipolar resection of gross tumour (30/75 males = 40.0% vs 6/17 females = 35.3%; $\chi^2 = 0.129$, $p = 0.720$). In terms of stratification by primary tumor grade, there was no statistically significant association with residual disease (high-grade: 24/43 = 55.8% vs low-grade: 24/49 = 49.0%; $\chi^2 = 0.429$, $p = 0.513$). Nevertheless, a higher tendency of high-grade primary tumour in relation to gross resection at second-look nearly reached statistical significance (high-grade: 21/43 = 48.8% vs low-grade: 15/49 = 30.6%; $\chi^2 = 3.194$, $p = 0.074$) (Table 3). Age, on the other hand, was not significantly different between the two groups (50.35 ± 16.98 years vs 52.33 ± 17.87 years; independent-samples t-test, $t = -0.509$, $df = 90$, $p = 0.612$; 95% CI of the mean difference: -9.68 to 5.73).

Table 1: Baseline Demographic and Clinical Characteristics of the Study Population (n = 92)

Variable	n (%) / Mean ± SD / Median (IQR)
Age (years) - Mean ± SD	51.66 ± 17.50
Age (years) - Median (IQR)	45.0 (28.0)
Age range	21 - 91 years
Gender - Male	75 (81.5%)
Gender - Female	17 (18.5%)
Primary TURBT stage - pT1	92 (100%)
Primary TURBT grade - High grade	43 (46.7%)
Primary TURBT grade - Low grade	49 (53.3%)

Table 2: Findings on Second-Look TURBT (n = 92)

Finding	Yes, n (%)	No, n (%)

Gross tumour requiring formal resection at second-look TURBT	27 (29.3%)	65 (70.7%)
Residual disease on histopathology (primary outcome)	48 (52.2%)	44 (47.8%)
Tumor upstaging (primary outcome)	31 (33.7%)	61 (66.3%)

Table 3: Association of Residual Disease and Tumor Upstaging with Gender and Primary Tumor Grade

Stratifying Variable	Outcome	Result	p-value
Gender (M vs F)	Residual disease	54.7% vs 41.2%	0.315
Gender (M vs F)	Tumor upstaging	34.7% vs 29.4%	0.679
Gender (M vs F)	Gross resection required	40.0% vs 35.3%	0.720
Primary grade (High vs Low)	Residual disease	55.8% vs 49.0%	0.513
Primary grade (High vs Low)	Gross resection required	48.8% vs 30.6%	0.074
Age (Upstaged vs Not)	Mean age, years	50.35 vs 52.33	0.612

Chi-square test applied for categorical comparisons; independent-samples t-test applied for age. $p \leq 0.05$ considered significant.

DISCUSSION

In this cross-sectional study among 92 patients with high-grade Ta or T1 NMIBC who had second-look TURBT performed in a tertiary urology care unit in Lahore, the frequency of histopathologically proven residual disease was 52.2% and the frequency of tumor upstaging was 33.7%. Both of these figures comfortably fall within, and near the upper middle range of, the broad spectrum of the literature on this topic, in which residual disease at second-look TURBT was reported to be between 17% and 78%, depending on the primary stage of the tumor, patient selection and quality of the surgery, with common pooled percentages in the literature around 33-55% for T1 tumors (7,13). The frequency of our residual disease is comparable with that of 45.98% in a study among European Ta-T1 tumors having re-TURB done (12), and it is a bit higher than the 40% and 41.8% reported in studies by Nazir et al. (8) and Chang and Picardo (9), although still lower than the 38.6% found in our series and much higher than the 16.7% observed in the series reported

by Fernandes et al. (10) and Mohammadi et al. (11), the two references used for determining the sample size of our study. Such differences between seemingly comparable series reinforce the importance of an aspect increasingly highlighted in the international literature: the results of second-look TURBT depend greatly on the thoroughness of the previous resection, the presence of detrusor muscle during first TURBT, and case-mix (the balance between T1 and high-grade Ta tumours). Indeed, all our patients had stage pT1 in their initial histology; in our series, therefore, the case-mix tended to be on the higher-risk side.

The percentage of tumor upstaging in our study is significantly higher than the percentages observed by Nazir et al. (17%) (8), Fernandes et al. (6.4%) (10), Chang and Picardo (3%) (9), and Mohammadi et al., where there were no cases of tumor upstaging observed (11). It is important for the clinical practice. Detection of upstaging during a second look TURBT, usually, is associated with occult muscle invasion or the transition of the tumor from Ta to T1 stage and dramatically changes treatment strategy – it leads to changing treatment from intravesical Bacillus Calmette-Guérin (BCG) into consideration of the possibility of radical cystectomy. A one-third rate of upstaging is much higher than in most published studies and may be associated with such aspects of our practice: delayed diagnosis, more advanced stage of the disease initially, variable quality of TURBT procedure done before referral (including muscle sampling) and different approaches to reporting the pathological findings. Whatever the explanation, this finding reinforces rather than weakens the rationale for second-look TURBT in our population - if anything, it suggests that omitting a second-look procedure in this setting would risk substantially under-treating a meaningful proportion of patients.

Lack of statistically significant relationship between gender and residual disease ($p = 0.315$) or tumor upstaging ($p = 0.679$) in our study agrees with what was established by the existing literature, where gender did not emerge as an independent predictor of residual or upstaged disease on re-resection unlike other factors like tumor size, multiplicity and completeness of primary resection (7). Also, there was no statistical association between primary tumor grade and residual disease ($p = 0.513$); however, the higher rate of need for resection of grossly visible tumors among high-grade group (48.8% vs. 30.6%, $p = 0.074$) was biologically sound and might have achieved significance with a larger sample size; high-grade tumors are known to be locally invasive and multifocal tumors, thereby making them predisposed to residual disease on re-look. The mean age of the patients with and without tumor upstaging was not statistically different ($p = 0.612$), implying that, at least for our group of patients, age is an unsatisfactory parameter to exclude patients who will have no tumor upstaging and who may have a second-look TURBT postponed – an observation that corresponds with the

guideline recommendations to base the decision to perform a re-resection on the stage, grade, and index TURBT adequacy rather than on patient demographics (6,13).

These results need to be evaluated in light of the debate surrounding the absolute necessity of performing second-look TURBT. Although both the 2021 EAU guidelines and the current AUA/SUO guidelines still recommend re-resection of all T1 tumors and high-grade Ta tumors (6,13), several recent reports have challenged this recommendation, indicating the possibility of omitting second-look TURBT in appropriately selected patients due to extra risk of surgery, cost, and delay of intravesical treatment.

However, our findings, with respect to residual tumor in more than half and upstaging in a third of unselected, consecutive high-grade Ta/T1 tumors, indicate that this recommendation should neither be modified nor relaxed in our setting; rather, it implies that excluding second-look TURBT in similar local conditions might result in inadequate staging and mismanagement of the upstaged patients, who may require more aggressive treatment than intravesical therapy. It should be noted that the present study seems to be the first one in Pakistan presenting such findings, which is why it bridges an important gap in the regional literature by providing locally generated evidence instead of applying data from predominantly European and East Asian populations to this setting.

LIMITATIONS

Several limitations are evident in this study and should be taken into account. First, the study was performed at one tertiary care center through the use of non-probability consecutive sampling, limiting the generalizability of the findings across other centers with potentially different referral patterns, surgeries, and patient population. Secondly, the use of cross-sectional research design provided the results of second-look only and not the longer follow-up that would help to determine the effect of residual disease or progression and upstaging on recurrence and survival. Thirdly, all patients included in the study had their staging done as pT1 based on histopathological results after TURBT surgery with no high-grade pTa tumors present during the study period. This patient population, although being the true reflection of our population, is difficult to compare with other studies which had high proportion of high-grade Ta tumors. Fourthly, the inter-observer variability in histopathological staging and grading at both primary and second look TURBTs was not investigated, and all histopathology reports were provided by one laboratory. Lastly, while all operations were done by consultant urologists with over five years of post-fellowship experience, differences in the adequacy of the index (primary) TURBT operation done prior to being referred – an aspect that has been shown to significantly contribute to residual disease rates in the literature – could not be standardised in this study.

CONCLUSION

In the current study group of patients with high-grade Ta/T1 stage non-muscle invasive bladder cancer under management in a tertiary urology center in Pakistan, second-look TURBT detected residual cancer in over 50% of the patients, with about 30% of patients exhibiting tumor upstaging. These results are in concordance with, and in the case of upstaging even higher than, many of the previously published international studies. None of the factors such as gender, age, or tumor grade could be used to predict which patients were less likely to exhibit these outcomes.

RECOMMENDATIONS

Multicentric, prospective studies are required to validate these results and determine the clinical implications of second look TURBT in terms of recurrence, progression and overall survival. The future studies must focus on the evaluation of the completeness of initial TURBT (as an independent factor) because it is known that this parameter affects the rate of residual disease, as well as tumor size, multifocality and time between initial and second look TURBT. The relationship between these parameters and residual disease or upstaging in the local population must be assessed because it was impossible to analyze them in the current study.

ETHICAL APPROVAL

The study was approved by the Institutional Ethical Review Committee prior to commencement, and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORS' CONTRIBUTION

[Author]: Concept, design, data collection, manuscript writing. Data analysis, literature search.Critical revision. [Supervisor]: Study supervision, final approval of manuscript.

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