The Research of Medical Science Review
ISSN: 3007-1208 & 3007-1216 Volume 3, Issue 7, 2025

FREQUENCY OF UPSTAGING AND UPGRADING OF NON-MUSCLE-INVASIVE BLADDER CANCER (NMIBC) ON REPEAT RESECTION AT 4-6 WEEKS

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DOI: https://doi.org/10.5281/zenodo.16351393

Keywords
Non-muscle invasive bladder cancer (NMIBC), transurethral resection of bladder tumors (TURBT), Tumor upstaging

Article History
Received on 22 April 2025
Accepted on 07 July 2025
Published on 23 July 2025

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Abstract

Objective: *To determine the frequency of upstaging and upgrading of non-muscle-invasive bladder cancer (NMIBC) on repeated transurethral resection of bladder tumor (TURBT).*

Study Design: *Cross-sectional study*

Place & duration of study: *Study was conducted at Sindh Institute of Urology & Transplantation from 18th May, 2023 to 1st January, 2025*

Methodology: *In this cross-sectional study, we included 62 patients with a pathological diagnosis of pTa/T1 urothelial carcinoma of the bladder on initial TURBT who had adequate muscularis propria present in the specimen. The follow-up TURBT (Re- TURBT) was performed 4 to 6 weeks after the initial procedure, allowing for the assessment of any upstaging or upgrading of the NMIBC or early recurrence. Gender, smoking status, hypertension, diabetes mellitus, tumor stage, histological grade, upstaging, and upgrading on repeat resection will be categorical data. This categorical will be repeated in terms of frequency and percentage. Upstaging was classified as occurring when the tumor was determined to be at a stage higher than previous stage. Early recurrence defined as new tumor found on the re-TURBT, despite complete resection on the initial TURBT*

Results: *The baseline study characteristics reveal that the average age of participants is 61.27±7.89 years. Among the study population, 46 patients (74.2%) were male. The average size of the tumors was 4.66±1.255 cm. Tumor upstaging was observed in 22 cases (35.5%). No early recurrence seen in our study population.*

Conclusion: *There is a high frequency of tumor upstaging and upgrading on repeated TURBT in patients of NMIBC. So, all patients after primary TURBT should be advised follow-up TURBT at 4 to 6 weeks, for the assessment of any upstaging or upgrading of the NMIBC.*

INTRODUCTION

Bladder cancer is one of the most frequently diagnosed cancers worldwide, with an estimated 550,000 new cases identified each year.[1] A significant portion of these cases consists of non-muscle invasive bladder cancer (NMIBC), which includes stages Ta, T1, and carcinoma in situ, representing roughly 75% of diagnoses at the outset.[2] In addition to T stage, tumor grade also play a role in staging, management, and prognosis. It is crucial to recognize that, despite being categorized as NMIBC, nearly all T1 tumors are classified as high grade (Grade 3), which means they have a heightened risk of evolving into muscle-invasive cancer and spreading to surrounding tissues.

The precise identification, classification, and prognosis of bladder cancer are primarily facilitated by the procedure known as transurethral resection of bladder tumors (TURBT). Achieving an accurate determination of the tumor's stage requires a comprehensive removal of the tumor, ensuring that the specimen includes the muscularis propria layer. It is not uncommon for patients with high-risk non-muscle invasive bladder cancer (NMIBC) to be inaccurately staged during their initial TURBT, leading to potential delays in receiving accurate diagnosis and appropriate treatment.[4] The frequency of upstaging of disease during repeat transurethral resection can vary significantly, with reported rates ranging from as low as 0% to as high as 28%.[5] In some studies, this rate may reach up to 49%, particularly when the muscularis propria is not present in the sample.[6] Additionally, the proportion of patients experiencing residual disease or early recurrence can be quite high, ranging between 21% to 78%. [7, 8] Given these concerning statistics, it is advisable for patients identified as high-risk, as well as those presenting with large or multiple tumors or cases where the initial transurethral resection was incomplete, to undergo a repeat procedure within 2 to 6 weeks. This approach helps determine the most appropriate management strategies.

The aim of this study was to determine the frequency and type of upstaging and upgrading of non-muscle-invasive bladder cancer (NMIBC) on repeated TURBT.

METHODS:

After taking approval from institutional ethical review committee, the samples were collected from 18 May 2023 to 01 January 2025. Based on previous estimate of upstaging rate was found to be 17.8% with margins of error 5% and confidence interval of 95%. A total sample size of 62 patients needed for the study. In our study, we included 62 patients with a pathological diagnosis of pTa/T1 urothelial carcinoma of the bladder on initial TURBT who had adequate muscularis propria present in the specimen. Patients with any previous history of TURBT, intra-vesical therapy, bimanually palpable growth at the time of TURBT, visibly incomplete initial TURBT, absence of detrusor muscle from the specimen, variant histology on initial or follow up TURBT, and those with incomplete record available, were excluded. Study participants were asked to provide informed consent.

Data regarding the patient's age, gender, co-morbids, smoking, occupational exposure of risk factors were taken in to account. All patients underwent baseline investigations and ultrasound kidney, ureter, and bladder (KUB). Data collected on standard Performa by principle investigator or one of the co-investigator. Data collected directly from patient and reviewing the medical records of patients from files and hospital medical information system (HMIS). Each patient underwent a cystoscopy and any papillary tumor growth identified in the bladder was completely excised, and label as initial TURBT. A consultant urologist performed the TURBT in all cases. The follow-up TURBT was performed 4 to 6 weeks after the initial procedure by a consultant urologist, and at least two biopsies were taken from previous resection site. The pathology specimen reviewed by same pathologist and grading and T staging assigned. Upstaging was classified as occurring when the tumor was determined to be at a stage higher than previous T stage. Upgrading defined as biopsy shown the grade higher than the grade seen at initial TURBT, as per WHO 1973 grading system. Early recurrence defined as, growth seen at follow- up TURBT which needs resection.

Data were analyzed using SPSS version 22. Mean values and standard deviations were calculated to summarize age, body mass index (BMI), and tumor size. Categorical variables, including gender, smoking,

hypertension, diabetes mellitus, tumor stage, histological grade, and upstaging and upgrading during repeat resections, were reported in terms of frequency and percentages.

RESULTS:

The baseline study characteristics reveal that the average age of participants is 61.27±7.89 years. The participants have a mean Body Mass Index (BMI) of26.29±2.50 Kg/m^2. Among the study population, 46 (74.2%) cases were male. Regarding co-morbidities, 29 (46.8%) of participants were smokers, while 13 (21.0%) had diabetes, and 34 (54.8%) patients had hypertension. In terms of clinical features, hematuria was reported by 55 (88.7%) participants, dysuria by 30 (48.4%), and clot retention by 7 (11.3%) cases. Besides this, urgency reported by 11 (17.7%) patients (Table I).

The laboratory findings revealed several key variables. The hemoglobin (Hb) level was measured at a mean of 12.09 g/dL with a standard deviation (SD) of 9.83. Total leukocyte count (TLC) showed a mean of 7.11 × 10^9 cells/L with an SD of 1.85. The mean urea concentration was found to be 27.90 mg/dL, accompanied by an SD of6.79. Lastly, creatinine levels averaged 1.22 mg/dL with an SD of 0.393 (Table II).

Table 3 outlines the tumor characteristics of the subjects studied. The average size of the tumors was 4.66±1.25 cm. In terms of the number of tumors present, 22 cases (35.5%) had a single tumor, 6 cases (9.7%) had two tumors, and the 34 cases (54.8%), exhibited multiple tumors. The primary risk scores indicated that 6 cases (9.7%) were classified as low risk, 3 cases (4.8%) as intermediate risk, and a significant 53 cases (85.4%) were considered high risk, as per EORTC risk calculator (2006). Follow-up cystoscopy at the 4-6-week follow-up, tumor upstaging was observed in 22 cases (35.5%). Among those who experienced upstaging, 10 cases (45.5%) progressed from Ta to T1, while 12 cases (54.5%) advanced from T1 to T2. Tumor upgrading was observed in 8 (12.9%) cases. Out of these 8 cases, 6 (75%) have progression from grade 2 to grade 3 [G2→G3], while 2 (25%) cases have upgrading from grade 1 to grade 2 [G1→G2]. No early recurrence seen at follow-up TURBT in our study population. (Table III)

Table I. Baseline Study Characteristics.

Variable	**Mean ± SD**
Age	61.27±7.89
BMI	26.29±2.50
Variable	**Frequency (Percentage)**
Male Gender	46 (74.2%)
Smoking	29 (46.8%)
Diabetes	13 (21.0%)
Hypertension	34 (54.8%)
Clinical Features	**Frequency (Percentage)**
Hematuria	55 (88.7%)
Dysuria	30 (48.4%)
Clot Retention	07 (11.3%)
Urgency	11 (17.7%)

Table II. Laboratory Findings.

Variable	Mean ± SD
Hb	12.09±9.83
TLC	$7.11x10^9$±1.85
Urea	27.90±6.79
Creatinine	1.22±0.39

Table III. Tumor Characteristics & Upstaging

Variable	Value
Size of Tumor (cm)	**4.66±1.25**
Number of Tumors	
01	22 (35.5%)
02	6 (9.7%)
Multiple	34 (54.8%)
Primary Risk Score (%) EORTC [2006]	
Low Risk	06 (09.7%)
Intermediate Risk	03 (4.8%)
High Risk	53 (85.4%)
Cystoscopy At 4-6 weeks Follow-up	
Tumor Upstaging	22 (35.5%)
Tumor Upgrading	8 (12.9%)
Type of Upstaging (Out of 22 cases)	
Ta to T1	10 (45.5%)
T1 to T2	12 (54.5%)
Type of Upgrading (Out of 8 cases)	
G1 TO G2	2 (25%)
G2 TO G3	6 (75%)

DISCUSSION:

TURBT plays a vital role in both diagnosing and managing NMIBC. Ensuring that the TURBT is thorough and executed correctly is crucial for achieving favorable outcomes.[9] A substantial body of research indicates that performing a re-TURBT for patients categorized as high-risk for NMIBC can significantly reduce the incidence of residual cancer and minimize the potential for incorrect staging.[10, 11]

In our study, the rate of tumor upstaging after primary TURBT was 35.5%. Akgul et al. reported tumor upstaging in 14% of cases, while Kinnaird et al. quoted upstaging rate of as high as 40% from major studies.[12, 13] In our study, all patients have muscle present in the specimen on initial TURBT and not a single case has early recurrence and this finding concurs with the findings of study by Chang et al., in which the patient who has muscle present at initial TURBT have no residual disease on re- TURBT. [14] These findings are consistent with our study.

A study carried out within the Canadian healthcare system revealed overall recurrence rates of 54.5% for patients diagnosed within six weeks, compared to a higher rate of 58.1% for those diagnosed after a period exceeding six weeks. Additionally, the upstaging rates were recorded at 6.8% for the six-week group, in contrast to 10.1% for the group with a delay beyond that timeframe.[13] Similarly, a prospective investigation conducted at a tertiary care

facility in India found an upstaging rate of 17.8% among patients diagnosed within four to six weeks. [15] While some studies have reported very low incidence rate of upstaging on repeated TURBT. A study by Soria et al. have upstaging rate of 7%, but they have included upstaging to muscle invasive disease only. [16] Another study by Chang et al. reported frequency of upstaging in 3.0% patients having NMIBC on repeated TURBT. [14]

Previous research has indicated a correlation between lower rates of sampling from the muscularis propria and an increase in both residual tumor presence and inaccurate tumor staging. [17] There is evidence to suggest that any remaining tumor after the initial transurethral resection of bladder tumor (TURBT) may adversely affect the effectiveness of BCG therapy. [14] As a result, the European Association of Urology has the recommendation for a repeat transurethral resection (re-TUR) within 2 to 6 weeks following the initial surgery as Grade A. [18] The ESMO guidelines recommended to have re-TURBT from 4-6 weeks. [19] In our study, we use this reference and our all patients underwent re-TURBT between 4-6 weeks. These guidelines apply specifically to high-risk tumors, including cases where the first resection may have been inadequate, those involving larger or multiple tumors, and situations where the initial resection specimens lacked muscularis propria. [18,19] To our knowledge, this study is the first in Pakistan to analyze compliance with the re- TURBT guidelines since they were established. Our focus is specifically on the rates of re-TURBT for high-risk non-muscle-invasive lesions, which are crucial for determining the necessity of following these guidelines.

The existing literature is considerably variable concerning the prevalence of residual disease after the initial transurethral resection of bladder tumor (TURBT). This discrepancy may stem from differences in the skill levels and techniques employed by the surgeons performing both the initial and subsequent resection procedures. [20]

In our study, all the initial and re-TURBT procedures were performed by very experienced surgeons in a single set up.

Despite being a thorough research on the subject studied, like all other studies our study also as few limitations. This a single center study with small sample size. All procedure performed by experienced urologist but by more than on urologists, so technical expertise may differ.

CONCLUSION:

There is a high frequency of tumor upstaging on repeated TURBT in patients of NMIBC. So, all patients after primary TURBT should be advised follow-up TURBT at 4 to 6 weeks, for the assessment of any upstaging, or early recurrence of the NMIBC.

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