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Original Research Article

A prospective observational study to evaluate the role of restaging transurethral resection of bladder tumour in patients with non-muscle invasive bladder cancer

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ABSTRACT

Background: Transurethral resection of bladder tumour (TURBT) is the primary treatment modality for Non-muscle invasive bladder cancer (NMIBC). Restaging transurethral resection of bladder tumour (RETURBT) is indicated to reduce risk of residual disease and correct staging errors after primary TURBT. The aim of the study is to evaluate the risk of residual tumour and upstaging in NMIBC after TURBT and to investigate the risk factors for the same.
Methods: A prospective observational study was carried out over 4 years and 87 patients were included in the study. Patients with NMIBC underwent RETURBT after 2-6 weeks of primary TURBT. The incidence of residual tumour and upstaging in RETUBRT was correlated with various histopathological and morphological parameters in primary TURBT.
Results: Out of 87 patients, who underwent RETURBT, residual disease was present in 51 patients (58.6%) and upstaging occurred in 22 patients (25.2%).On univariate analysis, T1 stage (p=0.01), high grade (p=0.01), Carcinoma in situ(CIS) (p=0.01) and multifocality (p=0.05) were predictive for residual disease in RETURBT. High grade (p=0.01), CIS (p=0.01) and absence of detrusor muscle in specimen (p=0.03) were risk factors for upstaging in RETURBT.
Conclusions: NMIBC have high incidence of residual disease and upstaging after primary TURBT. T1 stage, high tumour grade, CIS, and multifocality are risk factors for residual disease after primary TURBT. High tumour grade, CIS and absence of detrusor muscle are strongly associated with upstaging during RETURBT.

Keywords: Carcinoma in situ, Non-muscle invasive bladder cancer, Transurethral resection of bladder tumour, Restaging transurethral resection of bladder tumour

INTRODUCTION

Transurethral resection of bladder tumor (TURBT) is a crucial procedure in the diagnosis and treatment of urothelial cancer. The goal of TURBT in Non-muscle invasive bladder cancer (NMIBC) is to make the correct diagnosis and completely remove all visible lesions. Recurrence after TURBT can occur due to incomplete tumor resection, implantation of tumor cells, microscopic tumor remnant and aggressive tumor biology.[1] Certain critical manoeuvres are required to ensure complete resection. These include thorough inspection of bladder with 12 degree and 70-degree scope at the end of resection. The bladder volume should be maintained at approximately 50%-70% of its capacity to avoid over distension. This step is important, as a full bladder can

flatten the mucosa and make it more difficult to visualize areas of Carcinoma in situ (CIS).[2]

Biopsies from normal-looking mucosa is recommended when cytology is positive or when high-risk exophytic tumor is present (sessile appearance). Additionally, prostatic urethra biopsies are to be taken in cases of bladder neck tumor, when bladder CIS is present, when there is positive cytology without evidence of tumors in the bladder, or when abnormalities of the prostatic urethra are visible.[3] However, even after adoption of standardized resection technique, it is not always possible to do complete resection during TURBT. Residual tumor is present in 26% to 83% of patients during restaging transurethral resection of bladder tumor (RETURBT).[4] At the first resection, underestimation of pathologic stage occurs in 14-24% of cases depending on stage of tumour.[5]

Absence of detrusor muscle in tumor specimen leads to staging errors. The likelihood that muscle-invasive disease is detected by second resection of initially T1 tumor ranges from 4-25%, and it increases to 45% if there was no muscle in the initial resection.[6]

T1 stage, high tumor grade and sessile tumors have higher risk for upstaging and residual disease in RETURBT. CIS in primary TURBT correlates well with residual tumor while the absence of muscle in the primary TURBT specimen was significantly associated with upstaging to muscle invasive disease.[7]

Staging errors can occur due to errors during slide review by pathologist. Cautery artefacts, lack of uniform terminology, and difficult orientation of multiple fragmented pieces of tissue can lead to staging errors. Moreover, different patterns of invasion in cases of T1 tumors (broad-front or tentacular invasion) may contribute in these staging errors.[8]

According to latest European Urology guidelines, RETURBT is advised after incomplete primary resection, when muscle is absent in initial TURBT specimen and in all T1 tumors. When indicated it is advisable to perform RETURBT within 2-6 weeks of initial resection. Primary resection scar site should be included during RETURBT.[3]

The present study aims to evaluate the evaluate the risk of residual tumors and upstaging in NMIBC after TURBT and to investigate the risk factors for the same.

METHODS

This is a prospective observational study conducted over 4 years from January 2015 to December 2018 at Sri Sathya Sai institute of higher medical sciences, Puttaparthi. Out of 133 patients diagnosed in the initial TURBT as bladder cancer cases, 34 patients had muscle-invasive bladder cancer and 99 patients had NMIBC. 87 patients were included in the study after satisfying strict inclusion and exclusion criteria.

Inclusion criteria

- All patients with NMIBC who underwent complete resection during TURBT.

Exclusion criteria

- Bladder tumors other than transitional cell carcinoma.
- Bladder tumors with concomitant upper track transitional cell carcinoma.
- Recurrent bladder tumors.

Preliminary Cystoscopy was done to assess tumor size and focality. TURBT was done using 26 F monopolar resectoscope by experienced senior surgeons who have minimum experience of 60 TURBT cases. For tumors <1 cm whole of tumor was resected in one piece including bladder wall. For tumors >1 cm resection was performed in piece meal taking bladder wall with underlying detrusor muscle and edges of resection margin. In case of tumor arising from bladder neck and when abnormal areas in prostatic urethra was visible, additional biopsies from prostatic urethra was taken including precollicular portion (between 5 o'clock and 7 o'clock). After achieving hemostasis, Mitomycin C 40 mg dissolved in 20 ml normal saline was installed within 6 hours of surgery. Mitomycin instillation was deferred if bladder perforation/excessive bleeding occurred during TURBT. After instillation of Mitomycin C, per urethral catheter was kept clamped for 1 hour. Tumors were staged according to the 2017 TNM classification (Table 1) and graded according to the 2004 WHO classification (Table 2). Presence of carcinoma in situ (CIS), Lymphovascular invasion and detrusor muscle was noted during histopathological review.

RETURBT was performed 2-6 weeks following primary TURBT. During RETURBT, the bladder was assessed for any residual tumors or missed lesions. If no obvious tumor was found, scar biopsy was taken.

Persistence of malignancy in RETURBT was defined as residual tumor. Any progression in stage or grade during RETURBT was defined as tumor upstaging.

The analysis was focused on incidence of residual tumor and upstaging in RETURBT. The following parameters were analyzed for their role in residual disease and upstaging in RETURBT.

- T stage.
- Tumor grade.
- Tumor focality
- Absence of detrusor muscle
- Concomitant CIS.
- Lymphovascular invasion in sub epithelial connective tissue layer

Table 1: TNM classification of urinary bladder cancer.

T-Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma in situ
T1	Tumour invades subepithelial connective tissue layer
T2	Tumour invades muscle
	T2a Tumour invades superficial muscle
	T2b Tumour invades deep muscle
T3	T3 tumours -invade perivesical tissue
	T3a -microscopically
	T3b-macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
	T4a Tumour invades prostatic stroma, seminal vesicles, uterus or vagina
	T4b Tumour invades pelvic wall or abdominal wall
N-Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node in the true pelvis
N2	Metastasis in multiple regional lymph nodes in true pelvis
N3	Metastasis in common iliac lymph node(s)
M-Distant metastasis	
M0	No distant metastasis
	M1a Non-regional lymph nodes
	M1b Other distant metastasis

Table 2: WHO grading system of urinary bladder cancers.

WHO grading system of papillary bladder cancers
• Papillary urothelial neoplasm of low malignant potential
• Low grade papillary urothelial carcinoma
• High grade papillary urothelial carcinoma

Data collection

All the data were collected prospectively during the course of treatment.

Statistical analysis

Plan Continuous data with skewed or normal distribution was described as median (interquartile range) or mean (standard deviation) respectively after assessing for normality by D'Agostino-Pearson test for Normal distribution. Analytic statistics were obtained using the chi-square test and the differences were significant if $p<0.05$, however, fisher's exact f test was used where observed or expected counts were <5. All statistical analysis was performed using SPSS software (version 23, SPSS Inc., Chicago, IL, USA).

Ethical consideration

Institutional ethics committee approved the study. Protocol required no additional expense or therapeutic burden on the patient. Consent was sought for recruitment into study protocol and withdrawal at any stage was permitted. Patient identity was anonymized.

RESULTS

87 patients with diagnosis of NMIBC in primary TURBT underwent RETURBT. Mean age of the patient population was 61 years (range 20-83 years). Out of 87 patients who underwent TURBT, 74 were males and 13 were females with male: female ratio of 6:1.

The tumor characteristics on primary TURBT and their distribution in the study group are shown in Table 3. The outcome of RETURBT. (Table 4).

Table 3: Findings of primary TURBT.

Parameter	Distribution in study group
Tumour stage	Ta= 16
	T1= 71
Tumour grade	Low grade= 34
	High grade= 53
Tumour focality	Unifocal= 44
	Multifocal= 43
Carcinoma in situ	Absent= 75
	Present= 12
Muscle in specimen	Present= 60
	Absent= 27
Lymphovascular invasion	Absent= 85
	Present= 2

Table 4: Outcome of RETURBT.

Outcome measures of RETURBT	Present	Absent	Number (%)
Residual tumour	51	36	58.6%
Upstaging*	22	65	25.2%

Out of 87 patients who underwent RETURBT, residual disease was present in 51 patients(58.6%) and upstaging occurred in 22 patients (25.2%).Out of 22 patients who upstaged,20 had upstaged to muscle invasive bladder carcinoma, whereas 2 had upstaged from low grade to high grade disease. Authors also analyzed risk factors for residual disease and upstaging during RETURBT (Table 5 and Table 6).

On univariate analysis, T1 stage (p=0.01), high grade (p=0.01), CIS (p=0.01) and multifocality (p=0.05) were predictive for residual disease in RETURBT. High grade (p=0.01), CIS (p=0.01) and absence of detrusor muscle in specimen (p=0.03) were risk factors for upstaging in RETURBT.

Table 5: Univariate analysis of factors predictive for presence of residual tumour in RETURBT.

Prognostic histopathological and morphologic characteristics in primary TURBT		Residual tumours in RETURBT		p value
		Number	Number (%)	
Tumour stage	Ta	4	25%	0.01
	T1	47	66.2%	
Tumour grade	Low grade	13	38.2%	0.01
	High grade	38	71.7%	
Tumour focality	Unifocal	21	47.7%	0.05
	Multifocal	30	69.8%	
Carcinoma in situ	Absent	39	52.0%	0.01
	Present	12	100.0%	
Muscle in specimen	Present	31	51.7%	0.06
	Absent	20	74.0%	
Lymphovascular invasion	Absent	49	57.6%	0.5
	Present	2	100%	

Table 6: Univariate analysis of various histopathological and Morphologic Prognostic Factors predictive for upstaging in RETURBT.

Prognostic histopathological and morphologic characteristics in primary TURBT		Upstaging in RETURBT		p value
		Number	Number (%)	
Tumour stage	Ta	1	6.3%	0.06
	T1	21	29.6%	
Tumour grade	Low grade	3	8.8%	0.01
	High grade	19	35.8%	
Tumour focality	Unifocal	11	25.0%	1
	Multifocal	11	25.6%	
Carcinoma in situ	Absent	14	18.7%	0.01
	Present	8	66.7%	
Muscle in specimen	Present	11	18.3%	0.03
	Absent	11	40.7%	
Lymphovascular invasion	Absent	20	23.5%	0.06
	Present	2	100%	

DISCUSSION

Transurethral resection of bladder tumor is the standard of care for non-muscle invasive bladder urothelial carcinoma. Residual tumor after TURBT may occur due to a variety of reasons. These are summarized as below.

A) Incomplete tumor resection

Residual tumor can occur due to incomplete resection. Intra operative complications like hematuria can hamper vision leading to substandard resection. Obturator jerk during resection of lateral wall tumors result in early termination of procedure.

B) Implantation of tumor cells

It is believed that tumor cell implantation immediately after resection is responsible for many early recurrences.

This explains the reason why initial tumors most are commonly found on the floor and lower sidewalls of the bladder, whereas recurrences are often located near the dome as a result of flotation.[9]

C) Microscopic tumor remnant after TURBT

CIS being a flat tumor is easier to miss during TURBT. Positive margin after resection contribute to recurrence.

This is often overlooked during resection. It is recommended to take a minimum of 15 mm margin of healthy bladder mucosa to avoid undersection.[10]

D) Aggressive tumor biology

The field change theory of bladder cancer assumes a global change in urothelium with multiple transformed cells evolving into mature tumors separately. Therefore, even after complete resection of tumor, the remaining dysplastic urothelium can develop foci of cancer over time.

Residual tumor is present in 26% to 83% of patients during restaging transurethral resection of bladder tumor (RETURBT).[4] One of the first study on RETURBT was carried out by Herr et al who found residual disease in 75% of tumors. But the series included both new and recurrent bladder tumors and patients did not receive intravesical chemotherapy.[11] In a prospective examination of the outcome of RETURBT in 80 patients, Divrik et al, found residual cancer in 33.8% of cases.[12]

This study has reported 58.6% incidence of residual tumor. Even though only cases who underwent complete resection were taken up for the study, tumor implantation and microscopic tumor remnants may have contributed to residual disease. Residual T1 tumors after RETURBT have a worse prognosis compared to Ta tumors or no tumors. This information is useful for prognostication. Authors found upstaging risk 25.2% of in our study. Mahdi et al reported 38.7% upstaging rate in his study.[13] Dutta et al reported understaging risk of 40% when radical cystectomy was done for T1 high grade tumours.[14]

Upstaging to muscle invasive tumor changes treatment to radical cystectomy. Therefore, RETURBT will be extremely useful to detect muscle invasive tumors that have been missed during initial TURBT. Tumors that upstage during RETURBT have poor disease specific and overall survival compared to tumors that don't upstage. This is important prognostic information provided by RETURBT.[15]

According to current available evidence, T1 tumors which downstages to pT0 in RETURBT do not require intravesical BCG. It is possible that pT0 status after RETURBT carries a minimal risk for recurrence or progression and that intravesical BCG therapy is overtreatment for these patients. Thus, RETURBT gives information on this subgroup of patients, in whom BCG can be selectively avoided thereby avoiding adverse side effects of BCG and reducing economic burden on patients.[16] The value of pathological reinterpretation of tissue slides has long been questioned. Second review of transurethral bladder tumor resection specimens shows differences of interpretation in 26.7% to 33.3% of cases, which is sufficient to alter management.[17] Interobserver variability may be due in part to the use of varying grading systems, the lack of uniform terminology, and the variation in training and experience of the interpreting pathologist. Confusion of muscularis mucosa with muscularis propria may lead to over staging of superficial bladder cancer especially when muscle in scant in specimen. All our TURBT specimens were reviewed by a single experienced genitourinary pathologist, decreasing risk of error. Surgeon experience during TURBT correlates with disease recurrence. Inexperienced surgeons may not be competent to adequately resect tumor with underlying detrusor. This may lead to under staging and increased residual tumor risk. A report from Jancke et al, indicated that more experienced surgeons perform a more complete resection and have lower recurrence rates.[18] All our resections were done by senior consultant, thus the risks of incomplete resection due to surgeon inexperience doesn't come into question. In this study T1 tumors had higher rate of residual tumor in RETURBT compared to Ta tumors (66.2% vs. 25% p =0.01). Grimm et al reported T1 tumors to have higher residual tumor rate compared to Ta tumors (53% vs. 27%).[19] In another study residual tumors were found in 28% of the patients with Ta tumors and 54.2% of the patients with T1 tumours.[13]

High grade disease and CIS were significant risk factors for residual disease and upstaging in RETURBT. Gill et al reported T1 stage, high tumor grade and sessile tumors to have higher risk for upstaging and residual disease in RETURBT.[7] Since CIS difficult to visualize, there is high incidence of residual disease in tumors with CIS. Orsola et al showed that tumor size (>3cm) and CIS were significantly associated with tumor persistence.[20] Multifocality was found to be a strong risk factor for tumor persistence (69.8% vs. 47.7% p=0.05). Devasia et al, reported that 95% of the patients with solitary papillary lesions did not have any residual disease in RETURBT compared to 50% of the multiple papillary and 83.3% of the sessile group.[21]

Absence of detrusor muscle was significant predictor for upstaging to muscle invasive tumors in RETURBT (40.7% vs. 18.3% p =0.03). Similar observation was seen by Dutta et al who reported a 64% rate of under-staging in T1 tumor's if muscle was absent in the specimen versus only a 30% rate if muscle was present.[14] There are certain limitations in our study. T1 tumors without invasion of muscularis mucosa vascular plexus and those with unifocal invasion of lamina propria had decreased residual tumor rate in RETURBT.[22] Also, margin width is an important prognostic indicator for residual disease.[10] These parameters were not evaluated in our study. Newer modalities like fluorescent cystoscopy and narrow band imaging have led to improved detection rate of bladder cancer, indirectly leading to decreased residual tumor rate. The largest clinically important impact is on detection of CIS.[2] Use of these newer modalities was not undertaken in our study.

CONCLUSION

RETURBT helps in detection of residual disease and upstaging after Primary TURBT in NMIBC. T1 stage,

high tumor grade, CIS, and multifocality have high incidence of residual disease after primary TURBT. High tumor grade, CIS and absence of detrusor muscle are strongly associated with upstaging during RETURBT.

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