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ROLE OF RESTAGE TRANSURETHERAL RESECTION OF BLADDER TUMOR IN HIGH RISK NON MUSCLE INVASIVE BLADDER CANCER

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ABSTRACT

Background

Transurethral resection of the bladder tumor (TURBT) is the treatment of choice and gold standard for the treatment of clinical non-muscle invasive bladder cancer. Incomplete resection, tumor cell re-implantation, presence of subclinical tumors lead to recurrence of bladder cancer. According to guideline recommendations, restage TURBT is indicated 2-6 weeks after the initial TURBT in high-risk patients. The objective of the present study was undertaken to evaluate role of restage TURBT in high risk non-muscle invasive bladder cancer (NMIBC).

Objective

To identify the category of patients with high risk non-muscle invasive bladder cancer who may benefit from a routine restage TURBT procedure.

Materials and Methods

In this prospective observational study, biopsy proven NMIBC patients with gross total painless hematuria secondary to urinary bladder mass from October 2017 to June 2019 were enrolled. Patients with high risk disease on primary TURBT underwent re-TURBT within 2-6 weeks of primary procedure. Residual/ recurrent disease and tumor upstaging were recorded. Logistic regression analysis were used to explore risk factors associated with residual/recurrent disease and tumor upstaging during re-TURBT.

Results

A total of 250 patients (deep muscle involvement, n=237 and no muscle involvement, n=13) with histopathologically confirmed high risk disease following re-TURBT were included in the final analysis. During re-TURBT, 18% patients had residua or recurrent tumor. Presence of upper tract changes, presence of perivesical fat stranding and tumor size > 3cm, high grade histopathology and positive urine for malignant cytology were significantly associated with risk of residual or recurrent disease. Absence of muscle in primary TURBT specimen, presence of recurrent/residual growth in re-TURBT specimen, bladder tumor antigen increased the risk of upstaging.

Conclusion

Despite the low recurrence rate of tumor in re-TURBT, reTURBT within 2-6 weeks of primary TURBT is an essential step for the accurate diagnosis among NMIBC patients. This further aids in deciding the subsequent treatment step in patients with upstaging and recurrent/ residual tumor.

INTRODUCTION

Bladder cancer is the 9th most common cancer and 13th most common cause of death worldwide.[1,2] The incidence is higher among males than females and among Caucasians than Asians. The age-standardized mortality rates are 2–10 per 100,000 males and 0.5–4 per 100,000 females.[3]

There are three types of bladder cancer that begin in cells in the lining of the bladder:

Transitional cell carcinoma

- Cancer that begins in cells in the innermost tissue layer of the bladder. Most bladder cancers begin in the transitional cells. Transitional cell carcinoma can be low-grade or high-grade:
- Low-grade transitional cell carcinoma often recurs (comes back) after treatment, but rarely spreads into the muscle layer of the bladder or to other parts of the body.
- High-grade transitional cell carcinoma often recurs (comes back) after treatment and often spreads into the muscle layer of the bladder, to other parts of the body, and to lymph nodes. Almost all deaths from bladder cancer are due to high-grade disease.

Squamous cell carcinoma

- Cancer that begins in squamous cells (thin, flat cells lining the inside of the bladder). Cancer may form after long-term infection or irritation.

Adenocarcinoma

- Cancer that begins in glandular cells that are found in the lining of the bladder. Glandular cells in the bladder make substances such as mucus. This is a very rare type of bladder cancer.

Cancer that is in the lining of the bladder is called superficial bladder cancer. Cancer that has spread through the lining of the bladder and invades the muscle wall of the bladder or has spread to nearby

organs and lymph nodes is called invasive bladder cancer. Histologically, 90% of bladder cancers are of urothelial origin, 5% are squamous cell carcinomas, and less than 2% are adenocarcinoma or other variants. At initial presentation, nearly 80% of patients present with bladder cancers have tumors confined to the mucosa or submucosa, known as "non-muscle-invasive" bladder cancers and muscle involvement is seen in higher grades of cancer.[4] With higher risk of progression and recurrence in high grade tumors, early detection and initial management is of utmost importance. Treatment options available acco. to TNM staging

1.**Stage 0 (Noninvasive Papillary Carcinoma and Carcinoma in Situ)**
Treatment of stage 0 (noninvasive papillary carcinoma and carcinoma in situ) may include the following:

Transurethral resection
- with fulguration. This may be followed by one of the following:

Intravesical chemotherapy
- given right after surgery.
- Intravesical chemotherapy given right after surgery and then regular treatments with intravesical BCG or intravesical chemotherapy.

- Partial cystectomy
- Radical cystectomy
- A clinical trial of a new treatment.

2.Stage I Bladder Cancer
Treatment of stage I bladder cancer may include the following:

Transurethral resection
- with fulguration. This may be followed by one of the following:

Intravesical chemotherapy
- given right after surgery.
- Intravesical chemotherapy given right after surgery and then regular treatments with intravesical BCG or intravesical chemotherapy.

Partial cystectomy
- Radical cystectomy
- A clinical trial of a new treatment.

3.Stages II and III Bladder Cancer
Treatment of stages II and III bladder cancer may include the following:

- Radical cystectomy
- Combination chemotherapy
- followed by radical cystectomy. A urinary diversion may be done.

External radiation therapy
- with or without chemotherapy.

Partial cystectomy
- with or without chemotherapy.

Transurethral resection
- with fulguration.
- A clinical trial of a new treatment.

4.Stage IV Bladder Cancer
Treatment of stage IV bladder cancer that has not spread to other parts of the body may include the following:

- Chemotherapy
- Radical cystectomy
- alone or followed by chemotherapy.

External radiation therapy
- with or without chemotherapy.

Urinary diversion
- or cystectomy as palliative therapy to relieve symptoms and improve quality of life.

Stage 0 and stage i are superificial bladder tumour (non muscle invasive bladder tumour) while stage ii,iii and iv are invasive tumour(muscle invasive bladder tumour) .

Transurethral resection of bladder tumor (TURBT) is the first and gold standard treatment option for non-muscle invasive bladder cancer (NMIBC). TURBT eradicates all visible tumors and provides tissue for histopathological analysis. The quality of the primary TURBT specimen is paramount, and must include complete resection of tumor including suspected tumor and detrusor muscle to rule out muscle involvement and reduce the risk of disease progression and recurrence.[5] The International Bladder Cancer Group defines progression of NMIBC as an increase in the T stage not only as development of T2 or greater, but also as an increase in the T stage from CIS or Ta to T1.[6]

While TURBT is aimed at staging Ta, T1 and CIS and excising all endoscopically visible lesions, approximately 50% of T1 patients display residual tumors and approximately 25% cases result in upstaging during re-TURBT performed within 2-6 weeks, particularly in patients with high grade T1 and those with missing muscle in primary specimen.[7-10] Factors influencing the outcome of primary TURBT include, multiple tumors, a large tumor or a location with an unidentifiable margin, and effortless bleeding that can obstruct the surgeon's vision, the surgeon's experience and skill, the quality of the specimens, and the pathologist's evaluation. These subsequently result in underestimation of tumor in approximately 10-50% of cases with NMIBC following primary TURBT.[11]

Therefore, a second TURBT within 6 weeks after the primary TURBT is strongly recommended in patients with newly diagnosed T1 bladder cancer in various guidelines.[12, 13] While re-TURBT is often advised among bladder cancer patients, however, till date there are no clear indications for re-TURBT and it differs between institutions and authorities. Based on European Association of Urology (EAU) Guidelines 2014, absence of muscle specimen after primary resection, T1 tumors and in all high grade tumors should undergo re-TURBT within 2-6 weeks of TURBT, not only for accurate restaging, but also to evaluate the presence of residual cancer, for subsequent definitive treatment plan.[14] However, Re-TURBT is associated with limitations including bladder perforation, urethral stricture, higher cost and healthcare burden. Therefore, it is essential to identify subset of patients with definite indications for reTURBT.

With advances in technology and technique with time, incidence of stage progression or recurrence decreased with time is observed and rate of stage progression and recurrence previously studied needs to be re-evaluated. Also until now, few studies have investigated the efficacy of a second TURBT procedure for patients with high risk non muscle invasive bladder cancer. We will be conducting study to evaluate the role of restage TURBT in patients with high risk non muscle invasive bladder carcinoma and number of patients benefit by restage TURBT depending upon tumor characteristics and nature of tumor and to identify the subgroup where restage TURBT may be avoided. This will facilitate reduction in healthcare and patient burden by limiting re-TURBT only to subset of patients with increased risk of progression and/or recurrence.

MATERIAL AND METHODS

The present prospective observational study was conducted at Department of Urology at a tertiary care hospital from October 2017 to June 2019. Patients with gross total painless hematuria secondary to urinary bladder mass satisfying the eligibility criteria were included in the study. All consecutive patients diagnosed with

biopsy proven, high risk non-muscle invasive transitional cell carcinoma (TCC) of bladder following complete primary TURBT with high risk were enrolled in the study. Patients with low or intermediate risk, those with huge tumor burden not indicated for complete resection, patients with extravesical disease having radiological stage of ≥3 on CECT were excluded from the study.

The study was approved by institutional ethics committee of Dr RML Hospital & ABVIMS, New Delhi with number F.No.TP(DM/MCh)/IEC/PGIMER/RMLH 2094 dated 22nd December, 2017).

All patients signed an informed consent prior to enrollment. At enrollment, a detailed clinical history, physical examination including digital rectal examination, laboratory investigations including complete haemogram, blood urea, serum creatinine, random blood sugar, serum electrolytes, coagulation profile, bladder tumor antigen (BTA stat) test, urine routine and microscopic examination, urine culture and sensitivity, chest X-ray and electrocardiogram were carried out. An ultrasound of the kidneys, ureters and bladder region (KUB) was performed to assess the bladder mass size and location and to evaluate the upper tract. Contrast enhanced computed tomography (CT KUB)/ cystoscopy was done if needed.

Procedure

All enrolled patients underwent a primary complete TURBT. A pre-anaesthetic evaluation was carried out prior to admission/procedure in all patients. Patients were advised to take two tablets of laxative and an anxiolytic the previous night of surgery and fasting for 4-6 hours prior to admission. Following intravenous antibiotic administration, sedoanalgesia was admisistered for patients with for tumor size <3 cm and spinal/general anesthesia for tumor size ≥3cm. During initial cystoscopy, the operative details such as the number, configuration and site of lesions were mapped and recorded. TURBT was performed using a 26 Fr resectoscope and mono/bipolar cautery (settings 90 for pure cutting and 60 for coagulation). After complete TURBT, a deep biopsy from the base of the tumor was taken; the TURBT chips and biopsy specimens were sent separately for histopathological analysis. After complete resection of visibly seen tumor and achieving complete hemostasis, a 22 French tri-way catheter was inserted into the bladder, bulb inflated to a maximum of 15 ml, bladder was irrigated with 0.9% saline until clear effluent was seen. Within 72 hours postoperatively, Mitomycin-C (40 mg) was instilled into the bladder of all patients except those in whom bladder perforation/deep resection was suspected. Following discontinuation of irrigation for 2 hours, catheter was removed, patient was allowed to void and oral antibiotic was given for 3 days. Patients were discharged once the urine was clear.

Patients with high risk disease on primary TURBT were enrolled for second part of the study to undergo re-TURBT within a span of 2-6 weeks under sedoanalgesia. Same procedure followed in primary TURBT was followed. The following outcomes were noted: A) tumor on re-TURBT. B) Incidence of residual/recurrent disease and C) Incidence of tumor upstaging to T2. Patients with high risk disease & muscle free on re-TURBT HPE specimen were subjected to induction intravesical bacille Calmette-Guérin (BCG) 6 doses at 0 week followed by maintenance BCG at 6, 12, 18, 24, 36 weeks and Check cystopanendoscopy (CPE) 3 monthly for first 2 year then 6 monthly at next 2 year and the annually life-long.

STATISTICAL ANALYSIS

The statistical analysis was performed using SPSS package version 23. Continuous variables were expressed as mean and standard deviation (SD) and categorical variables were expressed as frequencies and percentages. Intergroup comparisons were carried out using Student's t test, analysis of variance (ANOVA), chi-square test or Fisher's exact test. Further, univariate and multiple logistic regression analysis was performed to explore risk factors that were associated with residual/recurrent disease and tumor upstaging following re-TURBT and results were reported as two-tailed odds ratio (OR) with 95% confidence interval (CI). For all analysis a significance level was set at 0.05.

RESULTS

From October 2017 to June 2019, a total of 1100 patients with suspected urinary bladder carcinoma were evaluated. Among these, 773 patients were BTA stat positive. A total of 250 patients HPE of primary TURBT suggestive of high risk disease who underwent re-TURBT within 2-6 weeks of primary TURBT were included in the final analysis. Based on presence or absence of deep muscle in primary TURBT specimen, patients were divided into Group A (deep muscle present): n=212 and Group B (deep muscle absent): n=38 and based on recurrence/residual growth on re-TURBT the patients were further divided into subgroup 1 and 2 (Figure 1). Following re-TURBT, 237 patients had deep muscle involvement and 13 patients had no muscle involvement. At 3 months during check CPE 43 patients had recurrent growth; among these, 35 patients were graded T1G3 (non-muscle invasive high grade) at primary TURBT and 8 patients were graded T1G1 (non-muscle invasive low group) at primary TURBT.

Demographic and patient characteristics

The mean age of patients was similar between muscle free and muscle involved group (56.2 years vs 53.0 years; p=0.373) and majority of patients belonged to the age range of 50-60 years. Overall the study population predominantly consisted of male population (84.8%). Gender distribution between muscle free and muscle involved group were not significantly different (p=0.117). On imaging the between group difference of urinary bladder (UB) mass was similar, whereas, presence of HDUN (3% vs 30.8% p<0.001) and presence of perivescical fat stranding and were statistically significant (14.3% vs 76.9%; p=<0.001). Compared to muscle free group, patients in muscle involved group had mean growth size >3cm (64.6% vs 92.3%; p=0.040). There was no significant difference in the number and type of growth between growths in the Primary TURBT, BTA stat test, urine cytology and histopathology between groups. Time for primary TURBT was longer than 30 minutes in muscle involved group (60.3% vs 92.3%; p=0.021). In the primary specimen, muscle was present in 84.8% in muscle free group and 46.2% in muscle involved group (p<0.001).

The mean interval for re-TURBT was 3.9 weeks in muscle free group and 4.2 weeks in muscle involved group. Cytology of re-TURBT showed recurrent/residual growth in 69.2% vs 15.6% patients in muscle involved and muscle free groups respectively (p<0.001). All patients in the muscle involved group were graded T2G3 during re-TURBT, while 75.5% had no tumor in muscle free group (p<0.001). CPE at 3 month follow up showed recurrent growth in 17.7% patients in muscle free group and none in muscle involved group.
On univariate and multivariate logistic regression analysis, factors such as perivescical fat stranding on imaging, presence of muscle in primary specimen and imaging of upper tract were associated with muscle involvement (Table 2). Since the number of outcomes was less, we penalised excessive variance as the results of the penalised logistic regression as shown in figure 2. Only Perivesical fat stranding and muscle present in primary specimen were significant predictors of muscle involvement. Cox regression analysis showed perivescical fat stranding in imaging, presence of muscle in primary specimen and imaging of upper tract as predictors of time to growth after primary TURBT (Table 3). Further, upper tract imaging, perivesical fat stranding, size of growth at the time of primary TURBT, BTA stat test, urine cytology for malignancy, time for primary TURBT, histopathology of primary and re-TURBT, muscle present in primary and re-TURBT specimen and CPE at 3 month follow up were associated with recurrence/residual of growth at the time of re-TURBT (Table 4).

DISCUSSION

TURBT has been the gold standard surgical procedure for the

management of NMIBC. In high risk patients, protocols and guidelines recommend taking a second look of TURBT after primary TURBT to check for recurrence, residual disease or upstaging.[12, 13] In This study, we compared only the selected parameters which are beneficial in predicting recurrent/residual and upstaging of disease. We also evaluated the role of routine reTURBT in T1 tumors, particularly those graded as high grade with no detrusor muscle involvement in the primary specimen.

In our study, total 270 patients were high risk on HPE after primary TURBT out of which 20 patient lost to follow up. Later 250 patients underwent re-TURBT within a span of 6-12 weeks after primary TURBT, with a mean of 3.9 weeks and 4.2 weeks in no muscle involvement and with muscle involvement groups. Total 212 patients (84.8%)had deep muscle in primary TURBT specimen and total 38 patients(15.2%) had deep muscle absent in primary TURBT specimen .Total 45 patients(18%) had recurrent growth on re-TURBT scopy :37 patients(82.2%) were high grade and 8 patients were low grade (17.8%) .Out of 13 (5%) patients who had disease upstaged to T2, 5(15.6%) patients were those who had recurrent growth on re-TURBT scopy and presence of deep muscle on primary TURBT specimen,4 patients (30.7%) were those patient had recurrent growth on re-TURBT scopy and deep muscle absent from primary TURBT specimen,3 patients(12%) we were those who had no recurrent growth on re-TURBT scopy but absent deep muscle in primary TURBT specimen and 1 patient(0.5%) who had no growth on re-TURBT scopy and deep muscle present on primary TURBT specimen. We assessed various characteristics associated with tumour upstaging risk at re-TURBT. Patients with tumour size more than 3 cm at primary TURBT, BTA positive , absence of deep muscle in primary TURBT specimen and presence of recurrent growth at re-TURBT cystoscopy were significantly associated with risk of upstaging disease at re-TURBT ($p<0.05$). Histopathological features of the primary TURBT, type of growth,number of growth,history of smoking & age did not have any significant association with tumour upstaging at re-TURBT.

Based on previous research, the rate of recurrent or residual disease in high risk NMIBC is 33-78% and risk of upstaging with muscle involvement is 2-28%, suggesting the need for reTURBT.[1,2,7,15,16]In our study, the rate of recurrence and upstaging in reTURBT was 18% and 5%, respectively. While in other countries patients are often referred to specialist center for second opinion, in lower and middle income countries such as in our study, patients are treated in a primary set up effectively. All primary and reTURBT procedures were carried out under supervision and meticulous methods which could have resulted in lower recurrence rate and upstaging in our study. Further, all patients received intravescical therapy with mitomycin within 72 hours of primary TURBT, which resulted in better outcome. However, we found no correlation between residual tumor and intravesical instillation (data not shown).

In our study, patients underwent re-TURBT within a span of 6-12 weeks after primary TURBT, with a mean of 3.9 weeks and 4.2 weeks in no muscle involvement and with muscle involvement groups, respectively which is in accordance with previously reported intervals of 2-6 weeks.[6, 8-10, 15] The rate of single tumor in primary TURBT (76%) was much higher than the 34-63% reported in other studies.[1,2, 16, 17] The higher rate of tumor could be related to convenient and cheap healthcare as well as timely diagnosis within 1 month of symptom onset.

Main aim of reTURBT is to improve the staging accuracy and detection and clearance of residual disease. ReTURBT also increases the recurrence and progression –free survival.[9, 18, 19] However, recently the benefits of reTURBT is questionable, particularly in T1 HG patients when the procedure is performed by an experienced urologist and in the presence of muscle in the primary sample as supported by observational study by Gontero et al.[20] In our study, upstaging was seen only in 5% of patients and the risk upstaging in primary sample with muscle involvement was only 1.6%. This could be due to meticulous technique used with ample deep muscle sample in the primary TURBT leading to definitive diagnosis. These results indicate the limited value of reTURBT in primary samples with muscle involvement and in cased where procedure is considered complete in primary TURBT. Some bladder tumors have tentacular growth pattern, therefore, a wider and deep dissection extending 2-3 cm over the tumor border is crucial in improving the quality of primary TURBT sample.[21] The inclusion of surrounding radius of up to 4cm is beneficial in removal of invisible lesions such as CIS and finger-like submucosal foci.

Perivesical fat stranding and hydroureteronephrosis (upper tract changes) on imaging indicative of spread of disease beyond muscle suggestive of invasive disease. These increase the risk of upstaging in ReTURBT. Previous studies have indicated the absence of muscle in primary TURBT, and solid tumor type as a risk factor of upstaging and BTA stat is a sensitive marker for urinary bladder growth.[6,8-10,15,22-24] Presence of recurrent/residual disease at reTURBT is also an indicator of upstaging.[8-10] Manmohan et al reported no relationship between size of growth and risk of upstaging.[25] In this study, factors affecting the risk of upstaging were upper tract changes, perivesical fat stranding, tumor, tumor >3cm, positive BTA stat test, absence of muscle in primary TURBT sample and presence of recurrent/residual growth in reTURBT. Similar to Jahnson et al, we found no relation between tumor grade and risk of subsequent upstaging.[26] In the penalized logistic regression analysis, presence of perivesical fat stranding on imaging was the most common factor associated with upstaging followed by presence of muscle in primary specimen, BTA stat test, urine for malignant cytology, presence of recurrent/residual disease at the time of re-TURBT & size of growth at time of primary TURBT.

In this study, during reTURBT, 18% had recurrent/residual disease and among the patients with upstaged disease, 69% had recurrent/residual disease. This is in accordance with previously reported studies and lower than 32% reported by Manmohan et al.[1,2,13,16,27,25] Risk factors for residual tumor in reTURBT may include presence of CIS, multiple tumors, stage and grade of tumor, size of tumor, interval between two resections, recurrence history, low surgeon experience, and others.[20, 28] Lower rate of residual tumor can be achieved by effective primary resection with muscle sample and subsequent treatment.

Previous studies have suggested that presence of muscle in primary specimen reduces the risk of residual tumor in re-TURBT.[29] Similar to Manmohan et al, we did not find a significant association of muscle presence in primary specimen and incidence of recurrent/residual disease in re-TURBT.[25] On the other hand, similar to Zapala et al, Diwedi et al and Kim et al we found significant association between high grade disease in primary TURBT specimen, increased tumor size (>3cm) and positive urine cytology for malignancy with recurrent or residual disease.[30,31,32] While, Katmulla et al found an association between number and growth of primary tumor and occurrence of residual/recurrent tumor, such association was not present in this study.[2]

At 3 month follow up, the tumor recurrence was 18% based on cystoscopy evaluation, which is similar to 10-45% reported by previous studies.[25, 33, 34] Comparatively lower rates of recurrence in this study could be attributable to meticulous resection by experiences surgeons during primary and reTURBT procedures followed by intravesical mitomycin treatment. Although less, the risk of recurrent/residual growth during restage TURBT is low, however, is necessary to carry out restage TURBT within 2-6 weeks of primary TURBT to rule out any missed diagnosis and appropriate management. Further, to avoid delay in definitive treatment, it is advised to repeat cystoscopy as well at the time of restage TURBT, particularly in high-risk patients, thereby avoiding repeated biopsies and healthcare and patient burden.

While our study shows the importance of good primary resection

including muscle presence in the primary sample, the study has some limitations. They include, observational nature of the study with its inherent observer bias, smaller sample size, selection bias as study was conducted at a tertiary referral center, thus limiting the generalizability of results. Psychosocial and/or social economic factors were not analysed in this study. Further, larger multicenter registry studies representing larger epidemiology of high risk NMIBC patients is warranted. Further studies with a large number of patients and longer follow up are warranted along with cost-benefit analysis of the procedures, particularly in developing countries.

CONCLUSION

Factors including presence of upper tract changes, perivesical fat stranding, larger tumor size, high grade tumor, BTA stat, positive urine for malignant cytology and absence of muscle in primary TURBT specimen are associated with disease upstaging and/or risk of recurrence or residual disease at re-TURBT. Despite the low recurrence rate, clinicians still cannot negate the important role of re-TURBT because it is useful in the early diagnosis of residual tumors and restaging, which could help us in deciding the subsequent treatment step if tumor was found.

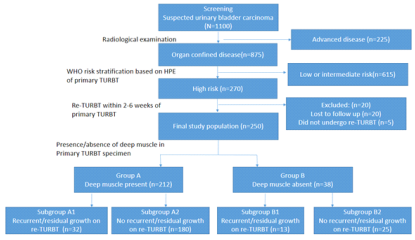

Figure 1: Patient disposition

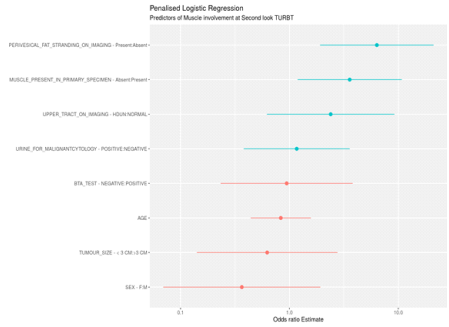

Figure 2: Effect plot showing predictors of muscle involvement at second look of TURBT

Table 1: Factors involving muscle involvement in bladder cancer

Variable	Muscle free N=237	Muscle involved N=13	P value
Mean (SD) Age, years	56.2 (13.1)	53.0 (18.3)	0.373
Age distribution 20-30 years	12 (5.1)	2 (15.4)	0.31
30-40 years	20 (8.4)	2 (15.4)	
40-50 years	39 (16.5)	2 (15.4)	
50-60 years	73 (30.8)	4 (30.8)	
60-70 years	66 (27.9)	1 (7.7)	
70-80 years	23 (9.7)	1 (7.7)	
80-90 years	4 (1.7)	1 (7.7)	
Sex emale	38 (16.0)	0 (0.0)	0.117
Male	199 (84.0)	13 (100.0)	
History of tobacco smoking and chewing No	103 (43.5)	4 (30.8)	0.368
Yes	134 (56.5)	9 (69.2)	
Imaging of UB mass Multiple growth	(15.2)	1 (7.7)	0.459
Single growth	201 (84.8)	12 (92.3)	
Imaging of upper tract HDUN	7 (3.0)	4 (30.8)	<0.001
Normal	230 (97.0)	9 (69.2)	
Perivesical fat stranding on imaging Absent	203 (85.7)	3 (23.1)	<0.001
Present	34 (14.3)	10 (76.9)	
Lymph node status on imaging Negative	237 (100.0)	13 (100.0)	NA
Size of growth during primary TURBT <3cm	84 (35.4)	1 (7.7)	0.040
>3cm	153 (64.6)	12 (92.3)	
No. of growth during primary TURBT Multiple	56 (23.6)	2 (15.4)	0.493
Single	181 (76.4)	11 (84.6)	
Type of growth Carpet	6 (2.5)	0 (0.0)	0.817
Papillary	189 (79.7)	11 (84.6)	
Solid	42 (17.7)	2 (15.4)	
BTA stat test Negative	83 (35.0)	2 (15.4)	0.146
Positive	154 (65.0)	11 (84.6)	
Urine cytology for malignancy Negative	153 (64.6)	7 (53.8)	0.433
Positive	84 (35.4)	6 (46.2)	
Time for primary TURBT <30 minutes	94 (39.7)	1 (7.7)	0.021
>30 minutes	143 (60.3)	12 (92.3)	
Postoperative intravesical MMC administration	237 (100.0)	13 (100.0)	NA
Histopathology of Primary TURBT CIS	2 (0.8)	0 (0.0)	0.443
T1G1	116 (48.9)	4 (30.8)	
T1G3	111 (46.8)	9 (69.2)	
TaG3	8 (3.4)	0 (0.0)	
Presence of muscle in Primary Specimen Absent	36 (15.2)	7 (53.8)	<0.001
Present	201 (84.8)	6 (46.2)	
Mean (SD) interval for re-TURBT, weeks	3.9 (0.7)	4.2 (0.7)	0.173
Cytology of Re-TURBT No growth	200 (84.4)	4 (30.8)	<0.001
Recurrent/Residual growth present	37 (15.6)	9 (69.2)	
Histopathology of Re-TURBT No tumor	179 (75.5)	0 (0.0)	<0.001
T1G1	5 (2.1)	0 (0.0)	
T1G3	53 (22.4)	0 (0.0)	
T2G3	0 (0.0)	13 (100.0)	
CPE at 3 month follow up (n=195) Recurrent growth	42 (17.7)	NA	

Table 2: Logistic regression analysis between Muscle free and muscle involved groups

Variable	Univariate	P value	Multivariate	P value
Age	0.98 (0.94-1.02)	p=0.406	0.99 (0.95-1.03)	p=0.688
Sex Female	Ref		Ref	
Male	20536473.26 (0.00-NA)	p=0.992	21611750.92 (0.00-NA,)	p=0.991
Tumor size <3cm	Ref		Ref	
>3cm	6.59 (1.26-121.06)	p=0.072	1.47 (0.17-31.45)	p=0.748
Perivesical fat stranding on imaging Absent	Ref		Ref	
Present	19.90 (5.76-92.19,)	p<0.001	14.92 (2.71-123.49,)	p=0.004
Presence of muscle in Primary Specimen Absent	Ref		Ref	
Present	0.15 (0.05-0.49,)	p=0.001	0.17 (0.04-0.68,)	p=0.012
BTA stat test Negative	Ref		Ref	
Positive	2.96 (0.77-19.45,)	p=0.164	0.47 (0.05-4.46,)	p=0.482
Urine cytology for malignancy Negative	Ref		Ref	
Positive	1.56 (0.49-4.85,)	p=0.437	1.39 (0.33-6.17,)	p=0.652
Imaging of upper tract HDUN	Ref		Ref	
Normal	0.07 (0.02-0.30,)	p<0.001	0.32 (0.05-1.92,)	p=0.203

Table 3: Factors predicting the time to growth after primary TURBT

Variable	Univariate	P value	Multivariate	P value
Age	0.99 (0.95-1.03)	p=0.601	1.00 (0.96-1.04)	p=0.906
Sex Female	Ref		Ref	
Male	88323572.24 (0.00-NA)	p=0.998	536652693.35 (0.00-NA)	p=0.998
Tumor size <3cm	Ref		Ref	
>3cm	7.46 (0.96-57.69)	p=0.054	1.53 (0.12-19.70)	p=0.745
Perivesical fat stranding on imaging Absent	Ref		Ref	
Present	18.73 (4.96-70.69)	p<0.001	14.73 (1.84-117.71)	p=0.011
Presence of muscle in Primary Specimen Absent	Ref		Ref	
Present	0.14 (0.05-0.42)	P<0.001	0.12 (0.03-0.47)	p=0.002
BTA stat test Negative	Ref		Ref	
Positive	2.73 (0.61-12.34)	p=0.191	0.22 (0.02-2.32)	p=0.210
Urine cytology for malignancy Negative	Ref		Ref	
Positive	1.65 (0.54-5.03)	p=0.377	1.76 (0.40-7.79)	p=0.459
Imaging of upper tract HDUN	Ref		Ref	
Normal	0.05 (0.01-0.20)	p<0.001	0.16 (0.03-0.73)	p=0.018

Table 4: Factors associated with recurrence/residual growth at time of re-TURBT

Variable	Muscle free N=237	Muscle involved N=13	P value
Mean (SD) Age, years	56.5 (12.9)	54.0 (15.6)	0.277
Sex Female	31 (15.2)	7 (15.2)	0.997
Male	173 (84.8)	39 (84.8)	
History of tobacco smoking and chewing No	88 (43.1)	19 (41.3)	0.820
Yes	116 (56.9)	27 (58.7)	
Imaging of UB mass Multiple growth	28 (13.7)	9 (19.6)	0.314
Single growth	176 (86.3)	37 (80.4)	
Imaging of upper tract HDUN	2 (1.0)	9 (19.6)	<0.001
Normal	202 (99.0)	37 (80.4)	
Perivesical fat stranding on imaging Absent	179 (87.7)	27 (58.7)	<0.001
Present	25 (12.3)	19 (41.3)	
Lymph node status on imaging Negative	204 (100.0)	46 (100.0)	NA
Size of growth during primary TURBT <3cm	80 (39.2)	5 (10.9)	<0.001
>3cm	124 (60.8)	41 (89.1)	
No. of growth during primary TURBT Multiple	43 (21.1)	15 (32.6)	0.094
Single	161 (78.9)	31 (67.4)	
Type of growth Carpet	5 (2.5)	1 (2.2)	0.247
Papillary	167 (81.9)	33 (71.7)	
Solid	32 (15.7)	12 (26.1)	
BTA stat test Negative	78 (38.2)	7 (15.2)	0.003
Positive	126 (61.8)	39 (84.8)	
Urine cytology for malignancy Negative	142 (69.6)	18 (39.1)	<0.001
Positive	62 (30.4)	28 (60.9)	
Time for primary TURBT <30 minutes	88 (43.1)	7 (15.2)	<0.001
>30 minutes	116 (56.9)	39 (84.8)	

Postoperative intravesical MMC administration	204 (100.0)	46 (100.0)	NA
Histopathology of Primary TURBT CIS	2 (1.0)	0 (0.0)	<0.001
T1G1	112 (54.9)	8 (17.4)	
T1G3	82 (40.2)	38 (82.6)	
TaG3	8 (3.9)	0 (0.0)	
Presence of muscle in Primary Specimen Absent	30 (14.7)	13 (28.3)	0.028
Present	174 (85.3)	33 (71.7)	
Mean (SD) interval for re-TURBT, weeks	3.9 (0.7)	3.9 (0.7)	0.987
Histopathology of Re-TURBT No tumor	179 (87.7)	0 (0.0)	<0.001
T1G1	2 (1.0)	3 (6.5)	
T1G3	19 (9.3)	33 (73.9)	
T2G3	4 (2.0)	9 (19.6)	
Presence of muscle in Re-TURBT Specimen Absent	200 (98.0)	37 (80.4)	<0.001
Present	4 (2.0)	9 (19.6)	

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