EVALUATION OF SECOND-LOOK TRANSURETHRAL RESECTION IN RE-STAGING OF PATIENTS WITH SUPERFICIAL BLADDER CANCER

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Abstract

Objective: *The Objective of this study was to evaluate the second-look transurethral resection (TUR) from the base of the previously resected bladder tumour in avoidance of staging errors, possibility of changing treatment strategy, and determination of risk factors of up-staging in patients with a diagnosis of superficial bladder cancer.*

Materials and Methods: *In this cross sectional study, 50 cases of superficial bladder cancers (pT_a and pT_1) were included where muscle coat were absent in histopathologic report of first TURBT. A second-look TUR from the tumour site were done after 4 weeks following the initial resection. At the second-look TUR, resection from the base of the previously resected area was performed for restaging. Finally, histopathologic findings of the second TURBT were compared with those of the initial one by appropriate statistical analysis.*

Results: *Out of 50 patients, 27 (54%) had residual malignant tissue in histopathological report of second-look TUR, while 23 (46%) were tumour free (no residual malignant tissue) at second-look TUR. In this study, total up-staging of tumour found in 18 (36%) patients. Out of them, 6 (12%) and 2(4%) patients were up-staged from pT_a to pT_1 and PT_2 respectively. 10 (20%) were up-staged from PT_1 to muscle-invasive (pT_2). So, total percentage of staging errors (under staging) detected in second-look TUR was 36% cases. Appearance (sessile), size (>3 cm) and stage (pT_1) of the tumour at the initial resection were independent risk factors for up-staging to muscle invasive disease detected at second-look TURBT.*

Conclusions: *Second-look TURBT is a valuable procedure for detection of residual tumour and accurate staging of non-muscle invasive bladder tumour. It also changed the treatment strategy of a significant proportion of patients. It is useful for tumours at high risk of recurrence and progression such as large size, sessile, multiple and T_1 high grade tumours, particularly when there is inadequate or no muscularis propria in the specimen.*

Key Words: *Bladder Tumour, Second Look Transurethral resection.*

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Introduction:

Urothelial cancer of the bladder is the second most common genitourinary malignancy, with over 60000 new cases annually in the United States and more than 13000 deaths from the disease per year[1]. Bladder cancer is nearly three times more common in men than in women. In men, it is the fourth most common cancer accounting for 7% of all cancers. In women, it is the ninth most common cancer accounting for 2.4% of all cancer. Bladder cancer is the eighth highest cancer related mortality rates in American men.

Bladder cancer presents as nonmuscle invasive (superficial) tumours in 70% to 80% of cases. Most cases are noninvasive papillary tumours (T_a) but a third is papillary or nodular tumours that invade the lamina

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propria (T_1) without involving the muscularis propria. In contrast to benign T_a tumours, T_1 cancers have a worse prognosis due to their predilection for muscle invasion, lymphnode or distal metastasis and higher mortality. Following initial Transurethral resection (TUR) and subsequent bladder sparing treatment for T_1 tumours, 70% of patients have recurrence, 30% to 50% have stage progression and a third eventually die of bladder cancer, usually within 5 to 10 years[2].

Transurethral resection of bladder tumour (TURBT) is the cornerstone of diagnosis and it is the gold standard treatment for patients with NMIBC (Nonmuscle-invasive bladder cancer). Without an adequate resection,with good quality of underlying detrusor muscle, the pathologist will not be able to fully differentiate between T_a, T_1, and T_2 bladder cancer[3]. The histopathologic diagnosis may be compromised by fulguration of the specimen, incomplete resection of the tumour, the pathologist expertise, and the difficult orientation of multiple fragmented pieces of tissue that may lead to staging errors. Moreover, different patterns of invasion in cases of T1 tumours may contribute in these staging errors[4].

It is well established that early recurrence (less than 3 months) is one of the most important prognostic factors in patients with NMIBC. Evidence is emerging, however, that a substantial number of so-called early recurrences simply constitute residual cancer rather than a true recurrence[5].

Benefits of second-look TURBT of NMIBC (Superficial bladder cancer) include not only complete resection of residual tumour, but also avoiding staging errors. Several studies reported that, at the first resection, underestimation of pathological stage occurs in 9% to 49% and the rate of residual tumour after initial TUR varies between 4% to 78%. This rate increases with the extent of infiltration noted on first resection and increases from 33% to 78% after initial resection of T1 tumour.[5-14]

As the treatment of a T_aT_1, high-grade tumour and a T_2 tumour is completely different, so correct staging is important. A second TUR may also change treatment strategy in patients with a diagnosis of NMIBC at initial TUR. In cases of upstaging to muscle infiltrating tumour (T_2) detected at second TUR, cystectomy or one of the bladder preservation protocols should be performed[15].

The fact that local tumour control and accurate tumour staging depend on a complete TURBT and reevaluation of the tumour base suggests that a second re-staging TURBT within 2 to 6 weeks may be of value in evaluating the patients with bladder cancer[4,7,14].

High recurrence rates and rapid progression are the major problems of superficial bladder tumour. It is not possible at presentation to accurately predict subsequent life threatening invasion of T_1 tumours. However, multiple tumours, grade 3 tumour, large size (> 3 cm), CIS and tumour at first follow up cystoscopy after treatment are associated with a greater risk of stage progression[6,9-11].

The optimal period to perform a second resection has not been established. Most authors seem to agree that endovesical visualization is better after 2-6 weeks as, by then, inflammation due to the first resection has subsided[14].

The purpose of this study was to evaluate the second-look transurethral resection (TUR) in avoidance of staging errors, possibility of changing treatment strategy, and determination of risk factors of up-staging in patients with a diagnosis of superficial bladder cancer

Materials and Methods:

This cross sectional study was done in the department of urology, BSMMU, Dhaka from December'2010 to May'2012, where 50 cases of superficial bladder cancers (pT_a and pT_1) were included where muscle coat were absent in histopathologic report of first TURBT. After counseling and taking concent, complete preoperative clinical evaluation including history, full physical examination, laboratory and radiologic investigations were performed. The morphologic and histopathologic findings of the first TURBT were recorded in the data sheet by complete evaluation of operation note, histopathological report and USG/CT findings at first TURBT, including appearance, size, number, stage and grade of the tumour. A second-look TUR were done after 4 weeks following the initial resection. At the second-look TUR, resection from the base of the previously resected area was performed for restaging. All data obtain from the second TURBT were recorded in a data sheet immediately after getting the histopathological report, including residual tumour and stage of the tumour. In this study, residual tumour was defined as presence of tumour in any stage (same stage or higher stage) in histopathological report of second-look TUR. Finally histopathologic findings of the second TURBT were compared with those of the initial one by appropriate statistical analysis and the differences were significant if $p < 0.05$.

Results and Observation

There were 50 patients, those in which muscle fibers were absent in histopathological report of initial TUR, underwent second-Look transurethral resection. Among them 35 (70%) were male and 15(30%) were female.

Out of 50 patients with superficial bladder tumour at initial TUR, 36 (72%) tumours were papillary and 14(28%) were sessile. Tumour size d" 3 cm were found in 33 (66%) cases and >3 cm were found in 17 (34%) cases. Total single tumours were 27(54%) and multiple tumour were 23(46%) cases.

Among the papillary tumours 20 were single and 16 were multiple, 28 were d" 3cm and 6 were > 3cm. Among sessile tumours 7 were single and 7 were multiple, 5 were d" 3cm and 11 were > 3cm.

Table-I

Pathlogical stage and grade of first TUR (N=50)

Pathologocal	Pathologocal grade		Total (%)
	Low Number (%)	High Number (%)	
pT_a	7 (14%)	14 (28%)	21(42%)
pT_1	5 (10%)	24 (48%)	29(58%)
Total	12 (24%)	38 (76%)	50(100%)

Out of 50 patients, 21(42%) were pT_a, of whom 7 (14%) were low grade and 14(28%) were high grade tumours. 29(58%) tumours were pT_1, of whom 5(10%) were low grade and 24(48%) were high grade tumours. Out of 50 patients total low grade tumours were 12 (24%) and high grade tumours were 38(76%).(Table-I)

Table-II

Second-look TUR Results of primary pT_a at first TUR (N=21)

Histopathological finding at second-look TUR	Stage	Number	(%)
Tumor free	-	11	52.38 %
Same stage	pT_a	2	9.52 %
Higher stage	pT_1	6	28.57 %
	pT_2	2	9.52 %
Total		21	100 %

Among 21 of original pT_a at initial TUR, 11(52.38%) had no residual tumour (Tumour free) at second-look TUR; 2(9.52%) had an identical pathological stage pT_a as in the initial TUR, while 8(38%) were up-staged (higher stage). Among 8 patients, 6(28.57%) were up-staged (higher stage) to pT_1 and 2(9.52%) had up-staged to PT_2.(Table-II)

Table-III

Second-look TUR Results of primary pT_1 at first TUR (N=29)

Histopathological finding - at second look TUR	Stage	Number	(%)
Tumor free	-	12	41.3%
Same stage	pT_1	7	24.13%
Higher Stage	pT_2	10	34.48%
Total		29	100%

Among 29 patients of original pT_1 at initial TUR, 12 (41.3%) had no residual tumour (tumour free) at second-look TUR; 7(24.13%) had an identical pathological stage pT_1 as in the initial TUR, while 10 (34.48%) were up-staged (higher stage) to muscle invasive (pT_2) tumour.(Table-III)

Table-IV

Percentage of residual and tumor free State found in second-look TUR (N=50)

Second-look TUR findings	Number of patients	**(%)**
Residual tumour	27	54 %
Tumor free	23	46 %
Total	50	100%

Out of 50 patients, 27 (54%) had residual malignant tissue found in histopathological report of second-look TUR, while 23 (46%) had tumour free (no residual malignant tissue) at second-look TUR. (Table-IV)

Table-V

Total up-staging (higher stage) of tumor found in second-look TUR (N=50)

Finding of first TUR	Finding of Second-look TUR	Number of up-staged	%
pT_a (21)	PT_1	6	12%
	PT_2	2	4%
pT_1 (29)	PT_2	10	20%
Total (50)		18	36%

Table-VI

Relation between various Morphologic and Histopathologic characteristics of primary tumours and patients with residual tumour at second look TUR.

At first-look TUR Morphologic and Histopathlogic characteristics of tumor at	Number of patients	At Second-look TUR Patients with residual tumours in 2nd look TUR(N=27) No. of patient	%	P Value	Odd Ratio initial TUR
Appearance					
Papillary	36	15	41.6	0.005*	8.4
Sessile	14	12	85.7		
Size					
≤ 3	33	11	33.3	0.000*	32
> 3	17	16	94		
Number					
Single	27	11	40.7	0.042*	3.3
Multiple	23	16	69.5		
Stage					
Ta	21	10	47.6	0.441	1.56
PT1	29	17	58.6		
Grade					
Low	12	2	16.6	0.003*	9.6
High	38	25	65.7		

*statistically significant

Among 50 patients, total up-staging of tumour found in 18 (36%) patients. Out of them, 6 (12%) and 2(4%) patients were up-staged from pTa to pT_1 and pT_2 respectively. 10 (20%) were up-staged from pT_1 to muscle-invasive (pT_2). So, total percent of staging errors (under staging) detected in second-look TUR was 36% cases. (Table-V)

Patients with residual malignant tumours at second-look TUR had a statistically significant correlation with appearance (sessile), size (>3 cm), number (multiple) and grade (high) of primary tumours. No statistically significant correlation was found between residual malignant tumours and stage (pT_1) primary tumour. (Table-VI)

Univariate analysis of different morphologic and histopathologic characteristics of primary tumours at initial TURBT reveals that there was a significant statistical relation between upstaged to muscle-invasive (pT_2) disease and presence of sessile tumours, size (>3 cm), stage pT_1 and high grade tumours detected at the initial resection (p<0.05). There was no statistically significant relation between multiple numbers of primary tumours and upstaged to muscle-invasive (pT_2) disease.

Table VII

Logistic regression analysis of the Different Histopathologic and Morphologic Risk factors for upstaging to Muscle-Invasive (pT_2) diseases in second look TUR

Logistic regression Table	Odd Ratio	*p* value
Variables		
Appearance(sessile)	31.8	0.006*
Size (>3 cm)	9.3	0.047*
Number (multiple)	3.5	0.349
Stage (PT_1)	3.8	0.05*
Grade (high)	4.7	0.406

* Statistically significant, OR= Odd Ratio

But in multivariate logistic regression analysis, the results shows that only appearance (sessile), size (>3 cm) and stage (pT_1) are independent risk factors for upstaging to muscle-invasive disease and it is statistically significant (p <0.05). Tumour with multiple numbers (OR=3.5), and high grade (OR=4.7) had considered risk for upstaging to muscle-invasive but were not statistically significant (p>0.05). (Table-VII)

Discussion

It is well established that early recurrence (less than 3 months) is one of the most important prognostic factors in patients with NMIBC. Evidence is emerging, however, that a substantial number of so-called early recurrences simply constitute residual cancer rather than a true recurrence. Benefits of second-look TURBT of NMIBC include not only complete resection of residual tumor, but also avoiding staging errors[18,19].

Complete tumor removal is not always possible, whether due to excessive tumor volume, anatomic inaccessibility, or risk of perforation. However, even in the absence of these circumstances repeat TUR is often indicated. When repeat TUR is performed within several days to several weeks of the original resection, residual tumor is identified at the site of the initial resection at least 40% of the time[7,13]. In several studies, it was reported that the rate of residual tumour after first endoscopic resection varies between 26-83%. This rate increases with the extent of infiltration noted on the first resection. It ranges from 33% to 78% after resection of T_1 tumour[14].

In this series of 50 patients, 27(54%) patient had residual tumour in the histopathological specimen of the second-look TURBT. Among them 10(20%) were pT_a and 17(34%) were pT_1 in the initial TURBT.In this study, the study result is close to those reported by Ali et al[6]. They reported that the overall rate of residual tumours in second resection was 58.2%.

Herr et al.[20] analyzed 150 cases consecutive second TURBT and found a high load of residual diseases, of the 150 cases 114(76%) had residual tumour.Mersdorf and associates[12] believed that a second TUR is a must. Among 94 cases with Ta and T1 tumors, about 80% of the cases had residual cancer on re-TURBT. Other authors, however, reported a rather lower rate of residual tumors in their studies. This rate could be explained by the quality of the initial TUR in these studies[13].

In different studies Schwaibold and Mersdorf [13,21,22] stated that the percentage of residual tumours increases with high grade, solid appearance and multiplicity. In this study, appearance, size, number, stage and grade had considered as prognostic or high risk factors to idenfy the patients in whom residual tumour might be found on second-look TURBT. Here size (>3cm), high grade, sessile and multiple tumour had found to the most important risk factors for presence of residual disease in second-look TURBT and this result is similar to previous studies. Few authors have evaluated the value of a second transurethral resection of the bladder in correcting staging errors. Miladi and associates[14] stated that, the stage of 9- 45% of tumours is underestimated at the first resection.

In an analysis, Herr[20] reported that of 38 cases with Ta disease, 23% had lamina propria invasion (pT_1) and 7.8% were upstaged to a muscle-invasive (pT_2) tumor; among the 58 cases with T_1 tumor, 27.5% were upstaged to muscle-invasive disease (pT_2) tumor. In Herr's study, second resection of those patients changed treatment in 28 (29%) cases upstaged from noninvasive to invasive tumour.

In this study, of 21 patients with stage pTa in second-look TUR, 6 patients (28.5%) had higher stage pT_1 and 2 patients (9.5%) had a higher stage pT_2. On the other hand, 29 patients with stage pT1, 10 patients (34.48%) had a higher stage.

In this study, among 50 patients, overall upstaging in second TUR was 36% that means total staging errors observed in 36% cases. This study results are comparable with the published results regarding correction of staging errors. In another study, Ali and associates showed that, of the 30 patients with stage pTa at the initial TUR, only 6 (20%) had a higher stage pT_1 at the second look TURBT. On the other hand, of the 61 patients with stage pT_1, 16 (26.2%) patients had a higher stage pT_2. Upstaging had changed treatment strategy in 22 (24.2%) cases. Brauers and colleagues[6] studied 42 patients with moderately or poorly differentiated T1 bladder tumor; 64% had residual tumors in their second resection and 24% were upstaged to muscle-invasive disease.

In a study Ali and associates[6] did a univariate analysis of the different histopathologic and morphologic risk factors at the initial TURBT revealed that there was a significant statistical relation between upstaging to muscle-invasive disease and presence of T_1, high grade, large size (>3 cm), nodular tumor detected at the initial resection ($p<0.05$). Furthermore, they used a multivariate logistic regression analysis to determine the independent prognostic or high-risk factors of NMIBC for upstaging to muscle-invasive disease at the second-look TURBT. They found that the risk of upstaging to muscle-invasive disease increases in patients with T1, high-grade, large size (>3 cm), and nodular tumor.

In this study, univariate analysis of different morphologic and histopathologic characteristics of primary tumour at initial TURBT reveals that there is a significant statistical relation between upstaging to muscle-invasive disease and presence of sessile tumour, size (>3 cm), Stage pT_1 and high grade tumour detected at the initial resection (p<0.05). There is no statistically significant relation between multiple tumour and upstaging. This result is similar with Ali's study. But, on the other hand, in multivariate logistic regression analysis, only sessile,large size and stage (pT_1) tumour are considered as independent risk foctors for upstaging detected at second-look TURBT (*p*d"0.05).

There are no studies available at present regarding the optimal timing of the second resection. Divrik et al.[23] performed a second TUR within 2 to 6 weeks following the initial resection if the histopathological evaluation revealed T_1 tumor. Schwaibold et al.[22] performed second TUR 4–6 weeks later. Manoharan[11] recommended that this should be performed within 1 to 4 weeks following the initial resection. May et al. reported that a delay of more than 12 weeks in muscle invasive bladder cancer led to significant upstaging[12] In this study, second-look TURBT were performed after 4 weeks so that patients recover physically, mentally, and financially for a second surgery.

Conclusion

Second TURBT from the previously resected tumour base is a valuable procedure for detection of residual tumour and accurate staging of non-muscle invasive bladder tumour. It also changed the treatment strategy of a significant proportion of patients. It is useful for tumours at high risk of recurrence and progression such as large size, sessile, multiple and stage pT_1 high grade tumours, particularly when there is inadequate or no muscularis propria in the specimen.

Conflict of Interest: None declared.

References

1 . Aldousari S, and Kassouf W. Update on the management of non-muscle invasive bladder cancer. J Can Uro Asso. 2010; 4: 56-64.

2. Andius P and Holmang S. Bacillus Calmette-Guerin therapy in stage Ta/T1 bladder cancer: Prognostic factors for time to recurrence and progression. Int. BJU, 2000; 98: 980.

3. Brauers A, Buettner R and Jakse G. Second resection and prognosis of primary high risk superficial bladder cancer: is cystectomy often too early? J Urol. 201; 165: 808.

4. Herr HW. Transurethral resection of bladder tumour. In: Lerner, SP, Schoenberg, MP and Sternberg CN, eds. Treatment and management of bladder cancer, United Kingdom, 2008; 1: 10.

5. Bostrom PJ, Rhijn BW, Fleshner N, Finelli A, Jewett M, Thoms J, Hanna S, Kuk C and Zlotta AR. Staging and staging errors in bladder cancer. J Eurol, 2010; 9: 2-9.

6. Ali MH, Ismail IY, Eltobgy A and Gobeish A. Evaluation of second-look transurethral resection in re-staging of patients with nonmuscle-invasive bladder cancer. J Endourology, 2010; 24: 2047-50.

7. Klan R, Loy V, Huland H. Residual tumor discovered in routine second transurethral resection in patients with stage T1 transitional cell carcinoma of the bladder. J Urol 1991; 146: 316–8.

8. Konety BR and Willams, RD 2004. Superficial transitional (Ta/T1/CIS) cell carcinoma of the bladder. Int BJU, 1991; 94: 18.

9. Konety BR and Carrol PR. Cancer of the bladder, ureter, and renal pelvis. In: EA, Tanasho, JW, McAhinch, eds. Smith General Urology. New Delhi: Tata McGraw-Hill, 2009; 308-327.

10. Kurth KH, Schroeder FH and Debruyne F. 'For the EORTC GU Group. long-term follow-up in superficial transitional cell recurrence rate, and survival. Final results of a randomized trial comparing doxorubicin hydrochloride, ethoglucid, and transurethral resection alone'. J Prog Clin Biol Res, 1989; 303: 481-90.

11. Manoharan M 2005. Optimal management of T1G3 bladder cancer. Urol. Clin N Am, 2006; 32: 133– 45.

12. May M, Nitzke T, Helka C, et al. Significance of the time period between diagnosis of muscle invasion and radical cystectomy with regard to the prognosis of transitional cell carcinoma of the urothelium in the bladder. Scand J Urol Nephrol, 2004; 38: 231-5.

13. Mersdorf A, Brauers A, Wolff JM, et al 1998. Second transurethral resection for superficial bladder cancer: A must? J Urol, 1998; 59 (Suppl): 143.

14. Miladi M, Peyromaure M, Zerbib M, Saighi D and Debre B. The value of a second transurethral resection in evaluating patients with bladder tumour. J Euro Endo, 2003; 43: 241-45.

15. Ba4.Herr HW. Transurethral resection of bladder tumour. In: Lerner, SP, Schoenberg, MP and Sternberg CN, eds. Treatment and management of bladder cancer, United Kingdom, 2008; 1-10.

16. Herr HW. Restaging Transurethral Resection of high risk superficial bladder cancer improves the initial response to Bacillus Calmette-Guerin therapy. J Urol, 2005; 174: 2134-2137.

17. Jemal A, Siegel R, Word E et al. Cancer statistics, 2007, CA Cancer. J Clin, 2007; 57: 43-66.

18. Cheng L, Neumann RM, Weaver AL . Grading and staging of bladder carcinoma in transurethral resection specimens. Correlation with 105 matched cystectomy specimens. Am J Clin Pathol, 2000; 113: 275-279.

19. Freeman JA, Esrig D, Stein JP, et al. Radical cystectomy for highrisk patients with superficial bladder cancer in the era of orthotopic urinary reconstruction. J Cancer, 1995; 76: 833-39.

20. Herr HW. The value of a second transurethral resection in evaluating patients with bladder tumors. J Urol 1999; 162: 74–76.

21. Dwivedi US, Kumar A, Das SK, et al. Relook TURBT in superficial bladder cancer: Its importance and its correlation with the tumour ploidy. Urol Oncol, 2009; 27: 514–519.

22. Schwaibold H, Sivalingam S, May F and Hartung, R. The value of a second transurethral resection for T1 bladder cancer. Int. BJU, 2006; 97: 1199-201.

23. Divrik T, Yildirim U, Eroglu A, Zorlu F and Ozen H. Is a second transurethral resection necessary for newly diagnosed pT1 bladder cancer? J Urol, 2006; 175: 1258-61.

Abbreviation:

TURBT : Transurethral Resection of Bladder Tumour
NMIBC : None Muscle Invasive Bladder Cancer