

Reliability of Assessing Grade and Stage of Urinary Bladder Tumours from Examining Trans-urethrally Resected Specimen: A retrospective Study

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Running title: Correlation of the stage and grade of Urinary bladder cancer determined from TURBT specimen and cystectomy specimen is very important.

Disclaimers : None

ABSTRACT

Urinary bladder tumours are common cancers among elderly males. Initial evaluation and management of these tumours is by TURBT. However, almost half of these become muscle invasive and require radical cystectomy. It is important to document the accuracy of tumour grade and stage assessed from TURB tissue, compared to that obtained from examination of the cystectomy specimen. This study aims to document the stage and grade of Urothelial bladder tumours of patients who underwent initial TURB followed by radical cystectomy, from both the TURB and the cystectomy specimens. Extent of correlation between them was assessed. We also sought for specific clinical protocol which might have enhanced matching of Grade and Stage between two categories of specimens. In a retrospective study, Physician, Surgeon and Pathologists of Medical College, Kolkata selected 52 patients of Radical cystectomy who had undergone previous TURB procedure in recent past. Fresh sections taken from their tissue blocks to determine stage and grade of tumour in both specimens. The results were analyzed for association between grade and stage using Wilcoxon log rank test and by Kappa for agreement between the results of TURB and cystectomy specimens. There was 44% agreement between T stage derived from TURB and cystectomy specimens. In most cases, the T stage found in cystectomy was higher than that found in TURBT with only 3.8% patients having a lower T stage in cystectomy compared to TURB. The agreement between tumour grade results derived from TURB and cystectomy specimens was 85%. There was marginal agreement between the T stage and grade as assessed by Kappa. In stage-matched cases, precisely labeled tissue obtained from base of lesion was submitted for histopathology evaluation in about 87% cases. Tumour stage and grade results between TURBT and cystectomy specimens vary significantly. Mostly the T stage is found to be higher in cystectomy specimens. Evaluation of specifically labeled tissue from base of lesion significantly hones staging precision in TURB. This factor should be taken in to consideration during decision making based on TURB specimens.

Key Words: Urinary Bladder, Urothelial Carcinoma, Transurethral resection of Urinary Bladder; Staging, Grading, Cystectomy

INTRODUCTION

Urothelial carcinoma of urinary bladder cancer is the fourth most common cancer in men and eighth most common malignancy in women in the Western world.^{1,2} In India, most of the epidemiological data come from tertiary Cancer care centers where large volume of patients with Bladder cancer are being treated. Two large series from different parts of the country have looked into the epidemiological aspects of bladder cancer. Gupta *et al*⁴ published a series of 561 bladder cancer patients treated between 2001 and 2008 at SGPGI,

Lucknow. In this series, the mean age was 60.2 ± 4.4 years (range: 18–90 years old) and the male to female ratio was 8.6:1. Transitional cell carcinoma was the most common histological variety (97.71%). A total of 26% of the patients had muscle invasive disease at the time of presentation³. Biswas *et al* published a retrospective epidemiological study of 88 patients diagnosed with carcinoma bladder at the Departments of Urosurgery and Pathology from CNMC and H, Kolkata, from December 2007 to November 2009. The median age of bladder cancer was 65–70 years. Moreover, there was a male preponderance (86.4% male vs. 13.6% female)⁴.

Yeole and Jussawalla reported data collected from the Bombay Cancer Registry and found that bladder cancer was very uncommon in the first three decades of life. However, after the age of 30, the incidence rates increase with age, in log-linear fashion, in both sexes⁵. The Indian figures differ from the Western literature, the incidence of bladder cancer per se is much more predominant in Indian males (8.9:1). This difference is lesser in the Western series (3:1–4:1).

In view of treatment and prognosis, obviously precise grading and staging system is crucial to stratify patients in various prognostic groups. To that end WHO has developed Pathologic classification of Urothelial Neoplasm-WHO/ISUP 2004.

As initial TURB diagnosis is vital for such categorization of patient population, it is essential to determine extent of correlation of Grade and stage between those that obtained from TURB specimen and those that obtained from final Cystectomy specimen.

In past, number of researchers tried to correlate such findings of TURB and final cystectomy specimen. However a number of such studies were conducted on small number of cases. Heavy reliance on review of pathology reports for grading and staging, inherent heterogeneity of natural history of Urothelial carcinoma of Urinary Bladder (due to long time interval between the TURB and Final cystectomy has impaired effectiveness of such studies⁶⁻²⁰).

In the present study, we tried to determine efficacy of Grading and Staging of Urothelial Neoplasm of Urinary bladder by comparing such parameters with that of Final Cystectomy specimens of the same patients. Additionally, we sought for specific clinical information which could have helped in more precise corroboration of such parameters. As heterogeneity of natural history of the disease is inherent and can hardly be obliterated, we tried to limit such variable factor by limiting the study interval to 100 days in majority of cases (between TURBT and Final Cystectomy).

MATERIALS AND METHODS

The study population consisted of 52 patients who were finally treated with radical cystectomy. In this retrospective study (conducted between 2010 and 2015), we selected only those patients who underwent TURB followed by Final Cystectomy. Interval between TURB and Cystectomy in our study varied from 2 to 266 days. Most patients underwent Final cystectomy within 100 days of the TURBT. Clinical data including copy of histopathology requisition slips were collected from tertiary treatment center in Kolkata. Fresh Copy of Haematoxylin and Eosin stained tissue sections of TURB and Cystectomy specimens were prepared from paraffin blocks. Team of physicians, surgeons and

Pathologist in Medical College, Kolkata went through the clinical data and tissue sections as per previously fixed protocol and parameters.

Cases in which histologic slides from TURB specimens were not available for review were excluded. We reviewed all histology slides of TURB and cystectomy specimens. Grading was performed by the team pathologist according to the WHO /ISUP classification system TNM (tumor, lymph nodes, and metastasis) system was used for pathologic staging.

Copy of original Histopathology reports were reviewed to select those cystectomy specimens which were examined by representative tissue sections and followed internationally standardized guideline for Macroscopic/Gross examination. From the histopathology requisition slip in TURB specimens, we identified patients where surgeon obtained tissue specifically from base of the lesion and submitted for histopathology examination after designating it with similar specification.

The association between histologic grade and pathologic stage was assessed with the Wilcoxon rank sum test. The agreement between TURB and cystectomy specimens for grade and stage was assessed based on calculating kappa statistics. For the ordinal stage variables (Ta, T1, T2 or more), a weighted kappa statistic was calculated that ascribed more weight to smaller degrees of disagreement. The kappa statistic is a chance-corrected measure of agreement that represents the proportion of agreement beyond that expected due to chance alone and is scaled to vary from –1.0 to 1.0; a value less than 0.4 signifies poor or marginal agreement, and values between 0.4 and 0.75 denote fair to good agreement. A significant P value indicates that the kappa value is significantly greater than zero. All calculated P values were 2-sided, and a P value of less than .05 was considered statistically significant.

RESULT

The median age of the patients was 63 years (range, 41-82 years) at TURB. The male: female ratio was 6:1. The median interval from TURB to cystectomy was 17 days (range, 2-266 days). Ninety-four percent of patients under-went cystectomy within 100 days after TURB.

In TURB specimens, pathologic stages were as follows: Ta, 5 patients; T1, 22 patients; and T2, 17 patients; and in cystectomy specimens, Ta, 3 patients; T1, 9 patients; T2, 9 patients; T3a, 10 patients, T3b, 13 patients; and T4, 8 patients. The histologic grade was low-grade (6 patients) and high-grade (46 patients) in TURB specimens; and low-grade (8 patients) and high-grade (44 patients) in cystectomy specimens. Histologic grade at TURB was associated with pathologic stage at cystectomy ($P < .001$).

Total 40 of Cystectomy patients was in Stage PT2 or more. Of them 27 (51.9%) were under staged by TURB. Of total 52 patients, in 23 (44.2%) cases, stage was matched between TURB and Final Cystectomy. In 2 (3.8%) Cystectomy showed lower stage carcinoma. Differentiation between PT2 and PT3 was not done in TURBT.

Among the stage-matched TURB specimens of 23 patients, in 20 (86.9%) cases, surgeon submitted specifically labeled tissue obtained from base of lesion for histologic evaluation

Cancer invading into the muscle wall (pT2) could not be distinguished from that invading beyond the muscle wall (pT3 or more) by examination of TURB specimens. 18 (69.2%) of 26 patients with stage T1 carcinoma at TURB had advanced stage carcinoma (pT2 or more), including 9 whose cancers were not organ-confined (pT3 or more) at cystectomy.

There was marginal agreement between TURB and cystectomy for pathologic stage (44% agreement; kappa =0.31; $P < .001$) and histologic grade (85% agreement; kappa =0.38; $P =.002$) (Table 1 and 2).

Table 1: Correlation of histologic Grade between Transurethral Resection of Urinary bladder (TURB) and Cystectomy specimen

	Transurethral Resection of Urinary bladder(TURB)	Cystectomy Specimen of Urinary Bladder
Low Grade	6	8
High Grade	46	44

Table 2: Histologic grade and Stage of Tumor at Final Pathologic Stage of Cystectomy specimen

	Cystectomy					
	Ta	T1	T2	T3a	T3b	T4
Low Grade	2	2	1	1	2	0
High Grade	1	7	8	9	11	8

Table 3: Histologic staging of Transurethral Resection of Urinary bladder(TURB)

	Transurethral Resection of Urinary bladder(TURB)					
	Ta	T1	T2	T3a	T3b	T4
Low Grade	3	9	16	-	-	-
High Grade	3	17	5	-	-	-

DISCUSSION

In past, the necessity for standardization of categorization of Urothelial Neoplasm of Urinary Bladder was perceived,⁶ and such was addressed by World Health Organization on 2004. We found that WHO grading and Staging system was very significant prognostic determinant in TURB specimens for predicting final Pathologic Grade and Stage in cystectomy specimen. Obviously, understaging with TURB is a long standing scenario in Urothelial carcinoma of Urinary bladder. Several studies have compared the clinical stage and final pathologic stage at cystectomy and found a substantial staging error (approximately 50%), similar to our results.⁷⁻²¹ Amling *et al* found an overall staging error in 56% of the patients, including clinical understaging in 31%. They have reviewed 220 patients who underwent cystectomy for bladder carcinoma.⁷ In concordance to other study, Pagano *et al* found an overall staging error of 56% in their study of 261 patients.⁸ The overall accuracy of staging by TURB was 46% in the report by Yaman *et al* of 65 patients who were treated by cystectomy.⁹ Freeman *et al* studied 182 patients of TIS, Ta, and T1 Urothelial Neoplasm. They found understaging in TURB specimens in 34% cases. Their study revealed 40% of T1 stage were upstaged to T2 or more during evaluation of final cystectomy specimens.¹⁰ Chen *et al* studied Non-invasive(Ta) Papillary Urothelial Neoplasm according to WHO classification system. In 164 cases, they categorized study population into prognostically different groups. They found seven years cancer (stage) progression –free survival for patients with Ta Papillary Urothelial Neoplasm of Low malignant potential, Low grade, and high grade carcinoma was 93,82 and 61 percent respectively.²² The strength of present study was in moderate sized cohort with short interval between TURB and final Cystectomy procedure in majority (and thereby less influence on natural history of the disease), fresh review of Histopathology tissue section by pathologist (which excluded reliance of heterogeneity of reporting bias - as found in previous studies) as well as use of standardized and internationally accepted system of Grading and Staging of tumour. We, a team of clinicians and pathologist, also combed through the Histopathology requisition slips to search for any crucial clinical data which might have influenced precise matching of Grade and stage of TURB and final Cystectomy specimen. Such specific attempt was possibly not done before. Histologic Grade of Urothelial malignant tumors were matched between TURB and final cystectomy Specimens in almost all cases. We find understaging in TURB specimen in 51.9% cases. In about 44.2% cases perfect matching of Tumor stage was noted. In 86.9% of such matched –staged cases, we found, while performing TURB Procedure, surgeons

have taken sample separately from base of the lesion, labeled the tissue sample specifically as such, before submission for histopathological evaluation (in addition separately identified tissue from tumor bulk) Our study however could not find precise categorization of T2 and T3 stage tumor in TURB specimens.

In conclusion, our study revealed that pathologic understaging of the tumor in TURB specimen occurs in a significant number of patients with Urothelial Malignant Neoplasm of Urinary Bladder. However, histologic evaluation with precisely marked sample obtained from base of the lesion during TURB procedure improves Tumor Stage of such Neoplasm of Urinary Bladder.

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