Study of grading and staging of bladder carcinoma in transurethral resection of urinary bladder

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Abstract

Introduction: Urinary bladder carcinoma is one of the most common malignancies causing morbidity and mortality. The most common form of bladder cancer that accounts for about 90% of the bladder cancer is urothelial carcinoma.

Aims of the study: Grading of urothelial carcinoma according to WHO 1999 grading system and evaluation of its prognostic significance on transurethral resection specimens. Evaluation of prognostic significance of stage on transurethral resection specimens Evaluation of transurethral resection of bladder as staging technique.

Material and Methods: Patients, who underwent transurethral resection of bladder tumours were identified from histopathological files of our institute, during the period from 2010 to 2014. The cases that were diagnosed as urothelial carcinomas on transurethral resection specimen and which were followed for 3 years since the lesion first appeared were included in the study. The rest all the cases not fulfilling the above criteria were excluded from the study of recurrences progression of lesions. Staging was done under TNM system and Grading was carried out according to WHO grading system 1999.

Results: High grade tumors (grade 2 & 3) are associated with high risk of early progression and metastasis. Low grade tumors are recurrent with slower progression. Higher stages are associated with increased risk of metastasis. WHO 1999 grading system can classify urothelial carcinoma into prognostically different groups, which is statically significant. ($p<0.01$)

Conclusion: Thus, grade is important prognostic factor for superficial urothelial carcinomas and can predict patient outcome and modify patient's management. The stage is important prognostically parameter in muscle infiltrating carcinomas. Under staging is a problem with transurethral resection specimens of urinary bladder with diagnostic accuracy is 66.66% and staging error of 45.46%.

Key-words: Urothelial Carcinoma, Transurethral resection, TNM staging.

Introduction

Urinary bladder carcinoma is one of the most common malignancies causing morbidity and mortality. According to cancer registry maintained by out institute, total 109 cases were newly diagnosed among 9807 cancer patients in 2010.(1) But, we eventually came down to 70 cases with confirmed and histological diagnosis of bladder carcinoma. The most common form of bladder cancer that accounts for about 90% of the bladder cancer is urothelial carcinoma. (Previously widely used term was Transitional cell carcinoma).(2) This phenotype represents papillary; low grade disease for which transurethral resection and selected use of chemotherapy with routine follow up is a standard course of treatment. Tumour recurrence with superficial disease is standard course of treatment. Tumour recurrence with superficial disease is quite common and can be as high as 50% to 70% following local resection. Approximately 10% to 30% of recurrent cancers progress to invasive disease. Although most urothelial carcinomas present as superficial disease and are amenable to transurethral resection, nearly 30% of the urothelial cancers are muscle invasive at the time of their initial presentation. The invasive phenotype of the bladder cancer is usually high grade and is treated with radical cystectomy or radical radiotherapy. The locally advanced diseases are treated with radiotherapy. Metastatic diseases are treated with chemotherapy with or without palliative cystectomy or palliative radiotherapy. Thus urinary bladder carcinomas represent a spectrum of neoplasm that can be grouped into three categories: Superficial, Invasive and Metastatic. Each differs in clinical behaviour, prognosis and primary management.(2) therefore, accurate examination of Transurethral Resection Specimens is important, as it is the most common procedure carried out by urologists.(3) At present date, grading and pathological staging are two most important prognostic parameters in urothelial cancers. Tremendous efforts have gone into development of molecular prognostic markers but to date, no marker has emerged that plays a role in routine management of bladder cancer patients.(4) However, no uniformly accepted grading system for bladder cancer exist and under staging is common problem with transurethral resection of bladder tumours. In this study a grading system published by WHO in 1999 has been used and accuracy of transurethral specimens is evaluated.

Methods

Patients who underwent transurethral resection of bladder tumours were identified from histopathological

files of our institute, during the period from 2010 to 2014. The cases that were diagnosed as urothelial carcinomas on transurethral resection specimens were included in the study. Staging was done under TNM system and Grading was carried out according to WHO gradin system 1999. In this retrospective study, all histological slides were reviewed and classified without knowledge of previous results. Patients who were followed for 3 years since the lesion first appeared were included in the study; rest were excluded from the study of recurrences and progression of lesions. Progression was defined as the development of invasive carcinoma, distant metastases or death from bladder cancer. Recurrences were defined as reappearance of histopathologically confirmed urothelial neoplasm in bladder of any stage or grade. According to cancer registry maintained by out institute, total 109 cases were newly diagnosed among 9807 cancer patients in 2010.[(1)] But, we eventually came down to 70 cases with confirmed and histological diagnosis of bladder carcinoma. The time of bladder cancer diagnosis to progression or date of last follow up was calculated and survival estimates were obtained by Kaplan-Meier method on SPSS software. The association of each grade with time to progression was evaluated with log rank test. Because of limited numbers of cause-specific deaths and patients with multiple metastases were lost to follow up; the analysis was focused on progression free survival.

Transurethral resection of bladder:

It was perfectly done with good muscle relaxation to prevent obturator jerk and to prevent iatrogenic injury during resection. After preliminary cystoscopy, urethral dilation had been done up to 28 Fr, and then resectoscope was inserted. The superficial chips were taken using cutting current and homeostasis achieved with coagulating current. Then this part of specimen washed out and was sent as superficial tissue. Then resection of the bladder growth was done to include the base and part of the muscle layer consisting deep tissue was sent to histopathology laboratory to look for muscle invasion.

Histopathological material:

The tissues were fixed in 10% buffered solution, and all tissues were submitted for processing. Processed tissues were then embedded in paraffin and paraffin blocks were made. Then rotary microtome and sections cut sections of 4 microns were stained with Haematoxylin and Eosin stain. Whenever required, in difficult cases, Masson Trichrome special stain was carried out. To visualise the lymph vascular permeation immuohistochemical stains with anti-CD 34 and anti-factor VIII antibodies were performed in difficult cases.

Results

The final study group include 70 patients among whom 15 were female and 55 were male. The patient characteristics and pathological findings are summarized in table. Patients' characteristics and pathological findings Table 1 The mean age of the patients was 54.5 years with range of 25 to 80 years. The male to female ratio was 3.6: 1. Mean follow up period was 23.60 months. Among 70 patients, all had recurrence, 38 developed progressions. : Different grades, number of recurrences, tumour stage and their interrelationship are summarized Table 2 Recurrences occurred after initial diagnosis until progression- Table 3 Grade I carcinomas are more recurrent than high-grade carcinomas (mean 3.2). High-grade carcinomas progressed early and less recurrent (mean 1): Staging in TUR specimens and cystectomy specimens Table 4 Staging in TUR specimens Table 5 Sensitivity of TUR specimen is 80% and positive predictive value is 66.66% Among 70 patients, progression from intraepithelial lesion occurred in 38 patients from which grade I were 3, grade II were 11 and grade II were 24. No progression occurred in seven patients and disease was advanced at the time of diagnosis in 25 patients. The mean period from diagnosis to progression was 76.8, 19.2 and 3.5 months for grade II, grade III and grade I respectively. The progression free survival rates at one year are 100% for grade I, 42% for grade II and 5% for grade III. (Log rank test: $p < 0.001$) The data for calculation of progression free survival: Table 6 among 70 patients who underwent transurethral resection of bladder tumours, 44 patients took the treatment, 22 patients underwent radical cystectomy, 10 patients took external beam radiation, and 2 patients took chemotherapy for advanced disease. 26 patients did not take any further treatment. Lymph node status was evaluated in 58 patients with positive nodal status in 13 patients and negative nodal status in 45 patients. Nodal status not evaluated in 12 patients. Nodes were evaluated on USG, CTscan and on histological material. Metastasis was present at the time of diagnosis in 11 cases, among which 3 patients were of grade II and 8 were of grade III. Metastasis after radical cystectomy occurred in 8 cases. The findings are summarized in table. Cases with metastasis after radical cystectomy: Table 7 Thus Grade II and Grade III tumours area associated with risk of metastasis even after radical cystectomy. In grade III tumours metastasis occurred in patients with stage T2a and T2b (early invasion) while Grade III cancers, metastasis were associated with stage T2a, T3 and T4 (higher stages).

Table 1: Patients' characteristics and pathological findings

Age		**Stage (T)**	
<60	46	Cis (flat lesion)	01
60-69	15	T0	06
>/= 70	09	T1	26
		T2	26
Gender		T3	07
Males	55	T4	05
Females	15		
		Stage (lymph nodes)	
History of tobacco use		Positive	
User	66	Negative	
Nonusers	02	Not assessed	
Unknown	02		
		Metastasis	19
Presenting symptoms			
Haematuria	67		
Dysuria	02		
Abdominal lump	01		
Incidental finding	--		
Multifocality			
single	16		
>/=2	54		
Gross appearance		Histological grade	
Ulceroinfiltrative	09	Grade 1	05
Papillary	55	Grade 2	22
Polypoidal	06	Grade 3	43

	Stage					
	NOP (T0)	**LPI (T1)**	**MI (T2)**	**FI (T3) PWI, PI, UI (T4)**	**Mets**	
I	02	01	02	--	--	05
II	04	04	05	02	07	22
III	01	01	19	10	12	43
Total	07	06	26	12	19	70

Abbreviations: NOP: no progression; LPI: lamina propria invasion; MI: muscle infiltrative; FI: perivesical fat infiltrative; METS: metastasis, PWI: pelvic wall infiltration I: prostrate infiltrative; UI: uterus infiltrative. (p value < 0.005). Thus most patients are with grade III (61.42) and most muscle invasive carcinomas have grade III. Metastasis is seen with grade III and grade II.

Table 3: Recurrences occurred after initial diagnosis until progression

No of Recurrences	**Grade**			
	I	**II**	**III**	
00	--	03	22	25
01	--	10	17	27
02	02	04	03	09
03	--	04	--	04
04	03	01	01	05
	05	22	43	70

Table 4: Staging in TUR specimens and cystectomy specimens

TUR stage	Cystectomy stage				
	T1	T2	T3	T4	Total
MI	-	12	05	01	18
Mos	01	02	01	00	04
Total	01	14	06	01	22

Table 5: Staging in TUR specimens

Correct staging	12 (54.54%)
Overstaging	00
Understaging	10 (45.46%)
Total correlation found in	22

Table 6: The data for calculation of progression free survival

No.	Duration in months	1: progressed 0: not progressed (status)	Cumulative survival	Cumulative events	No. remained
Grade I tumours					
1	48	1	0.8000	1	4
2	72	1		2	3
3	72	1	0.4000	3	2
4	72	0		3	1
5	120	1	0.0000	4	0
Grade II tumours					
1	6	1	0.9091	1	14
2	7	1		2	13
3	7	1	0.7273	3	12
4	8	1	0.6364	4	11
5	10	1		5	10
6	10			6	9
7	10			7	8
8	10			8	7
9	10		0.5455	9	6
10	24	1	0.4545	10	5
11	60	0		10	4
12	72	0		10	3
13	72	0		10	2
14	72	0		10	1
15	96	1	0.0000	11	0
Grade III tumours					
1	1	1		1	25
2	1	1		2	24
3	1	1		3	23
4	1	1	0.8261	4	22
5	2	1		5	21
6	2	1		6	20
7	3	1	0.6957	7	19
8	3	1		8	18
9	3	1		9	17
10	3	1		10	16
11	3	1		11	15
12	3	1		12	14
13	3	1		13	13
14	3	1		14	12
15	3	1		15	11

16	3	1		16	9
17	3	1	0.3479	17	8
18	4	1	0.3044	18	7
19	5	1		19	6
20	5	1	0.2174	20	5
21	7	1		21	4
22	7	1		22	3
23	7	1	0.1087	23	2
24	10	1	0.0548	24	1
25	120	0		25	0

Table 7: cases with metastasis after radical cystectomy

Stage	Grade II	Grade III
T2a	--	01
T2b	01	02
T3	02	--
T4	02	--
Total	05	03

Table 8: Comparison of progression data with Holmang et al is given in it

	Progression from intraepithelial lesions	
Tumour grade (WHO 1999)	**Holmang et al**	**Present study**
Grade I	04%	04.29%
Grade II	20%	15.72%
Grade III	45%	34.28%
Total	69%	54.29%

Table 9: Comparison with other authors' study is given in it

TUR stage correlation with cystectomy stage		
	Cheng et al	**Present study**
Same stage	43.80%	54.54%
Understaging	52.38%	45.46%
Overstaging	03.81%	0

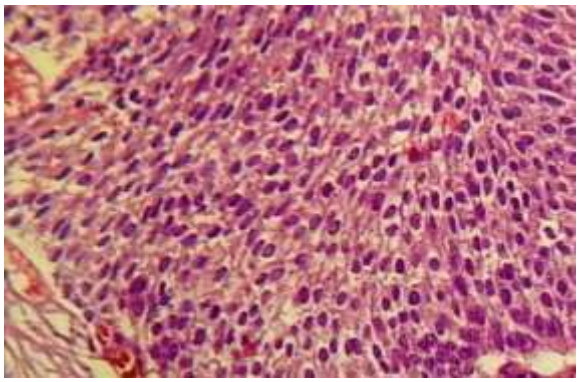

Fig. 1: Grade 1 urothelial carcinoma (40x) showing minimal crowding, loss of polarity, basal mitosis and inconspicuous nucleoli

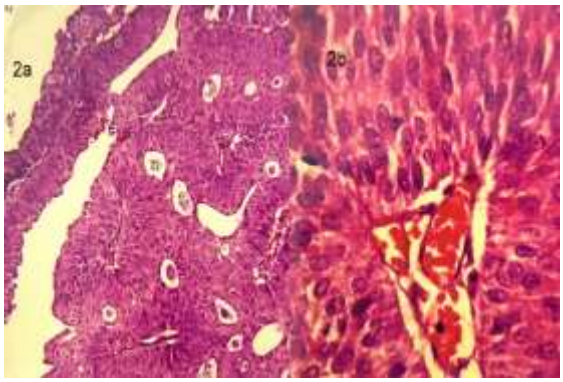

Fig. 2: (2a) Grade 2 urothelial carcinoma (10x) showing disordered architecture, but retention of some element of organisation; (2b): Grade 2 urothelial carcinoma (40x)

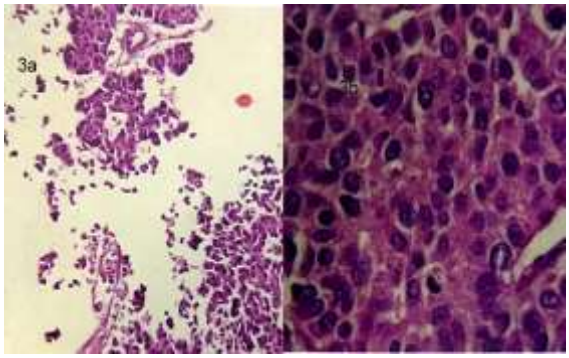

Fig 3: (3a) Grade 3 urothelial carcinoma (10x) showing discohesive cells with significant dysplasia; (3b) Grade 3 urothelial carcinoma (40x) showing nuclei are markedly pleomorphic, hyperchromatic and showing mitosis

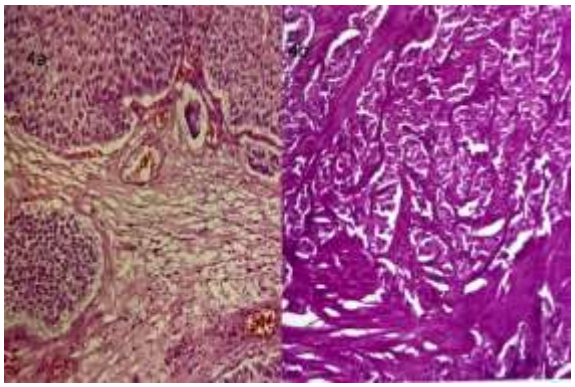

Fig. 4: Grade 4 urothelial carcinoma (10x); Grade 4 urothelial carcinoma (40x)

Discussion

In the study the pattern of recurrence and progression of disease diagnosed on transurethral resection specimen of urinary bladder were studied retrospectively to know the impact of grading and staging on them. The ability of transurethral resection specimen to stage the tumour accurately was also evaluated. It is found that WHO 1999 grading system stratify patients into prognostically significant group. Most urothelial carcinomas were of Grade III and at advanced disease because ours is a referral institute and most superficial tumours are usually treated in periphery. Almost all tumour grades showed recurrences except 7 cases that took intravesical chemotherapyin early non-invasive stage and are lost to follow up. Progression occurred in all groups. A difference was seen in progression-free survival. Because our patients were given adjuvant intravesical chemotherapy, the true natural history of tumours graded according WHO 1999 grading system may be underestimated. However, intra vesical chemotherapy given in 17 cases and they could not prevent progression in majority of cases, but they could prolong duration between recurrences, i.e. slowed the disease progression. Tumour grade is considered important prognostic factor for most patients. Like many studies, this study also showed that Grade can stratify patients into different groups. [5,6,7] The present study shows that progression occurred early in Grade III patients (mean 3.5 months), Grade II patients progressed in 1.5 years (mean) and Grade I patients progressed in 6.4 years (mean). This suggest those patient with Grade III and II requires close follow up programme to detect the disease in early manageable stage. Another opinion about management of these patients is to teat high grade superficial lesions with radical cystectomy or radiation therapy in this neo-bladder era, because even intravesical chemotherapy could not stop them progressing. [7] Grade is not a prognostic parameter in muscle invasive carcinoma.[1] After that progression depends on stage only. As present study shows, more or equal to half thickness muscle involvement in grade III tumours and full thickness muscle involvement or locally advanced tumours in grade II tumours are at high risk of developing metastasis, even after radical cystectomy. This finding is similar to Johnson et al.[8] This suggests that these patients should be treated with external beam radiation and chemotherapy after radical cystectomy. [7] As most of the patients presented with metastasis and locally advanced disease were lost to follow up soon, little information regarding specifics of biology of advanced disease was found.[8,10,11,12] Several limitations should be considered in this study. One is, histological grade was described in a relatively small number of patients with limited follow up. Small number of outcome events limited the discrimination ability of system. Despite, the limitations this study shows that, 1999 WHO grading system stratify patients into different prognostic groups with different clinical outcomes. Comparison of progression data with Holmang et al is given in it: Table 8 The stage is important prognostic factor in muscle invasion carcinomas. The under-staging by transurethral resection specimens was done in 45.46% of cases. This finding is little lower than Cheng et al, who found 52.38%. Accurate staging by computed tomography was done in 37.5% of cases, which is higher than Cheng et al[4] as mentioned (35%). Current TMN staging is based on examination of cystectomy specimens[5]. Examinations of trans-urethral specimens may yield a significant level of staging error[5]. In comparison with cystectomy specimen examination, TUR specimens cannot distinguish stage T2 cancer from stage T3, specimens even when cancer is extensive[4]. The assessment of TUR specimens in conjunction with imaging studies such as CT may improve accuracy of predicting pathologic stage. The limitation of this study are that the stage and grade of cystectomy specimens were modified by pre-cystectomy intravesical chemotherapy. Furthermore, sample size in present study was small. Comparison with other authors' study is given in it: Table 9 In summary, urothelial carcinomas occurred at the mean age of 54.5 years and were predominantly seen in males with history of smoking. Among 70 patients 7.14% were of Grade I, 3.43% were

of grade II and 61.43% of grade III tumours. Total 54.29% of tumours progressed, among which grade I within 6.4 years. Grade II within 1.5 years and grade III within 3.5 months. Thus, grade I tumours progressed slowly, grade III tumours progressed early in disease history and grade II tumours had intermittent time interval. 10% were not progressed because of early treatment with intravesical chemotherapy. 35.71 % patients were presented with advanced disease at the time of diagnosis among which all were grade III tumours. Metastasis occurred in 27.14% of patients among which 36.84% were of grade II and 63.16% were of grade III. No metastasis found in grade I tumours. Recurrences were more common in grade I tumours (more than three), while grade III tumours recurred once or advanced at the time of diagnosis. Metastasis developed in patients who invaded full thickness and more in grade II tumours and more than half thickness in grade III tumours at the time of cystectomy. Staging of TUR, specimens were correlated with cystectomy specimens in 31.43% of patients among which 45.46% were correctly staged and 54.54% were under-staged. None was over-staged.

Conclusions

High grade tumors (grade 2 & 3) are associated with high risk of early progression and metastasis. Low grade tumors are recurrent with slower progression. Thus, grade is important prognostic factor for superficial urothelial carcinomas and can predict patient outcome and modify patient's management. WHO 1999 grading system can classify urothelial carcinoma into prognostically different groups, which is statically significant. ($p<0.01$)Higher stages are associated with increased risk of metastasis. Thus, stage is important prognostically parameter in muscle infiltrating carcinomas.

Under staging is a problem with transurethral resection specimens of urinary bladder with diagnostic accuracy is 66.66 % and staging error of 45.46 %.

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