

Original Research Article

Correlation of P53 status with histological grading of urinary Bladder Transitional cell carcinoma

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Abstract: Bladder cancer is one of the most common urological malignancies. Ninety percent of the bladder tumors are transitional cell carcinomas. The most important molecular mechanism in the development of carcinogenesis is the Deletions or inactivation of the cancer suppressor genes. Several suppressor gene loci have been closely associated with bladder cancer. These include p53 on chromosome 17p, retinoblastoma (Rb) gene on chromosome 13q and genes on chromosome 9. Bladder cancers with p53 abnormalities appear to have more aggressive behaviour. The aim of the present study is to assess the p53 status in transitional cell carcinoma according to the histologic grade. A retrospective and prospective study with regard to the neoplastic lesions of the urinary bladder was done in the Department of Pathology. A total of 734 urinary bladder lesions were reported in the department of Pathology and among these, 419 (57%) were bladder tumors. In our study, Transitional cell carcinoma was the most common (81%, n=334) neoplasm. Out of 334 Transitional cell carcinoma cases, p53 status was done for 200 cases. P53 was positive in 74 (37%) lesions. P53 over expression correlated with tumor grading, the higher the grade more is p53 expression and poorer the prognosis.

Keywords: Urinary Bladder, Transitional cell carcinoma, P53 Expression, Tumor Grading

INTRODUCTION

Neoplastic lesions of the bladder are more common, compared to non-neoplastic lesions. Bladder cancer is nearly three times more common in men than in women [1]. In men, it is the fourth most common cancer after prostate, lung and colorectal cancers, accounting for 6.6% of all cancer cases [1]. In women, it is the ninth most common cancer, accounting for 2.4% of all cancers. Bladder cancer accounts for 3.0% of all cancer deaths in men and 1.5% in women.

Ninety percent of the bladder tumors are transitional cell carcinoma [2]. Age, gender and racial factors affect the survival and prognosis of patients with bladder cancer [3]. Recent studies concluded that a total of 40 to 45% of newly diagnosed bladder cancers are high-grade lesions, more than half of which show muscle invasion at the time of diagnosis [4]. P53 genes are the most frequently altered gene in human cancers [5]. Mutations of the p53 tumor suppressor gene are present in approximately 50% of all human cancers. The p53 protein can also be inactivated by mechanisms other than mutation, for example by complexing with viral or cellular proteins such as MDM2. It is clear that

the malfunction of this protein plays a central role in the development of cancer [6]. Bladder cancers with p53 abnormalities appear to have more aggressive behaviours [7]. This work is essentially undertaken to assess the incidence, age, sex distribution of the bladder lesions and p53 status in transitional cell carcinoma according to the histologic grade.

MATERIALS & METHODS

A study regard to the neoplastic lesions of the urinary bladder was done in the Department of Pathology in a detailed manner taking into account the following parameters: Age and sex of the patients, Gross appearance of the tumor, Histopathologic type of the lesion, Classification of lesions based on WHO Grading of urothelial carcinomas (1973) and Immunohistochemistry (p53 status) of transitional cell carcinoma. Sections were taken depending on the type of specimen. Core Biopsy Specimens were weighed collectively and all tissue embedded. In case of Cystectomy specimens, Sections were given from lesion proper. Routine tissue processing and H& E staining was done for histopathological examination. Immunohistochemistry for P53 status was done for

transitional cell carcinoma by Polymer-HRP (Horse radish Peroxidase) Method. For retrospective cases, stored slides were taken out and reviewed, one of the representative blocks were selected for IHC staining.

RESULTS

A total of 734 urinary bladder lesions were reported in the department of Pathology, from March 1993 to August 2011 (18 years study) and among these, 419 (57%) were neoplastic (6 were benign and 413 were malignant). (Tables 1&2)

Table-1: Incidence of urinary bladder lesions (N=734)

Lesion	Number of cases	Percentage (%)
Non- neoplastic	277	38
Pre- neoplastic	32	4
Neoplastic	419	57
Others (Cong. anomalies)	6	1

Table-2: Distribution of the neoplastic lesions of urinary bladder

Type of neoplasm	Number	Percentage
Benign	6	1.2%
Malignant	413	98.8%

Bladder tumours were classified according to the 1973 WHO classification. Among the malignant lesions (Table 3), Transitional cell carcinoma was the most common lesion (81%, n=334) followed by Squamous cell carcinoma (11%, n=46) and Adenocarcinoma (5%, n=20). Other lesions include neuroendocrine carcinoma small cell variant (0.7%, n=3), leiomyosarcoma (0.4%, n=2), poorly differentiated carcinoma (1%, n=3) rhabdomyosarcoma

(0.2%, n=1) and sarcomatoid carcinoma (0.6%, n=3), Lymphoma (0.2%, n=1). Mean age of the patients with neoplastic lesions was 55.6 years (youngest patient was 15 years female and oldest age was 90 years male). Majority of the bladder tumors in this study occurred in the sixth and seventh decades (55.7%) with a peak incidence between 51 and 60 years and male to female ratio 4:1. (Table 4)

Table-3: Distribution of individual malignant lesion (n = 413)

S.NO	Lesion	No	Percentage
1	Transitional cell carcinoma	334	81%
2	Squamous cell carcinoma	46	11%
3	Adenocarcinoma	20	5%
4	Other malignant lesions	13	3%

Table-4: Age & Sex distribution of malignant lesions

Age	TCC		SCC		Adeno		NEC		SMC		LMS		RMS		PDC		Lym		TOTAL
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	
1-10																			
11-20																			
21-30	4	2	1	1		1	1								1				10
31-40	14	1	2	2		0													18
41-50	46	7	5	7	4	2			1	2			1				1		74
51-60	83	2	10	5	6	2		1						1					129
61-70	79	1	5	2	5		1		1										103
71-80	48	8	3	1			1		1						1				60
81-90	8	1	2																11
TOTAL	282	5	28	18	15	5	2	1	2	1	2		1	1	2	1			413

(TCC - Transitional cell carcinoma, SCC – Squamous cell carcinoma , Adeno – Adenocarcinoma, NEC – Neuroendocrine carcinoma, SMC- Sarcomatoid carcinoma, LMS- Leiomyosarcoma, RMS- Rhabdomyosarcoma, PDC- Poorly differentiated carcinoma, Lym – Lymphoma)

Transitional cell carcinoma was the most common (81%, n=334) malignant neoplasm in our study of which 106 (31.7%) cases occurred in 6th decade followed by 90 (27%) cases in 7th decade and 59 (17.6%) cases in 8th decade. The Mean age was 58.5 years, M: F ratio was 5.4:1 with males comprising 282 (85%) of cases. The youngest patient was 22 yrs female and oldest age was 90 years male. Transitional cell carcinoma in situ was diagnosed in 7 cases youngest was 38 yrs male and oldest patient of 77yrs female. (Table 5) Squamous cell carcinoma was the second most common malignancy (11%, n=46), common in 5th to 7th decade with peak incidence in 6th decade. Adenocarcinoma was the third most common tumour (5%, n=20), common in 5th to 7th decade with peak

incidence in 6th decade accounting for 40%, with male to female ratio 3.2:1. Other rare malignant lesions seen in our study were leiomyosarcoma, rhabdomyosarcoma, neuroendocrine carcinoma, sarcomatoid carcinoma and lymphoma. leiomyosarcoma (0.4%, n=2) was seen in 5th decade.

Transitional cell carcinoma was graded according to WHOM 1973 and out of 334 Cases, 7 cases were carcinoma in situ & 327 cases were transitional cell carcinoma. Among 327 cases of TCC, a total of 95, 125 and 107 cases were classified as grade1, grade 2 and grade 3 lesions respectively and muscle invasion was seen in 86 cases. (Fig 1, 2)

Table-5: TCC Grading Based on WHO classification, 1973

GRADE	No of patients	Muscle invasion
Grade 1	95	-
Grade 2	125	37
Grade 3	107	49



Fig-1: Cystectomy specimens of Infiltrating Transitional cell carcinoma showing a) solid, gray white lesion infiltrating whole thickness of the bladder. (b) Large, exophytic growth infiltrating the wall of the urinary bladder with variegated appearance. Inset - cut section shows gray white areas with nodular exhibition with foci of hemorrhages and necrosis

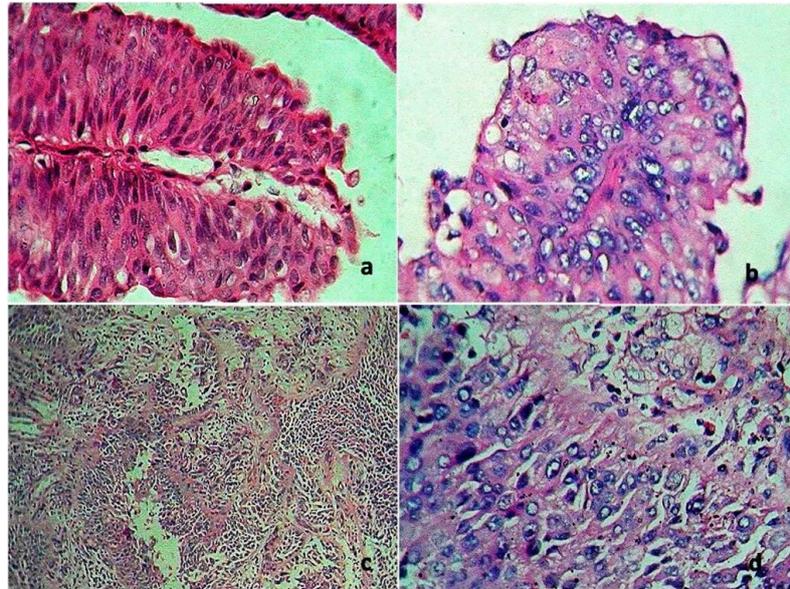


Fig-2: a) Grade1 transitional cell carcinoma with papillary structure lined by atypical transitional epithelium with stratification and without mitotic figures (H&E, x400) (b) TCC – Grade2, lined by pleomorphic transitional epithelium with few mitotic figures. (H&E, x400) (c,d) Transitional cell carcinoma Grade3 with invasion (H& E, x100 & x400).

IHC for P53 in TCC:

Out of 334 Transitional cell carcinoma cases, p53 status was done for 200 cases. P53 was positive in 74 (37%) lesions. IHC was done for 48, 74 and 78 cases of grade1, grade 2 and grade 3 lesions respectively and

it was positive in 7, 23 and 44 cases of grade1, grade2 and grade3 lesions respectively. P53 IHC was done for 62 cases with muscle invasion of them 41 cases (66%) shows positivity. (Table 6)(Fig 3)

Table-6: Immunohistochemistry for p53 in TCC

GRADE	No of patients	P53 positive	Percentage
Grade 1	48	7	9.4%
Grade 2	74	23	31%
Grade 3	78	44	59.4%

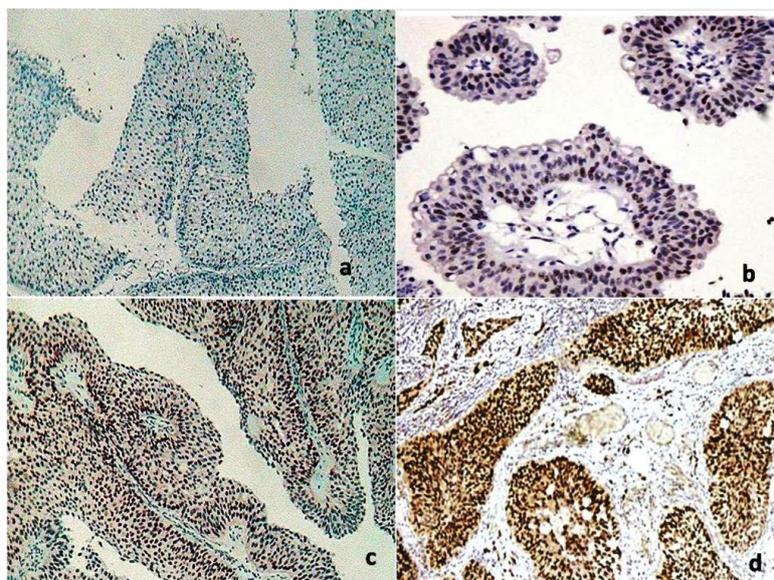


Fig-3: IHC of P53 in TCC of Urinary bladder. (a) Negative (b) Grade 1 positivity (c,d) High Grade (Grade 2&3) positivity. (H&E, x100)

DISCUSSION

According to the Indian cancer registry data in men, bladder cancer is one of the most common cancers accounting for 3.9% of all cancer cases [8].

Transitional cell carcinoma is most commonly noticed malignant urinary bladder lesion in our study accounting for 81% of cases and also most common urinary bladder lesion in general. Transitional cell carcinoma is rare among adults age below 40 years. In our study the incidence was 5.5%.

According to WHO 1973 TCC grading, the most common cases in our study belong to grade 2 (38.2%) followed by grade 3(32.7%) and grade 1 (29%). comparable with the study done by Messing *et al.*, 1995 (42.3%) [4], muscle invasion is seen in 26.7% of cases which is similar to study done by Parag Gupta *et al.* 2008(26%), lower compared to Christopher Ho Chee Kong *et al.* (41.4%) [9].

P53 positivity is seen in 74(37%) of total 200 cases, of which 7(9.4%) cases of grade 1, 23 (31%) cases of grade 2 and 44(59.4%) cases of grade3. The positivity for this antibody happened mostly in cases of staging progression. Most of the high degree TCCs showed immunostaining for p53 and no low-grade TCCs did. In our study the positivity with p53 is increasing with increase in the grade of the tumor comparable to other studies [10]. This p53 nuclear overexpression was correlated with tumor grade and p53 is considered as prognostic marker, in that the higher the grade, over expression and the poor prognosis. There was a strong positive correlation between the expression of mutant p53 and tumor grade.

P53 has been associated with prognostic parameters such as recurrence, tumor progression and metastasis-free interval. The expression of this antibody was associated with tumor progression in some studies [11-13]. Few authors did not observe the association between p53 and progression, due to low rate of antibody positivity. The histologic grade has also been related to p53 since studies have shown increased expression of this marker in higher grade tumors [14, 15]. In literature association of p53 with recurrence showed contradictory results. For some authors, p53 was associated with recurrence, for others there was no statistical significance in this regard [13]. The place of p53 immunoreactivity in predicting the prognosis of the tumor with regard to the grade and the stage, which is still controversial, will be understood better with the increase in the studies performed on larger series with a long term follow-up and at a molecular level. This study has undertaken to observe the p53 immunoreactivity on larger group to know the significance of staining patterns of P53 in tumor progression.

CONCLUSION

To Conclude, Transitional cell carcinoma was the commonest malignant lesion of urinary Bladder in the 6th decade with male predominance. P53 over expression correlated with tumor grading, the higher the grade p53 expression is more and poorer the prognosis. . The use of immunohistochemical markers, based on research data, may be useful as additional criteria in risk stratification of patients with non-invasive TCC. It is necessary to continue the studies to deepen the knowledge related to the use of biomarkers in patients with bladder cancer.

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