

Study of Urothelial Neoplasm in Central India With Reference to WHO/ISUP Grading

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Abstract

Introduction: Urothelial carcinoma is the most common bladder cancer, is often described as a polyclonal field change defect with frequent recurrence due to heightened potential for malignant transformation. Urothelial neoplasm runs the gamut from small benign neoplasm that may never recur to tumors of lower indeterminate malignant potential to lesions that invade the bladder wall and metastasize frequently. Hence histologic grading of these tumors to predict behavior has been subject of great debate as there is poor inter - observer reproducibility and no uniformity. **Material and Methods:** The present study was carried out in the Department of Pathology, L.N. Medical College, Bhopal, India. It was both a prospective and a retrospective study of 80 patients whose urinary bladder biopsy were studied. **Result:** 80 cases reported out of which 20 were transitional papilloma, 52 were cases of ransitional cell carcinoma and 8 cases were of squamous cell carcinoma. The majority of tumours are present in age group of 50-80 years. **Discussion:** Although World Health Organization classification system is most commonly used grading system but lack of detailed histological criteria motivated WHO and ISUP to publish a consensus classification for urothelial neoplasm of urinary bladder. The majority of the cases in this study belonged to the histologic grades of papillary carcinoma of low grade which corresponds to the WHO classification of transitional cell carcinoma grade II.

Key words: Transitional cell carcinoma, Urothelial neoplasm, WHO/ISUP grading

Introduction

Bladder cancer is a common urologic cancer that has the highest recurrence rate of any malignancy. According to a comprehensive analysis of 1476 radical cystoprostatectomy specimens, patients undergoing this procedure for bladder urothelial carcinoma commonly have incidental prostate cancers.^{1, 2} In North America, South America, Europe, and Asia, the most common type

of urothelial tumor diagnosed is transitional (urothelial) cell carcinoma (TCC); it constitutes more than 90% of bladder cancers in those regions. TCC can arise anywhere in the urinary tract, including the renal pelvis, ureters, bladder, and urethra, but it is usually found in the urinary bladder. Carcinoma in situ (CIS) is frequently found in association with high-grade or extensive TCC.³ Squamous cell carcinoma (SCC) is the second most common cell type associated with bladder cancer in industrialized countries. In the United States, around 5% of bladder cancers are

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SCCs⁴. Worldwide, however, SCC is the most common form of bladder cancer, accounting for 75% of cases in developing nations.

Approximately 2% of bladder cancers are adenocarcinomas. Nonurothelial primary bladder tumors are extremely rare and may include small cell carcinoma, carcinosarcoma, primary lymphoma, and sarcoma. Small cell carcinoma of the urinary bladder accounts for only 0.3-0.7% of all bladder tumors. High-grade urothelial carcinomas can also show divergent histologic differentiation, such as squamous, glandular, neuroendocrine, and sarcomatous features⁵.

Clinical and pathologic data indicate that at least 3 different phenotypes, as follows, exist in urothelial carcinoma^{4,6}

- Low-grade proliferative lesions that develop into non-muscle-invasive tumors; these account for approximately 80% of bladder cancers
- Highly proliferative invasive tumors with a propensity to metastasize
- CIS, which can penetrate the lamina propria and eventually progress

Divergent, yet interconnected and overlapping, molecular pathways are likely responsible for the development of noninvasive and invasive bladder tumors. Somatic mutations in fibroblast growth receptor 3 (FGFR-3) and tumor protein p53 (TP53) in tumor cells appear to be important early molecular events in the noninvasive and invasive pathways, respectively. FGFR-3, Ras, and PIK3CA mutations occur with high frequency in noninvasive tumors, leading to upregulation of Akt and mitogen-activated protein kinase (MAPK)^{7,8}. Loss of heterozygosity (LOH) on chromosome 9 is among the most frequent genetic alterations in bladder tumors and is

considered an early event⁹. Large numbers of genomic changes have been detected using karyotyping and comparative genomic hybridization (CGH) analysis in urothelial carcinoma. Numerically common are losses of 2q, 5q, 8p, 9p, 10q, 18q, and Y. Gains of 1q, 5p, 8q, and

17q are frequently present, and high-level amplifications can be found; however, the target genes in the regions of amplifications have not been conclusively identified.¹⁰

Up to 80% of bladder cancer cases are associated with environmental exposure. Tobacco use is by far the most common cause of bladder cancer in the United States and is increasing in importance in some developing countries. Smoking duration and intensity are directly related to increased risk.^{11,12,13} Risk of developing bladder carcinoma is 2-6 times greater in smokers than in nonsmokers. This risk appears to be similar between men and women¹⁴. Nitrosamine, 2-naphthylamine, and 4-aminobiphenyl are possible carcinogenic agents found in cigarette smoke.

Occupational exposure to aromatic amines or aniline dyes is presumed to be the cause of bladder cancer in up to 25% of cases. Numerous occupations associated with diesel exhaust, petroleum products, and solvents (eg. auto work, truck driving, plumbing, leather and apparel work, rubber and metal work) have also been associated with an increased risk of bladder cancer. People living in urban areas are also more likely to develop bladder cancer. The etiology in these cases is thought to be multifactorial, potentially involving exposure to numerous carcinogens.¹⁵

In many developing countries, particularly in the Middle East, Schistosoma haematobium infection causes most cases of bladder SCC. In a study from Egypt, 82% of patients with bladder carcinoma harbored S haematobium eggs in the bladder wall. In egg-positive patients, the tumor tended to develop at a younger age (with SCC predominant) than it did in egg-negative persons. A higher degree of adenocarcinoma has also been reported in schistosomal-associated bladder carcinomas.¹⁶

Material and Methods

The present study was carried out in the Department of Pathology, L.N. Medical College, Bhopal. It was both a prospective and a retrospective study of 80 patients whose urinary bladder biopsy were studied. For retrospective study, histopathology records of patients were studied up

to January 2011. Diagnosed cases of urinary bladder carcinoma were selected.

The paraffin blocks of these cases were retrieved. For prospective study urinary Bladder Biopsy, partial and total

cystectomy specimen received were processed, paraffin blocks of samples were sectioned and stained with haematoxylin and eosin and studied under microscope for staging.

Results

Table No. 1: Number of Cases of Various Urinary Bladder neoplasm

	Number of cases	Percentage
Transitional papilloma	20	25 %
Transitional cell carcinoma	52	65 %
Squamous cell carcinoma	8	10 %

As per Table 1 80 cases of urinary bladder tumors were studied, out of which 25% were of Benign transitional cell papilloma, 65% were of transitional cell carcinoma and 10% were of squamous cell carcinoma.

Table No. 2: Distribution of urothelial neoplasm (WHO grading)

Type of Lesion	Number of cases	Percentage
Papilloma	20	27 %
Transitional cell carcinoma Grade I	4	5.5 %
Transitional cell carcinoma Grade II	26	36.1 %
Transitional cell carcinoma Grade III	22	30.5 %

On classification as per WHO grading Papilloma were present in 27%. Higher grade transitional cell carcinoma was more common than lower grade carcinoma.

Table No. 3: Age distribution of patients with urothelial neoplasm

Age Distribution (Years)	Number of cases	Percentage
31-40 years	14	17 %
41-50 years	16	20 %
51-60 years	26	32 %
61-70 years	8	10 %
71-80 years	16	20 %

Table No. 4: Sex distribution of patients with urothelial neoplasm

Sex	Number of cases	Percentage
Male	72	90 %
Female	8	10 %

As per Table no. 3 and 4, majority of cases of urothelial neoplasm (32%) were in between the age of 51-60 years and majority cases (90%) were seen in male gender with only 10% in females.

Table No. 5: Type of tumor (WHO/ISUP grading)

Type of Lesion	Number of cases	Percentage
Papilloma	20	27 %
Papillary neoplasm of low malignant potential	4	5.5 %
Papillary carcinoma low grade	26	36.11%
Papillary carcinoma high grade	22	30.5 %

As per table no. 5 maximum number of cases of urothelial neoplasm studied according to WHO / ISUP consensus classification was of papillary carcinoma low grade.

Discussion

The progression of bladder cancer is dependent on the degree of anaplasia of tumour cells defined as increased cellularity, nuclear crowding, disturbance of cellular polarity, failure of differentiation from the base to the surface, pleomorphism, irregularity in cell size, variations of shape and chromatic pattern of the nuclei, displaced or abnormal mitotic figures and giant cells. This was the basis for the WHO Classification system proposing three tiered system of grade 1, 2 and 3.

Though well accepted by pathologist, urologist and oncologist, however, lacks detailed histological criteria hence recently described WHO / ISUP consensus flat and papillary pre invasive neoplasm in order to improve the reproducibility of grading among pathologists and to correlate grades with better defined prognosis. As per Indian cancer registry data in men, urothelial carcinoma is the ninth most common cancer accounting for 3.9% of all

cancer (Kurkure, 2001)¹⁷. Men are effected more often than women (3-4:1) (Reutor

VE, 2004)¹⁸. According to WHO (2004)/ISUP, Urothelial tumors may be of flat or papillary on the basis of the pattern of growth of the intraepithelial lesion, which may lead to invasive Urothelial carcinoma. Papillary tumors recognised in this classification are, Urothelial Papilloma , Urothelial neoplasm of low malignant potential, Papillary urothelial carcinoma low grade and Papillary urothelial carcinoma, high grade.

The higher incidence of urothelial tumors in male than in female is probably related to difference in smoking habits and occupational exposure (Gupta et al., 2009)¹⁹. Low grade tumors can be invasive but significantly lower than high grade papillary carcinoma (Grignon, 2009)²⁰. Pathological stage is the most important determinant of prognosis and treatment (Cheng et al).²¹

The majority of the cases of transitional cell carcinoma in the present study were between 50-80 years. This corresponds to the study of Jordan and Murphy et al (1987)²². This is similar to other study which showed that 80.6 % presents older than 50 years (Al-Bazzaz, 2009)²³. Younger patients frequently present with lower grade and lower stage tumors than their elder counter parts (Wan, 1989)²⁴. Incidence of bladder cancer increases with age with median age at diagnosis of around 70 years (Lynch & Cohen, 1995)²⁵. The median age was 60 years old in our study, similar to a study in India (Gupta et al., 2009).¹⁹ Males (90%) are involved more frequently than females. This corresponds to the study of Jordan & Murphy et al (1987)²². The male-female ratio in different parts of the world is varied.

In the present study most of the urothelial neoplasm 36.11% belonged to the histologic grade of papillary carcinoma of low grade according to WHO / ISUP Classification (1998).

Similar findings was also reported by Ahmed et al²² where 44% were low grade and 29.5% were high grade. However this does not correlate with study of Jordan and Murphy et al²² where 12.7% of the cases fall in grade 2 according to WHO classification.

In the present study invasive neoplasm (high grade) was constitute 30.5% of total cases. Result was similar to study by Ahmed et al (37.6%)²⁶. All the cases of this group of invasive neoplasm showed both nuclear and architectural features of high grade papillary neoplasm. Pathologic grade and muscle invasion are the most valuable prognostic predictors of survival.

This is supported by Blaveri et al²⁷, who evaluated the association between genomic instability and muscle invasive tumours and found that worse outcome is associated with muscle invasive tumors. Eight cases of squamous cell carcinoma were reported, which were associated with chronic irritation in bladder due to catheterization and stone and parasites due to bilharziasis.

Conclusion

In our study majority of urinary bladder tumours were present in age group of 50-80 years, though it can occur in younger age group also. The maximum cases were seen in males and correspond to low grade urothelial carcinoma. Urothelial neoplasm runs the gamut from small benign neoplasm that may never recur to tumors of lower indeterminate malignant potential to lesions that invade the bladder wall and metastasize frequently.

Hence histologic grading of these tumors to predict behavior has been subject of great debate as there is poor inter- observer reproducibility and no uniformity. Thus a reliable grading system and universally accepted classification should be used effectively by Pathologist, Urologist and Oncologist.

Although World Health Organization classification system is most commonly used grading system but lack of detailed histological criteria motivated WHO and ISUP to publish a consensus classification for urothelial neoplasm of urinary bladder.

Thus it is concluded that the recently proposed WHO / ISUP grading system defines more accurately grades in papillary urothelial neoplasm taking in account of both nuclear and architectural features.

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