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Urinary Bladder Tumors in Southern Pakistan: A Histopathological Perspective

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Abstract

Background: This study intends to determine the frequency and clinicopathological characteristics of different types of bladder tumors, particularly transitional cell carcinoma in cystoscopic bladder biopsies and resections in the local patient population and compare these findings with local and international reports.

Methods: The study was conducted in the Department of Histopathology, Sindh Institute of Urology and Transplantation, Karachi, Pakistan from December 1996 to December 2001. All patients with bladder growth who presented to the Urology Clinic of Sindh Institute of Urology and Transplantation (SIUT) during the study period and in whom a cystoscopy and bladder biopsy were performed, were included in this study. The clinical and demographic data and the pathological diagnoses were retrieved from the original surgical biopsy reports.

Results: Out of 500 patients, there were 421 (84.2%) males and 79 (15.8%) females. The mean age was 57.5±8.6 years (range: 4 to 82 years). Among the primary bladder tumors, transitional cell carcinomas were the most common (94.3%) malignancy. A majority of these cases (62%) presented with superficial disease, whereas in 38% the disease was muscle-invasive at initial diagnosis. Grading was possible in all except two cases, which contained only necrotic tumor tissue. A vast preponderance of tumors (74.5%) were well-differentiated, while 25.5% were poorly-differentiated.

Conclusion: This study demonstrates that the vast preponderance of bladder tumors is of urothelial origin and malignant. Benign tumors are very rare. The clinicopathological characteristics and frequency distribution of different types of bladder tumors in the local population are, in general, comparable to those reported in the world literature.

Keywords: Bladder tumors, Cystoscopy, Grading, Pakistan, Transitional cell carcinoma

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Introduction

Malignant tumors of the urinary bladder are common in urological practice and present significant diagnostic and therapeutic challenges to both the urologists and uropathol-

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ogists.[1,2] In addition, the incidence of bladder cancer is also increasing worldwide, especially in developed countries.[1] The incidence of bladder cancer varies between different countries of the world and even among different areas of the same country.[3-5] Local population-based data collected by national or regional tumor registries are still at a primitive stage in Pakistan.[6-8] A local multicenter hospital-based study showed that, overall, urinary bladder cancer is among the top ten cancers in males with hospital-to-hospital variation in rank order.[6] Urinary bladder cancer ranks fifth among males in a recent study of cancer patterns in Karachi division.[8] This may be an underestimate of the true incidence of the bladder tumors, as the aforementioned study did not include data from this center(SIUT), which is the largest tertiary care and referral center for diseases of the urogenital tract. Data from the US shows that over 51000 new cases of bladder cancer occur in the US each year with more than 10500 people dying of the disease.[2]

Since symtomatology of bladder cancer is quite non-specific, there is a need for a variety of diagnostic tests of which the cystoscopy and bladder biopsy are of paramount importance.[9] As for any other malignant tumor, a prompt and accurate diagnosis of bladder cancer is of critical importance, since a cure is only possible in the early stages; in the late stages, only palliative therapy can be provided.[1,2,9] Bladder biopsy plays a pivotal role in establishing the correct diagnosis, grading and local pathological staging of the bladder tumors, determining the optimal approach to the management and defining the prognosis. Both the histologic grade and the pathologic stage are the two most important prognostic variables in bladder tumors and these can only be accurately determined on the pathologic examination of an adequate biopsy material.[2,10-16]

The present study was conducted to determine the clinicopathological characteristics of bladder tumors diagnosed on cystoscopic bladder biopsies or resections in the local population and to determine the frequency of different types of bladder tumors in patients with bladder cancer.

Patients and Methods

We performed a retrospective study on all patients with bladder cancer who underwent cystoscopy and bladder biopsy and/or transurethral resection (TUR) of bladder growth in the urology department of Sindh Institute of Urology and Transplantation (SIUT) between December 1996 and December 2001. These biopsies were received and processed in the Department of Histopathology, SIUT, Karachi, Pakistan. Bladder biopsies and TUR specimens were received in 10% buffered formalin. Gross examination was performed after fixation and the entire biopsy material was submitted for tissue processing and paraffin embedding as per standard recommendations. Histologic sections were cut at a thickness of 3-4 µm and stained routinely with hematoxylin and eosin (HE), periodic acid-Schiff (PAS) and PAS with diastase, as described in our previous report.[12] Further serial sections and stains were obtained as and when required. Sections were examined by two pathologists under the light microscope to document the pathologic diagnosis by consensus. The WHO 1973 classification and grading system was used for grading papillary urothelial neoplasms.[13] Staging was done according to the American Joint Commission on Cancers (AJCC) staging methods.[14]

Patients' demographic and clinical data were collected from a review of the patients' original surgical biopsy reports. The pathological data items were also retrieved from a review of the original biopsy reports. Cystectomy specimens were excluded from the analysis. In many cases, multiple TURs were performed. In those cases we choose the most relevant biopsy or TUR result (i.e., one which showed all relevant histopathological parameters for standardized reporting of the bladder tumors).

Results

Patient characteristics

The demographic characteristics of patients are shown in Table 1. Of the total 500 patients, there were 421 (84.2%) males and 79 (15.8%) females, giving an overall male to female ratio of

5.3:1. The gender ratio was 5.4:1 for transitional cell tumors. The mean age was 57.5±8.6 years and there was a wide age range (4 to 82 years). However, the majority of patients (71.8%) belonged to the fourth to seventh decades of life. The study patients belonged mostly to the Southern part of Pakistan with some patients included from all regions of the country. Patients comprised both rural and urban populations.

Table 1. Overall patient characteristics.

All patients	500
Males	421 (84.2%)
Females	79 (15.8%)
Male to female ratio Age (years)	5.3:1
Mean ± SD	57.5 ± 8.6
Range	4 – 82

Pathological findings

The frequency distribution of different primary bladder tumors is shown in Table 2. The primary bladder tumors constituted the overwhelming majority (99%). In only 5 (1%) the urinary bladder was the seat of metastatic tumors that originated mostly from the gut. One was a squamous cell carcinoma (SCC) primary from the cervix in a middle-aged female. Among the primary tumors of the bladder, TCC was the most common malignancy that accounted for 93.4% of all tumors and 94.3% of the primary bladder tumors in this series (Table 2). It was more common in males than in females (male to female ratio: 5.4:1). Its peak occurrence was noted in the fourth through seventh decades. Pathologic staging was possible in 89.7% of the cases. A majority of these cases (62%) presented with superficial (muscle non-invasive) disease, while in 38%, the disease was muscle-invasive when first diagnosed. The pathological grading was possible in all except two cases, which contained only necrotic tumor. A vast preponderance of tumors (74.55%) were well to moderately-differentiated, while 25.5% were of

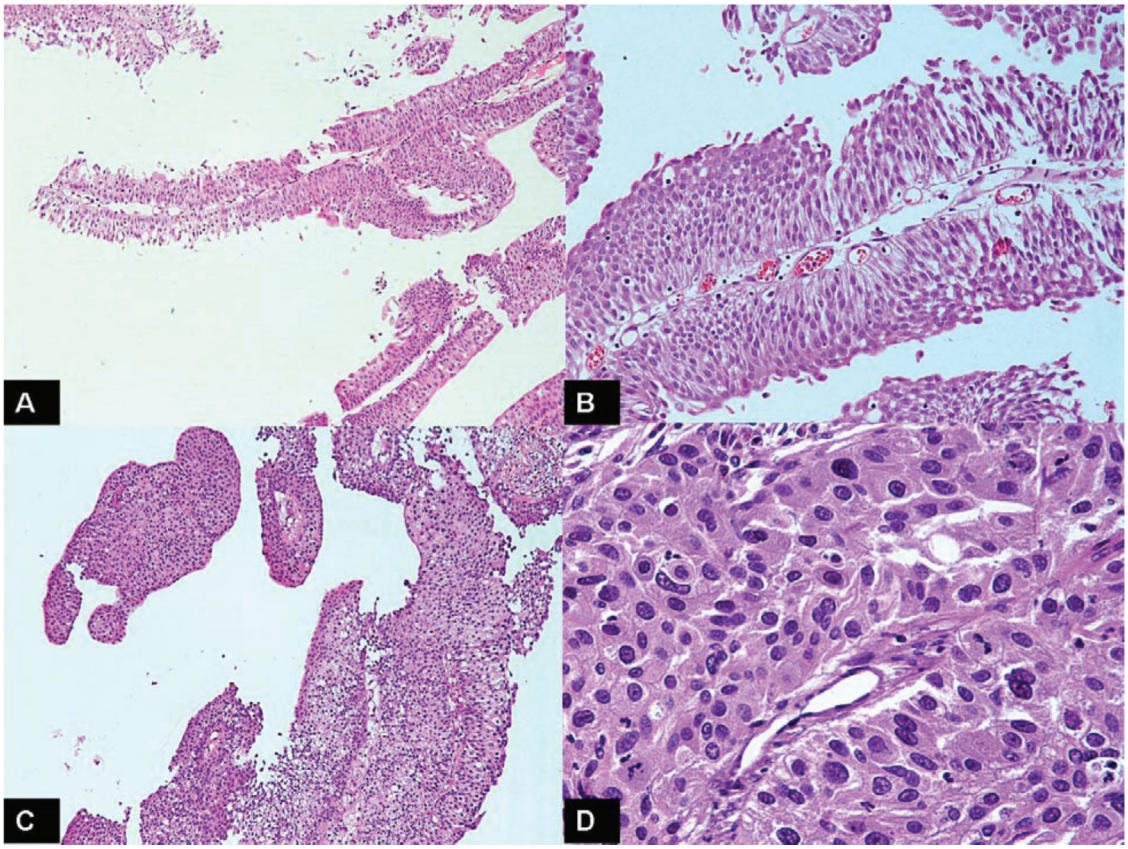

Figure 1. A. Thin delicate papillae lined by normal urothelium in a case of papilloma. (HE, 100x). B. Here the papillae are lined by mildly hyperplastic urothelium with minimal atypia in a case of grade 1 transitional cell carcinoma (TCC). (HE, 200x) C. Grade 2 TCC with marked hyperplasia and moderate atypia. (HE, 200x) D. Grade 3 TCC with marked cellular and nuclear atypia and increased mitoses. (HE, 400x)

Table 2. The frequency distribution of different primary urinary bladder tumors among 500 patients with bladder tumors.

Tumor type	Number	Percentage
Transitional cell carcinomas (TCC)	467	93.3
Adenocarcinoma	13	2.6
Squamous cell carcinoma (SCC)	10	2
Embryonal rhabdomyosarcoma	02	0.4
Inverted papilloma	01	0.2
Paraganglioma	01	0.2
Small cell carcinoma	01	0.2

grade 3 and belonged to the poorly-differentiated category (Table 3). The pure urothelial adenocarcinoma accounted for 2.6% of primary bladder tumors whereas SCC accounted for 2% of these tumors. Representative pictures of the different tumor types, their grading and staging are shown in Figures 1 and 2.

Discussion

This is the largest study from Pakistan on the spectrum of urinary bladder tumors diagnosed according to cystoscopy and bladder biopsy. A number of small-scale studies are available on this subject, but the number of patients and their origin from all parts of the country makes this study fairly representative of the prevalent urothelial tumors in this part of the world. However, there are some limitations in the study. This study represents a single center experience. The grading of urothelial tumors has been done according to

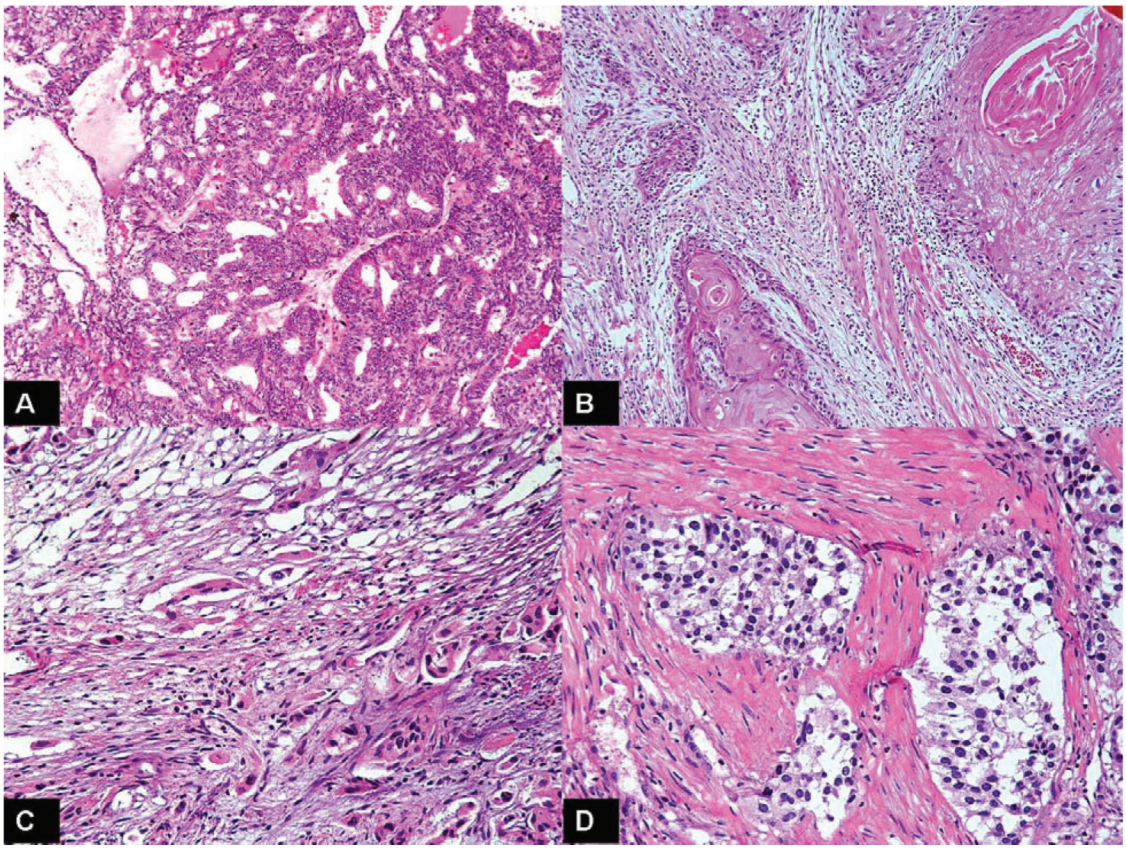

Figure 2. A. Malignant urothelial tumor composed of glands and classified as primary adenocarcinoma. (HE, 200x) B. Well-differentiated squamous cell carcinoma (SCC) of the urinary bladder forming keratin pearls. (HE, 200x). C. Individual cells and small clusters of tumor cells with intensely eosinophilic cytoplasm that infiltrated into the lamina propria. This tumor was staged as pT1. (HE, 400x) D. High grade transitional cell carcinoma that infiltrated into the detrusor muscle bundles, staged as pT2. (HE, 400x)

1973 WHO classification, which is still used, often along with newer WHO classifications in many centers of the world. We have also begun using the 1998 WHO/ISUP classifications and lately the 2004 WHO classifications along with the 1973 WHO classification, since the early 2000s. The 2004 WHO classification has not completely replaced 1973 WHO classification in many parts of the world. We are analyzing the results of the combined use of the above classifications and the results will be published in the near future.

The advent and widespread use of the fiberoptic cystoscopy has revolutionized the management of urinary bladder tumors. Bladder tumors are most reliably detected and monitored using some combination of cystoscopy, histology and urinary cytology. All methods have limitations and none can detect the presence of bladder tumors at every point in time.[10] Cystoscopy is particularly useful in localizing bladder tumors and detecting very low-grade papillary lesions. Certain areas of bladder are difficult to visualize and some tumors may be too small to see. Carcinoma is situ (CIS) cannot be reliably identified by cystoscopy. Determination of the depth of invasion and tumor grade represent further limitations of this method. Since bladder tumors are defined in histologic terms, the histology is the most accurate procedure for documenting the presence of a neoplasm during initial and follow-up examinations. Using this method, tumor type, grade and depth of invasion can be established.[1-9] We utilize all the three modalities, but in particular, cystoscopy and biopsy to detect and monitor urothelial neoplasms. Our center is the biggest urology, nephrology and transplant center in the country and receives a large number of patients from most areas of Pakistan. This study is based on an analysis of the clinicopathological characteristics of bladder tumors in cystoscopic bladder biopsies and we believe that this will be fairly representative of the prevailing tumor types and patterns in this country.

There was a wide age range of the patients in this series. However, the majority of patients (71.8%) belonged to the fourth to seventh decades of life, which was fairly concordant with local and international literature. The peak incidence of TCC was noted in the sixth decade. This was again in accordance with the studies from the West where bladder neoplasms are primarily encountered in men aged 50 to 70 years.[3,4,5,10] Only 26 cases of bladder neoplasms were detected in children and adults less than 35 years of age. Three of the later cases were embryonal rhabdomyosarcomas in children aged 4, 4, and 4.5 years. One case was of primary pure adenocarcinoma that arose from the urachus in a 35-year-old female. The remainder of the cases in the younger age group belonged to the low-grade non-invasive TCC category. This later finding was in concert with a previous study[17] which showed that the majority of tumors in younger age groups were low-grade, non-invasive TCCs.

Table 3. Histologic grading of the transitional cell carcinomas (TCCs) of the urinary bladder.

Histological grade	Number	Percentage
1	63	13.5
2	285	61
3	119	25.4

Overall, the male to female ratio in this series was 5.3:1. A ratio of 5.4:1 was observed in cases of TCCs of the urinary bladder. This was significantly lower than the 14:1 male to female ratio reported in a previous study from this institution.[7] This change in male to female ratio in favor of more females as compared to the early 1980's might be due to the fact that more women currently seek medical help. The sex ratio in the current series was, however, in good agreement with several worldwide studies, which have all shown a male to female predominance that ranged from 2:1 to 5:1.[10,12,14] A recent local study also found overall male to female ratio of 3.15:1 in bladder tumors.[18] Among the non-TCC (6.7%) neoplasms of the urinary bladder, a variety of neoplasms that included 13 (2.6%) cases of primary pure adenocarcinoma, 9 (1.8%) primary SCC, 3 (0.6%) cases of embrynol rhabdomyosarcoma, 3 (0.6%) poorly differentiated carcinoma cases, 2 cases of sarcomatoid carcinoma, and one

case each of paraganglioma, small cell carcinoma and inverted papilloma were observed (Table 2). This frequency distribution of bladder tumors was in good agreement with several other studies, which have shown TCC to be the most common malignant bladder tumor.[1,2,10,12,15,16] The few local studies available in the literature also showed a comparative distribution of major categories of bladder tumors in the local population.[18-20] A break up of histologic grade of TCC is shown in Table 3. The majority of these tumors were well-differentiated with 348/467 (74.5%) cases that belonged to grades 1 and 2. A total of 119 (25.4%) cases were grade 3 according to WHO 1973 classification. These figures were again in good agreement with numerous Western studies.[1,2] However, the majority of tumors (68%) were of higher grade (G3) in a local study.[18]

Adenocarcinoma of the urinary bladder denotes a malignant neoplasm derived from the urothelium and showing pure glandular phenotype on the histopathological evaluation. Bladder adenocarcinoma is uncommon, accounting for less than 2% of all malignant urothelial neoplasms in most series.[1,2,10,12] It includes two distinct topographic and histogenetic types, primary bladder adenocarcinoma and urachal carcinoma. This tumor has accounted for 2.6% of all malignant bladder tumors in this study, which was in good congruence with international studies. Two cases of adenocarcinoma were seen in young individuals, one of which in a female patient originated from the urachus.

The diagnosis of SCC should be reserved for those tumors that show a pure squamous cell phenotype on histopathological evaluation of the entire tumor. They constitute 2% to 7% of the urothelial cancers except in the Middle East, where, as a consequence of schistosomiasis, they are the most common form of cancer.[21] Squamous cell carcinomas are relatively more common in women: the male to female ratio in most series is less than 2 to 1.[10] A similar ratio has also obtained in a study by Siyal et al.[18] at Larkana. Among 9 cases of SCC in our series, one was metastatic from a primary cervical cancer in a female and the remaining 8 cases were of primary bladder origin. There were 6 cases observed in males and 3 in females, a finding similar to that in other reported series.[10,12,15]

During the last decade or so, attempts have been directed toward the discovery and application of immunohistochemical, omics and molecular genetic approaches to further refine the traditional morphology-based features for an accurate classification and prognostication of bladder tumors in general and TCCs in particular.[22]

Conclusion

In conclusion, this study demonstrates that the vast preponderance of bladder tumors is of urothelial origin and malignant in nature. Transitional cell carcinoma is the most prevalent tumor. Benign tumors are very rare. The clinico-pathological characteristics and frequency distribution of different types of bladder tumors in the local population are, in general, comparable to those reported in the world literature.

Conflict of Interest

No conflict of interest is declared.

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