

## ORIGINAL ARTICLE

## CLINICO-PATHOLOGICAL PATTERN, CLASSIFICATION AND STAGING OF URINARY BLADDER CARCINOMAS - A FIVE YEARS EXPERIENCE AT A TERTIARY CARE HOSPITAL IN CENTRAL PUNJAB

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**Background:** In Pakistan, urinary bladder carcinoma is the 8<sup>th</sup> commonest malignancy while being the fourth commonest cancer in men. The relative occurrence of a particular histological type of bladder carcinoma depends on the clinical setting. Both grade and stage of these cancers are highly correlated with recurrence, progression and patient survival rates. **Methods:** This cross-sectional study comprised of 122 patients with newly diagnosed operable primary bladder carcinomas who underwent cystoscopy associated transurethral resection of bladder tumour at the Urology Department of Punjab Employees Social Security Hospital, Lahore. All participants completed a detailed questionnaire and underwent an in-depth interview to obtain data. The surgical specimens were referred to the Pathology department. Gross observations of the tumour recorded. **Result:** A total of 114 cases, classified according to WHO/ISUP criteria, low-grade papillary lesions, comprising Papillary Urothelial Neoplasm of Low Malignant Potential (PUNLMP) and Papillary Low Grade carcinomas, accounted for 43% of tumours. Male to female ratio being 5.3:1 (74%). Lateral walls were involved in 44%, posterior wall in 25.3%, trigone in 10.7%, bladder neck in 7.2%, dome in 5.8%, ureteric orifice in 4.13%, anterior wall in 2% and left ureter in 0.87% cases. Tumour staging revealed an overall 11.5% of tumours with stage Ta and 31.5% with stage T3-4. About 29% tumours were non invasive. About n=13 of low-grade carcinomas and n=68 of high-grade carcinomas were invasive. For tumours classified by WHO/ISUP criteria, the percentage of women was larger for PUNLMP than for the other categories of urothelial tumours (*p*-value 0.006); no statistically significant difference was found by age or gender with respect to tumour stage (*p*-value 0.138 and 0.452). **Conclusion:** Transitional Cell Carcinoma (TCC) is the commonest among middle aged men.

**Keywords:** Urinary bladder carcinoma, Tumour, transitional cell carcinoma, urinary bladder

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### INTRODUCTION

Carcinoma of urinary bladder is one of the leading malignancies with approximately 356,000 new bladder cancer cases (274,000 males and 83,000 females) occurred worldwide in 2002.<sup>1</sup> But the burden of disease is on continuous rise in less developed areas of the world with a high incidence reported in South East Asia. This shift can be attributed to global changes in exposure to risk factors for urinary bladder carcinoma (UBC) and growth and aging of the world population.<sup>2</sup> In Pakistan, it is the 8<sup>th</sup> commonest malignancy while being the fourth commonest cancer in men. A frequency of 5.75% among men and 1.61% among women with an incidence of 5.4% was reported in North West Pakistan.<sup>3,4</sup> The relative occurrence of a particular histological type of bladder carcinoma depends on the clinical setting. Epidemiologically transitional cell carcinoma (TCC) represents 90-95% of cases in Europe while 5% represents mostly SCC of the bladder.<sup>5</sup> In more than 75% of patients, the most common sign is gross or microscopic painless haematuria. Thus, persistent painless haematuria must be investigated rigorously by excretory or retrograde urography.<sup>6</sup> A

number of factors have been implicated in the causation of TCC with tobacco smoking reported as the cause of approximately 50% of these cancers in men and 30% in women in epidemiological studies.<sup>7</sup> Occupation has been identified as the second most important risk factor after smoking and estimated to account for as much as 20% of all bladder cancer in industrialized countries.<sup>8</sup> How these influences to induce cancer is unclear, but a number of cytogenetic and molecular alterations have been observed. Furthermore, occupational risks of bladder cancer have changed over time and differ from population to population. A careful history of patients with bladder cancer is therefore important and useful process in helping to identify causal factor and, in more than one-half of the cases, a known relationship is found which makes bladder cancer a potentially preventable disease.<sup>9</sup>

Though majority of newly diagnosed bladder tumours are superficial, approximately one fourth of patients either present with or subsequently develop invasive cancers that will require aggressive management. Both grade and stage of these cancers are highly correlated with recurrence, progression and

patient survival rates.<sup>7</sup> The grading system to classify urothelial tumours was evolved from time to time till a popular World Health Organization (WHO) Classification was introduced in 1972 which divided the tumours into papilloma and grade I, II and III, transitional cell carcinomas (TCC). A recent classification which has been formulated by WHO Committee on urothelial tumours is called WHO/ISUP Consensus Classification. It has been proposed by the International Society of Urological Pathologists (ISUP) and Canadian Academy of Pathology in 1998. The aim of this classification is to develop a universally accepted system for bladder neoplasia and the diagnostic criteria of this classification system, however, have been profusely illustrated and described in literature to reduce the diagnostic variability and subjectivity among pathologists.<sup>10</sup> This study was aimed to know the frequency of different types of bladder cancers by classifying them according to the revised WHO/ISUP criteria and to relate it with the clinico-pathological pattern and TNM stages in population, including the factory workers, of Northern Punjab.

## MATERIAL AND METHODS

This was a cross-sectional study comprising 122 patients of bladder tumour at the Urology Department of Punjab Employees Social Security Hospital (PESSI) Lahore, Pakistan from January 2004 to July 2009.

Informed consent was taken from all the participants. All participants completed a detailed questionnaire and interviewed to obtain data including age, sex, residence, marital status, occupation, smoking history, exposure to carcinogenic chemicals, family history etc.

Relevant clinical and laboratory findings of these patients were recorded on separate *pro forma*. Cases with history of co-morbidity or taking medication/therapy for their malignancy, i.e., follow up cases were excluded. Preoperative staging work-up involved complete history and physical examination, complete laboratory workup, chest radiography, CT scan, or abdomenopelvic ultrasound (A/P U/S). Advanced diagnostic modalities including magnetic resonance imaging (MRI) and bone scan were undertaken where the clinical symptoms or diagnostic workup suggested advanced or metastatic disease.

The surgical specimens were referred to the Pathology department where after formalin fixation, about 4-7 $\mu$ m sections from each specimen were cut by rotary microtome and embedded in paraffin to prepare tissue blocks that were stained with haematoxylin and eosin (H&E). Gross observations of the tumour took account of size, location, colour, and consistency, areas of necrosis or calcification, depth of invasion and status of adjacent lymph nodes, if submitted. Microscopic features tabulated included patterns of growth, nuclear

features, mitoses, necrosis, and stromal reaction. All slides were reviewed by a group of four histopathologists and in the case of any difference in terms of final diagnosis; consensus was reached by computation of the votes of majority. Tumours without any papillary component were categorized as non-papillary (i.e., solid); all other tumours, either purely papillary or mixed papillary/solid, were categorized as papillary. Tumours were graded separately for each group first according to WHO Classification 1972 as papilloma, TCC Grade I, II, and III and later according to WHO/ISUP Consensus Classification 1998 as papilloma, papillary neoplasm of low malignant potential (PNLMP), low grade (Papillary LG) and high grade (Papillary HG) urothelial carcinoma. Tumour staging was done according to TNM criteria of the American Joint Commission on Cancer.<sup>11</sup>

Data was analysed using SPSS-17.0. Pearson Chi-square and Fisher Exact test were applied to observe associations, if any, between the qualitative variables. A *p*-value of <0.05 was considered as statistically significant.

## RESULTS

After confirmation of the final diagnosis, 4 cases were excluded for technical reasons or because malignancy was not definitively diagnosed and another 4 were segregated as SCC. Of the rest n=114 cases, classified according to WHO/ISUP criteria, we were able to classify the following subtypes and grades of TCCs (Table-1 and 2).

In brief, low-grade papillary lesions, comprising PNLMP and Papillary LG carcinomas, accounted for 43% of tumours.

There were 96 (84%) males and 18 (16%) females with mean ages of 57.5 $\pm$ 12.91 years (age range: 35-80 years) and 63.5 $\pm$ 13.62 years (age range: 43-84 years). Male to female ratio being 5.3:1. With reference to age, the number of male and female cases observed in the age groups of 30-40 years, 41-50 years, 51-60 years, 61-70 years, 71-80 years and >80 years were: 4 and 0, 10 and 2, 32 and 4, 35 and 9, 12 and 2; and 3 and 1 respectively.

Clinical history was more or less common in both genders with the maximum number of patients 84 (74%) presenting with haematuria with or without altered urinary habits including hesitancy, urgency, dribbling of urine etc. Other complaints were pain in abdomino-pelvic area in 64 (56%), dysuria in 54 (47%), palpable abdominal mass in 25 (22%), fever in 11(10%), and anorexia, weight loss or generalized weakness in 39 (34%) patients. History of smoking was present in 65 (57.4%) of patients. All patients were males. Exposure to carcinogens was found in 15 (13%) of patients. Family history was not present in any case. Regarding the sites of involvement, lateral walls were

involved in 50 (44%), posterior wall in 29 (25.3%), trigon in 12 (10.7%), bladder neck in 8 (7.2%), dome in 7 (5.8%), ureteric orifice in 5 (4.13%), anterior wall in 2(2%) and left ureter in 1 (0.87%) cases. The sex-wise distribution of the site of bladder carcinomas did not show much variation except that anterior wall, to some extent, was predominantly involved in females than in males (1.3% vs 0.7%). Tumour staging (Table-3) revealed an overall 11.5% of tumours with stage Ta and 31.5% with stage T3-4. About 29% tumours (including all PUNLMPs and CIS) were non invasive; among these n=17, n=03 and n=04 of the tumours representing grade I, 2 and 3 respectively. About n=13 of low-grade carcinomas and n=68 of high-grade carcinomas were invasive (n=81).

Differences in the distribution of gender and age were tested between tumours classified by tumour type and stage in each classification system. For tumours classified by WHO/ISUP criteria, the percentage of women was larger for PUNLMP than for the other categories of urothelial tumours (i.e. low-grade and high-grade papillary carcinomas) (*p*-value 0.006); no statistically significant difference was found by age or gender with respect to tumour stage (*p*-value 0.138 & 0.452).

**Table-1: WHO/ISUP classification of bladder carcinomas**

ISUP Tumour Grade	Number	Percentage
PUNLMP	22	19.2
LGPC	27	23.6
HGPC	45	39.4
CIS	11	9.6
NPUC	9	7.9
Total	114	

**Table-2: WHO grading of bladder carcinomas**

WHO Tumour Grades	Number	Percentage
I	41	35.9
II	29	25.4
III	44	38.6
	114	

**Table-3: AJCC Staging and WHO grading of invasive bladder carcinomas**

WHO Tumour Grades	Ta	T1	T2	T3-4	Total n (%)
I	10	3	0	0	13 (16)
II	2	4	8	12	26 (32)
III	0	0	18	24	42 (52)
Total	12 (10.5)	7 (6.14)	26 (22.8)	36 (31.5)	81 (71)

**DISCUSSION**

The data presented in this report are derived from a geographic location in the Southern Punjab which depicts a high incidence and morbidity rates related to bladder cancer. Patients included in the current study were mostly representing both rural and an urban, though a few, population including factory workers in this region.

Our observations were quite concordant to that of Hasan and colleagues, who reported Ca UB more common in males (72.09%) as compared to females (27.9%) with a male to female ratio of 2.5:1 and an age range of 24–78 years.<sup>6</sup> Khan from a local hospital based study reported an age range of patients from 43–72 years (mean:61 years).<sup>12</sup> As regards the histological type, TCC accounted 93.33 percent of all tumours while the SCC formed 3.2 percent which was exactly similar to the findings of Hasan. In a Sri Lankan study, 93.4% of primary bladder cancers were the TCC with a male predominance and a sex ratio of 6:19.<sup>13</sup> As reported by Rafique in his study population of 221 patients (172 male and 49 female) from January 1998 to June 2005, bladder carcinoma was evaluated in all patients with regards to clinical presentation, cystoscopic findings and histopathological data. The male-female ratio was 3.5:1 with a median age being 58 years (range 18–87 years) and TCC made the 96% of the tumours.<sup>14</sup>

In the present study, haematuria was also the commonest presenting symptom. The mean duration of symptoms was 7 months (6–8 months range) and maximum numbers of cases were having a tumour grade II to III. Our study findings were comparable to that of Agha Khan University Hospital reports where one can see a higher number of grade II tumours (67.60%) presented with longer duration of symptoms as compared to grade III in tumour (56.25%) ; although the finding were not statistically significant.<sup>15</sup>

TCC is a well-known tumour of the urinary bladder, yet its incidence in the ureters is rare, accounting for only 1% of all urinary tract neoplasms.<sup>16</sup> One of our study patients also reported with a ureteric TCC. The distribution of tumours in the present study reflects a significant proportion of the patient population reporting at this centre with higher stage and grade of bladder cancer. Concordant with this, Rafique also reported 63% patients with a muscle invasive disease at the time of presentation. Even in superficial bladder carcinoma, over 98% of his study patients had invasion of lamina propria (pT1 disease).<sup>14</sup> Tumour grade III formed 29.5% and 32% while grade II was found in 44% and 68% of patients reported by Hasan and Khan respectively.<sup>6,12</sup> Similar findings from Ather accounted 17%, 5%, 36%, 12% and 24% of patients with pT0, T1, 2, 3 and 4 respectively.<sup>15</sup> Conversely, the findings of Hasan depicted 17.85%, 64.28% and 10.72% patients with T1, 2 and 3 respectively.<sup>6</sup> Also Cheng<sup>17</sup> reported a higher number of patients with low grade carcinoma (67%) as compared to our and the observations of Wolf *et al.*<sup>18</sup> who found 47% patients with grade III while only 7% with grade I. We could not conceive any marked differences in histological characteristics by age or gender except that PUNLMPs were more common in females.

The geography of smoking is shifting from the developed to the developing world and many low and middle income countries are still in the early stages of the tobacco epidemic. This will result in a serious increase in bladder cancer incidence in these communities in the next decades.<sup>19</sup> As reported by Rafique, 65% men had history of cigarette smoking while 51% women had long history of smokeless tobacco (nasal snuff or chewable) use and therefore a significant dose-response relation was observed for increasing cigarette consumption, and a significant decrease in risk was shown for ex-smokers.<sup>14</sup> In our study, 33.3% (n=32) of men and 27.7% of women were chronic tobacco smokers with one female presented with a history of addiction to *charas* (cannabis) also.

Treatment with cytostatic drugs, especially cyclophosphamide, is associated with increased risk of bladder cancer, as is treatment with radiotherapy for uterine cancer.<sup>20</sup> Two of our female patients also reported a history of ovarian and uterine cancer and were currently on chemotherapy for more than 10 years in the former and less than 5 years in the latter.

The relationship between bladder cancer, occupation and exposure to a number of occupational agents could not be assessed because of the incomplete clinical data however it is conceivable that the results of this study may be extended in relation to histological patterns associated with exposure history, levels of industrialization, lifestyle or other demographic characteristics in the factory workers which may provide potential etiological clues.

## CONCLUSION

This study shows that commonest UB tumour is TCC and is of high grade at the time of diagnoses occurring mostly in middle and old age males. Persistent haematuria in the absence of symptoms must be investigated rigorously.

Awareness of risk factors like tobacco smoking in the population may significantly reduce the incidence of UB tumours

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