

## Pathological Spectrum of Urinary Bladder Tumours

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**Abstracts: Objective:** Recently few reports have reported high incidence of urinary bladder cancer in the Punjab region in India while others have shown high inorganic arsenic levels in the ground waters of the same region. Furthermore, the malignancy of the urinary bladder contributes significantly to the morbidity, mortality and thus adding to the burden on the healthcare and society. **Materials and Methods:** A retrospective analysis over a period of 4 years was undertaken to review all urinary bladder tumour biopsies, transurethral resection of bladder tumours (TURBT) and cystectomy specimens to study the histomorphological spectrum of the urinary bladder cancers according to the "WHO Classification of Tumours of the Urinary Tract". The records of Pathology department were probed for urinary bladder specimens. Further demographic characteristics, clinical diagnosis, cystoscopic findings were retrieved from the patient's files from the record section. The tissue section slides were then reviewed and results recorded. **Results:** In our cohort, 144 patients were from State of Punjab with about 50% belonging to the city where our hospital is located. Cystoscopic revealed papillary appearance in 112 out of 135 patients. Moreover, 111 cases (82.22 %) were unifocal. Urothelial neoplasms were the most common bladder tumours and Invasive Urothelial Carcinomas constituted the bulk of these. **Conclusions:** Our cohort comprised of relatively younger population with dominance of high grade urothelial carcinoma showing features of invasion on microscopy. Further, we observed that WHO/ISUP classification to be comprehensive and universally acceptable. The role of arsenic as a causative agent in urothelial neoplasms needs to be studied further. [Selhi P NJIRM 2014; 5(4): 25-29]

**Key Words:** Urothelial tumours, spectrum, bladder tumours

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**Introduction:** Urinary Bladder tumours are a heterogeneous group of neoplasms which contribute significantly to the overall human cancer burden. The origin of bladder cancer is multifactorial with tobacco smoking and other environmental factors reported to be the principal causes. Auerbach showed a sharp correlation between smoking habits and the occurrence of bladder cancer, Rehn observed that workers in factories producing aniline dyes were at a high risk for the disease complementing the epidemiological evidence<sup>1,2</sup>. High level of inorganic arsenic in drinking water has been known as an important environmental etiological factor for bladder cancer<sup>3</sup>. Recently, reports have emerged indicating a high incidence of bladder cancer in India particularly in the state of Punjab with high inorganic arsenic levels in the ground waters of the same region<sup>4,5,6,7,8</sup>. Histologically, more than 90% of bladder cancer cases are of epithelial differentiation with majority of them originating from the epithelial cells that line the bladder wall internally (urothelium)<sup>9</sup>.

This study was designed to review all urinary bladder tumour biopsies, transurethral resection of bladder tumours (TURBT) and cystectomy specimens to study the histomorphological spectrum of the urinary bladder cancers according to the "WHO Classification Of Tumours Of The Urinary Tract" and also to correlate these with cystoscopy findings.

**Material and Methods:** This is a retrospective analysis of all the urinary bladder tumours received in the Department of Pathology, Dayanand Medical College & Hospital, Ludhiana (Punjab, India) for histopathological examination over a period of four years. The department received 321 urinary bladder biopsy specimens during the time interval. The patient charts (Files) in the medical records department were accessed to record the age, sex, permanent residential address, cystoscopic findings and histopathological diagnosis. The details of the specimens received were recorded for gross and microscopic features. Tissue samples had been submitted either in the form of trans-urethral biopsies or radical cystectomy. The tumour base

was often submitted as a separate specimen so as to assess the depth of tumour invasion.

In case of biopsies, the entire tissue had been processed. The radical cystectomy specimens were received as whole bladder along with prostate gland, both seminal vesicles and ureters attached. These specimens had been processed according to standard ISUP guidelines<sup>10</sup>.

The data was collected from the requisition form, reporting form and signed out reports. Slides were reviewed by at least two pathologists and findings recorded. Urinary Bladder tumours were initially classified in accordance with the WHO classification of Tumours of the Urinary Tract and the urothelial neoplasms were further classified and graded on the basis of criteria laid down by the WHO / ISUP consensus conference held in 1998<sup>9,10,11</sup>.

**Observations And Results:** Of the 321 urinary bladder biopsy specimens received in four years, 182 (56.70 %) cases were neoplastic lesions. 118 (64.84 %) of the specimens in the study were trans-urethral resections of bladder tumours, 8 radical Cystectomy specimens and remaining 60 were bladder biopsy with no partial cystectomy or pelvic exenteration specimens. Our cohort had wide age range from 12 to 94 years with a mean of 60.9 years as about 70% of the cases were in the age range of 46-75 years. Of the 182 neoplastic specimens, 149 were males with an M: F ratio of 4.5:1 and the M: F ratio for urothelial tumours was the highest being 4.7:1.

**Table 1: Distribution of Urinary Bladder Tumours According To WHO Classification.**

| Type of Bladder Tumour     | Number of Cases | Percentage |
|----------------------------|-----------------|------------|
| Urothelial Tumour          | 166             | 91.20 %    |
| Squamous Cell Carcinoma    | 02              | 01.09 %    |
| Adenocarcinoma             | 03              | 01.64 %    |
| Undifferentiated Carcinoma | 07              | 03.88 %    |
| Metastatic Carcinoma       | 03              | 01.64 %    |
| Paraganglioma              | 01              | 00.55 %    |

According to "WHO classification of tumours of urinary tract"<sup>8</sup>, Urothelial Tumour were the commonest bladder tumours with 166 cases (91.20 %) while undifferentiated tumours (possibly urothelial origin) occupied the second place with 7 cases. As per features laid down by the WHO / ISUP consensus committee in 1998, all the urothelial tumour were graded as shown in table 2.

**Table 2: Distribution of Urothelial Neoplasms According To WHO/ISUP Classification.**

| Type of Urothelial Neoplasm according to WHO/ISUP classification | Number of Cases (n=166) | Percentage |
|--|-------------------------|------------|
| Low grade Intraurothelial Neoplasm                               | 2                       | 1.20%      |
| High grade Intraurothelial neoplasm                              | 3                       | 1.80%      |
| Papilloma  | 1                       | 0.60%      |
| PUNLMP   | 1                       | 0.60%      |
| Non-Invasive Papillary Urothelial Carcinoma, Low Grade           | 31                      | 18.67 %    |
| Non-Invasive Papillary Urothelial Carcinoma, High Grade          | 2                       | 1.20%      |
| Invasive Urothelial Carcinoma (LP invasion)                      | 56                      | 33.73 %    |
| Invasive Urothelial Carcinoma (MP invasion)                      | 70                      | 42.20 %    |

Of the non-invasive papillary urothelial neoplasms, Low Grade Papillary Urothelial Carcinoma constituted 18.67 % of all urothelial tumours and 88.57 % of non-invasive papillary urothelial tumours contributed the bulk. There was only one case each of Papilloma and Papillary urothelial neoplasm of low malignant potential (PUNLMP). Only 2 cases of High Grade Papillary Urothelial Carcinoma (1.20 %) did not show any invasion.

In the category of invasive urothelial carcinomas, lamina propria invasion was noted in 56 cases (33.67%) and muscularis propria invasion in 70 cases (42.2 %). This group accounted for the largest group amongst urothelial tumours. 58 out of the 70 cases had a classical morphology while 12 cases were high-grade morphological variants of invasive urothelial cancer.

**Table 3: Grading Of Invasive Carcinomas**

| Grade of Invasion           | Low Grade Urothelial | High Grade Urothelial | Adenocarcinoma | Undifferentiated | Total |
|-----------------------------|----------------------|-----------------------|----------------|------------------|-------|
| Lamina Propria Invasion     | 18                   | 37                    | 01             | 00               | 56    |
| Muscularis Propria Invasion | 00                   | 70                    | 00             | 04               | 74    |

**Table 4: Distribution of cases according to Districts of Punjab**

| Districts of Punjab | No. of Cases from the respective District |
|---------------------|---|
| Amritsar            | 3   |
| Barnala             | 6   |
| Bathinda            | 8   |
| Faridkot            | 4   |
| Fatehgarh           | 1   |
| Fazilka             | 1   |
| Ferozepur           | 5   |
| Gobindgarh          | 1   |
| Hoshiarpur          | 2   |
| Jalandhar           | 5   |
| Kapurthala          | 5   |
| Ludhiana            | 72  |
| Mansa               | 3   |
| Moga                | 6   |
| Mohali              | 1   |
| Mukatsar            | 4   |
| Nawansheher         | 2   |
| Patiala             | 3   |
| Sangrur             | 11  |
| Tarn Taran          | 1   |
|                     | Total = 144                               |

Cystoscopic findings were available in 135 of the total 182 cases with 112 lesions exhibiting a papillary appearance and 23 flat lesions spread out on the posterior wall & lateral walls (involving the ureteric orifices) of the urinary Bladder. Moreover, 111 cases (82.22 %) were unifocal and the rest 24 cases had multifocal lesions. Among the unifocal lesions, 104 cases were urothelial tumours exhibiting the entire morphological spectrum with maximum number of muscularispropria invasive papillary urothelial carcinoma, 5 cases of high-grade undifferentiated carcinomas and 2 cases of

adenocarcinoma. Amongst the multifocal lesions, 23 showed histomorphological features of Papillary urothelial carcinoma, (4 non-invasive and 19 invasive) with a solitary case of an undifferentiated high-grade carcinoma.

Residential addresses were available for 159 patients, of which 144 patients were residents of Punjab with maximum number of patients (72) from Ludhiana city.

**Discussion:** Urinary bladder neoplasms are one of the leading causes of cancer related deaths. Despite significant inroads into their origin and improved methods of diagnosis and treatment, they continue to exact a high toll in morbidity and mortality. Population based studies in different cities and states of India have placed bladder cancer in top ten malignancies especially in males.<sup>7,8,12,13</sup>

The incidence of bladder cancer increases with age and it is a rare malignancy in young adults<sup>14</sup>. More than 60% of the patients were in the age group of 46 – 75 years with the mean age being 60.9 + 14.9 years, which is similar to other studies<sup>15,16</sup>.

In our study, Intraurothelial neoplasms comprised 5 cases, Papilloma's and PUNLMP 1 case each, Non-invasive PUC Low Grade 31 cases, Non-invasive PUC High Grade 02 cases and Invasive Urothelial Carcinomas 126 cases.

Similarly the terms urothelial carcinoma, low grade and high grade, are highly predictive of their biological behaviour and prognosis, thus effectively guiding further therapy. This new classification system should have a significant impact on both research and the clinical aspects of this disease.

We further observed that 108 of 110 high-grade carcinomas were either invading the lamina propria or the muscularispropria. Laishram et al

from Manipur in India also reported muscle invasion in 75% of high grade carcinomas<sup>16</sup>. Murphy (1997) also reported similar findings of higher prevalence of high-grade urothelial carcinoma, which have a high propensity to invade the lamina propria and even muscularis propria<sup>17</sup>. Virtually all studies have concluded that tumour grade is one of the most powerful predictive factors for all patient outcome variables<sup>18,19,20</sup>.

The spectrum of microscopic forms of urothelial carcinoma has expanded to include several unusual histologic variants, which have been incorporated in the new WHO classification. The term variant is used to describe a distinctively different histomorphological phenotype of a neoplasm which may be associated with a different clinical outcome, and some of which have been incorporated into risk stratification models, while others may have a different therapeutic approach, and awareness of the unusual pattern may be critical in avoiding diagnostic misinterpretation. In our study there were 12 morphological variants of urothelial carcinoma, all of which showed their morphological variations in only focal areas of the tumours with rest of the tumour tissue exhibiting classical urothelial differentiation. A high grade and muscularispropria invasion was the rule in all of them.

In our study there were 2 cases of Primary squamous cell carcinoma with a mean age of 55 years, M: F ratio of 1:1 exhibiting clear-cut areas of squamous differentiation were high grade, muscle invasive with no evidence of urothelial differentiation. The category of undifferentiated carcinomas contains tumours that cannot be otherwise classified. Earlier the literature had included small cell carcinoma, giant cell carcinoma, and lymphoepithelioma like carcinoma in this category, but these tumours are now recognized as specific tumour variants. The 7 cases of undifferentiated carcinomas in our study showed a malignant epithelial tumour without squamous, urothelial, or glandular differentiation. All of these were high grade with muscularispropria invasion (3/7 cases) and lympho-vascular invasion (2/7 cases). In the remaining 4 tumours, invasion could not be assessed because the biopsy was composed of tumour tissue only.

We find that the classification of urothelial neoplasm proposed by WHO/ISUP consensus group parallels and slightly supersedes all the previous classification and grading systems as this reflects the biological potential of these and moreover, is universally accepted by pathologists, Urologists and oncologists.

Dose-response relationship has been established between the long-term arsenic exposure from drinking artesian well water and the incidence of lung cancer, bladder cancer, and cancers of all sites combined<sup>21</sup>. The WHO and US Environment Protection Agency recently established a new maximum contaminant level of 10 ppb for arsenic in drinking water<sup>3</sup>. Hundal et al (2009) reported in their study that groundwater is the primary source of drinking water for more than 95% of the population in Punjab and Arsenic content in hand pump water varied from 9 to 85 ppb with a mean value of 29.5 ppb<sup>4</sup>. According to the safe limit of arsenic, 54% and 97% water samples collected from deep-water tube wells and hand pumps, respectively, were not fit for human consumption<sup>4,22</sup>. The role of arsenic in drinking water and in addition fish as major component of diet has been postulated to be a risk factor by another study from India but from a different state<sup>23</sup>.

Our institution is the biggest integrated multispecialty health care provider in the region with patient drainage radius of more than 100 KM. 144 of 159 patients belonged to state of Punjab in north India and were from different major and minor cities of the state, although not representative of exact incidence but does show prevalence all over the state. The ground water remains major source of water supply even in urban areas in Punjab, thus exposing the population to contaminated water. However, no conclusion can be drawn as regards arsenic as causative factor from this study.

The histomorphological spectrum observed in our study corresponds with international literature; large number of cases in our series is significant, however, further investigation is required to confirm the role of arsenic in increased incidence of urinary bladder cancers in state of Punjab.

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