



HISTOPATHOLOGICAL PATTERN OF URINARY BLADDER TUMOURS IN TERTIARY CARE HOSPITAL, KASHMIR.

Pathology

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ABSTRACT

Urinary bladder cancer is one of the most common cancers worldwide, with the highest incidence in industrialized countries. A total of 225 cases of urinary bladder tumours were studied at the Department of Pathology, Government medical college Srinagar, Kashmir, India over a period of 4 years (Jan 2015 to Dec 2018). Tumours were evaluated as per Age, Sex, Histological type, grade of tumour and clinical features. Males were more commonly affected than females. Low grade Papillary urothelial carcinomas (PUC) were more common (66.4%) than high grade (28.5%). Peak age of incidence was 7th decade of life. Painless hematuria was the commonest symptom in high grade tumours and pain abdomen was mostly seen in high grade tumours. A definitive correlation between advancing grade of tumour and detrusor muscle invasion was observed.

KEYWORDS

Bladder tumour, Papillary carcinoma, Hematuria.

INTRODUCTION

Bladder cancer shows high incidence and mortality, that differs with gender, race and ethnicity. Moreover, the incidence and mortality rates vary across countries due to difference in risk factors, detection diagnostic practices and treatments. A recent global study show that incidence and mortality rates have decreased in most western countries but had increased in Eastern Europe and developing countries. This evidence confirms the need for continued surveillance and analysis of patterns and trends in bladder cancer¹. Keeping this background, the present study was taken up in the department of Pathology, Government Medical College Srinagar, Jammu and Kashmir, India to study the histopathological patterns of bladder tumours in Kashmir and to correlate the results with available clinical data.

The most common samples submitted for surgical pathology examination include small biopsies, larger transurethral, resection specimens and partial and radical cystectomies². Bladder cancer has the fifth highest incidence among all cancers in the United States and estimated 76,960 new cases of bladder cancer and 16,390 deaths from bladder cancer occurred in 2016³. It is also the 9th most common cancer and the 13th most common cause of death worldwide⁴. Each year approximately 110500 men and 70,000 women are diagnosed with new cases and 38,200 patients in the European Union and 17,000 US patients die from bladder cancer⁵. As per Indian cancer registry data in man it is the 9th most common cancer accounting for 3.9% of all cancer cases⁶.

Bladder cancer is more common in men than women with a male to female ratio of 3 to 4:1 however, in women it is diagnosed at a more advanced stage and has high mortality than men⁷. Smokers have 4 times greater risk of bladder cancer related to both the duration and amount of smoking. Cigarette smoking accounts for 1/3 to 1/2 off all bladder cancers⁸. Occupational exposure to aromatic amines and polycyclic aromatic hydrocarbons is other important risk factors. Impact of diet and environmental pollution is less evident. Increasing evidence suggest influence of genetic predisposition on incidence⁹. Bladder cancer most mostly affects patients in 6th or 7th decade of life and the most common presentation is hematuria in 80 to 85% of patients⁸.

MATERIALS AND METHODS:

Study design: Cross-sectional observational study

Duration of study:

A retrospective – prospective study of 4 years. 2 years retrospective from January 2015 to December 2016 and 2 years perspective from January 2017 to December 2018.

Inclusion criteria:

All cases of bladder biopsies, TURBT (transurethral resection of bladder tumours), partial cystectomy, total cystectomy and cysto prostatectomy specimens received in Department of Pathology Government Medical College, Srinagar, Kashmir from SMHS and other associated hospitals and District hospitals of Valley were included.

Exclusion criteria:

Known cases of urinary bladder tumour with history of recurrence.

Statistical methods:

The recorded data was compiled and entered in a spreadsheet (Microsoft Excel) and then exported to data editor of SPSS version 20.0.) Continuous variables be expressed as Mean±SD and categorical variables were summarized as frequencies and percentages. Graphically the data was presented by bar diagrams and pie diagrams. Chi-square test was employed for comparing categorical variables. A P value of less than 0.05 was considered statistically significant. All P values were two tailed.

RESULTS:

A total of 225 cases of urinary bladder tumours studied, who were registered in 4 years in the department of Pathology GMC Srinagar from Jan 2015 to Dec 2018. Clinical details, investigations and other relevant findings of all patients were recorded. The morphological features were studied in detail and findings were analyzed.

Table 1. Distribution of study patients as per specimens

Specimen Type	Frequency	Percentage
Biopsy	222	98.7
Cystectomy	2	0.9
Block	1	0.4
Total	225	100

Majority of cases were of biopsy specimens (98.7%), 2 cases were of radical cystectomy and 1 case of review of blocks.

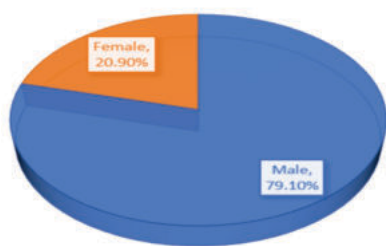
Table 2. Age distribution of study patients

Age (years)	Frequency	Percentage
20-29	16	7.1
30-39	15	6.7
40-49	35	15.6
50-59	40	17.8
60-69	64	28.4
70-79	30	13.3
≥ 80	25	11.1
Total	225	100

The age of the patients in the study ranged from 20 to 95 years with Mean± SD of 57.1±16.38 years. The maximum number of cases.

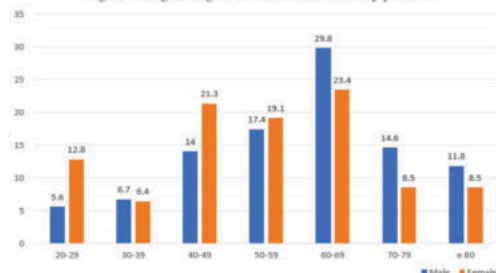
(28.4%) identified where is the 6th decade of life followed by a group of 5th decade. (17.8%).

Figure. 1. Gender distribution of study patients



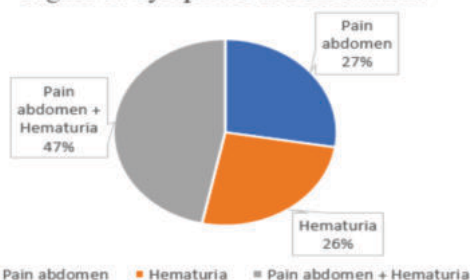
Out of 225, cases 178 (79.1%) were males and 47 (20.9%) were females with a male to female ratio of 3.8:1. Thus, males outnumbered females.

Figure. 2. Age and gender distribution of study patients



In males, majority of tumours were seen in age group of 60 to 69 years (29.8%), followed by 50 to 59 years (17.4%). In females, majority of cases were also identified in the age group of 62 to 69 years (23.4%), followed by 40 to 49 years (21.3%).

Figure 3. Symptoms at Presentation



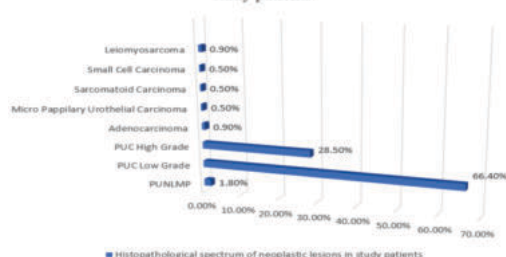
The most common presentation of the patients was pain abdomen plus hematuria (46.7%) followed by pain abdomen (27.6%) and hematuria (25.8%).

Out of 225 cases, 211 were neoplastic (93.8%) and 14 were non-neoplastic. (6.2%)

Table 3. Spectrum of bladder lesions

Histological Type	Frequency	Percentage
Neoplastic	211	93.8
Non-Neoplastic	14	6.2
Total	225	100

Figure 4. Histopathological spectrum of neoplastic lesions in study patients



Papillary urothelial carcinomas were further subdivided into low grade and high-grade, according to the microscopic findings. 140 cases (66.4%) of low grade non-invasive PUC were identified. 60 cases

(28.5%) of high-grade PUC were identified. There were (1.8%) of papillary urothelial neoplasms of low malignant potential (PUNLMP). Besides we have seen 2 cases, each of adenocarcinoma, and Leiomyosarcoma and 1 case, each of micropapillary urothelial carcinoma, sarcomatoid carcinoma, and small cell carcinoma.

Table 4: Histopathological spectrum of non-neoplastic lesions in study

Histopathological diagnosis	Frequency	Percentage
Cystitis cystica	7	50
Cystitis glandularis	4	28.57
Eosinophilic cystitis	1	7.14
Fibroepithelial polyp	2	14.29
Total	14	100

Among 14 Nonneoplastic lesions the majority 50% were cystitis cystica followed by cystitis glandularis (28.57%).

Table 5: Association of grade of tumour with gender in study patients.

Gender	High Grade- PUC		Low Grade- PUC		PUNLMP	
	No.	%	No.	%	No.	%
Male	51	82.3	112	80	3	75
Female	11	17.7	28	20	1	25
Total	62	100	140	100	4	100

Chi-Square=0.221; P-value=0.942 (Statistically Non Significant)

Among 140 low grade PUC cases, 112(80%) cases were males and 28(20%) were females. On the other hand, among 62 high-grade PUC cases, 51(82.3%) were males and 11 (17.7%) were females. Among 4 cases of PUNLMP, 3 (75%) were males, and 1(25%) female. Hence both types as well as low-grade tumours are more common in males than females.

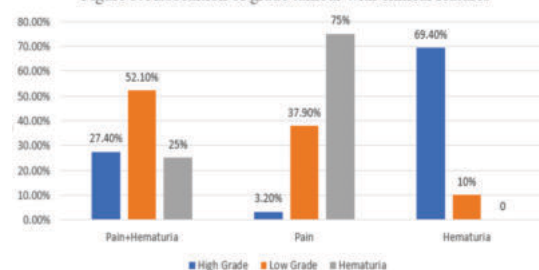
Table 5: Association of grade of tumour with age in study patients

Age (years)	High Grade		Low Grade		PUNLMP	
	No.	%	No.	%	No.	%
20-29	1	1.6	10	7.1	0	0
30-39	2	3.2	11	7.9	1	25
40-49	8	12.9	23	16.4	1	25
50-59	13	21	21	15	1	25
60-69	18	29	42	30	1	25
70-79	11	17.7	17	12.1	0	0
≥ 80	9	14.5	16	11.4	0	0
Total	62	100	140	100	4	100

Chi-square=10.079, P-value=0.614 (Statistically Non Significant)

Among 140 low grade PUC cases, the most common age group affected is 60-69 years (30% cases) followed by age group of 40-49(16.4% cases.). Among 62 high-grade PUC cases 18 (29%) were in the age group of 60-69 years followed by 13 cases (21%) in the age group of 50-59 years. Among 4 cases of PUNLMP, 1 case each (25%) was seen in a group of 4th, 5th, 6th and 7th decade. Low grade PUC is the commonest urothelial neoplasm irrespective of age and gender.

Figure 5. Association of grade tumour with clinical features



On analysing the association of grade of tumour with clinical features in our study patients, we found that hematuria was the commonest presenting symptoms among high-grade tumours (69.4% cases.) followed by pain abdomen+hematuria in 17 cases (27.4%). On the other hand, the most common presenting symptom among low-grade tumours was pain abdomen+hematuria (52.1% cases.) followed by pain abdomen in 53 cases. (37.9%). The most common clinical feature of PUNLMP was pain in 75% of cases. The difference in clinical presentation of different grades of tumour is statistically significant with P value<0.001. Out of 2 cases of adenocarcinoma, 1 was 65-year male and other 65 years female, both presented with pain abdomen as well as hematuria. Out of two cases of Leiomyosarcoma 1 was 65-

year-old male and other was 60 years male. Both presented with pain abdomen and hematuria. One case of small cell carcinoma was 60 years old male who also presented with pain abdomen and hematuria

Table 6: Grade and Muscle Invasion

Histological Grade	Muscle Invasion present	Muscle not invaded	Total
Low Grade	7 (6.25%)	105 (93.75%)	112
High Grade	27 (61.3%)	17 (38.7%)	44
Total	34	122	156

Among 202 cases of PUCs, invasion into muscularis propria would only be assessed in 156 cases, as the muscle was not present in the biopsy specimens of other cases. Muscle invasion was documented 27 cases. (61.3%) out of 44 cases of high-grade PUCs and 7 cases (6.25%) out of 112 cases of low-grade PUCs.

DISCUSSION

Urinary bladder tumours are a heterogeneous group with different subtypes having varied behaviour and outcomes.^{10,15} More than 95% tumours are epithelial, out of which majority are of urothelial origin and very few are other histological types². histopathological diagnosis is a gold standard for all bladder tumours. though ultrasonography, computer, tomography, and magnetic resonance imaging modalities have created a lot better understanding of bladder lesions, still histopathological diagnosis has remained important for the classification and management of lesions¹¹. As noted in various studies, incidence of bladder carcinoma, has marked geographic and clinicopathological variation. The present study was taken up to study the histopathological pattern of urinary bladder tumours in Kashmir valley.

Approximately 75% of newly diagnosed urothelial bladder cancers are non-invasive. Urothelial carcinoma (transitional cell carcinoma, TCC) is the most common histological sub type of primary bladder cancer, which accounts for greater than 90% of all bladder tumours. Other histological subtypes include squamous cell carcinoma, adenocarcinoma, small cell carcinoma, and some other rare non-epithelial subtypes. Among these squamous cell carcinoma, adenocarcinoma, and small cell carcinoma account for less than 5%, 2%, and 1% of all bladder tumours respectively¹¹. In conclusion it has been found that histological grade and muscle invasion are significantly associated with survival. It has been seen that high-grade tumours, invasive tumours and tumours with invasion and metastasis have poor prognosis resulting in poor clinical outcome.

Demographic Data

A Total number of 225 cases we studied. The age of patients ranged from 20 to 95 years with mean age being 57.1±16.38. Our results are comparable to other studies published in literature. Hussain NSA et al¹⁵ conducted the study of 106 cases in 2004-2005 and found the mean age of patients as 59.9 years. Zhang H et al²⁰ conducted the study of 658 patients during that time period of five years from 2006 to 2010 and found the mean age of patients as 61.59 years. Panchal J and Shreesha K¹¹ found the mean age as 57.1 years in their study of 225 patients, conducted during a period of 3 years from 2014-2014.

Majority of our patients were males 79.1% with a male to female ratio of 3.8:1. The results are comparable results obtained by various authors Laishram RS et al (2012), Vaidya S et al (2013)¹⁰, Goyal B et al (2018)¹² and Gupta P et al (2009)¹³. Higher incidence in males may be due to difference in smoking habits and occupational exposure.^{21,22}

On comparing the association of age and gender in our study, the peak incidence of urinary bladder carcinoma was seen in 7th decade both in males and females as well. Th youngest patient in our study was a 20-year female with low grade- PUC. The incidence of bladder carcinoma rises progressively, with peak incidence in 6th and 7th decade¹¹. Mungen NA et al²⁰ evaluated gender difference in bladder cancer prognosis, finding that survival in woman remained worse than men after adjusting that survival in woman remained worse than in men after adjusting for stage at presentation. Nevertheless, some studies did not find a significant association between gender and disease recurrence. In present study we haven't followed up the patients.

Clinical presentation.

In our study, we found that hematuria along with abdominal pain was the commonest presenting symptom seen in 46.7% of cases. Other symptoms being hematuria without pain 25.8% and abdominal pain

27.6%. Overall, hematuria was seen in 72.5% of the cases. Our findings are compatible to various other studies. In the study of 43 cases conducted by Panchal J and Shreesha K (2015)¹¹. The most common presenting symptom was Hematuria in 34 cases (79.3%), followed by abdominal pain in 4 cases (9.2%), increase in frequency of micturition in 2 cases (4.6%), one case (2.3%) each of abnormal vaginal bleeding, amenorrhea and urinary incontinence was seen. In a combined clinicopathological analysis of 658 urothelial carcinoma cases of urinary bladder conducted by Zhang H et al (2012)²⁰, hematuria was predominant presenting symptom in 76% of cases. None of the above cases presented with abdominal pain. More number of patients presenting with abdominal pain in our study maybe because of high percentage of low-grade tumours in our set up.

Diagnosis of study patients

Out of 225 patients, there were 211 (93.8%) neoplastic cases and 14 (6.2%) of non-neoplastic cases. Among them 140 cases (66.4%) were of low-grade PUC, whereas 60 cases (28.5%) where of high-grade PUC. These findings are similar to other studies like Laishram RS et al (2012)⁹ and Pudasaini et al.¹⁶ In a study conducted by a Laishram RS et al⁹ (2012), 53.9% cases were low grade, 34.6% were high grade, 7.7% were Papillomas, and 1 (3.9%) was papillary urothelial neoplasm of low malignant potential (PUNLMP). Some 18.2% of low-grade tumours and 75% of high-grade tumours in their study were invasive to detrusor muscle layer. They concluded that there is a definite correlation between advanced tumour grade and muscle invasion. In a study conducted by Vaidya S et al¹⁰ of 83 bladder tumours, 81(97.59%) cases were urothelial transitional tumours.

Transitional cell carcinoma (TCC) was most commonly the tumour which were seen in 67 cases (80.70%). 32 cases (47.76%) of TCC were low-grade while 35 (52.24%) were high grade. Ahmad Z et al²⁴ reported 55-60% of tumours are of low histological grade, but majority of patients with invasion were high grade. Micropapillary variant of urothelial carcinoma constitute approximately 0.6% to 2.2% of urothelial carcinoma²¹. We found one case of micropapillary urothelial carcinoma consistent with other studies. Studies have documented that these tumours have a prognosis and clinical course similar to other typical high grade non-invasive PUCs²³. Therefore, the WHO now strongly states that the designation as micropapillary variant should be restricted to individual carcinomas to avoid unnecessarily aggressive treatment²². Small cell carcinoma is rare and aggressive in urinary bladder, and its incidence varies between 0.3 to 1.88% in various studies^{16,17}, one case (0.4%) of small carcinoma was identified in our study. There two cases of primary adenocarcinoma in a 72-year-old male and 75-year female. Primary adenocarcinoma is a rare malignancy occurring in urinary bladder, secondary extension from colorectal carcinoma being more common^{10,12,14}.

Most important prognostic parameters are historical grade and stage of tumour^{10,12}. Detection of muscle invasion is of paramount importance because of its influence on therapy and prognosis¹⁸. This emphasises the need of submission of muscle tissue for optimal patient management.

Association of grade of tumour with gender.

In our study, high-grade PUC, low-grade PUC as well as PUNLMP were predominantly seen in males as compared to females. This trend is in accordance with most of other studies like Panchal J and Shreesha K (2015)¹¹.

Association of grade of tumour with age.

Younger patients frequently present low-grade and lower stage tumours than their older counterparts¹⁹. In a study conducted by Panchal J and Shreesha K (2015)¹¹ the most common age group affected among low grade tumours was 6th decade (mean 59.2 years). Similarly, among high grade tumours, the most common age group affected was 8th decade (mean 66.2 years). Our study also showed similar trend, with the majority of high-grade tumours seen an elderly group. Young patients in the age group 20 to 40 show mostly a low-grade neoplasm. This contrasts with common belief that the behaviour of cancer is more aggressive in younger age groups. More research should be carried out to know the reasons.

Association of grade of tumour with clinical features.

In our study, the main clinical presentation of high grade tumours was painless hematuria. On the other hand low grade tumours presented with abdominal pain along with hematuria as a predominantly

dominant clinical presentation. The results are somewhat different from other studies like by Panchal J and Shreesha K (2015)¹¹ found that hematuria as a predominant clinical presentation in both high as well as low grade tumours

Pathological grade and muscle invasion.

In our study muscle invasion into muscularis propria was seen predominantly in high grade tumours which is comparable to studies done Laishram RS et al⁹, Viadyia¹⁰ and Goyal B et al¹². Laishram RS et al⁹ in their study of 23 cases of urothelial carcinomas, muscle invasion was seen only in 19 cases (83%). 6 cases (75%) of high-grade PUC showed detrusor muscle layer invasion while only 2 cases (18.18%) of low grade PUC showed muscle invasion. Not including muscle layer in the biopsy specimens may lead to under-staging of tumours in many patients. The importance of including smooth muscle in the biopsy specimen needs to be emphasized. The authors also reported a high percentage of muscle invasions in higher grade tumours.^{24,25}

CONCLUSION

Bladder cancer is fairly common in Kashmir and is rare before age of 40, but its incidence steadily climbs thereafter in 6th and 7th decade of life. The peak incidence was seen in 7th decade with male dominance showing a male female ratio of 3.8:1. Overall, hematuria and abdominal pain were the most common presenting symptoms with painless hematuria being most common symptom in high grade tumour and pain abdomen in low grade tumours. There is a definite correlation between advancing tumour grade and muscle invasion with large percentage of high grade tumours showing muscle invasion. Grading of urothelial carcinoma is important for optimising the prognosis and treatment of bladder carcinoma. Therapeutic strategies should be based on histological grading.

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