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A clinicopathological study of neoplastic urinary bladder lesions with special emphasis on the role of urine sediment cytology in their diagnoses

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Abstract
Introduction: Neoplastic lesions of the urinary bladder constitute a diverse group of lesions. Bladder cancer is the 7th most common cancer worldwide. The present study is undertaken to study the spectrum of neoplastic bladder lesions and analyze their patterns with clinical features and urine sediment cytology.
Materials and Methods: 82 cases of neoplastic bladder lesions were categorized according to WHO classification (2016) and were correlated with demographic variables and clinical variables. In prospective cases urine sediment was analyzed and was correlated with histopathology.
Results: Out of 82 cases, majority of cases were infiltrating urothelial carcinoma. Analysis of urine cytology revealed a sensitivity of 86.67%, specificity of 83.3%, positive predictive of 92.86% and negative predictive value of 71.43%.
Conclusion: Neoplasms of urinary bladder are diverse in their presentation with urine sediment cytology proving to be a valuable adjunct in early diagnosis and treatment.

Keywords: Urinary bladder, non-neoplastic, neoplastic, histopathology, urine cytology

Introduction
Neoplasms of the bladder, a heterogenous group of tumors with different subtypes and varied behaviourial patterns and outcomes constitute one of the commonest urological conditions [1]. The neoplasms however pose significant clinical and biological challenges [2]. Bladder cancer is the second most common malignancy seen by the urologists. According to the Indian cancer registry data in men, it is the ninth most common cancer accounting for 3.9% of all cancer cases in India and the 7th most common cancer worldwide accounting for 3.2% of all cancers globally [3].
Urothelial (transitional cell) tumours constitute about 90% of all bladder tumours and range from small, benign lesions to aggressive cancers associated with high risk of mortality [1]. Despite significant developments into their origin and improved methods of diagnosis and treatment, neoplasms of bladder continue to extract a high toll in morbidity and mortality [2]. About 80% of patients are between the ages of 50 and 80 years [3]. Constitutional factors like age, gender, along with racial factors influence the survival and prognosis of patients with bladder cancer [3].
Cigarette smoking is demonstrated to be a major independent risk factor for urinary bladder cancer. Various epidemiologic studies conducted in different parts of the world have shown two to four times increased risk of developing bladder cancer in both male and female cigarette smokers when compared to nonsmokers. This risk increases proportionally with the frequency and duration of smoking [4]. Other important risk factors include long term use of analgesics, Schistosoma haematobium, industrial exposure to arylamines, prior exposure of the bladder to radiation and heavy long-term exposure to cyclophosphamides [1].
Over 90% of the patients with bladder neoplasm clinically present with painless haematuria. Prompt recognition of this ominous symptom can aid in the early diagnosis of bladder cancer [5]. Unfortunately, newly diagnosed bladder cancers are high grade lesions in approximately 40-45% of cases with more than half of them being muscle invasive at the time of diagnosis [3]. Recognition of this higher pathological grade and muscle invasion are valuable as they constitute prognostic prediction of significant importance [6].

Cystoscopy which allows a direct visualisation of the bladder mucosa and biopsying the suspected lesions is the primary diagnostic tool in patients suspected of having bladder tumors. Though it is the "gold standard" for the detection of de novo and recurrent bladder cancer, it is an expensive and invasive procedure. Because of high specificity of voided urinary cytology is considered a useful noninvasive adjunct to cystoscopy and it also has a comparatively high sensitivity at detecting high-grade lesions [7].

Urine specimens routinely obtained by relatively easier non-invasive techniques can be considered a liquid biopsy often mirroring the underlying pathological process in the urinary bladder [8]. Histopathological study of the biopsies along with urine sediment cytology constitutes the pillar stones of the diagnostic armamentarium in urinary bladder pathology.

The present study is undertaken to study the histopathological gamut of neoplastic lesions of urinary bladder and the role of urine sediment cytology as a diagnostic adjunct.

Objectives

1. To study the histopathological patterns of neoplastic urinary bladder lesions
2. To correlate the above lesions with various demographic variables like age, gender, tobacco consumption, occupation and clinical variables such as size, location of lesion and focality.
3. To cytologically analyze urine sediment of the above lesions in prospective cases and correlate the same with histopathology.

Methodology

The present cross-sectional study was conducted in the Department of pathology, ESIC Medical College and PGIMSR, Rajajinagar, Bangalore. Both retrospective and prospective cases were selected for the study. For retrospective cases, relevant slides, blocks and data from the preceding 4 ½ years (April 2010 to Oct 2014) retrieved from archived files of Department of Pathology and for prospective cases, samples received from the Department of Urology during the period of Nov 2014 to April 2016 were taken for study. A total of 82 cases were studied. Institutional ethical committee clearance was obtained. Complete clinicopathological details as per the proforma was collected. In all the prospective cases, in consultation with the urologists, cystoscopy findings like location, size and focality of the lesion was noted. Patients with abnormal cystoscopic findings were requested to give a freshly voided random urine sample prior to the biopsy procedure.

The cytological findings was compared with the histopathological findings using descriptive statistics and the role of urine sediment cytology in diagnosing neoplastic urinary bladder lesions was studied with histopathological diagnosis considered as gold standard.

Formalin fixed paraffin embedded sections of both archived and prospective cases was stained with hematoxylin and eosin stain and was studied histopathologically. The neoplastic lesions were categorized based on the WHO classification (2016). Morphological aspects of urothelial carcinoma like nuclear grade, differentiation, depth of lesion and muscular invasion was assessed. The above histological categories were correlated with clinical variables such as age, gender, occupation, tobacco consumption, tumor size, location, and focality.

Freshly voided random urine samples were collected prior to the biopsy procedure and centrifuged at 2500 rpm for 10 min. Papaniculoau and Giemsa/Leishman stained smears was prepared from the sediment. The presence of hematological cells and the morphology of exfoliated non-hematological cells with features of dysplasia, if and when present were noted.

Inclusion criteria

All cystoscopic guided transurethral resected bladder biopsies and cystectomy specimens.

Exclusion criteria

Nil

Statistical Analysis

Descriptive statistics using proportion, mean, standard deviation, percentage was used to describe the data. Chi-square tests of independence and goodness of fit was employed to determine the probability value. A p value of < 0.05 was considered as statistically significant.

Results

Eighty two cases of neoplastic bladder lesions were studied at the Department of Pathology, ESIC MC PGIMSR, Bangalore, over a period of 18 months (November 2014 to April 2016). Among them 7 cases were Radical cystoprostectomy and 75 cases were Transurethral Resection of Bladder Tumor (TURBT) specimens.

In relation to sex distribution, 64 (78.1%) were males and 18 (21.9%) were females. Male to female ratio was 3.5:1. Age of the patients ranged from 31 to 90 yrs with a mean age of 58.7 ± 11.2 years. Maximum numbers of cases were seen in the age group of 61 to 70 years (32.9%) (Table 1).

Table 1: Age and sex distribution of neoplastic lesions

Age Group In Years	Gender		No. Of Cases
	male	female	
31-40	2(3.1)	3(16.7)	5(6.1)
41-50	13(20.3)	4(22.2)	17(20.7)
51-60	17(26.6)	6(33.3)	23(28.1)
61-70	22(34.4)	5(27.8)	27(32.9)
71-80	9(14.1)	0(0.0)	9(11.0)
81-90	1(1.6)	0(0.0)	1(1.2)
Total	64(100.0)	18(100.0)	82(100.0)

Hematuria (93.9%) in combination with other symptoms was the most frequent complaint followed by pain abdomen, passing clots, dysuria, increased frequency of micturition and urgency in varying degrees of combination.

In relation to smoking habit, 58.5% had history of smoking with all of them being males and among the category of non- smokers (41.5%), 33.3% were males and 66.7% were females. In relation to use of smokeless tobacco, 46 cases (56.1%) had history of tobacco chewing with males being 37 (80.4%) and females being 9 cases (19.6%). Among the category of non-tobacco chewers (36 cases, 43.90%), 27 were males and 9 were females. In relation to alcohol consumption, 30 cases had history of alcohol consumption, accounting for 36.6% of total number of cases with all of them being males (100%). Regarding occupation, 32 cases

(39%) were labourers, 13 cases (15.9%) were drivers, 12 cases (14.6%) were farmers, 11 cases (13.4%) were garment workers, 7 cases (8.5%) were housewives and 7 cases (11.1%) belonged to other category.

With respect to size of lesion, 37 cases (45.12%) had bladder lesion with size less than 3 cm, whereas 45 cases (54.8%) had lesion with size greater than 3 cm. In our study, out of 82 cases of neoplastic lesions lateral wall (41 cases, 50%) was most commonly involved site of lesion followed by posterior wall (20 cases, 24.4%), anterior wall (5 cases, 6.1%), trigone (3 cases, 3.7%), dome (1 case, 1.2%) and base (1 case, 1.2%) of bladder. Multiple sites were involved in (11 cases, 13% of cases). Regarding focality of lesion, 71 cases (86.6%) had unifocal bladder lesions whereas 11 cases (13.4%) had multifocal bladder lesions. With respect to type of lesion, 43 cases (52.4%) had polypoidal lesion, 28 cases (34.1%) had papilliferous lesion, 6 cases (7.3%) had sessile growth, 4 cases (4.9%) had diffuse growth and 1 case (1.2%) had flat lesion.

Table 2: Distribution of Neoplastic lesions

Diagnosis		No. of cases	Percentage (%)
Urothelial Dysplasia (U Dys)		02	2.44
Urothelial Carcinoma in situ (U CIS)		01	1.22
Urothelial Papilloma (UP)		02	2.44
Inverted urothelial Papilloma (IUP)		03	3.66
Squamous cell papilloma (SP)		01	1.22
Papillary urothelial neoplasm of low malignant potential (PUNLMP)		08	9.76
Non invasive papillary urothelial carcinoma, low grade (PUC, LG)		21	25.60
Non invasive papillary urothelial carcinoma, high grade (PUC, HG)		12	14.63
Infiltrating Urothelial Carcinoma (IUC)	Lamina propria invasion (LP)	3	31.70
	Muscularispropria invasion (MP)	23	
Squamous Cell Carcinoma		06	7.32
Total		82	100.00

Among 82 neoplastic lesions, two cases were dysplasia (fig 1), 1 case of carcinoma in situ (fig 2), 2 cases of urothelial papilloma (fig 3), 3 cases of inverted papilloma (fig 4), 1 case of squamous cell papilloma, 8 cases of papillary urothelial neoplasm of low malignant potential (PUNLMP) (fig 5a), 22 cases of non invasive papillary urothelial carcinoma- low grade (fig 6a), 12 cases of non invasive papillary urothelial carcinoma- high grade (fig 7a), 24 cases of infiltrating urothelial carcinoma (fig 8a) and 6 cases of squamous cell carcinoma (fig 9 & 10) (Table 2). There were 16 recurrent cases. Out of which 5 cases (31.2%) were infiltrating urothelial carcinoma, 4 cases (25%) of non-invasive papillary urothelial carcinoma- high grade, 5 cases (31.25%) of non-invasive papillary urothelial carcinoma- low grade and 2 cases (12.5%) of PUNLMP.

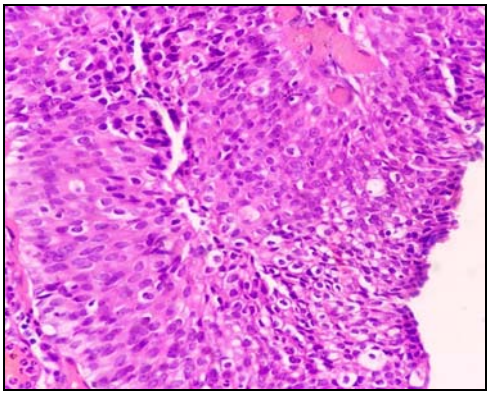

Fig 2: Microphotograph of Carcinoma in situ showing atypia in the entire thickness of epithelium [H&E 10x40]

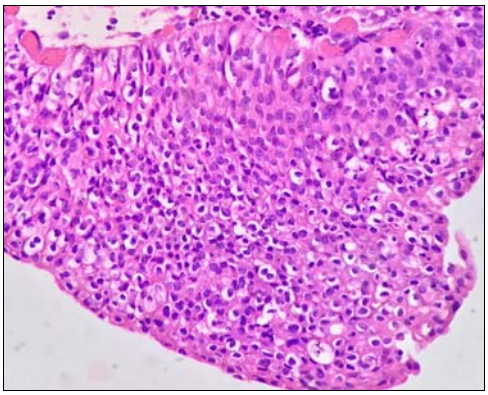

Fig 1: Microphotograph of Dysplasia showing nuclear atypia of lining epithelium [H&E 10x40].

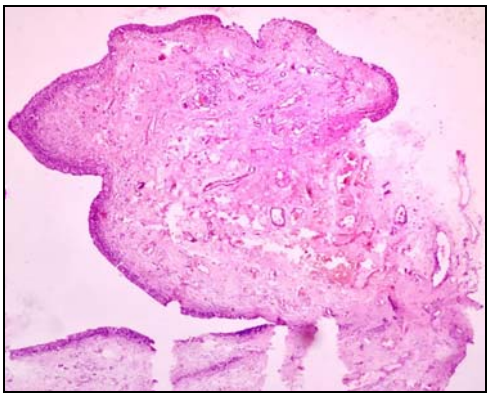

Fig 3: Microphotograph of urothelial papilloma showing papillary growth with central fibro vascular core [H&E 10x4]

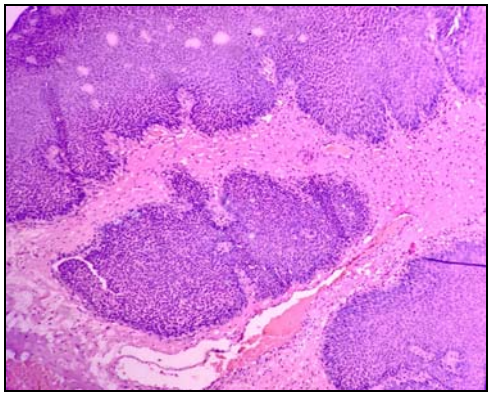

Fig 4: Microphotograph of Inverted papilloma showing inverted growth pattern [H&E 10x10].

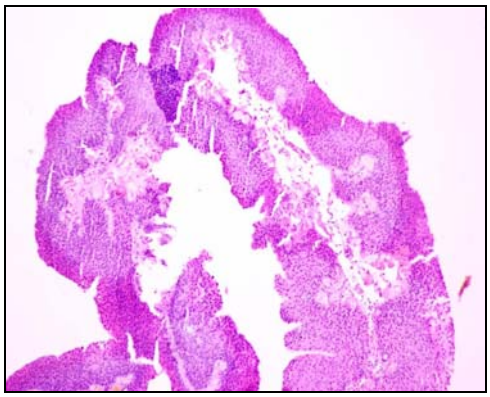

Fig 5a: Microphotograph of PUNLMP showing delicate papillae [H&E 10x10].

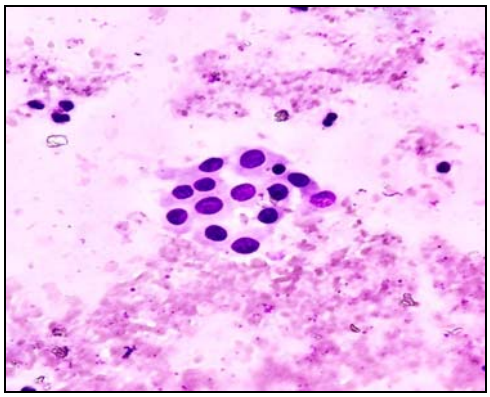

Fig 5b: Microphotograph of urine cytology of PUNLMP showing suspicious atypical cells [Leishman 10x40].

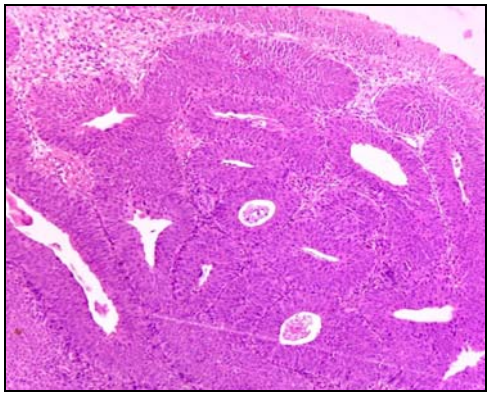

Fig 6a: Microphotograph of Papillary urothelial carcinoma- low grade: cells showing mild nuclear pleomorphism and inconspicuous nucleoli [H&E: 10x10.

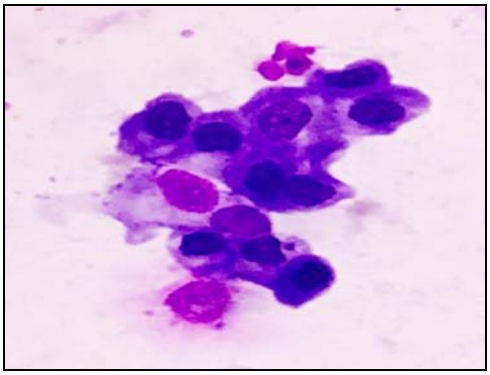

Fig 6b: Microphotograph of urine cytology of papillary carcinoma Low grade showing pleomorphic cells arranged in papillary clusters [Leishman 10x40].

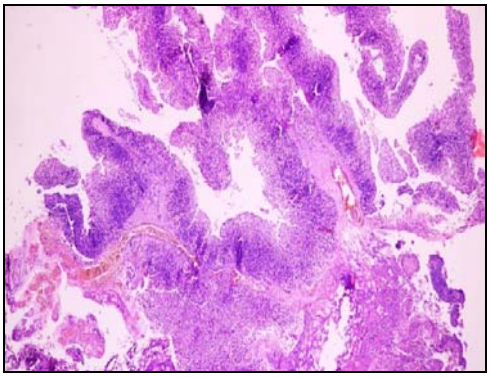

Fig 7a: Microphotograph of Papillary urothelial carcinoma- high grade [H&E 10x4].

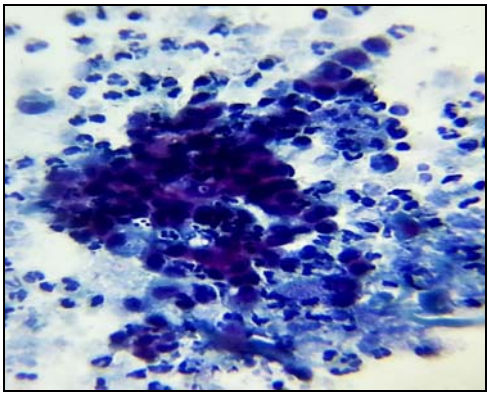

Fig 7b: Microphotograph of urine cytology of Papillary urothelial carcinoma high grade showing pleomorphic cells in small clusters [PAP stain 10x40]

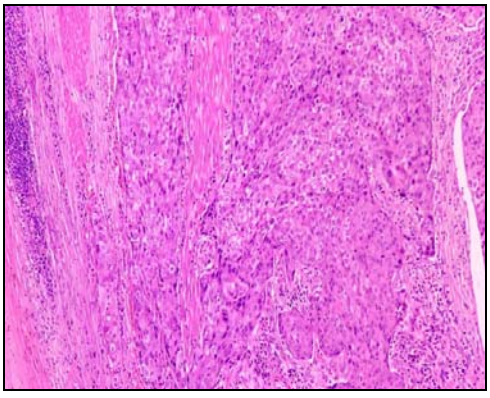

Fig 8a: Microphotograph of Infiltrating urothelial carcinoma showing invasion into muscle fibers [H&E 10x10].

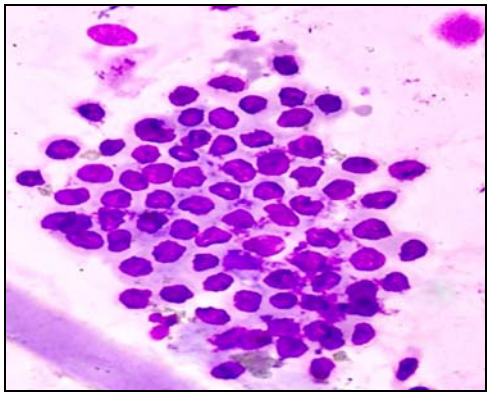

Fig 8b: Microphotograph of urine cytology of infiltrating urothelial carcinoma showing pleomorphic cells arranged in loosely cohesive sheet [Leishman 10x40]

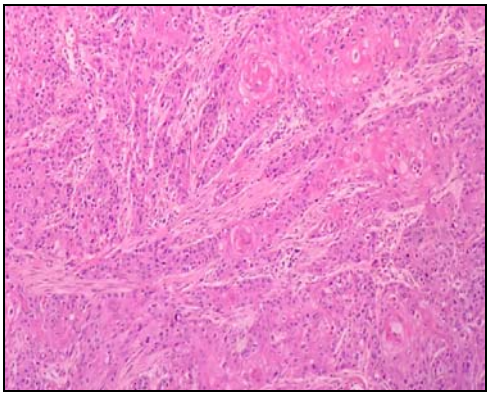

Fig 9: Microphotograph of Squamous cell carcinoma showing invasion into muscle [H&E 10x10].

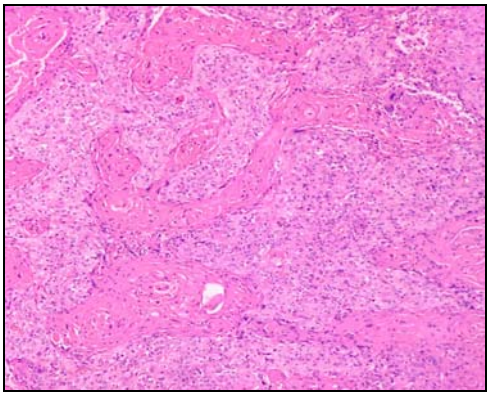

Fig 10: Microphotograph showing well diifferentiated Squamous cell carcinoma. [H&E 10x10]

Table 3: Correlation of neoplastic lesions with demographic variables.

Variables	U Dys N=2	UCIN N=1	UP N=2	IUP N=3	SP N=1	PUN LMP (N=8)	PUC, LG (N=21)	PUC, HG N=12	IUC LP N=3	MP N=23	SCC N=6
Age < 50 > 50	- 2	- 1	1 1	1 2	- 1	1 7 p=0.03	5 16 p=0.01	1 11 p=0.00	1 2	1 22 p=<0.01	5 1
Gender Male Female	2 -	1 -	1 1	1 2	1 -	6 2	16 5	8 4	3 -	20 3 p=<0.01	5 1
Smoking Yes No	2 -	1 -	- 2	2 1	1 -	5 3	13 8	6 6	3 0	19 4 p=<0.01	3 3
Tobacco chewing Yes No	2 -	1 -	- 2	2 1	1 -	4 4	10 11	6 6	1 2	17 6 p=0.02	4 2
Alcohol consumption Yes No	2 -	1 -	- 2	1 2	0 1	3 5	8 13	5 7	1 2	7 16	2 4
Occupation Labourers Drivers Farmers Garment House wife Others	2 - - - -	1 - - - -	- 1 - 1 -	1 1 - 1 -	1 - - - -	3 1 1 1 1 1	7 2 6 3 2 1	3 2 - 2 3 2	2 - - - - 1	9 4 5 2 1 2 p=0.04	3 2 - 1 - -

Upon correlation of neoplastic lesions with various demographic variables (Table 3), we found that majority of cases of PUNLMP (87.5%), papillary urothelial carcinoma-low grade (76.2%), papillary urothelial carcinoma- high grade (91.7%) and infiltrating urothelial carcinoma (IUC) with muscularis propria invasion (95.6%) were seen in the age group of > 50 years. The occurrence of these lesions in this age group was found to be statistically significant with p values of 0.03, 0.01, 0.00 and <0.01 respectively for the afore mentioned lesions. Infiltrating urothelial carcinoma with muscularis propria invasion was commonly seen in males (86.9%) which was documented to be statistically

significant (p value of <0.01). Smoking (82.6%) and tobacco consumption (73.9%) was seen to be significantly associated with IUC with muscularis propria invasion. With respect to occupation, IUC with muscularis propria invasion was commonly seen in labourers class of workers (39.1%) and this was seen to be statistically significant (p value = 0.04).

Table 4: Correlation of neoplastic lesions with clinicopathological variables

Variables	UDys N=2	UCIN N=1	UP N=2	IUP N=3	SP N=1	PUNLMP (N=8)	PUC, LG (N=21)	PUC, HG N=12	IUC LP N=3	MP N=23	SCC N=6
Predominant symptom Hematuria PA Dysuria Passing clots combined	2	1	2	3	1	7	20	11	3	23	4 2
Size <3cm >3cm	2 0	1 0	2 0	3 0	1 0	6 2	11 10	4 8	2 1	4 19 p <0.01	1 5
Location Lateral wall Posterior wall Anterior wall Trigone dome base ureteric orifice multiple	1 1	1	2	1 2	1	5 2 1 p=0.02	13 5 1 1 1 p=0.00	6 3 1 2 p=0.00	2 1	11 4 1 7 p=0.00	2 3 1
Focality Unifocal multifocal	2	1	2	3	1	8	21	10 2 p=0.02	2 1	16 7	5 1

Upon correlating neoplastic lesions with clinicopathological variables (Table 4), a statistically significant association was found between size of lesion and IUC with muscularis propria invasion, where majority of cases were of size >3 cm (82.6%). This association had a p value of <0.01. In PUNLMP, urothelial papillary carcinoma- low grade, urothelial papillary carcinoma-high grade and IUC with muscularis propria (MP) invasion, lateral wall was the commonest site involved with percentages being 62.5%, 61.9%, 50% and 47.8% respectively. This association was found to be statistically significant with a p value of 0.02 for PUNLMP and rest with a p value of 0.00. In Urothelial Papillary Carcinoma- high grade, IUC with MP invasion and Squamous cell carcinoma (SCC), majority of the lesions were unifocal (83.3%, 69.5% and 83.3% respectively), however a statistically significant association was seen only in Urothelial Papillary Carcinoma- high grade (p=0.02)

Regarding urine cytology findings in prospective lesions, there were 25 cases. Out of which 21 cases were from neoplastic lesions and 4 cases were from non-neoplastic lesions which showed features of chronic inflammatory infiltration. Urine cytology was positive in 7 cases of infiltrating urothelial carcinoma (Fig 8b), 2 cases of papillary urothelial carcinoma- high grade (Fig 7b) and 2 cases papillary urothelial carcinoma- low grade (Fig 7b). Three cases were reported as suspicious of malignancy in urine cytology and on histological examination, two cases were confirmed as malignant whereas one case was diagnosed as PUNLUMP (Fig 5b). Analysis of urine cytology as a diagnostic modality for bladder neoplastic lesions revealed a sensitivity of 86.67%, specificity of 83.3%, positive predictive of 92.86% and negative predictive value of 71.43%.

Discussion

Out of 82 cases, in our study most cases of neoplastic bladder lesions were seen in age group of 61 to 70 years with a mean age of 58.7± 11.2 years which is comparable with other studies done by Ray D *et al.* [5] and Ahmed Z *et al.* [9] who found a mean age of 57 and 59.1 years respectively. Incidence of cancer increases with age as reported by many studies [3, 5, 10, 11]. Bladder lesions are most frequently encountered in male gender owing to increased susceptibility to injurious personal habits. Studies conducted by Chinnasamy R *et al.* [12], Badar F *et al.* [13], Gupta P *et al* [3] and Joshi H N *et al.* [14] have documented that occurrence of neoplastic lesions is high in males with proportion being as high as 89.6% as reported by Gupta P *et al.* [3]. The present study also showed similar findings.

Shah PY *et al.* [15] and Selhi PK *et al.* [16] documented that among the various neoplasms of urinary bladder, IUC was the commonest one. The commonest lesion in the present study was also Infiltrating urothelial carcinomas. However, study by Srikoustubha *et al.* [2] documented low grade papillary carcinoma to be the commonest neoplasm with infiltrating urothelial carcinoma being third among all the neoplasms of the urinary bladder.

Hematuria and pain abdomen are the most frequently encountered clinical features in neoplastic lesions of the bladder. Joshi HN *et al.* [14] reported hematuria to be the most common clinical presentation followed by increased frequency, dysuria and urgency to micturate in neoplastic lesions. The present study shows concordance with findings of Joshi HN *et al.* [14] as hematuria being the commonest clinical presentation, however the present study also documented that pain abdomen was the next common clinical presentation.

Tobacco smoking is one of the most important predisposing factors for development of bladder tumors. Studies conducted by Chinnasamy *et al*. [12] and Joshi H N *et al*. [14] found a significant association between smoking history and presence of bladder neoplasm, like wise the present study also documented the same. Tobacco chewing has been considered to be one of the most important predisposing factors for development of bladder tumors. Smokeless tobacco can be consumed in various forms such as paan masala, tobacco leaves with betel nuts and chewing rolled dried leaves of tobacco. A study conducted by Chinnaswamy *et al*. [12] showed that majority of urinary bladder neoplasms were associated with tobacco chewing, whereas in a study by Rafique M *et al*. [17] it was seen that about 52% of cases of neoplastic origin were not associated with tobacco chewing. The present study revealed that 56.09% of urinary bladder neoplasms were associated with tobacco chewing.

Size of the tumor is a better predictor of the risk of metastases and probability of survival. In contrast to the present study, studies conducted by Chinnasamy R *et al*. [12], Kumano M *et al*. [18] and Chen Z *et al*. [19] demonstrated that majority of the neoplastic lesions of urinary bladder were < 3cm in size. The common location of bladder tumors in descending order of occurrence is lateral wall, posterior wall, trigone, neck, ureteric orifices, dome and anterior wall [20]. In the present study the most common location of neoplastic lesion was lateral wall, followed by posterior wall, multiple sites, anterior wall and trigone; which seems to be similar to a study conducted by Stephenson *et al.* [21]. Most of the bladder neoplasms were unifocal and these have been documented by studies conducted by Chinnasamy *et al* [12] and Kumano M *et al.* [18]. Study by Kumano M *et al*. [18] showed a statistically significant association between focality and bladder neoplasm (p=0.029). The present study also showed a statistically significant association between focality and bladder neoplasm (p=0.02).

Our study as compared to other studies by Chinnasamy *et al*. [12] and Selhi PK *et al*. [16] had varied type of lesions comprising polypoidal, papilliferous, sessile, diffuse growth and flat. Whereas Chinnasamy *et al*. [12] described lesions as polypoidal and sessile growth, whereas Selhi P K *et al*. [16] described lesions as papilliferous and flat growth. Our study had higher percentage of polypoidal growth which is comparable to study by Chinnasamy *et al*. [12].

Occupational exposure to chemicals is a well-established risk factor for urinary bladder cancer. It has been estimated that occupational exposure may account for 20% of all bladder cancers [22]. A study conducted by Amr S *et al*. [23] to determine the association between farming and bladder cancer revealed that men in farming who never smoke had an increased risk of development of bladder carcinoma. A study conducted by Biswas RR *et al*. [11] on the epidemiological factors associated with urothelial carcinoma, the authors documented that among the various occupation's labourers were at a higher risk for development of bladder cancer. A case control study was conducted by Khoubi J *et al*. [24] to determine the association between the high-risk occupations and bladder cancer in Iran. The authors concluded that there was a significantly increased risk of bladder carcinoma among truck and bus drivers, skilled agricultural workers, forestry and fishery workers, metal industry workers, domestic house keepers and construction workers. In the present study a significant statistical association was seen between infiltrating urothelial carcinoma and labourers [construction workers, mechanics and machine operators].

Urine cytology is the most established non-invasive method in the work up of hematuria and follow up of patients with history of bladder carcinoma and is used as an adjunctive to cystoscopy**.** In the present study urine cytology revealed a sensitivity of 86.6%, specificity of 83.3% which correlated with an Indian study by Siddappa S *et al*. [25]. However, studies by Planz B *et al*. [26] and Kumano *et al*. [18] showed a sensitivity of 38%, 50% and specificity of 98.3%, 91.7% respectively. In a literature review and meta-analyses study by Lotan Y *et al*. [27] the author arrived a sensitivity of 34% and specificity of 99%.

Conclusion

The study identified that among neoplastic lesions of bladder invasive neoplasms were more prevelent and were significantly found to be associated with risk factors like tobacco consumption and male gender. It was also observed that they were > 3 cm in majority of cases with a preponderance to unifocality, lateral wall involvement and hematuria symptoms. Exfoliative cytology of sedimented urine demonstrated a high sensitivity, specificity and positive predictive value for diagnosing neoplasms. Neoplasms of urinary bladder while diverse in their presentation, have distinct clinicopathological features to aid in their diagnosis with exfoliative urine sediment cytology proving to be a valuable adjunct in early diagnosis and prompt treatment.

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