Original Article

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Cystoscopic Biopsies of Bladder Neoplasms - A Snippet in Diagnosis

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ABSTRACT

Introduction: Urinary bladder neoplasms constitute an important source of clinical signs and symptoms which are more disabling than lethal. The present study aimed to study the prevalence of bladder neoplasms and to study the clinico-histomorphological features of various bladder neoplasms along with special emphasis on grading and staging of the bladder tumours.

Materials and Methods: The present study is a five years retrospective study. All patients who visited to urologyoutpatient department with lower urinary tract symptoms and obstructive bladder symptoms were subjected to cystoscopy. The detailed clinico-histomorphological features of cystoscopicbiopsies are studied using WHO/ISUP 2004 histological grading and TNM stagingwere used in classifying the bladder tumours.

Results: Out of 239 cystoscopic biopsies, the neoplastic lesions constituted 76.6%of the cases Among the neoplastic, benign lesions accounted for 12.9% of the cases (31 cases) and malignant lesions accounted for83 % of the cases (152 cases). Among the malignant lesions,urothelial carcinoma was the commonest accounting for 75.9% of the cases with increased prevalence of high grade papillary urothelial carcinoma (74.1%) and invasive papillary urothelial carcinoma accounting for 73.75% of the cases.

Conclusions: The present study has stressed the importance of histopathological examination with special emphasis on the study of serial sections and the importance of inclusion ofdetrusormuscle in the biopsy for accurate grading and staging so as to decrease the morbidity andmortality and initiate the early management of bladder tumours.

Keywords: *Bladder Neoplasms,High Grade,Low Grade, Urothelial Carcinoma.*

Introduction

Bladder neoplasms constitute one of the most common urologic disease accounting for significant morbidity and mortality [1,2]. It is the second most common neoplasm of genitourinary tract next to prostate and sixth most common cancer in the world wide. [3]

These neoplasms of bladder pose biological, clinical, diagnostic and therapeutic challenges to both urologist and uropathologist, as these bladder tumours represent a heterogeneous group of tumours with different subtypes and behavioral patterns. [4,5]

As per the data of Indian cancer registry, it is the ninth most common cancer and accounts for 3.9% of all cancers. [6] Since most of the bladder neoplasms are known for its recurrence, rapid progression to high grade and stage and it presents with various non-specific symptoms for which there is a need for accurate diagnostic tests. The significant diagnostic test includes cystoscopy, bladder biopsy and urine cytology for accurate diagnose, management and prognostic assessment of the patient.

Giving the importance of bladder neoplasms in genitor urinary pathology, the present study was undertaken to study the clinicopathological features of neoplasms with special emphasis on grading and TNM staging of bladder carcinoma.

Materials and Methods:

The present study is a retrospective type carried out in the department of pathology over a period of five years between June 2012 – June 2017 and included 239 cases in the study.

All the patients who visited the urology outpatient department (OPD) with lower urinary tract symptoms and obstructive urinary symptoms were included in the study. After the informed written consent of the patients, fiberoptic cystoscopic bladder biopsies was taken from the walls of the bladder. The cystoscopic bladder biopsies taken were fixed in 10% buffered formalin and then processed with embedding in paraffin wax. Three to four microns thick sections were taken and stained with regular Haematoxylin and Eosin stain (H and E). The study of biopsy specimens

along with the histomorphological changes under low and high power magnification were studied by light microscope. The WHO/ISUP – 2004 grading system was used to grade the bladder neoplasms and staging was done according to TNM staging. [7]

Inclusion Criteria: 1. Patients clinically and radiologically diagnosed to have bladder neoplasms. 2. All the transurethral resection of bladder tissue (TURBT) biopsies received in the department of pathology.

Exclusion Criteria: Autolysed and inadequate biopsies were excluded.

Results

Out of total 239 cases, 53.3% of the cases were males and 46.7% of the cases were females with peak age incidence was between 60-69 years as shown in graph 1. In the study, we found that the majority of the patients with benign lesions presented with lower urinary tract symptoms (LUTS) accounting for 82.7% of the cases and those with malignant lesions present with haematuria accounting for 90.8% of the cases as shown in graph 2. The details of the histomorphological diagnosis of bladder lesions are given in table 1. In our study, out of 239 cases, 56 were non neoplastic lesions and 183 cases were neoplastic. Among the neoplastic, we observed that majority of the bladder lesions were malignant constituting 63.59 % (152 cases) of the cases, among them the most common we found was urothelial carcinoma followed by squamous cell carcinoma and adenocarcinoma constituting 75.9%, 5.46% and 1.6% respectively. As per histological grading WHO/ ISUP (2004) used in the study we found high prevalence of high grade urothelial carcinoma followed by low grade urothelial carcinoma, urothelial papilloma and papillary urothelial neoplasm of low grade malignant potential (PUNLMP) accounting for 74.1.%, 22.3%, 12.9% and 3.6% respectively as shown in table 2.

In our study, we made an attempt to evaluate the pattern of tumour growth, its degree of differentiation, progression and associated mucosal changes. In 31 cases of urothelial papilloma, it is characterized by discrete papillary growth with a central fibrovasular core lined by urothelium of normal thickness and cytology (Figure 1). In five cases of Papillary urothelial neoplasm of low grade malignant potential (PUNLMP), histopathologically the tumour is characterized by delicate, orderly, tenuous papillary structures with orderly arrangement of cells within the papillae with minimal architectural abnormalities and nuclear atypia usually limited to basal layer irrespective of cell thickness (Figure 2).

The major distinction from papilloma is that in PUNLMP the urothelium is much thicker and nuclei are significantly enlarged. In 31 cases of low grade urothelial carcinoma, histologically it is characterized with papillary axes which are more compact, crowded, fused at the base and lined by unordered cells showing both architectural and cytological abnormalities with frequent mitosis (Figure 3).

In 103 cases of high grade urothelial carcinoma showed fused papillary axes over the large areas resulting in sheets and solid areas. The cells have enlarged, hyperchromatic, pleomorphic nucleus in full thickness of the epithelium with increased atypical mitosis (Figure 4).

As per TNM staging used in our study we observed majority of the bladder tumours were invasive accounting for 73.75% (Figure 5 and 6) as compared to non-invasive bladder tumours constituting 26.22% of the cases as shown in table 3.

Table1: Histomorphological diagnosis of bladder neoplasms.

Sl. No	Histomorphological diagnosis	No. of cases	Percentage
II	**Neoplastic**		
a.	**Benign**		
	Urothelial papilloma	31	16.9%
b.	**Malignant**	152	83.0%
1.	Urothelial carcinoma	139	75.9%
2.	Squamous cell carcinoma	10	5.46%
3.	Adenocarcinoma	3	1.6%
	Total	**183**	**100%**

Table 2: Histological grading of urothelial neoplasms as per ISUP/WHO 2004 [7].

Sl.No	Grade	No. of cases	Percentage
1.	Papilloma	31	12.9%
2.	PUNLMP	5	3.6%
3.	Low grade papillary urothelial carcinoma	31	22.3%
4.	High grade papillary urothelial carcinoma	103	74.1%

**PUNLMP – Papillary urothelial neoplasm of low grade malignant potential.*

Table 3: Staging of urothelial neoplasm as per TNM staging. [7]

Sl.No	Staging	No. of cases	Percentage
1.	pTa (Confined to epithelium)	48	26.22%
2.	pT1 (Invasion into lamina propria)	100	54.64%
3.	pT2 (Invasion into superficial muscle)	23	12.56%
4.	pT3 (Invasion into deep muscle)	7	3.82%
5.	pT4 (Invasion into organs)	5	2.73%
	Total	**183**	**100%**

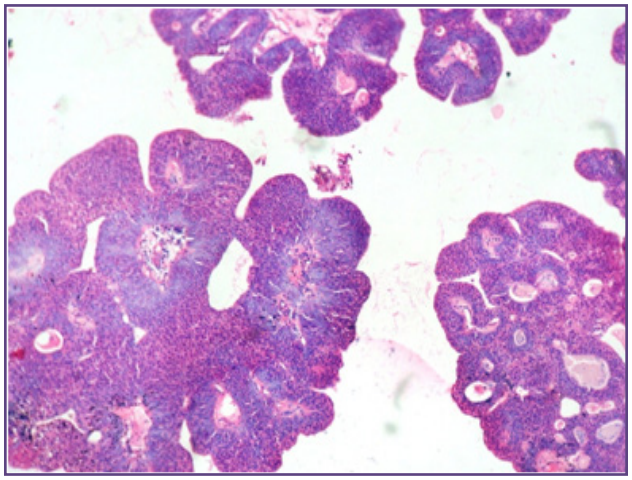


Fig. 1: Urothelial papilloma showing discrete papillae lined by normal thickened urothelium with normal cytology (H and E stain, 100X).

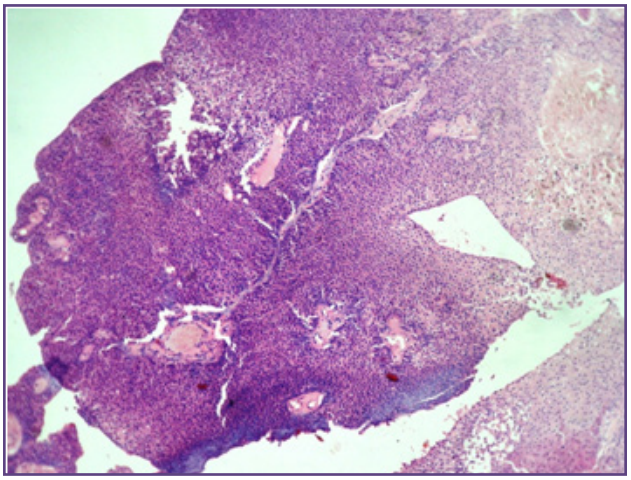


Fig. 2: Papillaryurothelial neoplasm of low malignant potential shows delicate papillae lined by hyperplastic urothelium with minimal nuclear atypia (H and E stain, 100X).

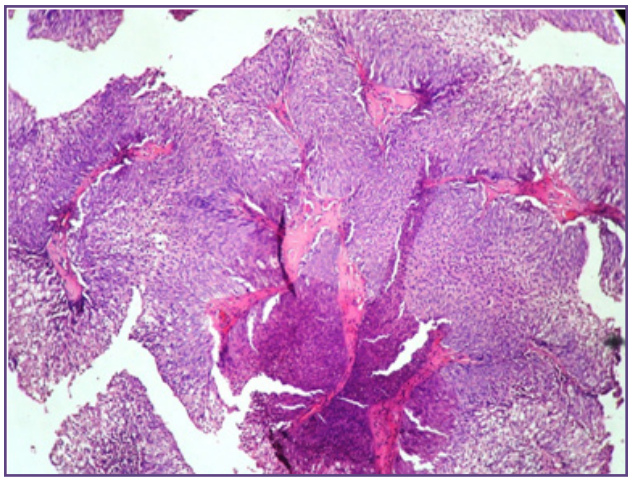


Fig. 3: Low gradepapillaryurothelial carcinoma shows compact, crowded papillae lined by hyperplastic urothelium with moderate nuclear atypia (H and E stain, 100X).

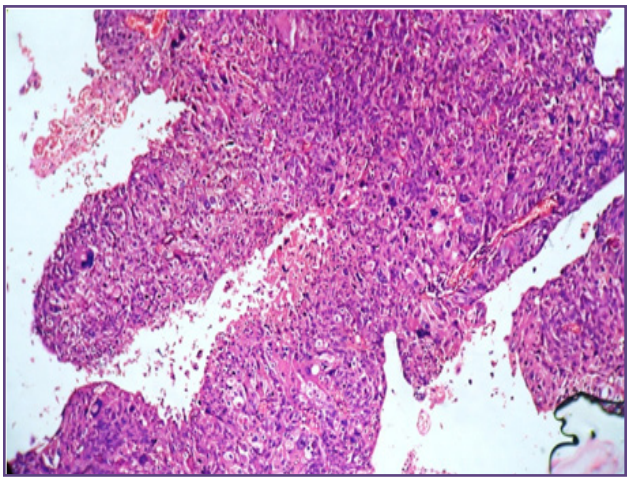


Fig. 4: High gradepapillaryurothelial carcinoma shows tumour cells in sheets and solid areas with marked cellular and nuclear atypia increased mitosis. (H and E stain, 400X).

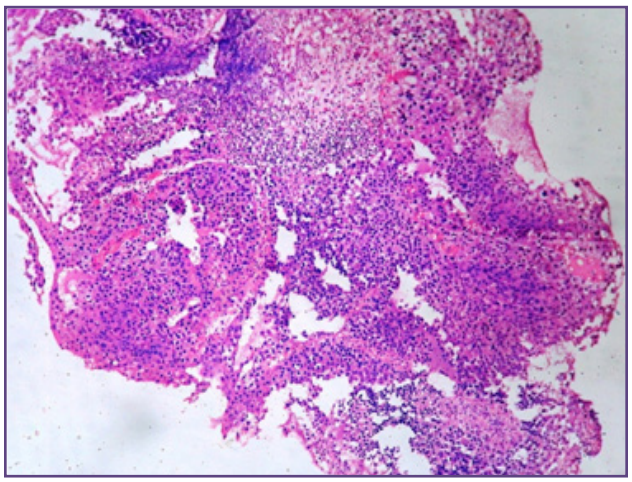


Fig. 5: Stage pT1showing tumour cells in clusters and singly infiltrating into the lamina propria. (H and E stain, 400X).

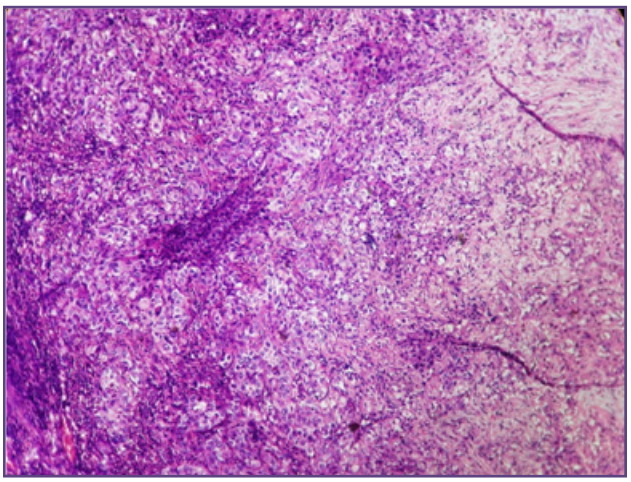
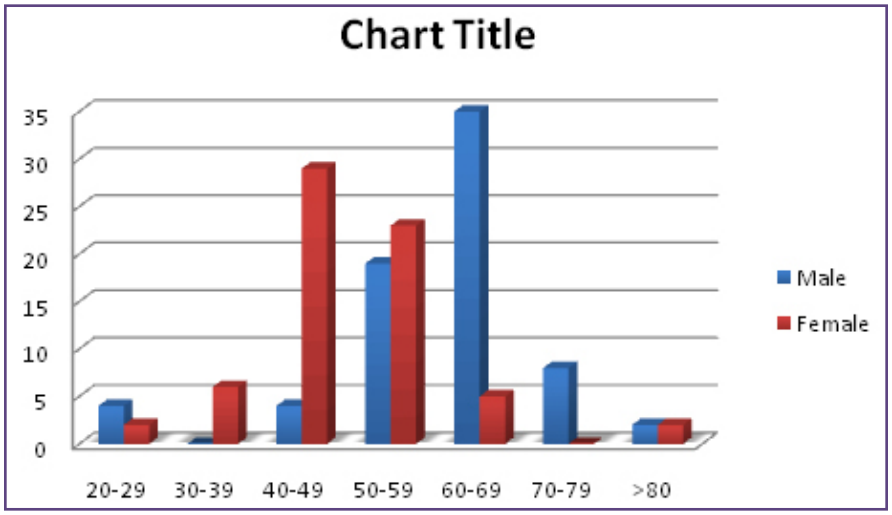
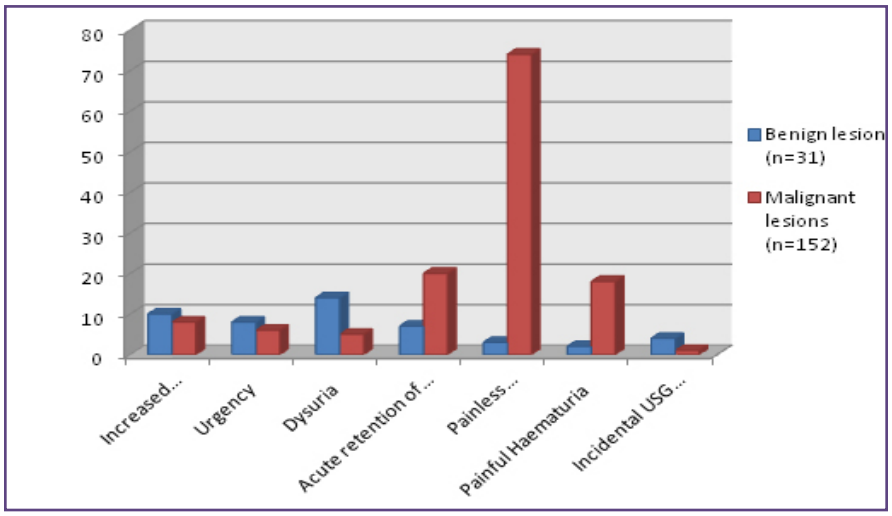


Fig. 6: Stage pT2 showing tumour cells infiltrating into the detrusor muscle bundles. (H and E stain, 400X).



Graph1. Age and gender wise distribution of bladder neoplasms.



Graph 2. Clinical presentations of the patients with bladder neoplasms

Discussion

The present study is undertaken to highlight the importance of histopathological examination in the diagnosis of bladder neoplasms. In recent days, the diagnosis and monitoring of bladder neoplasms are made by combination of cystoscopy, histopathology and urine cytology. [8] All these diagnostic methods have its own limitations and cannot diagnose the presence of bladder tumours at every point of time. [9] Advantages of cystoscopy are 1) helps in localizing the bladder tumours. 2) Detects low grade papillary lesions. Disadvantages are 1) Cystoscopy cannot visualize all the areas of bladder 2) Certain tumours like carcinoma insitu cannot be detected by cystoscopy. 3) It cannot comment on tumour grade and its depth of invasion.

Hence histopathology remains the gold standard method for diagnostic and therapeutic purpose. But it has its own limitations like friability nature of bladder tumours, there may be technical impediments and interpretation errors like electrocoagulation artifacts, retraction artifacts, exclusion of smooth muscle fibres from the mucosa pose difficulties in the histological grading and staging of the tumour. In such situations these limitations can be overcomed by studying, multiple serial sections, inclusion of detrusor muscle during cystoscopic biopsy and by the usage of special stains to ensure accurate and definitive diagnosis.

Various special stains which includes histochemical and immunohistochemical stains are used to differentiate other tumour like conditions mimicking carcinoma like inflammatory myofibroblastic tumour, pseudosarcomatous stromal reaction, pseudocarcinomatous proliferation, fibroepithelial polyps, collagen polyps, hamartoma etc can be differentiated that mimics carcinoma. Using special stains like Periodic Acid- Schiff (PAS), Periodic Acid-Siver methenamine (PEM) and Jones' methenamine Siver stain (JMS) are used for delineation of basement membrane and is used for detection of early invasive urothelial carcinoma. Gomori's trichrome stain (GMS), Massons Trichrome stain (MTS) are used for staining of smooth muscle and collagen like laminin which are usually advocated for detection of early stromal invasion. Histochemical stains for tenascin, an extra cellular matrix protein is strongly positive in invasive high grade carcinoma. Other stains like AgNOR, and Ki – 67 are used as proliferative markers that can differentiate between premalignant and malignant lesions of bladder. Immunohistochemical stains like CK–20, CK7, CK5/6, p53, and p63 stains are used as adjuvant for diagnosis of urothelial carcinoma.

In the era of modernization, robust techniques like flow cytometry, chromosomal analysis, genomics, proteomics and immunohistochemistry (IHC) applications are used for an accurate classification and prognostication of bladder tumours.[10] But these techniques are not routinely used due to lack of specificity, sensitivity and also due to exorbitant cost and inaccessibility to common people.

In our study, we have utilized all the three diagnostic modalities but emphasizing more on the histopathological diagnosis with respect to histological grading and staging of bladder tumours. We selected, WHO/ISUP (2004) classification for histological grading in the present study due to its various advantages like 1) Uniform terminology and common definition used and accepted by various urological pathologist. 2) Well defined criteria for preneoplastic and neoplastic bladder tumours leading to greater inter-observer reproducibility. 3) Terminologies of WHO/ISUP (2004) classification and terminologies of urine cytology are similar facilitating better cyto-histologic correlation. 4) Prevents over or under diagnosis of urothelial tumours. 5) Identification of distinct group of patients with high grade papillary urothelial carcinoma and carcinoma insitu for intravesical therapy. 6) Removes ambiguity in diagnostic categories. 7). It mainly shows prognostically significant categories. 8) It also gives idea regarding the recurrence rate, progression grade and stage and survival rates between tumours of different categories of non-invasive papillary urothelial neoplasms of bladder as given in table 4. [11]

In our study we observed that bladder lesions are common between the age group of 60-69 years constituting 48.64% of the cases and is in concordance with Vaidya et al [12] and Matalka et al study.[13] The bladder lesions showed male preponderance than female accounting for 53.3% and 46.7% of the cases respectively. Our observations are in accordance with Lim et al [14] and Vaidya et al.[12] The increased prevalence of bladder lesions in males observed in our study could be attributed to cigarette smoking, industrial exposure to acrylamine, schistosoma haematobium, cyclophosphamide, artificial sweetners and long acting analgesics. Various literatures state that the exact mechanism of inducing the cancer by these risk factors is unclear but a number of cytogenetic and molecular alterations are heterogenous. [15]

In the present study majority of the bladder lesions noted were malignant lesions accounting for 83.0% of the cases and our observations are in consistent with the Vibhav KG et al study (96.87%) and Vaidya S et al study (77.57%). [16,12] We have also observed that, among the malignant lesions of bladder the most common was urothelial carcinoma followed by squamous cell carcinoma and adenocarcinoma accounting for 75.9%, 5.46% and

1.6% respectively and our results are in accordance with Mohammad M et al (93.3%) and Vibhav KG et al study (93%) [8, 16] as shown in table 5.

We have encountered a wide spectrum of bladder lesions that includes non neoplastic lesions accounting for 23.4% of the cases and neoplastic lesions accounting for 76.6% of the cases. This wide spectrum of bladder lesions encountered in our study could be attributed to, free screening camps conducted by our centre. Our centre being one of the biggest institutes in which free cystoscopic bladder biopsies were carried out in suspected patients presenting with obstructive and lower urinary tract symptoms.

Present study showed increased prevalence of high grade urothelial carcinoma accounting for 74.1% and our results are in concordance with Vibhav KG et al, [16] Vaidya S et al, [12] Mahesh K et al study [17] and Satya et al [19] as shown in table 6.

*PUNLMP- Papillary urothelial neoplasm of low grade malignant potential; *LGPUC- Low grade papillary urothelial carcinoma.; *HGPUC- High grade papillary urothelial carcinoma.

Our study showed increased prevalence of invasive urothelial carcinoma than non-invasive urothelial carcinoma and our results correlates with Christopher et al [20] and Vaidya et al

study [12] as shown in table 7. The increased prevalence of high grade urothelial carcinoma in our study may be due to lack of awareness among the people, low socio-economic status and poor hygienic practices among the patients have contributed for the same.

In our study the diagnosed cases of invasive urothelial carcinoma were treated surgically with radical cystectomy with urinary diversion. Preoperative radiotherapy and adjuvant chemotherapy was given to patients with localized disease of urothelial carcinoma. Patients diagnosed as squamous cell carcinoma and adenocarcinoma were treated with radiotherapy.

Limitations of the study.

The study lacks the information regarding the post-operative follow-up of the patients. Hence the recurrence, grade, stage, progression and survival rate was not studied in our patients. Use of special stains, histochemical stains or immunohistochemical stains was not done in our study for accurate classification and prognosis of bladder neoplasms. However in our study, the data was collected from various records and the above mentioned limitations were beyond our control.

Table 4: Comparison of recurrence rate, grade and stage progression and survival rates of non-invasive papillary urothelial neoplasms. [11]

	Papilloma	Papillary neoplasm of low grade malignant potential	Low grade papillary urothelial carcinoma	High grade papillary urothelial carcinoma
Recurrence	0-8%	27-47%	48-71%	55-58%
Grade progression	2%	11%	7%	Not applicable
Stage progression	0%	0-4%	2-12%	27-61%
Survival rates	100%	93-100%	82-96%	74-90%

Table 5: Comparison of prevalence of various neoplastic neoplasms of bladder in different studies.

Neoplastic lesions	Matalka et al [13]	Mahesh K et al [17]	Mohammad M et al [8]	Vibhav KG et al [16]	Baidya et al [18]	Present study
Urothelial carcinoma	95.65%	28(46.6%)	467(93.3%)	93(93%)	109(33.65%)	139(75.9%)
Squamous cell carcinoma	1.73%	2 (3.33%)	13(2.6%)	2(2%)	0	10(5.46%)
Adenocarcinoma	2.60%	2 (3.33%)	10(2%)	1(1%)	1(0.3%)	(1.6%)

Table 6: Comparison of prevalence of different histological grades of bladder neoplasms in various studies.

Grading	Matalka etal [13]	Laishram et al [6]	Mahesh K etal [17]	Vaidya etal [12]	Satya etal [19]	Vibhav KG etal [16]	Baidya et al [18]	Present study
PUNLMP	0	7.69%	-	10.28%	-	4.1%	13(4.01%)	3.6%
LGPUC	60%	53.85%	42.85%	29.91%	25.0%	32.29%	54(16.67%)	22.3%
HGPUC	40%	34.61%	53.57%	32.7%	62.85%	60.41%	55(16.98%)	74.1%

Table 7: Comparison of prevalence of different stages of bladder neoplasms in various studies.

TNM stage	Matalka etal [13]	Christopher et al [20]	Laishram et al [6]	Vaidya et al [12]	Present study
pTa	54.5%	23(33.3%)	14(53.85%)	39(48.14%)	48(26.22%)
pT1	17.3%	15(20.0%)	4(15.38%)	18(22.22%)	100(54.64%)
pT2	20%	8(10.7%)	8(30.77%)	24(29.63%)	23(12.56%)
pT3	7.3%	9(12.0%)			7(3.82%)
pT4	0.9%	14(18.7%)			5(2.73%)

Conclusion

The early and definitive diagnosis with accurate grading and staging of bladder tumours can be done by gold standard histopathology method. The importance of including the smooth muscle in the biopsy, study of multiple serial sections and with usage of special stains needs to be emphasized for definitive diagnosis of bladder neoplasms. The pathological grade and muscle invasion are the most important predictors of survival.

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