

A Histopathological Insight into Gamut of Lesions in Urinary Bladder

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Abstract: ***Introduction:** Lesions arising from urinary bladder either non-neoplastic or neoplastic pose a major threat leading to significant morbidity and mortality all over the world. Adequate management warrants accurate diagnosis utilizing various procedures including cystoscopy and transurethral resection of bladder tumor (TURBT). Urinary bladder cancer is sixth most common cancer worldwide and encompasses a diverse array of neoplasms with high incidence in elderly males. The current study aims to analyze the histopathology of various lesions of the bladder through different modalities of biopsies like cystoscopic biopsies, TURBT and cystectomy specimens. **Methods:** This is a 2 year retrospective study of all consecutive biopsies assessed in the Department of Pathology, BJ Medical College, Ahmedabad, between 1st September 2020 to 30th September 2022. All the urinary bladder biopsies received in the department are included in the study. **Results:** Out of the 89 bladder biopsies, 54 were cystoscopic biopsies followed by 28 TURBT specimen. In our study, the share of neoplastic lesions is significantly higher amounting to 79 cases mostly affecting the male patients in the age group of 60-75 years. Urothelial tumours have the largest proportion amongst the neoplastic lesions. **Conclusion:** There is a wide spectrum of lesions occurring in urinary bladder that are scrutinized by the eyes of a pathologist. Histopathological analysis of bladder biopsies for diagnosing these lesions is essential and plays a crucial role in early management and prognosis of the patient.*

Keywords: Urinary bladder, TURBT, Urothelial tumors

1. Introduction

Urinary bladder lesions including both non-neoplastic and neoplastic, are responsible for significant morbidity and mortality throughout the world.[1] Diseases of the bladder, particularly inflammation (cystitis), constitute an important source of clinical signs and symptoms. Usually, however, these disorders are more disabling than lethal.[2] Tumors of the bladder are an important source of both morbidity and mortality. Amongst bladder tumors, urothelial carcinoma (UC) is a common malignant tumor of urinary bladder and comprises of 90% of primary tumor. These neoplasms of bladder create biological, clinical, diagnostic and therapeutic challenges to both urologist and pathologist. Urinary bladder cancer is the sixth most common cancer worldwide and represents a heterogeneous group of neoplasms. Bladder neoplasms account for 6% and 2% of the cancer incidences in men and women respectively.[3] The higher incidence of urothelial tumors in male than in female is probably related to difference in smoking habits and occupational exposure.[4] Important risk factors that have been implicated in the causation of bladder cancer include cigarette smoking, industrial exposure to arylamines, Schistosoma haematobium, long term use of analgesics, heavy long term exposure to cyclophosphamides and prior exposure of the bladder to radiation.[5]

Bladder cancer is a heterogeneous disease that demonstrates a wide spectrum of pathological features and clinical behaviors. Most UCs are noninvasive papillary carcinomas, which are characterized by slow disease progression but frequent cancer recurrence after local treatment. However, 20% to 30% of bladder UCs are presented as an invasive

disease, which is associated with rapid progression and poor clinical outcome.[6] Smooth muscle of indeterminate type (SMIT) may be applied, when pathologists are uncertain whether the smooth muscle tissue involved by bladder cancer represents the Muscularis mucosae or Muscularis propria.[6]

The upcoming WHO 2022 updates for urothelial neoplasm suggests reporting of papillary tumors as high grade when such components represent 5% of the tumor. Tumors with <5% high grade fraction are to be reported as low grade tumors with <5% high-grade component. Certain entities like Urothelial papillary proliferation of undetermined malignant potential are no longer recognized as a unique entity. Urothelial dysplasia is now considered as a part of urothelial carcinoma in situ.

As such, close and accurate disease surveillance is of paramount importance in the treatment of this malignancy and the prevention of progression to invasive disease. Diagnosis of bladder cancer has long relied on cystoscopy. This has been aided with the use of urine cytology but with significant limitations. The advent of noninvasive urine-based markers, including fluorescence in situ hybridization (FISH), nuclear matrix protein 22 (NMP22), bladder tumor antigen (BTA), Immunocyt, as well as other novel modalities, has yielded improved diagnostic accuracy.[7] Yet, Physical examination, cystoscopic evaluation and histopathological analysis of biopsy material are the mainstays of contemporary bladder cancer diagnosis and treatment.

Aims and Objectives

Volume 11 Issue 12, December 2022

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- 1) Describe histopathological features of various lesions in urinary bladder through different biopsy modalities.
- 2) Categorize neoplastic lesions according to WHO 2022/ISUP classification of urinary bladder tumors.
- 3) Study the frequency of different pathological lesions with regard to age and sex distribution.

2. Material and Methods

This study is a 2 year retrospective analysis of biopsies of urinary bladder carried out in the Department of Pathology, BJ Medical College, Ahmedabad and includes all the patients with urinary bladder lesions diagnosed on biopsy attending the hospital. The study period is 1st September 2020 to 30th September 2022. Patient's age, sex and other details have been retrieved from archived database from department of pathology. Clinical history and cystoscopic findings with the provisional diagnoses of all cases of urinary bladder lesion sent to the laboratory have been noted. The material for the study comprises of biopsy from Transurethral Resection of Bladder Tumor (TURBT)/Cystoscopic Bladder biopsy and cystectomy specimens.

Inclusion Criteria: All the urinary bladder biopsies and specimens received in the Department of Pathology, BJ Medical College, Ahmedabad.

Exclusion Criteria: Autolysed specimen and specimen with poor preservation.

All the specimen have been fixed in 10% formalin for 24 hrs. Surgical specimens are examined grossly concerning the size and shape of material and further subjected to standard paraffin embedding and hematoxylin and eosin staining. The slides are examined thoroughly with emphasis on age, sex and the detailed histomorphological examination is done using light microscopic technique. The objective of this study is to describe the histopathological features of various lesions in urinary bladder along with frequency of different types of lesions of the urinary bladder.

3. Results

A total of 89 cases of lesions of the bladder with maximum cystoscopic biopsy specimens followed by TURBT and cystectomy specimens have been reported during the study period. Among the array of 89 cases, 79 cases are neoplastic in origin whereas 10 cases are non-neoplastic.

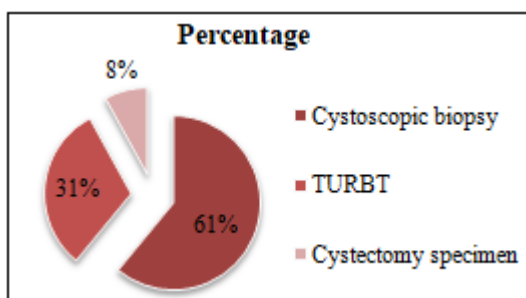


Figure 1: Types of Urinary Bladder biopsies

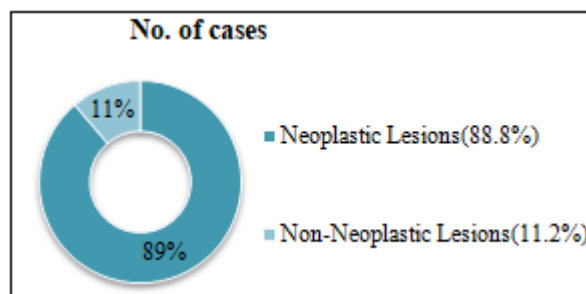


Figure 2: Lesion wise distribution of the bladder biopsies

Wide range of age group is observed in the study including patients aged between 1 year and 86 years. Male to female ratio is 8:1 which suggests predominant male population involvement. Mean age is 62 years in the cases analysed. Age group of 61-75 years (46.6%) is the most frequently affected followed by 46-60 years (29%). 76% (68 out of 89) patients are 45 years or older at the time of presentation.

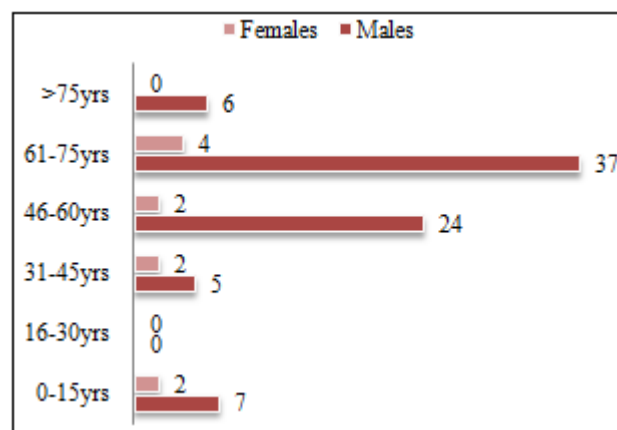


Figure 3: Age and Sex distribution of various lesions of urinary bladder

High grade papillary urothelial carcinoma with invasion (pT1 & pT2) has been found to be the commonest with 26 cases (33%) followed by low grade papillary urothelial carcinoma with invasion (pT1 & pT2) with nineteen cases (24%). Urothelial papilloma comprises of three cases (3.8%) and there are seven cases (8.9%) of PUNLMP (Papillary urothelial neoplasm of low malignant potential). 8 cases (10.3%) of Urothelial neoplasm with divergent differentiation showing squamous differentiation have been diagnosed. Poorly differentiated urothelial carcinoma amounts to 10 cases (12.3%) in the present study. 1 case each of neuroendocrine tumor, Adenocarcinoma and Malignant melanoma have been documented in the study.

Table 1: Spectrum of various neoplastic lesions with regard to age .

Age Group (years)	Non-Invasive			Invasive				Neuro-endocrine	Glandular Neoplasm	Melano-cytic tumor	
	Urothelial Papilloma	PUNLMP	Non.Inv. Urothelial Carcinoma (Low grade)	Infiltrating		Divergent differentiation	Lympho-epithelioma like	Poorly differentiated	Neuro-endocrine	Adeno-carcinoma	Malignant melanoma
				Infil. Urothelial Carcinoma, Low grade	Infil. Urothelial Carcinoma, High grade	Squa-mous	Sarcoma-toid				
0-9	1										
10-19											
20-29											
30-39	1	1				1					
40-49		1		4	3			1			
50-59	1	1	2	4	5	1			2	1	1
60-69		2		5	8		1		5		
70-79		2		7	6	1			7		
80-89					2	1					
Total	3	7	2	20	24	4	1	1	14	1	1

Pathological staging of the cases studied shows that maximum cases i.e 31 cases (39.2%) are in stage PT2 (muscle invasive carcinoma) followed by stage PT1 (lamina propria invasive carcinoma) with 21 cases (26.6%). Fourteen cases (17.7%) are in stage PTa. None of the papilloma and PUNLMP is invasive. Most of the high grade tumors (67%) are muscle invasive whereas the amongst low grade urothelial tumors, only 25% of the tumors are invasive to the muscularis propria.

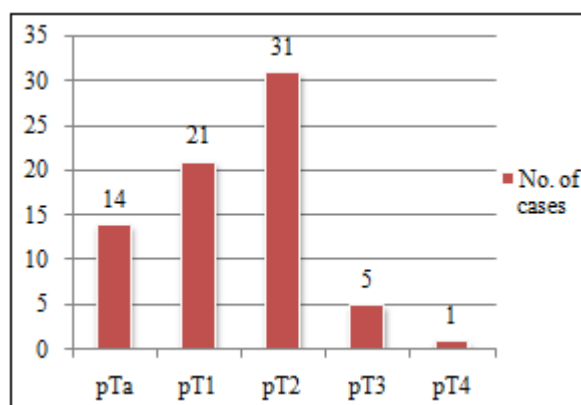


Figure 4: Pathological Stage of Urothelial tumors

Table 2: Grade and Muscularis propria Invasion in Invasive Neoplasm

Grade	Muscle Invasion	No Muscle Invasion	Not commented	SMIT
Low Grade	4	17	1	-
High Grade	18	9	1	1
Total	22	26	2	1

Table 3: Histologic features of urothelial papillary lesions

	Papilloma	Papillary neoplasm of low malignant potential	Low grade papillary carcinoma	High grade papillary carcinoma
Architecture				
Papillae	Delicate	Delicate. Occasional Fused	Fused, branching, and delicate	Fused, branching and delicate
Organization of cells	Identical to Normal	Polarity identical to normal. Any thickness Cohesive	Predominantly ordered, yet minimal crowding and minimal loss of polarity. Any thickness. Cohesive	Predominantly disordered with frequent loss of polarity. Any thickness. Often discohesive
Cytology				
Nuclear size	Identical to Normal	uniformly enlarged	Enlarged with variation in size	Enlarged with variation in size
Nuclear shape	Identical to Normal	Elongated, round-oval, Uniform	Round-oval. Slight variation in shape and contour	Moderate-marked pleomorphism
Nuclear chromatin	Fine	Fine	Mild variation within and between cells	Moderate-marked variation both within and between cells with hyperchromasia

Nucleoli	Absent	Absent to inconspicuous	Usually inconspicuous	Multiple prominent nucleoli
Mitoses	Absent	Rare, basal	Occasionally	Usually frequent
Umbrella cells	Uniformly Present	Present	Usually Present	May be absent

4. Discussion

Accurate cancer staging is crucial in the treatment of bladder cancer, as this complex disease demonstrates a wide variety of clinical behaviors. Bladder cancer can be staged clinically with cystoscopy, bimanual examination, and radiographic evaluation, but this clinical staging is often inaccurate, with understaging or overstaging reported in up to 40% of cases. Pathological stage based on histological examination of the cystectomy specimens is the gold standard in the management of bladder cancer and provides the additional information to the urologist that can have impact on the treatment.[6]Histopathology also poses limitations due to technical error and also interpretation errors from artifacts that mimic tumor. Excluding muscle fibers in cystoscopic biopsy can lead to incorrect histological grading and staging of the tumor. Most of the times these problems can be

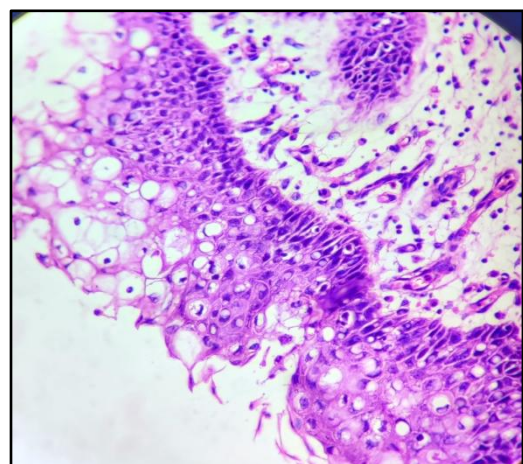
avoided by studying serial sections, using special stains and by encouraging inclusion of muscle layer during cystoscopic biopsy.

Out of 89 patients, 79 (88.8%) are males and 10(11.2%) are females with male to female ratio being 8:1.Among the neoplastic lesions out of 79 cases, 73(92.4%) are male and 6(7.6%) are females with male to female ratio being 12:1.Similar finding suggesting male preponderance are seen in several studies of cystoscopic biopsy. Bladder carcinoma is more commonly encountered in elderly males. The most common age groups of presentation of neoplastic lesion of the bladder are 60-69 years and 70-79 years, followed by 50-59 years. This is in concordance to that reported in the various existing literature by Srikousthubha et al [1], Shah et al [3] and Laishram et al [4].

Table 4: Comparison with other studies

	Present study	Srikousthubha et al[1]	Kumar et al[2]	Shah et al[3]	Laishram et al[4]	Vaidya et al[5]	Matalka et al[8]
Mean age	62	65	64	52.7	60	65	60.6
M:F	8:1	2:1	2.5:1	2.2:1	1.5:1	4.5:1	10:1
Tumor type	Urothelial	Urothelial	Urothelial	Urothelial	Urothelial	Urothelial	Urothelial
Tumor Grade	High grade (44.9%)	Low grade	High grade	High grade	Low grade	High grade (43.2%)	Low grade (60%)
Pathological Stage	pT2	pT1	pT2		pT2	pT1	pT2

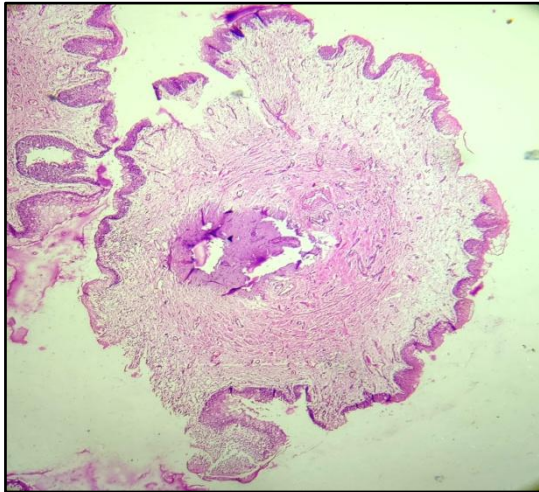
Out of 89 cases 10(11.2%) are non neoplastic lesions most common being exstrophy of bladder, all of which are reported in neonates which is followed by 3 cases of cystitis cystica and glandularis. Exstrophy of bladder is a congenital abnormality characterized by absence of the anterior vesicle and lower abdominal wall, with eversion of the posterior bladder wall.[9] In cystitis cystica, microscopically some cell nests show central cystic spaces which are lined by cuboidal epithelium. 1 case each of a Foreign body granulomatous inflammation, squamous metaplasia and fibroepithelial polyp showing normal-appearing urothelium have been diagnosed.



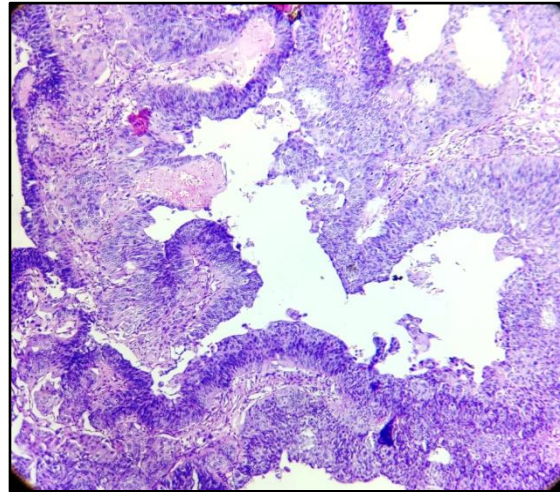
40x Picture of Cystitis cystitca



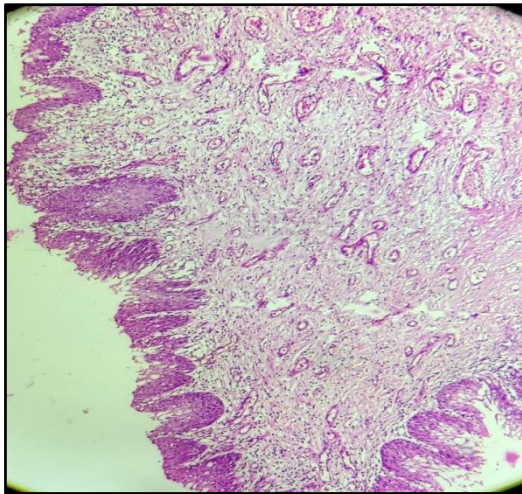
10x Picture of Cystitis cystitca



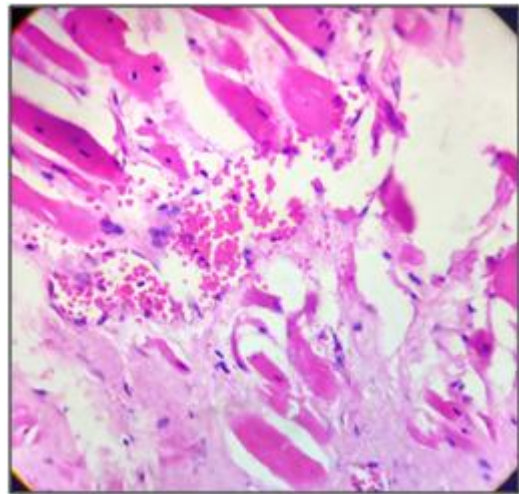
10x Picture of Fibroepithelial Polyp



10x Picture of High grade urothelial carcinoma



40x Picture of Fibroepithelial Polyp

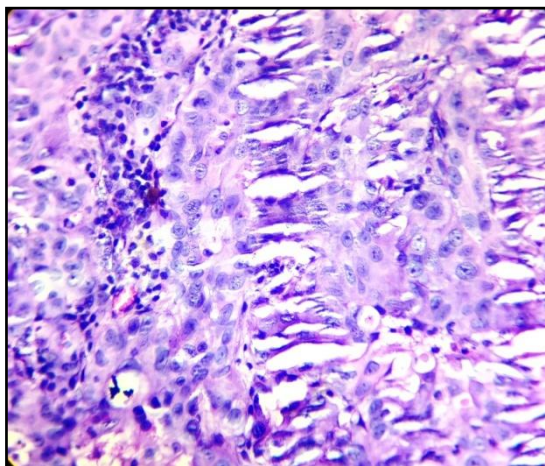


40x Picture of Muscularis propria invasion

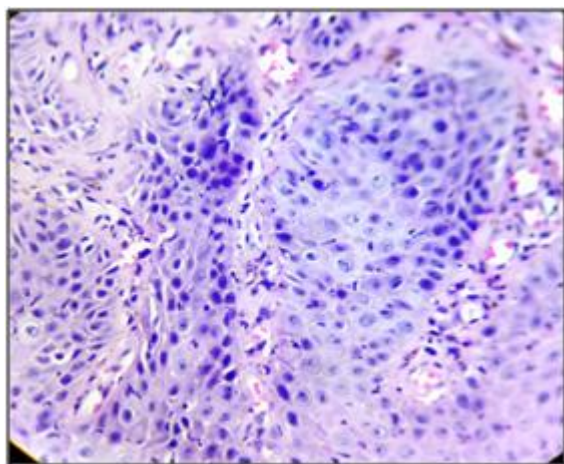
Majority of the lesions are of neoplastic nature contributing to 79 cases (88.8%). Among the neoplastic lesions urothelial neoplasms are most common consisting of 76(96.2%) cases. Non-invasive papillary lesions form 15% of the total neoplastic lesions i.e. 12 cases. There is no detrusor muscle in 2(3%) cases of urothelial neoplasm to assess the muscle invasion. Laishram et al [4] could also assess only 83% cases for invasion and out of that 42.1% cases show muscle invasion [4]. Comparable to these, in our study 40.5% of Urothelial Neoplasms show muscle invasion. About 70 % of all carcinomas of the urinary bladder are either non- invasive (pTa) or only minimally invasive (pT1) at the time of presentation. In our study 35 cases(44.3%) are in pTa and pT1 cumulatively and 31cases (39.2%) are invasive to muscularis propria(pT2). Correct histologic grading and tumor staging is crucial for proper and optimal patient management. The corner stone of bladder cancer diagnosis, treatment and staging is a high quality transurethral resection of the bladder tumor (TURBT) .

In our study most common urothelial neoplasm are Papillary Urothelial carcinoma, High Grade consisting 29(36.7%) out of 79 cases with 18 of them invading to muscularis propria. There are 22(27.8%) cases of Low grade papillary urothelial carcinoma with only 4 cases showing muscularis propria invasion. 7 cases of Papillary urothelial neoplasm of low malignant potential have been documented in the present study , none of which is invasive. A significant proportion of poorly differentiated urothelial carcinoma has been reported contributing to 14 cases with maximum incidence in age group 70-79yrs.

The study documents 4 cases of infiltrating urothelial carcinoma with squamous differentiation which in comparison to study by Vaidya et al[5] that shows 1 case of this entity. Lymphoepithelioma like variant of Infiltrating urothelial carcinoma has also been diagnosed in 1 of the biopsies received showing syncytial appearance with heavy lymphocytic infiltration. Bladder adenocarcinomas constitute approximately 2% of the malignant tumors of this organ.[9] A single case of adenocarcinoma has been reported in the given study period.



40x Picture of Lymphoepithelioma like Infiltrating urothelial carcinoma



40x Picture of urothelial carcinoma with neuroendocrine differentiation

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5. Conclusion

To summarize, neoplastic lesions form the bulk of the lesions in this study. The study reveals that urothelial neoplasms have the highest incidence amongst all bladder lesions. Elderly male population are predominantly affected with peak incidence in the seventh decade. Most of the tumors are invasive and invasion to the muscle layer is seen in more than half of the high grade tumors. There is a definite correlation between advancing tumor grade and muscle invasion. Hence, inclusion of detrusor muscle in the bladder biopsy is crucial for the correct pathological staging and prognosis of the patient which paves the route to appropriate management.

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