Original Article

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Pathology Section

Histopathological Spectrum of Neoplastic and Non Neoplastic Lesions of Urinary Bladder- A Retrospective Study

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ABSTRACT

Introduction: Urinary bladder encompasses a wide variety of lesions, both neoplastic and non neoplastic responsible for significant morbidity and mortality throughout the world. All bladder lesions require biopsy because of their lack of distinctive features. Urinary bladder cancer is the 9th most common cancer worldwide accounting for 6% and 2% of the cancer incidence in men and women, respectively.

Aim: To analyse the histopathological spectrum of bladder specimens with neoplastic and non neoplastic lesions, and categorising them according to recent 2016 World Health Organisation (WHO) classification.

Materials and Methods: The present study was conducted from January to June 2020 at Subharti Medical College, Meerut, Uttar Pradesh, India. Retrospective data was retrieved from a period of 10 years from January 2010-December 2019. Histopathological analysis of all the urinary bladder biopsies and radical cystectomy/cystoprostectomy specimens received during this period was done on basis of light microscopic examination of Haematoxylin and Eosin (H&E) stained slides. Lesions were categorised into non neoplastic and neoplastic. The neoplastic lesions were classified based on WHO classification 2016 and staging as per 8th edition of American Joint Committee on Cancer (AJCC). Descriptive data analysis was done.

Results: Total 252 cases were evaluated. A total of 200 (79%) cases were neoplastic and 52 (21%) cases were diagnosed as non neoplastic with majority of cases being cystitis. Male to female ratio was 7:1. The most common age group was 4th to 7th decade. In neoplastic category, urothelial tumours constituted 194 (97%) cases with Infiltrating Urothelial Carcinoma (IUC) being 118 (60.8%) cases. In non invasive lesions majority 27 (35.6%) cases were Papillary Urothelial Neoplasm of Low Malignant Potential (PUNLMP) followed by urothelial carcinoma *in situ* and papillary urothelial neoplasm of low grade. Entities other than urothelial tumours encountered in the present study were primary adenocarcinoma, small cell carcinoma, melanosis and metastasis from prostate. TNM staging showed lamina propria invasion (pT1) in 59 (37%) cases, followed by pT2 tumours invading muscle in 56 (35%) cases.

Conclusion: Proper knowledge of histologic characteristics of various bladder lesions is of utmost importance as few benign conditions mimic neoplastic and few serve as preneoplastic conditions, misdiagnosis may cause further any unnecessary treatment procedure. With a multidisciplinary approach, early diagnosis and immediate intervention can have a better survival and provide a more comfortable life to the patient.

Keywords: Cystitis, Cystectomy, Transurethral biopsies, Urothelial carcinoma

INTRODUCTION

Urinary bladder lesions cause significant morbidity and mortality [1]. Non neoplastic lesions like cystitis are barely lethal but they deteriorate the quality of life. On the contrary, malignant neoplasms of the bladder have therapeutic consequences.The bladder responds to chronic irritation through several reactive/metaplastic to hyperplastic/proliferative lesions which should be distinguished from malignant processes. Clinical, macroscopic, and radiologic findings for these entities may overlap; mandating a histologic evaluation [2].

Differentiating these lesions is also important because of differences in patient management and clinical outcome [3]. Cystoscopy is the primary diagnostic tool and useful in localising bladder tumours and biopsies of the suspected lesions [4]. Urinary bladder cancer is the 9th most common cancer worldwide accounting for 6% and 2% of the cancer incidence in the men and women respectively [5].

The 2016 WHO classification emphasises the ability of urothelial neoplasms to exhibit divergent differentiation, multiple morphologic variants and diverse genome, which may be utilised for selection of therapy [6,7]. Biopsy is the first line investigation for all cases with clinico-radiological features of bladder mass or diffuse bladder wall thickening. Many inflammatory and infectious diseases may mimic neoplastic conditions. The present study was therefore conducted with an aim to study the spectrum of non neoplastic and neoplastic lesions in urinary bladder. Also, due to paucity of studies in this region as per the recent updates in categorisation of the bladder neoplasms which has included new morphologic variants and better reproducible grading systems. The authors reviewed these lesions to classify and stage them according to the WHO classification 2016 and AJCC staging 8th edition [7,8].

MATERIALS AND METHODS

The present retrospective study was conducted from January to June 2020 at Subharti Medical College, Meerut, Uttar Pradesh, India. Retrospective data was archived for a period of 10 years (January 2010-December 2019). During this period, specimens submitted either in the form of transurethral biopsies or radical cystectomy/cystoprostectomy, were retrieved from the surgical Pathology department. The study was approved by Institutional Ethical Committee (reference number SMC/UECM/2021/231/146).

Inclusion criteria: All cystoscopic biopsies/cystectomy/cystoprostectomy specimen, received in Pathology department, were considered for the study.

Exclusion criteria: Inadequate/Inconclusive bladder biopsies were excluded.

Histopathological analysis was carried out on formalin fixed, paraffin embedded tissue sections of urinary bladder lesions stained with haematoxylin and eosin. The lesions were classified into non neoplastic and neoplastic lesions based on microscopic examination of H&E stained slides. The neoplastic lesions were further categorised based on the 2016 WHO classification of urinary bladder [6]. TNM staging was according to the 8th edition of AJCC [8].

STATISTICAL ANALYSIS

Data was entered in Excel sheet and descriptive data analysis was performed.

RESULTS

In this retrospective study 271 patients with urinary bladder biopsy/ Transurethral Resection of Bladder Tumour (TURBT)/ cystectomy/ cystoprostectomy procedures, were evaluated. Out of 271, 18 biopsies were inadequate/inconclusive, one biopsy showed no significant pathology, and in 252 cases pathologic diagnosis was made. Non neoplastic lesions were diagnosed in 52 cases (21%) and neoplastic lesions were detected in 200 cases (79%).

Most common age group was 4th to 7th decade with maximum 13 (25%) cases in 51-60 years age group for non neoplastic lesions and 65 cases (33%) in 61-70 years age group for neoplastic lesions. The male to female ratio was 7:1. In the present study, 39 (75%) cases and 183 (91.5%) cases were males in non neoplastic and neoplastic lesions, respectively [Table/Fig-1].

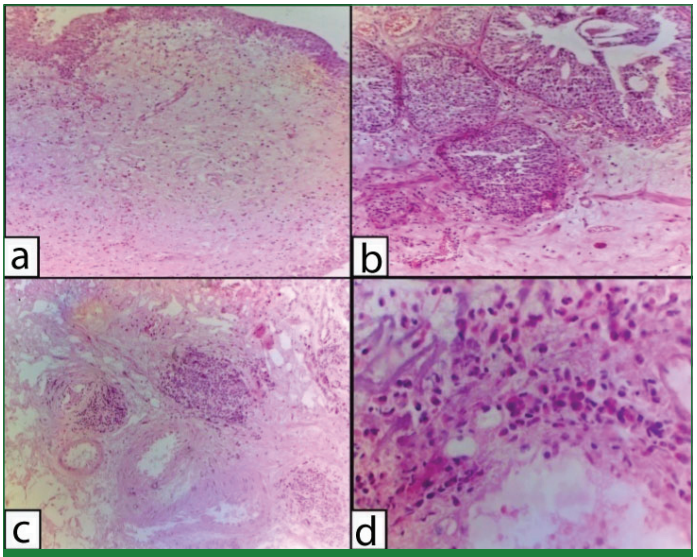
Age group (years)	Non neoplastic lesions				Neoplastic lesions			
	Male	Female	Total	(%)	Male	Female	Total	(%)
0-10	1	0	1	2	0	0	0	0
11-20	2	2	4	7	0	0	0	0
21-30	1	1	2	4	4	4	8	4
31-40	2	1	3	6	14	2	16	8
41-50	9	1	10	19	33	3	36	17.6
51-60	10	3	13	25	53	2	55	27.7
61-70	9	3	12	23	60	5	65	32.7
71-80	3	2	5	10	14	0	14	7
81-90	2	0	2	4	5	1	6	3
Total	39	13	52	100	183	17	200	100

[Table/Fig-1]: Age wise and gender wise distribution of both Non neoplastic and neoplastic lesions.

The spectrum of pathologic lesions revealed cystitis being most common among non neoplastic lesions constituting 43 cases (82.6%), majority were chronic non specific cystitis, followed by other variants like acute or chronic, eosinophilic and foreign body giant cell reaction. There were three cases of cystitis glandularis and two cases of urinary bladder diverticulum with one case each of inflamed urachal cyst, urethral caruncle, malakoplakia and cystitis cystica [Table/Fig-2,3]. Out of all neoplastic lesions of various histomorphological categories, urothelial tumours were most common with 194 cases (97%). Of 118 cases of IUC, conventional IUC constituted 88 (74.5%) cases while 30 (25.5%) cases were constituted by IUC with divergent differentiation. The various histologic entities with divergent differentiation were squamous (24 cases), glandular (two cases) poorly differentiated (two cases), micropapillary and mixed glandular and microcystic (one case each) variety. Two cases each of primary adenocarcinoma and metastasis from prostate, one case of small cell neuroendocrine carcinoma and melanosis were also seen. In non invasive lesions out of 76 cases, Papillary Urothelial Neoplasm of Low Malignant Potential (PUNLMP) constituted 27 (35.6%) cases followed by urothelial carcinoma *in situ* 16 (21%) cases, papillary urothelial neoplasm- low grade 16 (21%) cases and papillary urothelial neoplasm- high grade 8 (10.5%) cases [Table/Fig-4-6].

Type of lesion	Number of cases	%
Cystitis	43	82.6
• Chronic nonspecific cystitis	16	30.7
• Acute on chronic cystitis	14	26.9
• Eosinophilic cystitis	6	11.5
• Foreign body giant cell reaction	2	3.8
• Chronic granulomatous cystitis	1	1.9
• Acute cystitis	1	1.9
• Polypoidal cystitis	1	1.9
• Follicular cystitis	1	1.9
• Interstitial cystitis	1	1.9
Urinary bladder diverticulum	2	3.8
Inflamed urachal cyst	1	1.9
Urethral caruncle	1	1.9
Malakoplakia	1	1.9
Cystitis glandularis	3	5.8
Cystitis cystica	1	1.9
Total	52	100

[Table/Fig-2]: Histopathological spectrum of non neoplastic lesions.



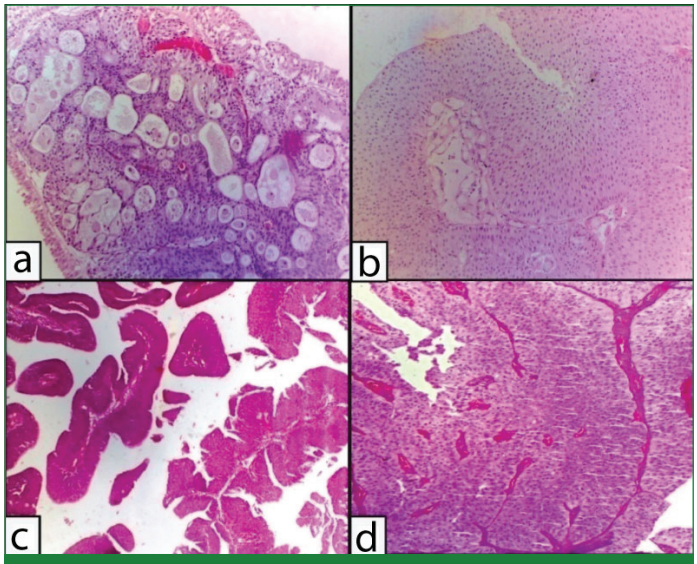
[Table/Fig-3]: Non neoplastic lesions: a) Interstitial cystitis (H&E, 4X), b) Cystitis glandularis (H&E, 10X); c) Follicular cystitis (H&E, 10X); d) Eosinophilic cystitis (H&E, 40x).

Out of 252 cases, there were 10 specimens of cystectomy/ cystoprostectomy. A 9/10 cases were diagnosed as invasive urothelial carcinoma while one case reported as urothelial carcinoma on biopsy from outside was reported as follicular cystitis with fibrosis after extensive sampling.

Of the total 200 neoplastic lesions, staging was rendered in 161 cases which had been diagnosed as invasive urothelial carcinoma, carcinoma-*in situ*, non invasive papillary urothelial carcinoma low and high grade, mucinous adenocarcinoma and small cell neuroendocrine carcinoma. Non invasive papillary carcinoma (pTa) was found in 24 (15%) cases while carcinoma *in situ* (pTis) was seen in 16 (10%) cases. Lamina propria invasion (pT1) was observed in 59 (37%) cases, followed by pT2 with tumours invading muscle 56 (35%) cases. pT3 and pT4 tumours were found in 2 (1.3%) and 4 (2.7%) cases respectively. In remaining 39 neoplastic cases AJCC, TNM staging was not done. These included five benign lesions comprising of urothelial papilloma in 1 (1.3%), inverted urothelial papilloma in 3 (4%), and melanosis 1 (0.5%). Tumours with unspecified, borderline or uncertain behaviour in 27 (35.6%) cases of PUNLMP, urothelial proliferation of uncertain malignant potential in 2 (2.6%) and urothelial dysplasia/atypia in 3 (4%) cases. 2 (1%) cases were metastasis from prostate.

Category	No. of cases	%
1. Urothelial tumours	**194**	97
• **Invasive/Infiltrating urothelial carcinoma**	**118**	60.8
a. Infiltrating urothelial carcinoma	88	74.5
b. Infiltrating urothelial carcinoma with divergent differentiation	30	25.5
• **Non invasive urothelial neoplasia**	**76**	39.2
Urothelial carcinoma in-situ	16	21
Papillary urothelial carcinomalow grade	16	21
Papillary urothelial carcinomahigh grade	08	10.5
Papillary urothelial neoplasm of low malignant potential	27	35.6
Urothelial proliferation of uncertain malignant potential	02	2.6
Urothelial papilloma	01	1.3
Inverted urothelial papilloma	03	4
Urothelial dysplasia/atypia	03	4
2. Glandular neoplasm	**04**	2
• Mucinous adenocarcinoma (Primary)	02	1
• Metastasis from prostate (Secondary)	02	1
3. Neuroendocrine tumour		
• Small cell neuroendocrine carcinoma	01	0.5
4. Melanocytic tumour		
• Melanosis	01	0.5
Total	200	100

[Table/Fig-4]: Histopathological spectrum of neoplastic lesions.



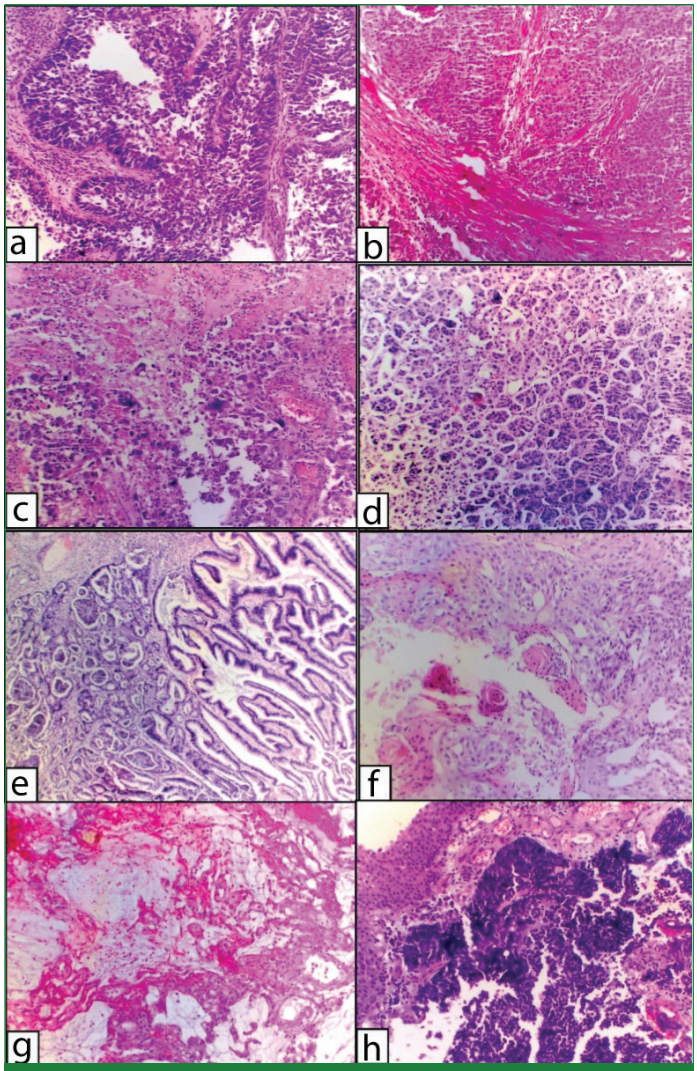
[Table/Fig-5]: Non invasive urothelial lesions: a) Urothelial papilloma with both endophytic and exophytic proliferation (H&E,10X); b) PUNLMP showing orderly arrangement of cells within papillae with minimum abnormality in architecture and atypia (H&E, 10X); c) Papillary urothelial carcinoma low grade showing isolated papillae (H&E, 4x); d) Papillary urothelial carcinoma high grade showing fused papillae, nuclear atypia (H&E, 40x).

DISCUSSION

In bladder cancer histomorphology is the most powerful tool to predict the risk of recurrence, progression and therapeutic response [9]. In most of the lesions, diagnosis is fairly easy, occasionally, it can pose diagnostic challenges. Therefore, pathologist play an important role in not just labelling the diagnosis but also to give additional information that can have an impact on the treatment [10]. The present study aimed to present the histopathological spectrum of bladder lesions.

The authors archived 252 cases of bladder pathology comprising of 242 bladder biopsies/TURBT and 10 cases of cystectomy/ cystoprostectomy.

In present study, the male to female ratio was 7:1, which was higher as compared to other studies conducted by Ploeg M et al., Vaidya S et al., Goyal VK et al., and Shah PY et al., however the difference in ratio in the present study as compared to others could be due to the low access of females to healthcare in this area or exposure to environmental factors [11-14].



[Table/Fig-6]: Urothelial carcinoma with invasion of lamina propria (H&E, 40x); b Muscle infiltrating IUC (H&E, 400x); c) IUC with poor differentiation and necrosis (H&E, 100x); d) IUC with micropapillary differentiation; e) IUC with glandular and microcystic differentiation (H&E, 100x); f) IUC with squamous differentiation showing keratin pearls (H&E, 100x); g) Mucin secreting adenocarcinoma showing muscle invasive pool of mucin with presence of atypical cells (H&E, 4X); h) Small cell neuroendocrine carcinoma with sheets of hyperchromatic cells lying below unremarkable urothelium (H&E, 10x).

Majority of the bladder lesions noted were neoplastic lesions accounting for 79.3% of the cases. This finding was well correlated with other studies done by Vaidya S et al., (77.57%), Goyal VK et al., (96.87%), and Dravid NV et al., (62.58%) [12,13,15]. Amongst the wide spectrum of non neoplastic lesions (20.6%) most common lesions observed was cystitis (82.6%) with histological variants like chronic non specific cystitis, acute on chronic, eosinophilic, granulomatous, follicular, polypoidal and interstitial cystitis. Similar distribution of non neoplastic lesions was documented by various other authors [1,14,16,17]. However, it is to be worth mentioning herein that one case reported as invasive papillary urothelial carcinoma on TURBT from outside, was diagnosed as follicular cystitis with fibrosis after extensive sampling of the cystectomy specimen. Follicular cystitis is a benign proliferative lesion usually secondary to bladder outlet obstruction or dysfunction. It can also be found adjacent to invasive or *in situ* bladder carcinomas representing a host response. Also, patients receiving intravesical chemotherapy or Bacillus-Calmette-Guerin therapy may develop follicular cystitis [18]. In the present case, entire tumour was possibly resected following TURBT with no residual tumour in cystectomy specimen.

Cystitis cystica and cystitis glandularis are reactive process in response to chronic irritation, infection, calculi, outlet obstruction and catheterisation. These are extremely common and seen in 60% of normal bladders at autopsy but majority of these cases are asymptomatic incidental findings therefore frequency in bladder biopsies is quite low [19,20]. However, these conditions are benign mimickers of invasive carcinoma so it is of utmost importance to diagnose these lesions correctly on histomorphology [15,21]. In the present study, the authors found 3 (5.8%) cases of cystitis glandularis and 1 (1.9%) case of cystitis cystica.

Bladder cancer has a lower incidence in women that reflects an approximate 3:1 male-to-female (M:F) ratio globally [22]. However, in present study this male:female ratio in neoplastic lesions was found to be 7:1, which was quite high as compared to various other studies. In studies by Srikoustubha et al., the male:female ratio was 5.25:1 and Shah PY et al., it was found to be 2.29:1 [1,14].

In the neoplastic category, most common tumour observed in the present study was urothelial tumour (97%). Among all the urothelial tumours, IUC (60.8%) was the most common subtype followed by PUNLMP and non invasive papillary urothelial neoplasm. These findings are comparable with other studies [13,17,23].

Non invasive tumours can be papillary or flat. Grading of urothelial tumours is important in Non invasive papillary neoplasms [6]. The PUNLMP is a low-grade, small, solitary neoplasm that neither invades nor metastasizes. In the present study out of total 76 cases of non invasive neoplasias, 35.5% were PUNLMP and 31.5% cases were papillary urothelial carcinoma, of which low grade cases were twice (21%) to high grade (10.5%). Distinction of PUNLMP from low-grade carcinoma may be difficult because approximately 35% of PUNLMPs recur and 11% progress in grade [7].

Conventional urothelial carcinoma constitutes about 75% of all cases [24]. The authors observed 88 (74.5%) cases of conventional IUC out of 118 IUC cases.

"Invasive urothelial carcinoma with divergent differentiation" was introduced in the recent WHO classification (2016) of bladder tumours. These tumours exihibit component of "usual type" urothelial carcinoma combined with other morphologies [7]. The divergent morphology include squamoid, glandular, small cell and trophoblastic differentiation [24,25]. Many of these variants have important prognostic or therapeutic implications worth knowing by the urologist and oncologist. Awareness of these unusual patterns is critical to avoid diagnostic misinterpretations [26]. In the present study, out of 118 cases of invasive urothelial carcinoma 30 cases (25.5%) exhibited features of divergent differentiation comprising 24 cases of squamous differentiation, 2 cases of glandular differentiation, 2 cases of poorly differentiated carcinoma and one case each of micropapillary and mixed glandular and microcystic variant.

Goyal VK et al., and Sushmitha S et al., also found majority cases of conventional urothelial carcinoma with 7.27% and 23% cases of divergent differentiation respectively [13,27]. The study conducted by Black PC et al., also stated that approximately 60% of tumours exhibit squamous differentiation and 10% of urothelial carcinomas contain foci of glandular differentiation [28].

In the present study, Glandular neoplasms comprised two cases each of primary mucinous adenocarcinoma and secondary adenocarcinoma (metastases from prostate). Studies have shown that Primary adenocarcinoma of bladder is uncommon and accounts for 0.5% -2% of all bladder tumours. Metastatic adenocarcinoma is commoner than primary tumours [29]. One case each of small cell neuroendocrine carcinoma and melanosis were also seen, although both are rare neoplasms with very few cases of both these entities documented in literature [30,31]. Most of the studies from India showed concurrence in prevalence of various carcinomas of bladder with the present study, the study done in West African region by Darre T et al., showed high prevalence of squamous cell carcinoma and adenocarcinoma as compared to urothelial carcinoma [32]. A plausible cause for this high prevalence could be association with urinary schistosomiasis and mechanical and chemical vesical irritant factors [33]. Comparison of prevalence of various carcinomas of bladder in different studies is shown in [Table/ Fig-7] [13,15,23,32,34-36].

Pathologic staging of bladder cancer is important to patient prognosis and treatment decision [37]. In the present study, invasive urothelial carcinomas, showed laminal invasion (pT1) in 37.3% cases while muscle invasion (pT2) was seen in 33.5% cases. Comparison of TNM staging in various other studies is shown in [Table/Fig-8] [12,15,38,39].

A new entity "urothelial proliferation of uncertain malignant potential" was introduced replacing the older term of urothelial hyperplasia and better categorisation of entity "urothelial dysplasia" was done in spectrum of flat and non invasive lesions of urinary bladder in the new WHO classification [7]. On re-assessment of biopsies according to the 2016 WHO classification [7] the authors found three cases of urothelial proliferation of uncertain malignant potential and two cases of urothelial dysplasia among 76 cases of non invasive urothelial neoplasia.

Neoplastic lesion	Mahesh Kumar U et al., [23] Bijapur, India (2012)	Darre T et al., [32] Africa (2014)	Goyal VK et al., [13] Bikaner, India (2015)	Dravid NV et al., [15] Dhule, India (2016)	Altaf J et al., [34] Pakistan (2017)	Mylsamy S and Kanakasabapathi D [35] Coimbatore, India (2017)	Agrawal S et al., [36] Moradabad, India (2019)	Present study, Meerut, India (2021)
Urothelial carcinoma	28 (46.6%)	25 (26.04%)	93 (93%)	77 (53.39%)	86 (90.5%)	38 (74.5%)	38 (84%)	118 (46.8%)
Squamous cell carcinoma	2 (3.33%)	36 (37.5%)	2 (2%)	7 (5.03%)	6 (6.3%)	5 (9.8%)	2 (4%)	Nil
Adenocarcinoma	2 (3.33%)	32 (33.3%)	1 (1%)	3 (2.15%)	3 (3.2%)	2 (3.9%)	1 (2%)	4 (1.6%)
Small cell carcinoma	Nil	Nil	Nil	Nil	Nil	Nil	Nil	1 (0.4%)

[Table/Fig-7]: Comparison of prevalence of carcinomas of bladder in different studies.

TNM stage	Kong CH et al., [38] 2010	Vaidya S et al., [12] 2013	Dravid NV et al., [15] 2016	Benhayoune K et al., [39] 2018	Present study 2021
pTa: Non invasive papillary carcinoma	23 (33.3%)	39 (48.14%)	20 (21.73%)	37 (23.7%)	24 (15%)
pTis: Carcinoma in situ	-	-	-	-	16 (10%)
pT1:Invades lamina propria	15 (20.0%)	18 (22.22%)	49 (53.26%)	35 (22.4%)	59 (37%)
pT2:Invades muscularispropria	8 (10.7%)	24 (29.63%)	18 (19.56%)	56 (36.2%)	56 (35%)
pT3:Invades perivesical tissue	9 (12.0%)	-	3 (3.26%)	15 (9.9%)	02 (1.3%)
pT4:Directly invades prostatic stroma, seminal vesicles, uterus or vagina, pelvic wall or abdominal wall	14 (18.7%)	-	2 (2.17%)	11 (7.2%)	04 (2.7%)

[Table/Fig-8]: Comparison of TNM stage of bladder neoplasms in various studies.

Limitation(s)

The limitation of present study is that clinicopathological correlation could not be, due to retrospective nature of study clinical details and follow-up was not available in all cases.

CONCLUSION(S)

Proper knowledge of histologic characteristics of the bladder lesions is utmost important as few benign conditions mimic neoplastic and few serve as pre-neoplastic conditions, tumour grading is a significant predictor for all patient outcome variables. The present study has potential areas of further research with the use of immunohistochemical stains which can aid to establish urothelial origin in bladder tumour with unusual histology and also to distinguish between reactive atypia and carcinoma in situ in difficult cases. This distinction is critical because of the therapeutic and prognostic implications.

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