

# BLADDER LESIONS IN CYSTOSCOPIC BLADDER BIOPSIES-A CLINICOPATHOLOGICAL STUDY ABSTRACT

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## ABSTRACT

### Introduction

In urinary bladder lesions, the clinical presentation is quite variable, the nonneoplastic lesions can mimic neoplastic and vice-versa bothering both clinicians and patients. The present study aims to study the clinic-pathological and histological features of various lesions of the urinary bladder in the specimens received through cystoscopic biopsy or transurethral resection.

### Objectives

The objectives of this study were to study the clinicopathological features of various bladder lesions and their frequencies and to correlate the clinical diagnosis with histological diagnosis.

### Methodology

The study was a descriptive cross-sectional involving patients with urinary bladder lesions requiring cystoscopic biopsy or transurethral resection conducted in the Department of Pathology of BP Koirala Institute of Health Sciences, Dharan over a period of one year (November 2016 to October 2017).

### Result

Among 40 patients, mean age was 56.40 years and male and female ratio was 1.5:1. The mean duration of symptoms was 3.49 months. The most common presenting feature for both neoplastic and non-neoplastic was frequency (75%), but hematuria was (86.36%) presenting feature in neoplastic cases and dysuria (88.88%) in non-neoplastic with each group accounting 55% and 45% respectively. Urothelial carcinoma (86.36%) was the commonest neoplastic lesion while cystitis (72.22%) was the commonest non-neoplastic lesion. NMIBC was the predominant lesion (78.95%) in urothelial tumor. Grading showed low grade (63.15%) and high grade (36.85%) respectively. The correlation analysis between clinical diagnosis and histological diagnosis revealed 100% correlation for non-neoplastic lesions and 73.33% correlation for neoplastic lesions having highly significant result ( $p < 0.001$ ).

### Conclusion

Urinary bladder is a common site of diverse lesions; with neoplastic being more common. Urothelial carcinoma was the most common type of neoplastic lesion and cystitis was the most common type of non-neoplastic lesion. Non-neoplastic lesions can mimic neoplastic lesions clinically. Histological diagnosis differs significantly from the clinical diagnosis indicating the importance of histological diagnosis in planning treatment.

## KEYWORDS

Cystoscopic biopsy; Dysuria; Urothelial carcinoma



## INTRODUCTION

The urothelium of the urinary bladder is considered to be lined by transitional cells, which can transform into a variety of benign and malignant tumors. Diseases of the urinary bladder both non-neoplastic and neoplastic are quite common. Non-neoplastic diseases of the bladder constitute an important source of clinical signs and symptoms.<sup>1</sup> They include hematuria, dysuria, frequency, urgency, nocturia and suprapubic pain. Usually, these disorders are more disabling leading to impairment in the quality of life and work performance. Sometimes, they can mimic neoplastic lesions clinically leading to mismanagement. Neoplasms of bladder pose biologic and clinical challenges and are responsible for significant morbidity and mortality throughout the world. Since urothelial cancer is a cancer of the environment and age, the incidence and prevalence rates increase with age, peaking in the eighth decade of life, and there is a strong association between environmental toxins and urothelial cancer evolution.<sup>2</sup> There is a geographic difference in bladder cancer incidence rates across the world, with the highest occurring in Southern and Eastern Europe, parts of Africa, the Middle East, and North America and the lowest occurring in Asia and underdeveloped areas in Africa.<sup>2,3</sup> An estimated 429,800 new cases of bladder cancer and 165,100 deaths occurred in 2012 worldwide<sup>4</sup>. There were 15,210 deaths recorded in 2013, including 10,820 men and 4390 women, and accounts for 3% of all cancer deaths in United States<sup>2,3,5</sup> Urothelial carcinoma is the most common tumor of the bladder, representing 90% of malignancies with this origin, 5% are squamous cell carcinomas, and less than 2% are adenocarcinoma or other variants. Urinary bladder cancer is the sixth most common cancer worldwide and the second most common malignancy of the genitourinary tract after prostate cancer. Bladder neoplasms account for 6% and 2% of the cancer incidence in men and women respectively.<sup>1</sup> Men are affected 3 to 4 times more often than women and about 80% of patients are between the age of 50 and 80 years. Hematuria is the most common presentation, but they can also present clinically as lower urinary tract symptoms similar to non-neoplastic lesions delaying diagnosis and treatment. So, accurate diagnosis of urinary bladder lesion is important to deliver proper treatment timely. Significant progress has been evolved in the non-invasive imaging and the scientists are continuing effort to identify and characterize potential markers or surrogate end points for bladder tumor. Still clinical examination, cystoscopic evaluation and histopathologic analysis of biopsy material are the mainstays of bladder cancer diagnosis and treatment.<sup>6</sup> Cystoscopy is the primary diagnostic tool for patients of bladder lesions. It provides information on appearance, number and location of bladder lesions and provides biopsy materials for histological evaluation for suspicious lesions. But, specimens obtained from cystoscopic biopsy is not sufficient for further characterizing neoplastic lesions in terms of depth of invasion and margin status. Transurethral

resection (TUR) of the bladder tumor is a therapeutic procedure that ensures the material necessary for histopathological diagnosis because it allows assessment of histological type and the degree of differentiation, depth of tumor invasion and other parameters which are useful in elaboration of diagnosis and subsequent treatment and prognosis.<sup>7</sup> In urinary bladder lesions, the clinical presentation is quite variable, the nonneoplastic lesions can mimic neoplastic and vice-versa bothering both clinicians and patients. We are also facing the conflicting scenario frequently in our institute, but no scientific study has been done on it, till date here.

The present study focus on the clinico-pathological and histological features of various lesions of the urinary bladder in the specimens received through cystoscopic biopsy or transurethral resection over a period of one year in a tertiary care hospital – BP Koirala Institute of Health Sciences, Dharan, Nepal.

## OBJECTIVES

To study the clinico-pathological features of various bladder lesions and their frequencies with sub-typing i. e. neoplastic vs non-neoplastic. To correlate clinical diagnosis with histological diagnosis.

## METHODOLOGY

The study is descriptive cross-sectional involving patients with urinary bladder lesions requiring cystoscopic biopsy or transurethral resection conducted in the Department of Pathology of BP Koirala Institute of Health Sciences, Dharan over a period of one year (November 2016 to October 2017). Purposive sampling technique was used for the study where patients with bladder lesions requiring biopsy were included. Informed consent was taken from the participants and the study was approved by Institutional Review Committee, BPKIHS (Ref. No. 334/073/074-IRC).

Sample size: Based on estimated proportion and desired precision (Aday et al. 2006)<sup>8</sup>. As reported by study of Pudasaini et al. neoplastic lesions were 55.6% in context of Nepal<sup>9</sup>,  $p=55.6\%$

$q(100-p)=44.4\%$

Permissible error (L)=10% of  $p=5.56$

Sample size  $(n_0)=Z^2 \cdot a/2^{pq} / L^2$   
 $= (1.96)^2 \times 55.6 \times 44.4 / (5.56)^2 = 306.775$

Based on the previous year (2015) medical records, 38 bladder biopsies were received so for the finite population,  $N=38$  Total sample  $(n)=n_0/1+n_0/n=307/1+307/38=34$

Droup out 10%=  $3.4 \sim 4$  Sample size=  $38 \sim 40$

**Inclusion criteria:** All the cystoscopic biopsies or transurethrally resected specimens received in the Department of Pathology, , BPKIHS, Dharan.

**Exclusion criteria:** Autolyzed specimen. Inadequate biopsies (Suboptimal biopsy in terms of processing and content)

**Study Procedure:** Data was collected on preformed proforma. Patients characteristics (age, gender and clinical



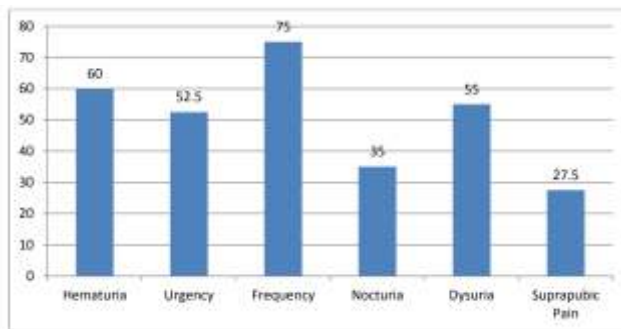
presentation), clinical diagnosis and cystoscopic findings was documented. Cystoscopic biopsy/TUR specimens was preserved in 10% Formaldehyde. Paraffin section was cut and stained by haematoxylin and eosin. Light microscopic technique was used for diagnosis. Special stains was applied, wherever required. Pathological diagnosis, its subtypes and degree of differentiation, grade and T stage of neoplastic lesions were also recorded. Data was initially entered into Microsoft Office Excel and appropriately coded. Statistical Analysis Statistical Package for Social sciences (SPSS version 20, IBM statistics license 1989 (2011) was used for data analysis. T-tests for continuous data and chi-square test and Fischer Exact test for categorical data was used. Chi-square test was used for correlation analysis. A p-value of <0.05 was considered significant.

**RESULTS**

Forty-two patients were included in the study. Two cases were excluded because the sample was inadequate. Finally 40 cases were available for the analysis ( Fig. 1). The mean age was 56.40± 15.87 years. For the neoplastic lesions, the mean age was 58.82± 13.33 years and 53.44±18.47 years for the non-neoplastic lesions. There were 24 males and 16 females ( M:F=1.5:1). They were 52.5% Hindus and 47.5% Buddhists. Most of the patients were house- wives by occupation ( 13/40, 32.5%) followed by farmers (11/40, 27.5%) and others (16/40, 40%). The mean duration of symptoms was 3.49±2.11 months (range 2 weeks to 8 months) [Table 1]. Frequency was the most common symptom (75%) followed by hematuria (60%) and dysuria (55%) [ Figure 2]. Hematuria was the most common symptom (19/22, 86.36%) in patients who had neoplastic lesions followed by frequency (18/22, 81.81%), urgency (12/22, 54.54) and nocturia (10/22, 45.45%). Similarly, dysuria was the most common symptom ( 16/18, 88.88%) among the non-neoplastic lesions followed by frequency (12/18, 66.66%), urgency (10/18, 55.55%) and nocturia (9/18, 50.00%).

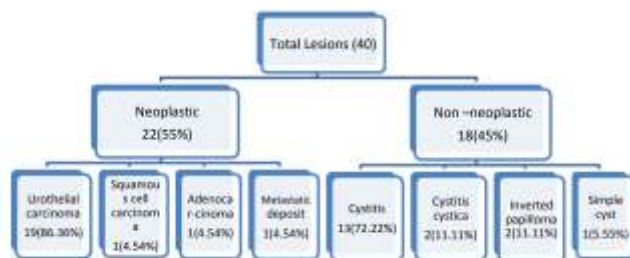
**Table 1:** Baseline Characteristics

Parameters	Mean ± SD /Radio
Age	56.40 ± 15.87 years
Duration of Symptoms	3.49 ± 2.11 months
Gender (M/F)	1.5:1



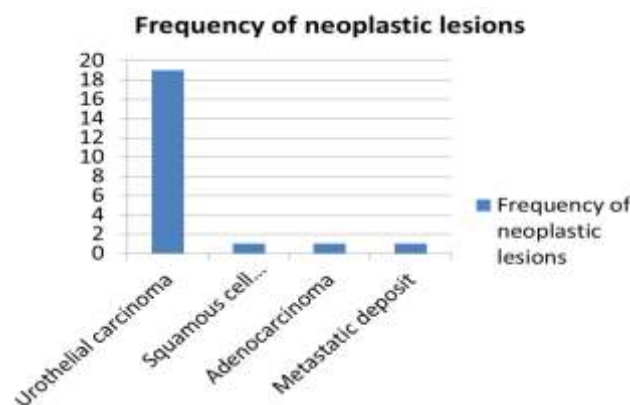
**Figure 2 :** Clinical features in the study population

Twenty-two specimens were TUR biopsy and 18 were cystoscopic biopsy. Thirty of the 40 biopsies (75%) were mass lesions and rest (25%) were suspicious area and among the mass lesions, majority were pedunculated (27/30, 90%) and only 3 (10%) were sessile. Postero-lateral was the most common location (14/30, 46.66%) followed by posterior (8/30, 26.66%) and neck region (5/30, 16.66%) for the mass lesions. Out of 40 cases, 22 were neoplastic (55%) and 18 were non-neoplastic (45%) [Fig.3].

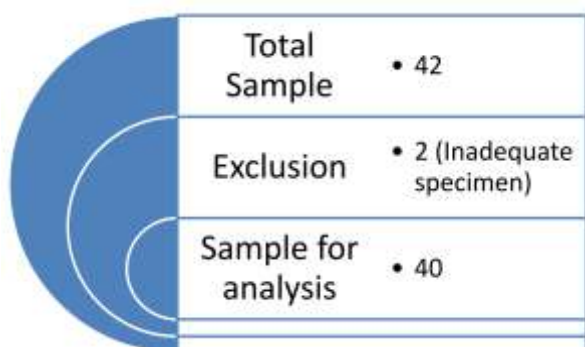


**Figure 3:** Spectrum of lesions identified.

Among the neoplastic lesions, urothelial carcinoma was the most common histological variant (19/22, 86.36%) followed by squamous cell carcinoma (1/22, 4.54%), adenocarcinoma (1/22, 4.54%) and metastatic deposit (1/22, 4.54%) [Fig.4].



**Figure 4:** Frequency of neoplastic lesions



**Figure 1:** Study procedure

Among the non-neoplastic lesions, cystitis was the most common (13/18, 72.22%), followed by cystitis cystica (2/18, 11.11%), inverted papilloma (2/18, 11.11%) and simple cyst (1/18, 5.55%)[Fig.5].

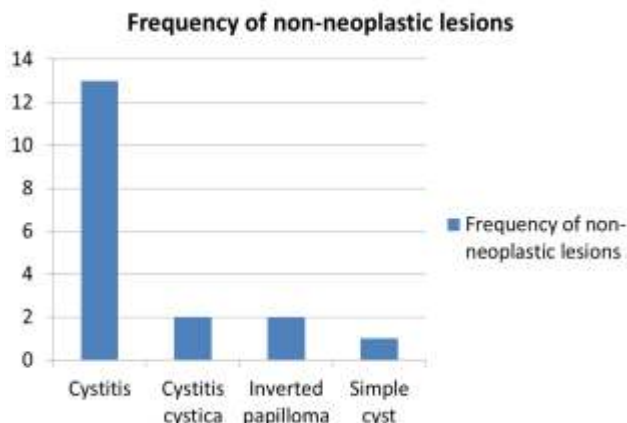


Figure 5: Frequency of non-neoplastic lesions

In patients with neoplastic lesions, more than half of them (13/22, 59.09%) were in 50-70 years age group, 22.72%(5/22) of them belonged to 70 plus age group and 18.18%(4/22) were below 50 years [Fig.6].

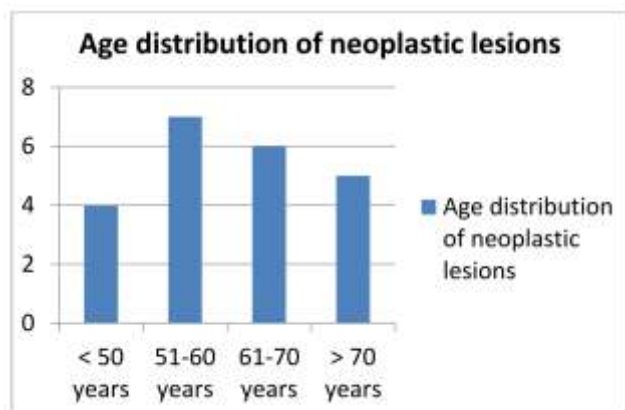


Figure 6: Age distribution of neoplastic lesions

NMIBC constituted 78.94% (15/19) and MIBC 21.05% (4/19). Papillary urothelial carcinoma was the most common lesion in NMIBC (12/15, 80%) followed by PUNLMP (3/15, 20%) [Table 2].

Urothelial Carcinoma	Number	Percentage
NMIBC	15	78.94%
NMIBC-PUNLMP	3	15.78%
NMIBC-papillary urothelial carcinoma, low grade	9	47.36%
NMIBC - papillary urothelial carcinoma, high grade	3	15.78%
MIBC	4	21.06%

The T staging of the tumors constituted Ta - 63.15% (12/19), T1- 15.78% (3/19) and T2- 21.05% (4/19) [Fig.7]. However, no CIS was detected in the lesions. In NMIBC, low grade urothelial tumor was seen in 60% (9/15) and 20% (3/15) were high grade with lamina propria invasion in high grade

cases. While all cases in MIBC were high grade and two of them showed lymphovascular invasion also. Thus overall grading of urothelial carcinoma shows 63.15% (12/19) low grade and 26.85% (7/19) high grade [Fig.8].

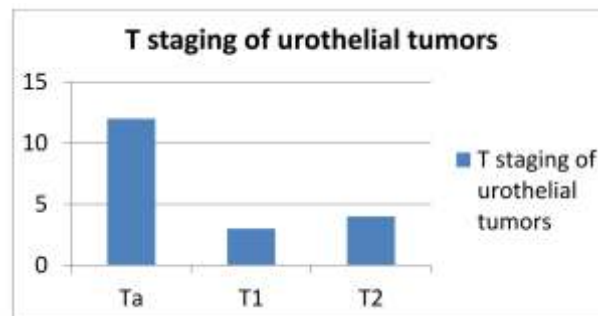


Figure 7: T staging of urothelial tumors

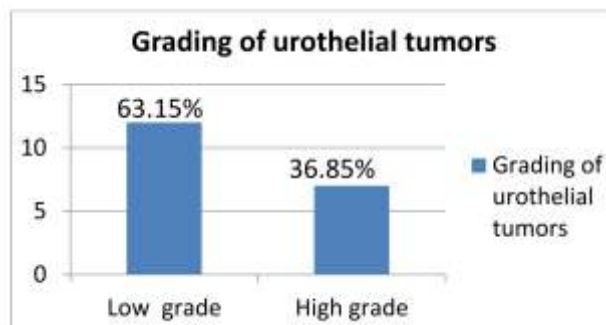


Figure 8: Grading of urothelial tumor

Patients with the non-neoplastic lesions, most of them were less than 50 years (7/18, 38.88%) followed by 51-60- and 60-70-year age group (4/18, 22.22% each) [Fig.9].

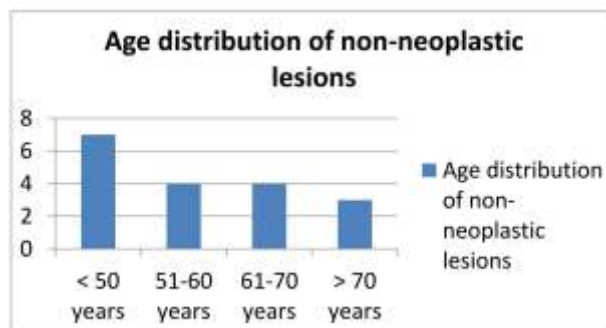


Figure 9: Age distribution of non-neoplastic lesions

In patients with cystitis, 3 had squamous metaplasia, 2 had eosinophilic cystitis and 1 had tubercular cystitis. The characteristic histology of non-neoplastic lesions is illustrated in the annexures.

The correlation of clinical diagnosis with histological diagnosis was 73.3% and 100% for neoplastic and non-neoplastic lesions respectively which differed significantly rejecting our research hypothesis (p-value<0.001) [Table 3]. Eight cases which were clinically diagnosed as neoplastic turned out non-neoplastic on histological diagnosis. They were cystitis cystica-2, inverted papilloma-2, tubercular cystitis-1, chronic cystitis-1 and eosinophilic cystitis-1. The patients were persistently symptomatic with symptom duration ranging from 3-6 months and cystoscopic evaluation revealed mass lesions suspicious for carcinoma.

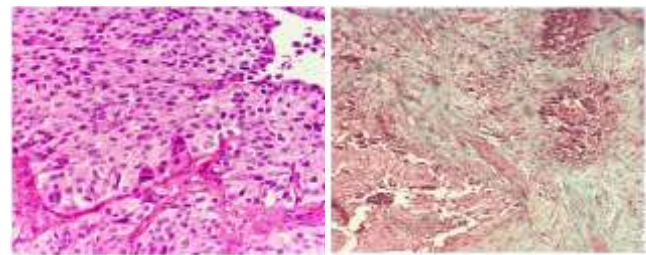




Table 3: Correlation of clinical diagnosis with histological diagnosis				
Clinical Diagnosis	Histological diagnosis	Correlation	Percentage	P-value
Non-neoplastic (10)	Non-neoplastic (10)	10/10	100%	<0.001
Neoplastic (30)	Neoplastic (22)	22/30	73.33%	

## DISCUSSION

Diseases of the urinary bladder both non-neoplastic and neoplastic are quite common. Non-neoplastic diseases of the bladder constitute an important source of clinical signs and symptoms.<sup>1</sup> They include hematuria, dysuria, frequency, urgency, nocturia and suprapubic pain. Usually, these disorders are more disabling leading to impaired quality of life and work performance. Neoplasms of bladder pose biologic and clinical challenges and are responsible for significant morbidity and mortality throughout the world. In this study, 40 cases of urinary bladder lesions were included. The mean age of the patients was 56.40 years with male predominance (M:F=1.5:1). The age of presentation in our study is similar to the study of Matalka et al where mean age was 60.6 years (range 19-91) and Goyal et al with mean age of 60.79 years (range 35- 85) respectively.<sup>10,11</sup> The gender ratio in our study was lower than the study of Goyal et al (5.25:1), Cheng et al (3.3:1.0), Hasan et al (2.58:1) and Vaidya et al (4.5:1) respectively.<sup>11-14</sup> This difference in gender ratio can be explained by shorter duration of study and lesser number of cases in our study. Painless hematuria was the most common symptom (86.26%) among the patients with neoplastic lesions. This is similar to the study Goyal et al. with 91% of patients presenting with painless hematuria and of Chinnasamy et al. where 83% of cases presented with painless hematuria.<sup>11,15</sup> Srikoouthubha et al reported 50% neoplastic and 50 % non-neoplastic lesions in cystoscopic bladder biopsies. Urothelial cancer was the most common malignant tumor (96%)<sup>1</sup>. Similarly, Pudasaini et al identified 56% neoplastic lesions and 44% non-neoplastic lesions in 35 cystoscopic bladder biopsies. Urothelial carcinoma was most common malignancy (89%) and 25% were muscle invasive in their study<sup>9</sup> ( Fig.10). In our study, 55% of cases were neoplastic with urothelial carcinoma constituting 86.26% and 45% were nonneoplastic which is comparable with above studies. But, Shruthi and colleagues reported 68% neoplastic and 32% non-neoplastic lesions in their specimens. Majority of malignant lesions were of urothelial origin.<sup>6</sup> Similar was the result in the study of Shah et al who detected 65% neoplastic and 35% non-neoplastic lesions in the bladder biopsy specimens. Urothelial tumor was most common malignancy ( 82.6%) and Forae et al reported 68% of neoplastic and 32% non-neoplastic lesions in their 75 bladder lesions received with urothelial carcinoma accounting 65%.<sup>16,17</sup> This slight higher incidence of neoplastic lesions in these studies compare to our findings can be due to difference in geography and patient habits.



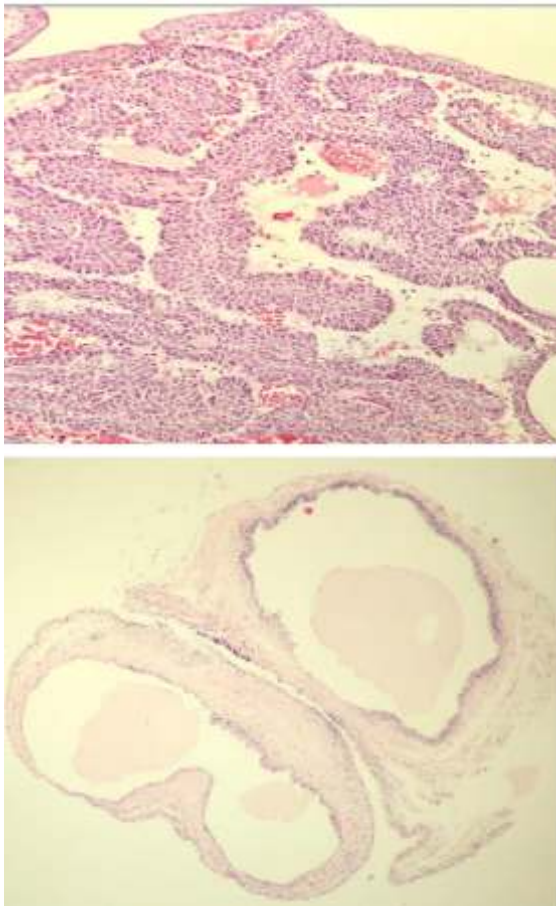
**Figure 10:** a) Papillary urothelial neoplasm (high grade,400X) b) Muscle invasive urothelial carcinoma(200X)

In this study, squamous cell carcinoma was seen in 4.54% of cases. It was a 54-year male who was on catheterization for about six months for refractory urinary retention. This result is similar to the results of Srikoouthubha et al. who reported 4% and Kumar et al. who reported squamous cell carcinoma in 6.25% of cases<sup>1,18</sup>. Similarly, adenocarcinoma was seen in 4.54% in our study comparable with 6.25% of Kumar et al. and 8.75% of Sathya et al respectively.<sup>18,7</sup> The adenocarcinoma in our case was in a 75 year male and it was primary mixed type comprising mixture of enteric and mucinous patterns. It was differentiated from urachal adenocarcinoma by the absence of location in dome/ anterior wall, absence of cystitis cystica/glandularis and clinical absence of primary elsewhere.<sup>19</sup> The results show both types are uncommon histological type of urinary bladder cancer. Metastatic deposit with adenocarcinoma was seen in a 35 year female who was treated for rectal cancer indicating colo-rectum is a rare site of origin for bladder metastasis as reported by Chang et al.<sup>20</sup> In our study, NMIBC was seen in 78.94% of cases and MIBC in 21.05% of cases. Our result is similar to the study of Wynder et al reporting NMIBC in 75% and MIBC in 20% of their cases.<sup>21</sup> Similarly, Sathya et al showed NMIBC in 75% and MIBC in 25% of cases.<sup>7</sup> Srikoouthubha et al reporting NMIBC in 87.5% and MIBC in 12.5% and Shruthi et al 87.75% and 12.25% respectively.<sup>1,6</sup> Papillary urothelial carcinoma was the most common lesion in NMIBC (80%) of which 60% were low grade and 20% were high grade respectively followed by PUNLMP (20%) in our study. Our results are compared with other available studies.

PUNLMP in our study is slightly higher than other studies possibly due to low threshold for cystoscopic evaluation and biopsy in our institution for suspected bladder lesions resulting in early-stage diagnosis. In current study, among the non-neoplastic lesions, cystitis was the most common (72.22%), followed by cystitis cystica (11.11%), inverted papilloma (11.11%) and simple cyst (5.55%). Out of which, 23.07% had squamous metaplasia, 15.38% were eosinophilic and 7.69% was tubercular. Srikoouthubha et al reported cystitis in 84% of their non-neoplastic lesions of which 71.40% were non specific, 14.28% tubercular and 4.76% eosinophilic. Here, squamous metaplasia was seen in 4% of cases<sup>1</sup>. Cases of cystitis were characterized by thickened bladder wall on ultrasonography and congested mucosa on cystoscopy but specimens under microscopic examination revealed normal urothelium and congested lamina propria with inflammatory infiltrates. Tuberculous cystitis showed ulcerations with the characteristic granuloma of epithelioid

cells, histiocytes, Langhan's giant cells, caseation necrosis and lymphocytes. Eosinophilic cystitis revealed intact mucosa with predominant eosinophilic infiltration in lamina propria. It can occur in association with allergic diseases or bladder trauma in the setting of catheterization.

Squamous metaplasia was characterized histologically by non-keratinizing stratified squamous epithelium and glycogen rich cells with clear cytoplasm. Cystitis cystica revealed solid invasion of surface epithelium into lamina propria with Von Brunn's nests some of which had cystic spaces lined by cuboidal epithelium. It is uncommon lesion occurring in the setting of trauma, calculus or inflammation. Two of our cases were inverted papilloma mimicking bladder cancer clinically. They show endophytic growth into lamina propria forming different sized epithelial nests and normal lining surface urothelium. They are uncommon lesions of urothelium accounting for 1.4%- 2.2% and mimic bladder cancer clinically.<sup>22</sup> One of our cases in a 74-year-old lady presented with cystic lesion in anterior bladder wall which was confirmed to be simple cyst on histopathological examination (Fig.11). Simple cyst of bladder is a rare finding and such cyst in anterior wall should be differentiated from urachal cyst which typically appears as midline echogenic swelling extending from umbilicus to dome of the urinary bladder in ultrasound and lined by pseudostratified columnar epithelium compared to cuboidal epithelium of simple cyst.<sup>23</sup>



**Figure 11:** a) Inverted papilloma (200X)  
b) Simple cyst of urinary bladder (200X)

While correlating clinical diagnosis with histological diagnosis, correlation was 100% for non-neoplastic lesions. But neoplastic lesions correlated in 73.33% of cases indicating histological diagnosis differed significantly from the clinical diagnosis ( $p < 0.001$ ).

## CONCLUSION

Urinary bladder is a common site of diverse lesions; both neoplastic and nonneoplastic with neoplastic lesions being more common. Urothelial carcinoma is the most common type of neoplastic lesion and cystitis is the most common type of nonneoplastic lesion. Non-neoplastic lesions can mimic neoplastic lesions clinically. High index of suspicion and timely and correct diagnosis is required to guide proper treatment which can reduce both morbidity and mortality. Histological diagnosis differs significantly from the clinical diagnosis indicating the importance of histological diagnosis in planning treatment. So, it is recommended and advised to have the histological diagnosis whenever applicable before starting treatment of bladder lesions.

## RECOMMENDATION

We further suggest to conduct similar studies with larger number of patients and for longer duration to see the outcomes of patients with histological markers for poor outcome. We also suggest studies involving Re-TUR specimens in high grade and T1 tumors to look for stage migration.

## LIMITATIONS OF THE STUDY

Limited duration of the study resulted in fewer number of patients in which we could not get CIS, variants of urothelial differentiation and radical cystectomy specimens. Availability of radical cystectomy specimen could provide further information on staging. We could not follow up of our patients with neoplastic lesions even one year post treatment to look for recurrence and progression. So we have limitations to comment on the outcome of patients with poor prognostic markers due to short follow up duration.

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## CONFLICT OF INTEREST

None, declared.

## FINANCIAL DISCLOSURE

We disclose that there was no financial support for the study by any means.

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