

## Histomorphologic study of cystoscopic urinary bladder biopsies: A gold standard

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### Abstract

**Introduction:** Urinary bladder lesions pose significant morbidity and mortality throughout the world. Cystoscopy, a widely accepted technique for diagnosing lower urinary tract lesions has its own limitations. Histopathology is gold standard for diagnosing, staging and to assess the microscopic invasion in malignant lesions. Thus present study was undertaken to study bladder biopsies and to correlate cystoscopic impression with histopathology and to know depth of invasion in malignant lesions.

**Materials and Methods:** It is an observational, prospective study of sixty cystoscopic guided urinary bladder biopsy done at tertiary care hospital over two year period.

**Results:** Out of total sixty biopsies 19 were non neoplastic (8 inflammatory, 9 metaplastic and 2 immune mediated) and 41 were neoplastic (2 benign, 39 malignant) on histopathology. Non neoplastic lesions (19/60) comprised of 4 follicular cystitis, 2 tuberculous cystitis, 2 eosinophilic cystitis, 4 cystitis cystica, 4 squamous metaplasia, one nephrogenic metaplasia and 2 amyloidosis. Neoplastic group (41/60) comprised of one papilloma, one papillary neoplasm of low malignant potential (PUNLMP), 28 transitional cell carcinoma (TCC), 3 adenocarcinoma, 6 squamous cell carcinoma, one small cell carcinoma and one embryonal RMS. Muscle invasion was detected in 8 and vascular invasion in 2 cases respectively. Cystoscopic impression was non neoplastic and neoplastic in 14 /60 and 46/60 respectively accounting for five discordant cases where final diagnosis was offered on histopathology.

**Conclusion:** Cystoscopy and histopathological examinations are complementary to each other in evaluating bladder pathologies but histology remains gold standard.

**Keywords:** Cystoscopy, Urinary bladder, Biopsy, Histopathology, Transitional cell carcinoma.

### Introduction

Bladder cancer ranks ninth most common cancer worldwide and it is the second most common malignancies seen by urologists.<sup>1,2</sup> Bladder cancers has higher incidence in men than women.<sup>1,3</sup>

Urothelial carcinoma are the most common bladder cancers in developed countries and constitute more than 90% bladder cancers in Italy, France and USA whereas the frequency is lower in Eastern and Northern Europe, Africa and Asia.<sup>4</sup>

Conventional cystoscopy is the important diagnostic tool for investigating bladder abnormalities.<sup>5</sup> Endoscopic impressions are accurate and discriminate between presence and absence of malignancy. Despite the general reliability, popularity and ease of execution of cystoscopy, this technique has some distinct limitations. Previous studies have observed discrepancies between cystoscopic observations and histological findings, more so in non-neoplastic.<sup>6</sup> Cystoscopy alone is a relatively poor tool to assess the microscopic invasion in malignant lesions, which is essential for predicting the prognosis of malignant lesions. Cystoscopy and bladder biopsies together are important for early diagnosis and treatment of various bladder lesions.<sup>7</sup>

Keeping in mind importance of both diagnostic modalities present study was carried out on cystoscopic guided bladder biopsies and cystoscopic impression was correlated with histopathology. In addition depth of invasion and other features were assessed in the malignant lesions.

### Materials and Methods

It is an observational, prospective study of sixty adequate cystoscopic biopsies carried out in department of pathology in a tertiary care hospital of central India after taking institutional ethical clearance.

The present study was aimed to study histomorphology of bladder lesions and to correlate cystoscopic impression with histomorphology. Secondary aim was to know the depth of penetration and vascular & lymphatic invasion in case of neoplastic lesions.

After taking written consent, patients presenting with lower urinary tract symptoms like dysuria, abdominal pain, hematuria and recurrent urinary tract infections etc. were selected by urologists for diagnostic and therapeutic cystoscopy. Biopsy was done under spinal anesthesia, using 26 Ch Continuous Irrigation Sheath (Iglesias) and Baumrucker working element. Cystoscopic appearances and exact site of biopsy were provided by the surgeons. Cystoscopic images and video recording was done in interesting cases. All cystoscopic biopsies procured from surgical wards in our institute as well as those received for review in the histopathology section were studied. Only adequate biopsies with presence of sub mucosa and at least part of muscularis propria were included in the study. Superficial biopsies without sub mucosa were excluded from the study.

The biopsies were put on a wet filter paper with mucosal surface on the upper side to avoid curling of the tissue and fixed in 10% formalin followed by routine processing taking care to orient the section vertically. 4-5

serial sections of 5  $\mu$  were taken. Haematoxylin and eosin staining was done in all and if required, special stains like Congo red, acid fast stain, Masson trichrome etc. were done.

## Results

Of total 60 adequate cystoscopic bladder biopsies 19 were non-neoplastic and 41 neoplastic, which included benign and malignant lesions on histology. The age ranged from 1-90 years with average age being 56 years. M: F ratio was 46:14. Commonest symptom of presentation was hematuria (40%) in both non-neoplastic and neoplastic categories but was more common in neoplastic lesions. Hematuria and dysuria were noted with equal frequency in non-neoplastic categories.

Most common site to be involved was lateral wall of the bladder (30%), in which neoplastic lesions predominated (21.67%). The inflammatory lesions were distributed at lateral wall, trigone and ureteric orifice.

Cystoscopist described lesions as polypoidal, sessile, fungating, flat, nodular, elevated and papillary. On cystoscopy 14/60 were non-neoplastic and 46/60 were neoplastic (Table 1). They were further classified into inflammatory, metaplastic, benign and malignant neoplasm respectively. (Table 2) Overall nodular lesions predominated (21.65%). Polypoidal lesions predominated in neoplastic category (9/41; 15%).

Histopathology revealed 19/60 were non-neoplastic and 41/60 were neoplastic. (Table 1) Non-neoplastic were further categorized as inflammatory (8), metaplastic (9), immune-mediated (2), benign (2) and malignant (39) on histology. Of 8 inflammatory lesions 4 were of follicular cystitis, 2 of tuberculous cystitis and 2 of eosinophilic cystitis respectively. Of 9 metaplastic lesions 4 were cystitis cystica, 4 squamous metaplasia and one nephrogenic metaplasia. Two cases were of amyloidosis (immune-mediated lesions). Neoplastic group (41/60) comprised of one papilloma, one papillary urothelial neoplasm of low malignant potential (PUNLMP), 28 transitional cell carcinoma (TCC), 3 adenocarcinoma, 6 squamous cell carcinoma (SCC), one small cell carcinoma and one embryonal rhabdomyosarcoma (RMS). (Table 3) All low grade tumors were papillary in configuration whereas solid (6/15) or mixed (7/15) types predominated in high grade tumors. All the cases of SCC (6/6) were invasive and advanced when biopsied. Muscle invasion was detected in 8 cases and vascular invasion was seen in 2 cases.

Chi square test was performed with p value <.005 and was considered significant. Correlation of cystoscopy and histopathological diagnosis was assessed by calculating sensitivity, specificity and positive predictive value. Sensitivity was 100% and specificity was 73.68% and positive predictive value 89.13% respectively.

## Discussion

Cystoscopy allows direct visualization of bladder mucosa and is the primary diagnostic modality for diagnosis of bladder lesions. Though most of the lesions are quite easy to identify, but at times may pose diagnostic difficulties.

Pathologist is responsible for definitive diagnosis and also offers additional information like invasion which is important for treatment. Thus cystoscopy and biopsy together help in an early detection of bladder neoplasm and follow up.<sup>8</sup>

In present study of 60 adequate cystoscopic biopsies, most of the patients were in the age group of 51-60 (21.66%). The youngest was 1.6 years and oldest being 85 years. Neoplastic lesions were more common in age range of 61-70 (18.33%) whereas most of the non-neoplastic lesions occurred in the age group of 31-50 yrs (16.66%). Males predominated with M: F – 3:1.

The most common presentation were hematuria (28%) and dysuria (25%), followed by polyuria (11%), suprapubic pain (8%), urinary tract infection (UTI) (6%), retention of urine (1%) and renal stones (4%). Other symptoms like constipation, weight loss, loss of appetite etc. were seen in 25% patients.

We observed that the most common site affected was lateral wall (30%) in both non-neoplastic and neoplastic lesions. The inflammatory group showed equal distribution on lateral wall, trigone and ureteric orifice (3.33% each) whereas most of metaplastic lesion involved trigone (6.66%).

Neoplastic group showed lateral wall involvement predominantly (21.67%), followed by posterior wall, dome, anterior wall, orifice, neck and trigone. Ordóñez et al also reported lateral wall as the commonest site.<sup>9</sup>

Of four cases of follicular cystitis (FC) which showed lymphoid follicles with germinal center on histology (Fig. 1A), three were females and one was male, two of them presented with dysuria and two had history of recurrent urinary tract infection with history of bladder stone in one. Belman had noticed an association between mucosal changes and irritative symptoms.<sup>10</sup> Cystoscopy revealed two lesions were located in trigone, one each on anterior and lateral wall. 2/4 lesions were nodular whereas the other two were flat in appearance. Caner in review article emphasized on histological diagnosis and planning treatment in FC and that it is rare cystitis common in females with common location being trigone.<sup>11</sup>

We had two cases of eosinophilic cystitis (Fig. 1B) of age 32 and 45 years. One was female and other male. Both had dysuria, while one of them had recurrent hematuria. Itano et al in their study reported that 95% cases presented with irritative voiding symptoms, hematuria and suprapubic pain.<sup>12</sup> Association with allergic conditions, autoimmune disorders, transitional cell carcinoma, and parasitic infestation had been mentioned by Itano but no such association was seen in the present study.<sup>13</sup> Cystoscopy revealed shaggy fungating lesions, mimicking neoplastic mass in one and hypertrophied mucosa thrown in thick, transparent folds in second case of ours. Eosinophilic cystitis presenting as tumor like bladder lesion has been described by other authors.<sup>12,13</sup> The diagnosis of this entity is must because it may progress relentlessly, resulting in complete fibrosis of the bladder with secondary obstructive uropathy in both children and adults.

We had two cases of tuberculous cystitis; both were males with age 26 & 55 years who presented with dysuria, hematuria respectively. On cystoscopy, one was a flat lesion involving ureteric orifice with bladder wall thickening. Further investigations revealed renal tuberculosis. Other was a sessile mass at the ureteric orifice which was diagnosed as neoplastic lesion on cystoscopy but showed granulomas on histology (Fig. 1C). Both patients in present study responded well to anti Koch's therapy. Kulchavenya et al have staged bladder tuberculosis into Stage 1- tubercle-infiltrative bladder TB, stage 2 erosive-ulcerous bladder TB, stage 3 is spastic cystitis, and stage 4 contracted bladder up to full obliteration and also emphasized on importance histopathological and other diagnostic modalities and further treatment.<sup>14</sup>

We had three cases of cystitis cystica and one case of cystitis glandularis. The age ranged between 17-45 years with male preponderance (M: F, 3: 1). All presented with dysuria. One patient had hematuria and another had polyuria. Cystoscopy revealed trigone involvement in 2/4 patients with plaque like lesion in one and elevated mucosal lesions in the other. One patient had multiple tiny nodules near ureteric orifice and the other had a pedunculated mass near bladder neck which was highly suspicious of neoplasm, on cystoscopy (Fig. 2A-C). There are case reports of bladder mass which were misdiagnosed as neoplastic on cystoscopy, thus emphasizing importance of tissue diagnosis in such cases.<sup>9,15,16</sup> Neoplastic transformation of cystitis glandularis had been described, hence long term follow-up is advised.<sup>9</sup>

We had a 45 years male who presented with hematuria and bladder stone which on cystoscopy revealed papillary nodule on the lateral wall which was suspected by urologist to be neoplastic but histology revealed nephrogenic metaplasia. (Figure 2 D-F) Ducrocq had stated that the lesion may mimic malignancy on cystoscopy and resection and histology is the diagnostic modality of choice.<sup>17</sup>

We had four cases of squamous metaplasia with female preponderance (M: F, 1:3). Irritative voiding symptoms were seen in 2/4 other two had recurrent UTI. Two were at trigone and one each was seen on lateral wall and ureteric orifice. Two were nodular and other two were flat plaque like lesions. Flat lesion on histology revealed keratinizing type of squamous metaplasia where as other three were of non-keratinizing type. (Fig. 2G-I) Ranadive and Johansson have mentioned of female preponderance due to hormonal influence on bladder mucosa and trigone and bladder neck being the common site.<sup>18,19</sup> Non- keratinizing type was seen commonly in reproductive age group.<sup>19</sup> Long term follow up is advised as they have premalignant potential.<sup>18</sup>

We had two cases of amyloidosis. (Fig. 1D) Both were male with age 55 and 58 years. Amyloidosis is basically disease of elderly male although youngest case to be reported so far was 32 years old.<sup>20</sup> One of our case presented with gross hematuria and had a sessile tumefactive lesion on cystoscopy which showed Congo red positive amyloid emphasizing on importance of tissue diagnosis. Livneh et al had reported similar nodular lesion with diagnosis of carcinoma bladder on cystoscopy.<sup>21</sup> The second patient

presented with features of polyuria and dysuria. Cystoscopy revealed flat ulcerated lesion on the dome of bladder. Strong had reported a case with similar cystoscopy.<sup>20</sup>

We had 41 neoplastic lesions, on histopathology where TCC predominated. The neoplastic cases were two times that of non-neoplastic (61.33%:31.67%).

We had one case of exophytic papilloma in 53 years old male. (Fig.3A-B) Presenting symptoms were dysuria and polyuria. Cystoscopy revealed a single papilloma near orifice. Fern like, red elevated excrescences with fragmentation, necrosis, and hemorrhage had been described by Lerman et al, whereas most of the lesion appeared neoplastic in the case series of Cheng where 94% lesions were solitary.<sup>22,23</sup> Recurrence and malignant transformation was reported to be low in these patients and depended upon the multiplicity of the lesion and atypia.

A 60 years old patient who presented with hematuria, cystoscopy revealed a papillary lesion at the dome of the bladder proved to be PUNLMP on histology (Fig. 3C-D). Cheng have reported case series with male predominance and age range of 33-99 years and most of the lesions were located on the lateral wall of bladder. Long term follow up was recommended due to increased risk of recurrence as well as progression to transitional cell carcinoma.<sup>23</sup>

We had 28/60 (46.67%) cases of TCC. Out of these, 13(46%) were low grade and 15(54%) were high grade tumors. Age ranged between 31-90 years with male preponderance (M: F - 8:1). Presenting complaint in the present study was hematuria in 22/28 (35%) followed by dysuria (27%), suprapubic pain (14%), polyuria (5%) and others (19%). Ordonez reported 90% of bladder tumors to be transitional cell carcinoma and common age after 50 years but they are known to occur at younger age and common complaint being hematuria.<sup>9</sup> Most common location in our study was lateral wall (35.71%) which correlated with Ordonez and Stephenson.<sup>9,24</sup> Stephenson also mentioned, lower grade lesions were located on lateral wall or orifice and high grade lesion were located on dome and that tumors located near neck carried a worse prognosis. Histology in all the low grade lesions showed papillary configuration (Fig. 3E-F) whereas high grade lesions were either solid (6/15) or a combination of solid and papillary (7/15). (Fig. 3 G-H) Papillary lesion carried a better prognosis as compared to solid or mixed type of lesion and this classification has prognostic importance.<sup>24</sup>

We noticed lamina propria invasion in 4/13 low grade tumors and all (15/15) high grade tumors. Invasion of the lamina propria carries worse prognosis.<sup>25</sup> Invasion of muscularis mucosa was seen in 5/15 high grade lesion. Younes said that the tumors invading only the muscularis mucosa had a more favorable course than tumors invading beyond it.<sup>26</sup> Muscularis propria invasion was seen in a single case of high grade TCC. (Fig. 3I) Muscle invasion was important for therapy and prognosis.<sup>9</sup> Vascular invasion was seen in 2/15 high grade TCC. (Fig. 3J) Vascular invasion was associated with a higher rate of recurrence.<sup>9</sup> Other findings noted were clear cell change in two high grade tumors with metastases in omentum in one of these

lesions, indicative of poor prognosis.<sup>9</sup> Squamous differentiation, inflammatory infiltrate and areas of necrosis were the other features noted.

We had 3 cases of adenocarcinoma. Age ranged between 55-70 years and M: F; 2:1. Of which one was a known case of carcinoma of rectum who presented with history of malena and hematuria whereas other two had only hematuria. Adenocarcinoma of bladder is a rare tumor comprising of 0.5-2% of all bladder neoplasm.<sup>27</sup> Direct extension of tumor from adjacent sites like prostate, colon, and ovary has been described and is reported to be more common than primary adenocarcinoma of bladder.

Cystoscopy revealed location of two tumors on posterior wall and one on ureteric orifice, two were flat lesions and one was elevated mucosal lesion. Two of our cases on microscopy showed glandular pattern with columnar cells and pure signet ring type in a known case of carcinoma rectum. (Fig. 4 C-D) Cystoscopic appearance of adenocarcinoma is either solid or papillary.<sup>25,28</sup> Grignon et al noticed flat lesions and reported that 6/8 case of signet ring type were located in posterior wall or trigone or both. He also recommended random biopsies if cystoscopy revealed only edematous/elevated mucosa in clinically suspected malignancies and that signet ring type behaved in an aggressive fashion.<sup>29</sup> We noticed muscle invasion in 1/3 cases. Anderstrom found all tumors in his study were invasive at the time of diagnosis and carried a worse prognosis than TCC.<sup>25</sup> We also noticed von Brunn's nests in 1/3 cases. Progression of cystitis cystica to adenocarcinoma had been reported by Ansari.<sup>15</sup>

We had 6 cases of SCC. (Fig. 4A) Age ranged between 45-81 years and M: F, 4:2 with chief complaint of hematuria (5/6cases). 3 had recurrent urinary tract infection and 2 had bladder stones. 4/6 were located on trigone and posterior wall, one each was located on lateral wall and there was diffuse thickening of bladder wall in one of the cases similar to Sharfi.<sup>30</sup> 4/6 were nodular and two were fungating masses. All showed invasion up to muscularis propria indicating poor prognosis.<sup>31</sup>

We found a single case of small cell carcinoma in an 80 year old male patient who had hematuria, dysuria and polyuria. (Fig. 4B) Cystoscopy revealed a large fungating, ulcerated mass on the lateral wall of bladder. Histology revealed diffuse infiltration of lamina propria, muscularis propria by monotonous population of small round cells along with vascular invasion. The patient succumbed within four days of diagnosis, indicating a poor prognosis of the tumor. Although the tumor had been described to be aggressive in nature, it is potentially curable if adequately resected before metastasis has occurred.<sup>32</sup>

We had a single case of RMS in male child aged 1.6 year who presented with abdominal lump. Cystoscopy revealed a large polypoidal mass involving whole of the posterior wall similar to Ghazali.<sup>33</sup> Microscopy revealed embryonal type of RMS. (Fig. 4E-F) Masson trichrome stain was contributory. According to Miettinen embryonal/botryoid/alveolar types are more common in pediatric age group whereas pleomorphic type was common

in adults.<sup>34</sup> Ghazali had mentioned a better prognosis for polypoidal type of lesions than any other variety.<sup>33</sup>

All histopathologically confirmed neoplastic lesions were correctly categorized as neoplastic (benign or malignant) on cystoscopy. As non in the neoplastic category were missed/ misdiagnosed thus sensitivity of cystoscopy for diagnosing a neoplastic lesion, in the present study was 100%. Histopathology and cystoscopy correlated in 55/60 cases (91.67%) and was not correlated in 5/60 cases (8.33%). Thus predictive value of cystoscopy for diagnosing the neoplastic lesions was 89.13%. In 5 of our discordant cases cystoscopic impression was of benign neoplasm, but histology proved them to be non-neoplastic (1each of tuberculous cystitis, eosinophilic cystitis, cystitis cystica, nephrogenic metaplasia and amyloidosis respectively). 14/19 benign lesions was correctly diagnosed on cystoscopy. Thus the specificity of cystoscopy was 73.68%. P value was <.005, which was highly significant. Cystoscopy was of no help in evaluating grade, invasiveness and histological categorization of the bladder tumors. As all these parameters are important from therapeutic and prognostic point of view, histopathology was mandatory for proper & timely management of the patients. This finding was correlated with the study conducted by Cina and Mitropoulos.<sup>35,36</sup> Except for few inadequate biopsies and thus decreasing the sample size a bit there were no obvious limitations in our study.

**Table 1 Cystoscopic and histopathologic categorization of various lesions**

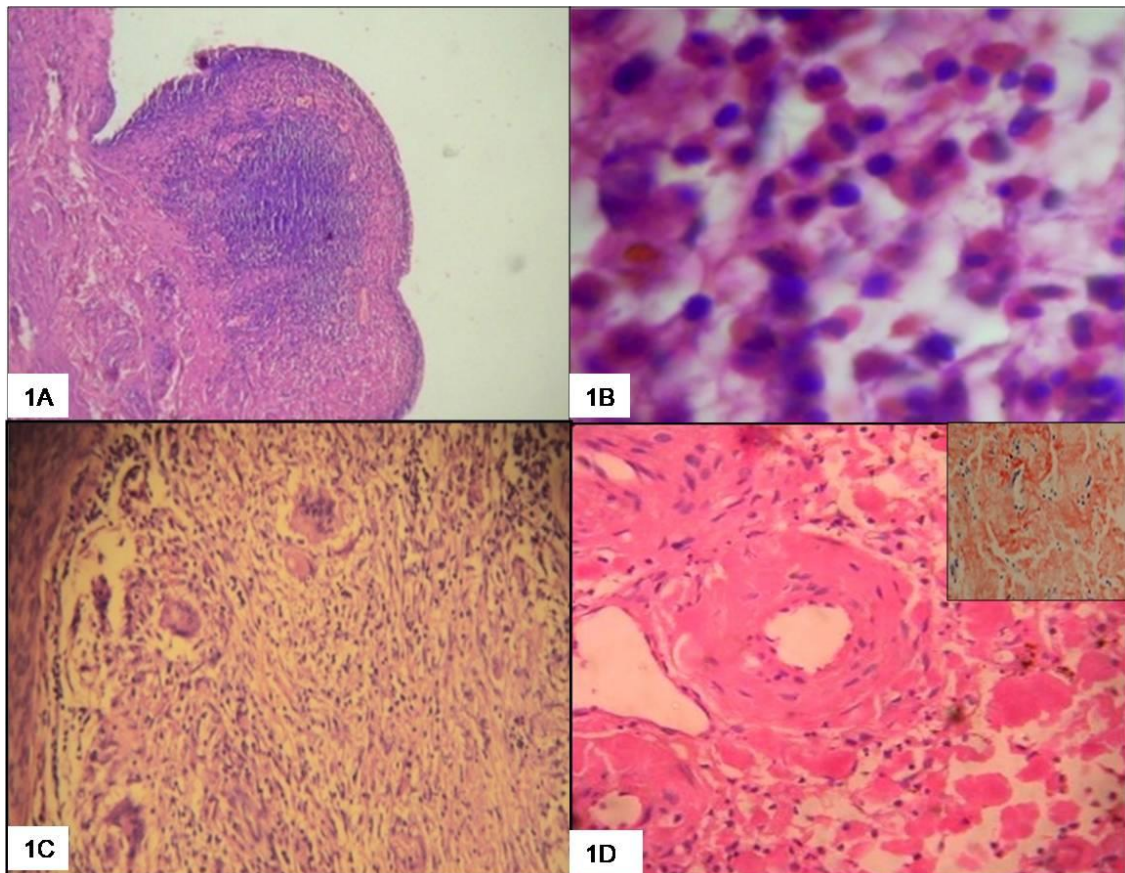
Category	Cystoscopy	Histopathology
Non neoplastic	14	19
Neoplastic	46	41

**Table 2 Cystoscopic categorization of lesions**

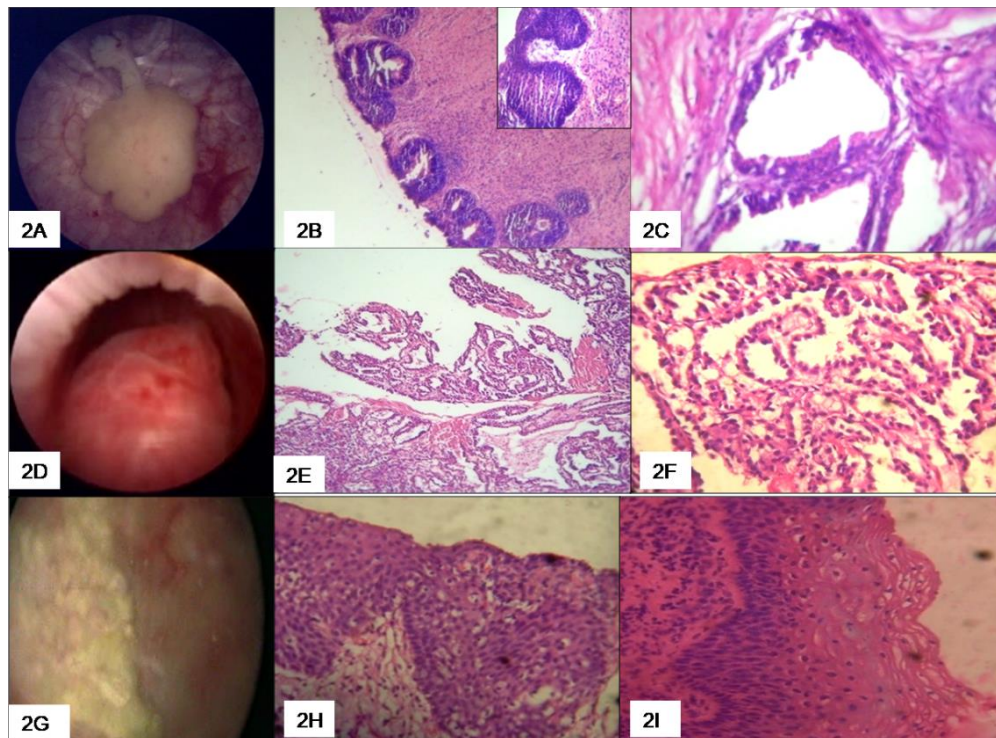
Diagnosis on cystoscopy	No. of cases	Percentage
Inflammatory	6	10%
Metaplastic	7	11.67%
Benign Neoplasm	7	11.67%
Malignant Neoplasm	39	65%
Unclassified	1	1.66%
Total	60	100%

**Table 3 Histopathologic categorization of lesions**

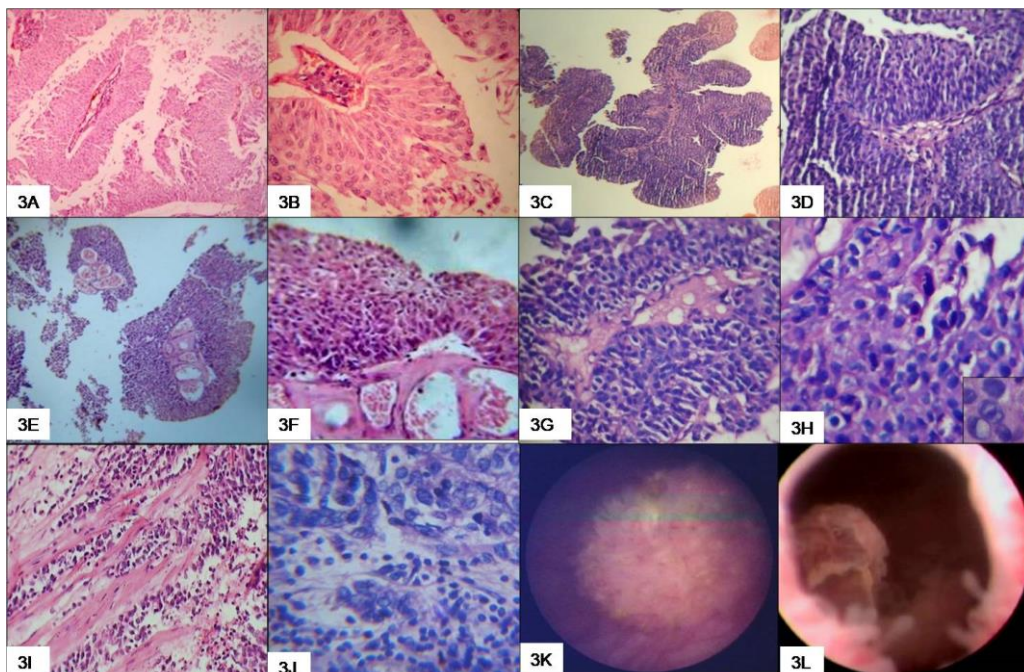
S. No.	Category	Histopathologic diagnosis	No. of cases (60)	Percentage (100%)
1.	Inflammatory lesions (8/60; 13.33%)	Follicular cystitis	04	6.67%
		Tuberculous cystitis	02	3.33%
		Eosinophilic cystitis	02	3.33%
2.	Metaplastic lesions (9/60; 15%)	Squamous metaplasia	04	6.67%
		Cystitis Cystica	04	6.67%
		Nephrogenic Metaplasia	01	1.66%
3.	Immune mediated lesions (2/60; 3.34%)	Amyloidosis	02	3.34%
4.	Neoplastic lesions 41/60; 68.33%)	Papilloma	01	1.66%
		PUNLMP	01	1.66%
		Low grade TCC	17	28.35%
		High grade TCC	11	18.34%
		Adenocarcinoma	03	05%
		SCC	06	10.0%
		Embryonal RMS	01	1.66%
		Small cell carcinoma	01	1.66%



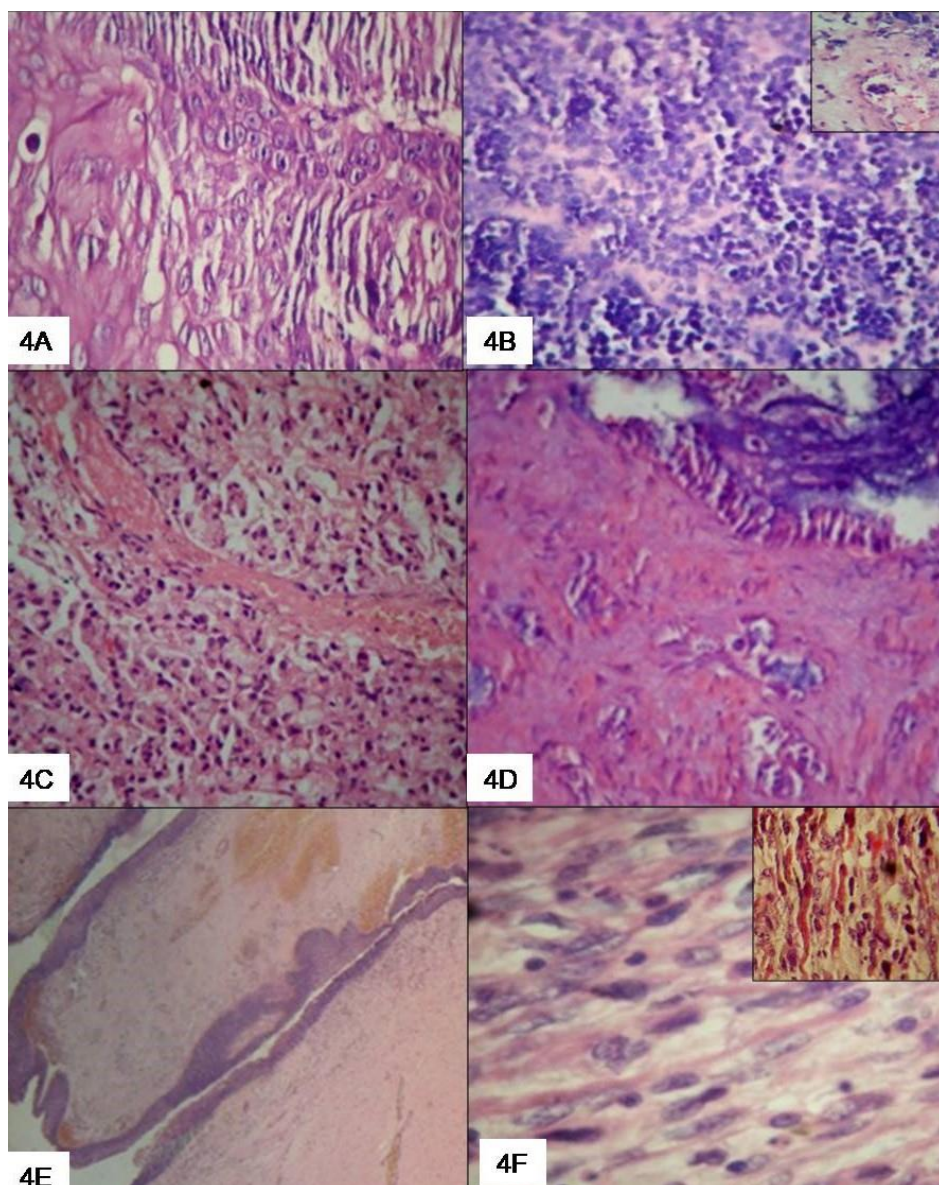
**Fig. 1A-D (H & E) - 1A: (10 X) FC - lymphoid follicles in lamina propria; 1B: (100X) Eosinophilic cystitis-eosinophilic infiltration of lamina propria; 1C: (40 X) Tuberculous cystitis - epithelioid granulomas with langhans giant cells; 1D: (40X) Amyloidosis - eosinophilic deposits in vessel wall and interstitium. Inset- positive Congo red**



**Fig. 2A:** Cystoscopy - nodular lesion; **2B:** (H & E 10 X) von Brunn's nests in cystitis cystica; **2C:** (H& E 40 X) Cystitis cystica glandularis; **2D:** Cystoscopy - nodular lesion; **2E & F:** (H& E 10X, 40 X) Nephrogenic metaplasia - hobnail cells in glands; **2G:** Cystoscopy - flat, white plaque. **2H,I:** (H& E 40X) Non keratinizing and keratinizing squamous metaplasia



**Fig. 3A–J:** (H & E) **3A,B:** (5X, 40 X) Papilloma - oriented cells, lack of atypia & mitosis; **3C,D:** (5X, 40X) PUNLMP maintained nuclear polarity and enlarged nuclei; **3E,F:** (5X, 40 X) Low grade TCC- Fused papillae, minimal loss of nuclear polarity & few umbrella cells; **3G,H:** (10X, 40X) High grade TCC -Loss of polarity, atypical mitosis (inset- nuclear pleomorphism, intranuclear vacuoles), **3I, J** Muscular and vascular invasion; **3K,L:** Cystoscopy -shaggy fungating, nodular masses



**Fig. 4A-F: (H & E) – 4A: (40X) SCC; 4B: (40X) Small cell carcinoma -hyperchromatic, mononuclear cells with scanty cytoplasm, vascular emboli; 4C: (40X) Adenocarcinoma -signet ring cells in lamina propria; 4D: (40X) Glands with mucin infiltrating in muscle; 4E,F: (10X, 40X) Embryonal RMS - polyp with prominent cambium layer, pleomorphic spindle cells, inset positive Massons trichrome**

### Conclusion

We conclude that there are certain non-neoplastic tumefactive urinary bladder lesions which can be mistaken for neoplasm on cystoscopy and needs tissue confirmation. Few non neoplastic lesions like cystitis cystica, squamous metaplasia, are known for their premalignant nature and need correct and timely diagnosis. In addition to histology being gold standard for diagnosis, it is mandatory to type, grade and look for depth of invasion in neoplastic lesions. Thus cystoscopic impression and biopsies together help in an early diagnosis of bladder neoplasm and follow up.

**Conflict of Interest:** None.

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