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Case Series

Histopathological Spectrum of Urothelial Carcinoma of Urinary Bladder – Study of 160 Cases: Experience in a Tertiary Care Hospital

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Abstract

Introduction: Ninety to 95 percent of urothelial carcinomas occur in the Urinary bladder. The current study aimed to classify urothelial carcinoma based on the TNM AJCC classification 2010 and the WHO 2016 classification system by analysing its histopathological features and correlating them with clinical features and radiological findings.

Materials and Methods: 160 cases of all bladder biopsies and TURBT from bladder tumours diagnosed as urothelial carcinoma were observed over a 9-year period. Cystectomy specimens obtained as a follow-up of the aforementioned cases in a tertiary referral hospital. The tumours were examined for histopathological details and they were correlated with clinical characteristics and cystoscopy.

Results: Out of the 160 cases that were included, 127 were TURBT and 33 were biopsies. Male preponderance (80.0%) was observed and majority of cases were in the 5th to 7th decade. Gross hematuria (80%) was most common presenting symptom. Infiltrating urothelial carcinoma accounted for 56.9% of all cases. Squamous differentiation was found to be the most prevalent type of divergent differentiation. Muscle invasion was observed in 22 cases (24.17%). Statistical analysis using Chi square tests revealed a significant correlation between tumour size and grade. We received 14 cystectomies specimen from above cases subsequently and the grade, invasiveness and differentiation of the tumour showed concordance with the previous histopathology findings.

Conclusion: The study showed uniformity in the diagnosis of the cystectomy specimen with their respective diagnosis on biopsies and TURBT and also emphasized on mentioning a note about the muscle invasion and differentiation of urothelial carcinoma as it has both prognostic and therapeutic implication.

Keywords: urinary bladder, urothelial Carcinoma, biopsy, histopathology.

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Introduction

Ninety to 95 percent of urothelial carcinomas occur in the Urinary bladder [1].It ranks as the ninth most frequent cancer, making up to 3.9% of all malignancies, according to data from the Indian Cancer Registry [2] . Bladder cancer typically strikes men between the ages of 65 and 70 [3]. The multicentricity and high recurrence rate of urothelial carcinomas are well established [1]. The main risk factors for bladder epithelial tumours are smoking, extended cyclophosphamide therapy, industrial exposure to arylamines and Schistosomiasis. Microscopic haematuria is seen in the majority of individuals with invasive urothelial carcinoma; however, the severity of symptoms varies depending on the tumour site and stage [4]. Painless gross haematuria, urgency, nocturia, dysuria are the most typical clinical symptoms. In later stages, urinary obstructive symptoms may also be present [5]. Cystoscopy is a useful technique, but it also has some clear drawbacks. For example, it is not very good at determining the microscopic invasion of malignant lesions, which is crucial for prognostic prediction and further treatment. Therefore, for the early identification and treatment of different bladder lesions, cystoscopy and bladder biopsies work well together [6]. In the end, prognosis and treatment are greatly influenced by the pathological staging and grading of bladder urothelial malignancies. Therefore, early identification can greatly increase the survival rate [7]. In light of this, a study was conducted to examine the histological characteristics of

urothelial carcinoma, correlate them with clinical characteristics and radiological findings and classify them using the WHO 2016 classification system. Additionally, we wanted to examine the architectural pattern, histopathological variants, muscle invasion, grading, presence of any divergence, such as squamous or glandular differentiation on biopsies and transurethral resection of bladder tumours. We also wanted to compare these characteristics with the results in cases where radical cystectomy was later performed. Special stains and immunohistochemistry were employed in a few instances to help with the diagnosis.

Material and Methods

This study was carried out in a tertiary urban referral hospital in western India during a nine-year period, from January 2016 to December 2024. There were 160 cases included - 127 cases of transurethral resection of bladder tumour (TURBT), 33 biopsies, and 14 cystectomy specimens for bladder cancer obtained from the aforementioned TURBT and biopsy cases. All cases of PUNLMP (papillary urothelial neoplasm of low malignant potential), non-neoplastic bladder lesions, non-urothelial carcinomas, papillomas, and insufficient biopsies were excluded. The patient's record and histopathological forms were used to gather the comprehensive clinical history, which included age, gender, radiological tests, and any noteworthy preoperative or surgical findings. Following the typical procedure for surgical grossing of resected materials, the biopsies, TURBT, and cystectomy specimens that were obtained were preserved in 10% formalin. The College of American Pathologist (CAP) 2017 protocol was followed in the examination of radical cystectomy specimens. Following standard processing, 5 µm-thick paraffin slices were stained with hematoxylin and eosin (H and E) for histological analysis. Immunohistochemistry and special stains were used as needed. The TNM AJCC classification from 2010 and the WHO classification from 2016 were used to analyse the tumours. Histopathological categorization and grading descriptive statistics were examined and displayed as percentages with a 95% confidence range. The Chi-square test of significance was used to determine whether the proportional differences were statistically significant.

Results

The study included 160 cases of bladder urothelial carcinoma, most of which were in the 5^{th} -7^{th} decade range. The mean age was 64 years with a SD of +/- 12.47. There was male preponderance with 80.0% cases in males and male to female ratio of 4:1. The study cases ranged in age from 32 to 85 years with the bulk falling between the 5^{th} and 7^{th} decades, there was a cluster of 50 cases (31.25%) in age group of 56-65 years, followed by 48 cases (30.0%) in 66-75 years and least in 26-35 years being 7 cases (4.35%). The key presenting feature being haematuria was noticed in 80% of the cases followed by dysuria, increased frequency of micturition and passage of clots in varying combinations. Variable features such as exophytic papillary mass (64.3%), solid mass (28.6%) and erythematous plaque (5.1%) were found during cystoscopic examination. 32.9 %of these tumours originated on the bladder lateral wall followed by multifocal tumours 28.6% and 24.3% were on the posterior wall, while the remaining tumours were observed on the anterior wall, trigone and the dome of the bladder. 53.75% cases had tumour sizes of >3.0 cm and 46.25% cases had tumour sizes of <3.0 cm.

The distribution of cases by TURBT and biopsy diagnosis is shown in (Table 1). 56.9% of patients had Infiltrating High Grade Urothelial Carcinoma (Fig 2), with Non Invasive Low Grade Urothelial Carcinoma (Fig 1) accounting for 28.7% of cases. There were 23 noninvasive cases of high grade urothelial carcinoma. All 160 cases had deep muscle biopsies sent for screening, and 34 cases (21.25%) had muscle invasion (Fig 3) and 57 cases (35.6%) had lamina propria invasion. In cases with muscle invasion, the stroma displayed inflammatory (46.4%), desmoplastic (14.3%) and myxoid change (10.7%) as stromal responses. Microscopy revealed lymphovascular emboli in nine cases of invasive high grade urothelial carcinoma.

The distribution of Infiltrating Urothelial Carcinoma variants and differentiation is shown in Table 2. Out of the 91 cases with infiltrating urothelial carcinoma, 71 were pure urothelial carcinoma, 13 had squamous differentiation, 3 had sarcomatoid, and 1 each of the following variants: glandular, neuroendocrine, nested, plasmacytoid, and giant cell (Fig 4). 14 cystectomy specimens (gross: Fig 5,6) were obtained from the cases of infiltrating urothelial carcinoma detected on TURBT and from biopsy were examined and categorized using the TNM classification, which revealed that the majority of cases were in the pT2 (42.86%) and pT3 (35.72%) stages. The grade and differentiation of the cases aligned with the results of the biopsy and TURBT and showed concordance. Within the 14 cystectomy cases, lymphovascular emboli with regional lymph node metastasis was seen in 3 cases and Carcinoma in situ (CIS) in adjacent mucosa was seen in four out of 14 cases on histology. On further clinical follow up, out of 160 cases, 10 cases were repeat TURBT. These all recurrence cases were from previous 23 cases, diagnosed as Noninvasive High Grade Papillary Urothelial Carcinoma. All of these 10

cases showed recurrence with high grade histology with three cases showed muscle invasion. This disease progression was observed after 3 to 4 year of initial diagnosis on clinical follow up. Out of these 10 recurrent cases, 8 were showing multifocal tumour morphology on initial presentation.

Table 1: Distribution of Cases according to diagnosis of Biopsies

Type of Lesion	Frequency	Percentage
Infiltrating Urothelial Carcinoma	91	56.90 %
Non Invasive Papillary Urothelial Carcinoma Low Grade	46	28.7 %
Non Invasive Papillary Urothelial Carcinoma High Grade	23	14.4 %
Total	160	100.00%

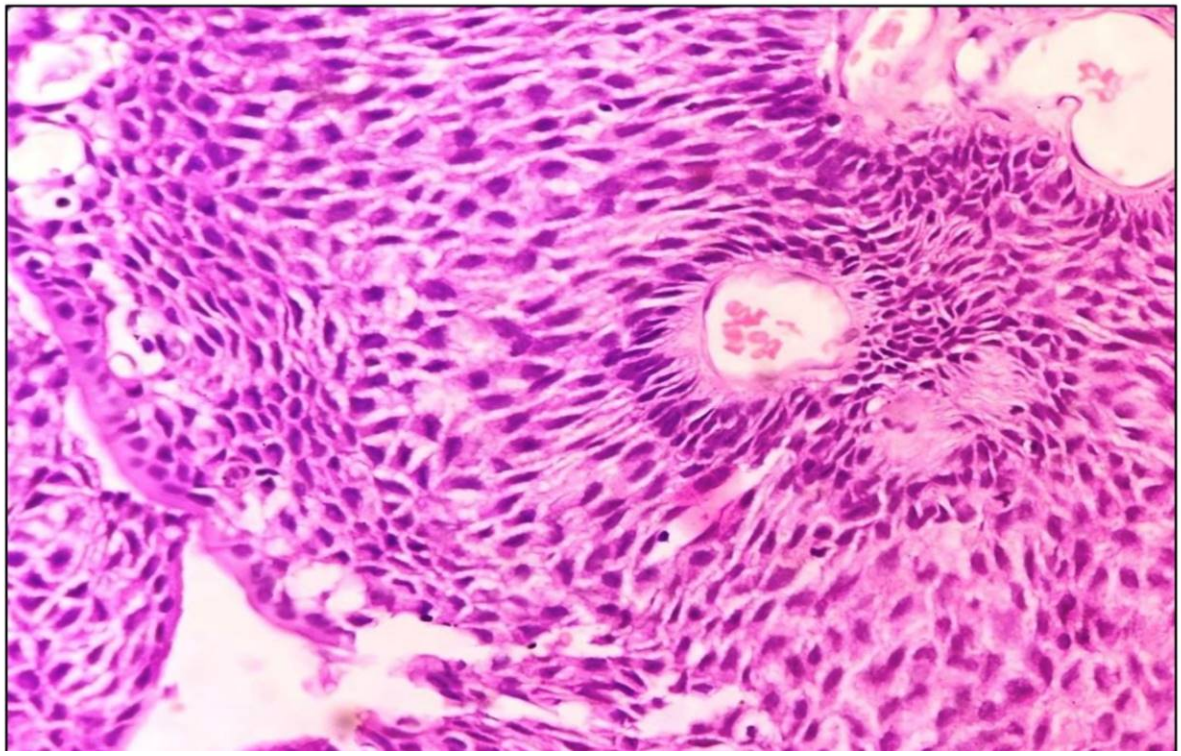

Fig 1: **"LGUC": The tumor shows monotonous population of cells with mild nuclear enlargement but the polarity is maintained as noted in low grade urothelial carcinoma. (H&E 100 X)**

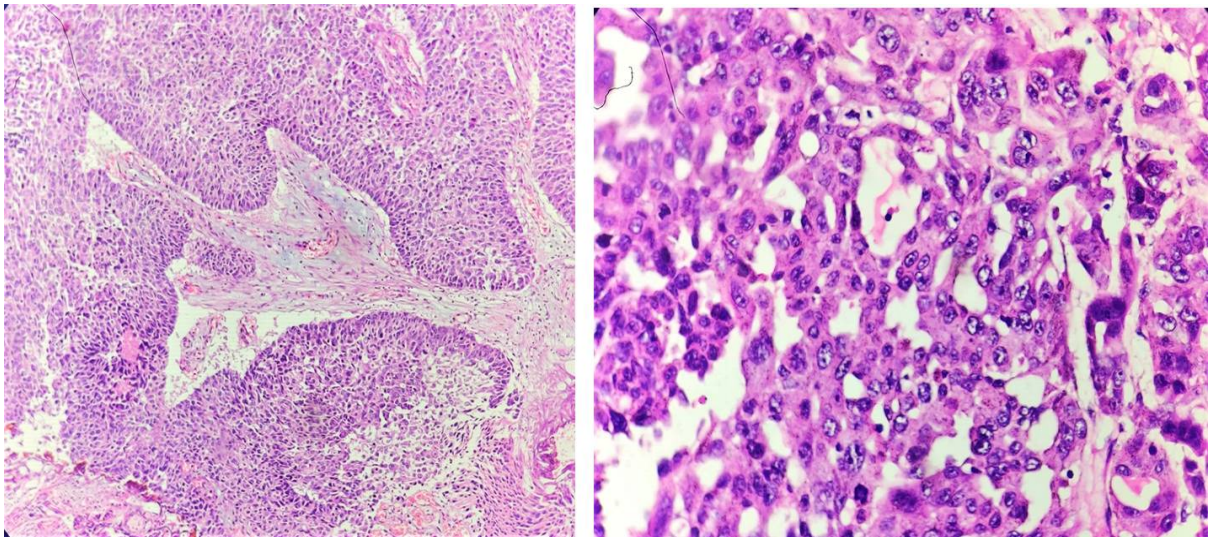

Fig 2: "HGUC": The tumor shows papillary fronds which has significantly disordered architecture and loss of polarity (H&E 100 X) (A). The tumor cell shows enlarged hyperchromatic nuclei with anaplasia, prominent nucleoli and atypical mitotic figures as seen in HGUC (B) (H&E 400 X).

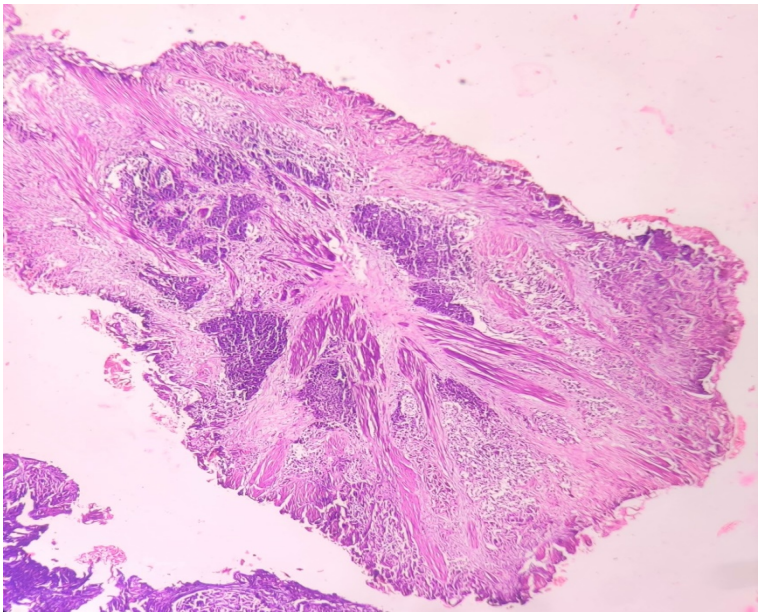

Fig 3: Depicts tumor arranged in nested pattern showing detrusor muscle invasion (H&E 100 X).

Table 2: Distribution of variants and Differentiation of Infiltrating Urothelial Carcinoma

Infiltrating Urothelial Carcinoma	Frequency	Percentage
Pure	71	78.08 %
Squamous Differentiation	13	14.28%
Sarcomatoid	03	2.19%
Glandular Differentiation	01	1.09 %
Nested	01	1.09 %
Neuroendocrine	01	1.09 %
Giant cell	01	1.09 %
Plasmacytoid	01	1.09 %
Total	91	100.00%

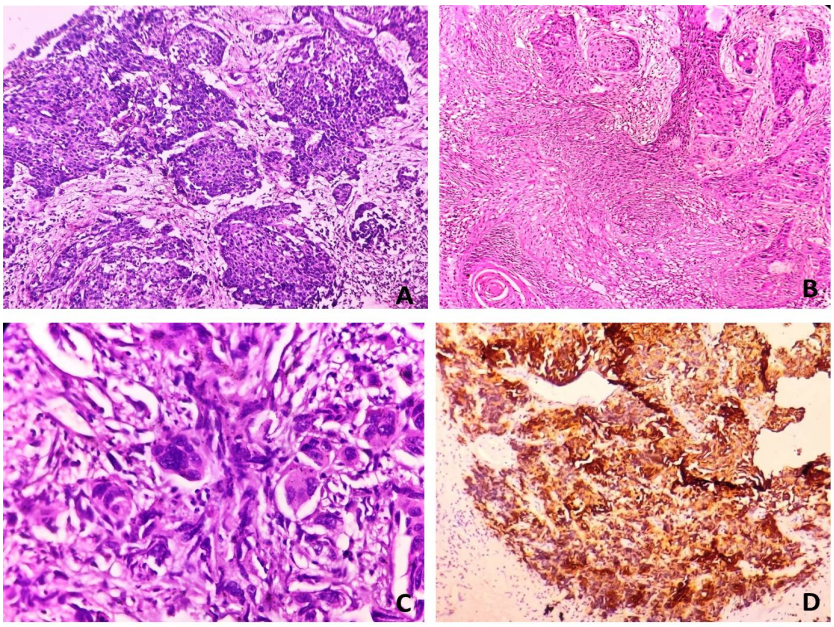

Fig 4 : Histomorphology differentiation : Nested pattern of Urothelial carcinoma-Large nests of tumor cells with irregular borders (A) (H&E 100 X),HGUC with squamous differentiation (B) (H&E 100 X), Giant cell variant of Urothelial carcinoma-Tumor cells are large, bizzare, bi/multinucleated with pleomorphism (C) (H&E 400 X), Neuroendocrine variant of Urothelial carcinoma- small tumor cells with scant cytoplasm, fine stippled chromatin showing Synaptophysin positivity on IHC ining (D)

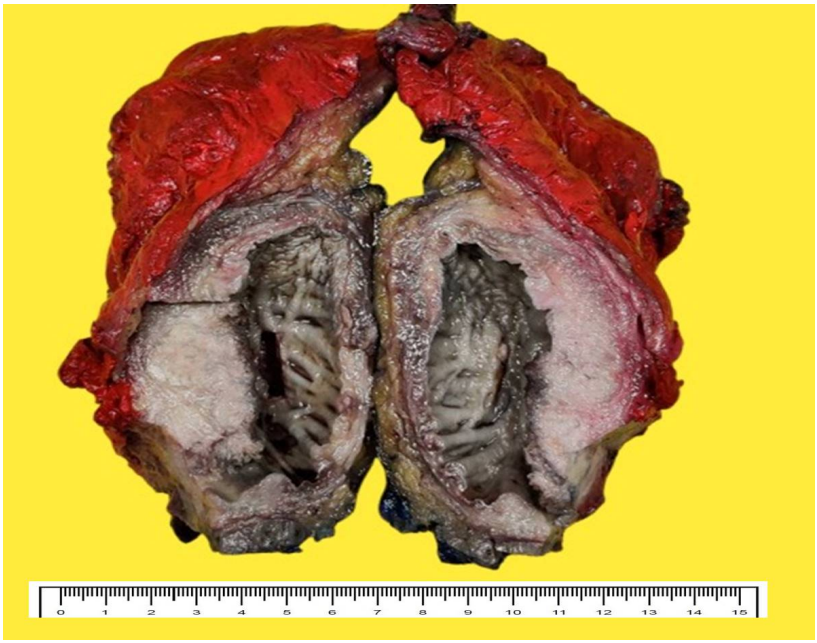

Fig 5: **Cut open Cystectomy specimen showing solid tumour measuring 4x3x2.5 cm arising from lateral wall of Urinary Bladder**

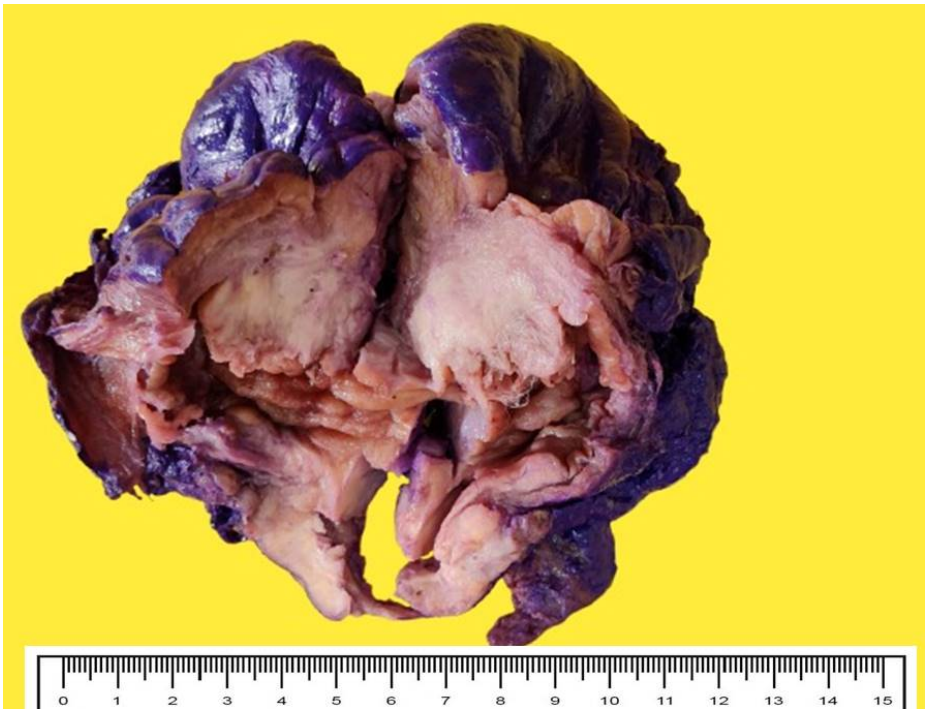

Fig 6: Cut open Cystectomy specimen showing papillary grey white tumour measuring 5.5x4x2 cm arising from posterior wall of Urinary Bladder

Table 3: Distribution of Cases According to the Diagnosis of Biopsies and Comparison with Other Studies

Type Of Lesion	Our Study (N=160)	S Sushmita et al [16] (N=48)	Shruti.H.P et al [17] (N=76)	Bhavana Grandhi M.D et al [18] (N=48)
Infiltrating Urothelial Carcinoma	56.90 %	60.71 %	25.4 %	56.25 %
Non Invasive Papillary Urothelial Carcinoma Low Grade	28.7 %	17.86 %	33.3 %	21.875 %
Non Invasive Papillary Urothelial Carcinoma High Grade	14.4 %	7.14 %	27.4 %	18.75%

Table 4: Comparison of Distribution of Divergent Differentiation of Invasive Urothelial Carcinomas

Infiltrating Urothelial Carcinoma	Our Study (N=91)	Goyal VK et al [2] (N= 89)
Pure	71	82
Squamous Differentiation	13	05
Sarcomatoid	03	-
Glandular Differentiation	01	01
Nested	01	01
Neuroendocrine	01	-
Giant cell	01	-
Plasmacytoid	01	-
Total	91	89

Discussion:

The histological characteristics of urinary bladder tumours are diverse, and approximately 90-95% of all primary bladder tumours are urothelial carcinomas [8]. The study primarily emphasized the significance of the histological analysis in bladder cancer diagnosis. The study comprised 160 cases of bladder urothelial carcinoma (127 TURBT, 33 biopsies) and 14 cystectomy specimens from biopsies and TURBT cases that were diagnosed. These findings were consistent with a research by Laishram et al. [9] and another by Goyal VK et al [2]. Compared to their elder counterparts, younger patients often present with malignancies that are lower grade and stage [10, 11]. Our study had 80% of men contributing the majority resulting in male: female ratio of 4:1 this correlated with a study by Cheng et al [12] (male: female ratio of 3.3:1) and Vaidya et al [13] (male: female ratio of 4.5:1), but these results were found to be slightly lower than studies by Lam et al [14] (5:1). Gross haematuria was the predominant symptom in combination with few other symptoms like dysuria, increased frequency of micturition and lower abdominal pain in varying combinations. Cystoscopy, the primary screening tool allowing the direct visualization of the bladder mucosa illustrated a maximum number of exophytic papillary mass followed by solid mass and erythematous plaque. This finding was similar to the observations made by Goyal VK et al[2] The present study showed alike observations with the incidence of tumours being most common in the lateral wall (32.9%) followed by multifocal (28.6%) with that of Husain N et al [15]study results. Concordance of the present study results with the other studies by S Sushmita et al [16], Shruti.H.P et al [17], and Bhavana Grandhi M.D et al [18] was seen with regards to the percentage of cases in each category of urothelial carcinoma (Table 3). Majority of the cases were pure urothelial carcinomas without any divergent differentiation (71 cases with 78.08%), followed by those with squamous differentiation, then glandular differentiation and a single case each of sarcomatoid, nested, plasmacytoid, neuroendocrine variant and giant cell variant (Table 4). To validate the diagnosis, immunohistochemistry markers synaptophysin and p63 were performed on Neuroendocrine variant, (p63 was negative and synaptophysin positive). According to recent estimates, squamous differentiation is the most prevalent kind of urothelial carcinoma occurring in 16.8% to 22.1% of cases [19]. The chi-square test was used to examine relationships between various clinico-pathological parameters such as tumour size and patient gender. Correlating the histopathological grade and the gender, no significant correlation could be seen ($P = 0.65$). The comparison between tumour size and the grade of tumour, it was found to be significant ($p<0.05$) thus concluding that tumour with size >3cm (86 cases 53.75%) had high grade histology.

When determining the tumours stage and the best course of treatment, deep muscle invasion is crucial. Out of 160, 34 cases (21.25%) in our study demonstrated deep muscle invasion which is consistent with findings from studies by Gupta et al [10] and Laishram et al [9]. It also showed high grade carcinomas had higher tendency to invade the deep muscle than low grade carcinomas. The cystectomy specimen diagnosis aligned with the TURBT and biopsy results. All fourteen of these cases had infiltrating urothelial carcinoma, three of which had squamous differentiation and one had sarcomatoid morphology.

Conclusion

This study underlined the significance of histopathological analysis in the diagnosis and management of individuals presenting with bladder urothelial malignancies. Since haematuria is the most common symptom, people who exhibit it should be examined in order to detect bladder tumours early. Bladder invasive urothelial carcinoma was the most prevalent histopathological type and because it has implications for prognosis and further treatment, it is crucial to include information in the histopathological report regarding the grade, presence of CIS, lamina propria/muscle invasion, differentiation and presence of lymphovascular emboli. The importance of deep muscle biopsy for assessing the muscle invasion was illustrated as it is a valuable

predictor of survival. Statistical analysis in our study showed significant association of tumour size and grade of tumour.

Limitations of our study was that we received only 14 cystectomies specimen of total Invasive urothelial carcinomas reported and cases reported in later part of study requires further follow up for progression and recurrences. Tumour grading and staging are currently the two major factors for recurrence, progression and for determination of treatment options for patients with urothelial bladder carcinomas.

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