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Histopathological Profiles of Neoplastic Urinary Bladder Lesions: A Retrospective Study

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Abstract

Context: Neoplastic urinary bladder lesions are one of the main reasons for morbidity and mortality across the world. Amongst these the urothelial carcinoma is the commonest entity. The objective of this study is to determine the profile of various neoplastic bladder lesions received in a tertiary care hospital at Mumbai within 10 years of period.

Aims & Objectives: To study the prevalence and histopathologic spectrum of neoplastic lesions of urinary bladder. To classify and compare bladder neoplasms by Old WHO 1973 and New 2004 WHO classification .To study the lamina propria invasion.

Material & Methods: A ten years retrospective histopathological study of neoplastic cystoscopic biopsies and radical cystectomy specimens was carried out in Department of Surgical Pathology, at a tertiary care hospital in Mumbai.

Results: Out of total 336 neoplastic cases, majority were Papillary Urothelial Carcinoma (64.3%) followed by Non Papillary invasive urothelial carcinoma (24.4%) and Papillary urothelial neoplasm of low malignant potential (PUNLMP-2.67%). Variants of Non Papillary invasive urothelial carcinoma encountered were: Nested variant (1.49%), Micropapillary variant (0.89%), microcystic variant (0.89%) and Osteoclast variant (0.60%) of invasive carcinoma .Carcinoma *in situ* was encountered in 0.60% of cases. Other carcinomas seen were Adenocarcinoma (0.89%), Squamous cell carcinoma (2.08%) and Round cell tumor (0.30%).

Conclusion: This article highlights the importance of histopathological study in evaluating neoplastic urinary bladder lesions. Majority of the neoplastic lesions were of urothelial origin. Cystoscopic studies and biopsies help in early detection of bladder neoplasms and they form the mainstay of the diagnosis and follow up of bladder neoplasms.

Keywords: Neoplastic, Urinary Bladder, Histopathology, Urot.

Introduction

The urinary bladder is the site of origin of variety of benign and malignant neoplasms. Among the malignant neoplasm, the most common and important vesical epithelial tumor is transitional cell carcinoma. Hence, cystoscopic biopsies are usually done on all the bladder

lesions for definite tissue diagnosis. To provide a rational basis for follow-up and treatment, a generally accepted system of clinicopathological classification is essential. The most widely accepted staging system is the tumor, node, metastasis (TNM) classification.

For histomorphological classification World Health Organisation (WHO) system is generally used. In WHO grading system, a sharp demarcation between different grades cannot be attained thereby causing considerable interobserver variability. Several efforts have been made to improve the existing or to develop a new grading system, which has led to extensive revision since the last century.

The recent one in use is WHO (1998), later revised in 2004, but it has not gained wide acceptance. Hence the comparison of Old WHO (1973) and New WHO (1998) /(2004) classification of urothelial carcinomas after reviewing histological sections is very important to understand the pitfalls in both the systems.

Hence we studied all the bladder lesions received in surgical histopathology section over a span of 10 years to analyse neoplastic lesions of urinary bladder by old and new WHO grading system.

Material and Methods

It is a 10 year retrospective study, in which the histopathology records of patients were screened for collection of data like age, sex, clinical history, type of surgery, gross, microscopic findings and final diagnosis. All details of the patients were used anonymously and identity of the subject was not revealed anywhere in the study. Material used for study was bladder biopsies or surgically resected bladder specimens received in surgical histopathological section. The cystoscopic biopsy specimens were fixed in 10% buffered formalin. The gross examination was done and specimens were embedded in paraffin. The sections were routinely stained with H&E and microscopic examination of the lesions was done. Light microscopy technique was used for diagnosis. Thereafter pathological grading of the bladder lesions was done following WHO (1973) and WHO/ISUP grading of urothelial papilloma.

Quantitative data has been represented in form of frequency and percentage and also using mean, median and interquartile range while qualitative data includes gender, type of malignancies, grading of malignancy, staging variables like age, etc. Association between qualitative variables has been assessed by chi- square test with continuity correction for all 2 X 2 tables and with or without continuity correction in rest and Fischer's Exact test for all 2 X 2 tables where p-value of chi-square test is not valid due to small counts (eg. Association between type of malignancies and gender) . Results have been graphically represented where deemed necessary.

Results

Prevalence of Bladder Lesions

On an average we received 5500-6000 specimens in surgical histopathology section every year. A total number of 53,621 surgical cases were received over a period of 10 years, of which 459 cases (0.86%) were of bladder lesions.

Neoplastic lesions were most predominant. Out of the total 459 bladder lesions studied, 336 cases (73.20%)were neoplastic and 123 cases(26.80%) were non neoplastic. The average numbers of bladder neoplastic lesions received per year were 25-35. Out of the total 336 neoplastic cases, most common cases were seen in the 5th and 6th decade, 38.7% were seen in the 5th decade and 28.57% in the 6th decade. The mean age of presentation was about 58 years. 78.6% of total were males and 21.4% were females. This variation in

the incidence of bladder lesions has been primarily attributed to a number of risk factors including occupational hazards smoking and other such bad habits to which the male population is exposed. The patients presented mostly with symptoms like hematuria (235 cases), dysuria (51 cases) and frequency of micturition (36 cases). Hematuria was the commonest presenting symptom.

According to the old WHO 1973 grading, 157 cases (52.86%) were in grade 2, 131 cases (44.11%) were in grade 3 and remaining 9 cases (3.03%) were in grade 1. In one case grading was not possible due to the crushing artifact**.(Table-1)**

Table: 1 WHO 1973 (Old) Grading

1973 WHO (OLD) CLASSIFICATION	Frequency	Percent
GRADE 1 TCC	9	3.03%
GRADE 2 TCC	157	52.86%
GRADE 3 TCC	131	44.11%
Total	297	100.00%

Legends; According to the old WHO 1973 grading, 157 cases (52.86%) were in grade 2, 131 cases (44.11%) were in grade 3 and remaining 9 cases (3.03%) were in grade 1. In one case grading was not possible due to the crushing artifact.

According to the new WHO/ISUP 2004 grading, 165 cases (55.55%) were High grade, 125 cases (42.09%) were Low grade and remaining 7 cases (2.36%) were PUNLMP (Papillary Neoplasm of Low Malignant Potential). In 1 case grading was not possible due to the crushing artifact. (**Table-2)**

Table: 2 Who/Isup 2004 (New) Grading

2004 WHO/ISUP (NEW) Grade	Frequency	Percent
HIGH GRADE UROTHELIAL CARCINOMA	165	55.55%
LOW GRADE UROTHELIAL CARCINOMA	125	42.09%
PUNLMP	07	2.36%
PAPILLOMA	00	0.00%
TOTAL	297	100.00%

Legends; According to the new WHO/ISUP 2004 grading, 165 cases (55.55%) were High grade, 125 cases (42.09%) were Low grade and remaining 7 cases (2.36%) were PUNLMP.

On comparison of the old WHO grading with the New WHO/ISUP 2004 grading, we arrived at the following observations.

Out of the total 9 cases of Grade 1 TCC ; 7 (77.8%) were categorized into PUNLMP and 2 cases(22.2%) into Low grade Urothelial Carcinoma.

Out of the total 157 cases of Grade 2 TCC ; 122 cases (77.7%) were categorised into Low grade Urothelial Carcinoma and 35 cases (22.3%) into High grade Urothelial Carcinoma.

Out of the total 131 cases of Grade 3 TCC; 130 cases (99.24%) belonged to High grade Urothelial Carcinoma and 1 case (0.76%) to Low grade Urothelial Carcinoma.

On reclassifying the bladder tumors, we found that there were maximum cases in grade 2. The morphology of grade 2 TCC was too broad and had grey zones. 35 cases of grade 2 papillary TCC were categorized into high grade urothelial carcinoma. The morphology of cases of grade 3 transitional cell carcinoma was similar to high grade urothelial carcinoma. Out of 9 cases of

grade 1 transitional cell carcinoma, 7 were categorized into PUNLMP. Hence, there were total 38 cases (12.8%) classified according to the old 1973 WHO classification which were reclassified according to the new 2004 WHO/ISUP consensus classification**. (Table-6)**

Discussion

Lesions in the bladder form a large group having a wide range of histopathological features. The urothelium of bladder has been reported to transform into benign as well as malignant tumors. In a clinicopathological and histological study of the bladder cancer Sathya and Chinnaswamy reported bladder cancer to be the most common genitourinary tract malignancy with 90% of it being represented by urothelial carcinoma.[1] More than 67,000 new cases of bladder cancer are reported to occur in India each year, with more than 13,700 people dying of the disease.[2] The list of bladder tumors is long including both epithelial and mesenchymal types out of which epithelial is the predominant group. On overall basis urinary bladder neoplasms are reported to represent a heterogenous group of tumors of various histopathological subtypes which makes their comparison relatively difficult.[3] Urothelial carcinoma has been reported to account for more than 90% of all primary cancers.[4]

Prevalence

Presently 459 cases of bladder lesions were encountered out of the total 53,621 surgical cases received over a period of 10 years. Thus it gave us a prevalence of 0.86% . However on worldwide bases the prevalence of urinary bladder cancers has been reported to account for approximately 3.2% of all the cancers.[5] According to Indian Cancer Registry urinary bladder malignancy accounts for 3.9% of all the cancers.[6] In comparison much less prevalence (0.86%) of bladder lesions has been documented presently.

Out of the total 336 neoplastic cases studied, Transitional cell carcinoma was diagnosed in 324 (96.4%) cases. As has been observed presently, it is reported to be the most common (80.72%) bladder neoplasm by Vaidya et al.[7] Out of these 64.29% cases were of papillary urothelial carcinomas while 22.32% cases were of non papillary urothelial carcinoma. In a study, Schned et al. reported 82.6% cases of papillary urothelial carcinomas and 10.1% cases of non papillary urothelial carcinomas.[8] Neoplastic urinary bladder lesions are reported to be responsible for significant morbidity and mortality throughout the world .[9] (**Table-3**)

Table 3: Neoplastic Lesions of The Bladder

S.No.	Histological Type	Frequency	%Age
1	Punlmp	09	2.67%
2	Papillary Urothelial Carcinoma	216	64.29 %
3	Non Papillary Invasive Urothelial Carcinoma	82	24.40 %
4	Carcinoma In Situ	02	0.60%
5	*Special Variants*		
	Micropapillary Variant	03	0.89%
	Nested Variant	05	1.49%
	Osteoclast Variant	02	0.60%
	Microcystic Variant	03	0.89%
	Sarcomatoid Carcinoma	01	0.30%
6	Squamous Cell Carcinoma	07	2.08%
7.	Adenocarcinoma	03	0.89%

8.	Round Cell Tumor	01	0.30%
9.	Tiny Tumor (No Opinion)	02	0.60%
	Total	336	100%

Legends; In our study, out of the total 336 cases, majority were of Papillary urothelial carcinoma (64.29%).

Our study comprises of 0.89% cases of adenocarcinoma. In a study by Vaidya et al 2% of bladder cancers have been reported to account for adenocarcinomas .[7] Most of the studies, have shown that adenocarcinoma is a rare variant of urinary bladder carcinoma.[10]

Presently, Squamous cell carcinoma was observed in 2.08% of the cases. According to a study conducted by Eble, et al., reported decline in the incidence of squamous cell carcinoma as compared to an increase in the incidence of urothelial carcinoma .[11]

Site of Neoplastic Lesions

Presently, malignancy was seen predominantly on the lateral wall (36.76%), posterior wall (23.53%), anterior wall (8.83%), dome (4.41%) and all over (23.53%). Stephenson et al., out of 914 bladder cancer cases reported that lateral wall accounted for 37.1% cases followed by posterior wall (17.9% cases). Comparatively lower proportion of cases were reported on the anterior wall (3.8% cases), dome (7.7% cases) and all over (12.6% cases) [12] Similarly, Srikoustubha et al. documented lateral wall as the commonest affected area (64%) followed by the posterior wall (28%) and the least common sites being the dome and ureteric orifice (4% each). The presently achieved results are in conformity to a large extent with the observations of Srikoustubha at al.[13].

Gross Specimen (Figure-1 & 2)

Cystoscopy and biopsy were the main diagnostic measures employed. Most of the specimens received were TURBT, biopsies and radical cystectomies.

A total of 51 radical cystectomy specimens were grossed. There was evidence of papillary, polypoidal and ulceroinfiltrative growths infiltrating the muscle wall and adjacent structures like prostate, seminal vesicles, etc.

Figure 1: Specimen of Bladder Showing An Exophytic Papillary Polypoidal Growth On The Wall

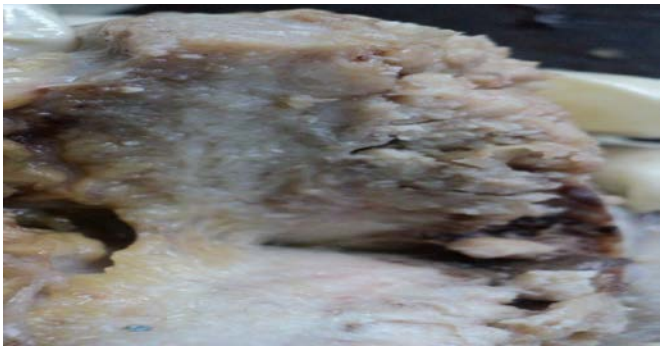

Figure 2: Cut Section Showing the Depth of the Growth With Growth Infiltrating The Muscle Wall

Papillary Urothelial Neoplasm Of Low Malignant Potential (N=7) (Figure-3 & 4)

Only 2.36% of the neoplastic cases represented this category in our study. Occasionally 7% to 10% of the lesions were reported to manifest as urothelial carcinoma, and in such a case close follow-up of the patient is required [14].

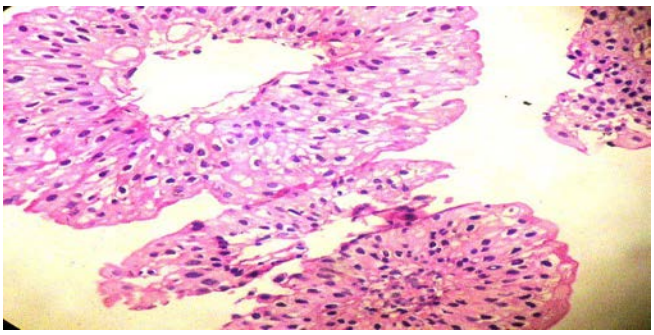

Figure 3: PUNLMP-section shows increased cell layers but cytologically the cells are arranged in orderly fashion and lack atypia . Umbrella cell layer seen. (H&E X100)

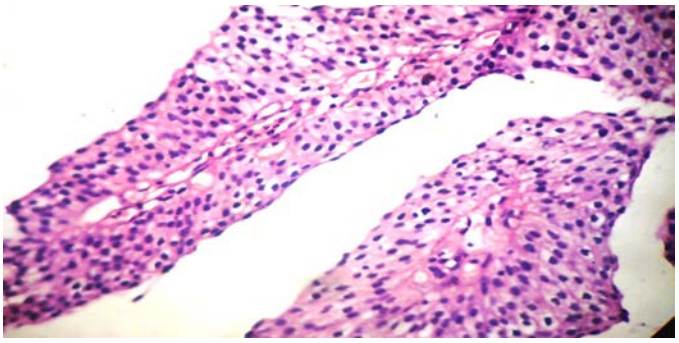

Figure 4: 1973 WhO , Papillary Grade 1 Tcc - 2004 Who ; Punlmp (H & E X 100)

Low-Grade Papillary Urothelial Carcinoma (N=125) (Figure-5, 6 & 7)

Low-grade carcinomas exhibit an overall orderly appearance but have variability in architecture or cytologic features. A high percentage of 42.09% of the neoplastic cases were categorised under this grade in this study.

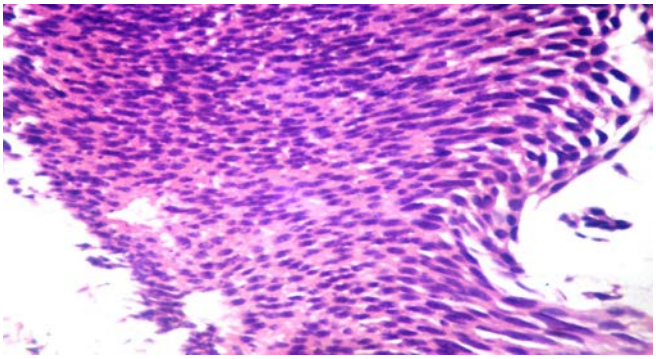

Figure 5: 1973 WHO , Papillary Grade 2 TCC- 2004 WHO; LOW GRADE Papillary Urothelial Carcinoma - section shows mild pleomorphic tumor cells not oriented in an orderly manner and showing mild cytologic atypia. (H & E X 100)

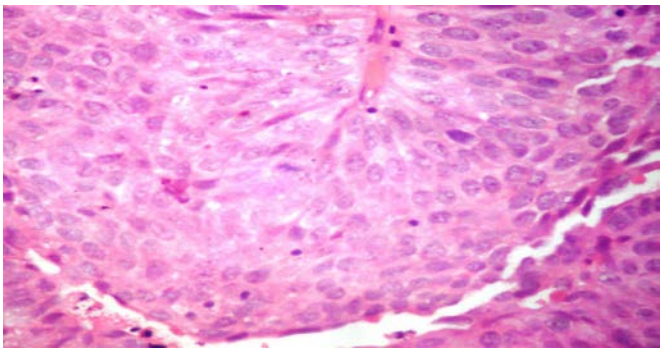

Figure 6: 1973 WHO ; Papillary Grade 2 TCC – 2004 WHO; Low Grade Papillary Urothelial Carcinoma (H & E X 400)

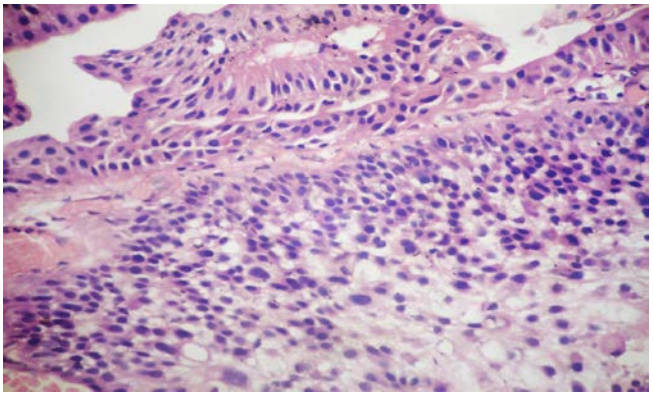

Figure 7: Papillary TCC showing Grade 2 Transitioning Into Grade 3 (H & E X 100)

HIGH-GRADE PAPILLARY UROTHELIAL CARCINOMA (n=165) (FIGURE-8, 9 & 10)

High-grade carcinomas are characterized by a disorderly appearance due to marked architectural and cytologic abnormalities. In our study, according to WHO(2004)/ISUP Grading high grade urothelial carcinoma cases were 55.55%.

Gupta et al. reported 44.7% of urothelial carcinoma cases exhibiting a low grade malignancy while 55.3% of the cases showing high grade malignancy [3]. Cheng et al. out of 105 TURBT specimens reported 12.3% showing low grade and 87.7% high grade carcinoma.[15]

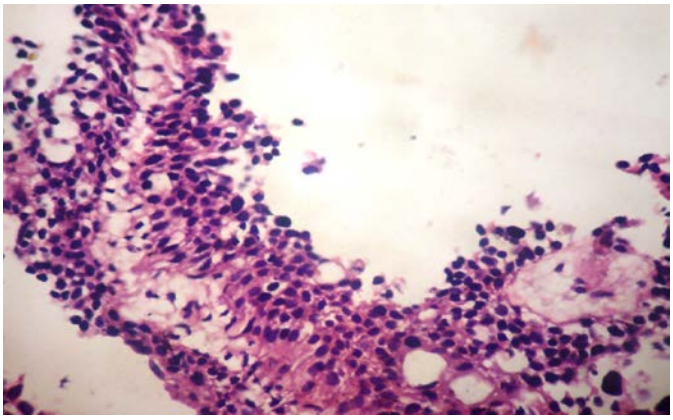

Figure 8: 1973 WHO, Papillary Grade 2 TCC – 2004 WHO: High Grade Papillary Urothelial Carcinoma (H & E X 100)

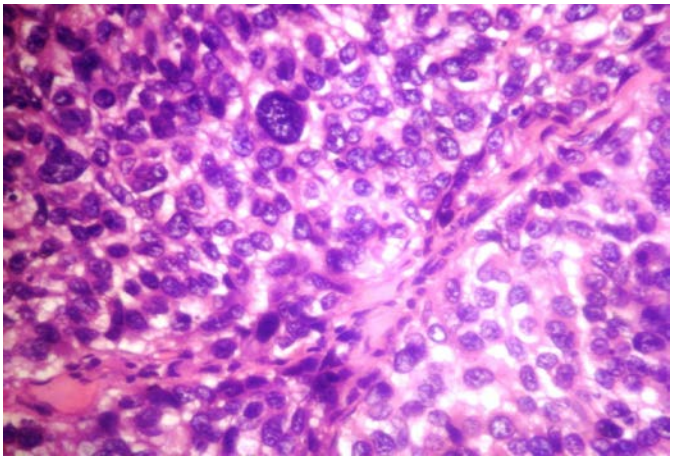

Figure 9: 1973 WHO; Papillary Grade 3 TCC - 2004 WHO; High Grade Papillary Urothelial Carcinoma (H & E X 400)

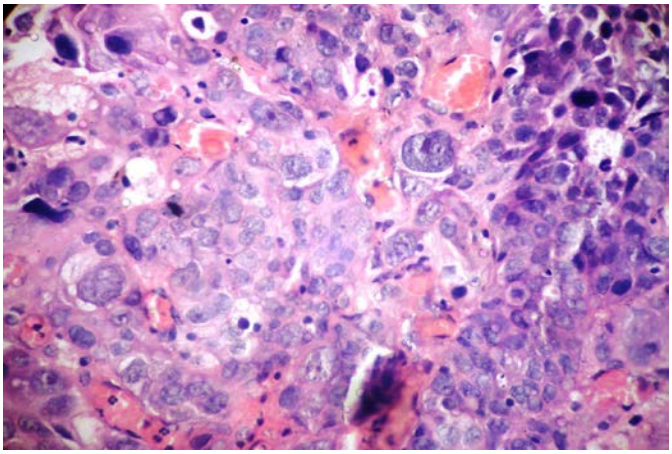

Figure 10: Invasive High Grade Urothelial carcinoma Of Bladder (H & E X 400) LAMINA PROPRIA INVASION (n=164) (FIGURE-11, 12, 13 & 14)

Out of the 336 neoplastic cases examined, lamina propria invasion was seen in 164 (48.8%) cases out of which 54 cases showed desmoplasia, 95 cases showed inflammation and 15 cases showed retraction clefts. The clue to identify lamina propria invasion is reported to be the presence of paradoxical differentiation, in which the invasive tumor cells are reported to acquire abundant eosinophilic cytoplasm.[16]

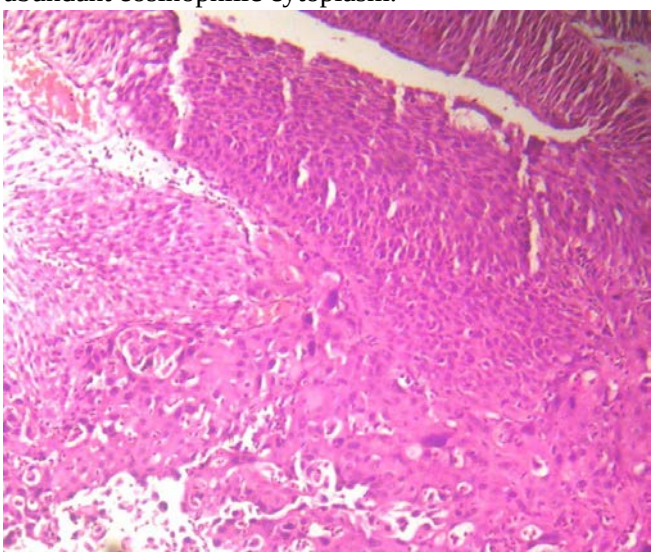

Figure 11: Papillary Urothelial Carcinoma Showing Lamina Propria Invasion (H & E X 100)

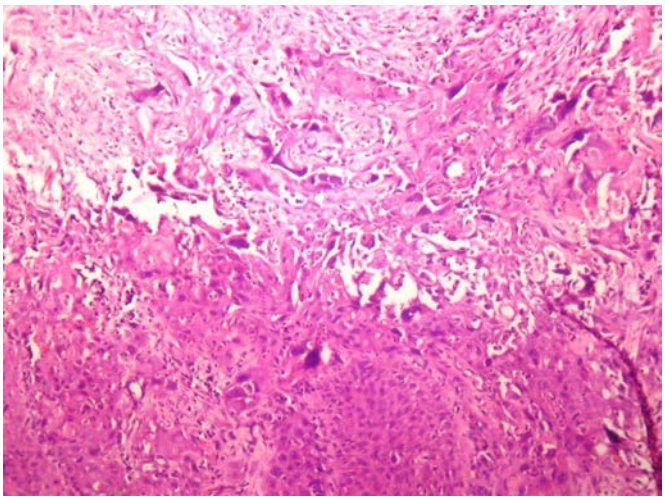

Figure 12: Grade 2 Papillary TCC With Lamina Propria invasion Showing Retraction Around The Tumor Cells.(H & E X 100)

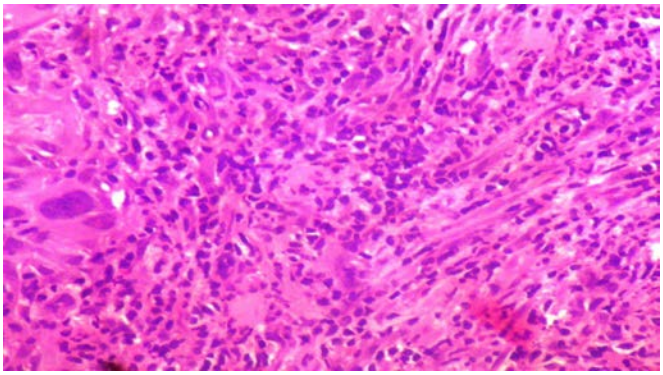

Figure 13: Papillary High Grade Urothelial Carcinoma With Lamina Propria Invasion. (H & E X 400)

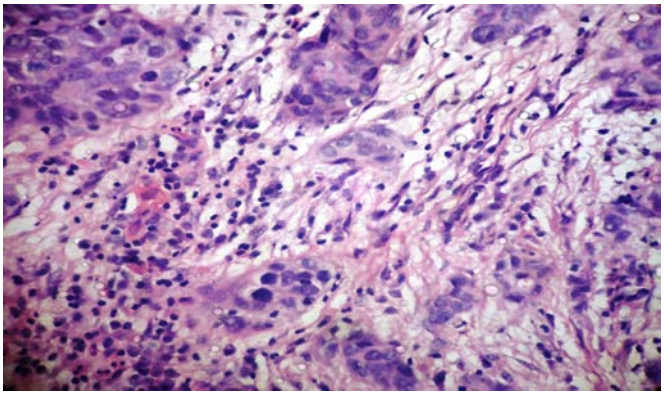

Figure 14: Lamina Propria Showing Invasion By Tumor Cells Surrounded By Lymphocytes And Desmoplasia.(H & E X 400)

Muscle Invasion (n=82) (FIGURE-15)

In our study, out of total 336 cases studied, muscle invasion was seen in 82 cases (24.4%). The results of the present observation is in consonance with the observation made by Gupta et al. who also reported 26% muscle invasion in urothelial carcinoma cases[3]

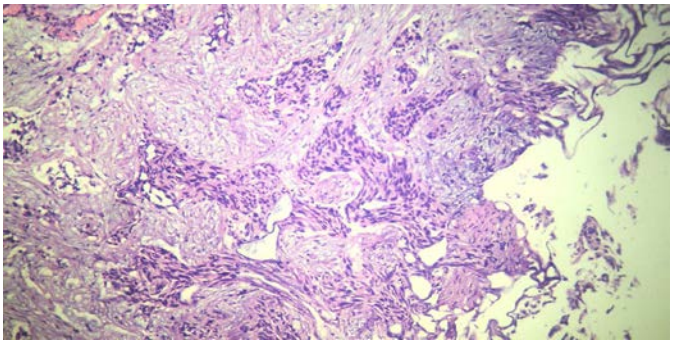

Figure 15: Urothelial Carcinoma With Muscularis Propria Invasion (H & E X 100)

Pathological Staging (Table 4 & 5)

Tumor grading and staging are the two major factors reported to be responsible for recurrence, progression and for determination of treatment protocol for bladder cancer patients. In our study, majority of the cases were of T2b stage (39.22%) followed by T1 stage (13.73%), Ta stage (11.76%) and T4a stage and T2a stage each (9.80%). In a study by Cheng et al., Pathologic staging in TURBT specimens with bladder carcinoma was reported in which14.3% (15 cases) cases were with Ta carcinoma,52.4% (55 cases) were with T1 carcinoma while 33.3% (35 cases) were with T2 carcinoma [15].

Table 4: Ajcc Cancer Staging For Bladder Cancer Cystectomies

AJCC Cancer Stage	Frequency	%Age
Tx-primary tumor cannot be assessed	0	0%
T0-no evidence of primary tumor	0	0%
Ta-noninvasive papillary carcinoma	6	11.76%
Tis-carcinoma-in-situ	0	0%
T1-lamina propria invasion	7	13.73%
T2a-superficial muscularis propria invasion	5	9.80%
T2b-deep muscularis propria invasion	20	39.22%
T3a-microscopic perivesical invasion	4	7.85%
T3b-macroscopic perivesical invasion	3	5.88%
T4a-invades prostate, uterus, vagina	6	11.76%
T4b-invades pelvic wall, abdominal wall	0	0.00%
Total Radical Cystectomies	51	100.00%

Table 5: TNM Staging For Bladder Tumors (Cystectomies)

Stage	No of Cases
0	6
I	7
II	25
III	7
IV	6
Total	51

Legends; Majority 39.22 % of the cases were in T2b stage, 13.73% of the cases were in T1 stage, 11.76% of cases were in Ta and T4a stage each and 9.80% of cases were in T2a stage

Comparison Of 1973 Who To 2004 WHO/ISUP Systems (Table 6)

Both the 1973 WHO system and the 2004 WHO/ISUP system divide papillary urothelial tumors into four categories. There is no one to one translation between the two classification systems, except for the tumors at the extremes of grades in 1973 WHO classification. In our study, 1973 WHO grade 1 carcinoma showing no cytologic atypia were reclassified as PUNLMP. Other 1973 WHO grade 1 tumors with definite yet slight cytological atypia were reassigned to low grade in 2004 WHO/ISUP classification.

Table 6: 1973 WHO Old Classification * 2004 Who/Isup Grade Crosstabulation

	1973 Who Old Classification * 2004 WHO/ISUP Grade Crosstabulation					
			2004 WHO/ISUP (New) Grade			Total
1973 Who (Old) Classification	G 1 TCC		High Grade	Low Grade	Punlmp	
		Count	0	2	7	9
		% Within Old Class	0.0%	22.2%	77.8%	100.0%
		% Within WHO/ISUP Grade	0.0%	1.6%	100.0%	3.0%
	G 2 TCC	Count	35	122	0	157
		% Within Old Class	22.3%	77.7%	0.0%	100.0%
		% Within WHO/ISUP Grade	21.2%	97.6%	0.0%	53.0%
	G 3 TCC	Count	130	1	0	131
		% Within Old Class	99.24%	0.76%	0.0%	100.0%
Total		% Within WHO/ISUP Grade	78.8%	0.8%	0.0%	42.9%
		Count	165	125	7	297
		% Within Old Class	55.5%	42.1%	2.4%	100.0%
		% Within WHO/ISUP Grade	100.0%	100.0%	100.0%	100.0%

Legends; out of the total 9 cases of grade 1 tcc ; 7(77.8%) were categorized into punlmp and 2 cases(22.2%) into low grade urothelial carcinoma. Out of the total 157 cases of grade 2 tcc ; 122 cases (77.7%) were categorised into low grade urothelial carcinoma and 35 cases (22.3%) into high grade urothelial carcinoma.out of the total 131 cases of grade 3 tcc; 130 cases (99.24%) belonged to high grade urothelial carcinoma and 1 case (0.76%) to low grade urothelial carcinoma.

Squamous Cell Carcinoma (n=7) (FIGURE-16)

Squamous cell carcinomas are reported to constitute 2% - 7% of urothelial cancers except in the Middle East where, as a consequence of the endemic nature of schistosomiasis, they are the most common form of cancer.[17] A recent study by Rogers et al. suggests that, squamous cell carcinomas of urothelial origin have better survival than do other unusual morphologic types such as adenocarcinoma .[18] In the present study, 7 cases out of the total 336 neoplastic cases were diagnosed as squamous cell carcinoma.

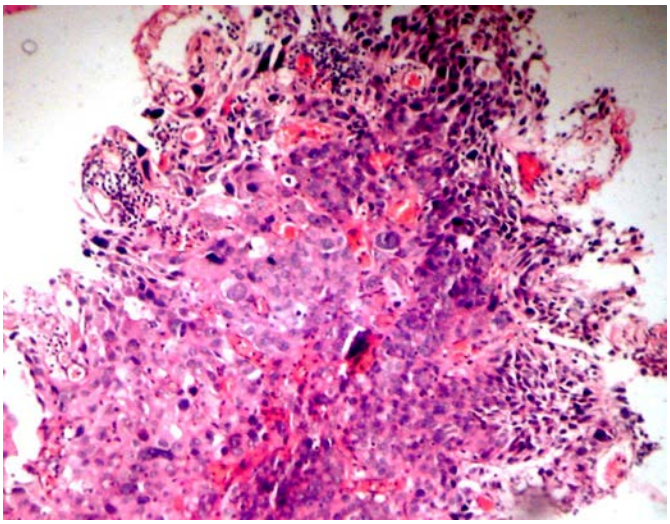

Figure 16: Invasive Squamous Cell Carcinoma of Urinary Bladder (H & E X 100)

Adenocarcinoma (n=3) (FIGURE-17)

They constitute up to 90% of carcinomas associated with bladder extrophy. In our study 3 cases of adenocarcinoma were reported forming 0.89% of the neoplastic lesions. Most adenocarcinomas are reported to have infiltrated deeply at the time of initial diagnosis, which most likely accounts for their poor prognosis. Stage for stage, they are reported to have survival similar to TCC .[19]

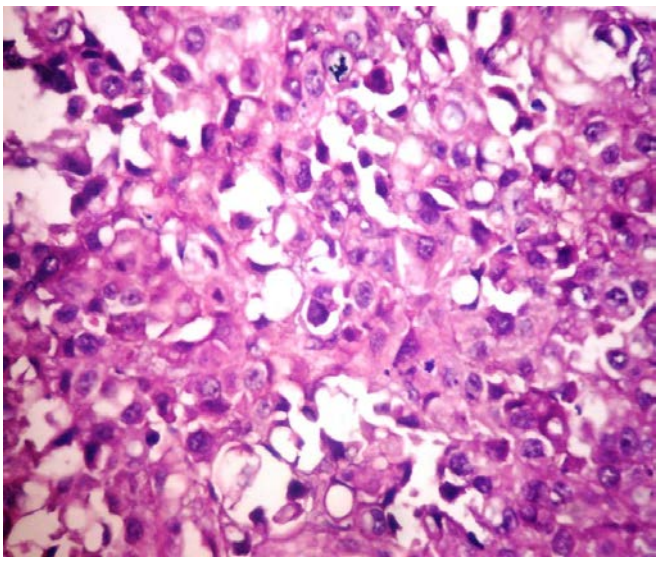

Figure 17: Adenocarcinoma Of Bladder- section shows tumor composed of glandular epithelium with signet cells (H & E X 400).

Other Variants Of Urothelial Carcinoma

There were some other variants of urothelial carcinoma including Sarcomatoid Carcinoma (n==1), Micropapillary Carcinoma (n=3) and Nested Variant of Urothelial Carcinoma (n=5), some cases of which were encountered during the present study.

Long back McDonald et al. documented high grade transitional cell carcinoma with atypical spindle cells which was later on described as ' Sarcomatoid Carcinoma' . In the present study, only 1 case of this variant was encountered. The pattern of cells in these cases have been reported to resemble leiomyosarcoma which is a storiform pattern reminiscent of that seen in malignant fibrous histiocytoma.[20]

Shah VB et al reported a case of Micropapillary Carcinoma of urinary bladder from India in 2008.[21] In the present study, 3 cases of micropapillary carcinoma were encountered forming 0.89% of the neoplastic lesions (FIGURE-18 & 19). Several authors have described a group of urothelial carcinomas that contained a micropapillary component[22].

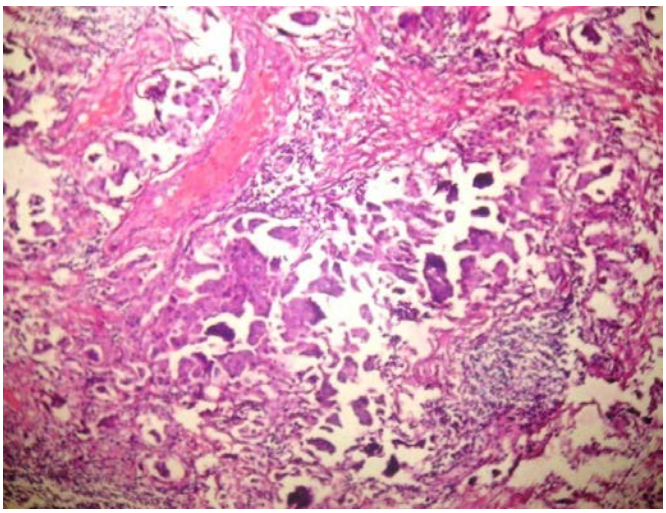

Figure 18: Micropapillary Carcinoma Of Bladder- numerous small cellular papillae & nests (H&E X 100)

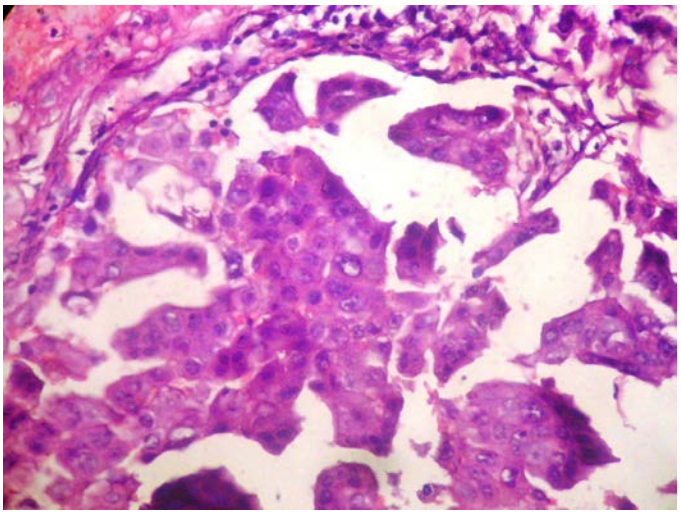

Figure 19: Micropapillary Carcinoma Of Bladder- (H&E X 400).

Nested Variant of Urothelial Carcinoma was first reported by Stern which was added to the WHO classification in 2004.[23] The large nested variant of urothelial carcinoma is reported to be a variant of urothelial carcinoma with a "pseudo-benign" appearance .[24] In the present study total 5 cases of nested variant of urothelial carcinoma were encountered forming 1.49% of the neoplastic lesions **(Figure-20)**.

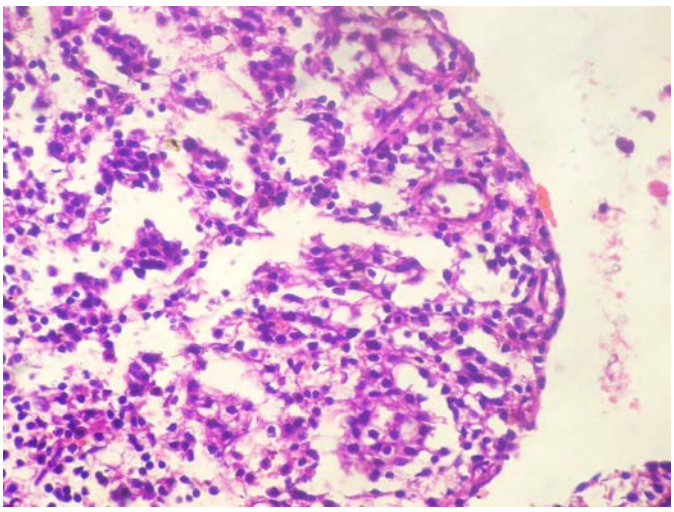

Figure 20: Nested Variant Of Invasive Carcinoma- section showing irregular and confluent nests of tumor cells infiltrating the lamina propria. - (H & E X 100)

Outcome of Urothelial Neoplasms

In our study, out of 336 patients 47 developed recurrence. Among these, 6 of 336 cases had recurrence and were diagnosed as Low grade urothelial carcinoma according to the 2004 WHO/ISUP classification and 41 of 336 cases recurred and diagnosed as High grade urothelial carcinoma. As many as 36 of 41 patients with recurrent High grade urothelial carcinoma also developed muscle invasive urothelial carcinoma. All the 48 patients with recurrence underwent radical cystectomy.

In the literature it is documented that PUNLMP has a more favourable outcome than Low grade papillary urothelial carcinomas. Recurrence rates of PUNLMP are reported to be between 17% - 62% which are significantly lower than those of Low grade carcinomas in most of the available comparative studies. In patients with Low grade papillary urothelial carcinoma tumor recurrence have been shown to occur in 34 - 77 % of the cases. The recurrence rate for non invasive high grade papillary urothelial carcinoma was reported to range from 43 - 74% [25]

Conclusion

Keeping in mind the aggressive management of High grade urothelial carcinoma, especially in residual disease or recurrence, grading is a paramount parameter for prognostication and guidance of therapy in urothelial neoplasm. Based upon the present study we can safely say that there are definite potential advantages of the current WHO/ISUP consensus classification system of urothelial neoplasms.

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