



Original Research Article

Clinicopathological study of urothelial neoplasms based on WHO Classification & its utility in patient management

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Abstract

Introduction: Outcome of patients with urothelial carcinoma is largely dependent on histopathological type & grade of tumor. WHO has proposed classification for diagnosing & grading papillary urothelial neoplasms in an attempt to more precisely predict progression of disease. Present study was undertaken to diagnose & classify urothelial neoplasms based on WHO classification 2022.

Results: The study included histopathological evaluation of urothelial neoplasm of bladder and was carried out in the department of pathology for 3 years from 2018 - 2020 which included 30 cases. Commonest age group was 61 - 70 years with a mean age of 62 years. Male preponderance was observed. Commonest clinical presentation was frequency of micturition 29 cases (96.6%) followed by hematuria in 18 cases (60%) and painful micturition in 16 cases (53.3%).

Histopathological diagnosis included low grade urothelial carcinoma 17 cases (56.6%), high grade urothelial carcinoma 7 cases (23.3%), muscle invasive urothelial carcinoma of high grade 3 cases (10.0%), PUNLMP 2 cases (6.6%) & squamous cell carcinoma with invasion in 1 case (3.3%). Divergent differentiation was seen in 2 cases in the form of squamous cell carcinoma (6.6%).

Conclusion: Clinicopathological profiling along with histopathological grading is very important for determining the prognosis in urothelial carcinoma of bladder.

Keywords: Urothelial neoplasms, Histopathological study, Clinicopathological correlation, WHO classification.

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1. Introduction

Urothelial carcinoma of the bladder is the most common carcinoma in the US. It is a heterogenous disease having variable natural history.¹ Overall incidence of bladder carcinoma has been increased by 10% since last 30 years.² Histopathological examination plays an important role in the outcome of the patients. Achieving accurate histopathological grading remains a crucial step in the management of urothelial carcinoma because histopathological classification & grading is of paramount factor for prognostification & guidance of therapy in these group of neoplasms.³ The current study of urothelial carcinomas is undertaken to diagnose cases of urothelial carcinoma on the basis of WHO classification of urinary

system with clinico- pathological correlation within a period of 3 years from 2018 - 2020.

2. Materials and Methods

The present study was hospital based cross sectional study and included all the cases of urothelial neoplasms diagnosed with transurethral resection of bladder tumors (TURBT) or cystoscopic biopsy from January 2018 to December 2020.

Inclusion Criteria was all the cases diagnosed as urothelial neoplasm in TURBT specimens or cystoscopic biopsy. Ethical clearance was obtained from the institutional ethical clearance committee before starting the study. Urothelial neoplasms of bladder were identified in 30 patients who met the inclusion criteria during histopathological

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examination, clinical data was obtained from the patient medical records. Specimen were grossed and fixed in 10% formalin for 12 hours. Standard protocol was followed for surgical grossing of specimens. Diagnosis of urothelial neoplasm was done on the basis of WHO classification of bladder tumors with clinicopathological correlation.

3. Results

The analysis of data from 2018 to 2020 revealed 30 patients diagnosed as urothelial neoplasms. This sample comprised of 28 male (93.3%) & 2 female patients (6.6%), M: F ratio being 14:1. **Table 1**

Table 1: Demographic data of patients with urothelial neoplasms.

Parameter	Number of cases (n=30)
Sex	
• Male	28 (93.3%)
• Female	02 (6.6%)
Age	
41-50 years	04 (13.3%)
51-60 years	05 (16.6%)
61-70 years	14 (46.6%)
71-80 years	07 (23.3%)

Commonest age group was 61-70 years with mean age of 62 years.

The most widely used intervention was TURBT used in 28 cases (93.3%) all of these cases were urothelial carcinoma. Cystoscopic biopsy was done in 2 cases (6.6%) which turned out papillary urothelial neoplasm of low malignant potential (PUNLMP). Commonest clinical presentation was frequency of micturition in 29 cases (96.6%) followed by hematuria in 18 cases (60%) & painful micturition in 16 cases (53.3%).

The tumor was arising from posterior wall of bladder in 16 cases (53.3%), lateral wall in 13 cases (43.3%) & trigone in 1 case (3.3%). All lesions were papillary. These cases were diagnosed on the basis of WHO classification of bladder neoplasms. Amongst these, 28 cases were of urothelial carcinoma & 2 cases were of PUNLUMP.

Table 2: Histopathological diagnosis of urothelial neoplasms.

Histopathological diagnosis	N=30	Percentage
PUNLMP	02	6.6%
Non-invasive papillary urothelial carcinoma		
• Low grade	17	56.6%
• High grade	07	23.3%
Invasive urothelial carcinoma	03	10%
Pure urothelial squamous cell carcinoma		
• High grade with invasion	01	3.3%



Figure 1: TURBT specimen showing grey white tumor tissue in fragments.

Low Grade Urothelial Carcinoma (LGUC) revealed mild loss of nuclear polarity & mild variation in nuclear size while High Grade Urothelial Carcinoma (HGUC) cases showed marked architectural and cytological atypia, loss of polarity, irregular pleomorphic nucleoli & high mitoses (**Figure 2a,b**)

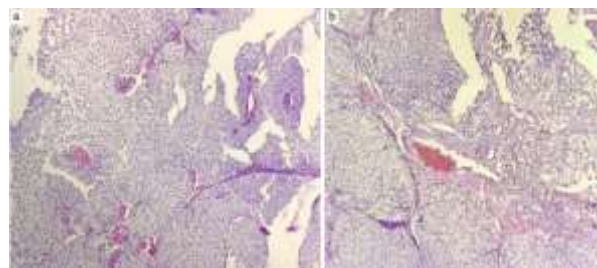


Figure 2: a,b: Microscopy of LGUC with papillary configuration and minimal nuclear atypia (100x H and E)

Tumor necrosis was seen in all three cases of invasive urothelial carcinoma & one case of high grade non-invasive urothelial carcinoma.

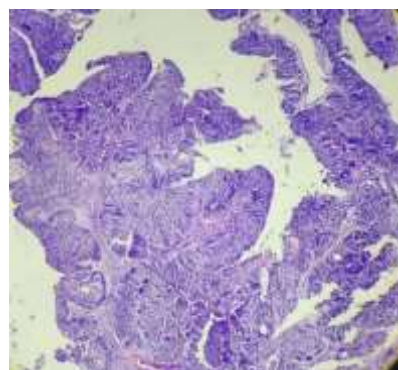


Figure 3: Microscopy of HGUC showing marked nuclear atypia (100x H and E)

Dense stromal inflammatory reaction was noted in all three cases of invasive urothelial carcinoma (**Figure 3**). All high grade invasive urothelial carcinoma revealed more than 5% high grade component (**Figure 4a,b**).

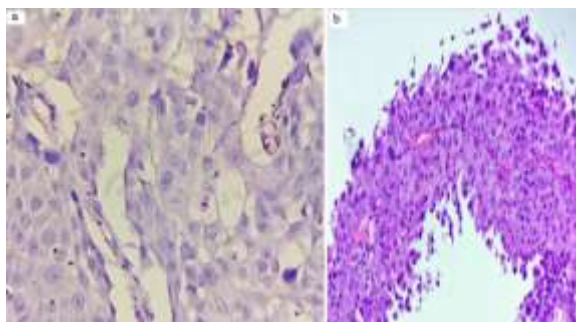


Figure 4: a,b: Microscopy of HGUC – marked nuclear atypia and mitotic figures (400x and 100x H and E).

Divergent differentiation of squamous cell component was admixed with invasive high grade urothelial carcinoma in 2 cases (6.6%). Squamous component was in the form of keratin pearls & highly atypical squamous cells (**Figure 5a,b**).

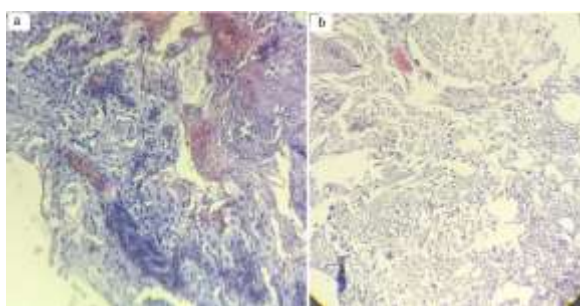


Figure 5: a,b: Urothelial carcinoma with squamous differentiation (100 x, H and E)

There was a single case of pure urothelial squamous cell carcinoma of high grade which revealed keratin pearls and highly atypical squamous cells (**Figure 6a,b**).

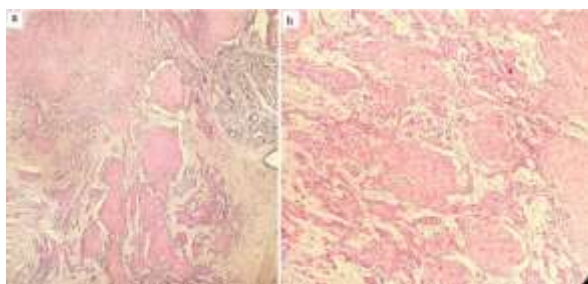


Figure 6: a,b: Pure urothelial squamous cell carcinoma (100x and 400x H and E)

4. Discussion

In this hospital based cross sectional study 30 cases of urothelial neoplasm were diagnosed & graded on the basis of WHO classification of bladder tumors & their clinicopathological profile was assessed.

Male preponderance was seen in our study, M:F ratio being 14:1. Similar observation was noted by other studies.^{4,5} This discussion could be explained by tobacco use &

smoking which is a significant risk factor in male patients. Also hormonal biology is different in two genders.

Commonest age incidence was found in the late age i.e. 61-70 years. A study of cases in New York observed highest incidence in the same age group. Another study by Gree Dalton Crossfield in Chicago revealed that commonest age for invasive urothelial carcinoma was 70 years.^{6,7,8}

Important risk factors for bladder cancer are smoking, schistosomiasis infection, occupational exposure to chemicals like arsenic, aniline dye, phenacetin as analgesic. *Schistosoma haematobium* ova infiltrate the bladder wall leading to chronic inflammation, squamous metaplasia, dysplasia & further progression to squamous cell carcinoma of urinary bladder.⁹ Our study also revealed a case of pure squamous cell urothelial carcinoma.

Urothelial carcinoma can arise anywhere in the bladder. In a series of 1000 cases, commonest location was lateral wall followed by posterior wall, trigone, neck, ureteric orifices, dome and anterior wall of bladder.¹⁰ In our study as well study by Ranu Biswas et al. posterior wall was the commonest location followed by lateral wall.

WHO has replaced the term transitional cell carcinoma with urothelial carcinoma.

WHO has classified bladder cancers based on differentiation as low grade & high grade urothelial carcinoma. This distinction has implications related to risk stratification & further treatment strategies. Also low grade and high grade urothelial carcinomas have different genetic alterations.¹¹ Low grade tumors have favorable progress. 15%-25% of invasive urothelial carcinoma cases show morphological variations.^{3,12} This can be seen as divergent differentiation such as squamous, glandular, trophoblastic or small cell/ high grade neuroendocrine differentiation in pure form or in combination.^{13,14,15} WHO has recommended to comment on percentage of divergent differentiation for diagnosis of high grade urothelial carcinoma. Percentage of high grade component must be 5% or more of the tumor, also with less than five percent high grade component this tumor should be reported as low grade urothelial carcinoma with less than five percent high grade component. Different studies have revealed that urothelial carcinoma account for 90-95% of bladder cancers, Adenocarcinoma accounted for two percent of cases and squamous cell carcinoma comprised of five to ten percent cases.⁸ Similar observations were noted in our study. Invasion of urothelial carcinoma into the muscularis propria is a significant factor in the morphological evaluation of tumor which was seen in ten percent of our case.⁵ PUNLMP reveals multilayering of urothelium with minimal or absent cytological atypia. They have excellent longterm prognosis with variable recurrence rate. Hence it is kept as a clinically relevant category.^{16,17} Molecular studies on muscle invasive bladder carcinoma had revealed six subtypes with different prognosis.^{18,19} Although at the present

time it is not possible to implement molecular classification of urinary tract neoplasms, it has potential impact for management of cases.

Prognosis of urothelial carcinoma depends on tumor type, grading, invasion of muscularis propria and divergent differentiation.²⁰ Management of non – muscle invasive urothelial carcinoma is based on risk stratification done after TURBT. Risk stratification relies on tumor size, aberrant histology, pathological grade and lympho-vascular invasion. Low risk patients are given single postoperative instillation of intravesical chemotherapy. Intermediate risk patients are given adjuvant intravesical therapy with BCG or chemotherapy for one year. High risk patients are restaged through TURBT in four to six weeks and based on results managed by intravesical BCG or radical cystectomy. Muscle invasive tumors are managed based on stage of disease either with combined cisplatin or radical cystectomy or TURBT chemoradiation. Stage 4 disease is managed with platinum base chemotherapy.

5. Conclusion

Identification of histopathological subtypes of urothelial carcinoma and divergent differentiation is most important and decides clinical management and guides prognostic stratification. Adjunctive molecular analysis may further enhance optimal and individualized therapy.

6. Conflict of Interest

None.

7. Sources of Funding

None.

References

- Gandhi J, Chen JF, Al-Ahmadie H. Urothelial Carcinoma: Divergent Differentiation and Morphologic Subtypes. *Surg Pathol Clin*. 2022;15(4):641-59.
- Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB. Cancer incidence in five continents. Vol. 8. Lyon (FR): IARC Publications; 2002.
- Cai T, Tiscione D, Verze P, Pomara G, Racioppi M, Nesi G et al. Concordance and clinical significance of uncommon variants of bladder urothelial carcinoma in transurethral resection and radical cystectomy specimens. *Urology*. 2014;84(5):1141–6.
- Biswas RR, Mangal S, Guha D, Basu K, Karmakar D. An Epidemiological Study of Cases of Urothelial Carcinoma of Urinary Bladder in a Tertiary Care Centre. *JKIMSU*. 2013;2(1):82-8.
- Syifa UI I, Imam S. Clinicopathological profile of urothelial carcinoma of the bladder: A five-year retrospective study *ROJ Med Pract*. 2023;18(3):147-51.
- Nik Ab Kadir MN, Mohd Hairon S, Yaacob NM, Ab Manan A, Ali N. Survival and Characteristics of Bladder Cancer: Analysis of the Malaysian National Cancer Registry. *Int J Environ Res Public Health*. 2021;18(10):5237.
- Nik Ab Kadir MN, Hairon SM, Yaacob NM, Ab Manan A, Ali N. Prognostic Factors for Bladder Cancer Patients in Malaysia: A Population-Based Study. *Int J Environ Res Public Health*. 2022;19(5):3029
- Zamzami Z, Yuliasri R, Juananda D. Characteristic of advanced stage bladder cancer managed with radiotherapy. *Int J Med Dev Ctries*. 2017;3(1):64-7.
- Matulewicz RS, Steinberg GD. Non-muscle-invasive Bladder Cancer: Overview and Contemporary Treatment Landscape of Neoadjuvant Chemoablative Therapies. *Rev Urol*. 2020;22(2):43-51.
- Stephenson WT, Holmes FF, Noble MJ, Gerald KB. Analysis of bladder carcinoma by subsite. Cystoscopic location may have prognostic value. *Cancer*. 1990;66(7):1630-5.
- Raspollini MR, Comperat EM, Lopez-Beltran A, Montironi R, Cimadamore A, Tsuzuki T et al. News in the classification of WHO 2022 bladder tumors. *Pathologica*. 2022;115(1):32-40.
- Wasco MJ, Daignault S, Zhang Y, Kunju LP, Kinnaman M, Braun T et al. Urothelial carcinoma with divergent histologic differentiation (mixed histologic features) predicts the presence of locally advanced bladder cancer when detected at transurethral resection. *Urology*. 2007;70(1):69–74.
- Moch H, Humphrey PA, Ulbright TM, Reuter VE. Urinary and male genital tumours. Lyon (France): International Agency for Research on Cancer; 2016. (WHO classification of tumours series, 4th ed.; vol. 8)
- Comperat E, Oszwald A, Wasinger G, Hansel DE, Montironi R, Kwast T et al. Updated pathology reporting standards for bladder cancer: biopsies, transurethral resections and radical cystectomies. *World J Urol*. 2022;40(4):915–27.
- Comperat E, Amin MB, Epstein JI, Hansel DE, Paner G, Al-Ahmadie H et al. The Genitourinary Pathology Society Update on Classification of Variant Histologies, T1 Substaging, Molecular Taxonomy, and Immunotherapy and PD-L1 Testing Implications of Urothelial Cancers. *Adv Anat Pathol*. 2021;28(4):196–208.
- Holmäng S, Hedelin H, Anderström C, Holmberg E, Busch C, Johansson SL et al. Recurrence and progression in low grade papillary urothelial tumors. *J Urol*. 1999;162(3):702–7.
- Holmäng S, Andius P, Hedelin H, Wester K, Busch C, Johansson SL et al. Stage progression in Ta papillary urothelial tumors: relationship to grade, immunohistochemical expression of tumor markers, mitotic frequency and DNA ploidy. *J Urol*. 2001;165(4):1124-8.
- Kamoun A, de Reyniès A, Allory Y, Sjö Dahl G, Robertson AG, Seiler R et al. A Consensus Molecular Classification of Muscle-invasive Bladder Cancer. *Eur Urol* 2020;77(4):420-33
- Mo Q, Nikolos F, Chen F, Tramel Z, Lee YC, Hayashi K et al. Prognostic Power of a Tumor Differentiation Gene Signature for Bladder Urothelial Carcinomas. *J Natl Cancer Inst* 2018;110:448–59. Erratum in: *J Natl Cancer Inst* 2019;111(11):1236.
- Brennan P, Bogillot O, Cordier S, Greiser E, Schill W, Vineis P et al. Cigarette smoking and bladder cancer in men: a pooled analysis of 11 case-control studies. *Int J Cancer*. 2000;86(2):289–94.

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