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Original Research Article

CLINICOPATHOLOGICAL PREDICTORS OF TUMOUR BEHAVIOUR IN UROTHELIAL CARCINOMA: ASSOCIATIONS WITH HISTOLOGICAL GRADE, TUMOUR STAGE, AND PROGNOSTIC PARAMETERS

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ABSTRACT

Background: Urothelial carcinoma of the urinary bladder is a significant global health concern with diverse clinical behaviour influenced by multiple histopathological factors. Accurate assessment of these parameters is essential for predicting tumour aggressiveness and guiding management. The aim is to evaluate the clinicopathological profile of urothelial neoplasms and to determine their correlation with histological grade, tumour stage, muscle invasion, lymphovascular invasion (LVI), and mitotic activity. **Materials and Methods:** This prospective observational study included 73 clinically suspected cases of urinary bladder neoplasms over a period of 18 months. Formalin-fixed, paraffin-embedded tissue specimens (TURBT and biopsy samples) were processed and stained with hematoxylin and eosin. Tumours were classified according to WHO criteria. Clinicopathological parameters including age, gender, presenting symptoms, smoking history, tumour type, grade, stage (pT), muscle invasion, LVI, and mitotic activity were analysed. Statistical analysis was performed using appropriate tests, with $p < 0.05$ considered significant. **Result:** The majority of patients were males (93.2%) with a peak incidence in the 61–70-year age group. Hematuria was the most common presenting symptom (72.6%). A significant association with smoking was observed (76.7%, $p < 0.0001$). Invasive tumours constituted 57.5% of cases, with conventional urothelial carcinoma being the predominant subtype. High-grade tumours were more frequent (76.6%, $p < 0.001$). Muscle invasion (65.6%, $p < 0.001$), lympho-vascular invasion (31.2%, $p = 0.003$), and high mitotic activity (62.5%, $p < 0.001$) showed significant association with tumour aggressiveness and advanced stage. **Conclusion:** Histological grade and tumour stage are strongly associated with adverse prognostic parameters and play a crucial role in predicting tumour behaviour. Comprehensive histopathological evaluation is essential for risk stratification and optimal patient management.

INTRODUCTION

Bladder cancer is a major global health concern and ranks among the most commonly diagnosed malignancies worldwide. According to recent global cancer estimates, more than 600,000 new cases were reported in 2022, reflecting a rising incidence compared to previous years.[1,2] The increasing trend highlights the growing burden of this malignancy across both developed and developing nations.[3]
Bladder cancer contributes significantly to global cancer mortality, accounting for over 200,000 deaths annually. A substantial number of patients continue

to live with the disease within five years of diagnosis, indicating its chronic clinical impact and recurrence potential.[4] The disease predominantly affects men, with a markedly higher incidence compared to women.[5]

Geographically, bladder cancer shows considerable regional variation, with Europe and Asia contributing the majority of global cases. This distribution is influenced by population demographics, environmental exposures, and healthcare infrastructure.[6] Lower reported incidence in Africa and Latin America may reflect underdiagnosis and limited access to healthcare services.[7]

Urothelial carcinoma (UC), also known as transitional cell carcinoma, accounts for more than 90% of all bladder cancers and arises from the urothelial lining of the urinary bladder.[8] Other histological types such as squamous cell carcinoma and adenocarcinoma are relatively uncommon and are often associated with chronic irritation, infections, or schistosomiasis.[9]

In India, bladder cancer is a relatively less common malignancy but contributes significantly to cancer-related morbidity.[10] It ranks lower in overall incidence but shows marked geographical variation, with higher prevalence reported in urban populations such as Delhi.[11] Environmental factors, smoking habits, and occupational exposures are important contributors to this variability.[12]

The urinary bladder wall is composed of multiple layers, including the mucosa (urothelium, lamina propria, and muscularis mucosa) and muscularis propria. The urothelium exhibits variable thickness depending on bladder distension and contains specialized umbrella cells that serve a protective function.[13]

Several risk factors are implicated in the pathogenesis of bladder cancer, including lifestyle, occupational exposure, and genetic predisposition. Among these, tobacco smoking is the most significant, accounting for nearly 50% of all cases.[14] The risk increases with both duration and intensity of smoking exposure.[15]

Carcinogenic compounds such as aromatic amines and polycyclic hydrocarbons present in cigarette smoke induce DNA damage in urothelial cells, leading to malignant transformation.[15] Occupational exposure to industrial chemicals in dye, rubber, and leather industries further contributes to bladder carcinogenesis.[16]

Cliinical presentations of these cases include painless gross hematuria which is often the earliest clinical manifestation. The likelihood of malignancy is significantly higher in patients presenting with macroscopic hematuria compared to microscopic hematuria. Other symptoms include urinary frequency, urgency, and dysuria, particularly in cases of carcinoma in situ. Tumors located near the bladder neck may lead to obstructive urinary symptoms, mimicking benign conditions and potentially delaying diagnosis.[17]

Advanced bladder cancer may present with systemic features such as abdominal pain, bone pain, and ureteric obstruction due to metastasis. These findings are associated with poor prognosis and indicate advanced disease stage.[18] According to WHO Classification 2022 of Urinary Bladder tumors - Urothelial tumors are the most common, others include Squamous cell neoplasms of the urinary tract, Glandular neoplasms, Urachal and diverticular neoplasm, Urethral Neoplasm and Tumors of Mullerian type.[19]

MATERIALS AND METHODS

The study was conducted in the Department of Pathology in collaboration with the Department of Urology at UPUMS, Saifai, Etawah. The sources of data for the study consisted of tissue samples preserved in 10% buffered formalin, either as TURBT chips or as bladder biopsies/specimens. After grossing and tissue processing Hematoxylin and eosin-stained sections were examined. This was a hospital based prospective analytical observational study. The study included a total of 73 cases who fulfilled all the inclusion and exclusion criteria and presented in the study duration.

Inclusion Criteria

- Clinically suspicious cases of CA Urinary bladder with chief complaints of hematuria, history of flank pain, abdominal mass, anorexia, weight loss, dysuria, nocturia, difficulty in starting and stopping the urine stream, overflow dribbling, poor urine stream, and other obstructive symptoms.
- Patients who had given consent to enroll in the study
- Patients of both genders and above 18 years of age were included.

Exclusion Criteria

- Patients who were unwilling to participate.
- Patients suffering from any other malignant disorders as evident from careful history, clinical examination and routine radiological investigation
- Patients suffering from any endocrinological disorders, any pathological lesion in prostate, kidney and gastrointestinal tracts.
- Patients suffering from any other pathological conditions of urinary bladder as evident from careful history, clinical examination and routine clinical investigation.

RESULTS

In the present study, total of 73 cases were studied, from which the maximum number of cases, 28 (38.4%), were observed in the 61–70 years age group, followed by 18 cases (24.7%) in the 51–60 years age group. This was followed by 10 cases (13.7%) in the 41–50 years age group and 8 cases (11.0%) in the 71–80 years age group. Fewer cases were seen in the younger and very elderly age groups, with 4 cases (5.5%) in the 31–40 years age group, 3 cases (4.1%)

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in the 81–90 years age group, and 2 cases (2.7%) in the 21–30 years age group. [Table-1]. The mean age of the study population was 59.5 years, and the median age group was 61–70 years, indicating a predominance of urinary bladder neoplasms in the older age population. [Table-1].In our study, urothelial neoplasms demonstrated a marked male predominance, with 68 cases (93.2%) occurring in males compared to only 5 cases (6.8%) in females. This corresponds to a male-to-female ratio of 13.6:1, highlighting a significant gender disparity in incidence. Out of the total 73 cases in our study, 56 cases (76.7%) had positive history for smoking while rest 17 cases (23.35) were non-smokers. Statistically significant ($p<0.0001$) correlation was observed between smoking and Urothelial Neoplasm. Among our study, maximum number of cases 53/73 (72.6%) presented with hematuria followed by increased frequency of urination in 14/73 cases (19.2%) and dysuria in 6/73 cases (8.2%).

In the present study, the majority of cases were invasive urothelial neoplasms, accounting for 42 cases (57.5%). Among these, invasive urothelial carcinoma was the predominant subtype, observed in 40 cases (54.8%), while urothelial carcinoma with squamous differentiation and pure squamous cell carcinoma were each identified in 1 case (1.4%). Non‑invasive urothelial neoplasms constituted 31 cases (42.5%). Within this category, low‑grade papillary urothelial carcinoma (LGUC) was the most frequent, comprising 15 cases (20.5%). Papillary urothelial neoplasm of low malignant potential (PUNLMP) was seen in 8 cases (10.9%), high‑grade papillary urothelial carcinoma (HGUC) in 7 cases (9.6%), and urothelial papilloma in 1 case (1.4%).

Table 1: Clinicopathological Profile and Histomorphological Characteristics of Urothelial Neoplasms with Statistical Analysis

Parameter	Category	No. of Cases (n)	Percentage (%)	p-value
Gender	Male	68	93.2	
	Female	5	6.8	
Presenting Complaints	Hematuria	53	72.6	
	Frequency	14	19.2	
	Dysuria	6	8.2	
Smoking History	Present	56	76.7	<0.0001
	Absent	17	23.3	
Non-Invasive Urothelial Neoplasms	Urothelial Papilloma	1	1.4	
	PUNLMP	8	10.9	
	Low-grade Papillary UC	15	20.5	
	High-grade Papillary UC	7	9.6	
Invasive Urothelial Neoplasms	Invasive Urothelial Carcinoma	40	54.8	
	UC with Squamous Differentiation	1	1.4	
	Squamous Cell Carcinoma	1	1.4	
	Total Invasive Tumours	42	57.5	0.002
Histological Grade	Low Grade	15	23.4	
	High Grade	49	76.6	<0.001
Tumour Extent (pT Stage)	pTa	22	34.4	
	pT1	20	31.3	0.004
	pT2	18	28.1	
	pT3 / pT4	4	6.2	
Muscle Invasion	Present	42	65.6	
	Absent	22	34.3	<0.001
Lymphovascular Invasion	Present	20	31.2	0.003
	Absent	44	68.8	
Mitotic Activity	High	40	62.5	
	Low	24	37.5	<0.001

The study population demonstrated a marked male predominance, with 68 cases (93.2%) in males compared to 5 cases (6.8%) in females, indicating a strong gender bias toward males in urothelial neoplasms. Hematuria was the most common presenting symptom, observed in 53 cases (72.6%), followed by urinary frequency in 14 cases (19.2%) and dysuria in 6 cases (8.2%), establishing hematuria as the predominant clinical presentation. A significant proportion of patients had a history of smoking, with 56 cases (76.7%) being smokers, while 17 cases (23.3%) were non-smokers, showing a highly significant association ($p < 0.0001$) between smoking and urothelial neoplasms.

Among non-invasive tumors, low-grade papillary urothelial carcinoma was the most frequent (20.5%), followed by PUNLMP (10.9%), high-grade papillary carcinoma (9.6%), and urothelial papilloma (1.4%), indicating predominance of low-grade lesions in this category. Invasive tumors constituted 57.5% of cases, with conventional invasive urothelial carcinoma forming the majority (54.8%), while rare variants such as urothelial carcinoma with squamous differentiation and pure squamous cell carcinoma were seen in 1.4% each, showing statistical significance ($p = 0.002$).

Histological Grade: High-grade tumors predominated in the study, accounting for 49 cases (76.6%), whereas low-grade tumors comprised 15

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cases (23.4%), demonstrating a highly significant predominance of high-grade lesions ($p < 0.001$).

Tumour Extent (pTStage): The most common stage was pTa (34.4%), followed by pT1 (31.3%) and pT2 (28.1%), while advanced stages pT3/pT4 were less frequent (6.2%), with the distribution being statistically significant ($p = 0.004$).

Muscle Invasion: Muscle invasion was present in 42 cases (65.6%), whereas 22 cases (34.3%) showed no muscle invasion, indicating a significant predominance of muscle-invasive disease ($p < 0.001$).

Lymphovascular Invasion (LVI): Lymphovascular invasion was identified in 20 cases (31.2%), while 44 cases (68.8%) did not show LVI, and this difference was statistically significant ($p = 0.003$).

Mitotic Activity: High mitotic activity was observed in 40 cases (62.5%), whereas low mitotic activity was noted in 24 cases (37.5%), indicating a significant predominance of highly proliferative tumors ($p < 0.001$).

DISCUSSION

The clinicopathological profile in the present study demonstrates patterns consistent with established epidemiological trends. A striking male predominance was observed, with 93.2% males and 6.8% females, which is in agreement with global literature reporting a strong male preponderance, as documented by the World Health Organization and studies by Antoni S et al.[20] This disparity is largely attributed to increased exposure to environmental and occupational carcinogens among males.[21]

Hematuria was the most common presenting symptom in our cohort, seen in 72.6% of cases, followed by frequency (19.2%) and dysuria (8.2%). This observation is consistent with reports by the European Association of Urology and Babjuk M et al,[22] who identified painless hematuria as the predominant clinical presentation.

A highly significant association with smoking was noted, with 76.7% of patients having a positive smoking history ($p < 0.0001$). This finding strongly correlates with data from the International Agency for Research on Cancer and Freedman ND et al,[23] which identify tobacco smoking as the most important etiological factor in urothelial carcinoma.[24]

The histopathological spectrum in our study revealed that 57.5% of tumors were invasive, with 54.8% being conventional invasive urothelial carcinoma, while rare variants such as squamous differentiation and pure squamous carcinoma accounted for 1.4% each ($p = 0.002$). These findings are comparable to those reported by Humphrey PA et al,[25] highlighting the predominance of invasive disease.

Among non-invasive lesions, low-grade papillary urothelial carcinoma (20.5%) was the most frequent, followed by PUNLMP (10.9%), high-grade papillary carcinoma (9.6%), and urothelial papilloma (1.4%), reflecting a distribution similar to that described in the World Health Organization Classification of Tumours.[26]

Histological grading demonstrated a significant predominance of high-grade tumors, with 76.6% high-grade and 23.4% low-grade lesions ($p < 0.001$). This aligns with established literature indicating that high-grade tumors are more frequently encountered in hospital-based cohorts.

Tumor staging showed that pTa was the most common stage (34.4%), followed by pT1 (31.3%) and pT2 (28.1%), while advanced stages pT3/pT4 were seen in only 6.2% of cases ($p = 0.004$). Similar distributions have been reported by Sylvester RJ et al,[27] supporting the reproducibility of stage patterns.

Muscle invasion was present in 65.6% of cases ($p < 0.001$), indicating a predominance of muscle-invasive disease. This finding is comparable to tertiary care–based studies such as those by Stein JP et al,[28] where advanced disease is frequently encountered.

Lymphovascular invasion was identified in 31.2% of cases ($p = 0.003$), while 68.8% of tumors did not show LVI, consistent with findings by Shariat SF et al,[29] who emphasized its prognostic significance.

Mitotic activity was high in 62.5% of tumors compared to 37.5% with low mitotic activity ($p < 0.001$), correlating strongly with aggressive tumor biology. Similar observations have been reported by Cheng L et al,[30] reinforcing the role of mitotic index as a marker of proliferation.

CONCLUSION

Histological grade and tumour stage remain the cornerstone determinants of tumour aggressiveness and clinical outcome. Their strong association with adverse prognostic parameters underscores their pivotal role in guiding therapeutic decisions.

Accurate and meticulous histopathological evaluation enables precise risk stratification of patients. This in turn, facilitates individualized treatment planning and improved prognostication. Ultimately, integrating these parameters into routine practice enhances patient care and clinical outcomes.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2022. CA Cancer J Clin. 2023;73(1):17–48.
2. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. Global Cancer Observatory: Cancer Today. Lyon: IARC; 2022.
3. Bray F, Laversanne M, Weiderpass E, Soerjomataram I. The global cancer burden 2020–2040. Nat Rev Clin Oncol. 2021;18(10):663–75.
4. Siegel RL, Miller KD, Jemal A. Cancer statistics. CA Cancer J Clin. 2023;73(1):7–33.
5. Antoni S, Ferlay J, Soerjomataram I, Znaor A, Jemal A, Bray F, et al. Bladder cancer incidence and mortality. Eur Urol. 2017;71(1):96–108.
6. Lenis AT, Lec PM, Chamie K, Mshs MD. Bladder cancer: epidemiology and risk factors. Urol Clin North Am. 2020;47(1):1–9.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

7. Islami F, Torre LA, Jemal A. Global trends of bladder cancer. Int J Cancer. 2018;142(4):673–84.
8. Humphrey PA, Moch H, Cubilla AL, Ulbright TM, Reuter VE. WHO classification of urinary tumors. Eur Urol. 2022;82(5):469–82.
9. Mostofi FK, Sobin LH, Torloni H. Histological typing of urinary bladder tumors. WHO; 1973.
10. National Cancer Registry Programme. Cancer statistics in India. ICMR; 2022.
11. Mathur P, Sathishkumar K, Chaturvedi M, Das P, Sudarshan KL, Santhappan S, et al. Cancer statistics, India. Lancet Oncol. 2020;21(12):1480–92.
12. Thun MJ, Linet MS, Cerhan JR, Haiman CA, Schottenfeld D. Cancer Epidemiology and Prevention. 4th ed. Oxford; 2017.
13. Standring S. Gray's Anatomy. 42nd ed. Elsevier; 2020.
14. Freedman ND, Silverman DT, Hollenbeck AR, Schatzkin A, Abnet CC. Smoking and bladder cancer. JAMA. 2011;306(7):737–45.
15. Cumberbatch MGK, Jubber I, Black PC, Esperto F, Figueroa JD, Kamat AM, et al. Epidemiology of bladder cancer. Eur Urol. 2018;74(6):784–95.
16. Burger M, Catto JWF, Dalbagni G, Grossman HB, Herr H, Karakiewicz P, et al. Epidemiology and risk factors of bladder cancer. Eur Urol. 2013;63(2):234–41.
17. Babjuk M, Burger M, Capoun O, Cohen D, Compérat EM, Dominguez Escrig JL, et al. EAU guidelines on bladder cancer. Eur Urol. 2022;81(1):75–94.
18. Messing EM, Young TB, Hunt VB, Gilchrist KW, Newton MA, Bram LL, et al. Hematuria screening. J Urol. 1995;154(1):57–61.
19. WHO Classification of Tumours: Urinary and Male Genital Tumours. 5th ed. Lyon: International Agency for Research on Cancer; 2022.
20. World Health Organization. WHO classification of tumours of the urinary system and male genital organs. 5th ed. Lyon: International Agency for Research on Cancer; 2022.
21. Antoni S, Ferlay J, Soerjomataram I, Znaor A, Jemal A, Bray F. Bladder cancer incidence and mortality: a global overview. Eur Urol. 2017;71(1):96–108.
22. Babjuk M, Böhle A, Burger M, Capoun O, Cohen D, Compérat EM, et al. EAU guidelines on non–muscle-invasive bladder cancer (TaT1 and CIS). Eur Urol. 2022;81(1):75–94.
23. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans: tobacco smoke. Lyon: IARC; 2012.
24. Freedman ND, Silverman DT, Hollenbeck AR, Schatzkin A, Abnet CC. Association between smoking and risk of bladder cancer among men and women. JAMA. 2011;306(7):737–745.
25. Humphrey PA, Moch H, Cubilla AL, Ulbright TM, Reuter VE. The 2016 WHO classification of tumours of the urinary system and male genital organs—part B: prostate and bladder tumours. Eur Urol. 2016;70(1):106–119.
26. World Health Organization. WHO classification of tumours of the urinary system and male genital organs. 4th ed. Lyon: International Agency for Research on Cancer; 2016.
27. Sylvester RJ, van der Meijden AP, Oosterlinck W, Witjes JA, Bouffioux C, Denis L, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables. Eur Urol. 2006;49(3):466–477.
28. Stein JP, Lieskovsky G, Cote R, Groshen S, Feng AC, Boyd S, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1054 patients. J Clin Oncol. 2001;19(3):666–675.
29. Shariat SF, Karakiewicz PI, Palapattu GS, Amiel GE, Lotan Y, Rogers CG, et al. Outcomes of radical cystectomy for transitional cell carcinoma of the bladder: a contemporary series. J Clin Oncol. 2006;24(18):2960–2967.
30. Cheng L, Montironi R, Davidson DD, Lopez-Beltran A. Tumor proliferation and grading in urothelial carcinoma: practical implications. Hum Pathol. 2010;41(2):157–165.

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