



A HISTOPATHOLOGICAL STUDY OF BLADDER TUMORS

Pathology

Mansi Khamesra*	MD Pathology, Senior Resident, Department of Pathology, Pacific Medical College and Hospital, Udaipur, Rajasthan-313001. *Corresponding Author
Lavish Tayal	MD Pathology, Senior Resident, Chamarajanagar Institute of Medical Sciences, Chamarajanagar, Karnataka.
Bhavana Garg	MD Pathology, Associate Professor, Pacific Medical College and Hospital, Udaipur, Rajasthan-313001.
Vijaya Mysorekar	MD Pathology, Professor, MS Ramaiah Medical College, Bangalore, Karnataka.

ABSTRACT

Background: The bladder is a common site for urinary tract malignancy. Urinary bladder carcinoma is of global concern and the histopathological types and variants are of relevance for their management. This study was carried out to assess the histopathological characteristics of bladder tumors.

Materials and methods: The data was collected retrospectively and prospectively to include a total of 140 urinary bladder tumor specimens. Detailed medical records of these subjects were collected, and histopathological examination was performed on the prospective samples.

Results: The most common symptom of bladder tumor was hematuria. Cystoscopy results found grossly visible tumor growths in about 76% subjects. Of the total sample, 84% patients underwent transurethral resection of bladder tumor (TURBT) surgery and the rest of them underwent cystectomy. Furthermore, the commonest histopathological type of urinary bladder carcinoma was invasive urothelial carcinoma. About 68.6% patients had high grade tumor. Most tumor growths were present on the lateral side (46.43%). In 52.86% specimens, deep muscles were involved in the tumor. Node involvement was positive in 11 (47.83%) patients. As per TNM classification, majority of the specimens were pT2bN2Mx (26.09%) and pT2bN0Mx (5, 21.74%). Tumors were detected in stage 2 (26.09%), stage 3 (30.43%) and stage 4 (39.13%).

Conclusions: The most common symptom observed in patients with urinary bladder carcinoma was hematuria. Cystoscopy results found 75.71% subjects to have grossly visible tumor growths. The major histopathological type of bladder carcinoma was invasive. In 52.86% specimens, deep muscles were involved in the tumor. About 68.6% patients had high grade tumor.

KEYWORDS

Carcinoma, cystectomy, transitional cell, urinary bladder neoplasm

INTRODUCTION

Bladder cancer is the tenth commonest type of cancer, globally. It is the malignancy of urinary tract that leads to significant mortality and morbidity.^[1] It constitutes about two-thirds of all urinary cancers in the world. Its occurrence is 4-5 times higher in males. Bladder cancer mostly occurs in patients over the age of 50 years but can also occur in children and younger adults.^[2] The predisposing factors for this cancer include smoking, chronic cystitis, pelvic irradiation, cyclophosphamide, genetic predisposition, occupations such as working in rubber, textile, leather, paint and print industries, aniline dyes, schistosoma infection and urachal remnants.^[3] Mostly, bladder cancers develop on the lateral wall or posterior wall (base) of the bladder. The growth pattern of urothelial tumors is of many types and it may be exophytic, endophytic or a combination of both. When exophytic, it could be papillary or solid/nodular.^[4]

Most common symptoms of bladder tumor include painless hematuria and associated urinary infections (frequency, urgency, dysuria). When the ureteral orifice is involved, pyelonephritis/hydronephrosis may follow leading to flank/abdominal pain.^[5] Urothelial tumors represent about 90% of all the bladder tumors and could range from benign papilloma's to anaplastic cancers. Several grading classification systems were proposed in the past to classify urothelial carcinomas and most widely used classification is the one developed by the World Health Organization/International Society of Urological Pathology (WHO/ISUP 1998).^[6] Urothelial cancers are known to show divergent differentiation and its histopathological types include invasive carcinoma, noninvasive carcinoma, squamous cell carcinoma (about 5% of the malignant tumor cases) and adenocarcinoma (rarely present).^[4]

Bladder tumors are often classified based on the stage and the staging system given by American Joint Committee on Cancer (AJCC).^[6,7] Cystoscopy procedure is the gold standard method for the detection of bladder tumor. The transurethral resection of bladder tumor (TURBT) method is used for diagnosis, prognosis and for therapy.^[8] The management of these cases depend on grade and stage of tumor. Till date, literature on bladder tumors from the Indian subcontinent are sparse. Therefore, the current study was planned to study the features of histologically confirmed bladder carcinoma cases.

MATERIAL AND METHODS

This study was conducted at a tertiary care hospital in Bengaluru, India and retrospective data was collected for 2 years and prospective data was collected for 2 years. A total of 140 bladder cancer cases were studied. Retrospective data comprised of 59 histologically confirmed tumor cases between Jun-2015 and May-2017. Histopathology requisition forms of all retrospective cases containing clinical information, along with paraffin blocks and stained slides were retrieved and reviewed. Prospective data comprised of 81 specimens collected from the Pathology Department between Jun-2017 and Oct-2019.

Urinary bladder biopsy and cystectomy specimens of patients with bladder carcinomas were collected. Cases with extensive tumor necrosis without sufficient viable tumor cells for accurate evaluation of tumor type and patients who received neoadjuvant therapy were excluded from the study.

Baseline and clinical data of patients regarding age, sex, specimen type, clinical symptoms along with ultrasonography/cystoscopy findings and medical records were noted. An extensive histopathological examination of the hematoxylin and eosin (H&E) stained sections was performed including histological typing, urothelial tumors grading and pathological staging.^[6,9,10] Grading of the urothelial cancers was done as per WHO/ISUP classification and tumour staging was done as per AJCC classification 8th edition.^[6] The data collected was tabulated and analysed.

Statistical analyses

Data was analyzed using statistical software R version 4.0.3. Categorical variables were presented in the form of frequency tables. Continuous variables were presented as mean±standard deviation. Chi square test was applied to check the significance between attributes. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 140 subjects with bladder cancer were recruited, of which 103 (73.57%) study subjects were men. Patients recruited were in the age range between 3 and 95 years with the average (mean±standard deviation) of 62.45±14.33 years. The most common symptom observed was hematuria (67.86%). Cystoscopy results found 75.71%

subjects to have grossly visible tumor growths. TURBT surgery was performed in 83.57% patients and rest of the sample underwent cystectomy (Table 1).

Table 1: Baseline characteristics and demographic variables of the study sample

Variables	Subcategory	Number of patients (%)
Age (years)	<40	10 (7.14)
	41-50	13 (9.29)
	51-60	30 (21.43)
	61-70	52 (37.14)
	71-80	25 (17.86)
	81-90	08 (5.71)
	91-100	02 (1.43)
	Mean±SD	62.45 ± 14.33
Gender	Female	37 (26.43)
	Male	103 (73.57)
Symptom	Hematuria	95 (67.86)
	Dysuria	27 (19.29)
	Frequent urination	08 (5.71)
	Lower abdominal pain	06 (4.29)
	Loin pain	04 (2.86%)
Type of Surgery	Cystectomy	22 (15.71)
	TURBT	117 (83.57)
Cystoscopy	Grossly visible	106 (75.71)
	No gross tumor	34 (24.29)
Histological types of bladder cancer	Invasive urothelial	113 (80.71)
	Non-invasive urothelial	14 (10.0)
	Adenocarcinoma	04 (2.86)
	Squamous cell carcinoma	04 (2.86)
	Neuroendocrine	02 (1.43)
	Embryonal Rhabdomyosarcoma	01 (0.71)
	Ganglioneuroma	01 (0.71)
	Spindle cell tumor	01 (0.71)
Involvement of deep muscles	Yes	74 (52.86)
	No	59 (42.14)
	Not tested	07 (5.0)
Involvement of lamina propria	Yes	125 (89.29)
	No	11 (7.86)
	Not tested	04 (2.86)
Site of origin	Right lateral	32 (22.86)
	Left lateral	33 (23.57)
	Anterior	10 (7.14)
	Posterior	24 (17.14)
	Dome	16 (11.43)
	Neck	07 (5.0)
	Base	3 (2.14)
	Multifocal	15 (10.71)
Tumor size	<5 cm	74 (52.86)
	>5 cm	25 (17.86)
	Not available	41 (29.29)
Grade	High grade	96 (68.57)
	Low grade	44 (31.43)

TURBT: Transurethral resection of bladder tumor.

The major histopathological type of bladder carcinoma was invasive urothelial type in 80.71% study specimens. The other types reported were noninvasive urothelial bladder cancer (14, 10.0%), adenocarcinoma (4, 2.86%), squamous cell carcinoma (4, 2.86%), neuroendocrine tumor (2, 1.43%), embryonal rhabdomyosarcoma (1, 0.71%), ganglioneuroma (1, 0.71%) and spindle cell tumor (1, 0.71%). In 52.86% specimens, deep muscles were involved in the tumor. The site of origin of tumor growth was left lateral in 23.57% study specimens followed by right lateral in 22.86% specimens. The tumor size was <5 cm in 74 patients (52.86%) while 25 patients (17.86%) had a tumor size of >5 cm. About 68.6% patients had high grade tumor while the rest had low grade tumor (Table 1).

Histopathological staining (H&E, 20 X) of urothelial carcinoma is depicted in Figures 1-3.

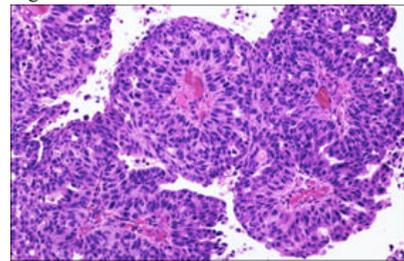


Figure 1: Microscopy of invasive urothelial carcinoma

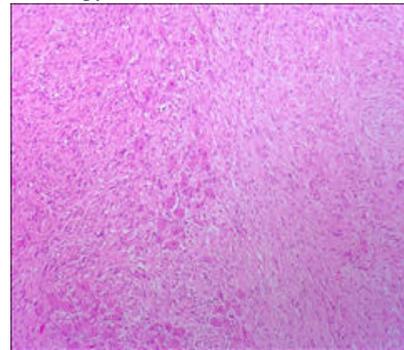


Figure 2: Microscopy of rhabdoid variant of urothelial carcinoma

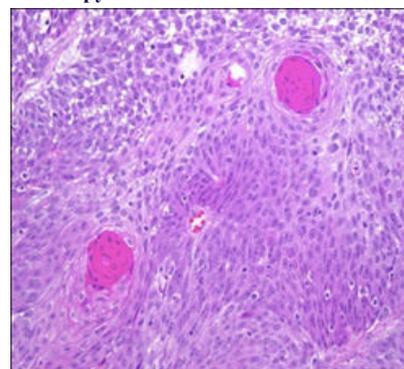


Figure 3: Microscopy of squamous variant of urothelial carcinoma

Table 2 presents the nodal status, TNM classification and stages of tumor for 22 cystectomy specimens included in the study. Node involvement was positive in 11 (47.83%) patients. As per TNM classification, majority of the specimens were pT2bN2Mx (6, 26.09%) and pT2bN0Mx (5, 21.74%). Tumors were detected in stage 2 (6, 26.09%), stage 3 (7, 30.43%) and stage 4 (9, 39.13%).

Table 2: Distribution of nodal status, TNM and stage in 22 cystectomy specimens

Variables	Sub-Category	Number of Patients
Nodal status	Negative	11 (47.83)
	Positive	11 (47.83)
TNM	pT1N0Mx	1 (4.35)
	pT2aN0Mx	1 (4.35)
	pT2bN0Mx	5 (21.74)
	pT2bN1Mx	1 (4.35)
	pT2bN2Mx	6 (26.09)
	pT3aN2Mx	2 (8.7)
	pT3N0Mx	2 (8.7)
	pT4aN0Mx	2 (8.7)
	pT4N1Mx	1 (4.35)
	pT4N2Mx	1 (4.35)
Stage	2	6 (26.09)
	3	7 (30.43)
	4	9 (39.13)

TNM: Tumor, nodes and metastases classification of malignant tumors.

DISCUSSION

Urinary bladder tumor is the tenth commonest type of cancer in the world.^[1] In USA, bladder cancer is the 4th and 12th most commonly present cancer in men and women, respectively. Bladder cancer accounts for 3.9% of all the tumor cases in India.^[2] The management of bladder tumor depends on its stage and grade. Till now, there have been very few bladder cancer histopathological studies conducted in India. Therefore, the current study was designed to analyze the characteristics of histologically confirmed urinary bladder carcinoma cases.

In the present study, mean age of the study subjects was approximately 62.5 years, and in line with previous literature, where age was in the range of 60 to 65 years.^[11] However, a significant difference was observed in case of gender ratio results in the current study (73.5% men) in comparison to previously published Indian studies, while it has been approximately same as the studies in patients from other countries such as North America, Europe and Australia.^[11,12] This gender ratio difference in India might be due to lesser number of women smokers and lesser number of working women, especially in industries who are exposed to industrial carcinogenic agents such as aniline dyes.

Hematuria was the commonly observed patient complaint, which is now considered as a major symptom of tumor growth in the urinary bladder.^[5] Goyal et al (2015), reported hematuria as the most common clinical symptom in 91% cases, while strangury (48%), burning (39%) and pain (38%) were also reported.^[13] Ajmera et al (2016), reported hematuria in 156 cases (59.7%) and other urinary complaints such as difficulty and burning micturition.^[14]

Tumor growth was reported on the lateral wall and posterior wall of the bladder, which was also observed in previous studies, in which majority of tumor growths occurred on the lateral wall.^[15] High grade urinary cancer was predominant in both TURBT (63.25%) and cystectomy (95.65%) procedures. These results were in concordance with the previous studies.^[12,15]

In the present study, the major histopathological type of bladder carcinoma was invasive urothelial type in 80.71% study specimens. Vaidya et al, reported squamous cell carcinoma as the most common type (80.72%) of urinary bladder cancer.^[16] The other types reported in the present study were noninvasive urothelial bladder cancer (14, 10.0%), adenocarcinoma (4, 2.86%), squamous cell carcinoma (4, 2.86%), neuroendocrine tumor (2, 1.43%), embryonal rhabdomyosarcoma (1, 0.71%), ganglioneuroma (1, 0.71%) and spindle cell tumor (1, 0.71%). Shah et al (2016), studied the histopathology and frequency of different type of lesions in the bladder and reported that the majority of lesions were papillary urothelial neoplasm (19 cases, 82.60%), among which 2 cases were squamous cell carcinoma (8.69%), 1 case was a poorly differentiated carcinoma of neuroendocrine differentiation (4.35%) and 1 case was a paraganglioma (4.35%).^[17] Goyal et al (2015) reported high-grade papillary urothelial carcinoma (58%) followed by low-grade papillary urothelial carcinoma (31%), low grade papillary urothelial neoplasm (4%), moderately differentiated squamous cell carcinoma (2%), and moderately differentiated adenocarcinoma (1%).^[13] Ajmera et al (2016) reported urothelial neoplasm as the most commonly occurring lesion (92.7%) in the urinary bladder.^[14] Adenocarcinoma (2%), squamous cell carcinoma (3%), small cell neuroendocrine carcinoma (0.4%) and sarcomatoid carcinoma (0.4%) were reported. Four cases of urothelial carcinoma with mixed epithelial features were reported. The most common histopathological diagnoses were high-grade, noninvasive papillary urothelial carcinoma (29.1%), infiltrating urothelial carcinoma (22.6%) and low-grade, noninvasive papillary urothelial carcinoma (20.3%).^[14] Pudasani et al (2014), reported cystitis (29%) and noninvasive papillary urothelial carcinoma, low-grade (29%) as the most common diagnoses on examining cystoscopic bladder biopsies.^[18] Histopathological examination observed that 51.6% of the cases were malignant lesions and among them 93.7% were urothelial tumors and 6.3% were glandular neoplasm.^[18]

In the present study, as per pathological grading, tumors from 22 patients who underwent cystectomy were reported in stages pT1, pT2a, pT2b, pT3, pT3a, pT4 and pT4a with a majority being pT2bN2Mx (6, 26.09%) and pT2bN0Mx (5, 21.74%). Laishram et al (2012), in a 10-year retrospective study, examined the histomorphological pattern of urothelial tumors of the urinary bladder

in Manipur and evaluated if a correlation exists between tumor grade and muscle invasion.^[19] In this study, 14 (53.9%) cases were low-grade, 9 (34.6%) were high-grade, 2 (7.7%) were papillomas and 1 (3.9%) was a papillary urothelial neoplasm of low malignant potential (PUNLMP). Pathological staging reported 14 (53.9%) in stage PTa, 4 (15.4%) PT1, and 8 (30.9%) PT2. Invasion into the detrusor muscle was observed in 18.2% low-grade tumors and 75% high-grade tumors.^[19]

In the present study, invasion of lamina propria was observed in 125 (89.29%) of patients. Muscle invasion was observed in 74 (52.86%) patients. Goyal et al (2015), reported invasion of lamina propria in 73.03% of cases while muscular invasion was observed in 62.92% of patients.^[13] Kundra et al (2017) found invasion in 39% of urothelial tumors and 61% were non-invasive in the age category <40 years. In patients >40 years, invasion was observed in 63% urothelial tumors and 37% were non-invasive.^[20]

The major limitations of this study are that the study did not screen for confounding factors in the onset of bladder tumours and did not evaluate the differences between various types of bladder cancers based on these factors.

CONCLUSIONS

The most common symptom observed in patients with urinary bladder carcinoma was hematuria. Cystoscopy results found 75.71% subjects to have grossly visible tumor growths. TURBT surgery was performed in 83.57% patients and rest of the sample underwent cystectomy. The major histopathological type of bladder carcinoma was invasive as reported in 80.71% study specimens. In 52.86% specimens, deep muscles were involved in the tumor. About 68.6% patients had high grade tumor.

REFERENCES

- Oeyen E, Hoekx L, De Wachter S, Baldewijns M, Amey F, Mertens I. Bladder Cancer Diagnosis and Follow-Up: The Current Status and Possible Role of Extracellular Vesicles. *Int J Mol Sci*. 2019; 20(4):821.
- Saginala K, Barsouk A, Aluru JS, Rawla P, Padala SA, Barsouk A. Epidemiology of Bladder Cancer. *Med Sci (Basel)*. 2020; 8(1):15.
- Jahrreis V, Pradere B, Laukhina E, Mori K, Shariat SF. Catalog of exogenous risk factors for bladder carcinogenesis. *Curr Opin Urol*. 2020; 30(3):449-456.
- Yakley JP. Urinary tract cancers: An overview for general practice. *J Family Med Prim Care*. 2016; 5(3):533-538.
- DeGeorge KC, Holt HR, Hodges SC. Bladder Cancer: Diagnosis and Treatment. *Am Fam Physician*. 2017; 96(8):507-514.
- Wang G, McKenney JK. Urinary Bladder Pathology: World Health Organization Classification and American Joint Committee on Cancer Staging Update. *Arch Pathol Lab Med*. 2019; 143(5):571-577.
- Magers MJ, Lopez-Beltran A, Montironi R, Williamson SR, Kaimakliotis HZ, Cheng L. Staging of bladder cancer. *Histopathology*. 2019; 74(1):112-134.
- Niraj T, Agbo CA, Agrawal CS. Transurethral resection of bladder tumour (TURBT): Experience of a Tertiary Centre. *Jos J of Med*. 2017; 11(1):17-9.
- Feldman AT, Wolfe D. Tissue processing and hematoxylin and eosin staining. *Methods Mol Biol*. 2014; 1180:31-43.
- Hurwitz M, Spiess PE, Rini B, Pisters LL, Redman BG. Urothelial and Kidney Cancers. <https://www.cancernetwork.com/view/urothelial-and-kidney-cancers> (accessed on 16-Feb-2021).
- Zhang L, Wu B, Zha Z, Qu W, Zhao H, Yuan J. Clinicopathological factors in bladder cancer for cancer-specific survival outcomes following radical cystectomy: a systematic review and meta-analysis. *BMC cancer*. 2019; 19(1):716.
- Yousef PG, Gabril MY. An update on the molecular pathology of urinary bladder tumors. *Pathol Res Pract*. 2018; 214(1):1-6.
- Goyal VK, Vyas SP, Kothari DC. Spectrum of lesions in urinary bladder biopsies: histopathological study. *Int J Dent Med Res* 2015; 1(6):42-46.
- Ajmera S, Ajmera R. Histopathological Study of Urinary Bladder Tumors-A 10 Year Study. *International Journal of Science and Research*. 2016; 5(7):93-95.
- Mainali N, Chaudhary P, Nepal N, Shrestha J. Spectrum of Urothelial lesions in Cystoscopic biopsies: a histopathological perspective. *J of Nob Med Col*. 2018; 7(1):6-10.
- Vaidya S, Lakhey M, K C S, Hirachand S. Urothelial tumours of the urinary bladder: a histopathological study of cystoscopic biopsies. *J Nepal Med Assoc*. 2013; 52(191):475-478.
- Shah PY, Nanavati M, Patel RG, Goswami HM. Spectrum of lesions in urinary bladder-a histopathological study. *International Journal of Current Research and Review*. 2016; 08(04):19-24.
- Pudasani S, Subedi N, Prasad KB, Rauniyar SK, Joshi BR, Bhomi KK. Cystoscopic bladder biopsies: a histopathological study. *Nepal Med Coll J*. 2014; 16(1):9-12.
- Laishram RS, Kippen P, Laishram S, Khurajam S, Sharma DC. Urothelial tumors of the urinary bladder in Manipur: a histopathological perspective. *Asian Pacific Journal of Cancer Prevention*. 2012; 13(6):2477-9.
- Kundra M, Hemapant. Urinary Bladder Tumors: A comparative histopathological study in patients less than 40 years and more than 40 years. *Indian J Pathol Oncol*. 2017; 4(4):507-510.