

Original Research Article

Histopathological Study of Urothelial Carcinomas and Association with Various Risk Factors

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ABSTRACT

BACKGROUND & METHOD: The aim of this study is to Histopathological Study of Urothelial Carcinomas and Association with Various Risk Factors. Detailed history of the cases regarding age, sex, personal history, site, type of procedure done were obtained for all 50 cases reported during the study period from surgical pathology records. All transurethral resection of bladder specimen were processed entirely and representative sections were taken from radical cystectomy specimen which were subjected for routine histopathological examination. The following clinical and pathological parameters were evaluated: age, gender, tumor site, size, tumor grade, tumor stage and invasiveness of the tumor.

RESULT: The patients found in tumor invasion 18 (56.25%) were muscularis propria and 14 (43.75%) cases were found in lamina propria. The maximum number of patients found in lymph node status 03 (75.0%) were negative status and 01 (25.0%) cases were found in positive status.

CONCLUSION: The current study emphasize the importance of investigating the etiology of the disease in the context of the communities where it arises. Identified risk factors, particularly smoking, given the double burden of the two highest reported cancer incidences: lung and bladder. Our results also highlight the need for both expanding research targeting bladder cancer in the country, and developing constructive preventive strategies to control incidence levels. Most data available are based on retrospective analyses, and each risk factor for UBC has to be seen in light of genetic environmental interactions to better evaluate its impact. It is evident; however, that UBC will remain frequent because of the ongoing high prevalence of smoking, which represents its main risk factor. The importance of primary prevention needs to be stressed, and smoking cessation programs should be encouraged and supported.

KEYWORDS: Histopathological, Urothelial, Carcinomas Risk Factors.

STUDY DESIGNED: Observational Study.

1. INTRODUCTION

Urothelial carcinoma of the bladder is one of the major causes of morbidity and mortality throughout the world. Urothelial carcinoma comprises approximately 90% of all primary bladder tumors and is typically seen in patients over 50 years of age but is occasionally seen in younger adults and is rare in children.¹

It is approximately three times as common in men as in women. The pathogenesis of these tumors depends on a combination of genetic and environmental factors.²⁻⁴ Among the latter, chemical factors are thought to be of great importance.⁴

Bladder tumors are common in industrial areas (especially in those associated with petrochemicals)⁵⁻⁶, and their incidence is increased with exposure to cigarette smoke and arylamines.⁷⁻⁸ Other environmental factors include aniline dyes (particularly benzidine and beta naphthylamine⁹⁻¹⁰, auramines, phenacetin and cyclophosphamide)¹¹⁻¹³.

Cigarette smoking is demonstrated to be a major independent risk factor for urinary bladder cancer. This risk increases proportionally with the frequency and duration of smoking.^[14]

Urothelial carcinoma is conventionally divided into two types, the papillary and nonpapillary (flat-sessile) types. This distinction reflects two genetic pathways believed to account for the majority of urothelial carcinomas.¹⁵ Noninvasive papillary carcinomas account for approximately 75% of newly diagnosed primary urothelial tumors of the bladder, 10% to 20% of these patients will however subsequently have an invasive tumor. Looked at from another angle, approximately 20% of patients with invasive bladder cancer have had prior noninvasive papillary lesions.¹⁶ Carcinoma in situ is most often seen with high grade papillary urothelial carcinoma; de novo carcinoma in situ accounts for only 1% to 3% of newly diagnosed urothelial carcinomas.¹⁷

The treatment of urothelial carcinoma is largely based on histological grade and stage.¹⁸

AIMS AND OBJECTIVES

1. To assess various types of urothelial carcinomas with regard to frequency, age and sex distribution, tobacco use, smoking, occupation, various other risks factors.
2. To describe the Histopathological features of various urothelial carcinomas.
3. To categorize the urothelial carcinomas according to W.H.O. (2016)/ ISUP classification.

2. MATERIALS AND METHODS

The present study is designed to conduct in Shyam Shah Medical College and Sanjay Gandhi Memorial Hospital Rewa (MP) over a period from Feb. 2021 to July 2022 (18 months) in histopathology section, department of pathology.

Sample size was approximately 50 specimen of urinary bladder urothelial carcinomas obtained in the form of TURBT biopsy and radical cystectomy urinary specimen.

All the urinary bladder biopsies, received at histopathology section will be fixed in 10% formalin followed by representative gross bits (1×1×0.2cm) thickness to be taken for study from the specimens. The tissue was processed and paraffin sections stained with

haematoxylin and eosin to be taken for microscopic examination. Tumors of urinary bladder were classified and studied according to WHO (2016)/ISUP Classification.

INCLUSION CRITERIA –

- All the urinary bladder neoplastic lesions received in the department of pathology, S.S.M.C. Rewa. Patients were contacted and detailed history regarding risk factors was taken.
- All cystectomy and trans-urethral resection of bladder specimen that was histologically diagnosed as urothelial carcinoma irrespective of age, gender, grade and stage was included in the study.

EXCLUSION CRITERIA –

1. Autolysed specimen.
2. Inadequate biopsies.
3. Non specific inflammatory conditions.
4. Non-neoplastic lesions of the urinary bladder.

METHOD OF DATA COLLECTION:

Detailed history of the cases regarding age, sex, personal history, site, type of procedure done were obtained for all 50 cases reported during the study period from surgical pathology records. All transurethral resection of bladder specimen were processed entirely and representative sections were taken from radical cystectomy specimen which were subjected for routine histopathological examination. The following clinical and pathological parameters were evaluated: age, gender, tumor site, size, tumor grade, tumor stage and invasiveness of the tumor.

STATISTICAL ANALYSIS PLAN –

Data were collected by using pre-tested and predesigned proforma. For quantitative data, mean, standard deviation etc were obtained and for qualitative data, proportion was obtained and analyzed by using statistical software or MS Excel.

3. RESULTS

Table 1- Gender wise distribution and demographic characteristic of urothelial bladder carcinoma patients

Age Group	Male		Female		Total	
	No	%	No	%	No	%
51-60	13	26.0	05	10.0	18	36.0
61-70	14	28.0	08	16.0	22	44.0
71-80	04	8.0	03	6.0	07	14.0
>80	02	4.0	01	2.0	03	6.0
Occupation						
Farmer	12	24.0	01	2.0	13	26.0
Housewife	-	-	10	20.0	10	20.0
Shopkeeper	09	18.0	-	-	09	18.0
Laborer	05	10.0	02	4.0	07	14.0
Driver	05	10.0	-	-	05	10.0
Teacher	01	2.0	03	6.0	04	8.0

Unemployed	01	2.0	01	2.0	02	4.0
Residence						
Urban	17	34.0	07	14.0	24	48.0
Rural	16	32.0	10	20.0	26	52.0

Table 2- Distribution of patients according to risk factor in urothelial cancer (n=50)

SNo.	Risk Factors	Total (n=50)	
		No	%
1	Tobacco Chewing	42	84.0
2	Analgesic Drug intake (Long term)	20	40.0
3	Schistosomahaematobium	-	-
4	Cement Exposure	4	8.0
5	Radiation exposure	2	4.0
6	Exposure to Phosphamide	-	-
Clinical Symptoms			
1	Haematuria	45	90.0
2	Frequency of micturition	48	96.0
3	Urgency	48	96.0
4	Dysuria	48	96.0
5	Pain in Abdomen	44	88.0

Table 3- Sex wise distribution of cases according to addiction

Addiction		Male		Female		Total	
		No	%	No	%	No	%
Addicted	Tobacco chewing	25	50.0	09	18.0	34	68.0
	Smoking	08	16.0	-	-	08	16.0
Non Addict		-	-	08	16.0	08	16.0
Total		33	66.0	17	34.0	50	100.0

Table 4- Distribution of patients according to Diagnosis (n=50)

SNo.	Diagnosis	Total (n=50)		
		No	%	
1	Non Invasive Urothelial Neoplasm (n=18)	Urothelial Ca in situ	03	6.0
		Urothelial papilloma	03	6.0
		Papillary Urothelial Ca High Grade	08	16.0
		Papillary Urothelial Ca Low Grade	04	8.0
2	Infiltrating Urothelial Carcinoma (n=32)	Infiltrating Urothelial Ca	13	26.0
		Infiltrating Urothelial Ca with Squamous Differentiation	19	38.0

Results: Age group starting from 50 to 85 was included in the study. Age 51-60 years were 18 (36.0%), 61-70 years were 22(44%), 71- 80 years were 7 (14%) and age >80 was 3

(6.0%). Mean age 64.66 ± 8.56 years. Male to female ratio were 2:1. Maximum numbers of urothelial cancer patients were found in 51 to 70 years (80.0%) age group (Table-1).

Among 50 cases, 12 cases were male farmer and 1 female farmer and 10 cases were housewife. 18.0% of the male patients were shopkeeper and 14.0% of the patients were laborer, 10.0% of the male patients were driver and 4.0% cases were found in unemployed. In rural area 26 (52.0%), Out of which 16 (32.0) were male patients and 10 (20.0%) were female patients. (Table-1) Tobacco chewing patients increase the risk factor of urothelial cancer as was seen in 42(84%) of patients. 20 (40.0%) cases were on analgesic drug from long term. Some patients had history of in cement exposure (8.0%) and radiation exposures (4.0%). Clinical symptoms patients found in 48 (96.0%) cases which were frequency of micturation, urgency and dysuria. 45 (90.0%) patients had haematuria and 44 (88.0%) patients had pain in abdomen. (Table-2)

The main risk factor of urothelial cancer of tobacco chewing in the maximum number of patients it was seen in 34 (68.0%), out of which 25 (50.0%) were male and 9 (18.0%) were female patients. 8 (16.0%) patients, all male, had addiction of smoking. Non addicted cases were 8 (16.0%) all were female. (Table-3)

The table 4 shows that the diagnosis of the case was found in 18 (36.0%) patients were non-invasive urothelial neoplasm and 32 (64.0%) were infiltrating urothelial carcinoma patients. In infiltrating urothelial carcinoma of the patients the most common 19 (38.0%) were infiltrating urothelial carcinoma with squamous differentiation and 13 (26.0%) infiltrating urothelial carcinoma. Non-invasive urothelial neoplasm with papillary urothelial carcinoma high grade 8 (16.0%) and papillary urothelial carcinoma with low grade 4 (8.0%) patients. (Table -4)

Table 5- Distribution of cases according to tumor invasion(n=32)

SNo.	Tumor invasion	Total (n=32)	
		No	%
1	Lamina propria	14	43.75
2	Muscularispropria	18	56.25
Lymph node status of urinary bladder (Radical Cystectomy) (n=4)			
1	Positive	01	25.0
2	Negative	03	75.0

The patients found in tumor invasion 18 (56.25%) were muscularispropria and 14 (43.75%) cases were found in lamina propria. The maximum number of patients found in lymph node status 03 (75.0%) were negative status and 01 (25.0%) cases were found in positive status. (Table - 5)

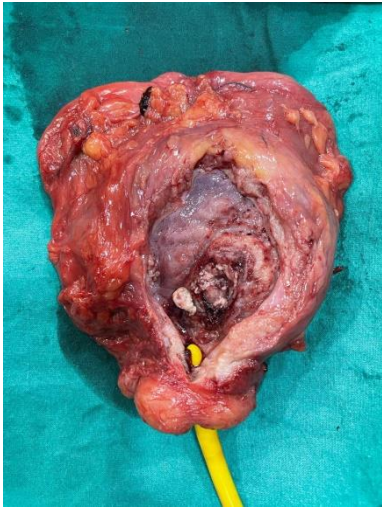


Fig A-

Fig-B

A- Resected Urinary bladder after radical cystectomy growth on lateral wall and posterior wall
B- - Urinary bladder gross features showing papillary like growth

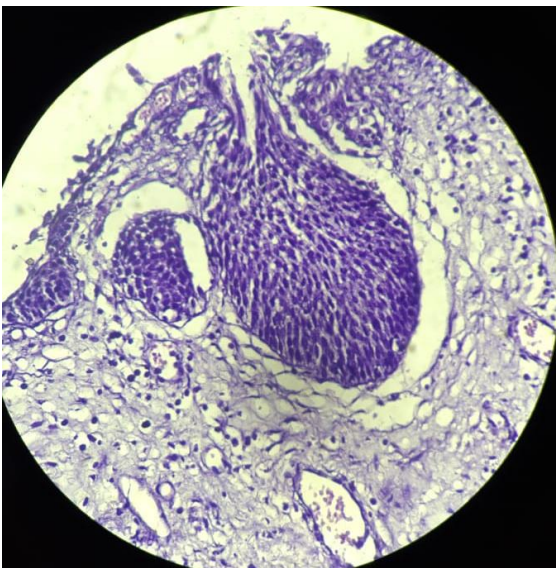


Fig.2- Carcinoma in Situ (40X). Malignant Urothelial cells (with in the bladder epithelial lining) does not invade the lamina propria.

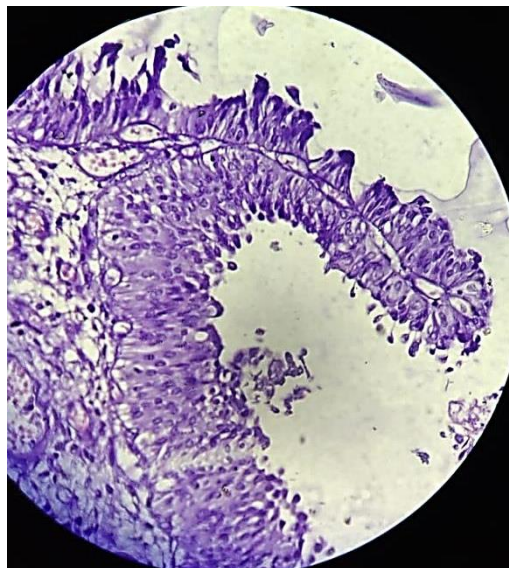


Fig.3- Papillary Carcinoma low grade (40X). Orderly arranged and fused papillae exhibiting nuclei which is larger than papilloma.

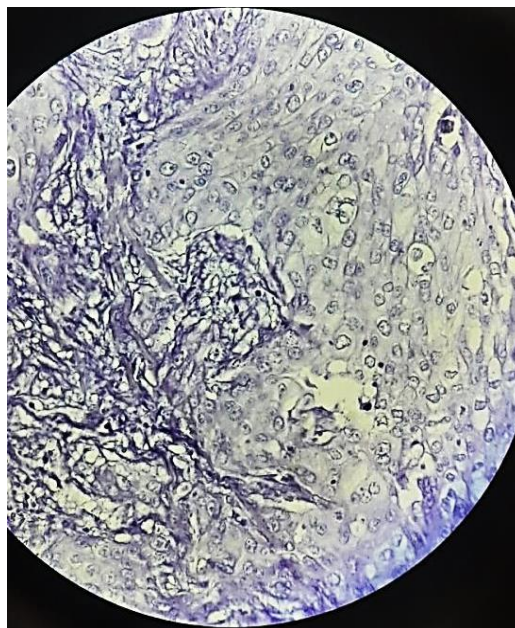


Fig.6- Infiltrating Urothelial Carcinoma with squamous differentiation (40X). The presence of intercellular bridges and/or

4. DISCUSSION

Sample size was approximately 50 specimen of urinary bladder urothelial carcinomas obtained in the form of urinary bladder biopsies.

Comparison of Age incidence with other studies

In our study the Age 51-60 years were 18 (36.0%), 61-70 years were 22 (44%), 71- 80 years were 7 (14%) and age >80 was 3 (6.0%). Mean age 64.66 ± 8.56 years. Male to female ration were 2:1. Maximum numbers of urothelial cancer patients were found in 51 to 70 years (80.0%) age group with higher age incidence noted in 6th and 8th decades. So the bladder pathology is more common in 6th and 7th decades of life. Median age at diagnosis of bladder cancer in our study was 60 years. Youngest patient affected was 52 years old, eldest patient was 83 years old.

Squires TS et al (1994) in their study found that most bladder cancers develop in later adulthood, with median age at diagnosis over 65 years of age.

Ray B et al¹⁹ (1973) described in their study that although uncommon, bladder cancer can develop in young patients and rarely in children. The vast majority of the later are low grade papillary lesions, but rare examples of aggressive epithelial tumours, have been described in the urinary bladder.

Among 50 cases of UC, majority of the patients were males 66% (n=33 cases) and above 60 years (58%, n= 29 cases). A similar observation regarding gender wise distribution of UC found in study done by Thakur et al²⁰ and age wise distribution was found in the other studies done by Gupta et al²¹ and Biswas RR et al,²² Mungan et al²³ and Quintero et al.²⁴

Bladder neoplasm was mostly seen in elderly age group (80% of the patients) which correlates with the finding of Nabi et al²⁵.

Comparison of Sex incidence with other studies

In our study, 33 cases (66.0%) were males and 17 cases (34%) were females. There was significantly greater number of males in the present study.

Boring CC et al²⁶ (1994) found that bladder cancer also has a distinctive gender distribution with a 2.7 fold higher incidence in men than women. This difference is reflected in a nearly double death rate in men.

According to Mungan et al²³ the incidence of urothelial cancer is 3 to 4 times more common in males than in females in the present study.

In our study male to female ratio is 2 : 1. In the study of Canter et al²⁷ it was 4 : 1 and the study by Nabi et al²⁵. It was 3.5:1.

Comparison of Occupation of all cases with other studies

In the present study 50 cases, 12 cases were male farmer and 1 female farmer and 10 cases were housewife. 18.0% of the male patients were shopkeeper and 14.0% of the patients were laborer, 10.0% of the male patients were driver and 4.0% cases were found in unemployed.

In the present study the maximum number of patients found in rural area 26 (52.0%), 16 (32.0) were male patients and 10 (20.0) were female patients. 24 (48.0%) were found in urban patients, 17 (34.0%) were male patients and 07 (14.0%) were female patients.

In 1954, Case et al.²⁸ reported a 200-fold increased bladder cancer risk for English and Welsh workers exposed to 2-naphthylamine.

In a Chinese cohort study, where 784 workers were exposed to benzidine, a 35-fold increase of bladder cancer risk was observed in Ma QW et al (2003)²⁹

Yu MC et al (2002)³⁰ Individuals with occupational exposure to hair dyes such as hairdressers and barbers experience enhanced risk of bladder cancer although it is unclear if other lifestyle aspects are responsible for the increase in bladder cancer risk.

Gago-Dominguez M et al (2001)³¹ In a large population-based case-control study in Los Angeles, personal use of hair dyes was assessed according to the types of hair dyes normally used and compared with people who did not use hair dyes.

Golka K et al (2004)³² An elevated bladder cancer risk was claimed for those who used permanent hair dyes at least once a month, for 1 year or longer. The risk increased to 3.3 for those who used permanent hair dyes at least once a month for 15 and more years. Hairdressers who performed their jobs for more than 10 years showed a 5-fold increased risk.

Risk Factor and Addiction

In the present study of the maximum number of patients found in 42 (84.0%) were tobacco chewing and smoking patients increase the risk factor of urothelial cancer and 20 (40.0%) cases were found in analgesic drug intake in long term use. Some patients found in risk factors for urothelial cancer in cement exposure (8.0%) and radiation exposures (4.0%).

The increased risk is similar in men and women and in different parts of the world. Nitrosamines and 2-naphthylamine are known bladder carcinogens that are present in cigarette smoke, but whether they contribute to the increased risk to tobacco smokers remains unknown.

In our study 42 patients were smokers and 08 patients were nonsmokers. All 33 patients were male and 9 were female patients. In our study, it is estimated that 84% of bladder cancer cases were related to smoking.

Clavel J et al³³(1989) estimated that 33% bladder cancer cases are related to tobacco smoke. Cigarette smokers have a 2 to 4 fold increase in risk of bladder cancer compared to non-smokers.

The risk of bladder cancer is generally more in smokers than non-smokers. We found the history of tobacco addiction for smoking in 84% and 16% in non-smokers.

Pietzaketal³⁴ suggested that smokers have three fold increased risk of developing bladder cancer than non-smokers.

Study done by Grotehivs et al³⁵ showed (50.9% / 18.8%) and Rink etal³⁶ (46.0% / 28.0%).

Alberg et al³⁷ showed the rate of bladder cancer was 22% in smokers and 52% in non-smokers whereas Tripathi et al³⁸ reported 23% in smokers and 39% in non-smokers.

Sturgeon et al³⁹ found that risks of each stage of bladder cancer increased with number of cigarettes smoked per day, but the more advanced the stage the higher the relative risk. Similarly, in this study we found that smokers were proportionally more likely than nonsmokers to be diagnosed with invasive disease and this difference was statistically significant.

Clinical Symptoms

In our study maximum number of clinical symptoms patients found in 48 (96.0%) cases which were frequency of micturation, urgency and dysuria. 45 (90.0%) patients had haematuria and 44 (88.0%) patients had pain in abdomen.

Most common clinical presentation was gross haematuria, 71% of patients which study by Nabi et al²⁵ i.e. 72%.

Roupret M et al (2018)⁴⁰The most common presenting symptom in two third of patients with UC is either gross or microscopic hematuria.

Comparison of urothelial cancer with other studies

The above table shows that the diagnosis of the case was found in 18 (36.0%) patients were non-invasive urothelial neoplasm and 32 (64.0%) were infiltrating urothelial carcinoma patients.

In infiltrating urothelial carcinoma of the patients the most common 19 (38.0%) were infiltrating urothelial carcinoma with squamous differentiation and 13 (26.0%) infiltrating urothelial carcinoma,

Non-invasive urothelial neoplasm with papillary urothelial carcinoma high grade 8 (16.0%) and papillary urothelial carcinoma with low grade 4 (8.0%) patients.

Incidences of muscular invasion in our study was found in 56% of muscularispropria and 44% in lamina propria invasion which shows our figures are slightly higher than the study by Karakiewicz et al⁴¹was found in 52% of muscularispropria and 48% in lamina propria invasion.

Histological distribution according to WHO grading reveals that the maximum number of cases (16.98%) observed TCC-low grade followed by high grade TCC with 16.67%. This correlates well with the study done by Matalaka et al (2008)⁴² which showed 40% cases of high grade TCC and 60% of low grade TCC.

Papillary urothelial Neoplasm of low malignant potential (PUNLMP) was seen in 4.01%. Jung-WeonShiam et al (2008)⁴³ showed 27.3% in his study. There was no seen in the our study.

5. CONCLUSION

In conclusion, results presented in the current study emphasize the importance of investigating the etiology of the disease in the context of the communities where it arises. Identified risk factors, particularly smoking, given the double burden of the two highest reported cancer incidences: lung and bladder. Our results also highlight the need for both expanding research targeting bladder cancer in the country, and developing constructive preventive strategies to control incidence levels. Most data available are based on retrospective analyses, and each risk factor for UBC has to be seen in light of genetic environmental interactions to better evaluate its impact. It is evident; however, that UBC will remain frequent because of the ongoing high prevalence of smoking, which represents its main risk factor. The importance of primary prevention needs to be stressed, and smoking cessation programs should be encouraged and supported.

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