

ORIGINAL ARTICLE

Impact of Smoking on High and Low-Grade Urothelial CarcinomaFIDA HUSSAIN¹, MUHAMMAD RAHIL KHAN², PARSAGHARI³, RIYASAT AHMED MEMON⁴, ZAHID ALI NOHRI⁵, AZHAR ALI⁶¹Lecturer pathology Department Bilawal Medical College for Boys Liaquat University of Medical and Health Sciences Jamshoro²Assistant professor Pathology Department Liaquat university of medical and health sciences Jamshoro Hyderabad³Resident Pathologist, Liaquat university of medical and health sciences Jamshoro Hyderabad⁴Assistant Professor, Pathology Department, Bilawal Medical College for Boys Liaquat university of medical and health sciences Jamshoro Hyderabad⁵Lecturer pathology Department Bilawal Medical College for Boys Liaquat university of medical and health sciences Jamshoro Hyderabad⁶Medical officer Rural health center Jhall MagsiCorresponding author: Fida Hussain, Email: fidahussain14942@gmail.com, Cell: +923360678576**ABSTRACT****Objectives:** This study was done to evaluate the role of smoking in high- and low-grade urothelial carcinoma.**Study design:** Cross-sectional descriptive study**Study setting:** This cross-sectional study was done at the Department of histopathology, Liaquat University of Medical and Health sciences, Jamshoro, Pakistan.**Methods:** Total 165 cases of urothelial carcinoma were included in this study. The clinical history of patients was taken from computer storage data followed by review of microscopic slides by two histopathologists. Excel 2021 and SPSS 22 were used for statistical analysis.**Results:** A total of 165 cases were enrolled in the study. 55.15% (n=91) were smokers. Smoking history was positive in most cases of low-grade urothelial carcinoma. Follow up of patients was taken at 24 months after biopsy or resection of tumor. Patient with high grade urothelial carcinoma poor outcome i.e., 53.3% dead at the follow up taken at 24 months.**Conclusion:** In conclusion, urothelial carcinoma is an aggressive malignancy which has strong association with smoking. Patients with positive smoking history present with higher stage and grade of disease. Early intervention in form of strict follow up and smoking cessation should be done in patients to ensure prompt treatment.**Keywords:** High grade urothelial carcinoma, Low grade urothelial carcinoma, Smoking**INTRODUCTION**

Urothelial carcinoma is subdivided as high- and low-grade urothelial carcinoma which can be muscle invasive or without invasion.^{1,2} Urothelial carcinoma exhibits a varied distribution of features. On histological staining various subtypes have been identified including micropapillary, microcystic, tumor with nests and sheet pattern, sarcomatous and plasmacytoid. These types have also been recognized as pure urothelial and non-urothelial types. These subtypes have been identified on hematoxylin and eosin sections. There has been increased awareness among the pathologist regarding various urothelial carcinomas. However, there has been inconsistency in diagnosis of urothelial carcinomas and upon second review, the diagnosis has been further classified into various types. In a study, almost 44% cases with variant histology have been missed by the primary pathologist. Various histologic subtypes in urothelial carcinoma have their own diagnostic and prognostic significance and their impact on therapeutic benefit is also varied. When the histology accurately predicts urothelial carcinoma subtypes, it guides the concerned physician on how the patients get specific treatment according to the subtype. The treatment approach in case of pure urothelial and variant urothelial carcinoma is different. Cases with variant histology are often very aggressive at presentation carry dismal prognosis however if treated early help in risk stratification of patient and carry equal prognosis as that of pure urothelial carcinomas. Few variants are quiet sensitive to chemotherapy such as small cell carcinoma where chemotherapy is the mainstay of treatment.³

Bladder cancer is a common entity worldwide. The tumors without muscle invasion were classified as superficial but this term is no longer used as such tumors have lamina propria invasion. Patient with low grade tumors often have near 50% risk of developing recurrence of tumor. With use of recent cystoscopy technologies, early diagnosis of urothelial tumors can be made and better management of patients can be done.⁴

Urothelial is regarded as the major cause of cancer related death. Almost 165000 deaths are reported annually. With first presentation, mostly patients only have non muscle invasive urothelial carcinomas where only submucosal or muscularis propria invasion is identified. These tumors however lately present with muscle invasive urothelial carcinoma. High grade urothelial carcinoma has higher risk of progressing to muscle invasive tumor.

High grade urothelial tumors have different clinical behavior. The management ranges from trans urethral resection to cystectomy. There has not been enough data published on how prognosis is defined in high grade urothelial tumor that are not muscle invasive. Lamina propria invasion also has impact on outcome while lymphovascular invasion and the size of tumor and age also indicate poor prognosis. Even though there are some defined prognostic indicators in urothelial carcinoma, still it is difficult to elaborate prognosis in these tumors.⁵

Urothelial tumors without muscle invasion have to be monitored and kept on long term follow up. Cystoscopy is often recommended for such patients. Urine sample cytology can also be done for the presence of atypical cells but it is highly subjective to the expertise of the histopathologist. Access to cystoscopy is often limited as it is a costly procedure and flat invasive lesions can be missed in almost up to 40% of cases. Few other noninvasive tests are also done but the diagnostic accuracy is not comparable to that of cystoscopy. There is a need to find such diagnostic modalities to improve the detection of such tumors.⁶

Bladder cancer with its high rate of recurrence poses socioeconomic burden on the society due to its high mortality and morbidity.⁷ The exact pathogenesis is not well defined. Smoking and industrial chemicals are considered as the causative agents in urothelial cancers.^{8,9} Despite improvements in the diagnosis of bladder lesions, there is still a need to find association of causative agents in urothelial tumors. This study was aimed to identify the impact of smoking in high- and low-grade urothelial tumors and to see outcome of patients at follow up of 2 years.

METHODS

This cross-sectional study was done at the department of histopathology, Liaquat university of medical and health sciences Jamshoro Sindh. Total 165 cases of urothelial tumors were retrospectively taken and included in the study. Two histopathologist reviewed the slides or confirmation of diagnosis. All the cases of urothelial carcinoma diagnosed at the dept of histopathology from 2019 to 2020 were included in the study. Excel 2021 and SPSS version 22 were used for statistical analysis. Descriptive statistics were applied to calculate frequency and percentages. Frequency and percentage were calculated for qualitative variables such as histopathological grades. This study

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RESULTS

A total of 165 cases were enrolled in the study. 55.15% (n=91) were smokers. Smoking history was positive in most cases of low-grade urothelial carcinoma. (table 1)

Table-1: Baseline characteristics of all cases

Grade	Smokers n (%)	Nonsmokers n (%)	Total
High grade urothelial carcinoma n (%)	56 (47.4)	62 (52.54)	118
Low grade urothelial carcinoma n (%)	35 (74.46)	12 (25.53)	47
Total	91(55.15)	74(44.84)	165

Follow up of patients was taken at 24 months after biopsy or resection of tumor. Patient with high grade urothelial carcinoma poor outcome i.e., 53.3% dead at the follow up taken at 24 months. (table 2)

Table-2: Association of outcomes among all cases

Patient outcome	High grade urothelial carcinoma (n=118)	Low grade urothelial carcinoma (n=47)
Alive	55 (46.6)	26 (55.3)
Dead	63(53.3)	21 (44.6)

DISCUSSION

Bladder cancer represents one of the most common malignancies with radical cystectomy the standard choice of treatment. Cystectomy is not only done in muscle invasive urothelial tumor but also in non-invasive tumors which have higher risk of recurrence. But it carries its own complications and morbidities. Along with industrial agents and other etiological chemical, smoking is regarded as a major risk factor in urothelial tumors. It is not only causative agent but is also an indicator of prognosis in the long-term prediction outcome of bladder cancers. Riccardo et al¹⁰ reported highest rate of pre and post op complications when the patients are chronic smokers. Not only the narcotic agents cause infections but also influence the outcome in terms of mortality. Awareness on cessation of smoking should be practiced in patients undergoing radical cystectomy and strict surveillance is recommended.¹⁰

Smoking carries up to 7-fold increased risk of developing urothelial tumors. Male gender, lynch syndrome and renal stones are some of the other known risk factors. Positive family history has little known impact on urothelial carcinoma.¹¹ Despite advancement in the screening tools, such tumors often present at later stages. A better understanding of these etiologies can definitely impact the long-term outcome of bladder tumors. Keng et al¹² reported a study where 864 cases were enrolled and long term follow up revealed increased disease burden and aggressive outcome in patients who were smokers. Such patients not only had metastatic disease at presentation but also had recurrent tumors ultimate undergoing radical urethrectomy. Another interesting factor in this study was the better outcome of patients who left smoking 10 years ago.¹²

Women often present with late and advanced disease as the diagnosed is often underestimated and the symptoms are correlated to urinary tract infections. Females with non-muscle invasive tumors have higher rate of recurrence as compared to male. Male carry an overall increased risk of developing these malignancies. The reason behind this is unknown. Almost half of the patients with urothelial carcinomas have a positive history of smoking. Aromatic amines and hydrocarbons in smoke are released from the body from kidneys and cause local damage in the transitional lining leads to DNA alteration and damage. They can lead to either muscle invasive or non-muscle invasive disease. Florian et al reported highest rate of smoking in southeast Asian men. Women tend to develop different smoking pattern as

compared to men and have lesser intake of carcinogen inside than males, however males take cigarette more frequently and the intake is also more as compared to male. These assumption are also theoretical findings and prove no authentic basis on the etiology of bladder cancer in male. But in the light of recent finding the number of females who smoke are increasing still it does not affect the gender discrepancy in pathogenesis of urothelial carcinoma. Certain genetic and environmental factors have been related to the incidence of urothelial carcinoma in both genders but females still present late in the course of disease and carry bad prognosis as compared to males. Few studies also correlate increased BMI to urothelial carcinoma but the evidences are very limited. Further studies also need to be done on evaluating any association between postmenopausal age¹³ and smoking. Alcohol intake and arsenic also known risk factors which have to be studied further.¹⁴

Known smokers with urothelial carcinoma have an aggressive course of disease.¹⁵ Not only they are at young age at presentation but also have dismal prognosis. The lesion is frequently high grade and with variant morphology and are associated with increased tumor size. Heavy smokers also have more risk of muscle invasion in comparison to patients with no positive history. Duration of smoking as well as the number of packs per year is also significant in tumor prognosis as it carries an impact on stage.¹⁶

CONCLUSION

In conclusion, urothelial carcinoma is an aggressive malignancy which has strong association with smoking. Patients with positive smoking history present with higher stage and grade of disease. Early intervention in form of strict follow up and smoking cessation should be done in patients to ensure prompt treatment.

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