



ORIGINAL RESEARCH PAPER

Pathology

CLINICAL RISK FACTORS OF URINARY BLADDER TUMORS: A ONE YEAR STUDY IN TERTIARY HEALTH CARE CENTRE

KEY WORDS:

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ABSTRACT

Introduction: Urinary bladder cancer is emerging as a major health issue among elderly population. It is the second most common urological malignancy after prostate cancer and represents a heterogeneous group of neoplasms. Bladder cancer is a complex pathologic process. Various factors are involved in its etiopathogenesis. The present study was conducted to evaluate various clinical risk factors associated with urinary bladder cancer. **Methods:** This was a cross-sectional, observational study carried out for a period of one year in the Department of Pathology and Urology, Indira Gandhi Medical College, Shimla. One hundred and ninety seven patients (TURBT and radical cystectomy) with primary epithelial urinary bladder cancer were included in the study. However, patients with inflammatory and metastatic lesions of urinary bladder and post chemoradiotherapy were excluded from the study. The various clinical risk factors like age (<60 years or ≥60 years), sex (male/female), grade (high/low), smoking and occupation history of the patients were evaluated. **Results:** The age of patients ranged from 36 to 89 years with mean age of 62 years. Male preponderance was observed with male to female ratio of 6.9:1. Most common clinical presentation was painless hematuria found in 173 (87.8%) patients. Majority, 141 (71.6%) patients, were smokers and 113 (57.4%) patients had agricultural background. Among urothelial tumors (193), majority, 126 (65.3%) cases, were high-grade urothelial carcinoma followed by 67(34.7%) cases of low-grade urothelial carcinoma. **Conclusions:** In the present study, majority patients were elderly males who were smokers and had agricultural background. Smoking and occupational exposure to various carcinogens present in fertilizers, pesticides could be the predisposing factor in bladder carcinogenesis. Prevention of these risk factors can lead to decreased burden of urinary bladder carcinomas.

INTRODUCTION

Diseases of urinary bladder both neoplastic and non-neoplastic, are an important public health problem. Urinary bladder cancer accounts for nearly 3.0% of all new cancer diagnosis and 2.1% of all cancer deaths globally¹. It is the tenth most common cancer in the world, ranking 6th among men and 17th in women². Worldwide, the lifetime risk of getting urinary bladder cancer is 1.1% in men and 0.27% in women³. However, significant variation in the incidence has been noted in different geographical regions; highest in Europe and North America whereas lowest rates are seen in Sub-Saharan Africa, Mexico and some middle Eastern and Central Asian countries⁴. It is the 19th most common cause of cancer death in India leading to 10,291 deaths in 2018⁵.

Various factors are involved in its etiopathogenesis⁶. Tobacco smoking is well established risk factor of bladder cancer both in men and women⁶. Tobacco increases the relative risk of developing bladder cancer by 3 to 4 times in smokers than in non-smokers^{6,7}. Association of tobacco smoking and bladder cancer varied from 75 to 80% in men and 35% in women⁸. Although specific carcinogen responsible for bladder cancer in tobacco smoke is not yet identified, however 4-aminobiphenyl and beta-naphthylamine have been implicated as the concentration of these compounds is high in the urine of smokers. Increase in p53 mutation in urothelial cells of smokers than non-smokers have been observed by some authors. Some of the studies have found that bladder cancer in smokers is often more invasive than in non-smokers^{9,10}.

Occupational exposure has been identified as the other most important risk factor for bladder cancer. Workers in tobacco, dye, rubber, printing, leather industries, chimney sweeps, aluminium workers, drivers, agriculture workers and oil workers are at increased risk for bladder cancer secondary to environmental exposure to aromatic amines and polycyclic aromatic hydrocarbons e.g. beta naphthyl amine, 4-amino biphenyl, 4-chloro-ortho-toluidine and benzidine^{11,12}. Increased risk of bladder cancer is related to the duration of exposure. There is approximately 3.6-fold increased risk with more than 10 years of employment^{13,14,15}. Chlorination of drinking water and trimethanes are also a risk factor of bladder cancer¹⁶.

Exposure to certain drugs like cyclophosphamide used in chemotherapy & heavy consumption of phenacetin containing analgesics, pioglitazone has also been shown to cause bladder cancer in humans¹⁷.

Chronic urinary tract infections particularly by Schistosoma hematobium are an important cause of bladder cancer especially in endemic areas. Others causes are catheterization, HPV, chronic lithiasis. Low hydration state, physical inactivity, eating processed meat, low levels of vitamin A, D and E, diabetes, obesity are also considered as potential risk factors for urinary bladder cancer¹⁸. However, alcohol intake does not increase the risk of bladder cancer¹⁸.

Nearly 7% cases of bladder cancer are familial. Most common hereditary links that increase the risk of bladder cancer are genetic-factors such as null GSTM-1 and slow NAT-2 polymorphism. N-acetyltransferase enzyme (NAT) inactivates the carcinogenic aromatic and heterocyclic amine compounds, so the germline polymorphisms in NAT-2 that lead to its slow activity; increase the risk of bladder cancer. Mutations involving TP53, RB, PTEN pathways are most commonly associated with invasive carcinoma¹⁹.

Majority of the bladder cancer cases are urothelial cancers comprising more than 90 percent of cases. Low grade papillary urothelial carcinoma are mostly non-invasive or limited up to lamina propria. High grade papillary urothelial carcinoma shows much higher frequency of muscle invasion as compared to low grade papillary urothelial carcinoma. None of the cases of papilloma or PUNLMP show invasion^{20,21}. Hence, the present study was conducted to evaluate the various clinical risk factors associated with urinary bladder cancer.

METHODS

This was a cross-sectional, observational study carried out between June 1, 2019 to May 31, 2020 for a period of one year in the Department of Pathology and Urology, Indira Gandhi Medical College, Shimla. Patient consent and ethical clearance from institutional ethical committee was taken. One hundred and ninety seven patients (TURBT and radical cystectomy) with primary epithelial urinary bladder cancer were included in the study. Patients with

inflammatory and metastatic lesions of urinary bladder and post chemoradiotherapy were excluded from the study.

Clinical presentation, smoking and alcohol history of these patients were noted. All samples were fixed in 10% neutral buffered formalin and paraffin embedded. Diagnosis was made as per WHO/ISUP classification (2004)²². Urothelial tumors were graded into low grade and high grade categories and their invasion into lamina propria and muscularis propria was assessed according to WHO/ISUP (2004) criterion.

RESULTS

One hundred ninety seven specimens including both TURBT (191) and cystectomy (6) were received in the Department of Pathology. The age of patients ranged from 36 to 89 years with mean age of 62 years. Male preponderance was observed in this study with male to female ratio of 6.9:1. Majority, 141 (71.6%) patients, were smokers and 113 (57.4%) patients had agricultural background. Most common clinical presentation was painless hematuria found in 173 (87.8%) patients followed by lower abdominal pain (5.6%), urinary flow obstruction (4.6%) and dysuria (2%).

Most common histological type found was urothelial carcinoma (98%) followed by other types such as squamous cell carcinoma (1%), small cell carcinoma (0.5%) and adenocarcinoma (0.5%). Among urothelial tumors (193), majority, 126 (65.3%) cases, were high-grade urothelial carcinoma followed by 67(34.7%) cases of low-grade urothelial carcinoma.

Out of 67 cases of low grade urothelial carcinoma (LGUC), in 11 cases no muscle tissue was included in the specimen. Hence, invasion was assessed in 56 cases. Out of 126 cases of high grade urothelial carcinoma (HGUC), in 4 cases no muscle tissue was included in the specimen. Hence, invasion was assessed in 122 cases. (Table 1)

Table 1. Invasion in different histological grades of urothelial tumors

Grade of tumor	Non-invasive	Invasive		Total Cases
		Invasion up to lamina propria	Invasion into lamina propria and muscle	
LGUC	46(82.1%)	10(17.9%)	-	56
HGUC	3(2.4%)	24(19.7%)	95(77.9%)	122

DISCUSSION

Majority of urinary bladder tumors are of urothelial origin (>90%) and exhibit diverse biological behavior, ranging from relatively benign to highly malignant.

Urinary bladder cancer is usually seen as a disease of advanced age with most patients more than 60 years old. However, with increased health awareness and advent of various newer diagnostic techniques many new cases of bladder carcinomas are being diagnosed at a relatively younger age^{7,20,21}.

Most studies have reported male to female ratio of 3 to 4:1. Higher incidence in males is probably due to difference in smoking habits, occupational exposure to various carcinogens, anatomical differences or hormonal influences. Androgenic hormones as opposed to estrogen may stimulate or do not inhibit oncogenesis. In women it is usually diagnosed at a more advanced stage and has high mortality than in men. The reasons for this could be multifactorial such as thinner bladder wall in women, hormonal differences or late presentation to health care services due to social reasons⁴.

The clinical presentation of bladder cancer is diverse.

Commonest clinical presentation is painless hematuria (>90%) which is due to direct hemorrhage of the tumor. Other symptoms that are also present but with much less frequency are dysuria, urgency, frequency, palpable pelvic mass, weight loss etc. Frequency, nocturia, and urgency are symptoms of vesical irritability which can be seen in association with hematuria. Flank pain can be a symptom of advanced bladder cancer due to invasion of bladder muscular wall or the ureter. Patients with large volume disease, muscle invasive tumors or metastatic disease may present with anemia, anorexia, weight loss and abdominal mass²³.

Smoking and occupational exposure to various chemical carcinogens are the most documented and established risk factors for urinary bladder cancer. Tobacco increases the relative risk of developing bladder cancer by 3 to 4 times. In the present study, history of smoking was present in 141 (71.6%) patients. Agriculture workers, workers in tobacco, dye, rubber, printing and leather industries etc. are at increased risk for bladder cancer secondary to environmental exposure to aromatic amines and polycyclic aromatic hydrocarbons e.g. beta naphthyl amine, 4-amino biphenyl, 4-chloro-ortho-toluidine and benzidine^{11,12}. Majority 113 (57.4%) patients in our study cohort had agricultural background. The presence of benzidine and dichlorodiphenyl-trichloroethane (DDT) in fertilizers, pesticides and herbicides could be the predisposing factor.

In the present study, among urothelial tumors (193), majority, 126 (65.3%) cases, were high-grade urothelial carcinoma followed by 67 (34.7%) cases of low-grade urothelial carcinoma. Papilloma and PUNLMP were not seen. Similar observations were made by Goyal VK et al²⁰ and Gupta A et al²¹.

Low-grade urothelial carcinoma are mostly non-invasive or limited up to lamina propria. High grade urothelial carcinoma shows much higher frequency of muscle invasion as compared to low grade urothelial carcinoma.

CONCLUSION

Urinary bladder cancer is a major health problem in elderly population and contributes towards significant morbidity and mortality. In the present study, majority patients were elderly males who were smokers and had agricultural background. Smoking and occupational exposure to various carcinogens present in fertilizers, pesticides could be the predisposing factor in bladder carcinogenesis.

Prevention of these risk factors can significantly decrease the overall burden of urinary bladder carcinomas.

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