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Role of smoking on pathological grading of bladder cancer: Retrospective study

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Abstract

Background: Bladder cancer being the fifth most prevalent cancer in males and twelfth most common cancer in females because of its lethality is known to account for three percent of cancer deaths. Besides the genetic factor, one of the main cause for occurrence of bladder cancer is the environmental factor. Smoking is one the main factor associated with the bladder cancer. It is also known to be resulting in increased prevalence of muscle invasive bladder cancer. The aim of our study is to evaluate the role of smoking and smoking history on the pathological grading of bladder cancer.

Material and Method: Retrospective data of 70 cases of bladder cancer was collected from January 2015 to January 2019 of the bladder cancer patients. And the data was analysed for the smoking history and the pathological grading and size of tumour on imaging.

Results: Amongst smokers there was found to be a total of 88.64% cases with invasive tumours of which 76.92% cases were high grade and 23.07% were low grade tumours while 11.36% were non-invasive tumours. While amongst non-smokers 69.23% cases were of non-invasive tumours while 30.76% were invasive tumours of which 75% were low grade tumours and 25% were high grade tumours. Also there was also found to be more prevalence of large size tumours on imaging amongst the smokers in comparison to non-smokers.

Conclusion: Smoking seems to be associated with worse pathological staging and large size bladder tumours.

Keywords: smoking, bladder cancer, pathological stage

Introduction

Urinary bladder cancer is the fifth most prevalent cancer among men and ranks twelfth among women. Bladder cancer being a lethal disease accounts for three percent of all cancer deaths [1]. The median age of bladder cancer diagnosis is 70 years for men and women, and the incidence of and mortality from the disease increase with age. Males are 3 to 4 times more likely to develop bladder cancer than females, presumably because of an increased prevalence of smoking and exposure to environmental toxins [1, 2]. Tobacco is the main known cause for urothelial cancer formation, particularly cigarette smoking, and accounts for 60% and 30% of all urothelial cancers in males and females, respectively [3, 4, 5, 6]. The relative risk of developing urothelial cancer from smoking is 2.8 and 2.73 in men and women, respectively [4]. Overall there is a two to six times greater chance of developing urothelial cancer with smoking, and the intensity and duration of smoking are linearly related to the increased risk, with no clear plateau level [5, 6]. If a person smokes for 1 to 10 years versus more than 40 years, the relative risk of bladder cancer is 1.2 versus 3.0, respectively [7]. If a person smokes for more than 60 years, he or she has a six fold increased risk of developing urothelial cancer compared with a non-smoker [8]. The risk of second hand smoke in bladder cancer formation is low and not statistically different from that for non-smokers [9]. Urothelial carcinoma is the most common malignancy of the urinary tract and is the second most common cause of death among genitourinary tumours. At initial presentation, 80% of urothelial tumours are non–muscle invasive. There are multiple growth patterns of urothelial cancer, including flat carcinoma in situ (CIS), papillary tumours that can be low or high grade, and sessile tumours with a solid growth pattern. The pathological grading and staging of bladder cancer determined by histopathological examination plays an important prognostic factor. Also it determines the severity of the tumour. In our present study the aim was to evaluate the role of smoking with the pathological grade of bladder tumour.

Methods

Retrospective data of patients diagnosed with bladder cancer was collected between January 2015 and January 2019 and the cases were reviewed. The details of the cases were reviewed. The age at first diagnosis, smoking status, grade of primary tumour and size of lesion were evaluated. Cases who had no details of smoking history were excluded from the study. Patients who were active smoker or former smoker were categorized into Group I and those who were non-smokers were categorized into Group II. Pathological staging and grading of both the groups was compared. The grading of samples was performed according to WHO system in 2004, and staging system was performed according to AJCC 8th edition TNM classification.

Statistical comparison of two groups were performed with a non-gaussian distribution. Pearson's chi square test and fisher's exact test were used to compare categorical variables. Logistic regression analysis was used when the independent variables include nominal measures and outcome variables was binary. This analysis was also used to interpret odds ratios with 95% confidence intervals. The statistical significance was accepted when $p<0.05$.

Results

Total 70 patients recorded were analysed between the duration from January 2015 to January 2019. Out of them 44 were smokers and 26 were non-smokers. The data was analysed regarding there first age of presentation with symptoms, smoking history, size of tumour and pathological staging of tumour.

Table 1: Age at presentation of first symptoms

Age at presentation of symptoms	Smokers	Non-smokers
Less than 30 years	1	0
30 to 45 years	4	2
45 to 60 years	8	5
More than 60 years	31	19

Out of 70 patients there were 50 cases (71.42%) whose age at presentation was more than 60 years, 13 cases (18,75%) with age at presentation to be between 45 to 60 years, 6 cases (8.5%) with age between 30 to 45 years and 1 case (1.42%) with age less than 30 years at initial presentation.

Table 2: Pathological grading

Pathological Grading	Smoker	Non-Smoker
Superficial non-invasive carcinoma	5	18
Invasive carcinoma	39	8
Low grade	9	6
High grade	30	2

Amongst the non-smokers 18 cases (69.23%) presented with superficial non-invasive tumours while 8 cases (30.76%) had invasive tumours of which 6 cases (75%) were low grade tumours while 2 cases (25%) were high grade tumours. Whereas in case of smokers 5 cases (11.36%) were superficial non-invasive tumours while 39 cases (88.64%) were invasive tumours of which 9 cases (23.07%) were low grade tumours while 30 cases (76.92%) were high grade tumours.

Table 3: Size of tumour on imaging

Size of tumour on imaging	Smoker	Non-smoker
Less than 3 cm	6	14
3 to 5cm	15	8
More than 5 cm	23	4

Amongst the non-smokers, 14 cases (53.84%) had size less than 3 cm, 8 cases (30.76%) size was between 3 to 5 cm and in 4 cases (15.38%) the size was found to be more than 5 cm. In case of smokers, 6 cases (13.63%) had size less than 3 cm while 15 cases (34.09%) and 23 cases (52.27%) had tumour size between 3 to 5 cm and more than 5 cm respectively.

Table 4: Smoking history

Smoking history	Superficial non-invasive	Low grade invasive	High grade invasive
Less than 10 years	4	4	3
10 to 20 years	1	6	5
20 to 30 years	0	3	7
More than 30 years	0	1	10

Of total 44 smokers, the cases presenting with superficial non-invasive tumours had 4 cases (80%) with smoking history less than 10 years and 1 case (20%) with duration between 10 to 20 years. Amongst the low grade invasive tumours 4 cases (28.57%) had duration less than 10 years of smoking while 6 cases (42.85%), 3 cases (21.42%) and 1 case (7.14%) had history of smoking duration 10 to 20 years, 20 to 30 years and more than 30 years respectively. For the high grade invasive cancer 2 cases (8%) had duration less than 10 years while 5 cases (20%) had duration between 10 to 20 years, 6 cases (24%) had duration between 10 to 20 years and 12 cases (48%) had duration more than 30 years.

Discussion

The occupational exposure to aromatic amines, polycyclic aromatic hydrocarbons, chlorinated hydrocarbons and smoking play an important role in development of bladder cancer. It has been also shown in various studies regarding high grade bladder tumours more likely to be developing in people with high risk occupations like working in dye, paint and metal industries, petroleum products industries. The association of cigarette smoking and bladder cancer has been known for more than 60 years and accounts for about 50% of cases [10]. Moreover, cigarette smoking increases the risk of recurrence and progression of non-muscle invasive bladder cancer [11].

There are two main mutation pathways responsible for development of bladder cancer. The Fibroblast Growth Factor Receptor-3 pathway and p53 oncogene pathway. The Fibroblast Growth Factor Receptor-3 (FBFR-3) mutation is significantly associated with lower grade tumour development. [12] The p53 oncogene mutation on the other hand is responsible for higher grade tumour development. Smoking is associated with development of higher grades of bladder cancer and this takes place through mutations from both the pathways. This being the reason for increased prevalence of aggressive cancer among smokers in comparision to non-smokers. In our study the prevalence of invasive tumours was around 88% in smokers when compared to non-smokers where prevalence was 30%.

Age and gender are also important factor regarding development of bladder cancer. It is more prevalent in males. However the prognosis in women is worse. Women who smoke have shown an increased risk of invasive bladder cancer when compared to men who smoke [13]. Bladder cancer mostly affects people in middle age and advanced age with more than 90% cases presenting at age of 60 years and above. Sturgeon *et al* [14] showed that cigarette smoking increased risk of muscle invasive tumours in patients younger than 60 years.

In a recent study, Jiang *et al*. [13] reported that incidence of advanced stage bladder tumours especially muscle invasive bladder tumours was higher in smokers. The same study also reported that, as smoking duration and intensity Increased high grade tumours and muscle invasive tumours were detected at twice the rate than low grade tumours. In our study also it was found that as the duration of smoking increased there was more incidence for higher grade and invasive tumours.

The risk of developing bladder cancer is directly related to the duration and intensity of cigarette smoking [15]. In a study showing relationship between smoking and bladder cancer stages and grades, it was reported that active smokers had higher grades and stage when compared to non-smokers and those who had quit smoking. The duration of smoking and quitting cigarette smoking affects risk of bladder cancer [16].

There is an association between the presence of the factor of smoking and also the duration of smoking with the occurrence of more aggressive form of bladder tumour. Measures to reduce the incidence of smoking in individuals over the years is resulting in decrease of morbidity and mortality from the bladder cancer.

Conclusions

Under the light of the data smoking seems to be associated with presentation of worse pathological features and more aggressive forms of bladder tumour.

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