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Original Articles

Evaluation of recurrence of non-muscle invasive urinary bladder cancer after transurethral resection among the smokers and non-smokers: A single centre experience

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Abstract

Background: Cigarette smoking is the most well-established risk factor for developing bladder cancer. **Objective:** To investigate the role of smoking as a risk factor for recurrence of non-muscle invasive transitional cell carcinoma (TCC) of the urinary bladder after transurethral resection. **Materials & Methods:** In this prospective comparative study from January, 2010 to December, 2013 with newly diagnosed non-muscle invasive transitional cell carcinoma of the urinary bladder recruited from Rajshahi Medical College Hospital were selected and divided into smokers (60 patients) and non-smokers (60 patients) group. Data were obtained from 120 patients during a prospective phase of 4 schedules of three monthly cystoscopic follow-up on the 3rd, 6th, 9th and 12th month after transurethral resection (TUR) to compare the recurrence rate between the smokers and non-smokers. Smoking status (obtained when entering the study) was matched with other known risk factors and the effect of smoking on size, number, presenting grade and stage of TCC in each group was evaluated. **Results:** Recurrence rate in smokers group was 36.67% and in non-smokers group was 23.33 %. **Conclusion:** Smoking not only induces bladder cancer, but also, once it develops, it can increase the post resection recurrence rate, resulting in worse prognosis. Another significant factor, that predicts a shorter recurrence free survival among the smokers compared with non-smokers. Painless haematuria is the most common presentation and greater awareness is needed not to overlook the bladder cancer.

Key Words: Urinary bladder cancer, Smoking, Recurrence, Survival.

Introduction

Urinary bladder is the most common site of involvement with cancer in the urinary tract system. Among the best established risk factors for the development of the urinary bladder cancer, there is a strong association between it and cigarette smoking. While specific industrial chemicals have been linked to the development of this disease, 60% of bladder cancers are estimated to result from smoking[1]. Therefore; cigarette smoking is the most important risk factor for the development of TCC of the urinary bladder[2]. Experimental evidence suggests that, nitrosamines, 2-naphthylamine and 4-aminobiphenyl might be the bladder carcinogens in cigarette smoke[3]. These amines cause oxidative DNA damage in the normal urothelium and induce bladder cancer[4]. The association between bladder cancer and smoking has been studied and evaluated from different aspects, especially in relation to gender[5,7], intensity and duration of smoking [8,9], ceasing smoking[8], environmental tobacco smoking[6,9], and cigarettes vs. other types of smoking[6,10]. It is not clear whether smoking contributes to the development of higher grades and stages of bladder cancer. Studies assessing this issue are few and have given conflicting results. Because, smoking has a well-known causal association with bladder cancer, one could hypothesize that, there is also a relationship between smoking status and clinical prognosis concerning the chances of recurrence and progression. This study was designed to evaluate the role of smoking in prognostic characteristics

of transitional cell carcinoma of the urinary bladder.

Materials & Methods

This study began in January, 2010 and concluded in December, 2013 (4 years) on patients presented with painless haematuria (sometimes with dysuria and frequency) and got admitted in Rajshahi Medical College Hospital. Those patients who revealed urinary bladder tumour(s) on abdominal ultrasonography with no abnormality elsewhere had undergone cystoscopic examination. When bladder cancer was identified on cystoscopy, the location, number and nature of the disease were recorded. A transurethral resection of the bladder tumor (TURBT) was performed using 1.5% Glycine as an irrigant. A deep biopsy was taken separately to include the detrusor muscle. Only the newly diagnosed non-muscle invasive transitional cell carcinoma of the urinary bladder obtained from cystoscopic biopsy was selected and divided into smokers (60 patients) and non-smokers (60 patients) group. Data were obtained from 120 patients during a prospective phase of 4 studies with 4 schedules of cystoscopic examinations. We reviewed the records of the 120 patients who had undergone transurethral resection of a bladder tumour and were diagnosed as non-muscle invasive bladder cancer. We documented their cigarette smoking habit, and patients were categorized into two groups accordingly, i.e. smokers and non-smokers. We then compared the grade and stage of cancer among these two groups. Grade-I and Grade-II tumors are considered as well and moderately differentiated respectively. For stage, Ta tumors indicate non-invasive papillary carcinoma and T_1 tumors invade the subepithelial connective tissue. Each patient was evaluated with bladder ultrasound and cystoscopy on the 3rd, 6th, 9th and 12th months (i.e. every three months for one year). At each cystoscopy, any tumor or abnormal looking urothelium was resected and the resected tissue was sent for histopathological examination to confirm the recurrence. Recurrences were considered early if they occur within the first 12 months of follow-up. After explanation of the study purpose, an informed consent was taken from the patients.

All clinical informations including history, physical findings and investigation reports were collected and recorded in a pre-designed data collection sheet. Data were expressed as mean ± standard deviation (SD) or number (%). Comparison between numerical data was performed using the unpaired student's 't' test while comparison between categorical data was done using the Chi square test. The SPSS (Statistical Package for Social Science) computer program (version 11 windows) was used for data analysis, *p value* less than or equal to *0.05* was considered significant.

Results

In our study, a total of 120 patients of non-muscle invasive transitional cell carcinoma of the urinary bladder were included whose complete records were available. Over 90% of patients presented with painless haematuria. The next most common symptoms were dysuria and frequency. The mean age at presentation was 61.74±13.64 years (range: 26-85 years).

Gender distribution of the patients

The male patients were 60 out of 60 patients (100%) and no female patient (00%) in the smokers group. On the contrary, in the non-smokers group, the male patients were 52 out of 60 patients (86.67%) and female were 8 out of 60 patients (13.33%). So, grand total was, male 112 (93.33%) and female 8 (6.67%). In our study regions, the male to female ratio for incident

bladder cancer was 15 **:** 1 based on a male standardized incidence rate of 93.33% (112 cases) and a female standardized incidence rate of 6.67% (8 cases). To determine the proportion of the male excess that may be due to cigarette smoking, we calculated the attributable risk for bladder cancer associated with cigarette smoking for men and women based on data from our study. The smokers were asked to report whether they typically inhaled into the mouth only, into the throat or into the chest. The magnitude of risk was higher for subjects who inhaled into the throat or chest compared with those who inhaled only into the mouth at each level of duration.

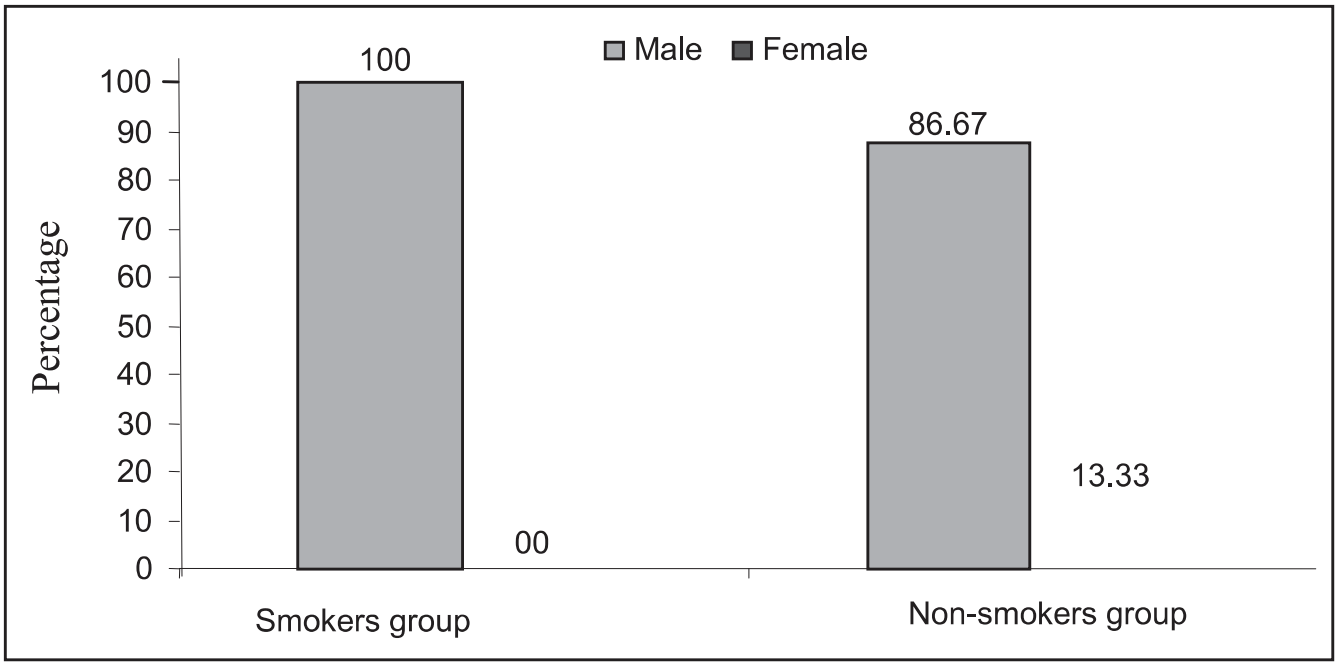

Fig. 01: Bar diagram showing distribution of gender among the respondents.

Smoking status was matched with the other known risk factors and the effect of smoking on the size, number, presenting grade and stage of TCC was evaluated.

Table 01 shows that, there was no recurrence when the size of the primary tumor was < 2 cm in both smokers and non-smokers group. On the other hand, recurrences were seen when the size of the primary tumor was ≥2 cm in both smokers and non-smokers group as 12 cases (20%) and 8 cases (13.33%) respectively.

Similarly, there were 4 cases (6.67%) of recurrent tumors in smokers and no recurrence in non-smokers group when the number of the primary tumor was 1-2. On the other hand, recurrences were seen when the number of the primary tumor were ≥3 in both smokers and non-smokers group as 8 cases (13.33%) and 4 cases (6.67%) respectively.

Modality of treated Group	Size of the primary tumor				Number of the primary tumor			
	Size of the primary tumor (cm)	Patients no. (%)	Recurrence no. %	Overall recurrence no.(%)	Number of theprimary tumor	Patients no. (%)	Recurrence no. %	Overall Recurrence no.(%)
Smokers group	<2	18 (30)	00 (00)	12 (20)	1–2	44 (73.33)	4 (6.67)	12 (20)
	≥2	42 (70)	12(20)		≥ 3	16 (26.67)	8 (13.33)	
Non-smokers group	<2	12 (20)	00 (00)	8 (13.33)	1–2	54 (90)	00 (00)	4 (6.67)
	≥2	48 (80)	8 (13.33)		≥ 3	6 (10)	4 (6.67)	

Table 01 : A comparison of smokers and non-smokers for tumor recurrence in relation to the size and number of the primary tumor among the respondents.

Table 02 shows that, there were 4 cases (6.67%) of recurrent tumors in smokers and 2 cases (3.33%) of recurrent tumors in non-smokers group when grade of the primary tumor was G-I. On the other hand, recurrences were seen when grade of the primary tumor was G-II in both smokers and non-smokers group as 8 cases (13.33%) and 6 cases (10%) respectively. Histopathologically, there was no progression of the grade of the recurrent tumors.

Similarly, there were 4 cases (6.67%) of recurrent tumors in smokers and 2 cases (3.33%) of recurrent tumors in non-smokers group when stage of the primary tumor was Ta. On the other hand, recurrences were seen when stage of the primary tumor was T1 in both smokers and non-smokers group as 6 cases (10%) and 4 cases (6.67%) respectively. Histopathologically, the "T" category of the recurrent tumors was same to that of the primary tumor.

Modality of treated Group	Tumor Grade				Tumor Stage			
	Primary tumor Grade	Patients no. (%)	Recurrence No. %	Overall recurrence no.(%)	Primary tumor Stage	Patients no. (%)	Recurrence no. %	Overall Recurrence no.(%)
Smokers group	G-I	28 (46.66)	4 (6.67)	12 (20)	Ta	28 (46.67)	4 (6.67)	10 (16.67)
	G-II	32 (53.33)	8 (13.33)		T1	32 (53.33)	6 (10)	
Non-smokers group	G-I	38 (63.33)	2 (3.33)	8 (13.33)	Ta	30 (50)	2 (3.33)	6 (10)
	G-II	22 (36.66)	6 (10)		T1	30 (50)	4 (6.67)	

Table 02 Shows the comparison between smokers and non- smokers for tumor grade and stage among the respondents. G-I tumors are considered as well differentiated and G-II tumors as moderately differentiated. On the other hand, Ta tumors indicate non-invasive papillary carcinoma and T_1 tumors invade subepithelial connective tissue.

Data were obtained from 120 patients during a prospective phase of 4 schedules of three monthly cystoscopic follow-up on the 3rd, 6th, 9th and 12th month after transurethral resection to evaluate the actual recurrence rate and also for statistical analysis.

Table 03 shows the recurrence status on the 3rd, 6th, 9th and 12th month of follow-up cystoscopy after transurethral resection of bladder cancer. There was no recurrence on the 3rd and 6th month of follow-up cystoscopy in both smokers and non-smokers group. In smokers group, it was 20% (12 cases) and in non-smokers group 13.34% (8 cases) on the 9th month. This result is statistically insignificant *(p> 0.05)*.

On the 12th month, the recurrence rate was 16.67% (10 cases) and 10% ((6 cases) in smokers and non-smokers group respectively. The difference is not significant in statistical analysis *(p>0.05)*. Those patients, who revealed recurrence on 9th month of follow-up cystoscopy, were recurrence free here(?). Overall, the recurrence rate in smokers groups was 36.67% and in non-smokers groups was 23.33 %.

Modality of treated group	**3rd** Month Recur-rence no.	**6th** Month Recur-rence no	**9th Month**						**12th Month**					
			Recurrence		Total	x^2	df	p	Recurrence		Total	x^2	df	p
			No no. (%)	**Yes no. (%)**	no. (%)				No no. (%)	**Yes no. (%)**	no. (%)			
Smokers Group	0	0	48 (80)	**12 (20)**	60 (50)	0.154	1	0.690	50 (83.33)	**10 (16.67)**	60 (50)	0.108	1	0.742
Non-smokers Group	0	0	52 (86.66)	**8 (13.34)**	60 (50)				54 (90)	**6 (10)**	60 (50)			
Grand Total	0	0	100 (83.33)	**20 (16.67)**	120 (100)				104 (86.67)	**16 (13.33)**	120 (100)			

Table 03: Recurrence status on the 3rd, 6th, 9th and 12th month of follow-up cystoscopy {n = 120 (Smokers Group = 60 and Non-smokers Group = 60)}

Discussion

The present study was conducted in Rajshahi Medical College Hospital, which is the biggest tertiary level hospital in the northern part of Bangladesh. The large number of patients with bladder cancer were from all regions of the north and south-west of Bangladesh, with no racial or ethnic discrimination. There was no significant difference between smokers and non-smokers in grade or stage, but the high-dose smokers had significantly more aggressive cancer (*p<0.05)*.

Although, it remains to be determined whether the non-smokers had other risk factors that might contribute to the induction of high-grade and high-stage bladder cancer, the insignificant difference between the groups could also be explained by the fact that smoking is a very common habit in Bangladesh and thus even non-smokers are commonly exposed to cigarette

smoke. Thus, from our results, we strongly advise heavy smokers to stop smoking, or at least to smoke fewer cigarettes per day, as we found that a greater dose of smoking was associated with the higher recurrence rate of bladder cancer. Solitary recurrences were seen on the 9th month of follow-up cystoscopy. Table 03 showed that, the number of recurrence was 12 in smokers group and was 8 in non-smokers group on the 9th month. The difference of recurrences in both groups are not significant *(p>0.05)*. Overall, the recurrence free rate was 80% in smokers group and 86.66% in non-smokers group. The recurrent tumors were resected. After taking biopsy, the base of the tumors was fulgurated. There was no evidence of progression in the specimen, confirmed by histopathological report. Those patients having recurrence on the 9th month were scheduled for follow-up on the 12th month and who revealed recurrence on the 9th month of follow-up cystoscopy, were recurrence free on the 12th month.

On the 12th month of follow-up (Table : 03), it was seen that, 10 cases in smokers group and 6 cases in non-smokers group were recurred, with recurrence free rate of 83.33% and 90% respectively. The recurrent tumors were resected. After taking biopsy, the base of the tumor was fulgurated. There was no evidence of progression in recurrent tumors, confirmed by histopathological report. The difference of recurrence among the groups is not significant *(p>0.05)*. In this study, follow-up of each patient was done for 1 year after initial TURBT. These analyses confirm the positive effect of smoking in the recurrence of transitional cell carcinoma of the urinary bladder.

Moreover, early recurrences were concentrated during the first 12 months in the smokers group (16.67%) compared to the non-smokers group (10%). Out of 120 patients (smokers group = 60 and non-smokers group = 60), in the smokers group 22 patients i.e.; 36.67% had recurrences during the first 12 months compared to only 14 patients i.e.; 23.33% of the non-smokers group; therefore, patients could have been spared cystoscopies on the 3rd, 6th and 9th months or substituted with other noninvasive procedures, such as bladder ultrasonography and urine cytology, in the non-smokers group which would have provided additional cost savings. However, after the 12 months, the follow-up schedule should be the same for both groups since overall recurrence was similar.

Smoking is a well known risk factor for developing a urinary bladder cancer and smokers have up to a 2-fold higher incidence rate of bladder cancer than the people who have never smoked[11]. The main purpose of this study was to evaluate this potential association. Mean age of the patients in our study was 61.74 ± 13.54 years with a minimum of 26 years and maximum of 85 years. There was no significant difference between the ages of the two groups. Mohseni et al. found that smoking was not only the most important risk factor for TCC of the urinary bladder, but was also associated with higher grades of the tumor[12]. Also, Marsit et al. reported that smoking not only induces bladder cancer, but also, once developed, it could increase the grade of the tumor, resulting in a worse prognosis [13].

Conclusion

While smoking is the most potential risk factor for bladder cancer as well as its post resection recurrence, the equality in the aggressiveness of the cancer between the smokers and non-smokers in the present population might be a result of the effect of passive smoking, in a country where smoking is a common habit or it might be the result of other risk factors. To answer these questions, a population-based study is needed, with more patients and studying all environmental

factors, including smoking. Finally, nearly the entire male excess in bladder cancer observed in Bangladesh with high sex ratios (i.e., male : female = 15:1) may be explained by the higher prevalence of smoking among the men compared with women, rather than occupational or environmental exposures to other bladder carcinogens. Awareness is also needed among the public and treating physicians as they tend to neglect the symptoms of haematuria resulting in an advanced stage of bladder cancer at presentation.

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