Smoking Cessation Rates of Patients with Bladder Cancer and Its Effect on Oncological Outcomes

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Abstract

ABSTRACT BACKGROUND: Smoking is the major risk factor for development of bladder cancer (BC). We evaluated the rate and the time of cessation of smoking in patients with BC and analysed the effect of ongoing smoking at recurrence and progression. METHODS: All patients were informed at the time of BC diagnosis about the correlation between smoking and BC and strictly warned to quit smoking. The demographic properties, pathologic characteristics and smoking status of the patients were evaluated retrospectively. Both the patients and the family members were questioned to evaluate the smoking status of the patient during the follow-up period. The disease recurrence and progression was correlated with the habitual attitude of patients in terms of smoking status. RESULTS: A total of 245 patients were included to the study. The mean follow-up period was 37.3±27.8 months (7-143 months). There were 102(41.6%) patients who were smoker and 143(58.4%) patients who were non-smoker at the time of diagnosis. Among the smoker patients, 34(33.3%) stopped smoking after the diagnosis of BC. The median smoking cessation time was 1.5 months and 64.7% of these patients stopped smoking in the first six months after the diagnosis. The Cox regression model did not show any relationship between the smoking status and recurrence/progression. CONCLUSION: The rate of cessation of smoking at BC patients was low. The first months of the diagnosis were the most suitable period for the patients to stop smoking. The smoking status after the diagnosis was not related with the tumor recurrence and progression.

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smoking in the first six months after the diagnosis. The Cox regression model did not show any relationship between the smoking status and recurrence/progression.

CONCLUSION: The rate of cessation of smoking at BC patients was low. The first months of the diagnosis were the most suitable period for the patients to stop smoking. The smoking status after the diagnosis was not related with the tumour recurrence and progression.

Key words: Bladder cancer, Smoking, Cigarette, Smoking Cessation, Oncological Outcome

WHAT IS ALREADY KNOWN ABOUT THIS TOPIC?

Smoking status and cumulative lifetime smoking exposure during bladder cancer treatment seem to affect disease recurrence, progression and survival.

WHAT DOES THIS ARTICLE ADD?

The rate of cessation of smoking in patients with bladder cancer was lower than we expected. It should be considerable for the medical team to promote smoking cessation especially at the first months after the diagnosis.

INTRODUCTION

Bladder cancer (BC) is the 9th most common cancer in the world with high mortality rates.[1] It is more common in developed countries but more mortal in developing countries.[2] Nearly 75% of the BC are diagnosed at the non-muscle invasive stage which are treated with local treatments. Nearly one-third of non-muscle invasive bladder cancers (NMIBC) become muscle invasive (MIBC) during the follow-up period.[3]Smoking, occupational carcinogen exposure, dietary factors, environmental carcinogens, socioeconomic factors and genetic factors are the main risk factors for BC in which smoking has a significant effect.[4-6] Several carcinogens like aromatic amines and nitrosamines are found in tobacco and cause DNA damage that is responsible for BC formation.[7,8]

Smoking is a prevalent bad habit in worldwide. Several social programs aim to decrease the smoking rate but smoking habit does not decline in many countries.[9] Not only for the formation of BC, smoking is also proposed to be a risk factor for recurrence and progression. For that reason, patients who are smokers at the time of diagnosis must stop smoking. One of the main responsibilities of the clinician is to inform their patients about the hazardous risks of smoking for their health. All clinicians recommend their patients to stop smoking as soon as they diagnose BC. On the other hand, the main question is; "does the patient understand and pay attention to this reality and do they really stop smoking?" Most of the studies reported the importance of cessation of smoking for the BC patients but there are limited data documenting the reality about the rate of cessation of smoking among BC patients.[10,11]

The primary aim of our study was to evaluate the behavior of BC patients in terms of cessation of smoking after the diagnosis. The secondary aim is to determine timing of patients to stop smoking after the diagnosis. The tertiary aim was to evaluate the effect of ongoing smoking on recurrence and progression of BC.

METHODS

With the permission of the local ethic committee, the patients who were diagnosed as BC in our clinic were included in the study. The demographic and clinical properties of the patients were evaluated retrospectively. Some of the patients were still smokers at the time of the diagnosis. According to our clinical policy, all patients were informed about the correlation between smoking and BC and strictly warned to quit smoking. Not only by verbal information, but a written brochure expressing the importance of cessation of smoking was given to the patients and their families. We also informed the patients for the possible progression risk of their disease with ongoing smoking. All patients confirmed that they understood the risks of smoking for their disease.

The patients underwent transurethral resection of bladder (TUR_B) and they were included to the treatment protocol according to pathologic stage and grade. In every visit, we checked if the patients gave up smoking

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and informed them repeatedly about the importance of cessation of smoking. In the last visit, we questioned the smoking habit of the patients. According to this data we grouped the patients as; "never smoked", "former smokers" and "current smokers". The former smokers group was divided into two as; former smokers that quit smoking before and after the diagnosis of BC. In order to remove the possible bias related to patient's declaration, we also asked the same questions to the family members of the patients. The patients who had less than 6 months follow-up and the patients who had irregular visits were excluded from the study. In order to standardize the study population, the patients with pathologic diagnosis other than transitional cell carcinoma were also excluded from the study.

SPSS version 20.0 software was used for statistical analysis. The normal distribution of continuous variables was assessed by applying the Kolmogorov-Smirnov test, and the data were expressed as mean ± standard deviation or medians, as appropriate. The differences between groups were assessed using Student's t tests for parametric data and the Mann-Whitney U test for non-parametric data. Differences in frequencies were tested using the ?2 test; p values of <0.05 were considered statistically significant. The effect of smoking habit on the recurrence and progression of BC was explored by Cox regression models. The time of follow-up was started with the time of initial transurethral resection of the BC. One-way Anova test was performed between groups that had more than 2 subgroups. The Cox regression model was formed with the variables; age, sex, stage, grade, tumor size and number of tumors which were accepted as BC prognosis factors.[12]

RESULTS

A total of 245 patients were included to the study. There were 208 (84.9%) male and 37 (15.1%) female patients with the male to female ratio of 5.6:1. The mean age of the study population was 63.6+-9.9 years. The mean ages of the male and female patients were 64.2+-9.4 and 60.6+-10.5, respectively (p=0.047). There were 28 (11.4%) patients who had MIBC at the time of diagnosis. The demographic and pathologic properties of the patients with NMIBC were shown at Table 1. The mean follow-up period was 37.3+-27.8 months (7-143 months).

TABLE 1 The demographic and pathologic characteristics of the non-muscle invasive bladder cancer patients according to smoking status

	Number of Patients n (%)	Never Smoked	Former Smoker (before diagnosis)	Former Smoker (after diagnosis)	Current Smoker
Gender					
Male Female	188(86.6%) 29(13.4%)	14 14	91 7	26 5	57 3
Pathologic stage					
Ta Low Grade	86(39.6%)	13 3 3 9	41 8 8 41	10 1 5 15	22 8 14 16
High Grade	20(9.2%)				
T1 Low Grade	30(13.8%)				
High Grade	81(37.3%)				
Number of Tumor					
1 2-7 [?]8	121(55.8%) 79(36.4%) 17(7.8%)	16 8 4	57 37 4	13 13 5	35 21 4
Tumor size					
<3 cm. [?]3 cm.	114(52.5%) 103(47.5%	17 11	54 44	18 13	25 35
Risk groups					

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	Number of Patients n (%)	Never Smoked	Former Smoker (before diagnosis)	Former Smoker (after diagnosis)	Current Smoker
Low	41(18.9%)	8 11 9	21 34 43	5 10 16	7 37 16
Intermediate	92(42.4%)				
High	84(38.7%)				

As we evaluated the smoking habits, we found that 102(41.6%) patients were smoker and 143(58.4%) patients were non-smoker at the time of diagnosis. Among the non-smoker group, only 31(21.7%) patients never smoked and 112(78.3%) patients stopped smoking before the diagnosis of BC. Of the 102 smokers, 34(33.3%) patients stopped smoking after diagnosis whereas 68(66.7%) patients were still smokers. The median smoking cessation time was 1.5 months ranging between 1 to 96 months. A total of 22(64.7%) patients were able to stop smoking in the first 6 months of the diagnosis. Postoperative smoking cessation times of each patient are shown in Figure 1.
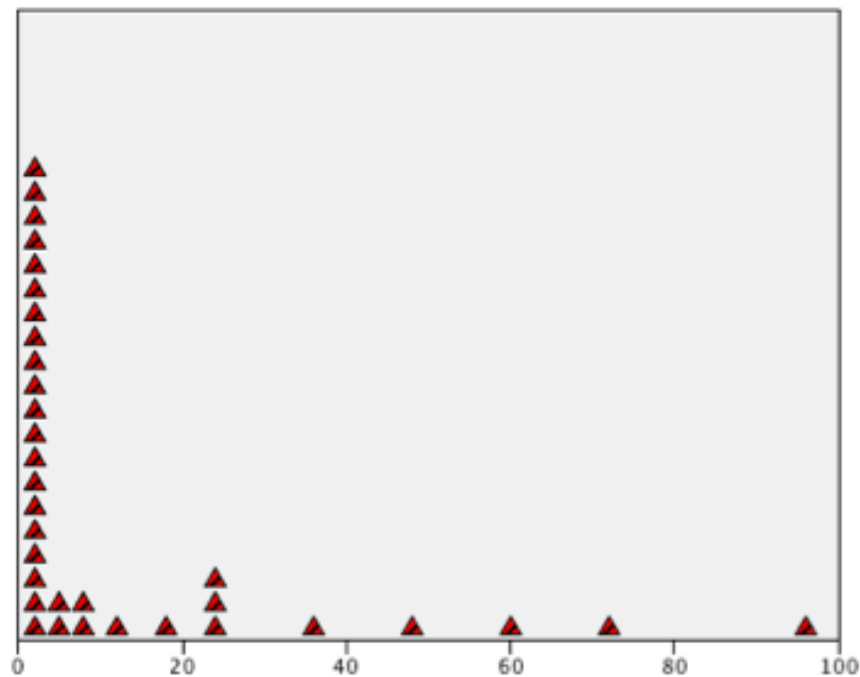

FIGURE 1 Postoperative smoking cessation of the bladder cancer patients according to times (months)

The rate of cessation of smoking at female patients was 40% whereas it was 30.4% at male patients (p=0.06). The mean age of the patients who stopped and did not stop smoking after the diagnosis were 60.5±8.7 and 60.4±10.4 years, respectively (p=0.966). The pre-diagnosis smoking frequency of patients who quit smoking was 22.1±11.4 cigarette/day, whereas it was 21.6±10.0 cigarette/day at patients who did not stop smoking (p=0.811). It was an elating finding that the frequency of still smokers decreased to 11.2±8.4 cigarette/day after the surgery (p<0.001). This data documented even they did not totally quit cigarettes, smoking frequency significantly decreased after the surgery. When we asked the reason of cessation of smoking, 32(94.1%) patients stated that the reason was the diagnosis of BC. Other 2(5.9%) patients reported that lower respiratory system symptoms were the reason.

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There were 28 patients with MIBC at the time of diagnosis. Of these patients, 21(75.0%) had local disease and underwent radical cystectomy. Among the patients who had MIBC, 11(39.3%) were smokers at the time of diagnosis. Surprisingly, the rate of cessation of smoking at these patients was 27.3% (3 of 11 patients).

The rate of recurrence and progression of NMIBC were 27.0% and 6.8%, respectively. The rates of recurrence and progression according to demographic and pathologic findings for NMIBC patients are shown at Table 2. The smoking status was not related with the recurrence and progression (p>0.05). The Cox regression model did not show any relationship between the smoking status and recurrence / progression (Table 3).

TABLE 2 The rates of recurrence and progression according to demographic, pathologic findings and smoking status for non-muscle invasive bladder cancer patients

	Recurrence (%)	p value	Progression (%)	p value
Gender				
Male Female	52/188(27.6%)	0.863	14/188(7.4%)	0.225
	7/29(24.1%)		0/29(0.0%)	
Ta Low Grade High	16/86(18.6%)	0.011	4/86(4.6%)	0.762
Grade T1 Low	4/20(20.0%		1/20(5.0%)	
Grade High Grade	11/30(36.6%)		2/30(6.6%)	
	29/81(35.8%)		7/81(8.6%)	
Number of tumors				
1 2-7 [?]8	24/121(19.8%)	0.018	8/121(6.6%)	0.510
	30/79(37.9%)		6/79(7.6%)	
	5/17(29.4%)		0/17(0.0%)	
Tumor size				
<3 cm. [?]3 cm.	25/114(21.9%)	0.047	6/114(5.2%)	0.638
	34/103(33.0%)		8/103(7.7%)	
Risk Groups				
Low Intermediate	6/41(14.6%)	0.088	3/41(7.3%)	0.547
High	25/92(25.8%)		4/92(4.3%)	
	28/84(33.3%)		7/84(8.3%)	
Smoking Status				
Never smoked	7/28(25.0%)	0.563	0/28(0.0%)	0.353
Stopped before	23/98(23.5%)		8/98(8.2%)	
diagnosis Stopped	11/31(35.4%)		1/30(3.3%)	
after diagnosis	18/60(30.0%)		5/60(8.3%)	
Current smoker				

Table 3 The Cox regression model according to smoking status

	HR	95% Cl	Number of events/patients at risk
Never smoked	1.00	Ref.	7/28
Stopped before diagnosis	0.82	0.64-1.02	23/98
Stopped after diagnosis	0.89	0.56-1.63	11/31
Current smoker	1.26	0.78- 1.63	18/60

DISCUSSION

Smoking is a significant risk factor for BC. It is a rich source for aromatic amines and nitroso compounds which have carcinogenic effect on bladder by damaging the DNA.[7] In a meta-analysis, the relative risk of BC

was found to be 3.47(95% confidence interval [CI] 3.07–3.91) for current smokers compared to non-smokers. Even the relative risk of BC for ex-smokers was 2.04 (95% confidence interval [CI] 1.85-2.25) compared to non-smokers.[4]The rate of patients who never smoked was 12.7% and the rate of still smokers were 41.6% in our study population. This data was not surprising that nearly 90% of our patients were still smokers or former smokers at the time of diagnosis.

The relation of smoking and the BC is a well-known phenomenon for the clinicians; on the other hand, patients learn this reality as soon as they are diagnosed as BC. At this situation all of the BC patients are advised to give up smoking. The main question is "do the patients really understand the importance of cessation of smoking and do they really give up smoking?" Nearly 40% of our study population was current smoker at the time of diagnosis. Two third of these patients were still smokers with a mean follow-up time of 37 months. All of the patients informed about the importance of cessation of smoking for their both general health and BC several times, but it was surprising that most of the patients did not understand this reality. Although the post-diagnosis smoking frequency decreased significantly compared to pre-diagnosis smoking frequency, the current smokers were still smoking 11 cigarettes per day. Similar results were also seen at Sfakianos et al study. In their 623 patient series, 138 patients were smoker at the time of diagnosis. The authors showed that 70% of patients were still smoker in a median follow-up of 80 months.[13] This data documented that only informing the patients to stop smoking is not enough to achieve the goal. Professional support and close follow-up might be necessary.

According to our knowledge this is the first study evaluating the postoperative time that the BC patients stopped smoking and the reason of this behavior. Nearly two thirds of the smoking quitters stopped smoking at the first month of their diagnosis. After this period, the rate of cessation of smoking decreased significantly. This behavior might be related with the immediate anxiety of the patients as they realized their disease. After a period of time, patients might get use to their disease and lose their apprehension to stop smoking. Nearly all the patients who gave up smoking after the diagnosis of BC declared that the reason was the diagnosis of BC. According to our study, the initial months of the BC diagnosis was very important for the patients to give up smoking and for the clinicians to achieve their goal. As the time passed, the probability of patients to stop smoking also decreased. For that reason, a professional work-up might be necessary as soon as the diagnosis was made. By this way, clinicians may increase their chance to ensure their patients to give up smoking.

The effect of smoking on disease recurrence and progression is debatable. Simonis et al stated that smoking status increased the risk of BC recurrence and progression. The authors concluded that heavy long-term smokers and patients who did not quit smoking were at risk for both recurrence and progression.[14] On the other hand, Sfakianos et al reported that smoking status was not associated with BCG response, disease recurrence and disease progression.[13] In another study, Kim et al also reported that smoking status was not a significant factor for BC recurrence.[15] Similar to these findings, van Osch et al reported that although the smoking cessation indicated a protective association with BC recurrence, the statistical analysis was not significant and the authors concluded that this relation could not be considered as strong.[16-17] We also observed that cessation of smoking was not related with BC recurrence and progression. The rate of recurrence and progression was similar at patients who stopped smoking after the diagnosis compared to still smokers.

Smoking status is also important for patients with MIBC.[18] Rink et al revealed that smoking status was associated with disease recurrence and cancer specific mortality at radical cystectomized patients.[19] Cacciamani et al stated that smoking was associated with lower neoadjuvan chemotherapy response before radical cystectomy. In addition, they also revealed smoking was related with higher recurrence and disease specific mortality rates at radical cystectomy patients.[20] As the authors showed it, stopping smoking was very important for patients with MIBC. We were expecting to find high rates of cessation of smoking in MIBC patients because these patients had to deal with major treatment protocols, which changed their life significantly. And the major responsible for this situation was smoking. Surprisingly the rate cessation of smoking among these patients was only 27.3 %. This data documented that patients with MIBC insisted to smoke

and the clinicians was not successful in terms of making their patients smoke-free. However, we predicted the smoking cessation rates would be higher. Because the patients follow up were more frequent so they had exposed much more suggestion about smoking cessation from our medical team. In addition, radical cystectomy is not a simple operation; it is the major oncological surgery. Therefore, the rates of cessation of smoking were far below our expectations and consequently the radical cystectomy patients should be much more encouraged for smoking cessation.

Our study had some limitations. The mean follow-up period of our study population was 37 months, which might be a short period of time. On the other hand, the main aim of this study to evaluate the rate and the time of cessation of smoking in which the follow-up period might be significant. The status of smoking was documented by self-reported questionnaire, which may be another limitation of the study. In order to overcome this possible personal bias, we cross-questioned the close relatives about the smoking habit of the patient. If there was an inconsistency about the answers patients were re-questioned.

CONCLUSIONS

The rate of cessation of smoking was low in our BC patients. Most of the patients gave up smoking at the initial months of the BC diagnosis. Therefore, it is important for urologists and other medical team to promote smoking cessation especially at the first months after the diagnosis. The clinicians must be aware of this data and act to lower the smoking rates with these finding. Even the effect of smoking cessation on oncological outcomes is still debatable; clinicians must perform more effort to decrease the rates of smoking of their patients.

CONFLICT OF INTEREST

The authors have no conflicts of interest to report.

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