Original Article
Smoking cessation rates of patients with bladder cancer and its effect on oncological outcomes

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Abstract: Objective: Smoking is a major risk factor for the development of bladder cancer (BC). We evaluated the rate and the time of cessation of smoking in patients with BC and analyzed the effect of ongoing smoking on BC recurrence and progression. Methods: All patients were informed at the time of BC diagnosis about the correlation between smoking and BC and were 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 were correlated with the habitual attitude of patients in terms of smoking status. Results: A total of 245 patients were included in the study. The mean follow-up period was 37.3±27.8 months (7-143 months). There were 102 (41.6%) patients who were smokers and 143 (58.4%) patients who were non-smokers 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 smoking status and recurrence/progression. Conclusion: The rate of cessation of smoking in 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 to the tumor recurrence and progression.

Keywords: Bladder cancer, smoking, cigarette, smoking cessation, oncological outcome

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 lethal in developing countries [2]. Nearly 75% of BC is diagnosed at the non-muscle invasive stage, which is 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. Not only for the formation of BC but smoking was also proposed to be a risk factor for the

recurrence and progression [7, 8]. The patients who were smokers at the time of BC diagnosis would be expected to stop smoking. However, the behavior of patients related to the cessation of smoking could be different from our expectations. There were very limited data in the literature documenting the patients' behavior in terms of the cessation of smoking after BC diagnosis [9-11].

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

Material and methods

With the permission of the Tekirdag Namik Kemal University local ethical committee

(Protocol Number: 220.147.06.09), the patients who were diagnosed as having 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 were strictly warned to quit smoking. Not only by verbal information but a written brochure expressing the importance of cessation of smoking was also given to the patients and their families. We also informed the patients of the possible progression risk of their disease with ongoing smoking. All patients confirmed that they understood the risks of smoking for their disease.

Patients who underwent transurethral resection for the first time with the diagnosis of BC were included in the study. The operations and pathological evaluations of the patients were performed in a single center. The patients who were still alive and had regular control visits were included in the study. The patients who died and had less than 6 months of follow-up were excluded from the study. In addition, the patients who had irregular visits and concomitant cancers were excluded. To standardize the study population, the patients with a variant pathologic diagnosis other than transitional cell carcinoma were also excluded from the study.

The status of smoking was the main observation indicator of the study. At every visit, we checked if the patients gave up smoking and informed them repeatedly about the importance of cessation of smoking. According to this data, we grouped the patients as; "never smoked", "former smokers" and "current smokers". The former smokers group was also divided into two groups; former smokers that quit smoking before and after the diagnosis of BC. To remove the possible bias related to the patient's declaration, we also asked the same questions to the family members of the patients.

The demographic and pathologic properties of the "never smoked", "former smokers" and "current smokers" were evaluated. The time of cessation of smoking, the rate of smoking, and the reason for the cessation of smoking among former smokers was analyzed. In addition, the effect of ongoing smoking on the recurrence and progression of BC was also evaluated.

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 χ^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. A 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 the number of tumors which were accepted as BC prognosis factors [12].

Results

A total of 245 patients were included in 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 in **Table 1**. The mean follow-up period was 37.3±27.8 months (7-143 months).

As we evaluated the smoking habits, we found that 102 (41.6%) patients were a 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 the 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

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	188 (86.6%)	14	91	26	57
Female	29 (13.4%)	14	7	5	3
Pathologic stage					
Ta					
Low Grade	86 (39.6%)	13	41	10	22
High Grade	20 (9.2%)	3	8	1	8
T1					
Low Grade	30 (13.8%)	3	8	5	14
High Grade	81 (37.3%)	9	41	15	16
Number of Tumors					
1	121 (55.8%)	16	57	13	35
2-7	79 (36.4%)	8	37	13	21
≥8	17 (7.8%)	4	4	5	4
Tumor size					
<3 cm	114 (52.5%)	17	54	18	25
≥3 cm	103 (47.5%	11	44	13	35
Risk groups					
Low	41 (18.9%)	8	21	5	7
Intermediate	92 (42.4%)	11	34	10	37
High	84 (38.7%)	9	43	16	16
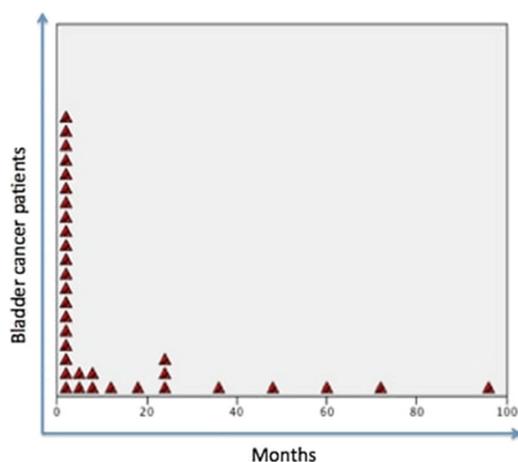
Figure 1. Postoperative smoking cessation of the bladder cancer patients according to times (months).

months of the diagnosis. Postoperative smoking cessation times of each patient are shown in **Figure 1**.

The rate of cessation of smoking in female patients was 40%, whereas it was 30.4% in 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 cigarettes/day, whereas it was 21.6±10.0 cigarettes/day for patients who did not stop smoking (P=0.811). It was an elating finding that the frequency of still smoking decreased to 11.2±8.4 cigarettes/day after the surgery (P<0.001). This data documented that even if they did not totally quit smoking, the frequency significantly decreased after the diagnosis. When we asked the reason for cessation of smoking, 32 (94.1%) patients stated that the reason was the diagnosis of BC. Another 2 (5.9%) patients reported that lower respiratory system symptoms were the reason.

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

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

Table 3. The Cox regression model according to smoking status

	HR	95% CI	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

Note: HR: Hazard ratio; CI: Confidence interval.

Surprisingly, the rate of cessation of smoking in these patients was 27.3 % (3 of 11 patients).

The rate of recurrence and progression of NMIBC was 27.0% and 6.8%, respectively. The rates of recurrence and progression according to demographic and pathologic findings for NMIBC patients are shown in **Table 2**. The smoking status was not related to 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**).

Discussion

Smoking is a significant risk factor for BC. It is a rich source of aromatic amines and nitroso compounds, which have a carcinogenic effect on the 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 smoking was 41.6% in our study population. This data was not surprising in that nearly 90% of our patients were

still smokers or former smokers at the time of diagnosis.

The relation between smoking and BC is a well-known phenomenon for clinicians. On the other hand, patients learn this reality as soon as they are diagnosed with BC. In 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 smokers 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 were informed several times about the importance of cessation of smoking for their both general health and BC. It was a surprising finding that most of the patients did not understand this reality. Although the post-diagnosis smoking frequency decreased significantly, the current smokers were still smoking 11 cigarettes per day. Similar results were also seen in Sfakianos' study. In their 623 patients, 138 patients were smokers at the time of diagnosis. The authors showed that 70% of patients were still smokers in a median follow-up of 80 months [13]. This data documented that only informing the patients to stop smoking was 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 post-operative time that BC patients stopped smoking and the reason for this behavior. Nearly two-thirds of the smokers quit smoking at the first month of their diagnosis. After this period, the rate of cessation of smoking decreased significantly. This behavior might be related to the immediate anxiety of the patients as they realized their disease. After a while, patients might get used 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 presence of BC. According to our study, the initial months of the BC diagnosis were very important for the patients to give up smoking. As time passed, the rate of cessation of smoking decreased. For that reason, a professional workup might be necessary as soon as the diagnosis is made.

In this way, clinicians may increase their chance to help their patients give up smoking.

The effect of smoking on disease recurrence and progression is debatable. Simonis 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 BC 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 was not considered as strong [16, 17]. We also observed that cessation of smoking was not related to BC recurrence and progression. The rate of recurrence and progression was similar in 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 in radical cystectomized patients [19]. Cacciamani et al stated that smoking was associated with the lower neoadjuvant chemotherapy response before radical cystectomy. In addition, they also revealed smoking was related to 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 responsibility for this situation was smoking. Surprisingly the rate of cessation of smoking among these patients was only 27.3%. This data documented that patients with MIBC insisted on smoking and the clinicians were 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, they were exposed to more suggestions about smoking cessation from our medical team. In addition, radical cystectomy is not a simple operation; it is a major oncological surgery. Therefore, the rates of cessation of smoking were far below our expectations, and consequently, radical cystectomy patients should be encouraged in 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. On the other hand, the main aim of this study was 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 a self-reported questionnaire, which may be another limitation of the study. To overcome this possible personal bias, we cross-questioned the close relatives about the smoking habits of the patient. If there was an inconsistency, the patients were re-questioned.

Conclusions

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

Disclosure of conflict of interest

None.

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