

EFFECTS OF SMOKING IN UROTHELIAL CARCINOMA OF BLADDER UNDERGOING RADIAL CYSTECTOMY

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Abstract: *The current study was designed to evaluate the impact of smoking status and cessation in bladder carcinoma patients undergoing radial cystectomy. A prospective study was conducted in the Department of Urology and Radiation Oncology of Shifa International Hospital, Islamabad and MMDC, Multan from January 2022- January 2023. A total of 190 patients with urothelial carcinoma of the bladder undergoing radial cystectomy were included in the study. Smoking history was noted for each patient before radial cystectomy. This history included smoking status, quantity, duration, and cessation in patients with former smoking history. The mean age of patients was 65.3 years. Among 190 patients, 87 were former smokers, 65 were current, and 38 were non-smokers. 58 patients (30.5%) had a pathological tumor stage 3. Multivariate analysis showed that duration of smoking, smoking cessation, and cumulative smoking exposure were predictors of tumor staging. Patients with more than 30 years of smoking were at higher odds of developing advanced tumor stage. Similarly, increased cumulative exposure was associated with greater odds of high tumor stage ($p < 0.001$). Duration of smoking cessation had an opposite relationship with the odds of advanced tumor ($p = 0.001$). Based on the results, it can be concluded that the current smoking status and cumulative smoking exposure are directly associated with disease development and recurrence in urothelial carcinoma of bladder patients. Smoking cessation has the opposite relationship respectively.*

Keywords: Urothelial carcinoma of the bladder, radial cystectomy, smoking, smoking cessation

Introduction

Nearly 30% of adults in the United States and Europe have a history of smoking besides being aware that tobacco smoke contains more than 50 carcinogens, causes cancer, and increases the risk of mortality (Jafari et al., 2021; Rocha et al., 2019; Yang et al., 2019). Among other types of cancers, cigarette smoking increases the chances of developing bladder cancer up to five times (Saginala et al., 2020). Smoking increases the risk of carcinogenesis and is associated with the development of tumors. Saginala et al. conducted a study on patients with urothelial carcinoma and found a strong association between the frequency and status of smoking and tumor development and stage (Saginala et al., 2020). Other studies on urothelial carcinoma of the bladder have also reported an association between smoking and disease progression and recurrence (Mori et al., 2020). Smoking cessation has been reported to manage this risk of disease progression in urothelial carcinoma of

bladder patients (Bassett et al., 2021). There has been sufficient research about the association between smoking and the development of urothelial carcinoma of the bladder, but there has been little to no evidence collected regarding the effects of smoking on the outcomes in such patients. This study evaluated the impact of smoking status and cessation in bladder carcinoma patients undergoing radial cystectomy.

Methodology

A prospective study was conducted in The Department of Urology and Radiation Oncology of Shifa International Hospital, Islamabad and MMDC, Multan from January 2022- January 2023. A total of 190 patients with urothelial carcinoma of the bladder undergoing radial cystectomy were included in the study. No patient received radiotherapy or chemotherapy preoperatively. Systemic

chemotherapy was administered in 38 patients (20%). All the patients gave their signed consent to be included in the study. The ethical committee of the hospital approved the study design.

All the surgical specimens were collected and analyzed according to standard procedures. A genitourinary pathologist examined the specimens and assigned a pathologic stage and tumor grade. The pelvic lymph node dissections were made and decided by the surgeon in charge. These dissections were analyzed closely, and the lymphoid tissues were examined histologically.

Smoking history was noted for each patient before radical cystectomy. This history included smoking status, quantity, duration, and cessation in patients with former smoking history. However, the former smokers who smoked at least 1 year before the procedure were regarded as current smokers. The patients were further divided into categories based on their cumulative exposure.

All the data were analyzed by SPSS version 23. X² test was performed to analyze the relationship between categorical variables. A multivariate logistic regression test was used to evaluate the association between disease progression and smoking. A p-value less than 0.05 was considered statistically significant.

Results

The mean age of patients was 65.3 years. Among 190 patients, 87 were former smokers, 65 were current, and 38 were non-smokers. 58 patients (30.5%) had a pathological tumor stage 3. All the pathological and clinical features of patients are shown in Table I.

Multivariate analysis showed that duration of smoking, smoking cessation, and cumulative smoking exposure were predictors of tumor staging. Patients with more than 30 years of smoking were at higher odds of developing advanced tumor stage. Similarly, increased cumulative exposure was associated with greater odds of high tumor stage (p<0.001). Duration of smoking cessation had an opposite relationship with the odds of advanced tumor (p=0.001) (Table II).

Smoking status was directly related to disease recurrence and mortality (p<0.001). However, no association was noted between smoking status and overall mortality. Current smokers had more changes of recurrence than non-smokers. The multivariate analysis predicting disease recurrence and mortality is shown in Table III.

Table I: Clinical characteristics of patients

	Total patients (n= 190)	Smoking status			P-value
		Never (n=38)	Former (n=87)	Current (n=65)	
Age (years)	65.3 (28.5-90.0)	63.4 (28.5-85.2)	65.2 (33.8-88.4)	66.0 (32.9-89.0)	0.002
Gender					0.277
Male	145 (76.3%)	30 (78.9%)	65 (74.7%)	50 (76.2%)	
Female	45 (23.7%)	8 (21%)	22 (25.3%)	15 (23.0%)	
Tumor stage					0.049
pT0	10 (5.2%)	2 (5.2%)	4 (4.6%)	4 (6.1%)	
pTa	9 (4.7%)	2 (5.2%)	2 (2.3%)	5 (7.7%)	
pTis	21 (11%)	5 (13.1%)	10 (11.5%)	6 (9.2%)	
pT1	22 (11.6%)	5 (13.1%)	9 (10.3%)	7 (10.8%)	
pT2	50 (26.3%)	8 (21.0%)	27 (31.0%)	15 (23.0%)	
pT3	58 (30.5%)	12 (31.6%)	26 (29.9%)	20 (30.7%)	
pT4	20 (10.5%)	2 (5.2%)	10 (11.5%)	8 (12.3%)	
Pathologic grade					0.268
No grading	10 (5.2%)	3 (7.9%)	2 (2.3%)	5 (7.7%)	
Low	5 (2.6%)	1 (2.6%)	2 (2.3%)	2 (3.0%)	
High	175 (92.1%)	35 (92.1%)	80 (91.9%)	60 (92.3%)	
Pathologic nodal status					0.775
Positive	40 (21.0%)	8 (21%)	19 (21.8%)	13 (20%)	
Negative	150 (78.9%)	30 (78.9%)	68 (78.1%)	52 (80%)	
Concomitant carcinoma in sit	81 (42.6%)	16 (42.1%)	37 (42.5%)	28 (43%)	0.622

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Lymphovascular invasion					0.439
Positive	57 (30%)	10 (26.3%)	28 (32.1%)	19 (29.2%)	
Negative	133 (70%)	28 (73.6%)	59 (67.8%)	49 (75.3%)	
Soft tissue margin status					0.332
Positive	12 (6.3%)	2 (5.2%)	6 (6.9%)	3 (4.6%)	
Negative	178 (94.7%)	36 (94.7%)	81 (93.1%)	62 (95.4%)	
Adjuvant chemotherapy	38 (20%)	7 (18.4%)	18 (20.6%)	13 (20%)	0.750

Table II: Multivariate analysis predicting tumor staging by smoking history

	pT3 and/or pN+, (n = 90)		pN+, (n = 22.6%)	
	Odds ratio	P value	Odds ratio	P value
Smoking status		0.688		0.677
Former	1.09 (0.81-1.42)		1.10 (0.74-1.50)	
Current	1.09 (0.80-1.45)		1.12 (0.80-1.60)	
No cigarettes smoked per day		0.059 (0.019)		0.130 (0.282)
11-20	1.28 (0.89-1.78)		1.19 (0.80-1.79)	
21-30	1.14 (0.87-1.67)		0.91 (0.61-1.40)	
More than 30	1.61 (1.10- 2.37)		1.50 (0.91-2.27)	
Duration of smoking		<0.001		0.002 (<0.001)
11-20 years	1.09 (0.77-1.58)		1.10 (0.60-1.66)	
21-30 years	1.68 (1.18-2.39)		1.60 (1.01-1.39)	
More than 30 years	1.72 (1.24-2.40)		1.79 (1.19-2.76)	
Duration of cessation, years		0.001 (0.054)		0.050 (0.070)
1-4	1.26 (0.86-1.78)		1.18 (0.77-1.78)	
5-9	1.17 (0.86-1.62)		0.91 (0.61-1.36)	
10 years or more	0.62 (0.47-0.88)		0.62 (0.42-0.91)	
Overall smoking exposure		<.001 (<.001)		.001 (.001)
Light short-term (20 CPD for 20 yr)	Reference			0.001 (0.001)
Heavy short term (>20 CPD for 20 yr)	1.29 (.95-1.95)		1.18 (.70-1.87)	
Light long term (20 CPD for >20 yr)	1.86 (1.32-2.62)		1.90 (1.27-2.96)	
Heavy long term (>20 CPD for >20 yr)	1.94 (1.36-2.71)		1.77 (1.16-2.68)	

Table III: Multivariate analysis to predict disease recurrence and mortality in smokers (n=152)

Variables	Disease recurrence		Cancer-specific mortality		Overall mortality	
	Hazar ratio	P value	Hazard ratio	P value	Hazard ratio	P value
Age	0.98 (0.99-1.00)	0.038	0.98 (0.99-1.01)	0.030	1.00 (0.99-1.01)	<.001
Female sex	1.50 (1.20-1.90)	<.001	1.57 (1.27-2.07)	<.001	1.59 (1.29-1.90)	<.001
Tumor stage		<.001		<.001		<.001

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pT0, non-invasive papillary carcinoma, carcinoma in situ, pT1	Reference		Reference		Reference	
pT2	1.88 (1.30-2.60)		1.86 (1.28-2.88)		1.68 (1.22-2.28)	
pT3	2.29 (1.59-3.29)		2.57 (1.67-3.97)		2.18 (1.57-3.09)	
pT4	3.26 (2.18-4.87)		3.39 (2.07-5.28)		2.87 (1.99-4.19)	
Lymphovascular space invasion	1.59 (1.27-2.08)	<.001	1.78 (1.37-2.27)	<.001	1.77 (1.47-2.28)	<.001
Lymph node metastases	1.39 (1.05-1.79)	.007	1.77 (1.38-2.28)	<.001	1.28 (1.01-1.66)	.017
Positive soft tissue surgical margin	2.29 (1.59-3.27)	<.001	2.65 (1.88-3.89)	<.001	2.49 (1.79-3.50)	<.001
Concomitant carcinoma in situ	1.17 (0.98-1.46)	.048	1.06 (0.88-1.39)	.257	1.19 (1.01-1.48)	.015
Adjuvant chemotherapy	1.59 (1.20-2.08)	<.001	0.99 (0.68-1.30)	.965	0.79 (0.59-1.08)	.348
Smoking status plus cessation period		<.001		<.001		.009
Current	Reference		Reference		Reference	
Former (less than 10 years)	1.01 (0.77-2.10)		1.01 (0.76-1.27)		1.01 (0.79-1.18)	
Former (10 years or more)	0.33 (0.27-0.58)		0.38 (0.19-0.57)		0.59 (0.48-0.88)	
Cumulative smoking exposure		<.001		.001		.032
Light short term	Reference		Reference		Reference	
Heavy short term	1.47 (1.01-2.09)		1.45 (1.01-2.28)		1.18 (0.88-1.59)	
Light long term	1.67 (1.19-2.28)		1.47 (1.01-2.18)		1.28 (0.98-1.79)	
Heavy long term	2.18 (1.57-2.98)		2.01 (1.33-2.90)		1.48 (1.09-1.97)	

Discussion

We conducted a study to analyze the effects of smoking and smoking cessation on disease progression and recurrence in patients with urothelial carcinoma of the bladder. The results showed that current smokers had high odds of advanced disease and its recurrence than patients who were non-smokers or had quit. Previous research also reported that current smokers were at high risk of developing the disease again compared to former smokers or non-smokers (Boeri et al., 2019; Brookman-May et al., 2019; Cacciamani et al., 2020). A study on UCB patients evaluating the effects of smoking in different genders found that smokers have a significantly higher mortality rate, both cancer-related and overall mortality, than non-smokers (Brookman-May et al., 2019). In our study, univariate analysis showed a positive relationship between smoking status and cancer-related deaths, but this changed when multivariate analysis was performed due to other risk factors. Also, the effects of these predictors were stronger than smoking status.

The disease recurrence and progression were lowest in the light short-term and highest in heavy long-term smokers. In addition, the patients with a duration of smoking cessation less than 10 years before radical cystectomy presented with less advanced tumors and an improved prognosis. Long-duration of cessation has also been proven to reduce the side effects of smoking that cause respiratory, cardiovascular, and gastrointestinal diseases (Caini et al., 2022; Serretta et al., 2020). Cessation combined with the change in lifestyle and environmental factors can reduce the risk of diseases (Sohlberg and Bergmark, 2020). In Pakistan, there is very little awareness about the effects of smoking. An international study also reported this lack of awareness, which noted that patients diagnosed with UCB are likely to quit smoking after the diagnosis and urologists' advice (Michael et al., 2022). Our study has some limitations. We have a short study period and a limited sample size. Secondly, we disregarded the disease history in patients and did not analyze its effects on the development of UCB. Lastly, we collected data from patients who reported their smoking history; no tests were performed to test smoking status.

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Conclusion

Current smoking status and cumulative smoking exposure are directly associated with disease development and recurrence in urothelial carcinoma of bladder patients. Smoking cessation has an opposite relationship respectively.

Conflict of interest

The authors declared absence of conflict of interest.

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