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## ASSOCIATION OF TOBACCO SMOKING AND ALCOHOL CONSUMPTION WITH URINARY BLADDER CANCER AGRESSIVENESS

### Abstract

**Objectives:** Bladder cancer is the most common malignancy in the urinary system and is associated with high incidence, recurrence, and mortality rates. The influence of common smoking and drinking habits on the urinary bladder cancer is still controversial. The main goal of our study was to identify the association of tobacco smoking and alcohol consumption on the tumor characteristics at the time of bladder cancer diagnosis.

**Methods:** We have evaluated selected data from 70 patients with confirmed urinary bladder cancer regarding their smoking and alcohol consumption. The clinicopathological tumor characteristics include: a number of vesical tumors revealed at first cystoscopy (single or multiple tumors), histopathological grade (G1, G2 and G3) and T-classification stage (binary categories: superficial and muscle-invasive).

**Results:** The patient's smoking habits were found to be statistically significantly associated with the histological grade of differentiation ( $p=0.027$ ) and T-classification ( $p=0.021$ ). Alcohol consumption was associated with the number of primary tumors at the cystoscopy ( $p=0.042$ ).

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All other comparisons between the clinicopathological data and patient's habits reveal differences that were not significant ( $p>0.05$ ).

**Conclusions:** The results suggest that smoking was associated with the histological grade of differentiation and T-classification grade as one of the most important indicators of tumor aggression in the patients with UBC. Alcohol consumption was associated with the number of primary tumors revealed by cystoscopy at the time of first diagnosis.

**Keywords:** urinary bladder cancer; tobacco smoking; alcohol consumption.

## INTRODUCTION

Bladder cancer is the most common malignancy in the urinary system and is associated with high incidence, recurrence, and mortality rates [1]. Urothelial (transitional cell) carcinoma is the most frequent histological type that accounts for nearly 90% of all bladder cancers.

According to GLOBOCAN, urinary bladder cancer (UBC) was the ninth most common malignancy worldwide in 2012, with 430,000 newly diagnosed cases [2]. In the Republic of North Macedonia, the mortality rate for this cancer type is 101 per 100,000 for the year of 2017, as reported by the Institute of Public Health [3].

It has been generally accepted that smoking is the most frequent risk-factor, implicated in approximately half of all bladder cancer cases [4]. According to the National Institutes of Health-AARP Diet and Health Study Cohort, cigarette smoking is a major risk factor for urinary bladder cancer, increasing the risk by 3.89 and 4.65, in men and women, respectively [5]. Other well-established risk factors are occupational exposure to aromatic amines and polycyclic aromatic hydrocarbons and genetic predisposition, while the links with dietary factors and environmental pollution are less evident. Some of the previous studies indicate that the intensity of smoking is significantly associated with more aggressive UBC at the time of diagnosis [6].

However, the association between alcohol consumption and bladder cancer incidence and major tumor characteristics are inconsistent among the studies. The results of an earlier, large meta-analysis of UBC cases indicated

a slightly increased risk of 1.3 for alcohol-drinkers, compared with non-drinkers [7]. Some recent case-control studies also suggested an increased risk for UBC in alcohol ever-drinkers [8]. The exact impact of alcohol on bladder carcinogenesis, including various alcoholic beverages, drinking pattern, and modification by other risk factors remains uncertain despite the relatively large number of published studies.

The aim of this study was to examine the association of tobacco smoking and alcohol consumption with some clinicopathological characteristics of tumor aggressiveness at the time of first diagnosis of UBC.

## MATERIALS AND METHODS

### *Study design and patient population*

In this retrospective, observational study we have evaluated a selected demographic and clinicopathologic characteristics of 70 patients with histopathologically confirmed UBC, treated by transurethral resection of bladder tumor (TURBT) at the University Clinic of Urology in Skopje between October 2009 and March 2011. Clinicopathological parameters that were evaluated included: the number of vesical tumors revealed at the first cystoscopy (single or multiple tumors), histopathological grade (G1, G2 and G3) and T-classification stage (superficial: pTa or pT1, and muscle-invasive: pT2 or pT3) according to WHO classification. For this study, considering the number of patients, we have used only the binary categories: superficial and muscle-invasive. Grading and tumor staging were considered at the time when the tissue sample from the primary tumor was obtained.

### *Assessment of patient tobacco smoking and alcohol consumption*

Patient data considering tobacco and alcohol consumption were obtained by a questionnaire.

For the purpose of this study, we have defined the smoking habits of the patients into the following four categories: non-smokers, light-smokers ( $\leq 20$  cigarettes/day), moderate-smokers (21-60 cigarettes/day) and heavy-smokers ( $> 60$  cigarettes/day).

Alcohol consumption was stratified into categories by using predefined levels: nondrinkers, moderate-drinkers ( $\sim 1$  drink/day) and heavy-drinkers

(>1 drink/day). The definition of a standard drink and the approximate frequency of drinking was according to the previously accepted criteria [10].

Only the patients with complete data regarding both clinicopathological and demographic parameters are recruited in this study. The study was approved by the Ethical Committee of the Urology Clinic at the Medical Faculty in Skopje (No. 03-1165 from December 28, 2009) and signed informed consent was obtained from each patient recruited for the study.

#### *Statistical analysis*

Correlations between the patient's habits and selected clinicopathological characteristics of tumor aggressiveness were analyzed by a Fisher's exact probability test (two tailed) using XLStat 2016 installed on Microsoft Excel 2016. A *p*-value less than 0.05 was considered statistically significant.

## RESULTS

In this study, we evaluated the data from 70 patients with histopathologically confirmed UBC regarding selected demographic and clinicopathological data (Table 1).

Table 1

Relevant demographic and clinicopathological patient characteristics

Age	Minimum	Maximum	Average	SD
	38	79	64.3	9,29
			n	%
Gender	Males		61	87.14
	Females		9	12.86
Smoking habit	Non-smokers		23	32.86
	Light-smokers		8	11.43
	Moderate-smokers		26	37.14
	Heavy-smokers		13	18.57
Alcohol consumption	Non-drinker		47	67.14
	Moderate-drinker		22	31.43

	Regular-drinker	1	1.43
<b>Histological grade of differentiation</b>	Grade 1	5	7.14
	Grade 2	42	60.00
	Grade 3	23	32.86
<b>T-classification</b>	Superficial	53	75.71
	Muscle-invasive	17	24.29
<b>Number of primary tumors at cystoscopy</b>	Single	42	60.00
	Multiple	28	40.00

The average age is  $64.3 \pm 9.29$  years (range 38-79). Males make up the majority of the group of patients (87.14%) and females were only 12.86% of the group.

It is obvious from the data shown that less than one-third of the patients are non-smokers (32.86%), while rest consume tobacco to various degrees.

Regarding alcohol consumption, more than two-thirds of the patients are non-drinkers, less than one-third consume moderate amounts of alcoholic beverages and an insignificant percent (1.43%) are regular-drinkers.

The association of tobacco smoking and alcohol drinking habits with the histological grade of tumor differentiation is presented in Table 2.

Table 2

Association of tobacco smoking and alcohol consumption with the histological grade of tumor differentiation

<b>Histological grade of differentiation</b>		<b>Grade 1</b>		<b>Grade 2</b>		<b>Grade 3</b>		<b>p *</b>
		<b>n</b>	<b>%</b>	<b>n</b>	<b>%</b>	<b>n</b>	<b>%</b>	
<b>Smoking habit</b>	Non-smokers	1	20.00	18	42.86	4	17.39	<b>0.027</b>
	Light-smokers	2	40.00	6	14.29	0	0.00	
	Moderate-smokers	2	40.00	13	30.95	11	47.83	
	Heavy-smokers	0	0.00	5	11.90	8	34.78	
<b>Alcohol consumption</b>	Non-drinker	5	100.00	26	61.90	16	69.57	1.000
	Moderate-drinker	0	0.00	15	35.71	7	30.43	
	Regular-drinker	0	0.00	1	2.38	0	0.00	

\* Fisher's exact test (two-tailed)

We found statistically significant differences between the patient's smoking habits and histological grade of differentiation ( $p<0.05$ ). Moderate and heavy-smokers are dominantly found in the subgroup of patients with Grade 3 tumors, while non-smokers and light-smokers are more frequently found with Grade 2 and 1 tumors.

However, differences considering alcohol drinking were not significant ( $p>0.05$ ).

Further analysis was performed considering superficial or muscle-invasive T-classification of the primary tumor.

The results of the analysis are presented in the Table 3.

Table 3

Association of tobacco smoking and alcohol consumption with the pathological T-classification of the primary tumor

T-classification of the primary tumor		Superficial		Muscle-invasive		$p^*$
		n	%	n	%	
Smoking habit	Non-smokers	20	33.33	3	35.71	<b>0.021</b>
	Light-smokers	8	8.33	0	9.52	
	Moderate-smokers	19	45.83	7	35.71	
	Heavy-smokers	6	12.50	7	19.05	
Alcohol consumption	Non-drinker	38	71.70	9	52.94	0.266
	Moderate-drinker	14	26.42	8	47.06	
	Regular-drinker	1	1.89	0	0.00	

\* Fisher's exact test (two-tailed)

We found that the differences between the subgroups of patients with superficial or muscle-invasive tumors regarding smoking habits are statistically significant ( $p<0.05$ ). By contrast, there are no significant differences regarding alcohol consumption habits.

Analysis of the cystoscopically detected number of primary tumors in association with smoking and alcohol drinking are presented in the Table 4.

Table 4

Association of tobacco smoking and alcohol consumption  
with the number of the primary tumors revealed by cystoscopy

Number of the primary tumors		Single		Multiple		<i>p</i> <sup>*</sup>
		n	%	n	%	
<b>Smoking habit</b>	Non-smokers	12	28.57	11	39.29	0.474
	Light-smokers	6	14.29	2	7.14	
	Moderate-smokers	15	35.71	11	39.29	
	Heavy-smokers	9	21.43	4	14.29	
<b>Alcohol consumption</b>	Non-drinker	32	76.19	15	53.57	<b>0.042</b>
	Moderate-drinker	9	21.43	13	46.43	
	Regular-drinker	1	2.38	0	0.00	

\* Fisher's exact test (two-tailed)

The differences between the distribution of patients with single vs. multiple primary tumors detected by cystoscopy regarding tobacco smoking habits are not statistically significant ( $p > 0.05$ ). Interestingly, those distribution differences are significant considering alcohol consumption ( $p < 0.05$ ).

## DISCUSSION

It is already established that tobacco smoke contains different carcinogenic compounds, including 4-aminobiphenyl, 2-naphthylamine, aromatic amines, and other substances which are associated with UBC in patients with smoking habits [10]. In addition, the risk of developing this cancer type increases with the number of cigarettes and the years smoked [11]. There is some evidence that smoking not only promotes carcinogenesis but also influences the tumor's behavior.

Alcohol (ethanol), however, has not been shown to be carcinogenic in animal studies. However, numerous epidemiological studies and meta-analyses suggest that alcohol consumption habits are associated with an increased risk for various types of malignant tumors including liver, laryngeal, and urothelial cancer [12]. Alcoholic beverages contain different compounds that, along with their metabolic products, are excreted through

the urinary tract. Some compounds, such as acetaldehyde, which could be detected in the urine of alcohol-drinkers have a potential for DNA damage and are thus classified as carcinogenic [13]. Indirectly alcohol may facilitate or promote the effects of other carcinogens that are present in the diet or other environmental exposures.

The current empirical concept of "field change" implies that UBC patients have a significantly higher risk of new cancer development elsewhere in the urinary tract [14]. In support of this thesis, patients with UBC often have *in situ* cancers or dysplasia at different urothelial locations, and these tumors are polyclonal and in various progressive stages. Some carcinogens in tobacco are eliminated by renal excretion and could have prolonged contact with the bladder urothelium.

In our study we have evaluated selected data from 70 patients with confirmed urinary bladder cancer regarding their smoking and alcohol consumption data.

The patients' smoking habits were found to be statistically significantly associated with a histological grade of differentiation ( $p=0.027$ ) and T-classification ( $p=0.021$ ) as one of the hallmarks of tumor aggression. This finding is concordant with growing evidence that tobacco smoking is a well-established risk factor in UBC development and tumor aggressiveness, negatively affecting the clinical outcome [6]. Many studies and meta-analyses that have been conducted over the last few decades support these conclusions, although there are also some discordant or inconsistent results in the literature.

In the retrospective study by Pietzak et al. (2015), they analyze a total of 740 tobacco-smoking patients who were diagnosed with bladder cancer from 1987 to 2009. The authors concluded that heavy smokers have a greater statistical risk of having high-grade tumors with invasion of the detrusor muscle upon first diagnosis [15]. A meta-analysis of 26 studies indicates that tobacco smoking is an important risk factor for the development of UBC, and this negatively affects further patient outcomes [16]. Conversely, Ros and collaborators found no association between smoking behavior and the aggressiveness of the UBC tumor among male patients, while the results were not consistent regarding the female patients [17].

Regarding alcohol consumption, in the present study we found evidence that this habit was associated with the number of primary tumors



at the cystoscopy ( $p=0.042$ ). Although several epidemiologic studies have been conducted to investigate the association between the alcoholic beverage consumption, UBC risk, and tumor aggressiveness, the results are not as clear and consistent as in the case of smoking.

The meta-analysis by Bagnardi et al. (2001) has found that alcohol consumption was not associated with increased risk of UBC [12]. A similar conclusion was inferred from a large meta-analysis of Pelucchi et al. (2012) and de Menezes et al. (2013) [18, 19].

However, an increased risk of UBC was found in heavy-drinkers in a large cohort study in the Netherlands. The results of this study, however, do not suggest that alcohol consumption is an important risk-factor for UBC [20]. Moderate alcohol consumption was found to be associated with overall cancer risk, including bladder cancer, in a recently conducted study from US cohorts [21]. The possible effects of alcoholic beverage consumption on UBC tumor aggressiveness still needs to be examined.

In conclusion, the results of our study suggest that habitual smoking was associated with the histological grade of differentiation and T-classification grade as one of the most important indicators of tumor aggression in patients with UBC. On the other hand, alcohol consumption was associated with the number of primary tumors revealed by cystoscopy at the time of first diagnosis. These results, along with a number of published studies, suggest it should be advised to avoid tobacco smoking and the consumption of alcoholic beverages in the patients with UBC.

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