 doi:10.20944/preprints201805.0320.v1

Effect of Smoking on Pathological Grade and Stage in Clinically Low-Risk Patients

Ercan Öğreden*, Ural Oğuz, Erhan Demirelli, Orhan Yalçın

Giresun University, Faculty of Medicine, Department of Urology, Giresun, Turkey

***Corresponding Author:** Ercan Ogreden

E mail: ercanogreden@gmail.com

Mobile Tel: +9 0 505 896 3960

Correspondence Address: Giresun University, Faculty of Medicine, Department of Urology. P.C: 28200, Giresun, Turkey.

Abstract

We investigated the effect of cigarette smoking on pathological staging in clinically low-risk patients. Data of 59 patients who were diagnosed with bladder tumor for the first time and had a single lesion radiologically and endoscopically smaller than 3 cm were investigated retrospectively. 33 patients who smoked were classified as Group I, and 26 patients who did not smoke were classified as Group II. Pathological diagnoses of the patients in both groups were compared. The mean age of the patients were 64.8 (20–86) years. In Group II, 5 (19.2%) were female and 21 (80.8%) were male ($p < 0.05$). Nine patients (27.3%) in Group I and 18 patients (69.2%) in Group II had Ta disease ($p < 0.05$). Nineteen patients (57.6%) in Group I and 5 patients (19.2%) in Group II had T_1 disease ($p < 0.05$). The number of patients with low grade (LG) tumor were 8 (24.2%) and 19 (73.1%) in Group I and in Group II, respectively ($p < 0.05$). The number of patients with high grade(HG) tumor were 25 (75.8%) and 7 (26.9%) in Group I and in Group II, respectively ($p < 0.05$). TaHG was detected in 9 (27.3%) patients in Group I. In contrast, no patients in Group II had TaHG disease ($p < 0.05$). The number of

 doi:10.20944/preprints201805.0320.v1

patients with T_1HG was 17(51.5%) patients in Group I and 2 (7.69%) patients in Group II ($p < 0.05$). Smoking is associated with pathologically HG and stage in patients with first time bladder tumor which is single and smaller than 3 cm.

Keywords: Smoking; Pathologic stage; Pathologic grade; Low risk

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 May 2018 doi:10.20944/preprints201805.0320.v1

1.Introduction

The bladder is the most common site for cancer in urinary system. Bladder cancer is the fourth most common type of cancer in men following prostate, lung, and colorectal cancers [1]. In bladder cancer, male/female ratio is 3.5:1 worldwide [2]. Association of smoking habit with bladder tumor has been well known. Smoking is the worst risk factor for bladder cancer and increases the risk of bladder cancer by 2 to 4 times [3]. Molecular changes associated with bladder cancer are crucial in determining the prognosis. The most important prognostic factor for bladder cancer is the pathological stage and the degree of tumor determined by histopathological examination [4]. Bladder cancer in patients who smoke and have a non-muscle-invasive disease is associated with advanced tumor stage and grade [5]. However, studies investigating the effect of smoking on stage and grade in clinically low-risk patients with bladder tumors that are smaller than 3 cm are limited. The aim of this study was to discuss the effect of cigarette smoking on pathological staging in patients with clinically low-risk bladder cancer.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 May 2018 doi:10.20944/preprints201805.0320.v1

2.Materials and Methods

The files of 154 patients who were diagnosed with bladder cancer for the first time between 2009 and 2013 were retrospectively reviewed in our clinic. Fifty-nine first-time patients with a single lesion, radiologically and endoscopically smaller than 3 cm in diameter were included in the study. Patients who were diagnosed with carcinoma in situ (CIS) in pathology specimens were excluded. Age at first diagnosis, smoking status, stage and grade of primary tumor, tumor diameter and number were noted documented. Patients who actively smoke cigarette were designated as Group I and lifetime non-smokers were designated as Group II. Group I was consisted of 33 patients and group II had 26 patients. Pathological diagnoses of the patients in both groups were compared. The grading of the samples was performed according to the World Health Organization (WHO) system in 1973 and the staging was performed according to Cancer Staging System of the 2002 American Cancer Staging Commission (AJCC).

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

2.1.Statistical Analysis

The data obtained in this study were analyzed with the SPSS 20 package program. Shapiro Wilk test was used while investigating the normal distribution of variables because of the unit numbers. The results were interpreted using significance level of 0.05. In the case of $p < 0,05$, it is stated that the variables do not come from the normal distribution, whereas in the case of $p > 0,05$, the variables were said to come from the normal distribution.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 May 2018 doi:10.20944/preprints201805.0320.v1

3.Results

The mean age of the patients were 66.4 (30-86) years and 62.7 (20-84) years, respectively (p = 0.427) (Table-1). All patients were male in Group I, while 5 (19.2%) were female and 21 (80.8%) were male in Group II (p <0.05). **(Table-1)**

The number of patients with pathologic stage Ta was 9 (27.3%) in Group I and 18 (69.2%) in Group II (p <0.05) (P <0,05). In the non-smoker group, the rate of detection of Ta tumor was significantly higher whereas the rate of detection of T1 tumor was significantly higher in smokers (p <0,05). Pathological T2 tumor rates were equally distributed in both groups (p = 1).

The number of patients with low grade tumor was 8 (24,2%) in group I and 19 (73,1%) in group II (p <0,05). The number of patients with high grade tumor was 25 (75.8%) and 7 (26.9%), respectively (p <0,05). It was found that cigarette smoking increased the grade of tumor. (Table-2)

When pathological grade and grade distributions of the groups are evaluated together; the number of Ta low grade patients was 11 (33,3%) and 15 (57,7%) in Group I and Group II respectively, while Ta high grade patients were 9 (27,3%) in Group I and zero in Group II. Smoking was not associated with low grade pathological stage (p = 0,108), and it was found to increase the risk of Ta high grade (p <0,05).

The number of patients with T1 low grade was 2 (6.1%) in Group I and 3 (11.54%) in Group II. However, the result was not statistically significant (p = 0.646). The number of patients with T1 high grade was 17 (51.5%) in Group I and 2 (7.69%) in Group II (p <0,05). It was found that smoking was associated with high grade in Ta and T1 stage tumors.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 May 2018 doi:10.20944/preprints201805.0320.v1

It was determined that association of smoking with tumor stage and grade in the muscle-invasive bladder tumors was similar to that of non-smokers (p=1). (**Table-2**)

Table 1.

								Mann Whitney U Test		
		n	**Mean**	**Median**	**Min**	**Max**	**ss**	**Rank Avg.**	**z**	**p**
Age	**Group I**	33	66,4	69	30	86	12,62	31,58	-0,795	0,427
	Group II	26	62,7	65,5	20	84	14,74	28		
	Total	59	64,8	68	20	86	13,6			

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 May 2018 doi:10.20944/preprints201805.0320.v1

Table 2.

		Group I		Group II		Total			
		n	%	n	%	n	%	Chi Square Test	p
Gender	Female	0	0	5	19,23	5	8,5	Fisher's exact	**0,013**
	Male	33	100	21	80,77	54	91,5		
	Total	33	100	26	100	59	100		
Ta	Absent	24	72,7	8	30,77	32	54,2	8,693	**0,003**
	Exist	9	27,3	18	69,23	27	45,8		
	Total	33	100	26	100	59	100		
T_1	Absent	14	42,4	21	80,77	35	59,3	7,343	**0,007**
	Exist	19	57,6	5	19,23	24	40,7		
	Total	33	100	26	100	59	100		
T_2	Absent	28	84,9	23	88,46	51	86,4	Fisher's exact	1
	Exist	5	15,2	3	11,54	8	13,6		
	Total	33	100	26	100	59	100		
Grade	LG	8	24,2	19	73,08	27	45,8	12,074	**0,001**
	HG	25	75,8	7	26,92	32	54,2		
	Total	33	100	26	100	59	100		
TaLG	Absent	22	66,7	11	42,3	33	55,9	2,6	0,108
	Exist	11	33,3	15	57,7	26	44,1		
	Total	33	100	26	100	59	100		
TaHG	Absent	24	72,7	26	100	50	84,7	Fisher's exact	**0,003**
	Exist	9	27,3	0	0	9	15,3		
	Total	33	100	26	100	59	100		
T_1LG	Absent	31	93,9	23	88,46	54	91,5	Fisher's exact	0,646
	Exist	2	6,1	3	11,54	5	8,5		
	Total	33	100	26	100	59	100		
T_1HG	Absent	16	48,5	24	92,31	40	67,8	10,863	**0,001**
	Exist	17	51,5	2	7,69	19	32,2		
	Total	33	100	26	100	59	100		
T_2LG	Absent	32	97,0	25	96,15	57	96,6	Fisher's exact	1
	Exist	1	3,0	1	3,85	2	3,4		
	Total	33	100	26	100	59	100		
T_2HG	Absent	29	87,9	23	88,46	52	88,1	Fisher's exact	1
	Exist	4	12,1	3	11,54	7	11,9		
	Total	33	100	26	100	59	100		

LG:low grade, **HG**:high grade

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 May 2018 doi:10.20944/preprints201805.0320.v1

4.Discussion

Occupational exposure and smoking are two important risk factors for developing bladder cancer. Occupational exposure of bladder carcinogens (2-naphthylamine, benzidine, 4-aminobiphenyl, etc.) are associated with the stage and grade of the disease. Tobacco contains more than 60 carcinogens, including benzidine derivatives and aromatic amines, as well as occupational exposure. These substances have an important role in bladder cancer. In addition, studies have shown that high-grade bladder tumors develop more often in people with high-risk occupations [6-8]. It is also known that cigarette smoking increases the risk of recurrence and progression of non-muscle-invasive bladder cancer (NMIBC) [9]. The association of cigarette smoking with bladder cancer has been known for 60 years and accounts for about 50% of cases [10].

Two main mutation pathways are responsible for bladder cancer development. One of these is the fibroblast growth factor receptor-3 (FBFR-3) mutation, which is associated with rather significantly lower grade tumor development. The other one responsible for the mutation is P53-oncogene and it is associated with the development of high grade tumors. Smoking is associated with higher grades of bladder cancer development by resulting mutations in both pathways. Therefore, the prevalence of aggressive tumors in smokers is higher than in non-smokers. In a study published recently, the rate of high grade tumors in smokers was 26% and in non-smokers was 13% and this difference was statistically significant ($p < 0.05$) [11]. In our study, the prevelance of high grade bladder cancer was significantly higher in smoking patients than non-smokers (91% vs. 7.7%).

Age and gender are an important risk factors for bladder cancer. Bladder cancer is detected more often in men, however, in women the prognosis is worse. Smoking women have shown an increased risk of invasive bladder cancer compared to smoking men [12]. Bladder cancers

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 May 2018 doi:10.20944/preprints201805.0320.v1

are usually middle-aged and / or advanced age disease. Approximately 90% of initially diagnosed bladder cancer patients are over sixty years of age. However, bladder cancer under the age of thirty-five is rare. Sturgeon et al. [13] showed that cigarette smoking increased the risk of muscle-invasive tumor in patients younger than 60 years, and there was no statistically significant relationship between smoking and stage of the tumor in patients aged 60 years or older. In our study, it was found that cigarette smoking did not significantly affect the risk of muscle-invasive tumor in clinically low risk patients. The average age of our study was 66.4 years and 62.7 years in the smoker and non-smoker groups, respectively. We did not detect any correlation between muscle-invasive tumor and cigarette smoking may be because there were no female patients in the smoker group and the mean age was over 60 years.

The relationship between cigarette smoking and the stage of tumor at initial diagnosis differs in various studies. Although some studies have reported that cigarette smoking does not affect the stage and grade of tumor, some other studies have reported that cigarette smoking is associated with high grade tumors, and in a study cigarette smoking is associated with low grade tumors. In a recent study by Jiang et al. [12] have reported that the incidence of advanced stage bladder tumors, especially muscle-invasive bladder tumors, was higher in smokers. The same study also reported that as smoking duration and smoking intensity increased, high grade tumors and muscle-invasive tumors were detected twice than low grade tumors. Nevertheless, Sturgeon et al. [13], who investigated the relationship between cigarette smoking and the grade of bladder cancer, have found that smoking was strongly associated with low-grade bladder cancer. Again, in the same study, they have found that high-grade bladder cancer was twice that low-grade bladder cancer. The authors did not explain the cause and result relation. Fleshner et al. [14], who reported that smoking did not affect tumor grade and stage, showed that smokers significantly increased the risk of detecting a tumor as large as 4 cm. In a recent study by Carpenter [15], he found that there was no significant difference

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 May 2018 doi:10.20944/preprints201805.0320.v1

in tumor stage and grade in smokers, but reported that recurrence was higher at the time, significantly. Su et al. [16], reported that smaller than 3 cm tumors tend to be less grade and stage than those larger than 3 cm in size. In our study, although the tumor size in both groups was smaller than 3 cm, it was found that high grade and stage tumors were more prevalent in the smoker group. These findings suggest that smoking increases the stage and grade of tumor regardless of its size.

The risk of developing bladder cancer is directly related to the duration and intensity of cigarette smoking [17]. In a study showing the relationship between smoking and bladder cancer stage and grade, it has been reported that active smokers have higher grades and stages of bladder cancer compared to those who have never smoked and have quit smoking and those who have quit smoking have higher stages and grades than those who never smoked. The duration of smoking and quitting cigarette smoking affects the risk of bladder cancer [18]. In our study, the duration of smoking was not specified and the effect of the disease on stage and grade was not investigated. This can be regarded as a limitation of our study.

4.1.Conclusions

Under the light of these data, significant associations were found between cigarette smoking and pathologically high-grade, high-stage tumors in patients who belong to low risk group.

Conflicts of interest

The authors declare no conflict of interest.

Author Contributions

Conception and design: Ercan Öğreden and Ural Oğuz.

 doi:10.20944/preprints201805.0320.v1

Administrative support: Orhan Yalçın, Erhan Demirelli.

Provision of study material or patients: Ercan Öğreden, Ural Oğuz, Erhan Demirelli, Orhan Yalçın.

Collection and assembly of data: Ercan Öğreden and Erhan Demirelli.

Data analysis and interpretation: Ercan Öğreden and Ural Oğuz.

Manuscript writing: All authors.

Final approval of manuscript: All authors.

Appendix

Table 1. Mann Whitney U test result on differences between groups in terms of age values.

Table 2. The relationship between the groups and the variables of the Chi Square Test result.

5.References

1. Jemal, A.; Siegel R.; Ward, E.; Murray, T,; Xu, J.; Thun, MJ. Cancer statistics. 2007. CA Cancer J Clin. 2007, 57, 43-66. https://doi.org/10.3322/canjclin.57.1.43.
2. Horstmann, M.; Witthuhn, R.; Falk, M.; Stenzl, A. Gender-specific differences in bladder cancer: a retrospective analysis. Gend Med. 2008, 5, 385-394. https://doi.org/10.1016/j.genm.2008.11.002.
3. Delclos, G.L.; Lerner, S.P. Occupational risk factors. Scand J Urol Nephrol Suppl. 2008, 58-63. https://doi.org/10.1080/03008880802284423.
4. Nilsson, S.; Ullén, A. Chemotherapy-induced bladder cancer. Scand J Urol Nephrol Suppl. 2008, 89-92. https://doi: 10.1080/03008880802291832.
5. Mitra, A.P.; Cote, R.J. Molecular pathogenesis and diagnostics of bladder cancer. Annu Rev Pathol. 2009, 4, 251-285. https://doi.org/10.1146/annurev.
6. Brooks, D.R.; Geller, A.C.; Chang, J.; Miller, D.R. Occupation, smoking, and the risk of high-grade invasive bladder cancer in Missouri. Am J Ind Med. 1992, 21, 699-713. https://doi.org/10.1002/ajim.4700210510.
7. Hecht, S.S. Tobacco carcinogens, their biomarkers and tobacco-induced cancer. Nat Rev Cancer. 2003, 3, 733-744. https://doi:10.1038/nrc1190.
8. Hayes, R.B.; Freidell, G.H.; Hoar Zahm, S.; Cole, P. Are the known bladder cancer risk factors associated with more advanced bladder cancer? Cancer Causes Control. 1993, 4, 157-162. https://doi.org/10.1007/BF00053157.
9. Figueroa, J.D.; Middlebrooks, C.D.; Banday, A.R.; Ye, Y.; Garcia-Closas, M.; Chatterjee, N. et al. Identification of a novel susceptibility locus at 13q34 and refinement of the 20p12.2 region as a multi-signal locus associated with bladder

cancer risk in individuals of European ancestry. Hum Mol Genet. 2016, 25, 1203-1214. https://doi.org/10.1093/hmg/ddv492.

10. Chavan, S.; Bray, F.; Lortet-Tieulent, J.; Goodman, M.; Jemal, A. International variations in bladder cancer incidence and mortality. Eur Urol. 2014, 66, 59-73. https://doi.org/10.1016/j.eururo.2013.10.001.

11. Pietzak, E.J.; Malkowicz, S.B. Does quantification of smoking history correlate with initial bladder tumor grade and stage? Curr Urol Rep. 2014, 15, 416. https://doi.org/10.1007/s1193.

12. Jiang, X.; Castelao, J.E.; Yuan, J.M.; Stern, M.C.; Conti, D.V.; Cortessis, V.K.; et al. Cigarette smoking and subtypes of bladder cancer. Int J Cancer. 2012, 130, 896-901. https://doi.org/10.1002/ijc.26068.

13. Sturgeon, S.R.; Hartge, P.; Silverman, D.T.; Kantor, A.F.; Linehan, W.M.; Lynch, C.; et al. Associations between bladder cancer risk factors and tumor stage and grade at diagnosis. Epidemiology. 1994, 5, 218-225. http://www.jstor.org/stable/3702364.

14. Fleshner, N.; Garland, J.; Moadel, A.; Herr, H.; Ostroff, J.; Trambert, R.; et al. Influence of smoking status on the disease-related outcomes of patients with tobacco-associated superficial transitional cell carcinoma of the bladder. Cancer. 1999, 86, 2337-2345. https://doi.org/10.1002/(SICI)1097-0142(19991201).

15. Carpenter, A.A. Clinical experience with transitional cell carcinoma of the bladder with special reference to smoking. J Urol. 1989, 141, 527-528. https://doi.org/10.1016/S0022-5347(17)40880-9.

16. Su, X.; Fang, D.; Li, X.; Xiong, G.; Zhang, L.; Hao, H.; et al. The Influence of Tumor Size on Oncologic Outcomes for Patients with Upper Tract Urothelial Carcinoma after

283 Radical Nephroureterectomy. Biomed Res Int. 2016, 2016, 4368943.
284 http://dx.doi.org/10.1155/2016/4368943.

285 17. Brennan, P.; Bogillot, O.; Cordier, S.; Greiser, E.; Schill, W.; Vineis, P.; et al.
286 Cigarette smoking and bladder cancer in men: a pooled analysis of 11 case-control
287 studies. Int J Cancer. 2000, 86, 289-294. https://doi.org/10.1002/(SICI)1097-
288 0215(20000415).

289 18. van Roekel, E.H.; Cheng, K.K.; James, N.D.; Wallace, D.M.; Billingham, L.J.;
290 Murray, P.G.; et al. Smoking is associated with lower age, higher grade, higher stage,
291 and larger size of malignant bladder tumors at diagnosis. Int J Cancer. 2013, 133, 446-
292 454. https://doi.org/10.1002/ijc.28017.