

Effect of Smoking on Prognostic Factors of Transitional Cell Carcinoma of the Bladder

MOHSENI MG*, ZAND S, AGHAMIR SMK

Department of Urology, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran

ABSTRACT

Purpose: This study was conducted to evaluate the effects of smoking on the clinical characteristics and growth trend of transitional cell carcinoma (TCC) of the bladder.

Material and Method: In a retrospective case-control study from February 2000 to March 2003, patients with TCC of bladder, referred to our clinic, were selected and divided into high-grade and low-grade groups. Groups were matched for other known risk factors and the effect of smoking on size, number, and presenting grade of TCC in each group was evaluated.

Results: A total of 185 patients, with a mean age of 65.1 ± 14.0 year, were included in this study, of whom 36 were females and 149 were males (male to female ratio of 4.1 to 1). Eighty-three patients were smokers (44.9%) with a mean 20.01 ± 11.09 pack-year (range 0.75 to 60) smoking history. History of smoking was positive in 36.1% of the patients with low-grade tumors; whereas, 90% of the patients with high-grade tumors were smokers ($P = 0.000$, OR = 15.9, 95% CI: 6.7-36.9). There was a statistically significant correlation between the history of smoking and size and number of tumoral lesions ($P = 0.000$, $P = 0.000$, respectively). Positive history of smoking was also associated with higher grades of tumor in both men and women (OR = 12.8 and 8.8, respectively).

Conclusion: This study showed that smoking not only induces bladder cancer, but also, once it develops, it can increase the grade of tumor, resulting in worse prognosis. Thus, smoking cessation might favorably alter the course of bladder cancer.

KEY WORDS: transitional cell carcinoma, smoking, tumor grade

Introduction

Bladder is the most common site of involvement with cancer in the urinary tract system. More than 53200 new cases of bladder cancer were diagnosed in 2000 in the United States,⁽¹⁾ which makes the bladder tumor as the fourth common tumor in men and the eighth one in women.⁽¹⁾ Among middle aged men, bladder cancer is the second common malignancy.⁽²⁾ Over 12200 cases of death have been reported during 2000 in United States.⁽¹⁾ It means that bladder cancer is the seventh common cause of death due

to cancer.⁽¹⁾

Several risk factors have been proposed for bladder cancer development, such as industrial chemicals,³ chemical materials,⁴ genetic disorders (p53 gene mutation,^(5,6) retinoblastoma gene⁽⁷⁾), cyclophosphamide,⁽⁸⁾ chronic urinary tract infection,⁽⁹⁾ and cigarette smoking.⁽¹⁰⁾ Parameters such as pathological grade and stage of the tumor can alter the natural history, prognosis, and survival rate of patients.^(11,12) Hence, describing factors, which may impact the grade or other prognostic factors in bladder cancer can help us improving the survival rate of patients.

This study was designed to evaluate the role of smoking in prognostic characteristics of bladder transitional cell carcinoma (TCC).

Received July 2003

Accepted May 2004

**Corresponding author: Department of Urology, Sina Hospital, Hassan-Abad Sq., Tehran, Iran.*

E-mail: mgmohseni@sina.tums.ac.ir

Materials and Methods

In a retrospective case-control study from February 2000 to March 2003, the referred patients to our clinic, suspected of bladder cancer, had undergone cystoscopic examination, if necessary. Those with documented TCC of bladder based on biopsy, were included in this study and divided into high-grade group (tumor grade III) and low-grade group (pathologic grade less than III), according to WHO grading system for TCC.⁽¹³⁾

Patients' age, sex, smoking status, history of other known risk factors of bladder cancer, and cystoscopic report of tumor characteristics such as size and number of lesions were recorded for each group. Tumors smaller than 2 cm were considered as small, 2 to 5 cm as moderate, and larger than 5 cm, as large. Statistical analysis was done using chi-square test, independent t test, and analysis of variance to compare variables in low-grade and high-grade groups. A P value less than 0.05 was considered significant.

Results

A total of 185 patients with TCC of the bladder were included in this study. Mean age of the patients was 65.1 ± 14.1 years, and of whom, 149 (80.5%) were men and 36 (19.5%) were women. Male to female ratio was 4.1 to 1.

There were 83 (44.9%) patients with a positive history of smoking, who had a mean of 20.01 ± 11.09 (range 0.75 to 60) pack-year history. Thirty patients were assigned in high-grade group (16.3%) and 155 (83.7%) in low-grade group (table 1). When gender and age of the patients were considered, there was no statistically signif-

TABLE 1. Patients and tumors' characteristics in low-grade and high-grade groups

		Low Grade		High Grade		Total %	P value
		No.	%	No.	%		
History of Opium consumption	Yes	6	3.8	4	13.3	10 (5.4)	0.059
	No	149	96.2	26	86.7	175 (94.6)	
Tumor size	Small	95	61.3	2	6.7	97 (52.4)	0.000
	Medium	38	24.5	13	43.4	51 (27.6)	
	Large	22	14.2	15	50	37 (20)	
Number of lesion	Single	134	86.5	14	46.7	148 (80)	0.000
	Multiple	21	13.5	16	53.3	37 (20)	
Gender	Male	123	79.4	26	86.7	149 (80.5)	0.354
	Female	32	20.6	4	13.3	36 (19.5)	
History of Smoking	Yes	56	36.1	27	90	83 (44.8)	0.000
	No	99	63.9	3	10	102 (55.2)	
Pack-year history of smoking		6.55±11.2		21.54±11.8			0.000
Total		155	83.7	30	16.3	185 (100)	

TABLE 2. Odds ratios for smoking in different groups

	Odds Ratio	95% CI
Smoking – Grade	15.9	6.7-36.9
Smoking – Grade in Men	12.8	5.7-28.7
Smoking – Grade (Age>50)	13.4	4.9-35.9

icant difference between smokers and non-smokers. Also, age and gender distribution differences were not statistically significant in high- and low-grade groups either.

Overall, 36.1% of the patients with low-grade tumors had a positive history of smoking; whereas, 90% of the patients in high-grade group were smokers (P = 0.000, OR = 15.9, 95% CI: 6.7-36.9).

Among non-smokers, 75.5% of the tumors were small in size, but 75.9% were moderate or large in smokers (P = 0.000). Of 102 non-smokers 93.1% had a single tumor lesion, but in smokers, 63.1% had multiple lesions (P = 0.000).

There was a significant difference in smoking rate between low-grade and high-grade groups, using analysis of variance test (P = 0.000)(table 1).

Mean smoking was 21.54 ± 11.8 pack-years in grade III and zero in grade 0. Bonferoni Post Hoc test demonstrated that that the difference mostly existed between grade III and II rather than the other grades (P = 0.000 vs. P = 0.002). On the other hand, cigarette smoking rate was statistically higher in patients with high-grade tumors. This difference could be seen in both men and women (P = 0.000 and P = 0.001, respectively) (table 2).

Discussion

Smoking is a well known risk factor of bladder cancer and smokers have up to a 2-fold higher incidence rate of bladder cancer than the people who have never smoked.⁽¹⁰⁾ However, there are few studies on evaluating the effect of smoking on the tumor growth pattern, pathological grade, and other prognostic characteristics. The main purpose of this study was to evaluate this potential association.

Mean age of the patients in our study was similar to that in the previous studies.⁽¹⁴⁾ Male to female ratio was 2.5 to 1 and 3 to 1 in other studies,^(1,15) which were slightly different from our findings (4.1 to 1).

The presence of larger tumoral lesions in smokers has also been demonstrated previously. Busto Catanon et al have shown that tumor lesions larger than 3 cm have higher grades.⁽¹⁶⁾ Raitanen et

al⁽¹⁷⁾ reported that recurrence rate is higher among patients with more than 3 tumoral foci. Our study not only showed that larger lesions had higher grade, but also demonstrated that smokers had larger and more lesions.

Patients with multiple lesions had higher mean smoking rate than those with a single tumor (20.89 vs. 6.01 pack-years). This finding suggests the probable smoking effect on tumor characteristics.

The main finding of our study was the relation between tumor grade and history of smoking. As we indicated, smokers had a higher chance of having high-grade tumors (OR=15.9). Thompson⁽¹⁸⁾ also suggested that there is a significant association between smoking history and stage, grade, and rate of recurrences; however, Fleshner et al⁽¹⁹⁾ did not find such a significant relation and reported that the frequency of each grade was not different between smokers and non-smokers.

Our study showed that the history of smoking was associated with up to 15.9 (95% CI: 6.7-36.9) fold higher chance of having high-grade tumors. This association also existed in both men and women. A greater impact of smoking on women has also been reported in another study.⁽²⁰⁾

Hence, it seems that smoking not only increases the risk of bladder cancer, but also it is associated with higher tumor grades.

Conclusion

While cigarette smoking is the most potent risk factor for bladder cancer, its effect on the natural history of the disease is also considerable. Consequently, we should bear in mind that patients with TCC of bladder who have a positive history of smoking may have high-grade tumors and a more rigorous follow-up program is necessary.

References

- 1- Greenlee RT, Murray T, Bolden S, Wingo PA. Cancer statistics, 2000. *CA Cancer J Clin.* 2000;50:7-33.
- 2- Feldman AR, Kessler L, Myers MH, Naughton MD. The prevalence of cancer. Estimates based on the Connecticut Tumor Registry. *N Engl J Med.* 1986;315:1394-7.
- 3- Morrison AS, Cole P. Epidemiology of bladder cancer. *Urol Clin North Am.* 1976;3:13-29.
- 4- Stadler WM. Molecular events in the initiation and progression of bladder cancer. *Int J Oncol.* 1993;3:549.
- 5- Esrig D, Elmajian D, Groshen S, et al. Accumulation of nuclear p53 and tumor progression in bladder cancer. *N Engl J Med.* 1994;331:1259-64.
- 6- Cordon-Cardo C. Mutations of cell cycle regulators. Biological and clinical implications for human neoplasia. *Am J Pathol.* 1995;147:545-60.
- 7- Cote RJ, Dunn MD, Chatterjee SJ, et al. Elevated and absent pRb expression is associated with bladder cancer progression and has cooperative effects with p53. *Cancer Res.* 1998;58:1090-4.
- 8- Morrison AS. Advances in the etiology of urothelial cancer. *Urol Clin North Am.* 1984;11:557-66.
- 9- Kantor AF, Hartge P, Hoover RN, Narayana AS, Sullivan JW, Fraumeni JF Jr. Urinary tract infection and risk of bladder cancer. *Am J Epidemiol.* 1984;119:510-5.
- 10- Burch JD, Rohan TE, Howe GR, et al. Risk of bladder cancer by source and type of tobacco exposure: a case-control study. *Int J Cancer.* 1989;44:622-8.
- 11- Holmang S, Hedelin H, Anderstrom C, Holmberg E, Johansson SL. The importance of the depth of invasion in stage T1 bladder carcinoma: a prospective cohort study. *J Urol.* 1997;157:800-3.
- 12- Millan-Rodriguez F, Chechile-Toniolo G, Salvador-Bayarri J, Palou J, Vicente-Rodriguez J. Multivariate analysis of the prognostic factors of primary superficial bladder cancer. *J Urol.* 2000;163:73-8.
- 13- Epstein JI, Amin MB, Reuter VR, Mostofi FK. The World Health Organization/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. Bladder Consensus Conference Committee. *Am J Surg Pathol.* 1998; 22:1435-48.
- 14- Lynch CF, Cohon MB. Urinary system. *Cancer.* 1995; 75(1 Suppl):316-29.
- 15- Wingo PA, Tong T, Bolden S. Cancer statistics, 1995. *CA Cancer J Clin.* 1995;45:8-30. Erratum in: *CA Cancer J Clin.* 1995;45:127-8.
- 16- Busto Catanon L, Sanchez Merino JM, Picallo Sanchez JA, Gelabert Mas A. Clinical prognostic factors in superficial cancer of the urinary bladder. *Arch Esp Urol.* 2001 Mar;54:131-8.
- 17- Raitanen MP, Tammela TL. Impact of tumour grade, stage, number and size, smoking habits and sex on the recurrence rate and disease-free interval in patients with transitional cell carcinoma of the bladder. *Ann Chir Gynaecol.* 1995;84:37-41.
- 18- Thompson IM, Peek M, Rodriguez FR. The impact of cigarette smoking on stage, grade and number of recurrences of transitional cell carcinoma of the bladder. *J Urol.* 1987; 137:401-3.
- 19- Fleshner N, Garland J, Moadel A, 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;86:2337-45.
- 20- Xavier B. Bladder cancer risk higher for women smokers [news]. *Br M J* 2001; 322:948.