RESEARCH ARTICLE

Are Bladder Neoplasms More Aggresive in Patients with a Smoking-related Second Malignancy?

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Abstract

Background: Relationships between smoking and bladder neoplasms, one of the common malignancies, are well-known. Different smoking-related malignancies may occur together. In this study, we evaluated the stage and grade of bladder neoplasms in patients also featuring lung or larynx cancer. Materials and Methods: From January 2006 to February 2012, patients who underwent surgery for bladder neoplasms in our clinic were screened retrospectively. In the evaluation, 5 patients had larynx cancer and 20 patients have lung cancer in addition, all having been smoking for a long time. The bladder tumor stage and grade were investigated in these 25 cases. Results: Mean age of patients was 66.8 (49-78). In the evaulation, all of 5 patients who had larnyx cancer also had high grade urothelial cancer. One had T2 urothelial, and 3 T1 urothelial cancer. In the same way, all of the 20 patients with lung cancer also have high grade urothelial cancer, three T2, and 13 T1. Bladder cancer stage and grade were determined to be significantly increased in patients with concomitant bladder and lung or larynx cancer. Conclusions: In the patients who have smoking releated second malignancy, bladder cancer prognosis appears more aggressive. We now need a larger series and multi-center studies for understanding relevant pathophysiology.

Keywords: Bladder neoplasm - lung cancer - larynx cancer - concomitant lesions - smoking - prognosis

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Introduction

Cancer of the urinary bladder is among the five most common malignancies in the Western world (Jemal et al., 2011; Siegel et al., 2013) and the frequency of transitional cell carcinoma (TCC), which accounts for 90% of bladder cancers (Jemal et al., 2011). Among men, it is the fourth most common tumour, and it is the ninth leading cause of death from cancer. The ratio of men to women that develop bladder cancer is approximately 3:1 (Jemal et al., 2011). When first diagnosed, more than 80% of bladder tumours are non-muscle invasive papillary tumours (Ta, T1) and 70% of them are non-invasive to lamina propria (Ta) that have an excellent prognosis (Millán-Rodríguez et al., 2000; Ahmadi et al., 2012; Cheng et al., 2013).

Tobacco consumption is the most important factor for the development of this disease, contributing to approximately 50% of all cases (Strope and Montie, 2008; Kobeissi et al., 2013). As the final recipient and reservoir of urine, the urothelium is inevitably exposed to carcinogens present in tobacco, which can create stepwise molecular alterations that eventually lead to transformation of urothelial cells (Martignoni, 2013).

Tobacco use is the single largest preventable cause of mortality and morbidity globally (Ezzati and Lopez, 2003). Tobacco kills a third to half of those who use it (Jha et al., 2008). As we told about bladdder cancer, tobacco use has been associated with many carcinomas too that including lung, esophagus, larynx, mouth, throat, kidney, pancreas, stomach, and cervix. Lung and larynx cancers are the commonest cancer associated with tobacco use accounting for up to 25% of tobacco-related mortality (Alberg and Samet, 2003). We hypotazied that patients' bladder tumor risk who have tabacco-related cancer is higher. And we evaulated the stage and grade of bladder neoplasm in patients with bladder neoplasm and lung or larynx cancer together.

Materials and Methods

We retrospectively analyzed data of the patients who underwent surgery for bladder neoplasm in our clinic between Jenuary 2006 to February 2012. Patients with upper urinary tract carcinomas, prostatic stroma invasion

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or metastatic bladder cancer at diagnosis were excluded from this study. The patients who had CIS, adenocarcinoma or squamose cell carcinoma on histopatologic results, chemoteraphy or radioteraphy were excluded too. Thus, 25 patients (22 men and 3 women) who have additional tabacco-related cancer as small-cell lung cancer or larynx cancer were enrolled in this retrospective study. These were included; age, gender, other tabacco-related cancer type, bladder tumor histologic stage, grade and pack-years of smoking (p/y).

The clinical staging of the 2002 TNM classification. Ta tumor was accepted as lower stage bladder carcinoma. T1 and T2 tumors were accepted as higher stage bladder carcinoma. Also, pathological grading adopted by World Health Organization (2004) grading system were used. The patients who had non-invasive papillary urothelial neoplasm of low malignant potential were accepted as low grade papillary urothelial papiller cancer. The institutional review board approved this study, and informed consent was obtained from each participant.

Continuous variables were expressed as median values and ranges. Categorical data and continuous variables were compared using the two-tailed Fisher exact test or q-square test. And statistical significance was defined as $p<0.05$. All analysis were conducted using SPSS version 15.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Among the 25 total patients analyzed in our study, there were 22 males (88%) and 3 females (12%). The mean age of patients was 68.28±6.87 and mean pack-years of smoking at this group was 62.28±27.49. Demographic analyses and clinicopathologic characteristics were demonstrated in Table 1.

In the evaulation, all five patients with larnyx cancer also had high grade urothelial cancer. One of these patients had T2 urothelial, and four of them had T1 urothelial cancer. In the same manner, among 20 patients who had lung cancer, 16 also had high grade urothelial cancer and four of them had low grade. Four of these patients had T2 urothelial, and 13 of them had T1 urothelial cancer (Table 2).

According to our data, bladder cancer stage was statistically determined to be significantly increased in patients with bladder neoplasm who also had lung or larynx cancer ($p<0.05$). As shown in Table 3, tobacco smoking was significantly associated with high histologic grade, and high pathologic stage, whereas age and gender were not.

The relationship of patients with additional tobacco related cancer and histopatological results of specimens at their transurethral resection of bladder tumour are given in Table 3. As can be seen, the risk of bladder tumours when patients have an additional tobacco-related cancer was significantly higher.

Table 1. The Patients and Tumor Characteristics

Variables		No	(%)
No. of patients		25	
Gender	Male	22	(88%)
	Female	3	(12%)
Age (mean±sd)		66.8	(49-78)
Lung cancer		20	
	Ta	3	(15%)
	T1	13	(65%)
	T2	4	(20%)
Larynx cancer		5	
	Ta	0	
	T1	4	(80%)
	T2	1	(20%)
Pathological grade	Low	5	(20%)
	High	20	(80%)

Table 2. Comparison of Characteristics of Patients

Age	Gender	P/Y	Additional Malignancy	Bladder Tumor Stage	Bladder Tumor Pathologic Grade
69	Man	160	Larynx Ca	T1	High Grade
62	Man	45	Lung Ca	T1	High Grade
49	Man	60	Lung Ca	T1	High Grade
78	Man	50	Lung Ca	T2	High Grade
72	Man	80	Lung Ca	T1	High Grade
66	Man	60	Lung Ca	T2	High Grade
68	Man	55	Lung Ca	T1	High Grade
64	Man	80	Larynx Ca	T1	High Grade
72	Man	60	Lung Ca	T2	High Grade
64	Man	60	Lung Ca	T1	High Grade
60	Man	120	Lung Ca	T2	High Grade
60	Woman	45	Larynx Ca	T1	High Grade
66	Man	60	Lung Ca	Ta	Low Grade
72	Man	45	Lung Ca	T1	High Grade
68	Man	50	Lung Ca	Ta	Low Grade
70	Man	60	Larynx Ca	T1	High Grade
75	Man	45	Larynx Ca	T2	High Grade
69	Man	80	Lung Ca	Ta	Low Grade
81	Man	45	Lung Ca	T1	High Grade
78	Woman	55	Lung Ca	T1	High Grade
67	Man	30	Lung Ca	T1	High Grade
73	Woman	40	Lung Ca	T1	High Grade
68	Man	44	Lung Ca	T1	High Grade
74	Man	48	Lung Ca	T1	Low Grade
62	Man	80	Lung Ca	T1	High Grade

*p/y: pack/year

Table 3. The Distribution of Histopathological Features of Patients

		Ta (Lower risk)	T1, T2 (Higher risk)
Stage	General population	56 %*	36 %*
	In our study PTRCB	12%	88%
Grade		Low grade	High grade
	In our study PTRCB	20%	80%

*Kirkali Z, Chan T, Manoharan M, et al (2005). Bladder cancer: epidemiology, staging and grading, and diagnosis. *Urology*, **66**, 4-34; **TRBC: patients who have an additional tabacco-related cancer to bladder cancer

Discussion

The objective of this study was to discover whether the risk of bladder cancer among persons with an additional tobacco-related cancer is significantly higher when compared to the general population.

In our study, we examined the data of patients admitted to our clinic because of bladder cancer and those patients who had previously been diagnosed with a smoking-related disease. Many diseases that might be associated with smoking have been described. They are mainly head and neck cancers, lung cancer, larynx cancer, and cancers of the urogenital system. In our study, we have included cancer patients whose illness we severely doubt was associated with smoking. Therefore, our preference was

small cell lung cancer and larynx cancer. When assessing the results of the first transurethral resection pathology due to bladder cancer of these patients, we assumed that the results were more invasive and had a higher grade than we could see in the general population. We have scanned the literature to establish whether there has been any previous such research and concluded that there was no similar past study.

Voluntary and passive smoking is the most clearly identified carcinogen for humans (Izarzugaza et al., 2010). The first results obtained by Doll et al. (2005) based on the research of British doctors followed up over a period of 50 years, had a great influence on the fall in the prevalence of tobacco use in general and cigarette smoking in particular (Doll et al., 2005). Recently, Lammers et al. (2011) demonstrated previous recurrences, multiplicity of tumours, and smoking status to predict recurrence-free survival of patients with non–muscle-invasive UBC in multivariate analyses (Lammers et al., 2011). A similar effect has been suggested for invasive UBC. Boström et al., found smokers to have lower rates of disease-free survival after radical cystectomy, but this was not an independent prognostic factor. Similarly, Yafi et al. (2011) found smoking to be independently associated with prolonged disease-specific and overall survival (Yafi et al., 2011).

Lung cancer is the paradigm of what smoking represents as a causal risk factor for the tumours studied. The clear relationship between the number of cigarettes smoked daily, degree of inhalation and age of initiation into smoking, on the one hand, and risk of developing lung cancer, on the other, has been established. In the meta-analysis conducted by Gandini et al. (2008), the estimated relative risk (RR) in current smokers was 8.96 (95% CI 6.63-12.11) for lung cancer, closely followed by laryngeal cancer (RR=6.98; 95% CI: 3.14-15.52) and, at a somewhat lower level, by bladder cancer at 2.80 (2.01-3.92): these risks are sufficiently important to justify prevalence of tobacco use being monitored in the population as a whole. Aside from tobacco, a number of other factors, such as asbestos, radon and occupation, exert an influence on the development of lung cancer. It is estimated that, among non-smokers and ex-smokers in several European countries, 15-24% of lung cancers are attributable to environmental tobacco smoke, with this factor being a major contributor to work-related exposure (Vineis et al., 2007). This is likewise applicable to bladder (González et al., 1989) and laryngeal (Smith et al., 1990; Hashibe et al., 2007; García-Pérez et al., 2009) cancers.

Cigarette smoking, the most common form of tobacco use, is known to be an important risk factor of laryngeal cancers (Anon, 2004). Comparison of hypopharyngeal and laryngeal cancer risk in relation to cigarette smoking has been investigated in several studies (Tuyns et al., 1988; Menvielle et al., 2004). The IARC international study of cancers of the hypopharynx and larynx in Europe showed that the effect of cigarette smoking was similar to all sites (Anon, 2004).

The risk of cigarette smokers correlates not only with number of pack-years smoked but also with duration of smoking and the depth of inhalation. Cigarette smoke is a rich source of chemical carcinogens and reactive oxygen species (ROS). Chemical carcinogens include polycyclic aromatic hydrocarbons, aromatic amines and N-nitroso compounds, which can produce DNA bulky adducts that may lead to DNA damage (Perera et al., 2012). As the final recipient and reservoir of urine, the urothelium is inevitably exposed to carcinogens present in tobacco, which can create stepwise molecular alterations that eventually lead to transformation of urothelial cells.

From the molecular point of view, evidence in the literature supports the existence of distinct pathogenetic pathways involved in bladder cancer development (Berber et al., 2013). By departing from this fact, we have proposed the hypothesis that the prognosis of bladder cancer may be worse in the presence of cancers associated with smoking and pathological stage especially if the histological grade is high.

The study had some shortcomings. The first of these was that the study was done retrospectively on a limited number of people. Although we think that it is possible to get more clear results, in this sole-based study, the number of patients with another cancer associated with smoking was restricted. Even in this limited study, the difference stands out statistically.

Secondly, this study has been performed on a population of Turkey; Smoking rates and bladder cancer data differ between societies. Of course, this also applies to other cancers associated with cigarette smoking. There are studies on smoking in Turkey. However, in the studies performed on the regional prevalence of bladder cancer, pathological evaluation and the relevant data on dissipation is not clear. Therefore, in this study, we have evaluated the frequency of bladder cancer, according to global data. In addition, although bladder cancer is closely related with smoking, there are also other factors associated with bladder cancer and influencing bladder cancer prognosis. Recurrent urinary tract infection, bladder stones, and schistosome infection are some of the well-known factors. Other factors are the genetic factors and liability. Significant gene environment interactions must exist that make the risks of smoking substantially greater in susceptible individuals. Indeed, a family history of bladder cancer alone did not increase the bladder cancer risk but a family history combined with smoking significantly increased the odds of bladder cancer (Lin et al., 2006). Multiple studies have explored the association between genetic polymorphisms and bladder cancer risk with inconsistent results (Cao et al., 2005; Gormally et al., 2006; Figueroa et al., 2007). The polymorphism most closely tied to an increase in bladder cancer risk has been the NAT1*14A allele and NAT2 slow acetylator phenotype (García-Closas et al., 2005; Kobeissi et al., 2013). We could not evaluate the genetic predisposition, and other factors in this study but we think that this will not affect the results.

Thirdly, there was no control group in our study. As mentioned earlier, there may be differences between our society and Western societies. But, since there was no large-scale data system about our society, we had to evaluate according to the global results. However, in our study, when the patients with smoking-related lung and

larynx cancer are compared, the pathological stage at the time of diagnosis has been found as 12% Ta and 88% T1 and T2. When we compared it with the values in the general population, these were 56% and 36%, respectively. There was a significant difference between these values. We can say that despite the deficiencies, our study is considered to be the first of is type and in this sense, it may well lead to future studies in this subject.

In conclusion, history of smoking-related secondary malignancies, the prognosis of patients with bladder tumours more aggressive outlook. To reveal the pathophysiology of larger series and multicenter studies are needed.

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