ASSOCIATION OF SMOKING WITH HIGH-GRADE TRANSITIONAL CELL CARCINOMA OF THE URINARY BLADDER

Mohammadghassem Mohseni MD•, Ali Nourbakhsh MD, Zinat-Nadia Hatami PhD

Background: Accurate staging and grading of bladder neoplasms, which are the most important guides for the treatment of transitional cell carcinoma (TCC), depend seriously on the interpretation of tumor biopsies by pathologists and are largely subject to inter- and intra-pathologist variations. Therefore, it appears that clinicians should have additional guides to appropriately diagnose and treat high-risk patients.

Objective: We evaluated the association of the grade of TCC of the urinary bladder with four patient’s variables, i.e., age, gender, cigarette smoking, and opium consumption, to find out if any of them could serve as a guide for clinicians.

Methods: A retrospective study was performed on 255 individuals in whom TCC was diagnosed. Correlations between the grade of TCC and clinical features were determined.

Results: Age was not correlated with tumor grade ($P = 0.59$), but cigarette smoking ($P = 0.032$) and male gender ($P = 0.029$) showed positive associations with higher grades. The association between male gender and higher grades is probably due to the higher incidence of cigarette smoking among men ($P < 0.001$), making this correlation spurious. Because opium consumption had a significant correlation with smoking ($P < 0.001$), its correlation ($P = 0.012$) with high grades of TCC could not be validated as accurate.

Conclusion: Cigarette smokers and males (according to a high prevalence of cigarette smoking among males) are more prone to develop high grades of urinary bladder TCC. In these high-risk groups, there should be a low threshold for the review of pathologic material if the primary pathological examination shows a low-grade carcinoma, for adjuvant treatment (intravesical therapy), and for careful follow-up after the treatment—especially when pathological differentiation between the grades is difficult.

Keywords: Cigarette smoking • grade • opium • transitional cell carcinoma (TCC) • urinary bladder

Introduction

There are various types of malignancies of the urinary bladder, with transitional cell carcinoma (TCC) or urothelial tumor, being the most common one.\(^1\) One of the important characteristics of TCC is that its prognosis seriously depends on the tumor histologic grade and stage when it is first diagnosed, making the tumor grade an important predictor for its behavior\(^1,3,6\). Based on the study of Oosterhuis et al., the prognostic value of the 1998 WHO/ISUP classification system for grading TCC of the urinary bladder has limitations in predicting progression-free survival, especially between papillary neoplasms of low malignant potential and high-grade papillary urothelial carcinomas.\(^7\) The analysis of new molecular parameters is of interest in predicting the prognosis of patients with bladder cancer, particularly in high-risk groups who are at risk of disease progression and recurrence, because clinical courses differ and current prognosticators are limited.\(^2\)

There are two main systems for grading these
lesions. The first is the World Health Organization (WHO) classification which classifies TCC into three grades. The second more recent classification system was created by the International Society of Urological Pathology (ISUP), which categorizes TCC into low malignant potential and two grades of carcinoma (low and high grades). High-grade TCC is mainly composed of grade III tumors and has a higher metastatic potentiality, lethality, recurrence rate, and level of invasiveness than the low-grade TCC.1

By considering the grade as a predictor of the prognosis, the relationship between their behavior and prognosis of the tumor can be assessed. This indicator of tumor grade through patient history can help us to determine which group of patients are at higher risk. Accurate diagnosis, staging, and grading of bladder neoplasms depend seriously on the interpretation of biopsies and transurethral resection (TUR) specimens. Coblentz et al demonstrated that the review of bladder pathologic materials before definitive therapy can impact clinical decisions significantly.8 Therefore, if the clinician can identify a high-risk group of patients, a review of their pathologic materials to avoid down-grading will be an obligation.

Pathological interpretations and their treatment are based on local pathology results. van Der Meijden et al proved that pathologic review is not mandatory in patients with low or intermediate risk, since it has little impact on the prognosis and treatment decision-making. In high-risk cases of grade III disease, however, the stage or grade is often changed, so that review remains essential in this subgroup.9

There is some evidence which proves the uncertainty of primary grading and staging of urothelial carcinoma of the urinary bladder. For example, Bol et al compared the original WHO criteria diagnosis with the reviewed one in stages Ta and T1 urothelial carcinoma. The consensus and original diagnosis agreed on stage and grade in only 68.5% and 62.3% of cases, respectively, and the prognosis was more compatible with the consensus diagnosis. At the end of the study, all pathologists expressed that they were regularly uncertain about the stage and grade assessment in an individual case in a considerable percentage of all cases.10

According to the above-mentioned studies, the clinician should have other aids, including patient history, to predict the grade and behavior of the carcinoma. Along side the pathological examination results, this can guide the physician to the best diagnostic procedure and treatment. Fitzpatrick mentioned that the natural history of superficial bladder carcinoma has an important bearing on the outcome of response to intravesical chemotherapy or immunotherapy. Many factors such as poor-grade and smoking history should alert the urologist to introduce intravesical therapy at an early stage.11

For the purpose of predicting the prognosis of invasive urinary urothelial carcinoma of the urinary bladder, Yang et al reviewed the medical records of patients with this carcinoma. Age and sex of patients were not significant predictors of the prognosis.12 Results from a study conducted by Fleshner et al showed that continued smokers experience worse disease-associated outcomes than patients who quit smoking.13

Cigarette smoking, opium consumption (a previously known risk factor for TCC14-16), age, and sex of the patient were examined for association with the grade of TCC. The purpose of this study was to assess the association of some patient’s risk factors with the grade of their bladder malignancy at the time of diagnosis.

Patients and Methods

The cases included biopsy-proven patients who were admitted to Sina Hospital with a diagnosis of TCC of the urinary bladder. Sina Hospital is one of the major referral centers in Tehran responsible for diagnosis and treatment of urological diseases. All results were confirmed by one expert pathologist. Samples were gathered between 1990 and 2000. The data were obtained by residents of urology during the study period through careful direct questioning. None of the patients had a previous history of urological problems.

Individuals were categorized into two groups according to their cigarette smoking habits: smokers as defined by smoking of at least ten cigarettes per day for the last three years, and nonsmokers who had no previous history of cigarette smoking. The criteria was based on the Smoker and Nonsmoker Guidelines (www.bisysinsurance.com) and also cigarette smoking habits in the country.

Opium consumption was defined as the inhalation of the smoke of ignited opium and/or eating opium in the crude form (both types are very common among the addicts and the separation
is rather impossible because almost all addicts have used both forms) at least three times per week for at least five years. Nonopium users were those who had no previous history of opium use. Criteria for the definition of opium consumption was arbitrary due to the lack of any internationally-acceptable consensus on this issue and was defined according to the opinion of epidemiologists and authors.

No exclusion criteria was assumed and all patients with a first-time diagnosis of TCC, admitted to Sina Hospital during the study period, were included. The WHO grading system was used.1

**Statistical analysis**

All the data were analyzed using the SPSS 10 software for Windows®. Chi-square test was used to assess the association of each patient’s feature with the grade of tumor.

**Results**

The total number of cases was 255. There were 39 (15%) patients with grade I, 146 (57 %) with grade II, and 70 (28 %) with grade III disease.

As shown in Table 1, while age was not associated with the grade of TCC (P = 0.59), male gender was statistically associated with the grade (P = 0.029). The percentage of smokers, when compared with nonsmokers, also showed a significant correlation with the grade (P = 0.032). Opium consumption was also significantly correlated with the grade (P = 0.012).

**Discussion**

The results showed that there was no association between the age and the grade of tumor (P = 0.59). Yang et al also have come out to the same conclusion and noted that age is not a significant predictor of the prognosis.12 Yossepowitch and Dalbagni also found that there was no difference in the pathological stage distribution or the rate of extravesical disease in young adults as compared to the older individuals.17

Smoking is not only the most important risk factor for TCC of the urinary bladder, but is also, according to our study, associated with higher grades of the tumor. There are some other studies that confirm this result. For example, Thompson et al showed a significant association between the smoking history and stage, grade, and the number of recurrences of transitional cell carcinoma of the bladder.18

These results indicate that cigarette smoking correlates with higher rates of progression, invasion, and lethality in patients. Additionally, after full investigation of the extent of the progression of the carcinoma, the benefits of adjuvant therapy (e.g., intravesical therapy) should be assessed and careful follow-up should be provided to this high-risk group. Review of the biopsy by the pathologist is also important if the first pathological diagnosis was a low-grade tumor.

The male gender was associated with higher grades of TCC. The correlation of higher grades of TCC and male gender (P = 0.009) suggests that men are more susceptible to the development of higher grade tumors and, therefore, have a poorer prognosis than women. However, in our study, this was probably due to the high correlation between the male gender and smoking incidence. Sixty-eight point three percent of the men who took part in this study were smokers, while only 3.6% of women smoked (P < 0.001). As previously mentioned, cigarette smoking was related to higher grades of the tumor (P = 0.032). In Yang et al’s study, there was no association between sex and prognosis of the tumor.12 Castelao et al investi-

**Table 1.** Clinical characteristics of 255 patients with TCC and the significance of their correlation with the grade of tumor.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>61.8 ± 10.3</td>
<td>63.2 ± 11</td>
<td>64.4 ± 9</td>
<td>0.59*</td>
</tr>
<tr>
<td>Sex</td>
<td>63</td>
<td>65</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>30 (77%)</td>
<td>134 (92%)</td>
<td>63 (90%)</td>
<td>0.029*</td>
</tr>
<tr>
<td>Female</td>
<td>9 (23%)</td>
<td>12 (8%)</td>
<td>7 (10%)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>18 (46%)</td>
<td>88 (60%)</td>
<td>50 (71%)</td>
<td>0.032*</td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>21 (54%)</td>
<td>58 (40%)</td>
<td>20 (29%)</td>
<td></td>
</tr>
<tr>
<td>Opium</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>User</td>
<td>4 (10%)</td>
<td>32 (22%)</td>
<td>5 (7%)</td>
<td>0.012*</td>
</tr>
<tr>
<td>Nonuser</td>
<td>35 (90%)</td>
<td>114 (78%)</td>
<td>65 (93%)</td>
<td></td>
</tr>
</tbody>
</table>

*Chi-square test; SD = standard deviation.
gated the possible sex differences in susceptibility to bladder cancer among smokers. They concluded that the risk of bladder cancer in women who smoke is significantly higher than that in men who smoke the same number of cigarettes.  

The frequency of opium consumption was much higher in the grade II than in the grade III patients ($P = 0.007$). Opium consumption was correlated with higher tumor grades. There are some studies which suggest opium is a risk factor for transitional cell carcinoma of the urinary bladder. It had also been mentioned, in a population in northeastern Iran, that ingestion of opium dross (sukhteh) can be a risk factor for esophageal cancer. It has also been suggested that the material, which is produced through burning opium and in particular its major alkaloid morphine, has high mutagenic activity. The major active ingredients in both sukhteh and opium smoke are aromatic hydrocarbons and primary aromatic amines. In another study, Sadeghi et al found that the correlation between cancer of the urinary bladder and opium use was much stronger than that of cigarette smoking. 

Unfortunately, there is little information about the mechanism of the mutagenicity of opium. The correlation of opium use with high-grade tumors can not be validated based on this study, as the majority of opium users were also smokers ($P < 0.001$) and any correlation detected between opium consumption and grade may be due to the considerable association between opium use and smoking.

Patients with a history of at least three years of smoking (at least ten cigarettes per day) in whom TCC is diagnosed should be considered at greater risk of developing higher grades of tumors. Further studies are needed to confirm the correlation between opium and the grade.

References