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A Combined Clinicopathologic Analysis of 658 Urothelial Carcinoma Cases of Urinary Bladder

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Key words: urinary bladder; urothelial carcinoma; tumor growth pattern; recurrence; progression

Objective To study the clinicopathological features of patients with urothelial carcinoma of the urinary bladder (UCB), and analyze the association of clinicopathological characteristics with tumor recurrence and progression.

Methods Altogether 658 UCB cases in Fudan University Shanghai Cancer Center were collected from January 2006 to December 2010. The histopathologic materials and the clinical records were reviewed. Univariate and multivariate analyses were preformed to detect the association.

Results The mean age of the patients was 61.97 ± 12.97 years (range, 20-90 years). Male to female ratio was about 5:1. A total of 517 cases (78.6%) were superficial at the time of diagnosis (stage Ta/T1). The mean follow-up period was 22.36 ± 24.92 months. Twenty-five patients lacking follow-up information were excluded in calculating recurrence and progression rates, the recurrence rate was about 37.0% (234/633), and progression rate about 6.2% (39/633). Three variables (grade, tumor growth pattern, and pathological stage) were found to be significant risk factors for tumor progression in univariate and multivariate analyses ($P < 0.05$).

Conclusions Most of the newly diagnosed UCB cases may be superficial diseases. Grade, tumor growth pattern, and pathological stage are associated with tumor progression of UCB.

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BLADDER cancer is the second most common malignancy encountered by urologists.¹ It is a significant cause of cancer morbidity and mortality. The incidence and pattern of this disease has geographical variation. In addition, age, gender, and racial factors all affect the survival and prognosis of patients with bladder carcinoma.² However,

the prognostic importance of various factors varies from one publication to another,³ including age, gender, tumor size, number of tumor, grade, pathological stage, carcinoma in situ, surgical margin, vascular invasion, and lymph node status.¹⁻⁷

The accurate prediction of clinical outcome is necessary for appropriate management of patients with urothelial carcinoma of the bladder (UCB). However, there were little relevant reports from China, especially with large samples. In the present study, we reviewed the clinicopathological features of 658 patients with UCB to detect the possible

prognostic factors associated with recurrence and progression of bladder cancer.

PATIENTS AND METHODS

Patients

658 UCB patients who underwent bladder tumor surgery in Fudan University Shanghai Cancer Center from January 2006 to December 2010 were included. The clinical information and pathological data of the patients were acquired from the hospital database involving age (≤ 55 years or >55 years), gender, pathological stage, grade, and tumor growth pattern (solid or papillary). To minimize interobserver variability, all histopathologic materials from the tumors were reviewed by 2 senior pathologists. Staging and grading of each tumor were performed according to the international tumor-node-metastasis grading system and the World Health Organization 2004 grading system, respectively. While analyzing the recurrence rate and the progression rate, 25 patients lacking follow-up information were excluded. Recurrence was defined as the reappearance of histopathologically confirmed UCB. Relapse within 3 months of primary diagnosis were excluded, considering the possibility of residual tumor. Progression was defined as an advance in stage or metastasis.

Statistical analysis

SPSS 17.0 software was used for statistical analysis. Univariate and multivariate analyses were adopted to assess the risk factors for tumor recurrence and progression. $P < 0.05$ was considered statistically significant.

RESULTS

Clinicopathological characteristics

In terms of gender feature, 83.3% (548/658) of the patients were male, with male to female ratio being about 5 : 1. The mean age was 61.97 ± 12.97 years (range, 20-90 years). Most patients were between 50-70 years of age (Fig.

1). The most frequent complaint was hematuria, recorded in 76.0% (500/658) of the patients, mainly painless hematuria. At initial diagnosis, 49.6% (326/658) of the patients had stage Ta tumors, and 29.0% (191/658) had stage T1 tumors. Muscle invasive urothelial carcinomas were presented in 84 patients (12.7%), including T2 in 56 patients (8.5%), T3 in 12 patients (1.8%), and T4 in 16 patients (2.4%). Based on the differentiation of neoplasm cells, the tumors were divided into two categories: low and high grade tumors. The percentages of low-grade and high-grade tumors were 49.9% and 50.1%, respectively.

Microscopically, based on the tumor growth pattern, the tumors were classified into papillary and non-papillary (solid) (Fig. 2). The papillary growth pattern was demonstrated as an exophytic tumor with a papillary stalk lined by dysplasia urothelium, while the solid growth pattern as an endophytic tumor composed of diffusely growing sheets of tumor cells without fibrovascular core formation. 69.6% (458/658) of the tumors in this study had papillary growth pattern. Most (77.6%) of the superficial (Ta/T1) UCB were papillary, and more than half of them (56.3%) were low grade, while muscle invasive UCB were mostly solid (82.1%) and high grade (95.2%). The clinicopathological characteristics of 658 patients with UCB at diagnosis are presented in Table 1.

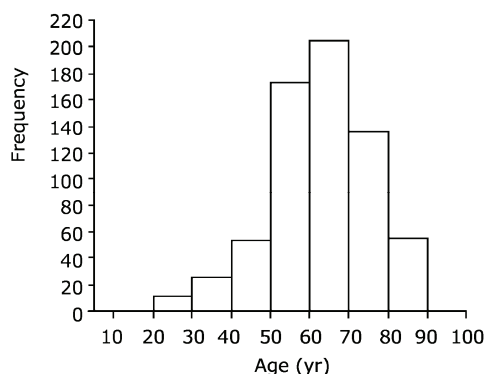


Figure 1. The age distribution of the 658 patients with urothelial carcinoma of the bladder (UCB).

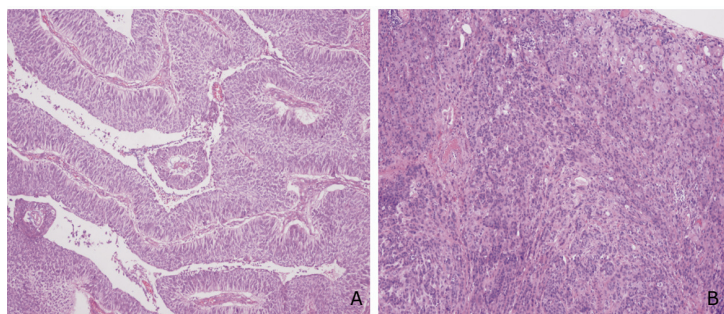


Figure 2. High-grade invasive papillary UCB (A) and high-grade invasive solid UCB (B). HE $\times 100$.

Table 1. Clinicopathological characteristics of 658 patients with UCB

Characteristics	Number	Percentage
Age		
≤55 years	183	27.8%
>55 years	475	72.2%
Gender		
Male	548	83.3%
Female	110	16.7%
Stage		
Tis	14	2.2%
Ta	326	49.6%
T1	191	29.0%
T2	56	8.5%
T3	12	1.8%
T4	16	2.4%
Uncertain	43	6.5%
Grade		
Low	328	49.9%
High	330	50.1%
Tumor growth pattern		
Papillary	458	69.6%
Solid	200	30.4%

Table 2. Clinicopathological characteristics of 234 recurrent patients

Characteristics	Number	Percentage
Age		
≤55 years	70	29.9%
>55 years	164	70.1%
Gender		
Male	189	80.8%
Female	45	19.2%
Stage		
Tis	5	2.1%
Ta	113	48.3%
T1	60	25.7%
T2	22	9.4%
T3	5	2.1%
T4	8	3.4%
Uncertain	21	9.0%
Grade		
Low	105	44.9%
High	129	55.1%
Tumor growth pattern		
Papillary	152	65.0%
Solid	82	35.0%

Recurrence and progression

After a follow-up period of 22.36 ± 24.92 months, recurrence was observed in 234 patients (37.0%, Table 2). Progression was seen in 39 patients (6.2%, Table 3). The most common extranodal site of metastases was bones (56.4%), followed by lungs (38.5%), livers (23.1%), pelvis (10.3%), and penis (7.7%). Nine patients had multiple metastases.

Association with recurrence and progression

According to univariate analysis, gender, age, grade, tumor growth pattern, and pathological stage were not associated with tumor recurrence, but multivariate analysis showed association between stage and recurrence ($P < 0.05$, Table 4). Gender, grade, tumor growth pattern, and pathological stage were associated with tumor progression in univariate analysis ($P < 0.05$); but in multivariate analysis, gender was not associated with progression (Table 4).

Table 3. Clinicopathological features of 39 progressive patients

Characteristic	Number	Percentage
Age		
≤55 years	7	18.0%
>55 years	32	82.0%
Gender		
Male	29	74.4%
Female	10	25.6%
Stage		
Ta	12	30.8%
T1	11	28.2%
T2	8	20.5%
T3	3	7.7%
T4	3	7.7%
Uncertain	2	5.1%
Grade		
Low	7	18.0%
High	32	82.0%
Tumor growth pattern		
Papillary	17	43.6%
Solid	22	56.4%

Table 4. The association of clinicopathological characteristics with tumor recurrence and progression detected by univariate and multivariate analyses

Characteristics	Association with recurrence (P value)		Association with progression (P value)	
	Univariate	Multivariate	Univariate	Multivariate
Age	0.830	0.606	0.630	0.371
Gender	0.268	0.208	0.035	0.111
Stage	0.170	0.045	<0.001	0.022
Grade	0.131	0.085	<0.001	0.028
Tumor growth pattern	0.244	0.184	<0.001	0.043

DISCUSSION

Some risk factors that are possibly associated with the recurrence and progression of UCB have been studied worldwide. In general, high grade, solid tumor growth pattern, and late pT stage were found to be risk factors closely associated with the unfavorable prognosis of UCB.^{6,8-10} In the present study, we analyzed the possible risk factors associated with the recurrence and progression of UCB based on the clinicopathological features of 658 UCB patients, and compared our findings with previous reports.

de Vere White et al⁸ reported that approximately 80% of the patients with newly diagnosed bladder carcinomas presented with superficial diseases (Ta/T1), about 20% of which were stage T1. Matalaka et al⁹ conducted a clinicopathological study with 115 UCB patients, the results of which revealed that 54.5% of the cases were stage pTa, 17.3% were pT1, 20% were pT2, 7.3% were pT3, and 0.9% were pT4. The percentages of Ta/T1 patients in the above two reports were similar with those in the present study. However, in the study by Rafique et al¹⁰ on the clinicopathological features of 221 bladder carcinoma patients in Pakistan, the majority (98%) showed invasion of lamina propria, and over 60% of the patients had muscle invasive diseases at the time of diagnosis. The difference might be a result of the patients not seeing a doctor in time.

Messing et al¹¹ reported that about 55%-60% of the newly diagnosed superficial UCB are of low histological grade, but majority of the patients with muscle invasive diseases have high histological grade. Pan et al¹² studied 1515 cases of non-muscle invasive urothelial tumors, concluding that 60.4% of the cases were low grade. Similarly, in the present study, 56.3% of the superficial tumors were of low grade while 95.2% of the muscle invasive tumors were of high grade.

Andius et al⁶ found that tumor growth pattern had independent prognostic value for predicting progression. They reported that solid tumor growth pattern was associated with an increased risk of progression in stage T1 patients in univariate and multivariate analyses. Moreover, Kikuchi et al¹³ found that the presence or absence of tumor stalk was a significant predictor for tumor recurrence. Gofrit et al¹⁴ showed that endophytic growth pattern was an independent prognostic factor of stage progression and disease-specific mortality. The finding of the present study also confirmed that the solid tumor growth pattern was a risk factor for tumor progression.

Research about the metastatic pattern of bladder cancer is relatively rare. Kishi et al¹⁵ investigated 87 au-

topsy cases of bladder carcinoma, and metastasis was noted in 58 cases (66.7%), frequently in lymph nodes (37.9%), livers (29.9%), lungs (29.9%), and bones (24.1%). Shinaqare et al¹⁶ found that the most common metastatic site was lymph nodes (69%), followed by bones (47%), lungs (37%), livers (26%), and peritoneums (16%). Metastatic sites in the present study are similar to the report by Shinaqare et al, but different from Kishi et al's, possibly due to racial difference.

The prognostic significance of gender in bladder cancer is controversial. A retrospective study with 1131 bladder cancer patients in Japan showed that gender was an independent risk factor for survival, in which female patients had a worse prognosis.¹⁷ Thieblemont et al¹⁸ reached a similar result after a study with 158 invasive urothelial bladder carcinoma patients. Mungan et al¹⁹ evaluated gender differences in bladder cancer prognosis, finding that the survival in women remained worse than in men after adjusting for disease stage at presentation. Nevertheless, some studies did not find a significant association between gender and disease recurrence.^{20, 21} In the present study, gender was associated with progression in univariate analysis, with female patients having a worse prognosis; but not associated in multivariate analysis. The prognostic significance of gender would require analysis with larger samples, and the possible reasons underlying the worse outcome in women require further study.

Other factors may also be associated with prognosis of bladder cancer. One study showed that tumors greater than 5 cm had a 35% progression rate, compared with a 9% rate for smaller tumors.²² In another study, tumor size greater than 3 cm was found as an independent risk factor for tumor recurrence in multivariate analysis.¹³ The number of tumors is also important in predicting recurrence. In one study by Pan et al,¹² patients with multiple tumors showed significantly higher recurrence rate compared with those with single tumors (47.1% vs. 26.0%, $P < 0.0001$). Recurrence rate in patients with single tumors range from 18% to 60%, while the rate in patients with multiple tumors is 40%-90%.²³

The prognostic factors studied in different publications vary. Kikuchi et al¹³ concluded that the presence or absence of tumor stalk, tumor multiplicity, tumor size, pathological stage, and grade were significant predictors of tumor recurrence. Pan et al¹² concluded that tumor grade, pT stage, patient age, and multiplicity were significant risk factors for recurrence in univariate analysis; tumor grade, pT, and patient age were significant prognostic factors for progression in univariate analysis and stepwise multivariate regression analysis. Lipponen et al²⁴ showed that T

category, N category, and M category were the most important clinical prognostic factors, followed by the age of the patient. In the present study, the pT stage was associated with tumor recurrence on multivariate analysis. Grade, tumor growth pattern, and pathological stage were significant prognostic factors for progression in univariate analysis and multivariate analysis; gender was associated with tumor progression in univariate analysis.

This study has its limitations. Foremost is the retrospective nature of the study. Another limitation is that this study did not cover some possibly important factors, such as the number and size of tumor, due to the lack of information in the reviewed medical records.

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