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ORIGINAL ARTICLE

Urothelial cancer of bladder in young versus older adults: Clinical and pathological characteristics and outcomes



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Abstract Bladder urothelial carcinoma is rare in young adults and occurs more commonly in older individuals. The aim of this study was to compare the clinical behavior, pathologic characteristics, and prognosis of urothelial carcinoma of urinary bladder in young versus older adults. A retrospective review of our records between 2007 and 2013 identified 56 patients (42 males and 14 females) with transitional cell carcinoma of the bladder who were less than 40 years old. Clinical and pathological parameters of patients who were less than 40 years of age were compared with those of a series of patients older than 40 years of age (the control group) during the same period. A survival analysis was performed using the Kaplan–Meier method and log-rank test, and Cox regression was performed to identify clinical parameters that affected the clinical outcomes. The mean age was 29.21 years (range, 5–40 years) for patients less than 40 years old and 61.66 years (range, 41–75) for those older than 40 years. The mean follow-up was 40.26 months (range, 12–65 months) for young patients and 42.57 months (range, 12–72 months) for the older patients. Young bladder cancer patients had smaller-sized tumors (less than 3 cm), less high-grade cancers, higher papillary urothelial neoplasms of low malignant potential, and low-grade tumors than patients older than 40 years. Multivariate logistic regression analysis predicted tumor recurrence in young patients with high-grade tumors [odds ratio (OR), 1.959; 95% confidence interval (CI), 1.235–2.965; $p = 0.046$] and tumors larger than 3 cm (OR, 1.772; 95% CI, 1.416–1.942; $p = 0.032$). The 5-year overall survival rate was 100% for young patients and 88.1% for older patients. No difference was observed in the recurrence-free ($p = 0.321$) and progression-free ($p = 0.422$) survival rates between the two groups. We concluded that although the

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clinical stage distribution, natural history, and outcomes of bladder urothelial cancer in young adults are similar to those in their older counterparts, clinicians must be aware that patients under 40 years of age presented with higher-grade and larger (>3 cm) tumors and are more likely to experience tumor recurrence.

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Introduction

Transitional cell carcinoma (TCC) of the bladder is uncommon below the age of 40 years (1%) [1,2]. There is no univocity on clinical outcomes of such neoplasms. According to some authors, such tumors are noninvasive low-grade tumors with low recurrence rate and, therefore, an improved prognosis [3–6]. In contrast, some studies have observed similar patterns in younger and older patients [1,7–9]. In our study, we evaluated clinical behavior, pathological outcomes, and disease recurrence and survival in patients with bladder TCC who were younger than 40 years of age. We compared our data with a matched cohort of older patients (older than 40 years) with bladder TCC.

Materials and methods

We retrospectively reviewed our medical records between May 2007 and June 2013, and identified 56 patients (42 males and 14 females) with TCC of the bladder who were less than 40 years old. Demographic data, including patients' age, sex, presenting symptoms, initial transurethral pathology, tumor diameter and locations, stages and grades at initial transurethral resection, recurrence events and disease progression to different stages or grades, and disease status, were collected. We also reviewed and selected a series of patients older than 40 years of age by a case-matched analysis as the control (comparison) group, with a case/control rate of 1:2, during the same period. The 2004 World Health Organization (WHO) International Society of Urologic Pathology and 2002 tumor-stage classification were used to evaluate the stages and grades of bladder cancer [10–12]. Patients with nontransitional bladder cancer, a history of known bladder cancer, and upper tract urinary cancer were excluded from the study. Disease recurrence was defined as the reappearance of the disease at any site of the bladder and progression was defined as conversion in tumor-stage classification of cancer. Additionally, recurrence- or progression-free periods were defined between the dates of initial diagnosis of bladder cancer and those of disease recurrence or progression.

Statistical analysis

Patients younger than 40 years old were divided into two subgroups according to age presentation: younger than 30 years old and between 30 and 40 years old. Data between groups were analyzed using the Chi-square test.

Recurrence-free, progression-free, and overall survival analyses were performed using the Kaplan–Meier method and log-rank test. Multivariate Cox proportional hazards analysis was performed to identify independent predictors of the recurrence of TCC of the bladder in patients less than 40 years old. These predictors included sex, tumor stage, tumor grade, multifocality, and tumor size. All statistical analyses were performed using SPSS ver.16.5 (Statistical Package for Social Sciences for Windows 16.5; SPSS Inc., Chicago, IL, USA). A p value of <0.05 was considered statistically significant.

Results

Between May 2007 and June 2013, 56 patients (42 males and 14 females) with TCC of the bladder who were less than 40 years old were included in the young group and 112 patients with TCC of the bladder who were more than 40 years old were included in the control group. For the two groups, the mean age at diagnosis was 29.21 years (range, 5–40 years) and 61.66 years (range, 41–75), with a male-to-female ratio 3:1 and 3.3:1, respectively. The mean follow-up time was 40.26 months (range, 12–65 months) for young patients and 42.57 months (range, 12–72 months) for older patients. A total of 25 patients (44.6%) were under the age of 30 years, and 31 (55.3%) were between 31 and 40 years of age. Macroscopic hematuria was the presenting symptom in 41 patients (73.2%) in the young group and in 79 patients (70.5%) in the older group. The clinical characteristics of younger patients and their older counterparts are presented in Table 1. Bladder urothelial cancer tumors occurring in patients 40 years or younger were predominantly ≤ 3 cm in size and of low grade. As shown in Table 1, the young group had significantly higher papillary urothelial neoplasms of low malignant potential, low-grade tumors (percentage of papillary urothelial neoplasms of low malignant potential, 28% vs. 16%; low-grade tumors, 64% vs. 49%; $p = 0.041$), tumors of ≤ 3 cm diameter (89% vs. 61%; $p < 0.001$), and a lower recurrence rate (30% vs. 47%, $p = 0.040$). Multivariate logistic regression analysis predicted tumor recurrence in young patients with high-grade tumors [odds ratio (OR), 1.959; 95% confidence interval (CI), 1.235–2.965; $p = 0.046$] and tumors larger than 3 cm (OR, 1.772; 95% CI, 1.416–1.942; $p = 0.032$) (Table 2).

The Kaplan–Meier method was used to estimate the recurrence-free, progression-free, and overall survival rates. The 5-year overall survival rate was 100% for young patients and 88.1% for older patients. No difference was observed in the recurrence-free ($p = 0.321$) and progression-free ($p = 0.422$) survival rates between the two groups (Fig. 1).

Table 1 Clinical characteristics of bladder urothelial cancer patients younger and older than 40 years.

	Young group (≤ 40 y)			Old group (>40 y)	<i>p</i>
	<30 y	31–40 y	Total		
Patients, <i>n</i> (%)	25 (44.6)	31 (55.4)	56 (100)	112	
Mean age (range, y)			29.21 (5–40)	61.66 (41–75)	
Mean follow up (range, mo)			40.26 (12–65)	42.57 (12–72)	0.136
Males/females, <i>n</i>	18/7	24/7	42/14	86/26	0.867
Clinical presentation, <i>n</i> (%)					
Microscopic hematuria	3	7	10 (17.8)	22 (19.6)	0.175
Macroscopic hematuria	20	21	41 (73.2)	79 (70.5)	
UTIs	2	3	5 (9)	11 (9.9)	
Stage at presentation, <i>n</i> (%)					
Ta	21	20	41 (73.3)	62 (55.4)	0.102
T1	4	7	11 (19.6)	22 (19.6)	
T2	0	3	3 (5.4)	22 (19.6)	
T3	0	1	1 (1.7)	6 (5.4)	
Grade at presentation, <i>n</i> (%)					
PUNLMP	7	9	16 (28.6)	19 (16.9)	0.041
Low	14	22	36 (64.3)	55 (49.2)	
High	1	3	4 (7.1)	38 (33.9)	
Multifocality (>1 lesions), <i>n</i> (%)	2	15	17 (30.3)	48 (42.8)	0.063
Tumor size, <i>n</i> (%)					
≤ 3 cm	25	25	50 (89.3)	69 (61.6)	<0.001
>3 cm	0	6	6 (10.7)	43 (38.4)	
Tumor recurrence, <i>n/N</i> (%)	5/25	12/31	17/56 (30.3)	53/112 (47.3)	0.040
Tumor progression, <i>n/N</i> (%)	4/25	8/31	12/56 (21.4)	26/112 (23.2)	0.661

PUNLMP = papillary urothelial neoplasms of low malignant potential; UTI = urinary tract infection.

Discussion

Urothelial carcinoma of urinary bladder in patients younger than 40 years of age is rare, with an incidence rate of only

Table 2 Multivariate logistic regression analysis of predictors for tumor recurrence in patients younger than 40 years old.

Variable	OR	95% CI	<i>p</i>
Sex			
Male	1.000	0.132–12.038	0.842
Female	1.260		
Tumor stage			
Superficial (Ta, T1)	1.000	0.890–1.981	0.056
Muscle invasive (T2, T3)	1.752		
Tumor grade			
PUNLMP	1.000	1.235–2.965	0.046
Low	1.000		
High	1.959		
Multifocality			
≤ 1	1.000	0.938–3.228	0.544
>1	2.324		
Tumor size			
≤ 3 cm	1.000	1.416–1.942	0.032
>3 cm	1.772		

CI = confidence interval; OR = odds ratio; PUNLMP = papillary urothelial neoplasms of low malignant potential.

0.8% [13]. There is a debate in the literature regarding the clinical behavior and outcomes of bladder urothelial neoplasms in younger patients compared with older patients. Our data confirm the results of previous studies and show that patients aged 40 years or younger have similar clinical presentation and disease outcome to their older counterparts, whereas some pathological parameters differ statistically.

In our study, younger patients had fewer high-grade cancers than older patients (7% vs. 33%) and fewer tumors >3 cm in size, which was similar to the findings of previous studies [13–16]. According to a recent review by Paner et al. [13], although there is a predominance of low-grade tumors in the first three decades of life, the grade distribution of bladder urothelial cancer in older patients is not exactly comparable to those in the fourth decade of life.

In our study, a male predominance was observed (male:female ratio 3:1) in patients below 40 years of age, which is similar to those reported in previous studies [7,17,18]. In both the young and the older groups, the major presenting symptom was macroscopic hematuria, and no significant difference was observed between the younger and older patients. In a review by Greenfield et al. [19] of 342 children with gross hematuria, causes of which include infection, urolithiasis, and malignancy, only three were diagnosed to have bladder urothelial carcinoma.

Furthermore, in the younger group, 17 patients (30%) had a recurrence and 12 of them progressed to higher stage, whereas in the older group, 53 (47%) had a recurrence and 26 progressed to higher disease; this finding is supported by previous study results [9]. We have indicated that stage distribution of patients aged 40 years or less with

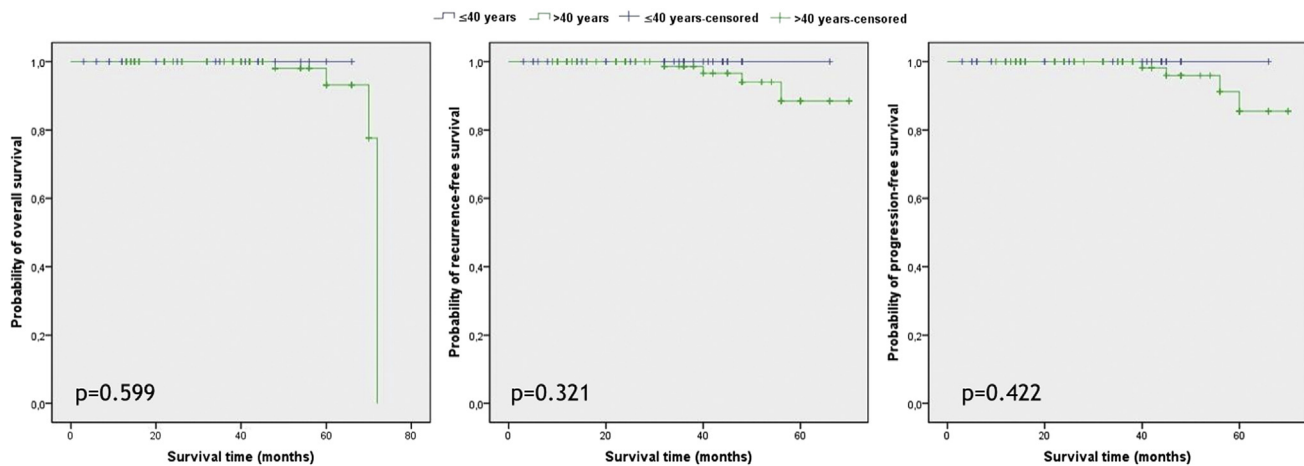


Figure 1. Survival curves for the young (≤ 40 years) and older (> 40 years) groups. (A) Overall survival probability in younger versus older patients ($p = 0.599$). (B) Recurrence-free survival probability in younger versus older patients ($p = 0.321$). (C) Progression-free survival probability in younger versus older patients ($p = 0.422$).

bladder urothelial carcinoma was not significantly different from their older counterparts, which is similar to the findings of some published studies. In contrast, older patients had higher invasive disease which some studies indicated were due to mutations on chromosomes 8, 9, 11, and 17 and often presented in older patients with a longer time to carcinogenesis [7,20,21]. Unfortunately, our study did not perform an extensive analysis because of the relatively small number of patients, lack of information, and short follow-up period, which are the major limitations of this retrospective review. Future studies are needed to confirm the exact clinical behavior and outcomes of bladder urothelial cancer in younger adults compared with those in their older counterparts.

Conclusion

Our results suggest that most of the patients younger than 40 years with urothelial bladder cancer have tumors that are ≤ 3 cm in size (89.3%) and of low grade (64.3%). Although the clinical stage distribution, natural history, and outcomes of bladder urothelial cancer in young adults are similar to those in their older counterparts, clinician must be aware that patients under 40 years of age presented with higher-grade and larger (> 3 cm) tumors are more likely to experience tumor recurrence.

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