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Transitional Cell Carcinoma of the Bladder in Young Adults: Presentation, Natural History, and Outcome of 158 Cases

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ABSTRACT

Background: The natural history of bladder transitional cell carcinoma (TCC) in young patients remains a matter of debate.
Purpose: To compare the clinicopathological characteristics and the prognosis of bladder TCC according to age in young adults.
Materials and methods: From 1993 to 2006, 158 patients ≤ 50 years with newly diagnosed bladder TCC were enrolled in this study. Patients were subdivided into 3 age groups: ≤ 30 years (group I, n = 10), ≤ 40 but > 30 years (group II, n = 37), and > 40 years (group III, n = 111). Data were analyzed with the Kaplan-Meier method to assess disease recurrence, progression, and survival.
Results: The study consisted of 140 males and 18 females. Eighty (50.6%) patients presented with pTa, 55 (34.8%) with pT1, and 23 (14.5%) with pT2-T3. The follow-up duration ranged from 36 to 158 months. The recurring tumors were stage Ta in 13 patients and stage T1 in 15. Five patients progressed to invasive cancer. The overall cancer-specific survival rate was 93%. The tumor size (p = 0.10), multiplicity (p = 0.71), tumor location (p = 0.60), T stage (p = 0.34), and tumor grade (p = 0.21) were similar in the 3 groups. The 5-year recurrence-free rates were 66.7, 77.4, and 81% (p = 0.76), respectively. The 5-year progression-free rates were 100, 96.8, and 95.8% (p = 0.74), respectively. The 5-year cancer-specific survival rates were similar in the 3 groups (p = 0.56).
Conclusion: Initial bladder TCC stage and natural history in young adults under 40 years old are similar to that in older patients.

INTRODUCTION

The incidence of bladder transitional cell carcinoma (TCC) is increasing in all Mediterranean countries [1], especially in Tunisia. It represents one of the most common cancers in the world, and accounts for 2.1% of all cancer-related deaths [2]. In Tunisia, it is second after pulmonary cancer, and the first urinary cancer in males [3]. It affects both genders, with a male-to-female ratio of 7:1, and it has the highest incidence in the sixth decade of life [4,5].

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Bladder TCC in the first 4 decades of life is distinctly unusual, with most described in case reports and small series. The reported incidence in the first 4 decades of life ranges between 0.4 to 1% [6].

A long debated and unresolved question is whether the age at diagnosis of bladder TCC has any prognostic value [7]. Even conflicting results have been reported. The purpose of the current study is to elucidate such conflicting data, and to evaluate the differences in bladder TCC characteristics and prognosis according to presentation age in young patients.

MATERIALS AND METHODS

From January 1993 to January 2006, 307 patients with newly diagnosed bladder TCC were treated in the department of urology of the Rabta University-Hospital in Tunis, Tunisia.

Study population and protocol

We retrospectively analyzed the data of 158 consecutive patients, younger than 50 years old, with newly diagnosed bladder TCC treated at our institution in the same period.

Exclusion criteria were concomitant or previous Tis (carcinoma in situ), previous bladder TCC, previous pelvic radiotherapy and/or chemotherapy, and the presence of another urinary cancer.

All patients submitted to a urinary culture, cystoscopy, and intravenous urography or ultrasonography. All patients included in the study had transurethral resection (TUR) with curative intent (complete TUR of the tumor and the underlying muscular layer). None of these patients had received therapy before surgery.

The pathologic stage of bladder cancer was assessed according to the tumor-node metastasis (TNM) classification [8]. The tumor grade was assessed according to the grading system established by the World Health Organization [9]. Non-muscle-invasive bladder TCC includes pTa and pT1 tumors. Muscle-invasive bladder cancer includes pT2, pT3, and pT4 tumors. The pathologic evaluation was carried out by 2 senior pathologists.

After surgery, patients with pTa/T1 tumors were treated by intravesical BCG instillations (21 to 28 days after TUR). A second look (a second TUR) was performed within 30 days for T1G3 tumors to exclude any understaging or an incomplete resection. The intravesical BCG therapy regimen consisted of weekly instillations for 6 weeks, and then monthly for 6 months.

Follow-up was performed by upper urinary tract ultrasound and cystoscopy (with a biopsy of any suspicious bladder lesions) after 3 months, then every 6 months in the first 5 years, and annually thereafter. Adverse events were documented throughout the study by the responsible physician. If a superficial tumor (Ta/T1 categories) recurred, TUR was repeated. If there was recurrence without muscle invasion, patients received a second intravesical BCG therapy regimen.

Parameters investigated included age, gender, presenting symptoms, endoscopic characteristics (size, aspect, multiplicity, and location) of bladder lesions, tumor stage, tumor grade, recurrences, and progression time from diagnosis to last follow-up. Radical cystectomy data and local and distal recurrence were recorded. Additional data, such as a history of smoking and professional exposure, were also obtained. For purposes of analysis, the study population was stratified into 3 subgroups according to their age at presentation: $\leq$ 30 years (group 1, n = 10), > 30 but $\leq$ 40 years (group 2, n = 37), and > 40 but $\leq$ 50 years (group 3, n = 111).

Clinical data, recurrence and progression events, radical cystectomy data, adjuvant therapies, and disease status were recorded and compared in the 3 groups.

Study endpoints

For efficacy parameter evaluation, we used 3 endpoints, including disease-free recurrence, disease-free progression, and disease-free survival. The recurrence-free interval is defined as the period between the date of resection and the date of histologically confirmed recurrence. Disease progression was defined as muscularis propria invasion of UC. The interval-to-progression was defined as the period between the date of the initial diagnosis and the date of proven progression. Patients without recurrence or progression were censored at the date of their last follow-up. Survival time was defined as the time from initial presentation to evidence of death due to bladder cancer. Living patients, or those who had died before recurrence or progression, were censored at the date of the last available follow-up cystoscopy.

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Statistical analysis

We investigated the correlation between the patient's age and clinical, pathologic, and prognostic features. The Chi-squared test was used to evaluate the statistical significance and difference of variables in the 3 groups, with a 95% confidence interval. Recurrence, progression, and survival were estimated using the Kaplan-Meier curves, and a log-rank test was performed to validate the differences among the 3 age groups. Data were analyzed using SPSS version 11.0 (SPSS Inc, Chicago, IL, USA). A p value of less than 0.05 was considered statistically significant.

RESULTS

The overall data

According to our data, the prevalence of bladder TCC in young patients under 40 years old was 15.3%. The mean age of patients at initial diagnosis was 42.8 years (range 20 to 50 years). The male-to-female ratio was 7.8:1 (140 males, 18 females). A history of cigarette smoking was obtained in the majority of patients (84.8%). None of the patients had a personal or family history of bladder cancer. Nineteen patients (12%) had a professional history associated with bladder carcinogenesis.

The most common presenting symptoms were gross hematuria in 130 patients (82.3%), LUTS in 30 (19%), and flank pain in 6 (3.8 %). The diagnosis of bladder tumor was fortuitous in only 4 patients. A digital rectal examination showed a normal prostate in all male patients and a normal posterior bladder wall in 150 patients (95%).

Cystoscopically, the majority of lesions (54.4%) were described as papillary and nodular in 30 cases (19%). A lesion's size ranged from 0.5 cm to 8 cm. Lesion locations were anterior (in 15 cases), posterior (21), lateral (69), trigonal (33), in the bladder floor (68), and in the urethra (5). The entire bladder mucosa was involved (bladder papillomatosis) in 9 cases. There were multiple lesions (2 or more) in 61 (38.6%) patients.

The initial cancer staging was as follows: pTa (n = 80), pT1 (n = 55), and pT2-T3 (n = 23). There were 98 (62%) low-grade and 60 (38%) high-grade cases. Patients with non-muscle-invasive bladder cancer (85.4%) underwent TUR of a bladder tumor, followed by intravesical instillation BCG therapy.

Twelve patients with invasive bladder cancer underwent radical cystectomy with an ileal conduit. Six of these 12 patients had adjuvant cisplatin-based chemotherapy, and 1 case was associated with radiotherapy.

Five patients with invasive bladder TCC were planned but preferred private hospitals to ours; thus, we have little follow-up information about them. The remaining 4 patients with invasive bladder cancer had poor performance status. They had liver, bone, and pulmonary metastases, and nothing was done. All of them died in 1 to 4 months.

Two patients (age > 40 years) with stage T2 were treated with BCG therapy, with no evidence of recurrence after 87 months of follow-up in the first case, and with superficial recurrence after 20 months in the second case. There was a total follow-up of 56 months.

The observation period was up to 158 months from which 147 cases (93%) had a minimum follow-up of 5 years. During the observation period, 11 patients (7%) were lost to follow-up, at a mean period of 41.7 months. The minimum observation period for these patients was 36 months.

The recurring tumors were of stage Ta in 13 patients and of stage T1 in 15 (T1G3 in only 2 cases). The median interval between the initial TUR and the first recurrence was 23.2 months (range 3 to 54 months). The median recurrence-free survival was 25.1 months (3 to 54). Twenty-four of the 29 recurring tumors after initial TUR and adjuvant intravesical BCG therapy responded to further treatment with BCG leading to bladder sparing. They maintained their bladders.

Five patients progressed with a median time interval of 9.6 months (range 3 to 34 months). Zero Ta and only 5 T1 recurrent lesions showed further progression. They underwent radical cystectomy with an ileal conduit (in 4 cases) and with cystoplasty in only 1 case.

The overall 5-year progression-free survival rate was 96.3%. One hundred and thirty-one patients (83%), managed with bladder sparing (TUR and BCG), are disease-free and maintain their intact bladders (including 2 patients with T2 bladder TCC).

A second primary tumor was revealed in only 1 case and it was a TCC of the renal pelvis. Fifteen patients (9.5%) died, 11 of them from bladder cancer. The overall 5-year survival rate was 90.5%. The overall 5-year cancer-specific survival rate was 93%.

Results by group

Bladder cancer was diagnosed between the ages of 20 and

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30 years in 10 (6.3%) patients, between 30 and 40 years in 37 (23.4%) patients, and between 40 and 50 years in 111 (70.3%) patients. The median age at initial diagnosis was 25.9, 37.6, and 46.1 years, respectively. The male-to-female ratio in the 3 age groups was 9:1, 4.3:1, and 10.1:1, respectively (p = 0.25). A history of cigarette smoking was reported in 90%, 75.6%, and 87.4%, respectively (p = 0.20). Professional exposition to bladder carcinogenesis was not different among the 3 groups (p = 0.10).

The consultation delay after the onset of symptoms for the 3 groups ranged from several hours to 5 years, and they were 7.6 months (2 to 12), 17.4 months (0 to 120), and 13.45 months (0 to 180), respectively. Four (40%), 10 (27%), and 38 (34.2%) patients, respectively, had a consultation delay longer than 1 year (p = 0.64).

Comparisons of clinical and pathologic characteristics according to age

Hematuria, the most frequent symptom, tended to decrease in older age groups (p = 0.24). A statistical analysis showed that clinical data (DRE) (p = 0.51), tumor size (p = 0.10), multiplicity (p = 0.71), the tumor aspect and extent of tumor base (p = 0.44, p = 0.11), tumor location (p = 0.60), T stage (p = 0.34), and tumor grade (p = 0.21) did not differ among the 3 age groups.

Among patients between 20 and 30 years, 9 had stage Ta-T1 disease, and 1 had stage T2 disease. Among patients 31-40 years, 31 had stage Ta-T1 disease, and 6 had stage T2-T3 disease. Among patients 41 to 50 years, 95 had stage Ta-T1 disease, and 16 had stage T2-T3 disease (p = 0.88). Initial stage Ta-T1, as well as muscle invasive tumors, were diagnosed in the 3 groups equally.

Serious adverse events of BCG-therapy

After analyzing all patient data, dysuria and burning micturition after intravesical instillation of BCG were very common and reported by almost all patients in the 3 groups. There were 2 cases of a serious adverse event showing systemic tuberculosis with severe asthenia, leading to change BCG therapy to mitomycin C in these patients. No patient experienced bladder shrinkage requiring urinary diversion.

Differences in recurrence-free and progression-free probabilities among age groups

Recurrence developed in 28 patients (20.7%) and progression in 5 patients (3.7%). The 5-year recurrence-free probability was 66.7%, 77.4%, and 81% in groups 1, 2, and 3, respectively (Figure 1).

Notably, the curves of disease-free recurrence showed no significant separation between the groups, especially with patients exhibiting pTa (p = 0.48) or pT1 (p = 0.27). This separation was also not significant when patients with GI or GII to III tumors were analyzed separately (p = 0.57 and p = 0.83).

The 5-year progression-free probability was 100%, 96.8%, and 95.8% (Figure 2). No difference was observed in the disease-free progression rate in patients who initially presented with non-muscle-invasive bladder TCC tumors.

Kaplan-Meier curves of disease-free recurrence and progression showed no difference between the 3 groups. Although statistically significant differences were not identified between the 3 age groups, disease progression of non-muscle-invasive bladder TCC tended to be more common in older rather than younger patients. Older age groups seem to have a poorer prognosis, but the difference was not significant.

Cystectomy

Of the 55 young patients who presented with initial stage T1 tumors, 5 ultimately underwent cystectomy due to progression of muscle invasion. The median time from presentation to cystectomy was 11 months (3 to 34). A higher (but not significant) proportion of older patients underwent cystectomy (p = 0.79).

Mortality

Five patients (2 in group II and 3 in group III) died from invasive bladder cancer after cystectomy, and 2 in group III died from superficial bladder cancer due to rapid tumor progression with bone metastasis. Four patients died from locally advanced and metastatic bladder tumors. They didn't receive any therapy or operations. In older patients > 40 years, 4 died from non-cancerous causes during the follow-up period.

The disease-specific 5-year survival rates were 95.7% and 91.9% in the young (< 40 years) and older (≥ 40 years) patients, respectively (p = 0.59). The overall 5-year survival rates were 93.6% and 89.1% in the young (< 40 years) and older (≥ 40 years) patients, respectively (p = 0.56). Table I shows a comparison of the study groups.

DISCUSSION

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original study

Figure 1. Recurrence-free survival curves in different groups.

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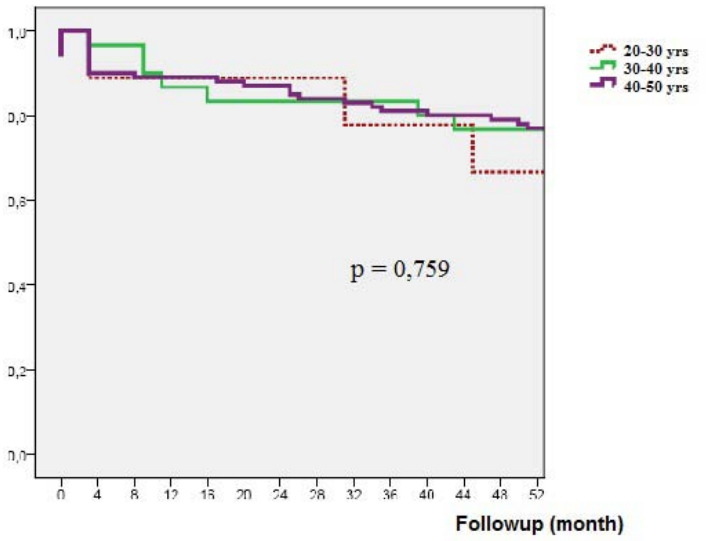

Figure 2. Progression-free survival curves in different groups.

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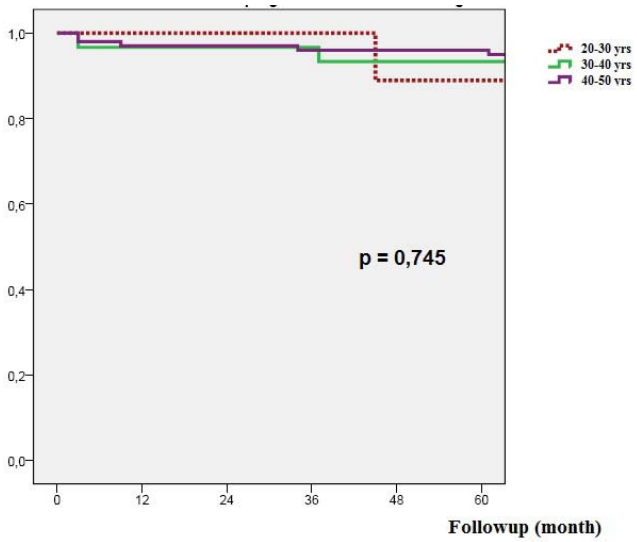

Urinary bladder cancer ranks ninth in worldwide cancer incidence [10]. In Tunisia, it is the second most common cancer in men and the twelfth in women [3]. Although bladder cancer can occur at any age, it is generally a disease of middle-aged and elderly people [3,11]. The most common form of bladder cancer remains TCC [3]. Non-muscle-invasive bladder TCC represents the main diagnosed stages, with stage pTa and pT1 accounting for 70 to 80% of all urothelial cancers in this site [5]. Bladder TCC in young people is rare and < 1% of cases develop in the first 4 decades of life [7].

Our study, showing a male-to-female ratio of 9.8:1, confirms the usual male predominance of bladder TCC. This ratio is similar to those in the reports of Wen et al. [12], Ozbey et al. [13], and Kurz et al. [14]. Interestingly, the male-to-female ratio was much lower in the young (< 40 years) rather than in more elderly patients (40 to 50 years) in our series, as already reported previously [6,7,14,15]. The reduction of the male-to-female ratio in young patients could be explained by a more homogeneous exposure to carcinogenic factors (environmental or occupational agents).

Although diagnosis tools and the treatment of bladder cancer have been well studied, conflicting data has been reported about the natural history, clinical behavior, and the prognosis of bladder TCC in young patients. The unresolved question is whether or not age at the time of diagnosis has any prognostic value. In this retrospective analysis, we evaluated the presentation and natural history of TCC of the bladder in young adults.

Why 40 years as a limit?

Two reasons prompted us and the other authors to choose 40 years as the threshold age to discriminate between young and old groups. First, the choice was supported by several epidemiological studies in which the data gradually changed from 30 years to 40 years, and then to 50 years [3,16,17]. Second, according to our data, the incidence of bladder cancer increases dramatically with age. Rates in those aged $\geq$ 70 years are about 2 to 3 times higher than those between 55 to 69 years, and 15 to 20 times higher than those between 30 to 50 years [3].

Cigarette smoking and specific professional exposures are the main known causes of bladder cancer with positive dose-response relationships. This dose would be higher in elderly patients, but in our series, we did not find a significant difference according to age.

Table 1. Comparison of the study groups.
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Parameters			p
Epidemiological data			
	Male/female		0.25
	Smoking		0.20
	Professional exposition		0.10
	Consultation delay		0.64
Clinical data			
	Hematuria		0.24
	DRE data		0.51
Edoscopic data			
	Tumor	Size	0.10
		Multiplicity	0.71
		Aspect	0.44
		Base	0.11
		Location	0.60
Pathological data			
	Tumor stage		0.34
	Tumor grade		0.21
Follow-up data			
	Recurrence-free rate		0.76
	Progression-free rate		0.74
	Cystectomy rate		0.79
	The disease-specific 5-year surviva		0.59
	The overall 5-year survival rates		0.56

Although the most common presenting symptom in the young adults in our study was gross hematuria, the findings of lower urinary tract symptoms should be carefully investigated to detect any bladder cancer. In our study, TCC bladder was multifocal in young patients despite reports in the literature (< 10%) [18].

Conflicting prognostic results have been reported. However, some authors have demonstrated that bladder TCC in younger patients tends to behave less aggressively and has a more favorable prognosis (lower disease recurrence and progression rates, as well as better overall survival), compared with older patients [6,10,17,19]. Others observed similar patterns of clinical behavior and prognosis for bladder cancer in young and older patients [6,7,14,16,20]. The latter did not note any proportional difference between non-muscle- versus muscle-invasive disease, or the likelihood of tumor recurrence or progression, as in our series.

Many authors [7,15,19] found that at a young age there is a tendency to have lower stages and grades at presentation with a significantly higher frequency of G1 and pTa. These data were not confirmed in the present study.

Concerning invasive tumors, the results are highly variable, depending on the series. Kutarski [16] did not find any invasive tumors in his study. Conversely, Aboutaieb [21] isolated 14 cases of invasive tumors in 25 TCC bladder tumors. In our series, invasive bladder cancer represented 14.9% of patients under 40 years old.

Our results did not show any differences in tumor characteristics and prognosis in patients with newly diagnosed bladder TCC according to age at presentation. Shi et al. [19] showed that the recurrence-free survival rate decreased with increased age. Kutarski [16] and Madgar et al. [22] reported that tumor recurrences were age-related and tended to occur more frequently in older rather than younger patients. Wen et al. [12] reported disease recurrence rates of 33.3% ($\leq$ 30 years) and 45.8% (31 to 40 years). Although this difference was not statistically significant, tumor recurrence does seem to be age-related. Fitzpatrick [17] reported a recurrence rate of 8% versus 54% in patients less and more then 30 year-old, respectively.

The results of the Migaldi series [15] shows that the outcome was significantly better in young rather than old (> 45 years) patients with TCC only when non-muscle-invasive tumors are considered. The recurrence rate was also lower in the young patients ($p < 0.001$), and Kaplan-Meier curves of disease-free survival separated significantly ($p < 0.005$) between the 2 groups. Thus confirming that bladder TCC behaves less aggressively in young patients.

Kutarski [16] has shown very clearly that the rate of progression was very different according to age. However, no difference was found in progression-free survival in our study and others [19]. Although differences were not found in recurrence-free and progression-free survival among the age groups, nomograms to predict recurrence and progression in patients with non-muscle-invasive bladder cancer included age as an important

determinant [23].

The lower rate of cystectomy in younger patients most likely reflects the presumed tendency of urologists to preserve the bladder in young patients with superficial disease [7]. In our series, 2 patients with T2 bladder TCC were treated successfully by endoscopic resection and BCG therapy.

The prognosis for patients with invasive bladder cancer is very poor. According to Yossepowitch and Dalbagni [7], the 5-year rate of disease-free survival after cystectomy was only 59%. According to Yossepowitch [7], 41% of young patients treated with cystectomy after 5 years had evidence of metastases. These rates were very low in our series.

The divergent conclusions in previous studies could be a result of comparing heterogeneous groups of patients with different inclusive age limits. In some studies [6], the dichotomous analysis was used exclusively, comparing patients aged < 30 years with those from older groups (< 40 years) [22]. In some reports, the study populations were too small to draw firm conclusions and valid statistical analyses (19 cases) [16]. Some studies included bladder in situ carcinomas, a pathological condition notoriously associated with a different clinical course [24] and genetic alterations [25] when compared with papillary urothelial tumors. The median follow-up is too short in some reports. Medical provider social influences include delayed diagnosis and less-aggressive therapy offered to, and selected by, elderly patients [26].

The study by Yossepowitch and Dalbagni (7) represents the first comparison of TCC in young and elderly patients. They compared 74 young and 75 elderly patients, and found a similar clinical behavior in the 2 groups. However, their study included bladder in situ carcinomas and the median follow-up was short (28.1 months). Thus, could explain why the conclusions obtained by those authors are not really crucial. A family history of bladder tumors in these young patients was reported previously [27]. In our series, no patient had a direct family history. However, the search for a family history of bladder tumors has not been systematic with each consultation. Thus, it is possible that some familial cases have escaped detection.

Cordon-Cardo et al. [28] underlined that alterations of cell-cycle regulation were among the main molecular keys determining the biological behavior of bladder TCC. Several retrospective studies [15,20,29] have found a high frequency of p53 overexpression (secondary to chromosome 17 alteration) in tumors of young patients. These alterations are typical of more aggressive tumors, which is not compatible with favorable clinical outcomes, as shown in our study. These results suggest that bladder TCC might develop, in young patients, through distinct molecular pathways from elderly patients. In addition, several studies have reported that aging appeared associated with a decreased response to intravesical BCG therapy [30].

Further studies are required to integrate molecular tumor markers into a comprehensive model of bladder carcinogenesis that may predict tumor behavior.

The strong points of the presenting study were the homogenous treatment in superficial bladder TCC groups (all of them underwent complete endoscopic resection followed by endovesical BCG instillations) and the long follow-up period.

This retrospective analysis had several biases. An important limitation was that a central review of the pathologic slides was not performed; consequently, interobserver differences in tumor grade and stage could not be excluded. The number of tumors was dichotomized as single or multiple. Therefore, we assigned the same risk to all multiple tumors (same for tumor size), which is not really true. Moreover, we studied only patients with newly diagnosed bladder TCC; therefore, a risk category for the previous recurrence rate was not included. Finally, the number of included patients was relatively small.

CONCLUSION

Bladder TCC in young adults is more common in males and is likely to manifest as hematuria. It has a clinical stage distribution at initial presentation and a natural history similar to that in older patients. Our study suggests that young patients who are ultimately treated with radical cystectomy have a particularly better prognosis.

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