

# Clinical behavior and survival outcome of urothelial bladder cancer in young adults

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## Abstract

**Background:** Bladder cancer (BC) is rare in young adults and therefore natural history of BC is still debatable. This study aimed to determine clinical behavior and prognosis of BC in patients <40 years.

**Materials and Methods:** We reviewed patients (<40 years) managed with urothelial BC from 2003 to 2019. Patients with nonurothelial histology were excluded. Clinical behavior and prognosis such as recurrence, progression, and survival were assessed. The recurrence is defined as a newly diagnosed occurrence of BC at previous or new site(s). Cancer progression is defined as an increase in staging or grade.

**Results:** Fifty-five patients inclusive of 45 males and 10 females with a median age of 30.0 (interquartile range [IQR]: 25.0–33.0) years were included. The median follow-up was 3.5 (IQR: 1.5–7.0) years. Fifty-one (92.72%) patients were diagnosed with nonmuscle-invasive BC while four (7.27%) patients were diagnosed with muscle-invasive disease. Three out of four patients with muscle-invasive BC died of metastatic disease. According to stage and grade, there were 42 (76.36%) Ta, 9 (16.36%) T1 and 4 (7.27%) having T2 stage while 41 (74.54%) low grade and 14 (25.45%) were having high grade disease. Thirty-six (65.45%) patients remained stable, 13 (26.63%) patients progressed, and 6 (10.90%) patients regressed to lower stage and grade. Higher stage and grade ( $P = 0.0431$ ) and tumor size >3 cm ( $P = 0.0454$ ) were significant for recurrence, and higher stage and grade ( $P = 0.0012$ ) and tumor size >3 cm ( $P = 0.0055$ ) were associated with tumor progression.

**Conclusion:** BC in younger adults is mostly low stage and low grade. We should be vigilant in patients with higher stage and grade as it is related with recurrence, progression, and metastatic disease.

**Keywords:** Bladder cancer, progression, recurrence, young adults

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## INTRODUCTION

Bladder cancer (BC) is a disease predominantly found in the elderly population. The median age at the time of diagnosis is 72 years,<sup>[1]</sup> and the incidence rate for the population younger than 40 years is reported to be <0.8%.<sup>[2]</sup> This

very low incidence of BC among the younger population has driven research to focus primarily on the elderly while information on the nature, progression, and survival for BC affecting a younger population can be found through small single-institution series.<sup>[3]</sup>

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Clinical prognosis of BC depends upon histopathological staging and grading. Although the treatment modality and prognostic factors have been extensively studied in the elderly, there are conflicting reports published about clinical behavior and cancer prognosis in younger adults. This might be due to rarity of the disease and differing ethnicities in younger patients.<sup>[4,5]</sup> Some researchers claimed that clinical behavior and survival outcomes of BC in younger adults are more favorable due to the lower grading and staging.<sup>[6,7]</sup>

On the contrary, others believe that BCs with higher grade and stage having lesser survival outcomes than with the elderly need to be approached with greater sensitivity.<sup>[8,9]</sup>

To better comprehend the clinicopathologic characteristics, survival outcome, recurrence, and progression of BC in younger patients in Saudi Arabia's population, we retrospectively evaluated a series of patients initially diagnosed with BC at 40 years or younger in our institution. Moreover, we also aimed to determine factors that influence the survival outcome of young patients with BC.

## MATERIALS AND METHODS

Our research proposal was approved by the Office of Research Assistant of King Faisal Specialist Hospital and Research Centre, Riyadh (RAC No. 5121091).

### Patient selection, inclusion, and exclusion criteria

We retrospectively collected the data of patients aged 40 or below who underwent transurethral resection of BC from 2003 to 2019. Patients with nonurothelial BC on histopathology and patients with upper tract involvement were also excluded from the study. Patients not tracked in the initial 5 years were also excluded. Data were collected from patients' records on demographics, age at the time of diagnosis, symptom presentation at first visit, smoking history, and family history of BC. Pathological findings such as staging and grading of tumor, size, multiplicity, number of recurrences, progression, BCG status, metastasis, and clinical outcome were collected.

### Pathological evaluation

All surgical specimens were processed according to standard pathological protocol and reviewed by our expert genitourinary histopathologist. The American Joint Committee on Cancer (AJCC) Classification 2010 and the World Health Organization 2016 were used to determine tumor stage and grade, respectively. Therefore, the patients who underwent surgery before these guidelines were reassessed for tumor stage and grade. Grade 2 tumors

according to the WHO 2004 classification were reassessed by the histopathologist to either low grade or high grade according to tumor characteristics based on the WHO 2016 classification.

### Postoperative protocol

According to department protocol, all patients received a single dose of mitomycin 40 mg intravesical within 6 h postsurgery. Re-transurethral resection of bladder tumor (TURBT) was done within 1 month in those patients who had T1G3 disease or high-grade disease, with no muscle in a specimen to exclude incomplete resection or understaging. Intravesical BCG was given to all high grades and patients who had recurrent disease. The intravesical BCG regimen included induction therapy with weekly instillations for 6 weeks. Maintenance therapy started 3 months after induction therapy and it is 3 weekly doses every 6 months for 3 years.

### Continuity of care protocol

Surveillance protocol is continued with either ultrasound or computed tomography (CT), urine cytology, and flexible cystoscopy. Cystoscopy protocol was stringent for high-grade disease with 3 monthly for the first 2 years and 6 monthly for the next 2 years and yearly thereafter. Follow-up cystoscopy for low-risk disease was performed initially with flexible cystoscopy at 3 months post-TURBT and then 6 monthly for 1 year and then yearly for 5 years.

### Statistical analysis

Illustrative data were presented as mean (standard deviation) and median (interquartile range [IQR]) were used for continuous variables. Fisher's exact test and Chi-square tests were used data analysis. *P* values under 0.05 were considered as statistical significance.

## RESULTS

Between January 2003 and December 2019, 55 patients with a median age at the time of diagnosis of 30.0 years with IQR of 25.0–33.0 years were diagnosed with BC. There were 45 males and 10 females with a male: female ratio of 4.5:1. Forty-three (78.18%) patients presented with intermittent painless gross hematuria, ten (21.82%) patients presented with lower urinary tract symptoms, and two (2.67%) patients were diagnosed on microscopic hematuria follow-up. The median follow-up of the patients was 3.5 (IQR: 1.5–7.0) years. Majority of the patients had low-stage Ta (76.36%) and low grade (74.54%). More than half of the patients (54.54%) were on cystoscopy surveillance, 32.72% of the patients were discharged, and 4 (7.27%) patients died due to metastatic

disease. Histopathologically, 51 (92.72%) patients had nonmuscle-invasive disease while 4 (7.27%) patients had muscle-invasive disease at the time of first diagnosis. As a part of hematuria workup protocol, urine cytology was positive in 23 (41.82%) patients while 32 (58.18%) patients had negative urine cytology in spite of the presence of BC on cystoscopy. The clinical and pathological characteristics of the patients are presented in Table 1.

Of the 55 patients, 27 (49.09%) patients had recurrence disease, in which 15 patients had Ta low grade (TaLG), 3 patients had Ta high grade (TaHG), 5 had T1LG, and 4 had T1HG. All patients received one dose of 40 mg of intravesical mitomycin within 6 h after TURBT. Thirteen (23.66%) of these recurrent patients received intravesical BCG therapy. Patients who had either

high-grade disease, carcinoma *in situ*, or low-grade disease with more than 2 recurrences in a year received intravesical BCG induction therapy weekly for 6 weeks and BCG maintenance therapy for at least 1 year for intermediate-risk disease and 3 years for high-risk disease. Four patients who died, three of them were diagnosed with either muscle invasive or metastatic disease and one patient progressed from T1G3 to muscle invasive and metastatic disease. The pathological finding of patients compared with recurrence is shown in Table 2.

Of the 55 patients, 13 (23.63%) patients progressed, 6 (10.90%) patients regressed, and 36 (65.45%) patients remained stable with respect to staging and grading. High stage and grade ( $P = 0.045$ ,  $P = 0.0012$ ) and increasing size  $>3$  cm ( $P = 0.005$ ) were the risk factors for progression of disease. Of the 13 patients who progressed, 4 patients died, 3 were discharged, 3 cystoscopy surveillance, 1 trimodal therapy, and 2 underwent radical cystectomy and ileal conduit formation. The histopathological findings of patients with progression of disease are shown in Table 3.

**Table 1: Clinical and pathological characteristics of the patients**

Characteristics	Patients (n=55), n (%)
Median age (IQR)	30.0 (25.0-33.0)
Gender	
Male	45 (81.81)
Female	12 (21.81)
Median follow-up (years)	3.5 (1.5-7.0)
Clinical presentation	
Gross hematuria	43 (78.18)
LUTS	10 (18.81)
Microscopic hematuria	2 (3.63)
Tumor size (cm)	
<3	28 (50.91)
>3	27 (49.09)
Tumor architecture	
Papillary	49 (89.09)
Sessile	6 (10.90)
Multiplicity	
Multiple	36 (65.45)
Single	19 (34.54)
Urine cytology	
BCG status	
Yes	15 (27.27)
No	40 (72.73)
Stage	
Ta	42 (76.36)
T1	9 (16.36)
T2	4 (7.27)
T3	0
T4	0
Grade	
LG	41 (74.54)
HG	14 (25.45)
Cancer progression/recession	
Progress	13 (23.63)
Recess	6 (10.90)
Stable	36 (65.45)
Final outcome	
Cystoscopy surveillance	30 (54.54)
Discharge	18 (32.72)
Chemotherapy	1 (1.81)
Cystectomy	2 (3.63)
Death	4 (7.27)

IQR: Interquartile range, LUTS: Lower urinary tract symptoms

## DISCUSSION

Urothelial bladder cancer is one of the common cancers of the urinary tract. The peak age of presentation is 60 years and rarely occurs in younger adults below the age of 40 years<sup>[10]</sup> and is reported to be approximately 0.8%.<sup>[11]</sup> BC is most commonly present in males as compared to females.<sup>[12]</sup> Males have a 4.5 times greater risk of developing BC compared with females.<sup>[13]</sup> The male: female ratio was 4.5:1 in our study. Similarly, Shi *et al.* found that there was a male-to-female ratio of 4.1 in patients aged  $<41$  years, but that ratio increased to 3.1 in patients aged  $<60$  years.<sup>[14]</sup> This reduction in ratio in young patients maybe due to more homogenous exposure to carcinogens.

Moreover, 43 (78.18%) patients presented with macroscopic hematuria, 10 (18.18%) had storage bladder symptoms, while only 2 (3.65%) patients had microscopic hematuria on urinalysis done for other reasons. As hematuria protocol, urine cytology, CT, and flexible cystoscopy were completed. Gunlusoy *et al.* found in their study that 78% of the patients presented with gross hematuria.<sup>[15]</sup> Urine cytology was positive in 23 (41.81%) patients. Although macroscopic hematuria was a predominant symptom in our study, the presence of lower urinary tract symptoms, especially storage bladder symptoms in younger adults, should be meticulously investigated to rule out BC. There are some factors that delay the diagnosis of BC in younger adults. One common factor might be the rarity of disease and symptoms

**Table 2: Association of pathological findings with recurrence of bladder cancer**

Variables	Recurrence	P
Ta stage		
TaLG	15	0.241
TaHG	3	
T1 stage		
T1LG	5	0.0431
T1HG	4	
Tumor size (cm)		
<3	2	0.0454
>3	25	
Tumor multiplicity		
Single tumor	5	0.0802
Multiple tumors	22	

LG: Low grade, HG: High grade

**Table 3: Association of pathological findings with progression of disease**

Variables	Progression	P
Ta stage		
TaLG	3	0.2141
TaHG	4	
T1 stage		
T1LG	1	0.0451
T1HG	1	
T2 stage		
T2HG	4	0.0012
Tumor size (cm)		
<3	3	0.0055
>3	10	
Tumor multiplicity		
Single tumor	2	0.1044
Multiple tumors	11	

TaLG: Low grade, HG: High grade

shared with other common entities such as urinary tract infection and stone disease. Other predominant causes for delay in diagnosis is a reluctancy toward cystoscopy by younger adults.<sup>[16]</sup>

Conflicting results have been reported regarding disease prognosis in younger patients with BC. It is important to mention that these patients have longer life expectancy, higher tension levels, and treatment expectations compared to their older counterparts. Therefore, treatment should be curative and improve life expectancy. Most of the authors found that bladder cancer in younger adults is usually low stage and grade, with prognosis being above average. All these studies are retrospectively reviewed.<sup>[17-19]</sup> In our study, 42 (76.36%) patients having Ta, 9 (16.36%) T1, and only 4 (7.27%) patients were having a T2 stage disease. According to the WHO 2016 bladder cancer grade and AJCC 2010 classification, 41 (74.54%) had low-grade disease while 14 (25.45%) had high-grade disease.

Considering risk stratification, Compérat *et al.*<sup>[20]</sup> found in their study on 152 patients <40 years that higher histological grade, stage, and multifocality were the strongest predictor

of tumor recurrence. Other studies<sup>[15,21]</sup> found that multifocality and higher stage were significantly associated with recurrence and progression in these younger patients. We found in our study that higher tumor grade, stage, and tumor size >3 cm were significant risk factors for tumor recurrence and progression.

In terms of prognosis, Gunlusoy *et al.*<sup>[22]</sup> found that tumor recurrence was significantly lower in younger age group when compared to older counterparts while rates of tumor progression were same. Therefore, they stressed clinicians to be vigilant while assessing invasiveness of tumors and warned not to delay the treatment in patients <40 years old. In our study, 51 (92.72%) patients had superficial bladder cancer while 4 (7.27%) patients had muscle-invasive disease. Twenty-seven (49.09%) patients developed bladder cancer recurrence. In muscle-invasive disease, three patients died of metastatic disease, suggestive of meticulous care and rigorous monitoring of patients. Janisch *et al.*<sup>[23]</sup> found similar results that young patients <40 years with muscle-invasive disease had a worse survival outcome after radical cystectomy in comparison to older counterparts. The relationship between age and prognosis of bladder cancer has always been controversial; this maybe due to different regional types of management, differences in ethnicities, socioeconomic backgrounds, and other factors which we may not include in our analysis.

From clinical point of view, some researchers found that BC in younger people <40 years tends to have lower cancer-specific mortality in comparison to their older counterparts,<sup>[24]</sup> suggesting that bladder-sparing approaches maybe a more viable option in young patients with muscle-invasive disease.<sup>[25-27]</sup> On the other hand, on a par to our results, researchers found no difference in survival outcome<sup>[8]</sup> or decreased survival outcome with heightened metastasis in younger patients,<sup>[28]</sup> suggesting that early definitive treatment and rigorous monitoring of these younger patients has more efficacy.

Our study has also few limitations. First, selection bias may obviously arise due to it retrospective and single-center study. Second, techniques of different surgeons and interobserver variability need to be considered due to the broad-spectrum period of study. Despite this being a cohort of consecutive patients, sample size is relatively small, especially in young patients with muscle-invasive disease. In our series, all patients consisted of Saudi population, as many studies revealed that ethnicity may influence the survival outcome in patients with urothelial BC.<sup>[29,30]</sup> Nevertheless, we think that our study represents that majority of the patients in the younger

population <40 years are low grade and low stage, but we also warrant timely delivery of definitive treatment and rigorous monitoring of patients with muscle-invasive disease or having high-risk factors in pathology.

## CONCLUSION

Bladder cancer in younger adults is mostly low stage and low grade. We need to be vigilant with patients in a higher stage and grade as it is related with recurrence, progression, and metastatic disease.

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## Conflicts of interest

There are no conflicts of interest.

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