

## Urothelial bladder cancer in young versus older adults: Presentations, clinical characteristics, and outcomes

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### Abstract

**Background and objective:** Urothelial bladder carcinoma is a common malignancy but rarely occurs at young ages and can occur more frequently in the older group. The majority of bladder cancer consist of urothelial bladder carcinoma. This study aimed to review the clinical presentation, histopathological features, staging, grading, and the progression and recurrence of urothelial bladder cancer in patients aged below 40 years compared with older patients.

**Methods:** We retrospectively analyzed and reviewed 105 newly diagnosed patients with urothelial bladder carcinoma between August 2014 to January 2020 in a private clinic and Rizgary Teaching Hospital, Erbil city, Iraq.

**Results:** The mean age  $\pm$  SD of the cases was  $56.2 \pm 19.37$  years, ranging between 18 – 85 years. Patients were divided according to age into two main groups, Group I (29 patients) were aged  $\leq 40$  years, and Group II (76 patients) were above 40 years. Most cases (72.4%) were males, but there was no significant gender distribution difference between the two groups ( $P = 0.327$ ). Gross hematuria was the most common presenting symptom in both groups. In Group I, the proportion of patients who ever smoked was 79.3%, and 47.4% in Group II ( $P = 0.003$ ). A significantly higher proportion of patients with lower grade and stage and small tumor size was detected in Group I than in Group II ( $P < 0.05$ ). The recurrence rate of Group II (36.8%) was significantly higher than that (6.9%) of Group I ( $P = 0.002$ ).

**Conclusion:** Urothelial bladder carcinomas among young patients were of lower grade, stage, and size than in older patients. The recurrence rate was higher among the older patients.

**Keywords:** Urothelial bladder carcinoma; Age; Erbil; Iraq; Presentation.

### Introduction

The urinary bladder is considered one of the most frequent organs that develop masses; these masses could be benign, which is fewer, or malignant, which form the majority.<sup>1</sup> Histologically, more than 90% of bladder masses are urothelial bladder cancer, which arises from the transitional cell lining of the bladder, nearly 5% of them are squamous cell carcinoma, and <2% are adenocarcinoma and other rare types.<sup>2</sup> Urothelial bladder cancer is the 9<sup>th</sup> most frequent malignancy globally, with 540,000 incident cases and 188,000 deaths in 2015 worldwide.<sup>3</sup> This cancer is the most

common cancer of the urinary tract and comes after prostatic cancer in the genitourinary system,<sup>4</sup> and it is more common in males than in females.<sup>5</sup> Urothelial bladder cancer could affect children and adolescents, but is extremely rare, with a prevalence of less than 1% in the first fourth decades of life.<sup>6</sup> The incidence is even lower at 0.003% in patients less than 20 years.<sup>7</sup> In patients younger than 10 years, fewer than 35 cases of urothelial bladder cancer have been mentioned in the international literature.<sup>8</sup> Usually, cancers in younger age groups

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tend to develop more aggressively. However, some studies show that bladder carcinoma is a low-grade, noninvasive tumor with a lower recurrence rate and better prognosis.<sup>7-9</sup> In contrast, other authors have mentioned similar patterns in younger and older patients.<sup>10,11</sup>

Usually, diagnosis of urothelial bladder cancer is suspected when hematuria occurs. About 13% to 34.5% of patients with gross hematuria have bladder cancer, while 0.5% to 10.5% of microscopic hematuria is associated with bladder cancer. In patients with irritative voiding symptoms, the risk can be doubled.<sup>3</sup>

Urothelial bladder cancer is expensive cancer to treat, with the cost of muscle invasive bladder cancer about \$150,000 per capita.<sup>12</sup> Tobacco is the main known reason for urothelial cancer development, especially cigarette smoking, which is about 60% and 30% of all urothelial bladder cancer in men and women, respectively. As a result, smoking raises the chance of developing urothelial cancer for about two to six times. The amount and duration of smoking are closely linked to the increased risk of bladder cancer with no clear plateau level.<sup>13</sup> Generally, over the last decade, the incidence rate of bladder cancer has been rising due to the slow rate of smoking cessation programs.<sup>13</sup>

Bladder cancer is ranked as the fifth most common cancer in Iraq. According to the annual report of the Iraqi Cancer Registry in 2016, there were 1419 new cases of bladder cancer (1059 male and 360 female cases), 142 male and 40 female cases were between the ages of 14-50 years.<sup>14</sup>

The incidence of bladder cancer in males and females in our country has decreased over the past years. According to the annual report of Iraqi Cancer Registry in 2016, in our country, there are 405 deaths from bladder cancer with a mortality rate of 5.35%.<sup>14</sup>

Improvements in diagnosis and treatment can raise survival, lower mortality rates and may define the drops in bladder cancer mortality noticed in men in many rich

countries.<sup>1</sup> Despite the focus on the subject in literature, no local research has studied the clinical and pathological nature of bladder cancer in young and middle-aged groups. Therefore, the researcher decided to carry out this study in Iraqi Kurdistan Region. This study aimed to review the clinical presentation, histopathological characteristics, staging, grading, and the recurrence and progression of urothelial bladder cancer in young patients (aged <40) compared with older ages.

## Methods

We retrospectively reviewed and analyzed our recorded cases of 105 newly diagnosed with urothelial bladder cancer between August 2014 to January 2020 in a private clinic and Rizgary Teaching hospital, Erbil city, Iraq.

We identified 29 patients (23 males and six females) with urothelial bladder cancer who were aged <40 years old. Data about personal characteristics (patient's age and gender), presenting symptoms, first transurethral pathology (tumor size, number, stages, and grades), recurrence events, and disease progression were collected and compared with the data of 76 patients aged ≥40 years old during the same period.

Exclusion criteria included patients with non-urothelial bladder cancer, history of previous bladder cancer, patients with concomitant upper urinary tract tumors, and secondary tumors in the bladder.

The tumor stage was defined according to the 2009 TNM system and the grade according to 1973 WHO grading system.<sup>15,16</sup>

*Progression* was defined as recurrent bladder cancer of a histologically higher stage than the initial tumor. *Recurrence* was defined as a newly appearing tumor in the bladder after proper initial tumor removal. The recurrence time was the interval between the initial treatment and the first cystoscopy showing a new urothelial bladder cancer.<sup>17</sup>

The study was approved by the ethics committee of Hawler Medical University.

### Statistical analysis

The statistical package for the social sciences (SPSS, version 25) was used for data analysis. For comparing proportions, the Chi-square test of association was used. Fisher's exact test was used when the expected count of more than 20% of the cells of the table was less than 5. A *P* value of  $\leq 0.05$  was considered statistically significant.

### Results

The total number of the studied sample was 105 patients affected by bladder cancer. Their mean age  $\pm$  SD was  $56.2 \pm 19.37$  years old, ranging between 18 to 85 years. The median age was 63 years

old. They were divided into two groups, Group I (29 patients) were aged  $\leq 40$  years, and Group II (76 patients) were aged  $\geq 40$  years old. The majority (72.4%) of the sample were males, as presented in Table 1, which shows the difference between the two groups in the gender distribution was not significant ( $P = 0.327$ ). The highest proportion (81%) of the sample presented with gross hematuria, and 10.5% presented with urinary tract infection (UTI). It is evident in Table 1 that there was a non significant difference between the two groups in the proportions of the clinical presentation ( $P = 0.777$ ). The proportion of smoking (including ex-smokers) in group I was 79.3%, which was significantly higher than the proportion of smoking (47.4%) in Group II ( $P = 0.003$ ).

**Table 1** Basic personal characteristics of the patients with urothelial bladder carcinoma according to the age group

Characteristic	Age (years)				Total		P value
	$\leq 40$		$> 40$		No.	(%)	
	No.	(%)	No.	(%)			
<b>Gender</b>							
Female	6	(20.7)	23	(30.3)	29	(27.6)	0.327†
Male	23	(79.3)	53	(69.7)	76	(72.4)	
<b>Clinical presentation</b>							
Micro-hematuria	3	(10.3)	6	(7.9)	9	(8.6)	0.777*
Gross hematuria	24	(82.2)	61	(80.3)	85	(81.0)	
UTI	2	(6.9)	9	(11.8)	11	(10.5)	
<b>Ever smoking</b>							
No	6	(20.7)	40	(52.6)	46	(43.8)	0.003
Yes	23	(79.3)	36	(47.4)	69	(56.2)	
Total	29	(100.0)	76	(100.0)	105	(100.0)	

\*By Fisher's exact test. †By Chi-square test.

Table 2 shows that the majority (72.4%) of the young patients (Group I) were of stage Ta compared with only 21.1% of the older patients (Group II), and the difference was significant ( $P < 0.001$ ). Nearly the same pattern can be observed for the grade, where the majority of the younger patients (72.4%) were of grade I compared with 27.6% of the older patients ( $P < 0.001$ ).

Around half (42.1%) of the tumors of the older patients were multi-focality compared with 20.7% of the tumors of the younger patients ( $P = 0.041$ ). The tumor size was more than three centimeters among 60.5% of the older patients compared with 13.8% of the younger patients ( $P < 0.001$ ), as shown in Table 2.

**Table 2** Tumor characteristics in the patients with urothelial bladder carcinoma

Characteristic	Age (years)				Total		P value
	≤ 40		> 40		No.	(%)	
	No.	(%)	No.	(%)	No.	(%)	
<b>Stage</b>							
Ta	21	(72.4)	16	(21.1)	37	(35.2)	
T1	7	(24.1)	43	(56.6)	50	(47.6)	
T2	1	(3.4)	8	(10.5)	0	(8.6)	
T3	0	(0.0)	7	(9.2)	7	(6.7)	
T4	0	(0.0)	2	(2.6)	2	(1.9)	<0.001
<b>Grade</b>							
G I	21	(72.4)	21	(27.6)	42	(40.0)	
G II	6	(20.7)	32	(42.1)	38	(36.2)	
GIII	2	(6.9)	23	(30.3)	25	(23.8)	<0.001
<b>Multi-focality</b>							
1	23	(79.3)	44	(57.9)	67	(63.8)	
> 1	6	(20.7)	32	(42.1)	38	(36.2)	0.041
<b>Size</b>							
≤ 3	25	(86.2)	30	(39.5)	55	(52.4)	
> 3	4	(13.8)	46	(60.5)	50	(47.6)	<0.001
<b>Total</b>	29	(100.0)	76	(100.0)	105	(100.0)	

The rate of recurrence was 36.8% of the older patients (Group II) in comparison with 6.9% of the younger patients (Group I), and the difference was significant ( $P = 0.002$ ). The rate of progression in Group II was also higher than the rate of Group I, but the difference was insignificant ( $P = 0.224$ ), as presented in Table 3. The rate of progression was higher among

those who continued smoking (21.4%) than those who stopped smoking (15.6%). However, the difference was not statistically significant ( $P = 0.688$ ). The rate of recurrence among those who were still smoking (57.1%) was significantly ( $P = 0.046$ ) higher than the rate for those who stopped smoking (24.4%), as presented in Table 4.

**Table 3** Outcome of the tumor in patients with urothelial bladder carcinoma

Outcome	Age (years)				Total		P value
	≤ 40		> 40		No.	(%)	
	No.	(%)	No.	(%)			
<b>Recurrence</b>							
No	27	(93.1)	48	(63.2)	75	(71.4)	0.002†
Yes	2	(6.9)	28	(36.8)	30	(28.6)	
<b>Progression</b>							
No	27	(93.1)	62	(81.6)	89	(84.8)	0.224*
Yes	2	(6.9)	14	(18.4)	16	(15.2)	
<b>Total</b>	29	(100.0)	76	(100.0)	105	(100.0)	

\*By Fisher's exact test. †By Chi-square test.

**Table 4** Progression and recurrence of the urothelial bladder carcinoma according to smoking status after the diagnosis

Status	Smoking				Total		P value
	Stopped smoking		Still smoking		No.	(%)	
	No.	(%)	No.	(%)			
<b>Progression</b>							
No	38	(84.4)	11	(78.6)	49	(83.1)	0.688*
Yes	7	(15.6)	3	(21.4)	10	(16.9)	
<b>Recurrence</b>							
No	34	(75.6)	6	(42.9)	40	(67.8)	0.046*
Yes	11	(24.4)	8	(57.1)	19	(32.2)	
<b>Total</b>	45	(100.0)	14	(100.0)	59	(100.0)	

\*By Fisher's exact test.

## Discussion

Urothelial bladder cancer in patients less than 40 years of age is sporadic, with 0.8% incidence rate.<sup>18</sup> The clinical behavior and outcomes of urothelial bladder cancer are debatable in the literature regarding patients younger than 40 years of age compared with older ages.

According to our data, younger patients had more low-grade cancer compared to older patients (72.4% in young age group vs. 27.6% in older age group) and fewer tumors size of >3 cm (13.8% in young age vs. 60.5% in older age group), which was similar to the results of prior studies.<sup>19</sup>

Also, in our study, male gender domination was detected (male to female ratio was about 4:1) in patients <40 years of age,<sup>20</sup> the ratio decreased with increasing age (about 2:1 in older age group). This indicates that the risk of urothelial bladder cancer in female patients is rising with increasing age, corresponding to those reported in prior studies.<sup>21</sup> The results showed irrelevant difference in the gender distribution in both groups.

Another study found that postmenopausal women had a higher risk of bladder cancer compared with premenopausal women.<sup>22</sup> Some authors described that estrogens inhibit the growth and development of bladder cancer in animals. Therefore, the hormonal level changes in the female gender could explain the reason for the increased risk of bladder cancer in older ladies.<sup>23</sup>

Furthermore, a new study revealed that androgens could advocate the initiation of bladder cancer.<sup>23</sup> As a result, these could have been the main reasons for the male dominance in bladder cancer in all groups.

Regarding presenting symptoms, our data confirms the results of prior research in which patients aged <40 years old have the same clinical presentation as their older counterparts, whereas some pathological parameters are statistically different. The major presenting symptom was macroscopic hematuria in both the young and the older age groups, with no obvious

significant difference between the young age and old ages (young 82.2% vs. 80.3% in old age group).<sup>21</sup>

In a review of a series of children presented with lower urinary tract infection, three of them were diagnosed with urothelial bladder carcinoma.<sup>24</sup> So, the presentation of macroscopic hematuria and lower urinary tract symptoms (LUTS) in young age groups leads to suspicion of more common causes like UTIs, nephrolithiasis, and/or nephropathies and less malignant cause.<sup>21</sup>

For stage and grade, in this study, the primary tumor stage was according to the 2009 TNM system, and the histologic grade was assigned using the 1973 World Health Organization histologic classification. The World Health Organization grading system is widely used and correlates well with patient survival.<sup>16,18</sup>

In our study, Ta stage lesions were presented in 35.2% of patients with young age group dominance (72.4% of young age vs. 21.1% of older age group), and 47.6% of patients presented with stage T1 lesions with older age group dominance (24.1% young age vs. 56.6% of older age group), which was comparable to the prior reported T stage distribution.<sup>21</sup>

Significant differences were detected in the distribution of the T stage among the two age groups. The pathologic results of our study revealed that significant differences were observed in the grade distribution between the two groups, with the percentage of well-differentiated malignancies declined with increasing age. Therefore, this finding is supported by a prior study.<sup>14</sup>

Apparently, our analysis showed that patients with age ≤40 year old often have a low-stage (72.4%) and low-grade (72.4%) tumor, which supports the previous evidence that patients in this age group had low stage and grade.<sup>21</sup>

Alabdulkareem et al.<sup>25</sup> concluded that 17 of 24 patients (70.8%) were of low grade tumors. Gunlusoy et al. also concluded that

82.4% of patients had low grade tumors in the young age group.<sup>11</sup>

These results supported the growing evidence in the literature that young patients mostly presented with low stage and low-grade bladder cancer.

In this study, 52.4% of patients had tumor size of less than 3 cm, mostly young age group (86.2%), and 47.6% of patients had tumors larger than 3 cm, mostly older age group (60.5%). A "3 cm" cut-off for size limit was used because it is the limit used in the EORTC Genitourinary Cancer Group scoring system and risk tables for predicting recurrence and disease progression.

Smoking habit is very common, and thus its epidemiologic impact is high. Around 56% of patients were smokers, with about 20-40 cigarettes per day for a variable period, making smoking the most common risk factor, especially in young age groups (79.3%), which supports the previous studies.<sup>26</sup>

Regarding recurrence and progression, two patients (6.9%) in the younger group had a recurrence, and both of them progressed to a higher stage. In the older age group, 28 (36.8%) of them had a recurrence, and 14 of them progressed to a higher stage, as prior study results support this finding.<sup>27</sup>

Recurrence is more frequent in the elder age group. The reason could be that bladder cancer in patients <40 years old tends to be well differentiated. Another explanation could be decreased host immunologic and other defense aspects in elderly patients.<sup>28</sup> Therefore, elderly patients with high-risk superficial urothelial bladder cancer should be precisely directed at the beginning regarding the natural history of their disease. Close surveillance is needed to observe the failure of initial intravesical therapy as soon as possible, in which case cystectomy must be recommended. Unlikely, superficial urothelial bladder cancer with low risk in younger age patients must have their therapy and follow-up protocol appropriate to their level of risk, and younger age

patients might well get benefit from a less-invasive treatment program.<sup>29</sup>

The proportion of patients with cancer progression was not associated with age. We did not find any statistically significant difference in the rate of progression between the two age groups.

The limitation of the present study is that it was done in only one center with a small number of cases. Further long-term multi-center prospective studies are recommended to explore the long-term results, recurrences, and progression of the diseases.

### Conclusion

The majority of patients were males. Gross hematuria was the most common presentation regardless of age. Urothelial bladder cancers among young patients were of lower grade, stage, and size than among older patients. The proportion of smokers was higher among the young than in the old age group. The recurrence rate was higher among the older patients. We recommend a prospective comparative study with a large number of patients for a prolonged period of follow-up to evaluate the effect of treatment modalities, tumor progression, tumor recurrence, and overall survival.

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### Competing interests

The author declares that he has no competing interests.

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