

# Urothelial Bladder Cancer in Young Age Group: Presentation, Clinical Behavior and Outcome

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(Submitted: 14 July 2022 – Revised version received: 03 August 2022 – Accepted: 21 August 2022 – Published online: 26 December 2022)

## Abstract

**Objectives:** The main aim of our study is to review the clinical presentation, histopathological features, staging and grading, as well as the recurrence, and progression (for 1 year) of UBC in patients less than 40 years age.

**Methods:** We retrospectively reviewed records of 42 newly diagnosed patients with UBC between May 2016 to May 2020 at the Rizgary Teaching hospital, and Zheen International hospital in Erbil city, Iraq.

**Results:** The mean age  $\pm$  SD of the sample were  $29.05 \pm 7.05$  years, ranging from 17 to 39 years. The median was 28.5 years. Patients were divided into three groups, Group I (6 patients) were aged  $\leq 20$  years, Group II (17 patients) were aged between 20–29 years old, and Group III (19 patients) were aged between 30–39 years old. The majority (78.6%) of the cases were males. Gross hematuria (73.8%) is the most common presenting symptom. The proportion of smoker patients was 61.9%. Significantly higher proportions of patients with lower grade and stage and small tumor size were detected that comparable with previous studies that support the bladder cancer in young-aged group with lower grade and stage. In one year follow up, the recurrence occurred in 6 (14.3%) of patients, just 2 of them progressed to a higher grade or stage.

**Conclusion:** The results suggested that young patients with UBC was expecting better prognosis than older patients.

**Keywords:** Urinary bladder neoplasms, young age group, presentation, clinical behavior, outcome

## Introduction

Frontal pelvic bladder. The organ is spherical when full but tetrahedral when empty.<sup>1</sup> The bladder wall has transitional epithelium, submucosa, and muscular layers.<sup>2</sup> The transitional epithelium has five to eight irregularly folded layers of urothelial cells, except at the trigone.<sup>3</sup> TE has dome-shaped, binucleate cells. The basal lamina, which is split into lamina propria and submucosa, separates the epithelium from the underlying connective tissue (Sm). 5 Muscular layer or detrusor muscle has three layers: inner, outer, and circular.<sup>2,3</sup> According to the **International Agency for Research on Cancer (IARC) 2020** data, the incidence rank of urinary bladder cancer among all cancers is number 6 in males and number 10 in both genders. While in Iraq According to **IARC** in 2020, 5th most common cancer in men and the 8th most common in both gender.<sup>4</sup> According to the Iraqi Cancer Registry's 2016 annual report, our country recorded 1419 new cases of bladder cancer, with an incidence of 3.75, ranking it as the 5th most common cancer. Male patients accounted for 1059 cases, representing 9.46% of all male cancer cases, with an incidence of 5.53, ranking it as the 2nd most common cancer in males. 360 female cases constitute 2.51% of all female cancer cases, making it the 10th most prevalent malignancy in females. 50 men and 19 women (0–40) had bladder cancer.<sup>5</sup> Low-grade Ta tumours recur 48% to 71% of the recurrence, while upstaging is rare (2% to 12%).<sup>6</sup> CIS with invasive tumours has a 5-year death rate of 45% to 65%.<sup>7</sup> UBC may occur at any age, but is primarily a disease of older ages, with the majority of patients over 60 years of age at the time of diagnosis and the median age of the initial diagnosis 69 and 71 years old for men and females respectively. In younger than 40-year-olds, its incidence is 0.8% to 1%, or 700 to 1700 cases a year.<sup>8</sup> UCB in young individuals is less aggressive and has a better prognosis, according to various studies.<sup>9</sup> Among women, longer age at menarche

(15 years), parity, and oestrogen or progestin medication are related with decreased UCB risk, suggesting sex steroid exposure decreases bladder cancer risk.<sup>10</sup> Androgen receptor (AR) contributes to bladder cancer growth and progression. AR downregulation causes advanced cancers.<sup>11</sup> Females are more likely to have advanced malignancies and a poor prognosis, despite BC being more common among men. Possible cause: late diagnosis.<sup>12</sup> UBC risk factors because the bladder is constantly exposed to environmental toxins and inflammation. Aromatic amines may be the main cancer-causing toxin in tobacco smoke. Tobacco use and employment cause most environmental dangers.<sup>13</sup> Tobacco causes 30–40% of urothelial cancers and doubles or triples BC risk.<sup>14</sup> UBC is linked to pipe and cigar smoking. Quitting early after a bladder cancer diagnosis is controversial. Chemical and dye workers are at danger, especially those who work with aromatic amines, such tobacco, dye, and rubber workers, hairdressers (due to hair dye exposure), painters, leather workers, and truck drivers (likely because of exposure to diesel fumes).<sup>15</sup> Valsalva motions may cause intermittent haematuria. Gross hematuria should be addressed even if urinalysis is normal. Antiplatelet and anticoagulant therapy for hematuria must be compared. *In situ* BC might produce irritable urination (frequency, urgency) (CIS). Half of individuals with severe hematuria have an identifiable cause, and cancer risk is 20.4%. Microscopic hematuria risk is 2.6% to 5.2%.<sup>16</sup> The main aim of our study is to review the clinical presentation, histopathological features, staging and grading, as well as the recurrence, and progression (for 1 year) of UBC in patients less than 40 years age.

## Methods

We retrospectively and prospectively analyzed 42 patients aged less than 40 years diagnosed with urothelial bladder cancer

(UBC) in Urology departments of Rizgary teaching hospital and Zheen International hospital in Arbil city from May 2016 to May 2020. After consent, medical records data included: Age, gender, and job. Hematuria, irritative voiding, discomfort, or other symptoms. Smoking, occupational, or environmental bladder tumour risk factors. BC genealogy. Ultrasound findings at presentation: abdominal and pelvic. Cystoscopy results without NBI (NBI). Histopathology. Intravenous infusion, Recurrences and advancement for 1-year follow-up cases (3 months, 6 months, 9 month & 12 month). Tumor size estimation either  $\geq 3$  cm or  $< 3$  cm according to largest diameter of the mass detected by ultrasonography or CT/MRI if done before cystoscopy, while the number, either unifocal or multifocal and the shape of lesion detected by cystoscopy done either under general or spinal anesthesia. Staging urothelial carcinoma was according to TNM classification in 2009 approved by the Union for International Cancer Control (UICC) updated in 2017 (8th Edition.) and grading according to WHO grading system in 1973. Patients were divided according to the age into three age groups: group I ( $\leq 19$ ) years, group II (20–29) years, group III (30–39) years. Exclusion criteria were patients with non-urothelial bladder tumor, patient with concomitant upper urinary tract tumor, and patients with follow up less than 12 months. Tumor stage and grade were defined according to the 2009 TNM system and 1973 World Health Organization grading system.<sup>17</sup>

## Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS, version 25). Numerical variables were summarized in the form of means and standard deviations (SDs), while frequencies and percentages were calculated to present the results of the categorical variables.

## Results

Forty-two patients with urothelial bladder cancer (aged less than 40 years) were included in the study. Their mean age  $\pm$  SD was  $29.05 \pm 7.05$  years, ranging from 17 to 39 years. The median was 28.5 years. Table 1 shows that the largest proportion (45.2%) of the sample were aged 30–39 years. The majority (78.6%) were males, and 4.8% had family history of cancer. Regarding the occupation, only 9.5% were working in risky occupations. More than half (61.9%) were smokers (Table 1).

It is evident in Table 2 that the majority of the patients (73.8%) presented with gross hematuria, 11.9% with micro hematuria, 9.5% with UTI, and only 4.8% were diagnosed during routine checkup. The majority of the tumors were diagnosed by ultrasonography (92.9%).

The cystoscopy shows that 76.2% of the patients had papillary growth, as presented in Table 3. The stage at presentation was Ta among 66.7% of patients, and the same is for the grade where 66.7% of patients had grade I & the majority (76.2%) of the tumors were unifocal (Table 3).

We had 33 (78.6%) with tumor size less than 3 cm, 9 (21.4%) larger than 3 cm detected by Imaging studies.

Intravesical therapy was given to two thirds (66.7%) of the patients, as presented in Table 4 which shows also that 6 patients (14.3%) developed recurrence. Only 4 patients (9.5%) continued smoking during treatment.

Table 1. Basic characteristics of the studied sample

	No.	(%)
Age (years)		
<20	6	(14.3)
20–29	17	(40.5)
30–39	19	(45.2)
Gender		
Male	33	(78.6)
Female	9	(21.4)
Family history		
No	40	(95.2)
Yes	2	(4.8)
Occupation		
Risky	4	(9.5)
Not risky	38	(90.5)
Smoking		
No	16	(38.1)
Yes	26	(61.9)

Table 2. Patient's presentation and investigation

	No.	(%)
Clinical presentations		
Gross hematuria	31	(73.8)
Micro hematuria	5	(11.9)
UTI	4	(9.5)
Routine checkup	2	(4.8)
Ultrasonography		
Not diagnosed by US	3	(7.1)
Diagnosed by US	39	(92.9)

About recurrence group Table 5, that they consist of 6 patients, 4 of them among 20 to 29 years of age groups, all of them were males, just one of them was in risky group occupation, 3 of them among prior smokers and 2 of them were continues smoking after recurrence or follow up period.

Furthermore, recurrence occurred in the sixth month in two patients, and in nine months in another two patients. Progression (upstaging or upgrading) of the tumor occurred among two out of the six patients.

About muscle invasion status, majority of the patients were NMIBC 39 (92.8%) of patients, as shown in Figure 1.

## Discussion

Between May 2016 and May 2020, 40 patients (33 men and 9 females) ranged in age from 17 to 39 at diagnosis. Our department diagnosed 28.5-year-olds with bladder urothelial cancer. In most earlier studies, age groups were defined as those under 40. Only one research with more than 100 UBC cases in young patients has been reported due to low incidence in this age group.<sup>18</sup> First, UBC risk is age-related.

Table 3. **Results of the cystoscopy and histopathology at presentation**

	No.	(%)
Cystoscopy finding		
Papillary growth	32	(76.2)
Non-papillary	10	(23.8)
Multifocality of the tumor		
Unifocal	32	(76.2)
Multifocal	10	(23.8)
Tumor size		
<3 cm	33	(78.6)
≥3 cm	9	(21.4)
Stage on presentation		
Ta	28	(66.7)
T1	11	(26.2)
T2	2	(4.8)
T3	1	(2.4)
T4	0	(0)
Grade on presentation		
G1	28	(66.7)
G2	11	(26.2)
G3	3	(7.1)

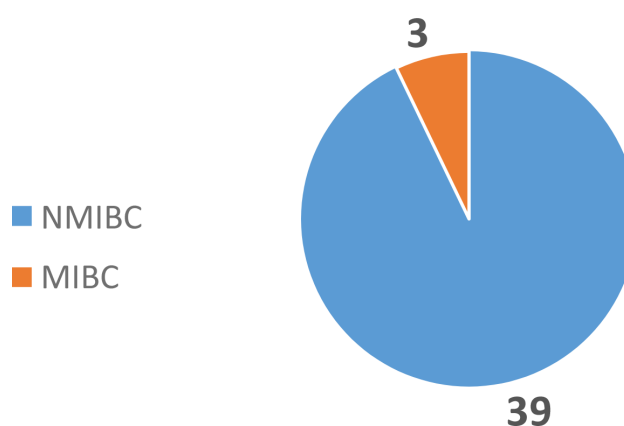
Table 4. **Intravesical treatment, recurrence and smoking continuity during treatment**

	No.	(%)
Intravesical therapy		
No	28	(66.7)
Yes	14	(33.3)
Recurrence		
No	36	(85.7)
Yes	6	(14.3)
Smoking continuity		
No	38	(90.5)
Yes	4	(9.5)

Smoking and long-term professional exposure are substantial environmental risk factors (could be up to 20 years).<sup>19</sup> About UBC instances in children were treated in children's hospitals or paediatrics departments, which might explain the absence of cases younger than 15 years in our analysis. Urothelial Bladder Cancer (UBC) in young individuals is a male-predominant illness; Eva Compérat et al. and F. Iori C. De Dominicis et al. observed male to female ratios of 2.9:1 and 3:1 respectively. Our study's male-to-female ratio was 3.5:1, similar to earlier research.<sup>20</sup> Almost all prior research found that UBC is more common in men than women, perhaps because to smoking, occupational risk, or the androgen impact. Miyamoto H, Yang Z, Chen YT, et al. found a link between androgens and bladder cancer.<sup>21</sup> We categorised the patients into 3 age groups; higher female proportion in group III (30–39 years) may be owing to late environmental

Table 5. **Recurrence and progression**

	No.	(%)
Age (years) (n = 6)		
<20	0	(0)
20–29	4	(66.7)
30–39	2	(33.3)
Gender (n = 6)		
Male	6	(100)
Female	0	(0)
Occupation (n = 6)		
Risky	1	(16.7)
Not risky	5	(83.3)
Smoking (n = 6)		
No	3	(50.0)
Yes	3	(50.0)
Smoking continuity (n = 6)		
No	4	(66.7)
Yes	2	(33.3)
Month of recurrence (n = 6)		
3 month	1	(16.7)
6 month	2	(33.3)
9 month	2	(33.3)
12 month	1	(16.7)
Progression (n = 6)		
No	4	(66.7)
Yes	2	(33.3)
Stage after recurrence (n = 6)		
Ta	4	(66.7)
T1	1	(16.7)
T2	1	(16.7)
T3	0	(0)
T4	0	(0)
Grade after recurrence (n = 6)		
G1	1	(16.7)
G2	4	(66.7)
G3	1	(16.7)

Fig. 1 **Muscle invasion status.**

exposure to carcinogen or oestrogen. In animals, oestrogen prevents BC growth and development, thus we agree that the rise in older females with UBC was attributable to hormonal changes.<sup>22</sup> Poor suspicion and low usage of invasive radiography analysis and cystoscopy led to delayed diagnosis.<sup>23</sup> This condition is more frequent in younger individuals because urothelial bladder cancer is less common and benign causes of hematuria are more common, creating unwillingness to undertake an invasive workup.<sup>24</sup> In many studies, 80–90% of patients presented with gross (visible) hematuria, while microscopic (non-visible) hematuria accounts for 5–15% of cases. About 10–15% patients present with lower urinary tract symptoms such as frequency, dysuria, urgency, lower abdominal or suprapubic pain, and recurrent UTI.<sup>25</sup> In our study, painless hematuria was the most common presenting symptom, either macroscopic (73.8%) or microscopic (11.9%). Irritative voiding symptoms, mainly dysuria and frequency, were the second most common (9.5%). Two (4.8%) patients were diagnosed during routine checkups or checkups for other complaints. Onur Telli et al. and S. Sasikumar had similar findings.<sup>26</sup> Common smoking has a strong epidemiologic effect. In our analysis, 26 (3 females and 23 men) patients (61.9%) smoked at least 15 cigarettes a day for various periods, making smoking the most prevalent risk factor. The sensitivity of ultrasound for detecting bladder tumours is over 80%, depending on size and location.<sup>27</sup> In our study, trans-abdominal ultrasonography detected a mass or thickening in 39 (92.9%) patients but not in 3 (7.1%). Muscle invasion staging is crucial before definitive treatment. Abdominal and pelvic CT scans are most common. CT (and MRI) can't distinguish bladder layers (superficial and deep muscle). In most situations, radiologic equipment cannot identify T2 and T3a cancers' microscopic extravascular expansion. T3b (macroscopic extravascular invasion) may cause bladder wall

irregularities. Local extension into prostate/seminal vesicles/vagina/uterus may be ignored because typical anatomic planes are not often noticed. If imaging is done one month after TURBT, postoperative responses might be confused with malignancy.<sup>28</sup> Low-grade tumours lead to a better prognosis for 'young' patients than 'older' patients, according to Migaldi et al. and Cho et al.<sup>28</sup> (66.7%) patients had grade I tumours, 11 (26.2%) had grade II, and 3 (7.1%) had grade III, which is consistent to past research.<sup>30</sup> Our data add to emerging evidence that young people have low-stage, low-grade bladder cancer. The frequency of urothelial cancers in young people rises with age, according to researchers.<sup>31</sup> Most young individuals' urothelial malignancies are noninvasive papillary neoplasms. Low-grade urothelial cancers diminish with age, but high-grade tumours rise.<sup>27</sup> Our findings matched earlier ones. Six individuals (14.3%) had recurrence. One patient recurred in three months, two in six, two in nine, and one in a year. Two of the six patients had tumour progression. Previous research confirms this.<sup>32</sup>

## Conclusion

The data show that most UBC patients under 40 years old are male, the most frequent presenting symptom is gross hematuria, and most tumours are 3 cm and grade I (G1) (66.7%). The clinical stage distribution, natural history, and outcomes of bladder urothelial cancer in young adults are similar to those with low grade and stage, so clinicians should be aware that patients under 40 years of age with higher-grade and larger than (3 cm) tumours are more likely to develop tumour recurrence.

## Conflict of Interest

None. ■

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