# Urothelial bladder cancer in young adults: Diagnosis, treatment and clinical behaviour

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## Abstract

**Introduction:** The aim of the study is to reveal pathologic characteristics and clinical behaviour of patients 40 years old or younger diagnosed with and treated for urothelial bladder carcinoma.
**Methods:** We retrospectively analyzed the clinical and pathologic data of 91 patients, initially diagnosed and treated at our institution from May 1996 to December 2014. Cancer recurrence was defined as new occurrence of bladder cancer at the same or different sites of the bladder. Cancer progression was defined as an increase in stage or grade in any of the recurrences.
**Results:** The mean age was 33.8 (range: 17–40) years. The pathological examination after transurethral resection revealed 83 (91.2%) patients with non-muscle invasive urothelial bladder cancer, and 8 (8.8%) patients with muscle invasive urothelial bladder cancer. According to the distribution of grade, there were 75, 4 and 12 patients with grade 1, grade 2 and grade 3 diseases, respectively. Initial cancer staging was: pTa with 40 patients (43.9%), pT1 with 43 patients (47.2%), pT2 with 7 patients (7.6%), and pT3 with 1 patient (1.2%). While 17 (18.6%) patients recurred in the follow-up, 10 (10.9%) patients had progression. There were no differences in recurrence and progression rates in the Ta and T1 stages between groups ($p = 0.233$, $p = 0.511$, respectively).
**Conclusion:** The risk of progression increased as the number of relapses increased. The clinical behaviour of high-stage and high-grade disease in younger patients is similar to the older group.

## Introduction

Urothelial bladder cancers (UBC) are among the most frequently diagnosed malignancies, usually seen in older patients. Tumour staging and grading are essential to determine the clinical prognosis of the disease. Low-grade papillary carcinomas have an advantage of longer survival rates, even though they frequently recur since they are usually not muscle invasive.[1] On the contrary, high-grade urothelial cancers tend to be invasive in nature and carry a serious risk of progression which can lead to metastasis. These tumour occurrence rates peak around the 6th decade of life.[2] The mean age of diagnosis is 69 in males and 71 in females.[3] UBC is quite rare before the age of 40. In a previous study, the rate of this cancer was below 1% during first 4 decades of life.[4]

Although bladder cancer is usually seen as a disease seen in advanced age, thanks to the developments in diagnostic techniques, suspicious cases can be diagnosed earlier. Biological behaviour and treatment of bladder cancer is well-studied, however there are controversial results regarding the natural prognosis of bladder cancers seen before the age of 40.[4,5] Some researchers reported that the clinical behaviour and prognosis of bladder cancer seen in younger patients are similar to those seen in elderly patients,[4,6] yet others reported lower recurrence, progression and higher survival rates in younger patients.[7,8]

In this study, our objective was to review the clinical symptoms, tumour stage and grade, tumour size and multiple foci properties of tumours in patients aged 40 or below who were diagnosed and operated in our clinic for UBC.

## Methods

Clinical and histopathological data of 91 patients aged 40 or below who were diagnosed with and operated for bladder cancer between 1996 and 2014 was retrospectively reviewed (Table 1). Patients with non-transitional pathologies and with upper urinary tract involvement were excluded from the study. Urinalysis, complete blood tests, urinary system x-rays, and urinary system ultrasound (USG) were obtained from patients with hematuria, irritative voiding symptoms, and infection for differential diagnosis. In patients with no definite differential diagnosis with basic imaging studies, we performed advanced imaging studies, such as computerized tomography (CT) and/or magnetic resonance imaging (MRI). After a thorough review of the results,


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

| Characteristic | Patients (n = 91) |
|---|---|
| Stage | |
| Ta | 40 (43.9%) |
| T1 | 43 (47.2) |
| T2 | 7 (7.6%) |
| T3 | 1 (1.2%) |
| T4 | 0 |
| Grade | |
| 1 | 75 (82.4%) |
| 2 | 4 (4.3%) |
| 3 | 12 (13.1%) |
| Tumour size | |
| >3 cm | 26 (28.5%) |
| <3 cm | 65 (71.5%) |
| Multiple tumors | 27 (70.3%) |
| Single tumors | 64 (29.7%) |
| Symptoms | |
| Hematuria | 71 (78%) |
| Irritative voiding symptoms | 12 (13.1%) |
| Urinary Infections | 6 (6.5%) |
| Pelvic pain | 2 (2.1%) |

patients with diagnosed or suspected bladder tumours and non-definitive hematuria underwent cystoscopy and transurethral resection.

The TNM and the World Health Organization (WHO) classification were used for pathological staging and grading, respectively. Tumour recurrence was defined as a new tumour formation at the same or different area of the bladder after treatment (Table 2). Disease progression was defined as the increase in tumour stage and grade with recurrence (Table 3).

Patients with non-muscle invasive tumours received intracavitary BCG or chemotherapy according to tumour stage and grade. All patients were followed up in 3-month periods during the first 2 years, 6-month periods during the following 2 years, and yearly thereafter with cystoscopy with cytology. Patients diagnosed with muscle-invasive disease after transurethral resection were treated with either radical cystectomy, radiotherapy, chemotherapy, or a combination thereof following tumour staging.

Chi-square test and Fisher's exact test were used for statistical analysis. Statistical significance was set at $p < 0.05$.

## Results

The mean age of patients was 33.8 (range: 17–40). There were 83 male and 8 female patients. The male-female ratio was close to 10:1. The most frequent symptom was hematuria (78%). In terms of staging, 40 (43.9%) patients had Ta, 43 (47.2%) had T1, 7 (7.6%) had T2, and 1 (1.3%) had T3 stage disease. According to tumour grades, 75 (82.4%) patients had grade 1, 4 (4.3%) had grade 2, and 12 (13.1%) had grade 3 tumours. In terms of tumour size, 65 (71.4%) patients had tumours smaller than 3 cm, while 26 (28.5%) had a tumour size >3 cm. When patients were classified clinically, 83 (91.3%) had non-muscle invasive disease and 8 (8.7%) had muscle-invasive tumours.

Of the 91 patients in this study, 17 (18.6%) had recurrence and 10 (10.9%) had tumour progression. Of the 17 patients with recurrent tumours, 4 had TaG1, 1 had TaG2, 1 had TaG3, 7 had T1G1, 1 had T1G2, and 3 had T1G3. There was no significant association between tumour grade and recurrence in patients with Ta disease ($p = 0.534$). There was, however, a significant relationship between tumour size and recurrence ($p = 0.031$). We also found that there was more recurrence in patients with single tumours than in those with multiple tumours ($p = 0.224$).

In patients with recurrent tumours (n = 17), 9 (52.9%) were treated with transurethral resection of bladder tumour (TURBT) and 7 (41.1%) required intracavitary treatment following TURBT. The remaining patient was diagnosed with muscle-invasive recurrence and underwent radical cystectomy.

Of the total number of patients in our study, 10 (10.9%) experienced tumour progression. In patients with Ta tumour,

**Table 2. Pathological findings of recurrent patients (n = 17)**

| | Tumour recurrence | *p* value |
|---|---|---|
| Ta stage | | 0.534 |
| TaG1 | 4 | |
| TaG2 | 1 | |
| TaG3 | 1 | |
| T1 stage | | 0.005 |
| T1G1 | 7 | |
| T1G2 | 1 | |
| T1G3 | 3 | |
| Tumour size | | 0.031 |
| >3 cm | 4 (23.5%) | |
| <3 cm | 13 (76.4%) | |
| Tumour type | | |
| Single tumours | 10 (58.8%) | 0.224 |
| Multiple tumours | 7 (41.1%) | |

**Table 3. Pathological findings of patients with progression (n = 10)**

| | Tumour progression | *p* value |
|---|---|---|
| Ta stage | | 0.260 |
| TaG1 | 5 | |
| TaG2 | 0 | |
| TaG3 | 1 | |
| T1 stage | | 0.028 |
| T1G1 | 1 | |
| T1G2 | 1 | |
| T1G3 | 2 | |
| Tumour size | | |
| >3 cm | 2 (20%) | 1 |
| <3 cm | 8 (80%) | |
| Tumour type | | 0.454 |
| Single tumours | 7 (70%) | |
| Multiple tumours | 3 (30%) | |

there was no significant difference in terms of tumour progression ($p$ = 0.260). Tumour progression was higher in patients with T1G3 tumors ($p$ = 0.028). Five patients with TaG1 tumour progressed to TaG2. One patient with TaG2 progressed to T1G1 tumour. Grade progression was observed in 2 of the 4 patients with T1 stage (T1G1 and T1G2 to T1G3). Two patients with T1G3 disease progressed to T2 tumour. There was no significant relationship between tumour size and progression ($p$ = 1). The progression rates in patients with multiple and single tumours were different, but not statistically significant ($p$ = 0.454). Out of the 10 patients with progression, 2 experienced tumour recurrence for the first time, while 8 had progression with repetitive tumour recurrences. Repetitive recurrences had a progression risk 28.4-times higher than average ($p \leq 0.001$, odds ratio 28.4, 95 confidence interval [5.2–153]).

In patients with tumour progression, 6 (40%) with superficial recurrence underwent TURBT and 4 (40%) received intravesical treatment following TURBT. Of 8 the patients with muscle-invasive disease, 6 underwent radical cystectomy, 1 received radiotherapy and 1 patient with no possible cure received chemotherapy. One of the patients who underwent radical cystectomy had lymph node metastasis in the pathological specimen and was treated with chemotherapy after radical cystectomy. And the other patient who was initially treated with radiotherapy had metastasis at follow-up and received chemotherapy.

## Discussion

UBC is usually seen in older patients and is rare in younger patients. It is not always easy to diagnose based solely on symptoms and patient complaints, due to the various other potential reasons for symptoms, including infection, urinary stone disease or nephropathy. Patients with macroscopic hematuria in addition to other irritative bladder symptoms are quite suspicious cases. Secondary irritative complaints also must not be overlooked. On the other hand, it is important to focus on identifying patients with microscopic hematuria who are at greater risk for bladder tumours.[9]

Similarly, macroscopic hematuria was the most common patient complaint (78%). USG and cystoscopy are complementary diagnostic methods in tumour diagnosis. For the initial approach, USG coupled with cystoscopy and cytology was the most suitable option in these cases. In younger patients, the diagnosis can be made late compared to elderly patients based on patient complaints. The main reason for this is the reluctance for cystoscopy in younger patients.[8] In this group, etiological studies are needed when macroscopic or repetitive microscopic hematuria coupled with irritative bladder symptoms are seen. In our study, irritative symptoms with hematuria in many patients were essential in the tumour diagnosis.

Bladder cancer is mainly seen in males.[10,11] Males have a 2.5- to 4-times higher risk of bladder cancer compared with females.[12-15] Shi and colleagues reported that even though this cancer type is more frequent in men, females become also more susceptible due to hormonal changes with advancing age.[11] In studying the incidence rates of UBC, Poletajew and colleagues found the male-female ratio of patients under 41 was 4:5, and a rate of 3:1 was seen in patients under 50.[16] Likewise, our study showed that the disease was more prominent in males (91.2%).

Disease prognosis is the most important issue for younger patients with bladder cancers. In such patients with long life expectancy, treatment should have curative properties and should improve quality of life. This younger patient group, with higher anxiety levels compared to older patients, had higher treatment expectations. Even though UBC in younger patients tends to be low-stage and have low-grade properties, regular cystoscopy and cytology studies are necessary. However, this patient group is more reluctant towards these procedures and has a low tolerance rate. Histopathological properties of the disease are crucial in determining the clinical behaviour of the disease. In their study with 152 UBC patients under 40, Comperat and colleagues reported that the most important factors that affect disease prognosis are histopathological grade and tumour stage.[1] In our study, we also determined that both tumour grade and stage affect recurrence and progression. Bladder cancers in younger patients were single-focused tumours.

Haukaas and colleagues reported that multicentric tumours during the initial diagnosis shorten the recurrence-free survival period; even if the tumour is low-grade and low-staged, it carries an important risk factor for recurrence.[17] Ozbey and colleagues reported a 64% single-focus tumour rate in the diagnosis of superficial tumours in younger patients.[9] In our study, 64 (70.3%) patients had a single focus and 27 (29.7%) patients had multicentric tumours. Another study reported that recurrence-free survival rates decrease with the age.[11] In a series by Madrid Garcia and colleagues, a 12.5% tumour recurrence rate without progression was found in patients under 40.[18] Another study described tumour grade as the only significant factor in determining recurrence rates in younger patients; however, tumour grade and stage are important factors in elderly patients.[19] In our study, 17 (18.6%) patients were diagnosed with recurrence. Of these, 4 were stage Ta, 12 were T1, and 1 was T2. According to tumour degree, 11 (64.7%) patients were diagnosed with Grade 1, 2 (11.7%) with Grade 2, and 4 (23.5%) with Grade 3 tumours. A study by Masuda and colleagues also described similar results; UBC tumours in younger patients were low-grade and low-staged.[20] This was explained by the fact that the risk of carcinogen contact, which may cause genetic mutation, is lower in younger patients compared to older patients. Although most of our patients had non-muscle

invasive tumours, 8 (8.7%) patients were diagnosed with muscle-invasive tumors. In treating these invasive tumours, even though we tried bladder-sparing treatment methods, we found that 7 patients still required radical cystectomy. In 3 of these patients, we used continent urinary diversion. The prognosis of high-stage and high-grade tumours is similar between younger and older patients.[8]

## Conclusion

Most bladder cancers in younger patients are low-stage and low-grade. In this group, the basic treatment approach should be curative and improving patient quality of life. However, one must not overlook the fact that clinical prognosis of the disease between younger and older patients is similar in high-stage and high-grade tumours.

**Competing interests:** The authors all declare no competing financial or personal interests.

This paper has been peer-reviewed.

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