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Young population bladder neoplasms

K. ÇIVI ÇETIN[1], S. ÖNER[2], B. ERDOĞAN[1], G. SIMŞEK[3], M. SEZER[3]

[1]Department of Pathology, Eskisehir City Hospital, Eskisehir, Turkey
[2]Department of Urology, Eskisehir Yunus Emre State Hospital, Eskisehir, Turkey
[3]Department of Pathology, Eskisehir Yunus Emre State Hospital, Eskisehir, Turkey

Abstract. – OBJECTIVE: Bladder urothelial carcinoma is a rare condition that primarily affects the elderly and is rare in people under 40 years of age. There is no definitive information about the prognosis and clinical behavior of bladder cancer in young individuals. In our study, we aimed to investigate the prognosis and clinicopathological features of bladder tumors in patients under 40.

PATIENTS AND METHODS: A retrospective analysis was performed on patients diagnosed with urothelial neoplasia who underwent bladder surgery between January 2008 and December 2020. The patient's medical records in our cancer database were collected. The study included stage, grade, multifocality, smoking habits, recurrence, and survival. The cases were divided into two groups: those under 40 (Group 1) and those over 40 (Group 2). The clinical and pathological features of young and old patients were compared.

RESULTS: 17 patients (14 men and 3 women) under 40 were identified. The age ranged between 19 and 40, and the average was 30.6. One infiltrating urothelial carcinoma (pT1), twelve papillary urothelial carcinomas (pTa), two papillary urothelial neoplasias with low malignant potential, and two urothelial papillomas were all identified by pathology. Dysuria was the primary symptom that initially manifested. Recurrence occurred in two of 12 patients with low-grade papillary urothelial carcinoma in the young patient group. In a similar group of patients over 40, recurrence was detected in 7 out of 10 patients. Patients with urothelial carcinoma under the age of 40 have been noted to have single, small tumors, unlike older patients. No tumor progression was detected in young patients. All young patients are still alive and have not experienced any recurrences. In the group of older patients, tumor progression was observed in 11 patients (16.4%).

CONCLUSIONS: Patients under 40 typically have low-grade and low-stage bladder urothelial cancer. Because urothelial tumors in young people frequently have a good prognosis and seldom recur, transurethral excision is the preferred treatment method for bladder tumors.

Key Words:
Urinary bladder, Neoplasm, Young population, Urothelial neoplasm.

Introduction

The fifth most common cancer is urothelial carcinoma of the bladder[1]. Male patients are affected more frequently than female patients, usually in the sixth or seventh decade[1]. Urothelial bladder neoplasms are rare in the young population. The number of young individuals with bladder cancer is increasing due to advances in diagnostic technologies and the introduction of early screenings[2-5]. Many studies have investigated the histological type of urothelial bladder cancer that develops in young people and how it behaves clinically[3-7]. Bladder urothelial carcinoma occurring in young patients typically has a low pathological stage and a low rate of progression and recurrence[1-6]. The clinical course of the disease is better in young people than in the elderly[8].

In this study, the clinicopathological characteristics of patients under 40 years of age with bladder urothelial neoplasia were examined. Additionally, this young patient group was compared with patients over 40.

Patients and Methods

The regional Ethics Committee approved this study. Between January 2008 and December 2020, 983 patients with urothelial neoplasia underwent bladder transurethral resection (TUR) surgery in Eskişehir Yunus Emre State Hospital were evaluated retrospectively. Age and gender demographics, smoking history, cystoscopic findings, tumor type, grade, stage, number of foci, tumor recurrence, progression events, intravesical treatment, treatment modalities, and clinical follow-up data were all analyzed in our cases. Bladder neoplasias were divided into urothelial, non-urothelial, and secondary neoplasias. The study group consisted of 921 patients diagnosed with urothelial neoplasia. The cases were then divided into two groups: those under 40 (Group 1) and those over 40 (Group 2). Patients

Corresponding Author: K.C. Çetin, MD; e-mail: kismet.civicetin@sbu.edu.tr

in Group 2 were randomly selected among those diagnosed in our department during the research period. Clinicopathological characteristics of young and elderly patient groups were determined, and these two groups were compared. The World Health Organization's 2016 grading scale determined the tumor grade. The emergence of the disease in any region of the bladder was referred to as disease recurrence. An increase in the quality or stage of any recurrent tumor was considered a sign of disease progression. All patients underwent cystoscopy every three to four months in the first year, every six months in the second year, and every year after that. Survival was the period between the initial presentation and the study's endpoint.

Statistical Analysis

Demographic, clinical, and laboratory characteristics were summarized using median (interquartile range) and percentages for continuous and categorical variables. Statistical analysis using IBM SPSS Statistics 25 (IBM Corp., Armonk, NY, USA) was used to examine the data. The mean, standard deviation, distribution, and median numbers summarize the data. A comparison of clinicopathological features between young and elderly patient groups was made using the Chi-square test. All p-values<0.05 are considered as statistically significant.

Results

Urothelial neoplasia was diagnosed in 921 patients. The histopathology of urothelial tumor patients was summarized in Table I. 17 patients (14 men, 3 women) diagnosed with urothelial neoplasia under 40 were identified. Group 1 was named the young patient group. The average patient age in the young patient group was 30.6 years (19-40 years). Two patients were under the age of 20. Five patients were between 20 and 30; the remaining patients ranged in age from 30 to 40. Microscopic hematuria was the most prevalent presenting symptom in 15 individuals (88.2%), followed by dysuria in 11 patients (64.7%), pollakiuria in 8 patients (47%), and pelvic pain in 4 patients (23.5 %). There were two multifocal tumors and 15 solitary tumors (88.2%). Most tumors (94.1%) were below 3 cm and located in the posterior region (47%). Thirteen patients (76.5%) had a history of smoking cigars, and one patient (5.9%) had chemical exposure. The patients had no prior history of schistosomiasis. The bladder tumor was treated by transurethral excision in all cases. Two papillary urothelial neoplasias with low malignant potential (PUNLMP), one infiltrating urothelial carcinoma (stage pT1), twelve papillary urothelial carcinomas (stage pTa), and two urothelial papillomas were diagnosed (Table II). Carcinoma *in situ* has not been identified in any patient. Intravesical Bacillus Calmette-Guerin (BCG) injections were performed in one patient. Recurrence occurred in 2 of 12 patients with low-grade papillary urothelial carcinoma within 1 and 7 months after surgery. Two (11.8%) recurrence patients were in the 30-40 age range. Recurrence was not found in people under the age of 30. No tumor progression was noted. With a mean follow-up time of 24.5 months, all patients were alive and free of recurrences (12-60 months). Group 2 was formed with 67 randomly selected patients over the age of 40 who were diagnosed with urothelial neoplasia in different categories and named as the elderly patient group. The clinical and pathological characteristics of the young and elderly patients are summarized in Tables III and IV. The two groups are compared in Table V.

Table I. Histopathology of urothelial tumors.

Urothelial neoplasms	Total	Females	Males
Carcinoma *in situ*	11 (1.2%)	2 (18.2%)	9 (81.8%)
High-grade dysplasia	3 (0.3%)	-	3 (100%)
Urothelial papilloma	18 (2%)	4 (22.2%)	14 (77.8%)
Low-grade dysplasia	55 (5.9%)	8 (14.5%)	47 (85.5%)
Papillary urothelial neoplasia with low malignant potential	15 (1.6%)	-	15 (100%)
Papillary urothelial carcinoma, low-grade	401 (43.5%)	33 (8.2%)	368 (91.8%)
Papillary urothelial carcinoma, high-grade	59 (6.4%)	10 (16.9%)	49 (83.1%)
Infiltrating urothelial carcinoma-low grade	60 (6.5%)	7 (11.7%)	53 (88.3%)
Infiltrating urothelial carcinoma-high grade	299 (32.5%)	26 (8.7%)	273 (91.3%)
Total	921	90 (9.8%)	831 (90.2%)

Table II. Bladder urothelial neoplasms in patients under 40 years of age.

Patients Number	Age	Gender	Histopathological Diagnosis	Stage
1	32	Male	Infiltrating urothelial carcinoma, high-grade	pT1
2	27	Male	Papillary urothelial carcinoma, low-grade	pTa
3	37	Male	Papillary urothelial carcinoma, low-grade	pTa
4	38	Male	Papillary urothelial carcinoma, low-grade	pTa
5	35	Male	Papillary urothelial carcinoma, low-grade	pTa
6	35	Male	Papillary urothelial carcinoma, low-grade	pTa
7	27	Male	Papillary urothelial carcinoma, low-grade	pTa
8	19	Male	Papillary urothelial carcinoma, low-grade	pTa
9	40	Male	Papillary urothelial carcinoma, low-grade	pTa
10	38	Male	Papillary urothelial carcinoma, low-grade	pTa
11	32	Male	Papillary urothelial carcinoma, low-grade	pTa
12	19	Female	Papillary urothelial carcinoma, low-grade	pTa
13	35	Female	Papillary urothelial carcinoma, low-grade	pTa
14	26	Female	Papillary urothelial neoplasms with low malignant potential	pT0
15	30	Male	Papillary urothelial neoplasms with low malignant potential	pT0
16	25	Male	Urothelial papilloma	pT0
17	26	Male	Urothelial papilloma	pT0

Discussion

Only 0.1% to 0.4% of urothelial tumors are discovered in individuals under 20, compared with 1.0 to 2.4% in patients under 40[9]. Bladder tumors rarely recur in young patients[10-12]. This age distribution implies that urothelial tumor incidence increases with age in young people. In the majority of studies, the age limit for young patients is considered to be 40 years old. However, the fact that some authors accept different age limits in their studies is one of the main problems of such studies. Two cases under the age of 20 years were found in our research. Our results show findings regarding the age and sex of young patients with urothelial neoplasms consistent with those of previously published research[2,4,6,7].

The fourth most prevalent cancer in men and the ninth most common in women in the US is bladder cancer.

In Western countries, it is more common in men than women and occurs in a ratio of 2:1-4:1[1]. Our investigation indicates a typical male preponderance of urothelial bladder neoplasms, with a male-to-female ratio of 4.7/1; this ratio is comparable to that in the reports of Wen et al[2] and Poletajew et al[13].

In our study, 88.2% of patients (15/17) had microscopic hematuria, the most typical presenting symptom in bladder urothelial carcinomas in young individuals[6,11,14]. In our study, dysuria, pollakiuria, and pelvic pain were frequently observed in young individuals. In the first four decades, multifocal bladder urothelial neoplasms are sporadic, while single tumors predominate[3,14,15]. In our analysis, 15 single tumors (88.2%) were found. Bladder cancer in young patients was low-grade and less than 3 cm in size[8]. Similar findings were obtained in our investigation. In the elderly patient group, a single tumor was detected in 46 patients (68.7%), and a tumor smaller than 3 cm was detected in 40 patients (59.7%).

According to Lara et al[16], there are racial/ethnic and socioeconomic disparities among adolescents and young adults diagnosed with bladder cancer in California. African Americans have significantly lower survival rates than those living in neighborhoods of the same socioeconomic status. Numerous environmental and genetic factors may play a role in the etiology of urothelial cancers in young children, even if the oncogenesis of these tumors is not fully understood. The risk of bladder cancer in older patients who smoke tobacco increases. Smoking tobacco is a significant and established risk factor for bladder cancer. Young individuals with bladder cancer have a high rate of tobacco use as well[6,17]; 58% of patients had a history of smoking, according to Stanton et al[17]; while according to Comperat et al[18], 41% of patients smoked. In line with the information published in the literature, we found that 76.5% of the young patient group smoked. In the group of elderly patients, 59.7% of them were smokers. Exposure to industrial solvents or workplace hazards is generally less in younger bladder cancer patients[3,17-20]. We detected chemical exposure in 1 patient (5.9%) in the young patient group.

According to earlier studies[19], urothelial papillomas represent 3-9% of urothelial malignancies

Table III. Clinicopathological characteristics of young patients.

Characteristics	Young patients (≤40) n (%) n=17	Urothelial papilloma (pT0) n=2	Papillary urothelial neoplasia with low malignant potential (pT0) n=2	Papillary urothelial carcinoma, low grade (pTa) n=12	Infiltrating urothelial carcinoma, high grade (pT1) n=1
Patients age	19-40 (30.64)	25-26	26-30	19-40	32
Males/females, n (%)	14 (82.3%)/3 (17.7%)	2/0	1/1	10/2	1/0
Smokers	13 (76.5%)	1	-	11	1
Chemical exposure	1 (5.9%)	-	-	1	-
Macroscopic hematuria	10 (58.8%)	1	-	8	1
Microscopic hematuria	15 (88.2%)	1	2	11	1
Dysuria	11 (64.7%)	-	2	8	1
Pollakiuria	8 (47%)	-	1	6	1
Flank pain	2 (11.8%)	-	1	1	-
Pelvic pain	4 (23.5%)	-	1	3	-
Localization:					
Posterior	8 (47%)	-	-	7	1
Trigone-posterior	3 (17.6%)	1	-	2	-
Right sidewall	3 (17.6%)	1	2	-	-
Left sidewall	1 (5.9%)	-	-	1	-
Left posterior-lateral	1 (5.9%)	-	-	1	-
Right sidewall-trigon superior	1 (5.9%)	-	-	1	-
Tumor size >3 cm	1 (5.9%)	-	-	1	-
Tumor size ≤3 cm	16 (94.1%)	2	2	11	1
Multifocality ≤1	15 (88.2%)	2	2	10	1
Multifocality >1	2 (11.8%)	-	-	2	-
Intravesical BCG administration	1 (5.9%)	-	-	-	1
Recurrence	2 (11.8%)	-	-	2	-
Progression	0 (0%)	-	-	-	-
Follow-up (months)	12-60 (24.5)	-	24-34	24-60	18

Table IV. Clinicopathological characteristics of elderly patients.

Characteristics	Elderly (>40) n (%) n=67	Urothelial papilloma (pT0) n=10	Papillary urothelial neoplasia with low malignant potential (pT0) n=7	Papillary urothelial carcinoma, low grade (pTa) n=10	Papillary urothelial carcinoma, high grade (pTa) n=10	Infiltrating urothelial carcinoma, low grade (pT1) n=10	Infiltrating urothelial carcinoma, high grade (pT1) n=10	Infiltrating urothelial carcinoma, high grade (pT2) n=10
Patients age	46-85 (67.16)	52-78 (64.3)	62-73 (67)	46-78 (62.3)	57-85 (70)	52-80 (69)	51-83 (65.4)	60-83 (72.4)
Males/females, n (%)	60 (89.6%)/7 (10.4%)	8/2	7/0	9/1	8/2	9/1	10/0	9/1
Smokers	40 (59.7%)	6	5	7	4	6	6	6
Chemical exposure	0 (0%)	-	-	-	-	-	-	-
Macroscopic hematuria	47 (70.15%)	4	3	6	7	8	9	10
Microscopic hematuria	67 (100%)	10	7	10	10	10	10	10
Dysuria	49 (73.1%)	4	4	9	7	8	7	10
Pollakiuria	46 (68.7%)	4	5	7	6	7	7	10
Flank pain	17 (25.4%)	-	-	1	2	4	1	9
Pelvic pain	25 (37.3%)	-	2	1	4	5	3	10
Localization:								
Posterior	20 (29.9%)	3	-	4	4	2	4	3
Trigone-posterior	6 (9%)	2	3	1	-	-	-	-
Right sidewall	9 (13.4%)	2	1	1	-	2	3	-
Left sidewall	11 (16.4%)	-	3	1	2	1	-	4
Left posterior-lateral	9 (13.4%)	1	-	2	2	2	2	-
Right sidewall-trigone-superior	12 (17.9%)	2	-	1	2	3	1	3
Tumor size >3 cm	27 (40.3%)	1	0	3	6	5	6	6
Tumor size ≤3 cm	40 (59.7%)	9	7	7	4	5	4	4
Multifocality ≤1	46 (68.7%)	7	7	7	6	6	6	7
Multifocality >1	21 (31.3%)	3	0	3	4	4	4	3
Intravesical BCG administration	10 (14.9%)	-	-	-	-	-	9	1
Recurrence	40 (59.7%)	3	2	7	4	7	8	9
Progression	11 (16.4%)	-	-	0	3	4	4	0
Follow-up (months)	12-120 (43)	12-144 (64.8)	24-48 (37.7)	24-120 (55.2)	12-24 (22.8)	12-48 (45.6)	24-84 (48)	12-36 (25.2)

Table V. Clinicopathological characteristics of the two cohorts.

Characteristics	Young (≤40) n=17 (20.2%)	Elderly (>40) n=67 (79.8%)	Total n=84	Group comparison *p*-value
Patients' age (mean)	19-40 (30.64)	46-85 (67.16)	19-85 (59.77)	-
Males/females, n (%)	14 (82.3%)/3 (17.7%)	60 (89.6% /7 (10.4%)	74 (88.1%)/10 (11.9%)	0.415
Smokers	13 (76.5%)	40 (59.7%)	53 (63%)	0.054
Chemical exposure	1 (5.9%)	0 (0%)	1 (1.2%)	0.039
Macroscopic hematuria	10 (58.8%)	47 (70.15%)	57 (67.86%)	0.889
Microscopic hematuria	15 (88.2%)	67 (100%)	82 (97.6%)	-
Dysuria	11 (64.7%)	49 (73.1%)	60 (71.4%)	1.000
Pollakiuria	8 (47%)	46 (68.7%)	54 (64.3%)	0.352
Flank pain	2 (11.8%)	17 (25.4%)	19 (22.6%)	0.336
Pelvic pain	4 (23.5%)	25 (37.3%)	29 (34.5%)	0.373
Localization				
Posterior	8 (47%)	20 (29.9%)	28 (33.3%)	0.275
Trigone-posterior	3 (17.6%)	6 (9%)	9 (10.7%)	
Right sidewall	3 (17.6%)	9 (13.4%)	12 (14.3%)	
Left sidewall	1 (5.9%)	11 (16.4%)	12 (14.3%)	
Left posterior-lateral	1 (5.9%)	9 (13.4%)	10 (11.9%)	
Right sidewall-trigone-superior	1 (5.9%)	12 (17.9%)	13 (15.5%)	
Tumor size >3 cm	1 (5.9%)	27 (40.3%)	28 (33.3%)	0.034
Tumor size ≤3 cm	16 (94.1%)	40 (59.7%)	56 (66.7%)	
Multifocality ≤1	15 (88.2%)	46 (68.7%)	61 (72.6%)	0.135
Multifocality >1	2 (11.8%)	21 (31.3%)	23 (27.4%)	
pT0 Urothelial papilloma	2 (11.8%)	10 (14.9%)	12 (14.3%)	
pT0 PUNLMP	2 (11.8%)	7 (10.6%)	9 (10.7%)	
pTa Papillary urothelial carcinoma, low-grade	12 (70.5%)	10 (14.9%)	22 (26.2%)	
pTa Papillary urothelial	-	10 (14.9%)	10 (11.9%)	
pT1 Infiltrating urothelial carcinoma, low-grade	-	10 (14.9%)	10 (11.9%)	
pT1 Infiltrating urothelial carcinoma, high-grade	1 (5.9%)	10 (14.9%)	11 (13%)	
PT2 Infiltrating urothelial carcinoma, high-grade	-	10 (14.9%)	10 (11.9%)	
Intravesical BCG administration	1 (5.9%)	10 (14.9%)	11 (13%)	0.000
Recurrence	2 (11.8%)	40 (59.7%)	42 (50%)	0.001
Progression	0 (0%)	11 (16.4%)	11 (13%)	0.113
Follow-up (months)	12-60 (24.5)	12-120 (43)	12-120 (40)	

in young individuals. We discovered 2 (11.8%) urothelial papillomas in our young patients.

PUNLMP is a common finding in patients with bladder cancer who are younger than 40 years old[3,16]. According to Varinot et al[21], 47% of the 44 patients with PUNLMP were under 30. Comperat et al[18] concluded that PUNLMP is dominant in the 30-year age group, and its frequency decreases in older age groups. In our study, two patients aged 26 and 30 (11.8%) in the young patient group were diagnosed with PUNLMP. No progression or recurrence was observed in these patients.

More information about these tumors' molecular anomalies is needed because of their rarity. Weyener et al[22] discovered that the early-onset group had a significantly greater prevalence of TP53 strongly positive papillomas, PUNLMPs, and pTa low-grade malignancies. They found a rare number of FGFR3 mutations and chromosome 9 deletions, in patients under 45 years of age compared to older patients[22]. According to Williamson et al[23], there are few or no mutations in the *FGFR3* and *TP53* genes in urothelial neoplasms of young individuals.

Younger patients typically have bladder urothelial carcinomas with lower-grade and stage tumors[4,6,7,13,24,25]. Young patients are less likely to be exposed to carcinogenic substances, resulting in fewer genetic mutations. It is thought[17] that the incidence of urothelial tumors increases with age. However, high-grade invasive urothelial carcinomas and poor clinical outcomes were observed in a group of patients[2,17,24,25].

Our young patient series included the diagnosis of 1 infiltrating urothelial carcinoma (stage pT1),

12 papillary urothelial carcinomas of low grade (stage pTa), 2 PUNLMPs (stage pT0), and two urothelial papillomas (stage pT0). In the young patient group, a tumor larger than 3 cm was detected in 1 (5.9%) patient, and multifocality was seen in 2 (11.8%) patients. In the elderly patient group, we observed tumors larger than 3 cm in 27 (40.3%) patients and multifocality in 21 (31.3%).

A prospective study by Demir et al[26] showed that the time from the first TUR to repeated TUR did not significantly affect relapse-free and progression-free survival rates. In our study, all patients underwent cystoscopy every 3-4 months in the first year, every six months in the 2nd year, and then once a year.

The time of tumor recurrence was longer in individuals under 40, and the recurrence rate was higher in older than younger patients[15]. With the increase in relapses, the risk of progression also increased[14]. In young patients, the prognosis for the urothelial bladder is generally favorable[13,17,18]. In our study, only one patient (pT1) in the young patient group had an invasive tumor. While no tumor progression was observed in any patient, recurrence was detected in 2 (11.8%) patients. In the elderly patient group, tumor recurrence was observed in 40 (59.7%) and progression in 11 patients (16.4%). Our findings show that younger urothelial carcinoma patients have a good prognosis, but this prognosis decreases with age.

Elderly patients may benefit from radical cystectomy for muscle-invasive or high-grade recurrent superficial bladder cancer. However, if this treatment is performed on young male patients, surgeons must be careful to prevent postoperative infertility and erectile dysfunction. Bladder preservation therapies treat bladder cancers in young individuals[15]. Young individuals with high-stage and high-grade urothelial neoplasias exhibit clinical behavior similar to older patients[7,14]. This may be partially explained by the variant histology in the young patient group with aggressive bladder cancer[24]. Janisch et al[27] did not find a better prognosis when comparing young patients with muscular invasive bladder carcinoma who underwent radical cystectomy with patients in other age groups.

Further research is needed in young adults with urothelial bladder neoplasms. In this study, we evaluated the clinicopathological findings of patients aged 40 and under with bladder urothelial neoplasms by comparing them with patients over 40. Such studies will provide important information about the diagnosis, treatment, and prognosis of tumors detected in young patients with bladder neoplasms.

Conclusions

Urothelial neoplasms are rare in children and young adults and typically present as low-grade, low-stage tumors. Hematuria, the most typical symptom, needs to be examined with cystoscopy. Due to their excellent prognosis and rare recurrence, transurethral resection is the preferred treatment for urothelial malignancies in young patients.

Conflict of Interest

The authors declare that they have no conflict of interest.

Authors' Contributions

Project planning, K.Ç.Ç.; article writing, K. Ç.Ç. and M. S.; collection and organization of data, S. Ö., and G. Ş.; statistical analysis, B. E.; coordination, M. S. All authors have read and agreed to the published version of the manuscript.

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Ethics Approval

The Eskişehir Osmangazi University Scientific Research and Publication Ethics Committee approved the study protocol (E-25403353-050.99-197012).

Informed Consent

Since the study was retrospective and the data were recorded, written consent of the patients was not required. Patient identification information: No name, ID number, or contact information was recorded. The study complies with the Declaration of Helsinki.

Data Availability

All data were contained within the manuscript.

ORCID ID

Kısmet Çivi Çetin: 0000-0001-5420-9211
Süleyman Öner: 0000-0002-0954-0914
Bahattin Erdoğan: 0000-0001-9884-1112
Gülay Şimşek: 0000-0001-9685-2563
Müge Sezer: 0000-0001-6226-8801.

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