

**Genç hastalarda invaziv olmayan mesane kanseri: Uzun dönem takip sonuçları***Non-invasive bladder cancer in younger patients: Results of long-term follow-up***Omer Bayrak, Haluk Sen, Erkan Sadioğlu, Ilker Seckiner, Sakip Erturhan**

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**Özet**

**Amaç:** Mesanenin transizyonel hücreli karsinomu 35 yaş altında nadir görülen bir hastalıktır. Çalışmamızda, genç yaştaki hastaların uzun dönem tedavi sonuçlarını ve takiplerini sunmayı amaçladık.

**Gereç ve Yöntem:** Yaşları 11-35 arası değişen, mesane tümörü tanısı almış 20 hastanın verileri retrospektif olarak incelendi. Tüm hastalara post-operatif ilk 12 saat içinde intravezikal epirubicin veya mitomicin kemoterapisi uygulandı. Hastalara evrelerine göre uygun protokolda kontrol sistoskopisi yapıldı. Hastalar yılda bir kez bilgisayarlı tomografi ve Nükleer Matriks Proteini-22 testi ile takip edildi.

**Bulgular:** Bir hastada mesane tümörünü taklit eden amiloidoz saptandı ve hasta çalışma dışı bırakıldı. Çalışma kapsamında değerlendirilen 9 erkek ve 10 kadın hastanın ortalama yaşı 25.1 (11-35) yıl, ortalama takip süresi 67.4 (42-96) ay olarak hesaplandı. Hastaların tamamında tek odakta tümör mevcut olup, ortalama tümör boyutu 2.55 (1-4) santimetre olarak ölçüldü. TNM sınıflamasına göre 2 (%10.5) hastada benin papilloma, 15 (%78.9) hastada Ta patoloji, 2 (%10.5) hastada T1 patoloji rapor edildi. Patoloji sonucu T1 olarak rapor edilen 2 (%10.5) hastaya intravezikal Bacillus Calmette Guerin (BCG) tedavisi uygulandı. Altı haftalık BCG uygulaması sonrası relaps meydana gelen bu hastalara BCG tedavisi yeniden başlandı ve takiplerinde nüks görülmedi. NMP-22 testi sadece relapsı olan 2 hastada pozitif olarak saptandı. Ayrıca 35 yaş altındaki bu hastaların hiçbirinde progresyon da izlenmedi.

**Sonuçlar:** Güncel literatürlerin ve mevcut çalışmaların sonuçlarına göre; mesanenin transizyonel hücreli karsinomunun, genç hastalarda düşük dereceli ve uzun dönem takiplerde iyi prognozlu olduğu görülmektedir.

**Anahtar Kelimeler:** Mesane kanseri, Patoloji, Prognoz, Genç hasta

**Abstract**

**Purpose:** The transitional cell carcinoma of the bladder (TCCB) is a rare disease below 35 years old patients. In our study, we aimed to present the treatment results and long-term follow-up process of younger patients.

**Materials and Methods:** A 20 patients aged between 11-35 years were reviewed retrospectively. Intravesical epirubicin or mitomycin was administered to all of the patients within the first 12 hours in the postoperative period. The patients were followed-up with cystoscopies according to the protocol. Abdominal computed tomography and Nuclear Matrix Protein-22 bladder control tests were performed once a year.

**Results:** Amyloidosis mimicked bladder tumor was detected in one patient and this patient was excluded from the study. The mean age of the 9 male and 10 female patients was calculated as 25.1 (11-35) years and the mean duration of follow-up was calculated as 67.4 (42-96) months. All of the patients had single tumoral focus and mean tumor size was calculated as 2.55 (1-4) centimeters. According to the TNM classification, 2 (10.5%) patients were reported as benign papilloma, 15 (78.9%) patients as Ta, and 2 (10.5%) patients as T1. Intravesical Bacillus Calmette Guerin (BCG) was administered to 2 (10.5%) patients whose pathologies were recorded as T1. After sixth doses of intravesical BCG, relapses occurred in these 2 patients. Intravesical BCG therapy was started again, and no relapses were observed in subsequent follow-ups. NMP-22 test yielded positive results only in 2 (10.5%) patients with relapses. In addition, progression was not observed in any of patients below 35 years old.

**Conclusions:** According to the related literature and the clinical results of the current study, TCCB appears as low grade in younger ages with better prognosis at long-term follow-up.

**Keywords:** Bladder cancer; Pathology; Prognosis; Younger patient

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**Introduction**

Urinary bladder tumors are the second most common malignancy of the urinary system (1). In 2012, the global age-standardised incidence rate (per 100,000 person/years) is reported 9.0 for men and 2.2 for women (2). Usually bladder cancers are seen in middle and old aged people. In United States, average age for getting diagnosis was 72 years. It was reported that 90% of new diagnosed patients were above 60 years and rarely below 35 years (3).

Bladder tumors relapse approximately 50-75% within 5 years after diagnosis and progressions occur in 10-20% of them (4). While the rate of five-years survival of organ-confined disease is 94%, the survival rates of locally invasive and metastatic tumor varied between 6-49% (5). In cases below 40 years of age, urothelial carcinoma of bladder is generally low grade and stage, five-year survival rate of stage I is reported as 97 % (6).

There are limited and small numbers of case series in the literature about young patients with bladder tumors. In this current study, we aimed to present treatment results and follow-up process of the patients with bladder tumors below 35 years old.

**Materials And Methods**

Between December 2007 and November 2012, twenty patients with bladder tumors aged between 11-35 years were reviewed retrospectively. Informed consent letters were obtained from the patients before the study. Detailed medical histories (average amount of tobacco among the smokers) along with occupational risk factors were recorded. Physical examination of the genitourinary system and general examination were completed; biochemical examinations, complete blood count and urine analysis were analyzed.

Urinary system ultrasonography and contrast-enhanced computerized tomography (CT) were performed on all patients pre-operatively. Then, cystoscopy was performed and tumoral tissues were resected endoscopically. Tumoral tissues and tumor bases were examined by pathologist. Localizations of the tumors and the pathological stages were recorded. Tumor grades were categorized according to the 2004 World Health Organization (WHO) classification as: urothelial papilloma or completely benign lesion (UP), papillary urothelial neoplasm of low malignant potential (PUNLMP), low grade papil-

lary urothelial carcinoma (LG), and high grade papillary urothelial carcinoma (HG) (7). Tumor stages were considered as: T1s; carcinoma in situ, Ta and T1; not invasive to muscle, and T2, T3, T4; muscle invasive tumors, according to the 2009 American Joint Committee on Cancer (AJCC) TNM classification (8, 9).

Intravesical epirubicin or mitomycin was administered to all of the patients within the first 12 hours in the postoperative period. In maintenance treatment, intravesical Bacillus Calmette Guerin (BCG) injections for 6 weeks and 6 months were planned to the patients with T1 pathology. Intravesical maintenance treatment was not planned to patients with Ta and PUNLMP.

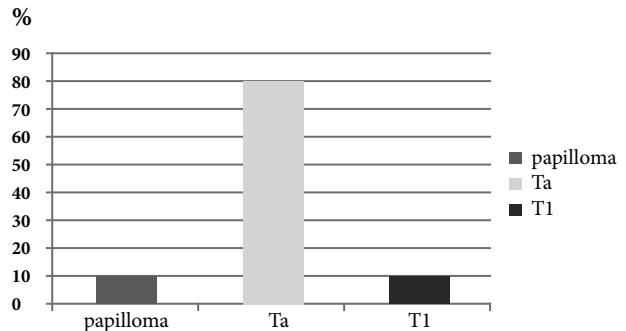
In the follow-up period, cystoscopies were performed once in every 3 months in the first year. In the second and the third years, cystoscopies performed once in every 6 months, and yearly thereafter. The patients underwent cystoscopies under general anesthesia. Tumor recurrence was accepted as a new tumor formation at the same or different region of the bladder. Abdominal CT and periodic Nuclear Matrix Protein-22 (NMP-22) bladder control tests were performed once a year (10).

Average, frequency and percentage values were given as descriptive statistics. SPSS Windows Version 11.5 (Chicago, IL) was used for analyses.

**Results**

None of the patients had a family history or occupational risk factors. Three (15%) patients had a smoking history. Amyloidosis mimicked bladder tumor was detected in one patient and this patient was excluded from the study. The mean age of the 9 male and 10 female patients was calculated as 25.1 (11-35) years and, the mean

**Figure 1:** Histopathological examination according to the TNM classification.

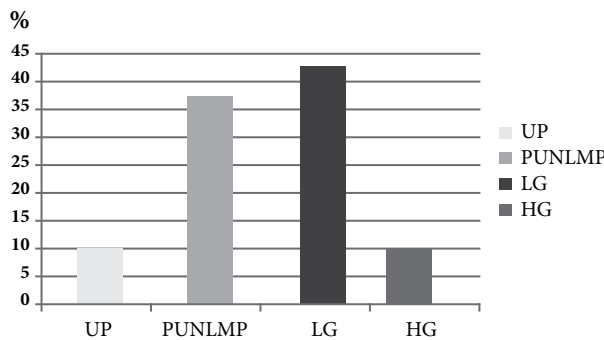


duration of follow-up was 67.4 (42-96) months. All of the patients had single tumoral focus and mean tumor size was found as 2.55 (1-4) centimeters.

As a result of the histopathological examination, superficial bladder carcinoma was determined in 17 (89.4%) patients and benign papilloma was stated in 2 (10.5%) patients. According to the TNM classification, 2 (10.5%) patients were reported as benign papilloma, 15 (78.9%) patients as Ta, and 2 (10.5%) patients as T1. T2 pathology was obtained in none of the patients (Figure 1). According to the WHO classification, UP was detected in 2 (10.5%) patients, PUNLMP in 7 (36.8%) patients, LG in 8 (42.1%) patients, and HG in 2 (10.5%) patients (Figure 2).

**Figure 2:** Histopathological examination according to the WHO classification.

(UP: Urothelial papilloma, PUNLMP: Papillary urothelial neoplasm of low malignant potential, LG: Low grade papillary urothelial carcinoma, HG: High grade papillary urothelial carcinoma).



n: number of patients, PUC: Papillary Urothelial Carcinoma  
 PUNLMP: Papillary Urothelial Neoplasms of Low Malignant Potential

Intravesical BCG was administered to 2 (11.1%) patients whose pathologies were recorded as T1. After sixth doses of intravesical BCG administration, relapses occurred in 2 patients with T1 pathology. Intravesical BCG therapy was started again, and no relapses were observed in subsequent follow-ups. In cystoscopic and radiological examinations during the follow-up period, no relapses were encountered in 15 (78.9%) patients with Ta pathology. In addition, progression was not observed in any of the patients.

Before the cystoscopy, NMP-22 test yielded positive results only in 2 (10.5%) patients with relapses. In the other patients, NMP-22 test resulted negative during the

follow-up periods. Pre-operative and post-operative data of the patients are shown in Table 1.

**Discussion**

The peak incidence of urothelial carcinoma of the bladder is stated in the sixth decade of life and less than 1% of the tumors are reported in the first four decades of life (11, 12). In addition, bladder tumor increases in both males and females in correlation with age. In the patients above 70 years old, bladder tumors are reported 2-3 times more than patients between 55-69 years old, and 15-20 times more than patients between 30-54 years old (13).

The progression and the recurrence of the tumor are very important parameters in the follow-up of the bladder tumors. The progression rates of bladder cancer have been reported as 5-50% and the recurrence rates have been reported as 50-80% (14). In studies conducted about cancer progression in younger patients, Yossepowitch and Dalbagni investigated the prognostic value of the age. By comparing 74 young patients below 40 years versus 75 elderly patients above 65 years who had transitional cell tumor of the bladder, they reported similar progression and recurrence rates. It was emphasized that poor outcomes were obtained in younger patients when radical cystectomy was performed due to the aggressive tumor (15). On the other hand, Benson et al. (16) and Madgar et al. (17) reported that the recurrences of transitional cell bladder cancer were related with age and occurred more frequently in the elderly when compared with the younger patients. In the meta-analysis which was carried out by Paner et al., recurrence and progression of the bladder tumors were not found frequent in the first two decades of life. They noted the rate of the high stage and high grade tumors increased in each following decade (18).

Nomikos M et al. stated that the prognosis was better in younger patients with bladder tumors if the tumors were superficial and low grade. Mortality due to disease was not encountered in an average of 38.52 (11-72) months follow-up period in 31 patients. However, the progression risk was found similar to elderly patients. The authors noted cystectomy was performed in none of the patients below 30 years old, but 3 (9%) patients underwent cystectomy between 31-40 years old (19). In the current study, no patient underwent cystectomy. In their study Migaldi et al. and Cho et al., the prognosis

**Table 1.** Pre-operative and post-operative data.

P	Sex	Age	Stage	Grade	NMP-22 pre/post operative	Recurrence	Progression
1	M	11	Papilloma	UP	-/-	-	-
2	F	19	Papilloma	UP	-/-	-	-
3	F	35	Ta	PUNLMP	-/-	-	-
4	F	34	Ta	PUNLMP	-/-	-	-
5	M	34	Ta	PUNLMP	-/-	-	-
6	F	19	Ta	PUNLMP	-/-	-	-
7	M	28	Ta	PUNLMP	-/-	-	-
8	M	29	Ta	PUNLMP	-/-	-	-
9	F	34	Ta	PUNLMP	-/-	-	-
10	M	28	Ta	LG	-/-	-	-
11	F	24	Ta	LG	-/-	-	-
12	M	30	Ta	LG	-/-	-	-
13	F	32	Ta	LG	-/-	-	-
14	M	26	Ta	LG	-/-	-	-
15	F	30	Ta	LG	-/-	-	-
16	F	18	Ta	LG	-/-	-	-
17	M	27	Ta	LG	-/-	-	-
18	M	26	T1	HG	-/+	+	-
19	F	32	T1	HG	-/+	+	-
20	F	31	Amiloidosis	-	-/-	-	-

F: Female, M: Male, Ta: Non-invasive papillary carcinoma, T1: Tumour invades subepithelial connective tissue, UP: Urothelial papilloma, PUNLMP: Papillary urothelial neoplasm of low malignant potential, LG: Low grade papillary urothelial carcinoma, HG: High grade papillary urothelial carcinoma

was stated better in younger patients (20, 21). Similarly, progression was not observed in any of the patients, and recurrence was observed only in two (11.1%) patients, in the current study. BCG was started again in these patients and no relapses were detected during the 2 years follow-up. The results of the current bladder cancer studies including patients below 40 years old are shown in **Table 2** (15, 16, 22-24).

In their study, Wang ZH et al. compared young versus elderly patients with bladder tumors, and they reported that the pathological stages were lower in patients below 20 years old (22). Garcia et al. (6) reported 75% of young patients with bladder tumors below 40 years old had grade I tumors, Fine et al. (23) emphasized 73% of the patients with bladder tumor below 20 years old had low grade urothelial carcinoma. In addition, Wen YC et al. noted that the patients younger than 40 years old with bladder carcinoma had low-stage and low grade tumors

(25). The authors stated that the survival rates of patients with invasive bladder cancer were no worse than patients with superficial urinary bladder carcinoma, in younger ages. Stanton et al. observed that non-invasive papillary carcinomas were usually detected in younger patients and had perfect prognosis (26). Nevertheless a small subset of young patients might present with HG invasive urothelial carcinomas with poor clinical outcomes.

Comperat et al. reported the results of clinicopathological data of 152 patients less than 40 years with bladder carcinoma. In their study, the authors emphasized that the histological grade of the tumors was the most important prognostic factor along with the stage. Multifocality was determined as one of the strong predictive factors of the recurrence. The majority of their patients had low grade lesions (PUNLMPs and pTa) similar to present study (27). Huang et al. showed that bladder transitional cell carcinomas had low grade, well prognosis and non-

**Table 2.** Studies including younger patients with bladder tumors.

	n	Grade (%)	Stage (%)	Recurrence (%)	Progression (%)
<b>Fine et al.</b> <sup>(26)</sup>	23	Papilloma, (8.6%) PUNLMP, (43.4%) Low Grade PUC, (34.7%) High Grade PUC, (13.1%)	Ta, (47.8%)	0	0
<b>Lerena et al.</b> <sup>(27)</sup>	6	PUC, (50%) High Grade UC, (50%)	Ta, (100%)	0	0
<b>Benson et al.</b> <sup>(19)</sup>	12	PUNLMP + Low Grade PUC, (100%)	Non-invasive, (100)	8.3	0
<b>Wang ZH et al.</b> <sup>(25)</sup>	82	PUNLMP, (%21.9) Low Grade PUC, (64.6%) High Grade PUC, (13.4%)	Ta, (24.3%) T1, (60.9%) T2, (13.4%)	23.1	3
<b>Yossepowitch and Dalbagni</b> <sup>(18)</sup>	74	Low Grade PUC, (48.6%) High Grade PUC, (51.3%)	Ta, (43.2%) T1, (35.1%) T2, (13.5%) T3-4, (4.05%) Tis, (4.05%)	38.7	16
<b>Our Results</b>	19	Papilloma, (10.5%) PUNLMP, (36.8%) Low Grade PUC, (42.1%) High Grade PUC, (10.5%)	Benign papilloma, (10.5%) Ta, (78.9%) T1, (10.5%)	10.5	0

n: number of patients, PUC: Papillary Urothelial Carcinoma  
PUNLMP: Papillary Urothelial Neoplasms of Low Malignant Potential

invasive characteristic in childhood. Moreover, these tumors were extremely rare with less aggressive behavior in the pediatric population (28). In the current study, a 12 years old boy had papilloma and excellent prognosis without recurrence.

The NMP-22 bladder control test is the first tumor marker that has been approved by FDA in the diagnosis of bladder tumor and in evaluation of recurrence after the surgery (8). In the study reported by Hwa Sub Choi et al., it was reported that NMP-22 test was more practical and highly sensitive in diagnosis of low grade bladder tumors than the invasive or high grade tumors (24). Conversely, in the present study, the NMP-22 test was positive only in 2 (10.5%) patients who had relapses with T1 pathology.

There are certain limitations in the current study. The study has retrospective nature and does not involve any sort of gene expression. However in the immunohistochemical study by Linn et al., p53 gene expression was found higher in bladder tumors with younger patients (29). In addition, Migaldi et al. stated that cycline-dependent kinase and MIB-1 (Proliferative activity) levels could play a role on recurrence risk in younger patients (20).

**Conclusions**

Bladder cancer is a rare disease below 35 years old patients. According to the related literature and the clinical results of the current study, urinary bladder tumors appear as low grade and with better prognosis in younger ages. It is uncommon to observe more aggressive bladder tumors in this age group. However, further studies are necessary to determine the prognosis of high grade tumors below 35 years old patients.

**Conflicts of Interest**

The authors have nothing to disclose.

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