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Original Article – Pediatric Urology

Low Grade Urothelial Bladder Neoplasms in Pure Pediatric Population and Long-Term Follow-up Data

Pediatrik Popülasyonda Düşük Dereceli Ürotelyal Mesane Neoplazmaları ve Uzun Dönem Takip Verileri

Short Title: Low-Grade Urothelial Neoplasms in Pediatric Bladder (Pediatrik Mesanede Düşük Dereceli Ürotelyal Neoplazmlar)

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Abstract

Objective: Urothelial carcinomas (UC) of the bladder in the pediatric population are rare and differ from adult papillary neoplasms in terms of clinical, pathological outcomes, and prognoses. Therefore, standardized recommendations have not been clearly defined for their management. In this study, we aimed to report our experience and long-term follow-up data with low-grade urothelial bladder neoplasms in pediatric patients.

Materials and Methods: The data of patients treated for bladder tumors in two tertiary centers between December 2018 and December 2024 were analyzed retrospectively. Patients who were younger than 18 years of age at the time of diagnosis and whose pathology was reported as UC were included in the study. Transurethral resection of the bladder tumors was carried out on all patients. Age, gender, presentation symptoms, tobacco use or exposure, imaging method, number of tumors, tumor size, histological findings, hospitalization time, complications, tumor recurrence, and follow-up data were examined.

Results: Four female and three male patients were included in the study. The mean age of the patients was 14.8 ± 2.1 (12–17) years. The most common symptom was hematuria. Mean tumor size was 20.5 ± 9.8 (14–40) mm, and all were low-grade. No recurrence was detected at a mean of 58 ± 13.8 (44–76) months after resection.

Conclusion: Urothelial carcinoma of the bladder is rare in the pediatric population. These neoplasms are usually low grade, and recurrence is rare. The most common recurrences are seen in the first year. Strict follow-up is essential in this period. Less invasive tools can be used for follow-up after the first year on low-grade neoplasms.
Keywords: adolescent, bladder tumor, pediatric, transurethral resection, urothelial carcinoma

Özet

Amaç: Pediatrik popülasyonda mesanenin ürotelyal kanserleri (UK) nadirdir ve klinik, patolojik sonuçlar ve prognoz açısından erişkin papiller neoplazmlarından farklıdır. Bu nedenle UK yönetiminde standart öneriler net bir şekilde tanımlanmamıştır. Bu çalışmada, pediatrik hastalarda düşük dereceli ürotelyal mesane neoplazmları ile ilgili deneyimimizi ve uzun süreli takip verilerimizi paylaşmayı amaçladık.

Gereçler ve Yöntemler: Aralık 2018 ile Aralık 2024 arasında iki üçüncü basamak hastanede mesane tümörü nedeniyle tedavi edilen hastaların verileri retrospektif olarak incelendi. Tanı sırasında 18 yaşından küçük olan ve patolojisi UK olarak raporlanan hastalar çalışmaya dahil edildi. Tüm hastalara mesane tümörlerinin transüretral rezeksiyonu yapıldı. Yaş, cinsiyet, başvuru semptomu, tütün kullanımı veya maruziyeti, görüntüleme yöntemi, tümör sayısı, tümör boyutu, histolojik bulgular, hastanede kalış süresi, komplikasyonlar, tümör nüksü ve takip verileri incelendi.

Bulgular: Çalışmaya dört kız ve üç erkek hasta dahil edildi. Hastaların ortalama yaşı 14.8 ± 2.1 (12-17) yıldı. En sık görülen başvuru semptomu hematüriydi. Ortalama tümör boyutu 20.5 ± 9.8 (14-40) mm idi ve hepsi düşük dereceliydi. Rezeksiyondan ortalama 58 ± 13.8 (44-76) ay sonra hiçbir hastada nüks izlenmedi.

Sonuç: Ürotelyal mesane kanseri pediatrik popülasyonda nadir görülür. Bu neoplazmalar genellikle düşük derecelidir ve nüks ihtimali düşüktür. En sık nüksler birinci yılda görülür. Bu dönemde sık takip gereklidir. Düşük dereceli neoplazmalarda birinci yıldan sonra takip için daha az invaziv araçlar kullanılabilir.
Anahtar kelimeler: adölesan, mesane tümörü, pediatrik, transüretral rezeksiyon, ürotelyal karsinom

Introduction

Urothelial papillary neoplasms of the bladder in children and adolescents are rare and differ from adult papillary neoplasms in terms of clinical, histological, and pathological outcomes and prognoses [1,2]. While 0.4% of urothelial carcinomas (UC) are observed in patients under 20 years of age, only 0.03% are witnessed in patients under 16 years of age [1].

The most common symptom at the time of diagnosis is hematuria. Dysuria, suprapubic pain, frequency, and obstructive symptoms are other less common symptoms [1]. Bladder tumors in the pediatric population are commonly detected by urinary system ultrasound (USG) [1,3]. A cystoscopy should be performed under general anesthesia for definitive diagnosis and treatment if a bladder tumor is suspected due to the patient's medical history and radiological imaging [4].

Urothelial carcinomas usually tend to be low grade and present a lower incidence of invasiveness in children and adolescents [2,5]. According to a World Health Organization

(WHO) classification in 2004, approximately 3% of pediatric cases are high-grade diseases, while most cases are papillary urothelial neoplasms of low malignant potential (PUNLMP) [1,6]. Therefore, the incidence and recurrence rates of invasive tumors diverge from those of adults. There is also a higher disease-free survival rate in pediatric cases [2,7,8]. The recurrence rate ranges from 8% to 15%, and more than two-thirds of recurrences occur in the first year [1,3,4,8].

Urothelial carcinomas are rare in the pediatric population, so standardized recommendations have not been clearly defined for their management. Although some authors state that the adult follow-up protocol may be preferred, uncertainty remains in the management of pediatric bladder UC, which differs significantly from adults in terms of clinical, histological, and prognosis [3,4].

In this study, we report our experience and long-term follow-up data with low-grade urothelial bladder neoplasms in pediatric patients.

Materials and Methods

Patients

The data of patients treated for bladder tumors in two tertiary centers between December 2018 and December 2024 were analyzed retrospectively. Four female and three male patients were included who were younger than 18 years of age at the time of diagnosis whose pathology was reported as a urothelial carcinoma, according to the 2004 WHO grading system (papilloma, PUNLMP, or low-grade urothelial neoplasm). The study excluded one patient with a papilloma and unclear follow-up data, as well as a five-year-old male patient whose pathology was reported as an inflammatory myofibroblastic tumor.

Urinary ultrasounds were used as the first imaging method before treatment in all patients. A computed tomography was applied in two patients with tumor sizes of 25 mm and 40 mm and in one patient with a hematoma in the bladder.

Age, gender, presentation symptoms, tobacco use or exposure, number of tumors, tumor size, histological findings, hospitalization time, complications, tumor recurrence, and follow-up data were examined.

Surgery and Follow-up

The patients were prepared for a cystoscopy, which was performed under general anesthesia in the lithotomy position. Cystoscopies were performed using a 9.5 Fr 13 cm pediatric cystoscope in two prepubertal patients and a 17 Fr rigid cystoscope in five adolescent patients with an appropriate urethral caliber. The transurethral resection of bladder tumors (TURB) was conducted using a 9 Fr 12 cm monopolar pediatric resectoscope in two prepubertal patients and a 24 Fr bipolar resectoscope in five adolescent patients with an appropriate urethral caliber.

After resection, a 10 Fr Foley catheter was inserted in two prepubertal patients, and an 18 Fr three-way Foley catheter was inserted in five adolescent patients. In patients without macroscopic hematurias, the catheter was removed on the first to third postoperative days, and the patients were discharged. In the second postoperative week, the patients were called for a pathology.

For recurrence control, a urinanalysis, urinary USG, and cystoscopy were performed postoperatively at the third, sixth, and 12th months. Subsequently, urinanalyses and ultrasounds were performed every six months.

Statistical Analysis

The SPSS, v.23.0 statistical software (SPSS, Inc., Chicago, IL, USA) package program was utilized for statistical analysis. Descriptive statistical analyses were assessed by mean, standard deviation, and minimum and maximum values. Hospitalization time was expressed as the median value due to the standard deviation.

Ethics and Consent to Participate

All procedures performed in this study involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Consent, according to the Helsinki Declaration, was taken from the Necmettin Erbakan University Faculty of Medicine Ethics Committee before the study (No: 2022/3711). Consent to participate was obtained from all parents before the study.

Results

Four female and three male patients were included in the study. The mean age of the patients was 14.8 ± 2.1 (12–17) years. The presenting symptom was painless hematuria in five (71.4%) patients, dysuria in one (14.3%) patient, and suprapubic pain in one (14.3%) patient. Both active smoking and passive tobacco exposure were present in three (42.8%) patients. In other patients, there was no exposure either way **(Table 1, Table 2)**. No lymph nodes or distant metastases were detected in three patients with preoperative computed tomography **(Figure 1)**.

While six (85.7%) patients had solitary papillary tumors, one patient with a total tumor diameter of 40 mm had three papillary tumors. The mean tumor size was 20.5 ± 9.8 (14–40) mm. According to the WHO classification (2004), papillomas were detected in two (28.6%) patients, PUNLMP in three (42.8%) patients, and non-invasive low-grade UC in two (28.6%) patients **(Table 1, Table 2)**.

Patients were discharged on a median of 3 (2–3) days without complications. Intracavitary instillations were not performed on any patients. No recurrence was detected in patients at a mean of 58 ± 13.8 (44–76) months after their resections **(Table 2)**.

Discussion

Urothelial bladder carcinomas are very rare in pediatric and adolescent groups, compared to adults. Although these two centers are tertiary referral centers in the region, only seven children were operated on for bladder UC in six years. All these patients had low-grade UC, similar to the literature. In addition, no recurrence was found in these patients during the long-term follow-up period. Most patients in our study had PUNLMP, which differed from low-grade UC, with minimal or no cytological atypia.

Most articles about pediatric bladder UC, including follow-up data in the literature, also include young adult patients. To the best of our knowledge, the largest pediatric series includes fewer than 20 patients [9]. According to the literature, approximately less than 5% of urothelial carcinomas in the pediatric group are high-grade tumors or have submucosal invasion [4,10]. In our study, most tumors were PUNLMP or low-grade UC, and no high-grade tumors were detected. Tumor genetics are thought to be the reason UCs have a benign course in the pediatric population, unlike adults. Wild et al. evaluated patients under 19 years of age. They stated that genetic changes such as FGFR 3 mutation, chromosome 9 alteration, aneuploidy, and TP53 mutation—high-grade tumors that are common in adults— are very rare in pediatric patients.

Therefore, it may cause differences in tumor biology [10]. In addition, genetic changes, such as low microsatellite instability and low expression of MIB-1, a proliferation index, have been associated with a lower grade and noninvasive course of pediatric Ucs [11,12]. The common hypothesis of different genetic studies is that pediatric UC has greater "genetic stability" than adult UC [13]. A genetically stable tumor that is less biologically aggressive may lead to less invasion and a lower-grade benign course of the disease.

Tobacco use is a well-known risk factor for adult bladder neoplasms. It facilitates tumorigenesis by causing DNA methylation in genes related to bladder tumors [14,15]. Nevertheless, in the current literature, smoking is not considered an exact risk factor for pediatric bladder tumors. However, it has been stated that the age of smoking initiation in children has been decreasing [16]. In our study, 42.8% of the patients were smokers. Smoking might also be regarded as a risk factor in the pediatric population. To reduce smoking-related health problems, such as bladder tumors, national and international policies regarding the prevention and cessation of smoking, especially in children and adolescents, should be carefully determined and followed.

The most common presenting symptom in our study, similar to the literature on pediatric UCs, is painless hematuria [1,3,4,8]. However, unlike in adults, hematuria in children rarely indicates an underlying malignancy. The most common etiological factors of hematuria in children are infection, glomerulonephritis, and hypercalciuria [17]. Although bladder tumors are a rare etiological factor, they should be considered in the differential diagnosis of recurrent hematuria in the pediatric population. Therefore, urinanalyses and urinary ultrasounds are essential tools for the diagnosis of bladder tumors in children with recurrent and/or resistant hematuria. In addition, a urine microscopy and the evaluation of red cell morphology may aid diagnoses. Isomorphic blood cells may suggest that hematuria has bladder-related origins rather than glomerular or tubular origins. Bladder USG has a higher sensitivity in children and adolescents than adults due to its thinner abdominal fat and muscle layer [3]. In the present study, all tumors were detected with USG. Subsequently, the diagnosis was confirmed by a cystoscopy.

The transurethral resection of bladder tumors is an essential procedure for the diagnosis and treatment of bladder neoplasms [18]. A complete resection with clear negative margins and obtained muscularis propria will lead to a quality pathological evaluation and, therefore, more accurate disease management [19]. In our study, complete TURB was performed with negative margins, and muscularis propria was obtained in all patients. We did not observe complications

in our patients. No residual tumors were detected in the long-term follow-up. Unlike adults, transurethral resections, especially in prepubertal patients, involve technical difficulties, such as the narrow urethral caliber and lack of drainage channels in the resectoscope. The narrow sheath of the resectoscope for the removal of resected materials is another challenging issue, especially in male patients. To overcome the drainage problem, we placed a feeding catheter into the urethra during resectioning in a prepubertal female patient.

Uncertainty related to follow-up remains [20]. The European Association of Urology (EAU) pediatric urology guidelines state that the adult follow-up protocol could be used for bladder UC follow-up in the pediatric patient group [18]. Conversely, some authors advocate that a less aggressive follow-up protocol could be applied in pediatric patients because pediatric UC has a lower recurrence rate than adults [9,21]. In addition, a cystoscopy is the gold standard for diagnosis; however, the use of a cystoscopy in follow-up is also controversial in pediatric patients [22]. It has disadvantages, such as being an invasive procedure and requiring anesthesia. Urinary cytology has high sensitivity (70%–80%) in high-grade UC, although sensitivity decreases to 6%–38% in low-grade tumors [23,24]. Because pediatric UCs on the bladder are usually low-grade tumors, cytology is far from routine [21,25]. The use of tomography in follow-ups is limited because of ionizing radiation [26]. Ultrasonography is a highly sensitive and non-invasive tool in diagnosing pediatric bladder tumors and is the most frequently used tool in follow-up [22].

In this series, we chose to perform a stricter follow-up. A cystoscopy, USG, and urinalysis were performed postoperatively at the third, sixth, and 12th months in the first year when recurrences were most commonly witnessed [22]. Since high-grade and invasive UC was not detected in our patients after the first year, we performed a urinalysis and USG every six months to protect the patients from anesthesia. We did not prefer cytology in the follow-up due to its low sensitivity. With this follow-up protocol, we did not observe recurring tumors.

The main limitation of our study was its few patients. Given the very low incidence of urothelium bladder neoplasms originating in the pediatric population, the current limitation applies to most studies in the literature. Another limitation is that patients' family history of bladder tumors is not adequately questioned. Genetic predisposition is not a definitive risk factor for pediatric UC and should be studied further. Finally, genetic changes, such as FGFR 3 mutation, chromosome 9 alteration, and TP53 mutation, which are frequently observed in bladder tumors, have not been investigated. The genetic origins of pediatric UC have not been clearly defined, and there is insufficient data in the literature on the suitability of genetic tests

for clinical use. Despite these limitations, the present study comprises purely pediatric UC patients with long-term follow-up data. We are confident that the data we share on the isolated pediatric population will contribute to the management approach of very rare bladder UC.

Conclusion

Urothelial carcinoma of the bladder is rare in the pediatric population. The most common symptom is hematuria. Cystoscopy and pathological evaluations of the tumor are crucial for diagnosis. These neoplasms are usually low grade, and recurrence is rare. The most common recurrences occur in the first year, and strict follow-up is essential in this period. Less invasive tools might be used for follow-up after the first year on low-grade neoplasms.

Ethics Committee Approval: Ethical approval for this study was obtained from Necmettin Erbakan University Faculty of Medicine Ethics Committee before the study (Ethics committee approval number: 2022/3711).
Informed Consent: An informed consent was obtained from all the patients.
Publication: The results of the study were not published in full or in part in form of abstracts.
Peer-review: Externally peer-reviewed.
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Table 1: Patients demographic and clinical data

	Age (years)	Gender (f/m)	Presenting Symptom	Tobacco exposure or use	Lymph node or distant metastases	Number of tumors (n)	Tumor size (mm)	Tumor stage	Tumor grade	Hospitalisation time (day)	Complication (Clavien)	Recurrence (n)	Follow-up (months)
Patient 1	12	F	Haematuria	-	-	1	15		Papilloma	3	-	-	76
Patient 2	13	M	Haematuria	-	NA	1	20		PUNLMP	2	-	-	64
Patient 3	14	F	Dysuria	+	-	1	25		PUNLMP	3	-	-	58
Patient 4	14	M	Haematuria	-	NA	1	14	Ta	Low Grade	2	-	-	44
Patient 5	17	F	Haematuria	+	-	3	40		PUNLMP	3	-	-	74
Patient 6	17	F	Supra pubic Pain	-	NA	1	10		Papilloma	1	-	-	46
Patient 7	17	M	Haematuria	+	NA	1	20	Ta	Low Grade	3	-	-	44

PUNLMP: papillary urothelial neoplasms of low malignant potential

Table 2: Descriptive statistical analyses of the patients

Age (years)	14.8±2.1 (12-17)
Gender (f/m)	4 female, 3 male
Presenting symptom (n/%)	Painless hematuria in 5 patients (71.4%) Dysuria in 1 patient (14.3%) Suprapubic pain in 1 patient (14.3%)
Tobacco exposure or use (n/%)	3 (42.8%)
Number of tumors (n/%)	6 (85.7%) solitary papillary tumors 1 (14.3%) multiple papillary tumors
Tumor size (mm)	20.5±9.8 (14-40)
Tumor stage (n/%)	2 Ta (28.6%)
Tumor grade (n/%)	2 Papilloma (28.6%) 3 PUNLMP (42.8%) 2 Low-grade (28.6%)
Hospitalisation time (day)	3 (2-3)
Complication (Clavien)	None
Recurrence (n)	None
Follow-up (months)	58±13.8 (44-76)

PUNLMP: papillary urothelial neoplasms of low malignant potential

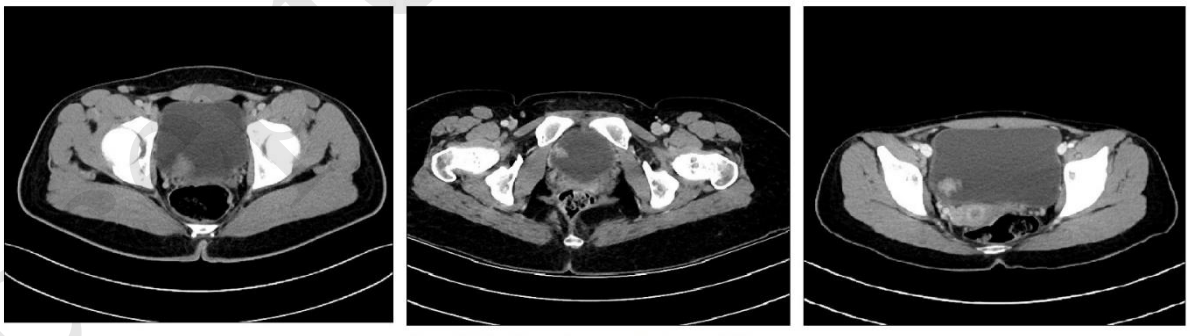

Figure 1: Patients Preoperative Computed Tomography Images

Figure 1. Patients preoperative computed tomography images