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Original Article

Evaluation of renal tumors in children

Çocukluk çağı böbrek tümörlerinin değerlendirilmesi

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ABSTRACT

Objective: Renal tumors are not uncommon in children. In this study, we aimed to evaluate the clinical and pathological features of renal tumors in children.

Material and methods: Between January 2008 and December 2017, the records of children with renal tumors in our institution were retrospectively analyzed. Data collected were composed of demographic and clinical characteristics including gender, age at time of diagnosis, symptoms, laterality of the tumor and pathological evaluation.

Results: A total of 48 children with renal tumor (28 males and 20 females) were included in the study. They were diagnosed at mean age of 53.26±46.64 months (range: 1-192) and the mean follow-up period was 73.45±48.92 months (range: 6-120). The most common symptom was a lump or mass in the area of the kidneys (45.8%), abdominal pain and hematuria (14.6%). Four patients (8.3%) were diagnosed at antenatal period. 68.8% of the children had Wilms tumor and the major histological groups of non-Wilms renal tumors were renal cell carcinoma (12.5%), congenital mesoblastic nephroma (10.4%) and angiomyolipoma (4.2%). 10.4% of the children had bilateral tumors and one patients had Wilms tumor with horseshoe kidney. 87.5% of the children were treated with surgery and of those 7 (14.5%) underwent nephron-sparing surgery. The patients had chemotherapy and radiotherapy (83.3% and 41.7%, respectively). Seven patients (14.6%) died during follow-up.

Conclusion: Wilms tumor is the most common pediatric renal neoplasm. On the other hand, we showed that considerable number of children with renal tumors had non-Wilms tumors including renal cell carcinoma, congenital mesoblastic nephroma and angiomyolipoma.

Keywords: Children; non-Wilms tumor; renal tumor; Wilms tumor.

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ÖZ

Amaç: Çocukluk çağı böbrek tümörleri nadir değildir. Bu çalışmada, çocukluk çağı böbrek tümörlerinin klinik ve patolojik özelliklerini değerlendirmeyi amaçladık.

Gereç ve yöntemler: Merkezimizde Ocak 2008 ve Aralık 2017 yılları arasında böbrek tümörü tanısı alan çocukların kayıtları retrospektif olarak değerlendirildi. Demografik ve klinik veriler (cinsiyet, tanı anındaki yaş, semptomlar, tümörün yönü ve patolojisi) analiz edildi.

Bulgular: Çalışmaya böbrek tümörü olan 48 çocuk (28 erkek ve 20 kız) dahil edildi. Tanı anındaki yaş ortalama 53,26±46,64 ay (1-192 ay) ve ortalama takip süreleri 73,45±48,92 aydı (6-120 ay). En sık gözlenen semptomlar karında kitle (%45,8), ağrı ve hematüriydi (%14,6). Dört hasta antenatal dönemde tanı aldı (%8,3). Hastaların %68,8'i Wilms tümörüydü. non-Wilms tümörler renal hücreli kanser (%12,5), konjenital mezoblastik lenfoma (%10,4) ve anjiyomyolipomdu (%4,2). Hastaların %10,4'ü bilateraldi ve bir hastada atnalı böbrekte Wilms tümörü saptandı. Hastaların %87,5'ine cerrahi uygulandı ve 7'sine (%14,5) nefron koruyucu cerrahi yapıldı. Hastaların %83,3'üne kemoterapi ve %41,7'sine radyoterapi uygulandı. Takiplerde 7 hasta (%14,6) eksitus oldu.

Sonuç: Çocukluk çağında en sık görülen böbrek tümörü Wilms tümörüdür. Diğer taraftan hastaların kayda değer bir kısmında non-Wilms tümör (renal hücreli kanser, konjenital mezoblastik nefroma ve anjiyomyolipom) gözlenmektedir.

Anahtar Kelimeler: Çocuklar; non-Wilms tümör; böbrek tümörü; Wilms tümörü.

Introduction

Nearly 6-7% of pediatric cancers consist of renal tumors, and 90% of them are Wilms tumors (WT).[1] Its annual incidence in Europe is 1/100,000 (100 new cases every year), and in the USA its incidence is 8,1/1.000,000 (500 new cases every year).[2,3] Nowadays two different protocols have been applied in the treatment of WT.[4] The main difference between these two protocols is related to whether staging is done with or without previous application of preoperative chemotherapy. In Europe most of the patients are given chemotherapy before surgery based on *Société Internationale d'Oncologie Pediatrique* (SIOP) WT 2001 Trial protocol, then the patients undergo nephrectomy, and staging is performed in consideration of the results of histopathology report. In Northern America according to National Wilms' Tumour Study Group/ Children's Oncology Group (NWTSG/COG) protocol, priorly surgeries are performed for staging, then chemotherapy is administered. In both protocols for all stages overall survival is above 90 percent.[5] Median age at diagnosis of WT is 3 years, while patients accompanied by bilateral, and congenital syndromes are diagnosed at an early age.

During childhood, renal tumors apart from WT are less frequently seen.[6] In children, the most frequently observed non-Wilms tumors (non-WT) include renal cell carcinoma (RCC), clear cell sarcoma of the kidney (CCSK), malignant rhabdoid tumor of the kidney (MRT), congenital mesoblastic nephroma (CMN), primitive neuroectodermal tumor (PNET), and renal lymphoma. Non-WT group seen in childhood has a heterogenous structure, and its tumoral behaviour can not be fully understood because of its rarity. Besides, their prognosis is worse than that of WT. In this study, demographic, and clinical characteristics of the patients treated, and followed up with the diagnosis of pediatric renal tumors (WT, and non-WT) in our center, and their treatment outcomes were evaluated.

Material and methods

A total of 48 pediatric patients who were followed up with the diagnosis of renal tumor by Mersin University, Division of Pediatric Oncology between the years 2008, and 2017 were included in the study, and their medical files were analyzed retrospectively. The study was realized in compliance with the principles of World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013). The patients with diagnosis based on histopathological analysis of trucut biopsy, nephron-sparing surgery (NSS) or nephrectomy specimens, and complete file records were included in the study. From patient files, the patients' gender, and ages, ages at the time of diagnosis, admission symptoms, laterality of the tumor (right-, and left-sided, bilateral), histopathology, stage of the tumor, and treatment outcomes were analyzed, and recorded. The patients without histopathological diagnosis, the patients lost to follow-up, and those with missing data were not included in the study.

Statistical analysis

Data of the patients were evaluated using descriptive statistical methods, and defined as mean±standard deviation (SD). For statistical evaluation *t*-test, and chi-square test were used. Kaplan-Meier curves were constructed to estimate progression-free, and overall survival rates. The time elapsed from the time of diagnosis to the disease progression or all-cause mortality was defined as progression-free survival time, while overall survival time was defined as the time passed between the establishment of diagnosis to the commencement of the study or death of the patient. $P<0.05$ was accepted as statistically significant threshold value.

Results

A total of 48 children [28 boys; 58.3%, and 20 girls; 41.7%] were included in the study Mean age at the time of diagnosis, and mean follow-up period were 53.26±46.64 months (range, 1-192 months), and 73.45±48.92 months (range, 6-120 months), respectively. Histopathologically the patients were diagnosed as WT (n=33; 68.8%), and non-WT (n=15; 31.2%) (Table 1). WT, and non-WT did not differ as for gender of the patients (p=0.636). Median age of the patients with WT was statistically significantly lower than that of non-WT patients (39.45±20.07 vs. 83.63±70.32 months, p=0.03). Laterality of the tumor did not differ between WT, and non-WT patients (p=0.654). Cases with bilateral renal cancer were either WT (n=4) or malignant epithelioid renal angiomyolipoma secondary to tuberosclerosis (n=1). Horseshoe kidney was detected in one case with WT (Table 2). In one case with RCC 6:11 translocation, and in another case with RCC Xp11 mutation were found.

The most frequently observed symptoms were abdominal distension, pain, and hematuria (Table 3). All families of the patients whose ultrasonographic diagnosis of CMN was made during antenatal period were informed that their babies had mass lesions originating from kidneys. In one of the patients with histopathological diagnosis of CMN, cellular variant of CMN was detected. Following excision of the mass, disease progression was detected and chemotherapy resulted in suc-

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Table 1. Tumor histopathology

Tumor types	n	%
Wilms tumor	33	68.8
Renal cell carcinoma	6	12.5
Congenital mesoblastic nephroma	5	10.4
Angiomyolipoma	1	2.1
Malignant epithelioid angiomyolipoma	1	2.1
Intrarenal neuroblastoma	1	2.1
Primitive neuroectodermal tumor	1	2.1

Table 2. Comorbid diseases accompanying patients with renal tumors

	n	%
Abscence of additional pathology	36	75
Hydrocele	3	6.1
Hypospadias	2	4.2
Tuberosclerosis	1	2.1
Horseshoe kidney	1	2.1
Neurofibromatosis	1	2.1
Beckwith-Wiedemann syndrome	1	2.1
Hemihypertrophy	1	2.1
Ureteral duplication + Hemihypertrophy	1	2.1
Idiopathic thrombocytopenic purpura	1	2.1

Table 3. Admission complaints of the patients

Symptoms	n	%
Abdominal mass	22	45.8
Abdominal pain, hematuria	7	14.6
Abdominal pain	5	10.4
Antenatal mass	4	8.3
Constipation, abdominal pain	3	6.2
Fever, weight loss, abdominal pain	3	6.2
Abdominal pain, hypertension	2	4.2
Enuresis	1	2.1
Incidental	1	2.1

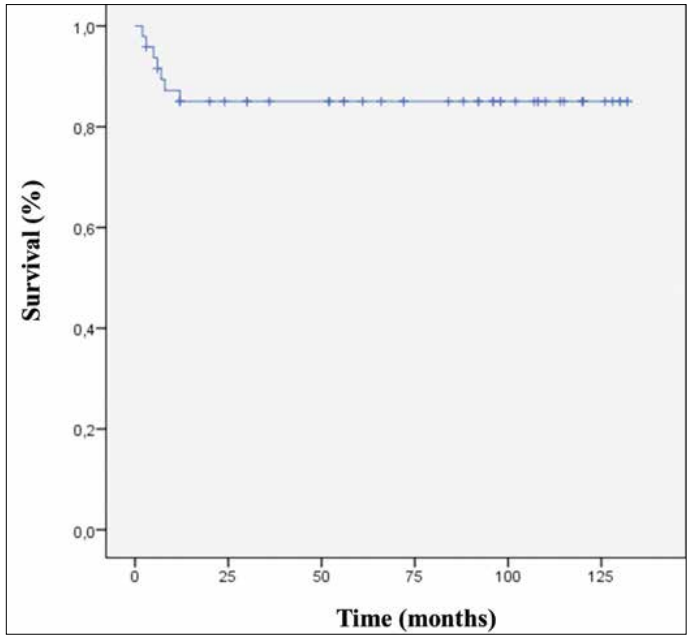

Figure 1. Kaplan-Meier curve of progression-free survival

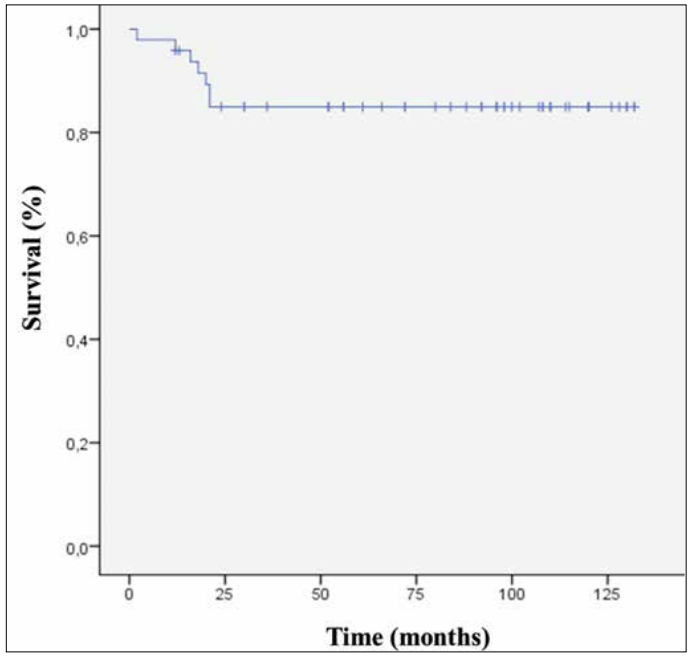

Figure 2. Kaplan-Meier curve of overall survival

cessful outcomes. The other patients underwent surgical treatments, and histopathologically they received the diagnosis of classical variant CMN. In these cases only surgical treatment sufficed, and any disease recurrence was not observed.

Distribution of all patients according to stages were as follows: Stages I (n=2; 4.3%), II (n=14; 30.4%), III (n=10; 21.7%), and IV (n=4; 30.4%). All cases diagnosed as WT were treated according to 2001 SIOP WT protocol, and 28 (70%) patients received radiotherapy. In three (6.5%) patients diagnosed as bilateral WT, radical nephrectomy was applied for the kidney with the largest mass lesion, while the contralateral kidney was treated with NSS. Seven (14.5%) cases with unilateral renal tumors underwent NSS. In all cases (WT and non-WT) 5-year progression-free survival rate was found as 85 percent (Figure 1). One year-overall survival rate was 95.8%, and after 5 years

of follow-up it decreased to 84.9 percent (Figure 2). During follow-up period 3 patients with WT, and 4 patients who individually received the diagnosis of malignant epithelioid angiomyolipoma, RCC, PNET, and intrarenal neuroblastoma lost their lives.

Discussion

Wilms tumor, in other terms, nephroblastoma is the most frequently seen solid renal tumor during childhood.[1,5] In a retrospective screening of medical files we performed in accordance with literature, we observed that nearly 70% of our cases received the diagnosis of WT, followed by RCC (12.5%), and CMN (10.4%). In 5-10% of the children with diagnosis of WT synchronous or metachronous bilateral tumors have been observed. In our study, all of bilateral tumors were synchronous tumors with a detection rate of 8.7% which was in accordance with the literature. Thanks to multidisciplinary, and multimodal treatments 5-year overall survival rates from 30%, and 75% in 1930s, and 1970s have nowadays climbed up to 90%.[7]

Contrary to adults, the most frequently observed symptoms in pediatric patients are abdominal mass, and swelling, followed by abdominal pain, hematuria, fever, and hypertension.[1,2] Also nearly half of our cases were brought into the hospital with the indication of abdominal mass, and in an important part of them one of symptoms of abdominal pain, hematuria, fever, constipation, weight loss, and hypertension were observed. All patients with histopathological diagnosis of CMN were detected during antenatal period.

Studies performed so far have demonstrated that majority of the pediatric renal tumors were diagnosed when they were younger than 5 years of age, and most of the cases diagnosed as WT were within the age range of 3-4 years.[5,8] Patients with bilateral WT, and those associated with congenital syndromes can be diagnosed at an early age. When we look at our series, WTs were diagnosed earlier than non-WTs. In our study, mean age of all cases was 53.26±46.64 months, while mean age of the cases with WT was 39.45±20.07 months. In a study performed by Miniati et al.[9] mean ages of the patients with WT, and non-WT were found to be 3.5±2.5, and 5.5±6.7 years, respectively, without any statistically significant difference between groups. On the other hand, in our study, age of WT patients at diagnosis was significantly lower than that of non-WT patients. Five to ten percent of the cases with WT may be accompanied by WAGR (WT, aniridia, genitourinary anomalies, and mental retardation), Denys-Drash syndrome, and Beckwith-Wiedemann syndrome.[5,8] In all of our cases, syndromic characteristics were present, while only 25% of them had additional pathologies.

Since non-WT seen in pediatric patients belongs to a heterogenous group, they have different malignancy potentials, treatment responses, and mortality rates. In a study by Zhuge et al.[10] most frequently reported pediatric non-WT renal tumors were RCC, CCSK, and MRT. In a case series reported by Miniati et al.[9] from the USA, CMN ranked on top, followed by CCSK, intrarenal neuroblastoma, and RCC. In a study from South Africa, most frequently CCSK was reported followed by CMN, cystic papillary differentiated nephroblastoma, MRT, and RCC.[11] In our series, RCC was most frequently observed in this group, while none of our patients was diagnosed as CCSK or MRT. After RCC, most frequently CMN, and angiomyolipoma secondary to tuberosclerosis were observed.[12]

For the management of renal tumors of the pediatric age, different treatment modalities have been used in Europe, and in the USA.[5] Despite different treatment protocols, overall survival rates exceed 90%. In Europe preoperative chemotherapy is performed based on SIOP protocol. However in the USA firstly surgery, then chemotherapy are applied according to COG protocol. We applied 2001 SIOP WT protocol in all of our patients. In our patient group 5-year overall survival rate for pediatric WT, and non-WT renal tumors was found as 84.5%.

Nephron-sparing surgery was performed for 7 patients. NSS performed for adult renal tumors has acceptable rates of surgical morbidity, cancer control rates resembling those of radical nephrectomy, and a potential of sparing renal tissue.[13] These advantages have revived the application of NSS in pediatric renal tumors. SIOP-WT 2001 protocol approves application of NSS in non-infiltrative tumors of those localized in renal poles.[4] Still in AREN0534 protocol of COG, NSS is recommended for patients with bilateral WT or those with genetic predisposition to the development of bilateral WT.[14] In a retrospective study performed by Cost et al.[15] NSS was performed in 15 patients with unilateral WT, and compared with those with the same disease stage who had undergone radical nephrectomy. Renal functions had been better preserved in the NSS group. In another retrospective study 15 patients with bilateral WT had undergone NSS, and an overall 4-year survival rate of 85.56% was reported.[16] Cozzi et al.[17] investigated the effects of nephrectomy, and NSS, and demonstrated that both of them had favourable effects on preoperative renal dysfunction in children with unilateral renal tumors. In a systematic review performed by Vanden Berg et al.[18] the

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authors detected similar long-term oncological outcomes in pediatric patients with WT who had undergone NSS or radical nephrectomy.

Important limitations of our study were its retrospective design, and scarce number of patient population. Besides, pre-, and post-operative renal function test results of the patients who underwent NSS or nephrectomy were not compared. Therefore, the effects of the differences between these two diverse surgical modalities on variations in renal functions could not be demonstrated.

In conclusion, in our study, WT was the most frequently seen renal tumor in childhood. On the other hand, in a substantial number of the cases non-WT was detected. RCC, CMN, and angiomyolipoma constitute an important proportion of pediatric non-WT cases. In this age group, during antenatal examinations of children presenting with abdominal mass, and swelling, as an important issue, renal tumors should be kept in mind. We think that as is the case with non-WT group, studies which provide data related to different tumor types, their incidence rates, and treatment outcomes are needed.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Written informed consent was obtained from the parents of the patients who participated in this study.

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