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ARAŞTIRMA / RESEARCH

Effect of risk group on survival in non-Wilms' renal tumors in children

Çocuklarda Wilms tümörü dışındaki böbrek tümörlerinde risk grubunun sağkalıma etkisi

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Abstract

Purpose: The aim of this study was to evaluate tne effect of the risk group on the clinical features of the disease, treatment strategies and especially survival in children with Non-Wilms' renal tumors (NWRTs).

Materials and Methods: Patients diagnosed with NWRTs followed up and treated between January 2012 and January 2022 were included in the study (n=29; 16 boys and 13 girls). They were categorized into high- and low-risk groups based on their histological type. Patient records were reviewed retrospectively. Clinical characteristics, treatments, and outcomes of these patients were analyzed.

Results: The high-risk group comprised clear cell sarcoma (CCSK) (n=8, 27.6%), malignant rhabdoid tumor (MRT) (n=3, 10.3%), renal cell carcinoma (n=2, 6.9%), non-Hodgkin lymphoma (n=1, 3.4%), and primitive neuroectodermal tumor (PNET) (n=1, 4%). The low-risk group comprised congenital mesoblastic nephroma (CMN) (n=9, 31%), angiomyolipoma (n=4, 3.8%), and hemangioma (n=1, 3.4%). Five patients died due to disease progression (mortality rate, 17%), all of whom belonged to the high-risk group (three patients with MRT, one with CCSK, one with PNET). The 5-year survival rate was 72% for the high risk group and 100% for the low risk group.

Conclusion: Although low-risk tumors are associated with excellent outcomes, the outcomes vary in high-risk tumors. Physicians should be wary of high mortality rates in children with MRT, CCSK, and PNET, and should design multidisciplinary treatments for NWRTs.

Keywords: Non-Wilms' renal tumors, children, risk groups, survival

Öz

Amaç: Bu çalışmanın amacı Wilms tümörü dışındaki böbrek tümörleri (WDBT'leri) olan risk grubunun hastalığın klinik özelliklerini, tedavi stratejilerini ve özellikle sağkalımı etkilerini değerlendirmektir.3323

Gereç ve Yöntem: Ocak 2012 ile Ocak 2022 tarihleri arasında takip WDBT tanısı ile takip ve tedavi edilen hastalar çalışmaya dahil edildi (n=29; 16 erkek ve 13 kız). Hastalar, histolojik tiplerine göre yüksek ve düşük risk grubu olarak kategorize edildi. Tüm hastaların dosya kayıtları geriye dönük olarak incelendi. Hastaların klinik özellikleri, uygulanan tedaviler ve tedavi sonuçları analiz edildi.

Bulgular: Yüksek risk grubundaki hastalar; berrak hücreli sarkom (BHS) (n=8, %27,6), malign rabdoid tümör (MRT) (n=3, %10,3), renal hücreli karsinom (RHK) (n=2, %6,9), Hodgkin-dışı lenfoma (HDL) (n=1, %3,4), primitif nöroektodermal tümör (PNET) (n=1, %4) iken, düşük risk grubundaki hastalar; konjenital mezoblastik nefroma (KMN) (n=9, %31), anjiomiyolipom (n=4, %3,8) ve hemanjiom (n=1, %3,4) olarak saptandı. WDBT'li 29 hastadan 5'i progresif hastalık nedeniyle kaybedildi; ölüm oranı %17 idi (n=5) ve kaybedilen tüm hastalar yüksek risk grubunda idi (3 hasta MRT, 1 hasta BHS, 1 hasta PNET). 5 yıllık sağkalım oranı yüksek risk grubu için %72, düşük risk grubu için %100 olarak saptandı.

Sonuç: Düşük riskli tümörler, mükemmel sonuçlarla ilişkilendirilirken, yüksek riskli tümörler değişken bir sonuca sahiptir. MRT, BHS ve PNET'li çocuklarda yüksek ölüm oranlarına karşı dikkatli olmalı ve WDBT'ler için multidisipliner tedavi planları tasarlanmalıdır.

Anahtar kelimeler: Wilms tümörü dışındaki böbrek tümörleri, çocuklar, risk grupları, sağkalım

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INTRODUCTION

Approximately 7% of childhood malignancies originate from the kidneys. Wilms' tumors account for as high as 90% of renal tumors[1]. Conversely, non-Wilms' renal tumors (NWRTs) are rarely encountered in children; however, the majority of NWRT cases are associated with higher mortality than Wilms' tumors[2]. The behavior of NWRT is more difficult to understand, since they are a heterogeneous group of tumors and their low incidence rate renders conducting clinical research on them difficult[3]. NWRT comprises clear cell sarcoma of the kidney (CCSK), malignant rhabdoid tumor (MRT), congenital mesoblastic nephroma (CMN), tumors occurring outside the kidney (Ewing's sarcoma/ primitive neuroectodermal tumor [PNET], lymphoma, neuroblastoma), and benign tumors (angiomyolipoma, hemangioma)[2].

There are no accepted optimal follow-up and treatment plans for this rare and heterogeneous group of tumors. The treatment ranges from surgery alone to multimodal approaches including chemotherapy, radiotherapy, immunotherapy. Due to their rarity, there are very few reports of these tumors in the literature. While the majority of cystic renal tumors have a good prognosis, clinicians should be aware of aggressive tumors such as MRT. The present study aims to identify the clinical features, treatment strategies and survival according to risk groups in children with NWRT who are followed up and treated at our institution.

MATERIALS AND METHODS

The study was conducted in accordance with the tenets of the Helsinki Declaration, patient rights regulations and ethical guidelines. The ethics committee approval with the decision number 124 dated 22.07.2022 was obtained from Çukurova University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee.

Sample

Patients under the age of 18 years who were diagnosed with NWRT and followed up and treated at the Pediatric Oncology Clinic of Çukurova University Hospital between January 2012 and January 2022 were included in the study.

The patients were categorized into high- and low-risk groups according to their histological type. Three patients with angiomyolipoma, a benign tumor, were diagnosed by ultrasonography and computed tomography. All the other patients were diagnosed histopathologically, via tru-cut biopsy, nephron-sparing surgery, or nephrectomy. All specimens were evaluated by the same pathologist. The data were obtained from the pediatric oncology patient files and hospital computer records retrospectively. The clinical characteristics, symptoms at the time of admission, diagnostic methods, stages, histological diagnoses, risk groups, treatments, and treatment outcomes of all the patients were analyzed. Since this was a retrospective study, the patients with missing data in their records, who went to another healthcare center after diagnosis or during the treatment process, and who did not have a radiologically or histopathologically proven NWRT diagnosis were excluded from the study.

Treatment procedures

The management of patients with renal tumors was performed according to the Turkish Pediatric Oncology Group (TPOG) protocol, which is routinely used in Turkey[4]. The standard treatment for CMN was surgical resection without adjuvant treatment. Chemotherapy with or without radiotherapy was given to recurrent CMN cases with local or metastatic disease. Standard treatment of CCSK consists of initial radical nephrectomy followed by aggressive chemotherapeutic regimens. This treatment method for CCSK was consistent with the regimen used for unfavourable Wilms' tumor with anaplasia. Patients with MRT were also treated with regimens used for Wilms' tumor. Nephrectomy alone was performed in patients with a diagnosis of low-grade RCC such as stage I and II. In advanced stage and metastatic tumors, chemotherapy was applied in the style of Wilms' tumor.

Statistical analysis

The SPSS 22 (Statistical Package of Social Science) package program was used to statistically analyze the obtained data. Categorical variables (such as gender) were analyzed using the chi-square test and normally distributed numerical variables (mean ages of groups) were analyzed using the Student's t-test. Kaplan–Meier survival analysis was also performed to assess survival rates. A p-value of <0.05 was considered statistically significant.

RESULTS

Between January 2012 and January 2022, 143 pediatric patients were diagnosed with renal tumors in our clinic. Of these, 110 (76.9%) were diagnosed with Wilms' tumor and 33 (23.1%) with NWRTs. Four patients were excluded from the study because they did not meet the inclusion criteria. A total of 29 patients (16 boys and 13 girls) with NWRT were included in the study. The tumor types of the patients are shown in Table 1, and the clinical characteristics of the patients according to tumor type are presented in Table 2. Overall, 15 patients were diagnosed with CCSK, MRT, renal cell carcinoma (RCC), non-Hodgkin lymphoma (NHL), and PNET in the high-risk group, and 14 patients were diagnosed with CMN, angiomyolipoma, and hemangioma in the low-risk group.

Table 1. Prevalence of non-Wilms' renal tumors

Tumor type	n	%
Congenital mesoblastic nephroma	9	31
Clear cell sarcoma of the kidney	8	27.6
Angiomyolipoma	4	13.8
Malignant rhabdoid tumor	3	10.4
Renal cell carcinoma	2	6.9
Non-Hodgkin lymphoma	1	3.44
Primitive neuroectodermal tumor	1	3.44
Hemangioma	1	3.44
Total	29	100

Table 2. Clinical characteristics of the patients by diagnosis

Tumor type	CMN n=9	CCSK n=8	AML n=4	MRT n=3	RCC n=2	NHL n=1	PNET n=1	HEM n=1
Gender								
Boy	4	6	2	2	-	1	-	1
Girl	5	2	2	1	2	-	1	-
Age (month)								
(min-max)	1–15	14–50	84–165	3–62	144–196	163	200	60
Mean±SD	4±5	30±16	116±34	27±31	170±37	-	-	
Stage								
I	7	-	4	-	1	-	-	1
II	1	4	-	-	1	-	-	-
III	1	3	-	2	-	-	1	-
IV	-	1	-	1	-	1	-	-
Treatment								
SUR	9	8	-	3	2	-	1	1
CT	2	8	-	2	1	1	1	-
RT	-	5	-	2	-	-	-	-
mTOR inh	-	-	2	-	-	-	-	-
Outcome								
Alive	9	7	4	-	2	1	-	1
Died	-	1	0	3	-	-	1	-

CMN: congenital mesoblastic nephroma, CCSK: clear cell sarcoma of the kidney, AML: angiomyolipoma, MRT: malignant rhabdoid tumor, RCC: renal cell carcinoma, NHL: non-Hodgkin lymphoma, PNET: primitive neuroectodermal tumor, HEM: hemangioma, SD: standard deviation, SUR: surgery, CT: chemotherapy, RT: radiotherapy, mTOR inh: mammalian target of rapamycin (mTOR) inhibitor therapy.

The most common complaint was abdominal distension (n = 5), followed by abdominal pain (n = 4), hematuria (n = 4), abdominal mass (n = 4), and mass detected in the prenatal period (n = 2). Three of the patients with angiomyolipoma, and one with hemangioma were diagnosed through imaging studies. Three patients with angiomyolipoma, RCC, and NHL each were diagnosed via tru-cut biopsy. The other patients (n = 22) were diagnosed using excisional biopsy. Of the patients diagnosed through

imaging studies, the one diagnosed hemangioma underwent nephrectomy and mass excision, and the patient with progressive angiomyolipoma underwent tru-cut biopsy during follow-up for the histopathological confirmation of the diagnosis.

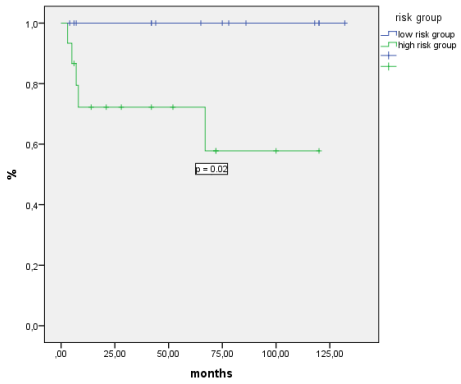

Figure 1. Overall survival rates of patients in the low-risk and high-risk groups

Except for the five patients diagnosed with angiomyolipoma and NHL, all other patients underwent surgery wherein mass excision was performed during nephrectomy. Two of the patients diagnosed with angiomyolipoma were followed up in the absence of any treatment, while the other two received mTOR inhibitors. Complete cure was achieved with chemotherapy alone in the patient diagnosed with NHL. Despite surgical excision of the mass during nephrectomy and administration of chemotherapy the patient with PNET died. Of the 29 patients with NWRTs, 3 patients diagnosed with MRT died due to disease progression and 1 patient with CCSK died due to relapse.

The mortality rate of NWRT was 17% (n = 5) and all the deceased patients belonged to the high-risk group (3 patients with MRT, 1 with CCSK, and 1 with PNET). Among the patients with CMN, two cases were diagnosed as classical type, two cases as mixed type, and the other five cases as cellular type. Disease progression was observed in 2 patients with cellular type CMN. These two patients also received chemotherapy after surgery. Complete cure was achieved in all the patients with CMN. The 5-year survival rate of the low-risk group was 100%. The overall survival rates of patients in the high- and low-risk groups are shown in Figure 1.

DISCUSSION

Although there have been several studies regarding Wilms' tumor, only a handful of studies regarding NWRT exists, which accounts for less than 20% of all renal tumors and less than 1% of pediatric cancers. The clinical characteristics and prognosis of these tumors vary depending on the diagnosis. Low-risk tumors are associated with excellent outcomes, while high-risk tumors have a poor prognosis[5].

In our center, 33% of renal tumors were NWRTs. The most common histopathological type of NWRT was CMN (31%), of which 90% were patients under 3 months of age. CMN is subdivided histologically into classical, mixed and cellular subtypes. The classic subtype is benign, but the mixed and cellular subtypes are thought to be associated with recurrent or metastatic disease[6]. In our series, the median age of the 9 patients diagnosed with CMN was 2 months. All the patients with CMN underwent mass excision by nephrectomy and complete cure was achieved in all. Chemotherapy was administered to the two patients with histologically cellular subtype who progressed after surgery. These two patients were Stages II and III CMN. Gooskens et al. showed in their review that the risk of recurrence is highest in Stage III disease at 23%, and that all these patients have a cellular subtype[7].

CCSK is the second most prevalent pediatric renal tumor (2%–5% of NWRTs) after Wilms' tumor[1]. Similar to Wilms' tumor, it is common in children aged 1–4 years and predominantly encountered in boys (ratio 2:1)[8]. In our series, the prevalence of CCSK was three times higher in boys and the age of incidence in patients was consistent with the literature.

Renal AML is the most prevalent benign renal tumor and tends to be more common in girls than boys, possibly due to estrogen effects[9-10]. The size of the tumors also tends to be larger in girls than in boys. AML can be seen in 50-75% of patients with tuberous sclerosis. Most angiomyolipoma cases are asymptomatic and usually do not require treatment.

Possible interventions include medical treatment with mammalian target of rapamycin (mTOR) inhibitor therapy, thermal ablation (radiofrequency ablation and cryotherapy), selective renal artery embolization, and surgical excision (total nephrectomy, partial nephron-sparing surgery)[10]. In our series, 2 of 4 AML cases were girls and were diagnosed with tuberous

sclerosis, and these two patients were treated with mTOR inhibitor therapy due to the progression of the lesion.

MRT of the kidney is a rare type of tumor having a poor prognosis and most commonly being observed in infants and young children, with 85% of the cases diagnosed within the first 2 years of life. The tumor is usually metastatic at the time of diagnosis[1]. In the present study, the patients were diagnosed at advanced stages and three patients died despite the multimodal treatments applied.

Reportedly, survival rates in pediatric RCC decrease as the stage of the disease progresses, with survival rates reported to be 90% for stage I, 80% for stage II, 70% for stage III, and 15% for stage IV[11]. The optimal treatment for pediatric RCC, however, remains unknown. Therefore, in accordance with the literature, the two patients with Stages I and II RCC were cured with surgery alone, based on excellent survival rates. Neoadjuvant chemotherapy was administered to one of the patients who was operated 4 weeks after chemotherapy and diagnosed with RCC. The patient was followed up without any treatment.

Primary PNET originating from the kidney is very rare. It is treated with multimodal methods, which is the standard treatment for Ewing sarcoma/PNET[12]. One patient in our study was diagnosed with PNET histopathologically via mass excision during nephrectomy; however, despite the surgery and subsequent chemotherapy, the patient died due to the disease progression.

The prevalence, treatment, and prognosis vary to a great extent among the different histopathological types of NWRTs. In a study by Qureshi et al., CCSK, RCC, MRT, and CMN were diagnosed at 39.4%, 19.3%, 12.8%, and 4.6%, respectively[4]. As in our study, the patients were divided into groups of high- and low-risk patients, with the worst prognosis being observed for MRT. The outcomes were more moderate for CCSK and RCC. For CMN, the overall survival rate in the abovementioned study was 100%, with an excellent outcome, similar to our study. However, in our study, CMN was the most prevalent type of NWRT, with an incident rate of 31%, followed by CCSK with an incident rate of 27.6%.

In a study by Zhu et al., the clinical and imaging characteristics of the 3 types of primary malignant NWRTs in 65 pediatric patients were investigated; MRT (41.6%) was found to be the most common, followed by CCSK (33.8%) and RCC (24.6%)[13].

In a similar study conducted in our country, in a center close to our institution, the main histological groups of NWRTs were reported as RCC (12.5%), CMN (10.4%) and angiomyolipoma (4.2%)[14].

In a study by Ünal et al., in which 20 children with NWRT were included, the mortality rate was found to be 30%. In our study, 29 patients were included and the mortality rate was found to be lower (17%)[15].

The 3- and 5-year overall survival rate in the present study of the high-risk group was 72%, whereas it was 100% for the low-risk group. In the study by Qureshi et al., the 3-year overall survival rate was reported to be 59% for the high-risk group and 100% for the low-risk group[5].

The most important limitation of our study is its retrospective nature. Other limitations are the small number of patients included in the study due to the rarity of tumors, and the lack of a homogeneous group due to tumor diversity.

In conclusion, MRT had the worst overall survival in our study. Physicians dealing with pediatric renal masses should be aware of the high mortality rates in pediatric MRT, CCSK, and PNET, and hence, should design multidisciplinary treatment plans for NWRTs.

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