Twenty children with non-Wilms renal tumors from a reference center in Central Anatolia, Turkey

Abstract

**Background/aim:** Non Wilms renal tumors (NWRT) are rarely encountered in children. The aim of this study is to determine the treatment strategies, prognosis, outcomes and survival of children with NWRT at Erciyes University, Kayseri

**Materials and methods:** Medical records of all patients (n=20) treated for NWRT over a 23-years period (1995-2018) were reviewed retrospectively.

**Results:** There was male predominance (female/male: 7/13); median age at the diagnosis was 3.2 years old (0.1-13.5 years old). The major histological groups included mesoblastic nephroma (MBN), (n:5, 25%); malignant rhabdoid tumor (MRT), (n:5, 25%); renal cell carcinoma, (n:3, 15%); inflammatory myofibroblastic tumor (n:2, 10%), multilocular cystic renal tumors (n:2, 10%), metanephric adenoma (n:1, 5%), renal neuroblastoma (n:1, 5%) and bilateral renal Ewing sarcoma/primitive neuroectodermal tumor (ES/PNET) (n:1, %5). All of the patients with NWRT had radical nephrectomy except the child with bilateral renal ES/PNET. Six children died because of progressive disease; the mortality rate was 30% (n:6).

**Conclusion:** We firstly report bilateral renal involvement of ES/PNET in the English medical literature. Physicians dealing with pediatric renal mass should be alert about the high mortality rate in children with MRT, MBN and ES/PNET; and should plan a substantial management plan for NWRT.

**Key words:** Non-Wilms renal tumor, children, management
1. **Introduction**

Wilms tumor is the most common pediatric renal tumor and accounts for approximately 6-7% of all pediatric malignancies [1]. Pediatric non-Wilms renal tumors (NWRT), constitutes less than 10% of all renal tumors and has a significantly higher mortality rate compared to childhood Wilms tumor [2-8]. There are controversies for optimal follow-up and treatment plan determination of this rare and heterogeneous group of tumors. In particular, while the majority of the cystic tumors have good prognosis; clinicians should be aware of the aggressive tumors such as malignant rhabdoid tumor. In general, NWRT include mesoblastic nephroma, malignant rhabdoid tumor, renal cell carcinoma, inflammatory myofibroblastic tumor, multilocular cystic renal tumors, and metanephric adenoma. In this review, the experience with pediatric NWRT followed at Erciyes University were presented. In addition to the classical tumor subtypes of NWRT, two interesting children with renal Ewing sarcoma/ primitive neuroectodermal tumor (ES/PNET), and neuroblastom were also added to this cohort.

2. **Materials and methods**

This study was carried out in the Department of Pediatric Oncology of Erciyes University in Kayseri, Turkey. Erciyes University Children’s Hospital is a tertiary hospital in the city of Kayseri, in Central Anatolia, Turkey. This hospital is the sole pediatric referral center, serving a wide population, including patients coming from the surrounding cities in the Cappadocia region. For 23 years (1995-2018) approximately 107 children were managed for renal tumors. The records of 20 (%18.7) non-Wilms’ renal tumors were reviewed. Using patient’s charts, patient demographics, presenting clinical symptoms and signs, tumor histology, treatment modalities and the outcome of treatment were analyzed.
Ethical permission for a review of all records was granted by the Ethics Committee of Erciyes University (number: 2018-146; date: 21.03.2018).

3. Result

Over a 23-years period; 20 children with NWRT were identified. The major histological groups were malignant rhabdoid tumor (figure 1) (25%), mesoblastic nephroma (figure 2) (25%), renal cell carcinoma (15%), inflammatory myofibroblastic tumor (10%), multilocular cystic renal tumors (10%), metanephric adenoma (5%), renal neuroblastoma (figure 3) (5%) and bilateral ES/PNET (figure 4). Patient’s demographics and clinical signs are summarized in table. There was male predominance (Female/Male:7/13). Female patients were mesoblastic nephroma, renal cell carcinoma, renal neuroblastoma and bilateral renal ES/PNET. Median age at the diagnosis was 3.2 years old (0.1-13.5 years old). The most seen presenting symptoms were abdominal mass, flank pain and hematuria. None of the patients have hypertension. In imaging studies there were no renal vena thrombus. Median tumor diameter was 8.9 cm (3-15 cm). From the 20 children only two patients with malignant rhabdoid tumor, renal cell carcinoma had distant metastasis at the time of diagnosis. One of the children with inflammatory myofibroblastic tumor both at renal and pulmonary involvement was reported previously [9]. All of the patients with NWRT had radical nephrectomy except the child with bilateral renal ES/PNET. Adjuvant chemotherapy was given to patients with malignant rhabdoid tumor, mesoblastic nephroma and bilateral renal ES/PNET. Different chemotherapy protocols were used for each types of tumors. Children with mesoblastic nephroma were treated similar to Wilms tumor consisted of Actinomycin-D (15 µg/kg intravenous (iv), on day 1–5), Vincristine (1.5 mg/m² iv on day 1), and Doxorubicin (50 mg/m² iv over 4 h on day 1). Children with
malignant rhabdoid tumor were managed with ifosfamide (2,000 mg/m$^2$ iv, on days 2, 3, and 4), carboplatin (targeted to the area under the curve (AUC) of 6 mg/mL-min iv, on day 1), and etoposide (100 mg/m$^2$ iv, on days 2, 3, and 4); alternating vincristine (1.5 mg/m$^2$ iv, on days 1, 8), doxorubicin (75 mg/m$^2$ iv, over 48 hours from day 1), and cyclophosphamide (1,500 mg/m$^2$ iv, on day 1). In addition, one child with ES/PNET received (1.5 mg/m$^2$ iv, on days 1), doxorubicin (20mg/m$^2$ iv, days 1-3), etoposide (100 mg/m$^2$ iv, on days 1-3). Two of the patients with mesoblastic nephroma were taken abdominal radiotherapy. One of the patient with inflammatory myofibroblastic tumor was treated with crizotinib. Two of the patients with mesoblastic nephroma and three of the patients with rhabdoid tumor, and the child with the bilateral renal ES/PNET died because of progression. Mortality rate was 30%.

4. Discussion

Pediatric NWRT constitute a very small part of childhood malignancies. Although they are very rare tumors it is important to define diagnosis, and start the adequate treatment immediately because of the high morbidity and mortality rates. In this group generally local stage and radical resection is associated with increased survival. Mesoblastic nephroma, malignant rhabdoid tumor, renal cell carcinoma, inflammatory myofibroblastic tumor, multilocular cystic renal tumors and metanephric adenoma are the most seen tumors of pediatric non-Wilms’ renal tumors. Renal neuroblastoma and bilateral renal ES/PNET are extremely rare entity among the NWRT [3,4,10]. Mesoblastic nephroma is the most frequent type of NWRT in the neonatal period. 90% percent of patients seen under the age of 3 months old. Total resection of the tumor is usually curative but local recurrences can be seen [11-13]. Cellular variants, and high mitotic index of mesoblastic nephroma have a poor outcome with bone and brain
metastases, and local recurrence [12,13]. Especially patients bigger than 3 months old, cellular variant and with residual tumor may benefit from chemotherapy. Two children with mesoblastic nephroma in our cohort died because of relapses after the end of the chemotherapies. This may be related to patient’s age (2.5, and 3.5 years old) and tumor size (maximal diameters were >10 cm).

Malignant rhabdoid tumor of the kidney is a rare aggressive cancer, occurring in infancy and early childhood and accounting for only 2% of all renal tumors in childhood [14]. The patients with malignant rhabdoid tumor of the kidney are characterized by young age and advanced stage at presentation. Metastases are usually to the lungs and brain. Hematuria, fever, infection, anemia and hypertension are the most presenting symptoms. Prognostic factors are sex, age at diagnosis, tumor stage and presence or absence of CNS lesions [15]. Patients under the age of two years have the worst prognosis because in this group relapses occur early and patients have a tendency to develop CNS tumors at the same time [14,15]. Hematuria is the most presenting symptom. Four of five patients had hematuria at the time of diagnosis. Chemotherapy and radiation therapy sensitivity is low but carboplatin, etoposide, doxorubicin and vincristine had been reported for multiagent chemotherapy. One of our patients 3 years old, with a 7.5 cm diameter tumor and stage 4 disease died during chemotherapy. Six-months old male patient with 9 cm diameter mass died 2 months after the completion of the chemotherapy. Three-years old boy with a 15 cm diameter tumor and stage IV disease died during receiving chemotherapy because of progressive disease with pulmonary metastasis and septic shock.

Renal cell carcinoma is a rare pediatric tumor that accounts for approximately 2% of all pediatric renal tumors, while it is the most common renal tumor in adults. The children with RCC generally present in 9-15 years of age; the ages of the presented
children in the current study at diagnosis were 5, 6, 11, and 13 years-old. Our patients
most presented with symptoms of hematuria, flank pain and abdominal mass. As other
subtypes of NWRT, patients with localized tumor have a good prognosis whereas
prognosis in metastatic cases is poor. Renal medullary carcinomas are highly aggressive
tumors and commonly presents as enlarged cervical lymph nodes. Surgical resection of
the tumor with radical nephrectomy is the mainstay of treatment. Adjuvant therapy is not
recommended for children with microphthalmia transcription factor translocation RCC,
papillary RCC and no residual tumor after resection [16-19]. No effective therapy for
disseminated disease is available. We did not give adjuvant chemotherapy to any children
with renal cell carcinoma, because of the complete tumor resection after surgery.

Inflammatory myofibroblastic tumor is a very rare benign reactive proliferative lesion. It
is rarely seen in the urinary tract. It has a low recurrence rate and rarely metastasizes
[9,20,21]. Lung is the most common site of the tumor. In the urinary tract, Inflammatory
myofibroblastic tumor most commonly occurs in the urinary bladder. [20]. Diagnosis
should be confirmed by histopathological study [21]. Fundamental treatment is complete
surgical resection. Local recurrence, malignant transformation and metastasis have been
reported rarely. Metastatic or recurrent cases should be treated with corticosteroids.
Approximately half of inflammatory myofibroblastic tumors carry rearrangements of the
anaplastic lymphoma kinase The inhibitor of anaplastic lymphoma kinase inhibitor,
crizotinib has been used in these patients [4]. One of the reported patient with
inflammatory myofibroblastic tumor had used crizotinib; and and showed complete
response [9].

Multicystic nephroma and cystic partially differentiated nephroblastoma are the two
histological subtypes [22-24]. It is non-heritable, benign lesion, and rare both in children
and adults [23]. Most of the children present with a painless abdominal mass. The sonographic appearance of multilocular cystic renal tumor includes multiple anechoic spaces traversed by thin septa and no solid elements [22-24]. No cases of aggressive behavior were documented. But surgery is required for diagnosis and differential diagnosis from cystic Wilms’ tumor, RCC or mesoblastic nephroma [4]. Recurrence can be occurred following incomplete resection. Two of our children with NWRT had diagnosed with multicystic nephroma and showed remission after complete resection.

Metanephric adenoma is a rare benign neoplasm, uncommonly seen in the pediatric population. They are usually asymptomatic lesions and detected incidentally on imaging studies performed for other indications [25, 26]. They generally appear as hypovascularized solid lesions. Diagnosis is made histologically. Partial nephrectomy is curative. Metastatic disease is very rare but should be considered [25]. Only a child had diagnosed with metanephric adenoma and showed remission after complete nephrectomy.

The primary intrarenal neuroblastoma is a rare condition. Intrarenal neuroblastoma typically results from direct renal invasion from an adrenal neuroblastoma, but true intrarenal neuroblastoma originates either sequestered adrenal rests during the fetal life or intrarenal sympathetic ganglia [27,28]. From our cohort of children with NWRT, only two-years old girl had diagnosed with primary intrarenal neuroblastoma. She was treated according to the national neuroblastoma protocol entitled “Turkish Pediatric Oncology Group Neuroblastoma Protocol 2009” as described by Ozguven et al. [29]. Our case was not MYCN-amplified, and showed remission after complete nephrectomy without further chemotherapy.

ES/PNET is a high-grade malignant neoplasm commonly affecting bones of the thoracic region. Primary ES/PNET of the kidney is extremely rare; it commonly affects young
adults and is rarely reported in children [10,30]. Our case was 3-months-old female with bilateral renal involvement. The pathological morphology was relevant for renal ES/PNET and FISH for $EWSR_1$ was positive. According to best of our knowledge, bilateral renal involvement of ES/PNET was not reported in the English medical literature.

The ultrasound guided renal biopsies showed a high effectiveness and safety but the we did not perform any renal biopsy in the presented children with NWRT to avoid upstaging of the disease [31]. Surgical nephrectomies were performed after discussion of each individual cases at multidisciplinary pediatric oncology council.

In conclusion, our series pediatric NWRT consist of 18.7% of all pediatric renal tumors. In this rare group of tumor mortality rate was found to be 30% in our series. The clinicians must be vigilant about different properties of these heterogenic group of tumors.

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References


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Figure legends:

Figure 1
Rhabdoid tumor of the kidney: A) Diffuse growth of neoplastic cells (Hematoxylin & Eosine x200), B) A sheet-like diffuse pattern of monomorphic neoplastic cells overrunning tubules (Hematoxylin & Eosine x400), C) the neoplastic cells are vimentine positive (vimentine x200)

Figure 2
Mesoblastic nephroma: A) Fascicles of fibroblastic cells dissect islands of native nephrons (Hematoxylin & Eosine x40), B) Fascicles of fibroblastic cells resembling fibromatosis dissect the native kidney (Hematoxylin & Eosine x200)

Figure 3
Neuroblastoma of the kidney: A) Coronal T2 HASTE image through abdomen demonstrates lobulated hyper intense mass arising from right kidney and infiltrating right adrenal region (arrow), B) Neuroblastoma cells adjust to the normal structures of kidney (Hematoxylin & Eosine x40), C) Neuroblastoma cells with neuro-fibrillary background (Hematoxylin & Eosine x200), D) The small round cells were positive for neuron spesific enolase (Neuron spesific enolase x20)

Figure 4
Bilateral Ewing Sarcoma/Primitive Neuroectodermal Tumor: Axial T2 HASTE image through upper abdomen demonstrates hypointense bilateral lobulated giant masses arising and infiltrating both kidneys (circles).
<table>
<thead>
<tr>
<th>Patient no</th>
<th>Sex</th>
<th>Age (year)</th>
<th>Presentation</th>
<th>Histology</th>
<th>Stage</th>
<th>Tumor diameter (cm)</th>
<th>Outcomes</th>
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<td>I</td>
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