

Our Six-year Wilms Tumor Results: A Single-center Experience

Altı Yıllık Wilms Tümör Sonuçlarımız: Tek Merkez Deneyimi

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Abstract

Objective: This study aimed to analyze the demographic, clinical, and pathological data of children diagnosed with Wilms tumor (WT) and operated on at a tertiary healthcare center.

Method: Our study is a retrospective, observational analysis of clinical records of patients diagnosed with WT at a tertiary pediatric center between May 2017 and June 2023. The patients were evaluated based on their age at diagnosis, gender, symptoms, associated anomalies, laboratory and radiological examinations, the affected kidney side, stage, postoperative treatment, and follow-up. Histopathological classifications and staging for all patients were performed according to the National Wilms Tumor Study Group (NWTSG). Chemotherapy treatment was determined based on the pathological stages and tumor histopathology. In cases with metastasis, if clinically appropriate, metastasectomy was performed and chemotherapy was administered. Treatment for recurrence included surgery, chemotherapy, and radiotherapy.

Results: The average age of these patients was 3.8 years, with an equal distribution of male and female patients. The most common symptoms were abdominal mass, hematuria, and fever. Right kidney involvement was found in 50% of patients, left kidney involvement in 40%, and bilateral involvement in 10%. Treatment protocols were determined according to the NWTSG guidelines, with unilateral radical nephrectomy performed on all patients except two, who received preoperative chemotherapy. Pathological evaluation revealed that all patients had nephroblastoma (triphasic type), with anaplastic features found in three patients. Two patients presented with pulmonary metastases. With an average follow-up of 2.15 years, no recurrences were observed during the study.

Öz

Amaç: Bu çalışmanın amacı, Wilms tümörü (WT) tanısı konulan ve üçüncü basamak bir sağlık merkezinde ameliyat edilen çocukların demografik, klinik ve patolojik verilerini analiz etmektir.

Yöntem: Çalışmamız, Mayıs 2017 ile Haziran 2023 arasında üçüncü basamak bir çocuk hastanesinde WT tanısı konulan hastaların klinik kayıtlarının retrospektif, gözlemsel olarak analiz edilmiştir. Hastalar, tanı anındaki yaşlarına, cinsiyetlerine, semptomlarına, ilişkili anomalilere, laboratuvar ve radyolojik muayenelerine, etkilenen böbrek tarafına, evresine, ameliyat sonrası tedavisine ve takibine göre değerlendirildi. Tüm hastalar için histopatolojik sınıflandırmalar ve evrelemeler Ulusal Wilms Tümörü Çalışma Grubu'na (NWTSG) göre yapıldı. Kemoterapi tedavisi, patolojik evrelere ve tümör histopatolojisine göre belirlendi. Metastazı olan olgularda, klinik olarak uygunsa metastazektomi yapıldı ve kemoterapi uygulandı. Tekrarlama tedavisi cerrahi, kemoterapi ve radyoterapiyi içeriyordu.

Bulgular: Bu hastaların ortalama yaşı 3,8 yıldır ve erkek ve kız hastalar arasında eşit dağılım vardı. En sık görülen semptomlar abdominal kitle, hematüri ve ateşti. Hastaların %50'sinde sağ böbrek tutulumu, %40'ında sol böbrek tutulumu ve %10'unda bilateral tutulum bulundu. Tedavi protokolleri NWTSG kılavuzlarına göre belirlendi ve preoperatif kemoterapi alan iki hasta hariç tüm hastalara unilateral radikal nefrektomi uygulandı. Patolojik değerlendirme tüm hastalarda nefroblastoma (trifazik tip) olduğunu ve üç hastada anaplastik özellikler bulunduğu görüldü. İki hastada pulmoner metastazlar görüldü. Ortalama 2,15 yıllık takip süresiyle çalışma sırasında hiçbir nüks gözlenmedi.



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Conclusion: WT treatment should be approached with a multidisciplinary strategy and executed with careful surgical techniques. This study supports the effectiveness of current methods in the treatment of WT and highlights their positive impact on survival rates.

Keywords: Child, experience, tumor, Wilms

Sonuç: WT tedavisi multidisipliner bir strateji ile ele alınmalı ve dikkatli cerrahi tekniklerle uygulanmalıdır. Bu çalışma WT tedavisindeki mevcut yöntemlerin etkinliğini ve sağkalım oranlarını desteklemektedir.

Anahtar kelimeler: Çocuk, deneyim, tümör, Wilms

Introduction

Wilms tumor (WT) is the most common renal tumor, accounting for approximately 6% of malignancies in infants and children (1). It is estimated that a germ cell mutation is responsible for about 10-15% of WTs (2). The most common clinical symptoms include abdominal mass, abdominal pain, hematuria, fever, and hypertension. The lungs are the most common site of metastasis (3). Evaluation of a child with suspected WT includes physical examination, complete blood count, blood biochemistry, urinalysis, and appropriate imaging, such as abdominal ultrasound (USG) or computed tomography (CT). However, a definitive diagnosis of WT can be made through a biopsy or surgical resection. Treatment protocols included surgical excision, chemotherapy, and radiotherapy in selected patients. Advancements in surgical techniques, anesthesia, and intensive care procedures, along with the chemotherapy and radiotherapy, have increased survival rates to over 90% (4).

This study aimed to examine the demographic characteristics, clinical and pathological findings, treatment processes, and follow-up outcomes of patients diagnosed with WT who underwent surgery at our tertiary pediatric hospital.

Materials and Methods

This retrospective observational study included the clinical records of patients diagnosed with WT at a tertiary pediatric hospital between May 2017 and June 2023. The study was approved by the Ethics Committee of the University of Health Sciences Turkey, Ümraniye Training and Research (protocol number B.10.1.TKH.4.34.H.GP.01/453) on 23.11.2023 and was conducted in accordance with the principles of the Declaration of Helsinki.

Patients who underwent surgery and were pathologically diagnosed with WT were included in the study and evaluated in terms of age at diagnosis, sex, symptoms, accompanying anomalies, laboratory, and radiological findings, affected side of the kidney, stage, postoperative treatment, and follow-up. Histopathological classification and staging of all patients were performed according to the

National Wilms Tumor Study Group (NWTSG) guidelines. The NWTSG-5 protocol has also been used for treatment (5).

Patients were evaluated by a multidisciplinary pediatric oncology board (comprising pediatric surgery, pediatric urology, pediatric hemato-oncology, radiation oncology, pediatric radiology, and pathology departments) based on their clinical findings, laboratory tests, and radiological imaging results. The treatment plan was determined. Chemotherapy was customized according to the pathological stage and tumor histopathology. In cases of metastasis, metastasectomy was performed, and chemotherapy was administered if the patient's clinical condition was acceptable. Recurrence treatment included surgery, chemotherapy, and radiotherapy. Preoperative chemotherapy was administered in cases in which surgery was deemed highly risky, the tumor could not be completely resected, or the presence of a thrombus in the inferior vena cava.

Statistical Analyses

In our study, simple statistics were used, and the mean \pm standard deviation (SD) and % values of the groups were calculated using Microsoft Excel.

In our study, basic statistical analyses were performed using Microsoft Excel. The results are presented as mean \pm SD and percentage values for each group. As the study did not involve any group comparisons, p-values were not reported.

Results

Ten patients were included in this study. Of the children, five were male and five were female: (M/F =1/1). The mean age at diagnosis was 3.8 years (46 months), with a range of 8-101 months. One patient (10%) exhibited an associated anomaly: Left undescended testis and right inguinal hernia. The most prevalent symptoms at diagnosis were intra-abdominal mass, hematuria, fever, burning sensation, abdominal pain, and fatigue. The findings are summarized in Table 1. The right kidney was affected in 5 patients (50%), the left kidney in 4 patients (40%), and the tumor was bilateral in 1 patient (10%) (Table 2).

Laboratory tests revealed normal alpha fetoprotein, human chorionic gonadotropin, lactate dehydrogenase, and ferritin levels. Doppler USG and CT imaging was performed to evaluate tumor invasion following the detection of a renal mass in patients undergoing abdominal USG. All patients exhibited normal echocardiographic findings.

A unilateral radical nephrectomy was performed in 9 patients with unilateral WT, and 2 of these received preoperative chemotherapy. One of these patients was a 7-year-old girl with lung metastasis at the time of diagnosis for whom chemotherapy was initiated at an external facility. The other patient was a 4-year-old girl with a thrombus in the renal vein and inferior vena cava (Figure 1).

In cases where preoperative CT or magnetic resonance imaging was performed, contralateral exploration was

conducted even in the absence of evidence of pathology in the contralateral kidney. A minimum of 5-7 samples was obtained from hilar and ipsilateral para-aortic or caval lymph nodes. A patient with bilateral WT underwent a left-sided nephrectomy and a right-sided biopsy. Given the pathological compatibility of the biopsied side with a WT, subsequent surgical procedures were performed, which entailed a nephrectomy and mass excision on the right side.

Variables such as age, sex, tumor side, tumor size, stage, presence of anaplasia, presence of nephrogenic rest, histology, and follow-up results are presented in Table 2. Postoperative bleeding requiring transfusion was not observed. One patient with bilateral tumors died postoperatively.

The pathology of all patients was reported as nephroblastoma (triphasic type). Anaplasia was identified in 3 patients, representing 30% of the study sample. Two patients exhibited evidence of lung metastasis (Figure 2). One of the 4 patients underwent chemotherapy and the others received radiotherapy. Eight children are currently being monitored for metastasis. The mean follow-up period was 2.15 years (range, 5 months-6 years).

Table 1. Clinical presentation

Symptoms	Number of patients (n)
Abdominal mass	7
Hematuria	3
Fever	2
Loss of weight	1
Fatigue	1
Abdominal pain	1

Table 2. Clinical and histopathological features

Patient	Age (month)	Sex	Side	Tumor size (cm)	Stage (COG)	Anaplasia	Nephrogenic rest	Histology	Follow-up
1	40	M	Right	8.7x7.5x7.3	III	Diffuse	Absent	Unfavorable	Disease free (3 years)
2	24	M	Right	14.5x12x9.8	II	Absent	Present	Favorable	Disease free (3 years)
3	36	M	Left	5x4.2x3.7	I	Absent	Absent	Favorable	Disease free (6 years)
4	58	F	Left	9x6x5	I	Absent	Absent	Favorable	Disease free (5 years)
5	8	M	Right	13x11.5x11	I	Absent	Absent	Favorable	Disease free (2 years)
6	32	F	Left	4.7x3x2.8	III	Absent	Present	Favorable Thrombus in renal vein and vena cava	Disease free (1 year)
7	45	F	Bilateral	Left 15x10x9 Right 10.5x5.5x4	III	Diffuse	Absent	Unfavorable	Exitus
8	84	F	Right	11.5x6x5	I	Absent	Absent	Favorable	Disease free (6 months)
9	30	M	Left	5.5x5x4.8	III	Focal	Absent	Unfavorable	Disease free (4 years)
10	101	F	Right	17x13x9	II	Absent	Absent	Favorable	Disease free (8 months)

COG: Children's oncology group

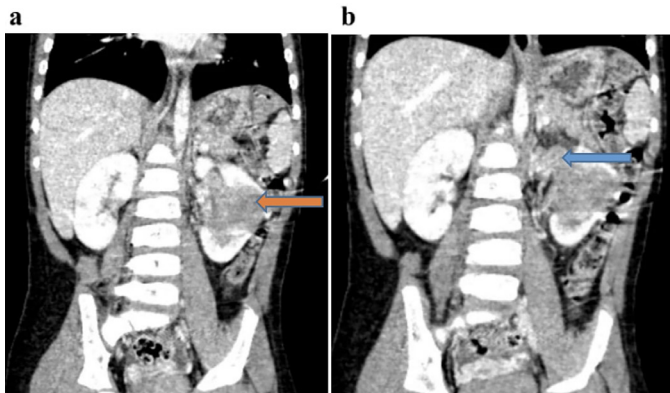


Figure 1. Coronal section CT image of the patient; a) CT image of a coronal section demonstrating a mass originating from the mid-pole of the left kidney (orange arrow), b) Left renal vein invasion (blue arrow)

CT: Computed tomography

Discussion

WT is the most prevalent renal tumor in children, affecting 1 in 10,000 children (6). According to the data, the age of onset of the tumor is 1-5 years in 78% of cases (7). The mean age of our patients was found to be 3.8 years, which is similar to that reported in the literature. Two patients (20%) were less than 5 years of age. The female-to-male ratio of the patients was 1:1. Analysis of the symptoms presented at the initial evaluation revealed that the most common finding was an abdominal mass (70%). The most common complaints were hematuria and fever. Abdominal mass is the most common presenting symptom of WT (8). In our series, abdominal mass was similarly identified as the most common presenting symptom.

Monophasic WTs may be difficult to distinguish from other tumors, in which case immunohistochemistry is helpful. WT1 was nuclear positive in 90% of cases. The blastemal component was positive for WT1, PAX8, and vimentin. The epithelial component was positive for cytokeratin, EMA, and CD56 expression. The stromal component is positive for vimentin, shows variable positivity for BCL2 and CD34, with weak expression or negativity for WT1(9). WT1 was negative in 2 of our patients. Although WT1 is specific and sensitive, it may be negative in 10% of the cases.

The diagnosis of WT is usually straightforward; however, monophasic WTs are difficult to distinguish from other histologically similar renal tumors. The pure blastemal type of WT must be differentiated from tumors such as neuroblastoma, primitive neuroectodermal tumor or Ewing sarcoma, desmoplastic small round cell tumor, and synovial sarcoma. Therefore, immunohistochemical and molecular

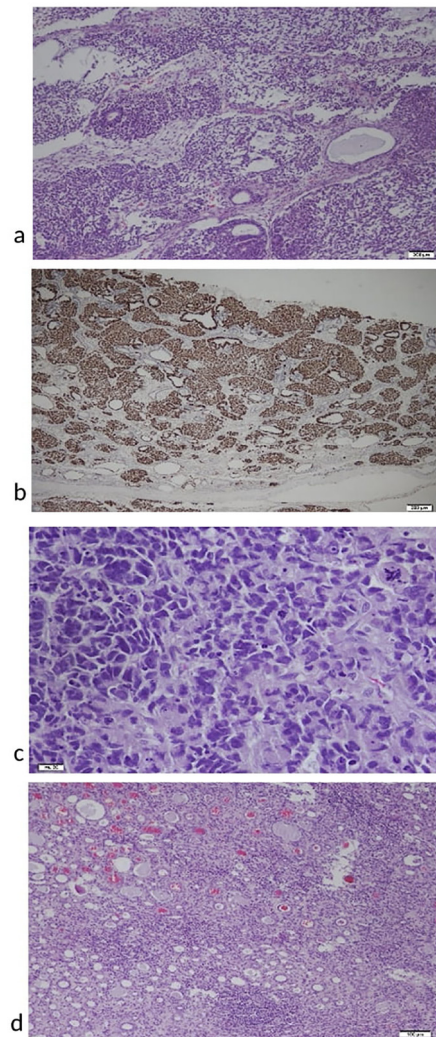


Figure 2. Triphasic Wilms tumor, staining in tumor cells with WT-1, anaplasia area, presence of nephrogenic rest

a) Triphasic Wilms tumor; stromal, blastemal and epithelial components (H&E, x4),

b) Staining of tumor cells with WT-1 (x4-WT-1),

c) Anaplasia area showing marked pleomorphism with numerous mitotic figures (H&E, x40),

d) Presence of nephrogenic rest in the renal parenchyma (H&E, x10)

WT: Wilms tumor, H&E: Hematoxylin and eosin

techniques are important. Blastemal components may show focal CD99 positivity, but this is not diffuse and membranous, as in Ewing sarcoma. Desmoplastic small round cell tumor is immunohistochemically similar to WT. The diagnosis should be made based on the EWS-WT1 t(11;22)(q13;q12) translocation. Neuroblastoma is characterized by high catecholamine levels and histological salt and pepper chromatin. Both tumors were positive for NSE and CD56; however, WT1, which is a marker

used in the characterization of tumors, was negative for indicating neuroblastoma. Pure epithelial WT should be differentiated from metanephric adenoma, renal cell carcinoma, and hyperplastic perilobar nephrogenic rest. The combination of CK7-, AMACR-, WT1+, and CD57+ favors metanephric adenomas. In the differential diagnosis of a pure stromal type WT, clear cell renal sarcoma and mesoblastic nephroma should be considered. Cystic WT should be distinguished from cystic nephroma (CN) and cystic partially differentiated nephroblastoma (CPDN). CN contains DICER1 mutations, whereas these mutations are absent in CPDN and WT. Since none of our patients had a monophasic histology, differential diagnosis was not necessary nor difficult. Triphasic components were found in all patients (10).

WT is similar to the histology of the developing kidney, and originates from the nephrogenic blastema. Histopathologically, it comprises blastemal, epithelial, and stromal components. The blastema component consists of undifferentiated cells with small and regular nuclei. The epithelial component contains differentiated elements, such as tubules and papillary structures. The stromal component may contain heterologous elements, such as adipose tissue and cartilage. Anaplasia, seen in 7-10% of WTs, is characterized by atypical multipolar mitotic figures, marked nuclear enlargement (at least 3-fold), and hyperchromasia. Anaplasia is divided into focal anaplasia, which is confined to the primary intrarenal tumor, and diffuse anaplasia, which extends beyond the tumor capsule. Focal anaplasia is defined as a clearly demarcated focus within the primary intrarenal tumor, but, in rare cases, multiple foci are allowed for diagnosis: up to 4 foci in the children's oncology group definition and up to 2 foci ≤ 15 mm according to the International Society of Paediatric Oncology (SIOP) definition.

In our series, focal anaplasia was found in 1 patient and diffuse anaplasia in 2 patients. One of the patients with diffuse anaplasia was also a patient with bilateral WT who died. In the patient with focal anaplasia, no recurrence was observed during 4 years of follow-up (11).

It has been reported that genitourinary abnormalities are common in patients with WT (12). In our series, the incidence of concomitant anomalies was 10%, occurring in 1 out of 10 patients. This is a low rate compared with data reported by some authors, who indicated a rate of 26%. In another study, the prevalence of all genitourinary malformations in patients with WT was found to be 5% (13).

In one patient, the incidence of WT on both sides was observed to be 10%. Right kidney involvement was found in 5 (50%) patients and left kidney involvement in 4 (40%) patients. According to some sources, left kidney involvement is more common (14); however, in our study, right-sided involvement was higher.

The most important prognostic factors in WT treatment are tumor stage, histopathological anaplasia, absence of preoperative rupture, and positivity for some biological markers (15). Regarding clinical staging, 4 (40%) of our patients were stage 3, 4 (40%) were stage 1, and 2 (20%) were stage 2. Favorable histology was observed in 3 (30%) patients. In a study by Breslow et al. (7), the rate of unfavorable histology was 11%, which was lower than that in our study. The remaining 7 (70%) had a favorable histology.

Nephrogenic rest is a precursor lesion of WT originating from various sites, such as blastemal, stromal, and embryonal nephroblastic tissue, and may be confused with other malignant tumors (16). Nephrogenic rests were found in 2 patients with favorable histology and without anaplasia.

In our 2 patients with lung metastasis, the survival rate 2-year follow-up period with treatment was quite high. However, the survival rate in WT cases is reported to be 75% in metastatic patients and over 90% in non-metastatic patients (17). With the current multidisciplinary treatment, chemotherapeutic drugs, and improvements in radiotherapy, significant progress have been achieved for WT (18). We agree with this view, and our results support this hypothesis.

In cases of horseshoe kidney, bilateral WT, thrombus in the hepatic vein or vena cava, solitary kidney, or respiratory distress due to lung metastases, NWTSG recommends preoperative chemotherapy (19). In our series, two patients with lung metastases and thrombus in the renal vein and inferior vena cava received preoperative chemotherapy.

The mean follow-up period of our patients was 2.15 years, and no mortality was observed during this period. Increased surgical experience, development of radiologic imaging techniques, and shrinkage of masses with chemotherapy have decreased the morbidity and mortality associated with WT.

In another study conducted in Turkey, the frequency of vascular invasion was 8% (20). In our study, the frequency of vascular invasion was 10%. There are reports that intravascular invasion of WT occurs in 20-35% of cases (21).

The most important aspect of WT surgery is to prevent tumor rupture and shedding intraoperatively (22). The surgical team was careful not to rupture the tumor capsule. We believe that this care was one of the reasons for the success of our follow-up.

In the present study, no recurrence was observed during the follow-up period. A recurrence rate of 4.3% for favorable histology and 42% for unfavorable histology has been reported in the literature (23).

When reviewing studies conducted in recent years, the outcomes of patients with focal anaplastic WT are comparable to those of identically treated patients with non-anaplastic intermediate-risk WT in SIOP studies. The outcomes for patients with high-stage diffuse anaplastic WT remain poor, presenting challenges for treatment and management. Recent studies have shown improvements in effectiveness with increased treatment, but also an increase in toxicity (24).

There are authors who argue that patients with stage I and II focal anaplastic WT have remarkably good survival rates when treated with doxorubicin and radiation. In their studies, they reported that intensification of therapy could improve survival in stage IV focal anaplastic WT, albeit with an increased risk of toxicity (25).

In a noteworthy recent study, the aim was to investigate prognostic factors for WT through peripheral blood cell profiling. It was found that overall survival and event-free survival were worse in patients with an absolute monocyte count below $0.325 \times 10^3/\mu\text{L}$ and those with stage IV disease (26).

It is well known that clinicians' evaluation of a patient's eligibility for postoperative radiation is crucial. Postoperative radiation has been shown to be associated with poor prognosis in patients with WT (27).

Moreover, some authors suggest that the rapid advancements in molecular biology, imaging, and radiotherapy will lead to better outcomes and reduced toxicity in WT patients. Advances in radiation techniques such as intensity-modulated radiation therapy have made it possible to explore heart protection strategies when delivering whole lung radiation (28).

A computer-aided prediction system was developed in a study to predict the response of WT to preoperative chemotherapy, using contrast-enhanced CT before treatment. It was reported that the designed program helped accurately identify WT cases, less likely to respond

to preoperative chemotherapy. Consequently, they argued that surgery could be recommended for these tumors in advance, thereby avoiding the drawbacks of preoperative chemotherapy (29).

Our primary goal is to ensure the best possible survival for these patients. In addition to all of this, recent studies have indicated that survival rates may vary according to race, ethnicity, metropolitan status, and age (30).

Study Limitations

One of the limitations of this study was the relatively small number of patients. However, the fact that the study was single-center and that all surgeons who performed the surgeries were experienced in tumor surgery is important and meaningful in terms of preventing inconsistencies in staging and pathology evaluation. Another one is, in the statistical analysis, p values were not reported because there was no comparison group. Because it does not possible to perform statistical analysis in a study group consisting of ten patients.

Conclusion

Patients with WT should be managed with a multidisciplinary approach, planned treatment, and close follow-up. Increased surgical experience, development of radiological imaging techniques, and shrinkage of masses due to chemotherapy have decreased morbidity and mortality in WT. As observed in our series, the number of patients detected in stage 1 was equal to the number of patients detected in stage 3. This finding supports our conclusions.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of the University of Health Sciences Turkey, Ümraniye Training and Research (protocol number B.10.1.TKH.4.34.H.GP.01/453) on 23.11.2023 and was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.Y., F.T.G., Z.İ., Concept: S.Y., Z.İ., Design: S.Y., F.T.G., F.T., Data Collection or Processing: S.Y., İ.T., F.T., Analysis or Interpretation: S.Y., İ.T., O.Ş., Z.İ., Literature Search: S.Y., F.T.G., F.T., O.Ş., Writing: S.Y., İ.T., O.Ş.

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