


30 Years of Wilms Tumor Experience at One Center in Türkiye's Central Anatolia Region

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ABSTRACT

Objective: The current study aims to evaluate the clinical presentation, treatment, and follow-up of children with Wilms Tumor (WT) who had been admitted to Erciyes University, Faculty of Medicine Department of Pediatric Hematology and Oncology hospital, a tertiary center in the central Anatolia region of Türkiye. The study assesses the survival data and features that have had an impact on survival.

Materials and Methods: The current study has been planned as a retrospective observational evaluation of patients admitted to the Pediatric Hematology and Oncology Center between 1991-2021.

Results: The study retrospectively evaluated a total of 48 patients in terms of demographic characteristics, presentation findings, tumor stages, histopathologies, and survival rates. Patients with an unfavorable histology had a 66.7% chance of both event-free survival (EFS) and overall survival (OS), which is lower than the respective 85.2% and 92.1% odds of EFS and OS for the favorable histology group. However, this is not statistically significant ($p = 0.20$ for EFS and $p = 0.05$ for OS). Regarding the impact of stage on survival rates, the EFS and OS for patients with the low-stage disease were 88% and 95.7%, respectively. These rates were significantly superior to those at an advanced stage of the disease, whose EFS and OS were 63.1% and 60.9%, respectively ($p = 0.042$ for EFS, $p = 0.005$ for OS).

Conclusion: Wilms tumor at an advanced stage and with an unfavorable histology are the major factors resulting in poor survival rates.

Keywords: Wilms Tumor, Event-Free Survival, Overall Survival, Unfavorable Histology

INTRODUCTION

Wilms tumor (WT), also known as nephroblastoma, is the most common cancer of the kidneys, accounting for 95% of all renal cases in children and also accounting for 5%-6% of all childhood cancers. The estimated incidence is 7.1 per million children under 15 years of age. Wilms tumor appears to be sporadic, with only 1%-2% of cases being familial. Most WT cases are presented with a solitary tumor; however, bilateral tumors take place in 5%-7% of patients. Also, WT may occur as synchronous (simultaneous) or metachronous (consecutive) WT (1-4).

Several prognostic factors associated with overall survival (OS) and event-free survival (EFS) are found upon initial diagnosis. These include tumor histology, stage, molecular and genetic markers, and age. These prognostic factors should be considered when selecting treatment (5,6).

This study's objective is to describe the epidemiology, clinical presentation, treatment, and follow-up of children with WT in the center, which is a tertiary reference center in the central Anatolia region of Türkiye.

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MATERIALS AND METHODS

The current research is an observational, retrospective study based on the evaluation of the files and medical records of 48 patients who had been admitted to Erciyes University, Faculty of Medicine Department of Pediatric Hematology and Oncology between 1991-2021. The study evaluates the age at diagnosis, sex, symptoms on admission, association with genetic disorders, unilateral or bilateral involvement, histological type and staging, chemotherapy, radiation therapy, surgical treatment strategies, disease course, and patient outcomes. Categorical outcome measures were compared using the χ^2 test or Fisher's exact test, as applicable, with a p -value < 0.05 being considered significant. Continuous outcome measures have been described as averages, standard deviations, and lower and upper quartiles. The events are defined as a relapsed, refractory, or progressive disease. OS and EFS rates have been estimated using the Kaplan-Meier and log-rank tests in the program SPSS 24.

The study was approved by the scientific Erciyes University, Faculty of Medicine (Approval No. 2023/365, dated 31.05.2023).

RESULTS

Of the 48 patients enrolled in the study, 24 are male and 24 are female, with a male-to-female ratio of 1:1. The median age at diagnosis is 4 years (Range: 3-165 months). The mean age of patients presenting an advanced disease on admission is 47 months (± 20 months), whereas the mean age of early-stage patients is 40 months (± 29 months). The difference between these two groups is not statistically significant ($p = 0.39$). The time from symptom to diagnosis was a median of 6.5 days (Minimum: 1 day; Maximum: 150 days) and a mean of 12.8 days (± 22.5 days). Of the patients, 20 (42%) presented with abdominal pain, 14 (29%) had a palpable mass in the abdomen, and 8 (16.7%) presented with hematuria on admission. Four patients were diagnosed incidentally by detecting a mass on their abdominal ultrasonography. One patient presented with clinical findings of an acute abdomen and was diagnosed with a renal mass during the operation. One patient had WAGR syndrome and presented with a palpable mass in the abdomen. Another patient was followed up with the diagnosis of Denys-Drash Syndrome, with a mass detected during a control USG test followed by admission. Three patients had bilateral disease, with involvement of the right kidney being observed in 43.8% ($n = 21$) and the left kidney in 50% ($n = 24$).

The staging system was evaluated according to the National Wilms Tumor Study (NWTs). The majority of patients presented with a low-stage tumor (i.e., Stages I or II). A Stage I tumor was observed in 13 patients (27.1%), and a Stage II tumor in 14 patients (29.2%). Six patients (12.5%) presented with Stage III tumors, while 12 patients (25%) were diagnosed with a Stage IV tumor. As mentioned before, three patients (6.3%) had Stage V tumors. Distant metastasis was determined in 21 of the admitted patients. Of these, 10 patients (50%) had lung metastases, four (20%) had liver metastases, and two (10%)

had both liver and lung metastases. The remaining five patients (20%) had disseminated disease findings involving lung, liver, and bone marrow metastases. The 5-year EFS for early-stage WT disease is 88%, while the EFS for advanced-stage WT disease is 63.1% ($p = 0.042$). Likewise, the 5-year OS for early-stage WT disease is 95.7% and for advanced-stage WT disease is 63.1% ($p = 0.005$). Patients who had been admitted with early-stage WT disease had significantly improved EFS and OS compared to those with advanced-stage WT disease (Figures 1a and 1b).

Primary surgery was performed on 41 patients (85.4%) while not on any of the others due to the risk of surgical rupture and patient risks associated with the operation. Of the patients who underwent primary surgery, 21 (51%) resulted without residual tumors, while the remaining 20 (49%) had microscopic residual tumors along the surgical margins. Histopathological results were favorable in 30 patients (62.5%) and unfavorable in 12 (25%). The 5-year EFS for the patient group with a favorable histology was 85.2% and 66.7% or the group with an unfavorable histology ($p = 0.2$). Likewise, the OS for the favorable group was 92.1%, whereas the unfavorable group demonstrated an OS of 66.7% ($p = 0.05$). The difference in EFS and OS rates between the two histological groups was not statistically significant. Patients who did not undergo primary surgery upon admission had neoadjuvant chemotherapy with regimens containing vincristine, doxorubicin, etoposide, and carboplatin. When considering treatment modalities, 50% ($n = 24$) of the patients had nephrectomy and chemotherapy, while the other half had nephrectomy, chemotherapy, and radiotherapy. Adjuvant chemotherapy was administered in 35 patients post-surgery. The mean cytotoxic treatment time was detected as 9.3 months (± 7.5 months), while the median cytotoxic treatment time was 6 months (Minimum = 1 month; Maximum = 43 months). The response to induction therapy was evaluated, and 27 patients (56%) were found to be in complete remission (CR). Ten patients (20.8%) were in partial remission (PR), while eight patients had stable WT disease with non-response, and three patients had progressive WT disease.

Table 1: Patient Characteristics

Patient Characteristics	N (%)	
Site	Right	21 (43,8%)
	Left	24 (50%)
	Bilateral	3 (6,3%)
Stage	I	13 (27,1%)
	II	14 (29,2%)
	III	6 (12,5%)
	IV	12 (25%)
	V	3 (6,3%)
Histopathology	Favorable	30 (62,5%)
	Unfavorable	12 (25%)
	Undetermined	6 (12,5)
Time of surgery	Primary nephrectomy	41 (85,4%)
	Second look surgery	3 (6,3%)
	No surgery	5 (10,4%)

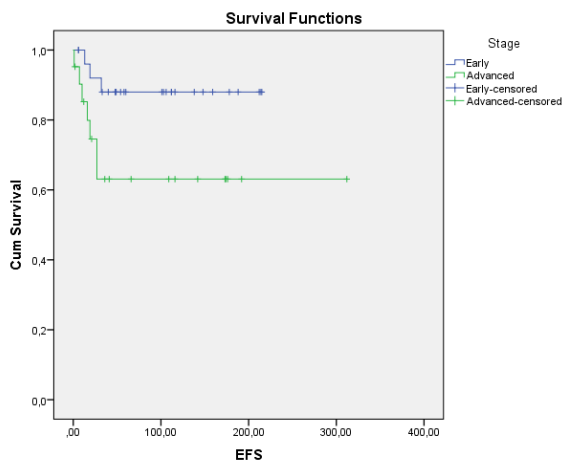


Figure 1a: Comparative EFS analysis by stage of disease on admission

EFS for the early stage: 88%. EFS for the advanced stage: 63,1% (p:0,042).

Second-look surgeries were implemented on three patients, of which two resulted with microscopic residual WT disease and one resulted with no residual disease. Radiotherapy (RT) was applied to 24 of the patients who continued their treatment in the current center. Regarding the RT sites, 16 involved primary tumors (66.6%), while the remaining was performed on both the primary tumor site as well as metastatic regions. Palliative RT was also implemented on four patients, two for lung metastases and two for bone metastases. The median time between surgery and RT is 19.3 days (± 15.9 days). Their 5-year EFS was 77.3%, and their OS was 80.3%.

DISCUSSION

Renal tumors are responsible for 3%-11% of all pediatric cancers. Wilms tumor, although the most common cancer of the kidneys in childhood, is still a rare entity (1-3,7,8). Generally, the mean age at diagnosis is 36 months with a range between 12-48 months. The mean age in the current study was older compared to the literature, which can be attributed to patients/families delaying the hospital admission. When verifying this, the mean age of the advanced-stage patients is also higher than in the literature. However, no statistically significant difference occurred between the early and advanced-stage groups, which can be attributed to the limited number of enrolled patients. WT less commonly develops under the age of 6 months, as observed in the current study. The most frequent symptoms presented upon admission in the present study were abdominal pain, followed by an asymptomatic palpable mass in the abdomen and hematuria. According to the literature, the most frequent symptoms in childhood consist of abdominal mass and swelling, followed by abdominal pain, hematuria, fever, and hypertension (9). One patient was also admitted with an acute abdomen and underwent an operation where the mass was detected intraoperatively. One should underline that a comprehensive diagnostic approach with imaging should be done as appropriately as possible in emergency circumstances.

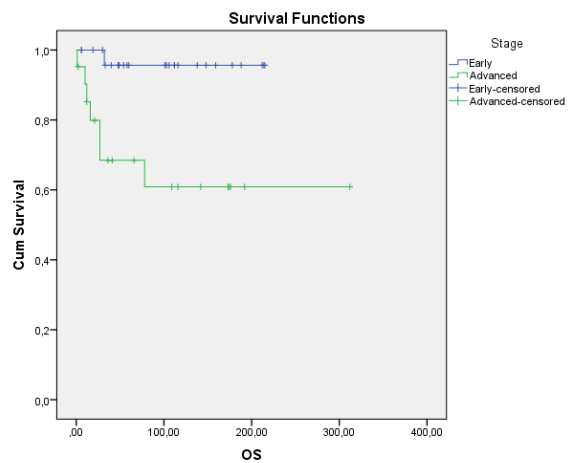


Figure 1b: Comparative OS analysis by stage of disease on admission

OS for the early stage: 95,7%. OS for the advanced stage: 63,1% (p:0,005).

A genetic predisposing syndrome has been determined in 5% of WT patients in the literature. In addition, congenital anomalies accompany 12%-15% of WT cases. Fundamentally, three genetic alterations are determined in WT, which consists of loss of WT1, activation of the WNT pathway, and increased expression of IGF2 (10). Mutations in the 11p13 region of the long arm of chromosome 16 and chromosome 1, where the WT1 gene is located, are associated with the development of WT. Apart from WT1, WT is also associated with loss-of-function mutations in several tumor suppressor and transcription genes, including p53, FWT1, and FWT2 genes and the 11p15.5 locus (11,12). Biallelic inactivation of the WT1 gene is related to WT development and has also been associated with genetic syndromes such as WAGR (Wilms tumor, aniridia, genitourinary anomalies, and mental retardation), Denys-Drash, and Frasier syndromes (10,13). Similar to the literature, 6.2% (n = 3) of the enrolled patients in the current study had predisposing syndromes. In the literature, bilateral WT generally accounts for 4%-13% of all tumors. Likewise in the present study, bilateral WT was found in 6.3% of all patients (5).

Staging and disease histology have key roles in the approach to diagnosing and treating WT. The staging system depends on the extension of the tumor beyond the kidney, tumor spillage or rupture, and involvement of lymph nodes, or peritoneal and hematogenous spread. Distant metastasis rates are reported as 10%-20% in the literature and the lungs are the most common site. However, 43% of patients in the current study had distant metastasis, with the lungs being the most common site, similar to the literature. As a result, the EFS and OS of the current study are slightly lower than reported recently and nationwide (3,14). On the other hand, both the 5-year EFS and OS were significantly higher in patients with the low-stage disease, with p-values of 0.042 and 0.005, respectively. According to the literature, age and stage of admission have a prognostic impact. The Children's

Oncology Group (COG) risk stratification system is based on stage, histology, age, tumor weight, lung nodule response, and loss of heterozygosity (LOH) at chromosomes 1p and 16q (15). The NWTS has demonstrated similar outcomes for the presence of LOH at chromosomes 1p and 16q (16).

Regarding the histopathological evaluation of WT, the histological features of the tumor should be underlined as being related to the chemotherapy response and survival. Anaplasia was demonstrated in 11.5% of patients treated with the Turkish Pediatric Oncology Group (TPOG) National Wilms protocol, which is a poor histological criterion (3). In the current study, both the 5-year EFS as well as the OS were higher in the favorable histology group compared to those with an unfavorable histology. However, the difference was not statistically significant, which can be attributed to the small size of the study population.

Among the large clinical study groups that have worked on WT, two lead the literature and have different management approaches. The main objectives of the two groups are to improve the remission rates while minimizing toxicity. The treatment strategies are adjusted according to the classification based on risk and histological type as proposed in the literature. Therefore, improvements have been made in recent years regarding EFS and OS through standardized management. Two different treatment approaches are available for WT. One of these has been proposed by the International Society of Pediatric Oncology (SIOP) and aims to reduce the tumor burden through pre-surgical chemotherapy, to facilitate surgery, and to reduce surgical risks (17). The other treatment modality is by COG and recommends primary surgery (18). The role of surgery is a highly studied topic on WT. Firstly, surgery provides tissue; hence, the histopathological evaluation becomes possible, and any later treatment can be stratified according to the individual risk. Radical nephroureterectomy is adequate for optimal local control (19). Patients who demonstrate very low-risk features like being younger than 2 years of age and having a Stage I favorable histology with a tumor weight < 550 g can be cured with surgery alone (20). The majority of patients (85.4%) in the present study underwent primary surgery upon admission, so chemotherapy protocols and staging were administered according to the NWTS guidelines. However, seven patients were unable to undergo the primary surgery due to individual risks. Therefore, one should underline that management should always be tailored to each patient individually.

Radiotherapy is a widely used treatment modality in WT, as well as in most other solid tumors that occur during childhood. However, patients should be evaluated carefully regarding the long-term side effects. When managing WT, RT can be exploited both for primary local control and for the control and palliation of metastasis (20). Current protocols have offered different approaches to the utilization of RT. In the COG approach, upfront surgery provides more reliable information about histology and tumor extent. Therefore, the intensity of adjuvant therapy can be decided. In the presence of a favorable histology, RT for local control is used in Stage III tumors. On the contrary, if histology results are unfavorable, RT is indicated

for all patients (21). The SIOP approach has also been recently revised as the Renal Tumor Study Group (SIOP-RTSG Umbrella) and recommends that the decision for adjuvant RT in localized tumors should be undertaken based on tumor stage and pathological findings after preoperative chemotherapy and surgical features such as the presence of residual disease, evaluation of resection margins, tumor spillage, lymph node involvement, and presence of drug-resistant viable tumor cells, as well as a histology risk stratification (22,23). Also, RT dosing levels have been highly studied in the literature. De-escalating the dose of RT has been demonstrated to have no negative impacts on oncological outcomes for local Stage III WT patients (23). The timing of RT has an essential effect on the outcome. A recent study from the National Cancer Database revealed that, in non-metastatic WT adjuvant, RT administered within 14 days (≤ 14 days) after surgery is related to improved survival (24). In the current study, the mean time between surgery and RT was 19.3 days, which is longer than in the literature and may affect the OS and EFS of the current study, which is slightly lower than the rates shown by recent data (7).

Cytotoxic chemotherapy in the current study has been fundamentally utilized based on the COG protocols. After the surgery, adjuvant chemotherapy was implemented in the patients according to the risk classifications that had been conducted based on histology, surgical features, and staging. Chemotherapy was intensified in the presence of anaplasia and advanced disease, and no chemotherapy-related side effects were observed.

CONCLUSION

The main goal of all protocols in the treatment of Wilms Tumor is to increase cure rates and minimize chemo-radiotherapy-related toxicity. The current article shares the treatment experience of a single tertiary center and has also revealed that advanced disease and unfavorable histology are associated with poor OS and EFS. Local treatment should be applied without delay; therefore, WT should be treated in experienced centers.

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Informed Consent: Written consent was obtained from the participants.

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C.E., Z.F.K., F.Ö., M.K.; Final Approval and Accountability- Ş.A., E.Ü., A.Ö., E.Y., M.K., G.P.O., E.Y., Z.F.K., F.Ö., H.A., A.B.D.

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