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Nephroblastoma treatment in children: A clinical retrospective analysis

Asmir Jonuzi[1], Nina Uzunović[2], Emir Milisic[1], Sanjin Glavas[2], Benjamin Kulovac[3], Almir Fajkić[4], Zlatan Zvizdic[1]

Abstract

Objectives: This study aimed to analyze the clinical presentation, diagnostic process, therapeutic approaches, pathological features, and treatment outcomes of children diagnosed with Wilms tumor (WT) and evaluate the time intervals from symptom onset to seeking medical attention and subsequent diagnosis.

Patients and methods: This retrospective study reviewed the records of 18 children (11 males, 7 females; median age: 3.72 years; range, 0.13 to 8.33 years) diagnosed with WT who underwent surgery between January 1, 2010, and December 31, 2023. Data on demographics, clinical presentation, treatment, and outcomes were collected and analyzed. All patients underwent radical nephrectomy and received preoperative and postoperative chemotherapy as per the UMBRELLA protocol of the International Society of Pediatric Oncology Renal Tumor Study Group.

Results: The median age at diagnosis was 37 months. The most common presenting sign was a palpable abdominal mass (100%), followed by abdominal swelling (61%) and distension (67%). The mixed histopathological type was most prevalent (50%). The median time from symptom onset to seeking medical attention was 13.9 days, and the median from initial medical consultation to diagnosis was 9.9 days. Complications occurred in three (17%) patients, and one (6%) patient experienced relapse. The survival rate was 94%.

Conclusion: This study's survival and relapse rates are comparable to global data, reflecting advances in the diagnosis and management of WT at our institution. However, further research is needed to address the study's limitations and enhance outcomes, particularly in resource-limited settings.

Keywords: Clinical presentation, diagnosis, survival, treatment, Wilms tumor.

Wilms tumor (WT) is the most common primary renal malignancy in children with an incidence of 10 out of 100,000 newborns.[1] About 93 to 96% of WT cases arise sporadically and unilaterally, with the peak age of presentation during the third year of life. Bilateral tumors are reported in 4 to 7% of cases, with a mean age of 2.6 years.[2] The most common clinical presentation of WT is abdominal enlargement due to the mass of the tumor. This mass tends to expand and compress other organs around it. This compression causes obstruction of the intestines and sometimes urinary bleeding, with respiratory suppression resulting in death.[3] Diagnosis and degree of tumor are two important aspects of determining the treatment modality. The most common tool of diagnosis that is widely used in children suspected of WT is ultrasonography. Computed tomography and magnetic resonance imaging re more accurate compared to ultrasonography.[4] The gold standard of WT diagnosis is a histopathologic examination of tumor tissues obtained by biopsy. The treatment is carried out using combination therapy consisting of chemotherapy, surgical intervention, and sometimes radiation.[5] Based on the results of previous national and international trials and studies, the Renal Tumor Study Group (RTSG) of the International Society of Pediatric Oncology

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Correspondence: Asmir Jonuzi, MD.

E-mail: jonuziasmir@hotmail.com

[1]Department of Pediatric Surgery, Clinical Center University in Sarajevo, Sarajevo, Bosnia and Herzegovina

[2]Department of Gastroenterohepatology, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina

[3]Department of Urology, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina

[4]Department of Pathophysiology, University in Sarajevo, Faculty of Medicine, Sarajevo, Bosnia and Herzegovina

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(SIOP) has developed a new research protocol for pediatric renal tumors: the 2016 UMBRELLA protocol. As in previous SIOP trials and studies, the UMBRELLA protocol mandates preoperative chemotherapy based on clinical and radiological diagnoses in most patients. All patients included in the study were treated with preoperative, as well as postoperative chemotherapy.[6] Wilms tumor is one of the most common childhood cancers where persistently innovating multimodal strategies have led to the conversion of almost uniformly fatal diseases to ones with excellent survival.[4] Surprisingly, despite such remarkable improvement in survival in developed countries, the outcome of WT in resource-challenged settings continues to be suboptimal.[7,8] Overall survival ranged from 70 to 97% in high-income countries, 61 to 94% in upper-middle-income countries, 0-85% in lower- middle-income countries, and 25 to 53% in low-income countries.[9] This prompted us to analyze our 14-year experience at a tertiary center. Hence, this study aimed to present and analyze the clinical presentation, diagnostic work-up, therapeutic approach, general and pathological characteristics, and the results of treating children with WT. With this work, we want to present and analyze the leading symptoms and signs, the period that elapsed from the onset of symptoms until reaching out to a physician (through primary health care institutions), and the time frame until the diagnosis was made.

PATIENTS AND METHODS

In this retrospective study, the comprehensive clinical database of the Clinical Center University of Sarajevo, Bosnia and Herzegovina, was searched for pediatric patients with WT who underwent surgery at the Department of Pediatric Surgery between January 1, 2010, and December 31, 2023. Patients whose files were incomplete were excluded from the study. Eighteen children (11 males, 7 females; median age: 3.72 years; range, 0.13 to 8.33 years) registered at our center were included in the study. Demographic, preoperative, intraoperative, and postoperative data were collected from patient's medical records. Due to the retrospective nature of the study, informed consent was waived. The study protocol was approved by the Ethical Committee of the Clinical Center, University of Sarajevo (date: 08.03.2024, No: 30-5-9017/24). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

Data were analyzed using Microsoft Excel (Microsoft Corp., Redmond, WA, USA). For continuous variables, mean and median were used as measures of central tendency, and standard deviation and range as measures of dispersion. The values of categorical variables were presented as numbers or percentages. Significance was assumed at a p-value <0.05.

RESULTS

The median age at diagnosis was 37 months. The demographic and other characteristics of the included patients are summarized in Table 1. Out of 18 patients, only one (6%) patient had a positive family history. In nine (50%) patients, the tumor was localized on the left kidney, and on the right kidney in eight (44%). One patient had a bilateral WT. Metastases were present in four (22%) patients, while 14 (78%) patients did not have metastases present. All patients were treated according to the SIOP RTSG UMBRELLA protocol, all received preoperative and postoperative chemotherapy, and all patients underwent radical nephrectomy. Chemotherapy according to the UMBRELLA protocol was administered both before and after surgery. Preoperative treatment includes actinomycin D at a dose of 15 μg/kg of body weight on three consecutive days, and again on the 15th to 17th day. Vincristine was given at a dose of 1.5 mg/m^2 on days one to eight and repeated on days 15 and 22. Surgery was performed on day 29. The result of preoperative therapy was tumor shrinkage or significant tumor necrosis. Postoperative chemotherapy continued seven days after the surgical procedure.[5] Radiotherapy was performed in two (11%) patients. In seven (39%) patients, Stage 1 disease was determined; in six (33%) patients, Stage 2; and in five (28%) patients, Stage 3. No patient had Stage 4 or Stage 5 disease. The most common pathohistological type in patients was the mixed type, which was found in nine (50%) patients, followed by blastema type in three (17%), anaplastic type in three, epithelial type in two (11%), and stromal type in one (6%) patient. Recurrence of the disease was found in one patient.

TABLE 1
Demographics and other characteristics of patients with Wilms tumor

Criteria	n	%
Sex		
Male	11	
Female	7	
Family history		
Negative	17	
Positive	1	
Side		
Right	8	
Left	9	
Both	1	
Metastases		
Present	4	22
Without metastases	14	78
Therapeutic treatment		
Radiotherapy	2	11
Preoperative chemotherapy	18	100
Postoperative chemotherapy	18	100
Nephrectomy	18	100
Stage		
1	7	39
2	6	33
3	5	28
4	0	0
5	0	0
Histopathology		
Anaplastic	3	17
Blastemic	3	17
Epithelial	2	11
Stromal	1	6
Mixed	9	50
Relapse		
Yes	1	6
No	17	94
Complications		
Yes	3	17
No	15	83
Mortality	1	6
Survival	17	94

Complications after surgery occurred in three patients (sepsis, pneumonia, and hiloabdomen). One patient died. The survival rate was 94%. The most common sign observed in our patients was a palpable mass in the abdomen, which was present in all patients (Table 2). Most subjects had swelling (n=11, 61%) and abdominal distension (n=12, 67%). Fever and abdominal pain were present in five (28%), nausea and macrohematuria in three (17%),

TABLE 2
Symptoms and signs of the disease (clinical presentation)

Symptoms and signs	n	%
Palpable mass	18	100
Swelling	11	61
Abdominal pain	5	28
Nausea	3	17
Constipation	2	11
Vomiting	1	5.5
Diarrhea	1	5.5
Fever	5	28
Macrohematuria	3	17
Microhematuria	1	5.5
Signs of blood vessels invasion	0	0
Abdominal distension	12	67
Dyspnea	0	0

constipation in two (11%), and microhematuria and vomiting in one (6%) patient. The median time from the onset of symptoms/signs to the presentation to the physician was 13.9 days, and the median time from the presentation to the physician to the diagnosis was 9.9 days (Figure 1).

DISCUSSION

Most studies have stated that there is no significant difference in the representation of patients between boys and girls. Some studies indicate that in certain Asian countries, girls have a higher chance of developing WT, even up to four times more than boys.[10] According to a study by Caldwell et al.,[11] girls get WT slightly more often than boys. According to research done in Pakistan (Rawalpindi), out of 84 cases, 40 (47.6%) were boys and 44 (52.4%) were girls.[12] Another study conducted in Pakistan (Lahore) stated that WT occurs more often in boys (55.9%) than in girls.[13] The results of our study are similar.

Most of the conducted studies indicate that the diagnosis is mainly made before the child is five years old,[10,14] while the median age of the child at the time of diagnosis is two to three years of age.[15,16] The average age at which WT is diagnosed is three years of age. The study[17] states that the diagnosis is established from the first to the fifth year of life

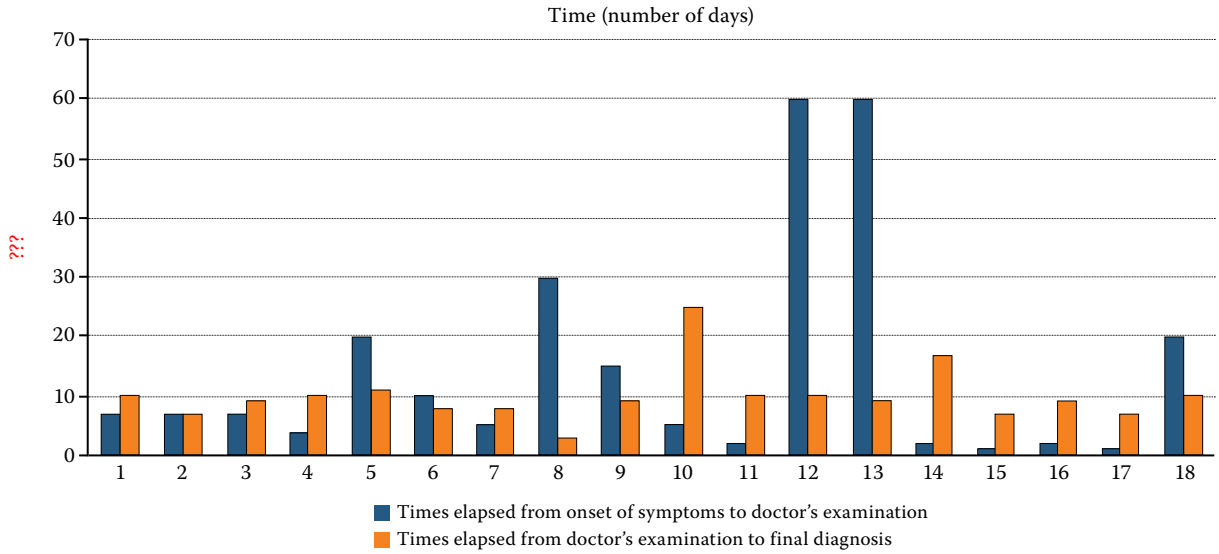

Figure 1. Time (number of days) elapsed from the onset of symptoms/signs to the time of reporting to the physician and the time from reporting to the physician to the diagnosis.

in 78% of respondents, dominantly between the third and fourth year of the child's life. In their work, Gooskens et al.[18] state that the age of the child is an extremely important prognostic factor. Age <2 years is considered a favorable prognostic factor, while age >2 years is regarded as a negative prognostic factor.[18] A study stated that younger age has a higher survival rate; in patients younger than seven months, the overall survival rate was 93.4%, and the incidence of metastatic spread was <1%.[19] At the time of diagnosis, the largest number of our respondents (39%) were in the age group of four to six years, and the median age of the respondents at the time of diagnosis was 37 months.

Wilms tumor can be related to genetic predisposition in 5 to 10% of cases.[20] If a predisposition is suspected before the diagnosis of WT, the tumor can be detected through a screening program.[20] Wilms tumor usually occurs sporadically, while in 1% of cases, it is present in the family.[21] In our study, one patient had a positive family history.

In a paper published by Paulino et al.,[22] they stated that abdominal pain was present in 28% of subjects, which is analogous to the results of this paper where pain was present in 28% of subjects. Additionally, Paulino et al.[22] stated that macrohematuria was present in 5 to 30% of subjects, while in this study, it was found in 17% of subjects. Mullen and Graf[23] confirmed that the most common sign at presentation was the presence of a palpable abdominal mass or swelling in otherwise healthy children. A study conducted in Lithuania found that the most common presenting symptom was pain (in 47.9% of subjects), while a palpable abdominal mass was present in only 14.3% of subjects.[24] Research in Johannesburg found that the most common presenting sign was the presence of an abdominal mass, with a rate of 60%. Abdominal pain is an occasional presentation, which most often occurs after trauma, causing bleeding or, less frequently, tumor rupture. Hypertension occurs in 25% of patients and is caused by the production of renin by tumor cells. Hematuria can be macroscopic, but it is most often microscopic and occurs in 15% of subjects.[17]

In our study, the most common sign was a palpable abdominal mass, found in 100% of subjects. Based on the medical documentation, it was concluded that the parents most often noticed the first signs of the disease while bathing or changing the children's clothes. Abdominal swelling and abdominal distension were also observed in most subjects, occasionally accompanied by elevated body temperature, abdominal pain, nausea, constipation, macrohematuria, and vomiting. None

of the subjects had signs of vascular invasion or dyspnea.

In our study, four (22%) subjects had associated congenital anomalies in addition to WT: unilateral or bilateral cryptorchidism, Perlman syndrome, and heart murmur. The presence of congenital anomalies was confirmed in other studies.[3,10,25]

Regarding the localization, in the study conducted by Alakaloko et al.,[26] WT was primarily localized in the right kidney in 57.5% of the subjects, while in the left in 42.5%. In Kalapurakal et al.'s[27] study, most patients had solid WT; 5 to 7% of patients had bilateral WT, while 10% had multifocal tumors in one kidney. In another study, the tumor was located in the right kidney in 39.2% of subjects and in the left kidney in 57.1%.[28] Only one subject had a bilateral tumor.[28] In our study, in nine (50%) subjects, the tumor was localized on the left kidney, and in eight (44%), it was located on the right kidney. One (6%) subject had a bilateral WT.

A study found that metastases were present in about 12% of cases with WT, of which 80% were located in the lungs.[29] The primary site of distant metastases for WT is the lungs, while liver metastases are much less common.[29] Rančelytė et al.[24] showed that WT was localized in 87.5% of subjects, while metastases were present in 12.5%. Most of these metastases were found in the lymph nodes around the kidneys, as well as in the lungs and liver. According to research by Vedaswari and Ariawati,[30] metastases were present in 10% of subjects, with the most common localization being the lungs. Hepatic and lymphatic metastases were much less common, and bone metastases were extremely rare.[30] In our study, metastases were present in four (22%) cases.

In a study, the median duration of symptoms was 2 (range, 1 to 8) months[28] The median time to diagnosis was 10 (range, 2 to 22) days from the first visit to the physician.[28] According to another study, the median time from the onset of symptoms to visiting a physician was 3 weeks (range, 1 day to 8 weeks).[31] In 66 (67.3%) patients, the onset of symptoms to the first pediatric examination was 30 days.[31] There are several factors that affect duration from initial medical consultation to diagnosis. Most common problems in healthcare systems are delays in imaging, long chains of referrals, or unavailability of pediatric specialists, as well as limited experience in primary care providers. In our sample, the median time from the onset of symptoms/signs to reporting to a physician was 13.9 days, and the median time from reporting to a physician to diagnosis was 9.9 days. Compared to other studies, the median time from the onset of symptoms/signs was shorter, while the median time to diagnosis was similar.[28,31] All of our patients were treated according to the SIOP protocol.

According to research conducted by Popov et al.,[32] the anaplastic type accounted for 5 to 8% of all WT types, indicating a higher incidence rate of anaplasia in our subjects. In a study that examined the treatment outcome of subjects with epithelial and stromal subtypes, out of 1,389 examined patients, 1% consisted of highly differentiated epithelial type, 4% epithelial subtype, 10% stromal subtype, and 85% other intermediate risk types.[33] Compared to this study, histologically, a higher incidence of the epithelial subtype (11%) and a lower incidence of the stromal subtype (6%) were determined in our subjects. In a study in China, out of 97 subjects, 40 (41.2%) had mixed type, 21 (21.6%) mesenchymal type, 14 (14.4%) epithelial type, and 22 (22.7%) blastemic type.[34] The most common type in our patients was mixed and was found in nine (50%) subjects, followed by the blastemic type in three (17%), the anaplastic type in three, the epithelial type in two (11%), and stromal type in one (6%) subject.

In a study, the relapse rate was 13%.[35] Therefore, the recurrence rate in our subjects was significantly lower (6%). According to another study, about 10% of patients from the intermediate risk group and up to 25% of patients with a high-risk tumor experienced disease relapse.[36] Another study that included 97 patients with WT of favorable histology found that the overall tumor recurrence rate was 17.5%.[37] Recurrence by WT subtypes was 45.5% for the blastemic type, 7.5% for the mixed type, 14.3% for the epithelial type, and 9.5% for the mesenchymal type.[34] In a study, the relapse rate was 23%.[37]

Examining the occurrence of complications after surgery, it was determined that three (17%) subjects had complications, while the rest of the subjects (83%) had no complications.

Complications that occurred include sepsis (*Pseudomonas aeruginosa* infection), pneumonia, and chyloabdomen.

The most common complications after nephrectomy due to WT are intestinal obstruction, extensive intraoperative hemorrhage, damage to visceral organs, wound infections, and vascular injury. In the study by Richey et al.,[38] 12.7% of subjects experienced complications after surgery. Intestinal obstruction was the most common complication (5.1%), followed by major bleeding (1.9%), wound infection (1.9%), and vascular injury (1.5%).[38] In this study, the authors state that the risk of complications was higher if the operation was performed by a general surgeon and not by a pediatric surgeon or a pediatric urologist.[38] The research carried out in Memphis described the complications arising during the surgical treatment of WT. Complications (infection, transient renal insufficiency, and intussusception) occurred in 36.4% of subjects.[39] In our study, the following complications occurred in three (17%) patients: *Pseudomonas aeruginosa* infection, pneumonia, and chyloabdomen.

The survival rate of patients with WT ranges between 80 and 90% of subjects.[22]A study showed a five-year survival rate of 94.6±3.7%.[40] In a study, the five-year survival rate was 75%.[26] According to research conducted in China, the five-year survival rate was 81.4%.[34] Based on the WT subtypes, the overall five-year survival rate of the dominantly blastemic subtype was 68.2%, mixed type was 88.9%, epithelial was 85.1%, and mesenchymal was 94.7%.[34] The authors stated that the dominant blastema subtype had a higher rate of disease recurrence and a lower five-year survival rate of subjects. In our study, the survival rate was 94%.

This study had some limitations. First, it was retrospective, lacking the validation of prospective studies. Second, it was a single-center study with a small sample size.

In conclusion, the clinicopathological profile of WT at the Clinical Center University in Sarajevo, Bosnia and Herzegovina, was generally similar to that of other studies from other countries. This study demonstrated that the survival and relapse rates were similar to those worldwide, indicating progress in treating patients with WT.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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