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PREDICTORS OF SURVIVAL OUTCOMES OF WILMS TUMOR TREATED FOLLOWING THE SIOP 2001, LAHORE PAKISTAN EXPERIENCE.

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Abstract

Background:

Wilms tumor is the most common pediatric renal neoplasm. Various histological subtypes, risks, and clinical stages are determined after preoperative therapy. The survival outcomes of different subtypes are excellent depending upon the patient's stage. In developed countries, overall survival and disease-free survival are remarkably high due to early presentation and close follow-up.

Methodology

A retrospective study was conducted at the Pediatric Hematology/Oncology Department, Children's Hospital Lahore. All diagnosed WT cases from 1st January 2014 who completed their treatment before 31st December 2018 were included. Entire management was based on SIOP 2001. Patients presenting before nephrectomy received four preoperative chemotherapy cycles depending on the clinical stage. After nephrectomy, the postoperative chemotherapy regimen was based on the patient's stage, risk stratification, and metastatic status. The survival outcomes of different histopathological subtypes, and stages were determined via Kaplan-Meier survival analysis, and the p-value was calculated via a log-rank test.

Results

The mean age of the 93 children was 44.4+ 30.92 months. The majority of the cases were males (55.9%) and commonly noted in the right-sided kidney (55.9%). Most patients completed the entire course of treatment (77.4%). The overall survival of the whole cohort was 88.2%, and event- free survival was 77.4%, at the 36-month follow-up. In our study, OS significantly dropped from 94.4% in stage II to 66.7% in stage IV disease (P< 0.001). Our study showed that there were more deaths of patients during the course of treatment by febrile neutropenia rather than relapse which affected treatment outcomes.

Conclusions

Our study showed that advanced-stage presentations and febrile neutropenia during treatment

contribute to the decreased OS and EFS seen in different histological subtypes and stages. Despite belonging to a low-middle-income class country and having an uneducated background, the majority of the patients completed the entire course of treatment, and relapse was fairly rare. The perks of the current study are that our hospital is the only pediatric tertiary care center in Lahore, which has investigated a variety of parameters influencing the course of WT treatment over three years.

Keywords: Wilms tumor (WT), (SIOP staging) Internal Society of Pediatric Oncology) National Wilm's Tumor Study Group (NWTS), Post chemotherapy.

Background

Wilms tumor (WT) or Nephroblastoma accounts for 85% of renal tumors and 6% of solid tumors in children.(1) The majority of WT are sporadic cases, however, 10% are found in genetic syndromes with bilateral presentation. The WT tumors are derived from nephrogenic rests, thus it is commonly seen under 5 years of age. (2) According to the annual statistical report of the World Health Organization (WHO), the median reported incidence is 15.1/million. The median incidence of WT in Asia is 7.6/million, hence, in Pakistan and India, the prevalence of WT is 3.6 and 4.8/million, respectively, with a small male predominance. (3) WT commonly presents with an abdominal mass and frequently metastasizes to the lungs and liver. 15 to 20% of WT cases are of stage IV disease. (4-5)

The advancement in WT treatment is one of the great achievements in pediatric oncology. At present, WT is managed by two treatment regimens, the National Wilms Tumor Study Group (NWTS), a part of the Children Oncology Group (COG), and the International Society of Pediatric Oncology (SIOP). The key distinction is the use of preoperative chemotherapy between NWTS and SIOP; nevertheless, no difference in Overall survival (OS) and Event-free survival (EFS) was found. Preoperative chemotherapy following the SIOP-RTSG Umbrella protocol categorized WT as low-risk (LR) tumors, Completely necrotic type (CN), intermediate risk (IR) tumors, Epithelial type (ET) (Fig.4), Stromal Type (ST), Mixed type (MT), Regressive type (RT), Focal Anaplastic type (FA). High-risk (HR) tumors; include Blastemal Predominant (BP) (Fig.3) and Diffuse Anaplastic (DA) subtypes. Bilateral tumors are stage V. (6-7)

By following SIOP 2001, WT is treated with prophylactic chemotherapy, surgery, and radiotherapy depending upon the localized or metastatic disease, and risk of WT. The assessment of clinical prognostic markers i.e., stage via NWTSG/SIOP has shown 90% survival in localized disease and 80% in metastatic patients and minimized treatment-related toxicities and omission of abdominal radiography in completely necrotic tumors. This report deciphers predictors of treatment outcomes of WT, and it is the first comprehensive research article regarding OS, and EFS during follow-up from the Lahore regional center. In our center, we are following the SIOP 2001 working classification based on pre-operative chemotherapy. The present study was carried out to determine the survival outcomes of histopathological subtypes and stages of WT treated as per the SIOP 2001 protocol. (8-12)

Methods

Study Population

This retrospective descriptive study was conducted at the Pediatric Hematology/Oncology

Department of Children's Hospital and Institute of Child Health, Lahore, Pakistan. The hospital ethical committee approved the study vide letter number approved by the Ethical Review Board vide letter No. 02/173/17 dated 01/02/2017, and informed consent was obtained from the parents of the patients. All the methods were performed according to relevant guidelines. All diagnosed cases of localized and metastatic WT registered from 1 January 2014; onward who completed their treatment before 31 December 2018 were included. Patients still on treatment at the time of data analysis and those who have not received any neoadjuvant chemotherapy were excluded. Four weeks of preoperative therapy consisting of vincristine (1.5mg/m^2) and Actinomycin D (45 mg/kg) in localized WT is administered. Doxorubicin (50mg/m^2) was added in metastatic cases with an extended time of six weeks. In the 5-6th week, nephrectomies were done by the surgical team, and specimens were sent to the Histopathology Department. Histopathological subtypes of WT, risks, and pathological staging were noted. Patients with localized WT completed 27 weeks of postoperative therapy with a combination of vincristine (1.5mg/m^2), Actinomycin D (45 mg/kg), and Doxorubicin (50 mg/$m^{2)}$. Patients with metastasis received 34 weeks of alternative blocks of chemotherapy (Cyclophosphamide 450 mg/m^2, doxorubicin 50mg/m^2, Etoposide 150 mg/m^2, and carboplatin 200 mg/m^2), and radiotherapy. After completion of treatment, patients were scheduled every two months for the first year, quarterly for the next two years, and biannually thereafter until five years post-treatment.

Data analysis:

For categorical and qualitative data, frequencies and percentages were determined. EFS is defined as the length of time after remission till the occurrence of an event as the progression of the disease, relapse, or death. OS was defined as the time from the day of diagnosis to the day of the last follow-up or death. Kaplan-Meier survival analysis was performed to analyze the survival of various histological subtypes and stages at 36 months follow-up. Survival differences were compared using the Log-Rank test, and a P-value <0.05 was considered statistically significant. Multivariate analysis by logistic regression was performed with prognostic factors having a P-value < 0.05.

Results

Patient demographics and clinical presentation

From January 2014 to December 2018, a total of 93 patients were included in our study. More than half of the patients presented under 36 months of age, with a male and right-sided preponderance of 55.9%. Majority of patients presented with abdominal masses. (Table 1)

Table: 1 The key demographics of patients with WT

Age at diagnosis		
• Mean age	44.4 months±30.92	
• Age range	6-180 months	
Various Age Groups	**Number 93 (n)**	**Percentage 100 (%)**
• Up to 36 months	50	53.7
• 37 to 72 months	29	31.1
• 73 to 108 months	9	9.6

• 109 to 143 months	4	4.3
• Above 144 months	1	1.1
Gender		
• Male	52	55.9
• Female	41	44.1
Primary tumor site		
• Right	52	55.9
• Left	37	39.8
• Unspecified side	4	4.3
Histological Subtypes		
• CN	12	12.8
• RT	20	21.3
• ET	18	18.1
• MT	21	23.4
• ST	11	11.7
• DA	1	1.1
• BP	10	10.7
Stage		
• Stage 2	36	38.7
• Stage 3	45	48.3
• Stage 4	12	12.9

Predictors of treatment outcome

The OS and EFS of the cohorts were 88.2%, and77.4%, respectively. In univariate analysis, the advanced stage of the tumor and metastatic disease adversely affected the treatment outcome. Stage II had the best treatment outcome. OS was 94.4%, 88.9%, and 66.7% in stage II, III, and IV disease, respectively (P< 0.001) (Fig. 1). EFS was 88.9%, 80.0%, and 33.3%in stage II, III, and IV disease, respectively (P< 0.001) (Table 2). A total of twenty-one (22.5%) patients expired during and after treatment, out of which mortality was more due to febrile neutropenia (n=11, 11.8%) than disease progression (n=10, 10.7%). As more than half of our patients were in the 36-month age group, the majority of events and deaths were recorded in this age group (n=10, 10.7%). Eight(8.6%) patients were lost to follow-up after the completion of treatment. Sex, age at

presentation, histological subtypes, and laterality did not show any association with treatment outcome, p >0.05. Multivariate analysis was performed for the following variables: stage of the disease and site of the tumor (Table 2). Histologically, the majority of cases were IR (n=70, 75.2%) and showed less than 65% necrosis, the MT subtype (n=22, 23.4%), and the least observed subtype was DA (n=1, 1.1%).

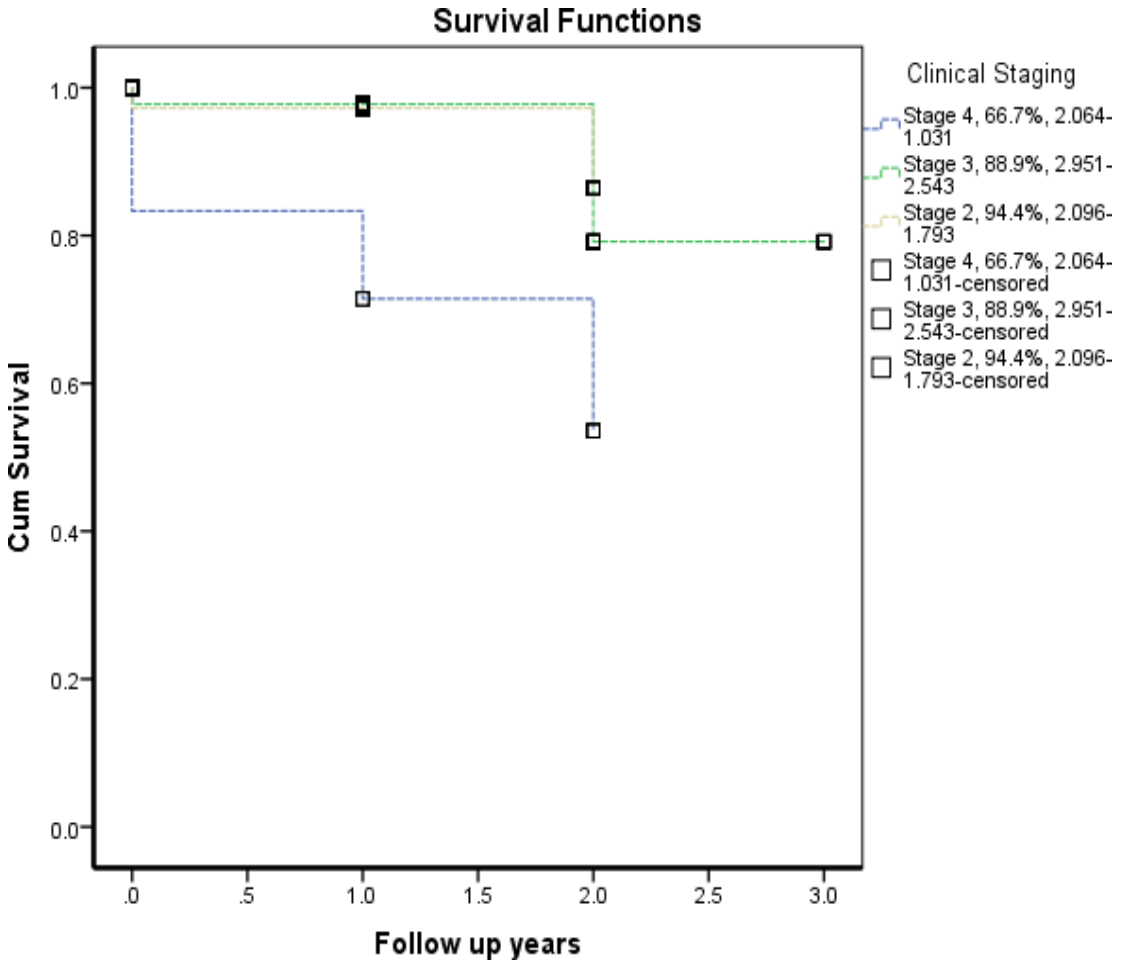

Fig: 1 OS of different clinical stages of WT following the SIOP-2001 Protocol (SPSS Version- 23)

Table: **2** Comparison of OS and EFS by clinical stage, histological subtype, tumor site, and age group in WT patients of both sexes at the 3-year follow-up

Clinical Staging	EFS 3 years	95% CI	Total events	P value	OS 3 years	95% CI	Total deaths	P value	Total cases
Stage4	33.3	.277 - .599	8	.031	66.7	1.031 -2.064	4	.000	12(12.9)
Stage3	80.0	.148 - 2.221	9		88.9	2.543 -2.951	5		45(48.3)
Stage 2	88.9	.088 - 1.716	4		94.4	1.793 -2.096	2		36(38.7)
Gender									
Male	85.7	2.344 2.877	7	.048	95.9	2.744 3.034	2	.014	
Female	68.2	1.834 2.526	14		79.5	2.137 2.730	9		
Histological Subtypes									
CN	58.3		5		91.7		1		12(12.8)
RT	70.0		6		85.0		3		20(21.3)
ET	83.3		3		83.3		3		18(18.1)
MT	81.0	-	4	.510	90.5	-	2	1.00	21(23.4)
ST	81.8		2		90.9		1		11(11.7)
DA	100.0		0		100		0		1(1.1)
BP	90.0		1		90.0		1		10(10.7)
Laterality									
Right	82.7	2.823-2.311	9		90.4	2.955-2.562	5		
Left	73.0	2.624-1.805	10	.299	86.5	2.908-2.237	5	.615	
NS	50.0	2.000-2.000	2		75.0	2.000-2.000	1		
Age									
36m	80.0		10		94.0		3		50(53.7)
37 to 72m	72.4		8		82.8		5		29(31.1)
73 to 108m	66.7	-	3	.730	66.7	-	3	.159	9(9..6)
109 to 144m	100.0		0		100.0		0		4(4.3)
Above 144m	100.0		0		100.0		0		1(1.1)

Completely necrotic type (CN), Epithelial type (ET), Stromal Type (ST), Mixed type (MT), Regressive type (RT), Blastemal Predominant (BP), Diffuse Anaplastic (DA)

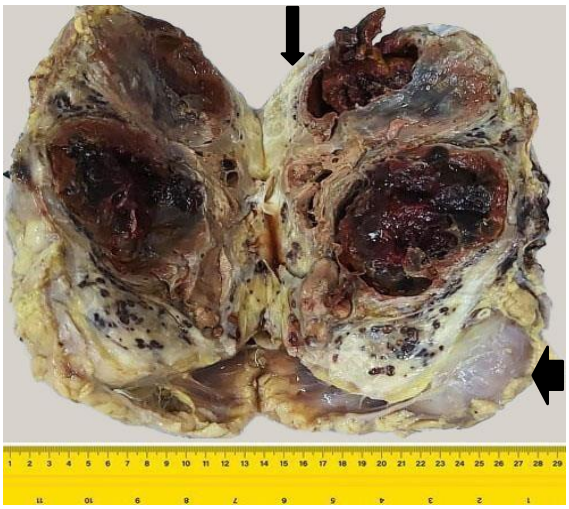

Fig: 2 Post-chemotherapy bivalve nephrectomy specimen showing variegated cut surface composed of solid and cystic areas. The periphery shows a dwarf kidney (left arrows).

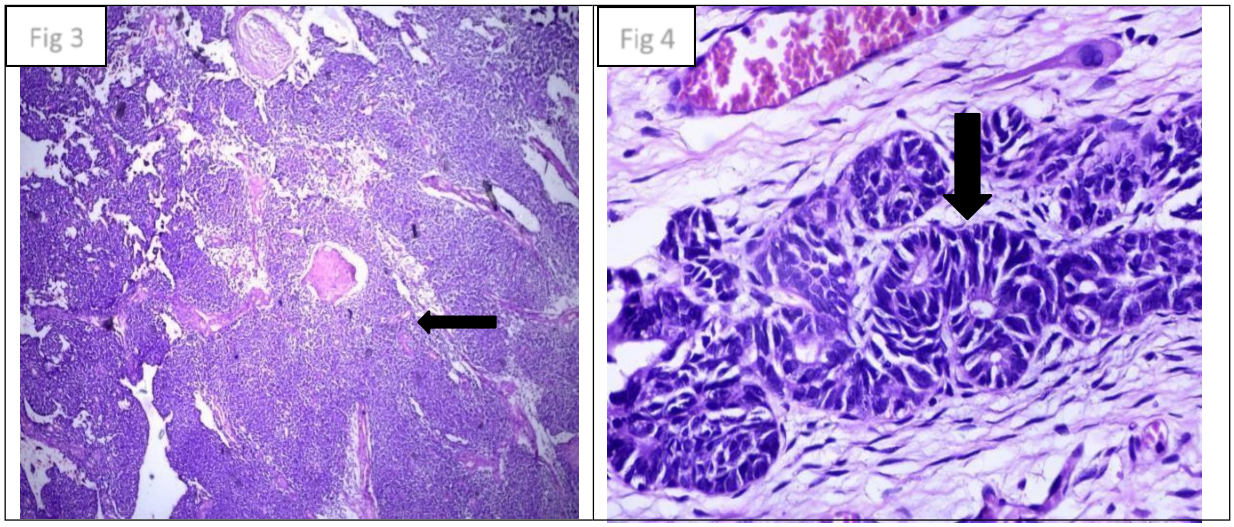

Fig: 3 Photomicrograph of H&E staining shows extensive viable residual tumor composed of the undifferentiated blastema (Blastema Predominant, High Risk) X 20.
Fig:4 Photomicrograph of H&E staining shows viable residual tumor composed of neoplastic tubules (Epithelial Predominant, Intermediate Risk) X 20

Discussion

Pakistan is a low-middle income country (LMIC) with 64 million (30.76%) children under 15 years of age. [20] Children's Hospital & Institute of Child Health Lahore is a pediatric regional center in Lahore that admits patients from all over Pakistan. There is a meager amount of exclusive Pediatric Hematology/Oncology healthcare facilities in the country. Apart from the in- house patient burden, a large number of patients also come for treatment from neighboring countries such as Afghanistan. There is a paucity of published data on pediatric renal tumors from Pakistan. [20] This single-center study deciphers the clinicopathological features and predictors of treatment outcome of WT.

In the present study, the mean age, sex, and right-sided kidney involvement were similar to those in local and international studies [14-25]. SIOP and NWTS are used to treat WT worldwide, while comparing both treatment protocols, the difference between OS and EFS is trivial. Our hospital is following the SIOP 2001 Protocol, and we calculated OS and EFS at the three-year follow-up of our patients. In our study, the OS was 88.2%, comparable to Khan MR et al. 83.8% and Ghafoor et al. 78.6%. [15, 21,20] However, Ekenze SO et al and D.K. Stones, et al. reported slightly lower rates of 53.3% and 67%, respectively. [17, 25] (Table 2) In our study, EFS was 88.2%, comparable to other authors. [17-21] In contrast, NWTS reported higher OS rates of 85.2% and 81%. 6-7,10, 29

Delayed presentation with advanced-stage metastatic disease is quite common in developing countries and is the major contributor to decreased EFS and OS. [19,26-29] In the present study, 12 (12.9%) patients had metastatic stage IV disease. This proportion of metastatic disease is higher than that reported from developed countries and similar to that reported from developing countries. The metastatic disease had significantly lower EFS and OS than localized disease. [26- 28-29,31

OS decreased from 94.4% in stage II to 66.7% in stage IV disease (P< 0.001) and EFS decreased from 88.9% in stage II to 33.3% in stage IV disease (P< 0.001). Very similar results were reported by a regional study. [14, 18, 20] In our study, the majority of patients had clinical stage III tumors (48.3%) (Table 2), similar to other local and international reports. [9,14-15,18-20,24,31]

The results in stage II disease are comparable to those documented in the Western world and low in advanced-stage disease. [20-31] Lack of resources and education is the main reason for delayed and advanced-stage disease. In our study, treatment-related mortality and progression of disease were comparable with other studies. [14,18- 20, 26-29]

The significance of the present study is that multiple factors, affecting the treatment outcomes of WT over an almost three-year period were thoroughly evaluated. Educating general pediatricians for expeditious referral to pediatric oncologists reduces the proportion of advanced-stage disease and improves both the OS and EFS of WT cases in our country. Furthermore, acquiring one uniform protocol in all pediatric Oncology treatment centers throughout the country, under the umbrella of the Pakistan Society of Pediatric Oncology will result in a congregant treatment strategy all over the country.

Conclusion

The stage is the most important prognostic predictor of Wilms tumor. Late presentations with superadded febrile neutropenia during treatments have a poor outcome.

Declarations

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Author contributions

Conception and design: Alia Ahmad, Madiha Ashraf
Interpretation of data: Fariha Sahrish
Drafting of the manuscript: Shehla Arshad, Naziha Azam
Critical revision of the manuscript for important intellectual content: Alia Ahmad, Amema Hafeez
All authors read and approved the final manuscript.

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from corresponding author Dr. Alia Ahmad repository on reasonable request.

Declarations Ethics approval and consent to participate
This study was approved by the Institutional Review Board of Children's Hospital & Institute of Child Health Lahore, vide letter No. 02/173/17 dated 01/02/2017, and informed consent was obtained from the parents of the patients.

Consent for publication

1. **Preprint Posting on Research Square:**
   This manuscript is also posted as a preprint on the Research Square platform (21 December 2022) during its earlier submission to BMC Scientific Reports. As such, there is some content overlap with the preprint version. The preprint is available at: https://doi.org/10.21203/rs.3.rs-2362164/v. I would like to emphasize that the content remains the original work of the submitting authors and I am fully committed to maintain ethical standards.

2. **Authorship Changes:**
   The current manuscript includes changes to the author list compared to the preprint version. These adjustments were made to reflect updated contributions during manuscript revision and finalization, by ICMJE authorship criteria and mutual agreement among collaborators.

3. **Sequential Data Publication:**
   This study is part of a longitudinal research effort that began in 2015. The dataset analyzed here builds upon earlier work, with new follow-up data and a distinct focus on survival outcomes under the SIOP 2001 protocol under the kind supervision of corresponding author Dr. Alia Ahmad.
   1.Histological Subtypes & Staging of Post-Chemotherapy Wilms Tumor According to SIOP 2001 Protocol: Study at the Children's Hospital, Lahore Proceedings S.Z.M.C., 2021
   Portions of the clinicopathological dataset (particularly Tables 1 and 2) were going to be published in the following article as accepted by Rawalpindi Medical College Journal
   Clinicopathological Features of Different Histopathological Subtypes and Stages of Wilms Tumor

4. **Conflicts of Interest:**
   I would like to emphasize that the content remains the original work of the submitting authors and I am fully committed to maintain ethical standards. The corresponding author acknowledges that changes in authorship between the preprint version and differences in institutional affiliations have been resolved by the International Committee of Medical Journal Editors (ICMJE) authorship guidelines with the approval of the Institutional Review Board. The corresponding author affirms that these factors have not influenced the integrity, analysis, or interpretation of the data presented in this manuscript.

List of abbreviations used in the articles

National Wilms Tumor Study Group (NWTS)
Children Oncology Group (COG)
International Society of Pediatric Oncology (SIOP)
Overall survival (OS)
Event-free survival (EFS)
Low-risk (LR)
Completely necrotic type (CN)
Intermediate risk (IR)
Epithelial type (ET)
Stromal Type (ST)
Mixed type (MT)
Regressive type (RT)
Focal Anaplastic type (FA)
High-risk (HR)
Blastemal Predominant (BP)
Diffuse Anaplastic (DA)

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