Original Article

Clinicopathological Features Of Different Histopathological Subtypes And Stages Of Wilms Tumor

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Article Processing
Received: 11/09/2022
Accepted: 01/01/2023

Cite this Article: *Ahmad, A., Anjum, A., Hashim, I., Hussain, M., Zaman, S., & Sahrish, F. (2023). Clinicopathological features of different Histopathological Subtypes and Stages of Wilms Tumor . Journal of Rawalpindi Medical College, 27(1).*
DOI: https://doi.org/10.37939/jrmc.v27i1.2040

Conflict of Interest: *Nil*
Funding Source: *Nil*

Abstract

Objective: Wilms tumor is the most common pediatric renal neoplasm. Following preoperative therapy, various histological subtypes, risks, and clinical stages are determined as per following SIOP 2001 protocol. To determine the clinicopathological features of different histopathological subtypes and stages of Wilms tumor after completing a course of preoperative as well as postoperative chemotherapy following SIOP 2001 protocol.

Methodology: This is a retrospective cross-sectional study, and the sample size was calculated by the non-probability technique. Ninety-three patients with abdominal masses in the Hematology/Oncology Department were included. After radiological and histopathological diagnosis, four weeks of preoperative chemotherapy were given to patients, followed by partial and radical nephrectomies by the surgical team. Specimens received in Histopathology Department were grossed and microscopically examined for different post-chemotherapy histological subtypes. Further risk categorization and clinicopathological staging in accordance with SIOP 2001, done after completion of treatment. Patients called for yearly follow up for the next five years. Categorical variables are presented as frequencies and percentages.

Results: Mean age of ninety-three children was 44.4 months $\pm$ 30.92 with a predominance of males (55.9%) and more common in right-sided kidneys (55.9%). The majority of patients completed the entire course of treatment (77.4%). The majority were intermediate-risk tumors (76.3%) and the most common histological subtype was the Mixed Tumor subtype (23.4%). In our study majority, of tumors were stage III (48.3%) and patients died due to febrile neutropenia (9.6%)

Conclusion: In our study, the majority of patients completed the entire course of treatment, and relapse was fairly less. Patients lost to follow-up after nephrectomy and deaths at home caused by febrile neutropenia were our major challenges.

Keywords: Wilms tumor (WT), Internal Society of Pediatric Oncology (SIOP 2001), Post chemotherapy.

Introduction

Pediatric renal tumors constitute 7% to 8% of solid malignancies out of which Wilms tumor (WT) is reported as 90% of malignant renal neoplasm. Mostly, WT affects children of age 0-4 years. The median reported incidence is 15.1 per Annual Statistical Report (ASR)/million and the interquartile range (IQR) is 11.8-18.7 by the World Health Organization (WHO), International Incidence of Childhood Cancer (IICC). The median incidence of WT in Asia is 7.6 ASR/million, whereas in Pakistan and India is 3.6 and 4.8 ASR/million respectively with a slight male predominance [1].

WT commonly presents as an asymptomatic abdominal mass or there can be abdominal pain, hematuria, hypertension, or genitourinary abnormalities. WT metastasizes to para-aortic lymph nodes and involves the lung and liver frequently in contrast to Neuroblastoma or Rhabdomyosarcoma, which commonly involves axial or appendicular skeleton [2]. Familial and sporadic cases are associated with the WT1 gene, present on chromosome 11p13, a transcription factor regulating genitourinary embryogenesis. Familial WTs are associated with Beckwith-Wiedemann Syndrome, Denys Drash syndrome, and WAGR syndrome. Differential diagnosis of abdominal mass in a child includes Neuroblastoma, Hepatoblastoma, Non-Hodgkins Lymphoma, and Germ cell tumors [3].

Grossly, upfront tumors show solid homogenous cut surfaces whereas post-treatment tumors exhibit a variegated appearance. WT shows triphasic morphology undifferentiated blastema, epithelial component, and stromal component. The nephrogenic rests in normal renal parenchyma considered precursors [4, 5, 6].

WT is currently managed by two treatment protocols, the National Wilms Tumor study group (NWTS) which comes under the Children Oncology Group (COG), and the International Society of Pediatric Oncology (SIOP). The use of pre-operative chemotherapy is the main difference between NWTS and SIOP, however, no difference in Overall survival (OS) and Disease-free Survival (DFS) was found. Upfront surgeries performed in less than six months infants, low-risk stage I cystic tumors [7, 8].

Post-operative chemotherapy is defined by SIOP-RTSG Umbrella protocol, given according to the local stage of the primary tumor, histology, size of a metastatic lesion, and the response of preoperative chemotherapy and surgery. This standard chemotherapy includes vincristine, actinomycin, and reduced doxorubicin whereas four-drug regimens include etoposide, carboplatin, cyclophosphamide, and doxorubicin. Vincristine and actinomycin-D without doxorubicin are used in Stage II and III Intermediate Risk (IR) tumors. However, Doxorubicin was added in large volumes (≥ 500 mL) to stage II-III IR tumors and High Risk (HR) blastemal tumors. Stage IV diseases are treated with a 6-week regimen of vincristine, dactinomycin, and doxorubicin. Surgically, radical nephrectomy and seven regional lymph nodes excision were done otherwise stage I-II tumors were rendered as stage III. Nephron-sparing surgery (NSS) is done in bilateral or recurrent WT. [9,10,11,12].

Preoperative chemotherapy following SIOP-RTSG Umbrella protocol categorizes WT as low-risk (LR) tumors, completely necrotic (CN), intermediate-risk (IR) tumors, Epithelial type (ET), Stromal Type (ST), Mixed type (MT), Regressive type (RT), Focal Anaplasia (FA) and high risk (HR) tumors, Blastemal predominant (BP) and diffuse anaplasia subtypes (DA). Stage V is bilateral tumors .[9, 10, 11, 12.] The strengths of this study are there is very limited data on WT from Pakistan, since in our center, we are following SIOP 2001 protocol in the treatment of WT it is a comprehensive study on clinicopathological profiles of WT.

Since our center is only pediatric tertiary care supra-specialty center, we treat WT in accordance with the SIOP 2001 protocol. The strength of our report is the comprehensive clinicopathological features of WT.

Aims and objectives: The present study was carried out to determine the clinicopathological features of histopathological subtypes and stages of WT treated as per SIOP 2001 protocol.

Materials and Methods

It is a retrospective cross-sectional study in accordance with SIOP 2001 protocol duly approved by Institutional Ethical Review Board. Ninety-three patients presented in the Oncology/Hematology from January 2014 to December 2017 included. After required diagnostic investigations and four weeks of pre-operative therapy, a combination of vincristine and actinomycin (dose 1.5-50 mg/m^2) in localized WT and doxorubicin (1.5mg/m^2) was added in metastatic cases. At the 5-6th week, nephrectomies were done by the surgical team and sent to the Histopathology

Department. A detailed gross and microscopic evaluation was done. Histopathological subtypes of WT, risks, and pathological staging were noted. Patients with localized WT completed 27 weeks of post-operative therapy combination of vincristine (1.5mg/m^2), actinomycin (0.5mg/m^2), and doxorubicin (1.5mg/m^2). Patients with metastasis took 34 weeks of chemotherapy in alternative blocks (cyclophosphamide and doxorubicin 50-250mg/m^2), (etoposide and carboplatin 150-200mg/m^2), and radiotherapy was given. After completion of treatment, patients called for yearly follow-ups with an ultrasound abdomen and baseline investigations.

Data analysis:

The data analysis was done on SPSS (Statistical Packages of Social Sciences) version 23. Qualitative variables like age, gender, different histopathological subtypes, clinicopathological staging and types of treatment received, and causes of death are presented in frequencies and percentages. No statistical association was found between any variables.

Inclusion criteria:

Children between 6-180 months of age, both genders, biopsy-proven cases of localized and metastatic WT. Post-chemotherapy radicals, partial nephrectomy specimens, and blocks for review were included.

Exclusion criteria:

Upfront and post-chemotherapy, bilateral partial nephrectomies, and autolyzed specimens were excluded.

Results

More than half of patients presented in first 36 months of age with a male predominance (55.9%). The majority of cases were seen in the right kidney (55.9%). The majority of cases received at our pathology department were unilateral radical nephrectomy specimens (95.7%) (Table 1).

Table-1: Main clinicopathological features of Wilms Tumor

Age		
Mean	44.4 months ±30.92	
Minimum age	6 months	
Maximum age	180 months	
Different Age Groups	**Number (n)**	**Percentage (%)**
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
Laterality		
Right	52	55.9
Left	37	39.8
Side not specified	4	4.3
Ureter		
Ureter involvement	1	1.0
Ureter not involved.	86	92.4
Not found grossly	6	6.4
Lymph nodes		
Lymph nodes involved.	2	2.1
Lymph nodes submitted.	33	35.4
Lymph nodes not submitted	58	62.3
Hilum		
Hilum involved by tumor	12	12.9

Hilum uninvolved by tumor	79	84.9
Types of specimens received		
Unilateral radical nephrectomies	89	95.6
Unilateral partial nephrectomies	2	2.1
Blocks received for review	2	2.1
Percentage of necrosis		
More than 65% of necrosis	34	37
Less than 65% necrosis	59	63

The main clinicopathological features are thoroughly described in Table 2. The majority of patients completed the entire course of treatment (81.7%) and few patients abandon treatment after nephrectomy (8.6%). The majority of patients received 27 weeks of chemotherapy (84.9%) and few patients received radiotherapy (10.7%). In our study total of 21(22.5%) patients expired, the majority died due to febrile neutropenia (9.6%), the cause of death, further elaborated in Figure 4. Our study concluded that the majority of patients were in clinical stage 3 (48.3%). Histologically, the majority of cases were IR (75.2%) and showed less than 65% of necrosis. The most commonly observed tumor subtype was the MT subtype (23.4%) as shown in Fig 2 and the least observed subtype was of DA (1.1%). Other miscellaneous clinicopathological findings include three cases of inferior vena cava thrombus (3.2%) and only 1 case of Denys-Drash syndrome.

Table-2: Type of treatment, outcomes, clinical staging and patients who abandon treatment in relation to different Risks and histopathological subtypes of Wilms tumor.

Risk Categorization	**Low Risk**	**Intermediate Risk**				**High Risk**		**Total**
	12(12.8%)	71(76.3%)				10(10.7%)		
Histological Subtypes	**CN (%)**	**RT (%)**	**ET (%)**	**MT (%)**	**ST (%)**	**DA (%)**	**BP (%)**	
Total cases	12(12.8%)	20(21.3%)	18(18.1%)	21(23.4%)	11(11.7%)	1(1.1%)	10(10.7%)	93
Maximum Tumor	12	11	12	16	15	10	12	-
Chemotherapy								
27 weeks	10	18	12	18	9	1	6	74(79.5)
34 weeks	2	2	6	23	2	0	4	19(20.4)
Radiotherapy								
Yes	0	2	3	2	2	0	1	10(10.7)
No	12	18	15	19	9	1	9	83(89.2)
Outcomes								
Rx completed	7	14	15	17	9	1	9	72(77.4)
Expired	5	6	3	4	2	0	1	21(22.5)
Clinical Staging								
Stage 1	0	0	0	0	0	0	0	0(0)
Stage 2	5	10	2	8	3	0	2	36(38.7)
Stage 3	5	8	7	10	7	1	7	45(48.3)
Stage 4	2	2	3	3	1	0	1	12(12.9)
Patients who abandon treatment								
No	11	19	16	18	10	1	10	85(91.3)
yes	1	1	2	3	1	0	0	8(8.6)

*CN; Completely Necrotic, RT; Regressive Type, ET; Epithelial Type, MT; Mixed Subtype, ST; Stromal Subtype, DA; Diffuse Anaplasia, BP; Blastema Predominant

Discussion

Pakistan is a low-middle-income country with limited resources where patients usually present with advanced disease and hence poor prognosis. In our study, we have compared patient characteristics with respect to loco-regional and international studies. The predominant chunk of our patients died due to febrile neutropenia at their homes rather than the progression of the disease. There were 28 cases of WT in the year 2018 in Pakistan to the annual registry of Shaukat Khanum Memorial Cancer Hospital Lahore. [1, 13].

The mean age of 93 children in our study was 44.4± 30.92 months similarly reported by loco regional authors[14-20]. No significant difference in mean age was noted regionally. (Table-1) Regarding sex, we had a majority of male patients (Table-1). This observation was similar to Guru Prasad et al, [14] Mazumder et al, [16] Anwar et al, [19] Ghafoor. T et al [20], Sayed et al [21] and Nuzhath.T et al [24]. In contrast, Faranoush et al [15], Verschuur.AC et al [22] and Shende SA showed female patients.[23]

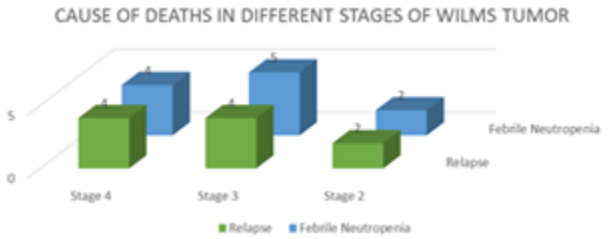

Figure-1 Details of causes of death in WT patients, febrile neutropenia and relapse seen in different stages

A right-sided kidney involvement seen in our index study (Table-1) is similar to Mazumder et al, [16] Anwar et al, [19,] and Ghafoor.T et al [20]. However, Wei Yao et al [17] and Sayed et al [21] observed predominantly left renal involvement. Bilateral tumors were excluded from our study, also reported by several authors such as Guru Prasad et al, [14] Anwar et al [19], Sayed et al [21,] and Pianezza et al [25].

The largest tumor size seen in our study was 16cm whereas Shende AS et al reported 35cm. The minimum tumor size seen in our study was 4cm similar to Shende AS et al[23].

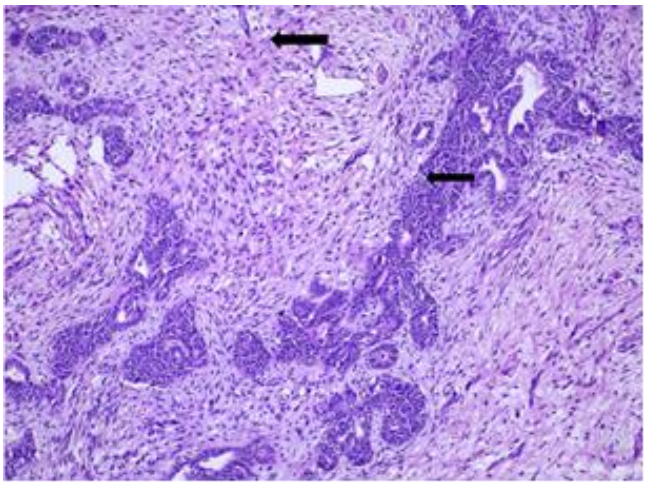

Figure-2 Photomicrograph shows residual post-chemotherapy tumor composed mesenchymal element and epithelial tubules (Highlighted by left arrows)

In our study relapse was seen in 10 (10.7%) of cases similar to Guru Prasad et al 10.7% whereas other authors showed much higher relapse rates Ghafoor.T et al (20.2%) and Faranoush et al (25.4%) [15,20].

In our study, 22.5% of deaths were observed whereas Ghafoor.T et al showed 16.6% of deaths. Our study showed the majority of deaths were due to febrile neutropenia (9.6%) rather than the progression of disease (4.3%) [20].

Conclusion

In our study, the majority of patients were clinical Stage III tumors (48.3%) (Table-2) similar to Guru Prasad et al[14] and Anwar et al[19]. The second most common stage was stage II (38.7%) similar to Faranoush et al [15]. MT subtype was the most common histological subtype (23.4%) seen after chemotherapy in our study followed by RT subtype (21.3%) (Table-2). Similarly, Mazumder et al[15], Shende et al [23] Sayed et al [21], Ran Naran Das [28], Pianezza et al [25], Hung IJ et al [29] and Vujanic et al [27] noticed majority cases of MT. In our study, the least observed case was of DA (1.1%) similar to Guru Prasad et al, Mazumder et al and Shende et al [14, 15, 23].

Limitations of our study

It was beyond the scope of this article to determine volume reductions in pre and post therapy kidneys and quantify radiological assessment of chemotherapeutic drugs in volume reductions of tumor.

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