



Histological Subtypes & Staging of Post-Chemotherapy Wilms Tumor According to SIOP 2001 Protocol: Study at the Children's Hospital, Lahore

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ABSTRACT

Introduction: Pediatric renal tumors constitute 7 to 8% of pediatric solid malignancies and most common is Wilms tumor. It usually presents as unilateral mass with sporadic and familial associations. It is currently treated by NWTS and SIOP protocols worldwide. In our hospital setup we follow SIOP 2001 protocol to subcategorize different histological subtypes and staging of Wilms tumor after completing four cycles of chemotherapy.

Aims & Objectives: To determine the frequency of histological subtypes of Wilms tumor (WT) in post chemotherapy nephrectomy specimens

Place and duration of study: Histopathology Section of Pathology Department, Children's Hospital and Institute of Child Health Lahore from January 2015 to June 2018.

Material & Methods: Ninety-three radical nephrectomy specimens of different histological subtypes i.e. Wilms Tumor (WT) consisting of blastemal predominant (BP), epithelial predominant (EP), stromal (ST), mixed (MT), regressive (RP), completely necrotic (CN) and diffuse anaplastic (DA) were analyzed. Risk categorization and staging proposed by SIOP 2001 was appraised. Data analysis was done using SPSS version 23.

Results: A total of 93 cases were included in the present study. Mean age of children recorded was 42 months with male predominance. Mean tumor size after chemotherapy was 7.25 cm. Majority cases were observed on the right side. Regarding the histological subtype there was a predominant group of MT while least observed was DA. Based on subtypes and necrosis, majority of WT were of intermediate risk (IR) and stage I tumors.

Conclusion: Majority of pretreated cases (n=80, 85.1%) were stage 1 tumors. Commonest histological subtype is MT followed by RP, CN, EP, BP, ST and DA.

Key words: Wilms tumor (WT), (SIOP staging) Internal Society of Pediatric Oncology) National Wilms Tumor Study Group (NWTS), Post chemotherapy WT.

INTRODUCTION

Pediatric renal tumors comprise 7 to 8 % pediatric solid malignancies in first 15 years of life. Most common renal tumor is Wilms tumor (WT), also known as nephroblastoma (N) which accounts for 85% of cases. It usually presents as palpable abdominal mass noticed by mother.^{1,2} Median age of children is 3-4 years.³ WT mostly presents as unilateral renal mass but 5-10 % cases are bilateral.⁴ WT1 gene located on chromosome 11p13 is associated with both familial and sporadic cases. Vast majority of WT are sporadic and only 10% are familial. Familial WT are associated with Beckwith Wiedemann Syndrome, Denys Drash syndrome and WAGR syndrome. No specific risk factor contributing towards WT has been identified uptill now.^{1,3,4}

Grossly most of the cases of WT are unicentric, whereas 5% WT are multicentric.⁵ Undifferentiated blastemal element, epithelial component and stromal component constitute classic WT. The potential precursor of WT are nephrogenic rests which are embryonic stem cells and are of perilobar and intralobar types.^{3,5}

WT is managed according to two protocols, National Wilms Tumor Study Group (NWTS) and International Society of Pediatric Oncology (SIOP) which are established over years of multicenter trials. These groups have enormous contributions towards the management and excellent prognosis of patients with WT.^{3,4,6,7,8}

The NWTS, established in 1969, completed 5 sequential trials from NWTS-1 to NWTS-5. It endorses the diagnosis of WT on radiological examination followed by core biopsy and prompt radical nephrectomy.² Currently, NWTS-5 is

analyzing genetic prognostic factors such as loss of heterozygosity on chromosome 1p and 16q.⁹

Shortly after NWTS, SIOP trials were started in 1971 and evolved from the SIOP 1 to SIOP 9 (1971-2001). It advocates prophylactic chemotherapy after initial diagnosis made on core biopsy. After cessation of chemotherapy course, it endorses radical nephrectomy in unilateral cases and partial nephrectomy in bilateral cases.^{10,11}

The histological classification of WT differs in NWTS and SIOP 2001 due to preoperative chemotherapy. Accurate histological subtyping and staging of WT is very important in further management and prognosis of patient.^{1,2}

According to NWTS, histology groups are divided on the basis of presence and absence of anaplasia in three groups. The favorable histology WT is cystic partially differentiated nephroblastoma (CPDN), standard risk (SR) histology group includes non-anaplastic WT and its variants and high risk (HR) diffuse anaplasia (DA). According to the SIOP WT 2001 classification the subtypes are classified on the basis of percentage of necrosis, presence of viable tumor, presence and absence of regressive changes and presence of focal and diffuse anaplasia. Low risk (LR) include completely necrotic (CN), intermediate risk (IR) include Epithelial predominant (EP), Stromal Type (ST), Mixed type (MT), Regressive predominant (RP), Focal Anaplasia (FA) and high risk (HR) tumors include Blastemal predominant (BP) and diffuse anaplasia (DA).^{3,10,11,12} In our centre we are following SIOP 2001 protocol.

The present study is carried out to determine the frequency and morphological features of WT according to SIOP 2001 protocol as our centre is following their protocol.

MATERIAL AND METHODS

The present study is a cross-sectional study approved by Ethical Review Board vide its letter No. 02/173/17 dated 01/02/2017 and carried out at the Histopathology Department of Children's Hospital and Institute of Child Health Lahore from January 2015 to June 2018.

Ninety-three radical nephrectomy specimens of children between 0-15 years of age in both genders of biopsy proven cases of WT tumor were included. Partial nephrectomy specimens and blocks received for review were excluded.

Different histological subtypes i.e. WT consisting of blastemal, epithelial, stromal, mixed, regressive, completely necrotic and anaplastic were analyzed.

Risk categorization and staging proposed by SIOP 2001 was appraised.

Radical nephrectomy specimens were meticulously sectioned as per protocol of American College of Pathologists. Specimen size, areas of suspected tumor rupture, capsular and perinephric invasion, sectioning of distal end of ureter, renal vein and artery for tumor metastasis and tumor thrombus was noted prior to opening of specimen at the department. Sectioning of tumor at one centimeter was done and assessment of necrotic areas, viable tumor areas and its relation to the normal kidney, capsule, renal hilum and renal sinus was done grossly. Additional sections from the tumor and normal kidney were taken to assess nephrogenic rests. Tissue slices were processed in the automatic tissue processor for 16 hours overnight dehydrated with ethyl alcohol, cleared by xylene, impregnated with paraffin wax and later on tissue blocks were made. Hematoxylin and eosin stains were done.

Statistical analysis:

Data analysis was done on SPSS (Statistical Packages of Social Sciences) version 23. Qualitative variables like age, gender, laterality, histological subtypes and staging were summarized as frequencies and percentages. No statistical association is determined between any variables.

RESULTS

A total of 93 cases were included in this study. The main clinical features of the study are presented in Table-1.

Age at diagnosis		
Mean	3.6 years	
Minimum age	6 months	
Maximum age	15 years	
	Number (n)	Percentage (%)
0 to 3 years	52	55.9
4 to 6 years	30	32.3
7 to 9 years	8	8.6
10 to 12 years	2	2.2
More than 12 years	1	1.1
Gender		
Male	52	55.9
Female	41	44.1
Laterality		
Right	52	55.9
Left	37	39.8
Tumor size in cm		
Mean tumor size	7.25	
Minimum tumor size	1.5	
Maximum tumor size	16	

Table-1: Principal clinicopathological features of Wilms Tumor

Majority of the patients were seen in first 3 years of age with a male predominance n=52(55.9%). Most cases were in right kidney (n=52, 55.9%) with mean tumor size 7.25cm. However, largest tumor size observed was 16cm after chemotherapy (Fig-1).

Regarding the histological subtype the commonest was MT (n=41, 44.1%), followed by RP (n=16, 17.2%). There were equal number of EP and CN (n=12, 12.9%). In addition, 9 cases (9.7%) were of BP, 2 cases (2.2%) of ST whereas only one case (1.1%) was of DA.

Considering necrosis, majority of the tumors (n=65, 69.9%) showed less than 66% necrosis and 28 cases (30.1%) showed more than 66% necrosis. On the basis of histological subtypes and necrosis, (76.3%) cases belonged to IR, whereas 12.9% cases were of LR and 10.8% cases were of HR according to SIOP staging protocol.

In the present study majority of the cases were limited to kidney, only in 7 cases hilum was involved. Capsule was involved in 2 cases and similar number of cases showed tumor thrombi in renal vein whereas in a single case inferior vena cava was involved by tumor thrombus clinically. Distal end of ureter, perinephric fat infiltration and nephrogenic rests were seen in one case each.

We received lymph nodes in 28 cases, which were all negative for metastatic disease. 80 cases (86%) had stage I, 11 cases (11.8%) had stage II and 2 cases (2.2%) had stage III.

The pathological features concerning histological subtypes, staging and largest tumor size is presented in Table-2.

Histological subtypes	Stage I n (%)	Stage II n (%)	Stage III n (%)	Largest Tumor size(cm)
Mixed type	34 (36.5)	6 (6.4)	1 (1.07)	16
Regressive predominant	14 (15)	2 (2.1)	0 (0)	10
Completely necrotic	11 (11.8)	1 (1.07)	0 (0)	14
Epithelial predominant	10 (10.7)	2 (2.1)	0 (0)	11
Blastemal predominant	8 (8.6)	0 (0)	1 (1.07)	14
Stromal predominant	2 (2.1)	0 (0)	0 (0)	6
Anaplasia – diffuse	1 (1.07)	0 (0)	0 (0)	10
Total No.	80 (79)	11(11.8)	2 (2.1)	81

Table-2: Histological subtypes, staging and largest tumor size according to SIOP 2001.

Concerning the stage distribution as shown in Table-2 the greater proportion of cases were of stage I with predominant histological type MT.

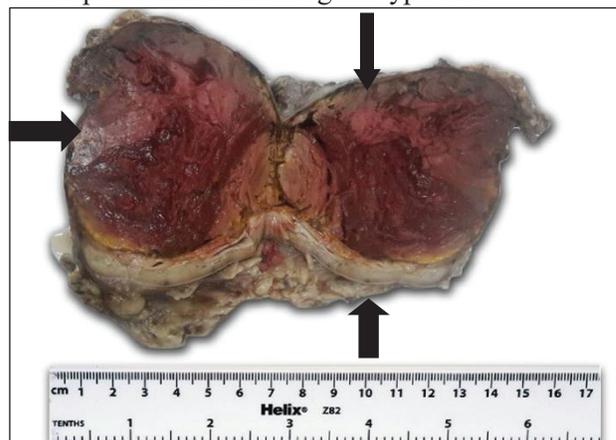


Fig-1: A post chemotherapy bivalved kidney shows a well circumscribed tumor with mahogany cut surface (down & right arrow), and periphery shows thin rim of normal renal parenchyma (up arrow)

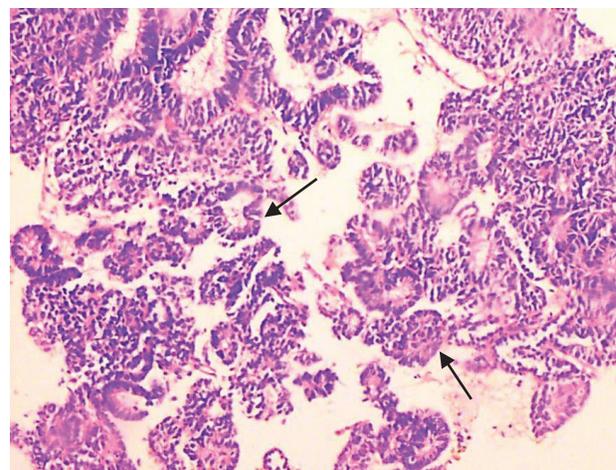


Fig-2: Photomicrograph of H&E staining showing neoplastic tubules (arrows) in residual Wilms Tumor X 20



Fig-3: Photomicrograph of H&E staining showing a renal hilum (right arrow), involved by Wilms Tumor (arrow) adjacent normal kidney parenchyma (elbow arrow) X 20

DISCUSSION

The prevalence of malignant pediatric tumors is remarkably higher in the developing countries as compared to the developed nations. In developing countries, pediatric malignancies prevalence is reported as 4.38% to 12.6% as compared to 2% in developed countries.¹³ It affects approximately one child in every 10,000 children, worldwide before the age of 15 years.⁴ According to World Health Organization (WHO), International Incidence of Childhood Cancer, the Incidence-age specific rate per million in Pakistan and India is 3.6 and 4.4 respectively.¹⁴ According to Annual Cancer Registry Report by Shaukat Khanum Cancer Hospital there were 27 cases of WT, NOS in 2018 in Pakistani population.¹⁵

We received 93 cases of post chemotherapy WT in approximately 3.5 years with the mean age of 3.5 years (Table-1). Similarly, Guruprasad et al. observed the mean age of 3.3 years in the duration of 6 years in Indian population.¹⁶ Mazumder et al. a peak age of approximately 4 years in a 20 patients cross sectional study,¹⁷ Anwar et al. had the observation of mean age of WT at the age of 3 years¹⁸ whereas Onuigbo noticed the peak age of WT lies between 2 years to approximately 5 years.¹⁹ Regarding sex, we had majority of the male patients (Table-1). This observation was similar to Gruparasad et al,¹⁶ Mazumder et al,¹⁷ Anwar et al,¹⁸ Onuigbo et al,¹⁹ Weirich et al¹¹ and Sayed et al²¹ whereas Shende SA showed female preponderance.²²

There was a predominately right sided renal involvement in our index study (Table-1). Similar to Mazumder et al,¹⁷ Anwar et al,¹⁸ Onuigbo et al¹⁹ and Basu et al.²⁰ However, Weirich et al¹¹ and Sayed et al²¹ observed predominantly left renal involvement. Bilateral WT was reported by Pianezza et al,²³ Gruparasad et al,¹⁶ Anwar et al¹⁸ and Sayed et al²¹ whereas bilateral WT was excluded in our study.

Regarding the histological subtype, there was a marked predominance of MT in our study and only 12% of the total cases were CN (Table-2). Similar to Mazumder et al who also observed predominantly tumors of MT in their study.¹⁷ Sayed et al. had the observation that most of the cases were of non-anaplastic type and had the MT histological picture followed by EP type.²¹ However, Vujanic et al. showed that in 258 of the total pretreated nephrectomy specimens, majority of the cases were of RP followed by MT.²⁴

Bocon-Gibond et al. showed majority as CN in their study.¹² In contrast, Vujanic et al studied 195 pre treated nephrectomy specimens and he noticed a

major chunk of MT and CN which was seen in 17% of the cases.²⁵

In our study majority were of Stage I tumors (Table-2) similar to Sayed et al,²¹ Vujanic et al²⁴ and Hung IJ et al.²⁷ In contrast, Faranoush et al. observed slight predominance of Stage II tumors²⁶ where as, Guruprasad et al¹⁶ and Anwar et al¹⁸ observed majority of the patients were in stage III.

Verschuur AC et al showed EP and ST showed excellent clinical outcomes which was beyond the scope of our case study.²⁸

CONCLUSION

Following SIOP 2001 protocol the commonest histological type is mixed subtype which has Intermediate risk. Majority of our tumors were of Stage I tumors.

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