Original Article

Grossing to reporting of Wilms tumor with emphasis on proper sampling in treatment-naive and postchemotherapy specimens and their clinicopathological correlation with outcome

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Abstract

Context: Emphasis on grossing to reporting for the assessment of histopathological parameters predicting outcomes in Wilms tumor.

Aims: To analyze various clinicopathological parameters that effect outcomes in treatment naïve and post chemotherapy Wilms tumor specimens.

Settings and Design: This was a retrospective observational study.

Subjects and Methods: All patients diagnosed with Wilms tumor between 2012 and 2018 at our institute will be included with their clinical findings, laboratory reports, and radiological findings. The patients will be categorized into two groups based on treatment protocol (Society of Pediatric Oncology (SIOP) or the National Wilms Tumor Study Group/Children's Oncology Group (COG) guidelines) used. Details of Grossing and reporting protocols used for the in pre treatment and post treatment specimens will be analyzed. Follow-up till December 2020 will be analyzed.

Statistical Analysis Used: Chi-square and Fisher's exact tests were used for statistical analysis.

Results: A total of 36 patients with the diagnosis of Wilms tumor were included in the present study. The mean age of presentation was 3.9 ± 0.7 years, and males were more common than females. Most of them presented as abdominal mass and few with isolated hematuria. Twenty-six (72%) patients were treated under SIOP protocol with preoperative neoadjuvant chemotherapy. Ten patients underwent upfront surgery as per COG protocol. In SIOP group patients, the mean tumor size was 9.3cm. Forty percent ($n = 10$) we mixed histological type followed by blastemal type constituting (32%, $n = 8$). Regressive and epithelial histological types constituted 16% ($n = 4$) and 12% ($n = 3$), respectively. In the SIOP group 72% ($n = 19$) had no anaplasia and 28% ($n = 7$) had anaplasia. Fifty seven percent ($n = 15$) cases were Stage I, followed by 26.9% $n = 7$)

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and 11.5% ($n = 3$) being Stage II and Stage III, respectively. Ten patients underwent upfront surgery as per COG protocol. The mean tumor size among this group was 8 cm ranging from 7 cm to 11 cm. Eight (80%) cases had favorable histology and two cases showed focal anaplasia. Heterologous differentiation is seen in 3 (70%). Out of the 10 cases, one case was Stage I, six were Stage 2, one was Stage III, and two were clinical Stage IV. None of the cases showed either vessel or lymph node metastasis. All the patients received adjuvant chemotherapy postsurgery and were followed up till December 2020 for (at least 3 years). Of 25 patients in the SIOP group, 18 (72%) had complete remission with no radiological evidence of residual disease. Of the 10 patients in the COG group, 6 (70%) had complete remission.

Conclusions: Histopathological evaluation of Wilms tumor is a critical aspect in the management of Wilms tumor, as tumor characteristics are different in the tumors treated under SIOP and COG protocols, which will ultimately affect the prognostic risk stratification. This necessitates the knowledge of the important grossing and reporting of these tumors under the two protocols.

Keywords: Grossing, reporting, treatment protocols, Wilms tumor

INTRODUCTION

Renal tumors account for approximately 6% of all pediatric malignancies and Wilms tumors account for 90% of all these which make them the most common renal tumors of pediatric age group.[1,2] Predominantly occurring in children with age < 6 years, more than 50% of cases occur below the age of 3 years. Commonly presenting as abdominal mass and hematuria, majority of these tumors are sporadic with only 1%–2% showing familial syndromic association. Microscopically, these tumors are composed of three components in various proportions that are undifferentiated blastemal, differentiating epithelial, and mesenchymal tissues. Based on the number of components, these tumors are classified into triphasic, biphasic, and monophasic Wilms.[3] 5%–10% of these tumors also show anaplasia which is defined by atypical, polypoid mitotic figures, large nuclear size, and hyperchromasia.[4] Based on the location and amount of these features, it was further classified into focal and diffuse anaplasia each showing a different prognosis as compared to tumors without anaplasia.[5,6] Tumors that lack anaplasia are designated as having "favorable histology." The last few decades have seen a significant improvement in the outcome of patients with a 90% survival owing to a multidisciplinary approach to diagnosis and treatment.[6,7] The multimodal approach includes a combination of surgery, chemotherapy and radiation.[6] Currently, two popular guidelines are being used in the management of Wilms tumor worldwide, namely the National Wilms Tumor Study Group/Children's Oncology Group (COG) and the International Society of Pediatric Oncology (SIOP).[8] The main difference between the two guidelines is that SIOP recommends neoadjuvant chemotherapy before surgery, whereas COG recommends upfront surgery before any kind of adjuvant chemotherapy or radiation. As these two treatment protocols employ two different approaches in the management of Wilms tumor, pathological evaluation of these tumors varies significantly. Irrespective of the method followed, the most important prognostic factors including age, histology, chemotherapy response, and clinicopathological stage are found to be the most significant prognostic factors in the assessment survival of these patients.[6] However, preoperative chemotherapy has a significant effect on the morphology of the tumor. As these tumors are already heterogeneous in their nature, the morphological response of different components of the tumor is different making it important to identify the histological features that are prognostically significant. Irrespective of the method followed, the most important prognostic factors including age, histology, chemotherapy response, and clinicopathological stage are found to be the most significant prognostic factors in the assessment survival of these patients.[6] As per SIOP guidelines, the tumor is treated with chemotherapy, and postsurgery, the chemotherapy response in the form of necrosis is quantified along with quantification of different components of the residual viable tumor. Based on the percentages of different components, the tumors are histological subtyped which in turn is used in assigning different histological risk groups to assess the prognosis [Table 1].[9] In COG protocol where patients undergo upfront surgery, the tumor is assigned a histological risk group which is slightly different from SIOP method [Table 2].[10] Both approaches have their own advantages and disadvantages. COG protocol facilitates immediate histological assessment unaltered by chemotherapy and accurate local staging, whereas SIOP protocol provides better surgical operability with shrunken tumor and fewer complications. Although both guidelines take radically different approaches in treating Wilms tumor, overall survival was found to be similar over 90%.[11]

The aim of this study was to analyze the clinicopathological parameters of Wilms tumor cases reported at our institute and to correlate with clinical outcomes.

Table 1: Histological criteria for Wilms tumor types in the International Society of Pediatric Oncology for pretreated cases

Tumor type	Histological features (%)**			
	CIC	Blastema	Epithelium	Stroma
Completely necrotic	100	0	0	0
Regressive	>66	0–100	0–100	0–100
Mixed***	<66	0–65	0–65	0–65
Mixed type	<66	11–65	0–89	0–89
Epithelial	<66	0–10	66–100	0–33
Stromal	<66	0–10	0–33	66–100
Blastemal	<66	66–100	0–33	0–33

**The percentage of the components of the viable tumor should add up to 100%, ***The presence of diffuse anaplasia in any of the above types supersedes the underlying types. Focal anaplasia also needs to be specifically mentioned in the diagnosis (for example, "focal anaplasia in mixed type"). CIC: Chemotherapy-induced changes

Table 2: Histologic risk classifications for Wilms tumor

	SIOP	COG
Low risk	Cystic partially differentiated nephroblastoma* Completely necrotic Wilms tumor	Cystic partially differentiated nephroblastoma*
Intermediate risk	Epithelial, stromal, mixed, regressive types Focal anaplasia	Favorable histology Wilms tumor No evidence of anaplasia
High risk	Diffuse anaplasia Blastemal type	Diffuse anaplasia Focal anaplasia

*Cystic partially differentiated nephroblastoma treated with surgery only. SIOP: International Society of Pediatric Oncology, COG: Children's Oncology Group

SUBJECTS AND METHODS

This was a retrospective study done on patients diagnosed with Wilms tumor between 2012 and 2018 at our institute. Clinical findings, laboratory reports, and radiological findings were collected from the institute laboratory information system and case sheets. Details of the surgery and chemotherapy were collected. All nephrectomy specimens received after NACT (SIOP protocol) were grossed, sampled, and reported as per datasets in which sampling of one full cross section of tumor is done in entirety for the assessment of chemotherapy response.[12] In cases where upfront surgery was done (COG protocol), grossing of the specimen with adequate tumor sampling along with adjacent structures was given. All the tumors were risk grouped and staged based on the respective protocols. Follow-up details of the patients till December 2020 (at least 3 years) were analyzed. Statistical analysis including Chi-square and Fisher's exact tests was done wherever necessary.

RESULTS

Thirty-six patients with the diagnosis of Wilms tumor were included in the present study.

Demography

Thirty-five out of 36 cases were aged < 10 years with one case presenting at the age of 24 years. The youngest age of presentation was 8 months, with the overall mean age of presentation being 3.9 ± 0.7 years (excluding the single case presenting at the age of 24 years). Males are more common than females (72.2% and 27.8%, respectively).

Clinical findings

Of the 36 cases, 50% ($n = 18$) of cases presented with only abdominal mass and 25% ($n = 9$) of patients presented with isolated hematuria. Twenty-three percent ($n = 7$) of patients presented with both abdominal mass and hematuria, whereas 5% ($n = 2$) of patients had neither of the two symptoms but presented with fever and the mass was later found on ultrasonography. No case was found to have any syndromic/familial association. Three patients had metastasis at the time of diagnosis. The right kidney was involved in 47% ($n = 17$) of cases, whereas 53% ($n = 19$) had involvement of the left kidney [Table 3].

Treatment

Twenty-six (72%) patients were treated under SIOP protocol with preoperative neoadjuvant chemotherapy using a combination of three drugs that are dactinomycin, vincristine, and doxorubicin. The duration of NACT was 4–6 weeks depending on the stage of the tumor. Out of 26 patients, 25 underwent nephrectomy post-NACT. One patient (who had metastasis) lost follow-up and was excluded from the study. Ten patients underwent upfront surgery as per COG protocol.

Gross and microscopy

In SIOP group patients, the mean tumor size was 9.3 cm (ranging from 5 cm to 19.5 cm) [Figures 1 and 2]. Forty percent ($n = 10$) showed mixed histological type followed by blastemal constituting (32%, $n = 8$). Regressive and epithelial histological types constituted 16% ($n = 4$) and 12% ($n = 3$), respectively [Figures 3 and 4]. Seventy-two percent ($n = 19$) had no anaplasia and 28% ($n = 7$) had anaplasia. Of the seven cases who had anaplasia, 1 showed diffuse anaplasia, with the rest showing focal anaplasia. Twelve of the 25 (48%) cases showed heterologous differentiation. Five cases showed differentiation toward skeletal muscle, whereas five showed differentiation toward both skeletal and smooth muscles. One case showed heterologous cartilaginous differentiation. One case showed skeletal muscle, smooth muscle, cartilage, and squamous differentiation. Renal capsular invasion was seen in 20% ($n = 5$) of cases. Five (20%) cases showed invasion into the renal sinus, whereas 3 (12%) showed lymph node metastasis. Fifteen cases were Stage I, whereas

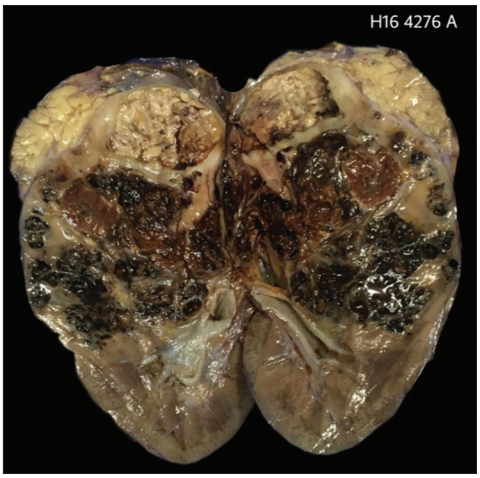

Figure 1: Gross picture of a postchemotherapy Wilms tumor

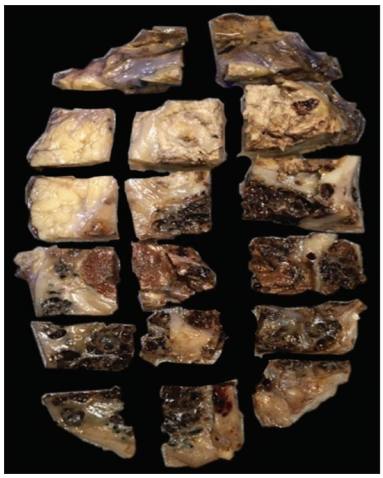

Figure 2: Gridding of one full cross section of tumor submitted for postchemotherapy assessment

Table 3: Clinicopathological characteristics of Wilms tumor cases in the present study

	SIOP (*n*=25), *n* (%)	COG (*n*=10), *n* (%)
Age <4	16 (64)	2 (20)
Age >4	9 (36)	8 (80)
Males: females	3:1	
Mean tumor size	9.3 cm (ranging from: 5–19.5 cm)	8 cm (ranging from: 7–11 cm)
Favorable histology (no anaplasia)	19 (73.1)	8 (80)
Unfavorable histology (anaplasia)	7 (26.9)	2 (20)
Blastemal	08 (32)	NA
Mixed	10 (40)	NA
Regressive	4 (16)	NA
Epithelial	3 (12)	NA
Stromal	0	NA
Renal capsular invasion	5 (19)	3 (30)
Renal sinus invasion	5 (19)	4 (40)
Lymph node metastasis	3 (11.5)	0
Stage I	15 (57)	1 (10)
Stage II	7 (26.9)	4 (40)
Stage III	3 (11.5)	1 (10)
Stage IV	0	2 (20)
Disease free at 3 years	18 (72)	6 (70)
Recurrence	7 (28)	4 (40)
Local recurrence	2 (8)	0
Lymph node metastasis	1 (4)	1 (10)
Liver metastasis	3 (12)	1 (10)
Lung metastasis	1 (4)	2 (20)
Death	1 (4)	1 (10)

NA: Not available, SIOP: International Society of Pediatric Oncology, COG: Children's Oncology Group

seven and three were Stage II and Stage III, respectively. Ten patients underwent upfront surgery as per COG protocol. The mean tumor size among this group was 8 cm ranging from 7 cm to 11 cm. Eight (80%) cases had favorable histology and two cases showed focal anaplasia. Heterologous differentiation is seen in 3 (70%) cases which had skeletal muscle differentiation. Three (30%) showed capsular invasion, whereas 4 (40%) showed invasion into the renal sinus. One (10%) case showed invasion into Gerota's fascia. None of the cases showed either vessel or lymph node metastasis. Out of the 10 cases, one case was Stage I, six were Stage 2, one was Stage III, and two were clinical Stage IV [Table 4].

Follow-up

All the patients received adjuvant chemotherapy postsurgery and were followed up till December 2020 for (at least 3 years). Of 25 patients in the SIOP group, 18 (72%) had complete remission with no radiological evidence of residual disease. Of the seven cases, two cases had local recurrence, and one presented with recurrence in regional lymph nodes. The remaining three cases presented with liver metastasis and one case presented with lung metastasis. One of the patients who had local recurrence died during treatment. Of the three cases who presented with liver metastasis, one had lymph node involvement and one had anaplasia. Of the two cases which had local recurrence, one had lymph node involvement at the time of surgery. The patient who presented with lung metastasis had lymph node involvement at the time of surgery. Of 10 patients in the COG group, 6 (70%) had complete remission. Of the four cases who had recurrence, one presented with metastasis to the liver, and one case presented with regional lymph node recurrence. Two patients presented with metastasis to the lung, of which one patient died during treatment. Three of these four cases had anaplasia.

DISCUSSION

This study aimed to look at clinicopathological characteristics and outcomes in patients diagnosed with Wilms tumor at our center. Most of the cases in the present study presented below the age of 10 years, with one patient presenting at the age of 24 years. There were only single case reports of adult Wilms in the literature.[13] Huszno *et al*. in their systematic review found the incidence of Wilms in adults to be around 3% and observed worse outcome when

compared to childhood cases, which was attributed to higher advancement age and higher stage at presentation.[14] However, our patient who presented with a COG Stage III tumor (core biopsy done before surgery) did not show any adverse event in 5-year follow-up. The clinical significance of age in Wilms tumor has been controversial. Currently, age is included in the risk stratification in COG studies, whereas SIOP trials include stage and histology. Gooskens *et al*. opined that although patients with higher age at presentation had worse outcome, age was not found to be an independent risk factor for adverse prognosis in various multivariate analyses.[15] In the present study, although there was a slightly higher incidence of recurrence in patients aged 4 years or above, the difference was not statistically significant ($P = 0.72$). No significant difference association between tumor size and adverse outcome was seen in the present study.

Weirich *et al*. in their study done on nonanaplastic Wilms treated under SIOP found that histological type had a significant impact on prognosis.[16] It has been observed that blastemal histological type had a higher incidence of recurrence over other types. Blastemal cells inherently are very responsive to chemotherapy, but the residual blastemal component after preoperative chemotherapy was found to be resistant to therapy and pertains to a higher incidence of recurrence. SIOP 2001 does recommend the use of more aggressive chemotherapy in cases with blastemal histology postchemotherapy. In the present study, the SIOP group had 32% ($n = 8$) of blastemal-type Wilms. There was a statistically significant difference in the recurrence in patients with blastemal histology (five of total eight cases) when compared to other histological types ($P = 0.01$). We also observed that blastemal type had a higher incidence of anaplasia. This observation, however, was not statistically significant ($P = 0.2$). Wilms tumor is traditionally classified into two major prognostic histological groups that are favorable and unfavorable histology which is defined by the presence of anaplasia which in turn is further classified based on its location and extent.[5] The prognostic importance of anaplasia was first recognized by Beckwith and Palmer who identified that tumors with anaplasia showed a higher incidence of adverse outcome and poor survival.[17] Anaplasia in Wilms tumor has been associated

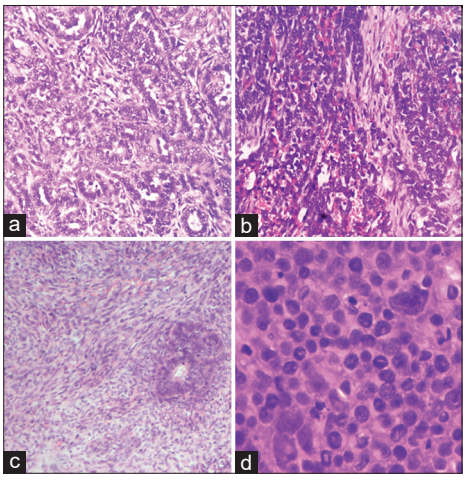

Figure 3: (a) H and E, ×400, Wilms tumor - epithelial component showing mature tubules. (b) H and E, ×400, Wilms tumor - blastemal component showing small round cells. (c) H and E, ×400, Wilms tumor - stromal component with spindle cells. (d) H and E, ×400, Wilms tumor - tumor cells showing anaplasia

Table 4: Statistical analysis of recurrence with different clinicopathological parameters

	No recurrence	Recurrence	*P*
Age (years)			
<4	15	4	0.7003
>4	11	5	
Tumor size (cm)			
≤10	19	7	0.4539
>10	6	4	
Blastemal histology (SIOP)			
Blastemal	3	5	0.0169
Nonblastemal	15	2	
Anaplasia			
Favorable	22	6	0.0207
Unfavorable	2	5	
Local stage			
I	12	3	0.258956
II	5	2	
III	1	2	

SIOP: International Society of Pediatric Oncology

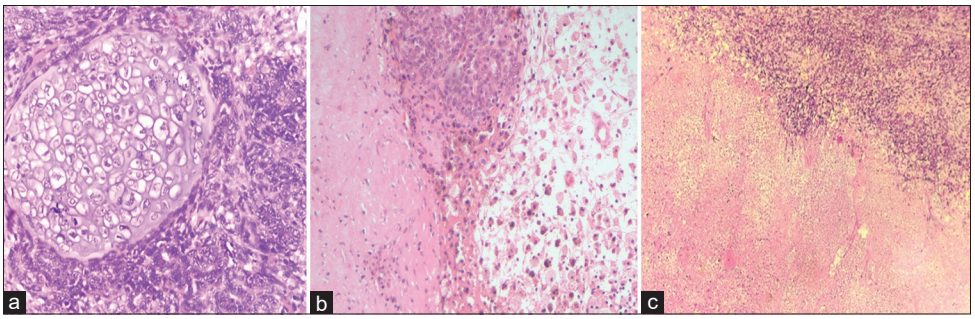

Figure 4: (a) H and E, ×400, Wilms tumor - heterologous chondroid differentiation. (b) H and E, ×40, Wilms tumor - postchemotherapy changes. (c) H and E, ×40, Wilms tumor - postchemotherapy necrosis

Table 5: Comparison of present study with findings of other studies

Author	Year	Findings	Present study
Gooskens *et al*.[15] (multivariate)	2016	Age not independent risk factor	Higher incidence of recurrence in older children but not significant
Weirich *et al*.[16]	2001	Blastemal histology - impact on prognosis (SIOP)	Blastemal histology had a higher incidence of recurrence Significant
Beckwith and Palmer[17]	1978	Anaplasia - adverse outcome and poor survival	Anaplasia had a higher incidence of recurrence Significant
Groenendijk *et al*.[20]	2021	COG - higher stage had high risk of recurrence SIOP - stage not independent risk factor	Not concordant Concordant

SIOP: International Society of Pediatric Oncology

Table 6: Comparison of outcomes of the present study and other studies

SIOP	Present study	Another study, John *et al*.[21]
Follow up	3 years	42 months
Event-free survival (%)	72	73
Overall survival (%)	96	80
COG	**Present study**	**Another study, Guruprasad *et al*.[23]**
Follow-up (years)	3	5
Event-free survival (%)	60	83
Overall survival (%)	90	85.2

SIOP: International Society of Pediatric Oncology, COG: Children's Oncology Group

with TP53 and MYCN mutations.[18,19] Currently, COG includes both focal and diffuse anaplasia in high-risk category. SIOP includes diffuse anaplasia in high-risk category and focal anaplasia in intermediate-risk category. In the present study, the incidence of anaplasia was 20%. There was a statistically significant high recurrence in cases with anaplasia in the present study ($P = 0.02$).

In the present study, we emphasize the importance of proper sampling of tumor in postchemotherapy specimens. In this study, we employed a protocol recommended by datasets where gridding is done on the largest surface area and one full cross section in entirety is submitted. In addition to this, additional representative sections of heterogeneous areas and areas suspected of incomplete resection and adhesion to adjacent structures are also sampled. This method helps in adequate quantification of each of the different components for better classification as per SIOP protocol. The average to tumor cassettes submitted in the present study ranged between 15 and 25.

Along with anaplasia, local stage is one of the important independent risk factors in patients with Wilms tumor. Groenendijk *et al*. observed that patients who had upfront surgery with COG Stage III and lymph node disease had an increased risk of recurrence. However, no significant difference in risk of recurrence was found in postchemotherapy cases among all SIOP stages in all previous studies when adjusted to other histological features such as blastemal type, anaplasia, and cytogenetic abnormalities.[20] Similar observations were made regarding lymph node involvement in SIOP trials. This finding was attributed to apparent chemotherapy effect on lymph nodes with tumor deposits. In the present study out of 10 cases in the COG group, two presented with Stage IV disease and had recurrence, of which one patient died during treatment. However, no significant statistical correlation was found between the stage and the outcome. We attribute this to the small number of patients treated under COG protocol. In the SIOP group, one case presented with Stage IV at presentation; however, postchemotherapy local stage was Stage II. In the present study like in the previous literature, no significant difference in the recurrence was seen among different stages. The overall 3-year survival in the present study in both the groups together was 94%, with event-free survival being 68%. The SIOP group had an overall survival of 96% and event-free survival of 72% which was similar to the findings of the study done by John *et al*. on South Indian population and was comparable to Western studies.[21,22] The COG group also had 90% overall 3-year survival but had 60% event-free survival which was lower than the study done by Guruprasad *et al*. on South Indian population.[23] There was no significant difference in the incidence of recurrence between the SIOP and COG groups [Tables 5 and 6].

CONCLUSIONS

Histopathological evaluation of Wilms tumor is a critical aspect in the management of Wilms tumor. As the tumor characteristics are different in the tumors treated under SIOP and COG protocols, the pathological factors to be assessed and prognostic risk classifications are also different. This necessitates the knowledge of the important prognostic parameters and application of different methods and grossing and reporting of these tumors under the two protocols. With this present study, we emphasize the importance of adequate sampling and appropriate reporting for better classification and quantification in both treatment-naive and postchemotherapy cases.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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