

Research Article

Effect of Preoperative Chemotherapy in Reduction of Tumor Volume in Wilms Tumor in Relation to Histology

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Abstract

Background: Wilms tumor (WT) is the most common renal tumor in children under 5 years. The survival rates of children with Wilms tumor have improved dramatically over a few decades.

Objective: To find out the effect of preoperative chemotherapy in the reduction of tumor volume in Wilms tumor and its correlation with tumor histology.

Methods: In this descriptive prospective study conducted from November 2019 to October 2020 in Pediatric Hematology Oncology Department, all patients diagnosed with WT under 15 years were enrolled. After a complete history and physical examination, all information including demographics, metastatic status, pre and post-chemotherapy volume, histology, postop stage and surgical complication was collected and entered on Performa. All patients received neo-adjuvant chemotherapy according to the SIOP protocol. Data was entered and analyzed in SPSS 23.

Results: Fifty-three patients were included. There were 33 (62.3%) male and the mean age was 4.45 +2.2 years. Thirty-two (60.4%) children had localized disease and 13 (24.5%) children had lung metastasis. There was a significant reduction of tumor volume of >500ml in 8 (15.1%) patients after preoperative chemotherapy and the majority 18 (34%) patients had 100-200 ml decrease in tumor volume. Intermediate risk histology 35 (66%) was most prevalent. During surgery, 35 (66%) children had no complications. Thirty-nine (73.5%) patients were cured, 4 (7.5%) patients were expired and 5 (9.4%) got left against medical advice (LAMA).

Conclusion: Our study infers that pre-operative chemotherapy reduces the tumor volume remarkably in WT making resection feasible.

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Introduction

Wilms tumor also called nephroblastoma is the most common primary renal tumor and the sixth

most common childhood malignancy. Incidence of WT is about 1/10000 in Europe and North America. The majority of children with Wilms tumor are diagnosed between 1-5 years of age with a median age of presentation 44 months. The most children are asymptomatic where abdominal mass may be an incidental finding or may present with abdominal pain, abdominal distension or occasional with hematuria.^{1,2,3}



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The initial imaging investigation is abdominal ultrasonography and then a CT scan abdomen and chest for confirmation of diagnosis and for staging purposes. A fine needle or true cut biopsy for histological diagnosis is not always required for diagnosis.^{4,5}

Management of Wilms tumor is multimodal including surgery, chemotherapy and radiotherapy. This multidisciplinary strategy with particular attention to risk stratification has markedly improved the cure rate for children with Wilms tumors over last few decades. The current 5-year event-free survival (EFS) and overall survival rates are 77.2 percent and 90 percent respectively in well-resourced countries where survival rates are still miserable in low-income countries.

The National Wilms Tumor Study Group/Children Oncology group (NWTSG/COG) and the International Society of Pediatric Oncology (SIOP) are two principal guidelines used for the management of Wilms tumors all over the world. The main difference between the two groups is the timing of surgery. SIOP recommends using preoperative chemotherapy and NWTSG/COG prefers using primary surgery before any adjuvant treatment. Both have different staging systems where COG relies on pathology analysis from a primary nephrectomy in most cases while SIOP staging is based on the results after preoperative chemotherapy. Despite these basic differences outcome is comparable in both groups.^{6,7,8,9}

In resource-limited countries delayed presentation with the advanced local disease is common and immediate surgical facilities might not be available at many centers. In these circumstances SIOP guidelines with the use of preoperative chemotherapy can lead to better outcomes with safe surgery and fewer surgical complications. At our center, we follow the SIOP protocol for Wilms tumor (WT) and this study aims to evaluate the effect of pre-operative chemotherapy on tumor volume reduction and the association of tumor volume reduction with histological type of WT in our population as certain histological types have better response to chemotherapy as compared to others and there is paucity of local data.

Methods

This descriptive prospective study was conducted over the period of one year starting from 1st November 2019 to 31st October 2020 in the Pediatric Hematology Oncology Department, at the Children's Hospital and Uni-

versity of Child Health Sciences, (UCHS) Lahore, Pakistan. It was done after the approval of the hospital's institutional review board (IRB). All the children under 15 years of age diagnosed as WT on initial radiological findings and later confirmed on histopathology of needle biopsy, presented in the department over the study period were included in the study. After initial history and physical examination all patient's data including demography, laterality, pre-chemotherapy volume and later post chemotherapy volume, histology, staging and post-operative complications were recorded on Performa. Patients with primary nephrectomy and those got treatment from other centers were excluded from the study. All patients received neo-adjuvant chemotherapy according to the SIOP protocol to reduce the tumor volume. This tumor volume was calculated using the ellipsoid formula, as described by Weirich et al,⁹: length into depth into thickness multiply by 0.523 by pediatric radiologist before and after chemotherapy. After completing pre-operative chemotherapy surgical resection was done in all cases and patients were followed for surgical complications and post-operative staging. According to the SIOP 2001 classification, histologic categories were defined as low, intermediate, or high-risk on nephrectomy samples. Tumors with epithelial and stromal predominance, as well as tumors with a mainly rhabdomyomatous component, were also found. Outcome variables were also measured. Data was entered in SPSS 23. Age, Tumor volume were presented as mean and standard deviation. Categorical data like Gender, Preoperative chemotherapy outcome were presented as frequency and percentages. Paired sample t test was applied on before after chemotherapy tumor volume and chi square test also apply to compare between the post chemotherapy tumor volume and age, histology, histology type of tumor. P value less than 0.05 considered as significant.

Results

The study included 53 patients who met the selection criteria. The male to female ratio among them was 1:0.65. The mean age of presentation was 4.45 ± 2.2 years. The prime age groups were 3-5 years 19 (35.8%) followed by 1-3 years of age 17 (32.1%) where as more than 5 years of age were 13 (24.5%) children Table: 1

Most of the patients had right sided tumor 37 (69.8%)

while 14 (26.4%) left sided and only 2 (3.8%) had bilateral Wilms tumor. Majority of the patients 32 (60.4%) had localized disease While 21 (40%) had metastatic disease and among them 13 (24.5%) children had lung metastasis, 3 (5.7%) had liver metastasis and 5 (9.4%) had both lung and liver metastasis. Table 1.

Table 1: Patients Characteristics

		Frequency (n)	Percentage (%)
Gender	Males	33	62.2
	Females	20	37.8
Age	<1 years	4	7.5
	1-3 years	17	32.1
	3-5 years	19	35.8
	>5 years	13	24.5
	Mean \pm SD	4.45 \pm 2.2	
Laterality	Right	37	69.8
	Left	14	26.4
	Bilateral	2	3.8
Meta-stasis	Non-metastasis	32	60.4
	Lung metastasis	13	24.5
	Liver metastasis	3	5.7
Stage	Both lung & liver	5	9.4
	Stage II	19	35.8
	Stage III	23	43.3
Histological type of risk	Low	6	11.3
	Intermediate	35	66
	High	12	22.6
Surgical complications	No complications	35	66
	Tumor Rupture	5	9.43
	Tumor spillage	9	16.8

There was significant tumor volume reduction documented after pre-operative chemotherapy. On presentation only 3 (5.7%) patients had less than 200 ml tumor volume, 14 patients (26.4%) had between 200-400 ml, 9 patients (17%) had 400-600 ml volume, whereas 10 (18.9%) patients had 600-800 ml tumor volume, 8 (15.1%) patients had 800-1500 ml and only 4 (7.5%) had greater than 1500 ml tumor volume. However after preoperative chemotherapy majority of patients 17 (32.1%) had less than 200 ml tumor volume followed by 14 (26.4%) and 12 (22.6%) having 200-400 ml & 400-600 ml tumor volume respectively, 2 patients (3.8%) had 600-800 ml volume, 1 (1.9%) had 800-1000 ml and 2 (3.8%) had greater 1500 ml tumor volume. Table 2.

The best documented response was >500 ml reduction

Table 2: Pre and Post Chemotherapy Tumor Volume

	Pre-Chemotherapy Tumor Volume	Post-Chemotherapy Tumor Volume
<200ml	3 (5.7%)	17 (32.1%)
200-400ml	14 (26.4%)	14 (26.4%)
400-600ml	9 (17%)	12 (22.6%)
600-800ml	10 (18.9%)	2 (3.8%)
800-1000ml	4 (7.5%)	1 (1.9%)
1000-1500ml	4 (7.5%)	0 (0%)
>1500ml	4 (7.5%)	2 (3.8%)
P value		0.002

in tumor volume in 8 (15.1%) patients after preoperative chemotherapy, 9 (17.0%) patients had 300-500 ml decrease while majority 18 (34%) patients had 100-200 ml decrease in tumor volume. While 3 patients (5.7%) had progressive disease with increasing tumor volume after preoperative chemotherapy.

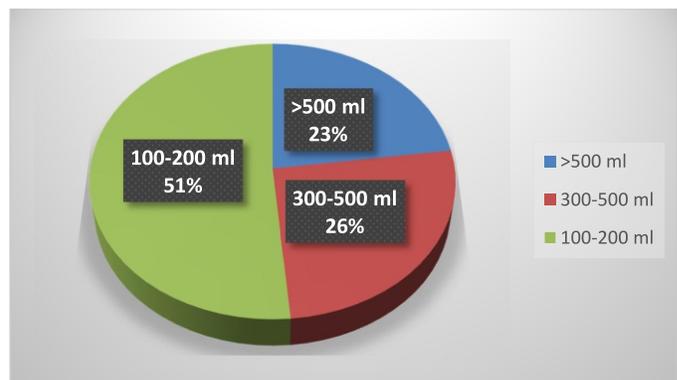


Figure 1: Tumor Volume Reduction after Pre-operative Chemotherapy

Post-operative histopathology risk stratification was done according to SIOP2001 guidelines. The vast majority of children 35 (66%) had intermediate risk histology while 12 (22.6%) had high-risk histology and only 6 (11.3%) patients had low risk histology. Among intermediate risk group mixed variety outnumbered i.e. 23 (43.4%) while 4 (7.5%) had epithelial and 8 (15%) patients had stromal variety.

In this study no significant correlation between histology and reduction of tumor volume was found. In the high-risk histology subgroup, only 2 out of 11 patients had a tumor volume decrease of less than 100 ml whereas 3 patients had a decrease of more than 200 ml, and 2 patients demonstrated a substantial reduction exceeding 500 ml in tumor volume. Likewise in intermediate risk 6 patients had more than 500 ml decrease in tumor

volume and 3 patients even had increase in the tumor volume after preoperative chemotherapy (Fig-2).

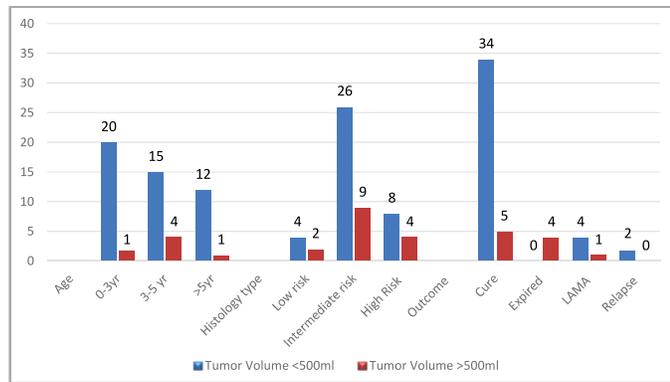


Figure-2 Post Chemotherapy Tumor Volume in Relation to age, Histology and Outcome

During treatment majority 35 (66%) children had no surgical complication, 5 (9.43%) patients had tumor rupture at the time of surgery, 9 (16.98%) had documented spillage, 4 (7.54%) had residual tumor.

The major bulk of patients were categorized in post-operative stage 2 and 3 of disease i.e. 19 (35.8%) & 23 (43.3%) respectively and only 5 (9.43%) patients had stage 4 disease. Two (7.7%) had high risk stage 4 disease and 10 (18.8%) patients had high risk stage 3 disease. Three (5.66%) patients had intermediate risk stage 4 and 13 (24.5%) patients had intermediate risk stage 3 and 19 (35.84%) patients had intermediate stage 2 disease. Only 6 (11.3%) patients had low risk stage 2 disease.

Thirty nine (73.5%) patients were cured, 4 (7.5%) patients were expired and 5 got LAMA (9.4%), two (3.7%) patients relapsed, and 3 (5.6%) patients lost to follow-up with missing record. Fig-2

There was a significant pre-operative chemotherapy response documentation ($p=0.008$) in terms of reduction in tumor volume >500 ml after preoperative chemotherapy. However, no significant correlation was found between pre-operative chemotherapy induced tumor volume reduction and histological type of Wilms tumor.

Discussion

Chemotherapy has played a key role in WT treatment and improved survival rate. Pre-operative chemotherapy is an integral part of the SIOP protocol which reduces tumor size and length of tumor, as well as the probability

of rupture of tumor during surgery.^{9,10,11}

In this study total fifty-three patients of Wilms tumor were enrolled. Age and gender distribution corresponds to other studies. In our study mean age at presentation was 4.45 ± 2.2 years with male's predominance 62% also documented by other studies.^{12,13} Though numerous studies have identified age less than two year as a good prognostic factor and increasing age as bad prognostic factor, our study found no association between age and the difference in tumor volume before and after chemotherapy. It was observed that only 6 patients showed good response to pre-operative chemotherapy in 0-5 years of age group, same observation noted by Oliveira P V et al showing insignificant association between age and chemotherapy induced reduction in tumor volume i.e., twenty-one (91.3%) of the 23 patients who represent good response to adjuvant treatment were over the age of two years.^{13,14}

Majority of patients (69%) were having right sided Wilms tumor in our study and 3.8% bilateral disease as reported in literature. Most of our patients (60%) presented with localized but advanced disease and forty percent with metastatic disease commonly with lung metastasis. In our study incidence of metastatic disease is higher than reported in the literature but one Moroccan study also reported similar observations with advanced local disease and metastatic disease in 32.6%.^{12,15}

There was a significant pre-operative chemotherapy response documentation in our study with marked reduction in tumor volume after preoperative chemotherapy in WT as many other studies had showed stage distribution with less rate of surgical complications in patients with Wilms tumor receiving delayed surgery compared to those having immediate nephrectomy.¹³ At baseline nearly fifty percent of patients were having tumor volume between 200-800 ml showing large tumors on presentation. While after receiving pre-operative chemotherapy 32% of patients had less than 200 ml tumor volume and about sixty percent had post chemotherapy tumor volume less than 400ml. Eight patients exhibited a prominent response, demonstrating a tumor volume reduction of more than 500 ml after chemotherapy and average response was 100-200ml decrease in tumor volume.

Similarly excellent response to pre-operative chemotherapy was reported by Taskinen S in his study in which

Wilms tumor total and viable tumor volumes were reduced after pre-operative chemotherapy by 68% and 97%, respectively and high proportion of blastemal cells in cutting needle biopsy was associated with the greatest decrease in Wilms tumor volume.¹⁶ Similar response to pre-operative chemotherapy has been seen with a significant downstaging of disease in many other studies.^{17,18}

Majority of our children 66% had post-operative intermediate risk histology mainly comprising of mixed variety and 22 % had high risk histology. As far as stage was concerned majority of patients were categorized in stage 2 and 3 of disease. Our study identified a notable number of post-operative complications in 18 children, with tumor spillage and rupture being the most prevalent factors. Other studies have highlighted that the utilization of pre-operative chemotherapy leads to a reduction in tumor volume and facilitates a more manageable and safer surgical removal of tumor with minimal surgical complications as well as prevents the deleterious effects of radiation and chemotherapy in young children.^{18,19}

According to one study, there is no significant relationship between histological risk & tumor volume statistically as in our study.²⁰ In contrast some studies had reported significant association between the histological type and tumor volume reduction. The degree of tumor necrosis after chemotherapy had a positive correlation with the proportion of blastemal component in one study.²¹

In our study about seventy three percent children were cured of disease with 7.5% mortality rate and all patients who expired had more than 500 ml tumor volume. Two patients died due to sepsis accompanied with severe malnutrition, two due to progressive disease and one of them was treatment defaulter. Tumor volume at presentation is alone a predictor of poor prognosis and increasing tumor volume increased risk of death in patients with WT.¹⁴

Conclusion

In conclusion, our study demonstrated significant pre-operative chemotherapy response in terms of reduction in tumor volume after pre-operative chemotherapy making these huge tumors resectable. Hence it's worth giving pre-operative chemotherapy in Wilms tumor in low-middle income countries like ours to minimize surgical complications while dealing with huge tumors.

However we need further studies to establish relationship between histology and tumor volume reduction as well as tumor volume as a predictive prognostic tool.

Ethical Approval: The Institutional review board of The Children's Hospital & Institute of Child Health approved the study vide letter No. Ref: 56187.

Conflict of Interest: The authors declare no conflict of interest.

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Authors' Contribution:

SA: Study concept & design, analysis of data & interpretation, literature search, writing manuscript

MS: Study design, data collection, data analysis, writing manuscript

MF: Literature search, data interpretation

AI: Data collection and analysis

SZ: Proof reading and literature review

MS: Critical review of the final article

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