

# The Relationship Of Tumor Volume After Preoperative Chemotherapy (Tvapq) And Before Preoperative Chemotherapy (Tvpbq) With Overall Survival Of Pediatric Patients With Wilms Tumor.

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## ABSTRACT

**BACKGROUND:** Wilms tumor is the most common renal malignancy in children worldwide affecting 1 in 10,000 before the age of 15 years. Most are diagnosed before the age of 5, with a peak incidence at 2-3 years. Prognosis has been improved dramatically during last few decades due to successful sequential advances in chemotherapy.

**METHODS:** It is an ambispective observational study. We studied the relationship of tumor volume after preoperative chemotherapy (TVAPQ) and before preoperative chemotherapy (TVBPQ) with overall survival of pediatric patients with wilms tumor. Clinical, histological and volumetric data were collected from the medical records and patients were followed for two years to study the prognosis and outcome. We excluded patients >14 years age and the one who were not willing.

**RESULTS:** Total 42 pediatric patients with Wilms tumor were enrolled during study period. Most commonly affected age group was 2 to 5 years [27(64.28%) patients]. Range of TVBPQ was found to be of 66.3ml to 2,380 ml and the median TVBPQ calculated is 572.5 ml and range of TVAPQ was found to be of 15 ml to 1,549 ml and the median TVAPQ calculated is 146 ml. Majority of patients with wilms tumor had tumor volume reduction > 40%(good response) [36(85.71%)] after preoperative chemotherapy. On statistical analysis, tumor volume after preoperative chemotherapy (TVAPQ) > 500 ml was significantly associated with death at 2 years (p value <0.001). On studying correlation between the difference between tumor volume before preoperative chemotherapy (TVBPQ) and after preoperative chemotherapy (TVAPQ) and outcome of patients with wilms tumor at end of 2 years, significant association between the difference between TVBPQ and TVAPQ and survival at end of 2 years (p value <0.001) was found. Overall survival in our study was 85.7% while mortality was 14.29 %.

**CONCLUSION:** Most common presenting age group for wilms tumor in our study was 2-5 years with slight female preponderance. Majority of patients with wilms tumor had tumor volume before preoperative chemotherapy (TVBPQ) between 500-1000ml and tumor volume after preoperative chemotherapy (TVAPQ) < 500 ml. Tumor volume after preoperative chemotherapy (TVAPQ) > 500 ml was significantly associated with death at 2 years. The relation between the difference between TVBPQ and TVAPQ and survival at end of 2 years was statistically significant. Overall survival was 85.71% at end of study.

## I. INTRODUCTION

Wilms tumor (WT) accounts for about 6% of all cancers of children and it is the most common malignant renal tumor of childhood.<sup>1</sup> Wilms tumor affects approximately one child per 10,000 worldwide before the age of 15 years. Most are diagnosed before the age of 5, with a peak incidence at 2-3 years. The majority of children have an asymptomatic and unilateral abdominal mass.

Currently, the most important predictive indicators of recurrence and mortality are staging and tumor histology. The most significant unfavorable factors are high stage and the presence of anaplasia, especially in the diffuse form, which is highly resistant to chemotherapy.<sup>2</sup> Based on the correlations between the histological features after surgery and survival, three prognostic groups of typical renal tumors of childhood were discerned in the *Société Internationale D'oncologie Pédiatrique* (SIOP) studies: low-risk, intermediate-risk and high-risk tumors. This classification is based on the percentage of overall necrosis and the predominant cell type in the residual viable tumor. They raise the possibility that the reduction of tumor volume, besides the classification of histological types of risk, could serve as a new prognostic parameter for the stratification of patients at the time of postoperative treatment. Currently only GPOH (German Pediatric Oncology and Hematology) uses tumor volume as a parameter for risk stratification.<sup>3</sup>

Tumor volume after preoperative chemotherapy (TVAPQ) could be considered alone as a predictor of poor prognosis regardless of the cutoff suggested in the literature, more studies are needed to replace the histology and staging by tumor size as best prognostic variable<sup>4</sup>. So we have selected this topic of study of tumor size and prognosis in pediatric patients with wilms tumor to enlighten more about prognosis of wilms tumor.

## II. MATERIALS AND METHODS

This hospital based ambispectiveobservational study was conducted in pediatric ward in government medical college and cancer hospital Aurangabad over a period of 2 years from October 2020 to October 2022. Institutional Ethical Committee approval was taken. All pediatric patients less than 14 years diagnosed with wilms tumor who have received preoperative chemotherapy were included in study and written informed consent was taken. All patient's history, clinical details, histology and volumetric data were collected from his/her medical records at the time of admission. Staging and risk stratification was done as per SIOP protocol<sup>7</sup>. After diagnosing wilms tumor, all patients underwent the SIOP protocol treatment of chemotherapy which uses neoadjuvant chemotherapy to reduce the tumor volume and the risk of intraoperative rupture. Tumor volume was calculated according to the ellipsoid formula: length  $\times$  depth  $\times$  thickness  $\times$  0.523<sup>5</sup> The TVBPQ (tumor volume before preoperative chemotherapy) was measured by noting size mentioned in ultrasound/ CT scan done before receiving first cycle of chemotherapy. After receiving full course of neoadjuvant chemotherapy, repeat USG/CT scan was done to calculate TVAPQ (tumor volume after preoperative chemotherapy) using the same ellipsoid formula. For the tumor volume, the patients were classified according to the reduction between the TVBPQ and TVAPQ in: (1) poor response (<40%) and (2) good response ( $\geq$ 40%).<sup>6</sup>

The relation of tumor volume after preoperative chemotherapy (TVAPQ) with outcome of patients at the end of 2 years was studied in all cases.

The relation according to the reduction between the tumor volume before preoperative chemotherapy (TVBPQ) and after preoperative chemotherapy (TVAPQ) with outcome of patients at end of 2 years was also studied in all cases.

Neoadjuvant chemotherapy with two or three drugs which includes vincristine weekly and actinomycin D +/- doxorubicin three weekly were given for a period of 4-6 weeks or maximum upto 12 weeks in some patients as per patient's tumor stage and response.<sup>7</sup> Regular follow up was done of enrolled patients upto 2 years. Outcome of all patients were noted in the form of 'survivor' or 'death'.

### Statistics and analysis

Continuous variables were represented by the median, while categorical variables were represented by a number (n) and percentage (%). The median value and range was calculated for TVBPQ and TVAPQ. The association between categorical variables was performed using the Fisher's exact test. The level of significance was set at 5%, and the analyses were performed using SPSSv 26.0.

## III. RESULTS

During study period, we enrolled 42 patients of wilms tumor.

Table 1 shows general characteristics of wilms tumor patients. Most commonly affected age group was 2 to 5 years [27(64.28%)patients]. There was a female preponderance with 22 (52.4%)patients being female and with male to female ratio of 0.9:1. Most of the patients were presented in stage III [23(54.7%)] in our study followed by 12(28.5%) in stage IV. On histological assessment, 19(45.2%)patients had intermediate risk histology followed by 18(42.9%) patient with high risk histology and only 5 (11.9%) patients with high risk histology.

**Table 1- general characteristics of patients with wilms tumor**

Characteristics	No of patients(n=42)	Percentage%
Age distribution (years)		
0-2	6	14.28
2-5	27	64.28
5-14	9	21.42
Sex distribution		
Male	20	47.6%
Female	22	52.4%
Stage at presentation		
I	2	4.7
II	3	7.1
III	23	54.7
IV	12	28.5
V	2	4.7
Histology		
Low risk	19	45.2%
Intermediate risk	18	42.9%
High risk	5	11.9

**Table 2-clinical profile of patients with wilms tumor**

Clinical findings	No of patients(n=42)	Percentage (%)
symptoms		
Abdominal mass	40	95.2
Abdominal pain	17	40.4
Fever	16	38
Hematuria	8	19
Burning micturation	13	30.9
Respiratory difficulty	8	19
Non specific symptoms	6	14.2
Clinical signs		
Abdominal lump	40	95.2
Hypertension	13	30.9
Abdominal tenderness	17	40.4
Respiratory distress	8	19
Altered sensorium	2	4.7
Bleeding diathesis	6	14.2

Table 2 shows clinical profile of patients with wilms tumor.

Most common presenting symptom was abdominal mass noticed by parents, found in 40 (95.2%) patients followed by abdominal pain in 17 (40.4%) patients. Similarly most common sign was abdominal lump in 40 (95.2%) patients.

**Table 3 showing TVBPQ (tumour volume before preoperative chemotherapy) of patients with wilms tumor and TVAPQ (tumour volume after preoperative chemotherapy) of patients with wilms tumor.**

TVBPQ	No of patients(n=42)	Median TVBPQ
<500ml	3	572.5ml
500-1000 ml	20	
1000-1500 ml	11	
1500-2000ml	6	
2000-2500ml	2	
TVAPQ	No of patients(n=42)	Median TVAPQ
<500 ml	34	146ml
500-1000 ml	5	
1000-1500 ml	2	
1500-2000ml	1	

2000-2500 ml	0	
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Table 3 shows, majority of patients with wilms tumor had tumor volume before preoperative chemotherapy (TVBPQ) between 500-1000ml, seen in 20 cases. On statistical analysis of this data, range of TVBPQ was found to be of 66.3ml to 2,380 ml and the median TVBPQ calculated is 572.5 ml. Majority of patients with wilms tumor had tumor volume after preoperative chemotherapy (TVAPQ) < 500 ml in 34 cases. On statistical analysis of this data, range of TVAPQ was found to be of 15 ml to 1,549 ml and the median TVAPQ calculated is 146 ml.

**Table 4- showing the percentage reduction of the tumor volume after preoperative chemotherapy (TVAPQ) compared to before preoperative chemotherapy (TVBPQ) in patients with wilms tumor**

Tumor volume reduction	No of patients(n=42)	Percentage (%)
<40%(poor response)	6	14.29
> 40%(good response)	36	85.71

Table 4 shows, majority of patients with wilms tumor had tumor volume of reduction > 40%(good response) i.e in 36 cases (85.71%) after preoperative chemotherapy.

**Table 5-showing relation between tumor volume after preoperative chemotherapy (TVAPQ) and outcome of patients with wilms tumor at the end of 2 years.**

Outcome	TVAPQ		P value
	<500ml	>500ml	
Death at 2 years	1	5	<0.001
Survivors at 2 years	35	1	

Table 5

shows, on statistical analysis tumor volume after preoperative chemotherapy (TVAPQ) > 500 ml was significantly associated with death at 2 years. (p value<0.001))

**Table 6 showing relation between the percentage reduction of the tumor volume after preoperative chemotherapy (TVAPQ) compared to before preoperative chemotherapy (TVBPQ) with outcome of patients with wilms tumor at end of 2 years.**

Outcome	Tumor volume reduction(n)		P value
	<40%(poor response)	>40%(good response)	
Death at 2 years	4	2	<0.001
Survivors at 2 years	2	34	

Table 6 shows, on statistical analysis, there is significant association between the difference between TVBPQ and TVAPQ and survival at end of 2 years. (P value <0.001)

**Figure 1 showing outcome of patients with wilms tumor at end of study (after 2 years)**

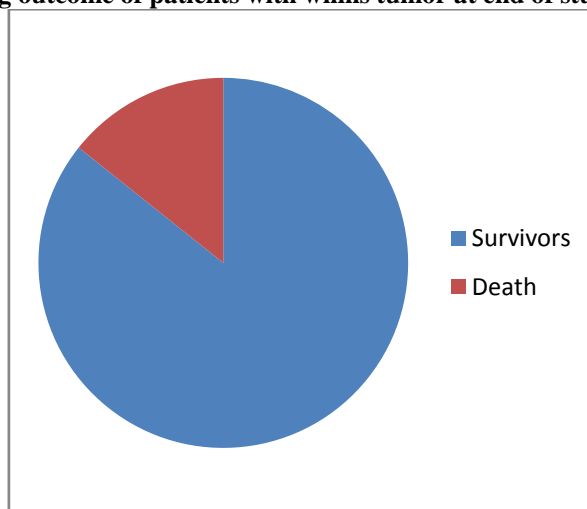


Figure 1 shows , out of 42 cases of wilms tumor, majority of patients survived i.e 36 cases (85.7%) and 6(14.29%) patients died.

#### IV. DISCUSSION

In present study, most common affected age group was between 2-5 years and was similar in many studies like Natasha et al (2022)<sup>8</sup>, Sah KP et al (2010)<sup>9</sup> and Guruprasad et al (2013)<sup>10</sup>. Literature also states that 78% of children with wilms tumor are diagnosed at 1-5 years of age, with a peak incidence occurring between 3 and 4 years of age.

In this study, there was a female preponderance with male: female ratio of 0.9:1 and was similar in many studies like Graf et al (2012)<sup>11</sup> with M: F ratio of 0.8: 1 and Natasha et al (2020)<sup>8</sup> with M: F ratio of 0.9:1. In contrast study conducted by Weirich et al (2004)<sup>5</sup>, they found the percentage of male patients (52.5%) was higher with M: F ratio of 1.1:1. The reason for higher incidence of wilms tumor in males in their study might be due to large sample size (n=440 cases). In study conducted by Valentina et al (2014)<sup>12</sup>, they found the percentage of male patients (53.1%) was higher with M:F ratio of 1.1:1. This gender difference in their study might be due to geographic difference as their study was conducted at Brazil.

In present study, most common symptom was abdominal mass in 40 cases (95.2%) which is followed by abdominal pain in 17 cases (40.4%). In the similar study by Okello et al (2020)<sup>13</sup>, all patients presented with an abdominal mass (100%). Similarly Natasha et al (2019)<sup>8</sup> observed most common symptom was abdominal mass (92%) followed by fever (24%) in patients with wilms tumor. On the contrary, in study done by Kioumehri et al (1989)<sup>14</sup>, most common symptom was abdominal pain (88%) which is followed by abdominal mass (40.4%). This difference in symptoms may be due to difference in age group studied in their study (15-84 years).

In present study, most common sign was abdominal lump in 40 cases (95.2%) which is followed by abdominal tenderness in 17 cases (40.4%). In similar study by Guru et al (2013)<sup>15</sup>, Majority of patients (92%) had an abdominal lump. Literature<sup>1</sup> also states that abdominal mass is the most common presenting sign.

In present study, majority of the patients with wilms tumor had low risk histology seen in 19 (45.2%) cases followed by intermediate risk histology in 18 (42.9%) cases followed by high risk histology in 5 (11.9%) cases. In similar study by Taran et al (2010)<sup>16</sup>, they observed most of cases of wilms tumor had histology of low risk (48%) followed by intermediate risk (43%) and high risk (9%). In contrast study, Graf et al (2012)<sup>11</sup> reported 95% cases with intermediate risk and 5% low risk histology. High risk histology cases were not included in their study for study purpose. Difference in histology may be due to large number of cases included in their study (n=594). In other contrast study by Sah kp et al (2010)<sup>9</sup> 50% children were classified as intermediate risk tumor followed by low risk tumor in 30% followed by high risk tumor in 20% cases. Difference in histology compared to our study may be due to the difference in geographical location (Nepal).

In the present study, majority of the patients were in stage III in 23 cases (54.7%). This finding was similar in studies like Sah kp et al (2010)<sup>9</sup> and Guruprasad et al (2012)<sup>15</sup>. In contrast study by Heba A. Sayeed et al (2012)<sup>17</sup>, majority of the patients were in stage I in 44 cases (48.4%). The difference in stage at presentation compared to our study may be due to large number of cases included in their study (n=91). In the other study done by Okello et al (2019)<sup>13</sup>, they found that majority of the patients were in stage II (48.4%) followed by stage III and stage I (21% each). This difference may be due to less number of cases included in their study (n=24) and also early stage at presentation in their study may be due to early referral of patients at their regional hospital where study was conducted.

In present study, Majority of patients with wilms tumor had tumor volume before preoperative chemotherapy (TVBPQ) between 500-1000ml, seen in 20 cases. Range of TVBPQ was found to be of 66.3ml to 2,380 ml and the median TVBPQ calculated was 572.5 ml. In similar study by Valentine et al (2014)<sup>12</sup>, median TVBPQ was 569.1ml (range 70.6 to 2,364.2ml). In other study by Graf et al (2012)<sup>11</sup>, they observed median Tumor volume at diagnosis (TVBPQ) was 439 ml. But Taran et al (2010)<sup>16</sup>, found median TVBPQ of 351.5 ml which was much low compared to our study may be due to wide range (24 to 5400 ml) in tumor size in their study which might be due to different geographical location of their study (Poland in Europe).

Majority of patients with wilms tumor in current study had tumor volume after preoperative chemotherapy (TVAPQ) < 500 ml in 34 cases. Range of TVAPQ was found to be of 15 ml to 1,549 ml and the median TVAPQ calculated was 146 ml and was similar in many studies like Valentine et al (2014)<sup>12</sup>, Graf et al (2012)<sup>11</sup>. Preoperative chemotherapy in patients with wilms tumor has shown to reduce tumor size and tumor volume.

In the present study, majority of patients with wilms tumor had tumor volume reduction > 40% (good response) (85.71%) after preoperative chemotherapy and 6 cases (14.29%) showed poor response i.e <40% reduction in tumor volume after preoperative chemotherapy and this finding was similar in studies like by Valentine et al (2014)<sup>12</sup> and Weirich et al (2004)<sup>5</sup>. On the contrary, in study by Graf et al (2012)<sup>12</sup>, Paired analyses on volume at diagnosis (TVBPQ) and after pre-operative chemotherapy (TVAPQ) showed no change in 3% and an increase in volume in 11% of the patients. Difference in response to preoperative chemotherapy may be due

to difference in histological subtype of tumor as 95% were with intermediate risk histology in their study while in our study majority were in low risk histology group.

In present study, tumor volume after preoperative chemotherapy (TVAPQ) > 500 ml was significantly associated with death at 2 years. ( $p < 0.01$ ). In similar study by Graf et al (2012)<sup>11</sup>, they observed that TVAPQ is the most important risk factor for recurrence and death. But Valentina et al (2014)<sup>12</sup>, showed there was no significant association of TVAPQ > 500 ml with death at 2 years. This difference might be due to difference in geographical location as their study was conducted at Brazil.

In the present study, there is significant association between the difference between

TVBPQ and TVAPQ and survival at end of 2 years. (P value < 0.001). Similarly Weirich et al (2004)<sup>5</sup> reported that patients who with reduction in TVAPQ < 40% had a statistically significant relapses. This indicates that less tumor volume reduction after preoperative chemotherapy results in significant number of relapses in future. In contrast study by Valentina et al (2014)<sup>12</sup>, they observed that the difference between TVBPQ and TVAPQ was not associated with death at 2 years. This difference might be due to difference in geographical location as their study was conducted at Brazil.

In the present study, out of 42 cases of wilms tumor, majority of patients survived i.e. 36 cases (85.7%) and 6 (14.29%) patients died. This observation is parallel to study reported by Valentina et al (2014)<sup>12</sup> in which 71.9 % cases survived at 2 years and 28.1% cases died. In contrast study by Okello et al (2019)<sup>13</sup>, mortality in their study was somewhat more (41% died and 59% survived at end of treatment). The low survival rates in their study may be to the high occurrence of diffuse anaplasia in their patients and due to the lack of radiotherapy services at their place which is required in management of advanced stage Wilms tumor.

## V. CONCLUSION

In our study most common age group in patients with wilms tumor was between 2-5 years. There was a slight female predominance with male: female ratio of 0.9:1. Abdominal mass (95.2%) was the most common symptom in wilms tumor and abdominal lump being most common sign (95.2%). Majority of the patients at presentation were in stage 3 (54.7%) and had low risk histology on biopsy (45.2%). Majority of patients with wilms tumor had tumor volume before preoperative chemotherapy (TVBPQ) between 500-1000 ml and the median TVBPQ calculated is 572.5 ml. Majority of patients with wilms tumor had tumor volume after preoperative chemotherapy (TVAPQ) < 500 ml and the median TVAPQ calculated is 146 ml. Majority of patients (85.7%) with wilms tumor showed good response to preoperative chemotherapy i.e tumor volume reduction > 40%. Tumor volume after preoperative chemotherapy (TVAPQ) > 500 ml was significantly associated with death at 2 years. ( $p < 0.001$ ). The relation between the difference between TVBPQ and TVAPQ and survival at end of 2 years was statistically significantly ( $p < 0.001$ ). Majority of patients survived at end of study (85.71 %). Hence our study indicates the positive relation between the difference between TVBPQ and TVAPQ and survival, still more studies with larger sample size are needed to state tumor size as best prognostic variable.

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