

## Intracaval and Intracardiac Extension of Wilms' Tumor. The Influence of Preoperative Chemotherapy on Surgical Morbidity

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### ABSTRACT

*Objectives:* The aim of this retrospective study is to compare surgical complications and long-term survival in children with Wilms' tumor (WT) and tumor thrombus receiving or not preoperative chemotherapy.

*Materials and Methods:* Review of the charts of 155 children with WT treated between 1983 and 2005, and analysis of 16/155 (10.3%) children with WT who presented cavoatrial tumor extension, being 8/16 IVC and 8/16 atrial thrombus.

*Results:* Median age was 54 months. 2/16 had cardiac failure as the first symptom. 11/16 (7 IVC and 4 atrial extension) (67%) were submitted to preoperative chemotherapy with vincristine plus actinomycin D, and 5/16 (1 IVC and 4 atrial) (33%) underwent initial nephrectomy and thrombus resection. So, 11 patients were submitted to preoperative VCR/ACTD and 2/11 (18.1%) had complete regression of the thrombus, 6/11 (54.5%) partial regression and 3/11 (27%) had no response. Among the partial responders, nephrectomy with thrombus removal was performed in all, including one patient with previous intracardiac involvement, without extracorporeal circulation procedures. In two of the three non-responders, cardiopulmonary bypass was necessary for thrombus removal. There were no surgical related deaths. Long-term survival is 91% in the group submitted to preoperative chemotherapy and 100% in the group who had surgery as first approach.

*Conclusion:* Preoperative chemotherapy was able to reduce thrombus extension in 8/11 (73%) treated patients and cardiopulmonary bypass was avoided in 2 patients with atrial thrombus. Surgical resection of tumor and thrombus was successful in all cases, receiving or not preoperative chemotherapy and overall survival was similar in both groups.

*Key words:* Wilms tumors; thrombus; vena cava; cardiac; chemotherapy; surgery

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### INTRODUCTION

Inferior vena cava (IVC) involvement by Wilms' tumor occurs in 4-10% of patients and right atrium thrombus extension in less than 1% (1). This complication does not influence on the prognosis of the malignancy, but it makes surgical procedures more challenging, mostly when there is intracardiac

involvement. Surgery used to be the first recommended approach, but some authors report the effectiveness of preoperative chemotherapy in reducing or eradicating the thrombus, and also reducing the tumor dimensions and making surgery easier to perform (2).

The aim of this retrospective study is to compare surgical morbidity and outcome of patients

with Wilms' tumor and cavoatrial thrombus who received or not preoperative chemotherapy.

## MATERIALS AND METHODS

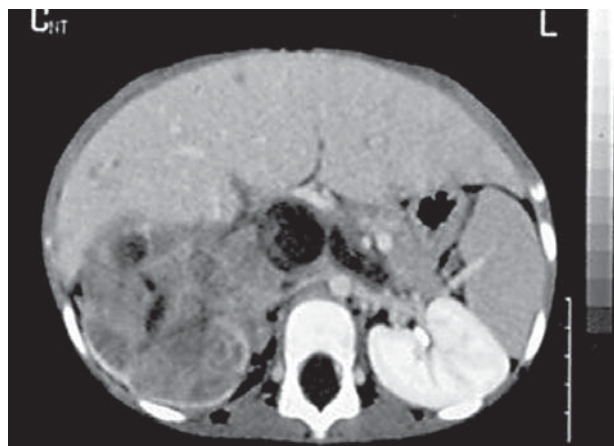
A retrospective review of the charts of 155 children with Wilms' tumor admitted to the University of Sao Paulo from June/1983 through April/2005 was performed in order to select those with intracaval (IVC) or intracardiac thrombus. Among them, 16/155 (10.3%) children presented intravascular thrombus, being the last one diagnosed in April/2001. The patients were treated with an institutional protocol from 1983-2001. These 16 patients were analyzed for the use or not of preoperative chemotherapy, effect of preoperative chemotherapy regarding thrombus extension, surgical morbidity, intraoperative time, use of cardiopulmonary bypass, postoperative complications, number of hospitalization days, transfusion amount and influence on disease outcome. Fisher's test, Mann-Whitney and Kaplan-Meier curve were employed for statistical analysis.

## RESULTS

Sixteen patients were selected. Eight had IVC (5.15%) and eight (5.15%) had atrial tumor involvement. There were nine females and seven males. Median age was 54 months, ranging from one year through 8 years. In 13 patients, the tumor arose from the right kidney and in 3 from the left. Hematuria was presented by 4/16 patients, hypertension by 2/16 and 2/16 had cardiac failure as first symptom. All thrombus were preoperatively detected by ultrasonography in 13/16 patients, Doppler echography in 5/16, abdominal CT in 3/16 (Figure-1) and IVU in 3/16.

Median tumor dimension at diagnosis was 120 X 80 mm. Stage II disease was observed in six patients, stage III in seven and stage IV in three. Histology was favorable in 13 patients and unfavorable in three.

Among the 8 patients with tumor extension into the IVC, in 5/8 the thrombus was infrahepatic and in 3/8 there was a suprahepatic involvement.



**Figure 1** – CT scan revealing thrombus in the vena cava in a patient with Wilms' tumor.

Preoperative chemotherapy with vincristine 1.5 mg/m<sup>2</sup>/day and 21 plus actinomycinD 1.5 mg/m<sup>2</sup>/day for four to six weeks was administered to 7/8 of these patients with IVC involvement and in 1/8 IVC thrombus, a primary surgical resection was carried out.

In the group of 8 patients with intracardiac thrombus extension, 4/8 were submitted to the same preoperative chemotherapy schedule and 4/8 went to surgery after diagnosis because of poor clinical situation (2 cardiac failure) or surgeon's preference (2 cases of the early 80's).

A total of 11/16 patients were submitted to preoperative VCR/ACTD for four to six weeks and 2/11 (18.1%) had complete regression of the thrombus, 6/11 (54.5%) partial regression and 3/11 (27.2%) had no response (Figure-2). There was no correlation between the duration of preoperative chemotherapy and response. Among the partial responders, nephrectomy with thrombus removal was performed without cardiopulmonary bypass in all, including one patient with previous intracardiac involvement, obviating the use of cardiopulmonary bypass. In two of the three non-responders cardiopulmonary bypass was necessary for thrombus removal (Table-1). Hypothermia was used in four patients with atrial thrombus. Radiotherapy was not used in any patient previously to surgery.

Transfusion mean amount was 803 mL ( $\pm$  678 mL) in the preoperative chemotherapy group and 1536

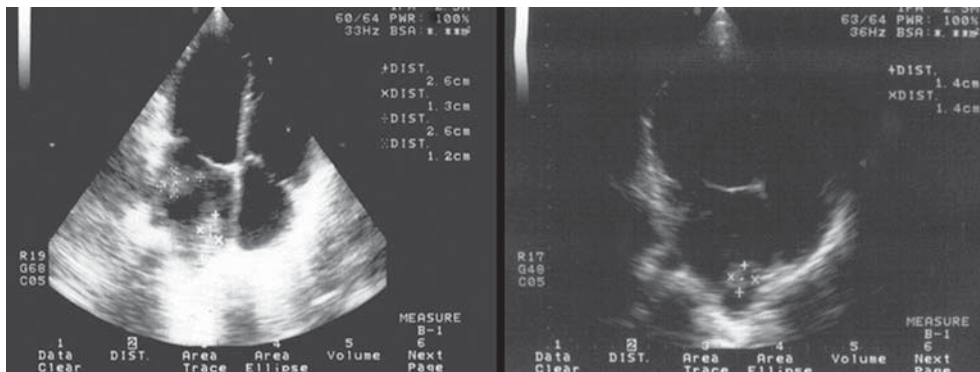


Figure 2 – Echocardiographic evaluation of a cardiac thrombus before and after preoperative chemotherapy: absence of response.

mL ( $\pm 1001$  mL) in the other group, statistically not different values ( $p = 0.2159$ ). Cardiopulmonary bypass was more frequently used in the non-preoperative chemotherapy group ( $p = 0.036$ ). Comparing patients not submitted to CBP with patients submitted to CBP, we have observed that the first group had lesser transfusion amount ( $p < 0.001$ ), shorter operative time ( $p = 0.001$ ) and shorter hospital stay ( $p = 0.001$ ).

Mean operative time was 227.7 minutes ( $\pm 89.2$  min.) in the preoperative chemotherapy group and 369 minutes ( $\pm 110$  min.) in the other one, revealing a quite longer time for the non- preoperative chemotherapy group ( $p = 0.0263$ ). Mean hospital stay was 5.72 days ( $\pm 7.1$  days) in the preoperative chemotherapy group and 9 days ( $\pm 4.9$  days) in the other one, a significant difference ( $p = 0.0342$ ).

Postoperative infectious complications were observed in two patients, one with and one without preoperative chemotherapy, resulting in a longer hospitalization period. No other complications were presented.

The histopathological analysis of the removed thrombus revealed viable tumor in 6/11 (54.5%) patients submitted to preoperative chemotherapy, all of them being favorable histology tumors.

Long-term survival was 91% in the previously treated group (one child with a chemotherapy resistant anaplastic tumor had a local relapse and died), and 100% in the group not submitted to preoperative chemotherapy. There was no difference between both groups regarding survival rate ( $p = 0.50$ ), Figure-3. The median follow-up is 177.3 months for the whole group.

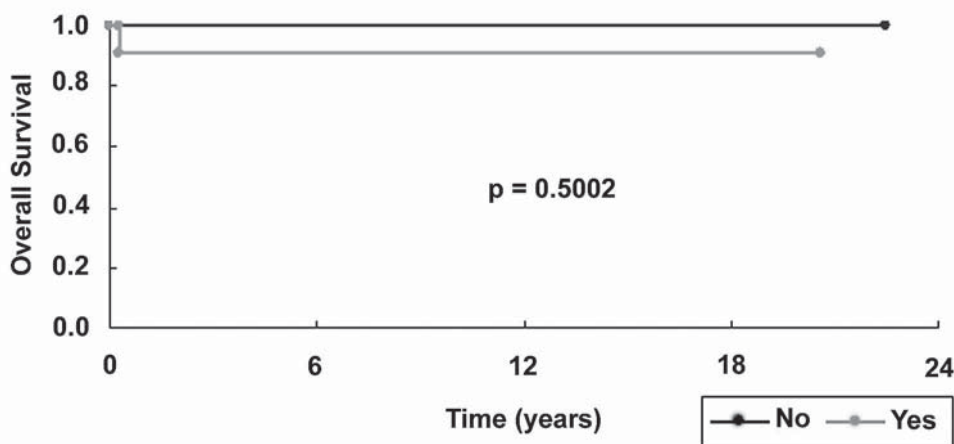


Figure 3 – Overall survival of patients with Wilms' tumor and intravascular thrombus, receiving or not preoperative chemotherapy.

**Table 1** – Study population: characteristics of the thrombus at diagnosis and at surgery, use or not of preoperative chemotherapy, cardiopulmonary bypass, hypothermia, transfusion amount, surgical time, hospital stay and stage.

Case	Thrombus Extension at Diagnosis	Preoperative VCR/ACTD	Response	Thrombus Extension at Surgery	CBP	Hypothermia	Transfusion (mL)	Surgical Time	Hospital Stay (d)	Stage
1	vena cava infrahepatic	yes	complete	-	no	no	-	4h	3	III
2	vena cava infrahepatic	yes	partial	vena cava infrahepatic	no	no	250	3h	5	II
3	vena cava infrahepatic	yes	partial	vena cava infrahepatic	no	no	-	3h30min	5	III
4	vena cava suprahepatic	yes	partial	renal vein	no	no	-	2h30min	4	II
5	vena cava infrahepatic	yes	partial	renal vein	no	no	-	3h	3	II
6	vena cava suprahepatic	yes	partial	vena cava infrahepatic	no	no	-	2h45min	2	II
7	vena cava infrahepatic	yes	none	vena cava infrahepatic	no	no	-	4h30min	3	IV
8	vena cava suprahepatic	no	-	vena cava suprahepatic	no	no	-	4h	4	III
9	right atrium	yes	partial	vena cava infrahepatic	no	no	-	3h	2	III
10	right atrium	yes	none	right atrium	yes	yes	600	6h	27	II
11	right atrium	yes	none	right atrium	yes	yes	1560	7h	6	II
12	right atrium	yes	complete	-	no	no	-	2h30min	3	IV
13	right atrium	no	-	right atrium	yes	yes	1750	5h	7	IV
14	right atrium	no	-	right atrium	yes	no	2900	8h45min	17	III
15	right atrium	no	-	right atrium	yes	yes	700	6h	7	III
16	right atrium	no	-	right atrium	yes	no	900	7h	10	III

## COMMENTS

The incidence of intravascular thrombus extension in our study population was 10.3%, similar to other authors' findings, but intracardiac involvement was 5.5%, a little higher than the reported experience (3,4). The thrombus occurrence represents a remarkable difficult factor for surgical procedures, increasing morbidity. In the NWTSG-4 intravascular tumor extension presented an increased risk for complications (odds ratio 3.8, 95% confidence interval) (5). It should be an elective procedure, performed by a multidisciplinary team. Tumor thrombus extending into the suprahepatic IVC (type III) and right atrium (type IV) requires cardiopulmonary bypass, with or without circulatory arrest, for removal (6). Cardiopulmonary bypass includes the use of median sternotomy, atriotomy and systemic anticoagulation (7). It elongates intraoperative time, exposing the patient to hypothermia, blood transfusion, cardiac arrest, pericardic-patch and to the complications related to these methods (8). Preoperative chemotherapy is recommended by many authors because it is able to promote significant tumor and thrombus shrinkage, and may facilitate the surgical approach and tumor resection, avoiding tumor rupture and neoplastic cells spillage (9), but in some cases, mostly in patients with cardiac thrombus, the risks of immediate cardiorespiratory dysfunction due to thromboembolism makes surgery the first recommended approach (10).

In our retrospective analysis, preoperative chemotherapy with VCR / ACTD has induced thrombus shrinkage in 8/11(72.7%) treated patients, but in 3/11(27.3%) it was ineffective regarding thrombus extension. Shamberger et al. reported a 79.5% incidence of tumor regression in similar cases (11). Tumor or thrombus progression or toxicity during preoperative chemotherapy is a concern for some authors, but it has not occurred in our patients (12,13).

The 7/8 patients with intracaval thrombus that were submitted to preoperative chemotherapy presented 1/7(14.3%) complete regression of the thrombus, 1/7(14.3%) failure and 5/7(71.4%) partial response. As CBP is the reason for a longer operative time ( $p < 0.001$ ), higher transfusion amount ( $p < 0.001$ ) and longer hospital stay ( $p < 0.001$ ), avoiding

CBP is the objective of the use of preoperative chemotherapy. Cardiopulmonary bypass was not necessary for thrombus removal in all cases of IVC thrombus and in 2/4 patients with intracardiac thrombus, who were supposed to be submitted to invasive surgical procedures with CBP, and after receiving preoperative chemotherapy presented a partial or total thrombus decrease. The remaining 2/4 presented no change in thrombus extension and surgery with cardiopulmonary bypass was performed with success. The other 4/8 children with intracardiac thrombus were treated exclusively with surgery, two due to critical clinical situation at diagnosis (cardiac failure) demanding prompt intervention and the two others due to surgeons' own decision. These cases were treated at the early 80's and a more aggressive initial approach was recommended at our hospital. All were successful procedures, with no intra or postoperative deaths.

The mean transfusion amount was similar in both groups ( $p = 0.2159$ ), but the group submitted to preoperative chemotherapy had advantages such as shorter operative time ( $p = 0.0263$ ) and shorter hospital stay ( $p = 0.0342$ ).

Complications like infection, tumor progression, tumor rupture, thromboembolism, hemorrhage and death are a major concern in this situation. The NWTSG-4 reports a complication incidence rate of 26% for children with initial surgical resection and 13.2% for those with preoperative chemotherapy ( $p = 0.053$ ) (11). The complications incidence rate in NWTSG-3 is 43% (14, 15). The SIOP/GPOH group reports 18.18% of complications in 33 children with Wilms' tumor and thrombus extension, 29/33 submitted to preoperative chemotherapy (16). The UKW3 trial reports 13.6% of hemorrhagic complications, including 3 deaths (17). In our study, 7/16 (44%) patients required blood transfusions due to the surgical procedures, and 2/16(12.5%) patients had infectious complications after surgery, one patient with and one without preoperative treatment. No intraoperative or postoperative deaths were observed.

This is a twenty-three-year experience and along this long period of time some changes in medical approach of this situation have occurred in our institution, including the patterns for indication of initial

surgery, the indication and the drugs used for preoperative chemotherapy and the postoperative management. Some authors recommend preoperative chemotherapy for those patients whose tumors are at or above the supra-hepatic vena cava (COG/NWTS), but many years ago, a surgical first approach was considered by some surgeons in our institution.

The five-year overall survival was 100% in the not treated group and 91% in the other, with one death due to local relapse in a patient with anaplastic tumor submitted to preoperative chemotherapy with partial response.

## CONCLUSION

In conclusion, preoperative chemotherapy was able to reduce thrombus extension in 8/11 patients and cardiopulmonary bypass was avoidable in at least two patients. Although surgical procedures were successful in all cases, receiving or not preoperative chemotherapy, the first group had some significant advantages such as shorter operative time and shorter hospital stay, suggesting the benefits of the preoperative use of VCR/ACTD in patients with Wilms' tumor and intravascular thrombus extension.

## CONFLICT OF INTEREST

None declared.

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## EDITORIAL COMMENT

Vascular extension in patients with Wilms' tumor occurs in 5 - 10%. This situation consists in a surgical challenge. Preoperative chemotherapy seems to benefit those patients, although there are few references about tumor vascular extension in literature (1,2). Both NWTS and SIOP protocols recommend that preoperative chemotherapy should be done. The presented paper shows that preoperative chemotherapy does not change the survival probability and have some advantages when compared to the non preoperative chemotherapy group, such as shorter operative times, blood loss and days of hospitalization. It also prevented some patients from cardiopulmonary bypass. However, the authors did not make any relation between blood loss and the type of procedure performed. They reported that 11 patients received preoperative chemotherapy. Four of those had extension until the right atrium, but only two needed cardiac bypass. The group of patients without preoperative chemotherapy (n = 5), four had extension until the right atrium and all of them were operated with cardiac bypass, which lead to a greater blood

loss (bias). Therefore, this paper shows one institution's experience in a rare situation and confirms the results of literature.

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