

Wilms tumor with intravascular tumor thrombus

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Abstract: Wilms tumor (WT) is one of the most common solid tumors in children. It is the second most common extracranial solid tumor after neuroblastoma. WT has a strong tendency to invade blood vessels in the form of tumor thrombus, into the renal veins, and inferior vena cava and even into the right atrium. Extension of tumor thrombus along to the renal vein into the inferior vena cava occurs in 4-10% of all patients. Tumor thrombus extending to the right atrium is less reported as 0.7-1%. WT with renal vein thrombus has been reported to be more common in the right kidney because of the shorter right renal vein. Most patients with tumor thrombus are asymptomatic and diagnosis is only made on imaging investigations. Several imaging modalities including computed tomography (CT), magnetic resonance imaging (MRI) and Doppler ultrasonography (USG) can demonstrate intravascular tumor thrombus before surgery. In addition to CT and MRI, Doppler USG is reliable in demonstrating the presence and extent of inferior vena cava tumor thrombus. The management of WT with tumor thrombus is determined by multiple factors such as extent of tumor thrombus, chemotherapy response of the tumor. Now, it is generally recommended to use preoperative chemotherapy to a patient presenting with intravascular tumor thrombus. This approach is helpful to decrease the extent of the vascular thrombus which facilitates surgical excision. Most intracaval and intraatrial thrombi in WT show a response to chemotherapy. Neoadjuvant chemotherapy causes tumor regression in nearly half of the patients. Most of them can be managed without the need for cardiac bypass surgery. The decision of initial surgery or preoperative chemotherapy should be carefully determined on every case. Primary surgery would only be indicated in a patient who is unstable because of thrombus that might dislodge and cause acute symptoms. Presence of tumor thrombus in WT needs for multidisciplinary care including pediatric oncologists, pediatric surgeons, and pediatric cardiac surgeons.

Keywords: Wilms tumor (WT); intravascular extension; tumor thrombus

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Wilms tumor (WT), also known as nephroblastoma, is the most common renal tumor in children. It accounts for more than 90% of all renal tumors in children.

The survival rates have greatly improved over the years, based on the currently available treatment protocols. Most of the patients with WT can expect to be cured of their disease following multimodal therapy (1,2).

Multicentre trials have been carried out both in Europe by Society of International Pediatric Oncology (SIOP) and in the United States by National Tumor Wilms Study Group (NTWSG) since 1980's. By using chemotherapy and radiotherapy, in addition to total nephrectomy, the

prognosis of WT has improved dramatically to more than 90% in recent years. The management of WT differs in Europe and North America. In Europe, WTs are treated according to the SIOP protocols. Use of preoperative chemotherapy provides tumor reduction prior to surgical resection in this approach. On the other hand, in North America, management of WT is according to the NTWSG regimens which advocate surgery prior to chemotherapy. Inoperable WT constitutes about 28% of total cases of WT. Large size of tumor, involvement of adjacent vital structures, and intracaval tumor thrombus are mostly accepted as inoperable criteria.

Table 1 Intravascular tumor thrombus in Wilms tumor

Author, reference	Number of cases	Age (years)	Tumor site	Thrombus extension	Preop chemo	Response	Surgery
Abdullah <i>et al.</i> (11)	9	6, 6	6R/3L	9 RA	8/9	2 complete	6 CPB; 2 T + N
Bader <i>et al.</i> (4)	10	6, 6	6R/2L/2B	2 RA, 2 diaphragm, 6 IVC	10	10 partial	10 CT
Aspiazu <i>et al.</i> (6)	7	3, 4	4R/3L	Sh IVC + RA 7	7	7 partial	1 N + T; 4 CPB; 2 CT
Hadley <i>et al.</i> (7)	40	4,5		10 RA, infrahep. 16, Retrohep 14	40	20 partial	7 CPB; 23 CT; 1 CCT
Cristofani <i>et al.</i> (12)	16	4, 5	13R/3L	8 IVC, 8RA	11	2 complete 6 partial	2 CPB; 13 N + T
Murthi <i>et al.</i> (13)	13	4	12R/1L	5 IVC, 8RA	11	3 partial	4 CT
Lall <i>et al.</i> (9)	59	3, 75	33R/24L, 2B	RA 10, Suprahep 9, retrohep 8, infrahepatic 26	52	35 partial	31 CT; 3 CPB

Abbreviations: R, right; L, left; B, bilateral; RA, right atrium; SH, supra hepatic; IH, infrahepatic; RH, retrohepatic; IVC, inferior vena cava; PR, partial response; CR, complete response; CPB, cardiopulmonary bypass; T, thrombectomy; CT, cavotomy; N, nephrectomy; CCT, cavectomy.

Overall survival and relapse free survival rates are almost same from different treatment strategies with both the NTWSG and SIOP approach.

WT has a strong tendency to invade blood vessels in the form of tumor thrombus, into the renal veins, and inferior vena cava and even into the right atrium. WT can extend into its venous drainage resulting in thrombus. Intravascular extension of WT to the renal vein has been reported to occur in up to 20% to 35% of patients (3-7). Extension of tumor thrombus along to the renal vein into the inferior vena cava occurs in 4-10% of all patients. Tumor thrombus extending to the right atrium is less reported as 0.7-1% (8-11) WT with renal vein thrombus has been reported to be more common (59-85%) in the right kidney because of the shorter right renal vein (Table 1).

Most patients with tumor thrombus are asymptomatic and diagnosis is only made on imaging investigations. Ritchey *et al.* in a retrospective review of 77 patients with intravascular extension, observed only five with clinical findings suggesting this condition (12). Preoperative identification of caval thrombus in patients with retroperitoneal tumors is very important for surgery. The accuracy of various imaging modalities in detection of tumor thrombus in children with WT has not been defined. Several imaging modalities including computed tomography (CT), magnetic resonance imaging (MRI) and Doppler ultrasonography (USG) can demonstrate intravascular tumor thrombus before surgery

(13,14). In addition to CT and MRI, Doppler USG is reliable in demonstrating the presence and extent of inferior vena cava tumor thrombus.

The current recommendation is that USG with color Doppler sonography should be performed for preoperative evaluation of tumor thrombus in WT. In patients with a suspected renal tumor, Doppler USG should be performed to detect tumor infiltration of renal vein and inferior vena cava and to assess patency of blood flow. Hadley *et al.* reported that they have found CT combined with Doppler USG to be useful in defining the presence and extent of tumor thrombus (7). But, on the other hand, some authors recently reported that CT can accurately identify cavoatrial tumor thrombus in their studies. McDonald *et al.* investigated the role of CT or MRI of abdomen over USG in children with WT. They concluded that CT or MRI added additional information in local staging of the patients (13). An echocardiogram will also add to the information on the extent of the intracardiac thrombus.

The classification of intracaval tumor thrombi is performed according to the upper extent of the tumor thrombus: level 1, infrahepatic thrombus; level 2, retrohepatic thrombus; level 3, suprahepatic thrombus; and level 4, atrial thrombus. The presence of cavoatrial tumor thrombus can lead to differences in management. The management of WT with tumor thrombus is determined by multiple factors such as extent of tumor thrombus, chemotherapy response of the

tumor (15-18).

In traditional concept, the recommended treatment of WT with tumor thrombus extending into the renal vein is open surgery to avoid tumor spread and minimize the risk of spillage. Primary surgery carries the risks of tumor thrombus with embolus and cardiac decompensation. In 1970's Wagget and Koop firstly suggested the use of neoadjuvant chemotherapy and radiotherapy in WT for providing tumor thrombus regression (19).

After this report, some patients received neoadjuvant chemotherapy followed by surgery whereas some patients underwent primary nephrectomy. The patients with thrombus located in the infrahepatic inferior vena cava can undergo primary resection while the patients located above the liver can usually require cardiopulmonary bypass (CPB).

Now, Both SIOP group and children's oncology group/NTWWSG recommend preoperative chemotherapy to a patient presenting with intravascular tumor extension. SIOP approach is helpful to decrease the extent of the vascular thrombus which facilitates surgical excision. Most intracaval and intraatrial thrombi in WT show a response to chemotherapy (Table 1). Neoadjuvant chemotherapy causes tumor regression in nearly half of the patients. Hadley *et al.* reported that there was a measurable tumor regression in 47% of their patients and in 30% of those with atrial thrombus (7). After preoperative chemotherapy, three children with atrial thrombus managed without use of CPB. Similarly, Cristofani *et al.* reported that preoperative chemotherapy was able to reduce thrombus extension 8/11 (73%) treated patients. Surgical resection of tumor and thrombus was successful in their cases, receiving or not preoperative chemotherapy. They resolve completely after chemotherapy or can be removed through a cavotomy (18).

Use of preoperative chemotherapy reduces the size of the tumor and provides easy surgical removal. WT with tumor thrombus can be managed without the need for cardiac bypass by preoperative chemotherapy. Even complete dissolution of tumor thrombus is possible. Very few cases require exploration under CPB.

Aspiazu *et al.* shared their experience and outcomes of children with WT and tumor thrombus. In their group, six of seven patients presented with tumor thrombus extending into the right atrium and only one patient with infrahepatic thrombus. After receiving neoadjuvant chemotherapy, tumor thrombus regression was observed in all cases. Nephrectomy and thrombectomy were performed in all cases, requiring CPB for the four patients with suprahepatic and right atrial thrombus (6).

As a result of preoperative chemotherapy, the size of tumor thrombus can decrease and thrombectomy and nephrectomy becomes easier and safer. But, if the thrombus invades the vessel wall, cavectomy is recommended as a treatment option. Riberiora *et al.* reported their experience in three patients treated with cavectomy and they concluded that cavectomy is a safe procedure for treating pediatric patients with WT (20). If thrombectomy is not possible, cavectomy can be preferred as a good surgical strategy. Generally, it has been recommended that if there is a renal tumor with intracaval tumor extension but without atrial extension, preoperative chemotherapy should be tried to shrinkage the tumor and tumor thrombus, firstly. After eight weeks of chemotherapy if the tumor still remains in the atria, it should be resected instead of persisting more chemotherapy.

Extension of the tumor to the retrohepatic vena cava or above would have required CPB and circulatory arrest to allow complete excision. CPB facilitates thrombus extraction in patients with suprahepatic vena caval and atrial extension. CPB is a complicated surgical procedure including the use of median sternotomy, atriotomy and systemic anticoagulation. It causes a longer operative time, higher transfusion amount and longer hospital stay.

Particularly, if atrial extension is still present after preoperative chemotherapy, most patients die with disease progression (7,10). Akyüz *et al.* reported that 14 patients received preoperative chemotherapy consisting of two-drug regimen. Akyüz *et al.* observed a high number of recurrences in children who had residual tumor thrombus. They concluded that surgical removal of the thrombus should be considered in the presence of life-threatening tumor thrombosis at diagnosis and in patients who had residual thrombus after chemotherapy (10). This finding shows the importance of complete resection. It seems that complete resection of all macroscopic disease should be tried. It has been recommended an aggressive approach to the management of patients with chemoresistant vena caval extension of their tumor. Murthi *et al.* reviewed their experience with surgical management of WT with persistent tumor thrombus. They used different approaches for excision of intravascular component such as local cavotomy in 3, extensive infra hepatic cavotomy without CPB in one and excision of cavoatrial tumor with CPB in nine patients (17).

Szavay *et al.* operated 24 patients who had tumor thrombus into the vena cava, in nine patients the thrombus reached into the right atrium. They used CPB in nine patients (15).

Presence of tumor thrombus does not cause a worse outcome if treated properly with preoperative chemotherapy and delayed resection. However, the presence of tumor thrombus increases the complication of primary resection. Complications are more frequent in the children with atrial extension than in those with extension limited to the inferior vena cava. The prognosis in children with WT and tumor thrombus is not affected by the presence or location of intravascular tumor thrombus, but an increased frequency of surgical complications has been reported. Chiappini *et al.* reported their results regarding 13 patients with an infradiaphragmatic tumor with thrombosis of the vena cava, the right atrium, or both underwent surgical resection with CPB, arrested circulation, and profound hypothermia. Postoperative complications were found in two patients (21).

In NTWSG-4, complications related to nephrectomy and tumor thrombectomy has been reported as 17.2% of cases with inferior vena cava extension and 36.7% of cases with atrial extension of tumor thrombus. Preoperative chemotherapy can lower the complication rate to 13%. The SIOP group reports 18% of complication in children with WT and thrombus extension (14,15). In children with extensive vascular invasion, particularly into the atrium, the best approach may be primary chemotherapy and delayed resection to minimize the risk of surgical complications.

It has been known that SIOP group recommends preoperative chemotherapy for most patients with presumed diagnosis of WT. Similarly, COG group also recommend preoperative chemotherapy for only patients with tumor thrombus. Preoperative chemotherapy has some advantages when compared to the initial surgery group such as shorter operative times, blood loss, and days of hospitalization.

But, the use of preoperative chemotherapy for patients with tumor thrombus has also some risks such as pulmonary embolism or tumor progression during preoperative chemotherapy. Vaideeswar *et al.* reported a case of sudden death due to hemorrhagic expansion of the intra-atrial component of WT after initiating of preoperative chemotherapy (22).

Schamberger *et al.* reported that complications during preoperative chemotherapy were seen in 5 of 69 patients such as tumor embolism, tumor progression (8).

Therefore, the decision of initial surgery or preoperative chemotherapy should be carefully determined on every case. Primary surgery would only be indicated in a patient who is unstable because of thrombus that might dislodge and cause acute symptoms.

The large series from the SIOP and NTWS groups

demonstrated that the patients with tumor thrombus have a similar relapse-free and overall survival rates compared to the patients without tumor thrombus.

In conclusion, presence of tumor thrombus needs for multidisciplinary care including pediatric oncologists, pediatric surgeons, and pediatric cardiac surgeons. Surgical excision of extensive tumor thrombosis is suggested in the case of life-threatening thrombosis even with CPB. Preoperative chemotherapy should be suggested in cases lacking clinical symptoms of thrombosis.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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