Chapter 4

Wilms Tumor and Its Management in a Surgical Aspect

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Abstract

Nephroblastoma [Wilms tumor (WT)] is a rare, but the most common, primary renal tumor in children. WT is usually diagnosed between the ages of 1 and 5, with the most common diagnosis at the age of 3. While imaging (ultrasound, computed tomography, and magnetic resonance) can accurately predict up to 95% of WTs, they cannot predict the histologic subtypes and require tissue examination. Surgery is one of the cornerstones of WT treatment. Other aspects of management include chemotherapy and radiation therapy. The Societe Internationale D'oncologie Pediatrique (SIOP) advocates primary chemotherapy in patients less than 6 months of age, whereas the

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Children's Oncology Group (COG) recommends primary surgery in all cases except those considered not resectable by the surgeon. In this chapter, the surgical therapy of WT is reviewed.

Key words: Nephroblastoma; Pediatric oncology; Surgery for Wilms tumor

Introduction

Wilms tumor (WT), also called nephroblastoma, was first described by Thomas F. Rance in 1814 (1, 2). In 1899, Carl Max Wilhelm Wilms, a German surgeon and pathologist, gave a detailed histological description and since then the tumor bears his name (1, 3). The incidence of WT is 1:10000 in children under 15 (4). WT is the most common renal malignancy in children, and it represents 6% of all childhood cancers. It is also the second most common intra-abdominal cancer, and it is an embryonal malignancy of the kidney (5). About 75% of children are diagnosed before the age of 5, and the median age is 3.5 years (6).

WT is primarily a sporadic disease, but family history exists in 1–2% of cases (7). There are a number of syndromes associated with WT, including WAGR (WT, aniridia, genitourinary anomalies, and mental retardation), Denys-Drash syndrome (progressive renal disease, male pseudohermaphroditism, and WT), and Beckwith-Wiedemann syndrome (8). While WAGR syndrome is associated with large deletion on the WT1 chromosome located on 11p13, Denys-Drash syndrome has point mutations on WT1 (9, 10). Beckwith-Wiedemann syndrome is a syndrome characterized by macrosomia, macroglossia, omphalocele, and growth retardation, and hemihypertrophy is caused by a mutation located on 11p15, also known as the WT2 gene locus (11). Normal kidneys complete differentiation at the end of the 36th week of gestation; however, in about 1–2% of newborns, nephrogenic blastemal cells, also called nephrogenic rests, persist. WT is thought to arise from these nephrogenic rests (12). These nephrogenic rests have been detected in almost 35% of unilateral and 100% of bilateral WT patients (13). The prognosis of WT is closely related to its histology. An unfavorable prognosis occurs when the tumor consists of anaplastic cells; the prognosis is favorable otherwise. This anaplastic type represents 11.5% of all WTs and is responsible for 52% of the mortality rate (14). However, for pretreated patients, there exist three subgroups: low-, intermediate-, or high-risk tumor, according to the Stockholm working classification of renal tumors used by the Societe Internationale D'oncologie Pediatrique (SIOP) (15). WT is associated with mutations in various tumor suppressor genes (16). In the anaplastic type of WTs, p53 mutation is frequent (17).

Clinical presentation

WT is usually unilateral, and the mean age of presentation is 3.3 years. In 4 to 7% of cases, they are synchronous bilateral and appear at a younger age (mean age of 2.6 years) (18). The most common clinical presentation of WT is an abdominal mass. Over 90% of children are referred with an abdominal mass. Other common symptoms are abdominal pain, macroscopic hematuria, fever, and hypertension (19). Abdominal pain can be a symptom of a rupture or intratumoral hemorrhage. Macroscopic hematuria may occur when the tumor has extended to the collecting system (20). Nonspecific symptoms, such as microscopic hematuria, urinary disturbances, malaise, weight loss, and anemia, may be present at initial presentation. If spermatic veins are occluded, varicocele can occur (3) and a thorough examination of the abdomen is necessary. Varicocele is always an alarming symptom, but even more if it occurs on the right side [symptom of inferior vena cava (IVC) thrombosis] or occlusion of the right spermatic vein by the lower part of the tumor (right spermatic vein goes directly to IVC). During the physical examination, a firm, nontender mass in the abdomen is usually identified. Due to elevated renin levels, a follow-up of the blood pressure is very important in WT patients. The most common intravascular tumor extension sites are the renal vein, IVC, and atrium (21). Although the lung is the most common metastatic site, respiratory symptoms are not common. In summary, during examination, the associated anomalies should be considered, and the patient should be examined for aniridia, hemihypertrophy, and genitourinary anomalies.

Diagnosis

Ultrasonography (US) is the primary diagnostic tool for children suspected of having WT. US allows for measuring the tumor size, identifying its origin, establishing the relationship between vena cava and aorta, as well as possible IVC or renal vein. The second important diagnostic tool is computerized tomography (CT). CT is recommended for WT along with US (Figure 1). During interpretation of the CT, and also the US, the contralateral kidney and the liver should always be carefully examined. Magnetic resonance imaging (MRI) is also helpful in detecting the vascular involvement. MRI, although requires longer general anesthesia in the preschool age, offers the most accurate imaging of the kidney. It serves best when nephron-sparing resection is considered or in case of the need to distinguish between WT and nephroblastomatosis. A plain chest X-ray is a routine procedure for the evaluation of pulmonary metastases. A routine pulmonary CT is still controversial (22); however, many physicians prefer the thoracic CT because of its high sensitivity. The definite diagnoses of WT and its subtypes are made by histological evaluation. The preoperative laboratory tests that should be performed are the total blood count, renal and liver function tests, calcium level examination, and urinary examination. In rhabdoid types, the serum calcium increases (23).

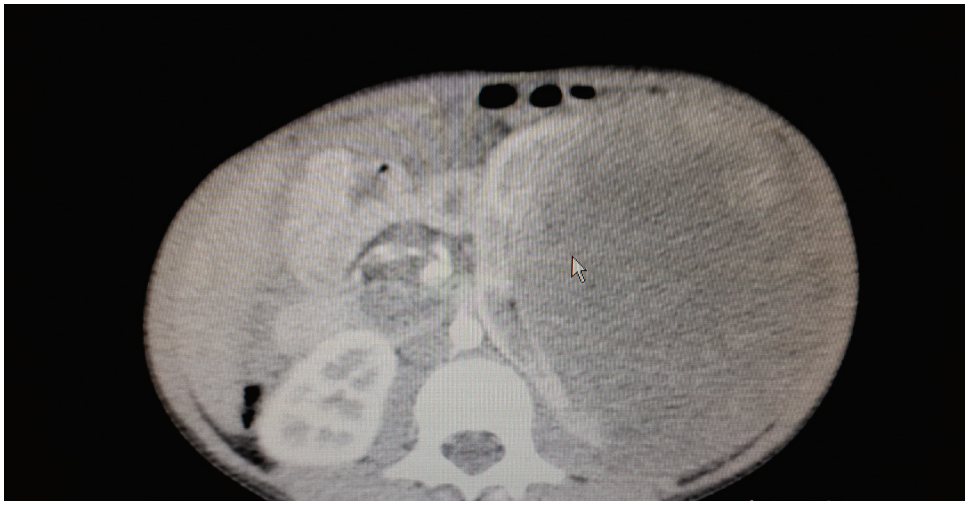

Figure 1. A CT scan of a left Wilms tumor.

In 8% of children with WTs, von Willebrand disease is a comorbidity (24). The routinely evaluated tumor markers include neuron-specific enolase, lactate dehydrogenase, alpha-fetoprotein, β-human chorionic gonadotropin, and ferritin. High-risk patients for the growth of WTs, such as patients with Beckwith-Wiedemann syndrome, should be routinely examined with an US (25). In addition, a 24-hour urine catecholamine test is essential to avoid misdiagnosing with neuroblastoma.

Staging

There are currently two major staging systems, the National Wilms Tumor Study (NWTS) and the SIOP, as summarized in Tables 1 and 2, respectively (26).

Surgical management

Surgery is the cornerstone for the treatment of WT. The Children's Oncology Group (COG) from North America, a group that conducted the NWTS trials, recommends surgery before chemotherapy, whereas SIOP in Europe suggests preoperative chemotherapy (26). As the SIOP group, the National Wilms Tumor Study Group (NWTSG) has concerns about performing a biopsy first because of the risk of tumor upstaging (27). The SIOP recommends preoperative chemotherapy to decrease the risk of intraoperative rupture, downstage the tumor, and to reduce the need for irradiation. The advantage of preoperative chemotherapy is the identification of chemoresistant high-risk blastemal predominant subtype that benefits from treatment intensification.

Table 1. The NWTS staging system*

Stages	Description
Stage 1	(a) Tumor is limited to the kidney and completely excised (b) The tumor is not ruptured before or during removal (c) The vessels of the renal sinus are not involved beyond 2 mm (d) There is no residual tumor apparent beyond the margins of excision
Stage 2	(a) Tumor extends beyond the kidney but is completely excised (b) No residual tumor is apparent at or beyond the margins of excision (c) Tumor thrombus in vessels outside the kidney is stage II if the thrombus is removed en bloc with the tumor
Stage 3	Residual nonhematogenous tumor is present and confined to abdomen (a) Lymph nodes in the renal hilum, the periaortic chains, or beyond are found to contain a tumor (b) Diffuse peritoneal contamination by the tumor (c) Implants are found on the peritoneal surfaces (d) Tumor extends beyond the surgical margins either microscopically or grossly (e) Tumor is not completely resectable because of local infiltration into vital structures
Stage 4	Hematogenous metastasis or lymph node metastasis
Stage 5	Bilateral renal involvement

*This system relies on surgical and pathological evaluation of a tumor in patients not submitted to the preoperative chemotherapy (4).

The management of WT requires a multidisciplinary approach with a pediatric radiologist, an oncologist, a surgeon, and a radiotherapist. First, the patient must be carefully evaluated using appropriate imaging techniques in the preoperative period to identify the origin of the tumor, its position in relation to the adjacent tissue, and vascular involvement. The bilaterality of the tumor, and presence of nephrogenic rests, must be evaluated. If the imaging is not suggestive of any bilateral lesion, there is no need to explore the contralateral kidney at surgery (28, 29). Among the results of WTSG-4, WT is detected in 7% of the patients whose preoperative abdominal CT of contralateral kidney is normal (30). An abdominal Doppler US is advised to check for possible thrombus in the renal vein and the IVC. In tumors with a renal vein and caval extension, it is advised to delay surgery and to start with chemotherapy (31). If the thrombus extends to the thoracic vena cava, an echocardiography should be performed. In case of the thrombus extending to the heart, the risk of pulmonary thrombosis produced by fragmented floating atrial/ventricular thrombus versus benefits of chemotherapy-induced regression must be carefully balanced. Some of these patients are cardiosurgical emergencies

Table 2. The SIOP staging system*

Stages	Description
Stage 1	(a) Tumor is limited to kidney and is completely resected (resection margins "clear") (b) The tumor may be protruding into the pelvic system and "dipping" into the ureter (but it is not infiltrating their walls) (c) The vessels of the renal sinus are not involved (d) Intrarenal vessel involvement may be present
Stage 2	(a) The tumor extends beyond kidney or penetrates through the renal capsule and/or fibrous pseudocapsule into perirenal fat but is completely resected (resection margins "clear") (b) The tumor infiltrates the renal sinus and/or invades blood and lymphatic vessels outside the renal parenchyma but is completely resected (c) The tumor infiltrates adjacent organs or vena cava but is completely resected
Stage 3	(a) Incomplete excision of the tumor, which extends beyond the resection margins (b) Any abdominal lymph nodes are involved (c) Tumor rupture before or intraoperatively (regardless of other criteria for staging) (d) The tumor has penetrated through the peritoneal surface (e) Tumor thrombi present at resection margins of vessels or ureter, transected or removed piecemeal by surgeon (f) The tumor has been surgically biopsied (wedge biopsy) prior to preoperative chemotherapy or surgery
Stage 4	Hematogenous metastases (lung, liver, bone, brain, etc.) or lymph node metastases outside the abdominopelvic region
Stage 5	Bilateral renal tumors at diagnosis

*This system relies on findings at postchemotherapy tumor nephrectomy and the microscopical examination of the whole sample.

and therefore an oncology-oriented pediatric surgeon and a cardiac surgeon are necessary, and the equipment must include the cardiopulmonary bypass device.

For unilateral WTs, a transperitoneal radical nephrectomy is the standard operation. Nephron-sparing surgery (NSS) is advocated only in selected cases of patients with solitary kidney or bilateral WTs (20).

Before the incision, rolled sterile pads should be placed under the patient in supine position. A nasogastric tube, a transient catheter, an arterial line, and a Foley catheter are placed in our center (Figure 2). A large transverse supraumbilical incision should be made, permitting the exploration of the entire abdomen and the contralateral kidney, if necessary (Figure 3). In patients with an intracardiac extension, where an upfront excision is not encouraged, a chevron incision or a combined transverse abdominal and sternal incision can be performed. Because the rupture of the tumor capsule and the spillage of the tumor increase with the tumor stage, and decrease survival, it is important to perform a suitably long incision to remove the tumor from the abdomen safely. At the beginning of the operation, the abdomen should be explored for any intra-abdominal implants. If deemed necessary based on preoperative imaging, the opening of Gerota fascia and careful exploration of the whole contra lateral kidney is recommended. Any suspicious areas should be biopsied. The peritoneum covering the tumor is opened as laterally as possible for easy closure of the peritoneum after the tumor resection (Figures 4 and 5). Most frequently, the best access to the right-sided WT is Kocher' maneuver, which offers a good exposition of the right renal vessels. For left-sided WTs, laterocolonal access is usually sufficient (Figure 6). The renal vein and the IVC should be palpated first to exclude thrombus. The nephrectomy should begin by ligating the renal artery to avoid thrombus embolism. Afterward, the renal vein should be ligated immediately (Figure 7). The ureter should be ligated as low as possible. Titanium clips are mostly used for the marking of the tumor area for possible further radiotherapy. An en bloc resection of the tumor without any tumor spillage is the most important aspect. Lymph node sampling is another important goal in WT surgery. Lymph node samples should be collected from the renal hilum, iliac, paracaval, or para-aortic areas for accurate staging. Spillage of the tumor or inadequate lymph node dissection results

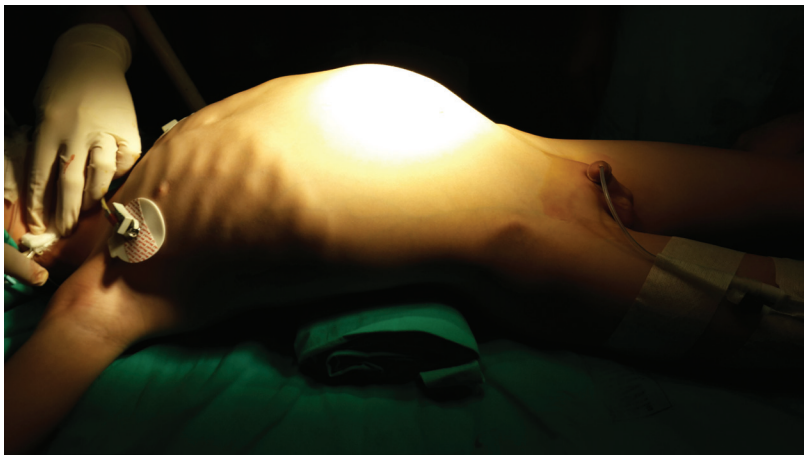

Figure 2. The position of the patient.

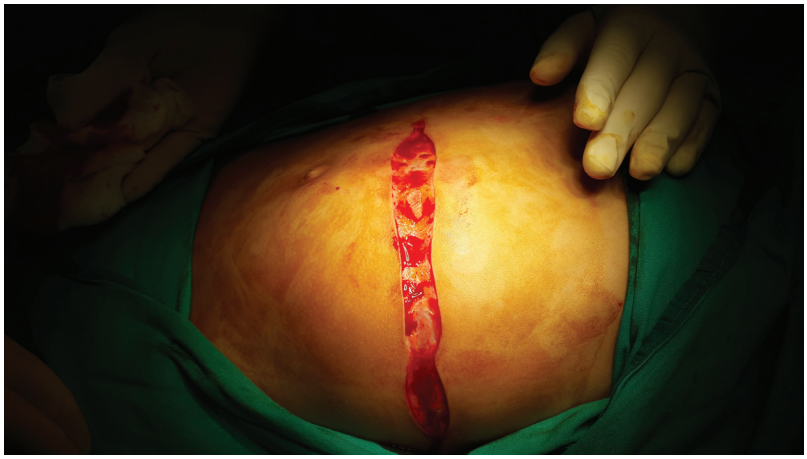

Figure 3. A large transverse supraumbilical incision, permitting the exploration of the entire abdomen and the contralateral kidney.

in incomplete chemotherapy and thus decreased survival rates. NWTS suggests seven regional nodes to get reliable information on lymph node involvement (32).

There is an emerging consensus on performing routine adrenalectomy during unilateral nephrectomy for WTs. One recent study proved that an adrenalectomy does not affect the 5-year survival rate, but it does increase the intraoperative spillage rates (33). Most surgeons leave the adrenal gland intact if it is not infiltrated by the tumor (34). In the study of van Waas et al. (35), it is stated that the removal of one adrenal gland does not result in clinical adrenal insufficiency.

Performing NSS by partial nephrectomy or enucleation in unilateral cases is also a matter of debate (36). We recommend this approach only in synchronous or metachronous bilateral cases or in solitary kidneys. Only less than 5% of all unilateral WTs are eligible for NSS because most of the tumors are locally advanced at the time of diagnosis (37). The surgical criteria for a partial resection are as follows: tumor is located in one pole and infiltrates approximately less than 1/3 of the kidney; no invasion of the renal vein; and the surgeon's experience in pediatric oncology (38). The SIOP WT 2001 trial reported 91 children (3%) with excellent survival rates in which NSS was performed (39). Minimally invasive nephrectomy can offer the same outcome as the classical laparotomic approach (40, 41).

For bilateral cases, the current approach is preoperative chemotherapy followed by bilateral NSS (42). Timing of surgery is important. Both COG/NWTSG and SIOP/RTSG recommend surgery after 9–12 weeks of chemotherapy. Where possible, both sides can be operated in the same session. In difficult cases, the easier side can be operated first. The more difficult

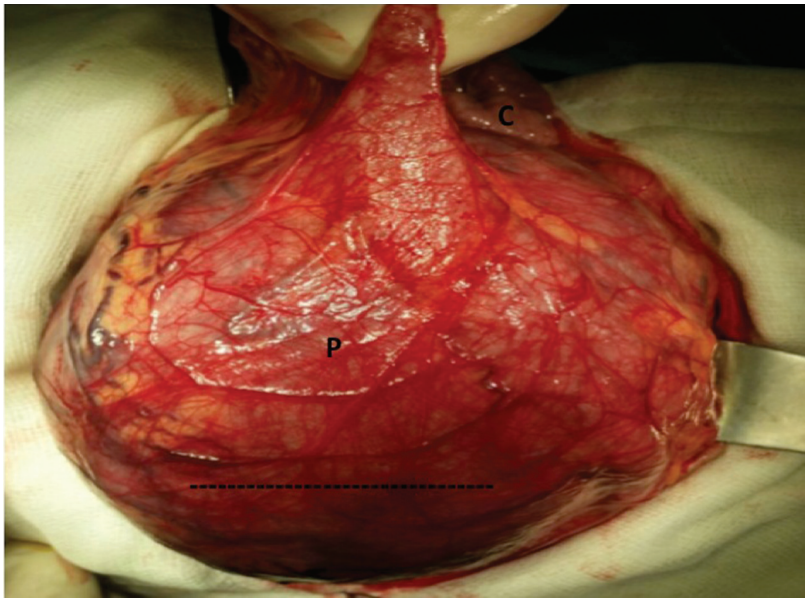

Figure 4. The peritoneal reflection covering a right Wilms tumor. P: peritoneum.

side can be operated after one or two courses of chemotherapy and stabilization of the renal function. The major goal of bilateral WT surgery is to achieve a cure by removing all tumoral renal tissue while preserving the maximum functioning kidney. Some authors suggest *in situ* topical cooling or perfusion with preservation solutions for meticulous dissection without the loss of renal function from ischemia. The ultrasonic scalpel is a useful tool in such resections (43). Millar et al. (44) reported 19 children with bilateral WT cases in which they achieved good results with appropriate chemotherapy and conservative NSS. They suggested a revision surgery if needed. Perioperative US is also a useful tool in NSS of bilateral cases for detecting the margins of normal renal tissue and the tumoral tissue.

Intracardiac extension of WT has been an important surgical challenge. First, an accurate preoperative radiological evaluation of the tumor and thrombus is necessary, and second, a multidisciplinary treatment plan by the cardiovascular surgeon and the pediatric surgeon is important. In general, upfront treatment with chemotherapy is advised. Then, surgical treatment can be considered as reported by SIOP group, which shows favorable results in patients who underwent surgery, including a cardiopulmonary bypass and hypothermia (45). Some surgeons have used this reported technique in pediatric WT cases (46–48).

Common surgical complications in primary nephrectomy patients with WT are ruptures, intestinal obstruction, bleeding, and surgical site infections. NWTSG conducted an

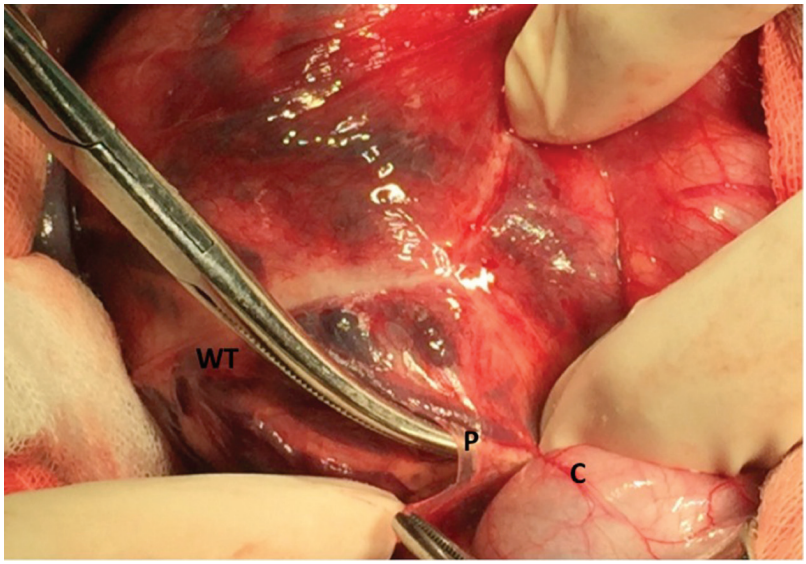

Figure 5. The lateral peritoneal reflection opened from an avascular area on the lateral side. WT: Wilms tumor, P: peritoneum, C: colon.

analysis on 3335 children who received primary nephrectomy for WT. They observed surgical complications in 12.7% of the patients. These complications were intestinal obstruction (5.1%), excessive bleeding (1.9%), surgical site infection (1.9%), and major vascular injuries (1.5%). Also, the risk of complications increased when the tumor size had exceeded 10 cm (49). The risk of tumor rupture was 15% in NWTSG for primary surgery and 3% for chemotherapy-pretreated cases in SIOP. This was replicated by a randomized study in UK (50). Godzinski (51) reported that not only the intraoperative tumor rupture but also other surgery-related complications became rare after the pretreatment. The rate of these complications did not exceed 8% in the pretreated patients. In selected cases, preoperative biopsy was considered. Tru-cut biopsy instead of a needle biopsy may be used to avoid upstaging of the tumor. Preoperative chemotherapy is advised in most bilateral cases, inoperable tumors, and tumors with an intracaval/cardiac extension (43).

Recurrent disease

About 10–15% of WT results in recurrence (52). Spillage occurs in almost every 10 unilateral nephrectomies and is correlated with right-side and larger tumors (53). The recent analysis of COG demonstrated that a relapse in the flank or abdominal site occurred in only 7.4% and 9.5%, respectively, of stage II WT patients with spill, whereas it occurred in 2.5% and 3%, respectively, for those without spill (54). According to SIOP trials, even though

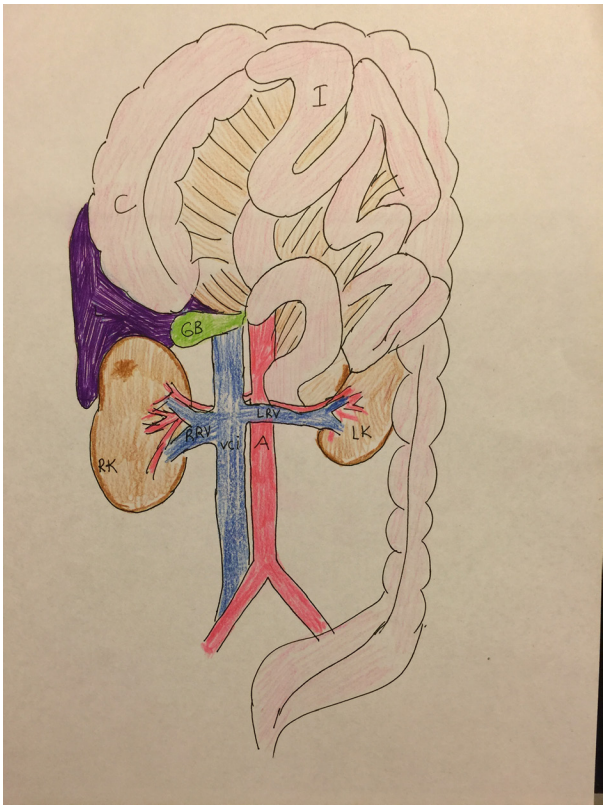

Figure 6. Image showing access to the right-sided WT in which the colon is reflected medially. C: Colon, I: ileum, GB: gall bladder, RK: right kidney, LK: left kidney, RRV: right renal vein, LRV: left renal vein, VCI: vena cava inferior, A: aorta.

the rupture frequency was much less in prechemotherapy group, event-free follow-up or overall survival rate was reported similarly (55). Drugs such as platinum compounds, ifosfamide, cyclophosphamide, etoposide (ICE), and their combinations are used in relapsed WT. Postrelapse survival rates of 50–60% have been reported with ICE chemotherapy (56). Survival rates also depend on the initial stage, initial treatment, metastatic burden, and the relapse-free interval (57). A complete resection of the recurrent lesion(s) has also been shown to be a favorable prognostic factor.

Conclusion

Whether chemotherapy is given preoperatively or not, surgery comprises the main part of the WT surgery. WT patients need a multimodal, multidisciplinary treatment with a close follow-up.

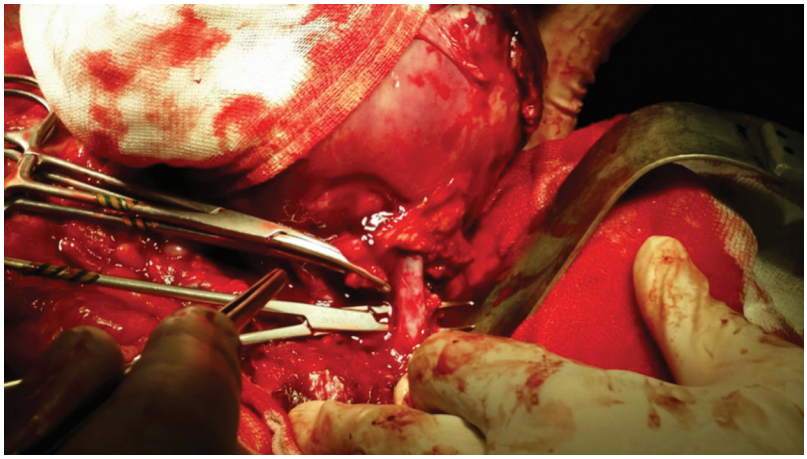

Figure 7. The ligation of the renal vein.

Conflict of Interest

The author declares no potential conflicts of interest with respect to research, authorship and/or publication of this article.

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