Surgical Management of Wilms Tumor (Nephroblastoma) and Renal Cell Carcinoma in Children and Young Adults

Natalie M. Lopyan, MD[a], Peter F. Ehrlich, MD, MSc[b,*]

KEYWORDS

- Pediatric Wilms tumor • Pediatric renal cell carcinoma
- Treatment and surgical management

KEY POINTS

- Well-designed surgical protocols exist that impact both event-free and overall survivals in children and young adults with renal tumors and should be followed in detail.
- Wilms tumor is the most common renal tumor in childhood and has an excellent survival rate.
- The treatment of Wilms tumor focuses both on oncologic cure and reduction of late effects of treatment.
- Renal cell carcinoma is the second most common pediatric renal malignancy.
- Renal cell carcinoma tends to present at advanced stages with poor outcomes in children and young adults.

INTRODUCTION

Renal tumors are the second most common abdominal tumor seen in infants and children, behind neuroblastoma, contributing to 7% of all newly diagnosed pediatric solid malignancy cases.[1,2] The most common renal tumor is a nephroblastoma or Wilms tumor (WT) accounting for 90% of solid renal tumors in children. Renal cell carcinoma (RCC) variants are the second most frequent. These are found more commonly in adolescents. Although surgery remains the mainstay of treatment, the management of renal tumors has evolved over the last 4 decades into a multimodal, risk-based

[a] C.S. Mott Children's Hospital Section of Pediatric Surgery, 1540 East Hospital Drive, Ann Arbor, MI 48109, USA; [b] University of Michigan, C.S. Mott Children's Hospital Section of Pediatric Surgery, 1540 East Hospital Drive, SPC 4811, Ann Arbor, MI 48109, USA
* Corresponding author.
E-mail address: pehrlich@umich.edu

Surg Oncol Clin N Am 30 (2021) 305–323
https://doi.org/10.1016/j.soc.2020.11.002
surgonc.theclinics.com

approach consisting of surgery, chemotherapy, and radiotherapy. Improved treatment is now focused on multiple risk factors in addition to pathology and stage, including age, response, and genetics. Staging and risk stratification have become more personalized and have helped improve overall survival and event-free survival.

WILMS TUMOR

WT is the most frequent tumor of the kidney in infants and children, with an incidence of 600 to 650 cases a year in North America. The mean age at diagnosis is 36 months, with the majority of children presenting between the ages of 12 and 48 months.[2] African American children are at greatest risk, followed by Caucasian and then East Asian populations. Most children present with unilateral tumors, although synchronous bilateral tumors occur in approximately 10% of patients. The frequency of bilateral disease is increased in familial cases, and such cases are often associated with an earlier age of onset. Nearly 10% of all WT cases arise in the setting of a well-described syndrome (eg, Beckwith–Wiedemann syndrome). WT represents one of the great success stories in modern medicine, with survival rates increasing from 5% in 1900 to more than 90% currently.[3] This increase reflects in large part the systematic data collection and analysis facilitated by multinational consortiums—the National Wilms Tumor Study Group, now a part of the Children's Oncology Group (COG) and the Société Internationale d'Oncologie Pédiatrique (SIOP)—which supported several large controlled trials in children with WT.

Clinical Presentation and Imaging

A renal tumor is often detected as an asymptomatic abdominal mass. Renal tumors a may present with hematuria—gross in 18.2% and microscopic in 24.5% of patients.[4] Overall, 20% to 25% of patients present with hypertension and 10% with fever. Rarely, a child may have abdominal trauma and demonstrate pain out of proportion to what is expected, and an abdominal mass is found that cannot be attributed to the trauma. Renal tumors can extend through the renal vein (11%), inferior vena cava (IVC) (4%), and right atrium (4%), or down through the ureter.[5] The common sites of metastatic spread include the lungs and the liver. Ultrasound examination is a good screening examination to determine if a mass is renal or extra renal in origin. A computed tomography (CT) scan of the abdomen or MRI will further define the tumor. Although there are no pathognomonic radiographic findings of a WT or other renal tumor. A "claw sign" is characteristic of a primary renal tumor (**Fig. 1**). In addition, WT tend to push other structures away whereas a neuroblastoma grows in and around structures. Vascular tumor extension is best detected by Doppler ultrasound examination or CT scan (**Fig. 2**).[6] A CT scan of the chest is the best method to detect the presence of pulmonary disease (**Fig. 3**).

Pathophysiology

Nephrogenesis in the normal kidney is usually complete by 34 to 36 weeks of gestation. The presence of nephrogenic rests (NRs)—persistent metanephric tissue in the kidney after the 36th week of gestation has been associated with the occurrence of WT. NRs are considered precursor lesions to WT. The presence of multiple or diffuse NRs is termed nephroblastomatosis. NRs may be further classified by their growth phase, which has been separated into 3 phases: (1) incipient or dormant, (2) hyperplastic NRs, which are composed of epithelial elements with nodular expansive growth, and (3) sclerosing rests, which consist of stromal and epithelial elements with few blastemal nephrogenic elements. Most NRs are dormant or in the sclerosing phase, and the majority will resolve

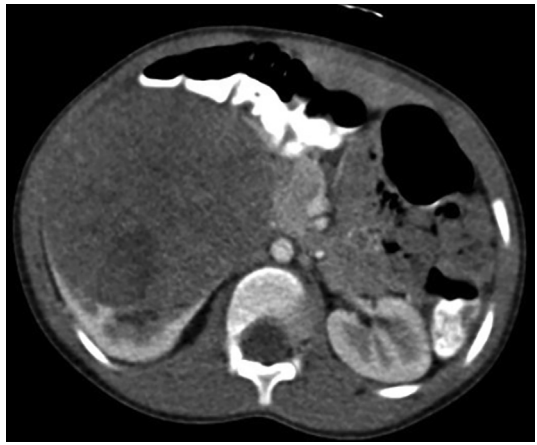

Fig. 1. CT scan showing the classic "claw" sign for a WT.

spontaneously. The pathologic distinction between NR and WT can be very difficult. In fact, it is impossible to distinguish a hyperplastic NR from a WT based on an incisional or needle biopsy specimen that does not include the margin between the NR and the remaining kidney.[7] Most hyperplastic nodules lack a pseudocapsule at their periphery, whereas most WTs will have one (**Fig. 4**). It is very difficult to diagnose NRs on imaging. Although MRI may be helpful, there is no gold standard.[8] Diffuse hyperplastic perilobar nephroblastomatosis is a unique category of nephroblastomatosis in which the rests form a thick rind around the periphery of the kidney (**Fig. 5**). Infants with diffuse hyperplastic perilobar

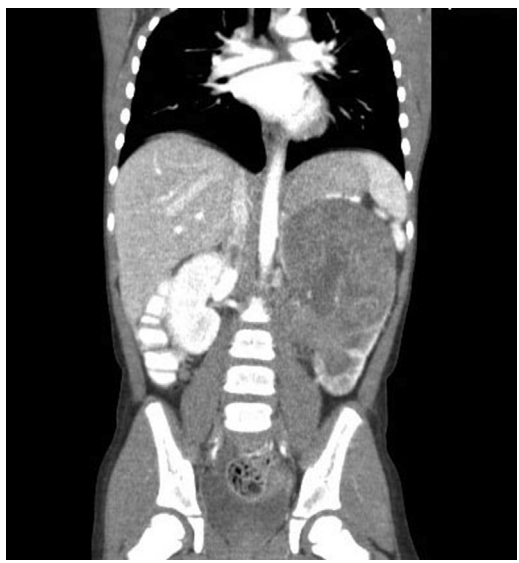

Fig. 2. CT scan showing tumor extension up the IVC to the atrium.

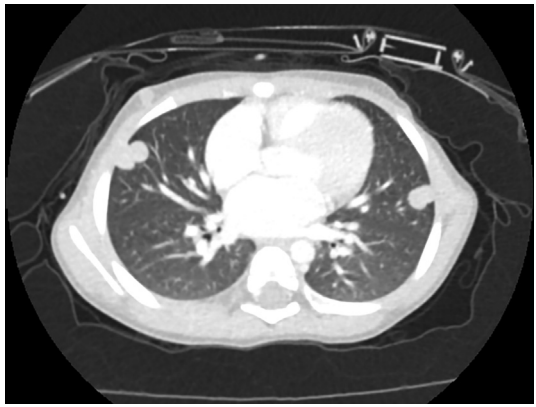

Fig. 3. CT scan of a pulmonary metastatic lesion in a patient with WT.

nephroblastomatosis may initially present with large unilateral or bilateral flank masses and are considered premalignant lesions.[9]

Staging and Prognostic Factors

Staging

WT staging occurs either at the time presentation (primary nephrectomy or biopsy) for children treated on COG protocols or after neoadjuvant therapy and nephrectomy on SIOP protocols (**Table 1**). Patients are given a local stage and a disease stage ranging from I to V for bilateral disease. The local stage defines the extent of abdominal disease, and the disease stage considers both the local extent of disease and distant metastasis. Both factors determine therapy. Therapeutic modalities can include

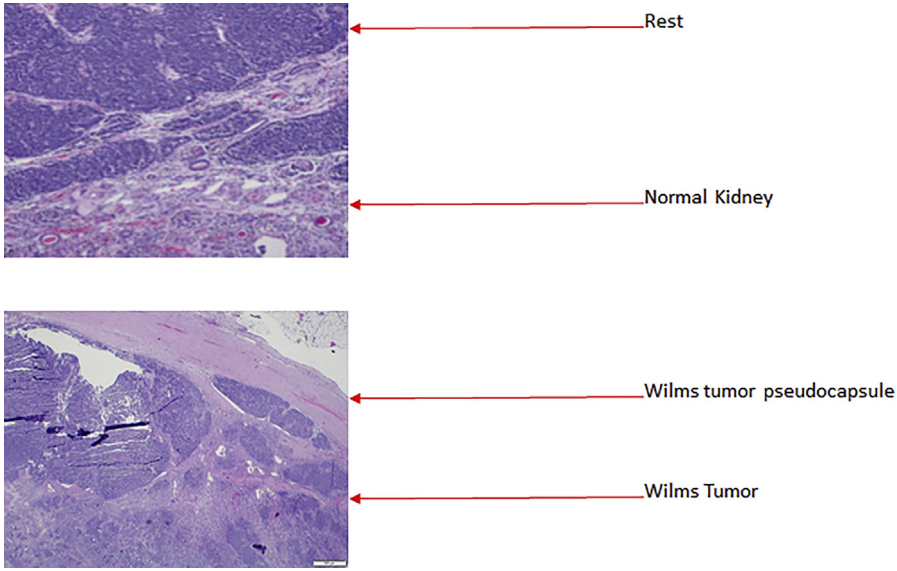

Fig. 4. High-power hematoxylin and eosin–stained slide showing the differences between a NR and a WT.

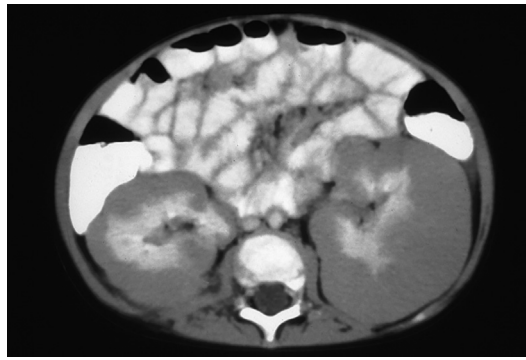

Fig. 5. CT scan of the abdomen demonstrating diffuse perilobar hyperplastic nephroblastomatosis.

surgery alone, chemotherapy regimens and/or radiation therapy to the flank, abdomen, or lungs.[10]

Prognostic factors

The current prognostic factors used in COG trials are histology, stage, age (<2 years), tumor weight (<550 g), response to therapy, and loss of heterozygosity (LOH) at 1p and 16q. The 2 most important factors continue to be the pathology and the stage of the tumor.[11,12] **Table 2** shows the risk stratification for the COG system. The SIOP risk classification was revised in 2010 based on a review of the histologic appearance of the tumors at resection (after neoadjuvant chemotherapy) and the corresponding outcomes[13] (**Table 3**).

Pathology

WTs are classified as either favorable or unfavorable. Favorable histology comprises 90% of the tumors. These tumors are the classic WT consisting of 3 elements: blastemal, stromal, and epithelial tubules. The proportion of these 3 elements in WTs have been studied, but have not been shown to predict outcomes before neoadjuvant treatment. However, data from SIOP (where prenephrectomy chemotherapy is routinely is used) the amount of blastemal elements that remains is predictive of outcome. Blastemal predominantsubtypes are considered high risk tumors.[14,15] Unfavorable tumors (unfavorable histology) are those with focal or diffuse anaplasia.[7,16] Anaplasia is defined by multipolar polyploid mitotic figures, marked nuclear enlargement (giant nuclei with diameters at least 3 times those of adjacent cells), and hyperchromasia.[17] Anaplasia can be either focal or diffuse.[11]

Molecular genetics

There are 3 major epigenetic and genetic changes observed in WT: (a) WT 1 loss, (b) WNT pathway activation, and (c) IGF2 overexpression (most common) without WT-1. The *WT1* gene, a tumor suppressor gene, was the first gene to be linked with WT development.[18,19] Wild-type *WT1* is involved in cell growth, differentiation, and apoptosis.[20] Patients heterozygous for *WT1* germline mutations are predisposed to WT, and *WT1* is inactivated in tumors (eg, WAGR). Based on this observation, it would be expected that many patients with sporadic WT would have a mutation in the *WT1* gene. Surprisingly, the incidence of mutations of *WT1* associated with WT in the sporadic form of the disease is low (10%–20%).[20,21]

Table 1
Comparison between the COG and the SIOP staging systems

Stage	COG	SIOP
I	The tumor is limited to the kidney and has been completely resected. The tumor was not ruptured or biopsied before removal. No penetration of the renal capsule or involvement of renal sinus vessels. Lymph node status is known and negative.	The tumor is limited to the kidney or surrounded with a fibrous pseudocapsule if outside the normal contours of the kidney; the renal capsule or pseudocapsule may be infiltrated with the tumor but it does not reach the outer surface, and it is completely resected. The tumor may be protruding (bulging) into the pelvic system and dipping into the ureter, but it is not infiltrating their walls. The vessels of the renal sinus are not involved. Intrarenal vessels may be involved.
II	The tumor extends beyond the capsule of the kidney but was not completely resected with no evidence of tumor at or beyond the margins of resection. There is penetration of the renal capsule. There is penetration of the renal sinus vessels. Lymph node status is known and negative.	The tumor extends beyond the kidney or penetrates through the renal capsule and/or fibrous pseudocapsule into the perirenal fat, but is completely resected. The tumor infiltrates the renal sinus and/or invades blood and lymphatic vessels outside the renal parenchyma, but it is completely resected. The tumor infiltrates adjacent organs or vena cava, but is completely resected. The tumor has been surgically biopsied (wedge biopsy) before preoperative chemotherapy or surgery.
III	Gross or microscopic residual tumor remains postoperatively including: inoperable tumors, positive surgical margins, tumor spillage surfaces, regional lymph node metastasis, positive peritoneal cytology or transected tumor thrombus. The tumor was ruptured or biopsied before removal.	Incomplete excision of the tumor, which extends beyond resection margins (gross or microscopic tumor remains postoperatively). Any abdominal lymph nodes are involved. Tumor rupture before or during surgery (irrespective of other criteria for staging). The tumor has penetrated the peritoneal surface. Tumor implants are found on the peritoneal surface. The tumor thrombi present at resection, margins of vessels or ureter transected or removed piecemeal by surgeon.
IV	Hematogenous metastases or lymph-node metastases outside the abdomen (eg, lung, liver, bone, brain).	Hematogenous metastases (lung, liver, bone, brain, etc.) or lymph node metastases outside the abdominopelvic region.
V	Bilateral renal tumors at diagnosis. Each side has to be substaged according to above classifications.	Bilateral renal tumors at diagnosis. Each side has to be substaged according to above classifications.

IGF2 (WT2) was the second set of genes to be associated with WT gene location was identified by linkage analysis in children with Beckwith–Wiedemann syndrome.[22] This site is not a single gene, but contains several genes that may play a role in tumor development. In patients with Beckwith–Wiedemann syndrome, it was found that the

Table 2
COG risk stratification for WTs

Age	Tumor Weight, g	Stage	LOH 1p and 16q	Rapid Response	Pathology	Risk Group
<2	<550	I	Any	N/A	FH	Very low
Any	≤550	I	None	N/A	FH	Low
≥2	Any	I	None	NA	FH	Low
Any	Any	II	None	N/A	FH	Low
≥2	Any	I	LOH +	N/A	FH	Standard
Any	≤550	I	LOH +	N/A	FH	Standard
Any	Any	II	LOH+	N/A	FH	Standard
Any	Any	III	None	Any	FH	Standard
Any	Any	III	LOH +	Any	FH	Higher
Any	Any	IV	LOH +	Any	FH	Higher
Any	Any	IV	None	Yes	FH	Standard
Any	Any	IV	None	No	FH	Higher
Any	Any	1-IV	Any	Any	UH	Higher
Any	Any	V	Any	Any	FH/UH	Bilateral

Abbreviations: FH, favorable histology; UH, unfavorable histology.

maternal allele of 11p15 was uniformly lost.[23] The process that causes this loss is termed genomic imprinting, whereby 1 allele is imprinted, in a parental-specific manner, to be functionally inactive. Recent studies suggest the loss of imprinting caused by hypermethlyation leading to WT is primarily located in the IC1 gene.[24–26] A LOH at 1p and 16 is used to risk stratify patients. Event-free survival and overall survival in patients with WT tumor with LOH at 1p and 16q were noted to be lower than those without LOH.[27] Prospective studies showed that increasing therapy could reverse those differences in event-free survival and overall survival.[28] Despite these exciting improvements, LOH is found in only 5% of patients. Chromosome 1q gain is found in up to 30% of patients with WT.[29–31] Recent retrospective studies have shown that 1q gain is associated with inferior outcomes across all stages of favorable

Table 3
SIOP postchemotherapy risk stratification

Risk	Histology
Low	Completely necrotic Favorable histology
Intermediate	Nephroblastoma epithelial type Nephroblastoma stromal type Nephroblastoma mixed type Nephroblastoma regressive type Nephroblastoma focal anaplasia type
High	Nephroblastoma blastemal type Nephroblastoma diffuse anaplasia type

histology WT.[32,33] In the upcoming COG studies, the augmentation and reduction of therapy will be based on the presence or absence of a 1q gain.

Age and weight

The current prognostic factors used in COG trials are histology, stage, age (<2 years), tumor weight (<550 g), response to therapy, and LOH at 1p and 16q. The 2 most important factors continue to be the histology and the stage of the tumor.[11,12] Children less than 2 years of age and had tumors that weighed less than 550 g with a favorable histology can be treated by surgery alone.[34]

Rapid response

Rapid response to chemotherapy was recently tested on ARENO533, which evaluated children in whom CT evidence of pulmonary metastases resolved after 6 weeks. In these patients, it was shown to be safe to avoid pulmonary radiation.[35]

Renal cell carcinoma

RCC is the second most common renal malignancy diagnosed among pediatric and adolescent patients, accounting for 2% to 6% of renal cancers. In contrast with patients with WT, those with RCC are generally older, with a median age at diagnosis of 12.9 years. RCC associated with familial syndromes (eg, Von Hippel–Lindau disease) typically presents with a higher proportion of multifocality and bilaterality.[36] Syndrome-associated RCC often presents at a younger age. In an investigation by Selle and colleagues[37] of the German Childhood Cancer Registry, one-third of patients with RCC were found to have an underlying medical condition, such as tuberous sclerosis, or previous treatment (eg, chemotherapy). Although uncommon as a secondary malignancy, RCC has been reported in children diagnosed with other cancers, neuroblastoma in particular.[38] RCC in children displays gross and histologic features similar to those seen in adults. Subtypes of RCC include papillary, medullary, translocation cell, clear cell, chromophobe, collecting duct, multilocular cystic, and unclassified. In a report from the COG translocation, RCC was the most common form of RCC.[39] Staging of RCC combines the TMN classification as well as stages I to IV. The clinical stage at the time of diagnosis is the most important prognostic factor, and the identification of renal vascular invasion does not seem to be an adverse predictor in children with RCC. Radical nephrectomy and regional lymphadenectomy have been the primary modality for cure, and children with distant spread have a very poor prognosis. The overall survival is much worse than for WT, with the best prognosis for those with complete resection and no metastatic disease. RCC is remarkably resistant to chemotherapy, preventing cure in most children with metastatic disease. The recent use of monoclonal antibody therapy for metastatic disease has been promising.[40] The first prospective study of pediatric and adolescent RCC was performed by the COG between 2006 and 2012. Surgery was the main treatment for localized disease and the investigator could choose any neoadjuvant therapy. Sixty-eight patients were enrolled, and the event-free survival rate was 80.2%; the overall survival rate was 84.8% (stage I = 92, stage II = 100%, stage III = 79.5, and stage IV = 33.3%).[41]

There are some subtle differences between the surgical management of RCC in adults and children. First, there are fewer partial nephrectomies performed and that is because WT are far more common than RCC and a biopsy will upstage WT. Second in adults, lymph node disease is based on cross-sectional imaging and not pathologic confirmation. This approach is not supported in pediatric RCC. Lymph node disease is common and observed among patients with small primary tumors. Using a size cutoff of 1 cm, imaging detection of lymph node involvement had a sensitivity of 57.14% (20

of 35 cases; 95% confidence interval, 39.35%–73.68%) and a specificity of 94.59% (35 of 37 cases; 95% confidence interval, 81.81%–99.34%).[39] Owing to the relative frequency of translocation RCC and the poor outcomes in high stage disease in both adolescents and young adults, the National Institutes of Health sponsored a combined study between the COG and adult cancer groups comparing double monoclonal antibody therapy in patients with translocation RCC.[42] That study is currently open and accruing.

Surgical management of renal tumors

The goals of primary surgery for unilateral renal tumors include clearance of all local disease, accurate nodal staging, and complete pathologic evaluation. While achieving these goals, the surgeon must avoid actions, that may require more intensive postoperative therapy, such as biopsy or tumor spillage, or that result in avoidable complications, such as the unneeded resection of surrounding organs. Unilateral radical nephroureterectomy with lymph node sampling is the recommended procedure and is supported by multiple cooperative trials.[43–45] In COG trials, a primary nephrectomy is preferred and in SIOP upfront neoadjuvant therapy is preferred for WT. In children less than 7 months of age who have a renal tumor, both cooperative groups agree that primary nephrectomy is associated with better outcomes.[46]

Preparing the child for the operating room

A complete blood count and typing is needed because children can have anemia at presentation. Coagulation studies are also important owing to the possibility of acquired von Willebrand disease. Acquired von Willebrand disease has been reported in patients with WT and other malignancies and has important implications for the surgeon.[47,48] Initially thought to be clinically insignificant, recent reports of profuse intraoperative bleeding that only stopped after ligation of the renal vessels have contradicted this assumption. The mechanism of acquired von Willebrand disease in WT is unknown, but the initial sign was a prolonged prothrombin time and partial thromboplastin time. When found, acquired von Willebrand disease should mandate collecting a further history for bleeding and factor analysis. Although correction of factor levels before surgery seems to help in most cases, it does not guarantee that significant intraoperative bleeding will not occur. Preoperative embolization should be considered as a management strategy.

Incision

A transabdominal or thoracoabdominal incision is used, because other incisions have been shown to increase the risk of tumor spillage and limit necessary staging evaluation. Complete peritoneal exploration and sampling of hilar and aortocaval nodes are mandatory. If preoperative imaging suggests any possibility of a contralateral lesion, the opposite kidney should be evaluated before nephrectomy.[43–45,49,50] The renal pelvis or ureter can be involved with the tumor and should be divided at the most distal level possible, with care taken to avoid tumor spillage.[51] The presence of hematuria may suggest involvement of the ureter and cystoscopy could be considered. The renal vein requires evaluation by palpation and/or intraoperative ultrasound examination to rule out tumor thrombus, which should be resected en bloc when present, avoiding spillage.[5]

WT can be adherent to, but rarely invades, the surrounding organs. Upfront hepatectomy or en bloc resection of the surrounding organs for metastasis or direct spread is unwarranted, because this practice increases complications and confers no benefit in survival.[43,44,49,52] Ipsilateral adrenalectomy, previously standard, is no longer

recommended if the gland is easily separated from the tumor; a retrospective study showed tumor invasion in fewer than 5% of ipsilateral adrenal glands.[53] Resection of small portions of diaphragm or other nonvital structures to avoid rupture is recommended. Surgical treatment combined with imaging, pathologic, and biological data is used to assign the patient an appropriate local and disease stage. All the factors are then combined to determine the patient's risk group and subsequent therapy. The risk of long-term renal failure in unilateral WT and other renal tumors is less than 1% and does not justify nephron-sparing surgery.

There are a few indications when WT tumors are considered unresectable. These indications are (1) a solitary kidney, bilateral WT, or genetic risk factors for the development of bilateral WT; (2) pulmonary compromise owing to extensive pulmonary metastases; (3) a tumor with extension of the tumor thrombus into the IVC that extends to the level of the hepatic veins (owing to an associated 26% increase in massive bleeding[5]); and (4) contiguous structure involvement, whereby the only means of removing the kidney and tumor requires removal of the other structures (eg, spleen, pancreas, colon, but excluding the adrenal gland and diaphragm). Finally, should the surgeon or anesthesiologist feel that upfront resection would incur unnecessary morbidity or mortality, neoadjuvant chemotherapy with a reevaluation at 6 weeks is an option.[54] Neoadjuvant chemotherapy generally leads to regression tumor shrinkage in the situation of caval or atrial thrombus with a low risk of progression or embolism.[5,44,55]

In patients with a known or suspected diagnosis of RCC, a partial nephrectomy should be attempted if possible. Furthermore, effective cytoreductive therapy is not available for patients with RCC and therefore may require more aggressive surgery to remove the primary mass.

Specific Surgical Conditions

Vascular extension

Vascular extension of the tumor thrombus to the IVC has been reported in 6% to 10% of patients, with atrial extension in 1%[5] (**Fig. 6**). For patients with WT, the overall survival is comparable with similarly staged patients without vascular extension, and survival is comparable whether the thrombus is resected upfront or after initial chemotherapy.[5,55] Vascular extension above the hepatic veins increases the risk of bleeding complications, and neoadjuvant chemotherapy is currently recommended in cases where the thrombus extends into the retrohepatic cava.[5,43,44] CT scans and Doppler ultrasound examinations are equally useful for assessing vascular extension to inform presurgical planning,[6] but intraoperative IVC and/or renal vein palpation remains essential to avoid transecting an unidentified thrombus. Intraoperative ultrasound can also be used if preoperative imaging and intraoperative palpation is unclear at defining the presence or extension of intravascular disease. In the National Wilms Tumor Study-4, 87% of patients with IVC extension and 58% of patients with atrial extension had significant regression of their tumor thrombus with initial chemotherapy, and complications during neoadjuvant treatment were rare.[5] Excision of vascular extension of tumor requires proximal and distal control, which may require cardiopulmonary bypass in cases of persistent atrial thrombus. Intraoperative ultrasound examination and hepatic mobilization may help with mapping of the thrombus. Most often, the tumor thrombus can be gently delivered out of the affected vein, but venotomy and curettage may be necessary for large or adherent thrombi. Division of the tumor thrombus constitutes spillage and consequent upstaging to stage III, so all efforts should be made to resect it in continuity with the primary tumor.

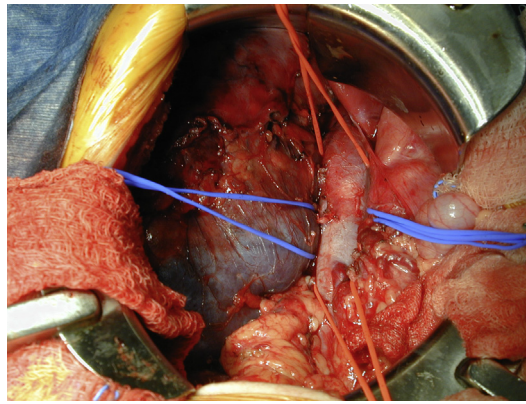

Fig. 6. Intraoperative photograph of a WT with IVC tumor.

Horseshoe kidney

WT or RCC presenting in a horseshoe kidney is rare. In patients with a renal tumor arising in a horseshoe kidney, care must be taken to identify anomalous vasculature, collecting system, and ureteral anatomy on preoperative imaging and at the time of surgical exploration. Complete resection of the affected renal moiety and the isthmus is recommended, and care should be taken to ensure hemostasis after division of the isthmus. As with all unilateral WT or RCC resections, complete resection, adequate nodal sampling, and avoidance of spillage are paramount. A horseshoe kidney does not increase the risk of having a bilateral tumor. This misconception is common, especially in children with WT.

Surgical Management of Wilms Tumor Metastases at the Time of Presentation

Intra-abdominal metastases

Peritoneal metastasis may be encountered in a patient with WT. Any suspicious site in the abdomen or liver should be biopsied or resected (if easily removed) at exploration to determine the nature of the mass, because it will affect tumor stage and therapy (particularly the extent of radiotherapy). The resection of liver masses or tumor that would require removal of intra-abdominal organs and bowel is not indicated as a primary procedure. If residual intra-abdominal metastatic disease remains at week 12 of chemotherapy, it should be resected only if complete resection is feasible. If complete resection is not feasible, then the residual disease should be reassessed for feasibility of resection at the completion of therapy.

Pulmonary metastasis

The lung is the most frequent site of metastatic disease. The treatment of pulmonary disease has changed. In the past, all patients with pulmonary disease received pulmonary radiation. However, the results of the ARENO533 study demonstrated that up to 40% of patients with pulmonary disease will completely respond to chemotherapy after 2 cycles and do not require pulmonary radiation. There are 3 situations in which a surgeon may be needed for the management of pulmonary metastases. First, if there is any doubt regarding the nature of the pulmonary nodule(s) at presentation, these nodules should be biopsied. As many as one-third of small (<1 cm) lesions may not be metastatic tumor. Second, if at the end of 2 cycles or 6 weeks of chemotherapy doubt remains about the nature of the pulmonary lesion, a biopsy should be performed before proceeding with pulmonary radiation. Third, if there are 3 or fewer lesions remaining on a single side that are able to be removed by thoracoscopic resection,

this procedure should be performed. Depending on the pathology of these lesions, such patients may be spared pulmonary radiation. Note, however, that it is only for patients with local stage I and II tumors that it is critical to define the nature of small pulmonary lesions at diagnosis. Patients with stage III and IV disease will receive identical chemotherapy regimens for the first 6 weeks. Patients with residual pulmonary lesions and viable tumor at the 6-week time period will receive whole lung radiation and intensified chemotherapy. If pulmonary nodules remain after week 12 of chemotherapy and irradiation, they should be resected if complete resection is feasible. If complete resection is not feasible, then imaging studies should be repeated at the end of protocol therapy to reassess for the feasibility of resection.

Management of tumor extension in the ureter

Extension of WT into the ureter is a rare event and can be difficult to detect on preoperative imaging. In the National Wilms Tumor Study-5, the incidence of ureteral extension was 2% and preoperative imaging detected the ureteral involvement in only 30% of the cases. Clinical findings of ureteral involvement can include gross hematuria, passage of tissue per urethra, hydronephrosis, and a urethral mass. If these findings are encountered, ureteral involvement should be suspected. Cystoscopy with a retrograde ureterogram may aid in the preoperative evaluation. When encountered or suspected, the ureter with tumor extension should be resected with clear margins when possible.

Bilateral Wilms tumors

Bilateral WT occur in up to 13% of patient with WT .[56,57] In addition, there is a population of children with either genetic disorders or tumor-specific features that increase their risk for synchronous and metachronous tumors.[58] In these patients, nephron-sparing surgery is a goal along with oncologic cure. Historically, when compared with patients with unilateral WT, patients with bilateral WT have lower event-free survival and overall survival, higher rates of renal failure, and often undergo protracted courses of chemotherapy and radiotherapy. The 4 year event-free survival for all patients with bilateral WT on the National Wilms Tumor Study-5 was 56%. Recently, the first prospective trial of patients with bilateral WT and unilateral high-risk tumors was published and has greatly improved our understanding of bilateral WT. The primary aims related to patients with bilateral WT were to improve the 4-year event-free survival to 73%, to prevent complete removal of at least 1 kidney in 50% of patients by using a prenephrectomy 3-drug chemotherapy regimen (vincristine, dactinomycin and doxorubicin), and to perform definitive surgical treatment in 75% of children with bilateral WT by 12 weeks after the initiation of chemotherapy. For the 189 patients with bilateral WT enrolled on this study, the 4-year event-free survival and overall survival were 82% and 95%, respectively.[57] Sixty-one percent of the patients required complete nephrectomy of at least 1 kidney. Definitive surgical treatment (partial or complete nephrectomy, or wedge resection in at least 1 kidney) was achieved in 84% of patients by 12 weeks after the initiation of chemotherapy, meeting the goals of the study. A similar excellent result was obtained for those patients with unilateral tumors with a predisposition syndrome.[59]

Wilms tumors in adults

WTs occur rarely in adults and, in most cases, the diagnosis is made on pathology after nephrectomy for a presumed RCC.[60] The outcomes in adults have been mixed. For those patients treated on one of the standard stage risk-based pediatric protocols, the outcomes are equivalent to the pediatric population.[61,62] For those treated on individual plans, outcomes are poorer. In 2011, the SIOP and COG oncologist performed a

systematic review and developed protocols for adults with WT.[60] Surgical recommendations are identical to those in the pediatric population, as are the chemotherapy regimens and radiation therapy recommendations. The major changes are to dosing, because the toxicity profiles are different in adults and children.

Treatment outcomes

The excellent 5-year event-free survival and overall survival for favorable histology WT have allowed for a decrease in the intensity of treatment, possibly mitigating late effects. Despite this progress, late effects are still noted. Renal failure, congestive heart failure, hypertension, pulmonary disease, pregnancy complications, and second malignancies are reported in survivors. At 25 years after therapy, a WT survivor's cumulative incidence of severe chronic health conditions is 65.4% compared with 24.2% of the general population.[63] The long-term risk of renal failure at 20 years after treatment among the standard, unilateral, nonsyndromic favorable histology WT patients is 0.6%. The major risk factors for renal failure were exposure to radiation, bilateral WT, and congenital syndromes. Congestive heart failure and hypertension are related to the cumulative doxorubicin dose ($P<.001$), lung irradiation ($P = .037$), and left abdominal irradiation ($P = .013$).[64,65] Nearly 15% of female survivors of WT who were treated with pulmonary radiation therapy developed invasive breast cancer by age 40 years. Pregnancy complicated by hypertension, premature labor, and malposition of the fetus were all statistically more frequent among irradiated women and were related to the radiation therapy dose.[66] The risk of second malignant neoplasms (leukemia and solid tumors) is 6.7% by age 40.[67]

Neoadjuvant Therapy for Wilms Tumor and Renal Cell Carcinoma

Chemotherapy

WT was the first malignant pediatric solid tumor with a demonstrated response to dactinomycin.[68] The current COG chemotherapeutic regimens for unilateral WT are presented in **Table 4**. Adjuvant therapy for RCC in the pediatric population has been varied and determined by the treating physician. Recently, the National Institutes of Health sponsored a pediatric and adult phase II trial for translocation RCC. Efficacy data for vascular endothelial growth factor receptor tyrosine kinase inhibitor (axitinib) and programmed death 1/programmed death ligand 1 targeted therapy (nivolumab), 2 key RCC therapeutic targets, will be assessed prospectively as a 2-arm randomized trial assessing axitinib and nivolumab in combination or nivolumab alone.[42]

Radiotherapy

The 3 principle fields for radiation therapy for renal tumors are whole abdominal, flank, and lung (metastatic lung disease). Favorable histology tumors are generally very radiosensitive. Current guidelines for radiation therapy for WT in the North American protocols are based on the results of prior cooperative group studies.[69,70] Abdominal radiation is used for stage III or higher disease. In most cases, flank radiation of 10 Gy is used. Currently, for favorable histology WT whole abdominal radiation is only used in (1) peritoneal seeding, (2) preoperative tumor rupture, and (3) an intraoperative spill that is widespread in the opinion of the operating surgeon. The role of radiation therapy has yet to be properly clarified for liver metastasis and a retrospective review showed that, for liver metastasis, some children did not receive radiation therapy, some received only flank radiation, and some received a radiation boost to the liver.[52] The treatment portal includes that portion of the liver involved on CT scan or MRI studies. The whole liver is treated in children with diffuse hepatic metastases. The

Table 4
Standard chemotherapy regimens for the COG WT

Regimen	Agents
VAD	Vincristine, dactinomycin, doxorubicin (maximum 12 wk)
EE-4A	vincristine and dactinomycin (19 wk)
DD-4A	Vincristine, dactinomycin, doxorubicin and radiation therapy (with or without radiation therapy) (25 wk)
Regimen I	Vincristine, dactinomycin, doxorubicin, cyclophosphamide, and etoposide, as well as radiation therapy (with or without radiation therapy) (28 wk)
Regimen M	Vincristine, dactinomycin, doxorubicin, etoposide and cyclophosphamide (31 wk) with or without radiation therapy
Regimen VI	Vincristine and Irinotican
UH-1/revised UH-1	Vincristine, dactinomycin, doxorubicin, cyclophosphamide carboplatin, etoposide and radiation (31 wk)

improvement in focal radiation therapy strategies are playing more important roles in treatment, because more precise targeting and sparing of uninvolved tissue is becoming a reality.[71,72]

The management of pulmonary disease in children with WT has become more complicated. Using CT scans results in several lung nodules being identified, not all of which may be WT.[73–76] Pulmonary radiation is used for lesions that do not completely disappear after 6 weeks of 3 drug chemotherapy.[77] To date there are no guidelines for the routine use of radiation therapy in patients with RCC.

CLINICS CARE POINTS

- Renal tumors in children although ofter large are easiely resectable.
- Renal tumors in chilsren have both a local and disease stage that affects treatment and short and long term toxicities.
- Failure to sample lymph nodes is the most common mistake made by surgeons treating pediatric renal tumors.

DISCLOSURE

The authors have nothing to disclose.

REFERENCES

1. Howlander N, Noone A, Krapecho M. SEER cancer statistics review 1975-2008 2008. Available at: http://seer.cancer.gov/csr/1975_2008.
2. Breslow N, Olshan A, Beckwith JB, et al. Epidemiology of Wilms tumor. Med Pediatr Oncol 1993;21:172–81.
3. Dome JS, Perlman EJ, Ritchey ML, et al. Renal tumors. In: PA P, DG P, editors. Principles and practice of pediatric oncology. 7th edition. Philadelphia (PA): Lippincott Williams and Wilkins; 2015. p. 753–72.
4. Chu A, Heck JE, Ribeiro KB, et al. Wilms' tumour: a systematic review of risk factors and meta-analysis. Paediatr Perinat Epidemiol 2010;24(5):449–69.

5. Shamberger RC, Ritchey ML, Haase GM, et al. Intravascular extension of Wilms tumor. Ann Surg 2001;234(1):116–21.
6. Khanna G, Rosen N, Anderson JR, et al. Evaluation of diagnostic performance of CT for detection of tumor thrombus in children with Wilms tumor: a report from the Children's oncology group. Pediatr Blood Cancer 2012;58(4):551–5.
7. Perlman EJ. Pediatric renal tumors: practical updates for the pathologist. Pediatr Dev Pathol 2005;8(3):32–338.
8. Sandberg JK, Chi YY, Smith EA, et al. Imaging characteristics of nephrogenic rests versus small Wilms tumors: a report from the children's oncology group study AREN03B2. AJR Am J Roentgenol 2020;214(5):987–94.
9. EJ P, P F, A S, et al. Hyperplastic perilobar nephroblastomatosis: long term survival in 52 patients. Pediatr Blood Cancer 2006;46:203–21.
10. Grundy PE, D JS, Ehrlich PF, al e. Renal tumors classification, biology and banking studies. Available at: https://memberschildrensoncologygrouporg/Prot/AREN03B2/AREN03B2DOCpdf. 2016. p. 18–33.
11. Dome JS, Fernandez CV, Mullen EA, et al. Children's oncology group's 2013 blueprint for research: renal tumors. Pediatr Blood Cancer 2013;60(6):994–1000.
12. Dome JS, Graf N, Geller JI, et al. Advances in Wilms tumor treatment and biology: progress through international collaboration. J Clin Oncol 2015;33(27):2999–3007.
13. Vujanic G, Sandstedt B. The pathology of Wilms' tumour (nephroblastoma): the International society of paediatric oncology approach. J Clin Pathol 2010;63:102–9.
14. Reinhard H, Semler O, Bürger D. Results of the SIOP 93-01/GPOH trial and study for the treatment of patients with unilateral nonmetastatic Wilms Tumor. Klin Padiatr 2004;216(3):132–40.
15. Pasqualini C, Furtwangler R, van Tinteren H, et al. Outcome of patients with stage IV high-risk Wilms tumour treated according to the SIOP2001 protocol: a report of the SIOP renal tumour study group. Eur J Cancer 2020;128:38–46.
16. Scelo G, Hofmann JN, Banks RE, et al. International cancer seminars: a focus on kidney cancer. Ann Oncol 2016;27(8):1382–5.
17. Zuppan CW, Beckwith JB, Luckey DW. Anaplasia in unilateral Wilms tumor. A report from the National Wilms tumor study pathology center. Hum Path 1988;19:1199–209.
18. van den Heuvel-Eibrink MM. Wilms tumor. Brisbane (Australia): Codon; 2016.
19. Yang Y, Han Y, Sauez Saiz F, et al. A tumor suppressor and oncogene: the WT1 story. Leukemia 2007;21(868):876.
20. Deng C, Dai R, Li X, et al. Genetic variation frequencies in Wilms' tumor: a meta-analysis and systematic review. Cancer Sci 2016;107(5):690–9.
21. Huff V. Wilms' tumours: about tumour suppressor genes, an oncogene and a chameleon gene. Nat Rev Cancer 2011;11(2):111–21.
22. Ping AJ, Reeve AE, Law DJ, et al. Genetic linkage of Beckwith-Wiedemann syndrome to 11p15. Am J Hum Genet 1989;44(5):720–3.
23. Riccio A, Sparago A, Verde G, et al. Inherited and sporadic epimutations at the IGF2-H19 locus in Beckwith-Wiedemann syndrome and Wilms' tumor. Endocr Dev 2009;14:1–9.
24. DeBaun MR, Niemitz EL, McNeil DE, et al. Epigenetic alterations of H19 and LIT1 distinguish patients with Beckwith-Wiedemann syndrome with cancer and birth defects. Am J Hum Genet 2002;70(3):604–11.

25. Alexandrescu S, Akhavanfard S, Harris MH, et al. Clinical, pathologic, and genetic features of Wilms tumors with WTX gene mutation. Pediatr Dev Pathol 2017;20(2):105–11.
26. Carraro DM, Ramalho RF, Maschietto M. Gene expression in Wilms tumor: disturbance of the Wnt signaling pathway and MicroRNA biogenesis. In: van den Heuvel-Eibrink MM, editor. Wilms tumor. Codon Publications: Brisbane (AU). 2016.Chapter-10.p.150-162.
27. Grundy PE, Breslow N, Li S, et al. Loss of heterozygosity for chromosomes 1p and 16q is an adverse prognostic factor in favorable-histology Wilms tumor: a report from the National Wilms tumor study group. J Clin Oncol 2005;23(29):7312–21.
28. Dix DB, Fernandez CV, Chi YY, et al. Augmentation of therapy for favorable-histology Wilms tumor with combined loss of heterozygosity of chromosomes 1p and 16q: a report from the Children's Oncology Group studies AREN0532 and AREN0533. J Clin Oncol 2015;33(15 supplement):10009.
29. Bown N, Cotterill SJ, Roberts P, et al. Cytogenetic abnormalities and clinical outcome in Wilms tumor: a study by the U.K. cancer cytogenetics group and the U.K. Children's cancer study group. Med Pediatr Oncol 2002;38(1):11–21.
30. Segers H, van den Heuvel-Eibrink MM, Williams RD, et al. Gain of 1q is a marker of poor prognosis in Wilms' tumors. Genes Chromosomes Cancer 2013;52(11):1065–74.
31. Chagtai T, Zill C, Dainese L, et al. Gain of 1q as a prognostic biomarker in Wilms tumors (WTs) treated with preoperative chemotherapy in the international society of paediatric oncology (SIOP) WT 2001 trial: a SIOP renal tumours biology consortium study. J Clin Oncol 2016;34(26):3195–203.
32. Gratias EJ, Dome JS, Jennings LJ, et al. Association of chromosome 1q Gain with inferior survival in favorable-histology Wilms tumor: a report from the children's oncology group. J Clin Oncol 2016;34(26):3189–94.
33. Gratias EJ, Jennings LJ, Anderson JR, et al. Gain of 1q is associated with inferior event-free and overall survival in patients with favorable histology Wilms tumor: a report from the Children's oncology group. Cancer 2013;119(21):3887–94.
34. Shamberger RC, Anderson JR, Breslow N, et al. Long-term outcomes for infants with very low risk Wilms tumor treated with surgery alone in National Wilms tumor study-5. Ann Surg 2010;251(3):555–8.
35. Verschuur A, Van Tinteren H, Graf N, et al. Treatment of pulmonary metastases in children with stage IV nephroblastoma with risk-based use of pulmonary radiotherapy. J Clin Oncol 2012;30(28):3533–9.
36. van der Beek JN, Geller JI, de Krijger RR, et al. Characteristics and outcome of children with renal cell carcinoma: a narrative review. Cancers (Basel) 2020;12(7):1776.
37. Selle B, Furtwangler R, Graf N, et al. Population-based study of renal cell carcinoma in children in Germany, 1980-2005: more frequently localized tumors and underlying disorders compared with adult counterparts. Cancer 2006;107(12):2906–14.
38. Gupta S, Vanderbilt CM, Leibovich BC, et al. Secondary renal neoplasia following chemotherapy or radiation in pediatric patients. Hum Pathol 2020. https://doi.org/10.1016/j.humpath.2020.07.014.
39. Geller JI, Ehrlich PF, Cost NG, et al. Characterization of adolescent and pediatric renal cell carcinoma: a report from the Children's oncology group study AREN03B2. Cancer 2015;121(14):2457–64.

40. Lalani AA, Li H, Heng DYC, et al. First-line sunitinib or pazopanib in metastatic renal cell carcinoma: the Canadian experience. Can Urol Assoc J 2017; 11(3–4):112–7.
41. Geller J, Cost NG, Chi YY, et al. A prospective study of pediatric and adolescent renal cell carcinoma: a report from the children's oncology group (COG) study AREN0321. Cancer 2020;26(23):5156–64.
42. Geller JI, Cost NG, Dome JS, et al A Randomized Phase 2 Trial of Axitinib/Nivolumab combination therapy vs single agent Nivolumab for the treatment of TFE/Translocation Renal Cell Carcinoma across all age groups. 2020.
43. Ritchey ML, Kelalis PP, Breslow N, et al. Surgical complications after nephrectomy for Wilms' tumor. Surg Gynecol Obstet 1992;175(6):507–14.
44. Ritchey ML, Shamberger RC, Haase G, et al. Surgical complications after primary nephrectomy for Wilms' tumor: report from the National Wilms' Tumor study group. J Am Coll Surg 2001;192(1):63–8 [quiz 146].
45. Ehrlich PF, Anderson JR, Ritchey ML, et al. Clinicopathologic findings predictive of relapse in children with stage III favorable-histology Wilms tumor. J Clin Oncol 2013;31(9):1196–201.
46. van den Heuvel-Eibrink MM, Paul G, Norbert G. Characteristics and survival of 750 children diagnosed with a renal tumor in the first seven months of life: a collaborative study by the SIOP/GPOH/SFOP, NWTSG, and UKCCSG Wilms tumor study groups. Pediatr Blood Cancer 2008;50(6):1130–4.
47. Baxter PA, Nutchtern JG, Guillerman RP, et al. Acquired von Willebrand syndrome and Wilms tumor: not always benign. Pediatr Blood Cancer 2009;52: 392–428.
48. Coppes MJ, Zandvoort SW, Sparling CR. Acquired von Willebrand disease in Wilms' tumor patients. J Clin Oncol 1992;10(3):422–7.
49. Shamberger RC, Guthrie KA, Ritchey ML, et al. Surgery-related factors and local recurrence of Wilms tumor in National Wilms Tumor Study 4. Ann Surg 1999; 229(2):292–7.
50. Ehrlich PF, Ritchey ML, Hamilton TE, et al. Quality assessment for Wilms' tumor: a report from the National Wilms' Tumor Study-5. J Pediatr Surg 2005;40(1):208–12.
51. Ritchey M, Daley S, Shamberger RC, et al. Ureteral extension in Wilms' tumor: a report from the National Wilms' tumor study group (NWTSG). J Pediatr Surg 2008; 43(9):1625–9.
52. Ehrlich PF, Ferrer FA, Ritchey ML, et al. Hepatic metastasis at diagnosis in patients with Wilms tumor is not an independent adverse prognostic factor for stage IV Wilms tumor: a report from the Children's oncology group/national Wilms tumor study group. Ann Surg 2009;250(4):642–8.
53. Kieran K, Anderson JR, Dome JS, et al. Is adrenalectomy necessary during unilateral nephrectomy for Wilms Tumor? A report from the Children's oncology group. J Pediatr Surg 2013;48(7):1598–603.
54. Kieran K, Ehrlich PF. Current surgical standards of care in Wilms tumor. Urol Oncol 2016;34(1):13–23.
55. Nakayama DK, Norkool P, deLorimier AA, et al. Intracardiac extension of Wilms' tumor. A report of the National Wilms' tumor study. Ann Surg 1986;204(6):693–7.
56. Coppes MJ, de Kraker J, van Dijken PJ. Bilateral Wilms' tumor: long-term survival and some epidemiological features. J Clin Oncol 1989;7(3):310–5.
57. Ehrlich P, Chi YY, Chintagumpala MM, et al. Results of the first prospective multiinstitutional treatment study in children with bilateral Wilms tumor (AREN0534): a report from the children's oncology group. Ann Surg 2017;266(3):470–8.

58. Coppes MJ, Beckwith JB, Ritchey ML, et al. Factors affecting the risk of contralateral Wilms tumor development (a report from the national Wilms tumor study group). Cancer 1999;85(7):1616–25.
59. Ehrlich PF, Chi YY, Chintagumpala MM, et al. Results of treatment for patients with multicentric or bilaterally predisposed unilateral Wilms tumor (AREN0534): a report from the children's oncology group. Cancer 2020;126(15):3516–25.
60. Segers H, van den Heuvel-Eibrink MM, Pritchard-Jones K, et al. Management of adults with Wilms' tumor: recommendations based on international consensus. Expert Rev Anticancer Ther 2011;11(7):1105–13.
61. Kalapurakal JA, Nan B, Norkool P, et al. Treatment outcomes in adults with favorable histologic type Wilms tumor-an update from the National Wilms Tumor Study Group. Int J Radiat Oncol Biol Phys 2004;60(5):1379–84.
62. Reinhard H, Aliani S, Ruebe C. Wilms' tumor in adults: results of the society of pediatric oncology (SIOP) 93-01/society for pediatric oncology and hematology (GPOH) study. J Clin Oncol 2004;22(22):4500–6.
63. Termuhlen AM, Tersak JM, Liu Q, et al. Twenty-five year follow-up of childhood Wilms tumor: a report from the childhood cancer survivor study. Pediatr Blood Cancer 2011;57(7):1210–6.
64. Green DM, Grigoriev YA, Nan B, et al. Congestive heart failure after treatment for Wilms' tumor: a report from the National Wilms' Tumor Study group. J Clin Oncol 2001;19(7):1926–34.
65. Green DM, Grigoriev YA, Nan B, et al. Correction to "Congestive heart failure after treatment for Wilms' tumor". J Clin Oncol 2003;21(12):2447–8.
66. Green DM, Lange JM, Peabody EM. Pregnancy outcome after treatment for Wilms tumor: a report from the national Wilms tumor long-term follow-up study. J Clin Oncol 2010;28(17):2824–30.
67. Breslow N, Lange JM, Friedma n DL, et al. Secondary malignant neoplasms after Wilms tumor: an international collaborative study. Int J Cancer 2009;127:657–66.
68. Farber S. Chemotherapy in the treatment of leukemia and Wilms' tumor. JAMA 1966;198:826–36.
69. D'Angio GJ, Evans AE, Breslow N, et al. The treatment of Wilms' tumor: results of the National Wilms' tumor study. Cancer 1976;38:633–46.
70. D'Angio GJ, Tefft M, Breslow N, et al. Radiation therapy of Wilms' tumor: results according to dose, field, post-operative timing and histology. Int J Radiat Oncol Biol Phys 1978;4:769–80.
71. Kalapurakal JA, Pokhrel D, Gopalakrishnan M, et al. Advantages of whole-liver intensity modulated radiation therapy in children with Wilms tumor and liver metastasis. Int J Radiat Oncol Biol Phys 2013;85(3):754–60.
72. Choi M, Hayes JP, Mehta MP, et al. Using intensity-modulated radiotherapy to spare the kidney in a patient with seminoma and a solitary kidney: a case report. Tumori 2013;99(2):e38–42.
73. Green DM. Use of chest computed tomography for staging and treatment of Wilms' tumor in children. J Clin Oncol 2002;20(12):2763–4.
74. Ehrlich PF, Hamilton TE, Grundy PE, et al. The value of surgery in directing therapy of Wilms tumor patients with pulmonary disease. a report from the national Wilms tumor study group (NWTS -5). J Pediatr Surg 2006;41(1):162–7.
75. Lange JM, Takashima JR, Peterson SM, et al. Breast cancer in female survivors of Wilms tumor: a report from the national Wilms tumor late effects study. Cancer 2014;120(23):3722–30.

76. Green DM, Lange JM, Qu A, et al. Pulmonary disease after treatment for Wilms tumor: a report from the national Wilms tumor long-term follow-up study. Pediatr Blood Cancer 2013;60(10):1721–6.
77. Kalapurakal JA, Li SM, Breslow N, et al. Influence of radiation therapy delay on abdominal tumor recurrence in patients with favorable histology Wilms' tumor treated on NWTS-3 and NWTS-4: a report from the National Wilms' Tumor Study Group. Int J Radiat Oncol Biol Phys 2003;57:495–9.