HHS Public Access

Author manuscript

J Pediatr Surg. Author manuscript; available in PMC 2020 October 08.

Published in final edited form as:

J Pediatr Surg. 2019 March ; 54(3): 390–397. doi:10.1016/j.jpedsurg.2018.09.005.

SUMMARY ARTICLE: UPDATE ON WILMS TUMOR

Jennifer H. Aldrink, MD[1,*], **Todd E. Heaton, MD MPH**[2,*], **Roshni Dasgupta, MD MPH**[3], **Timothy B. Lautz, MD**[4], **Marcus M. Malek, MD**[5], **Shahab F. Abdessalam, MD**[6], **Brent R. Weil, MD**[7], **Daniel S. Rhee, MD**[8], **Reto Baertschiger, MD**[9], **Peter F. Ehrlich, MD**[10] **American Pediatric Surgical Association Cancer Committee**

[1]Department of Surgery, Division of Pediatric Surgery, Nationwide Children's Hospital, The Ohio State University College of Medicine, Columbus, OH

[2]Department of Surgery, Division of Pediatric Surgery, Memorial Sloan Kettering Cancer Center, New York, NY

[3]Division of Pediatric General and Thoracic Surgery, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, OH

[4]Department of Surgery, Division of Pediatric Surgery, Northwestern University Feinberg School of Medicine, Chicago, IL

[5]Department of Surgery, Children's Hospital of Pittsburgh, University of Pittsburgh Medical Center, Pittsburgh, PA

[6]Department of Surgery, Division of Pediatric Surgery, University of Nebraska Medical Center, Omaha, NE

[7]Department of Surgery, Division of Pediatric Surgery, Boston Children's Hospital, Harvard Medical School, Boston, MA

[8]Depatment of Surgery, Johns Hopkins School of Medicine, Baltimore, MD

[9]Department of Surgery, Children's Hospital at Dartmouth, Dartmouth-Hitchcock Medical Center, Lebanon, NH

[10]Department of Surgery, Division of Pediatric Surgery, C.S. Mott Children's Hospital, University of Michigan, Ann Arbor, MI

Abstract

This article reviews of the current evidence-based treatment standards for children with Wilms tumor. In this article, a summary of recently completed clinical trials by the Children's Oncology

COORESPONDING AUTHOR Jennifer H. Aldrink, M.D., FACS, FAAP, Associate Professor of Clinical Surgery and Pediatrics, The Ohio State University College of Medicine, Nationwide Children's Hospital, Department of Surgery, Division of Pediatric Surgery, 700 Children's Drive, FB Suite 6B.1, Columbus, Ohio 43205, Tel: 614-722-0440, Fax: 614-722-3903, Jennifer.aldrink@nationwidechildrens.org.

*co-1st authors, equal contribution

DECLARATIONS OF INTEREST: None

Group are provided, the current diagnostic evaluation and surgical standards are discussed, and the surgical impact on current risk stratification for patients with Wilms tumor is highlighted.

LEVEL OF EVIDENCE—This is a review article of previously published and referenced LEVEL 1 studies, but also includes expert opinion LEVEL V, represented by the American Pediatric Surgical Association Cancer Committee.

Keywords

Wilms tumor; surgery

1.0 INTRODUCTION

Long-term survival for patients with Wilms tumor (WT) has steadily improved over the last several decades, and now exceeds 85%. [1, 2] However, specific subgroups of patients, including patients who relapse, those with anaplastic histology, and those with bilateral or unilateral high-risk tumors, continue to have poor event free survival (EFS) and are at risk for significant late effects from therapy. [1] Chronic health conditions secondary to treatment impact nearly one-quarter of survivors of WT and include renal failure, infertility, cardiac toxicity, restrictive pulmonary disease, and the development of subsequent malignancies. [1, 3] [4]

In this summary, we review the most recent literature and results from prospective cooperative group studies, with specific focus on the implications for surgical care of children with WT. Through these data, the importance of risk stratification based upon clinical, surgical, and biologic factors will be highlighted, and the relevance for future investigations will be considered.

2.0 SUMMARY OF RECENT CHILDREN'S ONCOLOGY GROUP (COG) STUDIES

2.1 Impact on surgical care

As the COG Renal Tumor Committee prepares to launch its next generation of trials, a review of recently closed trials and their significant findings is warranted. Table 1 summarizes the most important recently completed COG studies.

AREN03B2 Renal Tumor Biology, Banking and Classification is currently the only COG Renal Tumor study open for accrual, and it will soon be encompassed by the COG registry *Project: EveryChild*, an overarching cancer registry and biorepository that collects clinical and biological data and determines eligibility for and stratification on specific treatment study arms, and establishes a tissue bank. The AREN03B2 umbrella study classifies patients by imaging, histology, stage, age, tumor weight, response to therapy, and biological markers (e.g. loss of heterozygosity [LOH] of 1p and 16q; 1q gain). These criteria determined eligibility for therapeutic studies. With an enrollment of more than 6000 patients to date, the database will serve as a repository for future investigation into potential refinements of risk stratification and therapeutic options.

Four therapeutic clinical trials: AREN 0532, AREN 0533, AREN 032, and AREN 0534 (Table 1) were performed under the umbrella of AREN 03B2. AREN 0532 studied very-low-risk, low-risk, and standard-risk favorable histology Wilms tumor (FHWT). One of the primary objectives of AREN0532 was to demonstrate excellent outcomes for patients younger than 2 years of age with small, stage I FHWT after treatment with nephrectomy alone. An additional objective was to correlate relapse with known biomarkers LOH 1p and 16q, and 1q gain. This trial also incorporated a treatment arm for patients of any age with FHWT and LOH at 1p and 16q, and the results have been reported by Fernandez and colleagues. [5] The analysis demonstrated a 4-year event free survival (EFS) of ≥85% and a 4-year overall survival (OS) of ≥95%. Of 116 nephrectomy-only patients enrolled, 12 experienced disease relapse at a median of 4.2 months, leading to a 4-year EFS of 89.7% and 4-year OS of 100%. [5] The majority of those whose disease relapsed in the nephrectomy-only group had LOH 1p and 16q or 1q gain. The use of these markers in risk stratification and treatment schemes will allow for future expansion of the nephrectomy-only population by easing the current tumor size and age limits while excluding patients with these adverse markers. These findings further emphasize the role of proper upfront surgical resection and local staging, including lymph node sampling, for accurate risk stratification at diagnosis.

AREN0533 examined COG-enrolled patients with higher-risk FHWT [6]. This study stratified therapy for patients with unilateral FHWT and pulmonary metastases based on the response of the metastases to initial chemotherapy. The primary objectives of this study were to demonstrate that patients with complete resolution of pulmonary metastases following 6 weeks of DD4A chemotherapy (rapid complete responders) would have a 4-year EFS of 84% without administration of whole lung radiation therapy (WLRT), and that patients without resolution of pulmonary metastases by 6 weeks (slow incomplete responders) would have a 4-year EFS of 85% with intensification of chemotherapy (regimen M) and WLRT. The results for rapid complete responders indicated that WLRT can be eliminated with maintenance of excellent EFS. Nearly 40% of patients in this study were spared WLRT, potentially avoiding late radiation effects [7]. For surgeons, this study encourages biopsy of pulmonary lesions that are radiographically uncertain in their origin, or lack of regression during the first six weeks of chemotherapy. A definitive histopathological evaluation in this setting may potentially eliminate inappropriate and intensive therapy for benign lesions or post-treatment scar.

Anaplastic WT and other high-risk histologies remain an intense focus of study, given their poor outcomes. AREN0321 intensified therapy for patients with anaplastic WT using the revised UH-1 regimen[8] (see Table 1), but with increased toxicity. Future trials will investigate novel agents for treatment of these high-risk groups with the goal of improving outcomes and minimizing toxicity. Surgical resection for this high-risk group remains an important component of therapy.

Incorporating specific surgical aims into upcoming COG therapeutic studies is extremely important. Specific surgical aims will focus on identifying the ideal number and location of lymph nodes removed for local staging and risk stratification, expanding the surgery only

arm to include older patients with larger tumors, and the biopsy or resection of specific metastatic sites to eliminate toxic therapies in certain subsets of patients.

3.0 MODERN IMAGING AND DIAGNOSIS

Initial imaging of a renal mass usually includes abdominal ultrasound to identify the organ of origin, followed by cross-sectional chest/abdominal/pelvis imaging with either CT or MRI to further evaluate the primary site and to identify any metastases. Additional data provided by these scans include the status of the contralateral kidney, tumor involvement of the renal veins or inferior vena cava, presence of retroperitoneal adenopathy, preoperative tumor rupture, and the existence of ascites. [9, 10] Imaging characteristics, however, are not always correlated with operative or pathologic findings and should not replace surgical exploration and tissue analysis for local and disease staging. [10, 11] Advances in imaging such as 3-D computer reformatting and printing models may assist in planning operative approaches, particularly for patients in whom nephron sparing surgery is appropriate.

4.0 RISK STRATIFICATION

Accurate local and overall staging of WT is critical for appropriate risk stratification and risk-based therapy. AREN03B2, described above, provided prompt central review of pathology, radiology, and surgery records to stratify patients into appropriate therapeutic studies, and showed that central review changed the risk stratification in approximately 20% of patients[2]. In recent COG trials for the treatment of FHWT, risk stratification was based upon age at diagnosis, local and overall stage, tumor weight, and LOH of 1p and 16q. Grundy et al prospectively identified tumor-specific LOH 1p in 11.3% and LOH 16q in 17.4% of patients with FHWT, the frequency of which varied by age. [8] Patients with LOH 1p or 16q had a significantly increased risk of relapse (relative risk 1.56 and 1.49, respectively), stratified by stage. The greatest effect was noted with combined LOH. [8] These findings have led to the incorporation of LOH into the risk stratification for FHWT.

While LOH information is useful in predicting relapse, the overall incidence is relatively low, with combined LOH present in only 4.6% of FHWT. [8] More recently, gain of chromosome 1q, present in nearly 30% of FHWT, has been demonstrated to predict an inferior EFS and OS across all stages. [1] This prognostic marker will be studied as a marker for risk stratification in upcoming trials using both peripheral blood analysis as a “liquid biopsy” as well as tumor tissue. One concern about utilizing 1q gain is that recent studies have shown that expression is not uniform throughout a tumor specimen. [1, 12] Age of the patient, local and overall tumor stage, histopathology, and these tumor markers will be incorporated into the new prospective phase III COG trials for patients with WT, with the goal of optimizing survival while minimizing late effects through an individualized risk-based approach.

5.0 GOALS OF SURGERY FOR UNILATERAL DISEASE

The impressive advances in risk-stratified adjuvant treatment and overall survival in FHWT have been predicated on upfront, safe, and complete resection of unilateral WT. The goals of

primary surgery for unilateral WT include clearance of all local disease, accurate nodal staging, and complete pathologic evaluation. While achieving these, the surgeon must avoid actions, such as biopsy or tumor spillage that may require more intensive post-operative therapy, or result in avoidable complications, such as the unneeded resection of surrounding organs. Unilateral radical nephroureterectomy with lymph node sampling is the recommended procedure supported by multiple cooperative trials. [13-15] A transabdominal or thoracoabdominal incision is used, as 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 pre-operative imaging suggests any possibility of a contralateral lesion, the opposite kidney should be evaluated prior to nephrectomy [13-17]. The renal pelvis or ureter can be involved with tumor and should be divided at the most distal level possible, with care taken to avoid tumor spillage [18]. The presence of hematuria may suggest involvement of the ureter. The renal vein requires evaluation by palpation and/or intraoperative ultrasound to rule out tumor thrombus, which should be resected en-bloc when present, avoiding spillage [19]. CT has been shown to be equally sensitive to doppler ultrasound for diagnosing the presence of thrombus in the renal vein or vena cava [9]. WT is frequently adherent to, but rarely invades, surrounding organs. Upfront hepatectomy or en-bloc resection of surrounding organs for metastasis or direct spread is unwarranted, as this increases complications and confers no benefit in survival [13, 14, 16, 20]. Ipsilateral adrenalectomy, previously standard, is no longer recommended if the gland is easily separated from the tumor, as a retrospective study showed tumor invasion in <5% of ipsilateral adrenal glands [21]. Resection of small portions of diaphragm or other non-vital structures to avoid rupture is still encouraged. This resection with complete nodal evaluation provides all the pathologic information necessary to assign the patient an appropriate local stage, and together with the image-based metastatic evaluation, can define the patient's risk group and ensuing post-operative treatment.

Contraindications to upfront resection are few and include patients with a high long-term risk of renal failure, an unacceptable anesthesia risk due to disease burden, and an increased risk of operative morbidity. The risk of long-term renal failure in unilateral WT is <1% and does not justify neoadjuvant chemotherapy or nephron-sparing surgery. [54] However, patients with a solitary kidney, bilateral WT, or genetic risk factors for the development of bilateral WT are at a much higher risk and must be treated differently, as will be discussed later [22]. Rarely, massive pulmonary disease burden and/or very large abdominal tumors can pose an unacceptably high surgical or anesthetic risk. Should the surgeon or anesthesiologist feel that upfront resection would incur unnecessary morbidity/mortality, neoadjuvant chemotherapy with re-evaluation at 6 weeks is an option [23]. NWTS retrospective analyses have shown that IVC tumor thrombus to the level of the hepatic veins increases the risk of massive intra-operative hemorrhage and is a now a contraindication to upfront resection (Figure 1). Upfront chemotherapy generally leads to regression of caval/atrial thrombus in most patients, and the risk of progression or embolism during neoadjuvant therapy is low, so neoadjuvant treatment is now recommended for these cases [14, 19, 24]. In general, operative contraindications are few, and the overwhelming majority of WT patients should undergo upfront resection.

6.0 SURGICAL IMPACT ON RISK STRATIFICATION

NWTS and COG support upfront resection because it provides the necessary biologic information for risk stratification and selection of appropriate therapy. Tailoring of therapy according to biologic risk factors can minimize long-term side effects for low-risk patients and improve survival in higher-risk patients. Lymph node involvement is an important element of risk stratification and has been shown repeatedly to affect survival in prospective trials [15, 25-27]. Although early European studies showed no benefit for complete nodal dissection [28], nodal involvement remains an important determinant of risk. Failure to perform lymph node sampling despite COG recommendations occurs in 9-17% of cases and increases the relative risk of relapse. Lymph node involvement was the sole stage III component in up 41% patients. Stage I and II patients who did not undergo sampling of nodes are at the highest risk of under-treatment [16, 17]. There are no current recommendations on the minimum number of nodes to be removed, but recent evidence shows that the likelihood of finding a positive node increases with sampling of ≥7 nodes. [29] In a recent review of 5000 nephrectomies from AREN03B2, the number of lymph nodes sampled ranged from 0 to 10 and the location was rarely documented. Kieren et al, using data from the NWTS-5 study, showed that the likelihood of finding a positive lymph node increased as more nodes are sampled.[30] Zhuge et al showed that 5-year OS was significantly lower for patients without any nodal sampling and that better survival correlated with increased number of nodes removed (87% for 0 nodes vs. 91% for 1–5 nodes; 93% for 6–10 nodes; 95% for >10 nodes, P=0.005), a finding confirmed with multivariate analysis.[31] En bloc sampling of hilar, paracaval or paraaortic (depending on tumor side), and aortocaval nodes has also been shown to increase the number of lymph nodes harvested.[32] Chyle leak and other complications of nodal resection are exceedingly rare and should not limit sampling [14, 32].

Tumor spillage, whether confined to the flank or occurring throughout the peritoneum, is another important factor for staging. Spillage is more common in right-sided tumors, tumors larger than 12cm in diameter, and tumors removed via paramedian or flank incision [33], and may include imaging evidence of pre-operative retroperitoneal or intra-abdominal rupture, preoperative open or core-needle biopsy, bloody ascites found on exploration (regardless of cytology results), intra-operative biopsy, intra-operative tumor rupture, removal of the tumor in multiple pieces, transection of tumor within the ureter, or transection of intravascular tumor thrombus (whether remaining thrombus is removed or not). Any tumor spillage and its extent must be documented in detail to guide future therapy. Risk stratification of patients with spillage has evolved over time. Early NWTS studies showed that spillage adversely affects prognosis for stage I-III patients [26, 34, 35], and that lower radiation doses to the area of spillage were an effective treatment [36, 37]. More recently, NWTS studies showed stage II patients with spillage had 4.5x the risk of local recurrence [16], and found a 12.4% rate of local relapse among stage II-III patients not treated with radiation compared to 0% for stage II-III patients who received radiation [38]. Pritchard-Jones et al reported on the risk of local relapse with upfront biopsy in the United Kingdom trial. [39] The hazard ratio was 1.8 (95%CI: 0.97-3.32). Although the p-value was 0.06, the wide confidence interval is extremely concerning, again raising caution about the impact of

biopsy on local relapse. These findings culminated in the current recommendations that any spillage merits stage III classification and treatment with 10Gy of radiation to the area of contamination (flank or whole abdominal), reinforcing the importance of avoiding spillage whenever possible. One exception to this exists for patients with bilateral tumors who may undergo biopsy for histologic confirmation in accordance with AREN0534, are not given routine flank radiation unless final local stage requires it.

Ten percent of WT patients present with metastases, most commonly in the lung or liver. Metastatic disease is not a contraindication to upfront surgery and does not impact local tumor staging or the resection discussed above. The biologic factors and the local stage delineated by upfront surgery determine the need for further local therapy, but the presence of metastases may escalate the disease stage and ensuing systemic therapy. For example, a patient with local stage II disease without genetic risk factors, but with lung metastases, would receive escalated systemic therapy and possibly lung irradiation for control of the metastatic disease but no further local abdominal therapy after resection. The treatment of metastatic disease has evolved with the focus on chemotherapy and radiation [40-42]. One of the primary aims of COG AREN0533 was to limit the need for WLRT in patients who had a CR of all pulmonary lesions after 6 weeks of chemotherapy. A total of 302 patients were enrolled in the study, 105 had complete resolution of their pulmonary disease at 6 weeks and did not receive WLRT. These patients had excellent EFS and OS.[6] There were 20 patients with recurrences, 2 died, both from non-pulmonary related disease. Of importance, the 18 who experienced recurrence were successfully treated and salvaged with regimen M and radiation therapy. In the SIOP 93-1 study, 234 WT patients had pulmonary metastases and 148 (67.3%) achieved CR at 6 weeks with combination chemotherapy alone. An additional 37 patients required surgical resection of one or more pulmonary nodules to achieve CR. The five-year EFS was 84% (OS, 92%) among those who required surgical resection of residual nodules to achieve CR.[43] Those patients with necrotic disease had an OS of 100%. Ehrlich et al also showed that up to 50% of residual pulmonary nodules may not be tumor, and this finding was corroborated on AREN0533.[44] In addition, 49% of patients on AREN0533 whose pulmonary metastases did not completely respond to chemotherapy had fewer than 10 lesions, and 89% (83 of 93 patients) had between 1-3 residual lesions.[45] A retrospective review of the chest CT images for these patients suggested that in 35 percent of the patients, the gross residual disease would have been amenable to thoracoscopic resection. These data support pulmonary metastasectomy in FHWT as an important diagnostic modality in all patients with few, easily accessible pulmonary lesions of questionable etiology. This approach may spare patients more intensive therapy if the lesions prove to be fully necrotic or benign on biopsy.

The treatment of hepatic metastases is also based primarily on chemotherapy and radiation [42]. Upfront hepatic metastasectomy has demonstrated no clear benefit, as up to 16% of hepatic metastases achieve complete remission with chemotherapy alone, and only abdominal radiation appears to improve survival [20].

7.0 SPECIFIC SURGICAL CONDITIONS

7.1 Vascular Extension

Vascular extension of tumor thrombus to the IVC has been reported in 6-10% of patients, with atrial extension in 1% (Figure 1) [19]. Overall survival of these patients is comparable to similarly staged patients without vascular extension, and survival is comparable whether the thrombus is resected upfront or after initial chemotherapy [19, 24]. 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 [13, 14, 19]. CT and Doppler ultrasound are equally useful for assessing vascular extension to inform presurgical planning [9], but intraoperative IVC and/or renal vein palpation is still essential to avoid transecting an unidentified thrombus. Intraoperative ultrasound can also be utilized if preoperative imaging and intraoperative palpation is unclear at defining the presence or extension of intravascular disease. In NWTS-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 [19]. Excision of vascular extension requires proximal and distal control, which may require cardiopulmonary bypass in cases of persistent atrial thrombus. Intra-operative ultrasound and hepatic mobilization may help with mapping of the thrombus. Most often, 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 tumor thrombus constitutes spillage and consequently upstaging to stage III, so all efforts should be made to resect it in continuity with the primary tumor.

7.2 Horseshoe Kidney

WT presenting in a horseshoe kidney occurs in 0.5% of WT and presents specific surgical challenges because of the fusion of the renal moieties and variability in the anatomy of the vascular and collecting systems. A retrospective analysis of NWTS patients from 1969 to 1998 found 41 patients with WT in a horseshoe kidney. The anatomic abnormality was not identified on pre-operative imaging in 13 patients, and the group had a 15% complication rate, consisting mostly of urine leaks and ureteral injuries [46]. In patients with WT arising in a horseshoe kidney, care must be taken to identify anomalous vascular, collecting system, and ureteral anatomy on pre-operative 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 resection, complete resection, adequate nodal sampling, and avoidance of spillage are paramount.

8.0 BILATERAL WILMS TUMOR

Bilateral Wilms tumor (BWT) occurs in up to 13% of patient with WT (Figure 2).[47, 48] In addition, there is a population of children with either genetic disorders or tumor-specific features (Beckwith-Wiedemann Syndrome, multi-centric tumors) that increase their risk for synchronous and metachronous tumors.[49] One hurdle in treating BWT was that, until 2009, there had not been a dedicated study of the treatment of children with BWT. However,

the recent COG AREN0534 study focused on BWT and unilateral high-risk tumors and has greatly improved our understanding of BWT.

The balance to be achieved in treating these children is to maximize their overall survival with concomitant renal preservation. Historically, when compared to patients with unilateral WT, patients with BWT have lower EFS and OS, higher rates of renal failure, and they often received protracted courses of chemotherapy and radiotherapy. The four-year EFS for all patients with BWT on NWTS-5 was 56%. For BWT patients with favorable histology, focal anaplasia, and diffuse anaplasia, four-year event free estimates were 65%, 76%, and 25%, respectively.[8, 50, 51] European studies from the International Society of Pediatric Oncology (SIOP) reported a 10-year OS of only 69% for patients with synchronous BWT who were treated with either preoperative radiotherapy and/or chemotherapy.[47, 52, 53].

End stage renal disease (ESRD) is also more prevalent in children with BWT, [54, 55] with an incidence of 12% overall and much higher incidence in children with genetic syndromes such as Denys-Drash Syndrome (DDS) (75%) or WAGR Syndrome (50%). [54] One unique feature of BWT is that relapse may occur later than relapse of unilateral WT, at 3 years vs 6-18 months, respectively. For patients with BWT who developed ESRD within 5 years after treatment, the cause in 94% was a second nephrectomy for disease recurrence. [51] In addition, some children with BWT on NWTS-4 and 5 received chemotherapy regimens that lasted between 37 and 50 weeks, exposing them to both acute and long-term toxic events, but with little apparent effect on renal preservation or overall treatment outcome. [56]

Several factors contributed to the poor outcomes in children with BWT [56-58], including lack of a dedicated treatment protocol, under-staging which resulted in under-treatment, delay in local disease control, and an increased incidence of anaplasia. Biopsy, both open and core needle approaches, often fail to identify focal or diffuse anaplasia [58], resulting in some patients being treated for extended periods of time with inappropriate chemotherapy protocols. It has also been shown that tumors may not change in size on imaging after chemotherapy because the tumor may have differentiated or undergone rhabdomyomatous changes with no residual malignant elements. [59]

The COG AREN0534 study was the first cooperative group trial dedicated to children with BWT and unilateral high-risk patients. The primary aims related to patients with BWT were to improve 4-year EFS to 73%, to prevent complete removal of at least one kidney in 50% of patients by using a pre-nephrectomy three-drug chemotherapy regimen (vincristine, dactinomycin and doxorubicin [VAD]), and to perform definitive surgical treatment in 75% of children with BWT by 12 weeks after initiation of chemotherapy. For the 189 patients with BWT enrolled on this study, the 4-year EFS and OS were 82% and 95%, respectively. [48] Sixty-one percent required complete nephrectomy of at least one kidney. Definitive surgical treatment (partial or complete nephrectomy, or wedge resection in at least one kidney) was achieved in 84% of patients by 12 weeks after initiation of chemotherapy, meeting the goals of the study. A recent single institutional study and follow-up report by Davidoff and colleagues demonstrated that the renal function in children undergoing partial nephrectomies for BWT remains adequate over time.[60] Historically, the nephron sparing surgery (NSS) rate was 33% in children with BWT, based on the Surveillance,

Epidemiology, and End Results database. [61] While the goal of AREN0534 was to improve NSS to 50%, this was not achieved despite excellent EFS and OS. Failure of NSS in most cases in this study was due to the volume of the tumor or its central location. BWT cases are rare, and while few surgeons have a wide range of experience, more experienced surgeons have higher reported rates of NSS.[48, 60, 62] Moving forward, consultation and case review with a surgeon who has substantial NSS experience may be beneficial to guide decision-making and optimize NSS in patients with BWT.

9.0 SURGERY AND THE IMPACT ON LATE EFFECTS

The excellent 5-year EFS and OS for FHWT have allowed reduction in the intensity of treatment, possibly mitigating late effects. As previously mentioned, select stage I patients only require surgery, and select stage IV patients do not require pulmonary radiation therapy. This is crucial as late effects of WT treatment impact overall health, renal function, pregnancy/fertility, cardiac function, thoracic function and the risk of a subsequent malignancy. At 25 years after therapy, a WT survivor's cumulative incidence of severe chronic health conditions is 65.4% compared to 24.2% of the general population [3]. Long-term risk of renal failure 20 years after treatment among the standard, unilateral, non-syndromic FHWT patients is 0.6%.[51] The major risk factors for renal failure were exposure to radiation, BWT, and congenital syndromes.

The NWTS long-term follow-up study evaluated 700 maternal/offspring pairs.[63] 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. Regimen M, used for high-risk stage III and IV patients, contains cyclophosphamide, which has a profound effect on fertility in both men and women. Congestive heart failure is related to the cumulative doxorubicin dose ($P < 0.001$), lung irradiation ($P = 0.037$), and left abdominal irradiation ($P = 0.013$).[64, 65] The late effects of pulmonary radiation include pneumonitis, restrictive lung disease, scoliosis, kyphosis, reduced lung capacity, and subsequent tumors.[7, 66] Nearly 15% of female survivors of WT who were treated with pulmonary RT developed invasive breast cancer by age 40 years. It is clear that surgical decisions made during therapy greatly impact FHWT treatment and the patient's long-term health. Fertility preservation options should be presented to the patient at the time of diagnosis. It is also clear that large tumors should be resected whenever safe to do so, and lymph nodes must be adequately sampled to ensure the best short and long term outcomes for these patients. [17] [33] [17, 67] [5, 15, 45]

10.0 FUTURE CONSIDERATIONS

Despite the excellent overall outcomes for children with renal tumors, distinct patient populations exist which continue to have poor overall survivals, a high risk for late effects, or the possibility of significant treatment reduction. Surgical goals in upcoming studies of renal tumors include reducing the failure of lymph node sampling by requiring a minimum sample of 5 nodes from the regional nodal basin and instituting a surgical checklist that will be completed during the operation. An additional goal is to encourage thoracoscopic removal of pulmonary metastatic disease in patients with 3 or fewer lung lesions in FHWT

patients after 6 weeks of therapy with continued chemotherapy, potentially avoiding WLRT. More research is needed to understand and manage patients with nephrogenic rests. Tumor biology, in addition to stage and pathology, has become increasingly important in risk stratification and will continue to be evaluated in future studies.

10.1 Tumor Biology

NWTS-5 prospectively confirmed that patient EFS and OS with (LOH) at 1p and 16q were at least 10% lower than those without LOH. [8] COG studies AREN0532 and AREN0533 increased therapy for stages I to IV FHWT with LOH at 1p and 16q with improved outcomes. Despite these exciting improvements, LOH is found in only 5% of patients. Alternatively, chromosome 1q gain is found in up to 30% of patients with Wilms tumor and will be studied in future clinical trials.

10.2 Novel Therapeutic Agents

In the last several years, patients with relapsed WT have been treated on several developmental therapeutic studies based upon good response in preclinical models. Unfortunately, to date many of these encouraging results have not shown promise *in vivo*. In contrast, the combination of vincristine and irinotecan has been active in both preclinical and clinical models, and will be widely utilized in the upcoming COG renal tumor phase 3 clinical trials. [68]

10.3 Imaging

The advancing technology of functional MRI may add relevant information to imaging characteristics. Whether this advanced imaging will discriminate nephrogenic rests from WT remains to be seen. An interesting report by investigators from Denmark details the use of real-time magnetic resonance urography (MRU) as an overlay to assist with operative planning for NSS, but the clinical utility of this technology has yet to be fully explored.[69]

Acknowledgments

FUNDING SOURCES: None

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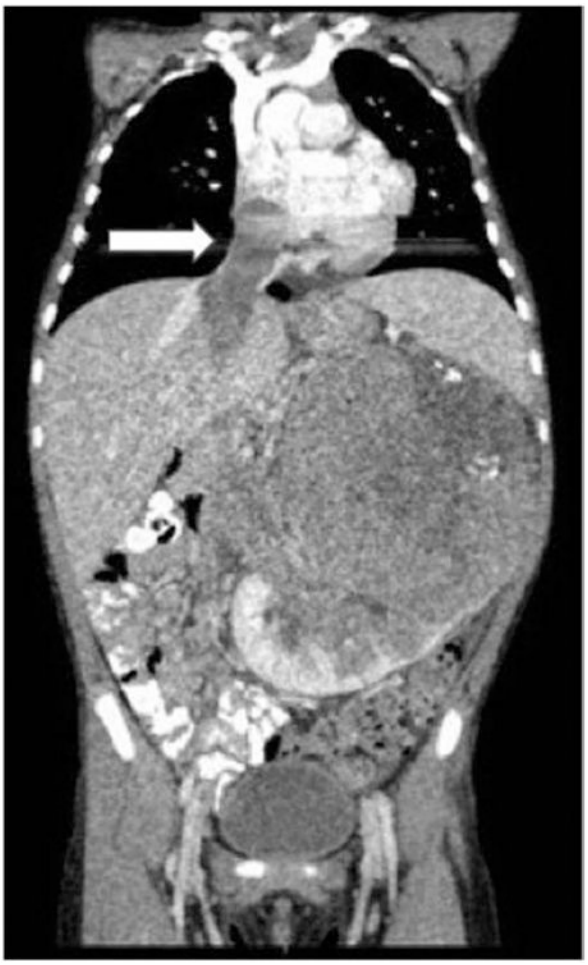

Figure 1:
Coronal computed tomography (CT) image of a large left renal mass with vascular extension (arrow) to the suprahepatic inferior vena cava and into the right atrium.

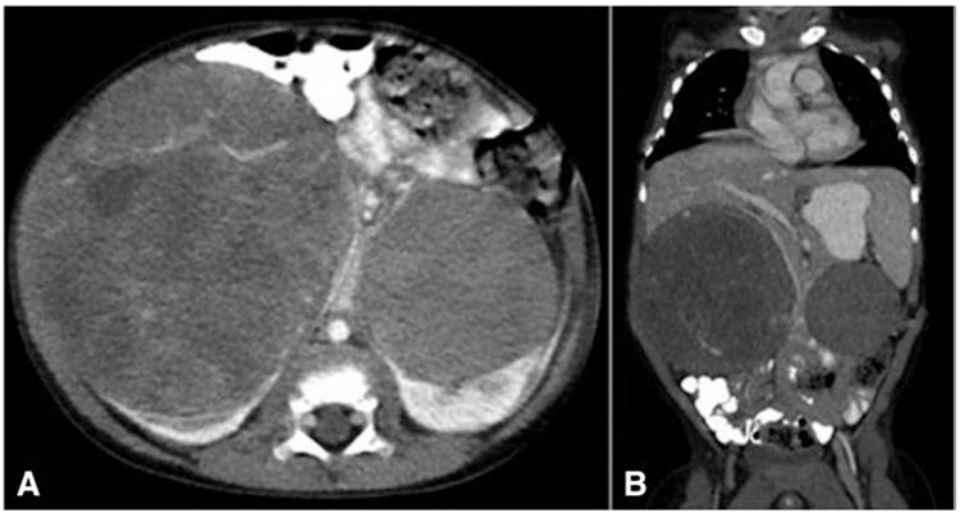

Figure 2:
Axial (A) and coronal (B) computed tomography (CT) images of bilateral renal masses in a patient with bilateral Wilms tumor.

Table 1:

Outcomes of Recent Children's Oncology Group Trials for Patients with Renal Tumors

STUDY	PRIMARY SPECIFIC AIMS	KEY STUDY CONCLUSIONS
AREN03B2 Renal Tumors Classification, Biology, and Banking Study	To classify patients with renal tumors by histological categorization, surgicopathological stage, presence of metastases, age at diagnosis, tumor weight and loss of heterozygosity for chromosomes 1p and 16q, to thereby define eligibility for a series of therapeutic studies. To maintain a bank of biological samples to be made available to scientists for evaluation of additional potential biological prognostic variables and for the conduct of other research.	Central Radiology, Pathology and Surgical reviews are feasible and improve standardization of risk assignment. Tumor size > 15cm is associated with a high risk of intraoperative rupture. Surgical Protocol Violations that potentially result in additional exposure to chemotherapy and radiation therapy are not uncommon in children undergoing resection of renal malignancies and can be used as a surrogate marker of surgical quality resection of renal malignancies and can be used as a surrogate marker of surgical quality Translocation RCC is the most common form of pediatric and adolescent RCC. Lymph node disease is common and observed among patients with small primary tumors. Imaging has a high specificity but relatively low sensitivity for the detection of such lymph node disease. Failure to sample LNs results in incomplete staging and potentially inadequate disease control for younger patients with RCC. CT and MRI have similar diagnostic performance for detection of lymph node metastasis and capsular penetration, however sensitivity and specificity are too low for clinical use. CT has moderate specificity but relatively low sensitivity in the detection of preoperative Wilms tumor rupture. CT can accurately identify cavoatrial tumor thrombus that will impact surgical approach. Routine Doppler evaluation, after CT has already been performed, is not required in Wilms tumor.
AREN0532 Treatment for Very Low and Standard Risk Favorable Histology Wilms Tumor	To demonstrate that very low risk patients treated by nephrectomy and observation alone will have a 4-year EFS of ≥ 85% and 4-year OS ≥ 95% To improve the current 4-year EFS for patients with Stage I and II FHWT with LOH of 1p and 16q by adding doxorubicin but not radiotherapy.	4-year EFS was 89.7% (95% CI:84.1-95.2%) and OS was 100%. Increased therapy (doxorubicin) for children with LOH at 1 p and 16q resulted in an improved 4-year EFS from 75% on NWTS-5 to 84%
AREN0533 Treatment of Newly Diagnosed Higher Risk Favorable Histology Wilms Tumors	To demonstrate that patients with Stage IV FH WT with pulmonary mets only, who have complete resolution of lesions after 6 weeks of DD4A (called Rapid Complete Responders – RCR), will have at least an 85% 4-year EFS after therapy with additional DD4A and without whole lung irradiation. To demonstrate that regimen M for stage IV FHWT patients whose lung lesions did not completely respond to chemotherapy at 6 weeks, an increase in therapy will improve 4-year EFS from over 74% and OS 86% from NWTS-5 To improve the 4-year EFS to 75% for patients with Stage III or IV FHWT with LOH of chromosomes 1p and 16q	105 patients were rapid responders and did not require pulmonary radiation therapy there were 20 failures and 4-year EFS was 78%, within the statistical goal of study 163 patients with SIR at week 6 and subsequently treated with regimen M, the estimated 4-yr EFS is 88%, and OS is 92% For stage III and IV patients, increased therapy improved 4- year EFS from 66% to 96%.
AREN0321 Treatment in High Risk Renal tumors	To evaluate whether a treatment regimen UH-1/revised UH1 improves the event-free and overall survival of patients with stage II-IV diffuse anaplastic Wilms tumor as compared to historical controls. To evaluate, in a Phase II—window study, the anti-tumor activity of a combination of vincristine and protracted-schedule irinotecan against metastatic diffuse anaplastic Wilms tumor. To evaluate whether a treatment regimen UH-2 improves the event-free and overall survival of patients with malignant rhabdoid tumor (MRT) as compared to historical controls. To maintain the excellent event-free survival of patients with Stage I clear cell sarcoma of the kidney (CCSK) without the use of abdominal irradiation.	66 patients were treated; 4-yr EFS was 75% and OS was 76%. Stage II 4-yr EFS was 86% Stage III 4-yr EFS was 85% Stage IV 4-yr EFs was 54% Results not yet available Results not yet available

STUDY	PRIMARY SPECIFIC AIMS	KEY STUDY CONCLUSIONS
AREN0534 Treatment for Patients with Bilateral, Multicentric, or Bilaterally-Predisposed Unilateral Wilms Tumor	To improve 4-year EFS to 73% for patients with bilateral Wilms tumor (BWT). To prevent complete removal of at least one kidney in 50% of patients with BWT by using pre-nephrectomy 3-drug chemotherapy induction with vincristine, dactinomycin, and doxorubicin. To have 75% of children with BWT undergo definitive surgical treatment by 12 weeks after initiation of chemotherapy.	the 4-year EFS and OS were 82.1% and 94.9%. This is a significant improvement over NWTS-5 In this group, 61% required complete nephrectomy of at least one kidney. Of the 189 BWT patients, 163 (84.0%) underwent definitive surgical treatment (partial or complete nephrectomy or wedge resection in at least one kidney) by 12 weeks after initiation of chemotherapy.

Abbreviations:

EFS: event-free survival

OS: overall survival

LOH: loss of heterozygosity

Regimen M: Vincristine, Dactinomycin, Doxorubicin, Cyclophosphamide, Etoposide, radiation therapy

DD4: Vincristine, Dactinomycin, Doxorubicin, radiation therapy

UH-1: Vincristine, Doxorubicin, Cyclophosphamide, Carboplatin, Etoposide, radiation therapy

UH-2: Vincristine, Doxorubicin, Cyclophosphamide, Carboplatin, Etoposide, Irinotecan, radiation therapy