Published in final edited form as:
Curr Opin Pediatr. 2009 June ; 21(3): 357–364. doi:10.1097/MOP.0b013e32832b323a.

WILMS TUMOR

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Abstract

Purpose of review—Wilms tumor accounts for nearly six percent of all pediatric cancers and more than 95 percent of all kidney tumors in children. Fortunately, survival for patients with Wilms tumor is generally excellent. This review will outline the results of prior clinical trials that have lead to this excellent outcome and how information gleaned from these trials has lead to the development of the current series of clinical trials for the management of children with Wilms tumor.

Recent findings—Tumor stage and histologic subtype have long been recognized as important prognostic factors in Wilms tumor. More recent evidence suggests that in certain instances patient age, tumor size, response to therapy, and genetic abnormalities, specifically the loss of genetic material on chromosomes 1p and 16q, provide additional prognostic information. These factors have, therefore, been incorporated into a new risk stratification system that is currently being used to assign patients with Wilms tumor to specific protocol-based therapies.

Summary—Survival for patients with Wilms tumor when considered as a whole, once <30%, is currently greater than 90%, with this dramatic improvement being due, in part, to the systematic manner in which the approach to therapy has evolved. Further refinement in therapy is being undertaken, with the current trials aiming to maintain the excellent survival for children being treated for Wilms tumor, while minimizing therapy-related toxicity.

Keywords

Wilms tumor; protocols; surgery

Introduction

Wilms tumor is the second most common intraabdominal cancer of childhood and the fifth most common pediatric malignancy overall. It represents approximately six percent of all pediatric cancers and accounts for more than 95 percent of all tumors of the kidney in the pediatric age group.[1,2] In the United States there are approximately eight cases of Wilms tumor per million children less than 15 years of age per year, with the total number of new cases being estimated at about 500 cases per year.[3] Approximately 75 percent of the cases occur in children less than five years of age with a peak incidence at two to three years of age. Survival for patients with Wilms tumor when considered as a whole, once <30%, is currently greater than 90%, making it one of the real successes of modern medicine. This dramatic improvement in survival is due, in part, to the systematic manner in which the approach to therapy has evolved. Surgery is a critical component of this therapy and the role of the surgeon is central in the treatment of these patients. However, the addition and

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refinement of chemotherapy, and, in certain circumstances, radiation therapy, have also had a significant impact on achieving improved survival rates. There are a number of excellent papers that provide overviews of Wilms tumor and the current clinical management of children with this disease.[4–12] This review will focus on describing the results of prior clinical trials that have lead to the excellent outcome for children with Wilms tumor and how these results have lead to the development of the current series of clinical trials. The current risk stratification and general treatment approaches for patients with Wilms tumor, and the critical role that the surgeon plays, will be highlighted.

National Wilms Tumor Studies

Due to the rarity of Wilms tumor, organized clinical investigation was limited until the establishment of the National Wilms Tumor Study (NWTS) in 1969. This represented a cooperative effort among several groups to treat patients in a clearly defined manner so that statistically relevant comparisons of treatment variations could be made. Five sequential trials have been completed, with the basic goal of each successive NWTS trial having been to maintain a high cure rate for patients with Wilms tumor, while reducing the intensity and duration of therapy, based on surgical stage and histologic evaluation. Although the importance of surgery in the treatment of Wilms tumor has long been recognized, the roles for chemotherapy and radiation therapy have evolved based on the results of the NWTS trials.

NWTS-1 showed that postoperative abdominal radiotherapy was not necessary for children who were less than two years of age and whose tumors were limited to the kidney and completely resected.13 In addition, the combination of vincristine and dactinomycin was shown to be more effective for the treatment of children with tumors that extended beyond the kidney than either drug alone. NWTS-2 demonstrated that six months of combination chemotherapy with vincristine and dactinomycin was effective treatment for children with tumors limited to the kidney and completely resected, none of whom received abdominal radiation. The addition of adriamycin to the combination of vincristine and actinomycin D was found to improve the relapse-free survival of other patients.14 The separation of Wilms tumor into distinct histopathologic categories based on prognosis was used to stratify patients in NWTS-3.15 NWTS-4 examined the utility of dose intensive scheduling to cut down on the duration of therapy.[16] The more recently concluded NWTS-5, a single-arm therapeutic trial designed to evaluate the prognostic value of certain biologic markers in Wilms tumor, demonstrated that loss of heterozygosity (LOH) for genetic material on chromosomes 1p and 16q in stage I and II favorable histology Wilms tumor was associated with a poorer prognosis.[17] This information, loss of heterozygosity of 1p and 16q, is now being used to further stratify patients in the current Children's Oncology Group (COG) trial for Wilms tumor.

Current protocols

Historically, the most important prognostic variables for patients with Wilms tumor have been the histopathologic tumor classification and surgical stage.[18] Survival statistics based on these factors, which have largely guided treatment, are shown in Table 1. The staging system developed by the NWTS and currently in common use, is shown in Table 2. Because appropriate therapy, as well as prognosis, is based on tumor stage, accurate staging of patients with Wilms tumor at the time of diagnosis is imperative and includes histologic assessment of regional lymph node involvement. There are two distinct histopathologic types of Wilms tumor, favorable and unfavorable.[19] The unfavorable group comprises Wilms tumors with anaplasia (extreme nuclear and cytologic atypia). Anaplasia is present in about 5 percent of Wilms tumor and is more common in older children, reaching a peak at

approximately five years of age.[20] This histopathologic variant is also more frequent in African-American patients than in Caucasian patients. There are two additional, distinct renal tumors that can occur in children, each characterized by sarcomatous stroma and a poor outcome. They are clear cell sarcoma of the kidney and malignant rhabdoid tumor of the kidney.19 As these are distinct from Wilms tumor, they will not be discussed further in this review.

It has recently been recognized that a Wilms tumor risk stratification system based on histology and stage alone does not accurately identify all patients at risk for recurrence. New clinical and genetic risk factors for recurrence have been validated and have now been incorporated into the assigning of therapy in the current COG clinical trials for patients with Wilms tumor. These factors include patient age at the time of diagnosis, tumor weight, histologic response to therapy and the allelic status of chromosomes 1p and 16q in resected tumors.

Since 2006, four clinical trials have opened within COG for the treatment of patients with Wilms tumor. Together these protocols cover the entire spectrum of Wilms tumor. Central to the approach to therapy for these patients is a risk classification scheme, which is defined in Table 3. To facilitate accurate and timely risk assessment, enrollment in an overarching tumor collection and biology classification protocol, AREN03B2: Renal Tumors Classification, Biology, and Banking Study, is a pre-requisite (Figure 1). Patients are then enrolled on one of the therapeutic protocols.

AREN0532: Treatment for Very Low and Standard Risk Favorable Histology Wilms Tumor

Only patients with non-metastatic, favorable histology disease are eligible (Figure 2). The “very low” risk arm of this protocol proscribes surgery alone as definitive treatment for children less than 2 years of age with stage I disease where the tumor weight is less than 550gm. Children with stage I (or II) disease who do not qualify for surgery alone are still considered “low risk” but in addition to surgery, are started on treatment with 22 weeks (7 cycles) of two-drug chemotherapy (vincristine and dactinomycin) on regimen EE-4A. These patients are technically not treated “on” a protocol but are followed on AREN03B2. However, if the tumor from these patients is subsequently found to have LOH of both 1p and 16q, these patients are switched to “standard” risk therapy consisting of 28 weeks (9 cycles) of three-drug chemotherapy, in which doxorubicin is added to vincristine and dactinomycin, on regimen DD-4A. Stage III patients whose tumors do not have 1p and 16q are also treated with “standard risk” DD-4A, plus radiation therapy. However, if their tumor is subsequently found to have both 1p and 16q LOH, these patients with stage III disease, are considered “higher risk” and are switched to AREN0533 (see below).

AREN0533: Treatment of Newly Diagnosed Higher Risk Favorable Histology Wilms Tumors

Patients eligible for this protocol have favorable histology tumors and either stage III disease that is found to have 1p and 16q LOH, or stage IV (metastatic) disease (Figure 3). Those with stage III disease and 1p and 16q LOH are treated for 33 weeks (11 cycles) with vincristine, dactinomycin and doxorubicin plus cyclophosphamide and etoposide on regimen M, as well as abdominal irradiation. Patients with stage IV disease without 1p and 16q whose pulmonary lesions respond “rapidly and completely” (see later discussion) are treated with regimen DD-4A chemotherapy and no pulmonary irradiation. All other patients with metastatic disease (those with 1p and 16q LOH, those with “slow, incomplete” response of their pulmonary disease [see later discussion], or those whose metastases are extra-pulmonary are treated with regimen M and radiation to the site(s) of metastatic disease.

AREN0321: Treatment of High Risk Renal Tumors

All patients with anaplastic Wilms tumor are treated on this protocol. For risk assessment and treatment purposes, a distinction is made between focal (anaplasia confined to one or a few discrete loci within the primary tumor, with no anaplasia or marked nuclear atypia elsewhere) and diffuse anaplasia. Patients whose tumors have focal anaplasia, stage I-III, or diffuse anaplasia, stage I, are treated with regimen DD-4A. Patients with stage IV focal anaplasia, stage II-III diffuse anaplasia, and stage IV diffuse anaplasia without measurable disease are treated for 30 weeks with cyclophosphamide/carboplatin/etoposide and vincristine/doxorubicin/cyclophosphamide plus radiation therapy (regimen UH-1). Patients with stage IV diffuse anaplasia with measurable disease are treated with 1–2 cycles of irinotecan/vincristine as window therapy to evaluate tumor response and determine whether this combination should be added to the backbone treatment with UH-1.

AREN0534: Treatment for Patients with Bilateral, Multicentric, or Bilaterally-Predisposed Unilateral Wilms Tumor

Due to an increased risk of renal failure in patients with bilateral Wilms tumor, these patients receive neoadjuvant therapy with three drug chemotherapy of regimen DD-4A in an effort to shrink the tumors prior to surgery and facilitate the preservation of renal parenchyma, thereby preserving renal function. Also eligible for enrollment on this protocol are patients with Wilms tumor arising in a solitary kidney or those patients less than one year of age with a unilateral Wilms tumor who are at an increased risk for a metachronous tumor. Patients with a number of genetic syndromes, particularly those associated with abnormalities of the Wilms tumor 1 (WT1) and Wilms tumor 2 (WT 2) genes on the short arm of chromosome 11, carry this risk (see Table 4). Patients with unilateral Wilms tumor and a Wilms tumor predisposition syndrome are treated with regimen EE-4A if their disease is stage I-II but DD-4A if the disease is stage II-IV.

Surgery for Wilms tumor

The role of surgery in the therapy of Wilms tumor is paramount since a meticulous and well performed procedure will accurately determine the stage of the patient and their future therapy. A poorly performed procedure can lead to inadequate therapy if patients are not appropriately staged or to unnecessarily intensive therapy if operative spill of the tumor occurs or if incomplete resection of the primary tumor is carried out. The main responsibility of the surgeon is to remove the primary tumor completely, without spillage, and to accurately assess the extent to which the tumor has spread, with particular attention to adequately assessing lymph node involvement.

Timing of surgery

One of the main controversies in the treatment of children with Wilms tumor is whether or not to administer preoperative chemotherapy, as suggested by the International Society of Pediatric Oncology (SIOP).[21–26] The surgeon considering the use of preoperative chemotherapy should realize that there can be significant adverse affects on staging and histological evaluation in children who receive preoperative chemotherapy which could lead to either over treatment or under treatment. Evidence to support the dangers of under treatment is a SIOP study that showed an increased incidence of infradiaphragmatic relapses in patients who did not receive postoperative radiation therapy.27 Likely, patients with lymph node involvement were missed due to preoperative chemotherapy.

Proponents of preoperative therapy suggest that the tumor is easier to resect with a decreased incidence of tumor spill and a lower mortality and morbidity. However, the

morbidity and mortality following tumor resection in NWTS is extremely low, and the incidence of tumor spill was less than ten percent.

Despite the arguments given above against the use of preoperative therapy, specific patient groups can be identified who would seem to benefit from preoperative chemotherapy. These are patients with bilateral tumors, those patients with IVC and intra-atrial involvement and patients with massive tumors considered by the operating surgeon to be unresectable without undue risk to the patient.

Surgical exploration

A radical nephrectomy should be carried out through a generous transverse, transperitoneal incision. A thoracic extension may be necessary but has been associated with a higher complication rate.[28] Isolation of the hilar vessels prior to mobilization of the primary tumor is no longer recommended since major vascular injury to the mesenteric arteries, celiac vessels, and aorta have been reported.[29] Palpation of the renal vein prior to dividing it is recommended to exclude the possibility of a tumor thrombus, as occurs in about 10% of cases. Biopsy of the primary tumor should not be carried out prior to removal and a meticulous dissection to avoid rupture of the tumor capsule with spillage of tumor cells is imperative, as tumor spill is strongly associated with recurrence.[30] During tumor resection the ureter is ligated and divided as low as possible but complete removal of the ureter down to the bladder is not necessary. Intra-operative inspection of the liver and the contralateral kidney are no longer required, unless lesions had been identified on pre-operative imaging studies, because of the high accuracy of current imaging modalities. However, lymph node sampling is critically important, despite the absence of abnormal nodes on pre-operative imaging, or upon gross inspection during operative exploration, since a review of lymph node sampling by the NWTS demonstrated a false negative rate of 31 percent and a false positive rate of 18 percent based on pre-operative and intra-operative assessment.[31] Unfortunately, there is currently a fairly high incidence of inadequate intra-operative staging, primarily due to failure to sample lymph nodes.[32]

Wilms tumors rarely invade surrounding structures but frequently adhere to adjacent organs. If the tumor cannot be cleanly separated from adjacent structures then excision of the tumor with surrounding structures can be carried out in continuity if the operating surgeon feels that all tumor tissue can be completely removed. Since patients with small residual disease respond well to present chemotherapy and since an increased incidence of complications has been associated with tumor resections that include adjacent structures, radical resection is only indicated if all tumor can be removed. In the case of hepatic invasion a resection of part of the liver along with the primary tumor can usually be carried out. However, a formal hepatectomy is rarely indicated.

There are reports of surgeons performing unilateral partial nephrectomy and laparoscopic nephrectomy (radical or partial) for Wilms tumor, particularly in Europe where children routinely receive pre-operative chemotherapy.[33–37] However, the appropriateness and adequacy of these approaches has not been confirmed and they are not currently endorsed by COG.

Very low risk favorable histology Wilms tumor

Children less than two years of age with unilateral, favorable histology, stage I tumors that weighed <550gms were felt to be at such low risk for recurrence that the risks of adjuvant chemotherapy might outweigh the risks of recurrence. Therefore, in NWTS-5, these patients were treated with surgery alone. However, because the two-year event free survival (EFS), 86.5%, did not meet the required EFS of 90%, this arm of the trial was stopped. Subsequent

evaluation of the data, in which the overall survival of the patients who suffered a relapse was 91% with adjuvant therapy, higher than the expected salvage rate of 50%,[38] has renewed enthusiasm for this approach which has been re-instituted. It should be noted that a critical component of the entry criteria is that adequate lymph node sampling be performed at the time of tumor resection to ensure accurate confirmation of stage I disease.

Bilateral Wilms tumor

Synchronous disease in both kidneys at presentation occurs in approximately five percent of children with Wilms tumor. Unfavorable histology is seen in approximately ten percent of the cases, and there can be discordant histology. However, because tumor biopsy, regardless of the technique, is very unlikely to document anaplastic histology[39] and because there are few other things, other than Wilms tumor, in the differential diagnosis for a child with bilateral renal masses, biopsy at presentation is now discouraged by COG.

As surgery is a critical component in the treatment of Wilms tumor, the challenge in the management of patients with bilateral disease is to achieve a high cure rate while maintaining adequate long-term renal function. Several studies have demonstrated that patients with bilateral Wilms tumor are at risk for developing renal failure.40–43 The exact etiology of renal failure is not always clear and is likely multifactorial.41,43 However, because of an increasing appreciation of the potential for renal failure in these patients, the management of synchronous bilateral Wilms tumor has evolved from primary kidney resection to renal-preserving surgical approaches, facilitated by the use of preoperative chemotherapy. We have recently reviewed our experience at St. Jude Children's Research Hospital and found that we were able to perform bilateral partial nephrectomies in nearly all patients (>90%) with favorable histology disease, despite occasionally foreboding pre-operative imaging.[44] Complications were minimal and long-term renal function and survival have been excellent. Definitive operative intervention should be done early, by twelve weeks after initiation of chemotherapy, since little significant further change in tumor size is likely45 and it is important to determine the exact tumor histology.39,46 The finding of either anaplasic or blastemal predominant histology would mandate intensification of therapy if not stage I disease, while certain other circumstances would allow for discontinuation of doxorubicin.

Intravascular tumor extension

Vena cava and intraatrial extension of Wilms tumor can occur in patients with Wilms tumor, with an incidence of approximately 5%. Survival does not appear to be affected and the prognosis is comparable stage by stage to children without intravascular involvement. Localization of the thrombus should be determined prior to operation utilizing real-time ultrasonography, echocardiography; sometimes MRI scanning can provide additional information. Surgical excision of the primary tumor and thrombus is recommended when technically feasible. An intraabdominal approach is sufficient for infrahepatic lesions with extraction of the caval thrombus after proximal and distal control of the vena cava are obtained. Free-floating thrombi that are easily removed are classified as Stage II but thrombi that invade the vessel or are extremely adherent to the wall of the vessel are classified as Stage III. Patients with atrial extension of a tumor thrombus require cardiopulmonary bypass for thrombus removal. In these patients a midline abdominal incision with a median sternotomy can be used. Alternatively, strong consideration should be given to the use of preoperative chemotherapy.[47–50]

Metastatic disease

The primary distant site for Wilms tumor metastases is the lungs; hepatic metastases are much less common. Approximately 12 percent of Wilms tumor patients will have evidence

of hematogenous metastases at diagnosis, with 80% having pulmonary metastases. Patients with Stage IV favorable histology tumors at diagnosis still have a good prognosis while unfavorable histology patients and patients who relapse with metastatic disease have a grave prognosis. Approximately 20% of favorable histology patients will relapse following therapy with a majority of relapses being in the lungs. Patients with pulmonary metastases usually can be managed by combined chemotherapy and radiation therapy;[51] pulmonary resection is rarely indicated because chemotherapy is extremely effective. Although histologic confirmation of pulmonary relapse may be indicated, complete removal of pulmonary metastases at relapse does not increase survival.

A new response-based approach is now being taken for patients with stage IV disease in AREN0533. Those patients, treated with regimen DD-4A, who have complete radiographic disappearance of their lung metastases (or who have tissue confirmation that residual nodules do not contain viable tumor) at the week 6 reevaluation will be considered “rapid responders,” will continue on DD-4A and will not receive pulmonary irradiation. Patients who do not have complete resolution of pulmonary nodules will be considered “slow, incomplete responders,” will be switched to regimen M and will receive whole lung irradiation. Those patients who, at the time of diagnosis have pulmonary metastases confirmed histologically and have the lesions completely resected (and therefore have no residual disease available for response monitoring) will be treated with DD-4A but will also be required to receive whole lung irradiation. Therefore, consideration must be given to the implications of resecting pulmonary lesions at the time of diagnosis. If the lesions are found to be benign, the patient will have been spared doxorubicin (if local stage I–II) and pulmonary irradiation. However, if the lesions are metastatic Wilms tumor and are removed completely, the patient will have lost the opportunity to be considered a rapid responder and avoid whole lung irradiation.

Conclusion

Significant improvement has been made in the treatment of children with Wilms tumor. New protocols are in place designed to maintain a high rate of cure for these patients while minimizing toxicity, based on refinement of the risk stratification system. Surgeons play a critical role in the management of children with Wilms tumor and it is imperative that they understand the directives of these new protocols and how the conduct of an operation can influence therapy and outcome for these patients.

Acknowledgments

Supported by grant CA 021765 from the National Institutes of Health and by the American Lebanese Syrian Associated Charities (ALSAC).

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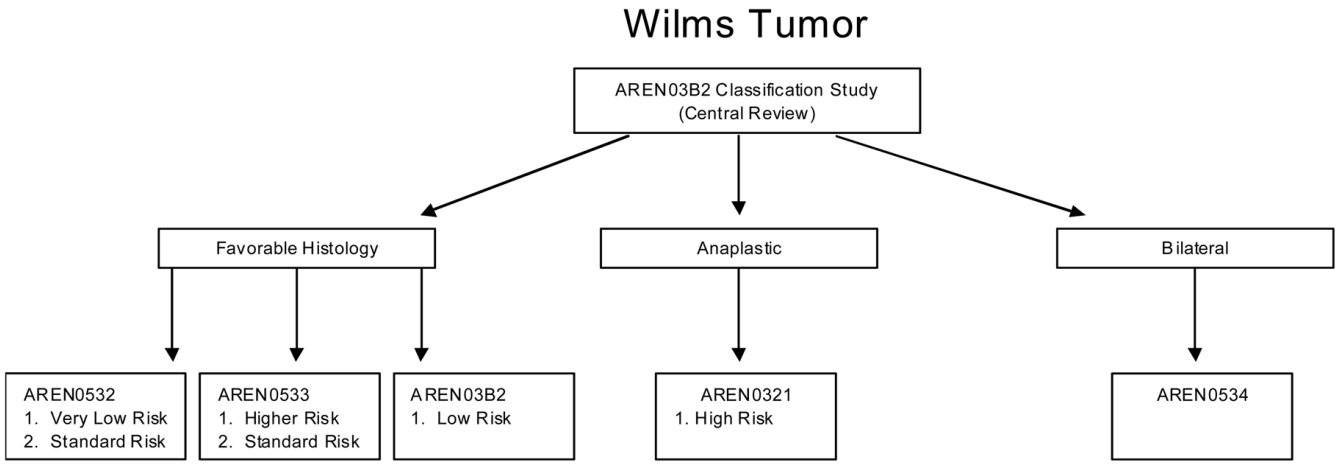

Figure 1.
COG protocols for patients with Wilms tumor. Patients being treated for low risk disease (Stage I-II, favorable histology, without 1p and 16q LOH are treated with regimen EE-4A and are followed on AREN03B2.

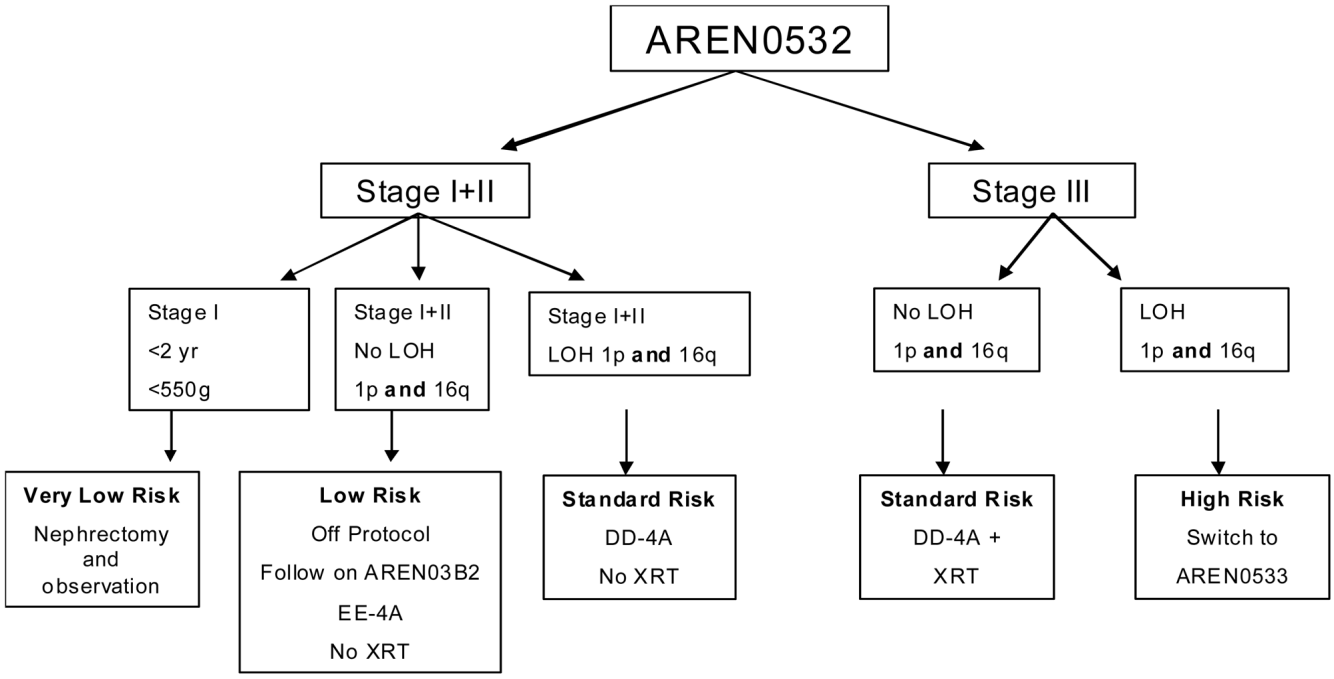

Figure 2.
Treatment outline for patients with favorable histology Wilms tumor on AREN0532: Treatment for Very Low and Standard Risk Favorable Histology Wilms Tumor.

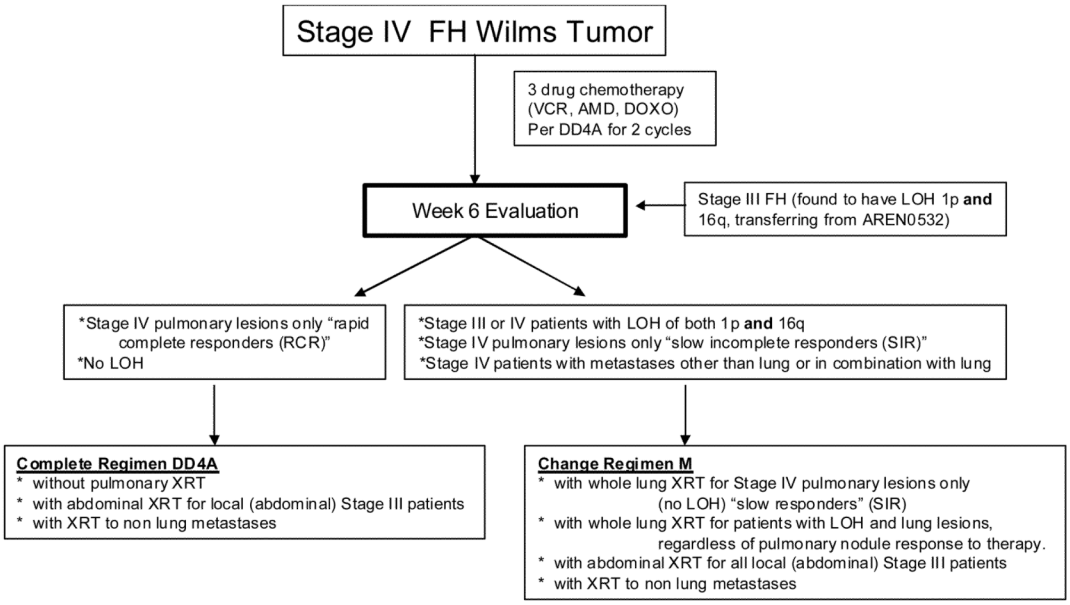

Figure 3.
Treatment for patients enrolled on AREN0533: Treatment of Newly Diagnosed Higher Risk Favorable Histology Wilms Tumor.

Table 1

Ten-Year Outcomes for Patients with Wilms Tumor treated on NWTS-4

Histology	Stage	10 yr Relapse Free Survival (RFS)%	10 yr Overall Survival (OS)%
Favorable	I	91	96
	II	85	93
	III	84	89
	IV	75	81
	V	65	78
Anaplastic	I	69	82
	II–III	43	49
	IV	18	18

Table 2

Wilms Tumor Staging System

I. Tumor limited to kidney and completely excised. The surface of the renal capsule is intact. Tumor was not ruptured before or during removal. There is no residual tumor apparent beyond the margins of excision.

II. Tumor extends beyond the kidney, but is completely excised. There is regional extension of the tumor; ie, penetration through the outer surface of the renal capsule into perirenal soft tissues. Vessels outside the kidney substance are infiltrated or contain tumor thrombus. There is no residual tumor apparent at or beyond the margins of excision.

III. Residual nonhematogenous tumor confined to abdomen. Any one or more of the following occur:

1. Lymph nodes on biopsy are found to be involved in the hilus, the periaortic chains or beyond.
2. There has been peritoneal contamination by tumor such as by biopsy or rupture of the tumor before or during surgery, or by tumor growth that has penetrated through the peritoneal surface.
3. Implants are found on the peritoneal surfaces.
4. The tumor extends beyond the surgical margins either microscopically or grossly.
5. The tumor is not completely resectable because of local infiltration into vital structures.

IV. Hematogenous metastases. Deposits beyond Stage III; ie, lung, liver, bone, and brain.

V. Bilateral renal involvement at diagnosis. An attempt should be made to stage each side according to the above criteria on the basis of extent of disease prior to biopsy.

Table 3

Risk Stratification and Treatment Study Assignment for patients with favorable histology Wilms tumor

Patient Age	Tumor Weight	Stage	LOH	Rapid Response	Final Risk Group	Treatment Study
<2 yrs	<550g	I	Any	N/A	Very Low	AREN0532
Any	≥550g	I	None	N/A	Low	None
≥2 yrs	Any	I	None	N/A	Low	None
Any	Any	II	None	N/A	Low	None
≥2 yrs	Any	I	LOH	N/A	Standard	AREN0532
Any	≥550g	I	LOH	N/A	Standard	AREN0532
Any	Any	II	LOH	N/A	Standard	AREN0532
Any	Any	III	None	Any	Standard	AREN0532
Any	Any	III	LOH	Any	Higher	AREN0533
Any	Any	IV	LOH	Any	Higher	AREN0533
Any	Any	IV	None	Yes	Standard	AREN0533
Any	Any	IV	None	No	Higher	AREN0533
Any	Any	V	Any	Any	Bilateral	AREN0534

Table 4

Syndromes related to the WT1 and WT2 loci

Syndrome	Locus	Genetic Lesion	Phenotype	Wilms tumor risks
WAGR	11p3	Deletion WT1 gene	Aniridia, genitourinary anomalies, delayed-onset renal failure	30%
Denys-Drash	11p3	Point mutation in zinc-finger regions of WT1 gene	Ambiguous genitalia, diffuse mesangial sclerosis	90%
Beckwith-Wiedemann	11p3	Precise genetic lesion unclear; loss of imprinting of several genes including IGF2, H19, and $p57^{kip2}$ implicated	Organomegaly, large birth weight, macroglossia, omphalocele, hemihypertophy, ear pits and creases, neonatal hypoglycemia	5%

Adapted from: Dome JS, Coppes MF. Recent advances in Wilms tumor genetics. Curr Opin Pediatr. 2002 Feb; 14(1):5–11. [5]