Wilms Tumor (Nephroblastoma), Version 2.2021

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ABSTRACT

The NCCN Guidelines for Wilms Tumor focus on the screening, diagnosis, staging, treatment, and management of Wilms tumor (WT, also known as nephroblastoma). WT is the most common primary renal tumor in children. Five-year survival is more than 90% for children with all stages of favorable histology WT who receive appropriate treatment. All patients with WT should be managed by a multidisciplinary team with experience in managing renal tumors; consulting a pediatric oncologist is strongly encouraged. Treatment of WT includes surgery, neoadjuvant or adjuvant chemotherapy, and radiation therapy (RT) if needed. Careful use of available therapies is necessary to maximize cure and minimize long-term toxicities. This article discusses the NCCN Guidelines recommendations for favorable histology WT.


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Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

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Disclosures for the NCCN Wilms Tumor (Nephroblastoma)

At the beginning of each NCCN Guidelines Panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Wilms Tumor (Nephroblastoma) Panel members can be found on page 977. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.
INTRODUCTION TO WILMS TUMOR

All patients with suspected Wilms tumor (WT) should be managed by a multidisciplinary team with experience managing renal tumors; consulting a pediatric oncologist is strongly encouraged.

The NCCN Guidelines for Wilms Tumor (Nephroblastoma) only address favorable histology Wilms tumor (FHWt) at this time.

Epidemiology of Wilms Tumor
- WT accounts for 5% of childhood cancers and is the most common primary renal tumor in children (accounts for >90% of renal tumors in patients <20 years). Five-year survival for these patients is >90% with appropriate treatment. However, outcome of some groups, particularly those with diffuse anaplastic WT, remains poor. This guideline does not include anaplastic WT at this time.
- Incidence of WT is highest among African American children, followed by Caucasian children, and children of Asian descent have the lowest incidence.1
- >70% of WT present between 1–5 years (most commonly 3 years).2
- Most patients have a solitary tumor at presentation. However, 5%–13% have bilateral tumors, and 10% have multifocal tumors in a single kidney.3,4
- For unilateral tumors, the median age at diagnosis is 35 months for boys, and 42 months for girls.1
- For bilateral tumors, the median age at diagnosis is 23 months for boys, and 28.5 months for girls.1

Clinical Presentation
- Most patients present with abdominal distention and/or presence of an abdominal mass (83%) with or without abdominal pain (37%), fever (23%), hematuria (21%–25%), and hypertension (20%–25%). Less common symptoms include: varicocele, hernia, enlarged testicle, congestive heart failure, hypoglycemia, Cushing syndrome, pleural effusion, and acute abdomen.
- A healthy-appearing child is more likely to have WT, whereas an ill-appearing child may have neuroblastoma.
- Calcification of the tumor appears in approximately 5%–10% of WTs, versus approximately 60%–70% of neuroblastomas.
- Almost 10% of patients with WT have coagulopathy (acquired Von Willebrand disease).5,6
- Most common sites of hematogenous metastases include: lung (81%), lung and liver (15%), other (4%).7 Spread to regional lymph nodes (NLs) also occurs.
- WT is associated with genetic predisposition syndromes, such as Beckwith-Wiedemann syndrome (macroglossia, hemihyperplasia, gigantism, and umbilical hernia); WAGR syndrome (WT, aniridia, genitourinary abnormalities, and range of developmental delay); and Denys-Drash syndrome (male pseudohemaphroditism and glomerulopathy), in 10%–15% of cases.8,9
- Aniridia is present in 1% of children with WT, and hemihyperplasia appears in 2%–3% of WT patients.10,11
- Genitourinary malformations (ie, cryptorchidism, hypospadias, fused [horsehoe] kidneys) are found in 5% of patients with WT.12
- If predisposition is present, routine screening for WT is recommended with physical exam and renal US every 3 months until at least 8 years of age.13,14
- Children with multifocal/bilateral disease present at a younger age than children with unilateral disease, and are often identified as part of a surveillance program.15

Treatment
- Treatment for WT ranges from observation after surgery only, to intensive chemotherapy, radiation, and surgery, depending on whether the WT is unilateral or bilateral, local stage, presence of metastases, patient age, tumor weight, biologic risk factors, histology, and clinical response to therapy.
- Consulting a radiation oncologist is recommended at time of diagnosis of WT.
- Studies of long-term survivors show these therapies are effective; however, judicious use of available therapies is necessary to maximize cure while minimizing long-term toxicities.
- Appropriate assignment of therapy to balance these goals employs an evolving system of risk stratification.
- Referral to Cancer Predisposition Consultation is appropriate for all patients with WT and strongly encouraged for patients with multifocal or bilateral WT.
- Recommend referral to infertiltiy risk/ferility preservation counseling for all patients treated with chemotherapy; strongly encourage prior to treatment with regimen M or whole abdominal irradiation (WAI).16,17

Overview

Wilms tumor (WT), also known as nephroblastoma, is the most common primary renal tumor in children. In the United States, approximately 650 children are diagnosed with WT each year.1 WT accounts for more than 90% of primary renal tumors in patients younger than 20 years and for 5% of all childhood cancers. Most children (75%) present with WT between 1 and 5 years of age, most commonly at 3 years.1,2 The incidence of WT is highest among African American children, followed by Caucasian children, and then Asian children.3–6 Five-year survival is more than 90% for children with all stages of favorable histology WT (FHWt) who receive appropriate treatment.7–10 However, survival remains poor for children with higher-stage diffuse anaplastic WT.11,12 Most children present with resectable disease in one kidney, and upfront unilateral nephrectomy is recommended for most children.9 These NCCN Guidelines for Wilms Tumor (Nephroblastoma) were first published in 2021 and only address FHWt at this time. These NCCN Guidelines will be updated at least once a year by the NCCN Wilms Tumor Panel.

Clinical Presentation

There are 2 primary ways children can be diagnosed with WT. Most children present with signs suggesting the presence of a renal condition, including abdominal swelling and/or a suspicious mass (see “Presentation,” WILMS-1 in the algorithm). Many of these children are asymptomatic, and the abdominal mass is discovered by a caretaker during routine activities such as bathing, or during examination by a pediatrician. Importantly, the abdominal mass should not be vigorously or frequently palpated to avoid rupturing the tumor. The other method of detection is through planned radiologic screening for children who have been identified as having a genetic predisposition condition and/or congenital anomalies (see “Genetic Predisposition Conditions,” page 947). Tumors discovered on routine imaging are almost always small asymptomatic lesions. Other rare presentations are found incidentally at surgery for another cause (eg, trauma, appendicitis).

Most children present with a solitary tumor in one kidney. However, 5%–13% of children have bilateral tumors and 10% have multifocal tumors in a single kidney. Most patients present with abdominal swelling and/or presence of an abdominal mass (83%) with or without abdominal
pain (37%), fever (23%), hematuria (21–25%), and hypertension (20–25%). Left-sided renal tumors can be confused on clinical examination with splenomegaly, and right-sided tumors with hepatomegaly. Less common symptoms include varicocele, hernia, enlarged testicle, congestive heart failure, hypoglycemia, Cushing syndrome, pleural effusion, acute abdomen, and acute rupture, bleeding, and shock. A healthy-appearing child is more likely to have WT, whereas an ill-appearing child with an abdominal mass may have neuroblastoma. Calcification of the tumor appears in approximately 5–10% of WT, versus approximately 60–70% of neuroblastomas. Almost 10% of patients with WT have coagulopathy (acquired von Willebrand disease). WT can extend locally to perirenal soft tissues, renal vein, and vena cava. The most common sites of hematogenous metastases include lung (81%), lung and liver (15%), and other sites (4%); spread to regional lymph nodes also occurs. However, WT rarely metastasizes to bone and brain, unlike clear cell sarcomas or other kidney cancers. Extrarenal tumors are a rare but well-recognized entity and usually are diagnosed by histology of a tumor occurring outside the kidney.

Genetic Predisposition Conditions

Genetic conditions predisposing children to develop WT may be present in 10%–20% of cases. Congenital anomalies such as aniridia, genitourinary abnormalities, gigantism, hemihyperplasia, macroglossia, or overgrowth may suggest the presence of certain genetic predisposition syndromes (see “Syndromes and Congenital Anomalies Associated with Wilms Tumor,” WILMS-I, in the algorithm). These genetic predisposition syndromes include Denys-Drash (associated with male pseudohermaphroditism, glomerulopathy), WAGR syndrome (WT, aniridia, genitourinary abnormalities, range of developmental delay), Beckwith-Wiedemann syndrome (associated with macroglossia, hemihyperplasia, gigantism, umbilical hernia), and other syndromes (see Syndromes and Congenital Anomalies Associated with Wilms Tumor [pages 970–972 in the algorithm]).

The most common germline variants involve WT1, which codes a transcription factor that is essential for normal kidney/genitourinary function.
located within 11p13 and is found in WAGR syndrome, Denys-Drash syndrome, and Frasier syndrome, and is associated with bilateral WT. WT2 is a gene located within 11p15 and results in overexpression of IGF2; it occurs in Beckwith-Wiedemann syndrome.

Numerous somatic genetic variants are associated with WT; the most common are CTNNB1, DROSHA, WT1, WTX (AMER-1), DGC8, SIX1, BCORL1, MLLT1, MYCN, SIX2; TP53 is associated with anaplastic WT. WT predisposition genes by exome sequencing include REST, TRIM28, FBXW7, NYNRIN, KDM3B, XPO5, CHEK2, and PALB2. Familial WT gene mutations (FWT1/FWT2) are rare (1%–2% of WT) and are not associated with the WT1 mutation. For children with WT, their siblings will rarely get WT (<1%). FWT1 is on chromosome 17q; FWT2 is on chromosome 19q.

Children with genetic predisposition syndromes should receive routine screening for possible development of WT. The goal is to identify and treat the WT at an early stage when the tumor is small and asymptomatic; this may hopefully be accomplished by partial nephrectomy, preserving renal tissue. It is important to note that the presence of a genetic predisposition syndrome does not mean that a child will develop WT. The different genetic syndromes are associated with various levels of risk for WT. Children with Denys-Drash have approximately a 90% risk of developing WT; Perlman syndrome, approximately a 75% risk; and WAGR syndrome, approximately a 50% risk. Approximately 10% of children with Beckwith-Wiedemann syndrome who have germline hypermethylation of 11p15 have the highest risk (24%) of developing WT. Other syndromes with a greater than 1% risk include Simpson-Golabi-Behmel at 5%–10%; Mosaic Variegated Aneuploidy (BUB1B or TRIP13), >25%, and Bohring-Opitz (ASXL1) at 7%. Germline testing should be considered for children with physical findings consistent with a predisposition condition.

The American Association for Cancer Research recommends screening in all children with a greater than 1% risk of developing WT. The NCCN Panel recommends that screening include physical examination and renal ultrasound every 3 months until children are at least 8 years of age based on the available data and clinical experience.
syndrome and often have been identified as part of a surveillance program.16-31

**Diagnosis**

The differential diagnosis for children with abdominal swelling and/or a suspicious mass includes assessment for WT, renal tumors other than WT, extrarenal tumors, and benign renal conditions (see “Principles of Abdominal Mass Evaluation” [WILMS-A] in the algorithm). Initial testing recommended for children with a suspicious abdominal mass includes (1) history and physical examination, including blood pressure measurement along with assessment for genitourinary malformations (ie, cryptorchidism, hypospadias) and other congenital anomalies associated with WT; (2) blood chemistry tests, including renal function, liver function, complete blood count, and assessment of coagulation; and (3) imaging, including abdominal ultrasound and abdominal CT or MRI (see “Initial Evaluation” [WILMS-1] in the algorithm).

Abdominal ultrasound is typically the first imaging modality used, because it is usually easily obtained, can be performed without sedation, and can most often quickly ascertain both the presence of a mass and organ of origin.54-55 Abdominal CT or MRI is then often used to evaluate the extent and involvement of the renal mass identified on ultrasound.56,57 Additional CT imaging of the pelvis may be indicated if the mass extends into the pelvis (see “Principles of Imaging” [WILMS-B] in the algorithm). The goal of imaging is to differentiate tumors of primary renal origin from extrarenal tumors and from benign renal conditions; imaging will also determine whether a child has unilateral or bilateral kidney disease and whether metastatic disease is present (see “Principles of Imaging” [WILMS-B] in the algorithm). It is also important to assess for ascites, which may raise concern for tumor rupture.

If a diagnosis of WT or any malignant renal tumor is suspected, assessment for metastatic disease should be performed. Chest CT should be done to evaluate for pulmonary nodules, which is the most common site of metastatic disease. It is always preferable to perform a chest CT unversed, and before any other sedation, to avoid the complication of atelectasis complicating the evaluation. If the organ of origin of the abdominal mass is not clear, then additional testing should be considered, such as urine catecholamines, alpha-fetoprotein, or beta-human chorionic gonadotropin. Surgery is recommended for most children with suspected unilateral WT at diagnosis. Although a

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* Conditions that predispose to the development of WT include genetic disorders such as Beckwith-Wiedemann, WAGR, Denys-Drash, Frazier, and Perlman syndromes; contralateral nephrogenic rests in children <12 months. Ten percent to 20% of WT occur in children with predisposing conditions. Children with known predisposing conditions should be screened for WT with PE and abdominal US every 3 months until at least 8 years of age. See Syndromes and Congenital Anomalies Associated with Wilms Tumor (WILMS) Consider germline testing for patients with physical findings consistent with a predisposition condition.

* Renal tumors may be unresectable at diagnosis because of tumor size, tumor thrombus extending above the hepatic veins, bilateral tumors, involvement of surrounding organs, or pulmonary function compromise from extensive metastatic disease.

* For tumors <2 cm, consider close surveillance given the challenge of differentiating WT from proliferating nephrogenic rests.

* Available online, in these guidelines, at NCCN.org.

* Pathologic confirmation of WT must be achieved by examination of the primary tumor specimen; see “Initial Treatment” [WILMS-2] in the algorithm.

* Nephrectomy and regional LN sampling are recommended as initial therapy for resectable tumors. LN sampling MUST be performed for adequate staging; recommend obtaining minimum >5 (nodes) from areas in renal hilum anatomically expected to represent nodes associated with kidney.

* See Principles of Pathology (WILMS-C).

* See Principles of Surgery (WILMS-D).

* See COG Staging of Wilms Tumor (ST-1).

* Biopsy is recommended (preferred) for diagnosis and so that molecular biomarker testing can be done earlier and used for treatment decisions. See Principles of biopsy (WILMS-E).

* Biopsy is not indicated for patients with bilateral Wilms and/or predisposing syndrome.

* Perform molecular analysis to identify loss of heterozygosity (LOH) of 1p, 16q, 11p, and 11q gain. If tumor is not WT, refer to appropriate specialist or NCCN Guidelines, if available. Other malignant renal tumors include clear cell sarcoma of the kidney, rhabdoid tumor, congenital mesoblastic nephroma, renal cell carcinoma, or renal medullary carcinoma.
clinical stage is determined before surgery, confirming the diagnosis of WT and complete staging occurs after surgery. The surgical tissue is used for complete pathologic evaluation, to assess histology, and to measure molecular markers; this information is used to determine the most appropriate postoperative treatment regimens.

Renal tumors other than WT include clear cell sarcoma of the kidney, congenital mesoblastic nephroma, renal cell carcinoma (including renal medullary carcinoma), rhabdoid tumor of the kidney, renal sarcoma, primitive neuroectodermal tumors, DICER1-associated sarcoma, desmoplastic small round cell tumors, renal neuroblastoma, and perivascular epithelioid cell tumors. Other intrabdominal malignancies that would produce a flank mass include Burkitt lymphoma, desmoplastic small round cell tumors, Ewing sarcoma, extrarenal WT, hepatoblastoma, neuroblastoma, rhabdomyosarcoma, malignant germ cell tumors, or other rare malignancies. Patients with nephroblastomatosis are at risk for WT development and those with cystic nephroma are at risk for transformation to renal sarcoma. Benign renal conditions need to be ruled out, including adrenal hemorrhage, angiomyolipoma, dysplastic kidney, hydronephrosis, metanephric tumors (ie, adenoma, stromal tumor, adenofibroma), multicystic kidney disease, polycystic kidney disease, renal hemorrhage, and renal vein thrombosis.

Pathology
To avoid potential tumor spread from malignant tumors, biopsy is not routinely recommended before upfront surgery. If the patient has a resectable unilateral renal tumor (outside the setting of known WT predisposition syndromes), upfront nephrectomy is recommended when feasible (see “Treatment of Unilateral Renal Tumor” [WILMS-2] and “Principles of Biopsy” [WILMS-E] in the algorithm). A biopsy to establish a pathologic diagnosis is strongly recommended for children with a unilateral, initially unresectable renal tumor but without a predisposing condition. For children with a biopsy showing FHWT, molecular testing on diagnostic tissue is also required to stratify therapy. Fine-needle aspiration is never recommended. Either core needle biopsies guided by interventional radiology or open biopsy can be considered.

Initiation of therapy without biopsy is the recommended approach for the subset of patients younger than 10 years with bilateral renal tumors, or patients with known predisposition syndromes and unilateral or bilateral renal tumors, because the likelihood of those tumors
representing WT is so high (and a secondary goal of therapy is to spare renal parenchyma). However, biopsy is recommended to confirm the diagnosis of FHWT (or WT without evidence of anaplasia) if a less than partial response to neoadjuvant chemotherapy is determined at week 6, especially if a biopsy was not performed at initial presentation.

Information that can be obtained through biopsy is limited. A diagnosis of FHWT obtained on a biopsy implies that focal or diffuse anaplasia is absent (see “Principles of Pathology” [WILMS-C] in the algorithm). It is important to know that anaplastic histology is often not identified in patients who had core needle or open wedge resection biopsy; however, anaplastic histology is identified when using tissue specimens from nephrectomy.58 As previously mentioned, these NCCN Guidelines only address FHWT at this time; anaplastic histology is less common.

Biopsies are also limited in distinguishing nephrogenic rests from WT. Nephrogenic rests are benign foci of embryonal kidney cells; they are precursors of WT. Hyperplastic nephrogenic rests are premalignant WT.38,59,60 Unless a rim of capsule or normal tissue is included in the sample, a core or needle biopsy cannot distinguish between nephrogenic rests and WT. In patients with small lesions suspicious for bilateral WT, it is difficult to distinguish nephrogenic rests from WT using imaging and percutaneous biopsies; MRI may be useful in this setting.61

Staging
WTs are staged both locally (reflecting abdominal spread of the tumor) and overall. Patients with any evidence of metastatic disease (most commonly lungs and liver) seen on imaging are staged as overall stage IV. Abdominal staging can be stage I (limited to renal parenchyma); stage II, demonstrating invasion into renal pelvis or renal capsule; or stage III (with tumor outside the capsule, remaining in the abdomen, including finding of positive margins, confirmation of preoperative or intraoperative tumor spill or rupture, positive lymph nodes, or tumor without upfront resection; see “Children’s Oncology Group (COG) Staging System of Wilms Tumor,” ST-1, available in this algorithm at NCCN.org). Staging is critical to overall risk stratification and therapy assignment, for both chemotherapy and RT.

The stage of renal disease is determined mainly by findings at surgery; imaging is useful but may overstage or understage patients.54–56,62 In North America, the Children’s Oncology Group (COG) staging system for WT is used (see ST-1, in the algorithm at NCCN.org). Lymph node
sampling is recommended in patients with resectable tumors to accurately stage the tumor (see “Principles of Surgery” [WILMS-D] in the algorithm).63 Local stage refers to the staging of the primary tumor, regardless of metastases (eg, stage IV with local stage III) and is used to determine the need for flank RT or whole abdominal irradiation (WAI) (see “Principles of Radiation Therapy for FHWT” [WILMS-H] in the algorithm).62

Treatment Overview

Treatment of WT ranges from surgery only to intensive chemotherapy, surgery, and RT, depending on whether the WT is unilateral or bilateral, local stage, presence of metastases, patient’s age, tumor weight, biologic risk factors, histology, and clinical response to therapy. A multidisciplinary evaluation with surgeons, pediatric oncologists, and radiation oncologists is recommended before treatment. Surgery is recommended at some point for most children with suspected WT, including those who are initially unresectable, or those with bilateral or metastatic disease. Risk assessment is done to determine the need for and type of adjuvant therapy after surgery (see Risk Assessment for FHWT [WILMS-F] in the algorithm).120,64 Most children have resectable unilateral kidney disease, and upfront unilateral nephrectomy is recommended for these children (see “Initial Treatment of Unilateral Renal Tumor” [WILMS-2] in the algorithm). Multifocal unilateral (10%) or primary bilateral renal tumors (5%–13%) are less common.

The goals of treatment are to maximize cure while appropriately risk stratifying patients to minimize long-term toxicity of therapy by selecting less-intensive treatment if possible. Long-term toxicity includes risk of secondary malignancy from chemotherapy and/or RT and development of end-stage renal disease among other long-term risks of surgery and RT. In cancer survivorship cohorts, with patients surviving many decades after diagnosis of WT, it has been shown that patients treated with historic regimens have an increased incidence (65%) of chronic health problems, 25 years after treatment; the incidence of severe conditions was 24%.65 The risk of long-term renal failure after treatment is only 0.6% in most patients with unilateral FHWT.20 The incidence of end-stage renal disease is higher (12%) in children with bilateral WT.20 Other risk factors for end-stage renal failure include radiation and congenital syndromes (eg, Denys-Drash, WAGR). Patients treated with RT have an increased risk for second malignancies.66–68
Neoadjuvant Chemotherapy
Neoadjuvant chemotherapy is recommended to shrink the tumors before surgery in children with bilateral WT, those with initially unresectable unilateral tumors, or those with predisposing conditions and either localized or metastatic unilateral renal tumors.69,70 Specific chemotherapy regimens are given for 6 weeks and then the tumor response is assessed (see “Principles of Chemotherapy” [WILMS-G] in the algorithm). Details are provided regarding neoadjuvant chemotherapy and regimens that are recommended for specific settings (see “Chemotherapy” [page 955] and “Neoadjuvant Chemotherapy” [page 956] in this Discussion).

Surgery
The surgical goals for WT include removal of all disease without rupturing the tumor(s) (ie, no gross tumor spill), accurate lymph node staging, and complete pathologic evaluation.71 Most patients with FHWt will have unilateral radical ureteronephrectomy. Surgery must include regional lymph node sampling.72–76 Nephron-sparing surgery (NSS) is reserved for patients with bilateral disease, those who are genetically predisposed, or those at other higher risk for renal failure.73,77–79 NSS is not recommended for unilateral disease if there is no genetic predisposition. In addition, testing is done on the surgical tissue specimens to confirm the diagnosis, assess for certain molecular markers (eg, loss of heterozygosity [LOH]), and to determine histology (eg, blastemal predominant, anaplasia); the results are used for risk stratification to select the appropriate adjuvant therapy.

Before treatment, it is essential to determine whether the tumor is resectable, the appropriate type and timing of surgery, and whether neoadjuvant chemotherapy is needed to shrink tumors before surgery (see “Principles of Surgery” [WILMS-D] in the algorithm). Although a clinical stage is determined before surgery, confirming the diagnosis of WT and complete staging occur after surgery. The evaluation of resectability includes assessment of the following: number and extent of tumors; and whether the patient is at risk for pulmonary compromise, tumor spill, or long-term renal failure. Contraindications to upfront surgery include tumor extension to contiguous structures; solitary kidney; extension of tumor thrombus above the hepatic veins; unacceptable anesthesia risk due to pulmonary metastases or very large abdominal tumors; and/or risk for significant morbidity or mortality, gross tumor spill, residual tumor, or long-term renal...
Metastatic unilateral renal tumor with predisposing condition

- Regimen VAD
  - (re-image week 6)
  - Partial or total nephrectomy with regional LN sampling, Pathology is FHWT
  - Unresectable
  - Continue Regimen VAD
    - (re-image week 12)

- Regimen DD4AP

- Switch to Regimen DD4AP
  - Not blastemal predominant
  - Blastic predominant

- Switch to Regimen P

- Post-op: Flank or whole abdomen for local stage III
  - Whole lung for lung metastases
  - Other sites

1 See Principles of Pathology (WILMS-C).
2 See Principles of Surgery (WILMS-D).
3 See Principles of Chemotherapy for FHWT (WILMS-G).
4 RT is often given 10 to 14 days after surgery. However, consider patient factors when deciding about the timing of RT (eg, age of patient, need to assess response of lung metastases to chemotherapy, when giving whole abdomen and whole lung RT). Local stage III refers to staging of the primary tumor regardless of metastases.
5 If feasible, resect metastatic tumors at the time of primary nephrectomy.
6 Reimaging primary and metastatic sites.
7 Uptake biopsy or resection is discouraged.
8 No surgery if there is a CR on reimaging.
9 If response is <PR at week 6, biopsy the tumor to confirm diagnosis of FHWT (or WT without evidence of anaplasia on biopsy), especially if biopsy not done at initial presentation.

Available online, in these guidelines, at NCCN.org.

Risk-Based Assessment

Risk stratification is used to determine the most appropriate therapy to minimize both risk of recurrence and long-term toxicity from treatment. Tumor histology, histopathologic and surgical stage, molecular markers (LOH of 1p and 16q), presence of metastatic and/or bilateral disease, and clinical factors, including age of the child, presence or absence of predisposition syndromes, and response of pulmonary lesions to neoadjuvant chemotherapy, are all used in risk stratification (see “Initial and Final Risk Assessment for Favorable Histology Wilms Tumor” [WILMS-F] in the algorithm). Risk stratification has evolved using data from large collaborative clinical trials. The presence of specific molecular biomarkers—such as LOH of 1p and 16q, 11p15, and 1q gain—identified in tumor tissue is associated with increased risk of relapse after initial therapy. Cytogenetic and molecular testing—for 1q gain and/or LOH of 1p and 16q—is recommended for all children with newly diagnosed FHWT. Other molecular markers may be reported after testing; however, at this time, data do not support the use of other markers for risk stratification. The use of specific molecular markers for risk-based assessment is evolving based on clinical trial data.
Several segmental chromosomal aberrations correlate with increased risk, including LOH of 1p and 16q, gain of 1q, and LOH and LOI of 11p15. To date, only alteration of therapy for combined LOH of 1p and 16 has been studied in a prospective clinical trial. However, the presence of certain unfavorable biomarkers clearly identifies children with potential increased risk when treated with therapy deintensification (patients classified with very-low-risk WT found to have LOH of 11p15, or patients with stage IV disease and rapid complete response of pulmonary metastases found to have 1q gain). Therefore, clinicians should consider assessing for all of these biomarkers in all children with FHWT.

Initial risk assessment is based on age and clinical, radiographic, surgical, and pathologic findings. Final risk assessment is based on the initial risk factors plus presence or absence of unfavorable molecular biomarkers and the response of the lung metastases at week 6, if applicable. Factors indicating need for more intensive therapy include: older age at diagnosis, unfavorable/anaplastic histology, higher stage, larger tumor weight, unfavorable molecular biomarkers, and incomplete lung nodule response to neoadjuvant chemotherapy at week 6. Excellent outcomes have been achieved for all stages of FHWT, including those patients with higher stage disease, unfavorable biomarkers, and adverse clinical factors, such as incomplete lung response; these patients are stratified to more intensive therapy with additional chemotherapy agents and RT.

Chemotherapy
Data show that neoadjuvant and/or adjuvant chemotherapy in combination with surgery (with or without RT) improves survival for most children with WT.11,61,91,92 Chemotherapy regimens include (1) EE4A (vincristine and actinomycin); (2) DD4A (vincristine, actinomycin, and doxorubicin); (3) VAD (vincristine, dactinomycin, and doxorubicin); (4) regimen M (vincristine, dactinomycin, doxorubicin, cyclophosphamide, and etoposide); and (5) regimen I (vincristine, doxorubicin, cyclophosphamide, and etoposide) (see “Principles of Chemotherapy” [WILMS-G] in the algorithm). Although many of the same agents are used in the different regimens, the schedule varies. Some of the chemotherapy regimens may be used for neoadjuvant or adjuvant chemotherapy. In the National Wilms Tumor Study (NWTS), chemotherapy was first given at week 0; however, COG chemotherapy

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starts at week 1. The number of doses of chemotherapy is the same.

In the EE4A regimen, 13 doses of vincristine and 7 doses of dactinomycin are administered over 18 weeks. In the DD4A regimen, 15 doses of vincristine (10 weekly, 5 every 3 weeks), 5 doses of dactinomycin, and 4 doses of doxorubicin (cumulative dose 150 mg/m²) are administered over 24 weeks with alternating doses of dactinomycin and doxorubicin every 3 weeks. In the VAD regimen, 6 to 12 doses of vincristine, 2 to 4 doses of dactinomycin, and 2 to 4 doses of doxorubicin (cumulative dose 70–140 mg/m²) are administered over 6 to 12 weeks based on treatment response and timing of surgery; this regimen is only used in the neoadjuvant setting for patients who are candidates for NSS. In the VAD regimen, dactinomycin and doxorubicin are given together. Regimen M consists of 9 doses of vincristine, 5 doses of dactinomycin, 5 doses of doxorubicin (cumulative dose 150 mg/m²), 4 courses of 5 daily doses of cyclophosphamide, and 4 courses of 5 daily doses of etoposide over 24 weeks. Dactinomycin and doxorubicin are given together, and cyclophosphamide and etoposide are given together. Regimen M starts at week 7 for tumors requiring augmentation of therapy based on molecular markers or response of lung metastases to 6 weeks of DD4A. Regimen I consists of 9 doses of vincristine, 4 doses of doxorubicin (cumulative dose 180 mg/m²), 7 courses of 3 to 5 daily doses of cyclophosphamide, and 3 courses of 5 daily doses of etoposide. Doxorubicin and 3 daily doses of cyclophosphamide are given together, and 5 daily doses of cyclophosphamide and etoposide are given together. Depending on when surgery is done, regimen I starts at week 7, 9, or 12 for tumors requiring augmentation of therapy based on histology.

**Neoadjuvant Chemotherapy**

Neoadjuvant chemotherapy regimens are used for patients with a contraindication to or inability to undergo upfront nephrectomy and include (1) EE4A, (2) DD4A, or (3) VAD (see “Principles of Chemotherapy” [WILMS-G] in the algorithm). The specific neoadjuvant regimens depend on the setting and are described in the algorithm (see “Principles of Chemotherapy” [WILMS-G] in the algorithm). At week 6 of neoadjuvant chemotherapy, the tumor(s) are reimaged to determine if they are now resectable. If present, pulmonary lesions can be used to assess response to neoadjuvant chemotherapy. Persistent pulmonary lesions may be considered for removal after 6 weeks of chemotherapy, if they can be removed without...
significant morbidity. In certain settings, if patients have a complete response at week 6 of chemotherapy then surgery is not needed. If there is less than a partial response after chemotherapy, an open biopsy should be considered to assess for anaplasia or to confirm diagnosis of WT. Chemotherapy is continued for a total of 12 weeks if the patient has a partial response at week 6 but is not a candidate for surgery at week 6, including NSS. However, surgery is recommended by week 12 of neoadjuvant chemotherapy based on clinical trial data showing that continuing chemotherapy beyond 12 weeks does not yield continued tumor shrinkage.70,95

Adjuvant Chemotherapy
Adjuvant chemotherapy regimens include (1) EE4A, (2) DD4A, (3) regimen M, and (4) regimen I (see “Principles of Chemotherapy” [WILMS-G] in the algorithm). The precise regimens that are used depend on the setting and risk stratification; for example, adjuvant chemotherapy with EE4A is recommended for children with unilateral FHWT at standard risk after upfront nephrectomy. Adjuvant chemotherapy should be initiated no later than 14 days after nephrectomy. As previously mentioned, risk stratification is used to determine the most appropriate adjuvant chemotherapy regimens for patients (see “Initial and Final Risk Assessment for Favorable Histology Wilms Tumor” [WILMS-F] in the algorithm). If RT is also required, then timing of adjuvant chemotherapy should be coordinated to avoid administering full doses of dactinomycin or doxorubicin with radiation.

Radiation Therapy
The NCCN Panel recommends consulting a radiation oncologist when WT is suspected to allow adequate time for radiation planning if needed, including coordination with chemotherapy administration. Adjuvant RT is recommended for patients at higher risk after surgery but not for those with low stage, lower risk disease. Depending on the setting, adjuvant flank RT or WAI with or without whole lung irradiation may be recommended. For example, adjuvant flank RT is recommended for patients who have local stage III FHWT or stage IV with local stage III.96 Local stage III refers to staging at the primary site regardless of metastases [see “Children’s Oncology Group (COG) Staging of Wilms Tumor,” available in these guidelines at NCCN.org]. Biopsy alone does not upstage a tumor to stage III for determining whether to give adjuvant RT. Testicular shielding is recommended for most boys receiving
adjuvant flank RT. WAI is recommended for patients with cytology-positive ascites, any preoperative tumor rupture, peritoneal seeding, and diffuse surgical spillage.\(^{81,97}\) Supplemental boost irradiation is recommended for gross residual disease that remains after adjuvant flank RT or WAI. For each setting, the algorithm provides detailed recommendations for adjuvant flank RT, WAI, and whole lung irradiation; the RT target volumes, techniques, and schedules are also provided in the supplementary pages (see “Principles of Radiation Therapy for FHWT” [WILMS-H] in the algorithm).

Adjuvant whole lung irradiation is recommended for patients with lung metastases; intensity-modulated RT (IMRT) or anteroposterior/posteroanterior (AP/PA) may be used.\(^{98-100}\) However, adjuvant whole lung irradiation can be delayed until week 6 of chemotherapy in select patients with FHWT who only have metastases in the lung. If patients with FHWT but no 1q gain and no LOH at 1p and 16q have a complete response of their lung metastases to 6 weeks of chemotherapy, then whole lung irradiation is not recommended; however, whole lung irradiation is recommended for patients with 1q gain or LOH at 1p and 16q. Studies show that starting RT later than 14 days after surgery is associated with an increased risk of abdominal recurrence in patients without metastases.\(^{101}\) The NCCN Panel recommends that RT should start ideally by day 10 after surgery but no later than day 14.\(^{102-103}\) However, patient factors should be considered when deciding about the timing of adjuvant RT, including age and need to assess the response of lung metastases to chemotherapy when giving WAI and whole lung irradiation. If RT is being considered, the timing of RT should be coordinated with chemotherapy to avoid the coadministration of full doses of dactinomycin or doxorubicin with RT (see “Principles of Chemotherapy” [WILMS-G] in the algorithm). Dactinomycin or doxorubicin can be administered at full doses before starting RT.

Treatment: Individual Settings

The NCCN recommendations for treatment of children with FHWT are based on clinical trial data from the COG, and older NWTS trials, that have been used to identify treatment regimens that can increase survival and decrease relapse, morbidity, and long-term adverse events.\(^{104}\) The clinical trials performed in Europe by the International Society of Pediatric Oncology (SIOP) have typically used neoadjuvant therapy followed by surgery even if the tumor was initially resectable. The only setting...
where NCCN recommendations are based on SIOP guidelines is the management of unilateral, initially unresectable tumors (see “Localized Unilateral Renal Tumor With a Predisposing Condition,” page 966). By treating for presumed diagnosis, SIOP accepts that a percentage of patients will be misdiagnosed as having WT (ie, false positive). NWTS/COG believe it is important to establish histology at the start because not all renal tumors are WT. COG treatments are also based on inclusion stage, and on genetic risk factors in the tumor at diagnosis, requiring tumor tissue. Most children with WT have unilateral disease and upfront nephrectomy with regional lymph node sampling is recommended followed by adjuvant therapy, which is selected based on an assessment of the risk after surgery (see “Initial and Final Risk Assessment for Favorable Histology Wilms Tumor” [WILMS-F] in the algorithm).

Molecular testing of tumor tissue (eg, LOH and 1q gain) is recommended to use in risk assessment for all newly diagnosed patients with FHWT. Risk Assessment for Favorable Histology Wilms Tumor” [WILMS-F] in the algorithm). Final risk assessment includes tumor biology and response of pulmonary nodules to initial therapy; final risk assessment is used when deciding whether to continue the initial chemotherapy or switch to more intensive (augmented) chemotherapy. The goal of therapy is to avoid relapse. Risk of toxicity with intensification needs to be balanced with risk of relapse, and consequent need for very intensive therapy, with much less chance of cure after relapse. If patients with FHWT relapse after initial treatment, the salvage rate depends on the number of drugs administered with initial chemotherapy and whether RT was given with the initial treatment. Posttreatment imaging surveillance should evaluate the chest and abdomen and may consist of CT, MRI, ultrasound, or chest X-ray, which is most often done every 3 months for 2 years and then every 6 months for an additional 2 years.
Clinical trial data used to support the NCCN recommendations in different settings of FHWT are described in the following sections. Patients with very-low-risk, low-risk, and standard-risk FHWT were studied in the NWTS-5 and AREN0532 trials.112,113 Patients with higher risk FHWT were studied in AREN0533.92 Clinical trial data from NWTS-5, AREN0532, and AREN0533 are used to support the NCCN recommendations for children with unilateral renal tumors who do not have predisposing conditions.105 Children with localized or metastatic unilateral renal tumor and a predisposing condition were studied in AREN0534.114 Patients with bilateral FHWT were also assessed in the AREN0534 trial.61

Unilateral Renal Tumors

Resectable Unilateral Renal Tumor With Very Low Risk

Clinical Trial Data
Children with resectable unilateral WT typically receive upfront nephrectomy followed by adjuvant therapy.115 However, data suggested that adjuvant therapy could be omitted in children who were deemed at very low risk after upfront nephrectomy.116 The National Wilms Tumor Study 5 (NWTS-5) trial assessed upfront nephrectomy followed by observation only in 77 children at very low risk after surgery.113 These children were deemed at very low risk because they were younger than 2 years, their tumor weight was less than 550 g, and they had stage I disease. These 77 children who only had surgery were compared with 111 children who had surgery plus adjuvant chemotherapy with EE4A. The estimated 5-year event-free survival for observation was 84% (95% CI, 73%-91%); it was 97% (95% CI, 92%-99%; P = .002) for EE4A. The children who relapsed after surgery alone were successfully treated with more intensive therapy than EE4A (doxorubicin and RT). The estimated 5-year overall survival for surgery only was 98% (95% CI, 87%-99%); it was 99% (95% CI, 94%-99%) for EE4A (P = .70). At 8 years, the overall survival was still excellent (98.7%).

Data suggested that certain molecular markers in the tumors could be used to identify children who might be at higher risk after surgery alone; adjuvant chemotherapy could be used to decrease the risk of relapse in this subset.90 The AREN0532 study assessed observation alone after upfront nephrectomy in children at very low risk after surgery.112 The trial assessed whether observation only after surgery alone was associated with an acceptable level of survival and whether certain tumor molecular markers...
were associated with increased risk of relapse. The goal was to avoid adjuvant chemotherapy with EE4A, if feasible, and thus decrease toxicity. For the 116 children observed after surgery alone, the overall survival was 100%; the estimated 4-year event-free survival was 89.7% (95% CI, 84.1%–95.2%). Tumors with 11p15 LOH or LOI were associated with a 20%–25% risk of recurrence, whereas the relapse risk was only 3% in tumors without 11p15 LOH or LOI. One patient who relapsed had combined LOH of 1p and 16q in addition to 11p15 LOH. The greatest difference between the NWTS very-low-risk cohort and the COG very-low-risk cohort was prospective central review for stage and histology, and requirement of lymph node sampling. Patients were not excluded for finding of unfavorable biology and outcomes were still excellent. Retrospective analysis showed impact of LOH/LOI of 11p15.

**NCCN Recommendations**

Children with FHWT fitting the criteria of the COG very-low-risk group can be observed without adjuvant therapy or receive adjuvant chemotherapy with EE4A (see “Unilateral FHWT, Primary Nephrectomy” [WILMS-3] in the algorithm). EE4A is recommended for children with very-low-risk clinical features but with unfavorable prognostic molecular markers (1p15 LOH or LOI or combined LOH at 1p and 16q). Observation only after surgery is recommended for children without these unfavorable biomarkers. Postoperative RT is not recommended for stage I disease.

**Low Risk Clinical Trial Data**

The NWTS-5 trial showed that certain unfavorable tumor molecular markers were associated with poorer relapse-free survival in children with stage I and II FHWT. When treated with adjuvant EE4A, children with stage I or II FHWT with combined LOH at 1p and 16q had a 4-year relapse-free survival of 74.9% versus 91.2% for those without these markers ($P = .001$). The AREN0532 and AREN0533 trials showed that intensifying (ie, augmenting) adjuvant therapy to DD4A improved relapse-free survival for patients with stage I or II FHWT with combined LOH at 1p and 16q compared with historical controls from NWTS-5.

For patients with stage I or II FHWT plus combined LOH 1p and 16q, the estimated 4-year event-free survival was 68.8% (95% CI, 55.2%–82.3%) with EE4A on NWTS-5.
and 87.3% (95% CI, 75.1%–99.5%) with DD4A on AREN0532 (P=.042). All 4 relapses occurred in patients with stage II FHWT who received DD4A. For patients with stage I or II FHWT and LOH at 1p and 16q, the estimated 4-year overall survival was 91.6% (95% CI, 83.6%–99.6%) with EE4A on NWTS-5 and 100% with DD4A on AREN0532 (P=.096). It is important to note that the AREN0532 and AREN0533 trials were not sufficiently powered to detect statistical differences in overall survival with augmented therapy (DD4A), because combined LOH 1p and 16q occurs at low frequencies (4.27% [49/1147]) in patients with stage I or II FHWT. The impact of intensification for finding of 1q gain has not been studied.

**NCCN Recommendations**

Children with FHWT at low risk after surgery can receive adjuvant therapy with regimen EE4A or switch to regimen DD4A (see “Unilateral FHWT, Primary Nephrectomy” [WILMS-3] in the algorithm). DD4A is recommended for children with low-risk tumors that express combined LOH 1p and 16q. EE4A can be continued for children with tumors that do not have these unfavorable biomarkers. Postoperative RT is not recommended for local stage I and II disease.

**Standard Risk and Higher Risk**

**Clinical Trial Data**

The NWTS-5 trial showed that certain unfavorable tumor molecular markers were associated with poorer relapse-free survival in children with stage III or IV FHWT. When treated with adjuvant DD4A, children with stage III or IV FHWT with combined LOH at 1p and 16q had a 4-year relapse-free survival of 65.9% versus 83% for those without these unfavorable biomarkers (P=.01). AREN0533 showed that augmenting adjuvant therapy to regimen M at week 7 improved relapse-free survival for 51 patients with stage III or IV FHWT plus combined LOH 1p and 16q compared with historical controls from NWTS-5. For patients with stage III WT plus combined LOH 1p and 16q treated with regimen M, the estimated 4-year event-free survival was 93.6% (95% CI, 84.6%–100%). For patients with stage IV WT plus combined LOH 1p and 16q treated with regimen M, the estimated 4-year event-free survival was 95.0% (95% CI, 84.9%–100%) and the estimated 4-year overall survival was 100%. Four relapses and two second malignancies occurred in patients with stage III or IV FHWT treated with regimen M.
For patients with stage III or IV FHWT plus combined LOH 1p and 16q treated with DD4A, the estimated 4-year event-free survival was 61.3% (95% CI, 44.9%–77.6%) for NWTS-5 and 90.2% (95% CI, 81.7%–98.6%) with regimen M on AREN0532 and AREN0533 (P < .001). For patients with stage III or IV FHWT plus combined LOH 1p and 16q, the estimated 4-year overall survival was 86.0% (95% CI, 74.5%–97.5%) with DD4A on NWTS-5 and 96.1% (95% CI, 90.5%–100%) with regimen M on AREN0532 and AREN0533 (P = .087). Some clinicians have concerns regarding the comparability of historical control data that were used to justify augmenting therapy with regimen M due to the historical control group that was used.

Due to the low frequency (6.01% [82/1364]) of combined LOH 1p and 16q in patients with stage III or IV FHWT, the AREN0532 and AREN0533 trials were not powered to detect statistical differences in overall survival with augmented therapy. A different molecular marker, 1q gain, occurs more frequently and is associated with inferior survival; 1q gain has been assessed in several studies, including patients with stage IV FHWT (8,89,92,119). The marker, 1q gain, identifies higher risk patients with isolated lung metastases (ie, lung-only metastases) who should receive whole lung irradiation even if their lung metastases have completely responded to initial DD4A. However, lung RT can be omitted in patients with lung-only metastases and no unfavorable markers (ie, no 1q gain, no combined LOH 1p and 16q) who have a complete response of their lung metastases to initial DD4A. Although 1q gain has been identified as an adverse prognostic factor, no prospective studies have been done to show that intensification of therapy is more effective. The impact of 1q gain is greatest in higher risk; it is up to the clinician and family to consider risks and benefits of intensification with known treatment regimens. 1q gain can be used to identify patients who are not appropriate for deintensification of therapy, such as patients with rapid complete response of lung nodules. Those with rapid complete response and 1q gain have a high risk of relapse if they are not treated with RT and DD4A (ie, event-free survival of 57%).

Regimen M may cause morbidity (eg, enhanced myelo-suppression) and late effects including secondary leukemia (caused by cyclophosphamide and etoposide) and infertility (caused by cyclophosphamide). How-ever, regimens to treat relapse are also associated with late effects, such as cardiomyopathy, second malignancy,
and renal insufficiency. In patients who have stage III FHWT and who relapse, the salvage rate is 50% or less. Thus, clinicians need to balance the possibility of late effects with regimen M versus the possibility of relapse without regimen M and also side effects associated with the salvage regimens. The NCCN Panel recommends referral for infertility risk/fertility preservation counseling for all patients treated with chemotherapy; counseling is strongly encouraged before treatment with regimen M or WAI.

**NCCN Recommendations**

DD4A is recommended as initial therapy for patients with stage III FHWT classified as standard risk after the initial risk assessment. At week 6 of DD4A, the results of molecular testing from diagnostic tissue are used to determine the final risk assessment and to select further therapy. Switching to augmented therapy with regimen M is recommended for patients with combined LOH of 1p and 16q who are at increased risk. Flank RT or WAI is recommended for patients with local stage III. If RT is being considered, the timing of RT should be coordinated with chemotherapy to avoid the coadministration of full doses of dactinomycin or doxorubicin with RT.

DD4A is recommended as initial therapy for patients with stage IV FHWT classified as higher risk. At week 6 of DD4A, results of molecular testing from diagnostic tissue and of imaging are used to determine the final risk assessment and to select further therapy. Switching to augmented therapy with regimen M is recommended for patients with (1) combined LOH of 1p and 16q; or (2) lung metastases that have slow incomplete response after 6 weeks of chemotherapy. DD4A is continued after week 6 in patients with lung-only metastases that respond completely after 6 weeks of chemotherapy and in patients with extrapulmonary metastases (with or without lung metastases). However, regimen M is associated with a greater risk of toxicity, including second cancers and infertility due to cyclophosphamide and etoposide. Although patients with extrapulmonary metastases were switched to regimen M in a recent study (AREN0533), the results have not been published yet; therefore, this regimen is not currently recommended in this setting.

Postoperative flank RT or WAI is recommended for patients with local stage III disease who have higher risk disease. Whole lung irradiation may also be recommended depending on the setting. For example, whole lung irradiation is recommended for patients with tumors that spread to the lungs. The timing of RT should be coordinated with chemotherapy to avoid the coadministration of full doses of dactinomycin or doxorubicin with RT.
that express 1q gain or combined LOH at 1p and 16q. Whole lung irradiation is recommended for all patients who present with pulmonary metastesas, with the exception of those patients with complete response of pulmonary lesions at 6 weeks, that also do not have either combined LOH of 1p and 15q, 1q gain, or other extrapulmonary metastesas.

Initally Unresectable Unilateral Renal Tumor With No Predisposing Condition

Clinical Trial Data

Clinical trial data from NWTS-5, AREN0532, and AREN0533 are used to support the NCCN recommendations for children with unilateral renal tumors that are initially unresectable if there are no predisposing conditions. Upfront biopsy with delayed nephrectomy should be limited to specific settings where upfront nephrectomy is contraindicated, such as patients with an inferior vena cava (IVC) thrombus above the level of the hepatic veins. Upfront biopsy is recommended for all patients meeting the criteria for delayed resection, to determine histology, establish a diagnosis of WT, and obtain molecular biomarkers to guide therapy. At week 6 of DD4A, the tumor is reimaged and depending on the tumor response, patients have either nephrectomy with regional lymph node sampling or continue with DD4A. Chemotherapy is continued for a total of 12 weeks if the patient has some response at week 6 but is not deemed a candidate for surgery. However, surgery is recommended for all patients at a maximum of week 12 of neoadjuvant chemotherapy based on clinical trial data showing that continuing chemotherapy beyond 12 weeks usually does not yield continued tumor shrinkage.

After pathology confirms that patients have FHW, molecular and imaging results are used to determine the final risk assessment and to select further therapy. Patients either continue regimen DD4A or switch to regimen M, depending on the risk assessment. Augmented therapy with regimen M is recommended for patients who are at
increased risk, including those with (1) combined LOH at 1p and 16q, or (2) metastases only in the lung that have slow incomplete response to neoadjuvant chemotherapy. Although patients with extrapulmonary metastases were switched to regimen M in a recent study (AREN0533), the results have not been published yet; therefore, regimen M is not currently recommended in this setting. Postoperative flank RT or WAI is recommended for patients with local stage III disease. Whole lung irradiation is recommended in patients whose lung metastases have not responded to 6 weeks of neoadjuvant chemotherapy, patients whose tumor expresses 1q gain or combined LOH at 1p and 16q, and patients with lung and extrapulmonary metastases. If RT is being considered, the timing of RT should be coordinated with chemotherapy to avoid the coadministration of full doses of dactinomycin or doxorubicin with RT.

Localized Unilateral Renal Tumor With a Predisposing Condition

Clinical Trial Data

The AREN0534 trial assessed neoadjuvant therapy with EE4A (or VAD if an upfront biopsy was done) for 6 weeks followed by either surgery or continuation of EE4A (or VAD) for an additional 6 weeks in 34 evaluable children who had localized unilateral renal tumor and who were predisposed to develop metachronous disease because of hemihyperplasia or a genetic predisposition syndrome, such as Beckwith-Wiedemann syndrome; the trial also included children with multiple renal tumors in one kidney (multicentric) and with unilateral renal tumor and contralateral nephrogenic rest(s) (of any size) in children younger than 12 months of age.114 This trial also assessed treatment in children with metastatic unilateral WT and bilateral WT (see “Metastatic Unilateral Renal Tumor With a Predisposing Condition,” page 969 and “Bilateral Renal Tumors,” page 970). Patients with localized unilateral renal tumor received neoadjuvant therapy with VAD if an upfront biopsy showed FHWT.

Goals of AREN0534 included performing surgery by week 12, improving the event-free survival (compared with NWTS-5), and decreasing the need for total nephrectomy by using NSS to preserve as much renal function as possible, because these children are at risk for end-stage renal failure.114 Surgery was done after either 6 weeks or 12 weeks of neoadjuvant chemotherapy based on the response at 6 weeks; continuing chemotherapy beyond
12 weeks usually does not yield continued tumor shrinkage. If there was a less than partial response at week 6, a total nephrectomy was performed before continuing chemotherapy based upon histology. Of the 32 patients who underwent surgery, 15 had surgery at week 6 and 17 had surgery at week 12. Orchidectomy can be done to determine the histology—FHWT or WT without evidence of anaplasia—before continuing with neoadjuvant chemotherapy. By 12 weeks of neoadjuvant chemotherapy, most patients had a partial response (62% [21/34]) or stable disease (32% [11/34]); 2 patients had a complete response; there was no progressive disease. Surgery included partial or total nephrectomy with regional lymph node sampling followed by determination of the pathology. A total nephrectomy was done if patients had a less than partial response to neoadjuvant chemotherapy at week 6. Partial nephrectomies were done in 63% (20/32) of patients.

After surgery, risk assessment was completed using histology results and stage to select further therapy including adjuvant chemotherapy with or without RT. Use of molecular biomarkers to direct therapy was not included in AREN0534; however, outcomes were excellent despite not augmenting chemotherapy for the presence of unfavorable biomarkers. The 4-year event-free survival was 94% (95% CI, 85.2%–100%) and the 4-year overall survival was 100%. Patients with stage I or II FHWT without blastemal-predominant histology are at lower risk of relapse after surgery; therefore, they continued receiving less intensive adjuvant therapy with EE4A and did not receive adjuvant RT. Patients with blastemal-predominant histology following neoadjuvant chemotherapy are at greater risk of relapse after surgery; therefore, they switched to more intensive adjuvant therapy with DD4A or regimen I, depending on the stage.

**NCCN Recommendations**

Neoadjuvant therapy with the EE4A regimen is recommended for children with a localized unilateral renal tumor and a predisposing condition. Upfront biopsy or resection is discouraged in this setting. However, if an upfront biopsy was done, then the VAD regimen is used as neoadjuvant therapy. At week 6 of EE4A (or VAD), the tumor is reimaged and depending on the response, patients (1) have no surgery if there was a complete response to EE4A (or VAD); (2) have partial nephrectomy with regional lymph node sampling if the tumor is...
now resectable; (3) continue with EE4A (or VAD) for a total of 12 weeks if the tumor is still unresectable but shows at least a partial response; or (4) have complete nephrectomy for those with less than a partial response. If there is a less than partial response at week 6, the tumor should be biopsied to confirm a diagnosis of FHWT (or WT without evidence of anaplasia) before continuing with EE4A (or VAD). Surgery is done at 12 weeks after neoadjuvant chemotherapy based on data showing that continuing chemotherapy beyond 12 weeks usually does not yield continued tumor shrinkage.14,95 A partial or total nephrectomy with regional lymph node sampling is recommended at week 12.61 The decision to do a partial versus total nephrectomy is based on tumor size, location in the kidney, extension into the kidney collecting system, and other factors. The only setting where NCCN recommendations are based on SIOP guidelines is the management of unilateral, initially unresectable tumors where COG has borrowed from SIOP data regarding the recommendation to change chemotherapy if histology is blastemal predominant at delayed nephrectomy. After pathology confirms that patients have FHWT, histology (ie, blastemal predominant) and staging are used to select further therapy (see “Children’s Oncology Group (COG) Staging of Wilms Tumor,” available in these guidelines at NCCN.org). If upfront biopsy was done and patients received VAD, the tumor is considered to be stage III for determining the adjuvant chemotherapy regimen. Patients either continue regimen EE4A, switch to regimen DD4A, or switch to regimen I, depending on the risk assessment. If patients have a complete response at 6 weeks to regimen EE4A, then they continue EE4A and do not receive RT.144 Switching to regimen DD4A is recommended for patients who are at increased risk, including those with (1) stage III FHWT without blastemal predominant histology; or (2) stage I FHWT with blastemal predominant histology. Augmented therapy with regimen I is recommended for patients with blastemal predominant histology and stage II or III FHWT, because they are at the greatest risk. Regimen M has not been studied in this population. RT is often given 10 to 14 days after surgery; the patient’s age and other factors are considered when deciding about the timing of RT. Local stage III refers to the staging at the primary tumor, regardless of metastases, and is used to determine the need for flank RT or WAI (see “Principles of Radiation Therapy for FHWT” [WILMS-H] in the algorithm). Neoadjuvant chemotherapy is not a criterion for upstaging to stage III in this setting. Biopsy alone in this situation
does not upstage a tumor to stage III for determining whether to give RT.

Metastatic Unilateral Renal Tumor With a Predisposing Condition

Clinical Trial Data

The AREN0534 study assessed neoadjuvant therapy with VAD for 6 weeks followed by either surgery or continuation of VAD for an additional 6 weeks in children who had metastatic unilateral renal tumor and who were predisposed to develop metachronous bilateral disease because of hemihyperplasia or a genetic syndrome, such as Beckwith-Wiedemann syndrome. One of the 32 patients who underwent surgery had stage IV disease. This trial also assessed treatment in children with localized unilateral WT and bilateral WT (see “Localized Unilateral Renal Tumor With a Predisposing Condition,” page 966 and “Bilateral Renal Tumors,” page 970). Additional details about AREN0534 are provided in the previous section (see “Localized Unilateral Renal Tumor With a Predisposing Condition,” page 966).

After surgery, risk assessment was done using histology results and stage to select adjuvant therapy, including RT. Use of molecular biomarkers to direct therapy was not included on AREN0534; however, outcomes were excellent despite not augmenting chemotherapy for the presence of unfavorable biomarkers. Patients without blastemal histology are at lower risk of relapse after surgery; therefore, they switched from VAD to adjuvant therapy with DD4A and adjuvant RT for local stage 3 disease. Patients with blastemal histology after neoadjuvant chemotherapy are at greater risk of relapse after surgery; therefore, they switched to more intensive adjuvant therapy with regimen I and adjuvant RT for local stage 3 disease.

NCCN Recommendations

Neoadjuvant therapy with the VAD regimen is recommended for children with a predisposing condition and a unilateral renal tumor that has metastasized. Upfront biopsy or resection is discouraged in this setting. At week 6 of VAD, the tumor is reimaged and depending on the response, patients (1) have no surgery if there was a complete response to VAD; (2) have partial nephrectomy at week 6 if the tumor is now resectable; or (3) continue with VAD for a total of 12 weeks if the tumor is unresectable but shows at least a partial response. If there is a less than partial response at week 6, the tumor should be biopsied to confirm a diagnosis of FHWT (or WT without...
evidence of anaplasia) before continuing with VAD. Surgery is done at 12 weeks after neoadjuvant chemotherapy based on data showing that continuing chemotherapy beyond 12 weeks usually does not yield continued tumor shrinkage. A partial or total nephrectomy with regional lymph node sampling is recommended at week 12. The decision to do a partial versus total nephrectomy is based on tumor size, location in the kidney, extension into the kidney collecting system, and other factors.

After pathology confirms that patients have FHWT, histology (ie, blastemal predominant) is used to select further therapy. Use of molecular biomarkers to direct therapy has not been studied in this setting; outcomes on ARENO0534 were excellent despite not augmenting chemotherapy for the presence of unfavorable biomarkers. Patients either switch to regimen DD4A or switch to regimen I, depending on the risk assessment. Switching to regimen DD4A is recommended for patients without blastemal predominant histology or those with a complete response at 6 weeks. Augmented therapy with regimen I is recommended for patients with blastemal predominant histology because they are at greater risk. Regimen M has not been studied in this population. RT is often given 10 to 14 days after surgery; the patient’s age and other factors are considered when deciding about the timing of RT. Local stage III refers to the staging at the primary tumor, regardless of metastases, and is used to determine the need for flank RT or WAI (see “Principles of Radiation Therapy for FHWT” in the algorithm). Biopsy alone does not upstage a tumor to stage III for determining whether to give RT. Neoadjuvant chemotherapy is not a criterion for upstaging to stage III in this setting. Omission of whole lung irradiation based on the response of lung metastases at week 6 of neoadjuvant chemotherapy has not been studied in this group of patients.

Bilateral Renal Tumors
Children with bilateral WT have a greater incidence of predisposition syndromes and a greater risk for developing a metachronous tumor after treatment, probably because of an increased incidence of nephrogenic rests. Children who present at a younger age are more likely to have multifocal/bilateral disease and their tumors are often identified as part of a surveillance program. When compared with unilateral WT, children with bilateral WT have decreased survival because of understaging and increased incidence of anaplastic histology.
SYNDROMES AND CONGENITAL ANOMALIES ASSOCIATED WITH WILMS TUMOR

- Other syndromes (cont.)
  - Perlman syndrome26 (MIM: 614184): Inheritance autosomal recessive (AR)
  - Gene DIS3L2
    - Affected children are large at birth, are hypotonic, and show organomegaly, characteristic facial dysmorphism (inverted V-shaped upper lip, prominent forehead, deep-set eyes, broad and flat nasal bridge, and low-set ears), renal anomalies (nephromegaly and hydronephrosis), frequent neurodevelopmental delay, and high neonatal mortality.
  - Bohring-Optiz syndrome27-28 (MIM: 605039)
    - Inheritance AD
  - Gene ASXL1
    - Malformation syndrome characterized by severe intrauterine growth retardation, poor feeding, profound mental retardation, trigonocephaly, prominent metopic suture, exophthalmos, nevus flammeus of the face, upslanting palpebral fissures, hirsutism, and flexion of the elbow and wrists with deviation of the wrists and metacarpophalangeal joints.
  - MULIBREY (Muscle, Liver, Brain, and Eyes) Nanism syndrome29 (MIML 605073, https://omim.org/entry/253250)
    - Inheritance AR
  - Gene TRIM37
    - Growth disorder with prenatal onset, including occasional progressive cardiomyopathy, characteristic facial features, failure of sexual maturation, insulin resistance with type 2 diabetes, and an increased risk for Wilms tumor

- Congenital anomalies associated with predisposition syndromes
  - Aniridia
  - Cryptorchidism
  - Hemihyperplasia
  - Horseshoe kidney (patients are twice as likely to develop WT)
  - Hypospadias
  - Renal duplication
  - Renal ectopia
  - Renal hypoplasia
  - Mesoblastic nephroma
  - Ureteral duplication

Surveillance recommendations for WT predisposition syndromes10,14
- The Pediatric Cancer Working Group of the American Association for Cancer Research recommends renal US every 3 mo up to age 8 y

Familial Nephroblastoma
- FWT1/FWT2 (Familial WT) gene mutations account for about 1%–2% of WT cases. These mutations are autosomal dominant with variable penetrance. They have no association with the WT1 mutation. FWT1 is found on chromosome 19q, whereas FWT2 is found on chromosome 11q.

References

Clinical Trial Data
The AREN0534 trial assessed neoadjuvant therapy with VAD for 6 weeks followed by either surgery or continuation of VAD for an additional 6 weeks in 189 evaluable children with bilateral FHWT.61 This trial also assessed treatment in children with unilateral WT and a predisposing syndrome (see “Unilateral Renal Tumors,” page 960). Goals of AREN0534 included performing surgery by week 12, improving the event-free survival (compared with NWTS-5), and decreasing the need for total nephrectomy by using NSS, if feasible, to preserve renal function. Surgery was done at either 6 weeks or 12 weeks after neoadjuvant chemotherapy based on the response at 6 weeks; continuing chemotherapy beyond 12 weeks usually does not yield continued tumor shrinkage.70,95 If there was a less than partial response at week 6, open renal biopsies in both kidneys were done to determine the histology—FHWT or WT without evidence of anaplasia—before continuing with VAD. However, bilateral renal tumors in children that are not WT are very uncommon. By 12 weeks, most patients had a partial response to neoadjuvant chemotherapy. Surgery was done with the goal of preserving as much renal function as possible, if feasible, and included (1) a partial nephrectomy on one or both sides; or (2) a total nephrectomy with regional lymph node sampling and a contralateral partial nephrectomy on one side. Data show that use of partial nephrectomy preserves renal function in patients with bilateral WT.125 Most patients (84%) had had surgery by 12 weeks; 61% of patients needed a complete nephrectomy in at least one kidney.

Histology results and stage were used to select further therapy including RT and/or adjuvant chemotherapy. To determine adjuvant therapy, risk assessment was done using the kidney with the highest stage. Patients with complete necrosis after neoadjuvant chemotherapy or with stage I FHWT without blastemal-predominant histology are at lower risk of relapse after surgery; therefore, they
received EE4A, which is less intensive adjuvant chemotherapy. Patients with blastemal-predominant histology are at greater risk of relapse after surgery; therefore, they received more intensive adjuvant therapy.61,122 For 11 children with bilateral FHWT and blastemal-predominant histology on ARE0534, the 4-year event-free survival was 81.8% (95% CI, 42.3%–100%) and the 4-year overall survival was 91% (95% CI, 64.1%–100%).61 For 140 children with bilateral FHWT but without blastemal-predominant histology on ARE0534, the 4-year event-free survival was 83.18% (95% CI, 73.2%–92.96%) and the 4-year overall survival was 97.7% (95% CI, 93.90%–100%).61 On the older NWTS-5 trial, 4-year event-free survival was 65% for patients with bilateral FHWT.11

**NCCN Recommendations**

**Localized Bilateral Renal Tumors With or Without a Predisposing Condition**

Neoadjuvant therapy with the VAD regimen is recommended for children with localized bilateral renal tumors with or without a predisposing condition.61 Upfront biopsy or resection is discouraged in this setting. Surgery is done at either 6 weeks or 12 weeks after neoadjuvant chemotherapy based on the response; data show that continuing chemotherapy beyond 12 weeks usually does not yield continued tumor shrinkage.70,95 NSS is recommended to preserve as much renal function as possible, if feasible, including (1) a partial nephrectomy on both sides; or (2) a total nephrectomy and a contralateral partial nephrectomy. In either case, regional lymph node sampling should be performed. At week 6 of VAD, the tumors are reimaged and depending on the response, patients (1) have no surgery if there was a complete response to VAD; (2) have bilateral partial nephrectomies at week 6 if the tumors are now resectable; or (3) continue with VAD for a total of 12 weeks if the tumors are still unresectable. If there is a less than partial response at week 6, renal biopsies in both kidneys are recommended to determine the histology—FHWT or WT without evidence of anaplasia—before continuing with VAD.
adjuvant chemotherapy regimen. Switching to regimen EE4A is recommended for patients with stage I FHWT without blastemal predominant histology, those with stage II FHWT with complete necrosis, or those with a complete response at 6 weeks of neoadjuvant chemotherapy. Switching to regimen DD4A is recommended for patients with (1) stage II or III FHWT without blastemal predominant histology; or (2) stage I FHWT with blastemal predominant histology. Augmented therapy with regimen I is recommended for patients with stage II or III FHWT with blastemal predominant histology, because they are at greatest risk.

RT is often given 10 to 14 days after surgery; the patient’s age and other factors are considered when deciding about the timing of RT. Local stage III refers to the staging at the primary tumor, regardless of metastases, and is used to determine the need for flank RT or WAI (see “Principles of Radiation Therapy for FHWT” [WILMS-H] in the algorithm). Upfront biopsy does not upstage a tumor to stage III for determining whether to give RT. Neoadjuvant chemotherapy is not a criterion for upstaging to stage III in this setting. Patients with a complete response at 6 weeks of neoadjuvant chemotherapy do not need RT.

Metastatic Bilateral Renal Tumors With or Without a Predisposing Condition

Neoadjuvant therapy with the VAD regimen is recommended for children with metastatic bilateral renal tumors with or without a predisposing condition.41 Upfront biopsy or resection is discouraged in this setting. At week 6 of VAD, the tumor is reimaged and depending on the response, patients (1) have no surgery if there was a complete response to VAD; (2) have partial nephrectomy at week 6 if the tumors are now resectable; or (3) continue with VAD for a total of 12 weeks if the tumors are still unresectable. If there is a less than partial response at week 6, the tumor should be biopsied to confirm a diagnosis of FHWT (or WT without evidence of anaplasia) before continuing with VAD. Surgery is done at either 6 weeks or 12 weeks after neoadjuvant chemotherapy based on data showing that continuing chemotherapy beyond 12 weeks usually does not yield continued tumor shrinkage.78,95 NSS is recommended to preserve as much renal function as possible, if feasible, including (1) a partial nephrectomy at one or both sides; or (2) a total nephrectomy and a partial nephrectomy on the contralateral side. In either case, regional lymph node sampling should be performed.

After pathology confirms that patients have FHWT, histology (ie, blastemal predominant) is used to select further therapy. Patients switch to regimen DD4A or regimen I, depending on the risk assessment. Switching to regimen DD4A is recommended for patients without blastemal predominant histology or those with a complete response at 6 weeks of neoadjuvant chemotherapy. Augmented therapy with regimen I is recommended for patients with blastemal predominant histology, because they are at greater risk. Use of molecular biomarkers to direct therapy has not been studied in this setting.

RT is often given 10 to 14 days after surgery; the patient’s age and other factors are considered when deciding about the timing of RT. Local stage III refers to the staging at the primary tumor, regardless of metastases, and is used to determine the need for flank RT or WAI (see “Principles of Radiation Therapy for FHWT” [WILMS-H] in the algorithm). Upfront biopsy does not upstage a tumor to stage III for determining whether to give RT. Neoadjuvant chemotherapy is not a criterion for upstaging to stage III in this setting. Patients with a complete response at 6 weeks of neoadjuvant chemotherapy do not need RT.

Whole lung irradiation is administered in patients with lung metastases, and extrapulmonary metastatic sites may also require radiation.

References


Wilms Tumor (Nephroblastoma), Version 2.2021


## Individual Disclosures for the NCCN Wilms Tumor (Nephroblastoma) Panel

<table>
<thead>
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<th>Panel Member</th>
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<th>Scientific Advisory Boards, Consultant, or Expert Witness</th>
<th>Promotional Advisory Boards, Consultant, or Speakers Bureau</th>
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The NCCN Guidelines Staff have no conflicts to disclose.