# In Brief

## Wilms Tumor

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Author Disclosure
Dr Friedman has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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Wilms tumor is responsible for 5% of pediatric malignant tumors or approximately 500 new cases each year in the United States, with equivalent frequency in boys and girls. The incidence is fairly uniform throughout the world, being somewhat more common in black children and less common in Asian compared with white children. The mean age at presentation is 3 years for sporadic and 2 years for hereditary cases.

Children who have Wilms tumor often present with an asymptomatic abdominal mass, found by caregivers or pediatricians. The differential diagnosis for a toddler who has an abdominal mass includes neuroblastoma, hepatoblastoma, sarcoma, lymphoma, and germ cell tumors, as well as benign conditions. At times, patients newly diagnosed as having Wilms tumor experience abdominal pain and hematuria from invasion of the renal pelvis or hypertension from compression of the renal artery, each consequence occurring in approximately 25% of cases.

The most common sites of metastasis of a Wilms tumor are abdominal lymph nodes, followed by asymptomatic parenchymal lung lesions and, less often, liver nodules. In contrast to neuroblastoma or sarcomas, Wilms tumor only rarely spreads to bone or bone marrow; as a result, patients do not experience bone pain, fractures, or low blood cell counts, and even children who have advanced stage disease often appear relatively well.

Wilms tumor is associated with several genetic syndromes that can affect the clinical presentation. The WAGR syndrome, consisting of Wilms tumor, aniridia, genitourinary (GU) anomalies, and developmental retardation, results from germline inheritance of a deletion at chromosome 11p13 that involves the *WT1* gene and neighboring genes that affect eye and cognitive development. *WT1* is a transcription factor that directs normal kidney and GU embryogenesis. GU anomalies associated with Wilms tumor include hypospadias, cryptorchidism, and gonadal dysgenesis. Some patients who have WAGR syndrome have normal mentation, potentially reflecting a smaller chromosomal deletion.

The prevalence of aniridia in patients who have Wilms tumor is approximately 0.8%; aniridia is rare in the general population otherwise and should prompt an ultrasonographic screen for Wilms tumor, with continued periodic evaluation. Because the risk for Wilms tumor diminishes greatly after age 9 years, it seems reasonable to stop radiographic screening at that time. Congenital *WT1* mutations are found also in Denys-Drash syndrome, which is characterized by diffuse mesangial sclerosis, leading to early nephrotic syndrome and renal failure by age 3 years, Wilms tumor, and gonadal dysgenesis with male pseudohermaphroditism or other gonadal developmental problems.

Wilms tumor occurs also in association with either hemihypertrophy of the extremities or Beckwith-Weidemann syndrome, which includes enlargement of the tongue, liver, kidney, and other organs. Loss of imprinting, and thus increased expression of insulinlike growth factor 2, is thought to produce cellular hyperplasia in affected patients. Approximately 3% of patients who have Wilms tumor have associated hemihypertrophy. As with aniridia, this physical finding is rare otherwise and should prompt screening for Wilms tumor. Patients who have Beckwith-Weidemann syndrome should, in addition, have $\alpha$-fetoprotein levels measured periodically because they are also at risk for hepatoblastoma and other cancers.

Approximately 5% of children who have Wilms tumor present with bilateral disease or develop a second Wilms tumor in the contralateral kidney at another time, and 7% of patients present with more than one primary tumor in a single kidney. These 12% of patients represent the hereditary cases and, as mentioned above, develop their tumors at a younger mean age than those who have sporadic disease. Some patients who have hereditary Wilms tumor inherit a point mutation or small deletion in one copy of their *WT1* gene. Because WT1 is a classic tumor suppressor gene,

loss of both copies is required for malignant transformation.

Children born having 1 copy of *WT1* missing in every cell throughout the body are at higher risk than the general population for more than 1 cell in each kidney, or 2 separate cells in 1 kidney, to mutate or lose both copies of *WT1*, accounting for bilateral or multifocal unilateral tumors, as well as for the younger age of patients who have hereditary disease.

Patients who have hereditary disease often are cured and may have children of their own; fortunately, the risk to their offspring is low. In genetic parlance, although 50% of their children inherit one mutated copy of the *WT1* gene, this genotype has low penetrance, so these offspring rarely develop the phenotype of Wilms tumor. This situation stands in sharp contrast to what happens to individuals who have anomalies of the other classic pediatric oncology tumor suppressor gene, *Rb*, which predisposes patients to bilateral retinoblastoma when mutated through the germline. Surviving patients who have hereditary retinoblastoma will transmit a mutant copy of *Rb* to half of their children, who then develop retinoblastoma with 98% penetrance.

At times, children who have hereditary Wilms tumor and come to clinical attention with a large, malignant tumor are found also to have multiple benign bilateral renal nodules, a situation termed *nephro*blastomatosis. Fortunately, most of these benign tumors regress and can therefore be monitored expectantly by computed tomography (CT) or magnetic resonance imaging (MRI). Typically, these tumors change from bright on T2 MRI to T2 dark as they involute. A nodule that remains bright and enlarges requires biopsy to look for malignant conversion.

Pediatricians who encounter an infant or toddler who has an abdominal mass often perform ultrasonography, which might reveal an intrinsic renal mass, prompting referral to a pediatric oncologist. Further evaluation will then include CT of the chest, abdomen, and pelvis to evaluate each kidney, abdominal nodes, lungs, and liver for primary tumor or metastatic involvement. Subsequent ultrasonography with Doppler flow evaluation of vasculature also should be performed because Wilms tumor at times enters the renal vein and inferior vena cava and in rare cases even reaches the right atrium, the so-called intracardiac Wilms tumor.

Bone marrow and bone scan evaluations are not needed, and positron emission tomography scans are not standard. Urinalysis is performed to assess for hematuria and proteinuria, and urine catecholamines often are measured to screen for possible neuroblastoma. The classic appearance of Wilms tumor on CT is a solid, intrinsic renal mass that displaces the normal renal parenchyma towards its rim, creating the so-called claw sign. In contrast to neuroblastoma, calcifications are rare, and the renal pelvis may be distorted, not just displaced inferiorly.

If the Wilms tumor is unilateral, the standard surgical approach in the United States is complete resection, after direct visualization of the other kidney to confirm its lack of involvement, with biopsy of regional lymph nodes and any suspicious liver masses. If resection would require damage to abdominal organs, simple biopsy is performed, with definitive resection deferred for 6 to 9 weeks to allow initial chemotherapy to reduce the tumor size.

Similarly, intracardiac disease is best approached by initial biopsy followed by chemotherapy. Pulmonary nodules do not require pathologic confirmation unless they have a nonclassic appearance on CT and thus potentially represent infectious or other nonmalignant causes. In some countries, all patients receive chemotherapy before definitive resection in the hope of minimizing spillage of tumor cells during surgery.

Pathologic evaluation of resected Wilms tumor reveals immature blasts intermixed with primitive glomeruli, tubules, and fibrous cells. Tumors are graded as having either favorable histologic findings, representing 96% of cases, or unfavorable histologic findings, characterized by nuclear anaplasia. At times, tumors will appear primarily favorable but have unfavorable histologic foci; such cases are classified as unfavorable because their anaplastic cells are likely to be of the most aggressive variety.

Besides Wilms tumor, several other malignant tumors present as intrinsic solid renal masses: mesoblastic nephroma occurs typically in infants younger than age 1 year and can be cured by surgical resection if localized; clear cell sarcomas can metastasize to bone; rhabdoid tumors arise from smooth muscle and occur also in the biliary tract and the central nervous system; and renal cell carcinoma may occur in teenagers, albeit rarely, more typically presenting during adulthood.

Staging of Wilms tumor depends on both radiologic findings and the results of surgery. Stage I tumors (37% of cases in one large study) are limited to the kidney and are excised completely. Stage II tumors (20% of cases) extend beyond the renal capsule or into the renal sinus but are excised completely. Patients who have Stage III tumors (20% of cases) have residual abdominal disease, either because the tumor was deemed too adherent to adjacent structures to resect or because of abdominal lymph node involvement or tumor spillage. Stage IV tumors (23% of cases) are those that manifest distant spread to the lung or liver.

Adjuvant therapy is guided by stage and histologic grade. The approach taken in the United States was developed through a series of national studies of Wilms tumor and is being optimized further through active Children's Oncology Group protocols. In brief,

patients who have stage I or II disease receive therapy with vincristine and actinomycin D. For stage III tumors, patients also receive doxorubicin and abdominal radiation therapy. Patients who have stage IV disease may also receive lung or liver radiotherapy. When unfavorable histologic findings exist, patients also may be treated with etoposide, cyclophosphamide, and carboplatin.

Cure rates with initial therapy are approximately 90% for stage I and II disease, 85% for stage III disease, and 66% for stage IV tumor or those having unfavorable histologic findings. Patients who experience tumor recurrence still can be cured: most patients who have low-stage disease and who relapse are cured with the use of more intense chemotherapy, and a subset of patients who have high-stage disease with recurrence may be cured by several cycles of more intense chemotherapy, followed by very high-dose chemotherapy combined with autologous stem cell rescue.

After completion of therapy for Wilms tumor, patients are monitored for pulmonary relapse with serial chest CT and for abdominal recurrence or development of a second primary tumor in the contralateral kidney by ultrasonography. In addition, patients are monitored for development of long-term adverse effects of therapy. Doxorubicin, an anthracycline, can damage cardiac myocytes; patients exposed to this agent are monitored with echocardiography and electrocardiography. Potential abnormalities include a diminished ejection fraction and a prolonged QTc interval. The risk of cardiac dysfunction increases with total lifetime anthracycline exposure, being uncommon below 200 mg/M$^2$; fortunately, patients who have Wilms tumor rarely exceed this threshold.

Anthracyclines, etoposide, and cyclophosphamide each place patients at risk for secondary leukemias, necessitating the monitoring of blood cell counts. External beam radiation can damage normal organs and induce leukemias or in-field solid tumors. For example, lung radiation affects both pulmonary and cardiac function and increases the risk of breast cancer and hypothyroidism, and both lung and abdominal radiation may affect nearby vertebrae, affecting adult height.

Immunizations are deferred until 6 months after completion of chemotherapy to allow the immune system to recover. Because chemotherapy for most cases of Wilms tumor is fairly mild, immunizations can then continue from the point at which the patient left off before diagnosis. Finally, patients treated for Wilms tumor should have their renal function and blood pressure monitored and should be counseled to avoid trauma to the remaining viable kidney.

## Comment:

Pediatricians all know nephroblastoma as Wilms tumor. But how many of us know anything about Dr. Wilms himself? I certainly didn't until Dr. Friedman's *In Brief* piqued my curiosity.

Max Wilms (1867-1918) was born into a Western German family of lawyers, and having begun his studies in law, he decided instead on a career in medicine. Graduating from the University of Bonn in 1890 with his doctorate, he worked initially as a pathologist in Giessen and Cologne with interests in the kidney and the development of tumor cells. In 1899 he was certified in surgery at Leipzig, moving to Basel and eventually to Heidelberg, where in 1910 he became the chairman of surgery. He was coauthor of an esteemed textbook of surgery that was translated into several languages and developed surgical techniques for the treatment of prostate disease and tuberculosis. In 1918, toward the end of World War I, he died of diphtheria, which he contracted from a French prisoner of war, whose life he had saved with a cricothyroidotomy.

Wilms argued, in an influential 1899 monograph, that the renal tumor cells he found in a cohort of children who had nephroblastoma were embryonic in origin, establishing his most prominent place in the history of medicine.

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Editor, In Brief

### Parent Resources from the AAP at HealthyChildren.org

The reader is likely to find material relevant to this article to share with parents by visiting this link:
http://www.healthychildren.org/English/health-issues/conditions/cancer/Pages/Childhood-Cancer.aspx

**Answer Key for July Issue:**
**Hemophilia:** 1. A; 2. C; 3. D; 4. C; 5. D
**Psychosis in Children and Youth:** 1. C; 2. D; 3. D; 4. A; 5. A
**Vomiting:** 1. C; 2. A; 3. B; 4. E; 5. E

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