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MEDICAL SPECIALTY SPOTLIGHT: ONCOLOGY

Wilms tumor and associated predisposing syndromes and conditions

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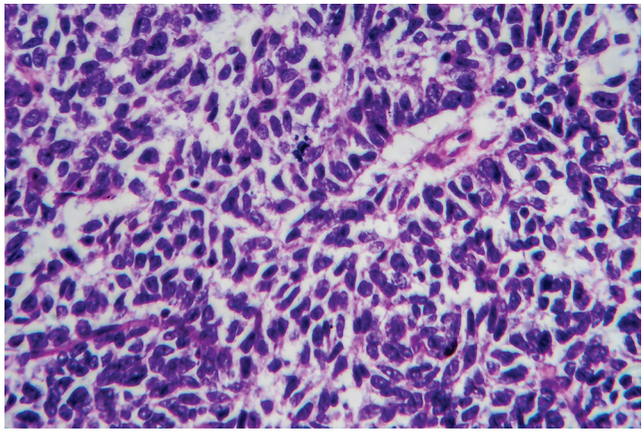
ABSTRACT

Wilms tumor, also known as nephroblastoma, is relatively rare but is the most common renal malignancy in children, accounting for about 5% of all childhood malignancies and 90% of all childhood renal malignancies. Advances in the understanding of the underlying cause and pathophysiology of Wilms tumor have significantly improved the prognosis and survival rates for children with Wilms tumor, but cases may occur sporadically and certain affected patients face higher rates of relapse and morbidity. The most common clinical presentation involves the identification of an abdominal mass or swelling without other signs or symptoms. The nonspecific nature of symptoms that can present can delay timely diagnosis and treatment. Numerous predisposing syndromes are associated with an increased risk for the development of Wilms tumor. Clinicians who recognize these syndromes and other conditions and understand the increased risk can provide the appropriate level of anticipatory guidance and use the optimal screening plan.

Keywords: Wilms tumor, pediatric, cancer, nephroblastoma, congenital syndromes, kidney

Learning objectives

- Describe the epidemiologic burden of pediatric cancer and Wilms tumor.
- Identify the risk factors and predisposing syndromes associated with Wilms tumor.
- List the appropriate screening precautions required for predisposing syndromes associated with Wilms tumor.
- Describe the common clinical presentation and diagnostic steps for a patient with Wilms tumor.



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According to the American Cancer Society (ACS), cancer is the second leading cause of death in the United States, with a projected incidence of more than 2 million and mortality of nearly 612,000 in 2024.[1] The National Cancer Institute estimates that 9,620 new cases of cancer will be diagnosed among children under age 15 years in 2024 and about 1,040 will die from their cancer.[2] Fortunately, the rate of cancers that arise in childhood represents a small subset of overall cancer diagnoses, but a cancer diagnosis can be especially devastating to families when it affects a child.[3] Although cancer risk increases with age and patients are most likely to receive a cancer diagnosis at age 65 years or older, this trend is beginning to change in the United States. The ACS also reported in 2024 that cancer patients are getting younger.[1]

Wilms tumor generally presents in children ages 3 to 5 years, with a median of 3.5 years.[4,5] It is the most common tumor of the kidney in infants and children. The incidence in the United States is 10.4 cases for every 1 million children under age 15 years and 0.2 cases per 10,000 infants. That is, about 650 cases of Wilms tumor are diagnosed each year in the United States.[6]

Wilms tumor generally develops in otherwise healthy children; however, about 10% of children with Wilms tumor have a congenital abnormality that predisposes them to the malignancy. The absolute risk of developing Wilms tumor differs based on the underlying condition or anomaly (**Table 1**). The main purpose of screening is to facilitate early detection of a small, localized tumor; to improve prognosis; and to enable a lower-intensity treatment plan.[7] Children with syndromes or conditions that significantly increase their risk of developing Wilms tumor generally undergo ultrasound screening every 3 months until at least

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Key points

- Nephroblastoma, also known as Wilms tumor, is the most common pediatric renal cancer.
- Wilms tumor is most common in Black children ages 1 to 4 years, often presenting as a unilateral, soft, nontender, smooth mass that does not cross the midline.
- Many conditions and syndromes are associated with increased risk for developing Wilms tumors and require routine surveillance.
- Physical examination of a patient with a suspected Wilms tumor should be conducted with extreme caution to prevent tumor rupture and spillage.
- Treatment and prognosis largely depend on histologic favorability, patient age, tumor size, and tumor stage, with treatment generally involving surgical resection with potential use of chemotherapy and/or radiation.

age 8 years.[6,7] High-risk conditions that warrant this screening include most children with Denys-Drash syndrome, WAGR syndrome, Beckwith-Wiedemann syndrome and other overgrowth syndromes, sporadic aniridia, and isolated hemihypertrophy.[6]

Although the clinical presentation can vary widely, most children with Wilms tumor present without symptoms but an abdominal mass. In children with known predisposition syndromes, renal tumors also may be found during routine screening. Clinicians should be alert to these clinical findings: a lump, welling, or pain in the abdomen; hematuria (gross or microscopic); hypertension; hypercalcemia; and constitutional symptoms.

Diagnosis can be challenging, given the nonspecific nature that often is a part of the clinical presentation. However, treatment of Wilms tumor is one of the major achievements in the field of childhood cancer. A key feature of this achievement is improved risk stratification, which allows clinicians to augment or reduce therapy based on the child's risk of relapse. Basing treatment on factors beyond tumor stage and histology alone, including newer clinical and biological prognostic factors, enables more tailored treatment and improved outcomes.[8]

This article presents an overview of latest expert guidance and consensus recommendations for screening and evaluating children with or at risk for Wilms tumor, including recommendations from the Children's Oncology Group.[4]

EPIDEMIOLOGY AND RISK FACTORS

Wilms tumor is the most common pediatric renal malignancy and accounts for about 5% of all pediatric malignancies and 90% of all pediatric renal malignancies. In comparison, renal cell carcinoma predominates in adults.[3] Globally, Wilms tumor accounts for 7.5 cases per million for children ages birth to 14 years, and 0.3 cases per million for those ages 15 to 19 years.[9] In the United States, Wilms tumor has an incidence of about 650 cases per year and accounts for about half of all pediatric deaths related to kidney and renal pelvis cancers.[4,10]

Presentation before age 1 year is rare, and patients most commonly present between ages 1 to 4 years, with a mean age of 3 years, and median age of 3.5 years.[9] About 90% of patients are diagnosed before age 6 years, and incidence is inversely proportional to age. Male incidence peaks at age 1 year; female incidence peak is between ages 1 and 3 years. Thus, we tend to see that cases diagnosed in the first year of life have predilection for the male sex. Wilms tumor prevalence is markedly higher among Black patients, and lower among those of East Asian and Pacific Islander descent.[4,9,11]

Environmental risk factors also may hold importance in the predisposition to Wilms tumor. The retrospective study, Etude Sur les Tumeurs Embryonnaires, Leucémies, et Lymphomes de l'Enfant (Study on Embryonic Tumors, Leukemias, and Lymphomas of Children [ESTELLE]), conducted in France, further explored this topic and reviewed 117 cases of Wilms tumor and 1,100 controls for such relationships.[12] Unlike other malignancies, Wilms tumor has not been associated with preconception or perinatal exposure to parental cigarette smoking or maternal alcohol consumption. However, data suggest a potential association between perinatal use of household pesticides and the development of Wilms tumor, especially when pesticides are used more often than once a month.[12]

CAUSES

Most cases of Wilms tumor occur sporadically, resulting from mutations leading to disturbances in embryonic renal organogenesis.[13] However, 1% to 2% of cases have an autosomal dominant inherited trait pattern.[13] With the use of large-scale genomic sequencing, mutations in a myriad of tumor suppressor and transcription genes have been implicated as predisposing factors.

PATHOPHYSIOLOGY

Embryonic nephrogenesis begins at 3 weeks gestation and consists of three mesoderm-derived stages: pronephros, mesonephros, and metanephros. The Wolffian duct, derived from the mesonephros, contains several ureteric buds surrounded by metanephric mesenchyme, called blastema. At about 5 weeks gestation, growth factors promote a reciprocal interaction between the ureteric buds and blastema. The blastema signal the ureteric buds to branch and give rise to the ureters, collecting ducts, and renal pelvis. In turn, the ureteric buds signal the mesenchymal-to-epithelial transition of blastema, ultimately forming the glomeruli and nephrons.[14]

A persistence of blastemal embryonic tissue in the postnatal phase is one of the primary mechanisms in the pathogenesis of Wilms tumor. These remnants of undifferentiated tissue, referred to as nephrogenic rests or nephroblastomatosis, are precursor undifferentiated cells that can develop into Wilms tumor if they do not regress.

TABLE 1. Surveillance recommendations and associated Wilms tumor risk of top predisposing congenital syndromes and conditions[17-26,40,41]

Predisposing syndrome	Wilms tumor risk	Surveillance/management
Denys-Drash syndrome	74%	Prophylactic bilateral nephrectomy and transplantation
Perlman syndrome	64%	Abdominal ultrasound every 3 to 4 months until age 5 years
WAGR syndrome	45% to 57%	Abdominal ultrasound every 3 months until age 7-8 years
Mosaic variegated aneuploidy	>20%	Abdominal ultrasound every 3 to 4 months until age 5 years
Fanconi anemia, subtype D1	20%	Abdominal ultrasound every 3 to 4 months until age 5 years
Simpson-Golabi-Behmel syndrome	10%	Abdominal ultrasound every 3 to 4 months until age 7 years
Beckwith-Wiedemann syndrome	7.5%	• Serum AFP every 6 weeks to 3 months until age 4 years • Abdominal ultrasound every 3 months until age 7 to 8 years
2q37 microdeletion syndrome	5%	Abdominal ultrasound at age 4 and again at puberty
Li-Fraumeni syndrome	<5%	• Abdominal ultrasound every 3 to 4 months until age 5 years • Whole-body and brain MRI every year starting at age 12 years
Hyperparathyroidism-jaw tumor syndrome	<5%	Abdominal ultrasound every 5 years or sooner if symptomatic
Mulibrey nanism	<5%	Abdominal ultrasound every 3 months until age 7 years
Trisomy 18	<5%	Abdominal ultrasound every 3 months until age 7 years
Bloom syndrome	<5%	• Abdominal ultrasound every 3 to 4 months until age 8 years • Whole-body and brain MRI every year starting at age 12 years
Isolated hemihypertrophy	<5%	• Serum AFP every 6 weeks to 3 months until age 4 years • Abdominal ultrasound every 3 months until age 7 years • Abdominal examination every 6 months after age 7 years
Sotos syndrome	<5%	No routine surveillance recommended, given estimated risk of about 1%
Multicystic dysplastic kidney	Limited data	Abdominal ultrasound every 3 months until age 4 to 6 years

This is supported by histopathologic similarities seen when comparing nephrogenic rests and biopsy-proven Wilms tumor tissue. In rare cases, patients with nephrogenic rests at birth do not develop Wilms tumor, because the tissue can spontaneously regress after birth.[13]

Most cases of Wilms tumor are unilateral; 5% to 8% of total cases are bilateral.[15] Moreover, unilateral Wilms tumor that recurs or metastasizes after diagnosis to the contralateral kidney only accounts for 0.85% of total cases.[15] Although only 35% of unilateral cases are expected to have nephrogenic rests on histology, 100% of bilateral cases will have nephrogenic rests.[15]

Lastly, extrarenal Wilms tumor, caused by ectopic nephrogenic rests outside the kidneys, is exceedingly rare. A retrospective study in 2020 reviewing 876 cases of Wilms tumor found that only 0.57% of cases were extrarenal, involving the retroperitoneum, gubernaculum testis, or sigmoid colon.[16]

ASSOCIATED SYNDROMES AND CONDITIONS

About 5% of patients with Wilms tumor have at least one concomitant predisposing syndrome that is linked to higher risk for the tumor. More than 100 syndromes have been identified, and most are characterized by genitourinary abnormalities or overgrowth.[15] Following are some of the well-established ones.

• *Denys-Drash syndrome* is characterized by progressive renal failure in infancy and male pseudo-hermaphroditism. In this syndrome, germline mutations of the *WT1* gene increase the chance of nephrogenic rests persisting after birth. The classic presentation includes proteinuria that can rapidly progress to acute renal failure. About 74% of patients develop concomitant Wilms tumor, and 20% have bilateral disease.[15] In many cases, prophylactic bilateral nephrectomy, followed by renal transplantation, is recommended.[17]

• *Perlman syndrome* is an autosomal recessive overgrowth condition associated with a mutation in *DIS3L2*. Characteristic findings include macrosomia, polyhydramnios, enlarged facies, and renal dysplasia.[18] Neonatal mortality is high but, among those who survive, about 64% develop Wilms tumor and 55% have bilateral disease.[15] Surveillance is recommended with abdominal ultrasound every 3 to 4 months until the patient is at least age 5 years.[19]

• *WAGR syndrome* results from congenital variable *11p13* deletion of the *WT1* gene. Clinical manifestations include aniridia, cryptorchidism, streak ovaries, ambiguous genitalia, prognathism, macrocephaly, cataracts, glaucoma, nystagmus, and intellectual disability. The incidence of concomitant Wilms tumor and WAGR syndrome is 45% to 57%, and 17% of patients have bilateral disease.[15] Surveillance with abdominal ultrasonography every 3 months until age 7 to 8 years is highly recommended.[20]
• *Fanconi anemia* is an autosomal recessive inherited disorder resulting in chromosomal instability that disrupts DNA repair pathways. Subtype D1, with homozygous *BRCA2* mutations, particularly predisposes patients to Wilms tumor. Clinical manifestations include pancytopenia, infertility, short stature, and café au lait spots.[21] Patients have a 20% risk of developing Wilms tumor, almost exclusively before age 5 years.[19] Surveillance with abdominal ultrasound is recommended every 3 to 4 months until the patient is at least age 5 years.[19]
• *Simpson-Golabi-Behmel syndrome*, an X-linked, recessively inherited overgrowth syndrome caused by deletions in the *GPC3* gene, confers a 10% risk of developing Wilms tumor.[22] Clinical manifestations include intellectual disability, motor milestone delay, speech delay, cleft lip, square face, macroglossia, tongue growth, and teeth malposition.[22] Surveillance is recommended with abdominal ultrasound every 3 to 4 months until the patient is at least age 7 years.[19]
• *Beckwith-Wiedemann syndrome* is the most common overgrowth syndrome, with an incidence of 1 in 13,000.[23] It is believed to be highly underdiagnosed because of the broad range of presenting symptoms. The syndrome results from disturbance of several genes on chromosome *11p15*, predisposing patients to Wilms tumor and hepatoblastoma. Hallmark features include hemihypertrophy, umbilical hernias, diastasis recti, omphalocele, exophthalmos, nevus flammeus (port-wine nevus), prominent mandible, anterior earlobe creases, and macroglossia. Hypoglycemia secondary to pancreatic islet cell hyperplasia and hyperinsulinemia is seen in 30% to 50% of patients.[23-25] About 7.5% of patients develop Wilms tumor, and 17.3% have bilateral disease.[15] Wilms tumor screening is recommended with abdominal ultrasound every 3 months until ages 7 to 8 years, and hepatoblastoma screening with serum alpha-fetoprotein (AFP) every 6 weeks to 3 months until the patient is age 4 years.[23,24]
• *Additional syndromes* include Li-Fraumeni syndrome, multicystic dysplastic kidney, Sotos syndrome, mosaic variegated aneuploidy, hyperparathyroidism-jaw tumor syndrome, Mulibrey nanism, trisomy 18 (Edwards syndrome), Bloom syndrome, isolated hemihypertrophy, and *2q37* microdeletion syndrome (**Table 1**).[26]

CLINICAL MANIFESTATIONS

As previously noted, the most common presentation of Wilms tumor is presence of an abdominal mass in an asymptomatic patient, usually presenting with a unilateral, firm, smooth, nontender abdominal mass that does not cross the midline. Between 20% and 30% of patients present with associated malaise, fever, abdominal pain, and gross hematuria.[27] Hypertension is reported in up to 50% of patients, as a result of compensatory renin-angiotensin-aldosterone system activation, leading to increased renin plasma concentration. Over time, this may lead to cardiac hypertrophy and heart failure.[28] Depending on tumor size and burden, 10% of patients present with signs and symptoms of surrounding organ compression, which are highly variable.[27]

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The most common site of metastasis is the lungs, accounting for 90% of metastatic Wilms tumor.[27] Presenting symptoms of pulmonary metastasis are nonspecific, including dyspnea and cough. Other sites of metastasis include the liver, bone, brain, and vasculature.[27] Vascular extension, often including the renal veins and vena cava, presents with ascites, hepatomegaly, and heart failure. Intra-atrial extension of Wilms tumor is rare, seen in 1% to 3% of patients, and most commonly involves the right atrium.[29]

Avoid excessive and aggressive palpation of a suspicious abdominal mass, because Wilms tumors are highly friable and can rupture, resulting in extrarenal tumor spillage, a medical emergency characterized by an acute abdomen and rapid onset of anemia. Tumor rupture and spillage upstages the tumor as well and confers an increased risk of postoperative recurrence and metastasis.[30]

Paraneoplastic syndromes have been reported and can result in atypical presentations including erythrocytosis, Cushing syndrome, hypercalcemia, and acquired Von Willebrand syndrome (AVWS).[31] Most notably, AVWS, seen in 8% of patients with Wilms tumor, results from plasma factors secreted by the tumor interacting with Von Willebrand factor to either inhibit its function or increase its clearance. These patients can be prone to bleeding and

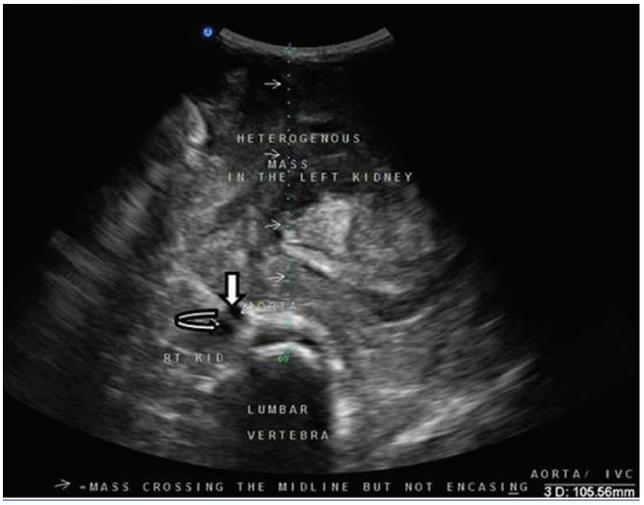

FIGURE 1. Abdominal ultrasound in a 3-year-old male, demonstrating left renal mass (small white arrows) with compression and displacement of the abdominal aorta (large white arrow) and inferior vena cava (white curved arrow)

Reproduced with permission from Ikhouriah T, Oboh D, Yakubmiyer M, et al. Wilms tumor: a case report with typical clinical and radiologic features in a 3-year-old male. *Radiol Case Rep.* 2023;18(5):1898-1904.

often respond well to conventional therapy including desmopressin (DDAVP) and IV immunoglobulin (IVIG).[32,33]

DIAGNOSIS

The differential diagnosis in a child presenting with a nontender, unilateral, smooth, abdominal mass includes Wilms tumor, neuroblastoma, renal cell carcinoma, renal medullary carcinoma, congenital mesoblastic nephroma, clear cell sarcoma of the kidney, and rhabdoid tumor of the kidney. The diagnostic highlights below are based on guidelines of the Children's Oncology Group.[34]

The initial diagnostic test of choice for a suspicious abdominal mass is an abdominal ultrasound (**Figure 1**). If a mass is visualized, findings suggestive of renal origin include mass movement with inspiration and distortion of the renal parenchyma, referred to as the *claw sign*. Varying degrees of echogenicity are seen, depending on the degree of hemorrhage and tissue necrosis. Evaluate the contralateral kidney for bilateral involvement and evaluate the hepatic cul-de-sac for metastasis. Subsequent imaging includes CT or MRI of the abdomen and pelvis to evaluate extent of disease and confirm renal origin (**Figure 2**). If bilateral disease is suspected, MRI is the preferred diagnostic test of choice over CT. Doppler imaging also is recommended to evaluate for intravascular extension. Initial laboratory tests are important to evaluate for pancytopenia, renal dysfunction, proteinuria, hematuria, and hepatic dysfunction.[34]

CT with IV contrast of the chest is recommended to evaluate for pulmonary metastasis, because about 20% of patients with Wilms tumor initially present with distant metastasis.[34] CT is recommended before surgery or any sedation, because postoperative atelectasis and pleural effusions may impede complete evaluation of lung parenchyma. Nodule size on imaging cannot exclude pulmonary metastasis alone, but favorable findings on CT include size greater than 5 mm, no calcifications, and sharp borders. Definitive confirmation or exclusion of a concerning nodule requires biopsy.[34]

In most cases, surgical resection precedes staging and is required for staging.

- Stage I involves only a single kidney and can be completely resected.
- Stage II involves renal sinus and capsule extension, can be completely resected, and does not involve lymph nodes.
- Stage III includes residual postsurgical disease, lymph node involvement, preoperative rupture or spillage, and extension to adjacent organs.
- Stage IV involves distant metastasis to lymph nodes and organs.
- Stage V involves bilateral disease present at diagnosis.[30,34]

MANAGEMENT

Surgery and chemotherapy remain at the forefront of managing patients with Wilms tumor. Radiation is reserved for higher stages and unfavorable histology, determined by the degree of tumor cell undifferentiation. For unilateral disease, the most common surgical technique used is the transperitoneal radical nephrectomy, allowing for complete exploration of the abdominal cavity and sampling of adjacent lymph nodes.[27] Sparing options, particularly for bilateral disease, are nephron-sparing surgery and minimally invasive surgery.[35] Regardless of technique, surgeons must avoid perioperative tumor spillage which carries a sixfold increased risk of recurrence.[27]

Children's Oncology Group protocols generally recommend surgical resection and staging before chemotherapy. However, neoadjuvant chemotherapy to reduce the risk of perioperative spillage is indicated if the patient has a large tumor burden. Common chemotherapeutic agents used are doxorubicin, vincristine, dactinomycin, cyclophosphamide, and carboplatin. The preferred regimen, duration of treatment, and use of adjunctive radiation depend on the patient's risk factors, tumor histology, and disease stage.[27,35]

Pulmonary metastatic nodules commonly are treated with chemotherapy and radiation. However, an argument can be made for the benefit of surgical resection, because untreated pulmonary nodules have a higher risk of pulmonary recurrence. Guidelines recommend surgical excision of pulmonary nodules only if they are refractory to chemotherapy and radiotherapy. This is supported by the finding that about 26% of biopsied pulmonary nodules are benign.[35]

Monitor patients for treatment-related adverse reactions during therapy. Of note, tumor lysis syndrome is an oncologic emergency characterized by cellular lysis of

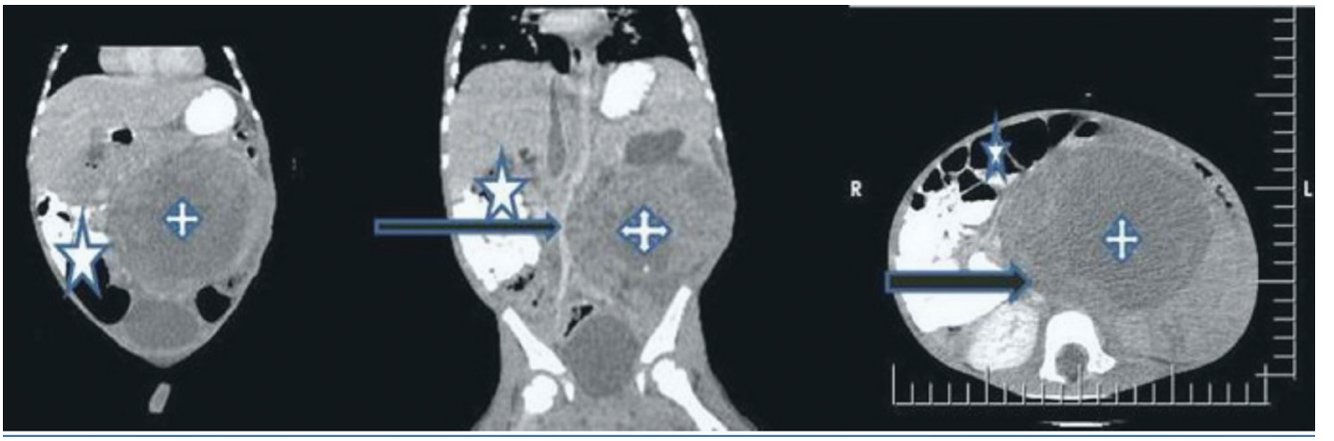

FIGURE 2. CT imaging of the abdomen and pelvis of a 3-year-old male patient. Axial (left and right) and coronal (center) views demonstrating left renal mass (white cross) with displacement of the abdominal aorta (black arrow) and bowel (white star).

Reproduced with permission from Ikhouriah T, Oboh D, Yakubmiyer M, et al. Wilms tumor: a case report with typical clinical and radiologic features in a 3-year-old male. *Radiol Case Rep.* 2023;18(5):1898-1904.

rapidly proliferating cancer cells. Although more commonly seen in patients with hematologic malignancies, it can occur in those with Wilms tumor, even in the operative setting. Hallmark laboratory findings include hyperkalemia, hyperuricemia, hyperphosphatemia, and hypocalcemia.[36]

PROGNOSIS

With significant advances in understanding of Wilms tumor pathophysiology, surveillance, and therapeutic options, survival rates have markedly improved over the past 30 years, especially for patients with favorable histology. Many risk factors play a role in risk stratification of patient prognosis. Studies have found that tumor size, patient age, surgical intervention, tumor stage, and tumor laterality are all independent prognostic factors that can guide patient therapy.[37] Recent studies during the COVID-19 pandemic have found that COVID-19 infection, concomitant with Wilms tumor and other pediatric tumors, is not a prognostic risk factor for mortality.[38]

About 15% of patients with Wilms tumor relapse, most commonly in the first 2 years off therapy; among these, pulmonary (58%) and abdominal (29%) recurrences are the most common.[34] The Children's Oncology Group recommends routine MRI or CT surveillance of the abdomen and pelvis in the first 2 years, and CT surveillance of the chest in the first 2 to 3 years off therapy.[34] Furthermore, clinicians today are better able to predict which tumors are at higher risk of relapse, depending on histologic favorability and other prognostic factors. Several studies suggest that patients with more favorable prognostic factors might be adequately monitored with an abdominal ultrasound and chest plain radiographs instead, to mitigate imaging radiotoxicity exposure.[34]

Depending on a patient's treatment course, monitor for late adverse reactions to treatment. Cardiotoxicity, often the result of cumulative doxorubicin dosing, predisposes patients to developing heart failure. Radiation, especially with higher doses, often predisposes patients to growth restrictions and pulmonary complications. Renal complications are more commonly seen among patients with the aforementioned predisposing syndromes, such as Denys-Drash syndrome. Secondary malignancies are seen in 6.7% of survivors as long as 40 years after initial diagnosis, and include breast cancer, melanoma, and hematologic malignancies.[27,35] Lastly, studies have highlighted that survivors of Wilms tumor have higher rates of social hardships, greater need for special education, and greater use of psychoactive medication.[39]

CONCLUSION

Wilms tumor is the most common pediatric renal malignancy. Although family history is a risk factor, most cases occur sporadically, highlighting the need for appropriate screening during well-care visits. Patients most commonly present between ages 1 and 4 years, and Wilms tumor is more common in males and Black patients. A patient presenting with a nontender, unilateral, firm, smooth, abdominal mass should be cautiously examined to avoid tumor rupture or spillage and should initially be evaluated with an abdominal ultrasound. Clinicians must remain cognizant of the various predisposing syndromes and their hallmark features, so that appropriate screening precautions may be incorporated into routine well-care visits. Patients who have a positive screening ultrasound should undergo abdominopelvic CT or MRI; preferably MRI if bilateral disease is suspected.

In patients with concomitant respiratory symptoms, be mindful of the potential for pulmonary metastasis and include a CT of the chest with IV contrast. Patient and family education is key, especially in the primary care setting, as is urgent outpatient pediatric hematology-oncology

referral. Surgery most often is the initial step in management, followed by neo-adjuvant chemotherapy. Postoperatively, the tumor will be further examined, allowing for histology identification and staging. Following treatment, patients require frequent imaging surveillance to assess for recurrence. **JAAPA**

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REFERENCES

1. American Cancer Society. 2024—first year the US expects more than 2M new cases of cancer. www.cancer.org/research/acs-research-news/facts-and-figures-2024.html. Accessed September 17, 2024.
2. National Cancer Institute. Childhood cancers. www.cancer.gov/types/childhood-cancers. Accessed September 17, 2024.
3. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA Cancer J Clin*. 2024;74(1):12-49.
4. Caldwell BT, Wilcox DT, Cost NG. Current management for pediatric urologic oncology. *Adv Pediatr*. 2017;64(1):191-223.
5. Leslie SW, Sajjad H, Murphy PB. Wilms tumor. Treasure Island, FL: StatPearls Publishing. www.ncbi.nlm.nih.gov/books/NBK442004. Accessed September 17, 2024.
6. National Cancer Institute. Wilms tumor and other childhood tumors treatment. www.cancer.gov/types/kidney/hp/wilms-treatment-pdq. Accessed September 17, 2024.
7. Murphy AJ, Davidoff AM. Bilateral Wilms tumor: a surgical perspective. *Children (Basel)*. 2018;5(10):134.
8. Nelson MV, van den Heuvel-Eibrink MM, Graf N, Dome JS. New approaches to risk stratification for Wilms tumor. *Curr Opin Pediatr*. 2021;33(1):40-48.
9. Libes J, Hol J, Neto JCA, et al. Pediatric renal tumor epidemiology: global perspectives, progress, and challenges. *Pediatr Blood Cancer.* 2022;70(1):e30006.
10. Surveillance, Epidemiology, and End Results. Mortality—kidney and renal pelvis, aggregated with age, total US (2016-2019). https://seer.cancer.gov/statfacts/html/kidrp.html. Accessed October 1, 2024.
11. Doganis D, Panagopoulou P, Tragiannidis A, et al. Childhood nephroblastoma in Southern and Eastern Europe and the US: incidence variations and temporal trends by human development index. *Cancer Epidemiol*. 2018;54:75-81.
12. Rios P, Bauer H, Schleiermacher G, et al. Environmental exposures related to parental habits in the perinatal period and the risk of Wilms' tumor in children. *Cancer Epidemiol*. 2020;66.
13. Huff V. Wilms' tumours: about tumour suppressor genes, an oncogene and a chameleon gene. *Nat Rev Cancer*. 2011;11(2):111-121.
14. Rosenblum S, Pal A, Reidy K. Renal development in the fetus and premature infant. *Semin Fetal Neonatal Med*. 2017;22(2):58-66.
15. Charlton J, Irtan S, Bergeron C, Pritchard-Jones K. Bilateral Wilms tumour: a review of clinical and molecular features. *Expert Rev Mol Med*. 2017;19:e8.
16. Liang H, He Y, Fu L, et al. Extrarenal Wilms tumor in children: a retrospective observational case series. *J Pediatr Urol*. 2020;16(5):664.e1-664.e7.
17. Lipska BS, Ranchin B, Iatropoulos P, et al. Genotype-phenotype associations in WT1 glomerulopathy. *Kidney Int*. 2014;85(5):1169-1178.
18. Morris MR, Astuti D, Maher ER. Perlman syndrome: overgrowth, Wilms tumor predisposition and DIS3L2. *Am J Med Genet C Semin Med Genet*. 2013;163C(2):106-113.
19. Scott RH, Walker L, Olsen ØE, et al. Surveillance for Wilms tumour in at-risk children: pragmatic recommendations for best practice. *Arch Dis Child*. 2006;91(12):995-999.
20. Duffy KA, Trout KL, Gunckle JM, et al. Results from the WAGR syndrome patient registry: characterization of WAGR spectrum and recommendations for care management. *Front Pediatr*. 2021;9:733018.
21. Garcia-de-Teresa B, Rodriguez A, Frias S. Chromosome instability in Fanconi anemia: from breaks to phenotypic consequences. *Genes*. 2020;11(12):1528.
22. Tenorio J, Arias P, Martinez-Glez V, et al. Simpson-Golabi-Behmel syndrome types I and II. *Orphanet J Rare Dis*. 2014;9:138.
23. Weksberg R, Shuman C, Beckwith JB. Beckwith-Wiedemann syndrome. *Eur J Hum Genet*. 2010;18(1):8-14.
24. Duffy KA, Grand KL, Zelley K, Kalish JM. Tumor screening in Beckwith-Wiedemann syndrome: parental perspectives. *J Genet Couns*. 2018;27(4):844-853.
25. Mussa A, Russo S, Larizza L, et al. (Epi)genotype-phenotype correlations in Beckwith-Wiedemann syndrome: a paradigm for genomic medicine. *Clin Genet*. 2016;89(4):403-415.
26. Liu EK, Suson KD. Syndromic Wilms tumor: a review of predisposing conditions, surveillance and treatment. *Transl Androl Urol*. 2020;9(5):2370-2381.
27. Szychot E, Apps J, Pritchard-Jones K. Wilms' tumor: biology, diagnosis and treatment. *Transl Pediatr*. 2014;3(1):12-24.
28. Miura H, Kawana S, Sugino S, et al. Successful management of an infant with hypertensive heart failure associated with Wilms' tumor: a case report. *JA Clin Rep*. 2020;6:12.
29. Sahu I, Ruhela M, Ola RK. Left atrial metastasis of a Wilms' tumor: a rare occurrence. *J Fam Med Prim Care*. 2020;9(8):4460-4462.
30. Zhang Y, Song H-C, Yang Y-F, et al. Preoperative Wilms tumor rupture in children. *Int Urol Nephrol*. 2021;53:619-625.
31. Coppes MJ. Serum biological markers and paraneoplastic syndromes in Wilms tumor. *Med Pediatr Oncol.* 1993;21(3):213-221.
32. Colonne CK, Favaloro EJ, Pasalic L. The intriguing connections between von Willebrand factor, *ADAMTS13* and cancer. *Healthcare*. 2022;10(3):557.
33. Michiels J, Schroyens W, Berneman Z, van der Planken M. Atypical variant of acquired von Willebrand syndrome in Wilms tumor: is hyaluronic acid secreted by nephroblastoma cells the cause? *Clin Appl Thromb Hemost*. 2001;7(2):102-105.
34. Servaes SE, Hoffer FA, Smith EA, Khanna G. Imaging of Wilms tumor: an update. *Pediatr Radiol*. 2019;49(11):1441-1452.
35. Milford K, DeCotiis K, Lorenzo A. Wilms tumor: a review of current surgical controversies. *Transl Androl Urol*. 2020;9(5):2382-2392.
36. Dhar M, Prakash S, Pandey V, Pai VK. Intraoperative tumor lysis syndrome in a child with Wilms' tumor. *Anesth Essays Res*. 2016;10(1):145-147.
37. Tang F, Zhang H, Lu Z, et al. Prognostic factors and nomograms to predict overall and cancer-specific survival for children with Wilms' tumor. *Dis Markers*. 2019;2019:1-11.
38. Dorantes-Acosta E, Avila-Montiel D, Klunder-Klunder M, et al. Survival and complications in pediatric patients with cancer and COVID-19: a meta-analysis. *Front Oncol*. 2021;10.
39. Foster RH, Hayashi RJ, Wang M, et al. Psychological, educational, and social late effects in adolescent survivors of Wilms tumor: a report from the Childhood Cancer Survivor Study. *Psychooncology*. 2021;30(3):349-360.
40. Andreas D, Glick R, Fish J, et al. Association of Wilms tumor in multicystic dysplastic kidneys: case report and review of the literature. *J Clin Urol*. 2021;16(4):360-363.
41. Kalish JM, Doros L, Helman LJ, et al. Surveillance recommendations for children with overgrowth syndromes and predisposition to Wilms tumors and hepatoblastoma. *Clin Cancer Res*. 2017;23(13):e115-e122.