An Approach to Renal Masses in Pediatrics

Alpin D. Malkan, MDa, Amos Loh, MDa, Armita Bahrami, MDb, Fariba Navid, MDc,d, Jamie Coleman, MD,e, Daniel M. Green, MDf, Andrew M. Davidoff, MDa, John A. Sandoval, MDa

abstract

Renal masses in children may be discovered during routine clinical examination or incidentally during the course of diagnostic or therapeutic procedures for other causes. Renal cancers are rare in the pediatric population and include a spectrum of pathologies that may challenge the clinician in choosing the optimal treatment. Correct identification of the lesion may be difficult, and the appropriate surgical procedure is paramount for lesions suspected to be malignant. The purpose of this article is to provide a comprehensive overview regarding the spectrum of renal tumors in the pediatric population, both benign and malignant, and their surgical management.

Renal cancers are rare in children, accounting for 6% to 7% of all childhood tumors.1 They can be detected by a parent bathing or holding the child, during routine physical examination or screening of children with known clinical syndromes with predispositions to renal disease,2 or incidentally during investigations for other intraabdominal processes.3–5 The key challenge is distinguishing malignant neoplasms from benign masses. A thorough understanding of the profile of common renal masses in children, as well as their associated clinical and imaging features, can facilitate accurate preoperative diagnosis and optimize patient care.

This article comprehensively reviews the approach to identifying renal cancers in children, individually summarizes the history, diagnosis, histopathology, and management of malignant and benign pediatric renal masses (Table 1), and provides the rationale for choice of the correct surgical procedure.

APPROACH

The priority of management is the differentiation of nonneoplastic processes from benign and malignant neoplasms (Fig 1). A thorough review of the patient’s clinical history and physical examination may reveal additional signs or symptoms to aid in the diagnosis. This may be useful in characterizing nonneoplastic renal pseudotumors, which are masslike imaging findings that mimic neoplasms.6 The presence of flank pain, fever, or pyuria, for example, is suggestive of an infective process, such as pyelonephritis, instead of a tumor. However, the absence of symptoms neither suggests nor refutes a diagnosis of malignancy. This will be particularly true of congenital anomalies such as prominent columns of Bertin or dromedary humps.

Although masslike renal lesions in children can sometimes be suspected on plain radiographs and evaluated with ultrasound, subsequent computed tomography (CT) is usually necessary for further characterization and confirmation of the diagnosis.7 Several image-based criteria can help to guide the differentiation of malignant from benign lesions.8 For solid lesions, once pseudotumors are excluded, the presence of contrast enhancement may be indicative of a neoplasm although...
several other abnormalities including infection (pyelonephritis) and abscess require consideration. The claw sign is classically seen as the tumor grows due to the normal kidney being splayed around the tumor and indicative of renal origin.9 CT and especially MRI can characterize the tissue composition of these solid lesions and can differentiate soft tissue from fat, fluid, or hemorrhage. On serial imaging, an enlarging mass can spur worries about a neoplasm, although absolute tumor size may not correlate well with malignancy risk.

For cystic masses, the Bosniak renal cyst classification is well established in the literature for malignancy risk prediction in image-detected renal cysts in adults.10 Based on this classification system, the lesion’s imaging (originally based on CT findings, but ultrasound and MRI are commonly applied) morphology and enhancements characteristics are used to categorize each lesion into 1 of 5 groups (I and II are benign and do not require further evaluation; IIF requires follow-up to prove benignity; III are indeterminate and considered surgical lesions although some may prove to be benign; IV are clearly malignant cystic masses that require surgical removal).8,11–13 A modified Bosniak classification has been shown to correlate fairly well with pathologic outcomes of complex renal cysts in children but has not been formally validated.14

**TABLE 1 Renal Lesions in Children**

<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiomyolipomas</td>
<td>WT</td>
</tr>
<tr>
<td>Renal pseudotumor</td>
<td>Renal cell carcinoma</td>
</tr>
<tr>
<td>MA</td>
<td>Clear cell</td>
</tr>
<tr>
<td>Multicystic nephroma</td>
<td>Medullary carcinoma</td>
</tr>
<tr>
<td>Metanephric stromal tumor</td>
<td>Multicystic</td>
</tr>
<tr>
<td>ORTl</td>
<td>Chromophil</td>
</tr>
<tr>
<td>Reninoma</td>
<td>Chromophobe</td>
</tr>
</tbody>
</table>

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
</table>

**FIGURE 1**

Renal mass algorithm.

**IMPLICATIONS FOR BIOPSY**

Despite thorough clinical and radiographic evaluation, some renal masses will remain indeterminate, and their management is subject to individual clinical opinions. Careful correlation of clinical and imaging findings may facilitate the preoperative diagnosis of most renal lesions. Although histologic evaluation is the gold standard for pathologic diagnosis, obtaining tissue biopsy via percutaneous (using Tru-cut biopsy, open biopsy, or fine-needle aspiration) or open surgical approach can have serious implications that require consideration. If a renal mass is suspicious for malignancy, the multidisciplinary team in addition to the surgeon typically determines the potential for complete resectability of the primary mass, and whether there is any evidence of metastatic disease on preoperative imaging. If the mass is determined to be unresectable then the issue of biopsy becomes more apparent to guide therapy.

In children, general anesthesia is typically needed to perform either an open or percutaneous biopsy. An open biopsy requires an incision, allows for large specimens to be obtained as compared with a percutaneous needle approach; however, this method inevitably causes the patient more discomfort, increased recovery time, and scarring. Even more problematic is obtaining an inadequate sample with potential for sampling error. In many cases, a percutaneous needle biopsy cannot differentiate renal lesions such as Wilms tumor (WT) from hyperplastic nephrogenic rests.15 More disturbing are the consequences of upstaging the tumor, which is used to describe a patient’s cancer from a lower stage (less extensive) to a higher stage (more extensive),15 necessitating administration of additional chemotherapeutic agents and/or radiation therapy. For instance, in
lower stage WT without anaplasia, complete resection of the mass, along with adjuvant chemotherapy, results in cure rates of over 90% at 5 years, whereas resection alone results in 20% long-term survival rate.\textsuperscript{16,17} A preoperative needle biopsy in this particular scenario would upstage the malignancy, and the possible need for more aggressive treatment, including chemotherapy and radiation.

An emphasis on the multidisciplinary approach is essential to the evaluation and treatment of these patients including the pediatrician, pediatric radiologist, pediatric surgeon, pediatric urologist, pediatric oncologist, pediatric radiation oncologist, and pathologist. The key characteristics of a comprehensive spectrum of pediatric renal masses are outlined below.

**MALIGNANT NEOPLASMS**

**Wilms tumor**

WT, also called nephroblastoma, is the most common pediatric renal malignancy,\textsuperscript{18–21} accounting for ~6% to 7% of all childhood renal cancers,\textsuperscript{18} and is observed at a frequency of 1:10 000 newborn infants,\textsuperscript{18,22} occurring mostly between 2 and 5 years of age.\textsuperscript{19} Most cases are sporadic, although it can occur in hereditary form with autosomal dominant inheritance, variable penetrance, and several affected generations.\textsuperscript{18} Symptoms may include abdominal pain, distension, and hypertension; however, the patient can also be asymptomatic. Bilaterality occurs in 4% to 13% of cases. WT may be associated with genitourinary anomalies and some congenital syndromes such as WAGR, Denys-Drash, and Beckwith-Wiedemann syndromes (BWS).\textsuperscript{15}

WAGR syndrome includes WT, aniridia (absence of the colored part of the eye), genitourinary abnormalities (gonadal tumors), and mental retardation.\textsuperscript{15} Interstitial deletion on chromosome 11p13 (prevalence of 0.4% of children with WT),\textsuperscript{15,23} and bilateral WT (15%) may be seen in association with WAGR syndrome.\textsuperscript{15,24} Denys-Drash syndrome is characterized by the triad of WT, pseudohermaphroditism, and chronic renal failure. Individuals with Denys-Drash syndrome manifest early nephrotic syndrome, which progresses to diffuse mesangial sclerosis and subsequent renal failure usually within the first 3 years of life. Germline missense mutations in the WT1 gene are responsible for most WTs that occur as part of the Denys-Drash syndrome\textsuperscript{25} including the 90% risk of developing WT.\textsuperscript{15,26} BWS includes macrognlossia, macrosomia (birth weight and length greater than the 90th percentile), midline abdominal wall defects (omphalocele, umbilical hernia, diastasis recti), ear creases or ear pits, and neonatal hypoglycemia. It is also characterized by the development of WT (bilateral),\textsuperscript{27} rhabdomyosarcoma, and hepatoblastoma.\textsuperscript{15} BWS results from constitutional loss of imprinting or heterozygosity of WT2.\textsuperscript{15} Approximately 1 of 5 patients with BWS and WT may present with bilateral disease; however, metastronous bilateral disease is also observed.\textsuperscript{15,28–30} WT typically appears as a large, smooth, well-defined intrarenal mass with uniform echogenicity that often displaces neighboring structures. WT is usually seen first on ultrasound, and subsequently with less enhancement on CT than adjacent normal parenchyma (Fig 2).\textsuperscript{7} Calcifications, fat density, patches of renal parenchymal enhancement, invasion of the renal collecting system, vascular invasion with tumor thrombus extension into the renal vein and inferior vena cava (most accurately evaluated on MRI), or the presence of distant lung metastases may be seen.\textsuperscript{7} Rarely, it may be largely cystic, an entity referred to as cystic partially differentiated nephroblastoma, that cannot be differentiated from cystic nephroma on imaging, but outcomes of both are favorable regardless of treatment.\textsuperscript{31} Current imaging modalities may fail to detect occult synchronous contralateral tumors at the time of initial diagnosis, but these occur in only a very small percentage of patients with WT, and outcomes for these patients have also been excellent.\textsuperscript{32}

Preoperative staging studies in patients suspected of having WT include CT (or MRI) scans of the chest, abdomen, and pelvis.\textsuperscript{15} The stage is determined by the results of imaging studies, as well as surgical and pathologic findings at time of nephrectomy, and is the same for tumors with favorable or anaplastic histology. In stage I (43% of patients) and II (20%) WTs, the tumor is completely resected without evidence of tumor at or beyond the margins of resection.\textsuperscript{15} Stage III (21%) and IV (11%) WTs have either residual nonhematogenous tumor present after surgery that is confined to the abdomen or hematogenous metastases or lymph node metastases outside the abdominopelvic region are present, respectively.\textsuperscript{15} Lymph node and major blood vessel involvement (encasement and/or thrombus) are reflective of advanced, potentially unresectable disease and higher stage (III or IV).\textsuperscript{15}

Histologically, WT can be separated into prognostic groups including favorable histology, anaplastic histology, and nephrogenic rests. Anaplastic histology is characterized by multipolar polypoid mitotic figures with marked nuclear enlargement and hyperchromasia and is the single most important predictor of response and survival.\textsuperscript{15} Anaplasia correlates best with responsiveness to therapy rather than to aggressiveness, and is most consistently associated with poor prognosis when it is diffusely distributed or identified at advanced stages.\textsuperscript{15} Nephrogenic rests are abnormally retained embryonic kidney precursor cells arranged in
clusters that are considered to increase the risk for tumor formation in the remaining kidney.\textsuperscript{15}

Unilateral WT is generally treated with nephrectomy followed by adjuvant chemotherapy. Neoadjuvant chemotherapy may be used to promote tumor shrinkage and is used in bilateral (Fig 3) or inoperable WTs and in selected treatment protocols. Postoperative radiation therapy may be administered to the tumor bed for local control, or to the whole abdomen in cases of gross spillage or dissemination. Metastatic disease and unfavorable histology are poor prognostic factors in WT.\textsuperscript{15,33}

Children with WAGR syndrome or other germline WT mutations require monitoring throughout their lifetime because of the increased risk of developing hypertension, nephropathy, and renal failure.\textsuperscript{15,33} Current screening recommendations for children with WAGR, Denys-Drash, and BWS or any genetic predisposition (overgrowth syndrome, sporadic aniridia, or isolated hemihypertrophy) that increases the chance of developing WT include abdominal ultrasounds every 3 months until 8 years of age.\textsuperscript{15,28,34–36} Approximately 5\% to 10\% of individuals with WT have bilateral or multicentric tumors, and those with genetic predisposition have an increased prevalence.\textsuperscript{15,37} Eighty-five percent of patients with either WAGR or BWS have unilateral tumors.\textsuperscript{15,37} Because ~10\% of patients with BWS will develop a malignancy, most commonly WT or hepatoblastoma, screening with abdominal ultrasound in addition to serum a-fetoprotein is recommended until age 4 (because most hepatoblastoma occur before this age), with renal ultrasounds thereafter.\textsuperscript{38} Currently, there is no standard approach for the treatment of those predisposed to developing bilateral WT.

Patients with Denys-Drash syndrome are faced with a significant challenge regarding the controversial need for early prophylactic bilateral nephrectomies as a means to diminish the potential development of WT,\textsuperscript{39–44} the adverse effects of chemotherapy, including the prolongation of time to consideration for transplantation, and to reduce metabolic and nutritional sequelae of chronic renal failure.\textsuperscript{40} Some authors propose careful monitoring of patients every 4 to 6 months by abdominal ultrasonography and performing nephrectomy after the onset of end-stage renal failure\textsuperscript{45,46}; however, others feel it is preferable to proceed with bilateral nephrectomies “early” rather than “late” in the course of the underlying renal disease.\textsuperscript{40}

**Clear Cell Sarcoma of the Kidney**

Clear cell sarcoma of the kidney (CCSK) is the second most common renal tumor in children, accounting for 3\% to 5\% of all childhood cancers.\textsuperscript{47–50} It commonly appears in children younger than 4 years of age.\textsuperscript{18,22,51} CCSK is an aggressive
tumor with a unique predilection for bone and brain metastasis, but can also spread to the lung and abdomen. Symptoms may include abdominal pain, hypertension, and hematuria. Typical presentation includes a large, unilateral, well-circumscribed, sharply demarcated mass that compresses the surrounding normal renal parenchyma and displaces the collecting system (Fig 4). CCSK is described as an enigmatic tumor type because its morphologic appearance does not resemble that of the kidney. It can mimic and be mimicked by WT, congenital mesoblastic nephroma, and rhabdoid tumor of the kidney.

The classic microscopic pattern includes cords of round or spindle-shaped cells with clear cytoplasm and ovoid to rounded vesicular nuclei with inconspicuous nucleoli. The cells are surrounded by fibrovascular septa ranging from a thin “chicken-wire” arrangement to broad sheets containing an arborizing capillary vasculature. Cytogenetic abnormalities involving recurring translocations in t(10;17)(q22;p13/p12) and deletion of 14q24q31 have been described in CCSK. Staging according to the National Wilms Tumor Study Group (NWTS) definition demonstrated that stages I to III are nearly equally represented (25%, 37%, 34%, respectively), whereas 4% present with stage IV and evidence of metastatic disease. 29% of CCSK cases may have evidence of lymph node metastases. Ipsilateral renal hilar lymph nodes are the most common site of metastases and underscore the importance of lymph node sampling in staging. Current multimodal treatment consists of radical nephrectomy for resectable tumors followed by intensive chemotherapy and radiotherapy.
The addition of doxorubicin to the treatment protocol has led to actuarial 6-year survival approaching 98% for localized disease.47

Renal Cell Carcinoma

Renal cell carcinoma (RCC) accounts for <0.3% of all childhood tumors,55 is the most common renal tumor in adolescents,56 and the average age of presentation is approximately 10–11 years old.57,58 RCC is a malignancy thought to arise from epithelial cells of the renal tubule.57 Several histologic subtypes of RCC exist, including clear-cell and medullary carcinoma (Fig 5), multicystic,59 chromophil, chromophobe,60 and collecting duct.2,61,62 Papillary and translocation, Xp11.263 (Fig 6) or the t(6:11), types are more common in children.18,64,65 RCCs are seen with greater frequency in childhood cancer survivors55,66,67 and in genetic syndromes such as von Hippel-Lindau disease, tuberous sclerosis,20,55,68 familial clear-cell renal cancer, hereditary papillary renal carcinoma, hereditary leiomyomatosis, and renal cell cancer syndrome, in individuals with cystic or end-stage renal diseases,69,70 sickle cell hemoglobinopathies, and in pediatric kidney transplant recipients.61

Unlike WT, RCC is rarely asymptomatic (only 12% of cases).56 Diagnostic clues may include the classic triad of gross, painless hematuria, flank pain, and the presence of a palpable mass.20,56,71,72 Metastases most commonly occur in the lungs (40% to 65%) and bones (10% to 42%); however, the liver (35% to 57%), bladder, brain, or pleura (7% to 15%) may also be involved.58 Abdominal ultrasound with a subsequent CT scan is used to better define the neoplasm.73 Distinguishing between RCC and other renal tumors requires histologic examination, and usually few if any hints come from imaging.56 Although on CT, RCC typically reveals a large, heterogeneous, solid mass with either well-circumscribed or poorly defined borders.7 Intravenous enhancement of the tumor is usually less than the adjacent normal parenchyma.7,51 RCC tends to be smaller than WT, invade tissues locally with distortion of normal renal architecture, and formation of a pseudocapsule that contain foci of calcification. Regional lymphadenopathy and vascular invasion are commonly seen.7 RCC histology demonstrates epithelial cells of renal tubule origin with moderate to large amounts of clear and variably eosinophilic cytoplasm with nested, solid, acinar, and/or tubulopapillary architectural growth.
patterns. Papillary growth pattern has been associated with advanced stage by some authors although there are no definitive conclusions regarding the role of histopathology on outcome. Translocation RCC is immunoreactive for TFE3 nuclear protein, and positive by reverse transcription-polymerase chain reaction for the ASPL-TFE3 fusion transcript. Additionally, renal medullary carcinoma is associated with sickle cell hemoglobinopathy and is most commonly seen in young adults. Histologically, it displays various morphologies including reticular, yolk sac, or adenoid cystic growth pattern and sometimes reveals neoplastic cells admixed with neutrophils in a desmoplastic background. Loss of heterozygosity at chromosome 22q11 and q12 and the lack of SMARCB1 protein expression are commonly seen.

Tumor stage appears to be the most important factor for survival. The 5-year survival for stage I is 90% or higher, for stages II and III it is 50% to 80%, and for stage IV is 9%, which is similar to the stage-for-stage survival in RCC in adults. Although the therapeutic value of complete retroperitoneal lymph node dissection is still controversial, the presence of lymph node disease is known to significantly worsen the survival of patients with RCC. The mainstay of treatment remains radical nephrectomy with regional lymphadenectomy; however, nephron sparing surgery has been performed with success. RCCs are generally resistant to traditional cytotoxic therapies and are poorly responsive to radiotherapy. Immunotherapy, such as interferon-α and interleukin-2, may have some effect on cancer control.

Several targeted agents (for example, sorafenib, sunitinib, bevacizumab, temsirolimus, pazopanib, and everolimus) have been approved for use in adults with RCC; however, these have undergone limited testing in pediatric patients.

Nephroblastomatosis

Closely associated with WT, nephroblastomatosis is an abnormality of renal development characterized by persistence of nephrogenic rests, which are foci of metanephrine blastema that persist into infancy. Metanephric blastema is an embryonic structure with cells derived from the intermediate mesoderm that normally mostly give rise to the nephron. These premalignant lesions are believed to give rise to the nephron. They are detected incidentally in 1% of infants and are associated with

FIGURE 6
Xp11.2 translocation RCC. A, Axial contrast-enhanced CT of the abdomen reveals a heterogeneous mass in the right kidney (white arrows). Central hypodensity likely reflects necrosis. Note also the thin crescent rim of hyperdense calcification (black arrow). B, Axial image reveals the heterogeneous renal mass (white arrow), as well as adjacent retroperitoneal lymphadenopathy consistent with metastatic disease (black arrows). C, Axial T2-weighted image from MRI on the same patient demonstrates heterogenous signal in the primary right renal mass (white arrow) with slightly more homogeneous signal in the adjacent lymphadenopathy (black arrow). D, A large well-circumscribed renal mass with a variegated surface and large necrotic and hemorrhagic areas in a 17-year-old boy. E, Hematoxylin and eosin section reveals epithelial cells with abundant eosinophilic cytoplasm with papillary architecture. F, Tumor cells are immunoreactive for TFE3 nuclear protein, and the ASPL-TFE3 fusion transcript was positive by reverse transcription-polymerase chain reaction.
BWS, hemihypertrophy and Perlman syndrome in their perilobar form, and with Denys-Drash syndrome, WAGR syndrome, and sporadic aniridia in their intralobar form.7

The diagnosis can be made radiographically and may appear on CT as low-attenuation, multifocal nodules located at the renal periphery with mild contrast enhancement or as diffuse nephromegaly with retention of the kidney’s reniform shape.22 MRI is particularly useful for diagnosis of nephroblastomatosis when it demonstrates homogeneity of the hypointense rindlike lesion on contrast enhancement, which differentiates it from WT.15 Microscopic findings range from benign small nests of blastemal cells to large areas with frank malignant transformation (WT), and is extremely difficult to differentiate between the 2 based on needle or even incisional biopsies alone.90,91 Current recommendations are for treatment with chemotherapy (vincristine and dactinomycin) until nearly complete resolution as determined by imaging.15 However, given the high incidence of bilaterality and the subsequent development of WT, renal sparing surgery is indicated (partial nephrectomy).15,89

**Rhabdoid Tumor**

Rhabdoid tumor of the kidney is a highly aggressive neoplasm accounting for <2% of all pediatric renal malignancies.18 This typically occurs in children younger than 2 years of age and is one of the most lethal, malignant solid tumors in children, with an overall survival rate <25%.92 A distinct clinical presentation with fever, hematuria, young age (mean age 11 months), and high tumor stage at presentation suggests a diagnosis of rhabdoid tumor of the kidney15,93; however, hypercalcemia due to elevated parathormone levels may also be found.7,22 Characteristic CT features include hemorrhage, necrosis, and tumor lobules lined by calcification.22,51 A peripheral subcapsular crescent with attenuation of fluid may be seen in 71% of patients (Fig 7).94 Synchronous or metachronous primary intracranial masses or brain metastases have been established as distinctive features.22 Germline mutations in SMARCB1 (also known as SNF5 or INI1) gene95,96 are seen in ~35%97 of patients with rhabdoid tumor consistent with a genetic predisposition.15,98 The most distinct histologic findings are rather large cells with large vesicular nuclei, a prominent single nucleolus, and in some cells, the presence of globular eosinophilic cytoplasmic inclusions.15,99 Treatment modalities include chemotherapy and nephrectomy; however, current therapy has limited efficacy for this patient population.100,101 Four-year overall survival rates for stages I and II are 42% and stage III and IV are 16%.92

**Congenital Mesoblastic Nephroma**

Mesoblastic nephroma, the most common solid renal tumor in infancy,20,21,102,103 is a low grade fibroblastic sarcoma most commonly affecting infants younger than 3 months, and >90% of cases appear within the first year of life.15,18,21 The associated manifestations include hypercalcemia with polyuria, congestive heart failure, and hypertension.7 Prenatal ultrasound may be helpful because in most cases the diagnosis can be made in the neonatal period as it can lead to polyhydramnios (71% of gestations associated with this tumor), and premature birth.21,104,105 A concentric hyperechoic and hypoechoic ring pattern known as the vascular “ring” sign may also be seen surrounding the tumor.106 Postnatal CT typically reveals a large, heterogeneous, solid intrarenal mass with smooth margins that enhances to a lesser degree than the adjacent normal renal parenchyma after intravenous contrast administration (Fig 8).7,104

Based on histopathologic appearances, congenital mesoblastic nephroma is subtyped into classic (24%), cellular (66%), and mixed (10%) types.103,105,107–109 The classic form is morphologically identical to infantile fibromatosis of the renal sinus109 with fusiform

![FIGURE 7](image-url)

Rhabdoid tumor. A, Axial contrast-enhanced CT of the abdomen demonstrates a hypodense solid mass in the right kidney (white arrow). B, Another image from the same CT reveals a second solid mass in the contralateral left kidney (white arrows). C, Axial gadolinium-enhanced T1 weighted image from this patient’s brain MRI confirms an enhancing mass in the left frontal lobe, in keeping with a synchronous atypical teratoid rhabdoid tumor.
spindle cells and rare mitoses. The cellular form is identical to infantile fibrosarcoma, is characterized by a highly cellular spindle cell proliferation with minimal intervening collagen/supporting stroma, and high nuclear-to-cytoplasm ratios. The cellular variant carries a specific translocation, t(12;15)(p13;q25), involving the ETV6 and NTRK3 genes, similar to the translocation seen in infantile fibrosarcoma. The mixed type is composed of areas of low (formed by elongated spindle cells resembling fibroblastic cells seen in benign myofibromas) and high cellularity. Complete surgical resection via radical nephrectomy is adequate therapy for most patients and reduces the risk of local recurrence. In stage III patients (incomplete resection and/or histologically positive resection margin), or those with cellular subtype, and aged 3 months or older at diagnosis are at increased risk for local and eventually metastatic recurrence. This select group of patients are recommended to have adjuvant chemotherapy. Five-year event-free survival rate is 94%, and the overall survival rate is 96% when diagnosed within the first 7 months of life.

Anaplastic Sarcoma

Anaplastic sarcoma of the kidney is a recently recognized pediatric tumor seen in children or adolescents younger than 15 years of age with a female predominance. Patients typically present with a large renal mass, and the most common sites of metastases are the lung, liver, and bones. The main histologic features are the presence of undifferentiated spindle cells arranged in short fascicles as well as undifferentiated small round primitive mesenchymal cells, very marked cellular anaplasia with giant pleomorphic cells, and usually prominent areas of benign or malignant cartilage or chondroid differentiation. Optimal therapy for this tumor is currently unclear.

Other Renal Neoplasms

Several other renal malignant tumors are even less common in children. Desmoplastic small round cell tumor (DSRCT) and Ewing sarcoma/primitive neuroectodermal tumor (PNET) of the kidney are extremely rare in children. DSRCT is aggressive, malignant, typically affects children 6 to 8 years of age but may also be seen in young adolescents and is diagnosed by its characteristic EWS-WT1 translocation. CT may reveal a hypovascular, heterogeneous, and well-circumscribed mass with internal punctate calcifications. It reveals similar histologic features as in the extrarenal sites consisting of nests, cords, or sheets of small undifferentiated cells with foci of necrosis, calcification, and desmoplasia. However, the definitive diagnosis of DSRCT is based on the presence of the typical translocation t(11;22)(p13;q12). Patients usually present at an advanced stage with a poor prognosis.

Ewing sarcoma/PNETs of the kidney are small round blue cell tumors. The tissue of origin is unknown; however, molecular profiling of these tumors suggests a mesenchymal cell origin. They are very aggressive, usually large and invasive, and typically have poorly defined margins with areas of hemorrhage and necrosis. The distinct vascular nature is manifested by an arborizing vascular pattern, perithelial arrangement of tumor cells, and perivascular pseudorosettes. More than 90% of renal Ewing sarcoma/PNETs have characteristic translocations involving rearrangement of the EWSRI gene on chromosome 22, t(11;22)(q24;q12). The treatment of these tumors is similar to their counterparts at other sites and includes a combination of chemotherapy, surgery, and/or radiation therapy. Synovial sarcoma of the kidney may present with an abdominal mass and flank pain. Histologically they demonstrate a monophasic, spindle cell appearance, with these stromal areas composed of relatively monomorphic, plump, ovoid spindle cells. This rare renal tumor is genetically characterized by translocation t[X;18](p11;q11).

RENAL TUMOR AS A SECOND MALIGNANCY

In pediatric patients with cancer, renal tumors may be detected on
imaging studies conducted during the course of their treatment or during cancer survivorship follow-up surveillance. RCC has been detected as a second malignancy during routine surveillance in survivors of leukemia, supratentorial PNET, WT, and neuroblastoma. In the Childhood Cancer Survivor Study, 51 kidney cancers were detected as second malignancies among 14,359 5-year survivors and another 28 as third or subsequent malignancies.

SECONDARY INVOLVEMENT OF THE KIDNEY

Primary lymphoma of the kidney is extremely rare. However, diffuse infiltration of the kidney may be observed in children with leukemia. Involvement of the kidney as seen in non-Hodgkin lymphoma and B-cell lymphomas is usually associated with hematogenous spread or direct extension of retroperitoneal disease. On imaging, lymphoma may appear in a variety of forms: as a solitary mass, diffuse nephromegaly, or bilateral multifocal nodules. The lattermost form may mimic nephroblastomatosis but is unusual in infants and young children. In contrast, leukemic involvement of the kidneys is seen on CT imaging as bilateral diffuse symmetric nephromegaly associated with decreased corticomedullary differentiation and decreased cortical enhancement. Adjacent or systemic lymphadenopathy is often also visualized on imaging when such renal lesions are detected.

BENIGN NEOPLASMS

Angiomyolipoma

Renal angiomyolipoma is considered a benign mesenchymal tumor, accounts for 3% of solid renal masses, and contains varying amounts of a disordered arrangement of blood vessels, smooth muscle, and adipose tissue. Although angiomyolipoma may occur sporadically, it is seen in up to 80% of patients with tuberous sclerosis (usually bilateral and/or multiple renal angiomyolipomas). It can be also seen in von Hippel-Lindau syndrome, neurofibromatosis, Sturge-Weber syndrome, autosomal dominant polycystic kidney disease, and pulmonary lymphangiomatosis. Presentation at extrarenal sites such as in the liver, spleen, abdominal wall, retroperitoneum, lung, and genital region may also be seen. Although largely asymptomatic, patients may present with flank pain, fever, nausea, vomiting, hematuria, hypertension, or even retroperitoneal hemorrhage due to aneurysm formation because of the abundant abnormal, elastin-poor vascularity of the tumor. Imaging appearance varies considerably based on the amount and type of histologic elements present. Diagnosis can usually be made by CT or MRI that reveals macroscopic fat; however, fat is not pathognomonic or unique to angiomyolipoma and is occasionally seen in WT and RCC. In fact, radiologic techniques using enhancement patterns and histogram analysis at CT and chemical shift MRI remain controversial to rule out RCC in histologically proven fat poor angiomyolipomas. A solid renal tumor without fat content on imaging studies is regarded as RCC and treated as such. Microscopically, angiomyolipomas are very cellular consisting mainly of myoid cells with vacuolated cytoplasm spinning off of large vessels in a background of mature fat. In asymptomatic lesions <4 cm, evaluation with abdominal ultrasound or CT scan should be performed biannually or yearly. In lesions that are >4 cm, symptomatic, or bilateral, arterial embolization and nephron sparing surgery are the treatments of choice because of the risk of hemorrhage. Angiomyolipoma of the kidney tumor remains a benign tumor with rare possibility of transformation to a malignancy; therefore, follow-up of these patients remains an important concern.

Follow-up evaluation requirement is proposed for asymptomatic patients with abdominal ultrasound or CT scan of the abdomen (risk of radiation exposure) or MRI at every 6- or 12-month intervals to monitor the number and size of lesions, and for aneurysm development. The modality used to image children remains a challenge. Ultrasonography is technically dependent, as compared with CT, which requires exposure to radiation, intravenous contrast, and the potential need for general anesthesia. Alternatively, MRI also requires intravenous contrast, with the potential need for general anesthesia and longer time required to complete imaging study. However, the significant advantage of MRI is its detailed imaging, and even more importantly is the elimination of radiation exposure, which makes this more optimal in children. Cost and the availability of these imaging modalities also impact the type of follow-up that may be provided.

Pseudotumors

Renal pseudotumors are masslike imaging findings (normal renal tissue) that mimic neoplasms. These are caused by a variety of conditions including renal congenital anomalies (prominent renal columns of Bertin, dromedary humps), inflammatory masses (focal pyelonephritis, renal abscesses), vascular structures (renal artery aneurysm or arteriovenous fistula), or abnormalities secondary to trauma or hemorrhage. A combination of patient demographics, clinical presentation, careful evaluation of specific imaging appearances on CT and/or MRI may provide useful information for evaluating this diverse group of etiologies. For example, a history of blunt abdominal trauma with microscopic hematuria may support a diagnosis of renal hematoma. CT features to support an
inflammatory process may include ill-defined margins and perinephric stranding, and abnormalities in the renal vasculature such as vessel hypertrophy may support a diagnosis of vascular malformation. In most cases, a familiarity with this group of masses in addition to a thorough clinical and radiologic evaluation should reveal the correct diagnosis.

**Metanephric Adenoma**

Metanephric adenoma (MA) is a rare, benign tumor of the renal cortex composed exclusively of epithelial and stromal elements. Patients can be asymptomatic or can have signs and symptoms related to polycythemia, hypertension, hematuria, dysuria, flank or abdominal pain, or a palpable abdominal mass. The lesion has radiologic similarities to RCC and WT, making preoperative diagnosis difficult. MAs have been diagnosed by using ultrasound or CT. Histologic features of MA reveal small uniform epithelial cells of an acinar, tubular, glomeruloid, or papillary growth pattern with a high nuclear-to-cytoplasmic ratio. MA due to the rarity of the tumor, potential for malignant degeneration, and inability to establish a diagnosis without histologic evaluation; therefore, nephron-sparing surgery or partial nephrectomy are considered sufficient in most cases. Although MA is considered benign with a good prognosis, reports of atypical histologic features, bone metastasis, and lymphatic dissemination may portend a poor prognosis.

**Cystic Nephroma**

Multicystic nephroma is an uncommon, noninheritable, unilateral, benign tumor that represents 2% to 3% of all primary renal tumors in children and is predominantly seen in boys. Children typically present with a painless, progressively enlarging, palpable abdominal or flank mass that has a variable growth rate and may be discovered incidentally. Flank pain, urinary tract infection or obstruction, hematuria, and hypertension may also be seen. CT may reveal a well-defined, nonenhancing cystic mass without solid components involving the kidney with multiple enhancing thin internal septa causing compression and stretching of the remaining enhancing renal parenchyma. The tumor is bulky, well-encapsulated, noninfiltrating, and composed of multiple noncommunicating, fluid-filled cysts. The presence of blastemal cells and poorly differentiated cells must be ruled out to diagnose this lesion. Complete resection either with nephrectomy or nephron-sparing surgery remains the treatment of choice because carcinomatous degeneration may occur within the wall of such tumors.

**Metanephric Stromal Tumor**

Metanephric stromal tumor is a benign stromal tumor of the kidney seen mostly within the first decade of life with a mean age at presentation of 2 years. The most common presentation is an abdominal mass. This tumor, MA, and metanephric adenofibroma represent a spectrum of well-differentiated nephroblastic lesions that appear to be related to WT. The most characteristic histologic features include an onion skin ring formation around entrapped tubules and blood vessels with vascular changes, including angiodysplasia/epithelioid transformation of medial smooth muscle and myxoid changes. It is composed primarily of spindle cells with a low proliferation index, and diffusely infiltrates the perirenal fat. Necrosis is usually curative, and patients have an overall excellent prognosis.

**Ossifying Renal Tumor of Infancy**

Ossifying renal tumor of infancy (ORTI) is a rare, benign renal tumor that may present as an abdominal mass typically in infants. Boys are more commonly affected, and gross hematuria is almost always observed due to bulging of the tumor into the pelvicalyceal system. A soft tissue mass with calcifications near the renal pelvis and no significant contrast enhancement may be seen on CT. Histologically, ORTI is characterized by 3 major components: an osteoid core, osteoblastlike cells, and spindle cells. The best treatment approach for this tumor involves resection with kidney preservation techniques.

**Reninoma**

Reninoma, also known as juxtaglomerular cell tumor, is a rare, benign cause of curable hypertension in children and adolescents. Patients may be found to have hypertension incidentally, which prompts further investigation leading to the discovery of clinical findings including hypokalemia, hyperaldosteronism, and high renin activity. Reninoma can be divided into typical, atypical, and nonfunctioning types depending on the blood pressure and serum potassium levels. Although ultrasound may in some circumstances be helpful, CT and even MRI remain the most useful imaging modalities to document the presence of a reninoma. It may appear isodense or hypodense as compared with the renal medulla; however, there is no definitive radiologic examination for the diagnosis of reninoma. Therefore, histopathologic evaluation with immunohistochemical staining aids in the correct diagnosis. Reninoma is composed of polygonal tumor cells within vascular stroma and thick-walled vessels. Immunohistochemical staining is particularly useful in differentiating reninoma from RCC and angiomyolipoma. Features
unique to reninoma include the tumor staining positively for CD34, and negatively for CD117, HMB-45, and S100 protein. Because these are usually small and rarely associated with metastasis, nephron sparing surgery is the standard treatment option allowing for preservation of renal function.

SUMMARY

Upon satisfactory exclusion of renal pseudotumors, renal neoplasms inevitably require some form of intervention to obtain a histologic diagnosis through biopsy or resection. Intervention for these masses is easily justified in view of their significant mass effect and the parental concern that such dramatic lesions would understandably generate. Management decisions need to be tempered with an understanding of the difference in profile of renal masses in children. Renal masses that are seen within the pediatric population, as discussed here, remain a delicate and sensitive issue. A combination of pathologic rarity, complexity, and uncertain malignant potential may lead to treatment that is either too aggressive, and, in retrospect unnecessary; or that is entirely too conservative when in fact aggressive measures are warranted. We encourage continued advancements in research to better define evidence-based approaches and treatment strategies for these challenging masses.

REFERENCES

27. Scott RH, Douglas J, Baskocom L, et al; Factors Associated with Childhood


[Review]


An Approach to Renal Masses in Pediatrics
Alpin D. Malkan, Amos Loh, Armita Bahrani, Fariba Navid, Jamie Coleman, Daniel M. Green, Andrew M. Davidoff and John A. Sandoval

Pediatrics originally published online December 1, 2014;

<table>
<thead>
<tr>
<th>Updated Information &amp; Services</th>
<th>including high resolution figures, can be found at: <a href="http://pediatrics.aappublications.org/content/early/2014/11/25/peds.2014-1011">http://pediatrics.aappublications.org/content/early/2014/11/25/peds.2014-1011</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>Permissions &amp; Licensing</td>
<td>Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: <a href="https://shop.aap.org/licensing-permissions/">https://shop.aap.org/licensing-permissions/</a></td>
</tr>
<tr>
<td>Reprints</td>
<td>Information about ordering reprints can be found online: <a href="http://classic.pediatrics.aappublications.org/content/reprints">http://classic.pediatrics.aappublications.org/content/reprints</a></td>
</tr>
</tbody>
</table>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2014 by the American Academy of Pediatrics. All rights reserved. Print ISSN: .
An Approach to Renal Masses in Pediatrics
Alpin D. Malkan, Amos Loh, Armita Bahrami, Fariba Navid, Jamie Coleman, Daniel M. Green, Andrew M. Davidoff and John A. Sandoval

Pediatrics originally published online December 1, 2014;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/early/2014/11/25/peds.2014-1011