# Chapter 10
# Pediatric Renal Tumors


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## Wilms Tumor

Wilms tumor is the most common primary renal malignancy in the pediatric population [1, 2]. Also known as nephroblastoma, Wilms tumor is comprised on the histological level of a classic pattern of three different cell types including blastemal, stromal, and epithelial elements [3]. Histopathology of Wilms tumor has important implications on outcomes and treatment as those tumors with unfavorable histologic features and anaplasia carry a poor prognosis even at low-stage disease and are more resistant to chemotherapy [4]. Outcomes for Wilms tumor have dramatically improved with survival rates approaching 90% in part due to multimodal therapy [5–7].

### *Epidemiology*

Each year approximately 500 new cases of Wilms tumor are diagnosed in the United States, with roughly 7.1 cases per one million patients younger than 15 years old and an equal distribution between male and female patients in unilateral cases [2]. The median age of onset for unilateral Wilms is 38 months; however, patients with bilateral disease typically present earlier in life (median 17–27 months) [2].

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## *Syndromes and Conditions Associated with Wilms Tumor*

Wilms tumor is typically sporadic; however, approximately 10% of children have an associated congenital anomaly [8]. Congenital syndromes associated with Wilms tumor can be separated into those with and without somatic overgrowth.

WAGR syndrome is characterized by Wilms tumor, aniridia, genitourinary anomalies, and mental retardation. This syndrome is associated with chromosomal deletions at 11p13 which contains the *WT1* gene [9]. Denys-Drash syndrome is another congenital disorder that is associated with mutations in the *WT1* gene and the development of Wilms tumor. Denys-Drash syndrome is otherwise characterized by male pseudohermaphroditism and renal failure [10]. The risk of developing Wilms tumor in Denys-Drash is approximately 90% [10].

Beckwith-Wiedemann is a somatic outgrowth syndrome that carries an increased risk of Wilms tumor in up to 10% of cases [11]. This syndrome is characterized by macroglossia, macrosomia, midline defects, skin creases near the ears, and neonatal hypoglycemia. Beckwith-Wiedemann syndrome is associated with abnormalities at chromosome 11p15 [11]. 9q22.3 microdeletion syndrome also carries an increased risk of developing Wilms tumor [12] and is characterized by metopic craniosynostosis, hydrocephalus, macrosomia, and developmental delay [13].

It is recommended that children at high risk of developing Wilms tumor be screened with an abdominal ultrasound every 3 months until 8 years of age [14, 15]. These syndromes that carry an increased risk of tumor development have helped gain important insight and greater understanding of the genetic cause of Wilms tumor.

A complete list of syndromes and conditions with associated cancer risk can be found in Table 10.1.

## *Genetics*

The *WT1* gene is located on the short arm of chromosome 11p13, and it is essential for normal genitourinary development [16, 17]. *WT1* mutations are identified in only 10–20% of cases of sporadic Wilms tumor [16, 18, 19]. Mutations in *WT1* have been found in WAGR syndrome, Denys-Drash syndrome, and Frasier syndrome [10, 20]. Somatic activation of the *CTNNB1* gene occurs in up to 15% of patients with Wilms tumor and is frequently found in association with *WT1* mutations [21, 22].

The *WTX* gene is located on the X chromosome at Xq11.1 and is altered in 15–20% of Wilms tumors [23, 24]. However, patients with germline mutations in *WTX* leading to osteopathia striata congenital with cranial sclerosis are not at increased risk of tumor development [25].

Loss of heterozygosity of 11p15.5, the *WT2* locus, is also frequently found in Wilms tumors, and approximately 80% of patients with Beckwith-Wiedemann syndrome have an abnormality of the 11p15 domain [26]. Children with sporadic Wilms tumor have been found to have 11p15 defects in 3% of cases without features of overgrowth with an increased risk of bilateral tumors [27].

**Table 10.1** Conditions and syndromes associated with Wilms tumor

| Syndrome or condition | Risk of Wilms tumor (%) | Clinical features |
|---|---|---|
| *Associated with overgrowth* | | |
| Beckwith-Wiedemann | 10% | Macroglossia, omphalocele, ear skin creases |
| Isolated hemihypertrophy | 6% | Overgrowth of one or more body part |
| Perlman | 40% | Fetal gigantism, renal dysplasia, nephroblastomatosis |
| Simpson-Golabi-Behmel | 10% | Macrosomia, macroglossia, diaphragmatic hernia |
| Sotos | 2–3% | Macrocephaly, central nervous system anomalies, developmental delay |
| 9q22.3 | Unknown | Craniofacial abnormalities, hydrocephalus, developmental delay |
| *Non-overgrowth associated* | | |
| Denys-Drash | 90% | Disorder of sexual differentiation, glomerulopathy |
| WAGR | >30% | Aniridia, genitourinary anomaly, mental retardation |
| Sporadic aniridia | 5% | Partial or complete absence of the iris |
| Bohring-Opitz | 7% | Distinctive facial features, microcephaly, hypertrichosis, severe myopia, nevus flammeus, unusual posture, intellectual disabilities |
| Familial Wilms | 2% | Genitourinary malformations |
| Bloom syndrome | Unknown | Short stature, sun-sensitive skin |
| Trisomy 18 | Unknown | Congenital heart disease |
| Fanconi anemia with biallelic mutations in BRCA2 or PALB2 | Unknown | Growth retardation, congenital anomalies, bone marrow failure, cancer predisposition |
| Li-Fraumeni | Unknown | Early-onset sarcomas |

Gain of chromosome 1q is found in approximately 30% of Wilms tumors and is associated with worse outcomes. In an analysis from the Children's Oncology Group of 1114 patients enrolled in NWTS-5, gain of 1q was associated with event-free survival across all stages of the disease [28]. With inferior survival, gain of 1q could potentially be incorporated into risk stratification and direct treatment intensity in the future. Additionally, loss of heterozygosity at chromosome 16q and 1p significantly increased the risk of relapse and death [29].

## *Diagnosis*

Wilms tumor typically presents as an asymptomatic abdominal mass found by the parents or primary care physician during routine exam [30]. However, abdominal pain may be present in approximately 40% of children [3]. Additionally, gross hematuria occurs in 18% of children, and microscopic hematuria is seen in 24%

[30]. Hypertension may also be a presenting symptom resulting from activation of the renin-angiotensin-aldosterone system which is seen in up to 25% of patients with Wilms [31].

Work-up following a diagnosis of Wilms tumor should include complete physical exam with a focus on identifying aniridia, hemihypertrophy, or other clues to an underlying syndrome. A panel of labs should be drawn including complete blood count, liver function test, renal panel, and urinalysis. Coagulation studies should be considered as 1–8% of patients with Wilms tumor will have acquired von Willebrand disease [32]. Surgical findings in conjunction with pathologic review are used to stage the tumor and are key components of risk stratification and placement into Children's Oncology Group (COG) protocols. The staging system for Wilms tumor is found in Table 10.2. An ultrasound is often the initial imaging modality obtained in these patients and should prompt further axial imaging. Computed tomography scan (CT) or magnetic resonance imaging (MRI) should be obtained of the chest, abdomen and pelvis. Identifying the extent of the tumor in regard to size, location, and presence of tumor thrombus and evaluation of the contralateral kidney are crucial in staging and management of Wilms tumor. Identification of a contralateral tumor on imaging studies increases the clinical stage and changes the initial management from immediate surgery to potential chemotherapy and nephron-sparing surgery. CT scan can accurately identify presence or absence of tumor thrombus which eliminates the need for Doppler ultrasound (Fig. 10.1) [33]. Biopsy prior to surgery is controversial in stage I and II Wilms as it will upstage a patient to stage III and may cause local tumor spread [34].

## *Pathology*

Wilms tumor consists of elements of the developing kidney including blastemal, epithelial, and stromal cell types [3]. Histologically Wilms tumor can be separated into two groups that have important prognostic implications: favorable histology and anaplastic histology. Anaplastic histology is found in approximately 10% of patients with Wilms tumor and is the most important histologic predictor of response and survival in patients with Wilms tumor [4, 35]. Tumors that harbor anaplasia are typically more resistant to chemotherapy. Patients aged 10–16 years with Wilms have a higher incidence of anaplastic histology [36]. Additionally, mutations in the *TP53* gene have been identified in anaplastic Wilms tumors [37]. This can serve as a molecular marker for anaplastic Wilms and have subsequent implications in treatment.

Nephrogenic rests are retained embryonic kidney cells that are arranged in clusters and are precursors to Wilms tumor [38]. Microscopic nephrogenic rests are found in about 1% of pediatric autopsies, and it is estimated that fewer than 1% of infants with microscopic rests will develop a Wilms tumor [39, 40]. There are two categories of rests currently recognized [38]. Perilobar nephrogenic rests are confined to the periphery of the kidney and frequently found in fetal overgrowth and overgrowth syndromes, whereas intralobar nephrogenic rests occur anywhere

**Table 10.2** Wilms tumor staging

| Stage | Criteria |
|---|---|
| I | Tumor limited to the kidney and completely excised |
| | Intact renal capsule |
| | No intraoperative rupture or prior biopsy |
| | No vascular extension |
| | Negative lymph nodes |
| | ~40% of patients |
| II | Tumor extends beyond the kidney but was completely excised |
| | Vascular extension may be present but was completely removed en bloc |
| | No evidence at or beyond margin of resection |
| | Negative lymph nodes |
| | ~20% of patients |
| III | Residual tumor present and limited to the abdomen |
| | Lymph node involvement in the abdomen or pelvis |
| | Tumor implants present on or through the peritoneal surface |
| | Incomplete tumor resection due to infiltration into adjacent structures |
| | Gross or microscopic tumor present at surgical margins |
| | Tumor rupture prior to or during surgery |
| | Renal biopsy prior to resection |
| | ~20% of patients |
| IV | Metastasis to the lungs, liver, or bones |
| | Lymph node involvement outside the abdomen and pelvis |
| | ~10% of patients |
| V | Bilateral tumors present at diagnosis |
| | ~5% of patients |

Adapted from www.childrensoncologygroup.org

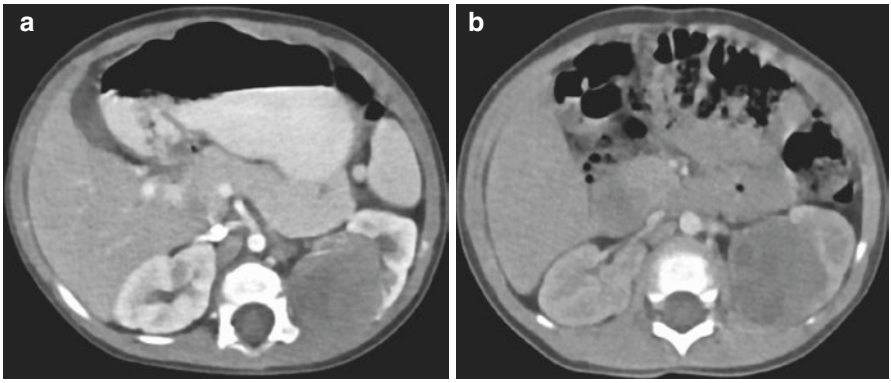


**Fig. 10.1** Wilms tumor in a 2-year-old male with WAGR syndrome. (**a**) Axial CT scan prior to chemotherapy. (**b**) CT scan following chemotherapy with no significant change in tumor size

within the renal lobe and renal collecting system. Intralobar nephrogenic rests contain multiple cell types and have an indistinct border. Additionally, intralobar nephrogenic rests are frequently associated with deletions or mutations in *WT1* [41]. Diffuse hyperplastic perilobar nephroblastomatosis represents a unique category with multiple perilobar nephrogenic rests in the hyperplastic phase. It is considered a pre-neoplastic condition where the renal unit is enlarged due to the rind of thick nephroblastic tissue oftentimes making difficult to distinguish on a biopsy this entity from Wilms tumor [42].

## *Treatment*

The initial treatment in the majority of unilateral Wilms tumors is radical nephrectomy with renal lymph node sampling using a transabdominal or thoracoabdominal incision [43]. Use of a flank incision is not typically recommended. Surgeons must be aware of the risk of intraoperative tumor rupture and through these approaches hopefully mitigate this risk and subsequent upstaging of the tumor.

The contralateral kidney does not need to be explored if preoperative imaging does not indicate a contralateral tumor. Preoperative or intraoperative biopsy should not be performed in the setting of unilateral resectable tumors as it would upstage the tumor [44]. There is a risk of ureteral involvement in Wilms tumors, and if present, the ureter should be taken en bloc to avoid tumor spill [45]. If preoperative gross hematuria is present, cystoscopy is recommended. Assessment of vascular extension into the inferior vena cava and renal vein should be conducted by palpation to check for tumor thrombus.

Treatment of patients with Wilms tumor should involve a multidisciplinary team that is well versed in pediatric malignancies. Additionally, patients with Wilms tumor should be considered for entry into a clinical trial. Risk stratification based on stage and pathologic findings dictates which treatment protocol patients are assigned. In the United States, the treatment of Wilms tumor is based on the results of clinical trials completed by the National Wilms Tumor Study (NWTS) group which has been incorporated into the Children's Oncology Group (COG) [4, 29, 46–48]. Results from NWTS and COG trials with rates of survival are provided in Table 10.3.

Bilateral Wilms tumors have had historically poor survival in comparison to unilateral favorable histology Wilms tumor [49]. A recent report from the COG investigated treatment of bilateral Wilms tumor in an effort to improve survival and preserve renal function [48]. Preoperative chemotherapy was intensified with the goal of performing bilateral partial nephrectomies and response was assessed on imaging after 6 weeks of treatment. Patients who did not respond received another two cycles of chemotherapy and open bilateral renal biopsies were performed in those who showed no evidence of response to asses for anaplasia. Postoperative chemotherapy and radiation were based on the kidney with the highest-stage local disease. Results of this trial are encouraging with bilateral favorable histology 4-year event-free survival and overall survival 84.2% and 97.3%, respectively.

**Table 10.3** Treatment of Wilms tumor

| Stage | Histology | Treatment | 4-year survival |
|---|---|---|---|
| I | FH <24mo, tumor weight < 550 g | Surgery with lymph node biopsy | 90% EFS, 100% OS[a] |
| | FH >24mo, tumor weight > 550 g | Nephrectomy + lymph node sampling followed by regimen EE-4A | 94% RFS, 98% OS[b] |
| | FA | Nephrectomy + lymph node sampling followed by regimen EE-4A and XRT | Data not available |
| | DA | Nephrectomy + lymph node sampling followed by regimen EE-4A and XRT | Data not available |
| II | FH | Nephrectomy + lymph node sampling followed by regimen EE-4A | 86% EFS, 98% OS[c] |
| | FA | Nephrectomy + lymph node sampling followed by abdominal XRT and regimen DD-4A | 80% EFS, 80% OS[d] |
| | DA | Nephrectomy + lymph node sampling followed by abdominal XRT and regimen I | 83% EFS, 82% OS[d] |
| III | FH | Nephrectomy + lymph node sampling followed by abdominal XRT and regimen DD-4A | 87% RFS, 94% OS[c] |
| | FA | Nephrectomy + lymph node sampling followed by abdominal XRT and regimen DD-4A | 88% RFS, 100% OS[d] |
| | FA (preoperative) | Preoperative treatment with DD-4A followed by nephrectomy +lymph node sampling and abdominal XRT | 71% RFS, 71% OS[d] |
| | DA (preoperative) | Preoperative treatment with regimen I followed by nephrectomy +lymph node sampling and abdominal XRT | 46% EFS, 53% OS[d] |
| | DA | Immediate nephrectomy +lymph node sampling followed by abdominal XRT and regimen I | 65% EFS, 67% OS[d] |
| IV | FH | Nephrectomy + lymph node sampling, followed by abdominal XRT, radiation to sites of metastases, bilateral pulmonary XRT, and regimen DD-4A | 76% RFS, 86% OS[c] |
| | FA | Nephrectomy + lymph node sampling, followed by abdominal XRT, radiation to sites of metastases, bilateral pulmonary XRT, and regimen DD-4A | 61% EFS, 72% OS[d] |
| | DA | Immediate nephrectomy +lymph node sampling followed by abdominal XRT, radiation to sites of metastases, whole-lung XRT, and regimen I | 33% EFS, 33% OS[d] |
| | DA (preoperative) | Preoperative treatment with regimen I followed by nephrectomy + lymph node sampling, followed by abdominal XRT, radiation to sites of metastases, and whole-lung XRT | 31% EFS, 44% OS[d] |
| V | Preoperative chemotherapy | Vincristine, dactinomycin, and doxorubicin for 6 or 12 weeks based on radiographic response followed by surgery. Further chemotherapy dictated by histology. Radiation dictated by the postchemotherapy stage | 82% EFS, 95% OS[e,f] |

(continued)

**Table 10.3** (continued)

Adapted from https://www.cancer.gov/types/kidney/hp/wilms-treatment-pdq
*FH* favorable histology, *FA* focal anaplasia, *DA* diffuse anaplasia, *RFS* recurrence-free survival, *EFS* event-free survival, *OS* overall survival
Regimen EE-4A = vincristine, dactinomycin for 18 weeks after nephrectomy
Regimen DD-4A = vincristine, dactinomycin, doxorubicin for 24 weeks
Regimen I = vincristine, doxorubicin, cyclophosphamide, etoposide for 24 weeks after nephrectomy
[a]Source: Fernandez et al. [47]
[b]Source: Shamberger et al. [46]
[c]Source: Grundy et al. [29]
[d]Source: Dome et al. [4]
[e]Source: Ehrlich et al. [48]
[f]In bilateral favorable histology

### *Late Effects of Therapy*

Children treated for Wilms tumor are at risk of developing sequelae of their treatment. Secondary malignancies in the form of digestive and breast cancers have been reported with radiation therapy identified as a risk factor [50, 51]. There is also an increased risk of congestive heart failure resulting from doxorubicin as well as radiation [52, 53]. Although Wilms tumor survivors are thought to have a low risk of end-stage renal disease, a recent study reported impaired glomerular renal function in a majority of patients emphasizing the need for long-term follow-through to adulthood [54].

## Renal Cell Carcinoma

Renal cell carcinoma (RCC) accounts for 2–5% of malignant renal masses found in children [55] and occurs most frequently in the second decade of life with an annual incidence of 0.01 per 100,000 [56]. Children and adolescents with RCC present with more advanced disease than those 20 to 30 years of age [57].

### *Diagnosis*

RCC is found incidentally in the pediatric population in only 12% of patients [58]. Children typically present with fevers, abdominal mass, pain, hematuria, and weight loss. Unlike for RCC in adults, pediatric RCC has not experienced a downward stage in recent years [57, 59]. This may be explained in part by less abdominal imaging in children in efforts to reduce radiation exposure.

Imaging findings of RCC in pediatric patients may help to distinguish this entity from the more frequently found Wilms tumor (Fig. 10.2). Miniati and colleagues analyzed CT scans of 92 pediatric patients and reported an accuracy of 82% for

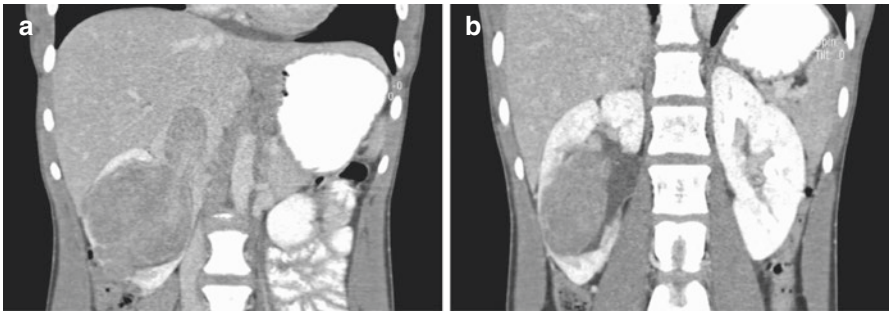


**Fig. 10.2** Renal cell carcinoma in a 13-year-old female. (**a**) Sagittal CT image shows a mass with heterogeneous appearance and tumor thrombus in the inferior vena cava. (**b**) The tumor can be seen invading the renal sinus

predicting tumor histology [60]. Calcifications on imaging are more frequent in RCC compared to Wilms tumor [61]. Preoperative identification of RCC, however, is essential in the pediatric population as neoadjuvant chemotherapy is typically administered for advanced Wilms and delay to surgery as first-line treatment for RCC is associated with increased mortality [57].

## *Pathology*

RCC in pediatric patients does not follow the typical distribution of tumor histologies observed in adults. More specifically, approximately 25% of pediatric RCCs demonstrate heterogeneous histologic features and cannot be classified as one of the common RCC subtypes [62]. Furthermore, papillary RCC is more common than the clear cell subtype and is frequently associated with aggressive disease [63, 64]. While histological features are used to classify pediatric RCC, another method currently being employed is molecular characterization. Specific genetic translocations can be identified in the majority of pediatric RCCs and can be used to classy tumors into distinct molecular subtypes [65].

## *Genetics*

Translocation-associated RCC is the most common form of pediatric and adolescent RCC [66]. The most frequently found translocation involves the *TFE3* transcription factor found on chromosome Xp11.2. Upon translocation, the *TFE3* gene can fuse with a number of other genes. To date, a total of five fusion partners of *TFE3* have been identified [67]. These include *PRCC*, *ASPSCR1*, *SFPQ*, *NONO*, and *CLTC* [3, 68, 69]. Grossly, Xp11.2 translocation RCCs resemble clear cell RCC, and all of the Xp11.2 translocation RCCs demonstrate expression of *TFE3*

[58, 67]. Other immunohistochemical expression patterns include low expression of cytokeratin and vimentin [67]. Another less common translocation subtype is the t(6;11)(p21;q12) [70, 71]. Few cases have been reported, and the clinical course is typically less aggressive than Xp11.2 translocation tumors.

### *Treatment*

The primary treatment for localized pediatric RCC is radical nephrectomy. There remains some debate over the utility of lymph node dissection during nephrectomy for pediatric RCC. Geller et al. reported on their experience with node-positive disease in combination with a review of the literature [72]. These authors found a 72.4% disease-free survival in node-positive patients and no improvement in disease-free or overall survival with adjuvant chemotherapy or radiation. They concluded that in the absence of clinical or radiographic evidence of disease, lymph node dissection does not confer any benefit. In contrast, Indolfi and colleagues reviewed their experience with 16 patients with RCC and node-positive disease and found that those who underwent a limited node dissection at the time of nephrectomy had significantly higher rate of relapse and mortality than those who underwent formal lymph node dissection [73]. Partial nephrectomy may be considered in select cases. In the setting of low-volume disease, well-selected patients have been found to have equivalent outcomes to those who had radical nephrectomies [74].

There is no standard treatment for unresectable metastatic RCC. Given the resistance of RCC to chemotherapy and radiation, metastatic disease remains difficult to treat. Despite this, there have been reports of advance disease treated with recombinant interleukin-2 [75, 76]. Additionally, the role of tyrosine kinase inhibitors continues to be defined in the pediatric population [77, 78].

## Clear Cell Sarcoma of the Kidney

Clear cell sarcoma of the kidney (CCSK) is a rare renal tumor which accounts for approximately 3% of malignant pediatric renal tumors [79]. The mean age of presentation is 3 years. CCSK has a high propensity to metastasize to bone as noted in several series [80, 81]. On imaging, CCSK appears as a heterogeneous mass with decreased enhancement compared to the contralateral kidney with internal hemorrhage and necrosis (Fig. 10.3). Additionally, the outcome of relapses of CCSK is poor with a frequent site of recurrence being the brain. It is postulated that the brain may be a sanctuary site for cells protecting them from chemotherapy [82]. Late relapses have decreased with longer duration of chemotherapy including

vincristine, doxorubicin, and dactinomycin; however, long-term survival is unchanged [83]. Important predictors of survival are low stage, older age at diagnosis, treatment with doxorubicin, and the absence of tumor necrosis [79].

## *Genetics*

Recent studies have identified several genetic changes associated with CCSK. The most frequently found are internal tandem duplications of the *BCOR* gene [84, 85]. In a recent series from Wong and colleagues, 10 of 11 tumors had *BCOR* exon 15 internal tandem duplications, and one had a fusion of the *BCOR* and *CCNB3* genes [86]. O'Meara et al. described the *YWHAE*-NUTM2 fusion in 12% of cases [87]. This gene fusion was found to be mutually exclusive of the *BCOR* internal tandem duplicates [88].

## *Treatment*

Patients with CCSK should be considered for entry into a clinical trial given the rarity of this tumor. Nephrectomy followed by chemotherapy and radiation therapy is the typical treatment course in this group of patients. A variety of

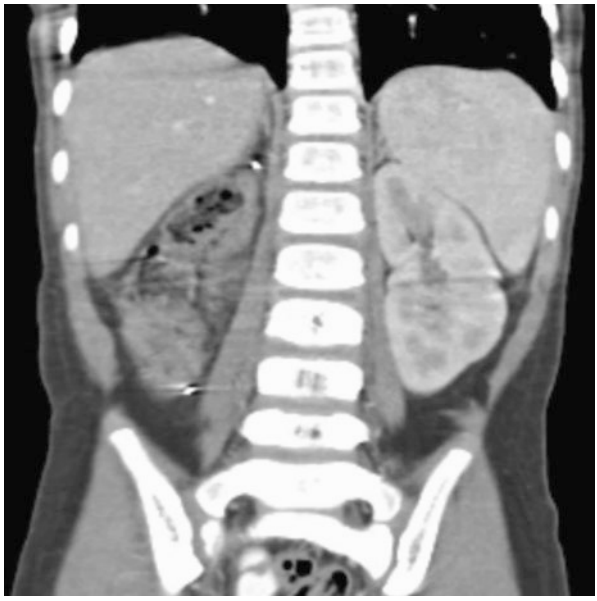

**Fig. 10.3** Clear cell sarcoma with a heterogeneous appearance on CT with areas of hemorrhage and necrosis

chemotherapeutic regimens in combination with radiation have been described for the treatment of CCSK [79, 83, 89].

## Rhabdoid Tumor of the Kidney

Rhabdoid tumors most commonly occur in the kidney and the central nervous system. Malignant rhabdoid tumor of the kidney (MRTK) is a rare highly aggressive malignancy. It accounts for about 2% of pediatric renal tumors [90]. The mean age at diagnosis is 11 months. In addition to young age of presentation, fever, hematuria, and advanced tumor stage suggest a diagnosis of MRTK [90]. MRTK has a propensity to metastasize to the lungs and the brain, with 10–15% of patients having lesions of the central nervous system [91]. This emphasizes the need for intracranial imaging and neurological monitoring for these patients. MRTK has a poor prognosis. Younger age at diagnosis and advanced stage significantly impact overall survival [91].

### *Genetics*

The majority of MRTK are characterized by loss of function of the *SMARCB1/INI1/SNF5/BAF47* gene located in chromosome 22q11.2 [92]. SMARCB1 is a member of the SWI/INF chromosome remodeling complex and has an important role in controlling gene transcription [92]. Inactivation of both alleles of *SMARCB1* leads to tumorigenesis, and it has been proposed as a novel tumor suppressor gene [93]. While the majority of cases are sporadic, a recent study found 35% of cases to have germline mutations of *SMARCB1* [92]. Therefore, genetic counseling should be involved in the treatment of these patients.

### *Treatment*

A multidisciplinary team well versed in treating renal tumors should dictate the treatment plan for patients with this rare tumor. Entry into a clinical trial should be strongly considered. Although preoperative chemotherapy especially with doxorubicin has been shown to decrease tumor volume, this may not translate to improved survival [94]. A recent report from the International Society of Pediatric Oncology renal tumor study group examined their experience with 107 patients with various stages of MRTK and varying pre- and postoperative chemotherapy regimens. They noted that although preoperative chemotherapy did decrease tumor volume significantly indicating chemosensitivity, overall survival was not improved [95]. Event-free survival was found to be 22% and overall survival was noted to be 26%.

## Congenital Mesoblastic Nephroma

Congenital mesoblastic nephroma accounts for approximately 5% of pediatric renal tumors and is generally considered to be a benign tumor occurring most commonly in the first year of life [96]. It is the most common tumor found in the newborn with a median age at diagnosis of 1–2 months. Mesoblastic nephroma occurs twice as often in males than females. The 5-year event-free survival rate is 94%, and overall survival is 96% when diagnosed in the first 7 months of age [5]. In a recent review of 276 patients with available outcome data, there were only 12 (4%) deaths found, 7 of which were related to treatment [97].

Mesoblastic nephroma can be divided into three histologic subtypes: classic, cellular, and mixed [98, 99]. In the cellular subtype, two genetic variants have been identified including translocation t(12;15) (p13;q25) resulting in fusion of *ETV6* and *NTRK3* as well as trisomy 11 [100].

### *Treatment*

Although congenital mesoblastic nephroma enjoys a high survival rate, the young age of these patients and potential adverse outcomes of treatment options cause some pause when deciding on timing and type of intervention. Nephrectomy is typically curative; however, the inherent risks of operating on an infant need to be taken into consideration. Patients with the cellular variant and stage III disease have a higher risk of recurrence and adjuvant chemotherapy is recommended for those greater than 3 months of age [98].

## Multilocular Cystic Nephroma

Multilocular cystic nephroma (MLCN) has a bimodal age distribution occurring in children less than 2 years old and adults 40–69 years old [101]. MLCN is a benign neoplasm of the kidney containing both mesenchymal and epithelial elements. Imaging typically demonstrates a unilateral mass with irregular cysts and septa of variable thickness. It must be noted, however, that it is not possible to distinguish MLCN from other cystic renal tumors. In a recent study by Doros and colleagues, loss of function of *DICER1* was identified as the key genetic event in cystic nephroma [102].

Treatment of MLCN is typically total nephrectomy. Partial nephrectomy can be accomplished in select cases with masses of appropriate size and location. Intraoperative biopsies should be considered in these instances to rule out malignancy that would prompt total nephrectomy.

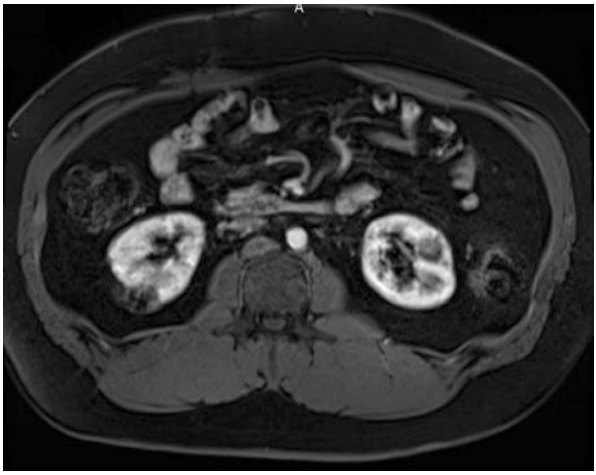

**Fig. 10.4** Angiomyolipoma of the right kidney in a patient with tuberous sclerosis complex

## Angiomyolipoma

Angiomyolipomas (AMLs) are hamartomatous lesions of the kidney that are associated with the tuberous sclerosis complex (TSC). AMLs are benign tumors composed of blood vessels, smooth muscle, and adipose tissue developing in up to 80% of TSC patients [103]. Mutations in the *TSC1* or *TSC2* gene are present in the majority of patients with TSC [104]. AMLs grow over time and lesions greater than 4 cm are at increased risk of hemorrhage (Fig. 10.4). In children with TSC, nephron-sparing approaches are necessary to preserve renal function due to the risk of development of new lesions. A recent study from Warncke and colleagues highlighted the often rapid and unpredictable growth of AMLs in children and emphasized the need for yearly ultrasounds for monitoring in hopes of identifying those at risk for future intervention [105].

## Conclusions

Pediatric renal tumors can demonstrate a broad range of pathologic behaviors from benign to locally invasive to metastatic. As we have explored, modifications to surgical approach and tailoring of chemoradiation protocols have led to improved outcomes for pediatric patients with renal tumors. With these improved outcomes, the focus of many in the field has now shifted toward preservation of renal function in these young patients, as well as enhanced quality of life and survivorship efforts.

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