Rare Tumors of the Urinary Tract

32

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32.1 Differential Diagnosis of Urinary Tract Tumors

Malignant renal tumors cover 6% of all childhood cancers (Pastore et al. 2006). Wilms tumor or nephroblastoma is largely the most common type of cancer in the kidney of children Graf and Bergeron 2012), accounting for more than 90% of primary renal tumors. Other tumors, like clear cell sarcoma of the kidney (CCSK), rhabdoid tumor of the kidney (RTK), renal cell carcinoma (RCC), renal medullary carcinoma, congenital mesoblastic nephroma (CMN), primitive neuroectodermal tumor of the kidney, adenoma of the kidney, and others, are much rarer. As their treatment and prognosis is quite different from Wilms tumor, an early timely diagnosis is crucial to deliver the best treatment to patients.

The typical presentation of a child with a kidney tumor is a painless mass in the abdomen. Other complaints are found in <20% of children (Graf and Wilms-Tumoren 2003; Brok et al. 2016), and may include hematuria and hypertension. It is well known that Wilms tumor may be associated with different syndromes (Scott et al. 2006; Srinivasan et al. 2019), and such syndromes can guide the way to a correct diagnosis. Children with tuberous sclerosis or von Hippel–Lindau disease are at risk for developing RCC or angiomyolipoma (Sausville et al. 2009). Cystic tumors, like cystic nephroma, may be encountered in children with DICER1-related syndrome (Schultz et al. 2018). Renal medullary carcinoma, a highly malignant tumor of the epithelial origin, occurs almost exclusively in adolescents and young adults with sickle cell trait or sickle cell disease (Swartz et al. 2002). Altogether there are no typical clinical signs or symptoms in children suffering from a specific renal tumor. Furthermore, there are no specific tumor markers available.

Imaging studies are important, although none of these rare tumors show a specific appearance in ultrasound, computed tomography (CT) scan, or magnetic resonance imaging (MRI), compared to nephroblastoma (Brisse et al. 2020; Watson et al. 2020). Even if RTKs are more lobulated, often showing peripheral subcapsular bleedings, more lymph node involvement, and more often lung metastases, they cannot be clearly distinguished from other renal neoplasm by imaging studies alone (Schenk et al. 2004, 2005; Watson et al. 2020). Only in addition with further information like the knowledge of lung metastasis in a small infant having a renal mass

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makes the diagnosis of a specific neoplasm more likely as RTK in the above case. However, abdominal cross-sectional imaging is key important: despite not being able to differentiate between the tumor types, it helps diagnosing tumor thrombus in the vessels (renal or Cava veins), the presence of abdominal metastases (lymph nodes, liver, peritoneum), or the presence of lesions in the contralateral kidneys. In all cases of a renal mass, a chest X-ray or computed tomography (CT) scan of the torax is needed for staging. Further staging procedures are mandatory in patients with specific diagnoses, and for this reason they should be performed after the histologic diagnosis is clear. In case of CCSK and RTK, an MRI of the brain should be performed as these tumors may develop brain metastasis in some patients (Smets and de Kraker 2010). Radioisotope bone scan (99 m-technetium-methylene diphosphonate) is recommended only in cases of CCSK and RCC to exclude bone metastasis (Smets and de Kraker 2010; Schenk et al. 2005).

Important to note, when the radiological and clinical picture cannot be orientative of a given tumor type or exclude a Wilms tumor, a percutaneous co-axial tru-cut biopsy is the most effective and safe method to reach a diagnosis (Irtan et al. 2019).

Diffusion-weighted MRI (DWI) may help in distinguishing between necrotic and vital tumor areas, above all after chemotherapy in cases of Wilms tumor, and in the follow-up of patients in defining response to treatment (Watson et al. 2020), but more research is needed to clarify their role in the diagnostic workup of rare kidney tumors in children (van den Heuvel-Eibrink et al. 2017). Experience with new imaging methods in non-Wilms tumors of the kidney is even more limited.

A correct diagnosis can only be done by histopathology (Vujanić et al. 2018). In case of a biopsy, one should send tumor material not only for pathological analysis but also for genetics as specific genetic aberrations can be found confirming the diagnosis (Vujanić et al. 2018).

Important to note, there are childhood malignancies that can arise close to the kidney or as primary renal lesion, and may mimic primitive renal tumors, like neuroblastoma, PNET, soft tissue sarcomas, and non-Hodgkin lymphomas.

32.2 Rare Kidney Tumors

Primary non-Wilms renal tumors represent a heterogeneous, although clinically relevant, group of malignancies accounting for <1% of pediatric tumors (Pastore et al. 2006; Ahmed et al. 2007; Magnani et al. 2001; Vujanić et al. 2018) (Fig. 32.1). Most of them are especially diagnosed in children aged <6 months or >12 years. The major histological groups include RCC, CCSK, and RTK. Renal primitive neuroectodermal tumor (PNET), desmoplastic small round cell tumor, anaplastic sarcoma of the kidney, and renal medullary carcinoma represent other clinically significant types of malignant tumors. The most frequent benign lesion is angiomyolipoma, while oncocytoma is extremely rare in children and adolescents (Ciftci et al. 2000). Lesions with low to borderline malignant potential are mesoblastic nephroma, cystic nephroma (to be distinguished from a cystic appearance of a Wilms tumor), and metanephric tumors. The group of metanephric neoplasms has been more recently described; basing on the extent/appearance of epithelium or stroma, the WHO recognizes three members of a family of metanephric neoplasms of the kidney: metanephric stromal tumor (pure stromal), metanephric adenoma (pure epithelial), and metanephric adenofibroma (biphasic, stromal-epithelial) (Arroyo et al. 2001). Metanephric neoplasms have an unclear etiology but have been postulated by many researchers to potentially represent the differentiated end of the Wilms tumor spectrum, based primarily upon overlapping morphologic features (including rare composite cases with features of metanephric neoplasms and Wilms tumor) and overlapping immunohistochemical profiles (specifically, WT-1 immunoreactivity). More recently, mutations in the BRAF gene (specifically V600E) have been identified in over 90% of MA cases (including pediatric MA cases) (Argani et al. 2016), while, importantly, the BRAF V600E mutation has not been identified in prior

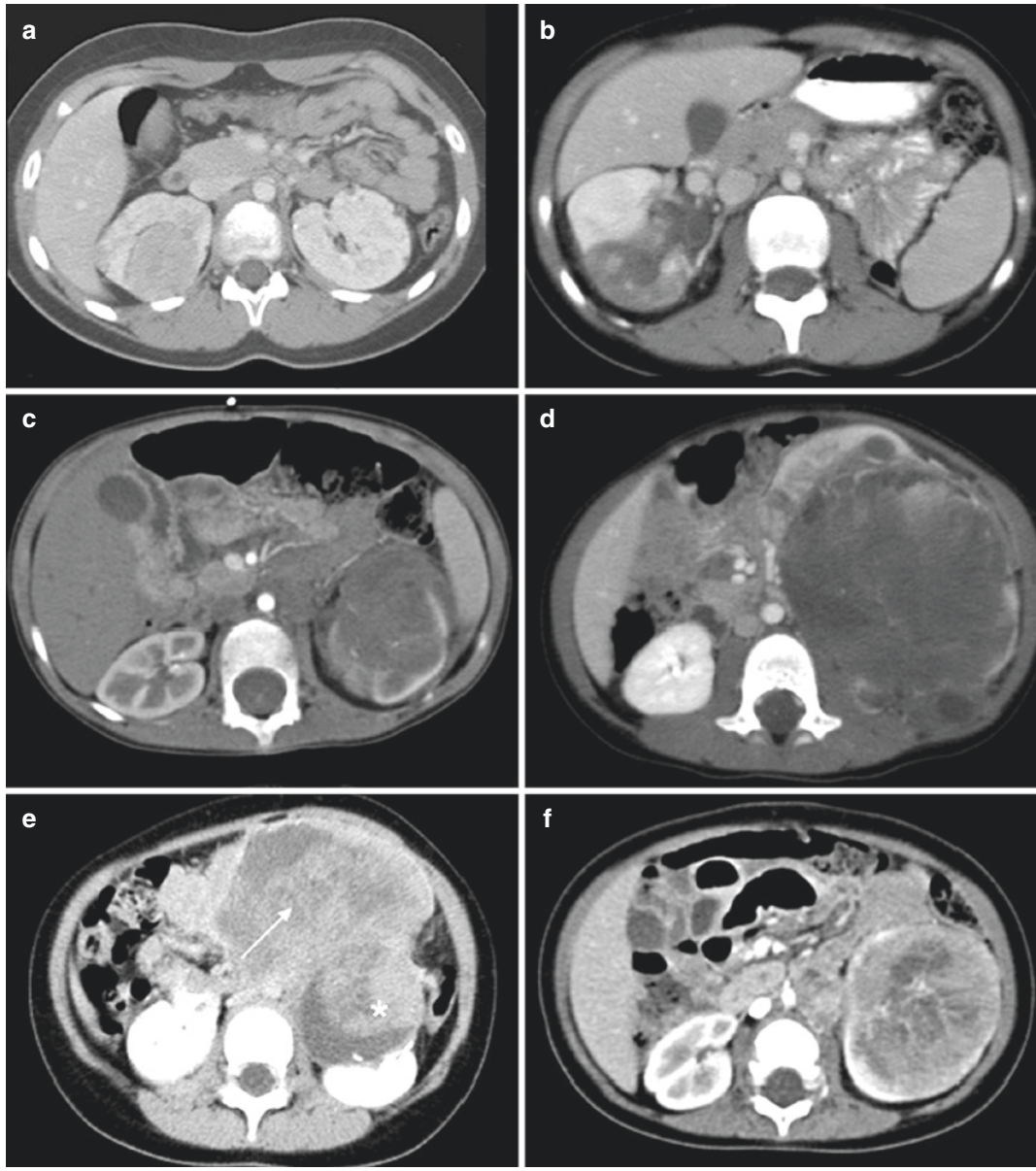

Fig. 32.1 Post-contrast CT imaging of (**a**) angiomyolipoma (male, 13-year-old); (**b**) primitive neuroectodermal tumor (female, 15-year-old); (**c**) Wilms tumor (male, 4-year-old); (**d**) clear cell sarcoma (male, 3-year-old); (**e**) 6-year-old female who displayed two rather distinct nodules that at microscopic examination turned out to be MiTF+RCC (*) and concomitant Wilms tumor (*arrow*); (**f**) Xp11.2 translocation carcinoma (female, 9-month-old)

sequencing analyses of Wilms tumor. The relationship—and sometime the association—between metanephric tumors and Wilms tumor or papillary RCC has been described and warrants further study to better elucidate potential common etiopathogenesis.

Other tumors, like non-Hodgkin lymphoma (mainly Burkitt lymphoma) or neuroblastoma,

may secondarily affect the kidney, but sometimes they are the only clinical disease manifestation.

Renal medullary carcinoma was originally described in 1995 and affects young adults (mean age is 20 years) of a Black ethnicity who have a sickle cell nephropathy (Davis et al. 1995). It is a rapidly growing tumor of the renal medulla, regarded as an aggressive variant of collecting duct carcinoma (Lopez-Beltran et al. 2009).

Angiomyolipoma most likely presents in children who carry a known diagnosis of the tuberous sclerosis complex. Although benign, these tumors may cause substantial morbidity if they increase in size or if cause hemorrhage. For this reason, careful imaging examination is recommended, either with computed tomography or MRI, in order to balance the proper time for surgery (conservative whenever possible) versus a wait-and-see approach. Sometimes the low burden of fat tissue (or even absence) renders the differential diagnosis with other malignant renal tumors (like Wilms tumor) very challenging.

PNET has been documented with increasing frequency in the kidney in the last decade (Findlay et al. 2019). PNET of the kidney is clinically aggressive and requires therapeutic approach like other tumors of the Ewing sarcoma family. Noteworthy, PNET is frequently misdiagnosed as Wilms tumor, both being monotonous round cell tumors (Shet and Viswanathan 2009).

While imaging has no specific radiological features that can reliably distinguish between the histological types of renal tumors (Srinivasan et al. 2019; Watson et al. 2020; Brisse et al. 2020), one useful criterion for suspecting among the types of tumor is the age of the children. More than 50% of children with RCC are diagnosed after the age of 15 years, whereas >80% of patients with CCSK and RTK are younger than 4 years at diagnosis (Zhuge et al. 2010). CMN is the primary diagnostic consideration for a renal mass in the neonate, and its incidence decreases quickly with advancing age (van den Heuvel-Eibrink et al. 2008). RTK represents the primary diagnostic consideration for a metastatic renal tumor in children <7 months of age.

Non-Wilms tumors tend to affect more boys under the age of 5 years while more girls above the age of 15 years (Zhuge et al. 2010).

Consistent with their rarity, there is a paucity of published reports of these tumors. The rarity of the different types of primary non-Wilms renal tumors and the importance of prescribing the correct type-specific adjuvant therapy—if any—render central pathology review fundamental for the correct and modern clinical assessment of pediatric renal tumors (Vujanić et al. 2009; Vujanić et al. 2018). A comprehensive analysis of the SEER registry pointed out that patients diagnosed with a non-Wilms tumor after 1989 had much improved survival compared with those diagnosed prior to 1989, likely reflecting improvement in the diagnosis and/or treatment (Zhuge et al. 2010). Entering homogeneous groups of tumors into centralized histological database facilitates the description and classification of new entities.

Molecular biology studies have helped us in recognizing that some renal tumors are identical to tumors of other sites (such as cellular mesoblastic nephroma and infantile fibrosarcoma of soft tissue, renal and extra-renal rhabdoid tumor) as well as that some tumors of other sites may also occur in the kidney (PNET, desmoplastic small round cell tumor, synovial sarcoma). These molecular new findings are helping researchers to move from a "kidney-oriented" classification to a classification system whose fulcrum is the tissue origin of the tumor, and or related biological driver pathways, more than the fact that they are in the kidney.

32.3 Renal Cell Carcinoma (RCC)

RCC is rare in the first two decades of life and accounts for only approximately 2–5% of pediatric renal tumors (Selle et al. 2006; Pastore et al. 2006; Silberstein et al. 2009; Argani and Ladanyi 2003a, b; Geller et al. 2018; Rialon et al. 2015; Spreafico et al. 2010). Important studies have suggested that the epidemiological and histological characteristics of pediatric RCC differ from their adult counterparts. The big

discovery regarding pediatric RCC has been the characterization of the translocation RCCs (Argani and Ladanyi 2003a, b; Argani and Ladanyi 2005, 2006). Since 2004, this is acknowledged by the WHO, which officially classified the translocation-type RCC (MiT-RCC), which mainly occurs in pediatric and young adult patients, as a specific entity (Cajaiba et al. 2018). MiT-RCC is characterized by translocations involving the *TFE3-gene* located on chromosome Xp11.2 and less frequently the *TFEB-gene* on 6p21, representing translocations of the microphthalmia transcription factor (MiT) family genes (Argani et al. 2005, 2006). It is likely that a large proportion of RCC in children (approximately one-third to two-thirds) belong to the translocation RCC (Argani and Ladanyi 2005, 2006; Sausville et al. 2009).

While much information is now available as far as the complementary treatment for RCC in adults, studies on children dealt with retrospective case reports, or mono- and pauci-institute series (Baek et al. 2010; Estrada et al. 2005; Geller and Dome 2004; Geller et al. 2009; Indolfi et al. 2003; Ramphal et al. 2006; Selle et al. 2006; Rao et al. 2009). The prognostic value and specific consequences for optimal treatment approach for these different histological subtypes remain however debatable. The potential bias inherent in non-consecutive case series and reports prevents a definitive formulation of standard therapeutic guidelines for RCC in children and adolescents (Spreafico et al. 2010), despite a recent study from the Children's Oncology Group reported on an extensive analysis of homogeneously and prospectively followed patients in the USA (Geller et al. 2015).

Radical nephrectomy is most important for therapy, while the role of extensive lymph node (LN) dissection—in the absence of LN spread—and of partial nephrectomy till remain clue issues for children as well.

Overall survival rates for childhood RCC are in the range of 50–60%, with outcomes worsening with advancing stages (Indolfi et al. 2003; Carcao et al. 1998; Geller and Dome 2004; Ahmed et al. 2007; Silberstein et al. 2009; Selle et al. 2006; Geller et al. 2015). Patients with tumor localized in the kidney with or without regional LN spread generally have a favorable prognosis, while outcome remains dismal for patients with distant hematogenous metastases. In the extensive review by Geller and Dome, stage-adapted survival rates for pediatric RCC were 92.5%, 84.6%, 72.7%, and 12.7% for modified Robson stages I to IV, respectively (Geller and Dome 2004). Children with LN+ M0 RCCs are likely to have an intermediate prognosis, with survival rate around 50–70% (Geller and Dome 2004, 2009; Geller et al. 2008; Indolfi et al. 2003; Selle et al. 2006: Rialon et al. 2015; Geller et al. 2015).

32.3.1 Epidemiology

The overall annual age-adjusted incidence is 0.01/100,000 children. Median age at diagnosis is 9–12 years, with equal prevalence in boys and girls (Geller and Dome 2004; Selle et al. 2006; Pastore et al. 2006; Silberstein et al. 2009; Indolfi et al. 2003; Ramphal et al. 2006). Despite RCC mostly occurs as a primitive renal tumor, it has been also recognized as a second neoplasm arising in children treated with chemotherapy (Schafernak et al. 2007; Argani et al. 2006). The association between RCC and neuroblastoma has been specifically described as a unique one, so that post-neuroblastoma RCC has been included in the 2004 WHO renal tumor classification as a distinct new category (Eble et al. 2004).

The strong association with the von Hippel–Lindau gene, known for adults (Rini et al. 2009), rarely occurs in children (Rao et al. 2011).

32.3.2 Diagnosis

Children with RCC may present with local or systemic symptoms, although current prevalent use of ultrasound and cross-sectional imaging is associated with an increasing incidental detection of asymptomatic small renal tumors (Estrada et al. 2005; Cook et al. 2006; Geller et al. 2015). Local signs and symptoms include

gross hematuria, flank pain, or a palpable abdominal mass. Rarely children present with the full abovementioned clinical triad (Indolfi et al. 2003; Geller and Dome 2004). Systemic symptoms may be due to metastases or paraneoplastic syndromes, such as hypercalcemia, fever, or hypertension, which are rarely diagnosed in children.

A 30% rate of metastatic disease has been reported in the pediatric population (Geller and Dome 2004; Silberstein et al. 2009). About 5–10% of adult RCCs extend into the venous vessels as tumor thrombi, often ascending the inferior cava vein (Rini et al. 2009), and this situation, which has important surgical implications, can be encountered in children as well despite no incidence estimation is available.

Similar to adults, tumor stage in pediatric RCC represents a good prognostic indicator. The TNM system is the more frequently adopted staging classification system, while stage designation according to modified Robson system (Carcao et al. 1998) is rarely adopted. Geller and Dome reported stage-specific incidence as follows: 43.2% low-stage tumors (stage I and II) and 56.8% high-stage tumors (stage III and IV). Such advanced presentation is probably reflective of LN+M0 status (modified Robson stage IIIb; TNM stage III or IV) (Geller and Dome 2004) (Fig. 32.2).

32.3.3 Pathology and Classification

Overall, the clear-cell type of RCC, predominant in adults, is much less frequent in children, where in turn the papillary forms are much more frequent (Bruder et al. 2004; Argani and Ladanyi 2003a, b; Sebire and Vujanic 2009; Cajaiba et al. 2018).

A large part of RCCs in children and young adults show peculiar morphology, immunophenotype and genetic alterations, and belong to the group of translocation RCCs (Argani and Ladanyi 2003a, b, 2005; Camparo et al. 2008; Cajaiba et al. 2018). It is realistic to presume that many RCCs reported as papillary or clear cell in previous pediatric series would turn on contemporary examination to be translocation RCCs.

32.3.4 TFE3/MiTF Translocation Family of RCCs

Translocations involving the TFE3 gene at Xp11.2 with varying partners (Argani and Ladanyi 2005) or the TFEB gene (at 6p21) in the translocation t(6;11)(q21;q13) (Argani et al. 2001) characterize these tumors. Fusion targets for TFE3 include PRCC in 1q21 (Argani et al. 2007), ASPL of alveolar soft part sarcoma in 17q25 (Argani et al. 2001, 2007), PSF in 1p34

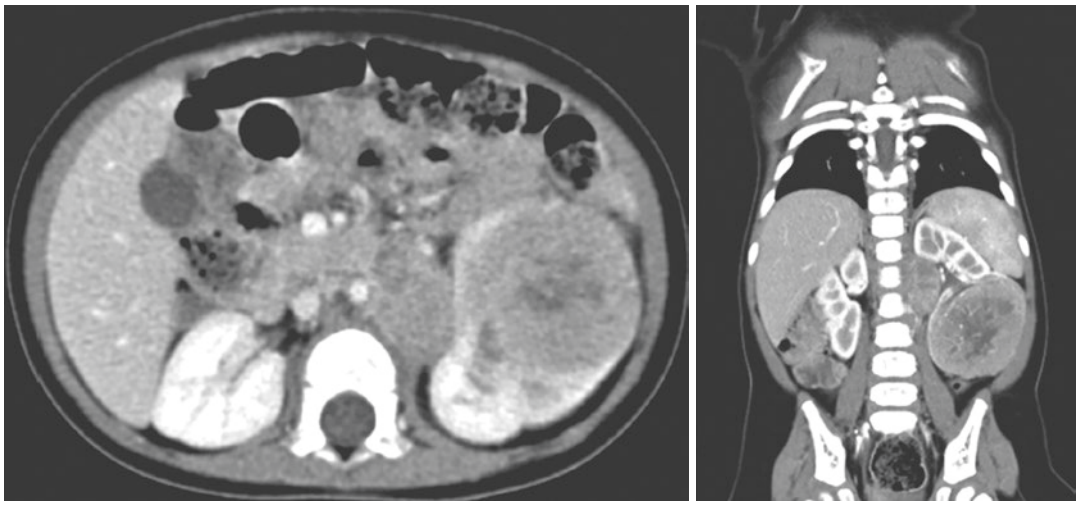

Fig. 32.2 Post-contrast CT scan of a Xp11.2 translocation carcinoma in a 9-month-old baby girl

(Argani et al. 2005), and CLTC in 17q23 (Argani and Ladanyi 2003a, b). TFE3 and TFEB are members of the microphthalmia transcription factor (MiTF) family (a subfamily of basic helix-loop-helix-leucine zipper transcription factors), together with MiTF and TFEC.

Many of these tumors show a high-grade (Fuhrman grade 3), type 2 papillary morphology and are made up by voluminous, large oxyphilic cells (Argani and Ladanyi 2005; Camparo et al. 2008; Ramphal et al. 2006). Cases with a solid, alveolar, nested, paraganglioma-like, or tubulopapillary pattern are reported as well. The immunophenotype is distinct and quite different from the adult-type RCCs. There is a variable, usually very low or even absent expression of epithelial markers, i.e., keratins 8, 18 (CAM5.2); keratin 7; and EMA. CD10 and racemase are usually expressed. Some cases express melanocytic markers, i.e., HMB-45 and Melan-A. In addition, there is nuclear reactivity for TFE3 or TFEB.

32.4 Principles of Treatment

The differences between childhood and adulthood RCC likely prevent a direct and consistent application and translation of therapies that have been validated for adults to children.

Because RCC is among the most resistant of tumors to systemic therapy and radiotherapy, the cornerstone of therapy for RCC in children remains surgery. Radical nephrectomy represents the standard surgical approach. Since nephron-sparing approaches that preserve healthy renal parenchyma are advocated for adults and demonstrated good long-term oncologic outcome for low-volume tumors (Ficarra 2007; Touijer et al. 2010), it is reasonable to consider them in children and adolescents as well (Cook et al. 2006), at least in cases carefully selected by experienced surgeons.

Question as to what is the more adequate extension of retroperitoneal LN dissection remains relatively unanswered (John et al. 2019). To our knowledge, no formal guidelines currently exist regarding the extent of LN dissection in adults as well (Margulis and Wood 2008; Blom et al. 2009). Nevertheless, while in adults lymphatic spread by RCC, and mostly by clear-cell RCC, certainly decreases outcome, it is likely not the same for children (Geller and Dome 2004; Geller et al. 2008; Selle et al. 2006; Renshaw 2005; Geller et al. 2015). From the available experiences, children with clinical evidence of regional LN metastases derive therapeutic benefit from involved LN dissection. It remains less clear, but worth to be analyzed thoroughly, whether children with clinically normal LNs can be targeted for lymphadenectomy as an adjunct to radical nephrectomy. Patients with unsuspected LN spread, in whom LNs randomly sampled turn out to be metastatic at microscopic examination, raise the dilemma of second-look lymphadenectomy.

Overall, chemotherapy has little to no role in the treatment of RCC (Escudier 2010, b), pending new insights on similarities between childhood RCC and alveolar soft part sarcoma, in which some chemotherapy agents may be effective (such as doxorubicin). Despite no result data have been published so far, it is worth to be mentioned that pediatric oncologists have used doxorubicin, gemcitabin, oxaliplatin, and irinotecan as isolated experience, with anecdotal responses in translocation RCCs.

Until 2005, only high-dose interleukin-2 (IL-2) had been approved by the Food and Drug Administration for the treatment of RCC in adults, and this approval was based on durable complete responses obtained in only 7–8% of patients with metastatic RCC. Thereafter, the landscape of systemic therapies in metastatic or advanced-stage RCC has been changed by the introduction of drugs designed to target tumor-related angiogenesis and signal transduction (Sun et al. 2010; Brugarolas 2007; Gulati and Vaishampayan 2020). These are the multitargeted receptor tyrosine kinase inhibitors (sorafenib, sunitinib, pazopanib, axitinib), the inhibitors of the mTOR pathway (temsirolimus, everolimus), and the anti-angiogenic monoclonal antibody bevacizumab (Gulati and Vaishampayan 2020). When used as first- and second-line therapies for metastatic RCC, these agents have demonstrated previously unprecedented response rates and

improvements in time to progression in phase III trials (Escudier et al. 2007; Escudier 2009, 2010; Motzer and Basch 2007; Motzer and Molina 2009; Hudes et al. 2007; Bellmunt and Guix 2009; Soulières 2009; Bukowski 2010). Systemic frontline therapy options now include immune checkpoint inhibitor-based combination therapies such as pembrolizumab/axitinib, nivolumab/ipilimumab, and avelumab/axitinib (Tenold et al. 2020; Thana and Wood 2020; Rassy et al. 2020; Gulati and Vaishampayan 2020). Despite the established efficacy of frontline immune checkpoint inhibitor-based combination, most patients will ultimately require additional lines of therapy, and oncologists must think carefully when switching to another therapy, particularly in situations of drug intolerance or apparent disease progression. Systemic therapy options after immune checkpoint inhibitor-based combination are generally tyrosine kinase inhibitor-based, and ongoing clinical trials will help optimize the treatment algorithm further. On the other hand, the utility of the abovementioned therapies in the adjuvant setting remains unproven.

Despite these several targeted therapies available for RCC, each with different profile of risk versus benefit, at the time of this writing, no prospective data have been published for pediatric age.

Many of the pediatric RCC series covered a very long time span—institutional and population-based reports may need as long as 20–40 years to accrue a significant number of children with this uncommon tumor—and mostly discussed results obtained prior to the more recently introduced targeted therapies (Geller and Dome 2004; Indolfi et al. 2003; Baek et al. 2010). Currently, the role of targeted agents such as tyrosine kinase inhibitors should be reserved to children with unresectable metastatic or advanced-stage RCC (Ambalavanan and Geller 2019; Geller et al. 2018; Craig and Poppas 2019). What might be recommended for metastatic pediatric RCCs is to adopt sequential treatment with VEGF pathway-targeted therapies, optimizing efficacy and safety results; however we are conscious that guidelines may rapidly change, basing on new data acquired in adults. The uncertain benefit of these therapies, together with their toxicity and the relatively better outlook for children and adolescents with completely resected LN+M0 RCC, support not currently using any adjuvant therapies in such pediatric RCCs (Escudier and Kataja 2010; Geller et al. 2018).

A further element which complicates the potential translation of therapeutic findings from adult to pediatric RCC relays in that a major proportion of RCCs included in adult clinical trials are clear-cell RCCs. On the other hand, the optimal therapy for the Xp11.2 translocation RCCs remains to be proven, but case report describing significant response to anti-angiogenics have been described (Joshi and Banerjee 2008; Malouf et al. 2010).

32.5 Rhabdoid Tumor of the Kidney (RTK)

Rhabdoid tumors of the kidney (RTKs) are rare and extremely aggressive malignancies that generally occur in infants and young children. These tumors tend to develop early metastasis. Besides the kidney, these tumors can arise in the CNS, the soft tissues, the liver, and at different sites in a single patient. This suggests a common genetic development including germline mutations (Schneppenheim et al. 2010; Kordes et al. 2014). They usually share biallelic SMARCB1 or rarely SMARCA4 inactivation (Versteege et al. 1998; Schneppenheim et al. 2010; Nemes and Frühwald 2018) and are characterized by a common histology and usually the loss of INI1 expression in immunostaining (Hoot et al. 2004; Hasselblatt et al. 2011).

The first description of this tumor entity was done by Haas et al. in 1981 (Haas et al. 1981). Despite a multitude of case series and single reports, much needs to be learned about this tumor as the prognosis remains dismal, with many relapses occurring early, often shortly after the end of treatment or even during treatment. Standard high-risk renal tumor regimens as well as regimens usually adopted for non-rhabdomyosarcoma soft tissue sarcomas have been unsatisfactory so far, resulting in 20–40%

OS (van den Heuvel-Eibrink et al. 2011; Tomlinson et al. 2005). Noteworthy, in vitro testing, case reports, and small series suggested sensitivity of RTK to anthracyclins (Waldron et al. 1999; Wagner et al. 2002; Lünenbürger et al. 2010; Furtwängler et al. 2014), alkylating agents, such as platinum derivates and oxazophosphorines (Gururangan et al. 1993), and radiation therapy (Furtwängler et al. 2014; Tomlinson et al. 2005; Palmer and Sutow 1983). A positive contribution of high dose chemotherapy with autologous hemopoietic stem cell rescue (HDSCT) has been reported in case series only (Koga et al. 2009), whereas comparable outcomes for patients with and without HDSCT could be shown in a retrospective analysis of 58 patients from Germany, Austria, and Switzerland, if patients were adjusted for early disease progression (Furtwängler et al. 2018).

Today, common therapeutic regimens include intensive anthracycline-based polychemotherapy and aggressive local therapy (Chi et al. 2009; Squire et al. 2007; Wagner et al. 2002; Waldron et al. 1999; Zimmerman et al. 2005). While there are multiple in vitro tests evaluating therapeutic targets for the treatment of malignant rhabdoid tumors, there is a paucity of phase I/II trials combining conventional chemotherapy with selective experimental agents (Nemes and Frühwald 2018; Bourdeaut et al. 2014).

32.5.1 Molecular Genetics

Common to rhabdoid tumors of any anatomical site are alterations in chromosome 22. The biallelic inactivation of SMARCB1 in chromosome 22q.11.23, or rarely (2–3%) SMARCA4 in chromosome 19p13.2, is rather typical of rhabdoid tumors. Apart from these mutations, no other genetic alterations that may explain clinical heterogeneity have been identified (Frühwald et al. 2016). Loss of genetic material from chromosome 22q11 in rhabdoid tumors has been demonstrated by molecular genetic analyses, fluorescence in situ hybridization, and loss of heterozygosity studies (Biegel et al. 1996; Rickert and Paulus 2004). The tumor suppressor gene SMARCB1 (hSNF5/INI1) resides on the long arm of chromosome 22. Versteege et al. isolated the gene SMARCB1 (hSNF5/INI1) from chromosome 22q11.2. SMARCB1 is a member of the SWI/SNF complex (Versteege et al. 1998). The gene contributes to gene transcription through chromatin remodeling (Zhang et al. 2002). Defects may cause a loss of function of the SWI/SNF-complex in chromatin compaction. This presumably causes easier access of polymerases to chromosomes and thus a non-specific activation of many downstream pathways involving among others sonic hedgehog pathways, Wnt-pathway, aurora-kinase pathway, and cell-cycle controls, e.g., cyclin D1, p16, and p14 (Venkataraman et al. 2012; Venneti et al. 2011; Smith et al. 2011; Algar et al. 2009). This is in contrast to the genetic stability of rhabdoid tumors, which harbor only very few mutations as compared to other tumors (Hasselblatt et al. 2013; Lee et al. 2012; McKenna et al. 2008) and show no oncogenic canonical pathway mutations (Kieran et al. 2012).

Transgenic mice heterozygous for SMARCB1 develop rhabdoid tumors and T-cell lymphomas (Roberts et al. 2000, 2002). SMARCB1 mutations have been detected in all nine exons (Biegel et al. 2002b) and show a broad mutational spectrum across tumors from different anatomical sites (Kordes et al. 2010). Today mutations can be detected at least in about 80% of cases on chromosome 22q11.2 (Biegel et al. 2002a; Jackson et al. 2009; Versteege et al. 1998). An additional 20–25% of tumors have reduced expression at the RNA or protein level, indicative of a loss-of-function event. It is unclear if this mutation indicates a common histogenesis of rhabdoid tumors (Parham et al. 1994; Weeks et al. 1989; Wick et al. 1995). Rarely (2–3%) biallelic SMARCA4 inactivation causes the lack of BRG1, another crucial subunit of the SWI/SNF complex.

Germline mutations in SMARCB1 do occur, and families are reported with more than one affected member, as well as patients with synchronous rhabdoid tumors of the CNS and the kidney (Proust et al. 1999; Sevenet et al. 1999; Taylor et al. 2000). Familial cases are summarized

under the term "rhabdoid tumor predisposition syndrome"—RTPS (Kordes et al. 2010; Louis et al. 2007). While the majority of the patients affected by the rhabdoid tumor predisposition syndrome are characterized by SMARCB1 mutations, one report describes a family with two affected children without mutation of SMARCB1 (Frühwald et al. 2006). Furthermore, there are family members described who carried a germline mutation and who did not develop any tumor (Ammerlaan et al. 2007; Janson et al. 2006). Nevertheless, genetic counseling appears mandatory in families with RTPS. In case of a mutation in SMARCB1 within the tumor, analysis of constitutional DNA from the blood of the patient needs to be done. If a germline mutation is detected, parents have to be informed about the potential risk in siblings of the affected patient (Fig. 32.3). A correlation between the mutational status of certain nucleotides and the clinical course of the disease has not been demonstrated. However, reports from the literature suggest that

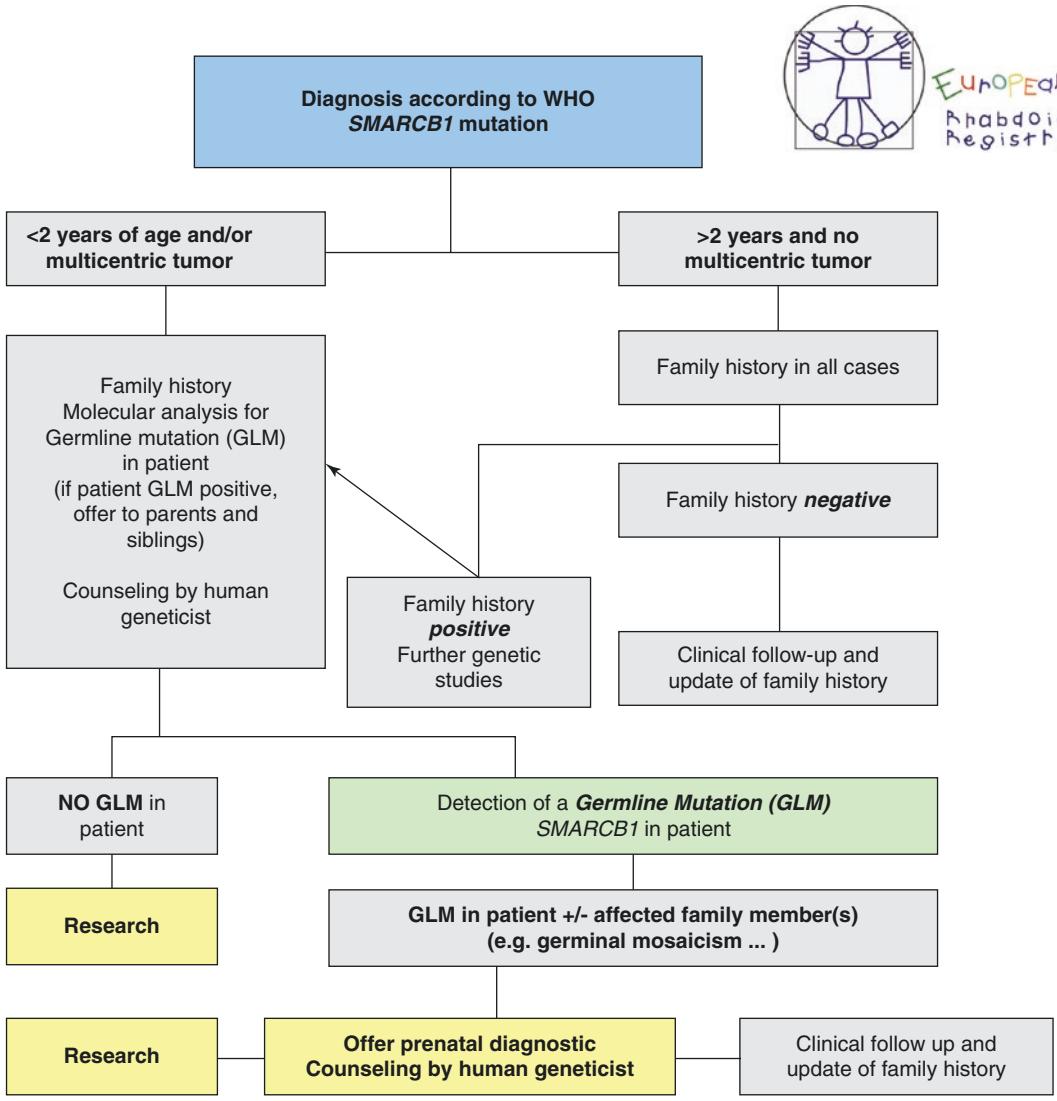

Fig. 32.3 Flow chart for genetic counseling of patients with suspected rhabdoid tumor predisposition. (From: Frühwald, M European Rhabdoid Registry protocol 2010)

patients with germline mutations are younger and are characterized by an almost inevitably fatal course (Kordes et al. 2010).

32.5.2 Diagnosis

RTKs constitute 2% of all kidney tumors in infants and children. Fever and hematuria in a young patient (mean age 11 months) with a high tumor stage should suggest the diagnosis of RTK. Tumor staging system is the same as in nephroblastoma but with a higher incidence of metastatic disease even in young infants. Among 639 cases of kidney tumors in the first 7 months of life with specified histology and stage, 9/11 stage IV tumors were RTKs, as reported by van den Heuvel-Eibrink et al. (2008). RTK tends to metastasize to the lungs and the brain. Up to 15% of patients with RTK also have brain lesions. Because of the coincidence with brain metastasis, a cerebral MRI is always indicated.

The diagnosis of RTK can only be done by histology. Today the diagnosis of RTK needs to be confirmed by immunohistochemical and/or molecular genetic techniques showing the loss of INI1 protein expression resulting from SMARCB1 mutations (Judkins 2007). In every case, tumor material should be stored for research to perform gene array and other experiments for gaining further knowledge (Huang et al. 2006).

32.5.3 Histopathology

Histopathologically, RTKs are characterized by cells with an eccentric nucleus and prominent nucleolus, abundant cytoplasm with eosinophilic inclusion bodies, and distinct cellular membranes, somewhat resembling the rhabdomyoblastic differentiation of rhabdomyosarcomas (Sotelo-Avila et al. 1986a, b). Rhabdoid differentiation may also be seen in a variety of other entities such as meningioma, melanoma, and lymphoma. Rhabdoid cells are characterized by expression of vimentin, EMA (epithelial membrane antigen), and cytokeratins, less commonly by SMA (smooth muscle actin) (Louis et al. 2007; Jackson et al. 2009; Tomlinson et al. 2005). The loss of INI1 protein confirms the diagnosis of rhabdoid tumors.

32.5.4 Treatment and Prognosis of RTK

Until now no randomized study comparing regimens has been conducted. However, several hints concerning the effect of specific drugs have been published. Waldron, Wagner, and colleagues reported three stage IV patients successfully treated with combinations of doxorubicin, cyclophosphamide, vincristine, ifosfamide, and etoposide (Waldron et al. 1999; Wagner et al. 2002). Anthracyclin-based treatment showed promising results in AT/RT in a report given by Chi et al. (2009), and anthracyclines have shown to induce volume decrease in the preoperative setting of MRTK (van den Heuvel-Eibrink et al. 2011; Furtwängler et al. 2014). However, Tomlinson et al. (2005) did not find a difference in survival based on the use of doxorubicin. The report fails to give details on the different cohorts to rule out a selection bias due to probable accumulation of higher stages in the doxorubicin receiving cohort. Alkylating agents, especially ifosfamide, seem to be important in the treatment of extracranial RT. In a series of 13 children from St. Judes, only those receiving ifosfamide survived (Gururangan et al. 1993).

Between 1984 and 1999, 70 children with rhabdoid tumors of any anatomical site were diagnosed in Germany. 35 children were below 1 year of age, 10 between 1 and 2 years, and 9 between 2 and 3 years. Only 10 children were older than 4 years. 32 tumors were localized in the kidneys, 25 in soft tissue (MRT), and 13 in the CNS (AT/RT). 20% of AT/RT and 40% of RTK patients demonstrated metastases at diagnosis. Treatment was according to the respective available protocols at that time (HIT, SIOP, CWS). Twenty-eight patients received radiotherapy (at a dose ranging between 30 and 40 Gy) in addition to surgery and chemotherapy. Of the 70 registered patients, 46 died within 2 years of diagnosis. Two additional patients succumbed to

the disease until the fourth year after diagnosis. More follow-up data are currently not available. The prognosis was dismal regardless of site of the primary tumor or the protocol used. The only statistically relevant negative prognostic factor was metastatic disease (Reinhard et al. 2008). The same risk factor could be shown in larger cohort of 58 patients with RTK from Austria, Switzerland, and Germany (Furtwängler et al. 2018) (Fig. 32.4).

In the United Kingdom, patients with RTK have been treated according to the Wilms tumor studies UKW2 and UKW3, containing a combination of vincristine, actinomycin-D, and doxorubicin (Grundy et al. 2004; Mitchell et al. 2006). The survival rate of 21 patients was 35% (SD ± 9%). All deaths occurred within 13 months following diagnosis. Two stage I patients survived; three patients with stage III died. Four of nine patients with stage III survived. Of seven patients with stage IV disease, there was only one survivor. Two of the stage III patients received radiotherapy.

In the United States, patients with RTK were enrolled into the National Wilms Tumor Studies (NWTS) until recently. These studies employed a drug regimen with vincristine, actinomycin-D, and doxorubicin with or without cyclophosphamide (D'Angio et al. 1989; Tomlinson et al. 2005). Despite high therapy intensity, the survival rate remained unsatisfactory with 4-year overall survival (OS) for stage I patients of 33%, stage II of 47%, stage III of 22%, and stage IV of 8% (Tomlinson et al. 2005). Similar results have been reported by the International Society of Paediatric Oncology (Vujanic et al. 1996) and the United Kingdom group (Grundy et al. 2004). To improve these results, the National Wilms Tumor Study-5 enhanced treatment by using carboplatinum and etoposide with cyclophosphamide (regimen RTK). This trial arm was preliminary closed because of poor outcome (26% survival rate). In a review of 142 patients from NWTS-1 through NWTS-5, stage and age were significant prognostic factors. Patients with stage I and stage II disease had an OS rate of 42%; higher stage was associated with a 16% OS. Infants younger than 6 months at diagnosis demonstrated a 4-year OS of 9%, whereas OS in patients aged 2 years and older was 41%. All except one patient with a central nervous system lesion died (Tomlinson et al. 2005).

Between December 2005 and June 2014, 100 patients from 12 countries with a diagnosis of

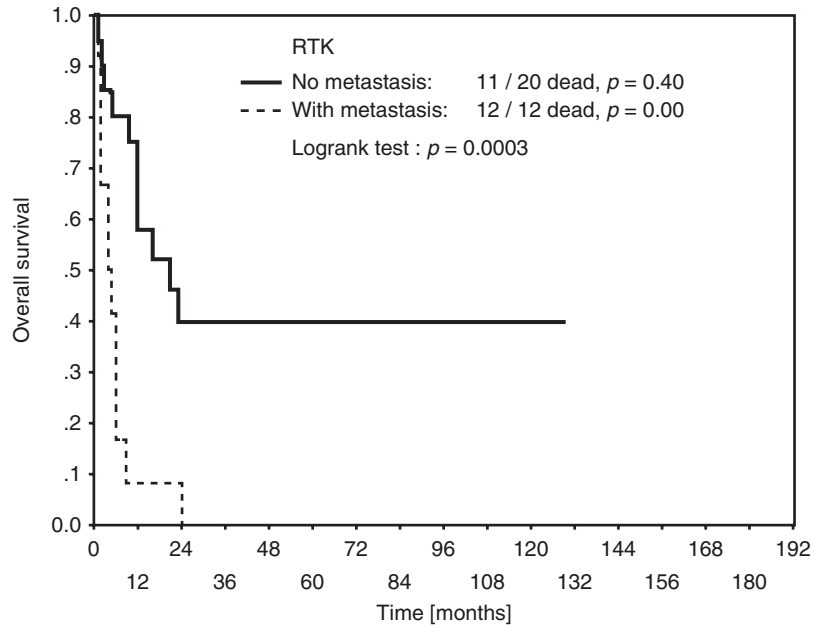

Fig. 32.4 Event-free survival (EFS) rates of patients suffering from localized, multifocal, or metastatic/stage IV disease, including one patient who did not receive any treatment. Note: Stage IV is defined as metastasis to the lungs or mediastinum (*n* = number of events/number of patients, x-axis in years) (Furtwängler et al. 2018)

rhabdoid tumors at an extracranial site were prospectively registered on the EpSSG Non-Rhabdomyosarcoma Soft Tissue Sarcoma 2005 Study (NRSTS 2005). They were all treated on a standard multimodal protocol of surgery, radiotherapy, and cyclophosphamide, carboplatin, and etoposide (CyCE) alternatively. Radiotherapy was recommended for all primary tumor sites and all sites of metastatic disease. For the whole cohort, the 3-year event-free survival (EFS) was 32.3% with a 3-year overall survival (OS) of 38.4%. Disclosed risk factors for death are patients ≤1 year of age and metastatic disease (Brennan et al. 2016).

Based on the currently available data, the role of radiotherapy in the treatment of RTK seems to be beneficial (Furtwängler et al. 2019, personal communication), but because of the rarity of the disease, the young age at diagnosis and the rapid progress of the tumor in many patients, conclusive results are not available. Sultan and colleagues, reporting on SEER data, showed a significant impact of RT on survival (HR 1.89; 1.29–2.78 95%CI; p = 0.0012) in multivariate analysis adjusted for age and stage, both being of significant influence too. But in 229 patients analyzed, only 45 had MRTK and the remaining patients AT/RT or MRT (Sultan et al. 2010).

32.6 European Rhabdoid Registry (EU-RHAB)

As prognosis of children with rhabdoid tumors is dismal, new diagnostic and therapeutic strategies are demanding. In Europe a European Rhabdoid Registry (EU-RHAB) has been launched as a registry for all rhabdoid tumors regardless of site. The EU-RHAB hopefully will build the basis for future therapeutic trials by contributing to improvements in the diagnostic and eventually therapeutic management of affected patients. The EU-RHAB contains treatment recommendations, which were generated from data derived from the current literature and the investigators' clinical experience. The EU-RHAB aims at giving a standardized therapeutic approach. A patient with RTK should be referred to a center for pediatric oncology and enrolled in a prospective trial or registry. Treatment planning by a multidisciplinary team of cancer specialists (pediatric surgeon or pediatric urologist, pediatric radiation oncologist, and pediatric oncologist) with experience treating renal tumors is required to determine and implement optimum treatment. Patients diagnosed with a RTK and registered in the UMBRELLA protocol for kidney tumors in children adolescents and young adults of the SIOP Renal Tumour Study Group are to be included into EU-RHAB to gain more knowledge about this tumor in many more patients around the world and thus being able to faster improve outcome in RTK.

32.7 Clear Cell Sarcoma of the Kidney (CCSK)

CCSK is an important primary renal tumor representing one of the most common unfavorable kidney tumors in childhood comprising 3–5% of all primary renal tumors in children (Argani et al. 2000; Ahmed et al. 2007). CCSK was initially recognized as a distinct clinicopathologic entity with a high propensity to metastasize to bone (Kidd 1970). Marsden and Lawler noted osseous metastases in 60% of patients with CCSK and coined the term "bone-metastasizing renal tumor" (Marsden and Lawler 1980). In addition to pulmonary and bone metastases, CCSK may also spread to brain and soft tissue. CCSK is associated with a significantly higher rate of relapse, even late relapse (Kusumakumary et al. 1997; Gooskens et al. 2012) and death than Wilms tumor. The prognosis for CCSK improved after the introduction of anthracyclines to modern treatment regimens, with survival rates approaching 90% for non-metastatic tumors (Gooskens et al. 2012, 2014; Furtwängler et al. 2013).

32.7.1 Molecular Genetics

Despite the fact that several chromosomal translocations and genetic alterations are described in

CCSK, the pathogenesis of this tumor remains unknown. There is no predisposition syndrome reported that occur in patients with germline genetic mutations explaining why familial cases of CCSK are not seen (Sotelo-Avilla et al. 1986a, b; Argani et al. 2000). In addition, correlations between gene mutations and outcome are not described.

Huang et al. (2006) could show that the most common malignant tumors arising in the kidney (Klatte et al. 2009) have distinct and different gene expression profiles despite their frequent histologic similarities, helping to provide much greater diagnostic confidence than only routine pathologic examination. The top eight upregulated genes they did find in CCSK are forkhead box F1 (FOXF1), tumor suppressor homeobox HB9 (HLXB9), DNA segment chromosome 4 (D4S234E), neuronal pentraxin I (NPTX1), forkhead box F2 (FOXF2), protocadherin 11 X-linked (PCDH11), engrailed homolog 2 (EN2), and neuronal pentraxin receptor (NPTXR) (Huang et al. 2006).

Cytogenetic studies of CCSK have repeatedly reported balanced translocations t(10;17)(q22;p13), t(10;17)(q11;p12), and del(14)(q24.1q31.1) (O'Meara et al. 2008). Although the tumor suppressor gene p53 is located at the chromosome 17p13 breakpoint, p53 abnormalities are rarely present in these tumors why p53 and abnormalities are controversially discussed (Argani et al. 2000; Brownlee et al. 2007). The t(10;17) breakpoint and deletion of chromosome 14q24 suggest that other genes are involved in tumor pathogenesis (Brownlee et al. 2007; O'Meara et al. 2008). O'Meara et al. (2008) found a rearrangement of YWHAE on chromosome 17 and FAM22 on chromosome 10 in 6 of 50 CCSKs tested. A study done by Gooskens et al. (2016) did not identify an explicit clinical phenotype of CCSK cases harboring the YWHAE-NUTM2B/E fusion transcript. Another recurring cytogenetic lesion in CCSK is an interstitial deletion of chromosome 14q (Punnett et al. 1989; Brownlee et al. 2002; Douglass et al. 1985). Also, t(1;6)(p32.3;q21) and t(2;22) have been reported (Taguchi et al. 2008; Kaneko et al. 1991).

Comparative genomic hybridization (CGH) studies revealed an absence of consistent genetic gains or losses in CCSK. Such analysis done by Schuster et al. revealed quantitative abnormalities in only 4 of 30 CCSKs. Two of them showed gain of 1q, one showed loss of 10q, and the other showed loss of terminal 4p. The remaining two cases demonstrated chromosome 19 loss and chromosome 19p gain, respectively. All 22 cases in their series informative for 11p15 showed retention of both alleles. Of 14 CCSKs informative for IGF2, 6 showed biallelic expression (Schuster et al. 2003). The high frequency of LOI for IGF2 in CCSKs (43%) is comparable to that reported in Wilms tumors. This suggests that IGF2, a potent growth factor, may play a role in the development or progression of CCSK (Schuster et al. 2003).

Cutcliffe et al. found in gene expression profiles of CCSK differentially expressed genes which they grouped into four categories: (a) a wide variety of neural markers, (b) members of the Sonic hedgehog pathway, (c) members of the phosphoinositide 3-kinase/Akt cell proliferation pathway, and (d) known therapeutic targets. In particular, they found that CD 117—an epidermal growth factor receptor—is upregulated at the protein level in many CCSKs, providing potential therapeutic targets. In addition, they claimed that nerve growth factor receptor represents a promising diagnostic tool for CCSK (Cutcliffe et al. 2005).

32.7.2 Diagnosis

CCSK constitutes about 4% of all kidney tumors in children. A male predominance has been noted in all large CCSK reports (average male to female ratio of about 2:1) (Argani et al. 2000; Gooskens et al. 2012, Graf et al. 2011). There is no distinct clinical presentation to differentiate it from nephroblastoma. Tumor staging is the same as in nephroblastoma. Only 2% of kidney tumors in the first 7 months of life are CCSKs (van den Heuvel-Eibrink et al. 2008). In a series of 50 patients from GPOH, the median age at diagnosis was 2.4 years, ranging from 2 months to 19.2 years with an excess of boys (male to female

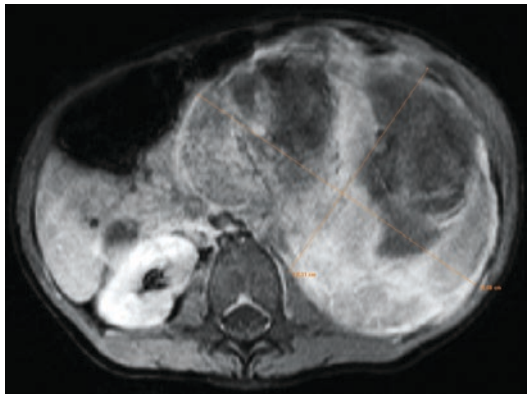

Fig. 32.5 MRI at the time of diagnosis in a 9-year-old girl with CCSK. Tumor volume at the time of diagnosis: 1370 mL with no regression after 4 weeks of preoperative chemotherapy according to the SIOP Wilms tumor protocol with vincristine and actinomycin-D

1.6:1) (Graf et al. 2011). This is in accordance with the findings of Argani et al. who found a male to female ratio of 2:1 and a mean age of 36 months in a series of 351 cases (Argani et al. 2000). Staging procedures have to be done as for nephroblastoma, with the addition of a bone scan and an MRI to the brain, as CCSKs do metastasize to the bone, lungs, and the brain. Imaging studies cannot differentiate between nephroblastoma, CCSK, and other renal tumors (Fig. 32.5).

32.7.3 Histopathology

Histologically, this tumor exhibits a great diversity of morphologic patterns that can mimic most other pediatric renal neoplasms, often leading to confusion and misdiagnosis (Kenny et al. 2016). Until recently, adjunct immunohistochemical and molecular genetic tests to support the diagnosis were lacking. The presence of internal tandem duplications in BCL-6 coreceptor (*BCOR*) and a translocation t(10;17) creating the fusion gene *YWHAE-NUTM2B/E* have now been well accepted (Aldera and Pillay 2020).

The classic pattern of CCSK is defined by nests or cords of cells separated by regularly spaced fibrovascular septa (Argani et al. 2000). Typical gross features included large size, a mucoid texture, foci of necrosis, and prominent cyst formation. Nine major histologic patterns were identified (classic, myxoid, sclerosing, cellular, epithelioid, palisading, spindle, storiform, and anaplastic) (Argani et al. 2000). Traditionally, the role of immunohistochemistry in the diagnosis of CCSK has largely been to exclude other pediatric renal tumors. Only vimentin is consistently immunoreactive in immunohistochemical stains. CCSK is consistently negative for epithelial markers (cytokeratins, epithelial membrane antigen), neural markers (synaptophysin, S100), vascular markers (CD34), muscle markers (desmin), membranous CD99, and WT1. The p53 gene product is rarely overexpressed in non-anaplastic CCSKs but strikingly overexpressed in anaplastic CCSKs (Argani et al. 2000).

Recently, diffuse strong nuclear staining with a commercially available BCL-6 coreceptor (BCOR) antibody has been shown to be highly sensitive and specific for the diagnosis of CCSK in the context of pediatric renal neoplasia (Kao et al. 2016; Argani et al. 2018). BCOR-related sarcomas, such as soft tissue undifferentiated small cell tumor of infancy and primitive mesenchymal myxoid tumor of infancy, also show diffuse, strong nuclear expression with BCOR immunohistochemistry. In the context of pediatric renal neoplasms, strong, diffuse nuclear staining with BCOR is a specific marker that can be useful in distinguishing CCSK from its mimics.

32.7.4 Treatment and Prognosis of CCSK

After the introduction of anthracyclines to the treatment protocol, the prognosis of CCSK has changed. Previously, relapses have occurred in long intervals after the completion of chemotherapy (up to 10 years). However, with current therapy, relapses after 3 years are uncommon (Seibel et al. 2004). An additional benefit could be found with the addition of alkylating agents, carboplatin and etoposide (Tournade et al. 2001; Furtwängler et al. 2013; Gooskens et al. 2018). Today 5-year overall survival rates are approaching 90% in localized diseases in all study groups as shown in Table 32.1. Even in patients with initial

Table 32.1 Treatment and outcome of CCSK in different study groups

Report	Study	Treatment		EFS	OS
		Chemotherapy	Radiotherapy		
Green et al. (1994)	NWTS 1-2	AMD/VCR (8 pt) AMD/VCR/DOX (58 pt)	0–37.8 Gy	25% (6y) 63.5% (6y)	25% (6y) 71.9% (6y)
Green et al. (1994)	NWTS 3	AMD/VCR/DOX (43 pt) AMD/VCR/DOX/CPM (30 pt)	0–37.8 Gy	64.4% (6y) 58.2% (6y)	71.3% (6y) 60.8% (6y)
Seibel et al. (2004)	NWTS 4	6m CT (AMD/VCR/DOX) (23 pt) 15m CT (AMD/VCR/DOX) (17 pt)	10.8 Gy	65.2% (5y) 87.8% (5y)	95.5% (5y) 87.5% (5y)
Seibel et al. (2006)	NWTS 5	VCR/DOX/CPM/VP-16 (110 pt)	Stage I–IV 10.8 Gy	79% (5y)	89% (5y)
Tournade et al. (2001)	SIOP 09	AMD/VCR/EPI(DOX)/IFO (16 pt)	Stage II/III 30 Gy	75% (2y)	88% (5y)
Furtwängler et al. (2013)	SIOP 93-01	St I-IV: VP-16/CARBO/IFO/EPI	Stage II/III 25.2–30 Gy	78% (5y)	86% (5y)
	SIOP 2001	St I: AMD/VCR/DOX St II-IV: VP-16/CARBO/CPM/DOX			
Mitchell (2000)	UKWT2	AMD/VCR/DOX (16 pt)	≥Stage III 30 Gy	82% (4y)	88% (4y)
Spreafico et al. (2014)	AIEOP-TW-2003	St I-IV: AMD/VCR/DOX; AMD/IFO; VP-16/CARBO	Stage I–III 25.2 Gy if <30 m, 34.2 Gy if >30 m	84% (5y)	91% (5y)

Abbreviations: *NWTS* National Wilms' Tumor Study Group; *SIOP* International Society of Pediatric Oncology; *GPOH* German Society of Pediatric Oncology and Hematology; *UKWT* United Kingdom Wilms Tumour Study Group; *AMD* actinomycin-D; *VCR* vincristine; *DOX* doxorubicin; *CPM* cyclophosphamide; *VP-16* etoposide; *IFO* ifosfamide; *CAR* carboplatin; *pt* patients; *EFS* event-free survival; *OS* overall survival; *y* year

metastasis 5-year EFS and OS is about 70% as shown for patients treated according to SIOP 93-01 1nd SIOP 2001 (Furtwängler et al. 2013). In comparison the estimated 5-year EFS and OS for the seven patients with stage IV disease in NWTS 5 were only 29% (95% CI: 0%–76%) and 36% (95% CI: 0%–75%), which may be attributed to a treatment protocol without carboplatin and the low number of stage IV patients also shown by the large confidence interval (Seibel et al. 2019).

Most remarkable is the relapse pattern that is seen today after multimodal treatment and high cure rates. In the largest series of relapsed CCSK patients (37 out of 236 CCSK patients) (Gooskens et al. 2014), 13 patients relapsed in the brain as the most common relapse site that was not seen before. Such a relapse pattern in the brain is reported by many other groups as well (Seibel et al. 2006; Radulescu et al. 2008), underlining that the brain is a frequent site of recurrent disease in CCSK and demanding brain scans at diagnosis and follow-up of patients with CCSK. Independent of the relapse site outcome of patients with a relapse is still poor with a 5-year EFS of 18% and a 5-year OS of 25% (Gooskens et al. 2014).

As prognosis of patients with CCSK in general is excellent today, if they receive adequate therapy, all patients with this tumor have to be referred to a center of pediatric oncology, and late effects of treatment (cardiomyopathy [anthracyclines], nephrotoxicity [ifosfamide, carboplatin], infertility [alkylating agents], and second malignancies [etoposide] need to be taken into consideration to improve future treatments. An excellent overview on the rationale for the treatment of children with CCSK in the UMBRELLA SIOP–RTSG 2016 protocol is given in a paper by Gooskens et al. (2018) in Nature Reviews Urology.

32.8 Differential Diagnosis and Treatment of Urothelial and Bladder Tumors

Pediatric tumors of the lower urinary tract are extremely rare and comprise dissimilar histological subtypes. Noteworthy, bladder tumor occurrence and histological subtypes differ considerably between adults and children (Gripp 2005).

Tumors arising from the bladder can originate from any of its four histological layers (urothelium, lamina propria, detrusor, and adventitia) and are divided into tumors that have an epithelial origin (arising from the urothelium) and those that have a non-epithelial origin (mesenchymal neoplasms) (Shelmerdine et al. 2017). Bladder tumors are usually of mesodermal origin in children <10 years, and tumor of the epithelial origin are extremely rare, above all below the age of 10 years (Alanee and Shukla 2010; Lopes et al. 2020). Papillary urothelial neoplasms of low malignant potential (PUNLMPs) and rhabdomyosarcoma (RMS) are the most common bladder malignancies in the pediatric population.

Macroscopic hematuria and symptoms of urinary tract infections often represent the initial presentation (Lerena et al. 2010; Fine et al. 2005; Dénes et al. 2013), but a significant proportion of these tumors are detected incidentally at imaging (Lopes et al. 2020). Boys are generally more affected than girls regardless of the histology (2–3:1).

With the exception of RMS, pediatric neoplasms of the bladder are associated with favorable benign behavior and outcomes after adequate therapy.

Urinalysis and urinary culture are mandatory to exclude or confirm concomitant urinary tract infection. Owing to the low sensitivity (low cell turnover related to the benign nature of many pediatric bladder lesions) and the absence of experience of pediatric pathologists in such situations, urinary cytology is rarely useful (Dénes et al. 2013). Ultrasonography is the most common initial examination: a full bladder during examination is advisable to avoid missing small lesions or making a misinterpretation (Mbeutcha et al. 2016). If malignancy is suspected, pelvic CT scan or—preferably—MRI is performed for better characterization of the location and extent of disease. Definitive diagnosis for pediatric tumors of the lower urinary tract is usually performed by cystoscopy, which also allows evaluation of tumor extensions, excision, or biopsy. Transurethral resection represents the treatment

of choice for papillary urothelial neoplasms. Interval cystoscopy has been advocated as the best method to follow these patients; however, while only cystoscopy allows for histological diagnosis, the need for general anesthesia and the risk of urethral manipulation make its limited use preferable, with ultrasound as a complementary imaging method. Work-up includes hemoglobin quantification in case of hematuria, assessment of inflammatory marker levels if suspicion of infection, and determining renal function if bladder tumor is associated with hydronephrosis.

The rarity of bladder tumors in children makes it very difficult to estimate their incidence and survival. A paper from the Surveillance, Epidemiology, and End Results (SEER) database focused on the incidence of pediatric bladder tumors. Among 140 identified cases of bladder neoplasms in children aged <18 years (over a 30 years time frame, between 1973 and 2003), PUNLMPs and embryonal RMS comprised 50.7% and 36.4% of the tumors, and transitional cell carcinoma (TCC) accounted for 9.3% (Alanee and Shukla 2010). Noteworthy, the incidence of a given histological subtype was related to the age at presentation. Embryonal RMS was the predominant type in children aged <12 years, being TCC extremely rare. It was around puberty when TCC was more common and overcame the other subtypes. The incidence of pediatric bladder tumors significantly increased over the period of the study; however, the authors warn that this can be due to the improved reporting to the SEER database more than to an actual increase. Survival calculated at 1 and 2 years after initial diagnosis was 93.6% and 97.5%.

Mesenchymal bladder tumors may exceptionally include, other than RMS, leiomyosarcoma, inflammatory myofibroblastic tumor (Berger et al. 2007; Houben et al. 2007; Lopes et al. 2020), leiomyoma, hemangioma (Wiygul and Palmer 2010), lymphangioma (Niu et al. 2010), and neuroendocrine tumors (pheochromocytoma, paraganglioma, neurofibroma) (Mou et al. 2008).

Inflammatory myofibroblastic tumors of the bladder (IMTBs) are rare (a quarter of these neoplasms occur in children) and are characterized by a benign and reactive proliferation of myofibroblasts. A review of 42 reported cases of pediatric IMTB showed equal prevalence in males and females. Clinical presentation includes hematuria, dysuria, or abdominal pain, and mean age at presentation is 7.5 years (range of 2–15 years). The etiology of IMTB is poorly understood and is attributed to infectious or traumatic causes or a possible clonal lesion mainly involving the anaplastic lymphoma kinase gene (*ALK-1*) or *NTRK*, *ROS1*, *PDGFR*, and *NTRK*, which are far more common in children and young adults (Martelli et al. 2016).

Urothelial neoplasms in children are rare and predominantly non-invasive. Lesions are classified in accordance with the 2004 WHO/International Society of Urological Pathology criteria as urothelial papillomas, PUNLMPs, low-grade urothelial carcinomas, and high-grade urothelial carcinomas. At presentation, the most common symptom is painless hematuria. In the presence of hematuria, ultrasound must be performed. If a bladder lesion is identified, transurethral resection of the bladder should be performed. The lesions are usually solitary, non-muscle invasive, and of low grade (mainly urothelial papilloma and PUNLMPs). There is no standard ideal follow-up protocol for these tumors, basing on the rarity of the disease. Recurrence or progression is uncommon in patients younger than 20 years, the reported recurrence rate is 7%, and a single case of progression has been reported so far (Lopes et al. 2020; Saltsman et al. 2018).

PUNLMPs are normally solitary and small (1–2 cm) lesions, commonly occur at the posterior lateral walls and ureteric orifices of the bladder, are non-invasive, and do not metastasize. About 35% of PUNLMPs reportedly recur after complete resection, and around 10% of them increase in size if they are not treated; therefore, regular imaging surveillance is advocated (Saltsman et al. 2018). PUNLMP seems to have excellent long-term survival (Fine et al. 2005; Alanee and Shukla 2010).

TCC of the bladder has a high incidence in adults, but it is uncommon in children and adolescents, and only small case series have been described in children (Lerena et al. 2010; Yossepowitch and Dalbagni 2002). Apart from

the SEER report, there are about 125 cases of patients <20 years of age reported in the literature, with only 20 of them in patients <10 years of age (reviewed in Lerena et al. 2010). Despite some genetic conditions seem to increase the risk of TCC of the bladder in adults, such as Cowden disease, hereditary non-polyposis colon cancer, and familial increased risk, none of these have been reported to be related to this cancer in children (Giedl et al. 2006). Adolescents and young adults with Costello syndrome are at higher risk of TCC of the bladder (Gripp 2005). A known past history of smoking in adolescents has been advocated as a possible risk factor. Hematuria is the most common symptom of presentation. This finding emphasizes the need to exclude urothelial tumors in all young patients who present with painless hematuria (Hoenig et al. 1996), even though gross hematuria in children most often has a benign cause. Urine cytology has a good sensitivity and specificity only in high-grade tumors, and since the great majority of TCC in children are well differentiated, urine cytology is not recommended for diagnosis and or follow-up in children.

Fine et al. reported on a relatively large series of patients younger than 20 years with urothelial neoplasms, diagnosed following modern clinicopathological classification (Fine et al. 2005; Eble et al. 2004). This analysis confirmed that these tumors are more common in males, are likely to manifest as hematuria, occur as solitary lesions, and are generally of low-grade histology, with low recurrence potential. Cystoscopically, the majority of the lesions were described as papillary. Lesions ranged between urothelial papilloma (2 cases), PUNLMP (10 cases), noninvasive low-grade papillary urothelial cancer (8 cases), and noninvasive high-grade papillary urothelial cancer (3 cases).

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