Rare Tumors of the Urinary Tract

40

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Contents

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40.1 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, 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, oncocytoma, 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 (Gutjahr et al. 1990; Graf et al. 2003). It is well known that Wilms tumor is associated with different syndromes (Scott et al. 2006). 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; Wiesbauer 2008). 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.

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Imaging studies are most important, although none of these rare tumors show a specific appearance in ultrasound, CT, or MRI, comparing to nephroblastoma. 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). Only in addition with further information like the knowledge of lung metastasis in a small infant having a renal mass makes the diagnosis of a specific neoplasm more likely as RTK in the above case. In all cases of a renal mass, a chest X-ray or computed tomography (CT) scan is needed for staging. Further staging procedures are mandatory in patients with specific diagnoses. In case of CCSK and RTK, an magnetic resonance imaging (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 in CCSK and RCC to exclude bone metastasis (Smets and de Kraker 2010; Schenk et al. 2005).

New imaging techniques like FDG-PET and diffusion-weighted MRI (DWI) may help in distinguishing between necrotic and vital tumor areas and in the follow-up of patients in defining response to treatment (Smets and de Kraker 2010), but more research is needed to clarify their role in the diagnostic workup of rare kidney tumors in children before these techniques are routinely used in the clinical setting. 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. 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 (Barroca 2008). For research purposes, genetic and molecular genetic analyses are mandatory and should always be initiated to find better treatments for these children.

40.2 Rare Kidney Tumors

Primary non-Wilms renal tumors represent a heterogeneous, although clinically significant, group of malignancies accounting for <1% of pediatric tumors (Pastore et al. 2006; Ahmed et al. 2007; Magnani et al. 2001). They 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 CMN, cystic nephroma (to be distinguish from a cystic appearance of a Wilms tumor), and metanephric tumors. The group of metanephric neoplasms has been recently described; basing on the extent/appearance of epithelium or stroma, they are classified into metanephric stromal tumor (pure stromal), metanephric adenoma (pure epithelial), or metanephric adenofibroma (biphasic, stromal-epithelial) (Arroyo et al. 2001). 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) (Kumar et al. 2010) or neuroblastoma, may secondarily affect the kidney but sometimes 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.

PNET has been documented with increasing frequency in the kidney in the last decade. 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 (Miniati et al. 2008), one of the most 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 (Ries et al. 2008; 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 (Vujanic et al. 2009). A recent 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 more than the fact that they are in the kidney (Fig. 40.1).

40.3 Renal Cell Carcinoma (RCC)

RCC is rare in the first two decades of life and accounts for approximately 5% of pediatric renal tumors (Selle et al. 2006; Pastore et al. 2006; Silberstein et al. 2009; Argani and Ladanyi 2003). The big discovery in recent years regarding pediatric RCC has been the characterization of the translocation RCCs (Argani et al. 2003; Argani and Ladanyi 2005, 2006). Translocations most frequently involve the TFE3 gene on chromosome Xp11.2 or, less commonly, the TFEB gene on chromosome 6p21. 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. 2008; Indolfi et al. 2003; Ramphal et al. 2006; Selle et al. 2006; Wu et al. 2008; Rao et al. 2009). 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.

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 around 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). Patients with tumor localized in the kidney with or without regional LN spread have a good 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; Geller et al. 2008; Indolfi et al. 2003; Selle et al. 2006).

40.3.1 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

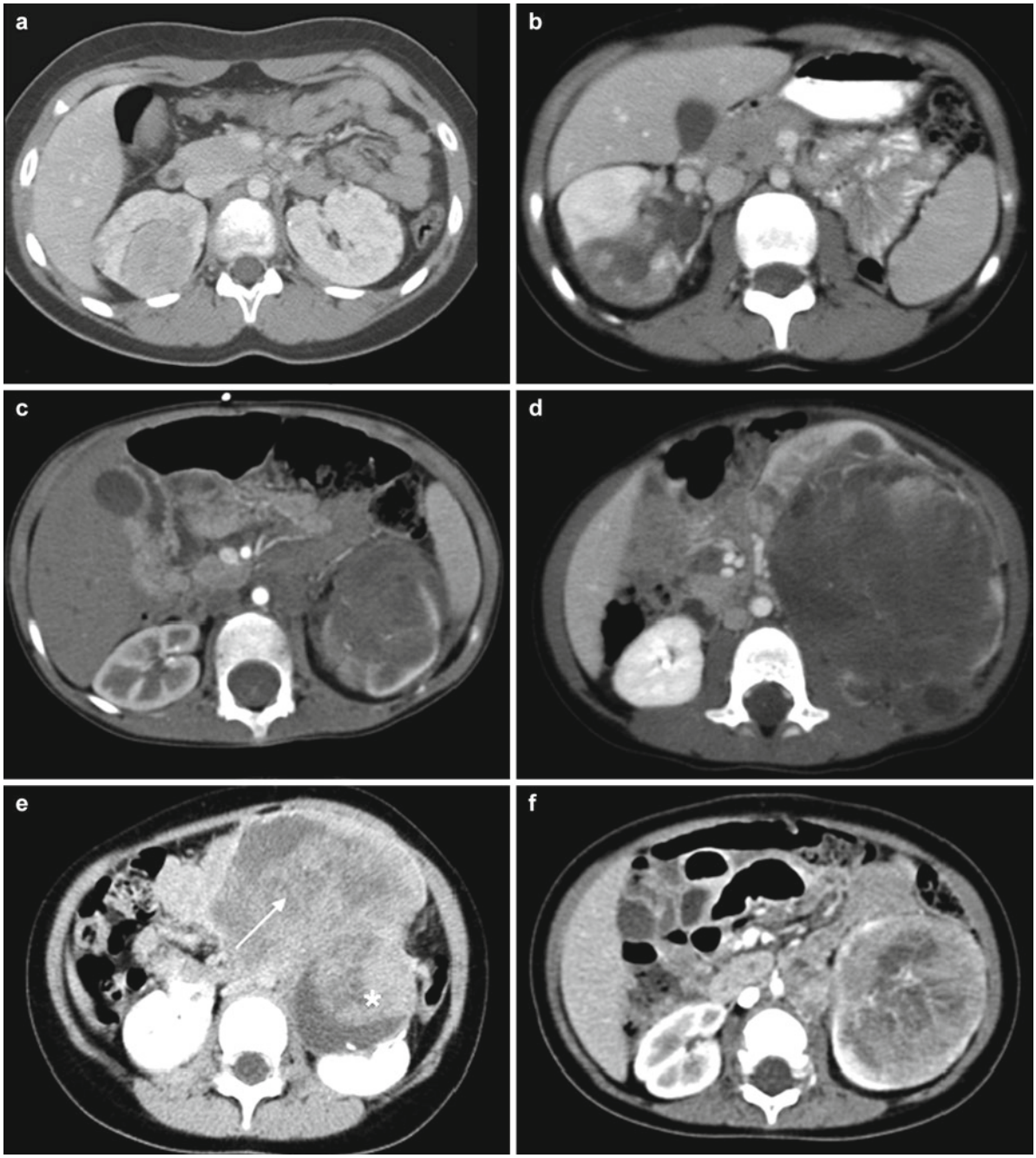

Fig. 40.1 Post-contrast CT imaging of: (**a**) angiomyolipoma (male, 13 year-old); (**b**) primitive neuroectodermal tumor (female, 15 year-old); (**c**) Wilms tumor (male, 4 year-old); (**d**) clear cell sarcoma (male, 3 year-old); (**e**) 6-year-old female who displayed two rather distinct nodules, that at microscopic examination turned out to be MiTF+RCC (*) and concomitant Wilms tumor (*arrow*); (**f**) Xp11.2 translocation carcinoma (female, 9-month-old)

(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

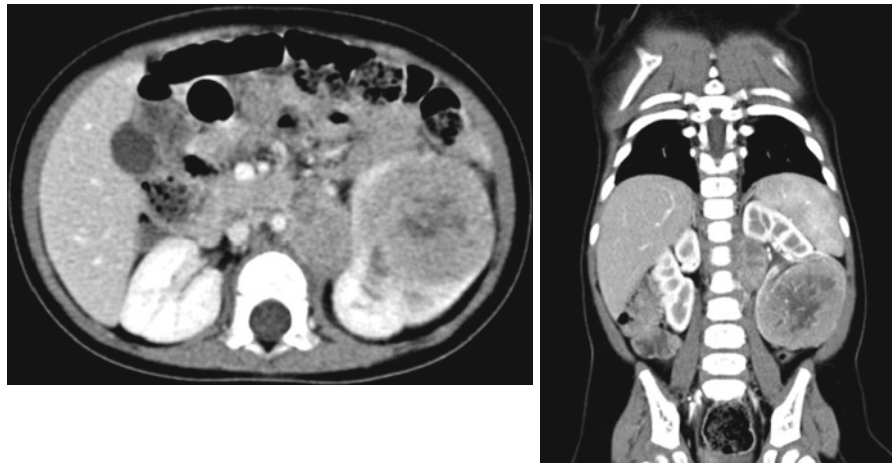

Fig. 40.2 Post-contrast CT scan of a Xp11.2 translocation carcinoma in a 9-month old baby girl

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.

40.3.2 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; Gill et al. 2010). Local signs and symptoms include gross hematuria, flank pain, or a palpable abdominal mass. Rarely children present with the full above mentioned 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.

Similar to adults, tumor stage in pediatric RCC represents a good prognostic indicator. The TNM system is the more frequently adopted, while stage designation according to modified Robson system (Carcao et al. 1998) is rarely encountered. 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. 40.2).

40.3.3 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 2003; Sebire and Vujanic 2009).

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 2003, 2005; Camparo et al. 2008). 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.

40.3.4 TFE3/MiTF Translocation 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. 2001b) 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. 2001a; Argani et al. 2007), PSF in 1p34 (Argani et al. 2005), and CLTC in 17q23 (Argani et al. 2003). 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 tubulo-papillary 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.

40.3.5 Principles of Treatment

The emerging differences between childhood and adulthood RCC probably prevent a direct 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 radical nephrectomy. Since nephron-sparing approaches that preserve healthy renal parenchyma are advocated for adults and demonstrated good long-term oncologic outcome (Ficarra 2007; Touijer et al. 2010), it is reasonable that they will be evaluated in children and adolescents as well (Cook et al. 2006), at least in cases very carefully selected by experienced surgeons.

Question as to what is the more adequate extension of retroperitoneal LN dissection remains relatively unanswered. 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. 2008). 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). 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 2010a, 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. The landscape of systemic therapies in RCC has been recently changed by the introduction of drugs designed to target tumor-related angiogenesis and signal transduction (Sun et al. 2010; Brugarolas 2007). These are the multitargeted receptor tyrosine kinase inhibitors (sorafenib, sunitinib, pazopanib), the inhibitors of the mTOR pathway (temsirolimus, everolimus), and the anti-angiogenic monoclonal antibody bevacizumab.

When used as first- and second-line therapies for metastatic RCC, these novel agents have demonstrated previously unprecedented response rates and improvements in time to progression in phase III trials (Escudier et al. 2007a, b, 2009, 2010; Motzer et al. 2007, 2009; Hudes et al. 2007; Bellmunt and Guix 2009; Soulières 2009; Bukowski 2010). On the other hand, the utility of these therapies in the adjuvant setting remains unproven. This uncertain benefit, together with their toxicity and the relatively better outlook for children and adolescents with completely resected LN+M0 RCC, support not currently using adjuvant therapies in such pediatric RCCs (Escudier and Kataja 2010).

Despite these several targeted therapies available for RCC, each with different profile of risk versus benefit, at the time of this writing, no 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 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. What might be recommended for metastatic pediatric RCCs is to adopt sequential treatment with VEGF pathway-targeted therapies, optimizing efficacy and safety results.

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).

40.4 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. Their prognosis remains dismal despite aggressive treatments. The first description is done by Haas et al. in 1981 (Haas et al. 1981). Despite a multitude of case series and single reports, very little is known about this tumor and done in prospective national or international clinical trials (Athale et al. 2009; Corey et al. 1991; Gururangan et al. 1993; Hirose et al. 1996). Common therapeutic regimens do use intensive anthracycline-based polychemotherapy regimens and aggressive local therapy (Chi et al. 2008; Squire et al. 2007; Wagner et al. 2002; Waldron et al. 1999; Zimmerman et al. 2005). Recent publications describe successful therapeutic approaches even in primarily metastasized or relapsed disease (Chi et al. 2008; Zimmerman et al. 2005).

40.4.1 Molecular Genetics

Common to rhabdoid tumors of any anatomical site (central nervous system, kidney, other soft tissues) are alterations in chromosome 22. 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). 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).

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. 40.3).

A correlation between the mutational status of certain nucleotides and the clinical course of the disease has not been demonstrated. However, reports from the

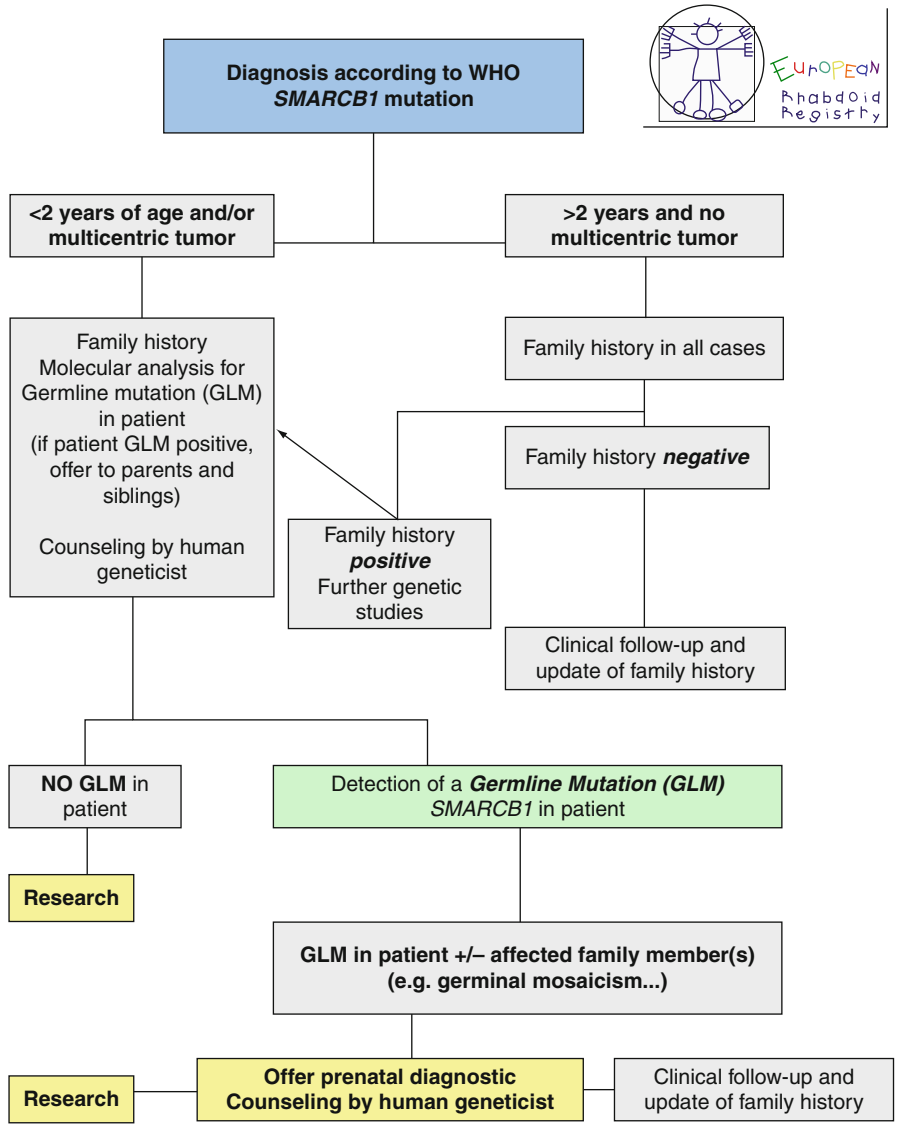

Fig. 40.3 Flow chart for genetic counseling of patients with suspected rhabdoid tumor predisposition (From: Frühwald, M European Rhabdoid Registry protocol 2010)

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

40.4.2 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).

40.4.3 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. 1986). 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.

40.4.4 Treatment and Prognosis of RTK

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 (Fig 40.4) (Reinhard et al. 2008).

In the United Kingdom, patients with RTK have been treated according to the Wilms tumor studies

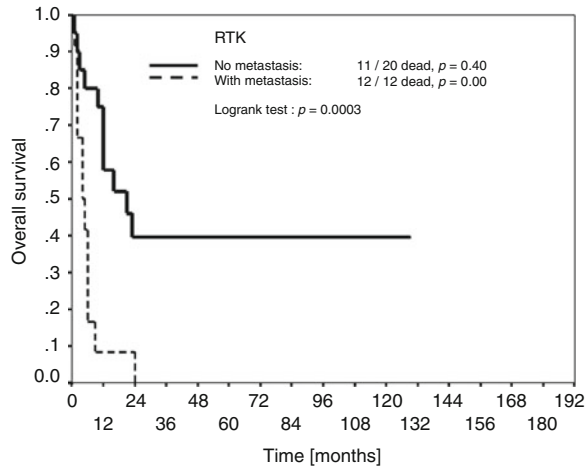

Fig.. 40.4 Outcome of RTK treated according to SIOP protocols in Germany

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) studies 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 (COG-Q9401) 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). Based on the currently available data, the role of radiotherapy in the treatment of RTK cannot be judged conclusively (Tomlinson et al. 2005). A recent window study using irinotecan in the induction was prematurely closed due to ineffectiveness (COG AREN0321).

40.4.5 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 Rhaboid 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, other than from the GPOH and SIOP studies for high-risk renal tumors, soft tissue sarcomas, and pediatric brain tumors. 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.

40.5 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 (Argani et al. 2000). 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) 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 (authors' unpublished data).

40.5.1 Molecular Genetics

Cytogenetic studies of CCSK have reported balanced translocations t(10;17)(q22;p13), t(10;17)(q11;p12), and del(14)(q24.1q31.1). Although the tumor suppressor gene p53 is located at the chromosome 17p13 breakpoint, p53 abnormalities are rarely present in these tumors. The t(10;17) breakpoint and deletion of chromosome 14q24 suggest that other genes are involved in tumor pathogenesis (Brownlee et al. 2007).

Comparative genomic hybridization 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).

Cutcliff 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). Huang et al.

could show that the most common malignant tumors arising in the kidney 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).

Correlations between gene mutations and outcome are not described yet. p53 abnormalities are controversially discussed (Argani et al. 2000; Brownlee et al. 2007).

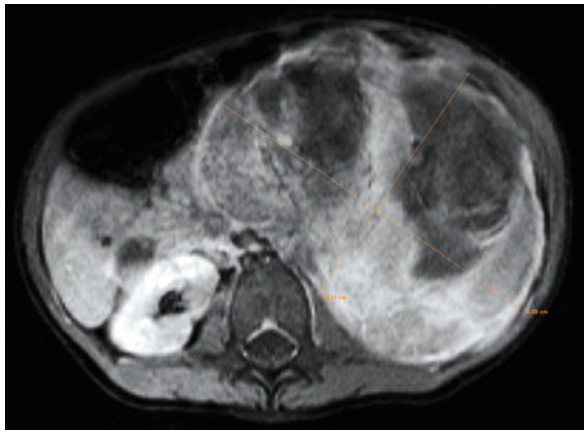

Fig. 40.5 MRI at the time of diagnosis in a 9-year-old girl with CCSK. Tumor volume at the time of diagnosis: 1,370 mL with no regression after 4 weeks of preoperative chemotherapy according to the SIOP Wilms tumor protocol with vincristine and actinomycin-D

40.5.2 Diagnosis

CCSK constitutes about 4% of all kidney tumors in children. 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 1.6:1) (Graf N 2010). 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 (Figs. 40.3 and 40.5)

40.5.3 Histopathology

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). Only vimentin is consistently immunoreactive in immunohistochemical stains. Consistently, negative results with other antibodies help to exclude other tumors. The p53 gene product is rarely overexpressed in non-anaplastic CCSKs but strikingly overexpressed in anaplastic CCSKs (Argani et al. 2000).

40.5.4 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). Overall survival is in the range of 70% today (Argani et al. 2000). A multivariate analysis done by Argani et al., including 182 patients from NWTSG trials 1–4 revealed four independent prognostic factors for survival: treatment with doxorubicin, stage, age at diagnosis, and tumor necrosis (Argani et al. 2000).

Over a period of 7 years, 50 patients were treated according to the SIOP 93-01/GPOH trial (Graf N 2010). Only three patients had metastatic disease at the time of diagnosis (all with multiple bone metastasis, one patient also with lung metastasis). Forty-one patients did receive preoperative chemotherapy

with vincristine and actinomycin-D for 4 weeks and, in addition, doxorubicin in case of metastatic disease for 6 weeks. Local stage after surgery was stage I: 27, stage II: 9, and stage III: 14. In 24 patients local histology was changed by reference histology, in 16 cases from a different histology to CCSK, and in 8 cases from CCSK to another histology. Most often, blastemal predominant Wilms tumor and RTK were misdiagnosed. None of the metastatic patients was in CR after preoperative chemotherapy. Postoperative high-risk chemotherapy with four drugs (carboplatin, etoposide, ifosfamide, and doxorubicin) was given to all patients for 34 weeks. Patients did receive postoperative local irradiation in stage II and III of 25.2 Gy and a boost in case of macroscopic remaining tumor or positive lymph nodes of 10.8 Gy. The 5-year event-free survival is 85% with a 5-year overall survival of 91% for this group of patients with a median follow-up of 68.4 months. Only five patients died, four because of tumor progression and one patient because of a cardiomyopathy. A multivariate analysis showed only a significant influence of stage III on event-free survival. No influence was found for age. As all patients did receive doxorubicin the influence of this drug to outcome could not be analyzed. This excellent result is also important as it shows that preoperative chemotherapy with only vincristine and actinomycin-D did not negatively influence the outcome. Two of the three patients with stage IV are in first CR for 4.5 and 5 years. Their treatment was intensified by high-dose chemotherapy with autologous stem cell transplantation in first line. The third patient with metastatic disease died of congestive heart failure due to doxorubicin and irradiation to the lungs and ribs.

Most remarkable is the relapse pattern. Out of seven relapses, six did occur in the brain. Two of them could be rescued with surgery, irradiation, and second-line therapy. They are in second complete remission for 7.4 and 8.8 years (Graf N 2010). Such a relapse pattern in the brain is also reported by other groups (Seibel et al. 2006; Radulescu et al. 2008), underlining that the brain is a frequent site of recurrent disease in CCSK.

As prognosis of patients with CCSK is excellent today, if they receive adequate therapy, all patients with this tumor have to be referred to a center of pediatric oncology.

40.6 Differential Diagnosis and Treatment of Urothelial and Bladder Tumors

Pediatric tumors of the lower urinary tract are extremely rare and comprise dissimilar histological subtypes. 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 2009).

Macroscopic hematuria and symptoms of urinary tract infections often represent the initial presentation (Patel et al. 2008; Lerena et al. 2010; Fine et al. 2005). Boys are generally more affected than girls regardless of the histology (2–3:1).

The rarity of bladder tumors in children makes it very difficult to estimate their incidence and survival. A recent 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 the past 30 years), papillary urothelial neoplasm of low malignant potential (PUNLMP) and embryonal rhabdomyosarcoma comprised 50.7% and 36.4% of the tumors, and transitional cell carcinoma (TCC) accounted for 9.3% (Alanee and Shukla 2009). Noteworthy, the incidence of a given histological subtype was related to the age at presentation. Embryonal rhabdomyosarcoma 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 rhabdomyosarcoma, leiomyosarcoma, inflammatory myofibroblastic tumor (Berger et al. 2007; Houben et al. 2007), hemangioma (Wiygul and Palmer 2010), lymphangioma (Niu et al. 2010), and pheochromocytoma (Mou et al. 2008).

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 (Patel et al. 2008; Lerena et al. 2010; Yossepowitch and Dalbagni 2002). Apart from the SEER report,

currently, 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 nonpolyposis colon cancer, 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 and Lin 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 revealed and 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. These neoplasms have low recurrence potential, with extremely favorable prognosis. 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).

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. Ultrasound is an excellent initial diagnostic tool for bladder tumor in children. 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. Although urothelial neoplasms in the younger age group may recur, these events are typically benign (papilloma) or low-grade lesions. PUNLMP seems to have excellent long-term survival (Fine et al. 2005; Alanee and Shukla 2009).

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