Non-Wilms Pediatric Renal Tumors

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Abstract

The vast majority of childhood renal tumors are Wilms tumors (nephroblastoma). All other pediatric kidney tumors comprise less than 15 % of childhood renal tumors and are therefore considered rare malignancies of childhood. The most frequently observed non-Wilms renal tumors include clear cell sarcoma of the kidney (CCSK), renal cell carcinoma (RCC), malignant rhabdoid tumor of the kidney (MRTK), and congenital mesoblastic nephroma (CMN). These tumor types are markedly heterogeneous in their clinical

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characteristics. CMN occurs mainly in early infancy, MRTK occurs in infants and young toddlers, CCSK occurs in toddlers and young school-age children, and RCC is most common in adolescents. The outcome of CMN is excellent, with overall survival rates over 95 % without adjuvant chemotherapy. By contrast, patients with MRTK have overall survival rates of only 20–25 %, even with intensive multimodality treatment regimens. The outcomes of CCSK and RCC are intermediate between CMN and MRTK. The non-Wilms renal tumors also have markedly different biological characteristics, each bearing distinct genetic mutations and translocations. This chapter provides an overview of the major non-Wilms renal tumors of childhood, including the ultra-rare entities of renal medullary carcinoma, metanephric tumors, and renal sarcomas.

14.1 Introduction

The vast majority of childhood renal tumors are Wilms tumors (nephroblastoma). All other pediatric kidney tumors comprise less than 15 % of childhood renal tumors and are therefore considered rare malignancies of childhood. The most frequently observed non-Wilms renal tumors include clear cell sarcoma of the kidney (CCSK), renal cell carcinoma (RCC), malignant rhabdoid tumor of the kidney (MRTK), and congenital mesoblastic nephroma (CMN). These tumor types are markedly heterogeneous in their clinical characteristics. CMN occurs mainly in early infancy, MRT occurs in infants and young toddlers, CCSK occurs in toddlers and young school-age children, and RCC is most common in adolescents. The outcome of CMN is excellent, with overall survival rates over 95 % without adjuvant chemotherapy. By contrast, patients with MRTK have overall survival rates of only 20–25 %, even with intensive multimodality treatment regimens. The outcomes of CCSK and RCC are intermediate between CMN and MRTK. The non-Wilms renal tumors also have markedly different biological characteristics, each bearing distinct genetic mutations and translocations. This chapter provides an overview of the major non-Wilms renal tumors of childhood, including the ultra-rare entities of renal medullary carcinoma, metanephric tumors, and renal sarcomas.

14.2 Clear Cell Sarcoma of the Kidney

Clear cell sarcoma of the kidney (CCSK) was considered a Wilms tumor variant until 1970 when it was recognized as a separate clinicopathologic entity by Kidd (1970). The distinctive histopathologic features of CCSK were reported simultaneously in 1978 by Morgan and Kidd, Marsden and Lawler, and Beckwith and Palmer (Beckwith and Palmer 1978; Marsden and Lawler 1978; Morgan and Kidd 1978). Currently, it is obvious that on the basis of histologic, ultrastructural, molecular, and clinical manifestations, CCSK should no longer be considered a variant of Wilms tumor (Sotelo-Avila et al. 1985).

14.2.1 Epidemiology

CCSK comprises approximately 4 % of all primary renal tumors in children (Beckwith 1983; Sotelo-Avila et al. 1985; Green et al. 1994; Argani et al. 2000b; El Kababri et al. 2004). The median age at presentation is between 2 and 3 years, and there is a male predominance, with a male to female ratio of about 2 to 1 (Morgan and Kidd 1978; Sotelo-Avila et al. 1985; Green et al. 1994; Argani et al. 2000b; Seibel et al. 2004; Stoneham et al. 2009). The youngest patient with CCSK reported in the literature was a fetus (at 31 weeks gestation) and the oldest was 58 years of age (Hung 2005; Adnani et al. 2006). CCSK is rarely reported in the first 6 months of life and in adults, in whom it has been the subject of only isolated case reports (Suzuki et al. 1983; Mishra et al. 1993; Newbould and Kelsey 1993; Oda et al. 1993; Toyoda et al. 1998; Amin et al. 1999; Bhayani et al. 2001; Benchekroun et al. 2002; Mazzoleni et al. 2003; Rosso et al. 2003; Hung 2005; Adnani et al. 2006; Kural et al. 2006; van den Heuvel-Eibrink et al. 2008).

14.2.2 Clinical Features

Common clinical presenting symptoms of patients with CCSK are similar to those of patients with Wilms tumor, including abdominal distention and hematuria. However, most CCSK patients present with additional clinical signs, such as abdominal pain, vomiting, decreased oral intake, bone pain, hypertension, fever, and constipation (Kagan and Steckel 1986; Wood et al. 1990; Kusumakumary et al. 1997; Parikh et al. 1998; Yumura-Yagi et al. 1998; Sharma and Menon 2001; Taguchi et al. 2008). Some studies suggest a predilection for the involvement of the right kidney (Sotelo-Avila et al. 1985; Sandstedt et al. 1987; Parikh et al. 1998). Most patients with CCSK present with stage I, II, and III disease; stage IV is uncommon at diagnosis, and stage V (bilateral disease) is extremely rare in CCSK (Morgan and Kidd 1978; Sotelo-Avila et al. 1985; Green et al. 1994; Argani et al. 2000b; El Kababri et al. 2004; Seibel et al. 2004, 2006; van den Heuvel-Eibrink et al. 2008). About 5–10 % of the patients have distant metastatic disease at presentation (Sotelo-Avila et al. 1985; Green et al. 1994; Argani et al. 2000b; El Kababri et al. 2004; Seibel et al. 2004). The most frequent site of distant metastases is the bone, but the tumor also spreads to the lungs, liver, mediastinum, brain, orbit, and soft tissue (Green et al. 1994; Argani et al. 2000b; Seibel et al. 2006; Brownlee et al. 2007; Radulescu et al. 2008).

14.2.3 Pathology

There is a spectrum of histological appearances seen in CCSK, all of which show admixture of cord cells, septal cells, stromal fragments, myxoid material, and blood vessels in various proportions (Argani et al. 2000b; Iyer et al. 2005). Iyer et al. also found small, pyknotic cells (Iyer et al. 2005). In total, nine histological patterns are identified. The most common pattern is the classic pattern, whose features are seen at least focally in over 90 % of tumors (Akhtar et al. 1989; Newbould and Kelsey 1993; Yun 1993; Parikh et al. 1998; Amin et al. 1999; Argani et al. 2000b; Mazzoleni et al. 2003; Hung 2005; Iyer et al. 2005; Radhika et al. 2005; Kural et al. 2006). The classic subtype of CCSK is characterized by round to oval cells arranged perivascularly and also in sheets and clusters intimately associated with a metachromatic matrix mucopolysaccharide material. The cells may show nuclear grooves (Drut and Pomar 1991; Krishnamurthy and Bharadwaj 1998; Radhika et al. 2005). CCSK is easily confused with other neoplasms because the classic pattern is often modified and may mimic other neoplasms to a sometimes striking degree. The pathologist unaware of these variant patterns is likely to diagnose CCSK as another neoplasm with different therapeutic and prognostic implications. Other patterns are myxoid, sclerosing, cellular, epithelioid, palisading, spindle, storiform, and anaplastic (Sotelo-Avila et al. 1985; Punnett et al. 1989; Kusumakumary et al. 1997; Argani et al. 2000b; Iyer et al. 2003, 2005). Immunohistochemistry shows varying degrees of vimentin immunoreactivity in nearly all samples, but other markers are consistently negative (Park et al. 1997; Argani et al. 2000b; Rosso et al. 2003; Kural et al. 2006). These include stains for epithelial markers (cytokeratins and EMA), neural markers (S100 protein), neuroendocrine markers (chromogranin, synaptophysin), muscle markers (desmin), CD34, CD117 (c-kit), and CD99 (MIC2).

14.2.4 Genetics and Biology

In contrast to nephroblastoma, CCSK does not appear to be associated with genetic predisposition syndromes (i.e., WAGR, Beckwith-Wiedemann, and Denys-Drash syndromes), and familial CCSK cases have not been reported so far (Sotelo-Avila et al. 1985; Sohda et al. 1997; Argani et al. 2000b). Cytogenetic studies of CCSK have revealed a recurrent t(10;17)(q22;p13) clonal balanced translocation in some tumors (Punnett et al. 1989; Rakheja et al. 2004; Taguchi et al. 2008). The breakpoints of the translocation were recently mapped and found to involve the *YWHAE* gene on chromosome 17 and the *FAM22* gene on chromosome 10. The *YWHAE-FAM22* transcript was detected in six of 50 CCSKs tested, showing an overall incidence of 12 % (O'Meara et al. 2012). The *YWHAE* gene encodes the 14–3–3 epsilon protein, which modulates phosphoserine-containing proteins and plays a role in various signal

transduction pathways, including Akt and MAPK (Muslin et al. 1996; Tzivion et al. 1998; Zuo et al. 2010). Comparative genomic hybridization (CGH) studies have found a high proportion of normal profiles in CCSK, with infrequent copy number variations. However, gain of chromosome 1q has been identified in several tumors, similar to findings in other malignancies (Barnard et al. 2000; Schuster et al. 2003). Other variations have been observed in chromosomes 4, 14, 10, and 19 (Barnard et al. 2000; Schuster et al. 2003).

The proto-oncogene *c-KIT* is overexpressed in CCSK but is not accompanied by gene amplification or activating mutations (Jones et al. 2007). In addition, dysregulation of the epidermal growth factor receptor (EGFR) pathway has been observed at multiple levels in clear cell sarcoma of the kidney (Little et al. 2007). Gene expression profiling studies have reported expression of neural markers (e.g., nerve growth factor receptor) and expression of member genes of the sonic hedgehog pathway and the phosphoinositide-3-kinase/Akt cell proliferation pathway in CCSK (Cutcliffe et al. 2005). Methylation analysis demonstrated loss of imprinting (LOI) of insulin-like growth factor-2 (IGF2) in 40–50 % of CCSKs, with retention of the normal somatic pattern at both the H19 and SNRPN loci (Sohda et al. 1997; Schuster et al. 2003). Consistent with LOI of IGF2, Yun et al. found high IGF2 expression (Yun 1993).

14.2.5 Treatment and Outcomes

The results of large cooperative group studies of CCSK are shown in Table 14.1. Historically, CCSK was treated using regimens used for nephroblastoma. Results from the first three National Wilms Tumor Studies (NWTS) suggested that the addition of doxorubicin to vincristine and dactinomycin improved the 6-year relapse-free survival (RFS) for patients with CCSK (Green et al. 1994). In NWTS-3, the addition of cyclophosphamide did not improve the 6-year RFS, but it should be emphasized that the cyclophosphamide dose and dose intensity were relatively low by today's standards (Green et al. 1994). Flank radiation therapy is considered part of standard therapy and has been used in the vast majority of NWTS patients.

In the fourth National Wilms Tumor Study (NWTS-4), patients with CCSK were randomized between 6 and 15 months of vincristine, doxorubicin, and dactinomycin chemotherapy. The results showed improved RFS with the longer course of therapy (8-year RFS of 87.8 % versus

Table 14.1 Treatment strategy and outcome of cooperative group studies of CCSK

Study	Chemotherapy (# patients)	Abdomen XRT	RFS (follow-up, years)	OS (follow-up, years)	Reference
NWTS 1-2	VA (8)	0 – >37.8 Gy (age based)	25 % (6 years)	25 % (6 years)	Green et al. (1994)
	VAD (58)		63.5 % (6 years)	71.9 % (6 years)	
NWTS 3	VAD (43)	0 – >37.8 Gy (age based)	64.4 % (6 years)	71.3 % (6 years)	Green et al. (1994)
	VADC (30)		58.2 % (6 years)	60.8 % (6 years)	
NWTS 4	VAD (6 months) (23)	10.8 Gy	60.6 % (8 years)	85.9 % (8 years)	Seibel et al. (2004)
	VAD (15 months) (17)		87.8 % (8 years)	87.5 % (8 years)	
NWTS 5	VDCE (110)	10.8 Gy	79 % (5 years)	89 % (5 years)	Seibel et al. (2006)
SIOP 9	VADI (10)	Stage II/III 30 Gy	75 % (2 years)	88 % (5 years)	Tournade et al. (2001)
SIOP 93-01	Stage I: VADI (27)	Stage II/III 30 Gy	–	91 % (5.9 years)	Furtwangler et al. (2005)
	Stage II-IV: IDECar (26)				
UKWT2	VAD (16)	Stage III 30 Gy	82 % (4 years)	88 % (4 years)	Stoneham et al. (2009)

Abbreviations: NWTS National Wilms Tumor Study Group, *SIOP* International Society of Pediatric Oncology, *UKWT* United Kingdom Wilms Tumor Study Group, *A* dactinomycin, *V* vincristine, *D* doxorubicin, *C* cyclophosphamide, *E* etoposide, *I* ifosfamide, *Car* carboplatin, *XRT* radiation therapy, *RFS* relapse-free survival, *OS* overall survival

60.6 %, $p=0.08$), but the overall survival (OS) was unchanged between the long and short chemotherapy regimens (8-year OS 87.5 % versus 85.9 %, $p=0.99$) (Seibel et al. 2004). NWTS-4 also compared the standard doxorubicin and dactinomycin administration schedules (doses divided over 3 days for doxorubicin and over 5 days for dactinomycin) with the "pulse-intensive" schedule (dose given on 1 day). The outcomes of the two schedules were equivalent, and patients experienced less severe hematologic toxicity and fewer physician and hospital encounters with the pulse-intensive schedule, which has now become the standard (Green et al. 1994; Seibel et al. 2004).

In the NWTS-5 protocol, patients with all stages of CCSK were treated with a radical nephrectomy followed by radiotherapy and chemotherapy with vincristine/doxorubicin/cyclophosphamide alternating with cyclophosphamide/etoposide for 24 weeks and flank radiation to a dose of 10.8 cGy (Seibel et al. 2006). Five-year event-free (EFS) and OS in NWTS-5 were 79 and 89 %, respectively. EFS by stage was 100 % (I), 87 % (II), 74 % (III), and 36 % (IV) (Seibel et al. 2006). The outstanding outcome for stage I disease confirms the previous review of 351 cases from NWTS 1-4, which showed a 98 % OS rate in patients with stage I disease, as defined by NWTS-5 staging definitions (Argani et al. 2000b). NWTS-5 updated stage I to designate tumors confined to the kidney, completely resected and without penetration of the renal capsule or involvement of the renal sinus vessels. Previously, stage I was defined by lack of tumor extension beyond the hilar plane, an imaginary line connecting the medial aspects of the upper and lower poles of the kidney. For CCSK, the updated definition identifies a group of patients with nearly 100 % survival (Kalapurakal et al. 2012).

In the SIOP-9 study, patients were treated with preoperative dactinomycin/vincristine and postoperative doxorubicin/dactinomycin/vincristine/ifosfamide. For local stage II or III disease, irradiation to the flank or abdomen was applied (Tournade et al. 2001; Furtwangler et al. 2005). With the SIOP-9 approach, the 2-year EFS was 75 % and 5-year OS was 88 % (Tournade et al. 2001). The SIOP 93-01/GPOH trial used a similar approach to SIOP-9, except that the postoperative chemotherapy regimen consisted of ifosfamide/etoposide/carboplatin/doxorubicin. On this study, the OS survival rate was 91 % (Furtwangler et al. 2005).

Treatment in the United Kingdom Children's Cancer Study Group 2 (UKCCSG-2) consisted of vincristine/dactinomycin/doxorubicin administered for 12 months. Patients with local stage I and II disease did not receive irradiation to the flank/abdomen, but patients with local stage III disease received 30 Gy (Mitchell et al. 2000). Four-year EFS and OS were 88 and 82 %, respectively. From the combined UKCCSG and French trials, 5-year EFS and OS were 63 and 75 %, respectively. Paradoxically, the OS for stage II disease (73 %) was inferior to the OS for stage III disease (86 %), suggesting the radiation therapy may be helpful for stage II (Stoneham et al. 2009).

14.2.6 Disease Recurrence in CCSK

Approximately 25 % of patients with CCSK will experience recurrence. Historically, late relapses were characteristic of CCSK, but in the NWTS-5 trial, only one of 21 relapses occurred beyond 3 years after diagnosis (Green et al. 1994; Charafe et al. 1997; Kusumakumary et al. 1997; Argani et al. 2000b; Seibel et al. 2006). Advanced stage, older age, lack of doxorubicin in upfront treatment, and absence of necrosis are important adverse prognostic factors for relapse (Argani et al. 2000b). The bone was historically the most frequent relapse site of CCSK (Morgan and Kidd 1978; Sotelo-Avila et al. 1985; Green et al. 1994; Argani et al. 2000b), but recent reports from the NWTSG and SIOP have indicated that the brain has surpassed the bone as the most common site of recurrence (Furtwangler et al. 2005; Seibel et al. 2006). The reason for the increase in central nervous system recurrences is unclear, but it is possible that the brain is a sanctuary site that allows tumor cells to avoid exposure to modern intensive chemotherapy. It is important to include the brain in imaging surveillance for patients who are off-therapy for CCSK. Notably, a case series of patients with recurrent CCSK with brain

metastases showed that six of eight patients had durable survival with a combination of ifosfamide/carboplatin/etoposide chemotherapy, surgery, and radiation therapy (Radulescu et al. 2008).

14.3 Malignant Rhabdoid Tumor of the Kidney

Malignant rhabdoid tumor of the kidney (MRTK) is a rare, highly aggressive type of cancer occurring in early childhood associated with rapid progression and a very poor prognosis. In the past, MRTK was classified as a subtype of Wilms tumor but in the early 1980s it was recognized as a distinct tumor type. To date, the exact cell origin of the MRTK has not been elucidated. Although MRTK was first described in the kidney, it is recognized to occur in many organs and soft tissues. MRTK arising in the brain is referred to as "atypical teratoid-rhabdoid tumor."

14.3.1 Epidemiology

The true incidence of MRTK is not known, but European data suggest that less than 0.5 per million children per year will suffer from MRTK, underscoring the rarity of the disease (Haas et al. 1981). The median age at presentation has been reported to vary between 10 and 18 months, and males and females are equally affected (Brennan et al. 2004; Tomlinson et al. 2005; Reinhard et al. 2008; van den Heuvel-Eibrink et al. 2011).

14.3.2 Clinical Characteristics

Patients with MRTK generally present with a palpable abdominal mass and have other symptoms such as hematuria (gross or microscopic), fever, infection, hypertension, and anemia (Amar et al. 2001). Hypercalcemia, caused by increased parathormone levels, is associated with MRTK, but is a nonspecific finding because hypercalcemia is seen in other non-Wilms renal tumors including congenital mesoblastic nephroma (Amar et al. 2001; Tomlinson et al. 2005). Most MRT cases present with a high tumor stage. Series of renal MRT consistently show that more than two-thirds of children have stage III or IV disease (Brennan et al. 2004; Tomlinson et al. 2005; Reinhard et al. 2008; van den Heuvel-Eibrink et al. 2011). By contrast, in Wilms tumor, only 33 % of children have stage III or IV (Amar et al. 2001). Common metastatic sites are regional lymph nodes, lungs, liver, bone, and brain.

It is difficult to discriminate MRTK from Wilms tumor based on imaging alone. Both tumors can present as a large intrarenal mass involving the renal hilum with invasion of the renal vein and inferior vena cava (Graf et al. 2000). MRTK on ultrasound appears as a large, heterogeneously, lobulated mass, due to hemorrhage, fat, necrosis, or calcification (Ahmed et al. 2007). Several CT findings are suggestive of MRT, including calcifications, subcapsular hematoma, and subcapsular fluid collections (Mitchell et al. 2006). However, these findings are also found in children with other renal tumors.

14.3.3 Histology

"Rhabdoid" tumor got its name based on its resemblance to rhabdomyoblasts, though it does not demonstrate muscle differentiation. On histology, MRTK is characterized by solid proliferations of monotone tumor cells with vesicular nuclei and prominent nucleoli, abundant eosinophilic cytoplasm, and intracytoplasmic inclusions (Vujanic et al. 1996; Biegel et al. 2002). Immunohistochemical analysis shows monophenotypic tumor cells, positive for vimentin and negative for actin, myosin, desmin, PAS, and cytokeratin (Graf et al. 2000; Kinoshita et al. 2001). The histological diagnosis can further be confirmed by INI1 (encoded by *SMARCB1*) staining, which is absent in cases of MRTK in contrast to other renal tumors and rhabdomyosarcoma (Hoot et al. 2004). Other tumors that may lack INI1 staining include renal medullary carcinoma, some liver tumors (there is debate as to whether these are rhabdoid tumors), epithelioid sarcomas, and schwannomas.

14.3.4 Genetics and Biology

It had long been debated whether renal, CNS, and extrarenal rhabdoid tumors are distinct cancers that possess similar histologic appearances or whether they are the same cancer in different anatomic locations. This issue was largely put to rest when the majority of rhabdoid tumors, regardless of anatomic site, were found to have biallelic inactivating mutations in *SMARCB1* (also known as *INI1*, *BAF47*, and *hSNF5*), located at chromosome 22q11.2 (Versteege et al. 1998; Biegel et al. 1999). Whereas previous studies showed that inactivating mutations in both copies of *SMARCB1* occur in about 75 % of malignant rhabdoid tumors, comprehensive analysis of the 22q11.1 locus has revealed that more than 95 % of tumors have detectable mutations (Jackson et al. 2009). Remarkably, up to 35 % of patients with seemingly sporadic rhabdoid tumor have a germline mutation in one allele of *SMARCB1* (Bourdeaut et al. 2011; Eaton et al. 2011). Carriers can present with more than one primary tumor.

SMARCB1 encodes a member of the SWI/SNF chromatin remodeling complex, which regulates transcription of specific targets by mobilizing nucleosomes and controlling access of the transcriptional machinery to promoters. Mice heterozygous for *Smarcb1* are predisposed to rhabdoid tumors that display a histological appearance identical to human rhabdoid tumor (Klochendler-Yeivin et al. 2000; Roberts et al. 2000; Guidi et al. 2001). While loss of *SMARCB1* occurs in the vast majority of human rhabdoid tumors, mutations of *SMARCA4* (*BRG1*), another member of the SWI/SNF complex, have been described in patients lacking *SMARCB1* mutations (Hasselblatt et al. 2011). Gene expression studies of rhabdoid tumor have identified multiple other genes/pathways with altered expression (Gadd et al. 2010).

14.3.5 Treatment

Historically, patients with MRTK were treated as Wilms tumor, using vincristine-/dactinomycin-/doxorubicin-based therapy. In more recent years, additional agents (cyclophosphamide, etoposide, carboplatin, ifosfamide) have been added, but the outcomes have remained poor, with overall survival rates not exceeding 30 %. Tomlinson et al. reviewed the outcomes of patients treated on NWTS 1–5 and found the overall survival rate to be only 23 % (Tomlinson et al. 2005). Patients with lower-stage disease fared better than those with advanced stage and age was an important prognostic factor. The 4-year overall survival rate was only 9 % in infants aged 0–5 months, compared to an overall survival rate of 41 % in children older than 2 years at diagnosis ($p < .0001$). Remarkably, patients treated on NWTS-5 fared no better than patients treated on the earlier studies, indicating the lack of progress achieved for this tumor (Tomlinson et al. 2005). Unlike CCSK, where the use of doxorubicin markedly improved outcome, this drug had no discernible effect for MRTK (Tomlinson et al. 2005).

Similar results were observed in the SIOP trials 93-01 and 2001 (van den Heuvel-Eibrink et al. 2011). Most patients received preoperative therapy with vincristine/dactinomycin followed by postoperative chemotherapy consisting of etoposide, carboplatin, ifosfamide, doxorubicin, and radiotherapy. Although responses to vincristine/dactinomycin were observed, response to preoperative therapy did not translate to improved overall survival. Despite this multi-agent treatment regimen, outcome was poor and the disease progressed early, underscoring the biological aggressiveness.

Despite the generally poor results with conventional cytotoxic therapies, there have been case reports of patients with advanced-stage disease who responded to chemotherapy and have had durable survival. Regimens containing ifosfamide/carboplatin/etoposide alternating with vincristine/doxorubicin/cyclophosphamide have been effective (Waldron et al. 1999; Wagner et al. 2002; Yamamoto et al. 2006). Some centers have advocated high-dose therapy with stem-cell rescue for extrarenal MRTK based on a few successfully treated cases (Madigan et al. 2007). There has also been some success with intensive chemotherapy for central nervous system (CNS)

atypical teratoid/rhabdoid tumors (Chi et al. 2009). It should be noted that although the genetics of CNS malignant rhabdoid tumor is similar to extra-CNS malignant rhabdoid tumor, the clinical picture differs. CNS malignant rhabdoid tumor rarely disseminates beyond the neuraxis, whereas extra-CNS malignant rhabdoid tumor is frequently diffusely metastatic.

Even if there are occasional patients who benefit from conventional cytotoxic agents, it has become clear that novel therapeutic approaches are urgently required to improve outcomes. The mechanism by which the SWI/SNF complex inactivation leads to rhabdoid tumor is multifactorial, but may provide clues regarding potential therapeutic targets. Accumulating evidence suggests that in its native form, the SWI/SNF complex inhibits cell cycle progression by transcriptionally repressing *CCND1* (encodes cyclin D1) and activating $p16^{INK4A}$ and $p21^{CIP}$ (Betz et al. 2002; Versteege et al. 2002; Isakoff et al. 2005). Based on this observation, therapies targeting cyclin D1 and CDK4 have been tested in preclinical models of MRT with some evidence of activity (Katsumi et al. 2011; Smith et al. 2011). Loss of *SMARCB1* has also been shown to activate expression of the mitotic regulator Aurora A kinase and the sonic hedgehog pathway (Jagani et al. 2010; Lee et al. 2011). Targets such as CXCR4, IGF2, and the INI1 pathway should be considered for future treatment strategies (Koga et al. 2009; Yanagisawa et al. 2009).

14.4 Renal Cell Carcinoma

Pediatric renal cell carcinoma (RCC) is an understudied tumor. Although the US Surveillance, Epidemiology, and End Results (SEER) program indicates that RCC is the second most common renal malignancy in children and adolescents (Howlader et al. 2011), most of the knowledge about childhood RCC comes from relatively small retrospective reviews and case series. The major cooperative groups for pediatric kidney tumors, the National Wilms Tumor Study Group (NWTSG), and the International Society of Pediatric Oncology (SIOP), historically did not focus on RCC. Until the current Children's Oncology Group (COG) AREN0321 study opened in 2006, there has not been a prospective analysis on the biology and treatment of RCC.

14.4.1 Epidemiology

The SEER program reports an age-adjusted incidence of RCC of 0.5 cases per million people under the age of 19 years (Howlader et al. 2011). Wilms tumor is more prevalent until the 15–19-year age group, at which point the incidence of RCC surpasses that of Wilms tumor. A German population-based study of childhood RCC showed the median age at diagnosis was 10.6 years, with a male to female ratio of 1 to 1.1 (Selle et al. 2006).

14.4.2 Clinical Features and Staging

The most common symptoms at diagnosis are pain (30–40 %), gross hematuria (30–40 %), and abdominal mass (20–25 %). Nonspecific constitutional symptoms such as fever, weight loss, and lethargy are seen in 15–40 % of children (Castellanos et al. 1974; Indolfi et al. 2003). Modern studies of pediatric RCC use the American Joint Committee on Cancer (AJCC) tumor/node/metastasis (TNM) staging system, which was last updated in 2010 (Edge et al. 2010), but the historical literature reported results based on the modified Robson classification (Table 14.2) (Carcao et al. 1998). Using the Robson system, more than half of pediatric RCC patients present with advanced-stage (III or IV) disease (Table 14.3) (Geller and Dome 2004). The most common sites of metastasis are lymph nodes, lung, bone, and brain.

14.4.3 Pathology

The histology of pediatric RCC is distinct from that of adult RCC. In the older literature, many cases of pediatric RCC were described as having clear cells with a papillary pattern (Dehner et al.

Table 14.2 Staging systems for pediatric RCC

Stage	Modified Robson	AJCC (2010)
I	Localized disease confined by the renal capsule	T1 N0 M0
II	Localized disease invading the renal capsule but confined by Gerota's fascia	T2 N0 M0
III	A. Involvement of renal vein or inferior vena cava	T1 N1 M0 or
		T2 N1 M0 or
	B. Regional lymph node involvement	T3 N0 M0 or
		T3 N1 M0
IV	Distant metastatic disease	T4 N0 M0 or
		T4 N1 M0 or
		Any T any N M1

AJCC American Joint Cancer Committee on Cancer
T primary tumor
TX primary tumor cannot be assessed
T0 no evidence of primary tumor
T1 tumor 7 cm or less in greatest dimension, limited to the kidney
T1a tumor 4 cm or less
T1b tumor more than 4 cm, but not more than 7 cm
T2 tumor more than 7 cm in greatest dimension, limited to the kidney
T2a tumor more than 7 cm but less than or equal to 10 cm
T2b Tumor more than 10 cm
T3 tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota's fascia
T3a tumor grossly extends into the renal vein or its segmental (muscle containing branches), or tumor invades perirenal and/or renal sinus fat but not beyond Gerota's fascia
T3b tumor extends into the vena cava below the diaphragm
T3c tumor grossly extends into vena cava above the diaphragm or invades the wall of the vena cava
T4 tumor invades beyond Gerota's fascia including continuous extension into the ipsilateral adrenal gland
N regional lymph nodes (Hilar, abdominal para-aortic, and paracaval nodes):
NX regional lymph nodes cannot be assessed
N0 no regional lymph node metastasis
N1 metastasis to regional lymph nodes
M distant metastasis
MX distant metastasis cannot be assessed
M0 no distant metastasis
M1 distant metastasis

1970; Lack et al. 1985). Renshaw described tumors with distinctive voluminous clear cytoplasm, which he proposed were a newly recognized type of RCC involving translocations of Xp11 (Renshaw 1999). In 2004, the World Health Organization officially recognized translocation RCC, which is associated with a family of translocations involving the *TFE3* or *TFEB* genes, as a distinct class of RCC (Eble et al. 2004). It is now estimated that translocation RCC accounts for 50–70 % of pediatric and young adult RCC (Ramphal et al. 2006; Geller et al. 2008). Other histologic types of RCC described in children include papillary RCC, chromophobe RCC, sarcomatoid RCC, collecting duct carcinoma, RCC arising from Wilms tumor, renal medullary carcinoma, RCC after neuroblastoma, and RCC not otherwise specified (Medeiros et al. 1999; Bruder et al. 2004; Ramphal et al. 2006; Geller et al. 2008). The clear cell (conventional) subtype, by far the most common type of RCC in adults, is uncommonly observed in children. A careful morphological and molecular analysis by Bruder included 6 pediatric patients with the histologic appearance of clear cell RCC (Bruder et al. 2004). However, none of these cases had LOH at chromosome 3p, the site of the *VHL* gene, or mutations of *VHL*, indicating that the clear cell RCC in children is distinct from adult clear cell RCC.

14.4.4 Genetics and Biology

Several genetic syndromes are associated with predisposition to RCC (Linehan et al. 2010). The best described is von Hippel-Lindau (VHL) syndrome (retinal angiomas, cerebellar and spinal hemangioblastoma, hemangiomas of various organs, clear cell RCC, pheochromocytoma, and pancreatic tumors), caused by mutations in the *VHL* gene at chromosome 3p25. *VHL* encodes a protein that regulates the level of the hypoxia-inducible factor (HIF) family of transcription factors. VHL is a component of a protein complex that promotes the ubiquitin-mediated degradation of HIF, which binds to promoters of genes involved in angiogenesis, erythropoiesis, energy metabolism, iron metabolism, cell proliferation, apoptosis, and other processes that are dysregulated in human cancer (Linehan et al. 2010). Tuberous sclerosis (skin lesions, seizures, mental retardation, multiorgan hamartomatous lesions)

Table 14.3 Recent series of pediatric RCC >10 patients

	Stage[a]				
	I	II	III	IV	Reference
% alive and relapse free (# of patients)	94 % (18)	100 % (2)	42 % (12)	0 % (9)	Indolfi et al. (2003)
	100 % (3)	50 % (2)	100 % (5)	0 % (3)	Geller and Dome (2004)
	91 % (11)	100 % (7)	75 % (4)	50 % (8)	Selle et al. (2006)[†]
	100 % (5)	100 % (3)	100 % (1)	75 % (4)	Ramphal et al. (2006)[†]
	100 % (3)	100 % (1)	33 % (3)	25 % (4)	Varan (2007)
	100 % (3)	100 % (1)	75 % (4)	33 % (3)	Geller et al. (2008)
Total	95 % (43)	94 % (16)	62 % (29)	29 % (31)	–

[a]Modified Robson stage except for studies marked with[†], which used the American Joint Committee on Cancer (AJCC) staging system. With the AJCC system, not all patients with stage IV disease had distant metastatic disease; more than 1 positive regional lymph node constituted stage IV in previous versions of the AJCC classification system. This may explain the better outcomes for stage IV disease in the series using the AJCC system instead of the Robson system

is caused by mutations in the *TSC1* and *TSC2* genes, which encode the hamartin and tuberin proteins, central regulators of the mammalian target of rapamycin (mTOR) pathway. The most common renal tumor in individuals with tuberous sclerosis is angiomyolipoma, but affected individuals are also susceptible to RCC with clear cell morphology (Bjornsson et al. 1996). Hereditary papillary RCC is caused by mutations in the *MET* oncogene, which encodes the hepatocyte growth factor receptor, which signals through the phosphatidylinositol 3-kinase (PI3K) pathway (Schmidt et al. 1997). The Birt-Hogg-Dubé syndrome (skin fibrofolliculomas, lung cysts, chromophobe RCC) is caused by mutations in *FLCN*, which encodes the protein folliculin, which interacts with the mTOR pathway (Nickerson et al. 2002). Individuals with germline mutations of two tricarboxylic acid (Krebs) cycle genes, fumarate hydratase (*FH*), and succinate dehydrogenase (*SDH*) are also susceptible to RCC. *FH* is the gene responsible for hereditary leiomyomatosis, a cancer predisposition syndrome in which patients develop uterine and cutaneous leiomyomas as well as papillary RCC (Tomlinson et al. 2002). Germline mutations of the *SDHB*, *SDHC*, and *SDHD* genes are responsible for familial paraganglioma and pheochromocytoma. Individuals with *SDHB* mutations are also at risk for early onset RCC (Neumann et al. 2004; Vanharanta et al. 2004). Mutations of the *FH* and *SDH* genes impair progression through the tricarboxylic acid cycle, thereby diminishing oxidative phosphorylation and leading cells to rely on glycolysis for energy metabolism even in normoxic conditions (Linehan et al. 2010).

Translocation RCC is associated with translocations involving genes that encode members of the microphthalmia (MiTF) family of transcription factors. The most commonly involved gene is *TFE3* on chromosome Xp11, which can fuse to several partners including *ASPL* (17q25), *PRCC* (1q21), *PSF* (1p34), *NonO* (Xq12), and *CLTC* (17q23) (Argani and Ladanyi 2005). The TFE3-ASPL translocation is the same translocation seen in alveolar soft part sarcoma (Argani et al. 2001a). A recent gene expression study has identified several novel genes that are differentially expressed between the Xp11 translocation carcinomas and conventional renal carcinomas and has shown that Xp11 translocation carcinomas may be more similar to alveolar soft part sarcoma than to conventional renal carcinomas (Tsuda et al. 2007). Additionally, gene expression profiling has identified potential therapeutic targets in the Xp11 translocation RCC. For example, the ASPL-TFE3 fusion protein transactivates the promoter of the MET receptor tyrosine kinase, leading to MET protein overexpression. Inhibition of the MET receptor tyrosine kinase may therefore be a potential avenue of targeted therapy for these RCC (Tsuda et al. 2007). Translocation RCC also express high levels of phosphorylated S6, a measure of mTOR pathway activation, which suggests that mTOR inhibition may be effective in this tumor type (Argani et al. 2010).

A less common type of translocation RCC involves a fusion of the untranslated *alpha* gene (11q12) to the *TFEB* gene (6p21) (Argani et al. 2001b; Davis et al. 2003). Interestingly, 15 % of translocation RCC occurs in individuals who were previously treated with chemotherapy for a variety of pediatric malignancies and nonmalignant conditions (Argani et al. 2006).

14.4.5 Treatment and Outcomes

Tumor resection is the mainstay of therapy for pediatric RCC. Most patients are presumed to have Wilms tumor and undergo radical nephrectomy and lymph node sampling according to Wilms tumor surgical guidelines. A role for radical lymph node dissection remains to be determined (Geller and Dome 2009).

Many patients with localized disease have fared well without adjuvant therapy. Among adults and children with translocation RCC, age ≥25 years, lymph node involvement, high Fuhrman grade, and presence of distant metastatic disease were associated with poor survival (Malouf et al. 2011). In pure pediatric series, however, local lymph node involvement was not associated with unfavorable outcome, even among patients who did not receive adjuvant therapy (Geller et al. 2008). The Children's Oncology Group AREN0321 study is prospectively evaluating the need for adjuvant therapy in children, adolescents, and young adults with RCC without distant metastatic disease. Patient outcomes reported in the large recent series of pediatric RCC are listed in Table 14.3.

Children with metastatic RCC have a poor prognosis (Table 14.3). Although successes with high-dose interleukin-2 have been reported (MacArthur et al. 1994), it is recognized in that non-clear cell renal cell carcinomas do not typically respond well to immunotherapy (Upton et al. 2005; Malouf et al. 2010). Emerging data on translocation RCC suggests that some tumors respond to vascular endothelial growth factor receptor (VEGF)-targeted therapy (sunitinib, sorafenib, ramucirumab) (Choueiri et al. 2010; Malouf et al. 2010). Among the agents reported, sunitinib seems to be most active. In one series, 7 of 14 patients (50 %) treated with sunitinib as either first- or second-line therapy for translocation RCC had partial or complete response (Malouf et al. 2010). Seven of 7 patients who had progressive disease on VEGF-directed therapy and switched to mTOR inhibitors showed at least transient disease stabilization, including one with a partial response. Responses to gemcitabine/doxorubicin alternating with gemcitabine/oxaliplatin have also been observed (Geller et al. 2008). Prospective studies to evaluate therapies for metastatic and recurrent childhood RCC are warranted.

14.5 Renal Medullary Carcinoma

Renal medullary carcinoma (RMC) is a renal epithelial neoplasm that has been described as the "7th sickle cell nephropathy" (Davis et al. 1995). It is an aggressive cancer that occurs in adolescent and young adult patients with sickle-cell trait or hemoglobin SC disease (Davis et al. 1995). The mean age of presentation is 19 years, with a reported range from 5 to 40 years. There is a male predominance, with a male to female ratio of 2 to 1 (Simpson et al. 2005). There is no single pathognomonic genetic abnormality seen in RMC, but *BCR-ABL* translocations or *ABL* gene amplification has been described in rare cases, as have *ALK* gene rearrangements (Stahlschmidt et al. 1999; Simpson et al. 2005; Marino-Enriquez et al. 2011). Absence of SMARCB1 (INI1/hSNF5) protein staining by immunohistochemistry has been observed in RMC, suggesting that rhabdoid tumor of the kidney and RMC may have common biological, as well as clinical, features (Cheng et al. 2008). Both are characterized by an aggressive metastatic pattern and relative chemotherapy resistance.

Patients with RMC almost always present with metastatic disease and have fatal outcomes (Davis et al. 1995; Simpson et al. 2005). Transient responses have been observed after treatment with methotrexate/vinblastine/doxorubicin/cisplatin (MVAC) or platinum/gemcitabine/taxane (Pirich et al. 1999; Simpson et al. 2005; Strouse et al. 2005; Bell 2006; Walsh et al. 2010). A patient

with RMC was shown to have a complete tumor response after treatment with the proteosome inhibitor bortezomib (Ronnen et al. 2006).

14.6 Congenital Mesoblastic Nephroma

14.6.1 Epidemiology

Congenital mesoblastic nephroma (CMN) is a rare tumor that accounts for about 3 % of pediatric renal tumors (Howell et al. 1982). The mean age at presentation is 3.4 months, but rare cases have been diagnosed in children up to 9 years of age (Howell et al. 1982). CMN is the most common renal neoplasm in the first month of infancy (van den Heuvel-Eibrink et al. 2008). Most large series show a predominance in boys, with a male to female ratio of about 2 to 1 (Howell et al. 1982; Furtwaengler et al. 2006). In the series from the National Wilms Tumor Study Group, 14 % of CMN were associated with congenital malformations including genitourinary and gastrointestinal anomalies, polydactyly, and hydrocephalus (Howell et al. 1982).

14.6.2 Clinical Features and Staging

Common presenting signs include abdominal mass, hypertension, and hematuria (Howell et al. 1982). Patients are usually asymptomatic and the mass is detected as an incidental finding. In some patients, the tumor is diagnosed on prenatal ultrasound (Furtwaengler et al. 2006). Approximately 12 % of patients present with hypercalcemia (Chan et al. 1987; Furtwaengler et al. 2006). Metastatic disease at the time of initial presentation is practically unheard of; among 101 patients in two of the largest series, there were no cases of lymph node involvement or distant metastatic disease (Howell et al. 1982; Furtwaengler et al. 2006). However, cases of metastasis to the brain and lung have been documented at the time of recurrence (Joshi et al. 1986; Heidelberger et al. 1993; Ali et al. 1994). The staging systems used for CMN are the same as those used for Wilms tumor, typically the NWTS/COG system or the SIOP system (Metzger and Dome 2005).

14.6.3 Pathology, Genetics, and Biology

There are two main histologic subtypes of CMN: classic (or conventional) and cellular (or atypical) (Joshi et al. 1986; Pettinato et al. 1989). It has been proposed that the term "atypical" is misnomer, because the majority of CMN have the cellular histology. Some CMN have a mixed pattern with features of both subtypes. Classic CMN tends to present in very young infants and neonates, whereas cellular CMN is seen in older infants (Furtwaengler et al. 2006).

Cellular CMN is morphologically similar to infantile fibrosarcoma (IFS), and both have the chromosomal translocation t(12;15)(p13;q25), which results in a fusion of the *ETV6 (TEL)* gene with the *NTRK3* gene (Knezevich et al. 1998a, b; Rubin et al. 1998). *ETV6* encodes a transcription factor with a helix-loop-helix protein dimerization domain and *NTRK3* encodes a receptor tyrosine kinase. The chimeric ETV6-NTRK3 protein is postulated to have constitutively active tyrosine kinase growth pathway signaling (Wai et al. 2000). A recent gene expression analysis of infantile fibrosarcoma/CMN showed that these tumors have a distinct gene expression profile compared to other pediatric renal tumors (Gadd et al. 2012). The expression pattern was consistent with receptor tyrosine kinase activation, with evidence of PI3-AKT, SRC, and MAPK activation. Interestingly, 4/14 cellular CMN manifested the gene expression pattern of CMN, but did not have detectable *ETV6-NTRK6* transcript, indicating that molecular mechanisms other than the *ETV6-NTRK6* fusion are responsible for the development of some cellular CMN (Gadd et al. 2012).

14.6.4 Treatment and Outcomes

Outcomes for patients with CMN are generally excellent when treated with nephrectomy only,

with overall survival rates of 95 % (Howell et al. 1982; Chan et al. 1987; Furtwaengler et al. 2006). The few tumors that recur are almost exclusively the cellular subtype. It remains to be established whether patients with stage III cellular CMN benefit from adjuvant chemotherapy. In a series published by the German Pediatric Oncology Group (GPOH), two of five patients with stage III cellular CMN developed recurrent disease, whereas only one of the remaining 45 patients had recurrence (Furtwaengler et al. 2006).

Studies of cellular CMN have shown that these tumors respond to regimens containing different combinations of vincristine, dactinomycin, doxorubicin, and cyclophosphamide (Loeb et al. 2002; Furtwaengler et al. 2006). This is not unexpected based on the sensitivity of infantile fibrosarcoma to similar sarcoma-directed therapy (Grier et al. 1985; Kurkchubasche et al. 2000; Orbach et al. 2010). Responses to ifosfamide/carboplatin/etoposide (ICE) have also been noted in patients with tumors refractory to the other agents (Loeb et al. 2002).

14.7 Metanephric Neoplasms

Metanephric tumors comprise a rare group of renal tumors that include a purely epithelial lesion (metanephric adenoma), a purely stromal lesion (metanephric stromal tumor), and a mixed stromal-epithelial lesion (metanephric adenofibroma) (Argani 2005). Metanephric tumors are thought to be related to Wilms tumor and some consider them to represent the most well-differentiated form of Wilms tumor. Patients with metanephric adenoma have ranged from 5 to 83 years of age, but typically occur in the fifth to sixth decades of life. They are often discovered incidentally, but can present with pain and hematuria. About 10 % of patients had polycythemia, which resolves once the tumor is resected. The differential diagnosis is epithelial-predominant Wilms tumor and the solid variant of papillary RCC. The tumors are benign and do not require adjuvant therapy. Metanephric stromal tumor (MST) presents at a median age of 13 months (range, newborn to 13 years). The lesion resembles the spindle cell stroma of classic congenital mesoblastic nephroma but is a distinct entity (Argani and Beckwith 2000). No cases of recurrence have been described, but three cases were associated with vascular abnormalities such as aneurysms and angiodysplasia (Argani and Beckwith 2000). Metanephric adenofibroma (MAF) has a median age of 30 months (range, 5–36 years) (Arroyo et al. 2001). MAF has been subclassified into a usual type, MAF with mitoses, MAF in the setting of Wilms tumor and MAF in the setting of papillary renal cell carcinoma. Most patients with MAF were treated with chemotherapy for Wilms tumor, so it is difficult to say how patients would fare without chemotherapy, though the histology suggests a benign behavior. In a series of 25 patients, no recurrences were observed (Arroyo et al. 2001).

14.8 Renal Sarcomas

Renal sarcomas are rare malignancies that comprise less than 1 % of all malignant renal tumors (Vogelzang et al. 1993; Lalwani et al. 2011). True sarcomas of the kidney are unusual at any age (Raney et al. 2008). According to the 2004 World Health Organization (WHO) classification, primary renal sarcomas are classified based on histopathology into three categories: mesenchymal neoplasms (clear cell sarcoma of the kidney, rhabdomyosarcoma, extra-skeletal Ewing's sarcoma, anaplastic sarcoma of the kidney), mixed mesenchymal and epithelial tumors (primary renal synovial sarcoma), and neuroendocrine tumors (primitive neuroectodermal tumor/Ewing sarcoma) (Lalwani et al. 2011; Eble et al. 2004 #1854).

14.8.1 Rhabdomyosarcoma (RMS)

The most frequent variety of soft-tissue sarcoma in children is RMS. Primary renal RMSs are extremely rare (Raney et al. 2008; Lalwani et al. 2011). The median age of pediatric RMS patients is 6.35 years (range, 2.6–17.8 years) (Raney et al. 2008). Usually, children with this disease present

with large tumors and may have metastases (Raney et al. 2008). The histological subtypes of RMS include embryonal, alveolar, and pleomorphic variants. Due to its origin, immunohistochemical stains are positive for desmin, myoglobin, and myogenin (Eble et al. 2004; Lalwani et al. 2011). Radical nephrectomy is the treatment of choice (Lalwani et al. 2011). Patients with localized renal RMS should be treated as having a form of unfavorable-site RMS and classified in Stage 2 or 3 (depending on diameter and regional lymph node involvement). Patients with metastatic disease should be treated on Stage 4 RMS protocols (Raney et al. 2008). Renal RMS is an aggressive neoplasm with unfavorable prognosis; in a series of 10 pediatric renal RMS patients, 4 patients died after a median of 0.57 years (Dalfior et al. 2008).

14.8.2 Anaplastic Sarcoma of the Kidney (ASK)

ASK is an exceptionally rare tumor (0.15 % of all pediatric renal tumors). The clinical features include a large renal mass and a female predominance. The age distribution is broad, ranging from infancy (10 months) to 41 years (Vujanic et al. 2007). Histologically, ASK shows a polyphenotypic mesenchymal pattern with both cystic and solid areas. Immunohistochemistry shows positivity for desmin. In the differential diagnosis, the most important tumor to be considered is anaplastic Wilms tumor (Vujanic et al. 2007). Although patients with ASK are treated according to different therapeutic protocols, the overall outcome is reasonably good (77 % 8-year overall survival). Previously, patients have responded well to treatment given to anaplastic Wilms tumors. Therefore, it is sensible to keep treating them the same way until more is known about the tumor's origin and pathogenesis (Vujanic et al. 2007).

14.8.3 Primary Renal Synovial Sarcoma

Primary synovial sarcoma (SS) of the kidney is very rare. Since its description in 1999, fewer than 70 cases have been reported in literature (Iacovelli et al. 2012). SSs affect patients between 17 and 61 years with a slight male predominance (Chen et al. 2001). Renal SS is characterized by a specific translocation t(X;18) (p11.2;q11.2), resulting in the fusion of SYT gene on chromosome 18 with an SSX family gene on chromosome X (Dassi et al. 2009; Iacovelli et al. 2012). Histologically, two different forms of SSs are seen: monophasic (only spindle cells) and biphasic (glandular elements and spindle epithelial cells). Spindle cells are immunoreactive for vimentin, CD99, and bcl2 (Argani et al. 2000a). Radical nephrectomy is the first approach for patients with metastatic and nonmetastatic disease. Response to chemotherapy (anthracyclines combined with ifosfamide) has been reported in patients with metastatic disease; however, the value of chemotherapy in the adjuvant setting has yet to be proven. About 35 % of the patients have local relapse or abdominal lymph node metastases after surgery, and the 5-year overall survival is 42–89 % (Lalwani et al. 2011; Iacovelli et al. 2012).

14.8.4 Primitive Neuroectodermal Tumor (PNET)/Ewing Sarcoma

PNET of the kidney is a rare tumor, with about 50 cases reported in literature (Pomara et al. 2004). PNETs are commonly seen in childhood or adolescence (median age 20 years) (Maccioni et al. 2000). It is very difficult to differentiate PNET and extraosseous Ewing sarcoma as separate entities. Both share common stem-cell precursor and unique chromosomal abnormality t(11;22) (q24;q12). However, the stages of differentiation in which the stem-cell precursor are blocked are different in both the tumors, explaining their different biological behavior and prognosis (Pomara et al. 2004). Diffuse CD99 positivity and strong membrane positivity for MIC2 are characteristic (Pomara et al. 2004). Renal PNET is more aggressive than in the other sites; it often recurs locally and metastasizes early to regional lymph nodes, lungs, liver, bone, and bone marrow, resulting in a poor prognosis (5-year overall survival 45–55 %) (Pomara et al. 2004). PNETs demonstrate a high response to a combination of surgery, irradiation, and chemotherapy (Miser et al. 1987).

14.9 Late Breaking Updates

Since this chapter was submitted, several new developments have occurred in the field of non-Wilms pediatric renal tumors. A large series of patients with CCSK ($n=191$) treated on the SIOP 9301 and 2001 studies was reported. Five-year event-free survival (EFS) and overall survival (OS) were 79 % and 86 %, respectively. Stage IV disease and young age were significant adverse prognostic factors for EFS (Furtwangler et al. 2013). The SIOP and Associazione Italiana Ematologia Oncologia Pediatrica groups reported a series of 37 patients with relapsed CCSK. The most common sites of relapse were the brain ($n=13$), lungs ($n=7$) and bone ($n=5$). Treatment of relapse consisted of chemotherapy ($n=30$), surgery ($n=19$) and/or radiotherapy ($n=19$). High-dose therapy with autologous stem cell transplant was used in 14 patients. Five-year EFS and OS after relapse were 18 % and 26 %, respectively (Gooskens et al. 2014). Ueno et al published a study on DNA methylation that resulted in a methylation profile that distinguishes CCSK from other pediatric renal tumors. A combination of four genes was sufficient to distinguish Wilms tumor, CCSK, CMN, MRTK and Ewing sarcoma. The methylation status of *THBS1* alone was sufficient to distinguish CCSK from other pediatric renal tumors (Ueno et al. 2013). Karlsson et al published a study reporting that CCSK demonstrates an embryonic signature indicative of a primitive nephrogenic origin and found remarkably few genetic imbalances (Karlsson et al. 2014). Next generation sequencing efforts are ongoing and may provide novel insight into clinically relevant prognostic markers and molecular targets.

Venkatramani et al reported a series of 21 patients with renal and extrarenal non-central nervous system malignant rhabdoid tumor who were treated at a single institution between 1983 and 2012 (Venkatramani et al. 2014). Starting in 2002, patients received a treatment regimen consisting of vincristine, doxorubicin and high-dose cyclophosphamide. The 5-year OS of patients treated before and after 2002 was 20 % and 54 %, respectively. Four patients who received high-dose therapy with autologous stem cell rescue were alive at last follow-up. The authors conclude that high-dose alkylator therapy followed by high-dose therapy/stem cell rescue is a promising treatment for malignant rhabdoid tumor. A caveat to concluding that there is benefit to autologous stem cell rescue is that there is likely a selection bias favoring those patients. In this series, the median time to progression was only 4 months; patients who were doing well long enough to get to stem cell transplant were likely an inherently more favorable group. Preclinical rhabdoid tumor models have provided leads to promising new biological agents, including an inhibitor of EZH2, a histone methyltransferase that is thought to be essential for viability in rhabdoid cells with *SMARCB1* mutations (Knutson et al. 2013). MRTK xenografts treated with an EZH2 inhibitor showed durable regression, even after cessation of drug administration.

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