NON–WILMS' RENAL TUMORS IN CHILDREN

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Renal tumors other than Wilms' tumor are infrequent in childhood. Wilms' tumors account for 6% to 7% of childhood cancer, whereas the remaining renal tumors account for less than 1%.[27] The most common non–Wilms' tumors are clear cell sarcoma of the kidney, rhabdoid tumor of the kidney (both formerly considered unfavorable Wilms' tumor variants but now considered separate tumors), renal cell carcinoma, mesoblastic nephroma, and multilocular cystic nephroma. Collectively, these tumors account for less than 10% of the primary renal neoplasms in childhood.

CLEAR CELL SARCOMA

Clear cell sarcoma of the kidney is currently considered a separate tumor distinct from Wilms' tumor, although in early National Wilms' Tumor Studies (NWTS) and International Society of Pediatric Oncology (SIOP) studies, it was considered an unfavorable histology pattern of Wilms' tumor (Table 1).[5] In these early NWTS series, 4% of registered renal tumors were designated clear cell sarcoma.[5, 18] The tumor was first described as a distinct entity in 1978 by three independent groups, Beckwith and Palmer,[5] Morgan and Kidd,[42] and Marsden and co-workers,[39] who labeled it "bone metastasizing renal tumor of childhood" in recognition of its well-known propensity for skeletal metastasis. Bone metastases occur in 40% to 60% of patients with clear cell sarcoma of the kidney, whereas they are found in less than 2% of patients with Wilms' tumor.[18, 26] This distinct clinical behavior is one of the features that has led to its designation as a separate tumor. Other clinical features include a lack of association with sporadic aniridia or hemihypertrophy.

Clear cell sarcoma of the kidney has not been reported to occur bilaterally and is not associated with nephroblastomatosis. It has been reported in infancy and adulthood, but the peak incidence is between 3 and 5 years of age. It has an aggressive behavior that responds poorly to treatment with vincristine and actinomycin alone, leading to its original designation by Beckwith as an unfavorable histology pattern. The addition of doxorubicin in aggressive chemotherapy regimens has improved outcome. Current 4-year survival is 75% in a group of 50 patients in NWTS-III.[17] In the ongoing NWTS-V protocols, clear cell sarcoma of the kidney at all stages is treated with the same regimen used for Wilms' tumor with diffuse anaplasia (excluding stage I), that is, radical nephrectomy followed by chemotherapy with cyclophosphamide, etoposide, vincristine, and doxorubicin for 24 weeks and radiotherapy.

RHABDOID TUMOR OF THE KIDNEY

As is true for clear cell sarcoma, rhabdoid tumor of the kidney was formerly categorized

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Table 1. SUMMARY OF CHARACTERISTICS OF NON–WILMS' RENAL TUMORS OF CHILDREN

Characteristic	Clear Cell Sarcoma	Rhabdoid Tumor	Renal Cell Carcinoma	Congenital Myoblastic Nephroma	CN/CPDN
Median age	4 Years	11 Months	12 Years	<3 Months	1–2 Years
Malignant potential	Yes	Yes	Yes	Cellular variant potentially malignant (rare)	Risk of local recurrence if tumor spill
Follow-up/ adjuvant therapy	Aggressive chemotherapy and radiotherapy	Aggressive chemotherapy and radiotherapy	? Immunotherapy for metastatic disease	Usually none Consider chemotherapy for cellular variant	Usually none Obtain follow-up imaging if intraoperative tumor spill
Unique characteristics	Bone metastases in 50%	Associated with medulloblastoma Propensity for brain metastases		Infiltrates renal parenchyma	
Prognosis	75% Survival	20% Survival	Good for localized disease Poor for metastatic disease	Excellent	Excellent

CN = cystic nephroma; CPDN = cystic partially differentiated nephroblastoma.

as an unfavorable histologic pattern of Wilms' tumor but is now considered a separate tumor.[5] It is rare, accounting for 2% of the renal tumors registered with NWTS. It may arise in extrarenal locations, although controversy remains regarding the exact identity of these extrarenal rhabdoid tumors.[46] Haas and co-workers[28] gave the tumor its present name and suggested its separate identity in 1981, but it was first described by Beckwith and Palmer in 1978 and referred to as a rhabdomyosarcomatoid neoplasm, reflecting the presence of cells with a rhabdomyoblast appearance.[5] On immunohistochemical staining, this resemblance appears to be deceiving, and evidence of a myogenic lineage is generally not found.[62] A diversity of phenotypic markers are expressed, but the most common and consistent are vimentin and cytokeratin.

Current thought is that rhabdoid tumor of the kidney is probably neurogenic in origin. The tumor is typically large and central/hilar in origin, often replacing the entire kidney. It presents early in life, with more than 50% of patients aged less than 1 year. The median age is 11 months.[61] Metastases may be found not only in the lungs and liver (as is true for Wilms' tumor) but also in the brain (unlike Wilms' tumor). In addition to brain metastases, primary brain tumors have been reported to occur in 10% to 15% of patients, the most common being medulloblastoma.[11, 61]

Rhabdoid tumor of the kidney is an aggressive lesion with a poor prognosis. Most patients present with advanced stage disease, the tumor responds poorly to current chemotherapy and radiotherapy, and overall mortality is 80%.[61] Even patients with completely resected tumors with negative lymph nodes have a 50% mortality rate. The current treatment protocol in NWTS-V is radical nephrectomy followed by chemotherapy with carboplatinum, etoposide, and cyclophosphamide for 24 weeks and radiotherapy.

RENAL CELL CARCINOMA

Renal cell carcinoma is the most common renal neoplasm in adults and occurs rarely in the pediatric patient. Approximately 1% to 2% of renal cell carcinomas occur in patients aged less than 21 years, and these lesions account for 2% to 5% of primary renal tumors in this age group. The earliest well-documented cases in the English language were reported by Boyd and Lisa[12] and McCurdy[41] in 1934. By 1960, more than 50 occurrences had been published as case reports. The first series of patients with renal cell carcinoma was reported by Dehner and co-workers[21] from the Armed Forces Institute of Pathology (15 patients) in 1970. The two largest series in the literature are 20 patients collected from four institutions reported on by Raney and co-workers[49] in 1983 and 22 patients from the Memorial Sloan-Kettering Cancer Center reported on by Aronson and co-workers[2] in 1996.

Renal cell carcinoma has been reported in infancy, but most patients are older, with a mean age of 9 to 15 years. During the second decade of life (age 10 to 20 years), patients presenting with a primary intrarenal tumor

are equally likely to have a Wilms' tumor or renal cell carcinoma.[29] Although one of the patients with renal cell carcinoma reported on in the series by Hartman and colleagues[29]had bilateral tumors, that feature is uncommon for this tumor.

It has been debated whether pediatric renal cell carcinoma is a different tumor than its adult counterpart. Caraco and co-workers[13] studied 16 pediatric patients from three children's hospitals in Canada and reported a higher incidence of papillary histology than seen in adult renal cell carcinoma and, perhaps more persuasively, cytogenetic translocations involving the X chromosome, which are rarely seem in adult tumors, in two of four patients with tumor karyotyping. The clinical behavior of pediatric renal cell carcinoma and adult tumor is similar; nevertheless, that is, the most significant prognostic variable for survival is complete resection and low-stage disease.[2, 49] Survival for patients presenting with stage I disease is greater than 90%, for patients with stage II and III disease approximately 50%, and for patients with stage IV disease almost 0%. The tumor is not responsive to radiotherapy, and there is no effective chemotherapy for nonlocalized or relapsed disease, although MacArthur and co-workers[38] reported a complete response to recombinant interleukin-2 in one child presenting with metastatic renal cell carcinoma. Renal cell carcinoma has been reported in children with tuberous sclerosis[51, 63] (also seen in adults), Beckwith-Wiedemann syndrome,[65] and von Hippel-Lindau syndrome,[60] and arising in a multicystic kidney.[7]

CONGENITAL MESOBLASTIC NEPHROMA

Congenital mesoblastic nephroma occurs in two forms—a typical or fibromatous type seen almost exclusively in infants under the age of 3 months that is benign and a second atypical or cellular variety usually seen in older children but also occurring in infants that is potentially malignant and capable of recurrence and metastasis.[55] Congenital mesoblastic nephroma is the most common solid renal tumor of the newborn period. Bolande and co-workers[9] first described the tumor as a separate entity in 1967, reporting eight cases in which evidence supported its categorization as a true neoplasm, albeit benign, that was related to Wilms' tumor. A larger series of 48 patients was reported in 1973. Clinicopathologic features included its occurrence in the neonatal period as an unencapsulated and locally invasive fibrous lesion that could be cured by nephrectomy alone ("no cases of tumor recurrence by metastasis having been documented").[10] Local recurrence as a result of incomplete resection could occur. In subsequent cases, patients with documented metastasis and a malignant course have been reported, and the histology of the tumors in these patients has been shown to contain atypical cellular features and a high mitotic index.[59]

The relationship of congenital mesoblastic nephroma to Wilms' tumor continues to be debated. It has been reported in a patient with Beckwith-Wiedemann syndrome who was noted to have cytogenetic rearrangements at chromosome 11p15, and adjacent normal renal tissue that may contain subcapsular tumorlets, supporting the association with Wilms' tumor.[50] Other investigators have noted that the cellular variant of congenital mesoblastic nephroma may metastasize to bone and brain and has histologic features more reminiscent of clear cell sarcoma of the kidney, stressing the latter tumor as a more probable association.[54]

Hypertension may occur and may be caused by entrapment of renal parenchyma by invading fibrous strands at the edge of the tumor and the resultant renin hypersecretion.[16] Hypercalcemia also has been reported owing to tumor secretion of prostaglandin.[55] Nephrectomy alone seems to be adequate treatment for infants less than 3 months of age and perhaps even older patients with typical fibrous histology and **complete** tumor resection.[31] Chemotherapy with a Wilms' tumor regimen should be considered for patients with incomplete resection, cellular features, and a high mitotic index, and certainly for any patient with evidence of metastasis or recurrence. Partial nephrectomy should not be performed because the risk of local recurrence would be high owing to the tumor's tendency to infiltrate surrounding renal parenchyma.

MULTILOCULAR CYSTIC NEPHROMA

A multilocular cyst in a child presents as a lesion that may range from a benign multilocular cyst to a multilocular cyst with partially

differentiated Wilms' tumor to a cystic Wilms' tumor. The first two entities are synonymous with the terms *cystic nephroma* and *cystic partially differentiated nephroblastoma,* respectively. These lesions are tumors representing neoplastic change rather than developmental dysplastic change.

Edmunds[23] is credited with the first published description of a multilocular cyst, reporting a cystic adenoma of the kidney in 1892. Powell and co-workers[48] outlined the generally recognized criteria for diagnosis of a multilocular cyst of the kidney in 1951: (1) unilateral involvement, (2) a solitary lesion, (3) a multilocular lesion, (4) no communication between individual cysts, (5) no communication between cysts and the renal pelvis, (6) cysts lined by epithelium, (7) no normal nephrons in the septa separating cysts, and (8) remaining normal renal parenchyma. These criteria have been modified slightly by Joshi and Beckwith[33, 34] in a more recent publication that stressed that, in a multilocular cyst, the only solid tissue present is the thin septa dividing the individual cysts. These septa conform to the spherical shape of the cysts and may contain mature renal tubules although not fully developed nephrons. The cysts may range in diameter from a few millimeters to many centimeters. The fluid contained within the cysts is clear, with a chemical content similar to serum. Typically, cytology of this fluid is normal.

Multilocular cysts occur in children and adults. In a review in 1991 of 187 previously reported cases. Castillo and co-workers[14] noted that 80% of children were between the ages of 3 and 24 months with 65% of these patients being male. Eighty-five percent of the adults were over 40 years of age, with 76% of these patients being female.[14] Castillo and colleagues also reported seven bilateral cases, in variance from earlier criteria set by Powell.

The distinction between multilocular cysts and multilocular cysts with partially differentiated Wilms' tumor, which are indistinguishable radiographically and grossly, is the histologic content of the septa. The septa of multilocular cysts are composed of fibrous tissue in which mature tubules may be present, whereas the septa of multilocular cysts with partially differentiated Wilms' tumor have blastema with or without other embryonic stromal or epithelial cells. Cystic Wilms' tumor differs from the previous two lesions in that, radiographically and grossly, there are solid portions of the tumor varying in amount in which triphasic Wilms' tumor is seen. There also must be epithelial lined cysts with clear serous fluid in distinction to cystic areas of hemorrhage or necrosis within an otherwise solid tumor for the lesion to be considered a cystic Wilms' tumor.

The treatment of multilocular cysts and multilocular cysts with partially differentiated Wilms' tumor is nephrectomy alone. Multilocular cysts are benign tumors. Recurrences or metastases have not been reported. Multilocular cysts with partially differentiated Wilms' tumor have been reported to recur locally; metastases have not been reported.[33] Cystic Wilms' tumor is a malignant tumor, although seemingly less aggressive than the more common solid Wilms' tumor. These tumors should be treated as any other Wilms' tumor, with the appropriate protocol for the particular stage.

ANGIOMYOLIPOMA

Angiomyolipoma is a well-recognized benign renal tumor occurring most commonly in adults. It occurs in a sporadic form and in association with the tuberous sclerosis complex, an entity involving mental retardation, epilepsy, glial nodules in the brain, adenoma sebaceum, phakoma of the retina, and hamartomas of the liver, heart, bone, or kidney.

Approximately 80% of patients with tuberous sclerosis have an angiomyolipoma of the kidney.[44] Angiomyolipoma of the kidney occurring in childhood is almost always associated with the tuberous sclerosis complex.[44] Tumors are frequently bilateral and multifocal. Although benign in histologic appearance and behavior (except for hemorrhage), they may extend into the renal vein, inferior vena cava, and right atrium and involve local lymph nodes.[8, 36, 53, 57] Hemorrhage is the most common complication. Its occurrence seems primarily related to size, with angiomyolipomas less than 4 cm in diameter having a low risk and lesions over 4 cm having an increasingly greater risk.[22, 45, 56] Management should be nonoperative, with periodic re-imaging for small asymptomatic lesions. Lesions that have bled and lesions greater than 4 cm may require surgical management. Partial nephrectomy, if possible, rather than total nephrectomy is the preferred surgical management. Angioinfarction of amenable tumors is also an option.

MISCELLANEOUS TUMORS OF THE KIDNEY

In addition to the uncommon tumors discussed previously, several additional tumors have been reported. In most cases, each of these tumors is so rare that relatively few recommendations can be made regarding their natural history and optimal treatment. Included in this group are several neural tumors—primitive neuroectodermal tumor, primary renal neuroblastoma, carcinoid, schwannoma, and paraganglioma.

Primitive neuroectodermal tumors occur most commonly in the chest and extremities, but 31 occurring within the kidney have been reported on by Roloson and Beckwith[52] in the NWTS pathology archives. These lesions resemble Wilms' tumor grossly and radiographically and may be confused with blastemal Wilms' tumor microscopically. They occur in adults and children and have an aggressive behavior.

Neuroblastoma has been reported as a primary renal tumor, arising within the renal parenchyma; however, a more common presentation is renal invasion by an adrenal neuroblastoma.[52] The behavior and treatment of renal lesions and of neuroblastoma in other locations are similar.

Renal medullary carcinoma is a recently described entity emerging as a distinct tumor from a nebulous group of collecting duct carcinomas reported on by Davis and co-workers[20] in 34 patients gleaned from the Armed Forces Institute of Pathology over 22 years. These tumors were found in patients ranging in age from 11 to 39 years, 11 of whom were under 20 years. All but one of these patients were believed to have sickle cell disease or sickle cell trait (30 patients) owing to the microscopic finding of drepanocytes, although only 10 carried this clinical diagnosis based on prior hemoglobin electrophoresis. Renal medullary carcinoma is a highly malignant tumor with metastases present at the time of diagnosis.[64] There have been no reported survivors.

Nephrogenic adenofibroma is a rare tumor first reported by Hennigar and Beckwith in 1992.[30] Five children from the NWTS archives were described with a mean age of 13 years and symptoms of polycythemia and hypertension. Nephrogenic adenofibroma is an unencapsulated but indolent-behaving tumor with no associated metastases. Nephrectomy is curative and resolves the symptoms.

Two cases of a tumor termed *ossifying tumor of the infantile kidney* have been reported by Chatten and co-workers.[15] Characterized predictably by occurrence in infancy and abundant bone and osteoid formation, they have a benign clinical behavior.

Juxtaglomerular cell tumor, also termed *reninoma*, is a benign renin-producing tumor seen most commonly in adolescents or young adults.[1] It is typically a small lesion several centimeters in size but capable of producing impressive clinical symptoms of malignant hypertension and hypokalemia (owing to hyperaldosteronism). Excision is curative.

Intrarenal **teratoma** has been reported in a child but must be distinguished from the more common teratoid Wilms' tumor by the presence of recognizable nonrenal organs or tissue, such as brain, skin, or gastrointestinal tract.[3]

Transitional cell carcinoma of the renal pelvis can also occur, generally as a low-grade papillary lesion.[35, 58] Various sarcomas arising in the kidney, including **leiomyosarcoma, fibroxanthosarcoma, and rhabdomyosarcoma** have been reported in children, as has one case of primary **melanoma** of the renal pelvis.[24, 26, 32, 37, 43]

SECONDARY RENAL TUMORS

Leukemia and lymphoma can metastasize to the kidney. Lymphoma may occur as a primary renal tumor as well.[60] Metastatic tumors usually infiltrate the kidney diffusely but may also appear as radiographically discrete lesions. Nephrectomy is usually not required if the tumor responds to systemic chemotherapy. Less commonly, osteogenic sarcoma has been reported to metastasize to the kidney in children, as has malignant melanoma.[4]

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