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Pediatric Genitourinary Tumors

Sharon M. Castellino, MD, MS, **Anibal R. Martinez-Borges, MD**, and **Thomas W. McLean, MD**
Department of Pediatrics Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA

Abstract

Purpose of review—We will review the 2007/2008 literature on pediatric genitourinary tumors.

Recent findings—Newly identified constitutional epigenetic defects in Wilms tumor (WT) genes extends the understanding of WT risks in children lacking syndromic features, and adds to the complexity of the pathogenesis of these tumor suppressor genes. Pediatric renal cell carcinoma (RCC) has distinct molecular characteristics and clinical associations from the adult counterpart. The pathway from *PAX3-FKHR* translocation to the development of rhabdomyosarcoma (RMS) tumors has been further elucidated.

Summary—Therapeutic strategies continue to be driven by developments in molecular diagnostics in pediatric GU tumors.

Keywords

genitourinary; childhood cancer; Wilms' tumor; rhabdomyosarcoma; germ cell tumor; testicle

Introduction

This review highlights recent developments in molecular and clinical diagnostics, treatment strategies and emerging late sequelae of therapy in pediatric genitourinary (GU) tumors. The differential diagnosis for renal and GU tumors varies by age in children. A recent report from the Children'sOncology Group (COG) highlights the trajectory of cooperative group approaches and treatment success in these childhood cancers[*1].

Wilms tumor

Wilms tumor (WT; nephroblastoma) represents 85% of pediatric renal tumors with a peak incidence in children under 5 years of age.

Diagnosis and Treatment

WT commonly presents as a painless abdominal mass, occasionally with associated hematuria [**2]. Surveillance screening in those with WT risk in excess of 5% may identify a few patients with genetic predisposition [3]. Current diagnostic workup remains abdominal ultrasound and CT, with no clear role for FDG-PET at this time [3]. Standard therapy for

Correspondence to: Sharon M. Castellino, MD, MS Department of Pediatrics Wake Forest University School of Medicine, Medical Center Blvd. Winston-Salem, NC 27157 Phone (336) 716-4085 Fax (336) 716-3010 scastell@wfubmc.edu.

WT is surgery, vincristine and dactinomycin, with the addition of adriamycin and/or radiation therapy (RT) based on tumor stage, histology (favorable (FH) versus anaplastic) and molecular factors.

Surgical staging to ascertain histology and assess extent of disease occurs at presentation in the North American COG (incorporating the National Wilms Tumor Study (NWTS) Group) approach, and following cytolytic therapy in the European (Societe Internationale d'Oncologie Pediatrique (SIOP)) experience. Over time significant overlap between approaches has evolved for defined risk groups [*4]. SIOP and COG/NWTS recommendations for renal tumors are concordant for the following clinical scenarios: immediate nephrectomy is advocated for those < 7 mo, due to the high likelihood of non-WT histology [5]; preoperative chemotherapy is utilized for bilateral WT (Stage V). Both cooperative group approaches agree that involvement of abdominal lymph nodes constitute stage III disease [*6]. Hence, adequate sampling of renal hilar and ipsilateral para-aortic or caval nodes is mandatory to accurate staging [**2].

Ureteral extension of tumor occurred in 2% of the NWTS5 cohort. Ureteral involvement of disease may not be apparent on imaging, and may be heralded by gross hematuria, hydronephrosis, or nonfunctioning kidney on imaging [7]. Hence, en bloc resection of tumor and ureter is recommended by the COG. Based on the risk of tumor spill and the importance of nodal evaluation to accurate staging, laparoscopic surgery is currently limited to removal of unilateral tumors pretreated with chemotherapy [**2, 8]. Bilateral nephron sparing approaches facilitated by preoperative chemotherapy are germane for those with Stage V disease, or in those with syndromes that predispose to late renal failure. Feasibility of nephron sparing is not always predictable from preoperative imaging and requires surgical expertise to minimize post op urine leak and to utilize techniques to ensure complete resection of all macroscopic disease [9].

The addition of RT and adriamycin weighed against their recognized late morbidities continues to be debated in the case of pulmonary involvement of WT. In follow-up to the SIOP approach, the United Kingdom WT group evaluated the feasibility of avoiding pulmonary RT in patients with favorable histology and chemoresponsive lung metastasis. In a cohort who received adriamycin based chemotherapy, the addition of 12 Gy of pulmonary radiotherapy reduced the risk of lung relapse (8% versus 23%, p=0.039), but overall survival was equivalent [10].

The role of hematopoietic stem cell transplant in WT is limited and is presently being studied as consolidation following ifosfamide, carboplatin, etoposide and topotecan (ICET) by the cooperative groups [11]. The combination of ICE added to vincristine, dactinomycin and adriamycin, with GFR dose adjustment of carboplatin, is a promising approach for unresectable and high-risk renal tumors [12]. A recently published Phase 2 trial with recombinant TNF-alpha and dactinomycin offers a novel combination for future investigation in children with recurrent WT [13].

Survival rates for WT exceed 90%, hence therapeutic focus is to minimize RT and anthracycline exposure for low stage FH patients, and to tailor intensive therapy for the rest.

COG protocols in development will evaluate an intensified 3 drug induction for high risk patients to improve survival and increase nephron sparing [14].

Molecular Genetics

The molecular genetics of WT continues to be elucidated (Table 1). Despite a favorable outcome for most patients with FH WT, the loss of heterozygosity (LOH) for chromosomes 1p and/or 16q (seen in about 5% of FH WT) and high telomerase expression are adverse prognostic factors. Mutations of the Wilms tumor genes, *WT1* (on chromosome 11p13) and *WT2* (on chromosome 11p15.5), have been associated with a minority of WT and other malignancies. The *WT1* gene encodes a transcription factor that may act as a tumor suppressor or, when over expressed, as an oncogenic protein. A recent study confirmed that mutations of *WT1* gene may be germline (constitutional) in addition to tumor-specific, and these patients have an increased risk of bilateral disease and recurrent disease [**15]. In addition, somatic (tumor specific) mutations of the cadherin-associated protein β1 gene *CTNNB1* are very common (33%). Despite less than optimal volumetric shrinkage to initial chemotherapy in WT mutated tumors, survival was not worse compared to patients with non *WT1*-mutated tumors.

Another relatively high risk group of patients are those with constitutional 11p15 abnormalities (*WT2*), which may result in a variety of clinical phenotypes including Beckwith-Wiedemann syndrome and other syndromes associated with abnormal growth and an increased risk of developing WT. Constitutional 11p15 abnormalities were found in 3% of patients with sporadic (nonsyndromic) WT [**16]. Specifically, epimutations in the *IGF2-H19* imprinting center were identified. Like the patients identified by Royer-Pokora, et al, these patients with constitutional 11p15 mutations have a higher rate of tumor recurrence compared to those without 11p15 mutations. The investigators suggest that all patients with WT should be screened for constitutional 11p15 mutations, although this is not yet common practice[14, **16].

The identification of *WTX, a WT* gene located on the X chromosome was found to be mutated in 15 of 51 (29%) of WT [17]. Tumors with *WTX* mutation do not have mutations in the *WT1* gene, previously the most common (15%) genetic mutation in WT. This discovery contributes to a paradigm of X-linked tumor suppressor genes, thus challenging the traditional “two hit” model. Furthermore, *WTX* has been confirmed to act as a tumor suppressor gene by negatively regulating WNT/β-catenin signal transduction, which is also seen in some cases of colon cancer and melanoma [18]. It is possible that mutations in WTX are involved in other malignancies as well, and that WNT/β-catenin signal transduction is a common end result of various other mutations, perhaps including mutations of *WT1* [19].

Nephrogenic rests are foci of embryonal cells rarely (<1%) found in normal infant kidneys and commonly (25-40%) found in Wilms tumor-bearing kidneys. They may be perilobar, intralobar or both, and they are widely considered to be precursors to WT. Although malignant transformation is believed to occur in ≤1% of nephrogenic rests, controversy exists regarding the management of coincidentally found nephrogenic rests [20-23].

Other pediatric renal tumors

Many histological variants of non-Wilms primary renal tumors are recognized, with prognosis and management varying by age and histology [*24]. Infants < 7 mos of age represent 7% of pediatric renal tumor populations, and have a different distribution of renal tumor histology, warranting special diagnostic consideration. Congenital mesoblastic nephroma (CMN) is the primary diagnostic consideration for a renal mass in the neonate, although its incidence decreases with increasing age within infancy [5]. Malignant rhabdoid tumor of the kidney (MRTK) is an aggressive histology, predominant in infancy, and the primary diagnostic consideration of a metastatic renal tumor in children < 7mo age [5].

In the second decade of life renal cell carcinoma (RCC) has an incidence that surpasses that of Wilms tumor, accounting for 4% of childhood primary renal neoplasms [25]. Xp11.2 translocation associated RCC is a distinct molecular subtype of RCC with a higher incidence in children, but significant morphologic overlap with other subtypes of RCC. Strong nuclear over-expression of TFE3 is diagnostic in these cases, which may present at a younger adolescent age, and have a propensity for delayed recurrence [*24, 26]. Pediatric RCC cases have associations with prior history of radiation for hepatoblastoma or neuroblastoma, and with tuberous sclerosis or family history of von Hippel landau syndrome. Clear cell RCC occurs with a lower incidence in children. A less common and less aggressive subtype type of RCC is that with the t(6;11)(p21;q12) translocation. The resultant fusion involves transcription factor EB gene (TFEB) at 6p21 [*24].

Prognosis for clear cell sarcoma of kidney (CCSK) has improved dramatically with current treatment, and ICE chemotherapy with RT and surgery is efficacious for salvage of brain metastases [27].

Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) originates from immature mesenchymal cells, and can commonly affect bladder, prostate, and paratesticular sites in children.

Diagnosis and Treatment

Embryonal (ERMS) histology is more common than alveolar histology (ARMS) in GU locations [*28]. Although focal and diffuse anaplasia is prevalent in GU, nonbladder/ prostate sites, the presence of anaplasia is not predictive of outcome in multivariate analysis from the centrally reviewed COG tumor registry [29]. Utilizing tumor size, node involvement and metastasis (TNM) staging criteria, bladder and prostate involvement is designated Stage 2 or 3, based on size (≥ or < 5cm), invasion of the primary tumor, or involvement of regional nodes. In the absence of distant metastases (Mo), non bladder, non prostate GU site is designated Stage 1, regardless of tumor size or nodal involvement [*28]. While current TNM staging uses a tumor size of 5cm based on the adult experience, a recent analysis of outcomes for childhood sarcomas indicates an interaction between tumor size and body size of the patient, suggesting an even lower tumor size cutoff may be warranted in smaller patients with a lower body surface area [30]. In combination with stage and histology, the International RMS Study Group (IRSG) also assigns treatment according to

post surgical grouping classification, based on residual disease following surgery. Pathologic confirmation of lymph nodes is critical to the planning of extent of radiotherapy, and germane to all boys with paratesticular RMS [*28]. Despite the therapeutic relevance of lymph node involvement in RMS, data for applicability of sentinel node biopsy in pediatric sarcomas is scarce, but recent experiences point to feasibility and limitations [31, 32].

Primary renal RMS is rare, and should be classified and approached as “unfavorable” site Stage 2 or 3 (based on size and nodes). A recent review of the IRSG experience showed 60% of these renal RMS cases are of ERMS histology [33].

Following local control with surgery, adjuvant chemotherapy with vincristine, dactinomycin, and cyclophosphamide (VAC) is the standard therapy approach. The additional benefit of irinotecan, doxorubicin, ifosfamide and etoposide is being studied for those who present with high risk disease [*28]. The role of second look surgery for group III disease and the need for RT as additional local control is validated, especially in pelvic primary tumors and tumors larger than 5cm at diagnosis [34].

Novel approaches for recurrent or metastatic ARMS have explored consolidative immunotherapy utilizing dendritic cell based vaccines targeted to the breakpoint region of the ARMS translocation (Table 1) [*35].

Molecular Biology

The more aggressive ARMS is associated with two reciprocal translocations: t(2:13)(q35;q14) and t(1;13)(p36;q14), which generate fusions of *PAX3* or *PAX7* and *FOXO1* (also known as *FKHR*), respectively (Table1). The *PAX3-FOXO1* fusion is present in 70% of cases of ARMS; the *PAX7-FOXO1* fusion is present in approximately 10–20% of cases of ARMS and has a more favorable prognosis compared to those with the *PAX3-FOXO1* fusion. Molecular applications with FISH and PCR allow less invasive procedures such as fine needle aspiration/biopsy for diagnosis [36]. Multiple other genetic changes have been identified in ARMS including aberrations in the function or expression of: telomeres; the genes *MYCN*, *p53*, *Rb*, *Cdkn2a p57Kip2*, $p16^{INK4A}$/$p14^{ARF}$; and insulin like growth factor signaling components [*37, 38]. In a retrospective study of 71 patients with RMS, the diffuse expression of myogenin was an independent adverse prognostic for survival [39]. The platelet-derived growth factor receptor-A has recently been shown to be a potential therapeutic target in ARMS [40].

Testicular Tumors

In addition to benign lesions, the differential diagnosis for a painless scrotal mass in a child/adolescent includes leukemia, rhabdomyosarcoma, and a primary testicular tumor (germ or non-germ cell). Yolk sac tumors (endodermal sinus tumors) and teratomas are the most common primary pre-pubertal testicular tumors. Embryonal carcinomas, teratocarcinoma, and mixed malignant germ cell tumors may occur in older children (typically teenagers). Gonadoblastoma, Leydig cell and Sertoli cell tumors are rare in children [41, 42]. Analysis of epidemiologic data shows that testicular germ cell tumors occur at a higher frequency in Asian/Pacific Islander boys compared to whites [43]. GCT histology and site remain the

most important clinical factors for treatment and prognosis, although gene expression profiles are being studied [44, *45]. Although the majority of yolk sac disease is clinical stage I, this tumor can spread by both blood and lymphatics. Prior to orchiectomy a serum alpha-fetoprotein (AFP) and beta human choriogonadotropin (β-HCG) should be obtained. Due to low rates of nodal involvement in children, retroperitoneal lymph node dissection is reserved for cases with persistently elevated tumor markers (AFP, β-HCG) or persistent retroperitoneal lymphadenopathy following radical inguinal orchiectomy and chemotherapy. For males with undescended testicle(s), orchiopexy before puberty decreases the risk of testicular cancer later in life [46]. For patient for whom chemotherapy is indicated, testicular GCTs are generally very chemosensitive to a variety of agents. Cisplatin and etoposide (with or without bleomycin) is currently the most common combination used [47]. In an attempt to reduce short and long-term morbidity, the COG is currently investigating reduced therapy for patients with low and intermediate risk extracranial GCTs (protocol ACOG0132).

Late Effects

Childhood cancer survivors who have received alkylating agents in isolation or in combination with radiation to a field involving the bladder require regular follow up for risks of long-term bladder fibrosis, neurogenic bladder, or secondary malignancy of the bladder. These risks vary by cumulative dose exposure; screening includes a careful voiding history an annual urinalysis to screen for microspcopic hematuria [*48]. Nephrotoxicity secondary to antineoplastic therapy can manifest as hypertension, proteinuria and varying degrees of renal insufficiency resulting from chemotherapy, nephrectomy or radiation to the kidney [*49]. Among child hood cancer survivors of nephrectomy GFR is more likely impaired among those who also received radiation [*49].

Data on second malignancy (SMN) risk continue to accumulate. In a large UK population based study of WT survivors treated between 1940 and 1991 the SIR of a second neoplasm was 6.7 (95%CI5-8.8), with a large number of second tumors within the abdomino-pelvic or thoracic radiation field [50]. The mean radiation doses employed in that treatment era far exceed that given in contemporary protocols. The cumulative incidence of a basal cell carcinoma in the RT field was 5.7% at 40 years of follow up.

Conclusion

Radiologic diagnostic have advanced the management of GU tumors [*6], yet no specific radiologic features reliably distinguish the histological types of these tumors [5, *24]. Molecular diagnostics continue to help refine therapy stratification, with a goal to maintain cure rates while minimizing late effects.

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Table 1

Common Cytogenetic Abnormalities in Pediatric GU tumors

Diagnosis	Tumor Cytogenetic Abnormalities	Tumor Specific Genes
Wilms Tumor (WT)		WT1* on chromosome 11p13
		WT2* on chromosome 11p15.5
		WTX on X chromosome
Clear Cell Sarcoma (CCSK)	t (10;17) Deletion 14 q	Unknown
Mesoblastic nephroma (CMN)	t(12;15)	ETV6 NTRK3
Alveolar RMS	t(1;13)	PAX7 on chromosome 1 FKHR on chromosome 13
	t (2;13)	PAX3 on chromosome 2 FKHR on chromosome 13
Renal Cell Carcinoma	t (X;17)	TFE3 on chromosome X
	t (X;1)	ASPL gene on chromosome 17
	t (6;11)	PRCC gene on chromosome 1 TFEB gene at 6p21

RMS: Rhabdomyosarcoma, WT1, 2: Wilm's Tumor geneland 2, ETV6: ETS variant gene 6, NTRK3: Neutrophic Tyrosine Kinase Receptor 3 gene, FKHR: Forkhead homolog 1 Rhabdomyosarcoma, PAX7 and 3: Paired Box gene 3 and 7. TFE3 and B: Transcription Factor E3 and EB, ASPL: Alveolar soft part sarcoma related gene, PRCC: Papillary Renal Cell Carcinoma gene.

*Some patients harbor germline mutations also.