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Pediatric Renal Tumors: Practical Updates for the Pathologist

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ABSTRACT

Pediatric renal tumors were targeted by the National Wilms Tumor Study Group for 4 decades with extraordinary success. Within this historic context, this review provides a summary of the new Children's Oncology Group renal tumor protocols that will be opening in the very near future, focusing on their pathologic requirements. All renal tumors must first be registered on the Renal Tumor Classification and Banking Protocol, followed by registration on 1 of 4 primary therapeutic protocols based on histology, stage, and molecular analysis. This requires prompt submission of samples for molecular analysis and central pathologic review. Changes in staging criteria include classification of all tumor spillage as stage III, and requirement of regional lymph node evaluation for eligibility for stage I Wilms tumors (WTs) weighing less than 550 g in infants younger than 24 months and for stage I clear cell sarcoma. Patients with unilateral favorable histology WT with loss of heterozygosity for chromosomes 1p and 16q will receive more aggressive chemotherapy at each stage. Patients with bilateral WT and patients with diffuse hyperplastic perilobar nephroblastomatosis will be eligible for a novel therapeutic protocol requiring pathologic classification based on response of tumor to previous therapy. Stage I anaplastic WT will be targeted with more aggressive chemotherapy than in the past. For the first time, pediatric renal cell carcinoma will be eligible for a cooperative group protocol. All rhabdoid tumors outside the central nervous system will be eligible for a single protocol. In conclusion, these new protocols bring considerable change in their overall organization, in eligibility, and in therapy.

INTRODUCTION

Pediatric renal tumors represent approximately 7% of all childhood cancers. Wilms tumor (WT) is the most common primary malignant renal tumor of childhood, with a total national incidence estimated at 500 cases per year. The different histologic subtypes of pediatric renal tumors are listed in Table 1. During the past 40 years cooperative groups targeting pediatric renal tumors have been remarkably successful. They have enabled the development of accurate diagnostic criteria, stage and histology-based therapeutic stratifications, and appropriate surgical techniques. In addition, they have demonstrated that irradiation in conjunction with several active chemotherapeutic agents are effective. The overall result has been a dramatic improvement in the prognosis for most patients with WT, from approximately 8% at the beginning of the century to approximately 50% in 1960 to greater than 90% in 2000 [1,2]. Most children in European countries are registered as patients in the International Society of Pediatric Oncology cooperative group protocols, which

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Table 1 Tumors eligible for Tumor Classification and Banking Protocol

Nephroblastic tumors
Nephroblastoma (Wilms tumor)
Favorable histology
Anaplasia, diffuse or focal
Nephrogenic rests and nephroblastomatosis
Cystic nephroma and cystic partially differentiated nephroblastoma
Metanephric tumors (adenoma, adenofibroma, stromal tumor)
Mesoblastic nephroma (cellular, classic, mixed)
Clear cell sarcoma of kidney
Rhabdoid tumor
Renal epithelial tumors of childhood
Clear cell renal tumors
RCC associated with Xp11.2 (TFE3) translocations
Other translocation–associated lesions
Conventional RCC
Papillary RCC
Renal medullary carcinoma
Oncocytic renal neoplasms after neuroblastoma
Other

RCC, renal cell carcinoma.

rely on the use of preoperative neoadjuvant chemotherapy and the provision of postoperative chemotherapy based on pathologic response. In contrast, the pediatric cooperative groups centered in North America have favored primary nephrectomy, with postoperative chemotherapy based on pathologic analysis of untreated tumors. Although these two approaches are difficult to compare, both have met with similar success in treating children with WT. This review provides a retrospective overview of the North American approach combined with a description of the new protocols that will govern the therapy of pediatric renal tumors in the near future. Emphasis is placed on changes in the pathologic evaluation that will be required by the new protocols. This report represents the most current information available regarding these future protocols. Modifications may occur during the in-depth review process of such therapeutic protocols which are still in progress.

PEDIATRIC RENAL TUMOR COOPERATIVE GROUP STRUCTURE

Historical perspective

The first cooperative group protocols for pediatric renal tumors in North America were designed, monitored, and reported by the National Wilms Tumor Study Group (NWTSG). The NWTSG was one of the first cooperative groups to develop and was uniquely successful due to its rigorous data-driven approach and its inclusion of all subspecialities that affect the care of children with renal tumors. This resulted in close collaboration between oncologists, radiation therapists, pathologists, radiologists, statisticians, and laboratory scientists. These experts guided 5 sequential NWTSG primary therapeutic protocols: NWTS-1 (1969 to 1973), NWTS-2 (1974 to 1978), NWTS-3 (1979 to 1986), NWTS-4 (1986 to 1993), and NWTS-5 (1995 to 2002). Although the therapies and goals outlined in each protocol differed, the overall structure for these protocols were quite similar. Patients with newly diagnosed renal tumors were evaluated at their local institutions according to recommendations provided in a single therapeutic protocol that contained multiple treatment arms. The patient was registered and treated on a particular regimen based on the diagnosis and stage provided by the institutional pathologist. The tumor was subsequently reviewed by the NWTSG Pathology Center, headed by Dr. J. Bruce Beckwith from 1969 to 2000. This continuity allowed for much of the progress that was contributed by the Pathology Center. The central pathology review was rapid, and the report was issued directly to the institutional pathologist. Discrepancies in diagnosis and staging between the central pathology review and institutional review were addressed by the local institution, at their discretion. It was the practice of the Pathology Center to provide the pathology review of all renal tumors rapidly and free of charge, regardless of their protocol registration status. This overall structure resulted in a "center of excellence" available to all patients. It respected the responsibility and authority of each pathologist, clinician, and institution for the care of their patients according to their best judgment.

Rationale for change in structure

The protocols that will open within the next few months will reflect significant modifications in the structure described above. These changes respond to a number of factors in the changing environment of the pediatric cooperative groups, the changing environment of health care, the changing environment of cooperative group funding, and, most of all, the evolving state of the science of cancer in general and pediatric renal tumors in particular. It is the overall goal of the Pathology Center to respond to these changes and preserve its strengths.

Change in cooperative group organization

One source of change is the overall restructuring of the organizations that oversee all pediatric therapeutic protocols. In 2000 the four pediatric cooperative groups based in North America (the NWTSG, the Intergroup Rhabdomyosarcoma Study Group, the Pediatric Oncology Group, and the Children's Cancer Study Group) developed an agreement to join and become a single large cooperative group, the Children's Oncology Group (COG). This new organization developed new policies and procedures responding to a number of needs and national pressures. Among these was the need to make clear the separation of the care of patients registered in nationally funded therapeutic protocols from those not registered. This resulted in a policy that COG will and should only support the central review of those patients registered and eligible for COG protocols. COG has mandated that the pathology review of nonregistered patients be through an official consultation. Pathologists are legally prevented from differentiating their charges for consultations based on patient differences. Further, new regulations concerning patient privacy and additional medicolegal pressures make it difficult for pathologists to provide consultations that are not clearly within the categories of clinical service or therapeutic protocols. All these factors result in the practical need for COG central pathology reviewers to approach all nonregistered patients within the United States as consultations associated with standard fees. The institution of this practice has the potential to result in the loss of availability of this "center of excellence" to all children with renal tumors. It is therefore important to note that, for strong scientific reasons, all pediatric renal tumors, as listed in Table 1, will be eligible for registration in the new COG Pediatric Renal Tumor Classification and Banking Protocol, whether or not the patient is subsequently registered in a specific therapeutic protocol. Therefore, the local institution may register any patient with a renal tumor and obtain central pathology review without an associated consultation fee, provided registration is accomplished in a timely fashion. The goal of the COG Renal Tumor Pathology Center is to continue the philosophy established by Dr. Beckwith and accommodate to the new environment.

Change in the therapeutic approach to cancer patients

The most important rationale for a change in the structure of the upcoming renal tumor protocols is to better respond to the current state of the art and science of cancer therapy. It is becoming increasingly evident that continued improvement in the outcome of patients with cancer at any site will depend on the identification of genomic and proteomic markers that (a) predict which tumors will respond to particular therapies, (b) identify patient characteristics that predict the ability to fully metabolize particular therapeutic agents, and (c) represent cancer-specific therapeutic targets that will enable the utilization of less toxic agents. This individualization of therapy will depend on our ability to combine multiple divergent pieces of information, including genomic or proteomic markers and standard histopathologic and radiographic features, to determine therapeutic stratification.

Summary of overall structure for new protocols

A summary of the major changes that will be made in the upcoming protocols is provided in Table 2. Rather than having a single large therapeutic protocol with multiple treatment arms, the new structure will have 4 different primary therapeutic protocols, each of which will require initial registration on an umbrella Tumor Classification and Banking Protocol. The purpose of this protocol is to gather all the required information necessary for starting the patient on the appropriate therapeutic protocol. After registration in the Tumor Classification and Banking

Table 2 Summary of major changes in renal tumor protocols

1. Overall Structure
a. All tumors must be registered in the Tumor Classification Protocol before registration in therapeutic protocols
b. Pathology Center will provide rapid review according to the COG guidelines
c. Tumors will be stratified based on central pathology review and molecular analysis
d. Tumors not registered in the Tumor Classification Protocol will be rapidly reviewed as consults
2. Staging
a. Rupture or spillage confined to the flank is now considered stage III
b. Biopsy (including fine needle aspiration) before removal of the kidney is considered to be local spillage and is therefore stage III
c. Two therapeutic protocols will require microscopic evaluation of lymph nodes for eligibility as stage I
i. Stage I: clear cell sarcoma of kidney
ii. Stage I: Wilms tumors <550 g in children <2 years
d. Renal cell carcinomas will be staged using a different system from other pediatric renal tumors (Table 9)
3. Overview of new approaches or changes in approach to therapy
a. FHWT: therapeutic stratification for therapy will be based on age, stage, and loss of heterozygosity for 1p and 16q
b. Bilateral Wilms tumor, syndromic patients with unilateral Wilms tumor, and patients with diffuse hyperplastic perilobar nephroblastomatosis: patients will receive preoperative chemotherapy and renal-sparing surgical approaches. Subsequent therapy will depend on posttherapy pathology classification (Table 7)
c. Focal and diffuse anaplasia: therapy will be more aggressive for stage I patients
d. Rhabdoid tumors: All non-CNS rhabdoid tumors will be registered in the Tumor Classification Protocol and treated with the high-risk renal tumor protocol
e. Pediatric renal cell carcinomas will be included in the high risk protocol

CNS, central nervous system; COG, Children's Oncology Group; FHWT, favorable histology Wilms tumor.

Table 3 New protocols for pediatric renal tumors

Tumor Classification and Banking Protocol (AREN0362)*
Therapeutic Protocols
Low- and standard-risk FHWT protocol (AREN0532)
High-risk FHWT protocol (AREN0533)
Bilateral Wilms tumor, unilateral Wilms tumor with high risk for renal failure, and nephroblastomatosis protocol (AREN0534)
High-risk renal tumors (CCSK, MRT, anaplastic Wilms Tumor, renal cell carcinoma) (AREN0321)

CCSK, clear cell sarcoma of the kidney; FHWT, favorable histology Wilms tumor; MRT, malignant rhabdoid tumor of all non–central nervous system sites

*All patients must be registered in the Tumor Classification and Banking protocol to be eligible for therapeutic protocols.

Protocol, institutions will submit a complete set of recut slides and frozen tumor to the Cooperative Human Tissue Network (CHTN) for central pathology review and molecular analysis. Based on the results of these studies, the patient will then be registered in a timely fashion into 1 of 4 therapeutic protocols listed in Table 3. The Pathology Center will review tumors of all patients registered on the Tumor Classification and Banking Protocol according to the COG guidelines for rapid review. In keeping with previous practices, a report will be faxed to the submitting institutional pathologist. In addition, the pathology information required for entry into the appropriate therapeutic protocol will be entered by the Pathology Center onto the Web-based

Table 4 Pathology requirements for tumor classification and banking protocol

	What is required
Central pathology review	1. Registration into the COG Cancer Registry
	2. Full set of recut slides
	3. Pathology report
	4. For rhabdoid tumors, renal cell carcinomas, and any tumor with unsure diagnosis, a paraffin block or unstained slides
Biology samples	1. Rapidly frozen tumor tissue for LOH analysis
	2. Rapidly frozen normal kidney
	3. Formalin fixed sections of tumor and normal kidney
	4. Other biology samples provided by oncologist (including patient blood, parental blood, urine, etc)

COG, Children's Oncology Group; LOH, loss of heterozygosity.

eRDA. This information coupled with the molecular analyses will therefore be available for the treating oncologist to determine the appropriate therapeutic protocol. All children with renal tumors are eligible for entry into the Tumor Classification and Banking protocol, whether or not they are registered on a therapeutic protocol. All tumors received by the Pathology Center from institutions within the United States that do not have a COG registration number will be considered to be a consultation and such reviews will be associated with the appropriate charges.

The greatest change that will be visible to submitting institutional pathologists is the need to register all patients with renal tumors on the Tumor Classification Protocol promptly, and the need to rapidly submit slides and tumor samples to the Cooperative Human Tissue Network. These requirements are outlined in Table 4. In the past, the institutional diagnosis was used for the protocol registration diagnosis. Therefore, as long as the diagnosis and stage were appropriate to the protocol for which the patient was registered, the patient was eligible. In the future, the central review diagnosis and the results of molecular studies will be used to determine eligibility for the therapeutic protocols; therefore, all tumors must be submitted rapidly for pathology review and molecular analysis. It should be noted that this is a structure that many protocols within the COG are moving toward, so it will be important that pediatric pathologists include the necessary changes to allow this within their clinical practices.

CLASSIFICATION AND STAGING OF PEDIATRIC RENAL TUMORS

Historical perspective

Nowhere is the progress made in the past 40 years more evident than in the evolution of the diagnostic classification of pediatric renal tumors, largely accomplished or supported by the Pathology Center [3–5]. This success has enabled the introduction of disease-specific therapy. Historically, clear cell sarcoma of the kidney (CCSK) and malignant rhabdoid tumor (MRT) were considered to be variants of WT and were managed with chemotherapeutic agents for WT. Anaplasia was first differentiated from favorable histology WT (FHWT) therapeutically in NWTS-3, whereas MRT was not treated with its own therapeutic regimen until NWTS-5. Although these distinctions aid in the selection of the most appropriate therapy for these more aggressive tumors, they also result in the ability to provide less therapy for most patients with FHWT. It is not within the scope of this review to discuss the pathologic criteria for each pediatric renal tumor. These criteria will not change in the new protocols. The reader is referred to recent extensive pathologic descriptions [6].

The criteria used for staging of pediatric renal tumors have evolved somewhat over the years, yet overall has remained rather stable. Stage I tumors are confined to the kidney, stage II tumors infiltrate locally beyond the confines of the kidney but are completely excised, stage III tumors show evidence of residual abdominal disease, whereas

Table 5 Staging of pediatric renal tumors

Stage I
Tumor limited to the kidney and completely resected
Intact renal capsule
No previous rupture or biopsy
Renal sinus vessels not involved
No evidence of tumor at or beyond margins of resection
Stage II
Tumor completely resected
No evidence of tumor at or beyond the margins of resection
Tumor extends beyond the kidney, as evidenced by one of the following:
Penetration through the renal capsule
Extensive invasion of the soft tissue of the renal sinus
Blood vessels within the nephrectomy specimen outside the renal parenchyma, including those of the renal sinus, contain tumor
Stage III
Residual nonhematogenous tumor confined to the abdomen is present after surgery as evidence by any one of the following:
Involvement of lymph nodes within the abdomen or pelvis
Penetration through the peritoneal surface
Tumor implants on the peritoneal surface
Tumor present at the margin of surgical resection
Tumor not resectable because of local infiltration into vital structures
Biopsy of tumor prior to removal of kidney
Tumor spillage of any degree or localization occurring before or during surgery
Tumor removed in greater than one piece
Stage IV
Hematogenous metastases (lung, liver, bone, brain, etc.)
Lymph node metastases outside the abdominopelvic region
Stage V
Bilateral renal involvement at diagnosis
Each side should be separately staged according to the above criteria

stage IV tumors demonstrate distant metastasis. The single largest change in staging was made in NWTS-5 and involved the criteria for distinguishing between stage I and stage II tumors [5]. At that time, tumor involvement of any vessel in the renal sinus became a basis for upstaging from stage I to stage II. This definition includes vessels located in the radial extensions of the sinus into the renal parenchyma but excludes other intrarenal vascular invasion. The renal sinus vessels represent the major portal of access by the tumor to the systemic circulation; therefore, identification of tumor in these vessels would be expected to be associated with increased risk for systemic spread.

Changes in classification and staging in new protocols

The pathologic criteria for the classification of all pediatric renal tumors remain unchanged from those used in NWTS-5. The major difference that will be seen is the inclusion of pediatric renal cell carcinoma (RCC) in the new protocols. Changes in the therapeutic approaches and the pathologic investigations that will be conducted centrally for each tumor will be discussed further in later sections. The staging system for WT, CCSK, and MRT will largely remain identical to that used in NWTS-5 and is listed in Table 5 (note that the staging used for pediatric RCC differs and will be considered

separately). Two relatively minor changes in the application of staging criteria are introduced in the new Tumor Classification and Banking protocol.

Local spillage

Previously, intraoperative tumor spillage or rupture that was deemed by the surgeon to be confined to the pelvis could be considered to represent stage II, whereas intraoperative spillage or rupture that was not confined was classified as stage III. This has been simplified in the new protocols due to the demonstration of increased relapse rate in patients with rupture or spillage previously classified as stage II and due to the difficulties and inconsistencies in applying this criterion. Therefore, going forward, a tumor that "spills" or ruptures preoperatively or intraoperatively should be designated as stage III, regardless of the degree or localization of the spillage. It remains important for the pathologist to be aware of situations in which spillage has occurred for the communication of stage to be accurate. Biopsy of the tumor (regardless of size or approach) before removal of the kidney is considered to be a form of local spillage and is likewise considered to be stage III.

Eligibility for stage I

Stage I tumors by definition are confined to the kidney. Previously, there has been no requirement for submission of regional lymph nodes for patients to qualify for stage I therapeutic protocols. However, in the upcoming protocols, there are two therapeutic arms that will provide decreased or no therapy for stage I tumors. These protocols include patients younger than 2 years with stage I FHWT that weigh less than 550 g (who will receive no adjuvant chemotherapy, discussed further below) and patients with stage I CCSK (who will receive no radiation therapy, discussed further below). In the upcoming protocols, for patients in these two groups to be eligible for decreased therapy, regional lymph nodes must be examined microscopically. This places a significant burden on both the surgeon and the pathologist, particularly considering the very small size of lymph nodes in infants with stage I tumors. Pathologists and surgeons will need to continually educate each other regarding this requirement. If lymph nodes are not separately submitted for pathologic evaluation and if none is grossly apparent, it is advisable to submit all hilar adipose tissue in search of microscopic lymph nodes at the time of the initial processing of the nephrectomy specimen. It is important to note that, although this staging requirement is currently limited to these two discrete groups of patients, its practical application to all patients with pediatric renal tumors would result in more accurate staging. The protocols will not define a particular number of lymph nodes that must be sampled; however, it will be required that sampling include regional lymph nodes (hilar, periaortic, and inguinal lymph nodes). Of note, mesenteric lymph nodes are not part of the lymphatic drainage of the kidney and will not constitute sampling of regional lymph nodes.

Recommended methods for assuring correct classification and staging

During NWTS-5, approximately 30% of CCSKs, 25% of MRTs, and 50% of anaplastic WTs were incorrectly classified by the institutional pathologist, resulting in ineligibility for many patients, particularly those with more aggressive tumors. In addition, approximately 15% of FHWTs were incorrectly staged. This reflects substantial improvement over previous NWTS studies, and these findings are largely to be expected with tumors that are rare. However, it also reflects opportunity for improvement through the use of rapid review. There are a few practices that, if instituted by the institutional pathologist, would enable a substantial decrease in errors.

Take most random tumor sections from the periphery of the lesion

Sections demonstrating the relation between the tumor and (a) the renal capsule, (b) the normal renal parenchyma, and (c) the renal sinus provide critical diagnostic and staging information, whereas sections taken from the center of the tumor, unless grossly distinctive, offer little information.

Submit sections that include the triangular interface between the intrarenal tumor pseudocapsule, the extrarenal tumor pseudocapsule, and the renal capsule

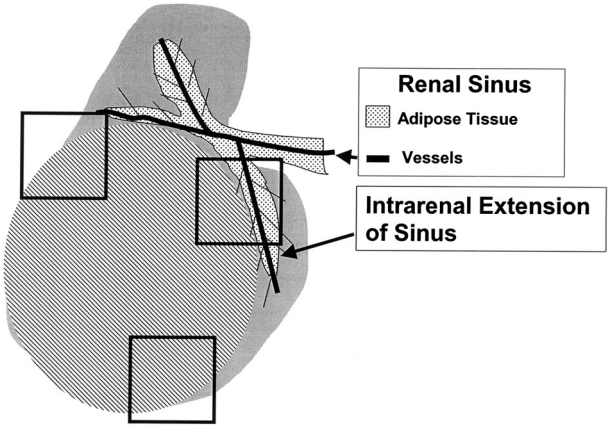

Figure 1. Schematic diagram of a pediatric renal tumor showing the relationship between the tumor and the components of the renal sinus. Boxes indicate sections that are particularly valuable in their ability to demonstrate the relationship between the tumor and the intrarenal extension of the sinus and between the tumor and the renal capsule.

This section will enable the accurate interpretation of the intactness of the renal capsule and will clarify the contribution of an acquired inflammatory pseudocapsule (Fig. 1).

Carefully consider the intrarenal extensions of the renal sinus

By far the most common reason for upstaging tumors that are otherwise stage I is the identification on central review of renal sinus vascular involvement. The renal sinus is the concave region on the medial aspect of the kidney that contains most of the pelvicaliceal system and through which most vessels and nerves of the kidney must pass. It is normally filled with fat and fibrous connective tissue. The interpretation of renal sinus vascular involvement is made difficult by the lack of recognition that the renal sinus extends into the contour of the kidney itself, following major vessels (Fig. 1).

Carefully evaluate lymph nodes

Nephroblastomas are often difficult to recognize within lymph nodes due to the similar staining properties and cellularity as lymphoid tissue. Particularly difficult are the small aggregates of tumor cells within the subcapsular sinus of the lymph node. These represent a common cause for upstaging on central review. Sometimes accumulations of Tamm-Horsfall protein within the nodal sinuses also contain sloughed renal tubular cells [7]. This should not be confused with tumor cell deposits. Moreover, be aware that CCSKs show a remarkably high incidence of regional lymph node involvement.

THERAPEUTIC APPROACHES TO UNILATERAL FAVORABLE HISTOLOGY WT (AREN0532, AREN0533)

Historical perspective

Actinomycin was the first chemotherapeutic agent shown to be effective in the treatment of children with WT [8]. Subsequently, other agents with activity against WT were identified, including vincristine, doxorubicin, and cyclophosphamide. Based on the activity of these drugs as single agents, the NWTSG initiated a series of clinical trials to evaluate the efficacy of different chemotherapy combinations against WT. The first 4 NWTSG protocols developed and refined the optimal drugs and dosages required for the therapy of FHWT [2,9–14]. At the close of NWTS-4, the overall survival rate for favorable histology WT had achieved a plateau of approximately 90%. This signaled the need to change approaches. It was the conclusion of the leaders of the NWTSG that the only way to significantly further improve the overall survival and quality of life for patients with WT was to identify novel molecular prognostic markers that could stratify FHWT. The discovery of such prognostic indicators would allow selective augmentation of therapy for those patients at high risk for tumor recurrence, thereby avoiding the adverse effects of additional therapy in most patients. NWTS-5 laid the groundwork for defining such prognostic markers by requiring the submission of biology samples. The rationale for risk stratification in NWTS-5 differed with tumor stage, as summarized below.

Stage I patients

During NWTS-4, a group of young patients with relatively small tumors was identified as having an excellent prognosis [15]. Therefore, an objective of NWTS-5 was to evaluate the necessity of chemotherapy for patients younger than 24 months with a stage I FHWT weighing less than 550 g. From 1995 to 1998, 75 such patients were treated without adjuvant chemotherapy, and 8 patients devel-

oped recurrence to the lung or operative bed and 3 patients developed metachronous contralateral WT, resulting in a 2-year disease-free survival estimate of 86.5% [16]. Based on predefined stopping rules, this arm of the study was closed early. Subsequent review of these patients revealed several factors that were not able to be considered in these predefined stopping rules. The most important factor was that the overall survival rate of these patients was much higher than estimated, suggesting that, even if these children relapse, the ability to successfully control the relapse was far greater than predicted [15]. Therefore, it has been concluded that observation only should remain a treatment consideration for this group of young patients in the new protocols.

Stage II–III patients

As the survival of patients with stages II and III FHWT improved, it became quite evident that the management of FHWT had reached a point at which the morbidity and mortality due to the therapy had to be balanced with the morbidity and mortality associated with relapse itself, which occurred in very few patients. In NWTS-4, stage II FHWT demonstrated a relapse-free survival rate that was lower than that of stage III FHWT, yet the overall survival rate for stage II patients continued to be higher than that of stage III FHWT [2]. Although it was recognized that providing more aggressive chemotherapy would result in an improved relapse-free survival rate for stage II patients, it was not clear that this would result in an increase in overall survival rate. Further, the toxicity associated with the provision of more aggressive therapy to all stage II patients would be greater than the benefit associated with decreasing the relapse-free survival rate. Conversely, it has been clear that most patients who have stage III FHWT do not require radiation therapy and doxorubicin, yet the provision of these agents for this group does improve the overall survival rate. Therefore, factors that predict specific risk subgroups within these groups would be quite useful. Analyses of different clinical and pathologic features for their ability to predict relapse in these 2 groups has resulted in an appreciation of the differences in aggressiveness and responsiveness among different histologic subtypes [17]. However, these have not demonstrated sufficient strength to prospectively stratify patients. Therefore, the NWTSG turned to the development of molecular markers to achieve this goal. NWTS-5 analyzed loss of heterozygosity (LOH) for chromosomes 1p and 16q, DNA ploidy, telomerase expression, and expression of multidrug resistance proteins, to mention a few. Many of these studies are still ongoing. Thus far, preliminary analysis of NWTS-5 data indicates an adverse prognosis in terms of relapse and death for patients with stage I to IV FHWT showing LOH for chromosomes 16q and 1p. These markers will therefore be used to prospectively stratify patients of all stages into low and higher risk categories in the upcoming protocols.

Treatment of FHWT in new protocols

The new protocols will use age, stage, and presence or absence of LOH for chromosomes 1p and 16q to determine the therapy that each child with FHWT will receive, as outlined in Table 6. Patients with unilateral tumors of all stages with LOH for chromosomes 1p and 16q will receive augmented chemotherapy. The only exception are stage I tumors weighing less than 550 g in patients younger than 24 months who will not be stratified by LOH status. It is important to note that the initial therapy provided to patients with FHWT of each stage is constant, regardless of LOH status. This window provides sufficient time for conducting the molecular analysis. Patients with stage IV tumors and pulmonary metastases whose lung lesions respond to chemotherapy will not receive pulmonary radiation therapy. Those whose tumors do not respond will receive pulmonary radiation therapy and will have cyclophosphamide and etoposide added to their chemotherapy regimen. The observation arm for patients younger than 24 months with stage I tumors weighing less than 550 g will again be offered.

THERAPEUTIC APPROACH FOR BILATERAL WT AND OTHER PATIENTS BENEFITING FROM RENAL-SPARING APPROACHES (AREN0534)

Historical perspective

Patients presenting with bilateral WT present particular therapeutic challenges. There is a high

Table 6 Therapeutic stratification of favorable histology Wilms tumor

Stage	LOH	Postsurgical treatment	Protocol
I (age <2 years tumor weight <550 g)	All	None	AREN0532
I (age ≥2 or tumor weight ≥550 g), II	Absence of LOH for1p or 16q	V, A	AREN0532
I (age ≥2 years or weight ≥550 g), II	LOH for 1p and 16q	V, A, D	AREN0532
III	Absence of LOH for 1p or 16q	V, A, D, Rx,	AREN0532
III	LOH for 1p and 16q	V, A, D, Rx, C, E	AREN0533
IV	Absence of LOH for 1p or 16q	V, A, D, Rx*	AREN0533
IV	LOH for 1p and 16q	V, A, D, Rx, C, E	AREN0533

A, actinomycin; C, cyclophosphamide; D, doxorubicin; E, etoposide; Rx, radiation therapy; V, vincristine;
*Patients with pulmonary metastases who do not respond after 6 weeks of VAD wil given C and E.

risk of renal failure in such patients, largely due to insufficient renal parenchyma after multiple surgeries [18]. Therefore, the therapy for patients with bilateral WT has depended on chemotherapy before surgery and on the use of renal-sparing surgical procedures, thereby decreasing the need for total nephrectomy [19–22]. This resulted in an overall 4-year survival of 82% in NWTS-4 patients [23]. It was stressed that positive margins did not invariably lead to recurrence. Despite these findings, the 10-year overall survival rate of patients with bilateral disease registered during NWTS-3 and NWTS-4 was lower than that for patients with unilateral FHWT. This suggests that patients with bilateral disease may benefit from more aggressive chemotherapy. Exacerbating this has been the lack of guidelines for decision-making in these complex cases, particularly with regard to the duration and type of therapy. Patients with residual masses after chemotherapy often receive prolonged courses of additional chemotherapy, often with no or little additional response.

New therapeutic protocols for bilateral WT (AREN0534)

The new protocol for bilateral WT will propose two major changes: it will increase the initial chemotherapy to include vincristine, actinomycin, and doxorubicin (VAD), and it will use histologic and radiographic responsiveness to therapy as a guideline for continued therapy early in treatment. It has long been recognized that the distribution of histologic subtypes is different after chemotherapy compared with primary surgery and that different histologic features after chemotherapy may be associated with different outcomes [20,22,24–26]. In AREN0534, guidelines are provided for the treatment of patients with bilateral FHWT that accomplish the following:

1. Patients with radiographic evidence of bilateral WT are treated with preoperative chemotherapy. Primary biopsy is not mandated for eligibility in the Tumor Classification and Banking protocol if the radiology is diagnostic.
2. The initial chemotherapy that will be provided includes 6 weeks of VAD. Historically, many of these patients received only vincristine and actinomycin.
3. After 6 weeks of VAD, bilateral partial nephrectomy is performed, if possible. If this is not feasible, radiographic studies are used to determine response to therapy. If there has been greater than 50% decrease in size, 6 more weeks of VAD is provided. If there has been less than 50% response, an open biopsy is performed to determine why the tumor has not responded. Each lesion showing less than 50% response should undergo biopsy, if possible. Subsequent therapy is based on the pathologic classification of the biopsy material, as outlined in Table 7. Patients with tumors that show anaplasia or blastemal predominant FHWT are switched to more aggressive regimens. Patients having only completely necrotic tumors may undergo excision immediately. Tumors that are in the intermediate category receive 6 more weeks of VAD therapy.

Table 7 Pathologic classification of post-chemotherapy Wilms tumor in AREN0534

Completely necrotic tumors
Less than 1% viable tumor tissue on gross and microscopic examination (the presence of scattered mature tubules is allowed).
Multiple blocks taken from different areas of a tumor according to recommendations (submission of ≥ one block/cm of tumor greatest dimension).
Approximately 10% of tumors are expected to fall into this category.
Intermediate tumors
Tumors may contain a variety of histologic features, including epithelial, stromal, and blastemal differentiation.
A spectrum of necrosis and regressive changes may likewise be present but fall short of complete necrosis.
Less than 66% of the viable tumor should be blastemal if the tumor is more than one third viable grossly.
Most tumors will fall in the intermediate-risk category.
Blastemal predominant tumors
The viable part of a tumor must comprise more than one-third of the tumor mass.
At least two-third of the viable tumor must consist of blastema.
Other components of nephroblastoma may be present in varying proportions.
Approximately 10% of tumors are expected to fall into this category.
Anaplastic tumors
Tumors demonstrating the criteria of focal or diffuse anaplasia.
Approximately 10% of tumors are expected to show anaplasia.

4. Patients who initially respond radiographically after 6 weeks (and do not require a biopsy) and patients who demonstrate intermediate risk tumor by pathology on their 6-week biopsy receive an additional 6 weeks of VAD and then undergo resection at 12 weeks. Resection options include wedge excision and partial nephrectomy if negative surgical margins are possible. Enucleation is an alternative in some situations but is contraindicated if anaplasia is present. Subsequent therapy is based on the pathologic classification of the resection specimen as outlined in Table 7 and Fig. 2.

In summary, the management of bilateral WT will require that pathologists use a new classification, outlined in Table 7. The application of this classification will be straightforward in most cases. The most significant difficulty is anticipated to be tumors that are blastemal predominant, due to the requirement to estimate the proportion of tumor that is viable in addition to the proportion of tumor that is blastemal. Pathologists in Europe have recommended the use of tumor mapping to aid in these determinations. The use of this classification is recommended for all post-therapy WT specimens, although this will only be used therapeutically for patients on AREN0534. The staging for post-therapy nephrectomy specimens differs only in the interpretation of areas of necrosis located outside the kidney. The presence of necrotic tumor or chemotherapy-induced change (in the absence of viable tumor) in the renal sinus and/or within the perirenal fat is not regarded as a reason for upstaging from stage I to stage II after chemotherapy, provided the tumor is completely excised and does not reach the resection margins. In contrast, the presence of necrotic tumor or chemotherapy-induced changes in a lymph node or at the resection margins is regarded as proof of previous tumor with potential microscopic residual disease, and therefore the tumor is assigned stage III.

Patients with unilateral WT and other syndromes

Although patients with synchronous bilateral WT have been targeted by AREN0534, other subgroups of patients with WT are also at increased risk for renal insufficiency due to a high risk of development of metachronous WTs [27]. These include patients with the Denys-Drash syndrome, Wilms tumor, Aniridia, Genitourinary anomalies,

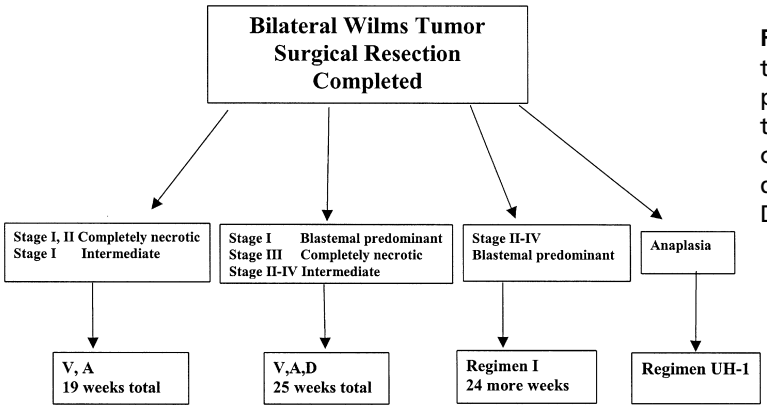

Figure 2. Schematic diagram of bilateral Wilms tumor therapy. The therapy provided to the patient after resection of the tumor depends on the stage and the histologic classification, as outlined in Table 7. Please refer to Table 8 for details of regimen 1 and UH-1. A, actinomycin; D, doxorubicin; V, vincristine.

Retardation (WAGR) syndrome, Simpson-Golabi-Behmel syndrome, aniridia, and a number of overgrowth syndromes including Beckwith-Wiedemann syndrome and idiopathic hemihypertrophy [28–30]. In addition, patients with unilateral WT and contralateral nephrogenic rest are at increased risk of developing metachronous WT [31,32]. These patients will also be eligible for AREN0534 to encourage renal-sparing approaches. Such patients will use the same schema described above for patients with bilateral renal masses, with the only exception being that they will initially receive only vincristine and actinomycin unless there is radiologic evidence of extrarenal spread (stage III or IV) at diagnosis, in which case they will receive VAD. This has the important result that all patients with bilateral renal masses, whether the contralateral mass is nephrogenic rest or WT, are eligible for AREN0534. Therefore, the often problematic distinction between nephrogenic rest and WT will have less significance.

Diffuse hyperplastic nephroblastomatosis

The other category that will be addressed within AREN0534 are patients with diffuse hyperplastic perilobar nephroblastomatosis (DHPLN), defined as nephroblastomatosis forming a thick rind around one or both kidneys. Histologically, the lesion consists of predominantly blastemal and epithelial components and often cannot be distinguished from WT by biopsy [31]. Radiologic studies are often more useful than biopsy in distinguishing nephroblastomatosis from WT [33–35]. DHPLN has not been formally studied by the NWTSG or the International Society of Pediatric Oncology. A retrospective series of 52 cases of DHPLN suggested that the use of vincristine and actinomycin results in decreased development of WT compared with patients who receive no therapy [36]. AREN 0534 represents the first effort to provide therapeutic recommendations for patients with DHPLN, as summarized below:

1. Initial biopsies are not mandated. Patients are eligible provided the radiology is diagnostic.
2. Patients will initially receive vincristine and actinomycin. Radiographic reassessment should be performed after 6 weeks of therapy. If there has been a partial response (> 50% decrease in tumor volume), patients are continued on vincristine and actinomycin for a total of 18 weeks and then followed with imaging at 3-month intervals.
3. If there is no response or if there is progression of disease while on therapy with development of new focal masses during therapy, surgery is performed.

An important component of the treatment of all patients on AREN0534 is the communication involving central pathology, radiology, and surgical review to allow for optimal therapeutic decisions.

THERAPEUTIC APPROACHES TO HIGH-RISK PEDIATRIC RENAL TUMORS (AREN0321)

Anaplastic WT, CCSK, and MRT comprise 7.5%, 3.5%, and 1.6% of pediatric renal tumors, respectively (data from NWTS-1 to NWST-5). Although RCC has not been included in previous NWTS studies, the National Cancer Institute's Surveil-

Table 8 Proposed therapy for high-risk renal tumors (AREN0321)

Histology	Stage	Regimen*
Focal anaplasia	I–III	VAD, Rx
Focal anaplasia	IV	UH-1
Diffuse anaplasia	I	VAD, Rx
Diffuse anaplasia	II–III and IV (no measurable disease)	U-1
Diffuse anaplasia	IV (measurable disease)	UH-2
CCSK	I	Regimen I
CCSK	II–III	Regimen I, Rx
CCSK	IV	UH-1
Rhabdoid tumor	I–II and III/IV (no measurable disease)	UH-1
Rhabdoid tumor	III/IV (measurable disease)	UH-2
Renal Cell Carcinoma	I–IV gross total resection	Surgery only
Renal Cell Carcinoma	I–IV, incomplete resection	Physician choice

CCSK, clear cell Sarcoma of the kidney; Rx, radiation therapy; VAD, vincristine, actinomycin, doxorubicin

Regimen I, cyclophosphamide/etoposide alternating with vincristine/doxorubicin/cyclophosphamide; UH-1, cyclophosphamide/carboplatin/etoposide alternating with vincristine/doxorubicin/cyclophosphamide and radiation therapy; UH-2, cyclophosphamide/carboplatin/etoposide; vincristine/doxorubicin/cyclophosphamide; vincristine/irinotecan and radiation therapy.

lance and Epidemiology and End Results (SEER) data indicate that RCC comprises 5.8% of (renal tumors in children and adolescents. This group of high-risk tumors accounts for a disproportionately large number of relapses and deaths among children with renal tumors and will be addressed within AREN0321.

Anaplastic WT

The single most important histologic predictor of response and survival in patients with WT is the presence or absence of anaplasia, first recognized in NWTS-1 and NWTS-2 [37]. Two histologic criteria for anaplasia were described, namely multipolar polyploid mitotic figures and marked nuclear enlargement with hyperchromasia [38]. Defined as such, anaplasia was shown to correlate best with responsiveness to therapy rather than to aggressiveness and was therefore most consistently associated with poor prognosis when it was diffusely distributed and when identified at advanced stages [39]. For this reason, pathologic and therapeutic distinctions have been made between *focal anaplasia* and *diffuse anaplasia*. NWTS-3 and NWTS-4 were the first cooperative group studies to prospectively evaluate the benefit of additional therapy for patients with anaplastic WT. These studies demonstrated an improvement in survival with the addition of cyclophosphamide [40]. NWTS-5 sought to build on these results by using vincristine, doxorubicin, and cyclophosphamide alternating with cyclophosphamide and etoposide for patients with stage II to IV diffuse anaplastic WT. The preliminary results indicate that the regimen is well tolerated and that patient outcomes are at least as good as with the previous regimen. For the upcoming AREN0321 study, the same chemotherapeutic agents will be used for patients with stage II to IV WT with anaplasia, although their dosages and administration will be modified (Table 8).

In NWTS-5, stage I WT with diffuse and focal anaplasia were managed with vincristine and actinomycin alone based on the excellent outcomes for this patient group in previous studies [40]. However, preliminary analyses of these groups within NWTS-5 indicate that the outcomes were not as favorable as in previous studies. To try to improve upon these results, AREN0321 will treat patients with stage I focal and diffuse anaplasia with VAD and radiation therapy (Table 8). As in previous protocols, the accurate distinction between stages I and II will continue to have major therapeutic implications to the patient.

Clear cell sarcoma of kidney

CCSK was recognized as a distinct clinicopathologic entity by Kidd in 1970, who noted its propensity to metastasize to bone. Although the histologic

appearance of CCSK is unique, it has a wide spectrum and often mimics other pediatric renal tumors, resulting in considerable diagnostic difficulty [41]. Specific immunohistochemical and genetic features that would aid in the diagnosis of CCSK continue to be elusive [41,42]. Analysis of patients registered in NWTS-1 to NWTS-4 has yielded comprehensive clinical data suggesting that the addition of doxorubicin to vincristine and actinomycin increased relapse-free survival [41,43,44]. NWTS-5 studied a regimen of cyclophosphamide and etoposide alternating with vincristine, doxorubicin, and cyclophosphamide (regimen I), and preliminary analysis is very promising for all but stage IV disease. None of the 14 patients with stage I have relapsed. Based on these results, AREN0321 will continue treating patients who have stage I to III CCSK with regimen I. Patients with stage IV CCSK will also receive carboplatin. Based on the excellent disease control that regimen I provides for patients with stage I CCSK, radiation therapy will be eliminated for this subset of patients. Of note, only patients who undergo lymph node sampling will be eligible to not receive radiation therapy because CCSKs have been shown to have a high frequency of lymph node metastases (29%) at presentation [41]. CCSK will continue to be a target for genomic studies to improve diagnostic accuracy and confidence and to identify therapeutic agents that target genetic changes specific to CCSK.

Rhabdoid tumor

MRT was initially described in 1978 as a variant of WT [45]. Since this original description, MRTs have been reported throughout the body, including the brain, liver, soft tissues, lung, skin, and heart. The recognition that MRTs of all sites contain deletions and mutations of the *hSNF5/INI1* gene supports the hypothesis that MRTs at different sites represent identical or very closely related entities [46,47]. Historically, patients with rhabdoid tumor of the kidney were treated in NWTSG trials with agents such as VAD, with or without cyclophosphamide, with very poor outcomes [48]. To try to improve upon these results, NWTS-5 adopted a different treatment strategy consisting of carboplatin and etoposide alternating with cyclophosphamide. Preliminary analysis of patients treated with this regimen has shown a cumulative survival to date of 25.8%. Similar results have been reported for central nervous system and extrarenal rhabdoid tumors [49,50].

Several case reports have documented the successful management of metastatic MRT of the kidney using ifosfamide and etoposide and using vincristine, doxorubicin, and cyclophosphamide [51,52]. In AREN0321, a modified form of this regimen will be used. In addition, two important changes will be introduced. First, all non–central nervous system MRTs will be eligible for AREN0321, enabling a more comprehensive analysis of tumors presumed to be biologically equivalent. Second, a component of this study will be central pathology review and central molecular genetic analysis to better define the entity of MRT and to investigate minimal diagnostic criteria. Recently, an immunohistochemical stain for the INI-1 protein product has demonstrated nuclear positivity for this antibody in all other categories of renal tumors, a variety of other pediatric sarcomas, and negativity in MRT [53]. This antibody will be evaluated for its diagnostic utility and will be performed centrally if it is not available at the local institution. In addition, frozen tumor will be analyzed for INI-1 mutation and deletion. It is important to note that no single immunohistochemical stain or profile will be considered to represent a diagnostic criterion for MRT in the upcoming protocols. It is therefore very important that unstained slides or paraffin blocks are available at the time of central pathology review for rapid review to be effective.

Pediatric Renal Cell Carcinoma

Malignant epithelial tumors arising in the kidney of children account for more than 5% of new pediatric renal tumors and are therefore more common than CCSK and MRT (SEER 1975 to 1999). Pediatric RCCs differ in their histologic appearance from those of adulthood and comprise a heterogeneous group of malignancies. They can be conceptually divided into 2 predominant subgroups based on histology, as recently reviewed [54].

Clear cell lesions

The first subgroup contains lesions that have a clear cell appearance. This is a genetically heterogeneous subgroup that includes rare tumors that

are true conventional adult-type RCC, complete with 3p25 (*VHL* locus) abnormalities, and tumors of patients with tuberous sclerosis. The clear cell–appearing subgroup also includes several translocation-associated RCCs that often have histologic appearances that closely resemble those of conventional RCCs. These translocation-associated RCCs preferentially affect children and young adults and by far outnumber conventional RCCs in this age group. The most common are tumors that show translocations involving the TFE3 gene at Xp11 and the PRCC gene of chromosome 1 [55–58]. There are many other variant translocations that involve TFE3, all of which result in overexpression of TFE3 [59,60]. There are other translocation-associated RCCs that involve different genes in the same transcription factor family, including TFEB [61,62].

Papillary RCC

The second subgroup of pediatric RCCs are the classic papillary RCCs [63–65]. These are not uncommon in children and show the same genetic features as those found in adults (gains of chromosomes 7 and 17). These tumors show a characteristic positivity for cytokeratin 7, which is of diagnostic utility [66]. Papillary RCC may also arise in the setting of WT, metanephric adenoma, and metanephric adenofibroma [54,67].

Other pediatric RCCs

Several additional rare epithelial tumors have been described. Renal medullary carcinomas are rare but highly aggressive malignancies that are associated with sickle cell hemoglobinopathy [68,69]. It is characterized clinically by a high stage at the time of detection, with widespread metastases and lack of response to chemotherapy and radiotherapy [68,70]. Survival ranges from 2 weeks to 15 months, with a mean survival of 4 months. Oncocytic RCCs have been described in patients several years after diagnosis and therapy for neuroblastoma [71]. Approximately 25% of pediatric RCCs are not able to be classified due to atypical histologic features [54].

Management and outcome of pediatric RCCs

Although it is difficult to compare the outcomes of childhood RCC with those in adults, they appear to be similar stage for stage. An important difference is the prognostic significance of local lymph node involvement. Adults presenting with RCC with involved lymph nodes have a 5-year overall survival rate of approximately 20%, whereas the literature would suggest that 72% of children with RCC and local lymph node involvement at diagnosis (without distant metastases) survived their disease [72]. Little is known about the management of childhood RCC. Neither chemotherapy nor radiation therapy have demonstrated activity in adult or pediatric patients with metastatic RCC. Similarly, the staging and grading systems that are most meaningful in pediatric RCC is currently unknown.

To address this lack of knowledge and experience, for the first time these tumors will be addressed in a cooperative group protocol within AREN0321. To enable comparison with adult tumors, the staging system proposed by the World Health Organization (Table 9) will be applied in AREN0321 for pediatric RCCs. Additional staging and grading systems will be applied centrally to address the optimal system for pediatric lesions. The relatively good survival rate for children with localized RCC combined with the relative inefficacy of the known adjuvant therapies support treating children without adjuvant therapy, as outlined in Table 8. However, the provision of adjuvant chemotherapy is at the discretion of the local physicians. Other specific objectives of AREN0321 include the following:

1. LOH at chromosome 3p25 (*VHL* gene)
2. Nuclear overexpression of TFE3 and TFEB using immunohistochemistry (translocations involving these loci result in nuclear overexpression)
3. Immunohistochemical profiles: a panel of markers will be investigated for their diagnostic utility:
   a. Papillary RCC: expression of cytokeratin 7
   b. Conventional RCC: coexpression of vimentin and low-molecular-weight cytokeratins (CAM 5.2); positivity for gp200 (RCC marker)
   c. Translocation-associated RCC: very low expression of vimentin and CAM 5.2; positivity for CD10, gp200 RCC marker
   d. Others: melan-A, HMB45, and S100 expression in angiomyolipomas and other rare translocation associated RCCs [61]

Table 9 Staging system for renal cell carcinoma in AREN0321

T—primary tumor			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
T1	Tumor ≤ 7.0 cm in greatest dimension, limited to the kidney		
T2	Tumor >7.0 cm in greatest dimension, limited to the kidney		
T3	Tumor extends into major veins or invades adrenal gland or perinephric tissues but not beyond Gerota fascia		
	T3a Tumor invades adrenal gland or perinephric tissues		
	T3b Tumor grossly extends into renal vein(s) or vena cava below diaphragm		
	T3c Tumor grossly extends into vena cava above diaphragm		
T4	Tumor invades beyond Gerota fascia		
N–Regional lymph nodes			
Hilar, abdominal para-aortic, and paracaval nodes; laterality has no effect			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in a single regional lymph node		
N2	Metastasis in more than one regional lymph node		
M—distant metastasis			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
Stage grouping			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1	N1	M0
	T2	N1	M0
	T3	N0, N1	M0
Stage IV	T1	N0	M0
	Any T	N0	M0
	Any T	Any N	M1

The accurate diagnosis of pediatric RCCs, and many of the studies listed above, will depend on the availability of immunohistochemical analysis. If the above antibodies are not available to the institutional pathologist, it is important that unstained slides or paraffin blocks accompany the routine slides stained with hematoxylin and eosin for rapid review.

OTHER PEDIATRIC RENAL TUMORS

The new structure of the upcoming protocols will, for the first time, allow for central monitoring and reporting of many rare renal tumors listed in Table 1. This will allow for treatment recommendations to be developed in the future. Two categories of tumors merit separate mention.

Cystic nephroma and cystic partially differentiated nephroblastoma

These lesions have long been hypothesized to represent one end of the spectrum of nephroblastoma but also have long been recognized to behave in a benign fashion. [73]. Patients with these lesions will be eligible for the Tumor Classification and Banking Protocol, with the recommendation that no adjuvant chemotherapy be provided.

Congenital mesoblastic nephroma

Congenital mesoblastic nephroma (CMN) comprises two histologic subtypes, one of which is potentially malignant (cellular CMN) and the other which is not (classic CMN). The accurate classification and the role of adjuvant chemotherapy, particularly for cellular CMN, has long been a concern [74]. In the past decade, documentation of the presence of the ETV6-NTRK3 fusion gene in cellular CMN and infantile fibrosarcoma has solidified the hypothesis that these are closely related or equivalent lesions [75]. In the new renal tumor protocols, patients with gross total excision of CMNs are eligible for the Tumor Banking and Classification Protocol and will be treated by careful monitoring without adjuvant chemotherapy. This is the same therapy recommended by the Non-Rhabdomyosarcoma Soft Tissue Sarcoma Committee for the biologically equivalent infantile fibrosarcoma arising in extrarenal locations that is described in protocol ARST03P1. Patients with renal cellular CMN with gross residual disease or cellular CMN after recurrence will be eligible for ARST03P1 and will receive adjuvant chemotherapy. This ensures that patients registered in COG protocols for the control of equivalent tumors receive equivalent therapy.

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