Protocol for the Examination of Biopsy Specimens From Patients With Wilms and Other Pediatric Renal Tumors

Version: 4.1.0.0
Protocol Posting Date: December 2022
The use of this protocol is recommended for clinical care purposes but is not required for accreditation purposes.
This protocol should be used for the following procedures AND tumor types:

Procedure	**Description**
Biopsy	Includes specimens designated core biopsy, incisional biopsy, or other
Tumor Type	**Description**
Wilms tumors	Includes pediatric patients with Wilms and other renal tumors

The following should NOT be reported using this protocol:

Procedure
Resection (consider Wilms Tumor Resection protocol)
Tumor Type
Renal cell carcinoma (consider the Kidney protocol)
Lymphoma (consider the Hodgkin or non-Hodgkin Lymphoma protocols)

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Accreditation Requirements
The use of this case summary is recommended for clinical care purposes but is not required for accreditation purposes. The core and conditional data elements are routinely reported. Non-core data elements are indicated with a plus sign (+) to allow for reporting information that may be of clinical value.

Summary of Changes
v 4.1.0.0

- WHO 5th edition updates
- Expert Consultation updated from Conditional to Optional

Replaced by version 5.0.0.0 on September 20, 2023, Obsolete as of June 2024 (8 months after newest release date)

Reporting Template

Protocol Posting Date: December 2022
Select a single response unless otherwise indicated.

CASE SUMMARY: (KIDNEY, PEDIATRIC RENAL TUMORS: Biopsy)
For bilateral tumors, complete a separate checklist for each kidney.

EXPERT CONSULTATION

+Expert Consultation (Note A)
___ Pending - Completion of this CAP Cancer Protocol is awaiting expert consultation
___ Completed - This CAP Cancer Protocol or some elements have been performed following expert consultation
___ Not applicable

SPECIMEN

Procedure (Note B)
___ Core biopsy
___ Incisional biopsy
___ Other (specify): _____
___ Not specified

Specimen Laterality (select all that apply)
___ Right
___ Left
___ Not specified

TUMOR

Histologic Type (Note C)
___ Wilms tumor, favorable histology
___ Wilms tumor, diffuse anaplasia
___ Congenital mesoblastic nephroma (cellular, classic, or mixed)
___ Clear cell sarcoma of kidney
___ Rhabdoid tumor
___ Other (specify): _____
___ Malignant neoplasm, type cannot be determined (explain): _____
+Histologic Type Comment: _____

+Relevant Immunohistochemistry (Note C)
___ Not performed
___ Specify findings: _____
___ Pending

+Ancillary Studies (Note D) (select all that apply)
___ Microarray
___ Specify findings: _____
___ Pending
___ FISH
___ Specify probe and findings: _____
___ Pending
___ Next generation sequencing (NGS)
___ Specify findings: _____
___ Pending
___ Other (specify): _____

ADDITIONAL FINDINGS

+Additional Findings (specify) (Notes D,E): _____

COMMENTS

Comment(s): _____

Explanatory Notes

A. Expert Consultation

Expert consultation is not required. This question has been added to annotate, if so desired, that the case has been sent out for consultation and thus items of the CAP protocol could not be completed pending expert consultation. Completion of the CAP protocol will then be performed following consultation.

B. Frozen Section and Biopsy Handling

With pediatric renal tumors, there are many issues that can interfere with making accurate diagnostic and staging decisions. The following guidelines are recommended to ensure that the necessary diagnostic features are preserved and properly examined.[1]

Because of the high number of false-positives, intraoperative frozen sections should be avoided unless the operative procedure will be altered by the result. Biopsies of pediatric renal tumors present significant potential for diagnostic error, even on permanent section. However, frozen sections from the bivalved nephrectomy specimen—to ensure tumor viability or to prompt other differential diagnostic studies—may be of value. See resection template notes for more detail.

For future potential molecular studies, viable tumor (1 gram or more) should be snap-frozen (liquid nitrogen or cold isopentane) in 2 or more vials, along with a separate portion of nonneoplastic kidney (at least 1 vial).[1] The latter serves as a useful control in molecular genetic studies and helps determine whether any detected genomic abnormalities are germline or intratumoral mutations. Nephrogenic rests may also be sampled and frozen for the same reasons.

References

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C. Microscopic Examination: Histology and Immunohistochemistry

Favorable Histology Wilms Tumor

Classic Wilms tumors present with a mixture of blastemal, stromal, and epithelial cell types. A common difficulty faced by pathologists interpreting a pediatric renal mass is the distinction between a hyperplastic perilobar nephrogenic rest and a Wilms tumor because these may be cytologically identical. The most helpful histologic feature is the absence of a peritumoral fibrous capsule in perilobar nephrogenic rests.

Many other neoplasms may have a histologic appearance similar to blastemal-predominant Wilms tumors. The most common tumors misdiagnosed as Wilms tumors are undifferentiated neuroblastoma, Ewing sarcoma, and synovial sarcoma. The most helpful feature that favors the diagnosis of Wilms tumor is the presence of overlapping nuclei with finely dispersed chromatin. Similarly, epithelial-prominent Wilms tumors show considerable histologic overlap with papillary renal cell carcinoma and metanephric adenoma. A more detailed diagnosis of pediatric renal tumors is provided elsewhere.[1,2,3]

Immunohistochemistry

For diagnosis of Wilms tumor, no single or panel markers can with 100% confidence either prove or exclude the diagnosis of Wilms tumor. WT1 is commonly positive in blastemal and epithelial elements but may be

negative in up to 20% of Wilms tumors. PAX8/PAX2 are expressed in Wilms tumor and this expression may exclude small blue cell tumors of the soft tissue that happen to present in the kidney.[3] Almost any other immunohistochemical marker may be found in Wilms tumors in the correct pathologic context.

Although some studies suggest that p53 immunostaining may be a more sensitive predictor of poor outcomes than histologic assessment of anaplasia[1], such studies are fraught with difficulties in interpreting the outside limits of "positivity" as well as with interinstitutional variability in immunostaining techniques. Furthermore, some p53 mutations by their nature do not result in abnormal protein accumulation. However, strong, unequivocal p53 protein accumulation identified in a tumor that is suspicious for anaplasia may contribute to the diagnosis.[2]

Anaplastic Wilms Tumor

Once a tumor has been diagnosed as Wilms tumor, it is necessary to determine if it is of favorable histology or if anaplasia is present. Although anaplasia is present in only 5% of all cases[4,5], it is the major prognostic indicator and will place a tumor in an unfavorable histologic category.

The presence of anaplasia is a significant prognostic factor in Wilms tumor and places the tumor in an unfavorable category. Although the mechanism for unfavorable prognosis is unclear, anaplasia may be a marker of chemotherapy resistance. A diagnosis of anaplasia requires both (1) gigantic polypoid nuclei with increased chromatin content and major diameters at least 3 times those of adjacent cells and (2) the presence of multipolar or otherwise recognizable polypoid mitotic figures. On a small biopsy, a single multipolar mitotic figure or an unequivocally gigantic tumor cell nucleus may be sufficient criteria for diagnosis. Severe nuclear unrest is defined as nuclear pleomorphism or atypia approaching the criteria of anaplasia. Care should be taken in the assessment of anaplasia cells exhibiting rhabdomyoblastic differentiation, as these cells may show nuclear enlargement, pleomorphism, and hyperchromasia akin to regenerating skeletal muscle. Such areas of "pseudoanaplasia" will have increased cytoplasmic volume and will lack atypical mitoses, as described above.

Criteria for focal versus diffuse anaplasia have been defined topographically and are rigorous.[5] This topographic definition of focal anaplasia makes it mandatory that pathologists carefully document the exact site from which every section is obtained (e.g., on a diagram, specimen photocopy, and/or photograph of the gross specimen).

Focal Anaplasia

Diagnosis of focal anaplasia is warranted if all of the following are true:

- No anaplasia should be present in tumors within renal vessels or outside the kidney.
- Anaplasia must be confined to 1 or 2 sharply localized regions, each less than 15 mm in diameter, within the primary intrarenal tumor site.[6]
- Each focus of anaplasia must be surrounded on all sides by nonanaplastic tissue. This may require mapping of the tumor during submission.
- The remaining nonanaplastic tumor must not show severe nuclear unrest.

(The same criteria apply to posttreatment nephrectomies. There is no evidence to suggest that either chemotherapy or radiation therapy results in anaplasia.)

Diffuse Anaplasia

Diagnosis of diffuse anaplasia is warranted if any of the following are true:

- Anaplasia is present in tumors in any extrarenal site, including vessels of the renal sinus, extracapsular infiltrates, or nodal or distant metastases. Also, anaplasia is present in intrarenal vascular involvement by tumor.
- Anaplasia is present in a random biopsy.
- Anaplasia is unequivocally identified, but the tumor fails any of the above criteria for focal anaplasia.

Posttherapy Classification of Wilms Tumor:

The response of a Wilms tumor to prior therapy may help guide the subsequent therapeutic strategy. For this reason, the Children's Oncology Group is using the overall categories (low, medium, high risk) utilized by the International Society of Paediatric Oncology (SIOP) when categorizing posttherapy tumors.[7] As outlined above, these categories are based on the proportion of the tumor that is viable and blastemal, and in COG only apply in favorable histology Wilms tumor. It is acknowledged that such quantitative analysis is quite difficult to reproduce and is highly dependent on how representative of the entire tumor the sections submitted are. The overall concept is that tumor that remains highly undifferentiated and proliferative following therapy will require more aggressive therapy going forward. Pathologists should, as always, use their best judgment. Staging of posttherapy nephrectomy specimens should be based on the resection specimen only. A prior pretherapy biopsy is not a criterion for assigning stage III to a post-therapy specimen.

Impact of Necrotic Tumor on Wilms Tumor Staging:

Necrosis outside of the kidney may be present in pretherapy resection specimens or posttherapy specimens. 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, providing the tumor (either viable or necrotic) 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.

Congenital Mesoblastic Nephroma

Congenital Mesoblastic Nephroma (CMN), a tumor of infancy, represents 2 morphologically/genetically distinct tumors: classic and cellular forms. The classic subtype is characterized by a whirled gross appearance and is composed of bland spindle cells with a low mitotic rate that are arranged in long, sweeping fascicles.[8,9] The cellular subtype has a fleshy and hemorrhagic gross appearance and is characterized by more densely cellular plump spindle cells with shorter to haphazard fascicles and a higher mitotic rate. Cases may also show a "mixed" histologic appearance with features of both classic and cellular CMN.[10,11] Cellular CMN may be positive for PAX8 and desmin and negative for CD34 and cytokeratins, but immunohistochemical markers are overall nonspecific.[11,12]

Approximately 10% of CMNs recur. Virtually all CMNs that recur are of the cellular subtype.[8,9,13] Recurrences occur very rapidly, often within the first month of diagnosis. Virtually all recurrences occur by the first year of age.[14] More than half are local recurrences; however, pulmonary metastases have been identified in 20% of patients who relapse. However, the primary determinant of outcome is the completeness of the excision. Surgeons should be educated and encouraged to secure wide margins, particularly medial margins, when resecting renal tumors in infants. Nonetheless, one can rarely be sure that the medial margin is clear; therefore, all patients should be followed closely. Monthly abdominal ultrasounds should be performed for 1 year, with the hope of catching recurrences early enough

to surgically excise them. Adjuvant chemotherapy is required when there is gross residual tumor.[13,14] Radiation has no demonstrable effect.

Clear Cell Sarcoma of the Kidney

Clear cell sarcoma of the kidney (CCSK) is capable of mimicking, or being mimicked by, every other major neoplastic entity in the pediatric kidney. Immunohistochemical stains for CCSK are non-specific but may be helpful to aid the diagnosis. CCSK may show variable but consistent expression for BCOR cyclin D1, and NGFR; other IHC may be useful to exclude other diagnoses.[15,16,17] Molecular features are described in Note G.

The histologic spectrum and clinical outcome of patients with CCSK have been reported by the National Wilms Tumor Study Group.[18] Nearly all patients with stage I CCSK survive. Conversely, patients with more advanced disease have a propensity for local recurrence and metastasis. Recurrences can occur from years to decades after the initial presentation, sometimes demonstrating bland histology that differs from the primary tumor. The metastatic pattern tends to be more widespread than that of Wilms tumor and includes bone, brain, and soft tissue. There is a high recurrence rate and death rate even when treated by combination chemotherapy, but survival can be greatly improved after treatment with doxorubicin, 11 which underscores the importance of identifying this neoplasm to facilitate early administration of more effective chemotherapy regimes.

There are several variants of CCSK, among which the following are most important:

Classic Pattern

The classic pattern of CCSK presents an evenly dispersed network of fine, arborizing vessels accompanied by a variable amount of spindle-cell stroma, subdividing the tumor into nests or cords of regular size, usually about 8 to 12 cells in width. The tumor cells are of regular size, usually with stellate cytoplasm, which often surrounds clear vacuoles. The nuclei are notably regular in size, with finely dispersed chromatin, and usually inconspicuous nucleoli. Mitotic activity may be sparse. Scattered preexisting tubules or glomeruli often are dispersed through the peripheral regions of the tumor. This pattern of growth, which isolates and separates individual nephronic units or collecting tubules, is an important clue that one is not dealing with Wilms tumor. The latter almost always has a sharply defined, “pushing” border.

Hyalinizing Pattern

The hyalinizing pattern of CCSK often has an osteoid-like, nonbirefringent matrix that separates tumor cells, giving an appearance reminiscent of osteosarcoma. A similar change may be seen in rhabdoid tumor of the kidney (RTK).

Epithelioid Pattern

The epithelioid pattern is the most deceptive of the patterns of CCSK, in which the tumor cells align themselves along vessels in a manner mimicking the tubules of Wilms tumor. Often these cells form filigree-like strands.

Rhabdoid Tumor of the Kidney

This distinctive renal neoplasm most commonly is encountered in infants younger than 1 year of age and is uncommon in patients older than 5 years.[19,20,21] It is extremely aggressive and is the prognostically unfavorable neoplasm of the kidney in early life. Rhabdoid tumors continue to present significant diagnostic

challenges, particularly when they do not show overt rhabdoid features. However, the growing appreciation that this tumor arises in sites other than the kidney and the central nervous system, and the increased appreciation of the wide histologic spectrum of rhabdoid tumors, have contributed to a marked increase in their correct diagnosis. Rhabdoid tumors of the kidney should not be confused with the true myogenic cells, which are often found in Wilms tumors.

The most distinctive features of rhabdoid tumor of the kidney (RTK) are rather large cells with large vesicular nuclei, a prominent single nucleolus, and the presence in at least some cells of globular eosinophilic cytoplasmic inclusions composed of whorled masses of intermediate filaments. Another distinctive feature is the extremely aggressive, invasive pattern of this lesion. RTK has a diverse immunohistochemical profile. Tumors may be positive for many supposedly incompatible epitopes for epithelial (keratins), myogenous, neural, and mesenchymal cell types. Epithelial membrane antigen (EMA) should be included in the routine panel applied to small blue cell tumors, largely because of the typical focal strong positivity for EMA (as well as a multiple of other markers) that rhabdoid tumors demonstrate.[2] RTKS consistently show loss of expression of INI-1/BAF47 (see Note G).[2]

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D. Ancillary Studies

The diagnosis of primary renal tumors in children remains largely based on examination of hematoxylin-eosin (H&E)-stained sections. However, a few ancillary studies may be employed for diagnostic or prognostic importance.

Wilms tumor molecular testing:

Molecular tests such as loss of heterozygosity (LOH) at chromosomes 1p and 16q, 1q gain, and 11p15 loss have prognostic significance in certain patient populations. Augmentation of therapy has been shown to be effective for WT with combined LOH at 1p and 16q, therefore analysis of these loci, most commonly by targeted or genome-wide SNP array, has become routine practice in North America.[1,2,3] While 1q gain is associated with adverse prognosis, the benefit of increased therapy is an area of active investigation. LOH and loss of imprinting of 11p15 have been associated with increased risk of relapse in young patients with stage I favorable histology WT that is treated with nephrectomy alone without adjuvant therapy.[4,5,6]

The molecular etiology of Wilms tumor is heterogeneous and more than a dozen genes have been found to be recurrently mutated in Wilms tumor tissue including genes involved in transcriptional regulation (*WT1, MYCN, SIX1, SIX2, MLLT1)*, microRNA processing *(DGCR8, DROSHA, DICER1, and XPO5*), and the

WNT signaling pathway (*AMER1 and CTNNB1*). TP53 mutations have been detected in 50-75% of anaplastic histology Wilms tumors. Additionally, approximately 70% of Wilms tumors have evidence of *IGF2* overexpression, which may arise via genetic or epigenetic changes at chromosome locus 11p15.[7] Some of these genes may also have germline mutations, which has implications for Wilms tumor predisposition and genetic counseling.

Other tumor molecular testing:

Congenital Mesoblastic Nephroma

CMN represents 2 genetically distinct tumors that correspond to the histologic subtypes. “Classic” CMN (24% of cases), which histologically resembles a type of fibromatosis has recently been recognized to harbor a*EGFR* activating mutations (most often internal tandem duplications).[8,9] These alterations may be detected by next generation sequencing (NGS). “Cellular” CMN (66% of cases), which is analogous to the soft tissue tumor, infantile fibrosarcoma, most commonly contains an *ETV6-NTRK3* gene fusion.

However, a variety of other variant MAP kinase pathway activating translocations or mutations may also be present.[10] *ETV6-NTRK3* fusions may be detected by FISH or NGS, while the less common alternative alterations may be detected by comprehensive NGS for mutations and fusions. Genetically, “mixed” CMN have most frequently demonstrated *EGFR* alterations similar to the classic subtype, with rare cases with genetic overlap to cellular CMN.[9]

Clear Cell Sarcoma of the Kidney

CCSK is characterized molecularly by BCOR internal tandem duplications or *YWHAE-NUTM2B* fusions.[11] The *YWHAE-NUTM2B* fusion was the first reported recurrent alteration in CCSK, but only accounts for approximately 15% of cases.[12] With increased use of NGS, the presence of the BCOR internal tandem duplication was confirmed in the majority of tumors that are negative for the fusion.[11,13] Rare renal tumors with a CCSK morphology have also been detected with *BCOR* gene fusions.[13,14,15] Fusions may be detected by FISH or by NGS-based RNA sequencing. The *BCOR* internal tandem duplication may be detected by NGS or by targeted PCR assays.

Rhabdoid Tumor of the Kidney

Both renal and extrarenal rhabdoid tumors carry homozygous deletions and/or mutations of the *SMARCB1* gene located at 22q11.2, which is a member of the SWI/SNF chromatin remodeling complex.[16] Furthermore, germline mutations have been identified in individuals with both renal and central nervous system rhabdoid tumors. The *SMARCB1* (INI1) gene causes conformational changes in the nucleosome, thereby altering histone-DNA binding and facilitating transcription factor access. Mutations in *SMARCB1* correspond to the loss of expression by immunohistochemistry using the INI-1/BAF47 antibody.[17] This antibody shows strong nuclear expression in normal tissues; however, nuclear expression is lost (aberrant expression) in rhabdoid tumor nuclei. Additionally, a variety of other tumors may also show loss of INI-1 by immunohistochemistry to include renal medullary carcinoma, epithelioid sarcoma, among several others. Molecular testing for SMARCB1 mutations is not necessary for the diagnosis of RTK, but may be utilized in the workup, particularly to identify germline mutations.

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E. Syndromes Associated with Wilms Tumor

The following syndromes are associated with Wilms tumor[1,2,3]:

- *REST*-related Wilms tumor
- *TRIM28*-related Wilms tumor
- WT1 disorder
- 1p15-related Wilms tumor (Beckwith-Wiedemann syndrome, hemi-hyperplasia)
- WAGR syndrome
- Perlman familial nephroblastomatosis syndrome
- Denys-Drash syndrome
- Trisomy 18
- Neurofibromatosis
- Bloom syndrome
- etc.

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