COLLEGE of AMERICAN PATHOLOGISTS

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

**Version:** Wilms Tumor Biopsy 4.0.0.0 **Protocol Posting Date:** February 2019

**Accreditation Requirements**
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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**Important Note**

- First priority should always be given to formalin-fixed tissues for morphologic evaluation.
- The second priority for tissue processing may include snap-freezing up to 1 g (minimum of 100 mg) of tumor for molecular studies (Note A).

For more information, contact: The Children's Oncology Group Biopathology Center. Phone: (614) 722-2890 or (800) 347-2486.

**Summary of Changes**
v4.0.0.0 - Biopsy and resection procedures separated into individual protocols

# Surgical Pathology Cancer Case Summary

Protocol posting date: February 2019

**KIDNEY, PEDIATRIC RENAL TUMORS: Biopsy**

**Note: This case summary is recommended for reporting biopsy specimens but is NOT REQUIRED for accreditation purposes. Core data elements are bolded to help identify routinely reported elements.**

*Note: For bilateral tumors, complete a separate case summary for each kidney.*

**Select a single response unless otherwise indicated.**

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

**Specimen Laterality (required for bilateral tumors only)**
___ Right
___ Left
___ Not specified

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

Comment(s)

## Explanatory Notes

**A. Frozen Section**
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.

For future potential molecular studies, viable tumor (1 g 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:
1. Knezevich SR, Garnett MJ, Pysher TJ, Beckwith JB, Grundy PE, Sorensen PH. ETV6-NTRK3 gene fusion and trisomy 11 establish a histogenetic link between mesoblastic nephroma and congenital fibrosarcoma. *Cancer Res.* 1998;58(22):5046-5048.

**B. Microscopic Examination**
Favorable Histology Wilms Tumor
Classic Wilms tumors present with a mixture of blastemic, 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, primitive neuroectodermal tumor, 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-predominant Wilms tumors show considerable histologic overlap with papillary renal cell carcinoma and metanephric adenoma. A more detailed differential diagnosis of pediatric renal tumors is provided elsewhere.[1,2]

Anaplastic Wilms Tumor
Once a tumor has been diagnosed as Wilms tumor, it is necessary to determine whether it is of favorable histology or if anaplasia is present. Although anaplasia is present in only 5% of all cases,[3] 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 polyploid nuclei with increased chromatin content and major diameters at least 3 times those of adjacent cells and (2) the presence of multipolar or otherwise recognizably polyploid 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. Anaplasia should not be assessed in cells exhibiting rhabdomyoblastic differentiation, as these cells may show nuclear enlargement, pleomorphism, and hyperchromasia akin to regenerating skeletal muscle.

Criteria for focal versus diffuse anaplasia have been defined topographically and are rigorous.[4] This topographic definition of focal anaplasia makes it mandatory that pathologists carefully document the exact site from which every section is obtained (eg, on a diagram, specimen photocopy, and/or photograph of the gross specimen).

*Focal Anaplasia (not applicable to biopsy specimens)*
Diagnosis of focal anaplasia is warranted if *all* of the following are true:
- No anaplasia should be present in tumor within renal vessels or outside the kidney.

- Anaplasia must be confined to 1 or a few sharply localized regions within the primary intrarenal tumor site.
- 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 result in anaplasia.)

*Diffuse Anaplasia*

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

- Anaplasia is present in tumor 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.

Congenital Mesoblastic Nephroma

There is a growing appreciation that congenital mesoblastic nephroma (CMN), a tumor of infancy, represents 2 genetically distinct tumors: the “classic” CMN (24% of cases), which may correspond to a type of fibromatosis; and “cellular” CMN (66% of cases), which corresponds to infantile fibrosarcoma and often contains the characteristic t(12;15), resulting in a fusion product detectable by reverse transcriptase polymerase chain reaction.[1] Absence of this translocation does not exclude the diagnosis of cellular congenital mesoblastic nephroma. Occasional cases (10%) are classified as “mixed” CMN, owing to the presence of both histologic types. Increasingly a subset of CMN, often but not exclusively “mixed” pattern, has been recognized to have *EGFR* activating mutations (most often internal tandem duplications).[6]

Approximately 10% of CMNs recur. Virtually all CMNs that recur are of the cellular subtype. Recurrences occur very rapidly, often within the first month of diagnosis. Virtually all recurrences occur by 1 year of age. 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 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. 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. CCSK is characterized molecularly by *BCOR* internal tandem duplications or *YWHAE-NUTM2B* fusions.[7] Immunohistochemical stains other than vimentin are inconsistent, but these negative results can help rule out other neoplasia in the differential diagnosis.

The histologic spectrum and clinical outcome of patients with CCSK have recently been reported by the National Wilms Tumor Study Group.[8] 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 initial presentation, sometimes demonstrating a 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,[8] which underscores the importance of identifying this neoplasia to facilitate early administration of more effective chemotherapy regimens.

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

*Classical Pattern*

The classical 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 preexistent 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 a 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 extremely uncommon in patients older than 5 years. It is extremely aggressive and is the most 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 tumor 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, 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 multitude of other markers) that rhabdoid tumors demonstrate.

Rapid advances in our understanding of the genetic events leading to the development of rhabdoid tumors have been made recently. It now is clear that both renal and extrarenal rhabdoid tumors carry homozygous deletions and/or mutations of the *hSNF5/INI1* gene located at 22q11.2.[9] Furthermore, germline mutations have been identified in individuals with both renal and central nervous system rhabdoid tumors. The *INI1* gene causes conformational changes in the nucleosome, thereby altering histone-DNA binding and facilitating transcription factor access. The *INI1* deletion can be evaluated with immunohistochemistry using the BAF47 antibody.[2] This antibody shows strong nuclear staining in virtually all cell types except rhabdoid tumor cells. Important exceptions are renal medullary carcinoma and epithelioid sarcoma, which also often show loss of INI-1 protein.

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