Wilms Tumor

Protocol applies to specimens from patients with Wilms tumor (nephroblastoma) or other renal tumors of childhood.

Protocol revision date: January 2004
No AJCC/UICC staging system

Procedures

- **Cytology** (No Accompanying Checklist)
- **Incisional Biopsy (Needle or Wedge)** (No Accompanying Checklist)
- **Partial Nephrectomy**
- **Radical Nephrectomy**

Authors
Stephen J. Qualman, MD
Department of Laboratory Medicine, Children's Hospital, Columbus, Ohio
Jay Bowen, MS
Department of Laboratory Medicine, Children's Hospital, Columbus, Ohio
Mahul B. Amin, MD
Department of Pathology, Emory University Hospital, Atlanta, Georgia
John R. Srigley, MD
Department of Laboratory Medicine, Credit Valley Hospital, Mississauga, Ontario, Canada
Paul E. Grundy, MD
Department of Oncology, Cross Cancer Institute, Edmonton, Alberta, Canada
Elizabeth J. Perlman, MD
Department of Pathology, Children's Memorial Hospital, and the Robert H. Lurie Comprehensive Cancer Center, Chicago, Illinois
For the Members of the Cancer Committee, College of American Pathologists

Surgical Pathology Cancer Case Summary (Checklist)

Protocol revision date: January 2004
Applies to specimens from patients with Wilms tumor (nephroblastoma) or other renal tumors of childhood
No AJCC/UICC staging system

KIDNEY: Resection for Wilms Tumor

Patient name:
Surgical pathology number:

Note: Check 1 response unless otherwise indicated.

MACROSCOPIC

Specimen Type
___ Partial nephrectomy
___ Radical nephrectomy
___ Other (specify): _____
___ Not specified

Laterality
___ Right
___ Left
___ Not specified

Kidney Size
Kidney dimension: ___ x ___ x ___ cm
Weight: ____ grams
Description of perirenal fat/Gerota's fascia: _____

***Tumor Site (check all that apply)**
*___ Upper pole
*___ Middle
*___ Lower pole
*___ Other (specify): _____
*___ Not specified

Tumor Characteristics
Number of tumor nodules: ___
For each nodule:
Greatest dimension: ___ cm
*Additional dimensions: ___x___ cm
Location(s) (specify): _____
___ Cannot be determined (see Comment)

* Data elements ***with asterisks*** are ***not required*** for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.

Macroscopic Extent of Tumor (check all that apply)
___ Gerota's fascia intact
___ Gerota's fascia disrupted
___ Renal vein invasion present
___ Renal vein invasion absent
___ Tumor extension into adrenal present
___ Tumor extension into adrenal absent

MICROSCOPIC

Histologic Type (check all that apply)
___ Wilms tumor, favorable histology
___ Wilms tumor, focal anaplasia
___ Wilms tumor, diffuse anaplasia
___ Congenital mesoblastic nephroma, classical
___ Congenital mesoblastic nephroma, cellular
___ Congenital mesoblastic nephroma, mixed
___ Clear cell sarcoma
___ Rhabdoid tumor
___ Other (specify): _____
___ Malignant neoplasm, type cannot be determined

Nephroblastomatosis
___ Nephrogenic rests, intralobar
___ Nephrogenic rests, perilobar
___ Nephrogenic rests, unclassified
___ No nephrogenic rests
___ Cannot be determined

Margins (check all that apply)
___ Cannot be assessed
___ Margins uninvolved by tumor
    Distance of tumor from closest margin: ___ mm
___ Margin(s) involved by tumor
    ___ Gerota's fascia
    ___ Renal vessels (specify): _____
    ___ Ureter

Renal Sinus (check all that apply)
___ No renal sinus involvement
___ Renal sinus soft tissue involvement
___ Renal sinus vascular involvement

* Data elements ***with asterisks*** are ***not required*** for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.

Regional Lymph Nodes
___ No lymph nodes submitted
___ Cannot be assessed
___ No regional lymph node metastasis
___ Regional lymph node metastasis
Specify: Number of lymph nodes examined: ___
Number of lymph nodes involved: ___

National Wilms Tumor Study Group (NWTSG) Staging System
(check all that apply under the appropriate stage)

Stage I
___ Tumor limited to kidney and completely resected
___ Renal capsule intact
___ Tumor not ruptured or biopsied prior to removal
___ Renal vein contains no tumor (intrarenal vessel involvement may be present)
___ No lymph node involvement or distant metastases

Stage II
___ Tumor extends beyond kidney but completely resected
___ Regional extension of tumor (vascular invasion outside the renal parenchyma or within the renal sinus, and/or capsular penetration with negative excision margin)
___ Operative tumor spillage confined to flank and not contaminating the peritoneum
___ Biopsy (except fine-needle aspiration) prior to surgery

Stage III
___ Nonhematogenous metastases confined to abdomen (eg, tumor in regional lymph nodes), including tumor implants on or penetrating the peritoneum
___ Gross or microscopic tumor remains postoperatively (tumor at margins of resection)
___ Tumor spill before or during surgery not confined to flank
___ Piecemeal excision of tumor (removal of tumor in more than 1 piece)

Stage IV
___ Hematogenous metastases or lymph node metastases outside the abdomino-pelvic region (beyond renal drainage system, eg, lung, liver)

Stage V
___ Bilateral renal involvement at diagnosis (each side should also be staged separately, according to above criteria, as I to IV)
Specify (both): Right kidney stage: ___
Left kidney stage: ___

***Additional Pathologic Findings**
*Specify: _____

***Comment(s)**

* Data elements ***with asterisks*** are ***not required*** for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.

Background Documentation

Protocol revision date: January 2004

I. Cytologic Material (Note **B**)

A. Clinical Information

1. Patient identification
   a. Name
   b. Identification number
   c. Age (birth date)
   d. Sex
   e. Race
2. Responsible physician(s)
3. Date of procedure
4. Other clinical information
   a. Relevant history (eg, previous diagnoses and treatment, family history of renal tumors)
   b. Relevant findings (eg, imaging studies)
   c. Clinical diagnosis
   d. Procedure (eg, fine-needle aspiration [FNA])
   e. Anatomic sites(s) of specimen (eg, kidney, metastatic site)

B. Macroscopic Examination

1. Specimen
   a. Unfixed/fixed (specify fixative)
   b. Number of slides received
   c. Quantity and appearance of fluid specimen
   d. Other materials received
   e. Results of intraprocedural consultation
2. Material submitted for microscopic examination (eg, smear, cytocentrifuge, touch or filter preparation, cell block)
3. Special studies (specify) (eg, histochemistry, immunohistochemistry, cytogenetic analysis) (Notes **A** and **C**)[1]

C. Microscopic Evaluation

1. Adequacy of specimen (if unsatisfactory for evaluation, specify reason)
2. Tumor, if present
   a. Histologic type, if possible (Notes **D** and **E**)
   b. Other features (eg, necrosis, anaplasia) (Notes **B** and **E**)
3. Other pathologic findings
4. Results/status of special studies (specify) (Note **C**)
5. Comments
   a. Correlation with intraprocedural consultation, as appropriate
   b. Correlation with other specimens, as appropriate
   c. Correlation with clinical information, as appropriate

II. Incisional Biopsy

(Needle or Wedge) (Note **B**)

A. Clinical Information

1. Patient identification
    a. Name
    b. Identification number
    c. Age (birth date)
    d. Sex
    e. Race
2. Responsible physician(s)
3. Date of procedure
4. Other clinical information
    a. Relevant history (eg, previous diagnoses and treatment, family history of renal tumors)
    b. Relevant findings (eg, imaging studies)
    c. Clinical diagnosis
    d. Procedure (eg, needle or wedge biopsy)
    e. Anatomic sites(s) of specimen (eg, left kidney)

B. Macroscopic Examination

1. Specimen
    a. Unfixed/fixed (specify fixative)
    b. Number of pieces
    c. Dimensions
    d. Descriptive features
    e. Orientation, if designated by surgeon
    f. Results of intraoperative consultation
2. Tissue submitted for microscopic examination, as appropriate
    a. Entire specimen
    b. Selected sample
    c. Frozen section tissue fragment(s) (unless saved for special studies) (Note **A**)
3. Special studies (specify) (eg, histochemistry, immunohistochemistry, molecular analysis [specify type], cytogenetic analysis) (Note **C**)

C. Microscopic Evaluation

1. Tumor
    a. Histologic type, if possible (Note **E**)
    b. Venous/lymphatic vessel invasion, if possible to determine (Note **E**)
    c. Extracapsular extension, if possible to determine (Note **E**)
2. Additional pathologic findings, if present
3. Results/status of special studies (specify) (Note **C**)
4. Comments
    a. Correlation with intraoperative consultation, as appropriate
    b. Correlation with other specimens, as appropriate
    c. Correlation with clinical information, as appropriate

III. Partial Nephrectomy

A. Clinical Information

1. Patient identification
   a. Name
   b. Identification number
   c. Age (birth date)
   d. Sex
   e. Race
2. Responsible physician(s)
3. Date of procedure
4. Other clinical information
   a. Relevant history (eg, previous diagnoses and treatment, family history of renal tumors)
   b. Relevant findings (eg, imaging studies)
   c. Clinical diagnosis
   d. Procedure
   e. Operative findings
   f. Anatomic sites(s) of specimen (eg, left partial kidney, upper pole)

B. Macroscopic Examination

1. Specimen (Note **D**)
   a. Organs/tissues included
   b. Unfixed/fixed (specify fixative)
   c. Type of specimen
   d. Kidney size (3 dimensions)
   e. Weight
   f. Orientation, if indicated by surgeon
   g. Weight of adrenal gland, if present
   h. Other organs/tissue(s) (weigh or measure, as appropriate)
   i. Results of intraoperative consultation
2. Tumor(s)[2]
   a. Number
   b. Location
   c. Sizes(s)
   d. Descriptive characteristics (eg, solid/cystic, color, consistency, necrosis)
   e. Extent of invasion (Note **E**)
   f. Venous/lymphatic vessel invasion (Note **E**)
3. Margins (Note **D** and **F**)
   a. Renal capsule
   b. Renal vessels/sinus
   c. Ureter
   d. Cut surface of kidney, if heminephrectomy
4. Regional lymph nodes
   a. Number
   b. Location, if possible
5. Tissues submitted for microscopic evaluation (Note **D**)
   a. Tumor (1 section for each centimeter of maximal tumor diameter and/or different gross appearances)[3]
   b. Non-neoplastic kidney (1 section minimum)

   c. Sections to document tumor extent
      (1) renal sinus
      (2) perirenal tissues/capsule
      (3) blood vessels
   d. All lymph nodes
   e. Margins, as appropriate (Note **D** and **F**)
   f. Adrenal gland (1 section minimum)
   g. Frozen section tissue fragment(s) (unless saved for special studies) (Note **A**)
6. Special studies (specify) (eg, histochemistry, immunohistochemistry, molecular analysis [specify type], cytogenetic analysis) (Note **C**)

C. Microscopic Evaluation[4]

1. Tumor
   a. Histologic type (Note **E**)
   b. Extent of invasion (Note **E**)
   c. Venous/lymphatic vessel invasion (Note **E**)
2. Margins (Note **D** and **F**)
   a. Renal capsule/sinus
   b. Renal vessels
   c. Ureter
   d. Cut surface of kidney, if heminephrectomy
3. Regional lymph nodes
   a. Number
   b. Number with metastasis (specify location, if possible; measure largest involved node)
4. Metastasis to other organ(s) or structure(s) (specify site) (Note **F**)
5. Additional pathologic findings, if present
6. Other tissue(s)/organs (eg, adrenal)
7. Results/status of special studies (specify) (Note **C**)
8. Comments
   a. Correlation with intraoperative consultation, as appropriate
   b. Correlation with other specimens, as appropriate
   c. Correlation with clinical information, as appropriate

IV. Radical Nephrectomy

A. Clinical Information

1. Patient identification
   a. Name
   b. Identification number
   c. Age (birth date)
   d. Sex
   e. Race
2. Responsible physician(s)
3. Date of procedure
4. Other clinical information
   a. Relevant history (eg, previous diagnoses and treatment, family history of renal tumors)
   b. Relevant findings (eg, imaging studies)
   c. Clinical diagnosis
   d. Procedure (eg, radical nephrectomy, with adrenalectomy, vena cava thrombectomy and lymphadenectomy)

e. Operative findings
f. Anatomic sites(s) of specimen (eg, left kidney)

B. Macroscopic Examination

1. Specimen
   a. Organs(s)/tissues(s) included
   b. Unfixed/fixed (specify fixative)
   c. Description of perirenal fat/Gerota's fascia
   d. Weight of adrenal gland, if present
   e. Kidney size (3 dimensions)
   f. Weight
   g. Length of ureter
   h. Other submitted tissues (weigh or measure, as appropriate) (eg, venous tumor thrombus, specimens from other organs)
2. Tumor(s) (including putative nephrogenic rests)
   a. Number
   b. Location
   c. Sizes(s)
   d. Descriptive characteristics (eg, solid/cystic, color, consistency, necrosis)
   e. Extent of invasion (Note **D**)
   f. Sinus invasion (Notes **D** and **E**)
   g. Renal vein invasion (Note **D**)
3. Margins (Notes **D** and **F**)
   a. Gerota's fascia
   b. Renal vessels
   c. Ureter
4. Regional lymph nodes (Note **F**)
   a. Number
   b. Location, if possible
5. Separately submitted tissues (specify)
6. Tissues submitted for microscopic evaluation
   a. Tumor (1 section for each centimeter of maximal tumor diameter and/or different gross appearances)[3]
   b. Uninvolved kidney (1 section minimum)
   c. Sections to document tumor extent (Note **D**)
      (1) sinus
      (2) ureter
      (3) renal capsule
      (4) perirenal tissues (including hilus and Gerota's fascia)
      (5) renal vessels (includes separately submitted tumor thrombus)
   d. All lymph nodes
   e. Margins, as appropriate (Note **D** and **F**)
   f. Adrenal gland (1 section minimum)
   g. Frozen section tissue fragment(s) (unless saved for special studies) (Note **A**)
   h. Other tissue(s), as appropriate
7. Special studies (specify) (eg, histochemistry, immunohistochemistry, molecular analysis [specify type], cytogenetic analysis) (Note **E**)

C. Microscopic Evaluation[5]

1. Tumor
   a. Histologic type (Note **E**)
   b. Extent of invasion (Note **E**)
   c. Venous/lymphatic vessel invasion (Note **E**)

2. Margins (Note **D** and **F**)
   a. Gerota's fascia
   b. Renal vessels
   c. Ureter
   d. Other(s), as appropriate
3. Regional lymph nodes (Note **F**)
   a. Number
   b. Number with metastasis (specify location, if possible; measure largest involved node)
4. Metastasis to other organ(s) or structure(s) (specify site) (Note **F**)
5. Additional pathologic findings, if present (Note **G**)
6. Other tissue(s)/organs
7. Results/status of special studies (specify) (Note **C**)
8. Comments
   a. Correlation with intraoperative consultation, as appropriate
   b. Correlation with other specimens, as appropriate
   c. Correlation with clinical information, as appropriate (Note **H**)

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 section 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 (up to 1 g or more) should be snap-frozen (liquid nitrogen or cold isopentane) in 2 or more vials, along with a separate portion of non-neoplastic kidney (at least 1 vial).[3] 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.

B. Fine-Needle Aspiration, Needle Biopsy, Wedge Biopsy

Fine-needle aspirations (FNA) of Wilms tumor specimens are of limited utility and are not encouraged, as the detection of anaplasia (Note **E**) may be obviated by sampling error. The distinction between a nephrogenic rest and Wilms tumor can seldom be made on the basis of needle biopsies. Moreover, in blastema-rich tumors, the characteristic triphasic histology of the tumor also may be absent due to sampling. In a tumor where histology remains the gold standard of diagnosis (Note **C**), FNA may not give one an accurate diagnostic classification. An otherwise stage I tumor is upstaged by performing a biopsy prior to nephrectomy.

C. Special Studies

The diagnosis of primary renal tumors in children remains largely based on the examination of hematoxylin-eosin (H&E)-stained sections. While some studies[1] suggest that p53 immunostaining may be a more sensitive predictor of poor outcome than histologic assessment of anaplasia, such studies are fraught with difficulties in interpreting the outside limits of "positivity," as well as with interinstitutional variability in

immunostaining techniques. Confirmation in larger studies using multiple techniques is needed.

No single cytogenetic or molecular abnormality has been consistently abnormal in Wilms tumor or its host, but constitutional deletions of the *WT-1* tumor suppressor gene at 11p13 often predispose the patient to development of Wilms tumors. WAGR syndrome (Wilms tumor, aniridia, genitourinary anomalies, and mental retardation) and Denys-Drash syndrome are characterized by the deletion or mutation of this gene. Intralobar nephrogenic rests (ILNR) are associated with WAGR and Denys-Drash syndrome. Perilobar nephrogenic rests (PLNR) are associated with Beckwith-Weidemann syndrome, Perlman syndrome, and hemihypertrophy.[6-8]

Genetic tests are often quite useful in the evaluation of several pediatric tumors arising in the kidney, which mimic Wilms tumor. These include the characteristic translocation of cellular mesoblastic nephroma, t(12;15), and peripheral primitive neuroectodermal tumor (PNET), t(11;22). Fluorescence in situ hybridization (FISH) study to detect the 22q11.2 deletion of malignant rhabdoid tumor of the kidney (RTK) may also be diagnostically useful. Neuroblastomas not infrequently present as renal primaries, and N-*myc* amplification detected by FISH may be important in such cases.

D. Handling of Renal Specimens

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 the necessary diagnostic features are preserved and properly examined.

1. *Nephrectomy specimens should be submitted intact by the surgeon.* The surface of the specimen should be photographed and inked prior to bivalving to facilitate the recognition of displacement artifacts from the smearing of tumor cells over the specimen surface during sectioning, as well as to evaluate margins. Bivalving will cause the capsule in a fresh kidney to retract, possibly altering the relationship between the tumor and the capsule or surgical margin.

2. The capsule from nephrectomy specimens must *never* be stripped. Invasion of the tumor into the capsule is a criterion in staging. In addition, nephrogenic rests are often subcapsular in location. The medial sinus margin is defined as the medial end of soft tissues surrounding the renal artery and vein.

3. Inspect the renal vein for tumor thrombus, as this is a common route by which Wilms tumor exits the kidney. Caution should be used in the evaluation of the margin of the renal vein that contains a thrombus. The vein often retracts after the surgeon sections it, leaving a protruding tumor thrombus, which may erroneously be considered a positive margin. If the thrombus itself is not transected, and if the margin of the vascular wall itself does not contain tumor, this surgical margin is interpreted as being negative.

4. The exact site from which each section or paraffin block is obtained may be documented by photograph, photocopy, or drawing. Often, this documentation is critical for recognizing staging problems and for the evaluation of focal versus diffuse anaplasia.

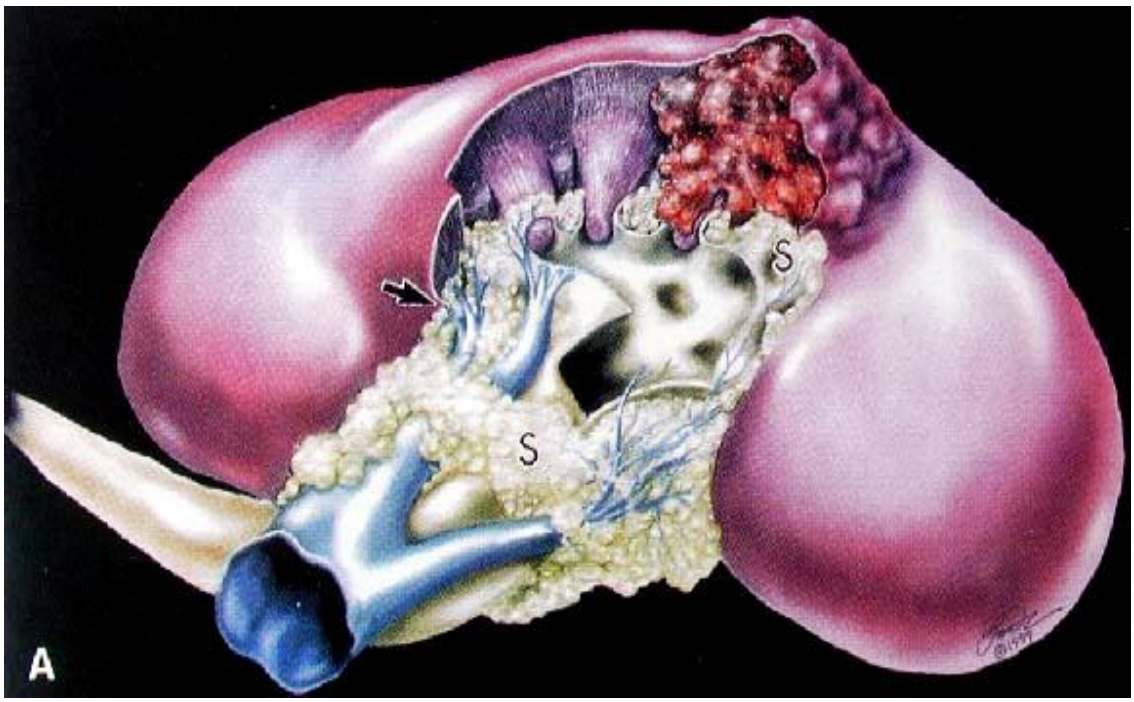

Figure 1A. Diagram showing the renal sinus fat (S) and its rich venous system that envelops the collecting system. The renal capsule terminates (arrow) just inside the vestibule of the hilus. (From: Bonsib SM, Gibson D, Mhoon M, Greene GF. Renal sinus involvement in renal cell carcinomas. *Am J Surg Pathol.* 2000;24(3):451-458. Reproduced with permission.)

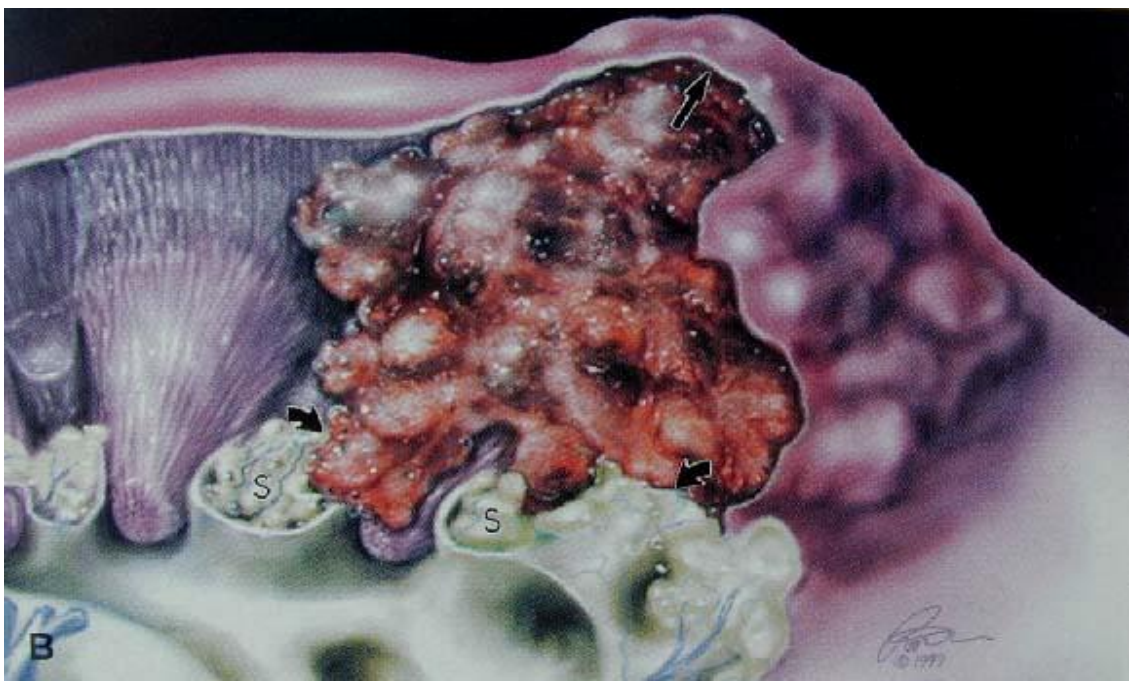

Figure 1B. A renal malignancy is constrained by the renal capsule (arrow), yet no fibrous capsule impedes its growth into the vascular tissue of the renal sinus (curved arrows). (From: Bonsib SM, Gibson D, Mhoon M, Greene GF. Renal sinus involvement in renal cell carcinomas. *Am J Surg Pathol.* 2000;24(3):451-458. Reproduced with permission.)

5. Take at least 1 microscopic section per centimeter of maximal tumor diameter, with additional sampling of any suspicious lesions.[3] The majority of random tumor sections should be taken from the periphery of the tumor, as this is where the invasive pattern of the tumor can be identified and its interface with the capsule and native kidney can be evaluated. Peripheral sections also demonstrate invasion of vessels within the intrarenal extension of the renal sinus. The renal sinus is that area in the hilum of the kidney occupied by the renal pelvis, as well as hilar vessels and fat (Figure 1). The renal cortex at the sinus lacks a capsule.[3] The most important sections are those taken from regions of the sinus adjacent to the tumor to demonstrate involvement (or lack of involvement) of sinus vessels.

6. For Wilms tumors that are multicentric, sample each nodule. More than 30% of Wilms nephrectomy specimens contain nephrogenic rests. Samples of native kidney with areas more pale than the usual parenchyma may reveal nephrogenic rests. Nephrogenic rests have important implications concerning the risk of contralateral Wilms tumor development and may have other syndromatic implications. At least 1 random section of normal kidney and possibly more may be taken to detect nephrogenic rests microscopically. The presence of multiple or diffusely distributed nephrogenic rests is termed “nephroblastomatosis.” Two fundamental categories of nephrogenic rests are recognized: intralobar (ILNR) and perilobar (PLNR). In addition to increased risk of tumor arising in the contralateral kidney, ILNR and PLNR have specific genetic implications (Note **C**). The topographic and microscopic distinction of PLNR and ILNR have been well described elsewhere.[6]

7. Nephrectomy weight may be an eligibility factor for some clinical trial protocols. Hence, this measurement is critical.

8. In addition to the capsular, vascular, and sinus sampling already described, routine sections taken for margins should include sampling of the distal ureter.

E. Microscopic Examination[4]

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 4% of all cases,[3] it is the major prognostic indicator and will place a tumor in an unfavorable histological category.

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. 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-predominate Wilms tumor. 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-predominate Wilms tumors show considerable histologic overlap with papillary renal cell carcinoma and metanephric adenoma (Note **G**).

Anaplasia
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 correlates with responsiveness to therapy rather than with aggressiveness. Therefore, tumors with anaplasia confined to the kidney, which are entirely excised, would be expected to demonstrate the same prognosis as favorable histology Wilms tumor of the same stage. Because of this distinction, criteria for focal versus diffuse anaplasia have been defined topographically and are rigorous. 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
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.
- Random biopsies are free of anaplasia.
- Anaplasia must be confined to 1 or more sharply localized regions within the primary intrarenal tumor site.
- Each focus of anaplasia must be surrounded on all sides by non-anaplastic tissue, and the remaining nonanaplastic tumor must not show severe nuclear unrest. (The same criterion holds for post-treatment nephrectomies.)

Diffuse Anaplasia
Diagnosis of diffuse anaplasia is warranted if *any* of the following are true.
- Anaplasia in tumor in any extrarenal site, including vessels of the renal sinus, extracapsular infiltrates, or nodal or distant metastases. Also anaplasia in intrarenal vascular involvement by tumor.
- Anaplasia in a random biopsy.
- Anaplasia unequivocally expressed in 1 region of the tumor, but with extreme nuclear pleomorphism approaching the criteria of anaplasia (extreme nuclear unrest) elsewhere in the lesion.

Renal Sinus Vascular Invasion
True tumor invasion is easy to confirm when the tumor fills the lumen or invades the vascular wall. Displacement artifact is also readily identified when it is present in arterial lumina, when it is accompanied by abundant displacement artifact elsewhere, or when ink is present within the aggregates. More difficult are foci of unattached tumor intermingling with fibrin and red cells, or free-floating rounded tumor fragments that are not associated with other displacement artifact. The presence of these foci in children with small, otherwise stage I tumors not treated with adjuvant chemotherapy are biologically significant and should upstage the patient. Intrarenal vascular invasion does not upstage a renal tumor.

F. Staging

The American Joint Committee on Cancer (AJCC) and International Union Against Cancer (UICC) TNM staging systems currently do not apply to Wilms tumor. The National Wilms Tumor Study Group (NWTSG) staging system for Wilms tumors is recommended and shown below.[5]

Stage I

- Tumor limited to kidney and completely resected.
- Renal capsule intact.
- Tumor not ruptured or biopsied prior to removal.
- No residual tumor apparent beyond margins of resection.
- Renal vein contains no tumor (intrarenal vessel involvement may be present).
- No lymph node involvement or distant metastases.

Stage II

- Tumor extends beyond kidney but completely resected.
- Regional extension of tumor (vascular invasion outside the renal parenchyma or within the renal sinus, and/or capsular penetration with negative excision margin).
- Operative tumor spill confined to flank (no peritoneal contamination).
- Tumor biopsy (except fine-needle aspiration) prior to surgery.

Stage III

- Nonhematogenous metastases confined to the abdomen (eg, tumor in regional lymph nodes), including tumor implants on or penetrating the peritoneum.
- Gross or microscopic tumor remains postoperatively (tumor at margins of resection).
- Tumor spill before or during surgery not confined to flank.
- Piecemeal excision of the tumor (removal in more than 1 piece).

Stage IV

- Hematogenous metastases or lymph node metastases outside the abdomino-pelvic region (beyond renal drainage system, eg, lung, liver).

Stage V

- Bilateral renal involvement at diagnosis. (Each side should also be staged separately, according to above criteria, as I through IV.)

G. Differential Diagnosis

Including Wilms tumor and its anaplastic variant, 3 other renal tumors – mesoblastic nephroma, clear cell sarcoma, and rhabdoid tumor – account for 95% of all primary renal tumors of childhood.[3] A more detailed differential diagnosis of pediatric renal tumors is provided elsewhere.[3,6]

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 corresponds to infantile fibromatosis; and “cellular” CMN (66% of cases), which corresponds to infantile fibrosarcoma and contains the characteristic t(12;15), resulting

in a fusion product detectable by reverse transcriptase polymerase chain reaction (RT-PCR).[9] Occasional cases (10%) are classified as "mixed" CMN owing to the presence of both histologic types. There is currently no consensus regarding the pathways through which mixed CMN may arise.

Approximately 10% of CMNs relapse. The substantial majority of CMNs that relapse are of the cellular subtype. Recurrences occur very rapidly, often within the first month of diagnosis. Virtually all relapses occur by 1 year of age. More than half are local recurrences; however, pulmonary metastases have been identified in 20% of those that relapse. Preliminary evidence suggests that renal sinus vascular involvement may be closely associated with lung metastasis. However, the primary determinant of outcome is the completeness of excision. Surgeons should be educated and encouraged to secure wide margins when resecting renal tumors in infants, particularly medial margins. Nonetheless, one can rarely be sure that the medial margin is clear; therefore, all cases 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. A genetic or histochemical feature specific to CCSK has been elusive. 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 has recently been reported by the National Wilms Tumor Study Group.[10] 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 following treatment with doxorubicin.[10] This underscores the importance of identifying this neoplasia to facilitate early administration of more effective chemotherapy regimens.

There are several variants of clear cell sarcoma of the kidney, among which the following are most important.

<u>Classical Pattern</u>

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 pre-existent 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 separates tumor cells, giving an appearance reminiscent of osteosarcoma. A similar change maybe seen in rhabdoid tumor of the kidney.

Epithelioid Pattern
The epitheliod pattern his 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 (RTK)
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 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. Rhabdoid tumor of the kidney 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.[11] 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 FISH, but no other diagnostically useful molecular tests are currently available.

H. Associated Syndromes[6-8]
Beckwith-Wiedemann syndrome
Perlman familial nephroblastomatosis syndrome
Denys-Drash syndrome
Trisomy 18

Neurofibromatosis
Bloom syndrome
WAGR syndrome (Wilms tumor, aniridia, genitourinary abnomalities, mental retardation)

References

1. Lahoti C, Thorner P, Malkin D, Yeager H. Immunohistochemical detection of p53 in Wilms tumors correlates with unfavorable outcome. *Am J Pathol.* 1996;148:1577-1589.
2. Coppes MJ, Arnold M, Beckwith JB, et al. Factors affecting the risk of contralateral Wilms tumor development: a report from the National Wilms Tumor Study Group. *Cancer.* 1999;85:1616-1625.
3. Zuppan CW. Handling and evaluation of pediatric renal tumors. *Am J Clin Pathol.* 1998;109(suppl 1):S31-S37.
4. Faria P, Beckwith JB, Mishra K, et al. Focal versus diffuse anaplasia in Wilms tumor - new definitions with prognostic significance: a report from the National Wilms Tumor Study Group. *Am J Surg Pathol.* 1996;20:909-920.
5. Beckwith JB. National Wilms Tumor Study: an update for pathologists. *Pediatr Dev Pathol.* 1998;1:79-84.
6. Beckwith JB. Renal neoplasms of childhood. In: Sternberg S, ed. *Diagnostic Surgical Pathology.* 3rd ed. Philadelphia, Pa: Lippincott, Williams and Wilkins; 1999:1825-1852.
7. Beckwith JB. Nephrogenic rests and the pathogenesis of Wilms tumor: developmental and clinical considerations. *Am J Med Genet.* 1998;79:268-273.
8. Charles AK, Brown KW, Berry PJ. Microdissecting the genetic events in nephrogenic rests and Wilms tumor development. *Am J Pathol.* 1998;153:991-1000.
9. Knezevich SR, Garnett MJ, Pysher TJ, et al. ETV6-NTRK3 gene fusion and trisomy 11 establish a histogenetic link between mesoblastic nephroma and congenital fibrosarcoma. *Cancer Res.* 1998;58:5046-5048.
10. Argani P, Perlman EJ, Breslow NE, et al. Clear cell sarcoma of the kidney: a review of 351 cases from the National Wilms Tumor Study Group Pathology Center. *Am J Surg Pathol.* 2000;24:4-18.
11. Biegel JA, Zhou J-Y, Rorke LB, et al. Germline and acquired mutations of INI1 in atypical teratoid and rhabdoid tumors. *Cancer Res.* 1999;59:74-79.

Bibliography

Husain AN, Pysher TJ, Dehner LP. The kidney and lower urinary tract (Chapter 18). In: Stocker JT, Dehner LP, eds. *Pediatric Pathology.* 2nd ed. Philadelphia, Pa: Lippincott, Williams and Wilkins; 2001.

Murphy WM, Beckwith JB and Farrow GM. Tumors of the kidney, bladder, and related urinary structures. In: *Atlas of Tumor Pathology*. 3rd series. Fascicle 11. Washington, DC: Armed Forces Institute of Pathology; 1994.