Intrarenal Extension into sinus 

Document Capsular Penetration

Renal Sinus Tumor

Precautions in handling pediatric renal tumor cases

1. Discourage frozen section diagnosis
2. Encourage surgeons to submit specimen intact
3. Weigh specimen and ink external surface
4. Identify any capsular breaks
5. Make a clean slice through center of kidney/tumor.
6. Wash knife blade between each cut to prevent knife metastasis
7. Take photographs before and after overnight fixation
8. Freeze tumor and normal kidney for Children's Oncology Group (COG) protocols (biology studies). Submit for cytogenetics and fluorescence in situ hybridization (FISH)/molecular studies where indicated
9. Submit multiple sections with most from tumor-kidney interface to evaluate renal sinus
10. Submit resection margins of renal vein, artery, and ureter
11. Map the sections submitted on the photograph or on paper for orientation
12. Evaluate all unusual areas of tumor
13. Submit sections of nontumoral kidney and any NR if present
14. In cases of resection after chemotherapy, map the sections to assess response to chemotherapy
Pediatric Renal Tumor Staging

**Stage I**
- Limited to Kidney & Completely Resected
- Intact Renal Capsule
- No Previous Rupture or Biopsy
- Renal Sinus Vessels Not Involved
- No Tumor At or Beyond Capsule

**Stage II**
- Tumor Completely Resected
- No Tumor At or Beyond Capsule
- Tumor Extends Beyond Kidney
  - Renal Capsule Penetration
  - Extensive Invasion of Renal Sinus Soft tissue
  - Vascular Invasion Outside Renal Parenchyma, Including Renal Sinus

**Stage III**
- Residual Hematogenous Tumor Confined to Abdomen Present After Surgery
  - Abdominal or Pelvic Lymph Nodes
  - Penetration Through Peritoneal Surface
  - Peritoneal Surface Tumor Implants
  - Nonresectable Tumor Infiltration of Vital Structures
  - Prior Biopsy
  - Tumor Spillage of Any Degree or Localization Before or During Surgery
  - Tumor Removed in Greater Than One Piece

**Stage IV**
- Hematogenous Metastases (Lung, Liver, Bone, Brain...)
- Lymph Node Involvement Outside Abdomen or Pelvis

**Stage V**
- Bilateral Renal Involvement at Diagnosis
- Each Side Should Be Staged Individually According to Staging Criteria
**Staging**

- Rupture or spillage is stage 3, regardless of degree or location
- Biopsy (including FNA) prior to removal of kidney is a criteria for stage 3
- Renal Cell Carcinoma uses a different staging system
- To be eligible as stage 1 for some treatment arms, lymph nodes must be available

**LOH at 1p and/or 16q**

- **Stage 1&2**
- **Stage 3&4**
### Major Change in New Protocols: FHWT: Stratification by LOH for 1p, 16q

<table>
<thead>
<tr>
<th>LOH Status</th>
<th># pts</th>
<th># relapses</th>
<th>4 yr RFS</th>
<th>RR</th>
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<tbody>
<tr>
<td>Neither</td>
<td>675</td>
<td>53</td>
<td>90%</td>
<td>----</td>
</tr>
<tr>
<td>1p only</td>
<td>51</td>
<td>8</td>
<td>81%</td>
<td>1.85</td>
</tr>
<tr>
<td>16q only</td>
<td>105</td>
<td>13</td>
<td>85%</td>
<td>1.46</td>
</tr>
<tr>
<td>Both</td>
<td>43</td>
<td>11</td>
<td>71%</td>
<td>5.11*</td>
</tr>
</tbody>
</table>

*p < 0.01

### Effect of LOH on Patient Outcome (NWTS-5)

<table>
<thead>
<tr>
<th>Stage/LOH status</th>
<th>4-yr RFS (%)</th>
<th>p</th>
<th>4-yr OS (%)</th>
<th>p</th>
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<tbody>
<tr>
<td><strong>Favorable histology stage I/II</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No LOH</td>
<td>91.2</td>
<td>98.4</td>
<td></td>
<td></td>
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<tr>
<td>LOH 1p only</td>
<td>80.4</td>
<td>0.02</td>
<td>91.2</td>
<td>0.02</td>
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<tr>
<td>LOH 16q only</td>
<td>82.5</td>
<td>0.01</td>
<td>98.1</td>
<td>0.6</td>
</tr>
<tr>
<td>LOH 1p and 16q</td>
<td>74.9</td>
<td>0.001</td>
<td>90.5</td>
<td>0.01</td>
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<tr>
<td><strong>Favorable histology stage III/IV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No LOH</td>
<td>83.0</td>
<td>91.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOH 1p only</td>
<td>89.0</td>
<td>0.37</td>
<td>97.6</td>
<td>0.36</td>
</tr>
<tr>
<td>LOH 16q only</td>
<td>85.3</td>
<td>0.67</td>
<td>92.0</td>
<td>0.76</td>
</tr>
<tr>
<td>LOH 1p and 16q</td>
<td>65.9</td>
<td>0.01</td>
<td>77.5</td>
<td>0.04</td>
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</table>

Abbreviations: LOH, loss of heterozygosity; RFS, relapse-free survival; OS, overall survival.
Tumor Classification Protocol

**Biology studies**
- Low risk FHWT
- High risk FHWT
- High risk renal tumors
- Bilateral Wilms

**Diagnosis, stage**
- Stage 1, 2
- Stage 3 + LOH, Stage 4
- CCSK, RCC, RT (all sites), Anaplastic WT
- Includes DHPLN

**Abbreviations:** yrs, years; LOH, loss of heterozygosity; FHWT, favorable histology Wilms tumor; DA, diffuse anaplastic; RCC, renal cell carcinoma; ECA, etoposide/cisplatin/actinomycin; H, hydroxyurea; V, vincristine; DA-IFRT, DA chemotherapy x 25 weeks; DA-IFRT/DA, DA chemotherapy followed by DA therapy; DHPLN, direct hyperplastic papillary nephroblastoma; DA-IFRT/DA-IFRT, DA chemotherapy followed by DA chemotherapy; DA-IFRT/DA-IFRT, DA chemotherapy followed by DA chemotherapy; DA-IFRT/DA-IFRT, DA chemotherapy followed by DA chemotherapy.

*This risk classification scheme was designed for treatment assignment in the context of clinical trials. Some of these treatment regimens are not established as standard of care.*
Children’s Oncology Group (COG)
Favorable histology Wilms tumor
No evidence of anaplasia

Focal anaplastic Wilms tumor
Anaplasia confined to one or more discrete sites within the primary tumor with no extrarenal involvement
No nuclear unrest outside anaplastic foci

Diffuse anaplastic Wilms tumor
Nonlocalized anaplasia
Anaplasia in invasive sites or extrarenal deposits
Localized anaplasia with severe nuclear unrest
Anaplasia in a random biopsy specimen
Anaplasia involving the edge of one or more sections
Non-Wilms renal tumors are excluded from this table.

International Society of Pediatric Oncology (SIOP)
Low-risk
Completely necrotic Wilms tumor
Cystic partially differentiated nephroblastoma

Intermediate-risk
Wilms tumor of epithelial, stromal, mixed, or regressive types
Focal anaplastic Wilms tumor (see COG definitions)

High-risk
Blastemal type Wilms tumor
Diffuse anaplastic Wilms tumor (see COG definitions)
Gain of 1q Is Associated With Inferior Event-Free and Overall Survival in Patients With Favorable Histology Wilms Tumor

A Report From the Children’s Oncology Group

![Graph 1](image1.png)

**Figure 1.** Event-free survival is shown stratified by 1q gain. MLPA indicates multiplex ligation-dependent probe amplification.

![Graph 2](image2.png)

**Figure 2.** Overall survival is shown stratified by 1q gain. MLPA indicates multiplex ligation-dependent probe amplification.

Molecular Profiling Reveals Frequent Gain of MYCN and Anaplasia-Specific Loss of 4q and 14q in Wilms Tumor

Richard D. Williams,1 Reem Alsadi,2 Rachael Nazrnan,1 Alan Mackay,1 Tanim Chughtai,1 Suzanne Little,4 Sandra N. Hing,1 Kerry Fenwick,1 Alan Ashworth,3 Paul Grundy,3 James R. Anderson,1 Jeffrey S. Dome,1 Elizabeth J. Portman,1 Chris Jones,1 and Kathy Pritchard-Jones1

![Graph 3](image3.png)

**Figure 3.** Fraction gained or lost.
MYCN Amplified in Anaplastic WT

WT1 Mutation and 11p15 Loss of Heterozygosity Predict Relapse in Very Low-Risk Wilms Tumors Treated With Surgery Alone A Children’s Oncology Group Study

Elizabeth J. Perelman, Paul E. Grady, James R. Andrews, Lawrence I. Sennings, Daniel M. Green, Jeffrey A. Dunn, Robert C. Steinberger, R. Curtis Rutanen, and Vital Wolf

Table 1: Mutation and LOH Analysis

<table>
<thead>
<tr>
<th></th>
<th>11p15 LOH</th>
<th>WT1 Mutation</th>
<th>11p15 LOH Methylation</th>
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<tr>
<td></td>
<td>LOH</td>
<td>H</td>
<td>ROH ND</td>
</tr>
<tr>
<td>Relapse n = 56</td>
<td>16</td>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td>No relapse n = 46</td>
<td>10</td>
<td>1</td>
<td>29</td>
</tr>
<tr>
<td>Lung n = 7</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>OR bed n = 3</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: LOH, loss of heterozygosity; H, constitutional homozygosity for all five loci; ROH, retention of heterozygosity; LOI, loss of imprinting; ROI, retention of imprinting; ND, not done; OR, operative.
New Therapeutic Approaches

- Stratification of Wilms tumor by histology, stage, age, and LOH for 1p and 16q
- Bilateral Wilms tumor will receive pre-operative chemotherapy, and subsequent therapy will depend on the pathology.
- Treatment for stage 1 anaplasia will be more aggressive
- Renal cell carcinoma is included
- ALL non-CNS rhabdoid tumors are included

FHWT <550g & <24 Months, Stage I

- NWTS5: 75 patients received no adjuvant therapy
  - 8 recurrences; 2 metachronous contralateral WT
  - 2 year disease-free survival of 86.5%
- Therapeutic arm closed prematurely
- Subsequently, overall survival shown to be 100%
  - (Green et al. J Clin Oncol, 2001)

Protocols contain a no-adjuvant therapy arm for “tiny tumors” if regional lymph nodes submitted.
Postoperative Therapy Determined by Pathology

- **Low Risk: Completely necrotic**
  - Rare non-proliferative tubules allowed
  - No further therapy if excised

- **High Risk: Blastemal predominant**
  - Viable tumor > 1/3 of mass
  - 2/3 of viable tumor blastemal
  - More aggressive chemotherapy

- **Intermediate Risk**
  - Everything else
  - Continuation of VAD for 6 more weeks

- **Anaplastic**
  - More aggressive chemotherapy

WT: Molecular Features

- WT1 & WT2 on 11p (10% of Tumors)
- PAX6 on 11p – Aniridia
- Familial WT Predisposition
  - FWT1 on 17q & FWT2 on 19q
- P53 – Adverse Outcome with High Expression
- LOH 1p &16q Adverse Outcome

- HER – Role in Renal Tubule Branching Morphogenesis – Associated with Epithelial Differentiation in WT
- Tumor Progression Genes
  - TRIM22, CENPF
  - MYCN, CTGF
  - RARRES3, EXH2
Diagnostic Difficulties in WT

- Biopsy – Difficult to Differentiate from Nephrogenic Rests (NR)
- Post-Chemotherapy – Difficult to Differentiate Treated WT from NR
- Blastemal Predominant WT – Difficult to Differentiate from Small Round Cell Tumor
- Pure Stromal WT – Confused with Mesoblastic Nephroma
- Frozen Section Discouraged
- Neuroblastoma Involving Kidney – May Require Immunostains (NB84, PGP9.5, WT1, etc)
CLEAR CELL SARCOMA OF THE KIDNEY

- 4% of Renal Tumors
- Peak 2nd Yr of Life
- 1.6M:1.0 F Gender Ratio
- Metastases: Bone (40% of cases at diagnosis), Brain, Lung, Skeletal Muscle, Spinal Cord
- “Bone Metastasizing Tumor of the Kidney”: Highly Aggressive Tumor

CLEAR CELL SARCOMA

- Monomorphic Polygonal Clear to Eosinophilic Cells
- Variants: Epithelioid, Spindled, Myxoid, Pericytomatos, Sclerosing, Palisading, Cystic & Anaplastic
- Difficult Dx When Presents at Distant Sites
- Vimentin Only
- Cytogenetics NonSpecific
- Origin: Medullary Pyramids or Central Renal Parenchyma
Clear Cell Sarcoma of Kidney

- CCSK six year Survival
  - 97-100% stage 1
  - 75% stages 2,3
  - 50% stage 4

- New Protocols: Radiation eliminated for patients with stage I disease if regional lymph nodes submitted