HANDBOOK FOR CHILDREN WITH RENAL TUMORS
Updated Spring 2014

This handbook is created from the COG Renal Biology Protocol, AREN 03B2, and clinical protocols. They are AREN 0532- Very Low, Low and Standard Risk Favorable Histology Wilms (closed Oct 2013), AREN 0533- Higher Risk Favorable Histology Wilms (closed May 2013), AREN0321- High Risk Renal Tumors, (closed Nov 2013) and AREN 0534- Bilateral Wilms. Even with no open clinical protocols, new patients with that category may still be enrolled on the Biology Protocol.

This handbook extracts and organizes surgically relevant information from all of these protocols into one document. It is organized around generalized topics of interest to the surgeon, and begins with a One Minute Review, which outlines the bare minimum facts necessary to proceed with surgery. There follows several sections with surgically relevant information delivered verbatim with citation. The table of contents at the left margin indicates bookmarks for a given section, so you can click on that topic for immediate review

Notable in these Renal Protocols?
-Staging from Biology: These protocols create risk based treatment groups on the basis of histopathology, surgical stage, loss of heterozygosity, and response to treatment. The Renal Tumors Biology concept is new, and mandatory. Enrollment on Biology will stratify the patient into one of the clinical protocols.
-Surgery Only: The Surgery Only stratus is reopened in the Very Low Risk protocol for children less than 2 years, tumor weight less than 550 gm. However, lymph nodes MUST be biopsied, and confirmed no disease to be enrolled. If not biopsied, then the child is not eligible.
-Contra lateral Exploration: Contra lateral exploration is not necessary if preoperative normal.
-Biopsy Rupture, spillage, and biopsy is Stage III, not Stage II.
-Bilateral Tumors treated with upfront 3 drug chemotherapy. Operation, with goal to spare normal renal parenchyma by partial nephrectomy, reserved for Week 6 or 12.
-Pulmonary Mets: Staged with Chest CT. If pulmonary mets present, chemotherapy will be given. XRT will be given only for residual pulmonary disease on repeat imaging at 6 weeks.

These documents will be updated periodically to reflect the opening of new protocols. Surgery Study members are listed below, and should be contacted for questions. Any and all suggestions for improvement are welcome. The Chair of the Renal Tumors Surgery Steering Committee is Peter Ehrlich.

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RENAL TUMORS- ONE MINUTE REVIEW

STAGES

I Tumor limited to kidney, completely resected.
II Tumor extends beyond kidney, completely resected.
III Residual non-Hematogenous tumor present, confined to abdomen or retroperitoneal lymph node involvement.
IV Hematogenous metastases (lung, liver, bone, brain) or extraabdominal LN metastases.
V Bilateral renal involvement.

SURGICAL PRINCIPLES

Stages I-IV

Complete abdominal exploration. Unilateral radical nephrectomy with lymph node sampling via transperitoneal incision. Avoid rupture or spillage by use of adequate incision. Flank incision should not be utilized. Palpate renal vein and IVC for extension. Visualization and palpation of contralateral kidney not necessary if imaging normal. Ureter is ligated and divided as low as conveniently possible. Titanium clips used only to identify residual tumor, margins of dissection, and suspicious areas. **Do not biopsy tumor.**

Lymph node sampling should include renal hilar, paraaortic and/or paracaval nodes, as well as any suspicious nodes. For tumors believed unresectable at initial operation, adequate biopsy should be performed.

Stage V

No initial biopsy. Start with upfront 3 drug Chemotherapy. Reevaluate at 6 wks for possible biopsy/resection (<50% reduction in size/resectable), vs continued chemotherapy with operation at 12 weeks.

TISSUE HANDLING

Do Not Bivalve or otherwise disrupt capsule in OR. **Send intact specimen FRESH**

STAGING

AREN 03B2 5.3.1 /AREN 0532 APPENDIX III

5.3.1.1 Wilms tumor, rhabdoid tumor of the kidney, clear cell sarcoma of the kidney:

Stage I - Tumor limited to kidney, completely resected. The renal capsule is intact. The tumor was not ruptured or biopsied prior to removal. The vessels of the renal sinus are not involved. There is no evidence of tumor at or beyond the margins of resection. NOTE: For a tumor to quality for certain therapeutic protocols as Stage I, regional lymph nodes must be examined microscopically.

Stage II - The tumor is completely resected and there is no evidence of tumor at or beyond the margins of resection. The tumor extends beyond kidney, as is evidenced by any one of the following criteria:

- There is regional extension of the tumor (i.e. penetration of the renal capsule, or extensive invasion of the soft tissue of the renal sinus, as discussed below)
- Blood vessels within the nephrectomy specimen outside the renal parenchyma, including those of the renal sinus, contain tumor.
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Note: Rupture of spillage confined to the flank, including biopsy of the tumor, is no longer included in Stage II and is now included in Stage III.

Stage III - Residual non-hematogenous tumor present following surgery, and confined to abdomen. Any one of the following may occur:

- Lymph nodes within the abdomen or pelvis are involved by tumor. (Lymph node involvement in the thorax, or other extra-abdominal sites is a criterion for stage IV),
- The tumor has penetrated through the peritoneal surface,
- Tumor implants are found on the peritoneal surface,
- Gross or microscopic tumor remains post-operatively (e.g., tumor cells are found at the margin of surgical resection on microscopic examination),
- The tumor is not completely resectable because of local infiltration into vital structures,
- Tumor spillage occurring either before or during surgery,
- The tumor was biopsied (whether, tru-cut, open or fine needle aspiration) before removal,
- Tumor is removed in greater than one piece (e.g. tumor cells are found in a separately excised adrenal gland; a tumor thrombus within the renal vein is removed separately from the nephrectomy specimen).

Stage IV - Hematogenous metastases (lung, liver, bone, brain, etc.), or lymph node metastases outside the abdomino-pelvic region are present. (The presence of tumor within the adrenal gland is not interpreted as metastasis and staging depends on all other staging parameters present).

Stage V - Bilateral renal involvement by tumor is present at diagnosis. An attempt should be made to stage each side according to the above criteria on the basis of the extent of disease.

5.3.1.2 Renal Cell Carcinoma Staging for Renal Cell Carcinoma is done in the TNM system:

T--Primary Tumor

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

T1 Tumor 7.0 cm or less in greatest dimension, limited to the kidney

T2 Tumor more than 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's fascia

- T3a Tumor invades adrenal gland or perinephric tissues but not beyond Gerota's fascia
- 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's 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 or N1	M0
Stage IV	T4	N0, N1	M0
	Any T	N2	M0
	Any T	Any N	M1

5.3.2 Surgical Principles

Stages I-IV. Complete abdominal exploration. A unilateral radical nephrectomy with lymph node sampling via transperitoneal incision is the surgical procedure. Palpate renal vein and IVC for extension. Do not biopsy tumor if a total nephrectomy can be performed since this is a criterion for Stage III. Avoid rupture or spillage by use of an adequate abdominal or thoracoabdominal incision. **Flank incisions should not be utilized.** Ureter is ligated and divided as low as conveniently possible. Titanium clips used to identify residual tumor. Lymph node sampling should include renal hilar and para-aortic, and/or paracaval nodes as well as any additional suspicious nodes. For tumors deemed inoperable at surgical exploration, adequate biopsy is obtained.

Stage V. (0534, Section 4.0 Treatment Plan)
Primary excision of the tumor at diagnosis is discouraged. However, patients with BWT who undergo nephrectomy or partial nephrectomy at diagnosis are eligible for enrollment. **Open renal biopsies at diagnosis are not recommended due to the risk of tumor spill and the designation of Stage III local disease after biopsy. Patients are eligible for enrollment on AREN03B2 without an initial biopsy at diagnosis.** If biopsies are obtained, a posterior approach needle biopsy is advised to limit contamination of the peritoneal cavity. Patients with multicentric unilateral Wilms tumor at risk for developing metachronous tumors should not undergo biopsy prior to treatment. Solitary peripheral renal lesions less than 2 cm in diameter, however, can be completely excised at diagnosis.

After six weeks of chemotherapy, the patient will be reimaged to determine response to chemotherapy. If there is less than 50% response to the chemotherapy, bilateral open renal biopsies are recommended. The 50% reduction in the tumor size as the cutoff for Week 6 surgery is based on the WHO criteria (bidimensional) outlined in the imaging section. Open biopsies are recommended because they are more accurate than percutaneous needle biopsies when assessing anaplasia. The goal of the biopsy is to assess tumor histology of nonresponding tumors. The

histology of the biopsy will determine whether additional chemotherapy is warranted before proceeding with surgery or if a change in the chemotherapy regimen is needed.

5.3.1.3 Tissue Handling
Operating Room personnel should not put the tissue into fixative. Tissues should be as sterile as possible and should be brought to the Pathology Department quickly (by special messenger if necessary). It may be appropriate to hold occasional meetings of surgical, laboratory, and clinical personnel to emphasize the urgency of processing these specimens rapidly, preferably within twenty minutes.

5.3.2 Operative Procedure for Primary Tumor

5.3.2.1 Primary Nephrectomy, Stage I-IV
A generous transabdominal, transperitoneal or thoracoabdominal incision is recommended for adequate exposure. Complete exploration of the abdomen should be performed. A radical nephrectomy is performed with the ureter divided as distally as possible. Routine exploration of the contralateral kidney is not necessary if technically adequate imaging does not suggest a bilateral process. (For surgical guidelines for bilateral tumors see next section) If the initial imaging studies are suggestive of a lesion on the contralateral kidney, the contralateral kidney should be formally explored to rule out bilateral involvement. This should be done prior to nephrectomy since the diagnosis of bilateral disease dramatically alters the therapeutic approach and may contra indicate initial nephrectomy. To do this exploration adequately, the colon and its mesentery should be mobilized from the anterior surface of the contralateral kidney, Gerota's fascia incised, and the kidney turned forward to palpate and visualize both its anterior and posterior surfaces. Any areas suggestive of bilateral involvement should be biopsied. See procedures for tumor biopsy below.

To expose the primary tumor, the lateral peritoneal reflection is then opened, and the colon is reflected medially. A plane is established outside of Gerota's fascia by sharp and blunt dissection. Before mobilizing the primary tumor, an attempt should be made to dissect, expose and ligate the renal vessels in order to lessen the chance of hematogenous spread of tumor cells while removing the tumor. **Preliminary ligation should not be pursued if technically difficult or dangerous**. The adrenal gland may be left in place if it is not abutting the tumor; but, if the mass arises in the upper pole of the kidney, the adrenal gland should be removed with the neoplasm. The ureter is ligated and divided as low as conveniently possible, but it is not necessary to remove the ureter completely. The tumor and the uninvolved portion of the kidney are mobilized and removed intact. Any enlarged or suspicious lymph nodes should be included with the specimen.

The use of titanium clips is strongly recommended to identify gross residual tumor. Clips should not be used for hemostasis and those placed for roentgenographic identification or radiation therapy portals should be limited to the minimum number necessary. Metallic clips can interfere with the CT scan. Clips are best applied by placing a non-absorbable suture in the structure to be marked, and attaching the clip to the suture. In general four small clips should be sufficient to delineate the margins of the tumor.

Any suspicious areas that could represent metastases should be biopsied, the site(s) identified with small titanium clips so that the locations can be determined later by roentgenograms.

The involved areas should be drawn on the diagram in the surgical checklist. The specimen should be specifically identified as to the site from which it was removed.

5.3.2.2 Contiguous Organs

Wilms tumors are frequently adherent to adjacent organs. In the majority of cases, there is not frank invasion by the tumor. Radical en bloc resection, e.g. partial hepatectomy is not generally warranted. Extensive resection including multiple organs, e.g. spleen, pancreas, and colon, is also not advised as this is associated with an increased frequency of complications. If removal of a small section of diaphragm, psoas muscle, or tip of the pancreas allows the tumor to be removed intact, then proceed.

5.3.2.3 Partial Nephrectomy (for Stages I-IV)

Partial nephrectomy is not indicated in the routine patient with unilateral Wilms tumor. The exception is the child with a Wilms tumor-predisposing syndrome (eg. WAGR, Beckwith Wiedemann, Denys Drash etc) who although presenting with a unilateral tumor is predisposed to the subsequent development of contralateral disease. Hence, such children need to be managed with a renal sparing approach as for bilateral tumors and should be enrolled and managed on AREN0534.

5.3.2.4 Lymph Node Documentation

The presence or absence of disease in hilar and regional lymph nodes is an extremely important factor in accurate staging and therefore appropriate treatment. Routine lymph node sampling from the renal hilum and the paracaval or paraaortic areas must be done for accurate staging and will be a requirement of eligibility for the surgery-only therapy strata on AREN0532. Involved or suspicious lymph nodes should be excised. Formal lymph node dissection is not recommended. Label the nodes carefully for separate microscopic examination. All lymph nodes removed should be identified on the surgical check list and the accompanying diagram.

5.3.2.5 Assignment of Surgical Stage

The surgeon should assign a "local-regional stage" to the tumor based solely on the operative findings and findings on pathologic examination. Knowledge of distant metastases does not influence local surgical staging. For example, the patient would be evaluated as "surgical stage III" if there were obviously positive lymph nodes even if it were known that pulmonary metastases were also present.

5.3.2.6 Tumor Biopsy

Routine pre-nephrectomy tumor biopsies are contraindicated. Studies have shown a higher risk of recurrence in patients who had tumor spills or ruptures irrespective of the cause or extent of the soiling. These events result in an increased risk of local recurrence and increased adjuvant

therapy with those attendant risks. Tumor biopsy prior to nephrectomy is considered local spill which results in children receiving additional chemotherapy (dactinomycin) and radiation therapy (10cGy).

Preoperative and intraoperative biopsies are therefore contraindicated and should only be performed when a tumor is deemed unresectable. If a biopsy is obtained, a posterior approach is advised to limit contamination of the peritoneal cavity. Needle biopsies are acceptable.

5.3.2.7 Tumor Spillage

It is important for accurate staging to document the extent of any peritoneal soilage by tumor since this will determine the extent of the need for radiation therapy. The peritoneum shall be considered "soiled" if there has been a biopsy (either pre operative or intra operative) in a tumor that is subsequently removed at initial surgery, if there has been preoperative rupture, if there is a tumor spill or if the tumor has been removed in more than one piece. Local spills are defined as those limited to the renal fossa. Diffuse spills are those occurring beyond these limits. All instances of soilage will be classified as stage III, but local soilage will be treated with flank irradiation only while diffuse soilage will be managed with whole abdominal irradiation field.

Spillage refers to transgression of the tumor capsule during operative removal whether accidental, unavoidable or by design. Tumors and adherent tissues that are removed en bloc should produce no tumor spill. However, tumor tissue may be cut across during removal of adherent structures or during removal of lymph nodes. Tumors that are removed in more than one piece, the neoplastic tissue having been cut across in the process, shall be considered to have spilled. Spill would also occur if the surgeon transected the renal vein or ureter at the site of tumor extension. In any of these instances, the surgeon should indicate whether in their opinion the peritoneal soilage was local (confined to the renal fossa) or diffuse.

Preoperative percutaneous needle biopsy from the anterior or posterior approach shall be considered local spillage. Open incisional biopsy prior to nephrectomy shall be considered a local spill unless, in the surgeon's judgment, the whole peritoneal cavity has been soiled in the process. The technique and timing of biopsy should be described fully in the operative note to assist reviewers in assessing the prognostic impact of such biopsies.

Rupture refers to either the spontaneous or post-traumatic rupture of the tumor preoperatively with the result that tumor cells are disseminated throughout the peritoneal cavity. Bloody peritoneal fluid shall be considered a sign of rupture, whether or not gross or microscopic tumor is identified in the fluid. There are times when the tumor may rupture posteriorly and the perforation is confined to the retroperitoneal space, thus qualifying as local soilage. When a hematoma is present, it is assumed that tumor cells will spread with the blood. If primary nephrectomy is undertaken, this increases the risk of contamination of the peritoneal space. Staging of such patients is problematic. The superior, inferior, medial and lateral margins of the associated hematoma should be described fully in the operative note, and the margins marked with titanium clips. Tumor may penetrate the kidney capsule, and the overlying peritoneum, the raw neoplastic tissue surface being in free communication with the peritoneal cavity. This shall be considered diffuse soilage. Separate, distinct nodules of tumor on the peritoneal or serosal surfaces, at a distance from the primary neoplasm ("satellite implants") shall be considered a sign of diffuse soilage.

Complete description of all techniques is essential. Please provide clear statements regarding how soilage of the peritoneal cavity occurred, and unequivocal opinion regarding whether soilage was diffuse or local.

When tumor extends into the renal vein or inferior vena cava, a precise description of the technique of removal should be given in the operative note. It must be stated in the operative report if the intravascular tumor extension was removed en bloc or if tumor was transected during the resection. It must also be clear whether the tumor thrombus has been removed completely and if there is evidence of either adherence or invasion of the vein wall.

5.3.2.8 Renal Vein/Inferior Vena Cava

Vascular invasion of the renal vein, cava and atrium presents special surgical challenges, and, since these tumors will often respond to preoperative therapy, management requires careful consideration. Renal vein involvement has been noted in 11% of cases (most often detected at operation) and caval and atria involvement in 5% of Wilms tumor cases. The pre operative ultrasound and CT scan will usually identify intravascular tumor extension but the renal vein and inferior vena cava should still be palpated carefully before ligation to rule out extension of the tumor into the vein.

Tumor extension into the renal vein and proximate inferior vena cava can in most cases be removed en-bloc with the kidney. However, primary resection of tumors that extend up the inferior vena cava above the level of the hepatic veins and particularly to the atrium is associated with higher operative morbidity. In these circumstances, preoperative chemotherapy decreases the size and extent of the tumor thrombus without increasing its adherence to the vascular wall, thereby facilitating subsequent excision.

The tumor that extends into the renal vein and cava may simply extend as a floating attachment and can then be “fished out”. Control of the renal vein and cava above and below the tumor with vessel loops is necessary. Silk 2-0 stitches can then be placed on either side of the renal vein. This will help with vascular control and limit bleeding. The tumor and kidney should be completely mobilized prior to removing vascular thrombus. A venotomy is then done and the tumor pulled out of the vein. A foley balloon technique can also be used to pull out the tumor. The tumor should not be transected.

In other instances the tumor may be fixed to the vascular lumen. Extraction is more difficult and a larger venotomy maybe required. A similar technique used for removing plaque for a carotid endarterectomy is helpful to lift the tumor off the vein wall. If after preoperative chemotherapy the tumor still extends above the hepatic veins, cardiopulmonary bypass is needed to remove the vascular extent of the tumor. The abdominal tumor is mobilized and removed first prior to administration of heparin. After placing the child on bypass the right atrium is opened and the tricuspid value inspected. The tumor is removed from the heart above and below at the same time to prevent tumor emboli.

5.3.3 Surgical Management of Metastases

5.3.3.1 Intra-abdominal Metastases

Any suspicious site in the abdomen or liver should be biopsied or resected at exploration to determine the nature of the mass as it will affect tumor stage and therapy. If residual intra-abdominal metastatic disease remains at week 12 of chemotherapy, it should be resected if complete resection is feasible. If complete resection is not feasible, then residual disease should be reassessed for feasibility of resection at the completion of therapy.

5.3.3.2 Pulmonary Metastases

It is strongly recommended that if there is any doubt about the nature of pulmonary nodules that these be biopsied since as many as one third of small (<1 cm) lesions may not be metastatic tumor. Note however, that stage III and IV patients enrolled and treated on AREN0533 will receive the same chemotherapy for the first six weeks. Only patients with residual pulmonary lesions at this time will receive whole lung radiation. Thus it is only for patients with local stage I and II tumors that it is critical to define the nature of small pulmonary lesions at diagnosis.

It is strongly recommended to biopsy residual pulmonary lesions at week six if there is any doubt about the nature of the lesions prior to committing the patient to whole lung radiation and intensification of chemotherapy. Patients will still receive intensified therapy however, even if all disease is surgically resected.

Most metastases are peripheral and superficial and can be removed thorascopically. For larger lesion (e.g. right middle lobe mass) or for those wishing to perform an open procedure, a standard posterior lateral thoracotomy incision for exploration of the chest can be used.

If pulmonary nodules remain after Week 12 of chemotherapy (and irradiation), they should be resected if complete resection is feasible. If complete resection is not feasible, then imaging studies should be repeated at the end of protocol therapy to reassess for feasibility of resection.

5.3.3.3 Bone Metastases

Surgical resection of bone metastases is rarely recommended and should be considered only if such would result in removal of all known disease. Bone metastases are treated with radiation therapy.

5.3.3.4 Brain Metastases

Surgical resection of brain metastases may be considered before the initiation of chemotherapy if complete resection is feasible.

5.3.4 Initially Unresectable Renal Tumors

Past experience in the NWTSG and the studies conducted by the International Society of Pediatric Oncology have shown that pretreatment with chemotherapy almost always reduces the

bulk of the tumor and renders it more safely resectable while often allowing preservation of the contiguous organs. However, this method does not result in improved survival rates, and does result in the loss of important staging information. It is recommended therefore that all patients undergo initial exploration to assess operability. It is only then that a tumor biopsy should be considered. Thorough exploration of the abdomen is necessary to detect evidence of extrarenal extension of tumor. If suspicious lymph nodes or other metastatic deposits are found, these should be biopsied to document tumor involvement. Patients who are staged by imaging studies alone are at risk for understaging and overstaging. If pre-nephrectomy therapy is given based on imaging alone, with or without a needle biopsy, the local tumor should be considered to be stage III. In general, radiographic reevaluation should be performed at week 6. The operative procedure can be performed shortly thereafter if sufficient tumor shrinkage has occurred. Serial imaging evaluation is helpful to assess response, but radiographic evidence of persistent disease can occasionally be misleading.

Tumors should be considered unresectable if:

- there is extension of tumor thrombus above the level of the hepatic veins. These patients should be considered for tumor resection when there is evidence of regression of the vena caval thrombus regardless of the degree of response of the primary tumor.
- the tumor involves contiguous structures whereby the only means of removing the kidney tumor requires removal of the other structure (e.g. spleen, pancreas, colon but excluding the adrenal gland). Note however, that Wilms tumors are frequently adherent to adjacent organs. In the majority of cases, there is not frank invasion by the tumor and the organs can be dissected freely from the tumor. Radical en bloc resection, e.g. partial hepatectomy is not generally warranted. If however, removal of a small section of diaphragm, psoas muscle, or tip of the pancreas allows the tumor to be removed intact, this is considered appropriate.
- if it is the surgeons' judgment that nephrectomy would result in significant or unnecessary morbidity/mortality, diffuse tumor spill, or residual tumor.
- if there is pulmonary compromise due to extensive pulmonary metastases.

The operative principles and operative approach is identical to that described above for a primary unilateral nephrectomy (Section 5.3.2.1).

SURGICAL RELAPSE

AREN 0532 13.6 Surgical Management of Patients Who Relapse After Primary Nephrectomy and observation (Very low risk arm)

13.6.1 Local recurrence
If a child on the AREN0532 very low risk arm (surgery only and observation) relapses with an intraabdominal mass, complete imaging of the abdomen and chest should be obtained to define the extent of recurrence. Recurrence should be confirmed by biopsy (percutaneous or open) and resection if feasible should be performed. Chemotherapy should be given using Regimen DD4A. If residual intra-abdominal metastatic disease

remains after Week 6 of chemotherapy, it should be resected, if complete resection is feasible. If complete resection is not feasible, then continue chemotherapy, with repeat imaging studies at Week 12. The feasibility of resection should again be assessed at that time and resection performed if feasible. If resection is not possible at Week 12, rebiopsy is strongly encouraged.Notify Study Chair.

13.6.2 Metachronous contralateral kidney "relapses"If a child develops a metachronous tumor, renal sparing surgery should be considered. Notify one of the Study Surgeons (Dr. Bob Shamberger, Dr. Michael Ritchey, Dr Peter Ehrlich, or Dr. Tom Hamilton). Each tumor should be reviewed by the local surgeon based on the tumor extent to determine the feasibility of renal sparing surgery. We also strongly recommend reviewing the renal sparing surgery protocol in AREN0534, the surgery protocol for Bilateral Wilms tumors and Unilateral High Risk tumors.

EXTRARENAL RHABDOID TUMOR

AREN 0321
14.3 Surgical Management of Extrarenal rhabdoid tumor
Extrarenal rhabdoid tumors can be found a variety of locations, including the soft tissues of the trunk, the extremities, head and neck, abdomen, pelvis and retroperitoneum, as well as in a variety organs including the thymus, liver, heart and bladder. The same general principles apply when encountering these tumors outside of the kidney as within the kidney. If feasible and safe, the tumor should be completely resected with good margins when first encountered. However, if the initial operation would be associated with significant morbidity (resection of organs or amputation of extremities), adjuvant therapy should be given to shrink the tumor. Such patients would be eligible to participate in the irinotecan/vincristine window study. If the tumor responds to window therapy, the patient will receive 6 weeks of therapy on Regimen UH-2 and then be evaluated for second-look surgery. If the tumor does not respond to window therapy, the patient will receive 12 weeks of chemotherapy on Regimen UH-1 and then be evaluated for second-look surgery.

Operative Procedure for Bilateral Tumors (AREN 0534, section 13.2)

13.2.1 Renal biopsies
Open exploration for staging and biopsy of the renal tumors is not required for entry in this study. Review of NWTSG data found that little meaningful staging information was obtained unless the patient was undergoing primary tumor resection, e.g. nephrectomy or partial nephrectomy. Studies have shown a higher risk of local recurrence in patients who had tumor spills or ruptures irrespective of the cause or extent of the soiling. In the COG renal treatment studies, all patients with tumor spill, including biopsy, will be considered Stage III. However, patients with favorable histology tumors who undergo biopsy will **NOT** require radiation therapy during therapy with this protocol unless there are other specific factors that warrant a designation of Stage III.

There are situations where the radiographic appearance of the tumor may lead to uncertainty in the diagnosis. If the treating clinician wants to obtain a tissue diagnosis before starting therapy, needle biopsies via a posterior approach to limit intraperitoneal spill are preferred (see Section 13.3.5 about spill risks).
After six weeks of chemotherapy the patient will be re-imaged to determine response to chemotherapy. If there is less than 50% response to the chemotherapy, bilateral open renal biopsies are recommended. The 50% reduction in the tumor size as the cutoff for Week 6 surgery is based on the WHO criteria (bidimensional) outlined in the imaging section. Open biopsies are recommended because they are more accurate than percutaneous needle biopsies when assessing anaplasia. The goal of the biopsy is to assess tumor histology of non-responding tumors. The histology of the biopsy will determine whether additional chemotherapy is warranted before proceeding with surgery or if a change in the chemotherapy regimen is needed.

13.2.2 Partial nephrectomy

Assessment of differential renal function prior to surgery is recommended to ensure that the kidney is salvageable. This assessment with radionuclide renal scan (e.g. DMSA scan) should also be repeated after surgery to assess the functional results of the renal sparing procedure. A transperitoneal incision is used. Inspect the renal hilar and periaortic area and sample lymph nodes to rule out lymphatic spread. Palpate the renal vein and IVC for evidence of tumor extension. Do not biopsy the tumor if a partial nephrectomy with margins can be performed since this is a criterion for Stage III. Avoid rupture or spillage by use of an adequate incision. Control of the renal vessels is recommended, but the surgery can be performed without hypothermia or vascular ischemia. In most children, manual compression of the kidney can be used to control bleeding during the dissection. Use of a harmonic scalpel or a similar device may help reduce blood loss and maintain hemostasis. Gerota's fascia is opened and the perirenal fat is dissected off the renal surface excluding the fat attached to the mass. A circumferential incision of the renal capsule around the surface of the tumor should be performed and the capsule peeled back to expose the adjacent renal parenchyma. A wedge or guillotine resection of the tumor is performed. The tumor should be excised with a 0.5 to 1 cm rim of normal parenchyma. After removal of the tumor any bleeding vessels can be suture ligated. If there is transection of the collecting system, a watertight closure with fine absorbable suture is recommended.

During the mobilization of the kidney and during dissection of the tumor, care must be taken not to place traction on the renal vessels. The small vessels in these young patients are prone to intimal injury which can lead to spasm and subsequent thrombosis.

Following any surgical procedure, if the specimen reveals diffuse anaplasia and there is incomplete resection, additional surgery is indicated to ensure complete resection of the tumor.

13.2.3 Enucleation

Enucleation of the tumor (removal of a tumor from the surrounding tissue) may be the only option for removal of some centrally located tumors. Tumors in this location do not have adjacent renal parenchyma to allow for a partial nephrectomy as described in Section 13.2.2. These tumors often compress the renal sinus and abut against both the renal vasculature and collecting system. After chemotherapy, these tumors are often firm with a capsule around the surface of the tumor. This allows for blunt dissection with enucleation of the tumor mass. This

procedure should be considered only for patients with **favorable histology** Wilms tumor. **If anaplasia is present, enucleation is contraindicated.** Clear margins are mandated for anaplastic tumors.

The surgical approach for enucleation is the same as for partial nephrectomy. A transperitoneal incision is used. Inspect the renal hilar and periaortic area and sample lymph nodes to rule out lymphatic spread. Palpate the renal vein and IVC for evidence of tumor extension. Do not biopsy the tumor if a partial nephrectomy with margins can be performed since this is a criterion for Stage III. During the mobilization of the kidney and during dissection of the tumor, care must be taken not to place traction on the renal vessels. The small vessels in these young patients are prone to intimal injury which can lead to spasm and subsequent thrombosis.

13.2.4 Nephrectomy (for Bilateral Protocol 0534)
Indications for nephrectomy:
• Bilateral Wilms tumor: partial nephrectomy is not feasible after 12 weeks of chemotherapy.
• Unilateral Wilms tumor at high risk for bilateral Wilms tumor:
    a. partial nephrectomy is not feasible after six weeks of chemotherapy and there has been less than a 50% response to chemotherapy.
    b. partial nephrectomy is not feasible after 12 weeks of chemotherapy.

A generous transabdominal, transperitoneal or thoracoabdominal incision is recommended for adequate exposure. Complete exploration of the abdomen should be performed. To expose the primary tumor the lateral peritoneal reflection is then opened, and the colon is reflected medially. A radical nephrectomy is performed with the dissection plane established outside of Gerota's fascia. Before mobilizing the primary tumor, an attempt should be made to dissect, expose and ligate the renal vessels in order to lessen the chance of hematogenous spread of tumor cells while removing the tumor. **Preliminary ligation should not be pursued if technically difficult or dangerous**. The adrenal gland may be left in place if it is not abutting the tumor; but, if the mass arises in the upper pole of the kidney, the adrenal gland should be removed with the neoplasm. The ureter is ligated and divided as low as conveniently possible but it is not necessary to remove the ureter completely. The tumor and the uninvolved portion of the kidney are mobilized and removed intact. Any enlarged or suspicious lymph nodes should be included with the specimen.

The use of titanium clips is strongly recommended to identify gross residual tumor. Clips should not be used for hemostasis and those placed for roentgenographic identification or radiation therapy portals should be limited to the minimum number necessary. Metallic clips can interfere with the CT scan. Clips are best applied by placing a non-absorbable suture in the structure to be marked, and attaching the clip to the suture. In general, four small clips should be sufficient to delineate the margins of the tumor.

Any suspicious area that could represent metastases should be biopsied, the site(s) identified with small titanium clips so that the locations can be determined later by roentgenograms.
The involved areas should be drawn on the diagram in the surgical checklist. The specimen should be specifically identified as to the site from which it was removed.

CENTRAL VENOUS LINE

AREN 0321 8.1 General Supportive Care Guidelines
8.1.1
A central venous catheter (single lumen port or externalized line for Regimens DD-4A; double lumen line for Regimens UH-1 and UH-2) is recommended prior to initiation of therapy.

PATHOLOGY REQUIREMENTS

AREN 03B2 5.0 METHODS
5.1 **Summary of Submission Requirements and Recommendations**

Submission (Specimens - BPC, imaging studies - QARC, surgical data -RDC, see protocol for details)	For all patients who are anticipated to enroll on a COG therapeutic study and who have had a biopsy or surgery prior to enrollment on AREN03B2	For all patients who are anticipated to enroll on a COG therapeutic study and who will not have a biopsy or surgery prior to enrollment on AREN03B2	For all patients who will not be enrolling on a COG renal tumor treatment study
Pathology Specimens for Central Review: • A complete set of recut H & E slides, including 2 H & E slides from each block which might affect staging decisions (lymph nodes, margins, etc.), and from all blocks containing tumor. • Representative formalin-fixed paraffin-embedded tissue block or if a block is unavailable, 10 unstained slides from a representative block of tumor • Institutional pathology report • Pathology checklist and Specimen Transmittal Form •	Required at enrollment	Required at any surgery while on study	Required at enrollment
Snap Frozen Tumor Tissue from primary - At least 1 g and up to 10 g if available (for **LOH** studies).	Required at enrollment Requested at relapse	Required at any surgery while on study. Requested at relapse	Requested at any surgery
5-10 mL of whole blood in purple	Required at enrollment	Required at enrollment	Requested at

top tube (for **LOH** studies)			any surgery
Diagnostic Imaging for Central Review: **Copies of films and institutional reports of CT/MRI abdomen, pelvis, chest; report only of color Doppler US**	Required at enrollment	Required at enrollment	Required at enrollment
Institutional surgical report(s)	Required	Required	Requested at any surgery
Snap Frozen Normal K**idney** T**issue** – At least 1 g and up to 10 g if available.	Requested at enrollment and any surgery	Requested at any surgery	Requested at any surgery
Snap Frozen Tumor Tissue from metastatic areas (<u>only if resected or biopsied</u>) – At least 1 g and up to 10 g if available.	Requested at enrollment and any surgery	Requested at any surgery	Requested at any surgery
Tumor Tissue in Formalin – "cassette sized"	Requested at enrollment	Requested at any surgery	Requested at any surgery
Serum (<u>PREOPERATIVELY</u>) - spun from 6mL of whole blood in red top tube	Requested at enrollment	Requested at enrollment	Requested at enrollment
Urine (<u>PREOPERATIVELY</u>) - 5-10 mL	Requested at enrollment	Requested at enrollment	Requested at enrollment
Peripheral blood (5-10mL) in purple top tube - end of therapy	Requested	Requested	
Peripheral blood (5-10mL) in purple top tube one year after end of therapy	Requested	Requested	
Set of H&E slides of tumor and snap frozen tumor (at least 1g and up to 10g) **at RELAPSE**	Requested	Requested	Requested

TREATMENT

CITED CHEMOTHERAPY REGIMENS include the following:

EE4A	Vincristine, Dactinomycin	19 weeks
DD4A	Vincristine, Dactinomycin, Adriamycin	27 weeks
Regimen I	Vincristine, Doxorubicin, Cyclophosphamide, Etoposide	28 weeks
UH I	Vincristine, Doxorubicin, Cyclophosphamide, Etoposide Carboplatin	31 weeks
UH II	Vincristine, Doxorubicin, Cyclophosphamide, Etoposide	37 weeks
	Vincristine and Irinotecan Windows	36 weeks

FAVORABLE (AREN 0532)

4.1 **Overview of Treatment plan**

Patient Age	Tumor Weight	Stage	LOH	Rapid Response	Risk Group	Treatment Study
< 2 yrs	< 550 g	I	Any	N/A	Very Low	AREN0532
Any	≥ 550 g	I	None	N/A	Low	AREN0532
≥2yrs	Any	I	None	N/A	Low	AREN0532
Any	Any	II	None	N/A	Low	AREN0532
≥ 2yrs	Any	I	LOH	N/A	Standard	AREN0532
Any	≥ 550 g	I	LOH	N/A	Standard	AREN0532
Any	Any	II	LOH	N/A	Standard	AREN0532
Any	Any	III	None	Any	Standard	AREN0532
Any	Any	III	LOH	Any	Higher	AREN0533
Any	Any	IV	LOH	Any	Higher	AREN0533
Any	Any	IV	None	Yes	Standard	AREN0533
Any	Any	IV	None	No	Higher	AREN0533
Any	Any	V	Any	Any	Bilateral	AREN0534

Bilateral Tumors

	STAGE I	STAGE II	STAGE III	STAGE IV
Complete response by imaging	EE4A	n/a	n/a	n/a
Completely necrotic	EE4A	EE4A	DD4A	DD4A
INTERMEDIATE RISK*	EE4A	DD4A	DD4A + XRT	DD4A + XRT
BLASTEMAL PREDOMINANT	DD4A	REGIMEN I	REGIMEN I + XRT	REGIMEN I + XRT
DIFFUSE ANAPLASIA	DD4A + XRT	REGIMEN UH-1 + XRT	REGIMEN UH-1 + XRT	REGIMEN UH-1 + XRT
FOCAL ANAPLASIA	DD4A + XRT	DD4A + XRT	DD4A + XRT	REGIMEN UH-1 + XRT
RHABDOID	REGIMEN UH-1 + XRT	REGIMEN UH-1 + XRT	REGIMEN UH-1 + XRT	REGIMEN UH-1 + XRT

RENAL TUMORS BACKGROUND and HISTOPATHOLOGY

APPENDIX I - HISTOLOGIC FEATURES OF PEDIATRIC RENAL TUMORS (AREN03B2)

I. FAVORABLE HISTOLOGY WILMS TUMOR

A variety of cell types differentiating toward blastema, epithelium, and stroma are present in most Wilms tumors.[33] The relative proportions of each cell or tissue type vary from specimen to specimen and the diverse cell types may each express various degrees of differentiation, resulting in an almost infinite variety of potential patterns. Triphasic patterns, containing blastemal, stromal, and epithelial cell types, are the most characteristic, but biphasic and monophasic lesions have often been observed. The *blastemal* cells are small, closely packed, and mitotically active with minimal evidence of differentiation into recognizable epithelial or stromal structures. Their nuclei are relatively small and regular with evenly distributed, slightly course chromatin and small nucleoli. A reliable feature of Wilms tumor is the prominent overlapping of adjacent nuclei. Blastemal cells occur in several distinctive patterns including diffuse, serpentine, nodular, and basaloid. *Epithelial* components are evident in a spectrum ranging from primitive rosette-like structures to well-differentiated tubular, papillary, and glomeruloid elements that recapitulate various stages of normal nephrogenesis. Heterologous epithelial differentiation may occur, the most common elements being mucinous and squamous epithelium. A variety of *stromal patterns* may occur and may cause diagnostic difficulty when blastemal and epithelial differentiation are absent. Smooth muscle and fibroblastic cells may be present and may show varying degrees of differentiation. Skeletal muscle is the most common heterologous stromal cell type and large fields often contain this pattern. More primitive myoblastic elements can also be found, including the condensed mesenchyme characteristic of the "cambium layer" of botryoid embryonal rhabdomyosarcomas. Almost any type of stromal differentiation, including adipose tissue, cartilage, bone and osteoid, mature ganglion cells, and neuroglial tissue, may be observed in nephroblastomas. While associations between histologic features and prognosis or responsiveness to therapy have been suggested, with the exception of anaplasia, none of these features have reached statistical significance and therefore do not direct the initial therapy.

II. ANAPLASTIC WILMS TUMOR

The single most important histologic predictor of response and survival in patients with Wilms tumor is the presence or absence of anaplasia. There are two histologic criteria for anaplasia, both of which must be present for the diagnosis:[34]

 The presence of multipolar polyploid mitotic figures. The mitotic abnormalities must reflect unequivocal increase in the total amount of DNA. In a true multipolar polyploid mitotic figure, each component is as large, or larger, than a normal metaphase. Simple lagging of chromosomes on an anaphase spindle may result in an "abnormal mitosis," but should not be a criterion for anaplasia. In a limited sample, such as a small biopsy, marked nucleomegaly with hyperchromasia alone may be sufficient to suggest anaplasia.

 Marked nuclear enlargement and hyperchromasia. The major dimension of affected nuclei meeting the criteria are at least three times that of apparently nonanaplastic nuclei in other areas of the specimen. Nuclear enlargement should involve all diameters of the nucleus and should not be confused with simple elongation. The enlarged nuclei must also be hyperchromatic, again indicating an unequivocal increase in DNA content.

Focal and Diffuse Anaplasia

Anaplasia correlates best with responsiveness to therapy rather than to aggressiveness. Accordingly, anaplasia is most consistently associated with poor prognosis when it is diffusely distributed and when identified at advanced stages. For this reason, pathologic and therapeutic distinction has been made between *focal anaplasia* and *diffuse anaplasia*.[1] Focal anaplasia is defined as the presence of one or a few sharply localized regions of anaplasia within a primary tumor, the majority of which contains no nuclear atypia. It is important to note that focal anaplasia has restrictive criteria. The following situations require a diagnosis of diffuse anaplasia:

a) Anaplasia in any extrarenal site, including vessels of the renal sinus, extracapsular infiltrates, nodal or distant metastases;

b) Anaplasia in a random biopsy specimen;

c) Anaplasia unequivocally expressed in one region of the tumor, but with extreme nuclear pleomorphism approaching the level of anaplasia elsewhere in the tumor;

d) Anaplasia in more than one tumor slide, unless: 1) it is known that every slide showing anaplasia came from the same region of the tumor; or 2) anaplastic foci on the various slides are small and surrounded on all sides by non-anaplastic tumor. This topographic definition of focal anaplasia requires careful documentation of the exact site from which every section is obtained (e.g. on a diagram, specimen photocopy, and/or polaroid photograph of the gross specimen).

Anaplasia in a Previously Treated Wilms Tumor

Anaplasia newly identified in a tumor previously treated as favorable histology Wilms tumor has the same implication as when found in untreated cases. There is presently no evidence that therapy causes cytological changes mimicking anaplasia.

III. CLASSIFICATION OF PRE-TREATED BILATERAL WILMS TUMORS

The treatment of bilateral Wilms tumors will utilize preoperative chemotherapy. Biopsies at diagnosis will not be mandated for such patients if they are confidently diagnosed by radiology. Following six weeks of chemotherapy, the patient will be reevaluated radiologically. Patients with at least a partial response (>50%) will receive six more weeks of therapy before second look surgery. Patients with less than partial response will undergo immediate surgery (biopsy or resection). Post-resection therapy in both cases will be based on the histology of the tumor. This therapy will depend on a number of variables, and the protocol should be referred to for details. However, the pathologic classification that will be utilized in all such situations is the same. Tumors following chemotherapy will be placed into three pathologic categories:

Completely Necrotic Tumors

These tumors must show less than 1% viable tumor tissue on gross and microscopic

examination of multiple blocks taken from different areas of a tumor according to recommendations (submission of at least one block per cm of tumor). The presence of scattered mature tubules is allowed as these may represent remnants of nephrogenic rests. Approximately 10% of tumors are expected to fall into this category.

Intermediate Tumors
The majority of tumors will fall in the intermediate category. These tumors may contain a variety of histologic features, including epithelial, stromal, and blastemal differentiation. A spectrum of proliferative changes may be present, and a spectrum of necrosis and regressive changes may likewise be present. However, if the viable part of the tumor comprises more than 1/3 of the tumor mass grossly, and if more than 66% of the viable tumor that remains is blastemal, the tumor is considered to be high risk (below).

Blastemal Predominant Tumors
The criteria for this category are the following:
a) The viable part of a tumor must comprise more than 1/3 of the tumor mass;
b) At least 2/3 of the viable tumor consists of blastema
c) Other components of nephroblastoma may be present in varying proportions

IV. STAGING CONSIDERATIONS OF NEPHRECTOMY SPECIMENS FOLLOWING CHEMOTHERAPY

The staging for post-therapy nephrectomy specimens is similar to that of pre-therapy nephrectomy specimens. The differences revolve around the interpretation of areas of necrosis 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 should not be regarded as a reason for upstaging a tumor following chemotherapy providing it is completely excised and does not reach the resection margins. Conversely, the presence of necrotic tumour or chemotherapy-induced changes in a lymph node or at the resection margins is regarded as proof of previous tumour with microscopic residue and therefore the tumour is assigned stage III.

V. NEPHROGENIC RESTS AND NEPHROBLASTOMATOSIS

Nephrogenic rests are abnormally persistent foci of embryonal cells capable of developing into nephroblastomas. The term *nephroblastomatosis* is defined as the presence of diffuse or multifocal nephrogenic rests. Nephrogenic rests and nephroblastomatosis are classified into perilobar (PLNR) and intralobar (ILNR) types. Patients with any type of nephrogenic rest in a kidney removed for nephroblastoma should be considered at increased risk for tumor formation in the remaining kidney. This risk decreases with patient age.

PLNRs are characterized by sharp circumscription and a location at the periphery of the lobule. *Dormant or incipient rests* show no evidence of proliferation, maturation, or involution. These contain well-formed tubular structures with few or no mitotic figures. When PLNRs begin proliferating, they become larger and oval in shape and may then

have one of several fates. Most commonly, the rest will regress, resulting in peritubular scarring, decreased proliferation, and sclerosis. Less commonly PLNRs may also undergo diffuse or focal proliferative overgrowth, resulting in *hyperplastic* rests. Hyperplastic PLNRs are composed of blastemal and poorly differentiated tubular components. Hyperplastic PLNRs are often not distinguishable from nephroblastoma by cytologic features alone. The most distinctive features of hyperplastic PLNRs are a 1) a tendency to preserve the original shape of the rest (usually non-spherical) and 2) a direct interface with the adjacent renal parenchyma. When a clonal expansion develops within a perilobar nephrogenic rest, the resulting nephroblastoma is recognized by its propensity for spherical expansile growth and a peritumoral fibrous capsule separating the neoplasm from the adjacent rest and normal kidney.

In rare patients, perilobar nephroblastomatosis forms a more or less continuous band around the surface of the kidney in a condition classified as diffuse perilobar nephroblastomatosis. Hyperplastic over-growth of diffuse perilobar nephroblastomatosis (DHPLN) results in massive renal enlargement. [35] These lesions are now treated according to a separate therapeutic protocol (AREN0534).

Intralobar nephrogenic rests (ILNRs) are typically located in the central areas of the lobule, and intermingle among the normal renal parenchyma. They are poorly circumscribed and composed of stromal elements as well as epithelial tubules. Like PLNRs, ILNRs may undergo hyperplasia, and this hyperplasia may involve stromal, epithelial, and/or blastemal elements. Nephroblastoma commonly develops with ILNRs, and are often separated from the underlying rest by a peritumoral fibrous capsule.

VI. CYSTIC NEPHROMA AND CYSTIC, PARTIALLY DIFFERENTIATED NEPHROBLASTOMA

Cystic nephroma (CN) and cystic, partially differentiated nephroblastoma (CPDN) are benign neoplasms considered to be a part of the spectrum of nephroblastoma. CN and CPDN are solitary, multilocular lesions sharply demarcated from an otherwise normal remaining kidney. Cysts range from a few millimeters to several centimeters in diameter and are filled with colorless fluid. The intervening septa must conform to the contours of the cyst and do not contain grossly identifiable nodular masses. The microscopic distinction between a cystic Wilms tumor, a CPDN and a CN is usually straightforward. CN by definition are composed of cysts with septae containing only mature elements. No nodular masses of mature or immature nephroblastic tissue should alter the contour of the cysts. CPDNs differ from CN only in that the septae contain blastemal or other poorly differentiated cell types. Any solid, expansile, nodular proliferations indicate a diagnosis of cystic nephroblastoma. Hemorrhage, necrosis, and calcification are not features of either CN or CPDN. Extension of the lesion beyond the renal capsule may occur and does not negate the diagnosis of CN and CPDN.

VII. BENIGN METANEPHRIC LESIONS

The benign metanephric lesions represent a spectrum of lesions that are derived from the metanephric blastema. The individual components of these lesions distinguish them pathologically from nephroblastoma. At one end of the pathologic spectrum are tumors

that are composed exclusively of epithelial nephroblastic cells, the *metanephric adenoma*, and at the other end are tumors that are composed exclusively of stromal elements, the *metanephric stromal tumors*. Tumors that include a composite of both have been termed *metanephric adenofibromas*. The vast majority of tumors within this family are classified as stage I. They may infiltrate the fibro adipose tissue of the renal sinus and entrap nerves, however vascular invasion has not been identified. While the lesions within this family of tumors behave in a benign fashion, either the epithelial or stromal component may show histologic progression. The epithelial component of metanephric adenoma or metanephric adenofibroma may show progression to either nephroblastoma or papillary renal cell carcinoma.

Metanephric adenomas are well circumscribed, but unencapsulated tumors consisting of small epithelial cells that form small acini in an acellular stroma. Tubular, glomeruloid, and papillary formations may also be seen, and calcospherites are common. Cytologically, the cells are quite bland with smooth nuclear contours and inconspicuous to absent nucleoli. Only very rare mitotic figures are evident, and vascular invasion precludes this diagnosis. The diagnostic criteria of metanephric adenoma include 1) absence of a peritumoral fibrous capsule with a direct interface between the lesion and normal kidney, 2) absent nucleoli, and 3) virtually absent mitotic activity. Metanephric adenoma is unusual for its negativity for epithelial membrane antigen and cytokeratin 7, both of which are positive in papillary renal cell carcinoma.

Metanephric stromal tumors are unencapsulated tumors composed of spindled to stellate cells. MST extend as tongues of stromal tissue into the surrounding renal parenchyma, often entrapping normal renal elements and causing dilatation and cyst formation. The degree of stromal cellularity in MST ranges from extreme hypocellularity with sclerosis, to extreme hypercellularity resembling cellular mesoblastic nephroma. The spindle cell stroma may show a number of architectural patterns, including a palisading pattern simulating the Verocay bodies of schwannoma, a storiform pattern, an epitheliod pattern, and a hemangiopericytomatous pattern. Mitoses are usually inapparent, but may reach up to 7 per 20 high power fields. MST show several distinctive, but not universally present features:

- Alternating regions of myxoid or sclerotic hypocellularity and fibroblastic hypercellularity resulting in a distinctive nodular appearance on low power.
- Concentric collarettes of stromal cells around renal tubules or blood vessels.
- Angiodysplasia of intratumoral arterioles.
- Nodules of heterologous tissue, most commonly including glial tissue

VIII. CONGENITAL MESOBLASTIC NEPHROMA

Congenital mesoblastic nephroma is a lesion virtually exclusively identified in infancy. The median age of diagnosis is 2 months and over 90 percent of cases appear within the first year of life. The diagnosis should be questioned when applied to individuals over 2 years of age.

Grossly, congenital mesoblastic nephromas appear as solitary, unilateral masses indistinguishable from nephroblastoma. Most mesoblastic nephromas are centered near the hilus of the kidney and nearly all involve the renal sinus soft tissue. Microscopically,

mesoblastic nephromas are predominantly monomorphic neoplasms composed of spindled mesenchymal cells of fibroblastic or myofibroblastic lineage. They can be divided into two major types: *classic and cellular*.

Classic mesoblastic nephroma closely resembles infantile fibromatosis in its pathologic features. It is characterized by intersecting fascicles of spindle cells resembling fibroblasts or myofibroblasts interspersed with collagen fibers. Dilated, thin-walled vascular spaces are often prominent. Mitotic activity is variable but generally less conspicuous than in the cellular pattern. The tumor margins are highly irregular with radiating bands of cells extending into the renal parenchyma and the perirenal soft tissue. Small nodules of hyaline cartilage are often encountered and extramedullary hematopoiesis is common in this subtype. Skeletal muscle differentiation is not a feature of mesoblastic nephromas. No consistent genetic abnormalities have been identified in classic mesoblastic nephromas. It has been suggested that classic mesoblastic nephromas may represent infantile fibromatosis, rather than fibrosarcoma, involving the kidney. This is supported by the strong histologic similarity between these two entities.

The *cellular mesoblastic nephroma* pattern is characterized by increased cellular density and plump cells with large, vesicular nuclei with a high proliferation rate. Lesions are usually sharply circumscribed without the interdigitating margins of classic lesions. However, a peritumoral fibrous capsule is seldom present. Mild to moderate nuclear pleomorphism may be present and the cells often grow in sheets reminiscent of fibroblast cell cultures. Rare tumors may show prominent nucleoli and necrosis, very closely resembling rhabdoid tumor. Many specimens closely resemble the spindle cells of the infantile fibrosarcoma. The potential linkage between infantile fibrosarcoma and cellular mesoblastic nephroma was established when both infantile fibrosarcoma and cellular congenital mesoblastic nephroma were shown to contain the same t(12;15)(p13;q25) chromosomal translocation. The cloning of the genes involved in this translocation (ETV6 and NTRK3) has allowed more reliable molecular detection assays to be applied on both formalin fixed and paraffin embedded sections.

Cellular and classic patterns may coexist, and such cases have been classified *as mixed mesoblastic nephroma*.

The risk for recurrence within congenital mesoblastic nephromas is closely associated with the presence of a cellular component and with stage.

IX. CLEAR CELL SARCOMA

Clear cell sarcoma of the kidney (CCSK) is a malignant mesenchymal neoplasm characterized by undifferentiated cells with abundant extracellular matrix separated into cords and nests from 6 to 10 cells in width by a vascular network.[36] These small vessels are accompanied by a variable component of spindle cells, often referred to as "septal" cells. The cord cells are uniform in size, loosely spaced and have indistinct cell borders. They are separated from their neighbors by extracellular, Alcian blue positive matrix that contributes to the pale appearance of most specimens. The nuclei of the cord cells contain finely dispersed chromatin without prominent nucleoli or chromatin condensation.

"Empty" appearing nuclei are frequent, and provide a valuable diagnostic clue for CCSKs. Most CCSKs are not composed entirely of clear cells but have at least some fields in which the cytoplasm is more condensed and acidophilic. The mitotic rate is variable but considerably lower than that in other malignant pediatric renal neoplasms.

A distinctive and diagnostically useful feature of CCSK is the microscopic appearance of the kidney-tumor interface. Although the tumor margin is sharply demarcated macroscopically and under low magnification, higher magnification reveals tumor cells subtly infiltrating for short distances, nibbling into the adjacent renal parenchyma. This is in contrast to nephroblastomas, which usually have either a sharply defined, pushing border or an aggressively invasive, widely infiltrating margin. This slowly infiltrative nature of CCSK characteristically results in entrapment and separation of individual nephrons, tubules, or collecting ducts at the periphery of the tumor, a feature virtually never seen in nephroblastomas but commonly seen in other sarcomas. The light microscopic features of the classic pattern of CCSK, described above, are present at least focally in over 90% of CCSKs. The diagnosis of CCSK is often made difficult by the presence of a large number of variant histologic patterns. The *myxoid pattern* results from the accumulation of mucopolysaccharide matrix, often obscuring the original classic pattern. In the *sclerosing pattern*, abundant acellular collagen develops, preserving vascular septa. The *cellular pattern* is characterized by decreased intercellular material with close spacing and overlapping of nuclei. Mitotic activity is often increased in this variant, providing the appearance of an undifferentiated small blue cell tumor. The *epithelioid pattern* results from condensation of the cord cells within the septa, forming ribbons, tubules, rosettes, and trabeculi. *Spindle cell patterns* may sometimes be prominent, resulting in a wide variety of histologic appearances reminiscent of other sarcomas, soft tissue, and fibrohistiocytic lesions. The primary contribution of immunohistochemistry in the diagnosis of CCSK is the exclusion of other pediatric renal neoplasms. No diagnostically useful genetic features have been identified.

X. RHABDOID TUMOR

Rhabdoid tumor is a rare, highly malignant neoplasm of infancy characterized by a monomorphous population of large, relatively non-cohesive cells with vesicular nuclei and large nucleoli.[37] After the description of rhabdoid tumor within the kidneys, it has become increasingly recognized that rhabdoid tumors often involve extrarenal sites, particularly the central nervous system. The unifying feature of infantile rhabdoid tumors at all sites is the presence of mutation or deletion of the *INI-1* gene located at chromosome 22q11.[26,38] Grossly, rhabdoid tumors are soft, pale, and relatively uniform. They are moderately well demarcated from the adjacent kidney, and usually lack a capsule. Microscopically, rhabdoid tumors have a monomorphous pattern composed of sheets of large, loosely cohesive cells with distinct cell borders often containing large whorls of intermediate filaments resulting in the appearance of acidophilic cytoplasmic inclusions. Cells have large nuclei with prominent nucleoli. The cells with characteristic cytoplasmic inclusions tend to be clustered rather than uniformly distributed and not all cells of any given neoplasm contain these structures. The growth pattern is characteristically highly infiltrative with frequent invasion of local blood vessels. Rarely,

tumor cells may be organized into fairly distinctive cords or tubule-like structures reminiscent of nephroblastoma. The stroma of rhabdoid tumors tends to be densely collagenous and may become hyalinized. Basophilic ground substance may accumulate to such a degree as to suggest chondroid differentiation. A large number of variant patterns have been described, including sclerosing, epithelioid, spindled, vascular and lymphomatoid, which can simulate other neoplasms.

Rhabdoid tumors are characterized by a polyphenotypic staining pattern. Vimentin immunoreactivity is uniform and intense; in addition tumor cells may stain simultaneously with a variety of markers including cytokeratin, EMA, desmin, and neurofilament. The staining pattern for these is characteristically patchy and strong, with small clusters of cells showing intense positivity. One particularly helpful pattern of staining is the presence of scattered clusters of intensely EMA or cytokeratin positive cells in a background of negative staining; few other pediatric tumors stain in this distinct fashion. Unfortunately, many rhabdoid tumors do not show the characteristic staining pattern mentioned above. Recently, an immunohistochemical stain for the INI-1 protein product has demonstrated nuclear positivity for this antibody in all other categories of renal tumors as well as a variety of other pediatric sarcomas, and negativity only in rhabdoid tumor.[39] This antibody will be evaluated for its diagnostic utility, and will be performed centrally if it is not available at the local institution.

NOTE: RHABDOID TUMORS MUST BE ACCOMPANIED BY UNSTAINED SLIDES OR PARAFFIN BLOCKS IN ORDER FOR AN ACCURATE CLASSIFICATION TO BE ACCOMPLISHED.

XI. PEDIATRIC RENAL CELL CARCINOMA

Malignant epithelial tumors arising in the kidney of children account for more than 5% of new pediatric renal tumors. Pediatric renal cell carcinomas differ in their histologic appearance from those of adulthood.[40] This is supported by genetic changes that have been reported in pediatric renal cell carcinomas in recent years. Given the currently available information, renal cell carcinomas in children most commonly fall into three distinct categories: *papillary renal cell carcinoma, renal medullary carcinoma, and renal cell carcinomas with clear cell features.* These categories will likely be refined and expanded in the next decade as knowledge of their pathologic spectrum and molecular pathogenesis increases.

The current protocol promises to greatly contribute to this knowledge, as it represents the first time these lesions are eligible for registration in the pediatric cooperative group protocols. It should be noted that the therapeutic protocols currently do not specify a particular therapy, and the staging as well as grading systems that will be most meaningful in pediatric tumors is currently unknown. In order to compare these tumors to those in adults, the staging system proposed by the World Health Organization, outlined earlier, is recommended. A number of staging and grading systems will be applied centrally in order to address these issues.

NOTE: THE REGISTRATION OF RENAL CELL CARCINOMAS MUST BE ACCOMPANIED BY UNSTAINED SLIDES OR PARAFFIN BLOCKS IN ORDER FOR ACCURATE CLASSIFICATION TO BE ACCOMPLISHED.

Papillary Renal Cell Carcinoma

Papillary renal cell carcinoma is the most common histologic subtype of renal cell carcinoma that is seen in children, and represents the counterpart of the typical basophilic papillary renal cell carcinoma found in adults.[41-43] The differential diagnosis includes differentiated epithelial nephroblastoma and metanephric adenoma. The most valuable histologic clues for distinguishing these similar lesions are the following:

Peritumoral pseudocapsule: The vast majority of epithelial nephroblastomas and papillary renal cell carcinomas have a prominent peritumoral pseudocapsule composed of compressed kidney and collagen. Papillary renal cell carcinomas characteristically show an abundant lymphocytic infiltrate around the periphery of their pseudocapsule. Metanephric adenomas by definition lack a peritumoral psuedocapsule.

Cytology: Nephroblastomas are proliferative lesions that contain at least occasional mitotic figures, whereas mitotic figures are absent in metanephric adenoma, and are often quite rare in papillary renal cell carcinoma. The cells of nephroblastoma are generally columnar with large, overlapping nuclei and finely dispersed chromatin. Cells of metanephric adenoma are oval, quiescent nuclei that lack prominent nucleoli. Papillary renal cell carcinomas commonly have prominent nucleoli. Aggregates of foamy macrophages and calcospherites may be seen in each of these tumors.

Immunohistochemistry: Papillary renal cell carcinomas are characteristically strongly and homogeneously positive for cytokeratin 7, a marker that is at most only focally positive in nephroblastoma and metanephric adenoma.[44] Metanephric adenoma is negative for epithelial membrane antigen.

Renal Medullary Carcinoma

Renal medullary carcinoma is a rare tumor that afflicts young individuals with sickle cell hemoglobinopathy.[45,46] While most reported cases have involved African Americans, patients have also been reported who have Caucasian European and Brazilian backgrounds, populations where a high prevalence of the sickle cell gene has been documented. All patients who have been tested contain the sickle cell gene. Renal medullary carcinoma is characterized clinically by a high stage at the time of detection with widespread metastases and lack of response to both chemotherapy and radiotherapy. Survival ranges from 2 weeks to 15 months with a mean survival of 4 months. Most tumors are poorly circumscribed, and predominantly involved the renal medulla. Intrarenal satellite tumors, representing local hematogenous spread, are grossly apparent in many cases. Microscopically, common growth patterns include cribriforming, microcystic, solid, and sarcomatoid. Stromal desmoplasia is present in the vast majority of tumors. Another common feature is the presence of a striking acute and chronic inflammatory infiltrate. Renal medullary carcinomas have strikingly infiltrative margins. Cytologically, the nuclei are large and vesicular with prominent nucleoli in most cases.

Eosinophilic cytoplasm is abundant and cytoplasmic lumina are occasionally identified. Cytoplasmic inclusions resembling rhabdoid tumor are noted in most cases. Drepanocytes (sickled cells) can be identified in the vast majority of cases, although some cases require a diligent search of the tissue. No consistent genetic changes have been noted in renal medullary carcinoma.

Renal cell carcinomas with clear cell features:
The most common renal cell carcinomas in the pediatric age group are those that have a clear cell appearance. This is a genetically heterogeneous group that includes rare tumors that are true conventional adult-type renal cell carcinomas, complete with 3p25 (*VHL* locus) abnormalities, and tumors of patients with tuberous sclerosis. However, the most common lesions within this clear cell-appearing subgroup are those associated with specific translocations. These often have histologic appearances that closely resemble conventional RCC. Since 1996 it has been recognized that many renal epithelial tumors in children have a nested or tubulopapillary morphology composed of cells with voluminous clear to acidophilic cytoplasm. Genetic analysis has documented a number of variant translocations involving the TFE3 gene located at Xp11.2.[47-52] TFE3 encodes a transcription factor, and the genes that partner with TFE3 in the variant translocations are involved with RNA splicing. The Xp11.2 renal cell carcinomas may demonstrate a broad spectrum of morphologic features, and their full histologic spectrum is not known. Grossly, the tumors are unencapsulated and infiltrate the surrounding kidney. Microscopically they demonstrate an organoid pattern of growth. Nests or papillary fronds of large, clear cells with voluminous cytoplasm and distinct cell borders are separated by thin fibrovascular septa. Nests may become discohesive in the center, resulting in an alveolar appearance. The nuclei contain a single prominent nucleolus and are often eccentrically placed. Small calcifications are often present. Occasional tumors show only small amounts of cytoplasm and a more trabecular appearance. An infiltrative border is present in most cases, with entrapment of native renal tubules and vascular invasion. Lymph node metastasis is common.

The immunohistochemical staining pattern of tumors with an Xp11.2 translocation differs from that of most other categories of renal cell carcinomas. These tumors are negative or only focally and weakly immunoreactive for epithelial membrane antigen, Cam5.2, cytokeratin 7, AE1/AE3 and vimentin.[40] An immunohistochemical marker for the TFE3 gene has been shown to demonstrate strong nuclear expression in tumors that contain translocations involving this gene. This marker will be performed at the time of central review.

The differential diagnosis of renal tumors containing the Xp11.2 translocation based on histologic appearance includes conventional renal cell carcinoma, which is rare in children without known genetic syndromes such as von Hippel-Lindau or tuberous sclerosis. In addition, epitheliod angiomyolipomas may closely resemble both conventional renal cell carcinoma as well as Xp11.2 renal cell tumors. The pure epitheliod variant of angiomyolipoma consists of polygonal oncocytic cells (perivascular epitheliod cells) with well-defined borders. These are commonly gathered in acini or nests; they frequently demonstrate considerable cytologic atypia, often resulting in the

diagnosis of renal cell carcinoma. Angiomyolipomas are positive for HMB45, S100 protein and melan-A and negative for epithelial markers.

Lastly, a small number of renal tumors in children have been described which are histologically quite similar to Xp11 translocation renal cell carcinomas. These differ only by the presence of a subpopulation of smaller cells that surround hyaline material which by EM represents basement membrane material. These tumors do not label for epithelial markers and do not demonstrate desmosomes. They may show very focal positivity for HMB45 and Melan A. These tumors demonstrate a recurrent t(6;11) (p21;q13) cytogenetic translocation, which involves the TFEB gene, a member of the TFE3 family.[53,54] Their histogenesis and biologic potential remains unclear.

In summary, in the absence of a genetic syndrome, the diagnosis of conventional renal cell carcinoma should be considered highly suspect in a patient less than 20 years of age. Immunohistochemistry to evaluate for the Xp11.2 translocation-containing renal cell carcinoma and for angiomyolipoma should be performed. A useful panel of markers for this purpose includes HMB45, S100 protein, epithelial membrane antigen, vimentin, AE1/AE3, Cam 5.2, gp200 (RCC marker), and cytokeratin 7.

SURGEON RESPONSIBILITIES

AREN 03B2 5.3.2.5 Assignment of Surgical Stage

The surgeon should assign a "local-regional stage" to the tumor based solely on the operative findings and findings on pathologic examination. Knowledge of distant metastases does not influence local surgical staging. For example, the patient would be evaluated as "surgical stage III" if there were obviously positive lymph nodes even if it were known that pulmonary metastases were also present.

AREN 03B2 5.3.1.4 Other Responsibilities of the Surgeon
Dictated Operative Report including:

- Demographics (name, date, surgeon, pre and postoperative diagnosis, operation)
- Clinical Summary (age, sex, symptoms and brief outline, preoperative treatments, indications and objectives of surgery)
- Operation-narrative summary (incision, general observations, description of procedure, extent of spread, placement of clips, presence of gross tumor residual, all specimens taken, staging biopsies, and blood loss)
- Completed AREN03B2 Surgical Checklist Form- Unilateral, Bilateral, or Subsequent Surgeries