39 Pediatric Tumors

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General Comments

A number of tumors are unique to children. These tumors frequently require special processing to ensure that the diagnosis can be established and appropriate treatment given. The Children's Oncology Group (COG) creates, monitors, and evaluates therapeutic protocols for pediatric tumors. In the United States, COG frequently requires that pathologic material be sent to review pathologists to verify the diagnosis and to further classify the tumor. Additional fresh and frozen tissue is often required for biologic studies, which are performed at specialized reference laboratories. If this tissue is not collected at the time of surgery, the patient may not be eligible for the appropriate treatment protocol. Furthermore, as knowledge is accumulated and protocols change, tissue requirements change. Therefore, pathologists who are processing pediatric tumors need to work closely with their pediatric oncologists to be aware of the current protocol requirements. Conversely, the entire specimen cannot be submitted for biologic studies. Sufficient tissue must be available to establish a histologic diagnosis. It is vital that the pathologist be responsible for the appropriate triage of this tissue. In many cases, tissue also needs to be submitted for ancillary diagnostic studies (such as electron microscopy and cytogenetic analysis). Despite these demands, pediatric tumors can be processed easily if a series of steps is routinely performed at the time of initial processing. Establishing a routine is particularly important because many biopsies are performed during off-hours.

Overall Guidelines

1. Ensure that *all* pediatric tumors are promptly received in the fresh state. This may entail processing during off-hours by on-call personnel.
2. Decide how much of the specimen is needed for routine histology. This will depend on the tumor type suspected and the size of the biopsy.
3. Submit tissue for electron microscopy if appropriate. It is good practice to put a small piece of every pediatric tumor in glutaraldehyde. This can then be embedded, and the decision of whether to section and process can be made at a later time.
4. Place ½ to 1 cc of minced tumor in Roswell Park Memorial Institute medium (RPMI) or equivalent tissue culture medium and refrigerate. This material can be submitted for cytogenetic analysis, flow cytometry, or mailed to a reference laboratory for special studies (such as ploidy, gene amplification studies, or fluorescence in situ hybridization).
5. Freeze a minimum of 1 cc of tumor tissue in liquid nitrogen. This can be submitted to reference laboratories for protocol studies or held locally in a tumor bank if available. Normal tissue should also be frozen. If you have limited tissue, remember that the frozen section control is often inadequate for permanent histology, yet if it is kept frozen it can be used for these studies.

Small Blue Cell Tumors of Childhood

Pediatric tumors are often embryonal neoplasms showing little or no differentiation by routine

histology. In particular, at the time of frozen section, these tumors appear to be primitive, small, round blue cell tumors. Their diagnosis often depends on ancillary studies such as immunohistochemistry, electron microscopy, and cytogenetics or molecular genetic analysis. If all pediatric specimens are processed as delineated in the first section, all necessary information should be available in a timely fashion. Table 39-1 lists the most common small blue tumors of childhood and their pertinent diagnostic features.

Pediatric Renal Neoplasms

Pediatric renal tumors are often primarily resected and must be carefully processed to ensure accurate staging.[19] Since these tumors are often bulky and friable and are therefore easily distorted, processing must be undertaken with care. (Refer also to Chapter 33.)

1. Photograph the nephrectomy specimen before bivalving. Carefully examine the contour of the kidney and the tumor, and identify potential sites of capsular penetration.
2. Ink the surface (do not strip the capsule).
3. Submit shave sections of the vascular and ureteral margins. The renal vein margin is particularly important.
4. Bivalve the specimen. The kidney should always be bivalved by the pathologist *after* steps 1–3 are performed, not by the surgeon and not in the operating room. Choose your plane of incision carefully, as the placement of the original incision determines your ability to document the relationship between the tumor and kidney, the tumor and the renal sinus, etc. The incision should be at or near the vertical midplane of the kidney. This cut should avoid sites of capsular penetration if possible.
5. Obtain fresh tissues needed for special studies (cytogenetics, frozen, etc.), as outlined previously. Photograph the bivalved specimen.
6. Make cuts parallel to the initial bivalving incision at 2- to 3-cm intervals. Submerge the specimen in a large container of formalin. If the formalin can be refrigerated, color preservation will be enhanced and autolysis slowed.
7. After a few hours or overnight fixation, the remaining sections may be obtained. Two slides should be prepared from all tissue blocks to expedite the mailing of slides to the external review pathologist. The majority of the routine tumor sections should be taken from the periphery of the lesion, showing the following:
   a. Nature of the tumor–kidney junction.

TABLE 39-1. Common small blue cell tumors of childhood and diagnostic parameters.

Tumor type	Immunohistochemistry				EM	Common cytogenetic changes
	NSE	Actin	CD99	CLA		
Neuroblastoma	+++	−	−	−	Neurosecretory granules, processes containing neurofilaments or neurotubules	1p del n-myc amplification
Peripheral neuroectodermal tumor	+	−	++	−	Scant neurosecretory granules, rare processes	t(11;22) and variants
Ewing's sarcoma	±	−	++	−	Glycogen lakes	t(11;22) and variants
Rhabdomyosarcoma						
Alveolar	±	++	±	−	Myofilaments	t(2;13), t(1;13)
Embryonal	±	++	±	−	Myofilaments	11p15 abnormalities
Lymphoblastic lymphoma	−	−	++	+	−	Variable
Burkitt's lymphoma	−	−	−	++	−	t(8;14)
Synovial sarcoma	−	−	±	−		t(X;18)
Desmoplastic small round cell tumor	±	±	±	−		t(11;22) (p13; q24)

CLA, common leukocyte antigen; EM, electron microscopy; MIC2, antibody to the protein coded for by the *MIC2* gene; NSE, neuron-specific enolase.

   b. Relationship of the tumor to the renal capsule, particularly in areas of concern for capsular penetration.
   c. Relationship of the tumor to the renal sinus.
   d. Areas of the tumor that appear different (e.g., necrosis, hemorrhage). Always indicate the exact site from which each section is taken. This is most easily done by taking Polaroid or digital photographs (see Chapter 4). Drawings are often insufficient.
8. Carefully section and inspect the normal kidney, particularly adjacent to the tumor. These areas may show microscopic foci of persistent embryonal tissue known as nephrogenic rests, the potential precursor lesion of nephroblastomas.
9. Carefully dissect the hilar and perinephric tissues for lymph nodes. Failure to submit regional lymph nodes may render patients ineligible for some low-stage protocols.

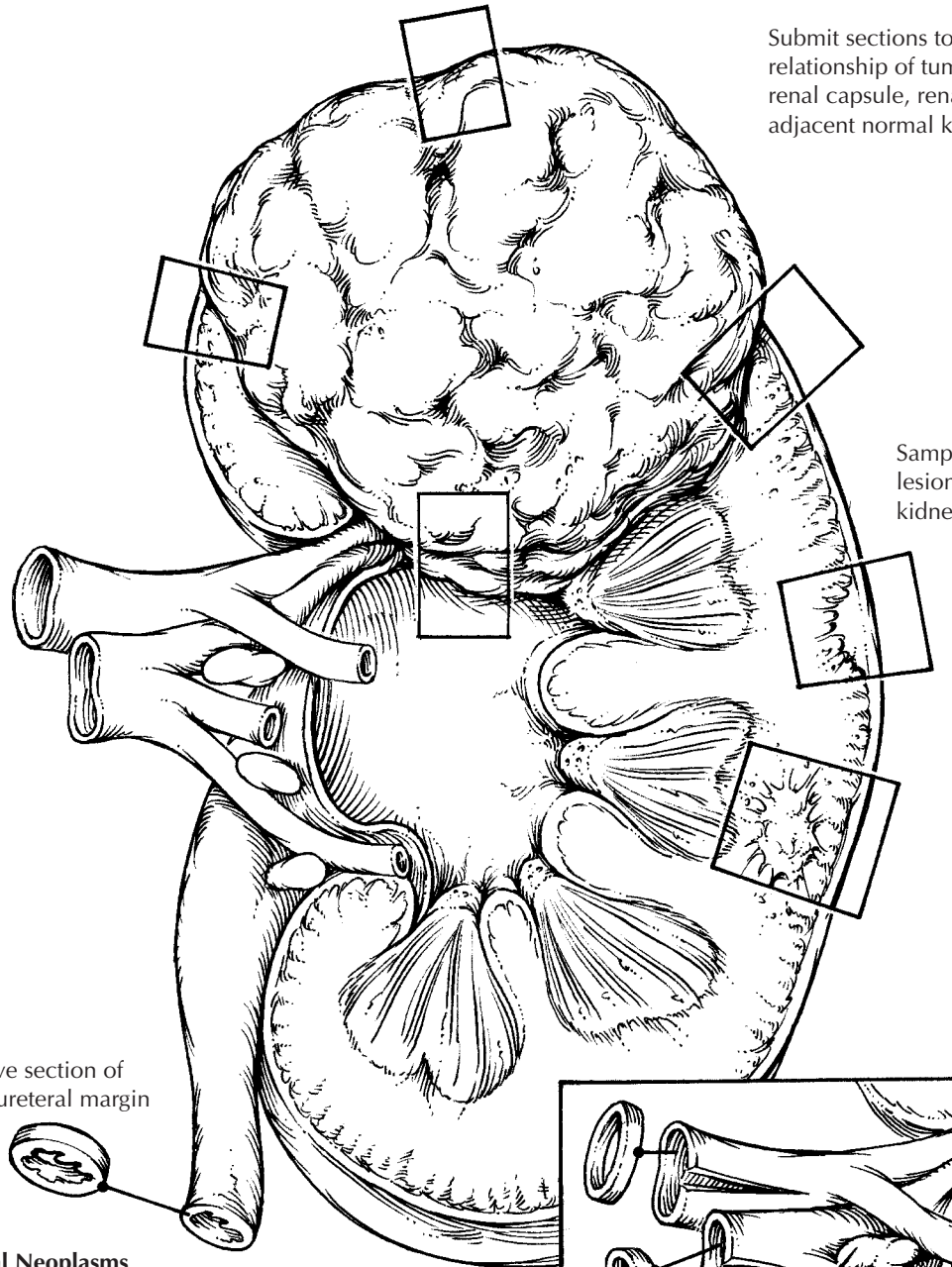
Using the above guidelines for submission of blocks, histologic evaluation should then provide the specific tumor diagnosis as well as the stage. The staging currently used for pediatric tumors is provided in Table 39-2. The diagnosis of stage II neoplasms depends on the identification of either renal capsular penetration or invasion of vessels of the ''renal sinus.'' The renal sinus is the principal portal of exit for tumor cells from the kidney and therefore deserves careful study. The renal sinus is the concave portion of the kidney that contains much of the pelvicalyceal system and the principal arteries, veins, lymphatics, and nerves that pass through this sinus. It is largely filled with vascularized adipose tissue. The renal sinus can be recognized histologically by the fact that the renal cortex lining the sinus lacks a capsule. A thick capsule surrounds the pelvicalyceal structures and continues to cover the medullary pyramids. The distinction between stage I and stage II tumors includes either penetration of the renal capsule or infiltration of vessels of the sinus. Some stage I tumors can distort the renal sinus and protrude with a smoothly encapsulated surface without invading the soft tissue of the renal sinus. Such tumors do not meet the criteria for upstaging, unless they show renal capsular penetration.

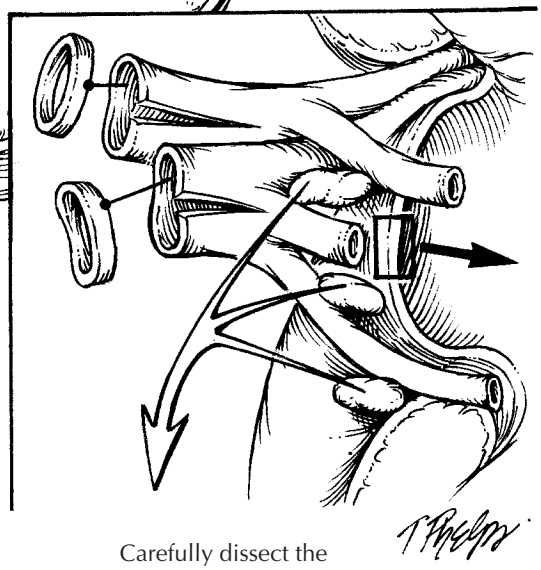
TABLE 39-2. Staging of pediatric renal neoplasms (From National Wilms' Tumor Study).

Stage I: Tumor confined to kidney, completely excised.
Intact renal capsule
Infiltrated but not penetrated renal capsule
Renal sinus vessels not infiltrated
Renal vein contains no tumor (intrarenal vessels may be involved)
Lymph nodes contain no tumor
No distant metastases
Stage II: Tumor extends out of the kidney but is completely excised, and there is no evidence of nodal or distant metastases.
Tumor penetrates renal capsule into perirenal fat
Tumor capsule biopsied, without diffuse peritoneal spillage
Tumor infiltrates renal sinus vessels
Tumor in renal vein, removed without cutting across tumor
Tumor infiltrates adjacent organs or vena cava, but is completely resected
Stage III: Tumor is incompletely excised.
Tumor incompletely excised
Surgical margins involved by tumor
Tumor in lymph nodes
Tumor thrombus transected
Peritoneal implants present
Tumor removed in more than one part

Important Issues to Address in Your Report on Pediatric Renal Neoplasms

- What procedure was performed, and what structures/organs are present?
- What type of neoplasm is present? The most common diagnoses in children are Wilms tumor, clear cell sarcoma of kidney, rhabdoid tumor, congenital mesoblastic nephroma, and renal cell carcinoma. If Wilms tumor, state whether the histology is *favorable* or *unfavorable*. Unfavorable histology is based on the presence of cells with nuclei four times the size of surrounding blastemal cells and the presence of aberrant, multipolar mitotic figures. If unfavorable histology (also called *anaplasia*) is present, comment on its extent (focal or diffuse).
- What is the size of the tumor (weight and greatest dimension)?
- Are any margins involved?
- Is the renal vein involved by tumor?
- Is renal capsular penetration present?
- Is renal sinus invasion present?
- Has the tumor metastasized to regional lymph nodes? Record the number of metastases and the total number of lymph nodes examined.





Pediatric Renal Neoplasms

1. Examine and photograph the specimen, and then ink the surface (do not strip the capsule).
2. Submit thin shave sections from the renal artery, renal vein, and ureter margins. Open and inspect the renal vessels.
3. Bivalve the specimen through the vertical midplane of the tumor.
4. Obtain fresh tissues for special studies as needed.
5. Submit sections of the tumor that demonstrate its relationship to the adjacent renal parenchyma, the renal capsule, and the renal sinus.
6. Do not forget to inspect the normal kidney carefully for additional lesions and the sinus for lymph nodes.