Protocol for the Examination of Specimens from Patients with Rhabdomyosarcoma

Protocol applies to rhabdomyosarcoma and related neoplasms.

No AJCC/UICC TNM Staging System
The Intergroup Rhabdomyosarcoma Study Postsurgical Clinical Grouping System is recommended
Protocol web posting date: October 2009

Procedure
• Resection or biopsy

Authors
D. Ashley Hill, MD*
Department of Pathology, Children's National Medical Center, Washington, DC
Jay Bowen, MS
Center for Childhood Cancer, Columbus Children's Research Institute, Columbus, Ohio
Cheryl M. Coffin, MD
Department of Pathology, Vanderbilt University Medical Center, Nashville, Tennessee
Stephen J. Qualman, MD[#]
Center for Childhood Cancer, Columbus Children's Research Institute, Columbus, Ohio
David M. Parham, MD†
Department of Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma
For the Members of the Cancer Committee, College of American Pathologists

*denotes primary author. † denotes senior author. All other contributing authors are listed alphabetically.

[#] Dr. Steve Qualman passed away during the completion of this work. Steve was an esteemed and valued colleague who contributed greatly to our understanding of the pathology and biology of pediatric sarcomas, especially rhabdomyosarcoma. He will be greatly missed by all of us.

Previous contributors: William Meyer, MD, Philip Branton, MD

The College of American Pathologists offers these protocols to assist pathologists in providing clinically useful and relevant information when reporting results of surgical specimen examinations of surgical specimens. The College regards the reporting elements in the “Surgical Pathology Cancer Case Summary (Checklist)” portion of the protocols as essential elements of the pathology report. However, the manner in which these elements are reported is at the discretion of each specific pathologist, taking into account clinician preferences, institutional policies, and individual practice.

The College developed these protocols as an educational tool to assist pathologists in the useful reporting of relevant information. It did not issue the protocols for use in litigation, reimbursement, or other contexts. Nevertheless, the College recognizes that the protocols might be used by hospitals, attorneys, payers, and others. Indeed, effective January 1, 2004, the Commission on Cancer of the American College of Surgeons mandated the use of the checklist elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. Therefore, it becomes even more important for pathologists to familiarize themselves with these documents. At the same time, the College cautions that use of the protocols other than for their intended educational purpose may involve additional considerations that are beyond the scope of this document.

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Important Note

First priority should always be given to formalin-fixed tissue for morphologic evaluation. Special studies (eg, reverse transcriptase polymerase chain reaction [RT-PCR]) are critical to the molecular work-up of rhabdomyosarcoma and require at least 100 mg of viable snap-frozen tissue as the second priority for work-up **(Note A)**.

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

Surgical Pathology Cancer Case Summary (Checklist)

Protocol web posting date: October 2009

RHABDOMYOSARCOMA AND RELATED NEOPLASMS: Resection or biopsy

Select a single response unless otherwise indicated.

Procedure (Note B)
___ Biopsy
___ Excision, local
___ Excision, radical
___ Excision, compartmentectomy
___ Amputation (specify type: _____)
___ Other (specify: _____)
___ Not specified

Specimen Laterality
___ Right
___ Left
___ Midline
___ Indeterminate
___ Not specified

Tumor Site
___ Bladder/prostate
___ Cranial parameningeal
___ Extremity
___ Genitourinary (not bladder/prostate)
___ Head and neck (excluding parameningeal)
___ Orbit
___ Other(s) (includes trunk, retroperitoneum, etc)
(specify): _____
___ Not specified

Tumor Size
Greatest dimension: ___ cm
*Additional dimensions: ___x____ cm
___ Cannot be determined (see Comment)

***Tumor Depth for Soft Tissue-Based Tumors (select all that apply)**
*___ Dermal
*___ Subcutaneous
*___ Subfascial
*___ Intramuscular
*___ Intra-abdominal
*___ Retroperitoneal
*___ Intracranial
*___ Organ based
*___ Other (specify): _____
*___ Cannot be assessed

Histologic Type (Note C)
___ Embryonal, botryoid
___ Embryonal, spindle cell
___ Embryonal, not otherwise specified (NOS)
___ Alveolar
___ Mixed embryonal and alveolar rhabdomyosarcoma
(specify percentage of each type): _____
___ Rhabdoid rhabdomyosarcoma
___ Sclerosing rhabdomyosarcoma
___ Undifferentiated sarcoma
___ Ectomesenchymoma
___ Other (specify): _____
___ Rhabdomyosarcoma, subtype indeterminate

Anaplasia (Note D)
___ Not identified
___ Focal (single or few scattered anaplastic cells)
___ Diffuse (clusters or sheets of anaplastic cells)
___ Indeterminate
___ Cannot be assessed

Margins (Note E)
___ Cannot be assessed
___ Sarcoma involvement of margins not identified
Distance of sarcoma from closest margin: ___ mm OR __ cm.
Specify margin: _____
___ Margin(s) involved by sarcoma
Specify margin(s): _____
___ Indeterminate

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Lymph Nodes

___ No regional lymph nodes sampled
___ Metastatic involvement of regional lymph nodes not identified
___ Regional lymph node metastasis present
Specify: Number examined: ___
Number involved: ___

Distant Metastasis

___ Not applicable
___ Distant metastasis present
*Specify site(s), if known: _____

The Intergroup Rhabdomyosarcoma Study Postsurgical Clinical Grouping System (Note F)

Note: Clinical information required to definitively assign stage group (eg, gross residual disease or distant metastatic disease) may not be available to the pathologist. Alternatively, this protocol may not be applicable to some situations (eg, group IIIA). If applicable, the appropriate stage group may be assigned by the pathologist.

___ Not applicable
___ Cannot be assessed (see Comment)

Group I
___ A Localized tumor, confined to site of origin, completely resected
___ B Localized tumor, infiltrating beyond site of origin, completely resected

Group II
___ A Localized tumor, gross total resection, but with microscopic residual disease
___ B Locally extensive tumor (spread to regional lymph nodes), completely resected
___ C Locally extensive tumor (spread to regional lymph nodes), gross total resection, but microscopic residual disease

Group III
___ A Localized or locally extensive tumor, gross residual disease after biopsy only
___ B Localized or locally extensive tumor, gross residual disease after major resection (greater than 50% debulking)

Group IV
___ Any size primary tumor, with or without regional lymph node involvement, with distant metastases, without respect to surgical approach to primary tumor.

***Modified Site, Size, Metastasis Staging for Rhabdomyosarcoma (for relevant stage) (select all that apply) (Note F)**

Note: Clinical information required to definitively assign stage (eg, nodal status or distant metastatic disease) may not be available to the pathologist.

*___ Not applicable
*___ Cannot be assessed (see Comment)
*___ Stage I (requires all of the following to be true)
    *___ Tumor involves orbit, head and neck or genitourinary site (excluding bladder, prostate and cranial parameningeal)
    *___ Tumor metastatic to distant site not identified
*___ Stage II (requires all of the following to be true)
    *___ Tumor does not involve orbit, non-parameningeal head and neck or non-bladder/non-prostate genitourinary tract
    *___ Tumor size ≤5 cm
    *___ Tumor involvement of lymph nodes not identified
    *___ Tumor metastatic to distant site not identified
*___ Stage III (select one if applicable)
    *___ Tumor involves bladder or prostate and is metastatic to regional lymph nodes but distant metastases are not identified
    *___ Tumor involves site other than orbit, non-parameningeal head and neck or non-bladder/non-prostate genitourinary tract and is >5 cm but distant metastases are not identified
*___ Stage IV
    *___ Distant metastases present

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

***Comment(s)**

Explanatory Notes

A. Submission of Tissue

A minimum of 100 mg of viable tumor should be snap-frozen for potential molecular studies.[1] If tissue is limited, the pathologist can keep the frozen tissue aliquot used for frozen section (usually done to determine sample adequacy and viability) in a frozen state (-80°C or lower) for potential molecular studies. Translocations may be detected using reverse transcriptase polymerase chain reaction (RT-PCR) or fluorescence in situ hybridization (FISH) on touch preparations made from frozen tissue. Alternatively, if no other tissue is available, then FISH may be performed on paraffin sections; some commercial laboratories prefer this material.

B. Procedures

Core needle biopsies can obtain sufficient material for special studies and morphologic diagnosis, but sampling problems may limit tumor subtyping. Open incisional biopsy is the generally preferred and most widely used technique because it consistently provides a larger sample of tissue and maximizes the opportunity for a specific pathologic diagnosis.[2] Excisional biopsy may not include an adequate margin of normal tissue even with an operative impression of total gross removal.[2]

Resection specimens may be intralesional, marginal, wide, or radical in extent. Intralesional resections extend through tumor planes, with gross or microscopic residual tumor identifiable at surgical margins. A marginal resection involves a margin formed by inflammatory tissue surrounding the tumor. A wide, radical resection has surgical margins that extend through normal tissue, usually external to the anatomic compartment containing the tumor. For all types of resections, marking (tattoo with ink followed by use of a mordant) and orientation of the specimen *(prior to cutting)* are mandatory for accurate pathologic evaluation.[2]

C. Histologic Type

The International Classification of Rhabdomyosarcoma is used to classify childhood rhabdomyosarcoma (RMS) into prognostically useful histologic categories.[3] Although undifferentiated sarcoma is a diagnosis of exclusion, its response to therapy is similar to alveolar RMS and was therefore included. This classification has been further modified by the Intergroup Rhabdomyosarcoma Study Group to include the anaplastic variant (Table 1).[4]

Botryoid Rhabdomyosarcoma

Botryoid RMS (sarcoma botryoides) is a favorable prognosis subtype of embryonal RMS and represents about 6% of cases submitted to the Intergroup Rhabdomyosarcoma Study Group. The term “botryoid” comes from the Greek word “*botryos*” meaning grapes, which describes its characteristic gross appearance of multiple nodules of soft, myxoid tumor growing into the lumen of a hollow viscus. Botryoid RMS by definition occurs in sites adjacent to an epithelial surface, particularly bladder, vagina, nasal cavity and sinuses, and biliary tract. Diagnosis of the botryoid variant requires at least 1 microscopic field demonstrating a cambium layer (condensed layer of rhabdomyoblasts) underlying an intact epithelium.

Spindle Cell Rhabdomyosarcoma

Spindle cell RMS, also considered a subtype of embryonal RMS, was described in detail in 1992.[5,6] It is uncommon, accounting for 3% of cases. Almost one-third of spindle cell RMS are located in the paratesticular region, where they account for 26.7% of RMS in this site, the remainder mostly being embryonal RMS, not otherwise specified (NOS). The 5-year survival for patients with spindle cell RMS in the paratesticular location is 88%. The favorable prognosis of spindle cell RMS does not apply to lesions outside the paratesticular and orbital regions, as tumors in these other locations have a prognosis similar to embryonal RMS, NOS. Spindle cell RMS is composed almost exclusively (minimum 80% of tumor) of elongated spindle cells in 1 of 2 recognizable patterns. The collagen-poor pattern has a whorled, fascicular growth of spindle cells without significant collagen and resembles a smooth muscle tumor both grossly and microscopically. The collagen-rich form shows spindle cells with variable myogenic differentiation in a dense collagenous stroma. The spindle cells have eosinophilic, fibrillar cytoplasm with distinct borders. Cells with cross-striations are easily found. A small component of embryonal RMS, NOS is seen in some cases, usually at the tumor periphery. Anaplasia is uncommon.

The primary differential diagnosis of spindle cell RMS includes embryonal RMS NOS, leiomyosarcoma, fibrosarcoma, malignant fibrous histiocytoma (MFH) and the more bland entities rhabdomyoma and leiomyoma and nodular fasciitis. In general, smooth muscle neoplasms are uncommon in childhood and adolescence. The presence of specific skeletal muscle antigens (eg, myoglobin, MyoD1, myogenin) and the ultrastructural presence of skeletal myofilaments helps in distinguishing spindle cell RMS from leiomyosarcoma, fibrosarcoma, and MFH.

Embryonal Rhabdomyosarcoma, Not Otherwise Specified

Embryonal RMS, NOS has an intermediate prognosis with a 5-year survival of 66% and accounts for approximately one-half of all RMS. These tumors are composed of mesenchymal cells that show variable degrees of cytoplasmic skeletal muscle differentiation. They are typically moderately cellular but may contain both hypo- and hypercellular areas with a loose, myxoid stroma. Either of these components may predominate, particularly in limited biopsies. Dense embryonal RMS, NOS may resemble solid alveolar RMS; its myogenin immunostaining pattern (focal, not diffuse) and testing for PAX3 translocations may assist in making this distinction. Perivascular condensations of tumor cells in the less cellular regions are common.

Embryonal RMS, NOS tumor cells may be rounded, stellate, or spindle-shaped. Nuclei are generally small with a light chromatin pattern and inconspicuous nucleoli. They typically have more irregular or spindled outlines that those of alveolar RMS. Many tumor cells contain generous amounts of eosinophilic cytoplasm, a feature of myoblastic differentiation. Cells with elongated tails of cytoplasm (“tadpole cells”) and cells with cytoplasm in the shape of a ribbon or “strap” are helpful in the light-microscopic diagnosis. Cross-striations can be seen in less than one-half of the cases and are not a prerequisite for diagnosis.

The differential diagnosis of embryonal RMS, NOS includes the botryoid and spindle cell variants and solid alveolar RMS. Ectomesenchymoma (discussed below) typically has embryonal RMS along with a neuroblastic/ganglion cell component. Undifferentiated

embryonal sarcoma of the liver has some morphologic and phenotypic overlap, but it generally does not express MyoD1 or myogenin by immunohistochemistry and contains characteristic cytoplasmic hyaline globules. Embryonal RMS-like differentiation is a common component of the multipatterned pediatric lung tumor pleuropulmonary blastoma. Occasional Wilms tumors show marked skeletal muscle differentiation and may even have a cambium layer in tumors abutting the renal pelvis. Well-differentiated embryonal RMS can also have some morphologic overlap with fetal rhabdomyoma. The finding of increased mitoses (>15 per 50 high-power fields), marked hypercellularity, a "cambium layer," and atypical nuclear features are more characteristic of RMS. Giant cell tumors of tendon sheath may lack giant cells, contain cells with eosinophilic cytoplasm, and show desmin positivity; however, they are strongly CD68-positive and myogenin-negative. Pseudosarcomatous fibroepithelial polyps of the lower female genital tract are particularly treacherous and should be considered in botryoid lesions occurring in adolescents and adults, particularly during pregnancy. These hypercellular lesions contain pleomorphic cells with a variable mitotic rate and frequently express desmin; however, they lack a cambium layer.

Alveolar Rhabdomyosarcoma

Alveolar RMS is a poor prognosis subtype with a 53% 5-year survival. These tumors are composed of malignant small rounded cells that are typically discohesive with a tendency to attach to and line up along thin fibrous septae. The tumor cells have some variation in size. Large, multinucleate cells can be found occasionally. Tumor cell nuclei are round and lymphocyte-like with coarse chromatin and one or more indistinct nucleoli. Tumor cells may show a thin rim of eosinophilic cytoplasm. Morphologic evidence of rhabdomyoblastic differentiation including strap cells or cells with cross-striations is often lacking, although multinucleate myoblasts may be seen. It is important to recognize the "solid variant," in which the tumor cells grow in solid masses of closely aggregated cells. With wide sampling, areas showing cleft-like spaces or a more classically alveolar pattern can usually be found, facilitating recognition of these tumors as alveolar RMS. Occasionally, an alveolar RMS pattern can be seen focally in a tumor that would otherwise be classified as embryonal RMS. These so-called mixed embryonal and alveolar RMS are currently included for classification purposes in the category of alveolar RMS when >50% of the tumor is composed of the alveolar pattern. It is unclear if the alveolar pattern seen in these mixed tumors is pathogenetically related to usual type alveolar RMS; typically these foci lack a PAX fusion.

The differential diagnosis of alveolar RMS includes the panoply of malignant small round cell neoplasms, particularly Ewing sarcoma/primitive neuroectodermal tumor (ES/PNET), poorly differentiated or undifferentiated neuroblastoma, desmoplastic small round cell tumor (DSRCT), poorly differentiated monophasic synovial sarcoma, and lymphoma. A panel of immunohistochemical stains including myogenin, desmin, Myo-D1, cytokeratin, CD99, WT1, synaptophysin, chromogranin, and leukocyte common antigen will distinguish alveolar RMS from these other entities, but unexpected staining with antigens such as cytokeratin may occur. Alveolar RMS shows diffuse and strong nuclear staining for myogenin. RT-PCR for PAX3- and PAX7-FKHR fusion gene products occur in approximately 85% of alveolar RMS cases and are recommended for difficult cases. The proper treatment and exact nature of PAX fusion-negative alveolar RMS is currently debated, so that histologic diagnosis remains the primary determinant for therapeutic protocol assignment.

Rhabdomyosarcoma with Rhabdoid Features

A rare type of RMS is one which shows abundant cells with large amounts of eosinophilic cytoplasm and intermediate-filament globular inclusions similar to those seen in malignant rhabdoid tumors (MRT).[7] Of 27 cases identified in IRS I-III, 22 had an embryonal histology and 5 had an alveolar histology. Tumors differed from MRT in their nuclear cytologic features; in rhabdoid RMS, the nuclear chromatin tended to be coarse instead of vesicular. Immunohistochemically, the inclusions were positive for vimentin and desmin, and the cytoplasm adjacent to the inclusion was positive for muscle specific actin and desmin. No significant survival difference was seen in this group but the numbers were small. Myogenin and INI-1 staining may be helpful in making the distinction between this neoplasm and true rhabdoid tumor.

Undifferentiated Sarcoma

Undifferentiated sarcomas, although they lack evidence of skeletal muscle differentiation, are included in the RMS classification system because historically they have been managed with therapy similar to RMS. These tumors are now treated on non-rhabdomyosarcomatous soft tissue tumor regimens in Children's Oncology Group studies. Undifferentiated sarcomas consist mostly of medium-sized cells with indistinct cytoplasm and oval nuclei with prominent chromocenters.[8] The cells are packed in sheets with no structure except perhaps a delicate fibrovascular septa or spindled-storiform pattern. Necrosis or inflammation is not prominent. Approximately three-fourths of tumors will stain with vimentin antisera. A combination of immunostains, electron microscopy, and cytogenetic/molecular studies are required to exclude other tumors from the undifferentiated category.

Ectomesenchymoma

Ectomesenchymoma is a rare malignant tumor that generally consists of a RMS component (embryonal greater than alveolar) and a neuroblastic component. The name originates from the belief that these tumors arise from pluripotent migrating neural crest cells or "ectomesenchyme." They have a similar age, sex, and site distribution and outcome to embryonal RMS and are treated with RMS-based therapy. Ectomesenchymomas are included in the risk stratification scheme for treatment of RMS based on the subtype of RMS seen.

Sclerosing Rhabdomyosarcoma

Several recent series have introduced a new morphologic type of RMS characterized by a dense hyalinizing collagenous matrix with rounded tumor cells arranged in small nests, single-file rows, and pseudovascular, alveolar profiles.[9-11] The tumors may have only focal positivity for desmin and myogenin but seem to be uniformly positive for MyoD1. This pattern has been termed sclerosing RMS and has morphologic overlap with sclerosing epithelioid fibrosarcoma, infiltrating carcinoma, osteosarcoma, and angiosarcoma. The relationship between sclerosing RMS and the more classic categories of embryonal and alveolar RMS is unknown at this time, although they appear to be PAX fusion-negative. Sclerosing RMS has been described in both children and adults. The prognosis relative to other categories of rhabdomyosarcoma is currently unknown.

Table 1. International Classification of Rhabdomyosarcoma[a]

Diagnosis[b]	Histology	Incidence (%)[c]	Five-year survival (%)	Prognosis
Embryonal, botryoid	Favorable	6	95	Superior
Embryonal, spindle cell	Favorable	3	88	Superior
Embryonal, not otherwise specified (NOS)	Favorable	49	66	Intermediate
Alveolar, NOS or solid variant	Unfavorable	31	53	Poor
Undifferentiated sarcoma	Unfavorable	3	44	Poor

[a] From Qualman et al.[4]
[b] Anaplasia can be found in any histologic subtype. Diffuse anaplasia is an unfavorable histology, with an incidence of 2% and a 5-year survival of 45%. The prognosis is poor.
[c] Total incidence is only 94% (including 2% RMS with diffuse anaplasia); some 6% of cases fall into the sarcoma NOS category because of insufficient or inadequate tissue to make a more specific diagnosis.

Immunohistochemistry

In cases where histological diagnosis of rhabdomyosarcoma is difficult, immunostaining with monoclonal antibodies against the intranuclear myogenic transcription factors MyoD1 and myogenin, and a polyclonal antibody preparation against desmin (P-DES) is suggested. Nearly all RMS tumors are positive for P-DES, myogenin, and MyoD1.[4,12] Polyclonal desmin is 35% more sensitive in the detection of RMS as compared with monoclonal desmin.[4] On occasion, anti-myogenin reacts with other spindle cell neoplasms,[13] and rare RMS cases may be myogenin-negative and desmin-positive.[14]

Chromosomal Translocations

The incidence of t(1;13) (resulting in a PAX7-FKHR gene fusion) and t(2;13) (PAX3-FKHR gene fusion) is strongly correlated with the alveolar subtype of rhabdomyosarcoma. These translocations may be found in as many as 85% of alveolar RMS cases.[2] Of these, approximately 30% are positive for PAX7-FKHR and the remaining 70% for PAX3-FKHR. Studies suggest that patients with alveolar RMS expressing the PAX3-FKHR gene product have a lower event-free survival than PAX7-FKHR-positive alveolar RMS,[4] but the significance of the translocations must still be elucidated. More recent data indicate that when gene fusion status is compared in patients with metastatic disease at diagnosis, a striking difference in outcome is seen between PAX7-FKHR and PAX3-FKHR (estimated 4-year overall survival of 75% for PAX7-FKHR and 8% for PAX3-FKHR; P=.002).[15]

Some tumors with alveolar histology lack a demonstrable PAX fusion. By gene array testing, they do not cluster with PAX fusion-positive tumors, so that they appear to have a different genetic signature that more closely resembles embryonal RMS.[16] Studies regarding the clinical significance of this finding are ongoing. At the present time, tumors with alveolar histology are treated accordingly on Children's Oncology Group protocols, independent of fusion status. However, fusion studies are extremely useful with limited or questionable material.

D. Anaplasia

Anaplasia is a histologic feature which may be found in any histologic subtype of RMS.[17] A recent retrospective review showed 13% of all samples analyzed had anaplasia.[18] Anaplastic tumors are defined using the Wilms tumor definition of large, lobate hyperchromatic nuclei (at least 3 times the size of neighboring nuclei) and atypical (obvious, multipolar) mitotic figures. Anaplasia is further defined as to the distribution of the cells: focal (group I) anaplasia, which consists of a single or a few cells, scattered amongst nonanaplastic cells; or diffuse (group II), in which clusters or sheets of anaplastic cells are evident. Anaplasia is more common in patients with tumors in favorable sites and less commonly observed in younger patients and in those with stage II, III, or clinical group III disease.[18] Regardless of focal or diffuse distribution, the presence of anaplasia negatively influences the failure-free survival rate (63% versus 77% at 5 years) and overall survival (68% versus 82% at 5 years) rates in patients with embryonal rhabdomyosarcoma.[14] This effect is most pronounced in children with intermediate-risk tumors but does not affect outcome in patients with alveolar tumors. Although it has predictive value for clinical outcome, current treatment protocols do not account for anaplasia in stratification of patients, as it has limited value as an independent survival marker.

E. Margins

The extent of resection (ie, gross residual disease versus complete resection) has the strongest influence on local control of malignancy.[19,20] The definition of what constitutes a sufficiently "wide" margin of normal tissue in the management of RMS has evolved over time from resection of the whole muscle to resection with a 2- to 3-cm margin.[16] For non-rhabdomyosarcoma soft tissue sarcomas, narrower margins (1 to 2 cm) may be adequate for low-grade tumors, whereas wider margins (greater than 5 cm) may be needed for higher-grade tumors.[20]

F. Clinical Grouping and Modified "TNM" Staging

The American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) TNM staging systems currently do not apply to RMS. The Intergroup Rhabdomyosarcoma Study Postsurgical Clinical Grouping System is recommended by this protocol. The Clinical Grouping System is used to plan radiation therapy and relies on pathologic examination.[21]

Also provided in this protocol is the "TNM" staging system modified for use with rhabdomyosarcoma. This system is based on a surgical, site-based, pretreatment assessment, which is used to plan chemotherapy. This modified staging system is predictive of outcome in rhabdomyosarcoma.[2,4, 21]

Clinical classification usually is carried out by the referring physician before treatment, during initial evaluation of the patient or when pathologic classification is not possible.

G. Relevant History

Relevant historical factors include any previous therapy, family history of malignancy, and the presence of congenital anomalies. If preoperative therapy has been given, assessment may be limited to the estimate of viable and necrotic RMS.[2] The tumor may also show extreme cytodifferentiation and nuclear pleomorphism. These factors may preclude accurate subtyping of the RMS.

There is a specific concern for increased risk of a familial cancer when the specific diagnosis of embryonal RMS or other soft tissue sarcoma is made within the first 2 years of life, especially in a male child.[22] Such syndromes include Li-Fraumeni syndrome, basal cell nevus syndrome, neurofibromatosis, and pleuropulmonary blastoma syndrome (pleuropulmonary blastoma plus associated malignancies).[2] A genetic predisposition to cancer is thought to be present in 7% to 33% of children with soft tissue sarcomas.[23]

Rhabdomyosarcoma is specifically associated with a variety of congenital anomalies.[24] These include congenital anomalies of the central nervous system, genitourinary tract, gastrointestinal tract, and cardiovascular system.

References

1. Qualman SJ, Morotti RA. Risk assignment in pediatric soft-tissue sarcoma: an evolving molecular classification. *Curr Oncol Rep.* 2002;4:123-130.
2. Coffin CM, Dehner LP. Pathologic evaluation of pediatric soft tissue tumors. *Am J Clin Pathol.* 1998;109(suppl 1):S38-S52.
3. Coffin CM. The new International Rhabdomyosarcoma Classification, its progenitors, and consideration beyond morphology. *Adv Anat Pathol.* 1997;4:1-16.
4. Qualman SJ, Coffin, CM, Newton WA, et al. Intergroup Rhabdomyosarcoma Study: update for pathologists*. Pediatr Dev Pathol.* 1998;1:550-561.
5. Cavazzana AO, Schmidt D, Ninfo V et al. Spindle cell rhabdomyosarcoma. A prognostically favorable variant of rhabdomyosarcoma. *Am J Surg Pathol.* 1992;16:229-35.
6. Leuschner I, Newton WA, Jr., Schmidt D et al. Spindle cell variants of embryonal rhabdomyosarcoma in the paratesticular region. A report of the Intergroup Rhabdomyosarcoma Study. *Am J Surg Pathol.* 1993;17:221-30.
7. Kodet R, Newton WA, Jr., Hamoudi AB, Asmar L. Rhabdomyosarcomas with intermediate-filament inclusions and features of rhabdoid tumors. Light microscopic and immunohistochemical study. *Am J Surg Pathol.* 1991;15:257-67.
8. Pawel BR, Hamoudi AB, Asmar L et al. Undifferentiated sarcomas of children: pathology and clinical behavior--an Intergroup Rhabdomyosarcoma study. *Med Pediatr Oncol.* 1997;29:170-80.
9. Mentzel T, Katenkamp D. Sclerosing, pseudovascular rhabdomyosarcoma in adults: clinicaopathological and immunohistochemical analysis of three cases. *Virchows Arch.* 2000;436:305-311.
10. Folpe AL, McKenney JK, Bridge JA, Weiss SW. Sclerosing Rhabdomyosarcoma in adults: Report of four cases of a hyalinizing, matrix-rich variant of rhabdomyosarcoma that may be confused with osteosarcoma, chondrosarcoma, or angiosarcoma. *Am J Surg Pathol.* 2002;26(9):1175-83.
11. Chiles MC, Parham DM, Qualman SJ et al. Sclerosing rhabdomyosarcomas in children and adolescents: a clinicopathologic review of 13 cases from the Intergroup Rhabdomyosarcoma Study Group and Children's Oncology Group. *Pediatr Dev Pathol.* 2004;7:583-94.
12. Parham DM. Pathologic classification of rhabdomyosarcomas and correlations with molecular studies. *Mod Pathol.* 2001;14:506-514.
13. Cessna MH, Zhou H, Perkins SL et al. Are myogenin and myoD1 expression specific for rhabdomyosarcoma? A study of 150 cases, with emphasis on spindle cell mimics. *Am J Surg Pathol.* 2001;25(9):1150-7.

14. Morotti RA, Nicol KK, Parham DM et al. An immunohistochemical algorithm to facilitate diagnosis and subtyping of rhabdomyosarcoma: the Children's Oncology Group experience. *Am J Surg Pathol* 2006;30(8):962-8.
15. Kelly KM, Womer RB, Sorensen PH, Xiong QB, Barr FG. Common and variant gene fusions predict distinct clinical phenotypes in rhabdomyosarcoma. *J Clin Oncol.* 1997;15(5):1831-6.
16. Davicioni E, Anderson MJ, Finckenstein FG et al. Molecular classification of habdomyosarcoma--genotypic and phenotypic determinants of diagnosis: a report from the Children's Oncology Group. *Am J Pathol.* 2009;174(2):550-64.
17. Kodet R, Newton WA Jr, Hamoudi A, Asmar L, Jacobs DL, Maurer H. Childhood rhabdomyosarcoma with anaplastic (pleomorphic) features: a report of the Intergroup Rhabdomyosarcoma Study. *Am J Surg Pathol.* 1993;17:443-453.
18. Qualman S, Lynch J, Bridge J, Parham D, Teot L, Meyer W, Pappo A. Prevalence and clinical impact of anaplasia in childhood rhabdomyosarcoma : a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. *Cancer.* 2008;113(11):3242-7
19. Marcus KC, Grier HE, Shamberger RC, et al. Childhood soft tissue sarcoma: a 20-year experience. *J Pediatr.* 1997;131:603-607.
20. Fletcher C, Kempson RL, Weiss S. Recommendations for reporting soft tissue sarcomas. *Am J Clin Pathol.* 1999;111:594-598.
21. Raney RB, Anderson JR, Barr FG et al. Rhabdomyosarcoma and undifferentiated sarcoma in the first two decades of life: a selective review of Intergroup Rhabdomyosarcoma Study Group experience and rationale for Intergroup Rhabdomyosarcoma Study V. *Am J Pediatr Hematol Oncol.* 2001;23(4):215-20.
22. Birch JM, Hartley AL, Blair V, et al. Cancer in the families of children with soft tissue sarcoma. *Cancer.* 1990;66:2239-2248.
23. Hartley AL, Birch JM, Blair V, et al. Patterns of cancer in the families of children with soft tissue sarcoma. *Cancer.* 1993;72:923-930.
24. Ruymann FB, Maddux HR, Ragab A, et al. Congenital anomalies associated with rhabdomyosarcoma. *Med Pediatr Oncol.* 1988;16:33-39.