

# Rhabdomyosarcoma

**Protocol applies to the examination of specimens from patients (children and young adults) with rhabdomyosarcoma. It excludes nonrhabdomyosarcomatous soft tissue sarcomas.**

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

## **Procedures**

- **Cytology** (No Accompanying Checklist)
- **Incisional Biopsy (Needle or Wedge)** (No Accompanying Checklist)
- **Resection**

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**Surgical Pathology Cancer Case Summary (Checklist)**

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

**RHABDOMYOSARCOMA AND RELATED NEOPLASMS:**

**Excision, Local or Wide; Compartmentectomy; Excision,  
Radical; Amputation (Type); Other (eg, Piecemeal)**

Patient name:

Surgical pathology number:

**Note: Check 1 response unless otherwise indicated.**

**MACROSCOPIC****Specimen Type**

- Excision, local or wide (\_\_\_ cm closest margin)  
 Compartmentectomy (\_\_\_ cm closest margin)  
 Excision, radical (\_\_\_ cm closest margin)  
 Amputation (type) (neural, vascular, soft tissue margins)  
 Other (piecemeal)  
 Not specified

**Tumor Depth (check all that apply)#**

- Dermal  
 Subcutaneous  
 Subfascial  
 Intramuscular  
 Intra-abdominal  
 Retroperitoneal  
 Other (specify): \_\_\_\_\_

# More than 1 tissue plane may be involved and should be indicated.

**Tumor Size**

Greatest dimension: \_\_\_ cm

\*Additional dimensions: \_\_\_x\_\_\_ cm

Cannot be determined (see Comment)

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

**Laterality (as appropriate)**

- Right  
 Left

**Tumor Site**

- Bladder/prostate  
 Cranial  
 Extremity  
 Genitourinary (not bladder/prostate)  
 Head and neck (excluding parameningeal)  
 Orbit  
 Parameningeal  
 Other(s) (includes trunk, retroperitoneum, etc)  
(specify): \_\_\_\_\_  
 Not specified

**MICROSCOPIC****Histologic Type**

- Embryonal, botryoid  
 Embryonal, spindle cell  
 Embryonal, not otherwise specified (NOS)  
 Alveolar, NOS or solid variant  
 Mixed rhabdomyosarcoma (specify percentage of each type):  
\_\_\_\_\_  
 Undifferentiated sarcoma  
 Other (specify): \_\_\_\_\_  
 Rhabdosarcoma, subtype cannot be determined

**Anaplasia<sup>#</sup>**

- Absent  
 Focal  
 Diffuse  
 Indeterminate

<sup>#</sup> *May be present in any histologic subtype*

**\*Mitotic Rate**

(X40 objective, most proliferative area)  
 /10 high-power fields

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

**\*Necrosis**

\*  Absent

\*  Present

\*Extent: \_\_\_%

**Regional Lymph Nodes**

Cannot be assessed

No regional lymph node metastasis

Regional lymph node metastasis

Specify: Number examined: \_\_\_

Number involved: \_\_\_

**Distant Metastasis**

Cannot be assessed

Distant metastasis

\*Specify site(s), if known: \_\_\_\_\_

**Margins**

Cannot be assessed

Margins uninvolved by sarcoma

Distance of sarcoma from closest margin: \_\_\_ mm

Margins involved by sarcoma

Specify margin(s): \_\_\_\_\_

**\*Venous/Lymphatic (Large/Small Vessel) Invasion**

\*  Present

\*  Absent

\*  Indeterminate

**The Intergroup Rhabdomyosarcoma Study Postsurgical Clinical Grouping System**

*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.

**\*Additional Pathologic Findings**

\*Specify: \_\_\_\_\_

**\*Comment(s)**

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

## Background Documentation

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Protocol revision date: January 2004

### I. Cytologic Material (Note B)

#### A. Clinical Information

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

#### B. Macroscopic Examination

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

#### C. Microscopic Evaluation (Note D)

1. Adequacy of specimen (if unsatisfactory for evaluation, specify reason)
2. Tumor, if present
  - a. Histologic type, if possible (subtype may also be suggested)
  - b. Other features (eg, anaplasia)
3. Other pathologic findings (eg, necrosis)
4. Results/status of special studies (specify)
5. Comments
  - a. Correlation with intraprocedural consultation, as appropriate
  - b. Correlation with other specimens, as appropriate
  - c. Correlation with clinical information, as appropriate

### II. Incisional Biopsy

#### (Needle or Wedge) (Note E)

#### A. Clinical Information

1. Patient identification
  - a. Name
  - b. Identification number
  - c. Age (birth date)
  - d. Sex
2. Responsible physician(s)

3. Date of procedure
4. Other clinical information
  - a. Relevant history (eg, previous diagnoses, treatment, family history) (Note C)
  - b. Relevant findings (eg, imaging studies)
  - c. Clinical diagnosis
  - d. Procedure (eg, core needle biopsy, wedge biopsy)
  - e. Anatomic sites(s) of specimen

**B. Macroscopic Examination**

1. Specimen
  - a. Unfixed/fixed (specify fixative)
  - b. Number of pieces
  - c. Dimensions
  - d. Descriptive features
  - e. Orientation, if designated by surgeon
  - f. Results of intraoperative consultation
2. Tissue submitted for microscopic examination, as appropriate
  - a. Entire specimen
  - b. Selected sample
  - c. Frozen section tissue fragment(s) (unless saved for special studies)
3. Special studies (specify) (eg, immunohistochemistry, electron microscopy, fluorescence in situ hybridization [FISH], reverse transcriptase polymerase chain reaction [RT-PCR], cytogenetic analysis) (Note A)

**C. Microscopic Evaluation (Note D)**

1. Tumor
  - a. Histologic type
  - b. Histologic subtype, if possible
  - c. Venous/lymphatic vessel invasion, if possible to determine
  - d. Evaluate for anaplasia, cambium layer
2. Additional pathologic findings, if present
3. Results/status of special studies (specify)
4. Comments
  - a. Correlation with intraoperative consultation, as appropriate
  - b. Correlation with other specimens, as appropriate
  - c. Correlation with clinical information, as appropriate

**III. Resection (Note F)****A. Clinical Information**

1. Patient identification
  - a. Name
  - b. Identification number
  - c. Age (birth date)
  - d. Sex
2. Responsible physician(s)/clinic(s)
3. Date of procedure
4. Other clinical information
  - a. Relevant history
    - (1) previous diagnoses
    - (2) surgery and date(s)
    - (3) radiation and date(s)
    - (4) chemotherapy and date(s)
    - (5) others (Note C)

- b. Relevant findings
- c. Clinical diagnosis
- d. Procedure (specify anatomic site[s])
  - (1) type of excision or resection (eg, cystectomy)
  - (2) list all anatomical structures removed
  - (3) lymph node dissection
- e. Operative findings (documentation of areas of concern marked by surgeon)
- f. Anatomic site(s) of specimen(s)

**B. Macroscopic Examination**

- 1. Specimen
  - a. Organ/tissues included
  - b. Unfixed/fixed (specify fixative)
  - c. Size (3 dimensions)
  - d. Descriptive features
  - e. Orientation, if indicated by surgeon
  - f. Results of intraoperative consultation (frozen sections or touch preparations)
- 2. Tumor
  - a. Anatomical site(s) involved by tumor
  - b. Size (3 dimensions)
  - c. Descriptive characteristics (eg, firm/soft, color, consistency, necrosis, biopsy scars)
  - d. Anatomic extent (structures involved by tumor and depth of invasion)
  - e. Relation to margins (Note **G**)
  - f. Additional tumors
- 3. Additional pathologic findings, if present
- 4. Lymph nodes submitted
- 5. Margins (Note **G**)
- 6. Tissues submitted for microscopic examination (1 section for each centimeter of maximal tumor diameter and/or different gross appearances)<sup>1</sup>
- 7. Special studies (specify) (eg, immunohistochemistry, electron microscopy, FISH, RT-PCR, cytogenetic analysis) (Note **A**)

**C. Microscopic Examination (Note **D**)**

- 1. Tumor
  - a. Histologic type
  - b. Histologic subtype
  - c. Venous/lymphatic vessel invasion, if possible to determine
  - d. Evaluate for anaplasia, cambium layer
  - e. Closest distance to margin (Note **G**)
  - f. Evaluate post-therapy tumors for differentiation, necrosis and fibrosis
- 2. Additional pathologic findings, if present
- 3. Results/status of special studies (specify) (Note **A**)
- 4. Comments
  - a. Correlation with intraoperative consultation, as appropriate
  - b. Correlation with other specimens, as appropriate
  - c. Correlation with clinical information, as appropriate (Notes **A** and **H**)

## Explanatory Notes

### A. Special Studies

#### Frozen Tissue

A minimum of 100 mg of viable tumor should be snap-frozen for potential molecular studies.<sup>2</sup> If the reservoir of 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.

#### Immunohistochemistry

In cases where histological diagnosis of rhabdomyosarcoma (RMS) 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.<sup>3,4</sup> Polyclonal desmin is 35% more sensitive in the detection of RMS as compared with monoclonal desmin.<sup>4</sup>

MIC-2 staining has also been used to rule out extraosseous Ewing sarcoma (EOE)/primitive neuroectodermal tumor (PNET).<sup>5</sup> Although some RMSs demonstrate immunopositivity to MIC-2,<sup>4</sup> it is often weakly granular and intracytoplasmic, as opposed to the distinct plasma membrane staining seen in EOE/PNET. Since some RMSs can demonstrate focal membranous MIC-2 staining, the MIC-2 immunostain should always be done in a panel that includes more specific myogenic stains, as defined above. MyoD1 and myogenin immunostaining have not been demonstrated in EOE/PNET.

The immunopositivity of RMS to p53 antibodies has been researched because of the association of some RMS with Li-Fraumeni syndrome.<sup>4</sup> Although immunopositivity is low amongst random RMS samples, strong immunopositivity to p53 antibody (grade 3 or 4 in immunopositivity) in RMS samples is strongly correlated with the presence of any anaplasia in alveolar RMS (ARMS) and diffuse anaplasia in embryonal RMS (ERMS).<sup>4,6</sup>

#### Chromosomal Translocations

The incidence of t(1;13) (PAX7-FKHR) and t(2;13) (PAX3-FKHR) is strongly correlated with the alveolar subtype of rhabdomyosarcoma (ARMS). The most common gene fusions are *PAX3-FKHR* and *PAX7-FKHR*, with the former being more prevalent. Studies suggest that patients with ARMS expressing the PAX3-FKHR gene product have a lower event-free survival than PAX7-FKHR-positive ARMS,<sup>4</sup> 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 PAX3-FKHR and PAX7-FKHR (estimated 4-year overall survival of 75% for PAX7-FKHR and 8% for PAX3-FKHR;  $P=.002$ ).<sup>2</sup> These translocations may be found in as much as 85% of ARMS cases.<sup>2</sup>

### B. Cytologic Material

A major limitation of a fine-needle aspiration (FNA) biopsy is that while criteria are usually sufficient to diagnose RMS (with supportive immunostains) (Note A), the RMS is not readily subclassified into spindle cell, botryoid, embryonal, or alveolar subtypes.<sup>7</sup> The presence of a monotonous, monomorphous nuclear cytology with coarse chromatin and prominent nucleoli is suggestive of a diagnosis of ARMS, with or without the presence of

giant cells; whereas a heterogeneous nuclear pattern with hyperchromatic irregular nuclei suggests a diagnosis of ERMS. However, either pattern may be missed due to sampling error in a mixed RMS, and even 1 focus of ARMS predicates a biologic course which requires therapeutic management as ARMS.<sup>8</sup> Moreover, histologic patterns, such as spindle cell RMS (SCRMS) or botryoid RMS (BRMS), are not well appreciated on FNA biopsy.<sup>7</sup> Since ultimately the gold standard for therapy in RMS is histologic subtyping and not grading,<sup>4</sup> FNA biopsy does not readily identify the therapeutic course that must be taken with a patient, even if a generic diagnosis of RMS is made. Another limitation of FNA biopsy is the inability to bank tissue for additional molecular diagnostic studies<sup>1</sup> (Note **A**). FNA biopsy does lend itself to use of fluorescent in-situ hybridization (FISH) studies for pertinent translocations but is still hampered by sampling error. Overall, FNA biopsy can provide a specific diagnosis of a suspected soft tissue sarcoma in about 20% of all cases.<sup>9</sup>

### C. 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.<sup>1</sup> 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 ERMS or other soft tissue sarcoma is made within the first 2 years of life, especially in a male child.<sup>10</sup> Such syndromes include Li-Fraumeni syndrome, basal cell nevus syndrome, neurofibromatosis, and pleuropulmonary blastoma syndrome (pleuropulmonary blastoma plus associated malignancies).<sup>1</sup> A genetic predisposition to cancer is thought to be present in 7% to 33% of children with soft tissue sarcomas.<sup>11</sup>

Rhabdomyosarcoma is specifically associated with a variety of congenital anomalies.<sup>12</sup> These include congenital anomalies of the central nervous system, genitourinary tract, gastrointestinal tract, and cardiovascular system.

### D. Histologic Type

The International Classification of Rhabdomyosarcoma is recommended.<sup>13</sup> Although undifferentiated sarcoma is a diagnosis of exclusion, its response to therapy is similar to ARMS and was therefore included. This classification has been further modified by the Intergroup Rhabdomyosarcoma Study Group to include the anaplastic variant (Table 1).<sup>4</sup>

The importance of accurate subtyping of RMS is evident in the superior prognosis of the botryoid and spindle cell variants to other types of embryonal RMS. Both types can show an extensive degree of rhabdomyoblastic differentiation. Diagnosis of the botryoid variant requires at least 1 microscopic field demonstrating a cambium layer (condensed layer of rhabdomyoblasts) underlying an intact epithelium. A gross demonstration of a botryoid configuration (“grape-like”) tumor is not required.

Spindle cell variants show a fascicular, spindled “leiomyomatous” pattern of growth that may also be nested or storiform. Some tumors demonstrate marked collagen deposition. Spindle cell tumors rarely occur outside the paratesticular region; association with intense chronic inflammation in the paratesticular region may be associated with improved prognosis,<sup>14</sup> although this has yet to be proven in a prospective study.

Classical ARMS presents with rhabdomyoblasts lining cleft-like spaces, but these diagnostic criteria may be obscured in the solid subtype; tumor cells may sit on or palisade about fibrovascular septae and fill these spaces. It is rare for solid ARMS to be present without evidence of cleft-like spaces somewhere in the specimen; therefore adequate sampling is imperative. Recognition of palisading tumor cells about septae necessitates greater vigilance. Although the prognosis for classic and solid variants is equally poor, improved recognition of the variation in histologies should improve the recognition of this tumor subtype.

Anaplasia is a histologic feature which may be found in any histologic subtype of RMS. Evidence of diffuse anaplasia may be significant in that retrospective studies are indicative of a poor prognosis<sup>4</sup> with presence of this nuclear change. This finding has added importance in that anaplasia is more common in ERMS, which normally has an intermediate to superior prognosis. Anaplasia was absent from earlier classification schemes due to its rarity (2% to 3% of RMS cases)<sup>4</sup> and a lack of a good definition prior to 1993.<sup>15</sup> The criteria are 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 now being studied prospectively in Children's Oncology Group Soft Tissue Sarcoma Clinical Trials to see if it warrants a separate therapeutic categorization in future studies.<sup>3</sup>

While undifferentiated sarcoma is a diagnosis of exclusion, it has a treatment regimen similar to that of ARMS and therefore is included here. This sarcoma consists mostly of medium-sized cells with indistinct cytoplasm and oval nuclei with prominent chromocenter. The cells are packed in sheets with no structure except perhaps a delicate fibrovascular septae or spindled-storiform pattern. Necrosis or inflammation is not prominent. Approximately three-fourths of tumors will stain with vimentin antisera, but no other diagnostic stains have been identified. Often a combination of immunostains, electron microscopy, and cytogenetic/molecular studies are required to exclude other sarcomas from the undifferentiated category.

### **Nonrhabdomyosarcomatous Soft Tissue Sarcomas (NRSTSs)**

Fewer than 1000 cases of pediatric soft tissue sarcomas are seen annually in the United States. One-half of these are RMS, for which a consensus treatment approach combining surgery, radiation therapy, and multi-agent chemotherapy has emerged.<sup>16</sup> In contrast, optimal management for NRSTS has been less clear. Combined-modality treatment approaches have not been evaluated systematically, however, due to the diversity of tumor types. An NRSTS grading system has been devised<sup>17</sup> (Table 2), which appears to predict clinical behavior.

A number of sarcomas which have a predilection for children<sup>1</sup> are not addressed in either the International Classification of Rhabdomyosarcoma or the NRSTS grading system. These include EOE/PNET, desmoplastic small round cell tumor, and malignant rhabdoid tumor. Currently, EOE/PNET is treated in the same manner as intraosseous Ewing sarcoma protocols; desmoplastic small round cell tumor and malignant rhabdoid tumor are consistently high-grade and aggressive lesions.

**E. Incisional Biopsy**

Core needle biopsies can obtain sufficient material for special studies and morphologic diagnosis, but sampling problems may limit tumor subtyping or grading.<sup>18</sup> 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.<sup>1</sup> Excisional biopsy may not include an adequate margin of normal tissue even with an operative impression of total gross removal.<sup>1</sup>

**F. Resection**

Resection specimens may be intralesional, marginal, wide, or radical in extent.<sup>19</sup> 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.<sup>1</sup>

**G. Margins**

The extent of resection (ie, gross residual disease versus complete resection) has the strongest influence on local control of malignancy.<sup>20,21</sup> 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.<sup>16</sup> For NRSTS, 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.<sup>16</sup>

**H. TNM Stage and Clinical Grouping**

The TNM staging system recommended by this protocol is a surgical, site-based, pretreatment assessment, which is used to plan therapy; the system is highly predictive of outcome<sup>1,4</sup> and has been specifically structured to assess RMSs. The American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) TNM staging systems currently do not apply to RMS. 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.

**Tumor (T)**

- T1 Tumor confined to anatomic site of origin
- T2 Tumor extension
  - a Tumor 5 cm or less in diameter
  - b Tumor greater than 5 cm in diameter

**Regional Lymph Nodes (N)**

- N0 Regional lymph nodes not clinically involved
- N1 Regional lymph nodes clinically involved
- NX Regional lymph node clinical status unknown

**Distant Metastasis (M)**

- M0 No distant metastasis
- M1 Distant metastasis present

**For Information Only**

**Pediatric • Rhabdomyosarcoma**

<u>Stage</u>	<u>Sites</u>	<u>T Invasiveness</u>	<u>T Size</u>	<u>Regional Nodes</u>	<u>Metastases</u>
I	Orbit	T1 or T2	a or b	N0,N1 or NX	M0
	Head and neck <sup>#</sup>	T1 or T2	a or b	N0,N1 or NX	M0
	Genitourinary <sup>##</sup>	T1 or T2	a or b	N0,N1 or NX	M0
II	Bladder/prostate	T1 or T2	a	N0 or NX	M0
	Extremity	T1 or T2	a	N0 or NX	M0
	Cranial parameningeal	T1 or T2	a	N0 or NX	M0
	Others <sup>###</sup>	T1 or T2	a	N0 or NX	M0
III	Bladder/prostate	T1 or T2	a	N1	M0
	Extremity	T1 or T2	b	N0,N1 or NX	M0
	Cranial parameningeal	T1 or T2	b	N0,N1 or NX	M0
	Others <sup>###</sup>	T1 or T2	b	N0,N1 or NX	M0
IV	All	T1 or T2	a or b	N0 or N1	M1

<sup>#</sup> Excluding parameningeal.

<sup>##</sup> Nonbladder/nonprostate.

<sup>###</sup> Includes trunk, retroperitoneum, etc.

The Intergroup Rhabdomyosarcoma Study Postsurgical Clinical Grouping System is shown below. The Clinical Grouping System is used to plan radiation therapy and relies on pathologic examination.<sup>1</sup>

<u>Clinical Group</u>	<u>Extent of Disease/Surgical Result</u>
I	A Localized tumor, confined to site of origin, completely resected
	B Localized tumor, infiltrating beyond site of origin, completely resected
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
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)
IV	Any size primary tumor, with or without regional lymph node involvement, with distant metastases, without respect to surgical approach to primary tumor

**Table 1. International Classification of Rhabdomyosarcoma<sup>a</sup>**

Diagnosis <sup>b</sup>	Histology	Incidence (%) <sup>c</sup>	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

<sup>a</sup>From Qualman et al.<sup>4</sup>

<sup>b</sup>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.

<sup>c</sup>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.

**Table 2. Pediatric Oncology Group Nonrhabdomyosarcomatous Soft Tissue Sarcoma Grading System<sup>a</sup>**

**Grade 1**

- Myxoid and well-differentiated liposarcoma
- Deep-seated dermatofibrosarcoma protuberans
- Well-differentiated or infantile (less than 4 years old) fibrosarcoma
- Well-differentiated or infantile (less than 4 years old) hemangiopericytoma
- Well-differentiated malignant peripheral nerve sheath tumor
- Extraskeletal myxoid chondrosarcoma

**Grade 2**

Sarcomas not specifically included in grades 1 and 3, in which less than 15% of the surface area shows necrosis, and the mitotic count is less than 5/10 high-power fields using a X40 objective; as secondary criteria, nuclear atypia is not marked, and the tumor is not markedly cellular

**Grade 3**

- Pleomorphic or round cell liposarcoma
  - Mesenchymal chondrosarcoma
  - Extraskeletal osteosarcoma
  - Malignant triton tumor
  - Alveolar soft part sarcoma
- Sarcomas not included in grade 1 and with greater than 15% of surface area with necrosis or with greater than 5 mitoses/10 high-power field using a X40 objective. Marked atypia or cellularity are less predictive but may assist in placing tumors in this category.

<sup>a</sup>From Parham et al.<sup>17</sup>

## References

1. Coffin CM, Dehner LP. Pathologic evaluation of pediatric soft tissue tumors. *Am J Clin Pathol*. 1998;109(suppl 1):S38-S52.
2. Qualman SJ, Morotti RA. Risk assignment in pediatric soft-tissue sarcoma: an evolving molecular classification. *Curr Oncol Rep*. 2002;4:123-130.
3. Parham DM. Pathologic classification of rhabdomyosarcomas and correlations with molecular studies. *Mod Pathol*. 2001;14:506-514.
4. Qualman SJ, Coffin CM, Newton WA, et al. Intergroup Rhabdomyosarcoma Study: update for pathologists. *Pediatr Dev Pathol*. 1998;1:550-561.
5. Ambros IM, Ambros PF, Strehl S, Kovar H, Gadner H, Salzer-Kuntschik M. MIC2 is a specific marker for Ewing's sarcoma and peripheral primitive neuroectodermal tumor: evidence for a common histogenesis of Ewing's sarcoma and peripheral neuroectodermal tumors from MIC2 expression and specific chromosome aberration. *Cancer*. 1991;67:1886-1893.
6. Bridge JA, Liu J, Qualman SJ, et al. Genomic gains and losses are similar in genetic and histologic subsets of rhabdomyosarcoma, whereas amplification predominates in embryonal with anaplasia and alveolar subtypes. *Genes Chromosomes Cancer*. 2002;33:310-321.
7. DeAlmeida M, Stastny JF, Wakely PE, et al. Fine-needle aspiration biopsy of childhood rhabdomyosarcoma: reevaluation of the cytologic criteria for diagnosis. *Diagn Cytopathol*. 1994;11:231-236.
8. Pappo AS. Rhabdomyosarcoma and other soft tissue sarcomas in children. *Curr Opin Oncol*. 1996;8:311-316.
9. Cost MJ, Campman SC, Davis RL, et al. Fine needle aspiration cytology of sarcoma: retrospective review of diagnostic utility and specificity. *Diagn Cytopathol*. 1996;15:23-32.
10. Birch JM, Hartley AL, Blair V, et al. Cancer in the families of children with soft tissue sarcoma. *Cancer*. 1990;66:2239-2248.
11. 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.
12. Ruymann FB, Maddux HR, Ragab A, et al. Congenital anomalies associated with rhabdomyosarcoma. *Med Pediatr Oncol*. 1988;16:33-39.
13. Coffin CM. The new International Rhabdomyosarcoma Classification, its progenitors, and consideration beyond morphology. *Adv Anat Pathol*. 1997;4:1-16.
14. Dishop MK, Anderson JR, Weiner E, Grier H, Crist W, Qualman SJ. Inflammatory infiltrate in paratesticular rhabdomyosarcoma: a comparison of histologic subtypes and correlation with survival. *Mod Pathol*. 2001;14:1P.
15. 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;17:433-453.
16. Wexler LH, Garvin JH Jr. Pediatric nonrhabdomyosarcoma soft tissue sarcomas: progress on clinical and biologic fronts. *J Pediatr*. 1997;131:508-509.
17. Parham DM, Webber BL, Jenkins JJ, Cantor AB, Maurer HM. Nonrhabdomyosarcomatous soft tissue sarcomas of childhood: formulation of a simplified system for grading. *Mod Pathol*. 1995;8:705-710.
18. Shives TC. Biopsy of soft-tissue tumors. *Clin Orthop*. 1993;289:32-35.
19. Conrad EU, Bradford L, Chonsky HA. Pediatric soft tissue sarcomas. *Orthop Clin North Am*. 1996;27:655-664.

20. Marcus KC, Grier HE, Shamberger RC, et al. Childhood soft tissue sarcoma: a 20-year experience. *J Pediatr.* 1997;131:603-607.
21. Fletcher C, Kempson RL, Weiss S. Recommendations for reporting soft tissue sarcomas. *Am J Clin Pathol.* 1999;111:594-598.

**Bibliography**

Coffin CM, Dehner LP, O'Shea PA, eds. *Pediatric Soft Tissue Tumors*. Philadelphia, Pa: Williams and Wilkins; 1997.