

## Protocol for the Examination of Specimens From Patients With Primitive Neuroectodermal Tumor (PNET)/Ewing Sarcoma (ES)

Protocol applies to pediatric and adult patients with osseous and extraosseous Ewing sarcoma family of tumors, including peripheral ES/PNET.

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Based on AJCC/UICC TNM, 7th edition

Protocol web posting date: June 2012

### Procedures

- Biopsy
- Resection

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*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.*

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## CAP PNET/Ewing Sarcoma Protocol Revision History

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### **Version Code**

The definition of the version code can be found at [www.cap.org/cancerprotocols](http://www.cap.org/cancerprotocols).

**Version:** PNET/EwingSarcoma 3.1.0.2

### **Summary of Changes**

The following changes have been made since the November 2011 release.

### **Explanatory Notes**

#### **M Category Considerations**

The word "checklist" was changed to "case summary."

### **Important Note**

Ewing sarcoma family of tumors includes both peripheral primitive neuroectodermal tumor (PNET) and Ewing sarcoma (ES), which occur both in children and adults. The malignancy may occur in both bone and soft tissue sites (including unusual sites such as skin or leptomeninges).<sup>1,2</sup> Because ES/PNET can occur in both bone and soft tissue, AJCC/UICC staging systems for both are included.

First priority should always be given to formalin-fixed tissue for morphologic evaluation. Special studies (eg, cytogenetics, fluorescence in situ hybridization [FISH], reverse transcriptase polymerase chain reaction [RT-PCR]) are critical to the molecular workup of ES/PNET and require at least 100 mg of viable, fresh or snap-frozen tissue as the second priority for workup (Note A).

This protocol is based on the experience of the Children's Oncology Group.  
For more information, contact The Children's Oncology Group Biopathology Center.  
Phone: (614) 722-2890 or (800) 347-2486.

## Surgical Pathology Cancer Case Summary

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Protocol web posting date: June 2012

### EWING SARCOMA/PRIMITIVE NEUROECTODERMAL TUMOR: Biopsy

Select a single response unless otherwise indicated.

#### Procedure (Note B)

- Core needle biopsy
- Incisional biopsy
- Excisional biopsy
- Other (specify): \_\_\_\_\_
- Not specified

#### Tumor Site

- Specify site (if known): \_\_\_\_\_
- Not specified

#### Tumor Size (Note B)

- Greatest dimension: \_\_\_ cm
- + Additional dimensions: \_\_\_ x \_\_\_ cm
- Cannot be determined (see "Comment")

#### + Extent of Osseous Tumors (select all that apply)

- +  Diaphysis
- +  Metaphysis
- +  Medullary cavity
- +  Tumor extension into soft tissue
- +  Other (specify): \_\_\_\_\_
- +  Not specified
- +  Cannot be determined

#### + Extent of Primary Extrasosseous Tumors (select all that apply)

- +  Dermal
- +  Subcutaneous/suprafascial
- +  Subfascial
- +  Intramuscular
- +  Intra-abdominal/pelvic
- +  Retroperitoneal
- +  Other (specify): \_\_\_\_\_
- +  Not specified
- +  Cannot be determined

#### Margins (for excisional biopsy only) (Note C)

- Cannot be assessed
- Margins negative for tumor
  - Distance of tumor from closest bone margin: \_\_\_ cm
  - Distance of tumor from closest soft tissue margin: \_\_\_ cm
- Margin(s) positive for sarcoma
  - Specify margin(s) \_\_\_\_\_

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

**+ Lymph-Vascular Invasion (Note D)**

- +  Not identified
- +  Present
- +  Indeterminate

**Prebiopsy Treatment (select all that apply)**

- No therapy
- Chemotherapy performed
- Radiation therapy performed
- Therapy performed, type not specified
- Unknown

**Necrosis Postchemotherapy (Note E)**

- Necrosis not identified
- Necrosis present
  - + Specify extent of total specimen: %
- Cannot be determined
- Not applicable

**+ Additional Pathologic Findings**

+ Specify: \_\_\_\_\_

**+ Ancillary Studies (Note F)**

+ Cytogenetics

+ Specify: \_\_\_\_\_

+  Not performed

+ Molecular Pathology

+ Specify: \_\_\_\_\_

+  Not performed

**+ Comment(s)**

## Surgical Pathology Cancer Case Summary

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Protocol web posting date: June 2012

### EWING SARCOMA/PRIMITIVE NEUROECTODERMAL TUMOR: Resection

Select a single response unless otherwise indicated.

#### Procedure (Note B)

- Resection  
 Amputation (specify type): \_\_\_\_\_  
 Other (specify): \_\_\_\_\_  
 Not specified

#### Tumor Site

- Specify site(s): \_\_\_\_\_  
 Not specified

#### Tumor Size (Note B)

- Greatest dimension: \_\_\_ cm  
 + Additional dimensions: \_\_\_x\_\_\_ cm  
 Cannot be determined (see Comment)

#### + Extent of Tumor (primary osseous tumors) (select all that apply)

- +  Diaphysis  
 +  Metaphysis  
 +  Medullary cavity  
 +  Tumor extension into soft tissue  
 +  Other (specify): \_\_\_\_\_  
 +  Not specified  
 +  Cannot be determined

#### + Extent of Tumor (primary extraosseous tumors) (select all that apply)

- +  Dermal  
 +  Subcutaneous/subfascial  
 +  Subfascial  
 +  Intramuscular  
 +  Intra-abdominal/pelvic  
 +  Retroperitoneal  
 +  Other (specify): \_\_\_\_\_  
 +  Not specified  
 +  Cannot be determined

#### Margins (Note C)

- Cannot be assessed  
 Margins negative for tumor  
     Distance of tumor from closest bone margin: \_\_\_ cm  
     Distance of tumor from closest soft tissue margin: \_\_\_ cm  
 Margin(s) positive for sarcoma  
     Specify margin(s): \_\_\_\_\_

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

**+ Lymph-Vascular Invasion (Note D)**

- + \_\_\_ Not identified
- + \_\_\_ Present
- + \_\_\_ Indeterminate

**Preresection Treatment (select all that apply)**

- \_\_\_ No therapy
- \_\_\_ Chemotherapy performed
- \_\_\_ Radiation therapy performed
- \_\_\_ Therapy performed, type not specified
- \_\_\_ Unknown

**Necrosis Postchemotherapy (Note E)**

- \_\_\_ Necrosis not identified
- \_\_\_ Necrosis present
  - + Specify extent of total mass: \_\_\_%
- \_\_\_ Cannot be determined
- \_\_\_ Not applicable

**+ Ancillary Studies (Note F)**

- + Cytogenetics
- + Specify: \_\_\_\_\_
- + \_\_\_ Not performed
  
- + Molecular Pathology
- + Specify: \_\_\_\_\_
- + \_\_\_ Not performed

**Pathologic Staging (pTNM) (Notes G and H)**TNM Descriptors (required only if applicable) (select all that apply)

- \_\_\_ m (multiple primary tumors)
- \_\_\_ r (recurrent)
- \_\_\_ y (posttreatment)

Primary Tumor (pT)*For Primary Osseous Tumors (Note G)*

- \_\_\_ pTX: Primary tumor cannot be assessed
- \_\_\_ pT0: No evidence of primary tumor
- \_\_\_ pT1: Tumor 8 cm or less in greatest dimension
- \_\_\_ pT2: Tumor more than 8 cm in greatest dimension
- \_\_\_ pT3: Discontinuous tumors in the primary bone site

*For Primary Extraosseous Tumors (Note H)*

- \_\_\_ pTX: Primary tumor cannot be assessed
- \_\_\_ pT0: No evidence of primary tumor
- \_\_\_ pT1a: Tumor 5 cm or less in greatest dimension, superficial tumor
- \_\_\_ pT1b: Tumor 5 cm or less in greatest dimension, deep tumor
- \_\_\_ pT2a: Tumor more than 5 cm in greatest dimension, superficial tumor
- \_\_\_ pT2b: Tumor more than 5 cm in greatest dimension, deep tumor

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Lymph Nodes

*Regional Lymph Nodes (pN)*

- pNX: Cannot be assessed
- pN0: No regional lymph node metastasis
- pN1: Regional lymph node metastasis
  
- No regional lymph nodes submitted or found

Number of Regional Lymph Nodes Examined

- Specify:  \_\_\_\_\_
- Number cannot be determined (explain): \_\_\_\_\_

Number of Regional Lymph Nodes Involved

- Specify:  \_\_\_\_\_
- Number cannot be determined (explain): \_\_\_\_\_

*Nonregional Lymph Nodes*

- Cannot be assessed
- No nonregional lymph node metastasis
- Nonregional lymph node metastasis
  
- No nonregional lymph nodes submitted or found

Number of Nonregional Lymph Nodes Examined

- Specify:  \_\_\_\_\_
- Number cannot be determined (explain): \_\_\_\_\_

Number of Nonregional Lymph Nodes Involved

- Specify:  \_\_\_\_\_
- Number cannot be determined (explain): \_\_\_\_\_

Distant Metastasis (pM)

*For Primary Osseous Tumors (Note G)*

- Not applicable
- pM1a: Lung
- pM1b: Metastasis involving distant sites other than lung  
+ Specify site(s), if known: \_\_\_\_\_

*For Primary Extraosseous Tumors (Note H)*

- Not applicable
- pM1: Distant metastasis  
+ Specify site(s), if known: \_\_\_\_\_

**+ Additional Pathologic Findings**

+ Specify: \_\_\_\_\_

**+ Comment(s)**

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.



## Explanatory Notes

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### A. Tissue Handling

Tissue specimens optimally are received fresh/unfixed because of the importance of ancillary studies, such as cytogenetics, which require fresh tissue. First priority should always be given to formalin-fixed tissues for morphologic evaluation, followed by submission of fresh tissue for cytogenetics and/or snap freezing a minimum of 100 mg of viable tumor for potential molecular studies.<sup>1</sup> When the amount 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 (-70°C is preferable). Translocations may be detected using RT-PCR on frozen or fixed paraffin-embedded tissue, or FISH on touch preparations made from fresh tissue or formalin-fixed paraffin-embedded tissue. Due to increased sensitivity of detection, snap-frozen tumor tissue is the preferred specimen type, and every effort should be made to procure it.

Note that classification of many subtypes of sarcoma is not dependent upon special studies, such as cytogenetics or molecular genetics, but frozen tissue may be required to enter patients into treatment protocols. Discretion should be used in triaging tissue from sarcomas. Adequate tissue should be submitted for conventional light microscopy before tissue has been taken for cytogenetics, electron microscopy, or molecular analysis.

### B. Procedures

#### Cytologic Material

Cytological material is usually sufficient to diagnose ES/PNET (with supportive immunostains) (Note F).<sup>2</sup> An important limitation of fine-needle aspiration biopsy is the limited amount of tissue for additional molecular diagnostic studies<sup>1</sup> and banking (see above).

If cytologic material includes fluid, such as pleural effusions or fluid from a liquefactive tumor, the fluid should be centrifuged and the resulting pellet fixed with formalin prior to making a paraffin block. The resulting cell block allows for histopathologic examination and immunocytochemical, RT-PCR, and FISH analyses.

#### Biopsy (Needle, Incisional, Excisional)

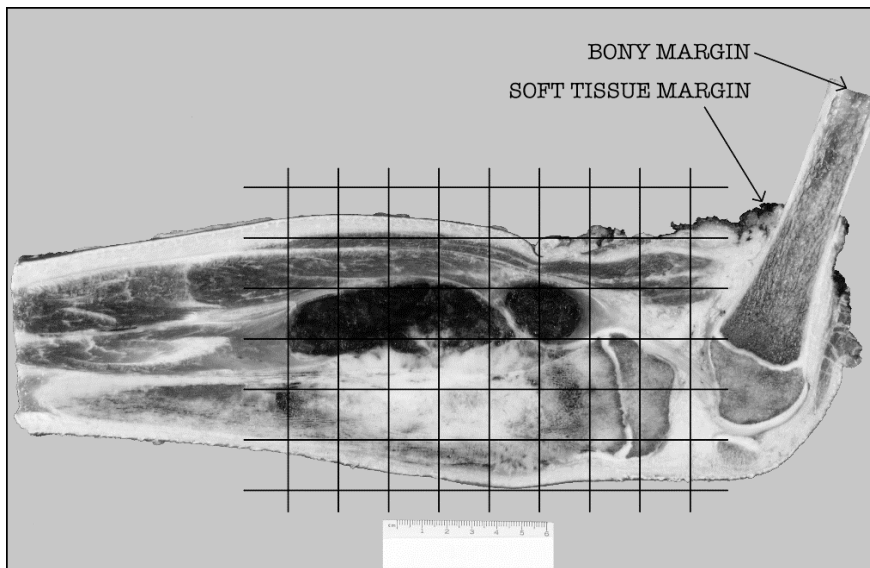
Core needle biopsies can obtain sufficient material for special studies and morphologic diagnosis. Open incisional biopsy is generally the preferred and most widely-used technique because it consistently provides a larger sample of tissue and maximizes the opportunity for a specific pathologic diagnosis.<sup>3</sup> Excisional biopsy may not include an adequate margin of normal tissue, even with an operative impression of total gross removal.<sup>3</sup>

In cases of nonexcisional biopsy (eg, core biopsy, incisional biopsy), the tumor size cannot be determined on pathologic grounds; therefore, imaging data (computed tomography [CT], magnetic resonance imaging [MRI], etc) can be used instead.

#### Tumor Resection

Resection specimens may be intralesional, marginal, wide, or radical in extent.<sup>4</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 reactive 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 highly recommended for accurate pathologic evaluation.<sup>3</sup> Full representative mapping of the specimen is also recommended,<sup>3</sup> as discussed below.

A full sagittal section of a bone tumor resection specimen<sup>5</sup> as illustrated in Figure 1 allows for mapping of the entire central face of the tumor and adjacent marginal tissue. Freezing of the specimen and cutting with a bone saw (with intraosseous specimens) may best achieve this result, although acceptable results can be obtained cutting the specimen fresh with a bandsaw if care is taken to attached soft tissue first. This face of the specimen can be documented by a black and white photograph or photocopy of the specimen when sealed in a plastic bag. As shown in Figure 1, this central full face of the specimen and lesion can be mapped and blocked postfixation (and decalcification as necessary) for complete microscopic examination, including estimate of percentage of tumor necrosis.



**Figure 1.** Grid diagram of histologic sections taken, superimposed on photograph of a sagittally-sectioned proximal tibia.

### C. Margins

The extent of resection (ie, gross residual disease versus complete resection) has the strongest influence on local control of malignancy.<sup>6,7</sup> The definition of what constitutes a sufficiently “wide” margin of normal tissue in the management of ES/PNET has evolved. In the current Children’s Oncology Group study of ES/PNET, the following margins are considered adequate.

- Bone margin: 2 to 5 cm
- Fascia, periosteum, and intermuscular septa: 2 mm
- Fat, muscle, and medullary bone: 5 mm

If the response to chemotherapy is poor, wider margins may be required. If margins are deemed inadequate by these criteria, postoperative radiotherapy may be indicated.

### D. Lymph-Vascular Invasion

Lymph-vascular invasion (LVI) indicates whether microscopic lymph-vascular invasion is identified in the pathology report. LVI includes lymphatic invasion, vascular invasion, or lymph-vascular invasion. By American Joint Committee on Cancer (AJCC) and International Union Against Cancer (UICC) convention, LVI does not affect the T category indicating local extent of tumor unless specifically included in the definition of the T category.

### E. Prognostic Factors

The typical case of ES/PNET shows a lobular growth pattern of tumor cells that are distinctly monotonous in their nuclear uniformity. Nuclei measure 10 to 15  $\mu\text{m}$  in diameter with distinct nuclear membranes, finely granular chromatin, and 1 to 2 inconspicuous nucleoli. Cytoplasm is poorly defined, scant, pale-

staining, and may be vacuolated due to irregular glycogen deposition. Atypical variants may show increased nuclear size or more pronounced atypia. Multinucleate giant cells are not seen. Large areas of perivascular tumor necrosis with “ghost cells” may be striking. Areas of neuroectodermal differentiation (Homer Wright rosettes; rarely Flexner-Wintersteiner rosettes or primitive neuroepithelium) may be evident in some tumors.

Currently, extraosseous ES/PNET is treated in the same manner as intraosseous Ewing sarcoma. There are no histological subtypes of established prognostic importance.<sup>8</sup>

A summary of the prognostic factors is detailed below.<sup>9</sup> Of the various prognostic factors listed, age at onset, size, site, and stage bear the most significant relationship to outcome.

Factor	Favorable Prognosis	Adverse Prognosis
Age	<10 years (EFS 69%); 10-17 years (EFS 74%)	≥18 (EFS 44%)
Site	Distal extremity (EFS 74%); Proximal extremity (EFS 62%)	Pelvis (EFS 50%)
Size	<8 cm greatest diameter (EFS 75%)	≥8 cm (EFS 55%)
Stage	Nonmetastatic (EFS approximately 70%)	Metastatic (EFS approximately 20%)
Histology posttherapy	Grades III-IV (see below)	Grades I, IIA, IIB (see below)
<i>EWS-FLI1</i> fusion transcript type	Type 1	Type 2

Definition: EFS, event-free survival.

Histologic response to chemotherapy is an excellent predictor of outcome in osteosarcomas and may also be of value in ES/PNET. This feature may be graded by the Huvos classification, as detailed below.<sup>10</sup> Details for evaluating tissue necrosis versus viability can be found elsewhere.<sup>11</sup>

Grade	Percent Necrosis	Description
I	0 (no necrosis)	No treatment effect identified
IIA	<50% necrosis	Partial / low effect
IIB	50%-95% necrosis	Partial / high effect
III	96%-99% necrosis	Only scattered viable tumor foci
IV	100% necrosis	No viable tumor, extensive sampling

In osteosarcomas, grades III and IV are considered favorable. Grades I, IIA, and IIB are considered to be failure of chemotherapy and will prompt a chemotherapy regimen change. Some authors consider any degree of necrosis greater than 90% to be favorable.<sup>11</sup>

A Childhood Cancer Group/Pediatric Oncology Group study of resected ES/PNET evaluated the response to preoperative chemotherapy using the following grading.<sup>12,13</sup>

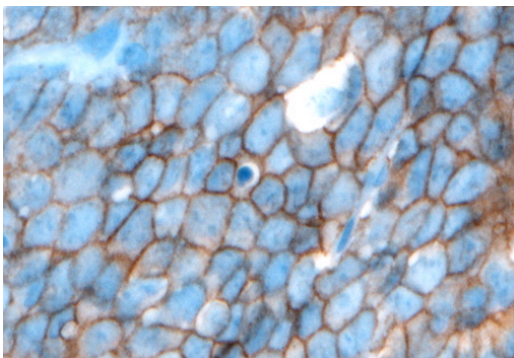
Grade	Description	3-Year Survival (%)
I	No chemotherapy effect	30%
IIA	1%-10% necrosis	30%
IIB	11%-90% necrosis	49%
III	91%-99% necrosis	73%
IV	100% necrosis	100%

Because the Huvos and Childhood Cancer Group/Pediatric Oncology Group grading schemes use similar numbering, but significantly different necrosis levels, it is important for the report to include the actual estimated percent necrosis rather than necrosis grade. This allows the oncologist and surgeon to interpret and translate the percent necrosis into the necrosis scheme used at their specific hospital(s).

## F. Special Studies

### Immunohistochemistry

Immunohistochemistry with monoclonal antibodies against the cell surface glycoprotein CD99, also known as MIC-2, is positive in virtually all cases of ES/PNET.<sup>14</sup> This glycoprotein is diffusely expressed in the vast majority of cases in a *membranous pattern* (Figure 2). The results of staining using monoclonal antibodies O13, HBA71, and 12E7 are similar, but individual tumors may exhibit better staining with one or another antibody.



**Figure 2.** CD99 staining in Ewing sarcoma/Primitive neuroectodermal tumor shows strong, diffuse membranous staining. (CD99 antibody O13 with hematoxylin counterstain.)

Lymphoblastic lymphomas/leukemias, rhabdomyosarcomas, synovial sarcomas, solitary fibrous tumors, malignant rhabdoid tumors, neuroendocrine tumors, desmoplastic small round cell tumors, and mesenchymal chondrosarcomas may also demonstrate immunoreactivity to MIC-2.<sup>8</sup> In some of these tumors, CD99 immunostaining is often weakly granular and intracytoplasmic; in others (lymphoblastic lymphoma/leukemia, occasional cases of poorly differentiated synovial sarcoma and alveolar rhabdomyosarcoma), distinct plasma membrane staining is present, as seen in ES/PNET. The MIC-2 immunostain should always be done in a panel, which usually includes muscle markers (desmin, muscle-specific actin, myoD1, myogenin), S-100, epithelial markers (epithelial membrane antigen, cytokeratin),

and lymphoid markers (CD45, CD30, Tdt, T-cell and/or B-cell markers). The value of other immunohistochemical markers for diagnosis, such as Ki-67, p53, and C-kit (CD117), has not been established at this time. ES/PNET is consistently vimentin immunopositive.

Approximately 90% to 95% of ES/PNET are positive for the *EWS-FLI1* fusion gene and as a result is diagnostically useful. In this regard, immunohistochemistry against the carboxy-terminus of the FLI-1 has been shown to be sensitive in the diagnosis of ES/PNET (see "Chromosomal Translocations" below), although the FLI-1 antibody will stain other tumor types,<sup>15,16</sup> including vascular tumors and lymphoblastic lymphoma.

### Chromosomal Translocations

It is now generally accepted that Ewing sarcoma and PNET form a single group of bone and soft tissue tumors. The characteristic translocations involve the *EWS* gene at 22q12 and either the *FLI1* gene at 11q24 or the *ERG* gene at 21q22. The presence of t(11;22) (*EWS-FLI1*) and t(21;22) (*EWS-ERG*) is strongly correlated with ES/PNET. The most common gene fusion is the *EWS-FLI1* (90% to 95% of patients). Investigations suggest that different types of *EWS-FLI1* fusions (type 1 versus type 2) may have prognostic implications.<sup>17</sup> Patients with type 1 fusions (in which *EWS* exons 1-7 fuse to *FLI1* exons 6-9) appear to fare better than patients with type 2 fusions (involving other sites within the relevant genes). The influence of fusion type on prognosis and response to therapy remains a subject of study. Treatment stratification does not currently take into account translocation type.

There are several tumor-defining translocations that are detected in a small percentage (<5%) of ES/PNET. These characteristic translocations include: t(7;22)(p22;q12) *EWS-ETV1*, t(17;22)(q12;q12) *EWS-E1AF*, t(2;22)(q33;q12) *EWS-FEV*, and t(1;22)(p36;q12) *EWS-ZSG*. Although these translocations are relatively rare with ES/PNET, the practicing surgical pathologist should be aware of these in the event that *EWS-FLI1* and *EWS-ERG* translocations are not detected by cytogenetics, RT-PCR, or FISH. Break-apart FISH probes for the *EWS* locus will still show 3 signals as the *EWS* gene has been disrupted in each of these translocations. It is possible to render a diagnosis of ES/PNET in the absence of a tumor-defining translocation, and the detection of ES/PNET-associated translocations is not mandatory to make such a diagnosis.

### Electron Microscopy

Ultrastructural studies are valuable despite the putative diagnostic power of immunohistochemistry and molecular studies.<sup>18</sup> These tumors usually have limited cytoplasmic organelles. Some cytoplasmic regions may contain an increased amount of polyparticulate glycogen. The latter correspond to the classical "dot-positivity" noted with the periodic acid-Schiff stain. Furthermore, one may also find intermediate filaments corresponding to vimentin and cytokeratin. In those tumors with neuroendocrine differentiation, neurosecretory granules may occur, but they are pleomorphic and larger than the 100-nm diameter spherical granules of neuroblastoma. Intermediate-type junctions are often present, but true desmosomes are not usually seen.

### G. TNM and Stage Groupings: Bone

The AJCC/UICC TNM staging system for bone tumors<sup>19,20</sup> is recommended for osseous tumors.

### Grading

All ES/PNET (either intraosseous or extraosseous) are classified as high grade, hence stage IA and IB below are excluded for ES/PNET.

### N Category Considerations

Lymph node involvement is rare in bone sarcomas. Staging of lymph nodes as NX is equivalent to N0 in stage grouping.

**Stage Grouping**

Stage IA	T1	N0, NX	M0#	Low grade
Stage IB	T2	N0, NX	M0	Low grade
Stage IIA	T1	N0, NX	M0	High grade
Stage IIB	T2	N0, NX	M0	High grade
Stage III	T3	N0, NX	M0	High grade
Stage IVA	Any T	N0, NX	M1a	Any grade
Stage IVB	Any T	N1	Any M	Any grade
	Any T	Any N	M1b	Any grade

# M0 denotes no distant metastasis.

**H. TNM and Stage Grouping: Soft Tissue**

The AJCC/UICC TNM staging system<sup>19,20</sup> for soft tissue is recommended for extraosseous tumors.

**T Category Considerations**

Superficial tumor is located exclusively above superficial fascia without invasion of fascia. Deep tumor is located either exclusively beneath superficial fascia or superficial to the fascia with invasion of or through the fascia. Retroperitoneal, mediastinal, and pelvic sarcomas are classified as deep tumors.

**Grading**

ES/PNET (either intraosseous or extraosseous) is classified as high grade.

**N Category Considerations**

Presence of positive nodes (N1) is considered stage III.

**M Category Considerations**

pMX and pM0 (no distant metastasis) are no longer case summary options as pM0 is often not known by the pathologist and the use of pMX provides no meaningful information to the clinician or cancer registrar and at times may create confusion in tumor staging.

**Stage Grouping**

Stage IA	T1a	N0, NX	M0	Low grade
	T1b	N0, NX	M0	Low grade
Stage IB	T2a	N0, NX	M0	Low grade
	T2b	N0, NX	M0	Low grade
Stage IIA	T1a	N0, NX	M0	High grade
	T1b	N0, NX	M0	High grade
Stage IIB	T2a	N0, NX	M0	High grade
Stage III	T2b	N0-1, NX	M0	High grade
Stage IV	Any T	Any N	M1	High or Low grade

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