Primitive Neuroectodermal Tumor (PNET) / Ewing Sarcoma (ES)

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

Protocol date: January 2005
Based on AJCC/UICC TNM, 6th edition

Procedures
• Cytology (No Accompanying Checklist)
• Biopsy (Needle, Incisional, Excisional) (No Accompanying Checklist)
• Resection

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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 the document. 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.
Summary

Protocol date: January 2005

This is a new protocol for 2005.

Important Note

Ewings sarcoma family of tumors includes both peripheral primitive neuroectodermal tumor and Ewing sarcoma, 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). Because PNET / ES 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 tissues for morphologic evaluation. Special studies (eg, reverse transcriptase polymerase chain reaction [RT-PCR]) are critical to the molecular work-up of PNET / ES and require at least 100 mg of viable snap-frozen tissue as the second priority for work-up (Note A). Tumor-defining translocations for Ewings sarcoma family of tumors may also be performed by RT-PCR and FISH on formalin-fixed tissue scrolls or tissue sections, respectively. Due to increased sensitivity of detection, snap-frozen tumor tissue is the preferred specimen type and every effort should be made to procure it.

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 (Checklist)

Protocol date: January 2005
Protocol applies to PNET / ES only
Based on AJCC/UICC TNM, 6th edition

PRIMITIVE NEUROECTODERMAL TUMOR / EWING SARCOMA (PNET / ES): Resection

Patient name:
Surgical pathology number:

Note: Check 1 response unless otherwise indicated.

MACROSCOPIC

Specimen Type
___ Resection
___ Amputation (specify type): ____________________________
___ Other (specify): ____________________________
___ Not specified

Tumor Site
Specify site(s): ____________________________
___ Not specified

Laterality (as appropriate)
___ Right
___ Left
___ Other (specify): ____________________________
___ Not specified

Tumor Size
Greatest dimension: ___ cm
*Additional dimensions: ___ x ___ cm
___ Cannot be determined (see Comment)
*Tumor Extent (check all that apply)
* ___ Dermal
* ___ Subcutaneous
* ___ Subfascial
* ___ Intramuscular
* ___ Intra-abdominal
* ___ Retroperitoneal
* ___ Bone
* ___ Other (specify): ____________________________
* ___ Not specified
* ___ Cannot be determined

MICROSCOPIC

Extent of Tumor Involvement
___ Limited to dermis
___ Other (specify): ____________________________
___ Cannot be determined

Pathologic Staging

Primary Tumor (pT)

For Primary Osseous Tumors
___ 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
___ pTX: Primary tumor cannot be assessed
___ pT0: No evidence of primary tumor
pT1: Tumor 5 cm or less in greatest dimension
___ pT1a: Superficial tumor (exclusively above superficial fascia)
___ pT1b: Deep tumor (exclusively deep to or extends across superficial fascia)
pT2: Tumor more than 5 cm in greatest dimension
___ pT2a: Superficial tumor (exclusively above superficial fascia)
___ pT2b: Deep tumor (exclusively deep to or extends across superficial fascia)
Lymph Nodes (check all that apply)

*Regional Lymph Nodes (pN)*
- ___ pNX: Cannot be assessed
- ___ pN0: No regional lymph node involvement
- ___ pN1: Regional lymph node involvement
  Specify: Number examined ___
  Number involved ___

*Nonregional Lymph Nodes*
- ___ Cannot be assessed
- ___ No nonregional lymph node involvement
- ___ Nonregional lymph node involvement
  Specify: Number examined ___
  Number involved ___

Distant Metastasis (pM)

*For Primary Osseous Tumors*
- ___ pMX: Cannot be assessed
- pM1: Distant metastasis
  ___ pM1a: Lung
  ___ pM1b: Other distant sites
    *Specify site(s): ____________________________

*For Primary Extraosseous Tumors*
- ___ pMX: Cannot be assessed
- ___ pM1: Distant metastasis

Necrosis Postchemotherapy
- ___ Absent
- ___ Present
  *Specify extent: ___%
  ___ Cannot be determined

Margins
- ___ Cannot be assessed
- ___ Margins uninvolved by tumor
  Distance of tumor from closest bone margin: ___ mm
  Distance of tumor from closest soft tissue margin: ___ mm
- ___ Margin(s) involved by tumor
  Specify margin(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.
*Venous/Lymphatic (Large/Small Vessel) Invasion (V/L)
* ___ Present
* ___ Absent
* ___ Indeterminate

*Additional Studies
*Specify: ____________________________

*Additional Pathologic Findings
*Specify: ____________________________

*Comment(s)
Background Documentation

Protocol date: January 2005

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. Imaging findings
      c. Procedure (eg, fine-needle aspiration [FNA], other)
      d. Anatomic sites(s) of specimen
B. Macroscopic Examination
   1. Specimen type
      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
   3. Other pathologic findings (eg, necrosis, other)
   4. Results/status of special studies (specify)
   5. Comments
      a. Correlation with intraoperative consultation, as appropriate
      b. Correlation with other specimens, as appropriate
      c. Correlation with clinical information, as appropriate

II. Biopsy
   (Needle, Incisional, Excisional) (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. Imaging findings
   c. Procedure (eg, core needle biopsy, wedge biopsy)
   d. Anatomic sites(s) of specimen

B. Macroscopic Examination
   1. Specimen
      a. Unfixed/fixed (specify fixative)
      b. Number of pieces
      c. Dimensions (range of largest dimension)
      d. Descriptive features (eg, soft tissue, bone, both)
      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. Venous/lymphatic vessel invasion, if possible to determine
      b. Additional pathologic findings, if present
   2. Results/status of special studies (specify)
   3. 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)

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

B. Macroscopic Examination
1. Specimen
   a. Resection type (intralesional, marginal, wide, or radical resection)
   b. Organ/tissues included (eg, intraosseous, extraosseous, other)
   c. Unfixed/fixed (specify fixative)
   d. Specimen x-ray (AP and lateral, if possible) for osseous lesions
   e. Descriptive features
   f. Orientation, if indicated by surgeon
   g. 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, bone present, color, consistency, necrosis, biopsy scars, calcification)
   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 full cut surface of the bone involved by the tumor) and specimen diagram (Note F)
7. Special studies (specify) (eg, immunohistochemistry, electron microscopy, FISH, RT-PCR, cytogenetic analysis) (Note A)

C. Microscopic Examination (Note D)
1. Tumor
   a. Closest distance to margin (Note G)
   b. Venous/lymphatic vessel invasion, if possible to determine
   c. Percentage of necrosis (Note H)
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. 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) for potential molecular studies. Translocations may be detected using reverse transcriptase polymerase chain reaction (RT-PCR) on frozen or fixed paraffin-embedded tissue, or fluorescence in situ hybridization (FISH) on touch preparations made from fresh tissue. FISH can be performed on tissue sections obtained from formalin-fixed paraffin-embedded tumor blocks as well, although sensitivity is reduced compared with tough preparations for FISH made from fresh or frozen tissue.

Immunohistochemistry
In cases where histological diagnosis of primitive neuroectodermal tumor (PNET) / Ewing sarcoma (ES) is difficult, immunostaining with monoclonal antibodies against the cell surface glycoprotein CD99, also known as MIC-2, is suggested. Nearly all PNET / ES tumors are positive for this antigen. This glycoprotein is diffusely expressed in the vast majority of cases in a membranous pattern. 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.

Lymphoblastic lymphomas/leukemias, rhabdomyosarcomas, desmoplastic small round cell tumor, synovial sarcomas, solitary fibrous tumor, extrarenal malignant rhabdoid tumor, neuroendocrine tumors, and mesenchymal chondrosarcoma may demonstrate immunoreactivity to MIC-2. In some of these tumors, CD99 immunostaining is often weakly granular and intracytoplasmic; in others (desmoplastic tumor, lymphoblastic lymphoma/leukemia), distinct plasma membrane staining is present, as seen in PNET / ES. The MIC-2 immunostain should always be done in a panel, which usually includes muscle markers (desmin, muscle-specific actin, myoD1, myogenin), neural markers (protein gene product 9.5 [PGP 9.5], S-100 protein, neuron-specific enolase [NSE], human natural killer-cell antigen [CD 57], synaptophysin, neurofilament protein), 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. PNET / ES is consistently vimentin immunopositive.

The prevalence of the EWS-FLI1 fusion gene in PNET / ES (90% to 95%) has been shown to be useful diagnostically. In this regard, immunohistochemistry against the carboxy-terminus of the FLI-1 has been shown to be sensitive in the diagnosis of PNET / ES (see “Chromosomal Translocations” below), although the FLI-1 antibody will stain other tumor types, including vascular tumors and lymphoblastic lymphoma.

In the past, PNET / ES has been a diagnosis of exclusion (of other primary and metastatic tumor types) without specific confirmatory markers. Immunostains (CD99, FLI1), while supportive of the diagnosis in the proper context, remain relatively nonspecific. Detection of the specific fusion gene (EWS-FLI1 or other variants) provides valuable molecular confirmation of the diagnosis unavailable by other technologies (see “Chromosomal Translocations” below).
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 PNET / ES. The most common gene fusion is the EWS-FLI1 (90% to 95% of patients). Recent investigations suggest that different types of EWS-FLI1 fusions (type 1 versus type 2) may have prognostic implications. Patients with type 1 fusions (in which EWS exons 1-7 link with FLI1 exons 6-9) fare better than patients with type 2 fusions (involving other sites within the relevant genes). This relationship remains under active investigation.

There are several tumor-defining translocations that are detected in a small percentage (<5%) of PNET/ES. 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 PNET / ES, 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. It is definitely possible to render a diagnosis of PNET / ES in the absence of a tumor-defining translocation and the detection of PNET / ES-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.11 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.

B. Cytologic Material
Cytological material is usually sufficient to diagnose PNET / ES (with supportive immunostains) (Note A). However, rhabdomyosarcomas may not be readily distinguished from PNET / ES in soft tissue lesions. An important limitation of fine-needle aspiration biopsy is the limited amount of tissue for additional molecular diagnostic studies and banking (Note A). FISH studies for pertinent translocations may be performed on fine-needle aspiration biopsy material, although it is still hampered by sampling error. In spite of these limitations, fine-needle aspiration biopsy can provide a specific diagnosis of a suspected PNET / ES in most cases.12

If cytologic material includes fluid, such as pleural effusions or fluid from aliquefactive 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.
C. Relevant History
Relevant historical factors include any previous therapy and family history of malignancy. If preoperative therapy has been given, assessment may be limited to the estimate of viable and necrotic tumor.

D. Histologic Type
The typical case of PNET / ES shows a lobular growth pattern of tumor cells that are distinctly monotonous in their nuclear uniformity. Nuclei measure 10 to 15 µm 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” (filigree pattern) 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 PNET / ES is treated in the same manner as intraosseous Ewing sarcoma. There are no histological subtypes of established prognostic importance. However, a neural pattern purportedly suggests a better prognosis, and a filigree pattern may confer a worse outcome. Unusual patterns like alveolar/rosette formations may be seen in treated tumors, but no prognostic implication for these patterns is known.

E. Biopsy Approach (Needle, Incisional, Excisional)
Core needle biopsies can obtain sufficient material for special studies and morphologic diagnosis, but sampling problems may limit diagnostic accuracy. 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. Excisional biopsy may not include an adequate margin of normal tissue, even with an operative impression of total gross removal.

F. Resection
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 highly recommended for accurate pathologic evaluation. Full representative mapping of the specimen is also recommended, as discussed below.

A full sagittal section of the resection specimen 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. This face of the specimen can be documented by a black and white photograph or photocopy of the specimen when vacuum-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.
G. Margins
The extent of resection (ie, gross residual disease versus complete resection) has the strongest influence on local control of malignancy.\textsuperscript{16,17} The definition of what constitutes a sufficiently “wide” margin of normal tissue in the management of PNET / ES has evolved. In the current Children’s Oncology Group study of PNET / ES, 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 often is indicated.

H. Prognostic Factors
A summary of the prognostic factors is detailed below.\textsuperscript{18} Of the various prognostic markers listed, age at onset, size, site, and stage bear the most significant relationship with outcome.
### Factor 
<table>
<thead>
<tr>
<th>Favorable Prognosis#</th>
<th>Adverse Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>Younger than 10 years (EFS 69%); 10-17 years (EFS 74%)</td>
<td>18 years or older (EFS 44%)</td>
</tr>
<tr>
<td><strong>Site</strong></td>
<td></td>
</tr>
<tr>
<td>Distal extremity (EFS 74%); Proximal extremity (EFS 62%)</td>
<td>Pelvis (EFS 50%)</td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td></td>
</tr>
<tr>
<td>Less than 8 cm greatest diameter (EFS 75%)</td>
<td>Greater than or equal to 8 cm (EFS 55%)</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
</tr>
<tr>
<td>Nonmetastatic (EFS approximately 70%)</td>
<td>Metastatic (EFS approximately 20%)</td>
</tr>
<tr>
<td><strong>Histology post-therapy</strong></td>
<td></td>
</tr>
<tr>
<td>Grades III-IV (see below)</td>
<td>Grades I, IIA, IIB (see below)</td>
</tr>
<tr>
<td><strong>EWS-FLI1 fusion transcript type</strong></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>Type 2</td>
</tr>
</tbody>
</table>

\# EFS = event-free survival

Histologic response to chemotherapy is an excellent predictor of outcome in osteosarcomas and may also be of value in PNET / ES. This feature may be graded by the Huvos classification, as detailed below.\(^\text{19}\) Details for evaluating tissue necrosis versus viability can be found elsewhere.\(^\text{20}\)

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

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. In the literature,\(^\text{20}\) some may consider any degree of necrosis greater than 90% to be favorable.

A recent Childhood Cancer Group/Pediatric Oncology Group study of resected PNET / ES evaluated the response to preoperative chemotherapy using the following grading.\(^\text{21}\)
<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>3-Year Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No chemotherapy effect</td>
<td>30%</td>
</tr>
<tr>
<td>IIA</td>
<td>1%-10% necrosis</td>
<td>30%</td>
</tr>
<tr>
<td>IIB</td>
<td>11%-90% necrosis</td>
<td>49%</td>
</tr>
<tr>
<td>III</td>
<td>91%-99% necrosis</td>
<td>73%</td>
</tr>
<tr>
<td>IV</td>
<td>100% necrosis</td>
<td>100%</td>
</tr>
</tbody>
</table>

Because the Huvos and CCG/POG 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).

I. TNM and Stage Grouping: Bone

The American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) TNM staging system for bone tumors is as follows.22,23

**Primary Tumor (T)**

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- T1: Tumor 8 cm or less in greatest dimension
- T2: Tumor more than 8 cm in greatest dimension
- T3: Discontinuous tumors in the primary bone site

**Regional Lymph Nodes (N)**

- NX: Cannot be assessed
- N0: No regional lymph node metastasis
- N1: Regional lymph node metastasis

**Distant Metastasis (M)**

- MX: Cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis
  - M1a: Lung
  - M1b: Other distant sites

**Grading**

PNET / ES (either intraosseous or extraosseous) is classified as high-grade, hence stage IA and IB below are excluded for PNET / ES.
J. TNM and Stage Grouping: Soft Tissue
The AJCC/UICC TNM staging system\textsuperscript{22,23} for soft tissues is as follows.

Primary Tumor (T)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor Size</th>
<th>Node Status</th>
<th>Metastasis</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Tumor 5 cm or less in greatest dimension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1a</td>
<td>Superficial tumor#</td>
<td></td>
<td></td>
<td>Low-grade</td>
</tr>
<tr>
<td>T1b</td>
<td>Deep tumor#</td>
<td></td>
<td></td>
<td>Low-grade</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor more than 5 cm in greatest dimension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2a</td>
<td>Superficial tumor#</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2b</td>
<td>Deep tumor#</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\# Superficial tumor located exclusively above superficial fascia. Deep tumor is located exclusively beneath superficial fascia or extends superficially into or through the fascia. Retroperitoneal, mediastinal, and pelvic sarcomas are classified as deep.

Regional Lymph Nodes (N)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Node Status</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Cannot be assessed</td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis</td>
<td></td>
</tr>
</tbody>
</table>

Distant Metastasis (M)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>Cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

Grading

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

Stage Grouping

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor Size</th>
<th>Node Status</th>
<th>Metastasis</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1a</td>
<td>N0, NX</td>
<td>M0</td>
<td>Low-grade</td>
</tr>
<tr>
<td></td>
<td>T1b</td>
<td>N0, NX</td>
<td>M0</td>
<td>Low-grade</td>
</tr>
<tr>
<td>IB</td>
<td>T2a</td>
<td>N0, NX</td>
<td>M0</td>
<td>Low-grade</td>
</tr>
<tr>
<td></td>
<td>T2b</td>
<td>N0, NX</td>
<td>M0</td>
<td>Low-grade</td>
</tr>
<tr>
<td>IIA</td>
<td>T1a</td>
<td>N0, NX</td>
<td>M0</td>
<td>High-grade</td>
</tr>
<tr>
<td></td>
<td>T1b</td>
<td>N0, NX</td>
<td>M0</td>
<td>High-grade</td>
</tr>
<tr>
<td>IIB</td>
<td>T2a</td>
<td>N0, NX</td>
<td>M0</td>
<td>High-grade</td>
</tr>
<tr>
<td></td>
<td>T2b</td>
<td>N0, NX</td>
<td>M0</td>
<td>Any grade</td>
</tr>
<tr>
<td>III</td>
<td>T2b</td>
<td>N0, NX</td>
<td>M0</td>
<td>Any grade</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
<td>Any grade</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>Any grade</td>
</tr>
</tbody>
</table>
References
19. Winkler K, Bielack S, Delling G, et al. Effect of intraarterial versus intravenous cisplatin in addition to systemic doxorubicin, high-dose methotrexate, and


**Bibliography**