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.

Based on AJCC/UICC TNM, 7th edition
Protocol web posting date: October 2009

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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Pediatric • PNET / Ewing Sarcoma

PNET/EwingSarcoma 3.0.0.0

CAP PNET/Ewing Sarcoma Protocol Revision History

Version Code
The definition of the version code can be found at www.cap.org/cancerprotocols.

Version: PNET/EwingSarcoma 3.0.0.0

Summary of Changes
No changes have been made since the October 2009 release.

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).1,2 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 (Checklist)

Protocol web posting date: October 2009

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

* 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.
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) ____________________________

*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 (Checklist)

Protocol web posting date: October 2009

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
*___ Intramuscular
*___ Intra-abdominal/pelvic
*___ Retroperitoneal
*___ Other (specify): ____________________________
*___ Not specified
*___ Cannot be determined

* 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.
**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): ____________________________

**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)**

*Cyto genetics
*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 (post-treatment)

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 (not including skip metastases)

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

Lymph Nodes

Regional Lymph Nodes (pN)
___ pNX: Cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1: Regional lymph node metastasis
Specify: Number of lymph nodes examined: ___
          Number of lymph nodes involved: ___

Nonregional Lymph Nodes
___ Cannot be assessed
___ No nonregional lymph node metastasis
___ Nonregional lymph node metastasis
Specify: Number of lymph nodes examined: ___
          Number of lymph nodes involved: ___

* 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.
Distant Metastasis (pM)

For Primary Osseous Tumors (Note G)
___ Not applicable
___ pM1a: Lung
___ pM1b: Metastasis involving distant sites other than lung *(including skip metastases)*
   *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)
Explanatory Notes

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. 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). An important limitation of fine-needle aspiration biopsy is the limited amount of tissue for additional molecular diagnostic studies 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. Excisional biopsy may not include an adequate margin of normal tissue, even with an operative impression of total gross removal.

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. 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. Full representative mapping of the specimen is also recommended, as discussed below.

A full sagittal section of a bone tumor 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, 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 sagitally-sectioned proximal tibia.](image)

**C. Margins**

The extent of resection (ie, gross residual disease versus complete resection) has the strongest influence on local control of malignancy. 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 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” may be striking. Areas of neuroectodermal differentiation (Homer Wright rosettes; rarely Flexner-Wintersteiner rosettes or primitive neuroepithelium) may be evident in some tumors.

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

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

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

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.10 Details for evaluating tissue necrosis versus viability can be found elsewhere.11
<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>&lt;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. Some authors consider any degree of necrosis greater than 90% to be favorable.\textsuperscript{11}

A Childhood Cancer Group/Pediatric Oncology Group study of resected ES/PNET evaluated the response to preoperative chemotherapy using the following grading.\textsuperscript{12,13}

<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 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.\textsuperscript{14} This glycoprotein is diffusely expressed in the vast majority of cases in a \textit{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.\textsuperscript{9} 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 \textit{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,\textsuperscript{15,16} 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 \textit{EWS} gene at 22q12 and either the \textit{FLI1} gene at 11q24 or the \textit{ERG} gene at 21q22. The presence of t(11;22) (\textit{EWS-FLI1}) and t(21;22) (\textit{EWS-ERG}) is strongly correlated with ES/PNET. The most common gene fusion is the \textit{EWS-FLI1} (90% to 95% of patients). Investigations suggest that different types of \textit{EWS-FLI1} fusions (type1 versus type 2) may have prognostic implications.\textsuperscript{17} Patients with type 1 fusions (in which \textit{EWS} exons 1-7 fuse to \textit{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) \textit{EWS-ETV1}, t(17;22)(q12;q12) \textit{EWS-E1AF}, t(2;22)(q33;q12) \textit{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. 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 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 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 checklist 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**

<table>
<thead>
<tr>
<th>Stage</th>
<th>T1a</th>
<th>N0, NX</th>
<th>M0</th>
<th>Low-grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1b</td>
<td>N0, NX</td>
<td>M0</td>
<td>Low-grade</td>
</tr>
<tr>
<td>Stage 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>Stage 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>Stage IIB</td>
<td>T2a</td>
<td>N0, NX</td>
<td>M0</td>
<td>High-grade</td>
</tr>
<tr>
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<td>T2b</td>
<td>N0-1, NX</td>
<td>M0</td>
<td>High-grade</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>High or Low grade</td>
</tr>
</tbody>
</table>

**References**


**Bibliography**