Protocol for the Examination of Specimens from Patients with Tumors of Bone

Protocol applies to malignant bone tumors. Hematopoietic neoplasms are not included.

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

Procedures
- Biopsy
- 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 these documents. At the same time, the College cautions that use of the protocols other than for their intended educational purpose may involve additional considerations that are beyond the scope of this document.

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Surgical Pathology Cancer Case Summary (Checklist)

Protocol web posting date: October 2009

BONE: Biopsy

Select a single response unless otherwise indicated.

Specimen (Note A)
Specify bone involved (if known): _____
___ Not specified

Procedure
___ Core needle biopsy
___ Curettage
___ Excisional biopsy
___ Other (specify): _____
___ Not specified

Tumor Site (select all that apply) (Note B)
___ Epiphysis or apophysis
___ Metaphysis
___ Diaphysis
___ Cortex
___ Medullary cavity
___ Surface
___ Tumor involves joint
___ Tumor extension into soft tissue
___ Cannot be determined

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

Histologic Type (World Health Organization [WHO] classification of bone tumors) (Note C)
Specify: _____
___ Cannot be determined

***Mitotic Rate (Note D)**
*Specify: ___ /10 high-power fields (HPF)
(1 HPF x 400 = 0.1734 mm^2; X40 objective; most proliferative area)

Necrosis (Note D)
___ Not identified
___ Present
Extent: ___%
___ 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.

Histologic Grade (Note D)
Specify: ___
___ Cannot be determined

***Lymph-Vascular Invasion (Note E)**
*___ Not identified
*___ Present
*___ Indeterminate

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

Ancillary Studies

Immunohistochemistry
Specify: _____
___ Not performed

Cytogenetics
Specify: _____
___ Not performed

Molecular Pathology
Specify: _____
___ Not performed

Radiographic Findings (if available) (Note F)
Specify: _____
___ Not available

***Comment(s)**

Surgical Pathology Cancer Case Summary (Checklist)

Protocol web posting date: October 2009

BONE: Resection

Select a single response unless otherwise indicated.

Specimen (Note A)
Specify bone involved (if known): _____
___ Not specified

Procedure (Note G)
___ Intralesional resection
___ Marginal resection
___ Segmental/wide resection
___ Radical resection
___ Other (specify): _____
___ Not specified

Tumor Site (select all that apply) (Note B)
___ Epiphysis or apophysis
___ Metaphysis
___ Diaphysis
___ Cortical
___ Medullary cavity
___ Surface
___ Tumor involves joint
___ Tumor extension into soft tissue
___ Cannot be determined

Tumor Size
Greatest dimension: ___ cm
*Additional dimensions: ___ x ___ cm
___ Cannot be determined
___ Multifocal tumor/discontinuous tumor at primary site (skip metastasis)

Histologic Type (World Health Organization [WHO] classification of bone tumors) (Note C, Note H)
Specify: _____
___ Cannot be determined

***Mitotic Rate (Note D)**
*Specify: ___ /10 high-power fields
(1 HPF x 400 = 0.1734 mm^2; X40 objective; most proliferative area)

* 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.

Necrosis (macroscopic or microscopic) (Note D)
___ Not Identified
___ Present
Extent: ___%

Histologic Grade (Note D)
Specify: ___
___ Not applicable
___ Cannot be determined

Margins (Note I)
___ Cannot be assessed
___ Margins uninvolved by sarcoma
Distance of sarcoma from closest margin: ___ cm
Specify margin (if known): _____
___ Margin(s) involved by sarcoma
Specify margin(s) (if known): _____

***Lymph-Vascular Invasion (Note E)**
*___ Not identified
*___ Present
*___ Indeterminate

Pathologic Staging (pTNM) (Note J)

TNM Descriptors (required only if applicable) (select all that apply)
___ m (multiple)
___ r (recurrent)
___ y (post-treatment)

Primary Tumor (pT)
___ 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)*

Regional Lymph Nodes (pN) **(Note K)**
___ pNX: Regional lymph nodes cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1: Regional lymph node metastasis
Specify: Number examined: ___
Number involved: ___

Distant Metastasis (pM)
___ Not applicable
___ pM1a: Lung
___ pM1b: Metastasis involving distant sites other than lung (*including skip metastases)*
*Specify site(s), if known: _____

* 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.

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

Ancillary Studies

Immunohistochemistry
Specify: _____
___ Not performed

Cytogenetics
Specify: _____
___ Not performed

Molecular Pathology
Specify: _____
___ Not performed

Radiographic Findings (if available) (Note F)
Specify: _____
___ Not available

Preresection Treatment (select all that apply)
___ No therapy
___ Chemotherapy performed
___ Radiation therapy performed
___ Therapy performed, type not specified
___ Unknown

Treatment Effect (select all that apply) (Note L)
__ Not identified
__ Present
*Specify percentage of necrotic tumor: _____%
__ Cannot be determined

***Comment(s)**

Explanatory Notes

These recommendations are used for all primary malignant tumors of bone except hematopoietic neoplasms, including lymphoma and plasma cell neoplasms.

A. Processing

Fixation
Tissue specimens from bone tumors optimally are received fresh/unfixed because of the importance of ancillary studies, such as cytogenetics, which require fresh tissue.

Tissue Submission for Histologic Evaluation
One section per centimeter of maximum dimension is usually recommended, although fewer sections are needed for very large tumors, especially if they are homogeneous. Tumors known to be high grade from a previous biopsy do not require as many sections as those that were previously diagnosed as low grade, as documentation of a high-grade component will change stage and prognosis in the latter case. Sections should be taken of grossly heterogeneous areas, and there is no need to submit more than 1 section of necrotic tumor (always with a transition to viable tumor), with the exception of chemotherapy effect on osteosarcomas and Ewing sarcoma/primitive neuroectodermal tumor (PNET).[1] Occasionally, gross pathology can be misleading, and areas that appear to be grossly necrotic may actually be myxoid or edematous. When this happens, additional sections of these areas should be submitted for histologic examination. When estimates of gross necrosis exceed those of histologic necrosis, the greater percentage of necrosis should be recorded on the surgical pathology report. In general, most tumors require 12 sections or fewer, excluding margins. Tumors with greater areas of heterogeneity may need to be sampled more thoroughly.

Fresh tissue for special studies should be submitted at the time the specimen is received. 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 needed 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.

Molecular Studies
It is important to snap freeze a small portion of tissue whenever possible. This tissue can be used for a variety of molecular assays for tumor-specific molecular translocations (see Table 1) that help in classifying bone tumors.[2,3] In addition, treatment protocols increasingly require fresh tissue for correlative studies. Approximately 1 cm^3 of fresh tissue (less is acceptable for small specimens, including core biopsies) should be cut into small, 0.2-cm fragments, reserving sufficient tissue for histologic examination. This frozen tissue should ideally be stored at -70^oC and can be shipped on dry ice to facilities that perform molecular analysis.

Table 1. Characteristic Cytogenetic and Molecular Events of Bone Tumors

Histologic Type	Cytogenetic Events	Molecular Events
Chondrosarcoma of bone	Complex	
Ewing sarcoma/PNET	t(11;22)(q24;q12)	*EWS-FLI1* fusion
	t(21;22)(q12;q12)	*EWS-ERG* fusion
	t(2;22)(q33;q12)	*EWS-FEV* fusion
	t(7;22)(p22;q12)	*EWS-ETV1* fusion
	t(17;22)(q12;q12)	*EWS-E1AF* fusion
	inv(22)(q12q12)	*EWS-ZSG*
Osteosarcoma		
Low grade	Ring chromosomes	
High grade	Complex	

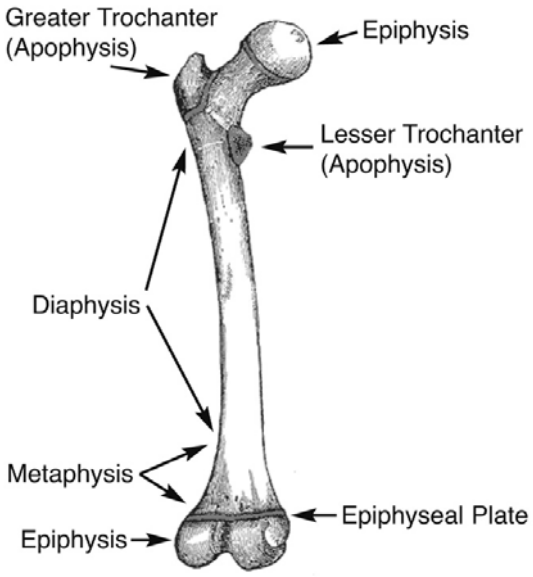
PNET indicates primitive neuroectodermal tumor.

B. Location of Neoplasms of Bone

Relevant Radiologic Findings

Radiographic imaging plays an especially critical role in the diagnosis of bone tumors, Close collaboration with an experienced musculoskeletal radiologist and orthopedic surgeon is recommended.

The figure is a diagrammatic representation of the “anatomic” regions of a long bone. These locations are very important in classifying bone tumors. For instance, chondroblastomas almost always arise in the epiphysis. Epiphyses and apophyses are secondary ossification centers, and therefore are embryonic equivalents. The greater and lesser trochanters are apophyses, while the epiphyses are at the ends of long bones.



Important anatomic landmarks for tumor diagnosis in long bones. Adapted from *Gray’s Anatomy of the Human Body.* Philadelphia, PA: Lea & Febiger; 1918.

C. Classification of Bone Tumors

Intraoperative Consultation

Histologic classification of bone tumors is sufficiently complex that, in many cases, it is unreasonable to expect a precise classification of these tumors based on an intraoperative consultation. A complete understanding of the surgeon's treatment algorithm is recommended before rendering a frozen section diagnosis. In the case of primary bone tumors, an intraoperative diagnosis of benign versus malignant will generally guide the immediate decision to curette, excise, or wait for permanent sections, and certain therapeutic options may be lost if the wrong path is pursued. Intraoperative consultation is useful in assessing if "lesional" tissue is present and whether or not this tissue is necrotic, and in constructing a differential diagnosis that can direct the proper triage of tissue for flow cytometry (lymphoma), electron microscopy, and molecular studies/cytogenetics. Tissue triage optimally is performed at the time of frozen section. In many cases, it is important that a portion of tissue be submitted for ancillary studies, even from fine-needle aspiration (FNA) and core needle biopsy specimens, once sufficient tissue has been submitted for histologic evaluation.

Tumor Classification from Biopsies

It is not always possible to classify bone tumors precisely based on biopsy material, especially FNA and core needle biopsy specimens. Whereas pathologists should make every attempt to classify lesions in small biopsy specimens, on occasion stratification into very basic diagnostic categories, such as lymphoma, carcinoma, melanoma, and sarcoma, is all that is possible. In some cases, precise classification is only possible in open biopsies or resection specimens.

WHO Classification of Malignant Bone Tumors

Classification of tumors should be made according to the World Health Organization (WHO) classification of bone tumors listed below.[4]

WHO Classification of Malignant Bone Tumors

- Cartilage Tumors
  - Chondrosarcoma
    - Central, primary, and secondary
    - Peripheral
    - Dedifferentiated
    - Mesenchymal
    - Clear cell
- Osteogenic Tumors
  - Osteosarcoma
    - Conventional
      - Chondroblastic
      - Fibroblastic
      - Osteoblastic
    - Telangiectatic
    - Small cell
    - Low grade central
    - Secondary

Parosteal
Periosteal
High grade surface

Fibrogenic Tumors
Fibrosarcoma

Fibrohistiocytic Tumors
Malignant fibrous histiocytoma (undifferentiated pleomorphic sarcoma)

Ewing Sarcoma/Primitive Neuroectodermal Tumor
Ewing sarcoma/PNET

Hematopoietic Tumors
Plasma cell myeloma
Malignant lymphoma, NOS

Giant Cell Tumors
Malignancy in giant cell tumor

Notochordal Tumors
Chordoma

Vascular Tumors
Angiosarcoma

Smooth Muscle Tumors
Leiomyosarcoma

Lipogenic Tumors
Liposarcoma

Miscellaneous Tumors
Adamantinoma
Metastatic malignancy

D. Grading

The grading of bone tumors is largely driven by the histologic diagnosis, and traditionally grading has been based on the system advocated by Broders, which assesses cellularity and nuclear features/degree of anaplasia.[5] The seventh edition of the *AJCC Cancer Staging Manual* recommends a 4-grade system.[6] G1, G2 are regarded as low grade and G3 and G4 as high grade. However, we advocate a more pragmatic approach to grading aggressive and malignant primary tumors of bone. Two bone tumors that are locally aggressive and metastasize infrequently, and thus are usually low grade, are low-grade central osteosarcoma and parosteal osteosarcoma. Periosteal osteosarcoma is generally regarded as a grade 2 osteosarcoma. Primary bone tumors that are generally high grade include malignant giant cell tumor, Ewing sarcoma/PNET, angiosarcoma, dedifferentiated chondrosarcoma, conventional osteosarcoma, telangiectactic osteosarcoma, small cell osteosarcoma, secondary osteosarcoma, and high-grade surface osteosarcoma.

Grading of conventional chondrosarcoma is based on cellularity, cytologic atypia, and mitotic figures. Grade 1 (low-grade) chondrosarcoma is hypocellular and similar histologically to enchondroma. Grade 2 (intermediate-grade) chondrosarcoma is more cellular than grade 1 chondrosarcoma; has more cytologic atypia, greater hyperchromasia and nuclear size; or has extensive myxoid stroma. Grade 3 (high-grade) chondrosarcoma is hypercellular, pleomorphic, and contains prominent mitotic activity. Mesenchymal chondrosarcoma, fibrosarcoma, leiomyosarcoma, liposarcoma, malignant fibrous histiocytoma (pleomorphic sarcoma, NOS) and other "soft tissue-type" sarcomas that rarely occur in bone can be graded according to the French Federation of Cancer Centers Sarcoma Group (FNCLCC) grading system[7] (see College of American Pathologists protocol for soft tissue tumors[8]).

Chordomas are locally aggressive lesions with a propensity for metastasis late in their clinical course and are not graded. Adamantinomas tend to have a low-grade clinical course, but this is variable. Fortunately, they are very rare. According to the WHO classification of tumors of bone, adamantinomas are considered low grade.

Bone Tumor Grades (Summary)

Grade 1 (Low Grade)
Low-grade central osteosarcoma
Parosteal osteosarcoma
Adamantinoma

Grade 2
Periosteal osteosarcoma

Grade 3 (High Grade)
Ewing sarcoma/PNET
Conventional osteosarcoma
Telangiectactic osteosarcoma
Mesenchymal chondrosarcoma
Small cell osteosarcoma
Secondary osteosarcoma
High-grade surface osteosarcoma
Dedifferentiated chondrosarcoma
Dedifferentiated chordoma
Malignant giant cell tumor

Variable Grade
Conventional chondrosarcoma of bone (grades 1 to 3)
Soft-tissue type sarcomas (eg, leiomyosarcoma)

TNM Grading
The seventh edition of the American Joint Committee on Cancer (AJCC) and International Union Against Cancer (UICC) staging system for bone tumors includes a 4-grade system but effectively collapses into high grade and low grade.[6,9] Grading in the TNM grading system is based on differentiation only and does not generally apply to sarcomas.

GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated
G4 Poorly differentiated or undifferentiated (4-tiered systems only)

For purposes of using the AJCC staging system (see note K), 3-grade systems can be converted to a 2-grade (TNM) system as follows: grade 1 = low-grade; grade 2 and grade 3 = high-grade.

E. Lymph - Vascular Invasion
Lymph-vascular invasion (LVI) indicates whether microscopic lymph-vascular invasion is identified. LVI includes lymphatic invasion, vascular invasion, or lymph-vascular invasion. By AJCC/UICC convention, LVI does not affect the T category indicating local extent of tumor unless specifically included in the definition of a T category.

F. Relevant Radiologic Findings
Radiographic imaging plays an especially critical role in the diagnosis of bone tumors. Close collaboration with an experienced musculoskeletal radiologist and orthopedic surgeon is recommended.

G. Definition of Procedures
The following is a list of guidelines to be used in defining what type of procedure has been performed. This is based on the surgeon's intent and not based on the pathological assessment of the margins.

Intralesional Resection
Leaving gross tumor behind. Partial debulking or curettage are examples.

Marginal Resection
Removing the tumor and its pseudocapsule with a relatively small amount of adjacent tissue. There is no gross tumor at the margin; however, microscopic tumor may be present. Note that occasionally, a surgeon will perform an "excisional" biopsy, which effectively accomplishes the same thing as a marginal resection.

Segmental/Wide Resection
An intracompartmental resection. A single piece of bone is resected, including the lesion and a cuff of normal bone.

Radical Resection
The removal of an entire bone, or the excision of the adjacent muscle groups if the tumor is extracompartmental.

H. Histological Classification of Treated Lesions
Due to extensive treatment effects, such as necrosis, fibrosis, and chemotherapy-induced and radiation-induced pleomorphism, it may not be possible to classify some lesions that were either never biopsied or where the biopsy was insufficient for a precise diagnosis.

I. Margins

It has been recommended that for all margins <2 cm, the distance of the tumor from the margin be reported in centimeters.[10] However, there is a lack of agreement on this issue. We recommend specifying the location of all margins <2 cm. Margins from bone tumors should be taken as *perpendicular* margins, if possible. If the tumor is >2 cm from the margin, the marrow can be scooped out and submitted as a margin.

J. TNM and Stage Groupings

The seventh edition TNM staging system for bone tumors of the AJCC and the UICC is recommended.[6,9]

The classification is to be applied to all primary tumors of bone. Anatomic site is known to influence outcome; therefore, outcome data should be reported specifying site. Site groups for bone sarcoma are the following: extremity, pelvis, spine. Pathologic staging includes pathologic data obtained from examination of a resected specimen sufficient to evaluate the highest T category, histopathologic type and grade, regional lymph nodes as appropriate, or distant metastasis. Because regional lymph node involvement from bone tumors is rare, the pathologic stage grouping includes any of the following combinations: pT pG pN pM, or pT pG cN cM, or cT cN pM

TNM Descriptors

For identification of special cases of TNM or pTNM classifications, the “m” suffix and the “y” and “r” prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

The “m” suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

The “y” prefix indicates those cases in which classification is performed during or following initial multimodality therapy (ie, neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a “y” prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The “y” categorization is not an estimate of tumor prior to multimodality therapy (ie, before initiation of neoadjuvant therapy).

The “r” prefix indicates a recurrent tumor when staged after a documented disease-free interval, and is identified by the “r” prefix: rTNM.

N Category Considerations

Because of the rarity of lymph node involvement in sarcomas, the designation NX may not be appropriate and could be considered N0 if no clinical involvement is evident.

Stage Groupings

Stage IA	T1	N0	M0[#]	G1,2	Low grade
Stage IB[##]	T2	N0	M0	G1,2	Low grade
Stage IIA	T1	N0	M0	G3,4	High grade
Stage IIB	T2	N0	M0	G3,4	High grade
Stage III	T3	N0	M0	G3,4	High grade
Stage IVA	Any T	N0	M1a	Any G	

Stage IVB	Any T	N1	Any M	Any G
	Any T	Any N	M1b	Any G

[#] M0 is defined as no distant metastasis.

[##] T3, N0, M0, G1,2 should be considered stage IB.

Additional Descriptors

Residual Tumor (R)
Tumor remaining in a patient after therapy with curative intent (eg, surgical resection for cure) is categorized by a system known as R classification, shown below.

RX Presence of residual tumor cannot be assessed
R0 No residual tumor
R1 Microscopic residual tumor
R2 Macroscopic residual tumor

For the surgeon, the R classification may be useful to indicate the known or assumed status of the completeness of a surgical excision. For the pathologist, the R classification is relevant to the status of the margins of a surgical resection specimen. That is, tumor involving the resection margin on pathologic examination may be assumed to correspond to residual tumor in the patient and may be classified as macroscopic or microscopic according to the findings at the specimen margin(s).

K. Lymph Nodes
Regional lymph node metastasis is extremely rare in adult bone sarcomas. Nodes are not sampled routinely, and it is not necessary to exhaustively search for nodes. When present, regional lymph node metastasis has prognostic importance and should be reported.

L. Response to Chemotherapy/Radiation Therapy Effect
It is essential to estimate neoadjuvant treatment effect in primary Ewing sarcoma/PNET and osteosarcoma of bone, as these have been shown to have prognostic significance.[1,11-14] An entire representative slice of the tumor taken through the long axis should be mapped using a grid pattern diagram, photocopy, or radiologic film to indicate the site for each tumor block. In addition, a section of tumor perpendicular to the long axis should be sampled at the rate of 1 section per centimeter. Areas of soft tissue extension and the interface of tumor with normal tissue should also be sampled. Prognostically significant therapy response in osteosarcoma, according to most series, is defined at 90%, with those tumors showing 90% therapy response associated with a favorable prognosis.[11,12] There are two protocols to assess response to therapy in Ewing sarcoma. Response can be assessed in the same manner as osteosarcoma or by the system of Picci which is expressed as grade I (macroscopic viable tumor), grade II (microscopic viable tumor), or grade III (no viable tumor).[13,14]

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