Protocol for the Examination of Biopsy Specimens From Patients With Primary Tumors of Bone

Version: 4.2.0.0
Protocol Posting Date: June 2024
The use of this protocol is recommended for clinical care purposes but is not required for accreditation purposes.

This protocol may be used for the following procedures AND tumor types:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy</td>
<td>Includes specimens designated core needle biopsy, curettage, or incisional biopsy.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary malignant bone tumors</td>
<td>Includes tumors arising in bone for which pTNM staging on the resection is clinically relevant.</td>
</tr>
</tbody>
</table>

The following should NOT be reported using this protocol:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resection (consider Bone Resection protocol)</td>
<td></td>
</tr>
<tr>
<td>Cytologic fine needle aspiration (FNA) without cell block or biopsy</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor Type - Best reported using other protocols</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric Ewing sarcoma (consider the Pediatric Ewing Sarcoma protocol)</td>
<td></td>
</tr>
<tr>
<td>Lymphoma / Leukemia (consider the Precursor and Mature Lymphoid Malignancies, Myeloid and Mixed / Ambiguous Lineage Neoplasms, or Plasma Cell Malignancies protocols)</td>
<td></td>
</tr>
<tr>
<td>Soft tissue primary sarcoma (consider the Soft Tissue protocol)</td>
<td></td>
</tr>
</tbody>
</table>

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With guidance from the CAP Cancer and CAP Pathology Electronic Reporting Committees.
* Denotes primary author.

Accreditation Requirements
The use of this biopsy case summary is recommended for clinical care purposes, but is not required for accreditation purposes. The core and conditional data elements are routinely reported for biopsy specimens. Non-core data elements are included to allow for reporting information that may be of clinical value.
Summary of Changes
v 4.2.0.0

- Cover page update
- Updates to content and explanatory notes, including WHO Histologic Types
- LVI question update from optional to required (core) and "Lymphovascular Invasion" to "Lymphatic and / or Vascular Invasion"
- "Mitotic Rate" answer update
- Addition of required (core) question “Tumor Laterality”
- Addition of conditional question “Multiple Sites (required only if applicable)”
- Addition of optional questions “Associated Syndrome”, “Other Clinical Findings”, “Decalcification Procedure”, and “Tumor Size (based on clinicoradiologic parameters)”
- SPECIAL STUDIES section update
Reporting Template
Protocol Posting Date: June 2024
Select a single response unless otherwise indicated.

CASE SUMMARY: (BONE: Biopsy)
Standard(s): AJCC-UICC 8
This case summary is recommended for reporting biopsy specimens, but is not required for accreditation purposes.

CLINICAL (Note A)

+Associated Syndrome
   ___ Li-Fraumeni syndrome
   ___ Mazabraud syndrome
   ___ Ollier disease
   ___ Maffucci syndrome
   ___ Hereditary multiple exostoses
   ___ Other (specify): _________________
   ___ Not specified

+Radiologic Findings (Notes A,B)
   ___ Specify: _________________
   ___ Not available

+Other Clinical Findings
   ___ Specify: _________________
   ___ Not available

SPECIMEN

Procedure (Note C)
   ___ Core needle biopsy
   ___ FNA core needle biopsy
   ___ Curettage
   ___ Incisional biopsy
   ___ Other (specify): _________________
   ___ Not specified

+Decalcification Procedure (Note C)
   ___ EDTA-decal or equivalent
   ___ Harsh acid decalcification

TUMOR

Multiple Sites (required only if applicable)
   ___ Not applicable
   ___ Multifocal tumor / discontinuous tumor at primary bone site
Additional primary bone site(s) present (specify for synchronous malignant tumors or polyostotic aggressive tumors): ____________________

Tumor Site (Note D)
___ Appendicular skeleton, trunk, skull, facial bones (specify): ____________________
___ Spine (specify bone, if known): ____________________
___ Pelvis (specify bone, if known): ____________________
___ Not specified

Tumor Laterality
___ Left
___ Right
___ Central
___ Polyostotic ipsilateral
___ Polyostotic bilateral
___ Cannot be determined

Tumor Location and Extent (Note B) (select all that apply)
___ Epiphysis or apophysis
___ Metaphysis
___ Diaphysis
___ Cortex
___ Medullary cavity
___ Surface
___ Involves joint
___ Extends into soft tissue
___ Cannot be determined: ____________________

+Tumor Size (based on clinicoradiologic parameters)
___ Greatest dimension in Centimeters (cm): ____________________ cm
___ Not specified
___ Cannot be determined: ____________________

Histologic Type# (Note E)
# The list is derived from the World Health Organization (WHO) classification of bone tumors, 5th edition, to include ONLY bone tumors of intermediate (locally aggressive and rarely metastasizing) potential and malignant bone tumors.
___ Chondrogenic tumors
___ Synovial chondromatosis
___ Atypical cartilaginous tumor
___ Chondrosarcoma
___ Chondrosarcoma secondary (specify): ____________________
___ Dedifferentiated chondrosarcoma
___ Periosteal chondrosarcoma
___ Clear cell chondrosarcoma
___ Mesenchymal chondrosarcoma
___ Osteogenic tumors
____ Osteoblastoma
____ Low-grade central osteosarcoma
____ Low-grade central osteosarcoma with high-grade transformation
____ Parosteal osteosarcoma
____ Parosteal osteosarcoma with high-grade transformation
____ Conventional osteosarcoma
____ Telangiectatic osteosarcoma
____ Small cell osteosarcoma
____ Periosteal osteosarcoma
____ High-grade surface osteosarcoma
____ Secondary osteosarcoma

+Precipitating Factor for Secondary Osteosarcoma: _______________

____ Undifferentiated small round cell sarcomas
____ Ewing sarcoma
____ Round cell sarcoma with EWSR1::non-ETS fusions (specify, if known): _______________
____ CIC-rearranged sarcoma
____ Sarcoma with BCOR genetic alterations

____ Fibrogenic / fibrohistiocytic / histiocytic tumors
____ Sclerosing epithelioid fibrosarcoma
____ Primary malignant giant cell tumor of bone
____ Secondary malignant giant cell tumor of bone
____ Giant cell tumor of bone
____ Langerhans cell histiocytosis

+System Involvement
____ Single system (specify): _______________
____ Multisystem (specify): _______________
____ Other (leukemic, atypical, or other, specify): _______________
____ Desmoplastic fibroma

____ Notochordal tumors
____ Conventional chordoma
____ Poorly differentiated chordoma
____ Dedifferentiated chordoma

____ Vascular tumors
____ Epithelioid hemangioma
____ Pseudomyogenic hemangioendothelioma
____ Epithelioid hemangioendothelioma
____ Angiosarcoma

____ Epithelial tumors
____ Adamantinoma of long bones
____ Osteofibrous dysplasia-like adamantinoma
____ Dedifferentiated adamantinoma

____ Other mesenchymal or tumors of uncertain differentiation
____ Leiomyosarcoma of bone
____ Rhabdomyosarcoma of bone (specify fusion, if known): _______________
____ TK-fusion (NTRK, ALK, BRAF) tumor, primary intraosseous (specify fusion, if known): _______________
Undifferentiated pleomorphic sarcoma
Cannot be determined:
Other histologic type not listed (specify):

**Histologic Type Comment:**

**Histologic Grade (Note F)**
G1, well-differentiated, low-grade
G2, moderately differentiated, high-grade
G3, poorly differentiated, high-grade
GX, cannot be assessed
Ungraded tumor / not applicable for this tumor type

**Mitotic Rate (Note G)**
Specify mitotic rate per mm2: mitoses per mm2
Specify mitotic rate per 10 high-power fields (HPF): mitoses per 10 high-power fields (HPF)
Cannot be determined (explain):

**Necrosis**
Not identified
Present
**Extent of Necrosis**
Specify percentage: %
Other (specify):
Cannot be determined (explain):
Cannot be determined

**Lymphatic and / or Vascular Invasion (Note H)**
Not identified
Present
Cannot be determined

**Tumor Comment:**

**ADDITIONAL FINDINGS**

**Additional Findings (specify):**

**SPECIAL STUDIES (Note E)**

**Immunohistochemistry**
Specify results:
Pending (specify):
Not performed:
Not applicable
Other (specify):
Cytogenetics
___ Specify results: _________________
___ Pending (specify): _________________
___ Not performed: _________________
___ Not applicable
___ Other (specify): _________________

Molecular Studies
___ Specify results: _________________
___ Pending (specify): _________________
___ Not performed: _________________
___ Not applicable
___ Other (specify): _________________

COMMENTS

Comment(s): _________________
Explanatory Notes

A. Scope of Guidelines
This checklist may be used for malignant chondrogenic tumors, osteogenic tumors, fibrogenic tumors, osteoclastic giant cell-rich tumors, notochordal tumors, myogenic tumors, lipogenic tumors, undifferentiated small round cell sarcomas, and other mesenchymal tumors arising in bone. Locally aggressive entities such as synovial chondromatosis, osteoblastoma, giant cell tumor of bone, epithelioid hemangioma, pseudomyogenic hemangioma, and desmoplastic fibroma may be reported using this protocol but are not staged. Radiologic parameters include bone involved, size and extent (compartment) of tumor, location of tumor and extent, radiologic intrinsic characteristics including matrix or mineralization in bone-forming tumors, and differential diagnosis. Clinical parameters include patient age, sex, exact anatomic location, size, solitary or polyostotic, syndromes, and other pertinent medical and surgical history, if clinically relevant.

B. Tumor Location and Extent
Radiographic imaging plays an especially critical role in the diagnosis of bone tumors. Close collaboration with an experienced musculoskeletal radiologist and orthopedic surgeon is advised.

Figure 1 is a diagrammatic representation of the “anatomic” regions of a long bone. These locations are very important in classifying bone tumors. For instance, chondroblastoma almost always arises in the epiphysis. Epiphyses and apophyses are secondary ossification centers and therefore are embryonic equivalents; “epiphyses” are found within joints, whereas “apophyses”, the sites of tendonous and ligamentous attachments, are not found within joints. The greater and lesser trochanters are apophyses, while the epiphyses are at the ends of long bones.

Figure 1. Important anatomic landmarks for tumor diagnosis in long bones. Adapted from Gray’s Anatomy.¹
C. Biopsy/Tissue Processing/Tissue for Genetic-Molecular Studies

The following is a list of guidelines to be used in defining pathologic diagnosis for biopsy.

**Biopsy**

It is best to obtain enough cores for H&E, immunohistochemistry, and molecular genetic studies. Tissue for frozen, flow, and/or cytogenetics should be taken after enough is submitted for permanent assessment. For microbiology cultures, it is best to go directly from the Operating Room to the Microbiology Laboratory. It is optimal to have more than one block for a biopsy so that one can be for immunostains and the other for molecular genetics studies, as needed.

**Fixation**

Tissue specimens from bone tumors optimally are received fresh/unfixed in case fresh tissue for ancillary studies, such as cytogenetics, are needed. All tissue should be processed in a manner that would allow molecular studies to be undertaken successfully. Decalcification using harsh acid reagents may be detrimental for nucleic acid-based molecular studies and therefore utilization of EDTA as decalcifying agent has been recommended. Freezing a portion of the sample and/or fixing soft portions of the lesion in buffered formalin is encouraged over EDTA decalcification for molecular studies.

**Tissue Submission for Histologic Evaluation and Genetic/Molecular Studies**

While it has been helpful and often required for clinical trials to have snap frozen tissue, approximately 1 cm³ of fresh tissue stored at minus seventy (-70° C) that can be shipped on dry ice to facilities to perform molecular analysis, most full work up of sarcomas can be made on formalin-fixed and EDTA decalcified paraffin-embedded tissue and tissue should be entirely submitted, separated into at least two blocks.

**ROSE or Intraoperative Assessment of Biopsy**

Histologic classification of bone tumors is sufficiently complex that it is unreasonable to expect a precise classification of these tumors based on a rapid assessment or intraoperative consultation; best to assess viability of sampling and defer to permanent.

References


D. Tumor Site

Given the strong association between the primary anatomic site and outcome, the 8th edition of the AJCC Cancer Staging Manual uses the following site groups for staging purposes:
• Appendicular skeleton, including trunk, skull, and facial bones
• Pelvis
• Spine

This site grouping is reflected by the provision of separate definitions for the primary tumor (T) for each anatomic site.

References

E. Classification of Bone Tumors
The list is derived from the World Health Organization (WHO) classification of soft tissue tumors, 5th edition,1 edited to include ONLY bone tumors of intermediate (locally aggressive and rarely metastasizing) potential and malignant bone tumors.

E.1. Classification of Bone Tumors
Atypical cartilaginous tumor/grade 1 chondrosarcoma:
This terminology should not be used when a pathologist cannot decide on the classification for the cartilaginous neoplasm.

Bone Primary Tyrosine Kinase Fusion Tumors:
While fusions involving the RAS::MAPK pathway are rare among bone tumors, these tumors have driver alterations in genes that encode tyrosine kinases and may respond to therapy targeting NTRK, ALK, BRAF, RET, RAF, FGFR1, or ABL1, etc. Notably, NTRK tumors fused with KANK1 or TPR have been demonstrated to exhibit higher-grade appearance, including spindled and pleomorphic characteristics, accompanied by necrosis and mitoses, leading to unfavorable outcomes. Consequently, it is advisable to conduct comprehensive RNA-based Next-Generation Sequencing (NGS) for fusions, particularly in spindled pleomorphic tumors occurring in individuals under 50 years old, especially those in soft tissue or intraosseous locations. This recommendation is especially pertinent with tumors that have variable ovoid spindled to epithelioid morphology, variable collagenous to myxoid stroma, variable gaping to staghorn vasculature and specifically focal CD34 and/or focal S100 protein, without any staining for SOX10. In these tumors, BRAF, ALK, or panTrk or other immunostain may be identified.2,3,4,5,6,7,8,9,10,11

Most Common Molecular/Genetic Findings:
The most common molecular/genetic findings in a subset of intermediate/malignant bone tumors are listed (Table 1).

Table 1: Subset of bone intermediate and malignant tumors with the most common diagnostic molecular/genetic findings.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Genes Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chondrosarcoma</td>
<td>IDH1/IDH2 mutation</td>
</tr>
<tr>
<td>Intraosseous extraskeletal myxoid chondrosarcoma</td>
<td>EWSR1/TAF15::NR4A3 fusion</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Genomic Alteration</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>Mesenchymal chondrosarcoma</td>
<td>HEY1::NCOA2 fusion</td>
</tr>
<tr>
<td>Secondary chondrosarcoma arising in enchondroma</td>
<td>IDH1/IDH2 mutation</td>
</tr>
<tr>
<td>Secondary chondrosarcoma arising in osteochondroma</td>
<td>EXT1/EXT2 mutation</td>
</tr>
<tr>
<td>Sclerosing epithelioid fibrosarcoma of bone</td>
<td>FUS::CREB3L2 fusion</td>
</tr>
<tr>
<td>Angiomatoid fibrous histiocytoma of bone/joint</td>
<td>EWSR1::CREB1 or EWSR1::ATF1 alternate</td>
</tr>
<tr>
<td>Primary malignant giant cell tumor of bone</td>
<td>H3F3A mutation</td>
</tr>
<tr>
<td>Leukemia/Multifocal atypical Langerhans cell histiocytosis</td>
<td>BRAF mutation</td>
</tr>
<tr>
<td>Poorly differentiated chordoma</td>
<td>SMARCB1 deletion</td>
</tr>
<tr>
<td>Low-grade central osteosarcoma</td>
<td>MDM2/CDK4 amplification</td>
</tr>
<tr>
<td>Parosteal osteosarcoma</td>
<td>MDM2/CDK4 amplification</td>
</tr>
<tr>
<td>Rhabdomyosarcoma of bone (adult)</td>
<td>FUS/EWSR1::TFCP2, MEIS1::NCOA2</td>
</tr>
<tr>
<td>Ewing sarcoma</td>
<td>EWSR1::FLI1 (85-90%), EWSR1::ERG (8-10%), others</td>
</tr>
<tr>
<td>CIC-rearranged sarcoma</td>
<td>CIC::DUX4</td>
</tr>
<tr>
<td>Round cell sarcoma with EWSR1::non-ETS fusion</td>
<td>EWSR1::PATZ1, EWSR1::NFATC2, FUS::NFATC2</td>
</tr>
<tr>
<td>Sarcoma with BCOR genetic alterations</td>
<td>BCOR::CCNB3 fusion</td>
</tr>
<tr>
<td>Epithelioid hemangioendothelioma of bone</td>
<td>WWTR1::CAMTA1 fusion</td>
</tr>
<tr>
<td>Angiosarcoma of bone</td>
<td>MYC amplification (post-irradiation)</td>
</tr>
<tr>
<td>Tyrosine-kinase fusion tumor</td>
<td>NTRK1/2/3, ALK, BRAF, etc. fusion (various fusion partners)</td>
</tr>
</tbody>
</table>

References


F. 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. The eighth edition of the AJCC Cancer Staging Manual recommends a 2-tiered system (low vs high-grade) for recording grading. Histologic grading uses a 3-tiered system: Grade 1 is considered low-grade, and Grade 2 and Grade 3 are grouped together as high-grade for biological grading. In bone sarcomas, the histologic subtype often determines the clinical behavior and grade. Therefore, a more pragmatic approach to grading aggressive and malignant primary tumors of bone can be used.

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, angiosarcoma, dedifferentiated chondrosarcoma, conventional osteosarcoma, telangiectatic osteosarcoma, small cell osteosarcoma, secondary osteosarcoma, and high-grade surface osteosarcoma.

Grading of conventional chondrosarcoma is based on cellularity, cytologic atypia, and mitotic figures, following the grading system proposed by Evans et al. Grade 1 (low-grade) chondrosarcoma is hypocellular and similar histologically to enchondroma. Grade 2 (intermediate-grade) chondrosarcoma is
myxoid and more cellular/atypical than grade 1 chondrosarcoma. Grade 3 (high-grade) chondrosarcoma is hypercellular, pleomorphic, and contains observed mitotic activity.

Mesenchymal chondrosarcoma, fibrosarcoma, leiomyosarcoma, liposarcoma, undifferentiated pleomorphic sarcoma of bone 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.5

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, these are very rare. Other tumors such as periosteal chondrosarcoma (grading does not predict behavior) or bone angiosarcoma (always considered high-grade behavior) are also not graded. According to the 2020 WHO classification of tumors of bone, adamantinomas are not graded.2,3,6

**Bone Tumor Grades (Most Common)**

**Grade 1 (Low-Grade)**
- Low-grade intramedullary (central) osteosarcoma
- Parosteal osteosarcoma
- Grade I chondrosarcoma
- Clear cell chondrosarcoma

**Grade 2**
- Periosteal osteosarcoma
- Grade II chondrosarcoma

**Grade 3 (High-Grade)**
- Ewing sarcoma
- Most round-cell sarcomas
- Sarcoma with BCOR genetic alterations
- CIC-rearranged sarcoma
- Conventional osteosarcoma
- Telangiectactic osteosarcoma
- Mesenchymal chondrosarcoma
- Small cell osteosarcoma
- Secondary osteosarcoma
- High-grade surface osteosarcoma
- Dedifferentiated chondrosarcoma
- Dedifferentiated chordoma
- Poorly differentiated chordoma
- Malignancy in giant cell tumor (primary and secondary malignant giant cell tumor of bone)
- Grade III chondrosarcoma
- Leiomyosarcoma
- Rhabdomyosarcoma
- Undifferentiated pleomorphic sarcoma
TNM Grading
The 8th edition of the American Joint Committee on Cancer (AJCC) and International Union Against Cancer (UICC) staging system for bone tumors includes a 3-grade system but effectively collapses into high-grade and low-grade. Other grading systems in (TNM) are based on differentiation, yet this is not applicable to primary intraosseous sarcomas.

GX Grade cannot be assessed
G1 Well-differentiated, low-grade
G2 Moderately differentiated, high-grade
G3 Poorly differentiated, high-grade

For purposes of using the AJCC staging system, 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.

References

G. Mitotic Rate
Mitotic rate is determined by counting mitotic figures in the most mitotically active area, away from areas of necrosis, in either 10 consecutive high-power fields (HPF) (use the X40 objective) (1 HPF x 400 = 0.1734 mm²) or in the appropriate number of HPF to encompass 1 mm² based on each individual microscope.

The area of 1 HPF originally used measured 0.1734 mm². However, the area of 1 HPF using most modern microscopes with wider 40x lenses will most likely be higher. Pathologists are encouraged to determine the field area of their 40x lenses and divide 0.1734 by the obtained field area to obtain a conversion factor. The number of mitotic figures in 10 HPF multiplied by the obtained conversion factor and rounded to the nearest whole number should be used for reporting purposes.

An important change in the 5th Edition of the WHO Classification of Tumours series is the conversion of mitotic count from the traditional denominator of 10 HPFs to a defined area expressed in 1 mm², as an attempt to standardize the area used for mitotic count. Table 2 shows the approximate number of fields required to encompass 1 mm² based on the field diameter and its corresponding area.
Table 2. Approximate number of fields per 1 mm² based on field diameter

Formula to calculate the area of one high power field of a specific microscope = \( \pi r^2 \text{/total magnification} = (\frac{1}{2} \text{ field diameter})^2 \times \pi \text{/total magnification} \)

Formula to calculate the field diameter = Objective Field Number/Objective Magnification

<table>
<thead>
<tr>
<th>Field diameter (mm)</th>
<th>Area (mm²)</th>
<th>Approximate number of fields per 1 mm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.40</td>
<td>0.126</td>
<td>8</td>
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<tr>
<td>0.41</td>
<td>0.132</td>
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<tr>
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<td>0.69</td>
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</tr>
</tbody>
</table>

References

H. Lymphatic and/or Vascular Invasion
Lymphatic or vascular invasion (LVI) indicates whether microscopic lymphatic or vascular invasion is identified. LVI includes lymphatic invasion or vascular invasion or both. This may not be detectable on a biopsy.