Protocol for the Examination of Biopsy Specimens From Patients With Soft Tissue Tumors

Version: Soft Tissue Biopsy 4.0.2.0

Protocol Posting Date: February 2020

Accreditation Requirements
The use of this protocol is recommended for clinical care purposes but is not required for accreditation purposes.

For accreditation purposes, this protocol should 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></td>
</tr>
<tr>
<td><strong>Tumor Type</strong></td>
<td><strong>Description</strong></td>
</tr>
<tr>
<td>Soft tissue sarcomas</td>
<td>Includes soft tissue tumors of intermediate (locally aggressive and rarely metastasizing) potential and malignant soft tissue tumors.</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 the Soft Tissue Resection protocol)</td>
<td></td>
</tr>
<tr>
<td>Cytologic specimens</td>
<td></td>
</tr>
<tr>
<td><strong>Tumor type</strong></td>
<td></td>
</tr>
<tr>
<td>Soft tissue tumors that may recur locally but have either no or an extremely low risk of metastasis</td>
<td></td>
</tr>
<tr>
<td>Carcinosarcoma (consider the appropriate site-specific carcinoma protocol)</td>
<td></td>
</tr>
<tr>
<td>Lymphoma (consider the Hodgkin or non-Hodgkin Lymphoma protocols)</td>
<td></td>
</tr>
<tr>
<td>Pediatric Ewing sarcoma (consider the Ewing Sarcoma protocol)</td>
<td></td>
</tr>
<tr>
<td>Pediatric rhabdomyosarcoma (consider the Rhabdomyosarcoma protocol)</td>
<td></td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal stromal tumor (consider the Gastrointestinal Stromal Tumor protocol)</td>
<td></td>
</tr>
<tr>
<td>Uterine sarcoma (consider the Uterine Sarcoma protocol)</td>
<td></td>
</tr>
</tbody>
</table>

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With guidance from the CAP Cancer and CAP Pathology Electronic Reporting Committees.

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Summary of Changes
Version 4.0.2.0
Modified Margins, changed the term sarcoma to tumor
Surgical Pathology Cancer Case Summary

Protocol posting date: February 2020

SOFT TISSUE: Biopsy

Note: This case summary is recommended for reporting biopsy specimens, but is not required for accreditation purposes. Core data elements are bolded to help identify routinely reported elements.

Select a single response unless otherwise indicated.

Prebiopsy Treatment (select all that apply)
___ No known prebiopsy therapy
___ Chemotherapy performed
___ Radiation therapy performed
___ Therapy performed, type not specified
___ Not specified

Procedure (Note A)
___ Core needle biopsy
___ Incisional biopsy
___ Excisional biopsy
___ Other (specify): ____________________________
___ Not specified

Tumor Site (Note B)
___ Head and neck (specify site, if known): ____________________________
___ Trunk and extremities (specify site, if known): _______________________
___ Abdominal visceral organ(s) (specify site, if known): __________________
___ Thoracic visceral organ(s) (specify site, if known): ____________________
___ Retroperitoneum (specify site, if known): ____________________________
___ Orbit (specify site, if known): ____________________________
___ Not specified

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

Mitotic Rate (Note D)
Specify: ___ /10 high-power fields (HPF)
(1 HPF x 400 = 0.1734 mm²; X40 objective; most proliferative area)

Necrosis (Note D)
___ Not identified
___ Present
   Extent: ___%
___ Cannot be determined

Histologic Grade (French Federation of Cancer Centers Sarcoma Group [FNCLCC]) (Note D)
___ Grade 1
___ Grade 2
___ Grade 3
___ Ungraded sarcoma
___ Cannot be assessed

The routinely reported core data elements are bolded.
Treatment Effect (Note E)
__ No known prebiopsy therapy
__ Not identified
__ Present
   Specify percentage of viable tumor: ____%
__ Cannot be determined

Margins (for excisional biopsy only) (Note F)
__ Cannot be assessed
__ All margins negative for tumor
   Distance of tumor from closest margin (centimeters): ___ cm
   Specify margin: ____________________________
   Specify other close (<2.0 cm) margin(s): ____________________________
__ Tumor present at margin(s)
   Specify margin(s): ____________________________

Lymphovascular Invasion (Note G)
__ Not identified
__ Present
__ Cannot be determined

Additional Pathologic Findings
Specify: ____________________________

Ancillary Studies (required only if applicable)

Immunohistochemistry (specify): ____________________________
__ Not performed

Cytogenetics (specify): ____________________________
__ Not performed

Molecular Pathology (specify): ____________________________
__ Not performed

Comment(s)
Explanatory Notes

A. Procedure / Tissue Processing

Fixation
Tissue specimens from soft tissue 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 per centimeter 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). 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 analyses for tumor-specific molecular translocations (see Table 1) that help in classifying soft tissue tumors.\(^1,2\) 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 minus (-)70°C and can be shipped on dry ice to facilities that perform molecular analysis.

### Table 1. Characteristic Cytogenetic and Molecular Events of Soft Tissue Tumors

<table>
<thead>
<tr>
<th>Histologic Type</th>
<th>Cytogenetic Events</th>
<th>Molecular Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alveolar soft part sarcoma</td>
<td>t(X;17)(p11;q25)</td>
<td>TFE3-ASPL fusion</td>
</tr>
<tr>
<td>Aneurysmal bone cyst</td>
<td>t(16;17)q22;p13)</td>
<td>CDH11-USP6 fusion</td>
</tr>
<tr>
<td>Angiomatoid fibrous histiocytoma</td>
<td>t(12;16)(q13;p11)</td>
<td>FUS-ATF1 fusion</td>
</tr>
<tr>
<td></td>
<td>t(12;22)(q13;q12)</td>
<td>EWSR1-ATF1 fusion</td>
</tr>
<tr>
<td></td>
<td>t(2;22)(q33;q12)</td>
<td>EWSR1-CREB1 fusion</td>
</tr>
<tr>
<td>Extraskeletal myxoid chondrosarcoma</td>
<td>t(9;22)(q22;q12)</td>
<td>EWSR1-NR4A3 fusion</td>
</tr>
<tr>
<td></td>
<td>t(9;17)(q22;q11)</td>
<td>TAF2N-NR4A3 fusion</td>
</tr>
<tr>
<td></td>
<td>t(9;15)(q22;q21)</td>
<td>TCF12-NR4A3 fusion</td>
</tr>
<tr>
<td></td>
<td>t(3;9)(q11;q22)</td>
<td>TFG-NR4A3 fusion</td>
</tr>
<tr>
<td>Clear cell sarcoma</td>
<td>t(12;22)(q13;q12)</td>
<td>EWSR1-ATF1 fusion</td>
</tr>
<tr>
<td></td>
<td>t(2;22)(q33;q12)</td>
<td>EWSR1-CREB1 fusion</td>
</tr>
<tr>
<td>Desmoplastic small round cell tumor</td>
<td>t(11;22)(p13;q12)</td>
<td>EWSR1-WT1 fusion</td>
</tr>
<tr>
<td>Dermatofibrosarcoma protuberans</td>
<td>Ring form of chromosomes 17 and 22</td>
<td>COL1A1-PDGFB fusion</td>
</tr>
<tr>
<td>Histologic Type</td>
<td>Cytogenetic Events</td>
<td>Molecular Events</td>
</tr>
<tr>
<td>-----------------</td>
<td>-------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Ewing sarcoma/PNET</td>
<td>t(17;22)(q21;q13)</td>
<td>COL1A1-PDGFB fusion</td>
</tr>
<tr>
<td>t(11;22)(q24;q12)</td>
<td>EWSR1-FLI1 fusion</td>
<td></td>
</tr>
<tr>
<td>t(21;22)(q12;q12)</td>
<td>EWSR1-ERG fusion</td>
<td></td>
</tr>
<tr>
<td>t(2;22)(q33;q12)</td>
<td>EWSR1-FEV fusion</td>
<td></td>
</tr>
<tr>
<td>t(7;22)(p22;q12)</td>
<td>EWSR1-ETV1 fusion</td>
<td></td>
</tr>
<tr>
<td>t(17;22)(q12;q12)</td>
<td>EWSR1-E1AF fusion</td>
<td></td>
</tr>
<tr>
<td>inv(22)(q12;q12)</td>
<td>EWSR1-ZSG fusion</td>
<td></td>
</tr>
<tr>
<td>t(16;21)(p11;q22)</td>
<td>FUS-ERG fusion</td>
<td></td>
</tr>
<tr>
<td>t(19;der)ins.inv(21;22)</td>
<td>EWSR1-ERG fusion</td>
<td></td>
</tr>
<tr>
<td>t(17;22)(q12;q12)</td>
<td>EWSR1-ETV4 fusion</td>
<td></td>
</tr>
<tr>
<td>t(6;22)(p21;q12)</td>
<td>EWSR1-POU5F1 fusion</td>
<td></td>
</tr>
<tr>
<td>t(1;22)(q36.1;q12)</td>
<td>EWSR1-PATZ1 fusion</td>
<td></td>
</tr>
<tr>
<td>t(2;22)(q31;q12)</td>
<td>EWSR1-SP3 fusion</td>
<td></td>
</tr>
<tr>
<td>t(20;22)(q13;q12)</td>
<td>EWSR1-NFATC2 fusion</td>
<td></td>
</tr>
<tr>
<td>t(2;16)(q35;p11)</td>
<td>FUS-FEV fusion</td>
<td></td>
</tr>
<tr>
<td>Undifferentiated round cell sarcoma (“atypical Ewing sarcoma”)</td>
<td>t(4;19)(q35;q13)</td>
<td>CIC-DUX4 fusion</td>
</tr>
<tr>
<td>Xp11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrosarcoma, infantile</td>
<td>t(12;15)(p13;q26)</td>
<td>ETV6-NTRK3 fusion</td>
</tr>
<tr>
<td>Trisomies 8, 11, 17, and 20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory myofibroblastic tumor</td>
<td>t(1;2)(q22;p23)</td>
<td>TPM3-ALK fusion</td>
</tr>
<tr>
<td>t(2;19)(p23;p13)</td>
<td>TPM4-ALK fusion</td>
<td></td>
</tr>
<tr>
<td>t(2;17)(p23;q23)</td>
<td>CLTC-ALK fusion</td>
<td></td>
</tr>
<tr>
<td>t(2;2)(p23;q13)</td>
<td>RANB2-ALK fusion</td>
<td></td>
</tr>
<tr>
<td>t(2;2)(p23;q35)</td>
<td>ATIC-ALK fusion</td>
<td></td>
</tr>
<tr>
<td>t(2;11)(p23;p15)</td>
<td>CARS-ALK fusion</td>
<td></td>
</tr>
<tr>
<td>t(2;4)(p23;q21)</td>
<td>SEC3L1-ALK fusion</td>
<td></td>
</tr>
<tr>
<td>t(2;12)(p23;p12)</td>
<td>PPFIBP1-ALK fusion</td>
<td></td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>Complex with frequent deletion of 1p</td>
<td></td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>Well-differentiated</td>
<td>Ring form of chromosome 12</td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>Myxoid/Round cell</td>
<td>Amplification of MDM2, CDK4, and others</td>
</tr>
<tr>
<td>t(12;16)(q13;p11)</td>
<td>FUS-DDIT3 fusion</td>
<td></td>
</tr>
<tr>
<td>t(12;16)(q13;p12)</td>
<td>EWSR1-DDIT3 fusion</td>
<td></td>
</tr>
<tr>
<td>Pleomorphic Complex</td>
<td>Low-grade fibromyxoid sarcoma</td>
<td>FUS-CREB3L2 fusion</td>
</tr>
<tr>
<td>t(7;16)(q33;p11)</td>
<td>FUS-CREB3L1 fusion</td>
<td></td>
</tr>
<tr>
<td>t(11;16)(p11;p11)</td>
<td>Malignant peripheral nerve sheath tumor</td>
<td>Complex</td>
</tr>
<tr>
<td>Histologic Type</td>
<td>Cytogenetic Events</td>
<td>Molecular Events</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Myxofibrosarcoma (myxoid MFH)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhabdoid tumor</td>
<td>Deletion of 22q</td>
<td>INI1(SMARCB1) inactivation</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alveolar</td>
<td>t(2;13)(q35;q14)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(1;13)(p36;q14), double minutes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(2;2)(q35;p23)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(X;2)(q35;q13)</td>
<td></td>
</tr>
<tr>
<td>Embryonal</td>
<td>Trisomies 2q, 8 and 20</td>
<td></td>
</tr>
<tr>
<td>Solitary fibrous tumor</td>
<td>Inversion chromosome 12</td>
<td>NAB2-STAT6</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monophasic</td>
<td>t(X;18)(p11;q11)</td>
<td>SS18-SSX1, SS18-SSX2 or SS18-SSX4 fusion</td>
</tr>
<tr>
<td>Biphasic</td>
<td>t(X;18)(p11;q11)</td>
<td>Predominantly SS18-SSX1 fusion</td>
</tr>
</tbody>
</table>

MFH, malignant fibrous histiocytoma; PNET, primitive neuroectodermal tumor.

**Definition of Procedures**

The following is a list of guidelines to be used in defining what type of procedure has been performed.

**Intralesional Resection**
Leaving gross or microscopic tumor behind. Partial debulking or curettage are examples or when microscopic tumor is left at the margin unintentionally in an attempted marginal resection.

**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, there is a high likelihood that microscopic tumor is present. If microscopic disease is identified at the margin, then it is an intralesional resection. Note that occasionally a surgeon will perform an “excisional” biopsy, which effectively accomplishes the same outcome as a marginal resection.

**Wide Resection**
An intracompartmental resection. The tumor is removed with pseudocapsule and a cuff of normal tissue surrounding the neoplasm, but without the complete removal of an entire muscle group, compartment, or bone.

**Radical Resection**
The removal of an entire soft tissue compartment (for example, anterior compartment of the thigh, the quadriceps) or bone, or the excision of the adjacent muscle groups if the tumor is extracomartmental.

**References**

**B. Tumor Site**
The 8th edition of the American Joint Committee on Cancer (AJCC) staging manual places a great emphasis on the anatomic primary site of soft tissue sarcomas, due to implications for local recurrence and risk of metastatic disease. Separate staging systems have been developed for soft tissue sarcomas (STSs) of the extremities and trunk, retroperitoneum, head and neck, and visceral sites. For the first two sites, outcomes are well characterized, and good predictive models based on staging data are available. However, for the latter two anatomic sites, data are more limited, and the proposed staging systems are meant to be a starting point for refining risk assessment. Additionally, changes were made to the AJCC staging system for orbital sarcomas.
Head and Neck
Includes STS arising in the neck (subcutaneous and deep structures, including neurovascular structures); oral cavity; upper aerodigestive tract, including laryngeal structures; pharyngeal areas; nasal cavity and paranasal sinuses; infratemporal fossa and masticator space; major salivary glands, thyroid and parathyroid glands; cervical esophagus and trachea; and peripheral and cranial nerves. Although these STSs usually are found at a smaller size than those arising in other anatomic sites, they often have a greater risk of local recurrence, and they usually present unique problems from an anatomic standpoint. Soft tissue sarcomas arising in the orbit have their own staging system (see below).

Trunk and Extremities
Includes STS arising in extremities and trunk, including breast.

Abdomen and Thoracic Visceral Organs
Includes STS arising from hollow viscera, including esophagus, stomach, small intestine, colon and rectum, as well as solid viscera such as the liver, kidneys, lungs, and heart. Sarcomas arising within the peritoneal, pleural, or mediastinal cavities, but not from a specific visceral organ, may be staged in a manner similar to that of retroperitoneal sarcomas.

Retroperitoneum
Approximately 10% of STS arise in this complex anatomic compartment. Sarcomas arising within the peritoneal, pleural, or mediastinal cavities, but not from a specific visceral organ, may be staged in a manner similar to that of retroperitoneal sarcomas.

Orbit
The orbit is a cone-shaped cavity surrounded by 7 bones. Numerous anatomic structures that support the globe and periorbital tissues, including the optic nerve and its meninges, lacrimal gland, extraocular muscles, fascial connective tissue, orbital fat, cranial and autonomic vessels, and blood vessels, can be the site of origin for a wide variety of primary orbital sarcomas.

References

C. Histologic Classification

Intraoperative Consultation
Histologic classification of soft tissue 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. Intraoperative consultation is useful in assessing if “lesional” tissue is present 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, after sufficient tissue has been submitted for histologic evaluation.

Tumor Classification From Biopsies
It is not always possible to classify soft tissue tumors precisely based on biopsy material, especially FNA and core needle biopsy specimens. Although 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 Tumors
Classification of tumors should be made according to the World Health Organization (WHO) classification of soft tissue tumors listed below. As part of the latest WHO classification of soft tissue tumors, a recommendation was
made to divide tumors into 4 categories: benign, intermediate (locally aggressive), intermediate (rarely metastasizing), and malignant.

WHO Classification of Soft Tissue Tumors of Intermediate Malignant Potential and Malignant Soft Tissue Tumors

Adipocytic Tumors

Intermediate (locally aggressive)
- Atypical lipomatous tumor/Well-differentiated liposarcoma

Malignant
- Dedifferentiated liposarcoma
- Myxoid/round cell liposarcoma
- Pleomorphic liposarcoma
- Mixed-type liposarcoma
- Liposarcoma, not otherwise specified

Fibroblastic/Myofibroblastic Tumors

Intermediate (locally aggressive)
- Superficial fibromatoses (palmar/plantar)*
- Desmoid-type fibromatoses*
- Lipofibromatosis*
- Giant cell fibroblastoma*

Intermediate (rarely metastasizing)
- Dermatofibrosarcoma protuberans
- Fibrosarcomatous dermatofibrosarcoma protuberans
- Pigmented dermatofibrosarcomatous protuberans
- Solitary fibrous tumor, malignant
- Inflammatory myofibroblastic tumor
- Low-grade myofibroblastic sarcoma
- Myxoinflammatory fibroblastic sarcoma/atypical myxoinflammatory fibroblastic tumor
- Infantile fibrosarcoma

Malignant
- Adult fibrosarcoma
- Myxofibrosarcoma
- Low-grade fibromyxoid sarcoma
- Sclerosing epithelioid fibrosarcoma

So-Called Fibrohistiocytic Tumors

Intermediate (rarely metastasizing)
- Plexiform fibrohistiocytic tumor*
- Giant cell tumor of soft tissues*

Smooth Muscle Tumors

Malignant
- Leiomyosarcoma

Pericytic (Perivascular) Tumors

Malignant glomus tumor

Skeletal Muscle Tumors

Malignant
- Embryonal rhabdomyosarcoma (including botryoid, anaplastic)
- Alveolar rhabdomyosarcoma (including solid, anaplastic)
- Pleomorphic rhabdomyosarcoma
- Spindle cell/sclerosing rhabdomyosarcoma
Vascular Tumors

Intermediate (locally aggressive)
- Kaposiform hemangioendothelioma*

Intermediate (rarely metastasizing)
- Retiform hemangioendothelioma
- Papillary intralymphatic angioendothelioma
- Composite hemangioendothelioma
- Pseudomyogenic (epithelioid sarcoma-like) hemangioendothelioma
- Kaposi sarcoma

Malignant
- Epithelioid hemangioendothelioma
- Angiosarcoma of soft tissue

Tumors of Peripheral Nerves

Malignant
- Malignant peripheral nerve sheath tumor
- Epithelioid malignant peripheral nerve sheath tumor
- Malignant Triton tumor
- Malignant granular cell tumor
- Ectomesenchymoma

Chondro-osseous Tumors

Malignant
- Extraskeletal mesenchymal chondrosarcoma
- Extraskeletal osteosarcoma

Tumors of Uncertain Differentiation

Intermediate (locally aggressive)
- Hemosiderotic fibrolipomatous tumor*

Intermediate (rarely metastasizing)
- Atypical fibroxanthoma*
- Angiomatoid fibrous histiocytoma*
- Ossifying fibromyxoid tumor
- Ossifying fibromyxoid tumor, malignant
- Mixed tumor
- Mixed tumor, NOS malignant
- Myoepithelioma
- Myoepithelial carcinoma
- Phosphaturic mesenchymal tumor, benign
- Phosphaturic mesenchymal tumor, malignant

Malignant
- Synovial sarcoma NOS
  - Synovial sarcoma, spindle cell
  - Synovial sarcoma, biphasic
- Epithelioid sarcoma
- Alveolar soft part sarcoma
- Clear cell sarcoma of soft tissue
- Extraskeletal myxoid chondrosarcoma
- Extraskeletal Ewing sarcoma
- Desmoplastic small round cell tumor
- Extra-renal rhabdoid tumor
- Malignant mesenchymoma
- Neoplasms with perivascular epithelioid cell differentiation (PEComa)
  - PEComa NOS, benign
  - PEComa NOS, malignant
- Intimal sarcoma
Undifferentiated/Unclassified Sarcomas

- Undifferentiated spindle cell sarcoma
- Undifferentiated pleomorphic sarcoma
- Undifferentiated round cell sarcoma
- Undifferentiated epithelioid sarcoma
- Undifferentiated sarcoma NOS

* Soft tissue neoplasms excluded from the AJCC staging system

References

D. Grading

Unlike with other organ systems, the staging of soft tissue sarcomas is largely determined by grade. Whilst nomograms assess multiple clinical and histologic parameters to calculate the probability of recurrence for a given patient,1 there is, however, no generally agreed-upon scheme for grading soft tissue tumors.2 The most widely used soft tissue grading systems are the French Federation of Cancer Centers Sarcoma Group (FNCLCC) and National Cancer Institute (NCI) systems.3,4 Both systems have 3 grades and are based on mitotic activity, necrosis, and differentiation, and are highly correlated with prognosis.5 However, in addition to these criteria, the NCI system requires the quantification of cellularity and pleomorphism for certain subtypes of sarcomas, which is difficult to determine objectively. The FNCLCC system is easier to use in our opinion, and it may be slightly better in predicting prognosis than the NCI system.6 Other systems with 2 or 4 grades also have been used. The 8th edition of the *AJCC Cancer Staging Manual* adopted the FNCLCC grading system. The revision of the American Joint Committee on Cancer (AJCC) staging system incorporates a 3-tiered grading system; however, grade 1 and grades 2 to 3 (effectively low and high) are used for stage grouping. Accurate grading requires an adequate sample of tissue, which is not always available from FNA or core needle biopsy specimens or in tumors previously treated with radiation or chemotherapy. However, given the importance of grade in staging and treatment, efforts to separate sarcomas on the basis of needle biopsies into at least 2 tiers (ie, low and high grade) is encouraged. In many instances, the histologic type of sarcoma will readily permit this distinction (ie, Ewing sarcoma, pleomorphic liposarcoma), whereas in less obvious instances, the difficulty of assigning grade should be noted. In general, multiple needle core biopsies exhibiting a high-grade sarcoma can be regarded as high grade, since the probability of subsequent downgrading is remote, but limited core biopsies of low-grade sarcoma carry a risk of upgrading.

**FNCLCC Grading**

The FNCLCC grade is based on three parameters: differentiation, mitotic activity, and necrosis. Each of these parameters receives a score: differentiation (1 to 3), mitotic activity (1 to 3), and necrosis (0 to 2). The scores are summed to produce a grade.

- Grade 1: 2 or 3
- Grade 2: 4 or 5
- Grade 3: 6 to 8

**Differentiation:** Tumor differentiation is scored as follows (see Table 2).

| Score 1: | Sarcomas closely resembling normal, adult mesenchymal tissue and potentially difficult to distinguish from the counterpart benign tumor (eg, well-differentiated liposarcoma, well-differentiated leiomyosarcoma) |
| Score 2: | Sarcomas for which histologic typing is certain (eg, myxoid liposarcoma, myxofibrosarcoma) |
| Score 3: | Embryonal sarcomas and undifferentiated sarcomas, synovial sarcomas and sarcomas of doubtful tumor type |
Tumor differentiation is the most problematic aspect of the FNCLCC system. Its use is subjective and does not include every subtype of sarcoma. Nevertheless, it is an integral part of the system, and an attempt should be made to assign a differentiation score.

Table 2. Tumor Differentiation Score According to Histologic Type in the Updated Version of the French Federation of Cancer Centers Sarcoma Group System

<table>
<thead>
<tr>
<th>Tumor Differentiation</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical lipomatous tumor / Well-differentiated liposarcoma</td>
<td>1</td>
</tr>
<tr>
<td>Well-differentiated leiomyosarcoma</td>
<td>1</td>
</tr>
<tr>
<td>Malignant neurofibroma</td>
<td>1</td>
</tr>
<tr>
<td>Well-differentiated Fibrosarcoma</td>
<td>1</td>
</tr>
<tr>
<td>Myxoid liposarcoma</td>
<td>2</td>
</tr>
<tr>
<td>Conventional leiomyosarcoma</td>
<td>2</td>
</tr>
<tr>
<td>Conventional fibrosarcoma</td>
<td>2</td>
</tr>
<tr>
<td>Myxofibrosarcoma</td>
<td>2</td>
</tr>
<tr>
<td>High-grade myxoid (round cell) liposarcoma</td>
<td>3</td>
</tr>
<tr>
<td>Pleomorphic liposarcoma</td>
<td>3</td>
</tr>
<tr>
<td>Dedifferentiated liposarcoma</td>
<td>3</td>
</tr>
<tr>
<td>Pleomorphic Rhabdomyosarcoma</td>
<td>3</td>
</tr>
<tr>
<td>Poorly differentiated/pleomorphic leiomyosarcoma</td>
<td>3</td>
</tr>
<tr>
<td>Biphasic / monophasic / poorly differentiated Synovial sarcoma</td>
<td>3</td>
</tr>
<tr>
<td>Mesenchymal chondrosarcoma</td>
<td>3</td>
</tr>
<tr>
<td>Extraskeletal osteosarcoma</td>
<td>3</td>
</tr>
<tr>
<td>Extraskeletal Ewing sarcoma</td>
<td>3</td>
</tr>
<tr>
<td>Malignant rhabdoid tumor</td>
<td>3</td>
</tr>
<tr>
<td>Undifferentiated pleomorphic sarcoma</td>
<td>3</td>
</tr>
<tr>
<td>Undifferentiated sarcoma, not otherwise specified</td>
<td>3</td>
</tr>
</tbody>
</table>

Note: Grading of malignant peripheral nerve sheath tumor, embryonal and alveolar rhabdomyosarcoma, angiosarcoma, extraskeletal myxoid chondrosarcoma, alveolar soft part sarcoma, clear cell sarcoma, and epithelioid sarcoma is not recommended. The case for grading malignant peripheral nerve sheath tumor is currently being debated.

Modified with permission from Coindre JM. 3

Mitosis Count: The count is made in the most mitotically active area, away from areas of necrosis, in 10 consecutive high-power fields (HPF) (1 HPF x 400 = 0.1734 mm²) (use the X40 objective). The area of 1 HPF originally used for mitotic count 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 grading purposes. If the mitotic rate is close to the cutoff between mitotic scores, the count should be repeated.

Score 1: 0 to 9 mitoses per 10 HPF
Score 2: 10 to 19 mitoses per 10 HPF
Score 3: >19 mitoses per 10 HPF
**Tumor Necrosis**: Evaluated on gross examination and validated with histologic sections.

<table>
<thead>
<tr>
<th>Score 0:</th>
<th>No tumor necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score 1:</td>
<td>&lt;50% tumor necrosis</td>
</tr>
<tr>
<td>Score 2:</td>
<td>≥50% tumor necrosis</td>
</tr>
</tbody>
</table>

**TNM Grading**

The 8th edition of the American Joint Committee on Cancer (AJCC) and International Union Against Cancer (UICC) staging system for soft tissue tumors recommends the FNCLCC 3-tiered system but effectively collapses into high grade and low grade. This means that FNCLCC grade 2 tumors are considered “high grade” for the purposes of stage grouping.

**References**


**E. Response to Chemotherapy/Radiation Therapy Effect**

Although agreement has not been reached about measuring the effect of preoperative (neoadjuvant) chemotherapy/radiation therapy in soft tissue tumors, an attempt should be made to quantify these effects, especially in the research setting. Therapy response is expressed as a percentage of total tumor area that is viable. Nonliquefied tumor tissue from a cross-section through the longest axis of the tumor should be sampled. At least 1 section of necrotic tumor (always with a transition to viable tumor) should be sampled to verify the gross impression of necrosis. Nonsampled necrotic areas should be included in the estimate of necrosis and the percentage of tumor necrosis reported. The gross appearance can be misleading, and areas that appear grossly necrotic may actually be myxoid or edematous. Additional sections from 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.

**F. Margins**

It has been recommended that for all margins <2 cm, the distance of the tumor from the margin be reported in centimeters. However, there is a lack of agreement on this issue. We recommend specifying the location of all margins <2 cm and the distance of the closest margin that is <2 cm. Margins from soft tissue tumors should be taken as perpendicular sections, if possible. If bones are present in the specimen and are not involved by tumor, or the tumor is >2 cm from the margin, the marrow can be scooped out and submitted as a margin.

**References**


**G. Lymphovascular Invasion**

Lymphovascular invasion (LVI) indicates whether microscopic lymphovascular invasion is identified. LVI includes lymphatic invasion, vascular invasion, or lymphovascular 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.