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

Protocol applies to soft tissue tumors of intermediate (locally aggressive) and intermediate (rarely metastasizing) potential and malignant soft tissue tumors.

Based on AJCC/UICC TNM, 7th edition
Protocol web posting date: June 2012

Procedures
• Biopsy
• Resection

Authors
Brian P. Rubin, MD, PhD, FCAP*
  Department of Anatomic Pathology, Cleveland Clinic, Lerner Research Institute and Taussig Cancer Center, Cleveland, Ohio
Kumarasen Cooper, MBChB, DPhil, FRCPA
  Department of Pathology, University of Vermont, Fletcher Allen Health Care, Burlington, Vermont
Christopher D.M. Fletcher, MD, FRCPA
  Department of Pathology, Brigham and Women’s Hospital, Boston, Massachusetts
Andrew Lawrence Folpe, MD, FCAP
  Department of Anatomic Pathology, Mayo Clinic, Rochester, Minnesota
Francis H. Gannon, MD, FCAP
  Department of Pathology, Baylor College of Medicine, Houston, Texas
Jennifer Leigh Hunt, MD, FCAP
  Department of Anatomic Pathology, Cleveland Clinic Foundation, Cleveland, Ohio
Alexander J. Lazar, MD PhD, FCAP
  Department of Pathology, Sarcoma Research Center, The University of Texas M. D. Anderson Cancer Center, Houston, Texas
Anthony G. Montag, MD
  Department of Pathology, University of Chicago Medical Center, Chicago, Illinois
Terrance D. Peabody, MD
  Department of Orthopedic Surgery, University of Chicago Medical Center, Chicago, Illinois
Raphael E. Pollock, MD, PhD
  Department of Surgical Oncology, Sarcoma Research Center, The University of Texas M D Anderson Cancer Center, Houston, Texas
John D. Reith, MD, FCAP
  Department of Pathology, Immunology, and Laboratory Medicine, University of Florida, Gainesville, Florida
Stephen J. Qualman, MD, FCAP**
  Department of Laboratory Medicine, Children’s Hospital, Columbus, Ohio
Andrew E. Rosenberg, MD, FCAP
  Department of Pathology, Massachusetts General Hospital, Boston, Massachusetts
Sharon W. Weiss, MD, FCAP
  Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, Georgia
Thomas Krausz, MD, FRCPA†
  Department of Pathology, University of Chicago Medical Center, Chicago, Illinois
For the Members of the Cancer Committee, College of American Pathologists

* Denotes primary author.  † Denotes senior author.  All other contributing authors are listed alphabetically.
** Deceased.
© 2012 College of American Pathologists (CAP). All rights reserved.

The College does not permit reproduction of any substantial portion of these protocols without its written authorization. The College hereby authorizes use of these protocols by physicians and other health care providers in reporting on surgical specimens, in teaching, and in carrying out medical research for nonprofit purposes. This authorization does not extend to reproduction or other use of any substantial portion of these protocols for commercial purposes without the written consent of the College.

The CAP also authorizes physicians and other health care practitioners to make modified versions of the Protocols solely for their individual use in reporting on surgical specimens for individual patients, teaching, and carrying out medical research for non-profit purposes.

The CAP further authorizes the following uses by physicians and other health care practitioners, in reporting on surgical specimens for individual patients, in teaching, and in carrying out medical research for non-profit purposes: (1) **Dictation** from the original or modified protocols for the purposes of creating a text-based patient record on paper, or in a word processing document; (2) **Copying** from the original or modified protocols into a text-based patient record on paper, or in a word processing document; (3) The use of a **computerized system** for items (1) and (2), provided that the Protocol data is stored intact as a single text-based document, and is not stored as multiple discrete data fields.

Other than uses (1), (2), and (3) above, the CAP does not authorize any use of the Protocols in electronic medical records systems, pathology informatics systems, cancer registry computer systems, computerized databases, mappings between coding works, or any computerized system without a written license from CAP. Applications for such a license should be addressed to the SNOMED Terminology Solutions division of the CAP.

Any public dissemination of the original or modified Protocols is prohibited without a written license from the CAP.

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” 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 required data 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.

The inclusion of a product name or service in a CAP publication should not be construed as an endorsement of such product or service, nor is failure to include the name of a product or service to be construed as disapproval.
CAP Soft Tissue Protocol Revision History

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

Version: SoftTissue 3.1.1.0

Summary of Changes
The following changes have been made since the November 2011 release.

Biopsy

Ancillary Studies
Added “required only if applicable” to this element.

Resection

Ancillary Studies
Added “required only if applicable” to this element.

Treatment Effect
Specify percentage of viable tumor: added “compared with pretreatment biopsy, if available.”

Explanatory Notes

M Category Considerations
The word “checklist” was changed to “case summary.”

Important Note
These recommendations are designed to be applied principally to soft tissue sarcomas in teenagers and adults, since pediatric sarcomas are, in general, treated under strict protocols that may differ significantly from the recommendations supplied herein.
Surgical Pathology Cancer Case Summary

Protocol web posting date: June 2012

SOFT TISSUE: Biopsy

Select a single response unless otherwise indicated.

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

Tumor Site
Specify (if known): __________________________
___ Not specified

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

Macroscopic Extent of Tumor (select all that apply)
___ Superficial
    ___ Dermal
    ___ Subcutaneous/suprafascial
___ Deep
    ___ Fascial
    ___ Subfascial
    ___ Intramuscular
    ___ Mediastinal
    ___ Intra-abdominal
    ___ Retroperitoneal
    ___ Head and neck
    ___ Other (specify): __________________________
___ Cannot be determined

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 determined

Margins (for excisional biopsy only) (Note E)
___ Cannot be assessed
___ Margins negative for sarcoma
    Distance of sarcoma from closest margin: ___ cm
    Specify margin: ________________________
___ Specify other close (less than 2.0 cm) margin(s): ________________________
___ Margin(s) positive for sarcoma
    Specify margin(s): ________________________

+ Lymph-Vascular Invasion (Note F)
+ ___ Not identified
+ ___ Present
+ ___ Indeterminate

+ Additional Pathologic Findings
+ Specify: ________________________

Ancillary Studies (required only if applicable)

Immunohistochemistry
Specify: ________________________
___ Not performed

Cytogenetics
Specify: ________________________
___ Not performed

Molecular Pathology
Specify: ________________________
___ Not performed

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

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important, but are not yet validated or regularly used in patient management.
Treatment Effect (Note G)
__ Not identified
__ Present
    + Specify percentage of viable tumor: ___% 
__ Cannot be determined

+ Comment(s)

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important, but are not yet validated or regularly used in patient management.
Surgical Pathology Cancer Case Summary

Protocol web posting date: June 2012

SOFT TISSUE: Resection

Select a single response unless otherwise indicated.

Procedure (Note H)
___ Intralesional resection
___ Marginal resection
___ Wide resection
___ Radical resection
___ Other (specify): ________________________
___ Not specified

Tumor Site
Specify (if known): ________________________
___ Not specified

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

Macroscopic Extent of Tumor (select all that apply)
___ Superficial
   ___ Dermal
   ___ Subcutaneous/suprafascial
___ Deep
   ___ Fascial
   ___ Subfascial
   ___ Intramuscular
   ___ Mediastinal
   ___ Intra-abdominal
   ___ Retroperitoneal
   ___ Head and neck
   ___ Other (specify): ________________________
___ Cannot be determined

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

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important, but are not yet validated or regularly used in patient management.
Mitotic Rate (Note D)
Specify: ___/10 high-power fields (HPF)
(1 HPF x 400 = 0.1734 mm²; X40 objective; most proliferative area)

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

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

Margins (Note E)
___ Cannot be assessed
___ Margins negative for sarcoma
    Distance of sarcoma from closest margin: ___ cm
    Specify margin: __________________________
    Specify other close (less than 2.0 cm) margin(s): __________________________
___ Margin(s) positive for sarcoma
    Specify margin(s): __________________________

+ Lymph-Vascular Invasion (Note F)
+ ___ Not identified
+ ___ Present
+ ___ Indeterminate

Pathologic Staging (pTNM) (Note J)

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

Primary Tumor (pT)
___ 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

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important, but are not yet validated or regularly used in patient management.
Regional Lymph Nodes (pN) (Notes J and K)
___ pNX: Regional lymph nodes cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1: Regional lymph node metastasis
___ No nodes submitted or found

Number of Lymph Nodes Examined
Specify: ___
___ Number cannot be determined (explain): ______________________

Number of Lymph Nodes Involved
Specify: ___
___ Number cannot be determined (explain): ______________________

Distant Metastasis (pM) (Note J)
___ Not applicable
___ pM1: Distant metastasis
   + Specify site(s), if known: ______________________

+ Additional Pathologic Findings
+ Specify: ______________________

Ancillary Studies (required only if applicable)

Immunohistochemistry
Specify: ______________________
___ Not performed

Cytogenetics
Specify: ______________________
___ Not performed

Molecular Pathology
Specify: ______________________
___ Not performed

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

Treatment Effect (Note G)
___ Not identified
___ Present
   + Specify percentage of viable tumor (compared with pretreatment biopsy, if available): ___%
___ Cannot be determined

+ Comment(s)

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important, but are not yet validated or regularly used in patient management.
Explanatory Notes

A. 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. In addition, treatment protocols increasingly require fresh tissue for correlative studies. Approximately 1 cm³ 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°C and can be shipped on dry ice to facilities that perform molecular analysis.

<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>EWS-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>Histologic Type</td>
<td>Cytogenetic Events</td>
<td>Molecular Events</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>-------------------------------------------</td>
<td>----------------------------------------</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 COL1A1-PDGFB fusion</td>
<td>COL1A1-PDGFB fusion</td>
</tr>
<tr>
<td>Ewing sarcoma/PNET</td>
<td>t(11;22)(q24;q12)</td>
<td>EWSR1-FLI1 fusion</td>
</tr>
<tr>
<td></td>
<td>t(21;22)(q12;q12)</td>
<td>EWSR1-ERG fusion</td>
</tr>
<tr>
<td></td>
<td>t(2;22)(q33;q12)</td>
<td>EWSR1-FEV fusion</td>
</tr>
<tr>
<td></td>
<td>t(7;22)(p22;q12)</td>
<td>EWSR1-ETV1 fusion</td>
</tr>
<tr>
<td></td>
<td>t(17;22)(q12;q12)</td>
<td>EWSR1-E1AF fusion</td>
</tr>
<tr>
<td></td>
<td>inv(22)(q12;q12)</td>
<td>EWSR1-ZSG fusion</td>
</tr>
<tr>
<td></td>
<td>t(16;21)(p11;q22)</td>
<td>FUS-ERG fusion</td>
</tr>
<tr>
<td>Fibrosarcoma, infantile</td>
<td>t(12;15)(p13;q26)</td>
<td>ETV6-NTRK3 fusion</td>
</tr>
<tr>
<td></td>
<td>Trisomies 8, 11, 17, and 20</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></td>
<td>t(2;19)(p23;p13)</td>
<td>TPM4-ALK fusion</td>
</tr>
<tr>
<td></td>
<td>t(2;17)(p23;q23)</td>
<td>CLTC-ALK fusion</td>
</tr>
<tr>
<td></td>
<td>t(2;2)(p23;q13)</td>
<td>RANB2-ALK fusion</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>Complex with frequent deletion of 1p</td>
<td></td>
</tr>
<tr>
<td>Liposarcoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well-differentiated</td>
<td>Ring form of chromosome 12</td>
<td>Amplification of MDM2,</td>
</tr>
<tr>
<td>Myxoid/Round cell</td>
<td>t(12;16)(q13;p11)</td>
<td>CDK4, and others</td>
</tr>
<tr>
<td>Pleomorphic</td>
<td>t(12;22)(q13;q12)</td>
<td>TLS-DDIT3 fusion</td>
</tr>
<tr>
<td>Low-grade fibromyxoid sarcoma</td>
<td>Complex</td>
<td>EWSR1-DDIT3 fusion</td>
</tr>
<tr>
<td>Malignant peripheral nerve sheath tumor</td>
<td>t(7;16)(q33;p11)</td>
<td>FUS-CREB3L2 fusion</td>
</tr>
<tr>
<td>Myxofibrosarcoma (myxoid MFH)</td>
<td>Ring form of chromosome 12</td>
<td></td>
</tr>
<tr>
<td>Rhabdoid tumor</td>
<td>Deletion of 22q</td>
<td>INI1 inactivation</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>Complex</td>
<td></td>
</tr>
<tr>
<td>Alveolar</td>
<td>t(2;13)(q35;q14)</td>
<td>PAX3-FOXO1A fusion</td>
</tr>
<tr>
<td></td>
<td>t(1;13)(p36;q14), double minutes</td>
<td>PAX7-FOXO1A fusion</td>
</tr>
<tr>
<td></td>
<td>t(2;2)(q35;p23)</td>
<td>PAX3-NCOA1 fusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PAX3-AFX fusion</td>
</tr>
<tr>
<td>Embryonal</td>
<td>Trisomies 2q, 8 and 20</td>
<td>Loss of heterozygosity at 11p15</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</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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.
B. Tumor Size
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.

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.4 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
   Intermediate (rarely metastasizing)
      Solitary fibrous tumor and hemangiopericytoma (including lipomatous hemangiopericytoma)
      Inflammatory myofibroblastic tumor
Low-grade myofibroblastic sarcoma
Myxoinflammatory fibroblastic sarcoma
Infantile fibrosarcoma
Malignant
Adult fibrosarcoma
Myxofibrosarcoma
Low grade fibromyxoid sarcoma/hyalinizing spindle cell tumor
Sclerosing epithelioid fibrosarcoma

So-called Fibrohistiocytic Tumors
Intermediate (rarely metastasizing)
Plexiform fibrohistiocytic tumor
Giant cell tumor of soft tissues
Malignant
Pleomorphic malignant fibrous histiocytoma (MFH) / Undifferentiated pleomorphic sarcoma
Giant cell MFH / Undifferentiated pleomorphic sarcoma with giant cells
Inflammatory MFH / Undifferentiated pleomorphic sarcoma with prominent inflammation

Smooth Muscle Tumors
Malignant
Leiomyosarcoma

Skeletal Muscle Tumors
Malignant
Embryonal rhabdomyosarcoma (including spindle cell, botryoid, anaplastic)
Alveolar rhabdomyosarcoma (including solid, anaplastic)
Pleomorphic rhabdomyosarcoma

Vascular Tumors
Intermediate (locally aggressive)
Kaposiform hemangioendothelioma
Intermediate (rarely metastasizing)
Reticiform hemangioendothelioma
Papillary intralymphatic angioendothelioma
Composite hemangioendothelioma
Malignant
Epithelioid hemangioendothelioma
Angiosarcoma of soft tissue

Tumors of Peripheral Nerves
Malignant
Malignant peripheral nerve sheath tumor
Epithelioid malignant peripheral nerve sheath tumor

Chondro-osseous Tumors
Malignant
Mesenchymal chondrosarcoma
Extraskeletal osteosarcoma

Tumors of Uncertain Differentiation
Intermediate (rarely metastasizing)
Angiomatoid fibrous histiocytoma
Ossifying fibromyxoid tumor (including atypical / malignant)
Mixed tumour / Myoepithelioma / Parachordoma

Malignant
Synovial sarcoma
Epithelioid sarcoma
Alveolar soft part sarcoma
Clear cell sarcoma of soft tissue
Extraskeletal myxoid chondrosarcoma (“chordoid” type)
Primitive neuroectodermal tumor (PNET) / Extraskeletal Ewing tumor
  Peripheral primitive neuroectodermal tumor (pPNET)
  Extraskeletal Ewing tumor
Desmoplastic small round cell tumor
Extra-renal rhabdoid tumor
Malignant mesenchymoma
Neoplasms with perivascular epithelioid cell differentiation (PEComa)
  Clear cell myomelanocytic tumor
Intimal sarcoma

* Since the last edition of the WHO classification, 2 cases of well-documented regional metastasis of kaposiform hemangioendothelioma have been reported, raising the issue of whether or not kaposiform hemangioendothelioma might be more appropriately included in the category of “intermediate (rarely metastasizing)” instead of “intermediate (locally aggressive).” This will undoubtedly be addressed in the next WHO classification of tumors of soft tissue.

D. Grading

Unlike with other organ systems, the staging of soft tissue sarcomas is largely determined by grade. Unfortunately, there is no generally agreed-upon scheme for grading soft tissue tumors. The most widely used soft tissue grading systems are the French Federation of Cancer Centers Sarcoma Group (FNCLCC) and National Cancer Institute (NCI) systems. Both systems have 3 grades and are based on mitotic activity, necrosis, and differentiation, and are highly correlated with prognosis. 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. Other systems with 2 or 4 grades also have been used. The seventh 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 staging groups. Accurate grading requires an adequate sample of tissue, which is not always available from FNA or core needle biopsy 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/PNET, 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 3 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
Score 2: Sarcomas of certain histologic type
Score 3: Synovial sarcomas, embryonal sarcomas, undifferentiated 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>Histologic Type</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well-differentiated liposarcoma</td>
<td>1</td>
</tr>
<tr>
<td>Myxoid liposarcoma</td>
<td>2</td>
</tr>
<tr>
<td>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>Fibrosarcoma</td>
<td>2</td>
</tr>
<tr>
<td>Myxofibrosarcoma (malignant fibrous histiocytoma [MFH])</td>
<td>2</td>
</tr>
<tr>
<td>MFH, pleomorphic type (patternless pleomorphic sarcoma)</td>
<td>3</td>
</tr>
<tr>
<td>Giant cell and inflammatory MFH (pleomorphic sarcoma, NOS, with giant cells or inflammatory cells)</td>
<td>3</td>
</tr>
<tr>
<td>Well-differentiated leiomyosarcoma</td>
<td>1</td>
</tr>
<tr>
<td>Conventional leiomyosarcoma</td>
<td>2</td>
</tr>
<tr>
<td>Poorly differentiated / pleomorphic / epithelioid leiomyosarcoma</td>
<td>3</td>
</tr>
<tr>
<td>Biphasic / monophasic synovial sarcoma</td>
<td>3</td>
</tr>
<tr>
<td>Poorly differentiated synovial sarcoma</td>
<td>3</td>
</tr>
<tr>
<td>Pleomorphic rhabdomyosarcoma</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>Ewing sarcoma / primitive neuroectodermal tumor</td>
<td>3</td>
</tr>
<tr>
<td>Malignant rhabdoid tumor</td>
<td>3</td>
</tr>
<tr>
<td>Undifferentiated sarcoma</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. From Guillou et al.\(^9\) Modified with permission. © 2003 American Society of Clinical Oncology. All rights reserved.
Mitosis Count: The count is made in the most mitotically active area in 10 successive high-power fields (HPF) \((1 \text{ HPF} \times 400 = 0.1734 \text{ mm}^2)\) (use the X40 objective).

Score 1: 0 to 9 mitoses per 10 HPF  
Score 2: 10 to 19 mitoses per 10 HPF  
Score 3: 20 or more mitoses per 10 HPF

Tumor Necrosis: Determined on histologic sections.

Score 0: No tumor necrosis  
Score 1: Less than or equal to 50% tumor necrosis  
Score 2: More than 50% tumor necrosis

TNM Grading  
The seventh 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-grade system but effectively collapses into high grade and low grade.\(^{10,11}\) This means that FNCLCC grade 2 tumors are considered “high grade” for the purposes of stage grouping.

E. Margins  
It has been recommended that for all margins <2 cm, the distance of the tumor from the margin be reported in centimeters.\(^{12}\) 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.

F. 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.

G. 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.

H. 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 thing 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 extracompartmental.

I. Histological Classification of Treated Lesions
Because of 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.

J. TNM and Stage Groupings
The TNM staging system for soft tissue tumors of the AJCC and UICC is recommended.10,11 The staging system applies to all soft tissue sarcomas except Kaposi sarcoma, gastrointestinal stromal tumors, fibromatosis (desmoid tumor), and infantile fibrosarcoma. In addition, sarcomas arising within the confines of the dura mater, including the brain, and sarcomas arising in parenchymatous organs and from hollow viscera are not optimally staged by this system.

Pathologic (pTNM) staging consists of the removal and pathologic evaluation of the primary tumor and clinical/radiologic evaluation for regional and distant metastases. In circumstances where it is not possible to obtain accurate measurements of the excised primary sarcoma specimen, it is acceptable to use radiologic assessment of tumor size to assign a pT category. In examining the primary tumor, the pathologist should subclassify the lesion and assign a histopathologic grade.

Definition of pT
Although size currently is designated within the TNM system as 5 cm or smaller versus larger than 5 cm, particular emphasis should be placed on providing size measurements. Size should be regarded as a continuous variable, with 5 cm as merely an arbitrary division that makes it possible to dichotomize patient populations.

Depth
Depth is evaluated relative to the investing fascia of the extremity and trunk. Superficial is defined as lack of any involvement of the superficial investing muscular fascia in extremity or trunk lesions. For staging, all retroperitoneal and visceral lesions are considered to be deep lesions.

Depth is also an independent variable and is defined as follows.

1. Superficial
   a. Tumor is located entirely in the subcutaneous tissues without any involvement of the muscular fascia. In these cases, pretreatment imaging studies demonstrate a subcutaneous tumor without involvement of muscle, and excisional biopsy pathology specimen demonstrate a tumor
located within the subcutaneous tissues without invasion into fascia (adopted from the seventh edition of the AJCC Cancer Staging Manual).

2. Deep
   a. Tumor is located partly or completely within 1 or more muscle groups within the extremity. Deep tumors may extend through the muscular fascia into the subcutaneous tissues or even to the skin, but the critical criterion is location of any portion of the tumor within the muscular compartments of the extremity or invasion of the muscular fascia. In these cases, pretreatment imaging studies demonstrate a tumor located completely or partly within the muscular compartments of the extremity. Finally, on pathologic evaluation, any tumor that is superficial to the muscular fascia, but invades the fascia, is considered deep (adopted from the seventh edition of the AJCC Cancer Staging Manual).
   b. All intraperitoneal visceral lesions, retroperitoneal lesions, intrathoracic lesions, and the majority of head and neck tumors are considered deep.

3. Depth is evaluated in relation to tumor size (T)
   a. Tumor 5 cm or less: T1a = superficial; T1b = deep.
   b. Tumor greater than 5 cm: T2a = superficial; T2b = deep.

**Regional Lymph Nodes (pN)**
Nodal involvement is rare in adult soft tissue sarcomas but, when present, has a very poor prognosis. N1 disease is classified as stage III. Patients whose nodal status is not determined to be positive for tumor, either clinically or pathologically, should be designated as N0.

**Restaging of Recurrent Tumors**
The same staging should be used when a patient requires restaging of sarcoma recurrence. Such reports should specify whether patients have primary lesions or lesions that were previously treated and have subsequently recurred. Reporting of possible etiologic factors, such as radiation exposure and inherited or genetic syndromes, is encouraged. Appropriate workup for recurrent sarcoma usually includes cross-sectional imaging (computed tomography [CT] scan or magnetic resonance imaging [MRI] scan) of the tumor, a CT scan of the chest, and a tissue biopsy to confirm diagnosis prior to initiation of therapy.

**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.
T Category Considerations
Superficial tumor is located exclusively above the superficial fascia without invasion of the fascia; deep tumor is located either exclusively beneath the superficial fascia or superficial to the fascia with invasion of or through the fascia. Retroperitoneal, mediastinal, and pelvic sarcomas are classified as deep tumors.

N Category Considerations
Presence of positive nodes (N1) is considered stage III.

M Category Considerations
pMX and pM0 (no distant metastasis) are no longer case summary options as the use of pMX provides no meaningful information to the clinician or cancer registrar and at times may create confusion in tumor staging.

Stage Groupings
Stage IA
T1a  N0  NX  M0  G1  Low
T1b  N0  NX  M0  G1  Low

Stage IB
T2a  N0  NX  M0  G1  Low
T2b  N0  NX  M0  G1  Low

Stage IIA
T1a  N0  NX  M0  G2  High
T1b  N0  NX  M0  G2  High

Stage IIB
T2a  N0  NX  M0  G2  High
T2b  N0-1  NX  M0  G3  High

Stage IV
Any T  Any N  M1  Any G  High or Low

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
With the exception of epithelioid sarcoma and clear cell sarcoma of soft parts, regional lymph node metastasis is uncommon in adult soft tissue sarcomas. Nodes are not sampled routinely, and it usually is not necessary to exhaustively search for nodes. When present, regional lymph node metastasis has prognostic importance and should be reported. The seventh edition of the AJCC Cancer Manual recommends that N1 M0 disease to be regarded as stage III rather than stage IV disease.
References


