

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

Version: Soft Tissue Resection 4.0.2.0

Protocol Posting Date: February 2020

CAP Laboratory Accreditation Program Protocol Required Use Date: November 2020

Includes pTNM requirements from the 8<sup>th</sup> Edition, AJCC Staging Manual

**For accreditation purposes, this protocol should be used for the following procedures and tumor types:**

Procedure	Description
Resection	Includes specimens designated intralesional resection, marginal resection, wide resection, and radical resection
Tumor Type	Description
Soft tissue sarcomas	Includes soft tissue tumors of intermediate (locally aggressive and rarely metastasizing) potential and malignant soft tissue tumors.

**This protocol is NOT required for accreditation purposes for the following:**

Procedure
Biopsy (Consider the Soft Tissue Biopsy protocol)
Primary resection specimen with no residual or viable cancer (eg, following neoadjuvant therapy)
Cytologic specimens
Tumor type
Soft tissue tumors that may recur locally but have either no or an extremely low risk of metastasis

**The following tumor types should NOT be reported using this protocol:**

Tumor Type
Carcinosarcoma (consider the appropriate site-specific carcinoma protocol)
Lymphoma (consider the Hodgkin or non-Hodgkin Lymphoma protocols)
Pediatric Ewing sarcoma (consider the Ewing Sarcoma protocol)
Pediatric rhabdomyosarcoma (consider the Rhabdomyosarcoma protocol)
Kaposi sarcoma
Gastrointestinal stromal tumor (consider the Gastrointestinal Stromal Tumor protocol)
Uterine sarcoma (consider the Uterine Sarcoma protocol)

## Authors

Javier A. Laurini, MD\*; Kumarasen Cooper, MBChB, DPhil; Christopher D.M. Fletcher, MD; Andrew Lawrence Folpe, MD; Francis H. Gannon, MD; Jennifer Leigh Hunt, MD; Thomas Krausz, MD; Alexander Lazar, MD, PhD; Anthony G. Montag, MD; Jordan Olson, MD; Terrance D. Peabody, MD; Raphael E. Pollock, MD, PhD; John D. Reith, MD; Brian P. Rubin, MD; Andrew E. Rosenberg, MD, PhD; Sharon W. Weiss, MD

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

\* Denotes primary author. All other contributing authors are listed alphabetically.

### Accreditation Requirements

This protocol can be utilized for a variety of procedures and tumor types for clinical care purposes. For accreditation purposes, only the definitive primary cancer resection specimen is required to have the core and conditional data elements reported in a synoptic format.

- Core data elements are required in reports to adequately describe appropriate malignancies. For accreditation purposes, essential data elements must be reported in all instances, even if the response is “not applicable” or “cannot be determined.”
- Conditional data elements are only required to be reported if applicable as delineated in the protocol.
- Optional data elements, are identified with “+” and although not required for CAP accreditation purposes, may be considered for reporting as determined by local practice standards

The use of this protocol is not required for recurrent tumors or for metastatic tumors that are resected at a different time than the primary tumor. Use of this protocol is also not required for pathology reviews performed at a second institution (i.e. secondary consultation, second opinion, or review of outside case at second institution).

### Synoptic Reporting

All core and conditionally required data elements outlined on the surgical case summary from this cancer protocol must be displayed in synoptic report format. Synoptic format is defined as:

- Data element: followed by its answer (response), outline format without the paired "Data element: Response" format is NOT considered synoptic.
- The data element should be represented in the report as it is listed in the case summary. The response for any data element may be modified from those listed in the case summary, including “Cannot be determined” if appropriate.
- Each diagnostic parameter pair (Data element: Response) is listed on a separate line or in a tabular format to achieve visual separation. The following exceptions are allowed to be listed on one line:
  - Anatomic site or specimen, laterality, and procedure
  - Pathologic Stage Classification (pTNM) elements
  - Negative margins, as long as all negative margins are specifically enumerated where applicable
- The synoptic portion of the report can appear in the diagnosis section of the pathology report, at the end of the report or in a separate section, but all Data element: Responses must be listed together in one location

Organizations and pathologists may choose to list the required elements in any order, use additional methods in order to enhance or achieve visual separation, or add optional items within the synoptic report. The report may have required elements in a summary format elsewhere in the report IN ADDITION TO but not as replacement for the synoptic report ie, all required elements must be in the synoptic portion of the report in the format defined above.

## 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: Resection

Select a single response unless otherwise indicated.

#### + Preresection Treatment (select all that apply)

- + \_\_\_ No known preresection therapy
- + \_\_\_ Chemotherapy performed
- + \_\_\_ Radiation therapy performed
- + \_\_\_ Therapy performed, type not specified
- + \_\_\_ Not specified

#### Procedure (Note A)

- \_\_\_ Intralesional resection
- \_\_\_ Marginal resection
- \_\_\_ Wide resection
- \_\_\_ Radical resection
- \_\_\_ Other (specify): \_\_\_\_\_
- \_\_\_ Not specified

#### Tumor Site (Note B)

- \_\_\_ Head and neck (specify site, if known): \_\_\_\_\_
- \_\_\_ Trunk and extremities (specify site, if known): \_\_\_\_\_
- \_\_\_ Abdominal visceral organs (specify site, if known): \_\_\_\_\_
- \_\_\_ Thoracic visceral organs (specify site, if known): \_\_\_\_\_
- \_\_\_ Retroperitoneum (specify, if known): \_\_\_\_\_
- \_\_\_ Orbit (specify site, if known): \_\_\_\_\_
- \_\_\_ Not specified

#### Tumor Size (Note C)

- Greatest dimension (centimeters): \_\_\_ cm
- + Additional dimensions (centimeters): \_\_\_ x \_\_\_ cm
- \_\_\_ Cannot be determined (explain): \_\_\_\_\_

#### Histologic Type (World Health Organization [WHO] classification of soft tissue tumors) (Note D)

- Specify: \_\_\_\_\_
- \_\_\_ Cannot be determined

#### Mitotic Rate (Note E)

- Specify: \_\_\_ /10 high-power fields (HPF)
- (1 HPF x 400 = 0.1734 mm<sup>2</sup>; X40 objective; most proliferative area)

#### Necrosis (macroscopic or microscopic) (Note E)

- \_\_\_ Not identified
- \_\_\_ Present
- Extent: \_\_\_%

#### Histologic Grade (French Federation of Cancer Centers Sarcoma Group [FNCLCC]) (Note E)

- \_\_\_ Grade 1
- \_\_\_ Grade 2
- \_\_\_ Grade 3
- \_\_\_ Ungraded sarcoma

+ Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.

Cannot be assessed

**Treatment Effect (Note F)**

No known presurgical therapy

Not identified

Present

+ Specify percentage of viable tumor (compared with pretreatment biopsy, if available): \_\_\_\_%

Cannot be determined

**Margins (Note G)**

Cannot be assessed

All margins negative for tumor

Distance of tumor from closest margin (centimeters): \_\_\_\_ cm

Specify closest margin: \_\_\_\_\_

Specify other close (less than 2.0 centimeters) margin(s) (if applicable): \_\_\_\_\_

Tumor present at margin(s)

Specify margin(s): \_\_\_\_\_

**+ Lymphovascular Invasion (Note H)**

+  Not identified

+  Present

+  Cannot be determined

**Regional Lymph Nodes (Note I)**

No lymph nodes submitted or found

Lymph Node Examination (required only if lymph nodes present in specimen)

**Number of Lymph Nodes Involved:** \_\_\_\_\_

Number cannot be determined (explain): \_\_\_\_\_

**Number of Lymph Nodes Examined:** \_\_\_\_\_

Number cannot be determined (explain): \_\_\_\_\_

**Pathologic Stage Classification (pTNM, AJCC 8<sup>th</sup> Edition) (Note J)**

*Note: Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. Only the applicable T, N, or M category is required for reporting; their definitions need not be included in the report. The categories (with modifiers when applicable) can be listed on 1 line or more than 1 line.*

Histologic type not appropriate for staging<sup>#</sup>

<sup>#</sup> *Note: Regardless of the anatomic site, certain specific types of locally aggressive soft tissue neoplasms, which may recur locally but have either no risk of metastatic disease or an extremely low risk of metastasis, are excluded from the AJCC soft tissue sarcoma staging system.*

TNM Descriptors (required only if applicable) (select all that apply)

m (multiple)

r (recurrent)

y (posttreatment)

**Primary Tumor (pT)**

Head and Neck

pTX: Primary tumor cannot be assessed

pT1: Tumor ≤2 cm

pT2: Tumor >2 to ≤4 cm

+ Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.

- \_\_\_ pT3: Tumor >4 cm
- \_\_\_ pT4: Tumor with invasion of adjoining structures
- \_\_\_ pT4a: Tumor with orbital invasion, skull base/dural invasion, invasion of central compartment viscera, involvement of facial skeleton, or invasion of pterygoid muscles
- \_\_\_ pT4b: Tumor with brain parenchymal invasion, carotid artery encasement, prevertebral muscle invasion, or central nervous system involvement via perineural spread

Trunk and Extremities

- \_\_\_ pTX: Primary tumor cannot be assessed
- \_\_\_ pT0: No evidence of primary tumor
- \_\_\_ pT1: Tumor 5 cm or less in greatest dimension
- \_\_\_ pT2: Tumor more than 5 cm and less than or equal to 10 cm in greatest dimension
- \_\_\_ pT3: Tumor more than 10 cm and less than or equal to 15 cm in greatest dimension
- \_\_\_ pT4: Tumor more than 15 cm in greatest dimension

Abdomen and Thoracic Visceral Organs

- \_\_\_ pTX: Primary tumor cannot be assessed
- \_\_\_ pT1: Organ confined
- \_\_\_ pT2: Tumor extension into tissue beyond organ
- \_\_\_ pT2a: Invades serosa or visceral peritoneum
- \_\_\_ pT2b: Extension beyond serosa (mesentery)
- \_\_\_ pT3: Invades another organ
- \_\_\_ pT4: Multifocal involvement
- \_\_\_ pT4a: Multifocal (2 sites)
- \_\_\_ pT4b: Multifocal (3-5 sites)
- \_\_\_ pT4c: Multifocal (>5 sites)

Retroperitoneum

- \_\_\_ pTX: Primary tumor cannot be assessed
- \_\_\_ pT0: No evidence of primary tumor
- \_\_\_ pT1: Tumor 5 cm or less in greatest dimension
- \_\_\_ pT2: Tumor more than 5 cm and less than or equal to 10 cm in greatest dimension
- \_\_\_ pT3: Tumor more than 10 cm and less than or equal to 15 cm in greatest dimension
- \_\_\_ pT4: Tumor more than 15 cm in greatest dimension

Orbit

- \_\_\_ pTX: Primary tumor cannot be assessed
- \_\_\_ pT0: No evidence of primary tumor
- \_\_\_ pT1: Tumor ≤2 cm in greatest dimension
- \_\_\_ pT2: Tumor >2 cm in greatest dimension without invasion of bony walls or globe
- \_\_\_ pT3: Tumor of any size with invasion of bony walls
- \_\_\_ pT4: Tumor of any size with invasion of globe or periorbital structures, including eyelid, conjunctiva, temporal fossa, nasal cavity, paranasal sinuses, and/or central nervous system

**Regional Lymph Nodes (pN) (required only if lymph nodes submitted in this case)<sup>#</sup>**

- \_\_\_ pN0: No regional lymph node metastasis
- \_\_\_ pN1: Regional lymph node metastasis

<sup>#</sup> When no lymph nodes are present, the pathologic 'N' category is not assigned (pNX is not used for soft tissue tumors) and should not be reported.

**Distant Metastasis (pM) (required only if confirmed pathologically in this case)**

- \_\_\_ pM1: Distant metastasis  
Specify site(s), if known: \_\_\_\_\_

**+ Additional Pathologic Findings**

+ Specify: \_\_\_\_\_

+ Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.

**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.<sup>1,2</sup> In addition, treatment protocols increasingly require fresh tissue for correlative studies. Approximately 1 cm<sup>3</sup> 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**

<b>Histologic Type</b>	<b>Cytogenetic Events</b>	<b>Molecular Events</b>
Alveolar soft part sarcoma	t(X;17)(p11;q25)	<i>TFE3-ASPL</i> fusion
Aneurysmal bone cyst	t(16;17)(q22;p13)	<i>CDH11-USP6</i> fusion
Angiomatoid fibrous histiocytoma	t(12;16)(q13;p11) t(12;22)(q13;q12) t(2;22)(q33;q12)	<i>FUS-ATF1</i> fusion <i>EWSR1-ATF1</i> fusion <i>EWSR1-CREB1</i> fusion
Extraskelletal myxoid chondrosarcoma	t(9;22)(q22;q12) t(9;17)(q22;q11) t(9;15)(q22;q21) t(3;9)(q11;q22)	<i>EWSR1-NR4A3</i> fusion <i>TAF2N-NR4A3</i> fusion <i>TCF12-NR4A3</i> fusion <i>TFG-NR4A3</i> fusion
Clear cell sarcoma	t(12;22)(q13;q12) t(2;22)(q33;q12)	<i>EWSR1-ATF1</i> fusion <i>EWSR1-CREB1</i> fusion
Desmoplastic small round cell tumor	t(11;22)(p13;q12)	<i>EWSR1-WT1</i> fusion
Dermatofibrosarcoma protuberans	Ring form of chromosomes 17 and 22	<i>COL1A1-PDGFB</i> fusion

<b>Histologic Type</b>	<b>Cytogenetic Events</b>	<b>Molecular Events</b>
Ewing sarcoma/PNET	t(17;22)(q21;q13)	<i>COL1A1-PDGFB</i> fusion
	t(11;22)(q24;q12)	<i>EWSR1-FLI1</i> fusion
	t(21;22)(q12;q12)	<i>EWSR1-ERG</i> fusion
	t(2;22)(q33;q12)	<i>EWSR1-FEV</i> fusion
	t(7;22)(p22;q12)	<i>EWSR1-ETV1</i> fusion
	t(17;22)(q12;q12)	<i>EWSR1-E1AF</i> fusion
	inv(22)(q12;q12)	<i>EWSR1-ZSG</i> fusion
	t(16;21)(p11;q22)	<i>FUS-ERG</i> fusion
	t(19;der)ins.inv(21;22)	<i>EWSR1-ERG</i> fusion
	t(17;22)(q12;q12)	<i>EWSR1-ETV4</i> fusion
	t(6;22)(p21;q12)	<i>EWSR1-POU5F1</i> fusion
	t(1;22)(q36.1;q12)	<i>EWSR1-PATZ1</i> fusion
	t(2;22)(q31;q12)	<i>EWSR1-SP3</i> fusion
t(20;22)(q13;q12)	<i>EWSR1-NFATC2</i> fusion	
t(2;16)(q35;p11)	<i>FUS-FEV</i> fusion	
Undifferentiated round cell sarcoma (“atypical Ewing sarcoma”)	t(4;19)(q35;q13)	<i>CIC-DUX4</i> fusion
Fibrosarcoma, infantile	Xp11	<i>BCOR-CCNB3</i>
	t(12;15)(p13;q26) Trisomies 8, 11, 17, and 20	<i>ETV6-NTRK3</i> fusion
Inflammatory myofibroblastic tumor	t(1;2)(q22;p23)	<i>TPM3-ALK</i> fusion
	t(2;19)(p23;p13)	<i>TPM4-ALK</i> fusion
	t(2;17)(p23;q23)	<i>CLTC-ALK</i> fusion
	t(2;2)(p23;q13)	<i>RANB2-ALK</i> fusion
	t(2;2)(p23;q35)	<i>ATIC-ALK</i> fusion
	t(2;11)p23;p15)	<i>CARS-ALK</i> fusion
	t(2;4)(p23;q21)	<i>SEC31L1-ALK</i> fusion
	t(2;12)(p23;p12)	<i>PPFIBP1-ALK</i> fusion
Leiomyosarcoma	Complex with frequent deletion of 1p	
Liposarcoma	Well-differentiated	Amplification of <i>MDM2</i> , <i>CDK4</i> , and others
	Ring form of chromosome 12	
	Myxoid/Round cell	<i>FUS-DDIT3</i> fusion
	Pleomorphic	<i>EWSR1-DDIT3</i> fusion
Low-grade fibromyxoid sarcoma	t(7;16)(q33;p11)	<i>FUS-CREB3L2</i> fusion
	t(11;16)(p11;p11)	<i>FUS-CREB3L1</i> fusion
Malignant peripheral nerve sheath tumor	Complex	



Histologic Type	Cytogenetic Events	Molecular Events
Myxofibrosarcoma (myxoid MFH)	Complex	
Rhabdoid tumor	Deletion of 22q	<i>INI1(SMARCB1)</i> inactivation
Rhabdomyosarcoma		
Alveolar	t(2;13)(q35;q14) t(1;13)(p36;q14), double minutes t(2 ;2)(q35 ;p23) t(X;2)(q35 ;q13)	<i>PAX3-FOXO1A</i> fusion <i>PAX7-FOXO1A</i> fusion <i>PAX3-NCOA1</i> fusion <i>PAX3-AFX</i> fusion
Embryonal	Trisomies 2q, 8 and 20	Loss of heterozygosity at 11p15
Solitary fibrous tumor	Inversion chromosome 12	NAB2-STAT6
Synovial sarcoma		
Monophasic	t(X;18)(p11;q11)	<i>SS18-SSX1</i> , <i>SS18-SSX2</i> or <i>SS18-SSX4</i> fusion
Biphasic	t(X;18)(p11;q11)	Predominantly <i>SS18-SSX1</i> fusion

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 extracompartmental.

### References

1. Ladanyi M, Bridge JA. Contribution of molecular genetic data to the classification of sarcomas. *Hum Pathol.* 2000;31(5):532-538.
2. Tomescu O, Barr FG. Chromosomal translocations in sarcomas: prospects for therapy. *Trends Mol Med.* 2001;7(12):554-559.

### B. Tumor Site

The 8<sup>th</sup> edition of the American Joint Committee on Cancer (AJCC) staging manual<sup>1</sup> 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.<sup>1</sup>

### 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

1. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017.

### **C. Tumor Size**

In situations in which an accurate measurement of the excised primary tumor cannot be obtained (ie, fragmented specimen), it is acceptable to use available imaging data (computed tomography [CT], magnetic resonance imaging [MRI], etc) to assess tumor size for the purposes of determining the pT category.

### **D. 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.

#### WHO Classification of Tumors

Classification of tumors should be made according to the World Health Organization (WHO) classification of soft tissue tumors listed below.<sup>1</sup> 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

- Extraskelatal mesenchymal chondrosarcoma
- Extraskelatal 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
- Extraskelatal myxoid chondrosarcoma
- Extraskelatal 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

#### Histologic 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.

#### References

1. Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F, eds. *WHO Classification of Soft Tissue and Bone Tumors*. 4th ed. Geneva, Switzerland: WHO Press; 2013.

#### **E. 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,<sup>1</sup> there is, however, no generally agreed-upon scheme for grading soft tissue tumors.<sup>2</sup> The most widely used soft tissue grading systems are the French Federation of Cancer Centers Sarcoma Group (FNCLCC) and National Cancer Institute (NCI) systems.<sup>3,4</sup> Both systems have 3 grades and are based on mitotic activity, necrosis, and differentiation, and are highly correlated with prognosis.<sup>5</sup> 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.<sup>5</sup> Other systems with 2 or 4 grades also have been used. The 8<sup>th</sup> edition of the *AJCC Cancer Staging Manual*<sup>6</sup> 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**

### Tumor Differentiation

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

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.<sup>4</sup> The case for grading malignant peripheral nerve sheath tumor is currently being debated.

Modified with permission from Coindre JM.<sup>3</sup>

**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 mm<sup>2</sup>) (use the X40 objective). The area of 1 HPF originally used for mitotic count measured 0.1734 mm<sup>2</sup>. 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.

- Score 0: No tumor necrosis  
 Score 1: <50% tumor necrosis  
 Score 2: ≥50% tumor necrosis

### TNM Grading

The 8<sup>th</sup> 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.<sup>6,7</sup> This means that FNCLCC grade 2 tumors are considered “high grade” for the purposes of stage grouping.

### References

1. Eilber FC, Brennan MF, Eilber FR, et al. Validation of postoperative nomograms for 12-year sarcoma-specific mortality. *Cancer*. 2004;101:2270-2275.
2. Oliveira AM, Nascimento AG. Grading in soft tissue tumors: principles and problems. *Skeletal Radiol*. 2001;30(10):543-559.
3. Coindre JM. Grading of soft tissue sarcomas: review and update. *Arch Pathol Lab Med*. 2006;130:1448-1453.
4. Costa J, Wesley RA, Glatstein E, Rosenberg SA. The grading of soft tissue sarcomas: results of a clinicohistopathologic correlation in a series of 163 cases. *Cancer*. 1984;53(3):530-541.
5. Guillou L, Coindre JM, Bonichon F, et al. Comparative study of the National Cancer Institute and French Federation of Cancer Centers Sarcoma Group grading systems in a population of 410 adult patients with soft tissue sarcoma. *J Clin Oncol*. 1997;15(1):350-362.
6. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017.
7. Brierley JD, Gospodarowicz MK, Wittekind C, et al, eds. *TNM Classification of Malignant Tumours*. 8th ed. Oxford, UK: Wiley; 2016.

### **F. 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.

### **G. Margins**

It has been recommended that for all margins <2 cm, the distance of the tumor from the margin be reported in centimeters.<sup>1</sup> 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

1. Recommendations for the reporting of soft tissue sarcomas. Association of Directors of Anatomic and Surgical Pathology. *Mod Pathol*. 1998;11(12):1257-1261.

## H. 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.

## I. Regional 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. For sarcomas arising in the trunk and extremities or retroperitoneum, the 8th edition of the *AJCC Cancer Manual* recommends that N1 M0 disease be regarded as stage IIIB rather than stage IV disease.

## J. Pathologic Stage Classification (pTNM and Stage Groupings)

The TNM staging system for soft tissue tumors of the AJCC and UICC is recommended.<sup>1,2</sup> The staging system applies to all soft tissue sarcomas of the extremities and trunk, abdomen, and thoracic visceral organs and retroperitoneum except Kaposi sarcoma, gastrointestinal stromal tumors, fibromatosis (desmoid tumor), and infantile fibrosarcoma. The staging system applies to all soft tissue sarcomas of the head and neck except angiosarcoma, rhabdomyosarcoma of the embryonal and alveolar subtypes, Kaposi sarcoma, and dermatofibrosarcoma protuberans. In addition, sarcomas arising within the confines of the dura mater, including the brain, are not optimally staged by this system.

Furthermore, regardless of the anatomic site, locally aggressive soft tissue neoplasms, which may recur locally but have either no risk of metastatic disease or an extremely low risk of metastasis, are *excluded* from the AJCC soft tissue sarcoma staging system. Examples of soft tissue lesions not staged using the AJCC staging system include:

- Desmoid tumor (deep fibromatosis)
- Superficial fibromatosis
- Lipofibromatosis
- Giant cell fibroblastoma
- Plexiform fibrohistiocytic tumor
- Giant cell tumor of soft tissues
- Kaposiform hemangioendothelioma
- Hemosiderotic fibrolipomatous tumor
- Atypical fibroxanthoma
- Angiomatoid fibrous histiocytoma
- Pleomorphic hyalinizing angiectatic tumor

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 criteria currently vary by anatomic site, particular emphasis should be placed on providing size measurements. Size should be regarded as a continuous variable, with the centimeter cutoffs as arbitrary divisions that make it possible to characterize patient populations.

### Depth

Due to the limited impact of depth on outcome and because the inherent inability to use depth in anatomic sites other than extremities and trunk, depth is no longer used in the 8th edition of the AJCC staging manual.<sup>1</sup> In previous staging systems, depth was evaluated relative to the investing fascia of the extremity and trunk. Superficial was defined as lack of any involvement of the superficial investing muscular fascia in extremity or trunk lesions. For staging, all retroperitoneal and visceral lesions were considered to be deep lesions.



### Regional Lymph Nodes (pN)

Nodal involvement is rare in adult soft tissue sarcomas but, when present, has a very poor prognosis. In the absence of metastatic disease, N1 disease is classified as stage IIIB. Patients whose nodal status is not determined to be positive for tumor, either clinically or pathologically, should be designated as N0. NX should not be used.

### 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

Tumor size criteria vary by anatomic site.

### N Category Considerations

Presence of positive nodes (N1), in the absence of metastatic disease, is considered stage IIIB.

### 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.

### References

1. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017.
2. Brierley JD, Gospodarowicz MK, Wittekind C, et al, eds. *TNM Classification of Malignant Tumours*. 8th ed. Oxford, UK: Wiley; 2016.