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

Version: 4.1.0.0
Protocol Posting Date: June 2021
CAP Laboratory Accreditation Program Protocol Required Use Date: March 2022
The changes included in this current protocol version affect accreditation requirements. The new deadline for implementing this protocol version is reflected in the above accreditation date.

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)

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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. For instance, the total number of lymph nodes examined must be reported, but only if nodes are present in the specimen.
- 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 (ie, 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

v 4.1.0.0

- General Reformatting
- New WHO 5th Edition Histological Updates
- Added Tumor Focality Question
- Revised Margins Section
- Revised Lymph Nodes Section
- Added Distant Metastasis Section
- Removed pTX and pNX Staging Classification

Reporting Template

Protocol Posting Date: June 2021
Select a single response unless otherwise indicated.

CASE SUMMARY: (SOFT TISSUE: Resection)
Standard(s): AJCC-UICC 8
This checklist applies principally to soft tissue sarcomas in teenagers and adults. In general, pediatric sarcomas are treated under strict protocols that may differ significantly from the recommendations for adult type sarcomas.

CLINICAL

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

SPECIMEN (Note A)

Procedure
___ Intralesional resection
___ Marginal resection
___ Wide resection
___ Radical resection
___ Other (specify): _____
___ Not specified

TUMOR

Tumor Focality
___ Unifocal
___ Multifocal
Number of Tumors
___ Specify number: _____
___ Other (specify): _____
___ Cannot be determined: _____
___ Cannot be determined: _____

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 site, if known): _____
___ Orbit (specify site, if known): _____
___ Not specified

Tumor Size (Note C)
___ Greatest dimension in Centimeters (cm): _____ cm
+Additional Dimension in Centimeters (cm): ____ x ____ cm
___ Cannot be determined (explain): _____

Histologic Type (World Health Organization [WHO] Classification of Soft Tissue Tumors) (Note D)
 # The list is derived from the 2020 World Health Organization (WHO) classification of soft tissue tumors, edited to include ONLY soft tissue tumors of intermediate (locally aggressive and rarely metastasizing) potential and malignant soft tissue tumors for which anatomical staging using the AJCC system is considered to be clinically relevant.

___ Adipocytic Tumors
Intermediate (locally aggressive)
___ Atypical lipomatous tumor
Malignant
___ Well differentiated liposarcoma
___ Dedifferentiated liposarcoma
___ Myxoid liposarcoma
+Percentage of Hypercellular Areas (formerly known as round cells)
___ Specify percentage: _____ %
___ Other (specify): _____
___ Cannot be determined
___ Pleomorphic liposarcoma
___ Epithelioid liposarcoma
___ Myxoid pleomorphic liposarcoma

___ Fibroblastic / Myofibroblastic Tumors
Intermediate (rarely metastasizing)
___ Fibrosarcomatous dermatofibrosarcoma protuberans
Malignant
___ Solitary fibrous tumor, malignant
___ Adult fibrosarcoma
___ Myxofibrosarcoma
___ Epithelioid Myxofibrosarcoma
___ Low grade fibromyxoid sarcoma
___ Sclerosing epithelioid fibrosarcoma

___ So-called Fibrohistiocytic Tumors
Malignant
___ Malignant tenosynovial giant cell tumor

___ Smooth Muscle Tumors
Malignant
___ Leiomyosarcoma

___ Pericytic (Perivascular) Tumors
Malignant
___ Malignant glomus tumor

___ Skeletal Muscle Tumors
Malignant
___ Embryonal rhabdomyosarcoma (including botryoid, anaplastic)
___ Alveolar rhabdomyosarcoma (including solid, anaplastic)
___ Pleomorphic rhabdomyosarcoma
___ Spindle cell / sclerosing rhabdomyosarcoma

___ Spindle cell / sclerosing rhabdomyosarcoma NOS
___ Congenital spindle cell rhabdomyosarcoma with VGLL2/NCOA2/CITED2 rearrangements
___ MYOD1-mutant spindle cell / sclerosing rhabdomyosarcoma
___ Intraosseous spindle cell rhabdomyosarcoma (with TFCP2/NCOA2 rearrangements)
___ Ectomesenchymoma

___ Vascular Tumors
Malignant
___ Epithelioid hemangioendothelioma with WWTR1-CAMTA1 fusion
___ Epithelioid hemangioendothelioma with YAP1-TFE3 fusion
___ Epithelioid hemangioendothelioma NOS

___ Peripheral Nerve Tumors
Malignant
___ Malignant peripheral nerve sheath tumor
___ Epithelioid malignant peripheral nerve sheath tumor
___ Malignant granular cell tumor
___ Malignant perineurioma

___ Chondro-osseous Tumors
Malignant
___ Extraskeletal osteosarcoma

___ Tumors of Uncertain Differentiation
Intermediate (rarely metastasizing)
___ Ossifying fibromyxoid tumor
___ Mixed tumor: _____
___ Mixed tumor NOS, malignant: _____
___ Myoepithelioma
Malignant
___ Phosphaturic mesenchymal tumor, malignant
___ NTRK-rearranged spindle cell neoplasm
___ Synovial sarcoma, biphasic
___ Synovial sarcoma, spindle cell
___ Synovial sarcoma, poorly differentiated
___ Synovial sarcoma NOS
___ Epithelioid sarcoma, classic type
___ Epithelioid sarcoma, proximal or large cell type
___ Alveolar soft part sarcoma
___ Clear cell sarcoma of soft tissue
___ Extraskeletal myxoid chondrosarcoma
___ Ossifying fibromyxoid tumor, malignant
___ Myoepithelial carcinoma
___ Extraskeletal Ewing sarcoma
___ Round cell sarcoma with EWSR1-non ETS fusions
___ CIC-rearranged sarcoma
___ Sarcoma with BCOR genetic alterations

___ Undifferentiated / Unclassified Sarcomas
___ Undifferentiated spindle cell sarcoma
___ Undifferentiated pleomorphic sarcoma
___ Undifferentiated round cell sarcoma

___ Undifferentiated sarcoma NOS

___ Other histologic type not listed (specify): _____

___ Cannot be determined: _____
+Histologic Type Comment: _____

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

Mitotic Rate (Note E)
___ Specify mitotic rate per mm^2: _____ mitoses per mm^2
___ Specify mitotic rate per 10 high-power fields (HPF): _____ mitoses per 10 high-power fields (HPF)
___ Cannot be determined (explain): _____

Necrosis (macroscopic or microscopic) (Note E)
___ Not identified
___ Present
Extent of Necrosis
___ Specify percentage: _____ %
___ Cannot be determined (explain): _____
___ Cannot be determined

Treatment Effect (Note F)
___ No known presurgical therapy
___ Not identified
___ Present
Percentage of Viable Tumor (compared with pretreatment biopsy, if available)
___ Specify percentage: _____ %
___ Cannot be determined (explain): _____
___ Cannot be determined

+Lymphovascular Invasion (Note G)
___ Not identified
___ Present
___ Cannot be determined: _____

+Tumor Comment: _____

MARGINS (Note H)

Margin Status
___ All margins negative for tumor
Closest Margin(s) to Tumor
___ Specify closest margin(s): _____
___ Cannot be determined (explain): _____

Distance from Tumor to Closest Margin
Specify in Centimeters (cm)
___ Exact distance: _____ cm
___ Greater than: _____ cm
___ At least: _____ cm
___ Less than: _____ cm
___ Less than 2 cm
___ Other (specify): _____
___ Cannot be determined: _____
Other Close Margin(s) to Tumor (less than 2 cm)
___ Specify other close margin(s): _____
___ Cannot be determined (explain): _____
___ Not applicable
___ Tumor present at margin
Margin(s) Involved by Tumor
___ Specify involved margin(s): _____
___ Cannot be determined (explain): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Not applicable

+Margin Comment: _____

REGIONAL LYMPH NODES (Note I)

Regional Lymph Node Status
___ Not applicable (no regional lymph nodes submitted or found)
___ Regional lymph nodes present
___ All regional lymph nodes negative for tumor
___ Tumor present in regional lymph node(s)
Number of Lymph Nodes with Tumor
___ Exact number (specify): _____
___ At least (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
Number of Lymph Nodes Examined
___ Exact number (specify): _____
___ At least (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

+Regional Lymph Node Comment: _____

DISTANT METASTASIS

Distant Site(s) Involved, if applicable (select all that apply)
___ Not applicable

___ Lung: _____
___ Other (specify): _____
___ Cannot be determined: _____

PATHOLOGIC STAGE CLASSIFICATION (pTNM, AJCC 8th Edition) (Note J)

Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. As per the AJCC (Chapter 1, 8th Ed.) it is the managing physician's responsibility to establish the final pathologic stage based upon all pertinent information, including but potentially not limited to this pathology report.

Pathologic Stage Classification

___ Not applicable (histologic type not appropriate for staging)#

 # 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. (Note J)

___ Histologic type appropriate for staging

TNM Descriptors (select all that apply)

___ Not applicable
___ m (multiple)
___ r (recurrent)
___ y (post-treatment)

pT Category

___ Head and Neck

pT Category

___ pT not assigned (cannot be determined based on available pathological information)
___ pT1: Tumor less than or equal to 2 cm
___ pT2: Tumor greater than 2 cm to less than or equal to 4 cm
___ pT3: Tumor greater than 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
___ pT4 (subcategory cannot be determined)

___ Trunk and Extremities

pT Category

___ pT not assigned (cannot be determined based on available pathological information)
___ 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

pT Category

___ pT not assigned (cannot be determined based on available pathological information)
___ pT1: Organ confined

pT2: Tumor extension into tissue beyond organ

___ pT2a: Invades serosa or visceral peritoneum
___ pT2b: Extension beyond serosa (mesentery)
___ pT2 (subcategory cannot be determined)

___ pT3: Invades another organ
pT4: Multifocal involvement
___ pT4a: Multifocal (2 sites)
___ pT4b: Multifocal (3 - 5 sites)
___ pT4c: Multifocal (greater than 5 sites)
___ pT4 (subcategory cannot be determined)

___ Retroperitoneum
pT Category
___ pT not assigned (cannot be determined based on available pathological information)
___ 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
pT Category
___ pT not assigned (cannot be determined based on available pathological information)
___ pT0: No evidence of primary tumor
___ pT1: Tumor less than or equal to 2 cm in greatest dimension
___ pT2: Tumor greater than 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

pN Category
___ pN not assigned (no nodes submitted or found)
___ pN not assigned (cannot be determined based on available pathological information)
___ pN0: No regional lymph node metastasis
___ pN1: Regional lymph node metastasis

pM Category (required only if confirmed pathologically)
___ Not applicable - pM cannot be determined from the submitted specimen(s)
___ pM1: Distant metastasis

ADDITIONAL FINDINGS

+Additional Findings (specify): _____

SPECIAL STUDIES

Immunohistochemistry
___ Specify: _____
___ Not performed: _____
___ Not applicable

Cytogenetics
___ Specify: _____
___ Not performed: _____
___ Not applicable

Molecular Pathology
___ Specify: _____
___ Not performed: _____
___ Not applicable

COMMENTS

Comment(s): _____

Explanatory Notes

A. Procedure / Tissue Processing

Fixation

Ideally, tissue specimens from soft tissue tumors are received fresh/unfixed in the pathology laboratory, in case fresh tissue for ancillary studies, such as cytogenetics, needs to be collected.

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 10 to 12 sections or fewer, excluding sections submitted to assess the status of surgical margins. Tumors with greater areas of heterogeneity may need to be sampled more thoroughly.

Although the ability to perform diagnostic molecular studies in formalin fixed paraffin embedded tissue has substantially diminished the need to collect fresh tissue on every case, frozen tissue may be needed to enter patients into treatment protocols.[1,2,3,4] Nevertheless, discretion should be used in triaging tissue from sarcomas. Adequate tissue should be submitted for conventional light microscopy before setting aside samples for cytogenetics, electron microscopy, or molecular analysis. Fresh tissue for special studies should be collected at the time the specimen is received.

Molecular Studies

It may be important to snap freeze a small portion of tissue as availability of frozen tissue may be a requirement for patient enrollment into clinical trials. In general, 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^oC and can be shipped on dry ice to facilities that perform ancillary testing.

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.
3. Jin L, Majerus J, Oliveira A. et al. Detection of fusion gene transcripts in fresh-frozen and formalin-fixed paraffin-embedded tissue sections of soft-tissue sarcomas after laser capture microdissection and rt-PCR, Diagn Mol Pathol . 2003 Dec;12(4):224-30
4. Smith SM, Coleman J, Bridge JA et al. Molecular diagnostics in soft tissue sarcomas and gastrointestinal stromal tumors. J Surg Oncol. 2015 Apr;111(5):520-31.

B. Tumor Site
The 8th edition of the American Joint Committee on Cancer (AJCC) staging manual[1] 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.[1]

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 2020 World Health Organization (WHO) classification of soft tissue tumors.[1] As part of the WHO classification system, soft tissue tumors are divided into 4 categories: benign, intermediate (locally aggressive), intermediate (rarely metastasizing), and malignant.
The provided list of histologic types is derived from the 2020 World Health Organization (WHO) classification of soft tissue tumors[1], edited to only include soft tissue tumors of intermediate (locally aggressive and rarely metastasizing) potential and malignant soft tissue tumors for which anatomical staging using the AJCC system is considered to be clinically relevant. The full reference contains information on additional soft tissue tumors.

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. In problematic cases, the grade of the pretreatment specimen (if available) should take precedence.

References
1. WHO Classification of Tumours Editorial Board. Soft Tissue and Bone Tumors. Lyon (France): International Agency for Research on Cancer; 2020. (WHO classification of tumours series, 5th ed.; vol. 3)

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,[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.[5] Other systems with 2 or 4 grades also have been used. The 8th edition of the *AJCC Cancer Staging Manual*[6] 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 1).

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 1. 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.[4] 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 either 10 consecutive high-power fields (HPF) (use the X40 objective) (1 HPF x 400 = 0.1734 mm^2) or in the appropriate number of HPF to encompass 1 mm^2 based on each individual microscope. If the mitotic rate is close to the cutoff between mitotic scores, the count should be repeated.

Table 2. Mitotic Count Score equivalence

Mitotic Score	# mitosis / 10 HPF (1 HPF= 0.1734 mm^2)	# mitosis / 1 mm^2 (see table 3)
Score 1	0 to 9 mitosis / 10 HPF	0 to 5 mitosis / 1 mm^2
Score 2	10 to 19 mitosis / 10 HPF	6 to 11 mitosis / 1 mm^2
Score 3	> 19 mitosis / 10 HPF	> 11 mitosis / 1 mm^2

The area of 1 HPF originally used for mitotic count measured 0.1734 mm^2. 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.

An important change in the 5th Edition of the WHO Classification of Tumours series[7] is the conversion of mitotic count from the traditional denominator of 10 HPFs to a defined area expressed in mm^2, as an attempt to standardize the area used for mitotic count. Table 3 shows the approximate number of fields required to encompass 1 mm^2 based on the field diameter and its corresponding area.

Table 3. Approximate number of fields per 1 mm^2 based on field diameter and its corresponding area

Field diameter (mm)	Area (mm^2)	Approximate number of fields per 1 mm^2
0.40	0.126	8
0.41	0.132	8
0.42	0.138	7
0.43	0.145	7
0.44	0.152	7
0.45	0.159	6
0.46	0.166	6
0.47	0.173	6
0.48	0.181	6
0.49	0.188	5
0.50	0.196	5
0.51	0.204	5
0.52	0.212	5
0.53	0.221	5
0.54	0.229	4
0.55	0.237	4
0.56	0.246	4
0.57	0.255	4
0.58	0.264	4
0.59	0.273	4
0.60	0.283	4
0.61	0.292	3
0.62	0.302	3
0.63	0.312	3
0.64	0.322	3
0.65	0.332	3
0.66	0.342	3
0.67	0.352	3
0.68	0.363	3
0.69	0.374	3

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 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.[6,8] This means that FNCLCC grade 2 and grade 3 tumors are considered "high grade" for the purposes of stage grouping.

References

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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. 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.

H. Margins

The most important predictor of local recurrence is the status of surgical excision margins.[1] Therefore, detailed reporting of surgical margins is a critical role of the pathologist. It has been recommended that for all margins located less than 2 cm, the distance of the tumor from the margin be reported in centimeters.[2] However, there is a lack of agreement on this issue. We recommend specifying the location of all margins located less than 2 cm and the distance of the closest margin that is less than 2 cm from the

tumor. 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 located more than 2 cm from the margin, the marrow can be scooped out and submitted as a margin.

References
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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 no lymph nodes are resected, the pathologic 'N' category is not assigned (pNX is not used for soft tissue tumors). 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.[1]

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

The TNM staging system for soft tissue tumors of the AJCC and UICC is recommended.[1,2] 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.[1] 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. When no lymph nodes are resected, the pathologic 'N' category is not assigned (pNX is not used for soft tissue tumors). 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

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