

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

Version: Soft Tissue Biopsy 4.0.2.0

Protocol Posting Date: February 2020

Accreditation Requirements

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

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

Procedure	Description
Biopsy	
Tumor Type	Description
Soft tissue sarcomas	Includes soft tissue tumors of intermediate (locally aggressive and rarely metastasizing) potential and malignant soft tissue tumors.

The following should NOT be reported using this protocol:

Procedure
Resection (consider the Soft Tissue Resection protocol)
Cytologic specimens
Tumor type
Soft tissue tumors that may recur locally but have either no or an extremely low risk of metastasis
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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Summary of Changes

Version 4.0.2.0

Modified Margins, changed the term sarcoma to tumor

Surgical Pathology Cancer Case Summary

Protocol posting date: February 2020

SOFT TISSUE: Biopsy

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

Select a single response unless otherwise indicated.

Prebiopsy Treatment (select all that apply)

- No known prebiopsy therapy
- Chemotherapy performed
- Radiation therapy performed
- Therapy performed, type not specified
- Not specified**

Procedure (Note A)

- Core needle biopsy
- Incisional biopsy
- Excisional biopsy
- Other (specify): _____
- Not specified

Tumor Site (Note B)

- Head and neck (specify site, if known): _____
- Trunk and extremities (specify site, if known): _____
- Abdominal visceral organ(s) (specify site, if known): _____
- Thoracic visceral organ(s) (specify site, if known): _____
- Retroperitoneum (specify site, if known): _____
- Orbit (specify site, if known): _____
- Not specified

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

- Specify: _____
- Cannot be determined

Mitotic Rate (Note D)

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

Necrosis (Note D)

- Not identified
- Present
 - Extent: ___%
- Cannot be determined

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

- Grade 1
- Grade 2
- Grade 3
- Ungraded sarcoma
- Cannot be assessed

Treatment Effect (Note E)

- No known prebiopsy therapy
- Not identified
- Present
 - Specify percentage of viable tumor: ____%
- Cannot be determined

Margins (for excisional biopsy only) (Note F)

- Cannot be assessed
- All margins negative for tumor
 - Distance of tumor from closest margin (centimeters): ____ cm
 - Specify margin: _____
 - Specify other close (<2.0 cm) margin(s): _____
- Tumor present at margin(s)
 - Specify margin(s): _____

Lymphovascular Invasion (Note G)

- Not identified
- Present
- Cannot be determined

Additional Pathologic Findings

Specify: _____

Ancillary Studies (required only if applicable)

Immunohistochemistry (specify): _____

- Not performed

Cytogenetics (specify): _____

- Not performed

Molecular Pathology (specify): _____

- Not performed

Comment(s)

Explanatory Notes

A. Procedure / Tissue Processing

Fixation

Tissue specimens from soft tissue tumors optimally are received fresh/unfixed because of the importance of ancillary studies, such as cytogenetics, which require fresh tissue.

Tissue Submission for Histologic Evaluation

One section per centimeter of maximum dimension is usually recommended, although fewer sections per centimeter are needed for very large tumors, especially if they are homogeneous. Tumors known to be high grade from a previous biopsy do not require as many sections as those that were previously diagnosed as low grade, as documentation of a high-grade component will change stage and prognosis in the latter case. Sections should be taken of grossly heterogeneous areas, and there is no need to submit more than 1 section of necrotic tumor (always with a transition to viable tumor). Occasionally, gross pathology can be misleading, and areas that appear to be grossly necrotic may actually be myxoid or edematous. When this happens, additional sections of these areas should be submitted for histologic examination. When estimates of gross necrosis exceed those of histologic necrosis, the greater percentage of necrosis should be recorded on the surgical pathology report. In general, most tumors require 12 sections or fewer, excluding margins. Tumors with greater areas of heterogeneity may need to be sampled more thoroughly.

Fresh tissue for special studies should be submitted at the time the specimen is received. Note that classification of many subtypes of sarcoma is not dependent upon special studies, such as cytogenetics or molecular genetics, but frozen tissue may be needed to enter patients into treatment protocols. Discretion should be used in triaging tissue from sarcomas. Adequate tissue should be submitted for conventional light microscopy before tissue has been taken for cytogenetics, electron microscopy, or molecular analysis.

Molecular Studies

It is important to snap freeze a small portion of tissue whenever possible. This tissue can be used for a variety of molecular analyses for tumor-specific molecular translocations (see Table 1) that help in classifying soft tissue tumors.^{1,2} In addition, treatment protocols increasingly require fresh tissue for correlative studies. Approximately 1 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 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

Histologic Type	Cytogenetic Events	Molecular Events
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

Histologic Type	Cytogenetic Events	Molecular Events
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
	t(12;16)(q13;p11)	<i>EWSR1-DDIT3</i> fusion
	t(12;22)(q13;q12)	
	Pleomorphic	Complex
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 8th edition of the American Joint Committee on Cancer (AJCC) staging manual¹ 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. 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.¹ 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

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.

D. Grading

Unlike with other organ systems, the staging of soft tissue sarcomas is largely determined by grade. Whilst nomograms assess multiple clinical and histologic parameters to calculate the probability of recurrence for a given patient,¹ there is, however, no generally agreed-upon scheme for grading soft tissue tumors.² The most widely used soft tissue grading systems are the French Federation of Cancer Centers Sarcoma Group (FNCLCC) and National Cancer Institute (NCI) systems.^{3,4} Both systems have 3 grades and are based on mitotic activity, necrosis, and differentiation, and are highly correlated with prognosis.⁵ However, in addition to these criteria, the NCI system requires the quantification of cellularity and pleomorphism for certain subtypes of sarcomas, which is difficult to determine objectively. The FNCLCC system is easier to use in our opinion, and it may be slightly better in predicting prognosis than the NCI system.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 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.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 10 consecutive high-power fields (HPF) (1 HPF x 400 = 0.1734 mm²) (use the X40 objective). The area of 1 HPF originally used for mitotic count measured 0.1734 mm². However, the area of 1 HPF using most modern microscopes with wider 40x lenses will most likely be higher. Pathologists are encouraged to determine the field area of their 40x lenses and divide 0.1734 by the obtained field area to obtain a conversion factor. The number of mitotic figures in 10 HPF multiplied by the obtained conversion factor and rounded to the nearest whole number should be used for grading purposes. If the mitotic rate is close to the cutoff between mitotic scores, the count should be repeated.

Score 1: 0 to 9 mitoses per 10 HPF

Score 2: 10 to 19 mitoses per 10 HPF

Score 3: >19 mitoses per 10 HPF

Tumor Necrosis: Evaluated on gross examination and validated with histologic sections.

- 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.^{6,7} 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.

E. Response to Chemotherapy/Radiation Therapy Effect

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

F. Margins

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

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.