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

Version: 4.2.0.0
Protocol Posting Date: June 2024
The use of this protocol is recommended for clinical care purposes but is not required for accreditation purposes.

This protocol may be used for the following procedures AND tumor types:

Procedure	Description
Biopsy	Includes specimens designated core needle biopsy, incisional biopsy, and others
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, excisional biopsy (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 / Metaplastic carcinoma / Sarcomatoid carcinoma (consider the appropriate site-specific carcinoma protocol)
Lymphoma / Leukemia (consider the Precursor and Mature Lymphoid Malignancies, Myeloid and Mixed / Ambiguous Lineage Neoplasms, or Plasma Cell Malignancies protocols)
Pediatric Ewing sarcoma (consider the Pediatric Ewing Sarcoma protocol)
Pediatric rhabdomyosarcoma (consider the Pediatric Rhabdomyosarcoma protocol)
Gastrointestinal stromal tumor (consider the Gastrointestinal Stromal Tumor protocol)
Uterine sarcoma (consider the Uterine Sarcoma protocol)
SMARCA4-deficient sarcoma (consider the Lung protocol or Organ-Site-Specific protocol)

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Accreditation Requirements
The use of this biopsy case summary is recommended for clinical care purposes, but is not required for accreditation purposes. The core and conditional data elements are routinely reported for biopsy specimens. Non-core data elements are included to allow for reporting information that may be of clinical value.

Summary of Changes

v 4.2.0.0

- Cover page update
- Updates to content and explanatory notes, including WHO Histologic Types
- LVI question update from optional to required (core) and “Lymphovascular Invasion” to “Lymphatic and / or Vascular Invasion"
- Addition of optional questions including "Associated Syndrome", “Radiologic Findings”, “Tumor Laterality”, Tumor Size (based on clinicoradiologic parameters)”, and “Tumor Extent and Depth of Invasion”
- Removal of “MARGINS” section
- SPECIAL STUDIES section update

Reporting Template

Protocol Posting Date: June 2024
Select a single response unless otherwise indicated.

CASE SUMMARY: (SOFT TISSUE: Biopsy)
Standard(s): AJCC-UICC 8
The use of this template is recommended for reporting biopsy specimens, but is not required for accreditation purposes.

CLINICAL

+Associated Syndrome
___ Li-Fraumeni syndrome
___ Neurofibromatosis type 1
___ Familial adenomatous polyposis
___ Other (specify): _____
___ Not specified

+Radiologic Findings
___ Specify: _____
___ Not available

SPECIMEN (Note A)

Procedure
___ Core needle biopsy
___ Incisional biopsy
___ Other (specify): _____
___ Not specified

TUMOR

Tumor Site (Note B)
___ Head and neck (specify site, if known): _____
___ Trunk, extremities, joint / intra-articular (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
___ Other (specify): _____

+Tumor Laterality
___ Left
___ Right
___ Central

___ Not specified
___ Cannot be determined

+Tumor Size (based on clinicoradiologic parameters)
___ Greatest dimension in Centimeters (cm): _____ cm
___ Not specified
___ Cannot be determined: _____

Histologic Type# (Note C)
 # The list is derived from the World Health Organization (WHO) classification of soft tissue tumors, 5th edition, to include ONLY soft tissue tumors of intermediate (locally aggressive and rarely metastasizing) potential and malignant soft tissue tumors.
___ Adipocytic tumors
- ___ Atypical spindle cell / pleomorphic lipomatous tumor
- ___ Atypical lipomatous tumor
- ___ 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, NOS
- ___ Epithelioid pleomorphic liposarcoma
- ___ Myxoid pleomorphic liposarcoma

___ Fibroblastic / myofibroblastic / fibrohistiocytic tumors
- ___ Solitary fibrous tumor
- ___ Desmoid-type fibromatosis
- ___ Lipofibromatosis
- ___ Plexiform fibrohistiocytic tumor
- ___ Giant cell fibroblastoma
- ___ Dermatofibrosarcoma protuberans
- ___ Fibrosarcomatous dermatofibrosarcoma protuberans
- ___ Myxofibrosarcoma
- ___ Low-grade fibromyxoid sarcoma
- ___ Sclerosing epithelioid fibrosarcoma
- ___ Myofibroblastic sarcoma
- ___ Superficial CD34-positive fibroblastic tumor
- ___ Myxoinflammatory fibroblastic sarcoma

___ Histiocytic / giant cell rich tumors
- ___ Giant cell tumor of soft tissue
- ___ Langerhans cell sarcoma
- ___ True histiocytic sarcoma
- ___ Malignant tenosynovial giant cell tumor
- ___ Dendritic reticulum cell sarcoma
- ___ Interdigitating reticulum cell sarcoma
- ___ Fibroblastic reticulum cell sarcoma

___ Tyrosine kinase fusion tumors, RAS-MAP pathway (Note D)
- ___ NTRK 1/2/3 fusion tumor
- ___ BRAF fusion tumor
- ___ RET fusion tumor
- ___ RAF fusion tumor
- ___ ALK fusion tumor, NOS
- ___ Inflammatory myofibroblastic tumor
- ___ Epithelioid inflammatory myofibroblastic sarcoma
- ___ Infantile fibrosarcoma

___ Pericytic / myopericytic tumors
- ___ Glomus tumor, atypical / uncertain biologic potential
- ___ Glomus tumor, malignant

___ Vascular tumors
- ___ Kaposiform hemangioendothelioma
- ___ Papillary intralymphatic angioendothelioma
- ___ Retiform hemangioendothelioma
- ___ Composite hemangioendothelioma
- ___ Pseudomyogenic hemangioendothelioma
- ___ Kaposi sarcoma
- ___ Epithelioid hemangioendothelioma with WWTR1::CAMTA1 fusion
- ___ Epithelioid hemangioendothelioma with YAP1::TFE3 fusion
- ___ Epithelioid hemangioendothelioma, NOS
- ___ Epithelioid angiosarcoma
- ___ Radiation-associated angiosarcoma
- ___ Lymphedema-associated angiosarcoma
- ___ Angiosarcoma, NOS

___ Smooth muscle tumors
- ___ EBV-associated smooth muscle tumor
- ___ Leiomyosarcoma

___ Skeletal muscle tumors
- ___ Embryonal rhabdomyosarcoma
- ___ Alveolar rhabdomyosarcoma
- ___ Pleomorphic rhabdomyosarcoma
- ___ Spindle cell / sclerosing rhabdomyosarcoma, NOS
- ___ Congenital spindle cell rhabdomyosarcoma with VGLL2/NCOA2/CITED2 fusions
- ___ Spindle cell / sclerosing rhabdomyosarcoma with MYOD1 mutation
- ___ Spindle cell rhabdomyosarcoma with FUS/EWSR1::TFCP2 or MEIS1::NCOA2 rearrangements
- ___ Ectomesenchymoma

___ Peripheral nerve sheath tumors
- ___ Malignant peripheral nerve sheath tumor, NOS
- ___ Epithelioid malignant peripheral nerve sheath tumor
- ___ Malignant triton tumor
- ___ Melanotic malignant peripheral nerve sheath tumor
- ___ Malignant granular cell tumor
- ___ Malignant perineurioma

___ Chondro-osseous tumors

___ Extraskeletal osteosarcoma
___ Mesenchymal chondrosarcoma
___ Chondrosarcoma arising in synovial chondromatosis
___ Tumors of uncertain differentiation / additional round and spindle cell tumors
___ Hemosiderotic fibrolipomatous tumor
___ Pleomorphic hyalinizing angiectatic tumor
___ Atypical fibroxanthoma
___ Pleomorphic dermal sarcoma
___ Angiomatoid fibrous histiocytoma
___ Myoepithelioma
___ Mixed tumor, malignant
___ Myoepithelial carcinoma
___ Ossifying fibromyxoid tumor (Note E)
___ Phosphaturic mesenchymal tumor, malignant
___ Synovial sarcoma
___ Epithelioid sarcoma, distal classic type
___ Epithelioid sarcoma, proximal large cell type
___ Alveolar soft part sarcoma
___ Clear cell sarcoma of soft tissue
___ Extraskeletal myxoid chondrosarcoma
___ Extraskeletal Ewing sarcoma
___ Desmoplastic small round cell tumor (DSRCT)
___ Round cell sarcoma with EWSR1::non-ETS fusions
___ CIC-rearranged sarcoma
___ Sarcoma with BCOR genetic alterations
___ PEComa, NOS
___ PEComa, TSC2 mutated
___ PEComa, TFE3 rearranged
___ Intimal sarcoma
___ Extrarenal rhabdoid tumor
___ Undifferentiated sarcomas
___ Undifferentiated pleomorphic 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)
___ G1, total differentiation, mitotic count and necrosis score 2 or 3
___ G2, total differentiation, mitotic count and necrosis score 4 or 5
___ G3, total differentiation, mitotic count and necrosis score of 6, 7, or 8
___ GX, cannot be assessed: _____
___ Ungraded sarcoma / not applicable for this tumor type

Mitotic Rate (Note E)
___ Specify mitotic rate per mm2: _____ mitoses per mm2

___ Specify mitotic rate per 10 high-power fields (HPF): _____ mitoses per 10 high-power fields (HPF)
___ Cannot be determined (explain): _____

Necrosis (Note E)
___ Not identified
___ Present

Extent of Necrosis
___ Specify percentage: _____ %
___ Cannot be determined (explain): _____
___ Cannot be determined

+Tumor Extent and Depth of Invasion (Note F) (select all that apply)
___ Dermis
___ Subcutis
___ Deep fascia
___ Skeletal muscle, intramuscular
___ Skeletal muscle, intermuscular
___ Bone
___ Other (specify): _____

Lymphatic and / or Vascular Invasion (Note G)
___ Not identified
___ Present
___ Cannot be determined: _____

+Tumor Comment: _____

ADDITIONAL FINDINGS

+Additional Findings (specify): _____

SPECIAL STUDIES

Immunohistochemistry
___ Specify results: _____
___ Pending (specify): _____
___ Not performed: _____
___ Not applicable
___ Other (specify): _____

Cytogenetics
___ Specify results: _____
___ Pending (specify): _____
___ Not performed: _____

___ Not applicable
___ Other (specify): _____

Molecular Studies
___ Specify results: _____
___ Pending (specify): _____
___ Not performed: _____
___ Not applicable
___ Other (specify): _____

COMMENTS

Comment(s): _____

Explanatory Notes

A. Procedure/Tissue Processing

Fresh tissue versus formalin 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. 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,[1,2,3,4] frozen tissue may be needed to enter patients into treatment protocols. 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 or molecular analysis. Microbiology specimens should go directly from operating room to microbiology laboratory. Fresh tissue can be sent for flow cytometry, if indicated. Additional cores for special studies, including at least two blocks of cores for permanent H&E, immunohistochemistry, molecular/genetic studies, should be collected at the time the specimen is received. If decalcification is required, best to use EDTA rather than harsh acid decalcification, for additional studies or to put soft tissue into a non-decalcified block for additional studies.

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 after reserving sufficient tissue for histologic examination. This frozen tissue should ideally be stored at minus seventy (-70° C) and can be shipped on dry ice to facilities that perform molecular analysis.

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 are usually 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. Mostly rapid or intraoperative review is used for assessing viable tissue and triage.

WHO Classification of Tumors
Classification of tumors should be made according to the World Health Organization (WHO) classification of soft tissue tumors, 5th edition.[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 World Health Organization (WHO) classification of soft tissue tumors, 5th edition,[1] edited to only include soft tissue tumors of intermediate potential, i.e., locally aggressive (including significant and problematic local recurrence and/or requiring oncologic management) and rarely metastasizing as well as malignant soft tissue tumors. The full reference contains information on additional soft tissue tumors. Table 1 lists the intermediate and malignant soft tissue tumors that demonstrate diagnostic molecular findings. Generally, the term well-differentiated liposarcoma has been used for groin/retroperitoneum and deep skeletal muscle tumors, due to their increased potential for de-differentiation, whereas atypical lipomatous tumor is preferred for superficial subcutaneous tumors with the same histology since these are generally cured by limited excision.

Table 1: Subset of Soft Tissue Tumors that Carry Diagnostic Molecular/Genetic Findings
Note: This list is not exhaustive. Only the most common molecular finding(s) is listed. Many molecular findings are not unique to a single entity.

Tumor	**Most common molecular genetic finding**
Atypical spindle cell/pleomorphic lipomatous tumor	*RB1* deletion
Atypical lipomatous tumor/well-differentiated liposarcoma	*MDM2* amplification
Dedifferentiated liposarcoma	*MDM2* amplification
Myxoid liposarcoma	*FUS/EWSR1::DDIT3* fusion
Solitary fibrous tumor	*NAB2::STAT6* fusion
Desmoid-type fibromatosis	*CTNNB1* or *APC* point mutation
Giant cell fibroblastoma	*COL1A1::PDGFB* fusion
Dermatofibrosarcoma protuberans	*COL1A1::PDGFB* fusion
Fibrosarcomatous dermatofibrosarcoma protuberans	*COL1A1::PDGFB* fusion
Inflammatory myofibroblastic tumor	*ALK* fusion (various partners)
Superficial CD34-positive fibroblastic tumor	*PRDM10* fusion (various partners)
Infantile fibrosarcoma	*ETV6::NTRK3* fusion
Low-grade fibromyxoid sarcoma	*FUS::CREB3L2* fusion
Sclerosing epithelioid fibrosarcoma	*EWSR1::CREB3L1* fusion
Malignant tenosynovial giant cell tumor	*CSF1* fusion
Pseudomyogenic hemangioendothelioma	*SERPINE1/ACTB::FOSB* fusion
Epithelioid hemangioendothelioma	*WWTR1::CAMTA1* fusion
	YAP1::TFE3 fusion
Angiosarcoma	*MYC* amplification (irradiation/lymphedema-associated angiosarcoma)
Malignant glomus tumor	*MIR143::NOTCH2* fusion *BRAF* mutation, *GLI-1* fusion
EBV-associated smooth muscle tumor	EBER transcripts
Alveolar rhabdomyosarcoma	*PAX3/7::FOXO1* fusion
Spindle cell/sclerosing rhabdomyosarcoma	*VGLL2/NCOA2* fusion (various partners)
	MYOD1 mutation
	EWSR1/FUS::TFCP2, MEIS1::NCOA2
Malignant melanotic nerve sheath tumor	*PRKAR1A* mutation
Hemosiderotic fibrolipomatous tumor	*TGFBR3* and *OGA* (*MGEA5*) breakpoints
Myxoinflammatory fibroblastic sarcoma	*TGFBR3* and *OGA* (*MGEA5*) breakpoints; *BRAF* fusion, *VGLL3* amplification
Pleomorphic hyalinizing angiectatic tumor of soft part	*OGA (MGEA5), TGFBR3* breakpoints

Phosphaturic mesenchymal tumor	*FN1::FGFR1* fusion
Angiomatoid fibrous histiocytoma	*EWSR1/FUS::ATF1/CREB1* fusion
Ossifying fibromyxoid tumor	*PHF1* fusion (various partners)
Myoepithelial carcinoma	*EWSR1/FUS::POU5F1/PBX1, PLAG1* fusion (various partners)
NTRK-fusion tumor	*NTRK1/2/3* fusion (various partners)
ALK-fusion tumor including inflammatory myofibroblastic tumor and epithelioid inflammatory myofibroblastic tumor	*ALK* (various partners)
BRAF-fusion tumor	*BRAF* (various partners with second fusion)
Synovial sarcoma	*SS18::SSX1/2/4* fusion
Epithelioid sarcoma	*SMARCB1* deletion
Alveolar soft part sarcoma	*ASPSCR1::TFE3* fusion
Clear cell sarcoma of soft tissue	*EWSR1::ATF1/CREB1* fusion
Extraskeletal myxoid chondrosarcoma	*EWSR1/TAF15::NR4A3* fusion
Mesenchymal chondrosarcoma	*HEY1::NCOA2* fusion
Desmoplastic small round cell tumor	*EWSR1::WT1* fusion
Extrarenal rhabdoid tumor	*SMARCB1* deletion
PEComa	*TSC2* mutation, *TFE3* fusion (various partners)
Ewing sarcoma	*EWSR1/FUS::FLI1/ERG* fusion
Round cell sarcoma with *EWSR1::non-ETS* fusion	*EWSR1::PATZ1, FUS/EWSR1::NFATC2*
CIC-rearranged sarcoma	*CIC::DUX4* fusion
BCOR altered sarcoma	*BCOR::CCNB3* fusion *BCOR* ITD (infants)
Epithelioid malignant peripheral nerve sheath tumor	*SMARCB1* deletion

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).

D. Tyrosine Kinase Fusion Sarcomas

While fusions involving the *RAS::MAPK* pathway are rare in mesenchymal tumors, these tumors have driver alterations in genes that encode tyrosine kinases and may respond to therapy targeting *NTRK, ALK, BRAF, RET, RAF, FGFR1, or ABL1*, etc. Notably, *NTRK* tumors fused with *KANK1* or *TPR* have been demonstrated to exhibit higher-grade appearance, including spindled and pleomorphic characteristics, accompanied by necrosis and mitoses, leading to unfavorable outcomes. Consequently, it is advisable to conduct comprehensive RNA-based Next-Generation Sequencing (NGS) for fusions, particularly in spindled pleomorphic tumors occurring in individuals under 50 years old, especially those in soft tissue or intraosseous locations. This recommendation is especially pertinent with tumors that have variable ovoid spindled to epithelioid morphology, variable collagenous to myxoid stroma, variable gaping to staghorn vasculature, and specifically focal CD34 and/or focal S100 protein, without any staining for SOX10. In these tumors, BRAF, ALK, or panTrk or no specific immunostaining is identified.[1,2,3,4,5,6,7,8,9,10]

References

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2. Hung YP, Fletcher CDM, Hornick JL. Evaluation of pan-TRK immunohistochemistry in infantile fibrosarcoma, lipofibromatosis-like neural tumour and histological mimics. *Histopathology.* 2018;73(4):634-644.
3. Agaram NP, Zhang L, Sung YS, et al. Recurrent NTRK1 Gene Fusions Define a Novel Subset of Locally Aggressive Lipofibromatosis-like Neural Tumors. *Am J Surg Pathol.* 2016 Oct;40(10):1407-16.
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5. Fanburg-Smith JC, Smith JD, Flemming DJ. Bone and soft tissue tumors: clinicoradiologic-pathologic molecular-genetic correlation of novel fusion spindled, targetable-ovoid, giant-cell-rich, and round cell sarcomas. *Skeletal Radiol.* 2023 Mar;52(3):517-540. doi: 10.1007/s00256-022-04244-w. Epub 2022 Dec 21. PMID: 36542130.
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E. Grading

Unlike with other organ systems, the clinical 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 separately grades 2 to 3 (effectively low and high, respectively) 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 (i.e., low and high-grade) is encouraged. In many instances, the histologic type of sarcoma will readily permit this distinction (i.e., 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 may 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 total score
Grade 2: 4 or 5 total score
Grade 3: 6 to 8 total score

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 (e.g., well-differentiated liposarcoma, well-differentiated leiomyosarcoma)
Score 2: Sarcomas for which histologic typing is certain (e.g., myxoid liposarcoma, myxofibrosarcoma)
Score 3: Embryonal sarcomas and undifferentiated sarcomas, synovial sarcomas, and sarcomas of uncertain 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
Myxoid liposarcoma	2
Conventional leiomyosarcoma	2
Myxofibrosarcoma	2
High-grade myxoid (round cell) liposarcoma	3
Pleomorphic liposarcoma	3

Histologic Type	Score
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: Tumors not included in the list, such as desmoplastic round cell tumor, alveolar rhabdomyosarcoma, and intimal sarcoma, are by definition high grade. Other tumors such as alveolar soft part sarcoma, clear cell sarcoma, epithelioid sarcoma, extraskeletal myxoid chondrosarcoma, low-grade fibromyxoid sarcoma, and sclerosing epithelioid fibrosarcoma are not assigned FNCLCC grade but may demonstrate late metastasis.[4,7] Grade is not used for angiosarcoma, as deceptively bland angiosarcomas may behave poorly, thus all are considered clinically "high-grade." The prognostic significance of FNCLCC grading in malignant peripheral nerve sheath tumor is unclear. Other tumors such as ossifying fibromyxoid tumor and solitary fibrous tumor are best categorized by risk stratification parameters (see Table 5).
Modified with permission from Coindre JM.[3]

Mitosis Count:
The count is made in the most mitotically active area, away from areas of necrosis. Mitoses may be scored as either 10 consecutive high-power fields (HPF) (40X objective) or in an area of 1 mm^2. If whole slide digital pathology is used, 1 mm^2 is measured directly on the digital image. The mitotic count is converted to a score (Table 3). If the mitotic rate is close to the cutoff between mitotic scores, the count should be repeated.

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 be higher. Therefore, pathologists are encouraged to either correct for the area of their 40X objective or score mitoses per 1 mm^2.

1) To correct for the area of a 40X objective: determine the 40X field area (Table 4) 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.
2) To determine to number of 40X fields equivalent to 1 mm^2, consult Table 4.

Table 3. Mitotic Count Score Equivalence

Mitotic Score	# mitosis / 10 HPF (1 HPF= 0.1734 mm^2)	# mitosis / 1 mm^2 (see table 4)
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

Table 4. Approximate number of fields per 1 mm^2 based on field diameter
Formula to calculate the area of one high-power field of a specific microscope = pr^2/total magnification = (½ field diameter)^2 x p/total magnification
Formula to calculate the field diameter = Objective Field Number/Objective Magnification

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.

Table 5. Risk Stratification for Solitary Fibrous Tumor[9]

Risk factor	Score
Age	
<55	0
>55	1
Tumor size (cm)	
<5	0
5 to <10	1
10 to <15	2
≥15	3
Mitotic count (/10 high-power fields)	
0	0
1-3	1
≥4	2
Tumor necrosis	
<10%	0
≥10%	1
Risk class	**Total score**
Low	0-3
Intermediate	4-5
High	6-7

As with other sarcoma risk assessment and grading schemes, evaluation of core biopsies may result in inappropriately lower risk scores, due to sampling bias. Full application of the risk stratification system would be reserved for carefully sampled resection specimens.

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F. Tumor Extent and Depth of Invasion

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. Tumor extent and depth of invasion for trunk and extremity tumors are included in this protocol as optional data elements.

References

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

G. Lymphatic and/or Vascular Invasion

Lymphatic and Vascular Invasion (LVI) indicates whether microscopic lymphatic and/or vascular 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.