

Protocol for the Examination of Specimens from Patients with Tumors of Soft Tissue

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

Based on AJCC/UICC TNM, 7th edition

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Procedures

- Biopsy
- Resection

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We dedicate this work to our esteemed and beloved colleague, Dr. Steve Qualman, who passed away during the writing of this document. Steve was a tireless investigator, academic leader, and compassionate physician who made significant and long-lasting contributions to our understanding of the pathobiology of sarcomas. He established the Biopathology Center (BPC) at Columbus Children's Hospital, which currently houses over 1,000,000 specimens and is an integral component of the Cooperative Human Tissue Network (CHTN) critical for translational research. Over the years he was an integral part of and force behind the Intergroup Rhabdomyosarcoma Studies, which produced the most comprehensive and authoritative work in this disease. His expertise, reflected in this body of work, has helped countless pathologists, clinicians, and childhood patients world-wide. Even though Steve is no longer with us, his legacy lives on.

Important Note

These recommendations are designed to be applied principally to soft tissue sarcomas in teenagers and adults, since pediatric sarcomas are, in general, treated under strict protocols that may differ significantly from the recommendations supplied herein.¹

Surgical Pathology Cancer Case Summary (Checklist)

Protocol web posting date: October 2009

SOFT TISSUE: Biopsy

Select a single response unless otherwise indicated.

Procedure (Note A)

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

Tumor Site

- Specify (if known): _____
- ☐ Not specified

Tumor Size (Note B)

- Greatest dimension: _____ cm
- *Additional dimensions: _____ x _____ cm
- ☐ Cannot be determined (see "Comment")

Macroscopic Extent of Tumor (select all that apply)

- ☐ Superficial
 - ☐ Dermal
 - ☐ Subcutaneous/suprafascial
- ☐ Deep
 - ☐ Fascial
 - ☐ Subfascial
 - ☐ Intramuscular
 - ☐ Mediastinal
 - ☐ Intra-abdominal
 - ☐ Retroperitoneal
 - ☐ Head and neck
 - ☐ Other (specify): _____
- ☐ Cannot be determined

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

- Specify: _____
- ☐ Cannot be determined

Mitotic Rate (Note D)

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

* Data elements with asterisks are not required. However, these elements may be clinically important, but are not yet validated or regularly used in patient management.

Necrosis (Note D)

- ☐ Not identified
☐ Present
 Extent: ____%
☐ Cannot be determined

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

- ☐ Grade 1
☐ Grade 2
☐ Grade 3
☐ Ungraded sarcoma
☐ Cannot be determined

Margins (for excisional biopsy only) (Note E)

- ☐ Cannot be assessed
☐ Margins negative for sarcoma
 Distance of sarcoma from closest margin: ____ cm
 Specify margin: _____
 Specify other close (less than 2.0 cm) margin(s): _____
☐ Margin(s) positive for sarcoma
 Specify margin(s): _____

***Lymph-Vascular Invasion (Note F)**

- * ☐ Not identified
* ☐ Present
* ☐ Indeterminate

***Additional Pathologic Findings**

*Specify: _____

Ancillary StudiesImmunohistochemistry

Specify: _____
☐ Not performed

Cytogenetics

Specify: _____
☐ Not performed

Molecular Pathology

Specify: _____
☐ Not performed

* Data elements with asterisks are not required. However, these elements may be clinically important, but are not yet validated or regularly used in patient management.

Prebiopsy Treatment (select all that apply)

- ☐ No therapy
- ☐ Chemotherapy performed
- ☐ Radiation therapy performed
- ☐ Therapy performed, type not specified
- ☐ Unknown

Treatment Effect (Note G)

- ☐ Not identified
- ☐ Present
 - *Specify percentage of viable tumor: _____%
- ☐ Cannot be determined

***Comment(s)**

* Data elements with asterisks are not required. However, these elements may be clinically important, but are not yet validated or regularly used in patient management.

Surgical Pathology Cancer Case Summary (Checklist)

Protocol web posting date: October 2009

SOFT TISSUE: Resection

Select a single response unless otherwise indicated.

Procedure (Note H)

- ☐ Intralesional resection
- ☐ Marginal resection
- ☐ Wide resection
- ☐ Radical resection
- ☐ Other (specify): _____
- ☐ Not specified

Tumor Site

- Specify (if known): _____
- ☐ Not specified

Tumor Size

- Greatest dimension: ____ cm
- *Additional dimensions: ____ x ____ cm
- ☐ Cannot be determined (see "Comment")

Macroscopic Extent of Tumor (select all that apply)

- ☐ Superficial
 - ☐ Dermal
 - ☐ Subcutaneous/suprafascial
- ☐ Deep
 - ☐ Fascial
 - ☐ Subfascial
 - ☐ Intramuscular
 - ☐ Mediastinal
 - ☐ Intra-abdominal
 - ☐ Retroperitoneal
 - ☐ Head and neck
 - ☐ Other (specify): _____
- ☐ Cannot be determined

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

- Specify: _____
- ☐ Cannot be determined

Mitotic Rate (Note D)

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

* Data elements with asterisks are not required. However, these elements may be clinically important, but are not yet validated or regularly used in patient management.

Necrosis (macroscopic or microscopic) (Note D)

- ☐ Not identified
☐ Present
 Extent: ____%

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

- ☐ Grade 1
☐ Grade 2
☐ Grade 3
☐ Ungraded sarcoma
☐ Cannot be determined

Margins (Note E)

- ☐ Cannot be assessed
☐ Margins negative for sarcoma
 Distance of sarcoma from closest margin: ____ cm
 Specify margin: _____
 Specify other close (less than 2.0 cm) margin(s): _____
☐ Margin(s) positive for sarcoma
 Specify margin(s): _____

***Lymph-Vascular Invasion (Note F)**

- * ☐ Not identified
 * ☐ Present
 * ☐ Indeterminate

Pathologic Staging (pTNM) (Note J)

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

- ☐ m (multiple)
☐ r (recurrent)
☐ y (post-treatment)

Primary Tumor (pT)

- ☐ pTX: Primary tumor cannot be assessed
☐ pT0: No evidence of primary tumor
☐ pT1a: Tumor 5 cm or less in greatest dimension, superficial tumor
☐ pT1b: Tumor 5 cm or less in greatest dimension, deep tumor
☐ pT2a: Tumor more than 5 cm in greatest dimension, superficial tumor
☐ pT2b: Tumor more than 5 cm in greatest dimension, deep tumor

Regional Lymph Nodes (pN) (Notes J and K)

- ☐ pNX: Regional lymph nodes cannot be assessed
☐ pN0: No regional lymph node metastasis
☐ pN1: Regional lymph node metastasis
 Specify: Number examined: ____
 Number positive: ____

* Data elements with asterisks are not required. However, these elements may be clinically important, but are not yet validated or regularly used in patient management.

Distant Metastasis (pM) (Note J)☐ Not applicable☐ pM1: Distant metastasis

*Specify site(s), if known: _____

***Additional Pathologic Findings**

*Specify: _____

Ancillary StudiesImmunohistochemistry

Specify: _____

☐ Not performedCytogenetics

Specify: _____

☐ Not performedMolecular Pathology

Specify: _____

☐ Not performed**Preresection Treatment (select all that apply)**☐ No therapy☐ Chemotherapy performed☐ Radiation therapy performed☐ Therapy performed, type not specified☐ Unknown**Treatment Effect (Note G)**☐ Not identified☐ Present

*Specify percentage of viable tumor: _____%

☐ Cannot be determined***Comment(s)**

* Data elements with asterisks are not required. However, these elements may be clinically important, but are not yet validated or regularly used in patient management.

Explanatory Notes

A. Tissue Processing

Fixation

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

Tissue Submission for Histologic Evaluation

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

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

Molecular Studies

It is important to snap freeze a small portion of tissue whenever possible. This tissue can be used for a variety of molecular analyses for tumor-specific molecular translocations (see Table 1) that help in classifying soft tissue tumors.^{2,3} In addition, treatment protocols increasingly require fresh tissue for correlative studies. Approximately 1 cm³ of fresh tissue (less is acceptable for small specimens, including core biopsies) should be cut into small, 0.2-cm fragments, reserving sufficient tissue for histologic examination. This frozen tissue should ideally be stored at –70°C and can be shipped on dry ice to facilities that perform molecular analysis.

Table 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)	<i>FUS-ATF1</i> fusion
	t(12;22)(q13;q12)	<i>EWSR1-ATF1</i> fusion
	t(2;22)(q33;q12)	<i>EWSR1-CREB1</i> fusion
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22;q12)	<i>EWS-NR4A3</i> fusion
	t(9;17)(q22;q11)	<i>TAF2N-NR4A3</i> fusion
	t(9;15)(q22;q21)	<i>TCF12-NR4A3</i> fusion
Clear cell sarcoma	t(12;22)(q13;q12)	<i>EWSR1-ATF1</i> fusion
	t(2;22)(q33;q12)	<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
	t(17;22)(q21;q13)	<i>COL1A1-PDGFB</i> fusion
Ewing sarcoma/PNET	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)(q12q12)	<i>EWSR1-ZSG</i> fusion
	t(16;21)(p11;q22)	<i>FUS-ERG</i> fusion
Fibrosarcoma, infantile	t(12;15)(p13;q26)	<i>ETV6-NTRK3</i> fusion
	Trisomies 8, 11, 17, and 20	
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
Leiomyosarcoma	Complex with frequent deletion of 1p	
Liposarcoma		Amplification of <i>MDM2</i> , <i>CDK4</i> , and others
Well-differentiated	Ring form of chromosome 12	<i>TLS-DDIT3</i> fusion
Myxoid/Round cell	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
Malignant peripheral nerve sheath tumor	Complex	
Myxofibrosarcoma (myxoid MFH)	Ring form of chromosome 12	
Rhabdoid tumor	Deletion of 22q	<i>INI1</i> inactivation
Rhabdomyosarcoma		
Alveolar	t(2;13)(q35;q14)	<i>PAX3-FOXO1A</i> fusion
	t(1;13)(p36;q14), double minutes	<i>PAX7-FOXO1A</i> fusion
	t(2;2)(q35;p23)	<i>PAX3-NCOA1</i> fusion
		<i>PAX3-AFX</i> fusion
Embryonal	Trisomies 2q, 8 and 20	Loss of heterozygosity at 11p15
Synovial sarcoma		
Monophasic	t(X;18)(p11;q11)	<i>SS18-SSX1</i> , <i>SS18-SSX2</i> or

Histologic Type	Cytogenetic Events	Molecular Events
Biphasic	t(X;18)(p11;q11)	SS18-SSX4 fusion Predominantly SS18-SSX1 fusion

MFH, malignant fibrous histiocytoma; PNET, primitive neuroectodermal tumor.

B. Tumor Size

In cases of nonexcisional biopsy (eg, core biopsy, incisional biopsy) the tumor size cannot be determined on pathologic grounds; therefore, imaging data (computed tomography [CT], magnetic resonance imaging [MRI], etc) can be used instead.

C. Histologic Classification

Intraoperative Consultation

Histologic classification of soft tissue tumors is sufficiently complex that, in many cases, it is unreasonable to expect a precise classification of these tumors based on an intraoperative consultation. A complete understanding of the surgeon's treatment algorithm is recommended before rendering a frozen section diagnosis. Intraoperative consultation is useful in assessing if "lesional" tissue is present and in constructing a differential diagnosis that can direct the proper triage of tissue for flow cytometry (lymphoma), electron microscopy, and molecular studies/cytogenetics. Tissue triage optimally is performed at the time of frozen section. In many cases, it is important that a portion of tissue be submitted for ancillary studies, even from fine-needle aspiration (FNA) and core needle biopsy specimens, after sufficient tissue has been submitted for histologic evaluation.

Tumor Classification from Biopsies

It is not always possible to classify soft tissue tumors precisely based on biopsy material, especially FNA and core needle biopsy specimens. Although pathologists should make every attempt to classify lesions in small biopsy specimens, on occasion stratification into very basic diagnostic categories, such as lymphoma, carcinoma, melanoma, and sarcoma, is all that is possible. In some cases, precise classification is only possible in open biopsies or resection specimens.

WHO Classification of Tumors

Classification of tumors should be made according to the World Health Organization (WHO) classification of soft tissue tumors listed below.⁴ As part of the latest WHO classification of soft tissue tumors, a recommendation was made to divide tumors into 4 categories: benign, intermediate (locally aggressive), intermediate (rarely metastasizing), and malignant.

WHO Classification of Soft Tissue Tumors of Intermediate Malignant Potential and Malignant Soft Tissue Tumors

Adipocytic Tumors

Intermediate (locally aggressive)

Atypical lipomatous tumor / Well-differentiated liposarcoma

Malignant

Dedifferentiated liposarcoma

Myxoid/round cell liposarcoma

- Pleomorphic liposarcoma
- Mixed-type liposarcoma
- Liposarcoma, not otherwise specified

Fibroblastic / Myofibroblastic Tumors

- Intermediate (locally aggressive)
 - Superficial fibromatoses (palmar / plantar)
 - Desmoid-type fibromatoses
 - Lipofibromatosis
- Intermediate (rarely metastasizing)
 - Solitary fibrous tumor and hemangiopericytoma (including lipomatous hemangiopericytoma)
 - Inflammatory myofibroblastic tumor
 - Low grade myofibroblastic sarcoma
 - Myxoinflammatory fibroblastic sarcoma
 - Infantile fibrosarcoma
- Malignant
 - Adult fibrosarcoma
 - Myxofibrosarcoma
 - Low grade fibromyxoid sarcoma/hyalinizing spindle cell tumor
 - Sclerosing epithelioid fibrosarcoma

So-called Fibrohistiocytic Tumors

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

Smooth Muscle Tumors

- Malignant
 - Leiomyosarcoma

Skeletal Muscle Tumors

- Malignant
 - Embryonal rhabdomyosarcoma (including spindle cell, botryoid, anaplastic)
 - Alveolar rhabdomyosarcoma (including solid, anaplastic)
 - Pleomorphic rhabdomyosarcoma

Vascular Tumors

- Intermediate (locally aggressive)
 - Kaposiform hemangioendothelioma[#]
- Intermediate (rarely metastasizing)
 - Retiform hemangioendothelioma
 - Papillary intralymphatic angioendothelioma
 - Composite hemangioendothelioma

Malignant

- Epithelioid hemangioendothelioma
- Angiosarcoma of soft tissue

Tumors of Peripheral Nerves

Malignant

- Malignant peripheral nerve sheath tumor
- Epithelioid malignant peripheral nerve sheath tumor

Chondro-osseous Tumors

Malignant

- Mesenchymal chondrosarcoma
- Extraskeletal osteosarcoma

Tumors of Uncertain Differentiation

Intermediate (rarely metastasizing)

- Angiomatoid fibrous histiocyoma
- Ossifying fibromyxoid tumor (including atypical / malignant)
- Mixed tumour / Myoepithelioma / Parachordoma

Malignant

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

Since the last edition of the WHO classification, 2 cases of well-documented regional metastasis of kaposiform hemangioendothelioma have been reported,⁵ raising the issue of whether or not kaposiform hemangioendothelioma might be more appropriately included in the category of “intermediate (rarely metastasizing)” instead of “intermediate (locally aggressive).” This will undoubtedly be addressed in the next WHO classification of tumors of soft tissue.

D. Grading

Unlike with other organ systems, the staging of soft tissue sarcomas is largely determined by grade. Unfortunately, there is no generally agreed-upon scheme for grading soft tissue tumors.⁶ The most widely used soft tissue grading systems are the French Federation of Cancer Centers Sarcoma Group (FNCLCC) and National Cancer Institute (NCI) systems.^{7,8} Both systems have 3 grades and are based on mitotic activity, necrosis, and differentiation, and are highly correlated with prognosis.⁹ 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.⁹ Other systems with 2 or 4 grades also have been used. The seventh edition of the *AJCC Cancer Staging Manual*¹⁰ adopted the FNCLCC grading system. The revision of the American Joint Committee on Cancer (AJCC) staging system incorporates a 3-tiered grading system; however, grade 1 and grades 2 to 3 (effectively low and high) are used for staging groups. Accurate grading requires an adequate sample of tissue, which is not always available from FNA or core needle biopsy or in tumors previously treated with radiation or chemotherapy. However, given the importance of grade in staging and treatment, efforts to separate sarcomas on the basis of needle biopsies into at least 2 tiers (ie, low and high grade) is encouraged. In many instances the histologic type of sarcoma will readily permit this distinction (ie, Ewing sarcoma/PNET, pleomorphic liposarcoma), whereas in less obvious instances the difficulty of assigning grade should be noted. In general, multiple needle core biopsies exhibiting a high-grade sarcoma can be regarded as high grade, since the probability of subsequent downgrading is remote, but limited core biopsies of low-grade sarcoma carry a risk of upgrading.

FNCLCC Grading

The FNCLCC grade is based on 3 parameters: differentiation, mitotic activity, and necrosis. Each of these parameters receives a score: differentiation (1 to 3), mitotic activity (1 to 3), and necrosis (0 to 2). The scores are summed to produce a grade.

Grade 1: 2 or 3

Grade 2: 4 or 5

Grade 3: 6 to 8

Differentiation: Tumor differentiation is scored as follows (see Table 2).

Score 1: Sarcomas closely resembling normal, adult mesenchymal tissue

Score 2: Sarcomas of certain histologic type

Score 3: Synovial sarcomas, embryonal sarcomas, undifferentiated sarcomas, and sarcomas of doubtful tumor type

Tumor differentiation is the most problematic aspect of the FNCLCC system. Its use is subjective and does not include every subtype of sarcoma. Nevertheless, it is an integral part of the system, and an attempt should be made to assign a differentiation score.

Table 2. Tumor Differentiation Score According to Histologic Type in the Updated Version of the French Federation of Cancer Centers Sarcoma Group System

Tumor Differentiation	
Histologic Type	Score
Well-differentiated liposarcoma	1
Myxoid liposarcoma	2
Round cell liposarcoma	3
Pleomorphic liposarcoma	3
Dedifferentiated liposarcoma	3

Histologic Type	Score
Fibrosarcoma	2
Myxofibrosarcoma (malignant fibrous histiocytoma [MFH])	2
Typical storiform MFH (sarcoma, not otherwise specified [NOS])	3
MFH, pleomorphic type (patternless pleomorphic sarcoma)	3
Giant cell and inflammatory MFH (pleomorphic sarcoma, NOS, with giant cells or inflammatory cells)	3
Well-differentiated leiomyosarcoma	1
Conventional leiomyosarcoma	2
Poorly differentiated / pleomorphic / epithelioid leiomyosarcoma	3
Biphasic / monophasic synovial sarcoma	3
Poorly differentiated synovial sarcoma	3
Pleomorphic rhabdomyosarcoma	3
Mesenchymal chondrosarcoma	3
Extraskeletal osteosarcoma	3
Ewing sarcoma / primitive neuroectodermal tumor	3
Malignant rhabdoid tumor	3
Undifferentiated sarcoma	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

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Mitosis Count: The count is made in the most mitotically active area in 10 successive high-power fields (HPF) (1 HPF X 400 = 0.1734 mm²) (use the X40 objective).

Score 1: 0 to 9 mitoses per 10 HPF

Score 2: 10 to 19 mitoses per 10 HPF

Score 3: 20 or more mitoses per 10 HPF

Tumor Necrosis: Determined on histologic sections.

Score 0: No tumor necrosis

Score 1: Less than or equal to 50% tumor necrosis

Score 2: More than 50% tumor necrosis

TNM Grading

The seventh edition of the American Joint Committee on Cancer (AJCC) and International Union Against Cancer (UICC) staging system for soft tissue tumors recommends the FNCLCC 3-grade system but effectively collapses into high grade and low grade.^{10,11} This means that FNCLCC grade 2 tumors are considered “high grade” for the purposes of stage grouping.

E. Margins

It has been recommended that for all margins <2 cm, the distance of the tumor from the margin be reported in centimeters.¹² However, there is a lack of agreement on this issue. We recommend specifying the location of all margins <2 cm and the distance of the closest margin that is <2 cm. Margins from soft tissue tumors should be taken as *perpendicular* sections, if possible. If bones are present in the specimen and are not involved by tumor, or the tumor is >2 cm from the margin, the marrow can be scooped out and submitted as a margin.

F. Lymph-Vascular Invasion

Lymph-vascular invasion (LVI) indicates whether microscopic lymph-vascular invasion is identified. LVI includes lymphatic invasion, vascular invasion, or lymph-vascular invasion. By AJCC/UICC convention, LVI does not affect the T category indicating local extent of tumor unless specifically included in the definition of a T category.

G. Response to Chemotherapy/Radiation Therapy Effect

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

H. Definition of Procedures

The following is a list of guidelines to be used in defining what type of procedure has been performed.

Intralesional Resection

Leaving gross or microscopic tumor behind. Partial debulking or curettage are examples or when microscopic tumor is left at the margin unintentionally in an attempted marginal resection.

Marginal Resection

Removing the tumor and its pseudocapsule with a relatively small amount of adjacent tissue. There is no gross tumor at the margin; however, there is a high likelihood that microscopic tumor is present. If microscopic disease is identified at the margin, then it is an intralesional resection. Note that occasionally a surgeon will perform an “excisional” biopsy, which effectively accomplishes the same thing as a marginal resection.

Wide Resection

An intracompartmental resection. The tumor is removed with pseudocapsule and a cuff of normal tissue surrounding the neoplasm, but without the complete removal of an entire muscle group, compartment, or bone.

Radical Resection

The removal of an entire soft tissue compartment (for example, anterior compartment of the thigh, the quadriceps) or bone, or the excision of the adjacent muscle groups if the tumor is extracompartmental.

I. Histological Classification of Treated Lesions

Because of extensive treatment effects, such as necrosis, fibrosis, and chemotherapy-induced and radiation-induced pleomorphism, it may not be possible to classify some lesions that were either never biopsied or where the biopsy was insufficient for a precise diagnosis.

J. TNM and Stage Groupings

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

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

Definition of pT

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

Depth

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

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

1. Superficial
 - a. Tumor is located entirely in the subcutaneous tissues without any involvement of the muscular fascia. In these cases, pretreatment imaging studies demonstrate a subcutaneous tumor without involvement of muscle, and excisional biopsy pathology specimen demonstrate a tumor located within the subcutaneous tissues without invasion into fascia (adopted from the seventh edition of the *AJCC Cancer Staging Manual*).
2. Deep
 - a. Tumor is located partly or completely within 1 or more muscle groups within the extremity. Deep tumors may extend through the muscular fascia into the

- subcutaneous tissues or even to the skin, but the critical criterion is location of any portion of the tumor within the muscular compartments of the extremity or invasion of the muscular fascia. In these cases, pretreatment imaging studies demonstrate a tumor located completely or partly within the muscular compartments of the extremity. Finally, on pathologic evaluation, any tumor that is superficial to the muscular fascia, but invades the fascia, is considered deep (adopted from the seventh edition of the *AJCC Cancer Staging Manual*).
- b. All intraperitoneal visceral lesions, retroperitoneal lesions, intrathoracic lesions, and the majority of head and neck tumors are considered deep.
3. Depth is evaluated in relation to tumor size (T)
- a. Tumor 5 cm or less: T1a = superficial; T1b = deep.
 - b. Tumor greater than 5 cm: T2a = superficial; T2b = deep.

Regional Lymph Nodes (pN)

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

Restaging of Recurrent Tumors

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

TNM Descriptors

For identification of special cases of TNM or pTNM classifications, the “m” suffix and the “y” and “r” prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

The “m” suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

The “y” prefix indicates those cases in which classification is performed during or following initial multimodality therapy (ie, neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a “y” prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The “y” categorization is not an estimate of tumor prior to multimodality therapy (ie, before initiation of neoadjuvant therapy).

The “r” prefix indicates a recurrent tumor when staged after a documented disease-free interval, and is identified by the “r” prefix: rTNM.

T Category Considerations

Superficial tumor is located exclusively above the superficial fascia without invasion of the fascia; deep tumor is located either exclusively beneath the superficial fascia or

superficial to the fascia with invasion of or through the fascia. Retroperitoneal, mediastinal, and pelvic sarcomas are classified as deep tumors.

N Category Considerations

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

M Category Considerations

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

Stage Groupings

Stage IA	T1a	N0	NX	M0	G1	Low
	T1b	N0	NX	M0	G1	Low
Stage IB	T2a	N0	NX	M0	G1	Low
	T2b	N0	NX	M0	G1	Low
Stage IIA	T1a	N0	NX	M0	G2	High
	T1b	N0	NX	M0	G2	High
Stage IIB	T2a	N0	NX	M0	G2	High
Stage III	T2b	N0-1	NX	M0	G3	High
Stage IV	Any T	Any N		M1	Any G	High or Low

Additional Descriptors

Residual Tumor (R)

Tumor remaining in a patient after therapy with curative intent (eg, surgical resection for cure) is categorized by a system known as R classification, shown below.

RX	Presence of residual tumor cannot be assessed
R0	No residual tumor
R1	Microscopic residual tumor
R2	Macroscopic residual tumor

For the surgeon, the R classification may be useful to indicate the known or assumed status of the completeness of a surgical excision. For the pathologist, the R classification is relevant to the status of the margins of a surgical resection specimen. That is, tumor involving the resection margin on pathologic examination may be assumed to correspond to residual tumor in the patient and may be classified as macroscopic or microscopic according to the findings at the specimen margin(s).

K. Lymph Nodes

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

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