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

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

This protocol does not apply to carcinosarcoma, lymphoma, pediatric Ewing sarcoma, pediatric rhabdomyosarcoma, Kaposi sarcoma, gastrointestinal stromal tumor, uterine sarcoma.

Based on:

AJCC/UICC TNM, 8th edition
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None

Summary of Changes:

This protocol is revised to the 8th edition of the AJCC Cancer Staging Manual and the current version of the CAP Cancer Protocol SoftTissue 4.0.0.0.

Procedures Covered in this Protocol:

- Biopsy
- Resection

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The purpose of the Protocols is to support Laboratory Personnel engaged in the macroscopic examination of cancer resection specimens. The Protocols are based on specified relevant source documents, drafted by pathologists' assistant experts, and supported by information provided by the College of American Pathologists (CAP) and the American Joint Committee on Cancer (AJCC). These Protocols are intended to serve patients by ensuring that the macroscopic examination of cancer resection specimens is compliant with CAP Cancer Protocols, the AJCC Cancer Staging Manual, and provide optimization of the pre-analytic steps necessary to promote appropriate molecular studies.

The AAPA cautions that the use of the Protocols in practice may require the use of additional considerations that are beyond the scope of the Protocols. The AAPA does not offer medical advice or diagnoses, or engage in the practice of medicine. The information provided in the Protocols is not intended or implied to be a substitute for the Laboratory Personnel's own training, professional medical opinion, diagnosis, or treatment advice. All content, including text, graphics, images and information contained in the Protocols are for the above stated purposes only. Laboratory Personnel are encouraged to confirm any information provided in these Protocols with other sources. The inclusion of a product name, organization, or service in an AAPA publication, including without limitation the Protocols, should not be construed as an endorsement of such product, organization, or service, nor is failure to include the name of a product, organization or service to be construed as disapproval.

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Ambiguous Terminology:

Excisional biopsy, marginal resection, and wide resections all refer to the complete removal of the tumor and its pseudocapsule with some adjacent tissue.

Molecular Considerations, Cytogenetics, and Electron Microscopy:

Soft tissue tumors should be received in the laboratory in the fresh state due to ancillary studies requiring fresh tissue.

First priority for tissue triage is adequate sectioning for light microscopy.

- Tissue triage is optimally performed at time of frozen section.
- Once sufficient tissue is reserved for histological examination, a 1 cm cube of fresh tissue (less is acceptable for small specimens, such as core biopsies) should be cut into small 0.2 cm cubes and snap frozen. The frozen tissue should be stored at -70 degrees C and shipped on dry ice if necessary for molecular analysis.
    - Analysis may include a variety of molecular assays for tumor-specific molecular translocations that help classify soft tissue tumors.
- Tissue should be submitted in transport medium (alpha MEM or RPMI) for cytogenetic analysis.
- Submit tissue in glutaraldehyde or other suitable fixative for electron microscopy.

Classification of many subtypes of sarcoma is not dependent on special studies, such as cytogenetics or molecular genetics, but frozen tissue may be required to enter patients into treatment protocols. Treatment protocols increasingly require fresh tissue for correlative studies.

Immunohistochemistry Considerations:

Immunohistochemical tests may be performed on formalin fixed, paraffin embedded tissue sections. The macroscopic description should provide the fixative used. 10% neutral buffered formalin is the preferred fixative. It is recommended that the duration of fixation be provided as well.

PROCEDURES AND GENERAL ANATOMIC CONSIDERATIONS:

- **Procedures Covered by this Protocol: ***

  - Biopsy
  - Resection

  **These recommendations are designed to apply principally to soft tissue sarcomas in teenagers and adults, since pediatric sarcomas are treated under strict protocols that may differ significantly from the recommendations supplied in this guideline.*

- **Definition of Terms:**

  - Core needle biopsy: withdrawal of a cylinder of abnormal tissue
  - Incisional biopsy: removing just a sample of tumor for the purpose of diagnosis
  - Intralesional resection: leaving gross or microscopic tumor behind (i.e., partial debulking or curettage)
  - Excisional biopsy: removing the entire tumor mass, plus a layer of surrounding normal tissue (same as marginal)
  - Marginal resection: removing the tumor and its pseudocapsule with a small amount of adjacent tissue (same as excisional)
  - Wide resection: tumor is removed with pseudocapsule and a rim or cuff of at least 2 cm of normal tissue surrounding the neoplasm (intracompartmental resection; same as excisional and marginal)
  - Segmental resection for bone: the portion of involved bone is removed with a cuff of normal bone
  - Radical resection: removal of an entire soft tissue compartment or bone, or the excision of adjacent muscle groups if the tumor is extracompartmental; this includes amputations and disarticulations

- **Specimen Size and Extent of Resection:**

  - Provide three dimensions of the specimen and divisions if known or included.
  - List the organs/structures included, and record measurements in three dimensions.
  - Record the specimen weight if applicable.

- **Specimen Integrity, Adequacy, and Triage:**

  - Soft tissue tumors are preferably received fresh due to the importance of ancillary studies, such as cytogenetic analysis, frozen tissue required for treatment protocols, and electron microscopy.
  - Provide an assessment of the specimen integrity. Identify and describe any defects or disruptions, specifically any that may involve the tumor or hinder the assessment of the surgical margins.
  - It may be beneficial to discuss complex resections with the surgeon to assure specimen orientation and to identify all anatomic landmarks.
  - A statement describing fascia integrity and relationship to the tumor is necessary.
    - Smooth or shaggy
    - Complete or incomplete

- Focally disrupted

TUMOR ("T" of TNM)

- **Tumor Size:**

  - Include three dimensions in cm.
  - If there are multiple tumors, include three dimensions for each.

- **Macroscopic Tumor Appearance and Sampling:**

  - A detailed description of the cut surface of the tumor is valuable to assess heterogeneity, necrosis, and treatment effect.

  - One section per centimeter of maximum dimension is recommended. Since documentation of high-grade component will change stage and prognosis, grossly heterogeneous areas should be well sampled.

  - Macroscopically necrotic tumor may be confused with myxoid or edematous changes; additional sections of these areas should be submitted.

  - Response to neoadjuvant therapy should be quantified. Therapy response is expressed as a percentage of viable tumor.

    - Non-liquefied tumor tissue from a cross-section through the longest axis of the tumor should be sampled.
    - At least one section of necrotic tumor with transitioning viable tumor should be sampled.
    - Non-sampled necrotic areas should be included in the estimate of necrosis and the percentage of tumor necrosis reported.

  - When estimates of macroscopic necrosis exceed those of histologic necrosis, the greater percentage of necrosis should be recorded on the surgical pathology report.

- **Tumor Site(s):**

  - State tumor anatomic site:
    - Head and Neck
    - Trunk and extremities
    - Abdominal visceral organ(s)
    - Thoracic visceral organ(s)
    - Retroperitoneum
    - Orbit

- **Explanatory Note:**

  The anatomic site is known to influence outcome, and therefore should be reported specifying the site. This is particularly applicable in the head and neck and visceral sites where grade or size may disproportionately drive prognosis relative to other staging criteria in comparison with sarcomas arising elsewhere in the body.

- **Tumor, Size and Relationship to Fascia and Attached Organs / Structures:**

Soft Tissue Sarcoma of the Head and Neck
Definition of Primary Tumor (pT)

pT Category	pT Criteria
pTX	Primary tumor cannot be assessed
pT1	Tumor ≤2 cm
pT2	Tumor >2 to ≤4 cm
pT3	Tumor >4 cm
pT4	Tumor with invasion of adjoining structures
pT4a	Tumor with orbital invasion, skull base/dural invasion, invasion of central compartment viscera, involvement of facial skeleton, or invasion of pterygoid muscles
pT4b	Tumor with brain parenchymal invasion, carotid artery encasement, prevertebral muscle invasion, or central nervous system involvement via perineural spread

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Soft Tissue Sarcoma of the Trunk and Extremities
Soft Tissue Sarcoma of the Retroperitoneum
Definition of Primary Tumor (pT)

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

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Soft Tissue Sarcoma of the Abdomen and Thoracic Visceral Organs
Definition of Primary Tumor (pT)

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

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Orbital Sarcoma
Definition of Primary Tumor (pT)

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

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. The ycTNM or YpTNM categorizes the extent of tumor actually present at the time of that examination.

The "r" prefix indicates a recurrent tumor when staged after a documented disease-free interval: rTNM.

Residual Tumor (R) Category

The absence or presence of residual tumor at the primary tumor site after treatment is denoted by the symbol R. The R categories for the primary tumor site are as follows:

R	R Definition
RX	Presence of residual tumor cannot be assessed
R0	No residual tumor
R1	Microscopic residual tumor
R2	Macroscopic residual tumor at the primary cancer site or regional nodal sites

The R classification is relevant to the status of the margins of a surgical resection specimen. 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).

- **Margins:**

  All surgical margins from soft tissue tumors should be assessed and sampled as perpendicular sections, if possible.

  - Margins bounded by a fascial plane or periosteum should be identified and described.
  - Apply ink to the margins of all intact specimens.
  - Specify if margins are uninvolved or involved by tumor; if involved, specify the margin.
  - Record the distance of tumor to each margin.
  - Specify the location and distance of all margins less than 2 cm from the tumor, and the distance of the closest margin.
  - If bone is present in the specimen and is not involved by tumor, or the tumor is greater than 2 cm from the margin, the marrow can be scooped out and submitted as a margin.
  - In re-excision specimens, the distance of scarring or granulation tissue from margins should also be measured.

- **Explanatory Notes:**

  Neurovascular and bone invasion should always be documented where possible. Even though neurovascular and bone invasion is not a determinant of stage, further studies may prove to be an independent prognostic factor.

- **World Health Organization [WHO] classification of soft tissue tumors**
  (see appendix, pp. 14-16)

  Classification of tumors should be made according to the World Health Organization (WHO) classification of soft tissue tumors, which as a recommendation, divides tumors into 4 categories: benign, intermediate (locally aggressive), intermediate (rarely metastasizing), and malignant.

  - Benign - complete resection is curative
  - Intermediate (locally aggressive) – wide resection is required for local control; do not metastasize
  - Intermediate (rarely metastasizing) – locally destructive and infiltrative growth pattern; may give rise to distant metastases
  - Malignant – locally destructive and infiltrative growth pattern; metastasis occurs in a high percentage of cases

LYMPH NODES ("N" of TNM)

- **Soft Tissue Sarcoma of the Head and Neck**
  Soft Tissue Sarcoma of the Trunk and Extremities*
  Soft Tissue Sarcoma of the Abdomen and Thoracic Visceral Organs
  Soft Tissue Sarcoma of the Retroperitoneum**
  Definition of Regional Lymph Node (pN)

pN Category	p Criteria
pN0	No regional lymph node metastasis or unknown lymph node status
pN1	Regional lymph node metastasis

*Presence of positive nodes (N1) is considered Stage IV - {N1, M0 = Stage IV}
{Any N, M1 = Stage IV}

**Presence of positive nodes (N1) is considered at least Stage IIIB – {N1, M0 = Stage IIIB}
{Any N, M1 = Stage IV}

Orbital Sarcoma
Definition of Regional Lymph Node (pN)

pN Category	p Criteria
pNX	Regional Lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Regional lymph node metastasis

Involvement of regional lymph nodes by soft tissue sarcoma is uncommon in adults, but, when present, has a very poor prognosis and should be reported. Patients, whose nodal status is not determined to be positive for tumor, should be designated as N0.

Lymph Node Sampling:

- Count lymph nodes identified.
- Specify site of lymph nodes identified.
- Measure lymph nodes in three dimensions.
- Describe the cut surface of the identified lymph nodes.
- Submit all lymph nodes for microscopic examination.
  - Submit small lymph nodes in toto.
  - Serially section and entirely submit larger lymph nodes.
- If possible, submit lymph node sections so that the long axis of the lymph node is demonstrated.
- Take steps to ensure that an accurate lymph node count can be rendered.

METASTASIS ("M" of TNM)

- **Metastasis:**

Soft Tissue Sarcoma of the Head and Neck
Soft Tissue Sarcoma of the Trunk and Extremities
Soft Tissue Sarcoma of the Abdomen and Thoracic Visceral Organs
Soft Tissue of the Retroperitoneum
Orbital Sarcoma

Definition of Distant Metastasis (pM) (required only if confirmed pathologically)

pM Category	pM Criteria
M0	No distant metastasis
pM1	Distant metastasis

Metastatic sites are often dependent on the original site of the primary tumor.

- The most common site of metastatic disease for patients with head and neck sarcomas and extremity and trunk sarcomas is the lung. Histologic subtypes, such as myxoid/round cell liposarcoma, commonly have extrapulmonary metastases, such as soft tissue and bone marrow sites.
- Brain metastases are rare, but may be seen in patients with leiomyosarcoma, angiosarcomas, and alveolar soft part sarcoma.
- Sarcomas of visceral origin typically metastasize to the liver or lung or within the involved body cavity.
- Pulmonary metastasis is the major site of dissemination in soft tissue sarcomas of the retroperitoneum, except in the case of leiomyosarcoma, which is frequently associated with liver and pulmonary metastases.
- Orbital metastases occur by hematogenous dissemination but spread via local periorbital lymphatics may occur if the eyelids, conjunctiva, and lacrimal gland are involved. Pulmonary metastases are the primary site of metastasis.

Appendix

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 dermatofibrosarcoma 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
    - Extraskeletal mesenchymal chondrosarcoma
    - Extraskeletal 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
- Extraskeletal myxoid chondrosarcoma
- Extraskeletal 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

*These soft tissue neoplasms are excluded from the AJCC staging system.

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