Soft tissue sarcoma of the extremities

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Soft Tissue Sarcomas of the Extremities
Soft Tissue Sarcomas: Definition

- Sarcomas are malignant tumors that arise from skeletal and extraskeletal connective tissue, mesenchymal cells, including:
  - adipose tissue
  - bone
  - cartilage
  - smooth muscle
  - skeletal muscle
Soft Tissue Sarcomas: Statistics

- Soft tissue sarcomas are rare and unusual neoplasms
  - about 1% of adult human cancers
  - 15% of pediatric malignancies
- Most commonly occur in the extremities (50%)
  - Also common in the abdominal cavity/retroperitoneum, trunk/thoracic region, and head and neck
## Soft Tissue Sarcomas: Histology

<table>
<thead>
<tr>
<th>Cell of origin</th>
<th>Sarcoma type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adipocyte</td>
<td>Liposarcoma</td>
</tr>
<tr>
<td>Fibrohistiocyte</td>
<td>Malignant fibrous histiocytoma</td>
</tr>
<tr>
<td>Fibroblast</td>
<td>Fibrosarcoma</td>
</tr>
<tr>
<td>Smooth muscle</td>
<td>Leiomyosarcoma</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>Rhabdomyosarcoma</td>
</tr>
<tr>
<td>Vascular</td>
<td>Angiosarcoma, Kaposi’s</td>
</tr>
<tr>
<td>Synovial</td>
<td>Synovial sarcoma</td>
</tr>
<tr>
<td>Melanocyte</td>
<td>Malignant melanoma</td>
</tr>
<tr>
<td>Unknown</td>
<td>Ewing’s sarcoma, Epithelioid sarcoma</td>
</tr>
</tbody>
</table>
Soft Tissue Sarcomas: Histology

- **Histopathology is determined by anatomic site**
  - Common subtypes in the extremity are liposarcoma and malignant fibrous histiocytoma
  - In the retroperitoneal location liposarcoma and leiomyosarcoma are the most common histiotypes
  - In the visceral location, gastrointestinal stromal tumors are found almost exclusively
Age as factor in histopathology

- In childhood, embryonal rhabdomyosarcoma is most common
- Synovial sarcoma is more likely to be seen in young adults (<35 years old)
- An even distribution of liposarcoma and malignant fibrous histiocytoma as the predominant types in the older population
Soft Tissue Sarcomas: Histology

- The biologic behavior of sarcomas is extremely variable.
- Histologic grade is a major prognostic determinant and is based on degree of mitosis, cellularity, presence of necrosis, differentiation, and stromal content.
Soft Tissue Sarcomas: Histology

- Low-grade sarcomas-better-differentiated, less cellular, tend to resemble the tissue of origin to some extent, cytologic abnormalities are less prominent, mitotic rate is low
- Grow slower, low risk of metastasis, a high risk of local recurrence after surgical removal
High-grade sarcomas—highly cellular, poorly differentiated mesenchymal cells with marked nuclear abnormality, high mitotic rate and anaplasia.

Grow rapidly, show extensive local invasion, metastasize early through bloodstream, usually fatal.
Soft Tissue Sarcomas: Histology

- Can be further characterized by cellular appearance:
  - well differentiated
  - undifferentiated
  - myxoid
  - round cell
  - pleomorphic
Soft Tissue Sarcomas: Risk Factors

- Genetic Predisposition
  - Neurofibromatosis - von Recklinghausen's disease
  - Li-Fraumeni syndrome
  - Retinoblastoma
  - Gardner's syndrome (familial adenomatous polyposis)

Radiation Exposure

Lymphedema
- Postsurgical
- Postirradiation
- Parasitic infection (filariasis)

Trauma

Chemical
- 2,3,7,8-Tetrachlorodibenzodioxin
- Polyvinyl chloride
- Hemachromatosis
- Arsenic

Soft Tissue Sarcomas: Risk Factors

Soft Tissue Sarcomas: Pathogenesis

- **Specific genetic alterations:**
  - fusion genes due to reciprocal translocations
  - specific point mutations

- **Nonspecific genetic alterations:**
  - genetic losses and gains

- **The tumor suppressor genes:**
  - $p53$ and $RB1$
Soft Tissue Sarcomas: Diagnosis

- Extremity sarcomas usually present with as a painless mass
- However, pain is noted at presentation in up to 33% of patients
- Delay in diagnosis is common, with the most common differential diagnosis for extremity and trunk lesions being a hematoma or a "pulled" muscle
Soft Tissue Sarcomas: Diagnosis

- Physical examination
  - should include assessment of the size of the mass and its relationship to neurovascular and bony structures

- Biopsy
  - Generally, in an adult, any soft tissue mass that is symptomatic or enlarging, any mass that is larger than 5 cm, or any new mass that persists beyond 4 weeks should be sampled

Soft Tissue Sarcomas: Diagnosis

- Usually incisional or core biopsy preferred
  - Extremity masses should be biopsied through a longitudinal incision
  - Entire biopsy tract can be excised at the time of definitive resection
- The incision should be centered over the mass in its most superficial location
  - No tissue flap should be raised
  - Meticulous hemostasis to prevent cellular dissemination by hematoma
Soft Tissue Sarcoma: Diagnosis

- **Tru-cut core needle biopsy**
  - Has been advocated as the first step in diagnosis
  - Ease of performance
  - Low cost
  - Low complication rate

- Incisional biopsy may be reserved for cases in which the core needle biopsy is inconclusive

- Biopsy is indicated only if the actual treatment will be altered by a definitive diagnosis

Soft Tissue Sarcomas: Diagnosis

- **Excisional biopsy**
  - Only for small (< 3 cm) cutaneous or subcutaneous tumors

- **Fine-needle aspiration**
  - Limited role in diagnosing extremity soft tissue tumors
  - May be of value in the documentation of recurrence.
Soft Tissue Sarcomas: Diagnosis

- Imaging
  - MRI preferred
    - enhances the contrast between tumor and adjacent structures
    - provides excellent three-dimensional definition of fascial planes

Soft Tissue Sarcomas: Diagnosis

- Imaging: Relative value of MRI and CT
  - No statistically significant difference between CT and MR imaging in determining tumor involvement of muscle, bone, joints, or neurovascular structures
  - Combination of CT and MR images did not significantly improve accuracy

Soft Tissue Sarcomas: Workup

- Evaluation for sites of potential metastasis:
  - Lymph node metastases occur in less than 3% of adult soft tissue sarcoma\(^1\)
  - For extremity lesions, the lung is the principal site for metastasis of high-grade lesions\(^2\)
  - For visceral lesions, the liver is the principal site\(^3\)

- Low-grade lesions are assumed to have a low <15% risk of subsequent metastasis

- High-grade lesions have a high >50% risk of subsequent metastasis

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Soft Tissue Sarcomas: Workup

- Low-grade extremity lesions require a chest radiograph
- High-grade lesions require a chest CT
- Visceral lesions should have the liver imaged as part of the initial abdominal CT or MRI
Soft Tissue Sarcomas: Staging

- **Staging systems focus on:**
  - Histologic grade of the tumor
  - Size of the primary tumor
  - Presence or absence of metastasis

- **Staging systems:**
  - apply to risk of metastasis
  - disease-specific survival
  - overall survival
  - almost exclusively confined to extremity lesions

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AJCC Staging - Soft Tissue Sarcoma

**Histopathologic Grade**

- **GX**: Grade cannot be assessed.
- **G1**: Well differentiated.
- **G2**: Moderately differentiated.
- **G3**: Poorly differentiated.
- **G4**: Undifferentiated.

**Primary Tumor**

- **TX**: Primary Tumor cannot be assessed.
- **T0**: No evidence of primary tumor.
- **T1**: Tumor 5 cm or less in greatest dimension.
  - **T1a**: Superficial tumor.
  - **T1b**: Deep tumor.
- **T2**: Tumor more than 5 cm in greatest dimension.
  - **T2a**: Superficial tumor.
  - **T2b**: Deep tumor.

**Note:** 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 or superficial and beneath the fascia. Retroperitoneal, mediastinal, and pelvic sarcomas are classified as deep tumors.
**Soft Tissue Sarcomas: Staging**

**Regional Lymph Nodes**

- **NX**: Regional lymph nodes cannot be assessed.
- **N0**: No regional lymph node metastasis.
- **N1**: Regional lymph node metastasis.

**Distant Metastasis**

- **MX**: Distant metastasis cannot be assessed.
- **M0**: No distant metastasis.
- **M1**: Distant metastasis.
# Soft Tissue Sarcomas: Staging

The above four components are combined into the following staging criteria.

## Stage Grouping

### Stage I

<table>
<thead>
<tr>
<th>Grade</th>
<th>Tumor Size</th>
<th>Node Status</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (Low grade, small, superficial and deep)</td>
<td>G1-2</td>
<td>T1a-1b</td>
<td>N0</td>
</tr>
<tr>
<td>B (Low grade, large, superficial)</td>
<td>G1-2</td>
<td>T2a</td>
<td>N0</td>
</tr>
</tbody>
</table>

### Stage II

<table>
<thead>
<tr>
<th>Grade</th>
<th>Tumor Size</th>
<th>Node Status</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (Low grade, large, deep)</td>
<td>G1-2</td>
<td>T2b</td>
<td>N0</td>
</tr>
<tr>
<td>B (High grade, small, superficial, deep)</td>
<td>G3-4</td>
<td>T1a-1b</td>
<td>N0</td>
</tr>
<tr>
<td>C (High grade, large, superficial)</td>
<td>G3-4</td>
<td>T2a</td>
<td>N0</td>
</tr>
</tbody>
</table>

### Stage III

<table>
<thead>
<tr>
<th>Grade</th>
<th>Tumor Size</th>
<th>Node Status</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>(High grade, large, deep)</td>
<td>G3-4</td>
<td>T2b</td>
<td>N0</td>
</tr>
</tbody>
</table>

### Stage IV

<table>
<thead>
<tr>
<th>Grade</th>
<th>Tumor Size</th>
<th>Node Status</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>(any metastasis)</td>
<td>Any G</td>
<td>Any T</td>
<td>N1</td>
</tr>
<tr>
<td>Any G</td>
<td>Any T</td>
<td>N0</td>
<td>M1</td>
</tr>
</tbody>
</table>
Soft Tissue Sarcoma: Treatment

- **Surgical excision:**
  - Greatest hope for cure
  - Whenever possible, function- and limb-sparing procedures should be performed
  - As long as the entire tumor is removed, less radical procedures do not adversely affect local recurrence or outcome
  - Goal is complete removal of the tumor with negative margins and maximal preservation of function

Soft Tissue Sarcoma: Treatment

- **Excision**
  - 1 to 2 cm margins
  - Amputation no longer standard of care
  - Meticulous dissection can prevent injury to major neurovascular structures

Soft Tissue Sarcoma: Treatment

- Wide excision alone adequate for:
  - Any size low-grade sarcoma
  - Subcutaneous or intramuscular high-grade sarcoma < 5 cm
- Otherwise adjuvant therapy is indicated

Soft Tissue Sarcoma: Treatment

- Adjuvant radiation should be added to the surgical resection:
  - If the excision margin is close
  - If extramuscular involvement is present
  - If a local recurrence would result in the sacrifice of a major neurovascular bundle or amputation

Soft Tissue Sarcoma: Treatment

- Adjuvant radiation
  - improves local control
  - brachytherapy for high-grade lesions
  - external-beam radiation therapy for large (>5 cm) high- or low-grade lesions

Soft Tissue Sarcoma: Treatment

- **Adjuvant chemotherapy**
  - depends on the histologic type of sarcoma; indicated for:
    - Ewing's sarcoma
    - rhabdomyosarcoma
      - High risk of microscopic metastasis at diagnosis and good response to chemotherapy

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Soft Tissue Sarcoma: Treatment

- **Adjuvant chemotherapy**
  - Controversial for other histologic subtypes
    - Has no measurable impact on overall survival
    - Small (10% to 15%) improvement in disease-free survival

Soft Tissue Sarcoma: Recurrent Disease

- Incidence of distant metastasis significant
  - Billingsley, et al: Of 994 patients with primary extremity soft tissue sarcomas distant metastasis developed in 230 patients (23%)\(^1\)
  - Median survival after the development of metastasis was 11.6 months
  - Lungs first metastatic site in 73%

Soft Tissue Sarcoma: Recurrent Disease

- Predictors of survival:
  - Extent of metastatic disease
  - Length of the disease-free interval
  - Presence of a preceding local recurrence
  - Age

Soft Tissue Sarcoma: Recurrent Disease

- **Local extremity recurrence**
  - Presents as a nodular mass or series of nodules arising in the surgical scar
  - If isolated should undergo re-resection
    - two thirds of these patients experience long-term survival benefit
  - Adjuvant radiation if feasible

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Soft Tissue Sarcoma: Recurrent Disease

- Resection of pulmonary metastases:
  - Primary tumors controlled or controllable
  - No extrathoracic disease
  - Medically fit for thoracotomy
  - Complete resection of all lung disease appears possible

- 20% to 30% 3-year survival rates after complete resection

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Soft Tissue Sarcoma: Recurrent Disease

- Role of chemotherapy
  - Unresectable pulmonary metastases
  - Extrapulmonary metastatic sarcoma in more than a single site
  - Uniformly poor prognosis
    - DTIC (doxorubicin, ifosfamide, dacarbasine) and MAID (mesna, ifosfamide, doxorubicin, dacarbasine) have a 47% response rate and a 10% complete response rate

- Palliative, not curative, therapy

Soft Tissue Sarcoma: Recurrent Disease

- Long-term follow-up
  - 9% of patients who were disease free at the end of 5 years would have further recurrence of the primary extremity sarcoma

Conclusions

- Sarcomas of the extremity can be extremely variable in terms of their histologic make-up, their natural history, and their biological behavior.
- Surgical resection is the mainstay of curative therapy.
- Multimodal treatment and salvage therapy have improved outcomes in a subset of patients.