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

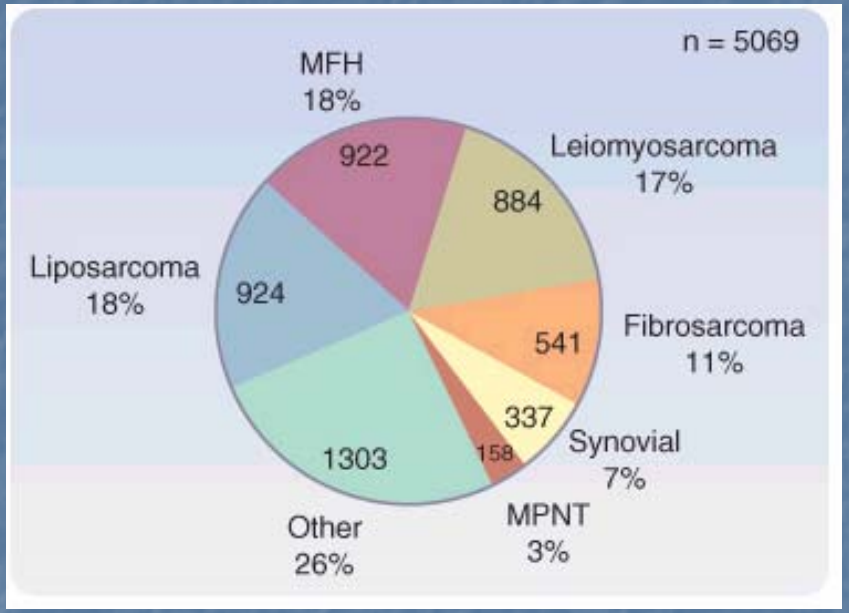
- Soft tissue sarcomas are rare and unusual neoplasms
  - about 1% of adult human cancers
  - 15% of pediatric malignancies
- Most commonly occur in the extremities (50%)
  - Also common in the abdominal cavity/retroperitoneum, trunk/thoracic region, and head and neck

Soft Tissue Sarcomas: Histology

Cell of origin	*Sarcoma type*
Adipocyte	Liposarcoma
Fibrohistiocyte	Malignant fibrous histiocytoma
Fibroblast	Fibrosarcoma
Smooth muscle	Leiomyosarcoma
Skeletal muscle	Rhabdomyosarcoma
Vascular	Angiosarcoma, Kaposi's
Synovial	Synovial sarcoma
Melanocyte	Malignant melanoma
Unknown	Ewing's sarcoma, Epithelioid sarcoma

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

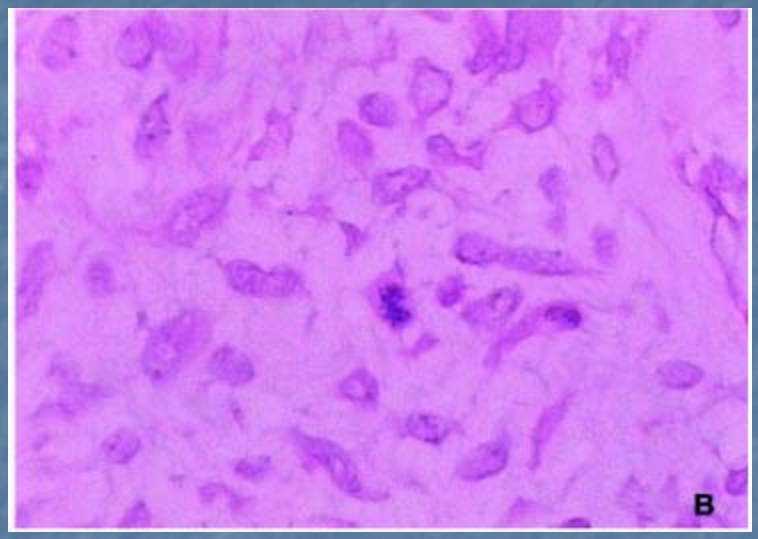


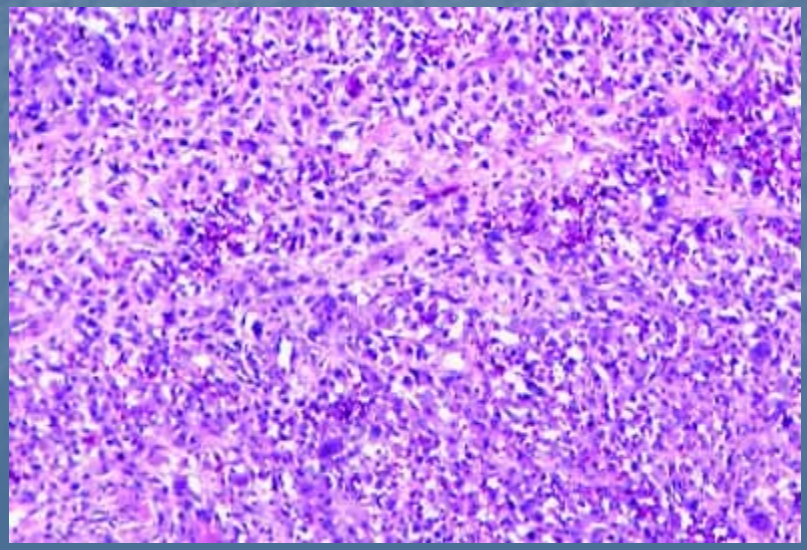
Soft Tissue Sarcomas: Histology

- 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

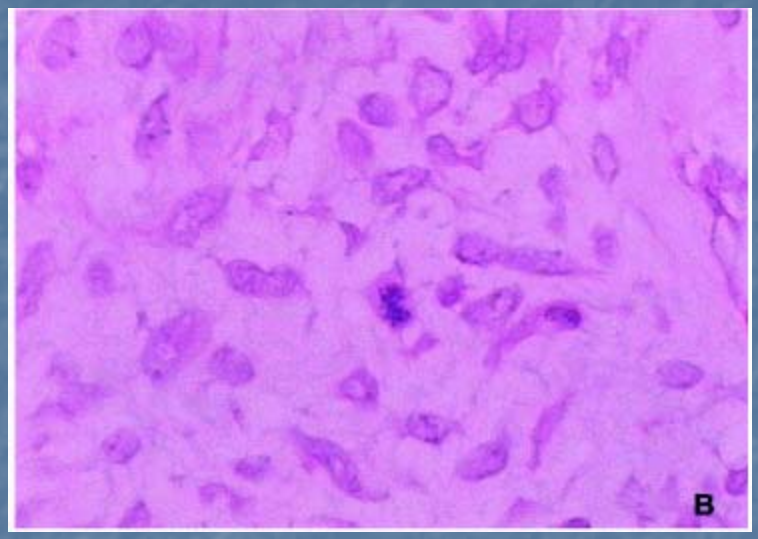
- The biologic behavior of sarcomas is extremely variable
- Histologic grade is a major prognostic determinant and is based on degree of mitosis, cellularity, presence of necrosis, differentiation, and stromal content

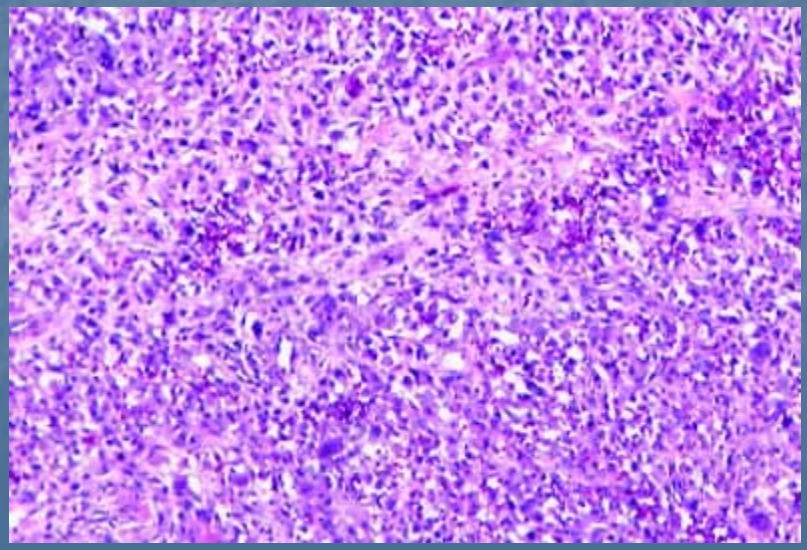




Soft Tissue Sarcomas: Histology

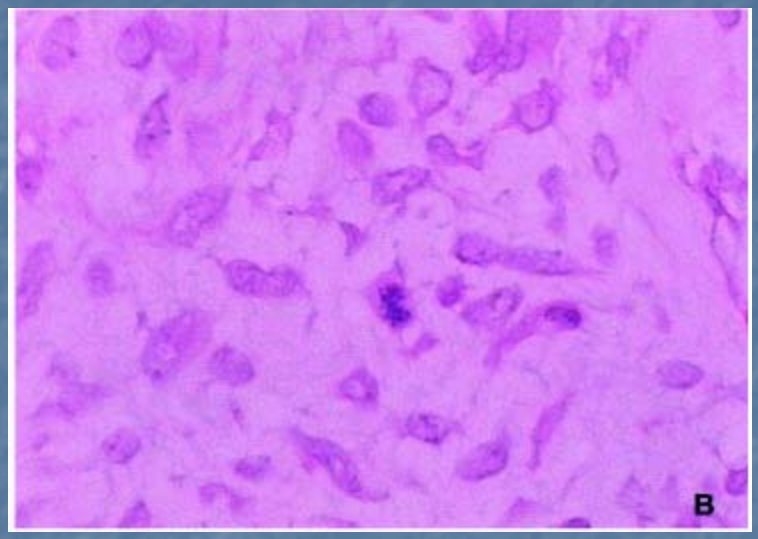
- Low-grade sarcomas-better-differentiated, less cellular, tend to resemble the tissue of origin to some extent, cytologic abnormalities are less prominent, mitotic rate is low
- Grow slower, low risk of metastasis, a high risk of local recurrence after surgical removal

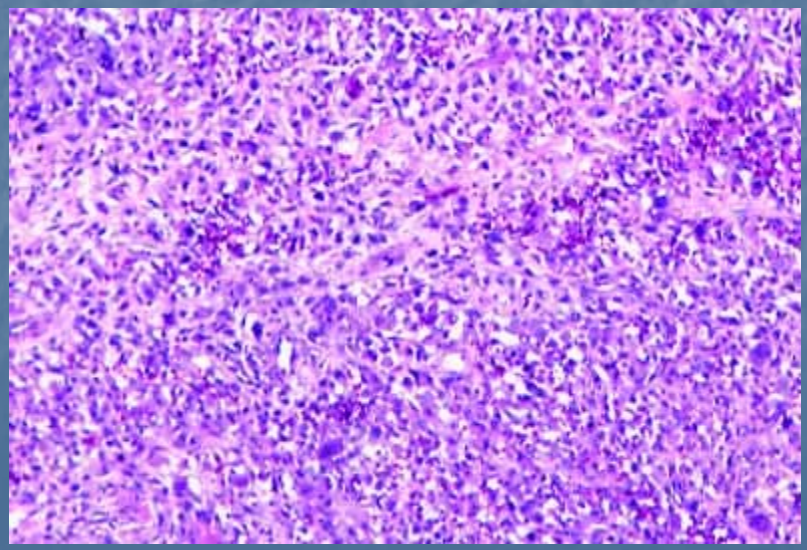




Soft Tissue Sarcomas: Histology

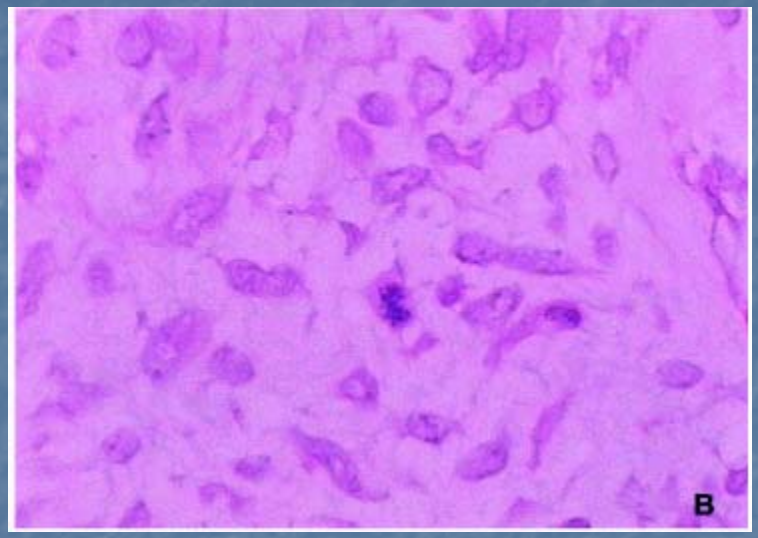
- High-grade sarcomas- highly cellular, poorly differentiated mesenchymal cells with marked nuclear abnormality, high mitotic rate and anaplasia
- Grow rapidly, show extensive local invasion, metastasize early through bloodstream, usually fatal

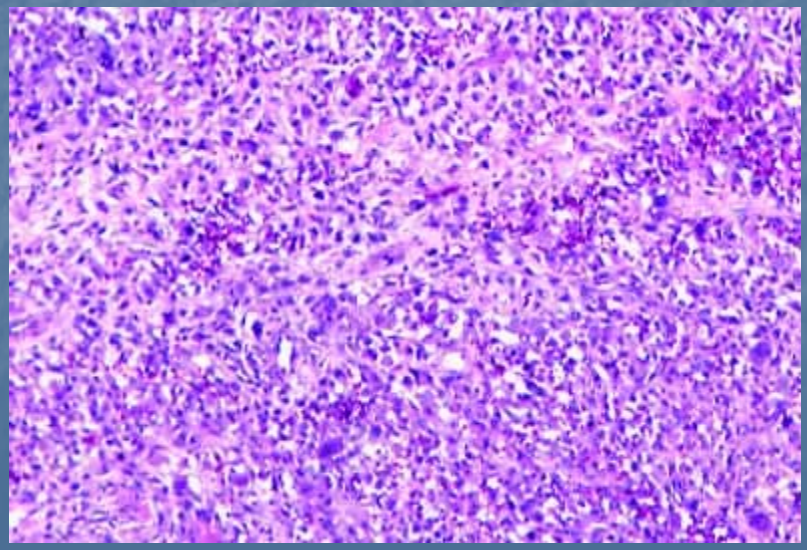




Soft Tissue Sarcomas: Histology

- 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)

[1] Barken D, Wright E, Nguyen D: Gene for von Recklinghausen neurofibromatosis is in the pericentromeric region of chromosome 17. Science 236:1100, 1987.
[2] Li FP, Fraumeni JF: Soft-tissue sarcomas, breast cancer, and other neoplasms: A familial syndrome? Ann Intern Med 71:747, 1969.
[3] Sorensen SA, Mulvihill JJ, Nielsen A: Long-term follow-up of von Recklinghausen neurofibromatosis: Survival and malignant neoplasms. N Engl J Med 314:1010, 1986

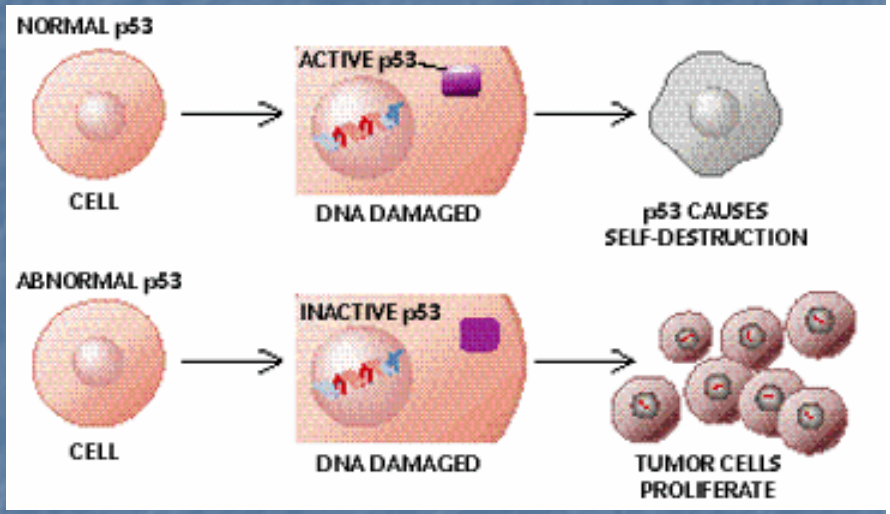
Soft Tissue Sarcomas: Risk Factors

- **Radiation Exposure** [1,2]
- **Lymphedema**
  - Postsurgical
  - Postirradiation
  - Parasitic infection (filariasis)
- **Trauma**
- **Chemical**
  - 2,3,7,8-Tetrachlorodibenzodioxin
  - Polyvinyl chloride
  - Hemachromatosis
  - Arsenic

[1] Brady MS, Gaynor JJ, Brennan MF: Radiation-associated sarcoma of bone and soft tissue. Arch Surg 127:1379, 1992.
[2] Brennan MF, Lewis JJ: Diagnosis and Management of Soft Tissue Sarcoma. London, Martin Dunitz, 2002.

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

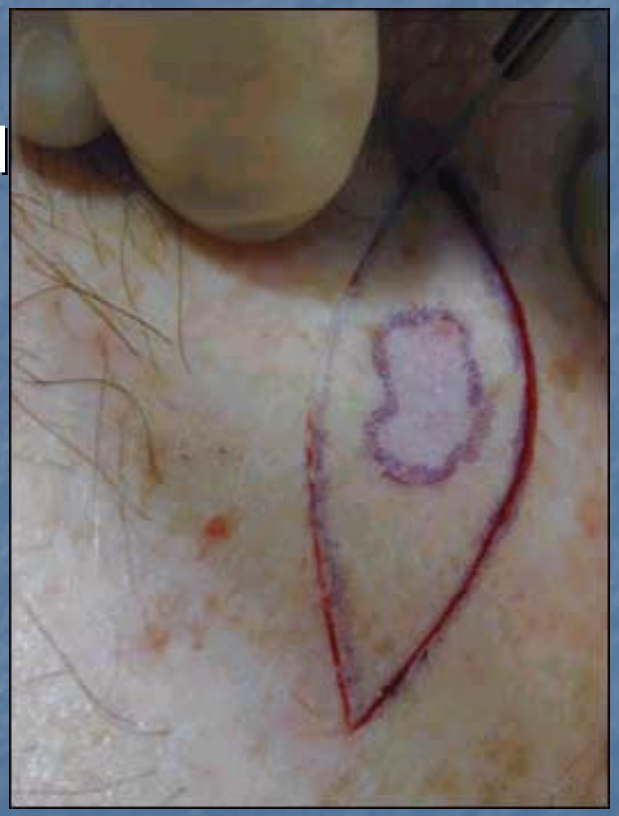
Soft Tissue Sarcomas: Diagnosis

- 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

Lewis J, Brennan MF: Soft tissue sarcomas. Curr Probl Surg 33:817, 1996

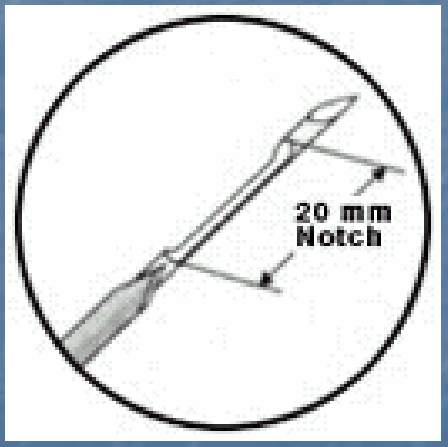
Soft Tissue Sarcomas: Diagnosis

- 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

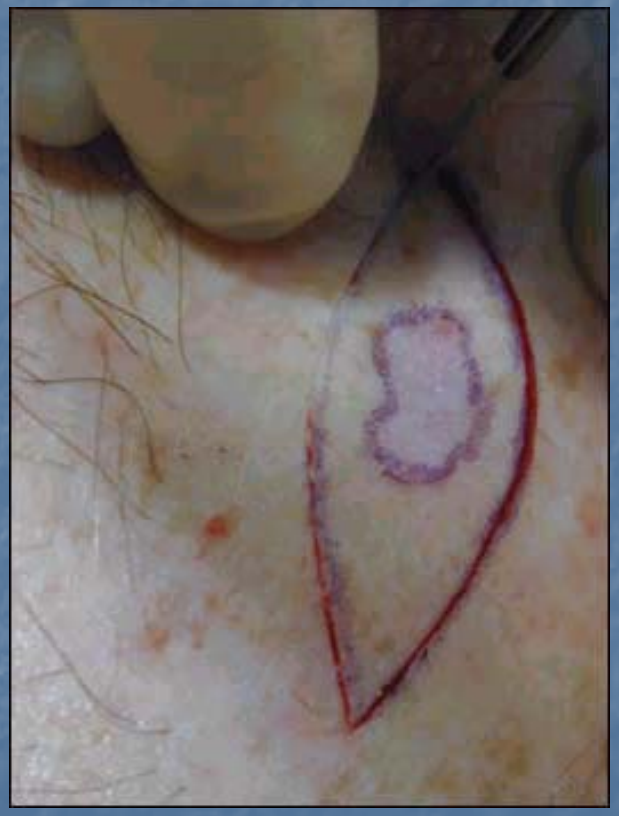
- Tru-cut core needle biopsy
  - Has been advocated as the first step in diagnosis
  - Ease of performance
  - Low cost
  - Low complication rate
- Incisional biopsy may be reserved for cases in which the core needle biopsy is inconclusive
- Biopsy is indicated only if the actual treatment will be altered by a definitive diagnosis



Heslin MJ, Lewis JJ, Woodruff JM, Brennan MF: Core needle biopsy for diagnosis of extremity soft tissue sarcoma. Ann Surg Oncol 4:425, 1997.

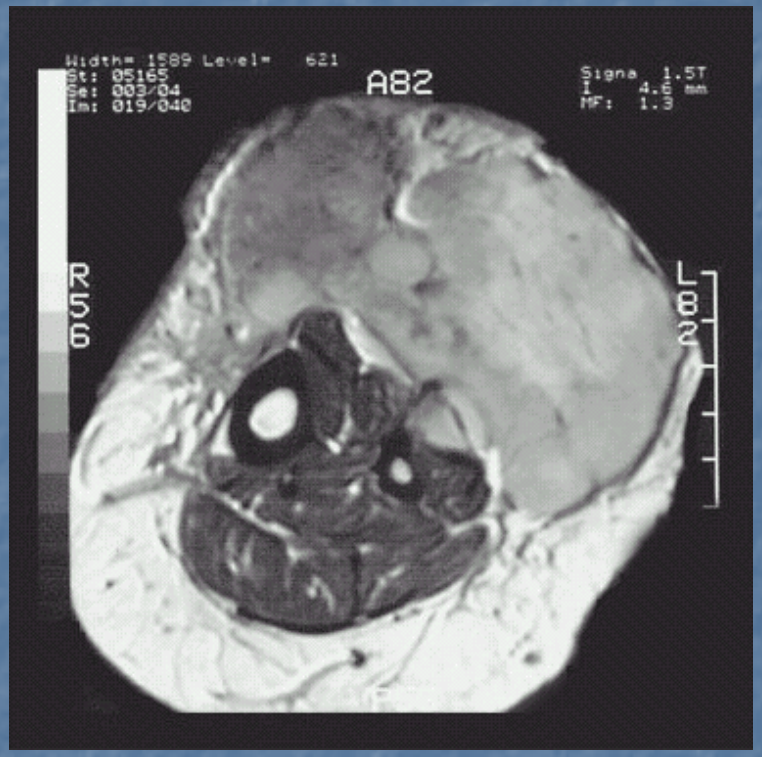
Soft Tissue Sarcomas: Diagnosis

- 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

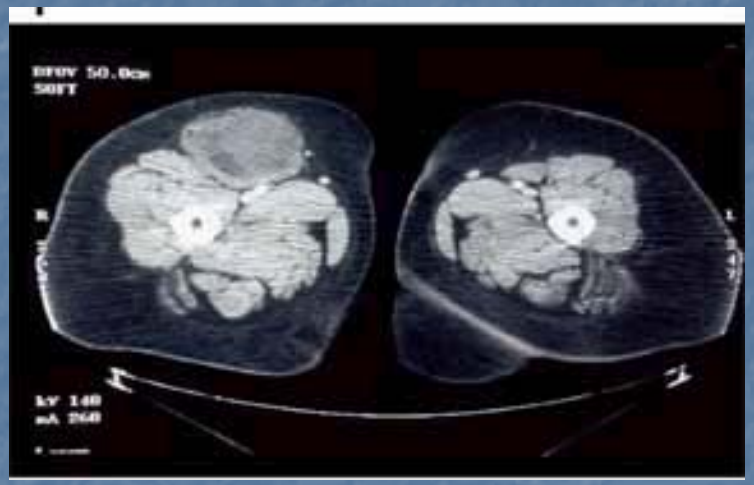


[1] Varma DG: Optimal radiologic imaging of soft tissue sarcomas. Semin Surg Oncol 17:2, 1999.

[2] Panicek DM, Go SD, Healey JH, et al: Soft-tissue sarcoma involving bone or neurovascular structures: MR imaging prognostic factors. Radiology 205:871, 1997.

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



Panicek DM, Gatsonis C, Rosenthal DI, et al: CT and MR imaging in the local staging of primary malignant musculoskeletal neoplasms: Report of the Radiology Diagnostic Oncology Group. Radiology 202:237, 1997

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

[1] Fong Y, Coit DG, Woodruff JM, Brennan MF: Lymph node metastasis from soft tissue sarcoma in adults: Analysis of data from a prospective database of 1772 sarcoma patients. Ann Surg 217:72, 1993.
[2] Gadd MA, Casper ES, Woodruff JM, et al: Development and treatment of pulmonary metastases in adult patients with extremity soft tissue sarcoma. Ann Surg 218:705, 1993.
[3] DeMatteo RP, Lewis JJ, Leung D, et al: Two hundred gastrointestinal stromal tumors: Recurrence patterns and prognostic factors for survival. Ann Surg 231:51, 2000.

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

[1] Brennan MF: Staging of soft tissue sarcomas. Ann Surg Oncol 6:8, 1999
[2] Greene F, Page D, Fleming I, Fritz A, et al (eds): AJCC Cancer Staging Manual, 6th ed. Heidelberg, Springer-Verlag, 2002.

Soft Tissue Sarcomas: Staging

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 superfacial 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					
	A (Low grade, small, superficial and deep)	G1-2	T1a-1b	N0	M0
	B (Low grade, large, superficial)	G1-2	T2a	N0	M0
Stage II					
	A (Low grade, large, deep)	G1-2	T2b	N0	M0
	B (High grade, small, superficial, deep)	G3-4	T1a-1b	N0	M0
	C (High grade, large, superficial)	G3-4	T2a	N0	M0
Stage III					
	(High grade, large, deep)	G3-4	T2b	N0	M0
Stage IV					
	(any metastasis)	Any G	Any T	N1	M0
		Any G	Any T	N0	M1

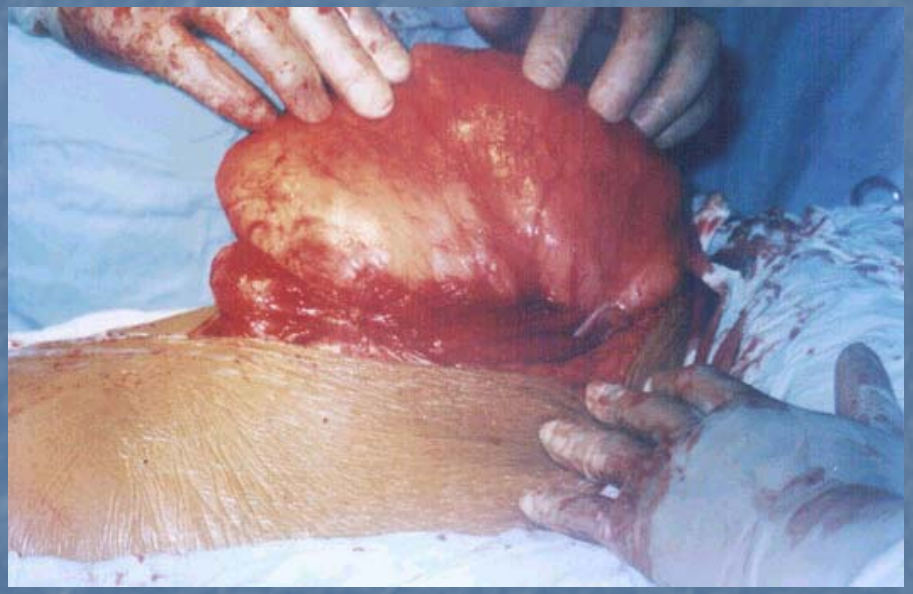
Soft Tissue Sarcoma: Treatment

- 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

Rosenberg SA, Tepper J, Glatstein E, et al: The treatment of soft-tissue sarcomas of the extremities: Prospective randomized evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. Ann Surg 196:305, 1982.

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



Williard WC, Collin C, Casper ES, et al: The changing role of amputation for soft tissue sarcoma of the extremity in adults. Surg Gynecol Obstet 175:389, 1992.

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

Yang JC, Chang AE, Baker AR, et al: Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. J Clin Oncol 16:197, 1998.

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

Yang JC, Chang AE, Baker AR, et al: Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. J Clin Oncol 16:197, 1998.

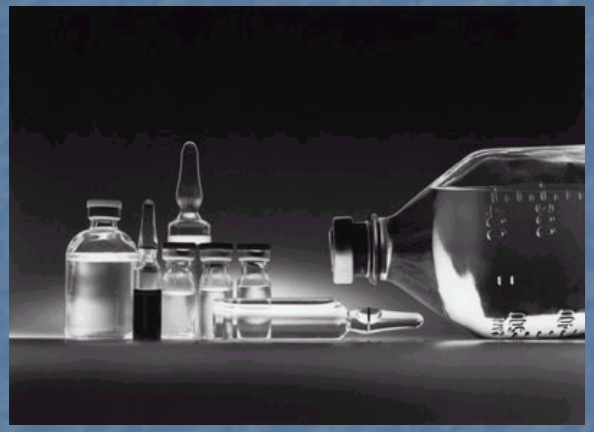
Soft Tissue Sarcoma: Treatment

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

[1] Yang JC, Chang AE, Baker AR, et al: Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. J Clin Oncol 16:197, 1998.
[2] Pisters PW, Harrison LB, Leung DH, et al: Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma. J Clin Oncol 14:859, 1996.

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 chemotherpy



[1] Baldini EH, Demetri GD, Fletcher CD, et al: Adults with Ewing's sarcoma/primitive neuroectodermal tumor: Adverse effect of older age and primary extraosseous disease on outcome. Ann Surg 230:79, 1999.
[2] Esnaola NF, Rubin BP, Baldini EH, et al: Response to chemotherapy and predictors of survival in adult rhabdomyosarcoma. Ann Surg 234:215, 2001.

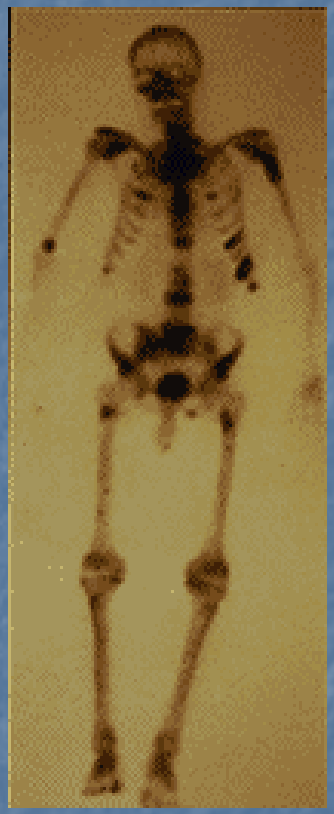
Soft Tissue Sarcoma: Treatment

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

[1] Bramwell V, Rouesse J, Steward W, et al: Adjuvant CYVADIC chemotherapy for adult soft tissue sarcoma-reduced local recurrence but no improvement in survival: A study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. J Clin Oncol 12:1137, 1994.
[2] Tierney JF, Stewart LA, Parmar MKB, et al: (Sarcoma Meta-analysis Collaboration): Adjuvant chemotherapy for localised resectable soft-tissue

Soft Tissue Sarcoma: Recurrent Disease

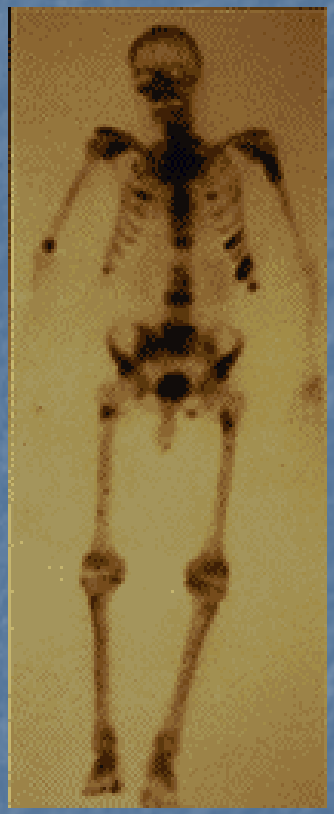
- Incidence of distant metastasis significant
  - Billingsley, et al: Of 994 patients with primary extremity soft tissue sarcomas distant metastasis developed in 230 patients (23%)[1]
  - Median survival after the development of metastasis was 11.6 months
  - Lungs first metastatic site in 73%



Billingsley KG, Lewis JJ, Leung DH, et al: Multifactorial analysis of the survival of patients with distant metastasis arising from primary extremity sarcoma. Cancer 85:389, 1999.

Soft Tissue Sarcoma: Recurrent Disease

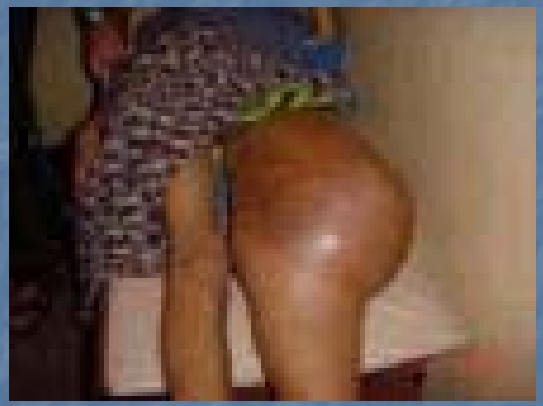
- Predictors of survival:
  - Extent of metastatic disease
  - Length of the disease-free interval
  - Presence of a preceding local recurrence
  - Age



Billingsley KG, Lewis JJ, Leung DH, et al: Multifactorial analysis of the survival of patients with distant metastasis arising from primary extremity sarcoma. Cancer 85:389, 1999.

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

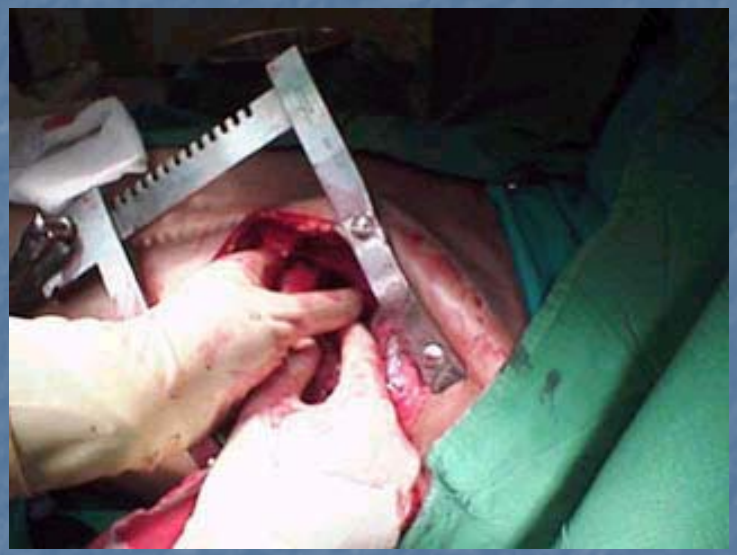


[1] Singer S, Antman K, Corson JM, Eberlein TJ: Long-term salvageability for patients with locally recurrent soft-tissue sarcomas. Arch Surg 127:548, 1992.

[2] Brennan MF: The enigma of local recurrence. The Society of Surgical Oncology. Ann Surg Oncol 4:1, 1997.

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



[1] Billingsley KG, Burt ME, Jara E, et al: Pulmonary metastases from soft tissue sarcoma: Analysis of patterns of diseases and post-metastasis survival. Ann Surg 229:602, 1999.

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

Benjamin RS, Rouesse J, Bourgeois H, van Hoesel QG: Should patients with advanced sarcomas be treated with chemotherapy? Eur J Cancer 34:958, 1998.

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

Lewis JJ, Leung D, Casper ES, et al: Multifactorial analysis of long-term follow-up (more than 5 years) of primary extremity sarcoma. Arch Surg 134:190, 1999

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