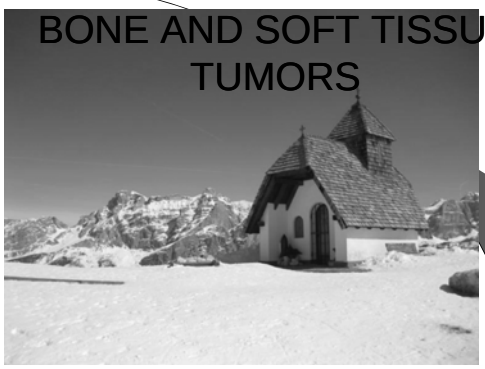
BONE AND SOFT TISSUE TUMORS



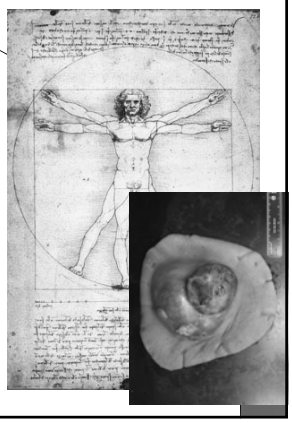
Fabrizio Remotti MD

CLASSIFICATION

- Purpose of classification is to link similar tumors in order to understand their behavior, determine the most appropriate treatment, and investigate their biology.
- However, purpose of a classification system is simplicity and reproducibility
- Therefore tumors are classified according to the cell type they resemble.
- Refinements are coming from cytogenetics, molecular, and gene expression studies.
- The majority arise from -or show differentiation toward- mesenchymal cells, but some show other differentiation (neuroectodermal, histiocytic).
- A small subset is of unknown histogenesis.

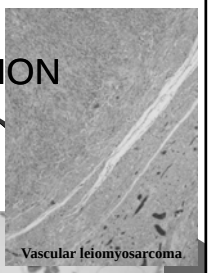
DEFINITION

- Soft tissue pathology deals with tumors of the connective tissues.
- The concept of soft tissue is understood broadly to include non-osseous tumors of extremities, trunk wall, retroperitoneum and mediastinum, and head & neck.
- Excluded (with a few exceptions) are organ specific tumors.

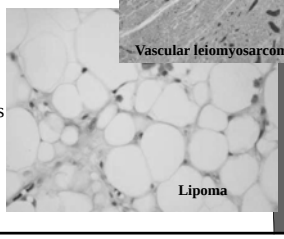


CLASSIFICATION

- Many tumors resemble tissues present in the region of origin.
- These tumors may be derived from stem cells that belong to local, organ-specific pools.
- Other involved stem cells may be bone marrow derived.



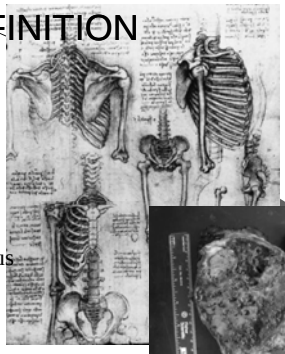
Vascular leiomyosarcoma



Lipoma

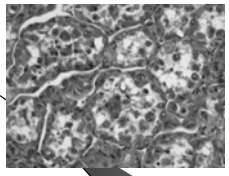
DEFINITION

- Bone pathology deals with tumors of the skeletal system.
- Included are subsets of tumors from extra-osseous sites that show osseous and cartilaginous differentiation.

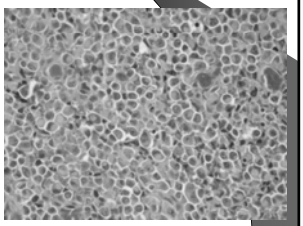


Alveolar soft part sarcoma

CLASSIFICATION



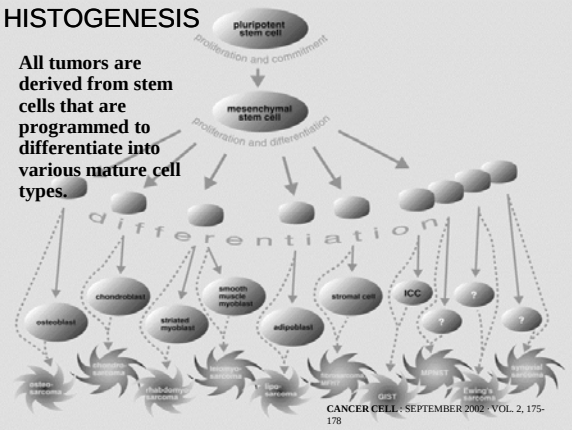
- Some tumors have no resemblance to normal tissue in the region (metaplastic foci within a tumor, or tumors of different histogenesis from the normal cells of the region)
- Some sarcomas have no normal cell counterparts, probably reflecting an unique genetic makeup.



Epithelioid sarcoma, proximal type

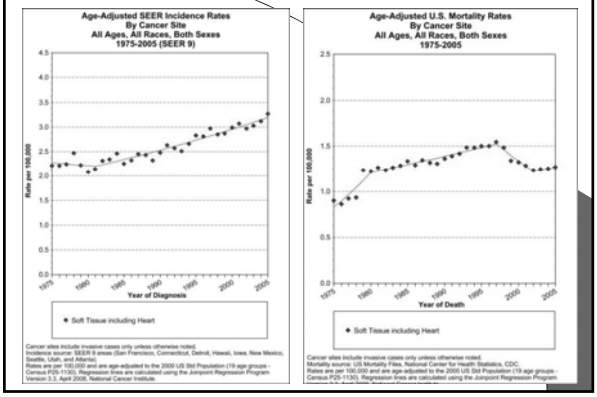
HISTOGENESIS

All tumors are derived from stem cells that are programmed to differentiate into various mature cell types.



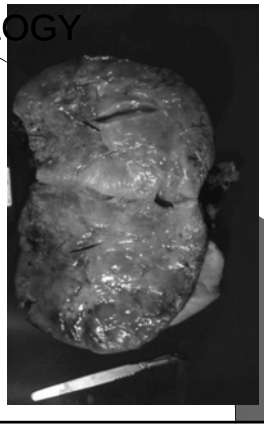
CANCER CELL - SEPTEMBER 2002 - VOL. 2, 175-178

EPIDEMIOLOGY



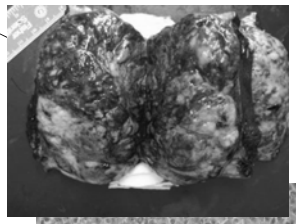
EPIDEMIOLOGY

- Soft tissue (ST) sarcomas are rare tumors compared to other malignancies: **8,700** new sarcomas in 2001, with **4,400** deaths.
- The incidence of ST sarcomas in the USA is approximately **3.3 cases per 100,000** people.
- This is roughly **5%** of each of some of the most common carcinomas (prostate, breast and lung), half of all brain tumors, and approximately equal to AML.

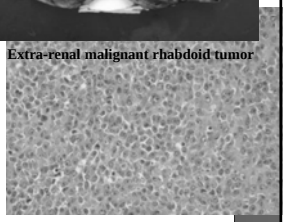


EPIDEMIOLOGY

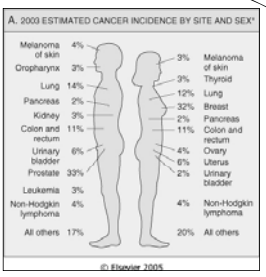
- There is a slight male predominance (with some subtypes more common in women).
- The majority of soft tissue tumors affect older adults (some sub-groups occur predominantly or exclusively in children).
- Incidence of benign soft tissue tumors not known, but probably outnumber malignant tumors **100:1**.



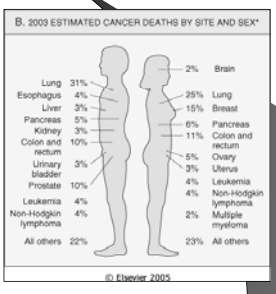
Extra-renal malignant rhabdoid tumor



SOFT TISSUE TUMORS

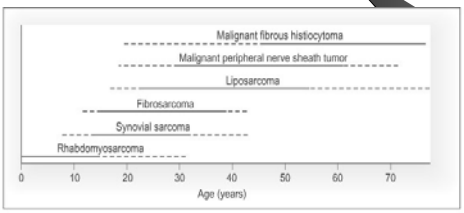


Nowhere in the picture…..



EPIDEMIOLOGY

- The knowledge of epidemiologic data may help in diagnosis.
- What you don't know may hurt you!



© Elsevier, Inc. 2008 Weiss and Goldblum. *Enzinger and Weiss's Soft Tissue Tumors*, 5th edition.

BONE TUMORS- EPIDEMIOLOGY

- Primary bone tumors are rare.
- Bone sarcomas account for 0.2% of all neoplasms (SEER Cancer Statistics Review, 1973-1996).
- Soft tissue sarcomas are approximately 10 times more common than primary bone sarcomas.

BONE TUMORS-

- The major
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  secondary
  metastatic
  - seco

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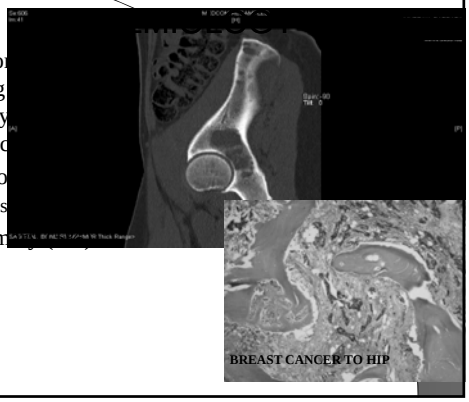
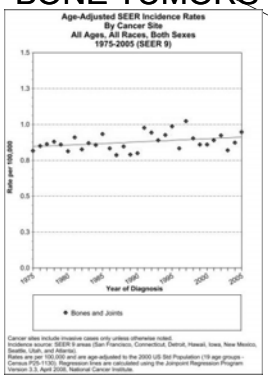
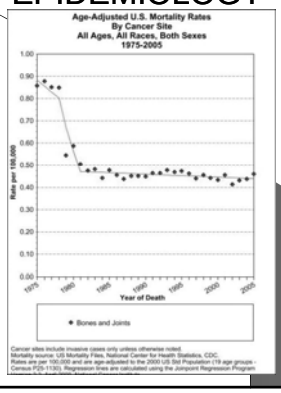


BREAST CANCER TO HIP

BONE TUMORS- EPIDEMIOLOGY

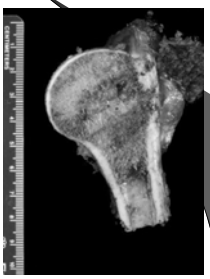




Secondary Tumors of Bone

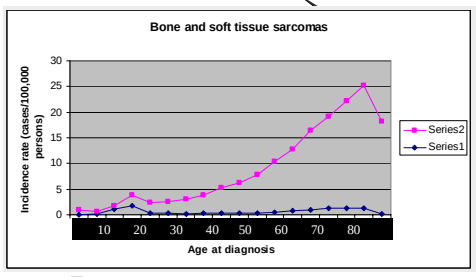
•The carcinomas most frequently involved with bone metastasis originate from:

- **Lung**
- **Breast**
- **Prostate**
- **G.I**
- **Kidney**
- **Thyroid**



MELANOMA TO
PROXIMAL HUMERUS

EPIDEMIOLOGY

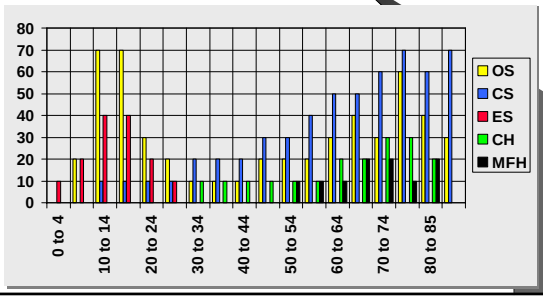


Soft tissue sarcomas

Bone sarcomas

BONE TUMORS

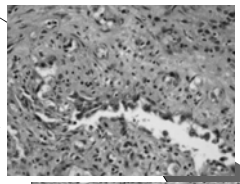
•Bone sarcomas as a group have a bimodal distribution.
•The first peak is in the second decade.
•The second peak occurs in patients older than sixty.

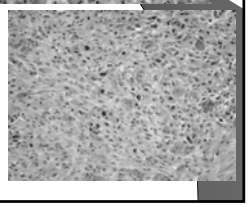


ETIOLOGY

- The etiology of sarcomas is poorly understood, and what is known apply only to a small fraction of the group.
- The known etiologic agents are ionizing radiation, oncogenic viruses, and chemicals.
- These agents are able to cause genetic alterations that can lead to tumorigenesis.

ETIOLOGY





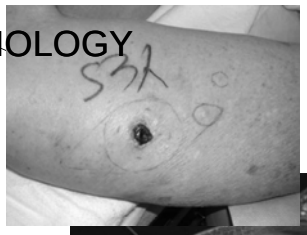
- Herbicides ("agent orange") and peripheral soft tissue sarcomas
- Retained metal objects (shrapnel, surgical devices) and OS, AS and MFH
- Vinyl chloride, inorganic arsenic, Thorotrast, anabolic steroids linked to AS and MFH.

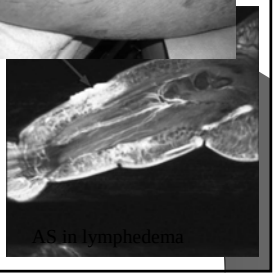
ETIOLOGY

- Radiation induced sarcomas develop in 1% of patients who have undergone therapeutic irradiation.
- The interval between irradiation and diagnosis of sarcoma varies between 5 and 10 years.
- The majority of radiation-induced sarcomas are high grade and poorly differentiated (MFH, FS, OS, and AS).

ETIOLOGY

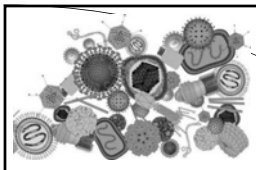
- Host factors may also play a role in the development of soft tissue sarcomas.
  - Immunosuppression, besides Kaposi's sarcoma, may be associated with sarcomas.
  - Lymphedema, congenital or acquired (post-mastectomy) is a rare cause of extremity-based AS.

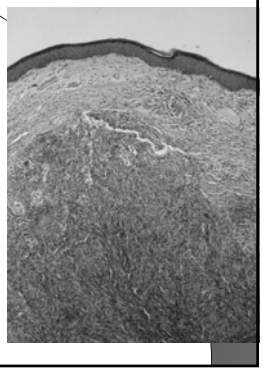




AS in lymphedema

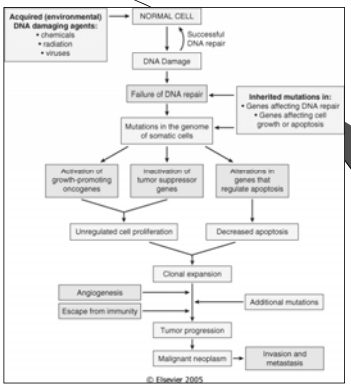
ETIOLOGY





- Oncogenic viruses introduce new genomic material in the cell, which encode for oncogenic proteins that disrupt the regulation of cellular proliferation.
- Two DNA viruses have been linked to soft tissue sarcomas:
  - **Human herpes virus 8 (HHV8) linked to Kaposi's sarcoma**
  - **Epstein-Barr virus (EBV) linked to subtypes of leiomyosarcoma**
- In both instances the connection between viral infection and sarcoma is more common in immunosuppressed hosts.

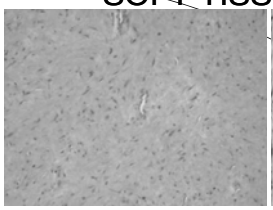
ETIOLOGY



CONGENITAL SYNDROMES ASSOCIATED WITH BONE AND SOFT TISSUE TUMORS

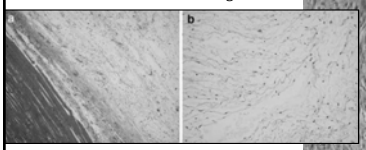
Disorder	Inheritance	Locus	Gene	Tumor
Albright hereditary osteodystrophy	AD	20q13	GNAS1	Soft tissue calcifications and osteomas
Bannayan -Riley- Ruvalcaba syndrome	AD	10q23	PTEN	Lipomas, hemangiomas
Beckwith- Wiedemann syndrome	Sp/AD	11p15	Complex	Embryonal RMS, myxomas, fibromas, hamartomas
Bloom syndrome	AR	15q26	BLM	Osteosarcoma
Carney complex (Familial myxoma syndrome)	AD	17q23-24 2p16	PRKAR1AK	Myxomas and pigmented schwannomas
Familial chordoma	AD	7q33	-	Chordomas
Costello syndrome	Sporadic	-	-	Rhabdomyosarcomas
Cowden disease (Multiple hamartoma syndrome)	AD	10q23	PTEN	Lipomas, Hemangiomas
Diaphyseal medullary stenosis	AD	9p21-22	-	MFH
Familial adenomatous polyposis	AD	5q21	APC	Craniofacial osteomas, desmoid tumors
Familial expansile osteolysis	AD	18q21	TNFRSF11A	Osteosarcomas
Familial infiltrative fibromatosis	AD	5q21	APC	Desmoid tumors
Langer- Giedion syndrome	Sporadic	8q24	EXT1	Osteochondromas, chondrosarcomas
Li-Fraumeni syndrome	AD	17p13 22q11	TP53 CHEK2	Osteosarcomas, RMS, other sarcomas
Familial multiple lipomas	AD	-	-	Lipomas
Symmetrical lipomatosis	Sporadic	-	-	Lipomas, lipomatosis of head and neck

SOFT TISSUE TUMORS

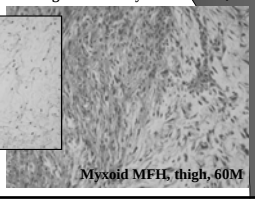


Fibroma of tendon sheath, finger

Low-grade fibromyxoid sarcoma, neck 19F



IM myxoma, thigh 65M

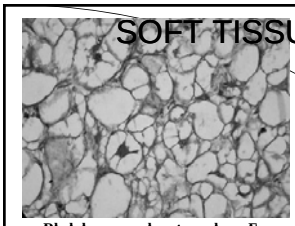


Myxoid MFH, thigh, 60M

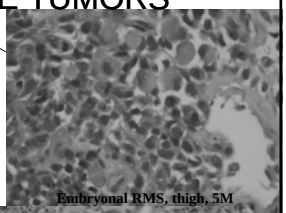
CONGENITAL SYNDROMES ASSOCIATED WITH BONE AND SOFT TISSUE TUMORS

Disorder	Inheritance	Locus	Gene	Tumor
Maffucci syndrome	Sporadic	-	-	Enchondromas, CS, hemangiomas, AS
Mazabraud syndrome	Sporadic	20q13	GNAS1	Fibrous dysplasia, OS, IM myxomas
McCune –Albright syndrome	Sporadic	20q13	GNAS1	Fibrous dysplasia, osteosarcomas
Multiple osteochondromas, non- syndromic	AD	8q24 11p11-12	EXT1 EXT2	Osteochondromas, chondrosarcomas
Myofibromatosis	AR	-	-	Myofibromas
Neurofibromatosis type 1	AD	17q11	NF1	Neurofibromas, MPNST
Neurofibromatosis type 2	AD	22q12	NF2	Schwannomas
Ollier disease	Sporadic	3p21-22	PTHR1	Enchondromas, chondrosarcomas
Paget disease of bone, familial	AD	18q21 5q31 5q35		Osteosarcomas
Proteus syndrome	Sporadic	-	-	Lipomas
Retinoblastoma	AD	13q14	RB1	Osteosarcomas, soft tissue sarcomas
Rhabdoid predisposition syndrome	AD	22q11	SMARCB1	Malignant rhabdoid tumors
Rothmund- Thompson syndrome	AR	8q24	RECQL4	Osteosarcomas
Rubinstein- Taybi syndrome	AD	16p13	CREBBP	Rhabdomyosarcomas
Venous malf. With glomus cells	AD	1p21-22	-	Glomus tumors
Werner syndrome	AR	8p11-12	WRN	Bone and soft tissue sarcomas

SOFT TISSUE TUMORS

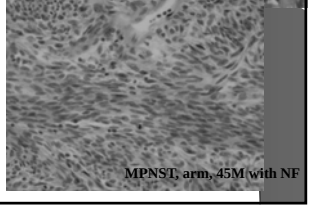


Rhabdomyoma, heart, newborn F



Embryonal RMS, thigh, 5M

Scwannoma, leg, 35F

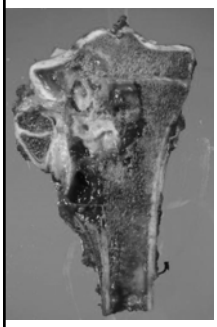


MPNST, arm, 45M with NF

SOFT TISSUE TUMORS CLASSIFICATION

MAJOR TYPES OF SOFT TISSUE TUMORS		
Cell type	Benign tumor	Malignant tumor
(Myo)fibroblast	Fibroma, myxoma	Fibrosarcoma, MFH
Adipocyte	Lipoma	Liposarcoma
Smooth muscle cell	Leiomyoma	Leiomyosarcoma
Skeletal muscle cell	Rhabdomyoma	Rhabdomyosarcoma
Endothelial cell	Hemangioma	Angiosarcoma
Schwann cell	Schwannoma, neurofibroma	MPNST
Cartilage cell	Chondroma	Chondrosarcoma
Interstitial cell	GIST	GIST
Histiocyte	JXG, GCTTS, RDD	True histiocytic sarcoma
Unknown	No benign counterparts	ES, SS, ES, ASPS

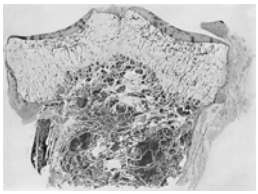
WHO CLASSIFICATION OF BONE TUMORS



Osteosarcoma

Cartilage tumors	Osteochondroma	
	Chondroma	Enchondroma
		Periosteal chondroma
		Mult. chondromatosis
	Chondroblastoma	
	Chondromyxoid fibroma	
	Chondrosarcoma	Central
		Peripheral
		Dedifferentiated
		Mesenchymal
		Clear cell
Osteogenic tumors	Osteoid osteoma	
	Osteoblastoma	
	Osteosarcoma	Conventional
		Telangiectatic
		Small cell
		Low grade central
		Secondary
		Parosteal
		Periosteal
		High grade surface
Fibrogenic tumors	Desmoplastic fibroma	
	Fibrosarcoma	
Fibrohistiocytic tumors	Desmoplastic fibroma	
	Fibrosarcoma	

WHO CLASSIFICATION OF BONE TUMORS

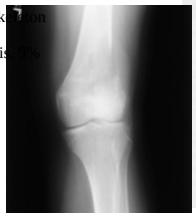


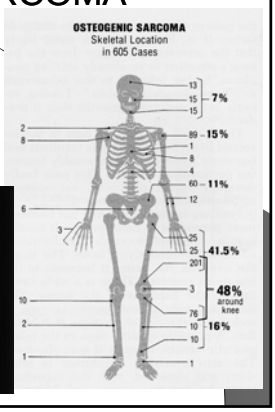
Aneurysmal bone cyst

Ewing/PNET	Ewing sarcoma
Hematopoietic tumors	Plasma cell myeloma
	Malignant lymphoma
Giant cell tumor	Giant cell tumor
	Malignant giant cell tumor
Notochordal tumors	Chordoma
Vascular tumors	Hemangioma
	Angiosarcoma
Smooth muscle tumors	Leiomyoma
	Leiomyosarcoma
Lipogenic tumors	Lipoma
	Liposarcoma
Neural tumors	Schwannoma
Miscellaneous tumors	Adamantinoma
	Metastatic malignancy
Miscellaneous lesions	Aneurysmal bone cyst
	Simple cyst
	Fibrous dysplasia
	Osteofibrous dysplasia
	Langerhans cell histiocytosis
	Erdheim -Chester disease
	Chest wall hamartoma
Joint lesions	Synovial chondromatosis

OSTEOSARCOMA

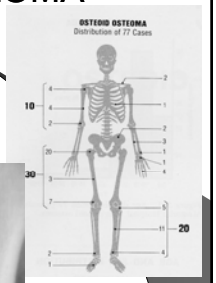
- Largely a disease of the young (60% <25 years)
- 30 % >40 years.
- In older people rule out predisposing conditions (e.g. Paget's disease of bone, radiation)
- Long bones of appendicular skeleton are favored
- 91% metaphysis 9% diaphysis

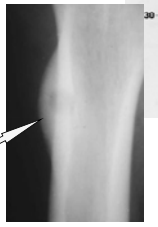




OSTEOID OSTEOMA

- Benign bone forming tumor.
- Small size, limited growth potential and disproportionate pain.
- Most common in long bones, but every bone may be affected.
- It may be painful on physical examination
- It may be associated with redness of skin and swelling.
- Lesions close to a joint may be associated with joint effusion.

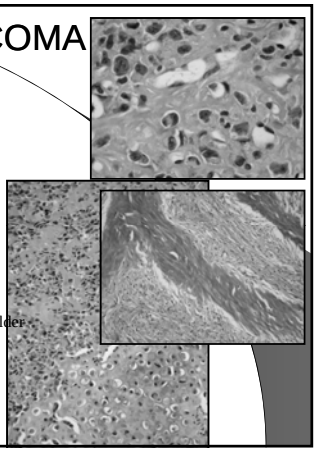




Nidus

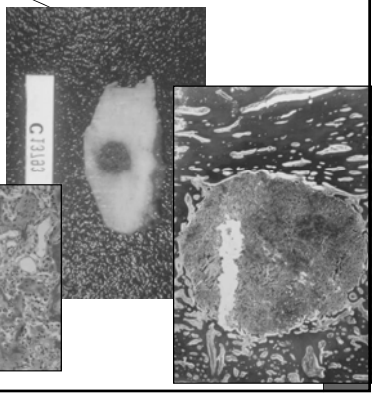
OSTEOSARCOMA

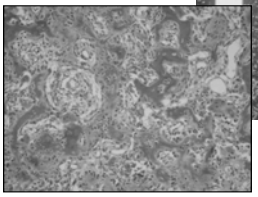
- Conventional:
  - Osteoblastic (50%)
  - Chondroblastic (<25%)
  - Fibroblastic (<1-2 %)
- Telangiectatic (<4%)
- Small cell (1.5%)
- Low grade central (<1%)
- Parosteal (4%)
- Periosteal (<2%)
- High-grade surface (<<1%)
- Secondary (20% of OS in patients older than 40)



OSTEOID OSTEOMA

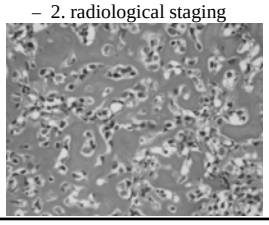
- Small, cortically based lesion, red and gritty, surrounded by sclerotic bone.
- The lesion is composed of a meshwork of osteoid trabeculae lined by plump osteoblasts.

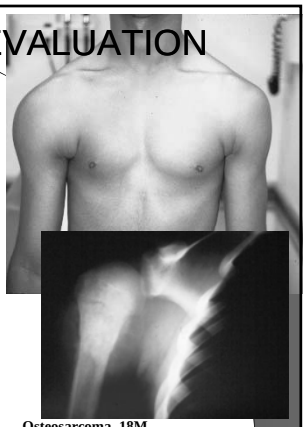




CLINICAL EVALUATION

- Clinical presentation
- Physical examination
- Pretreatment evaluation:
  - 1. biopsy
  - 2. radiological staging

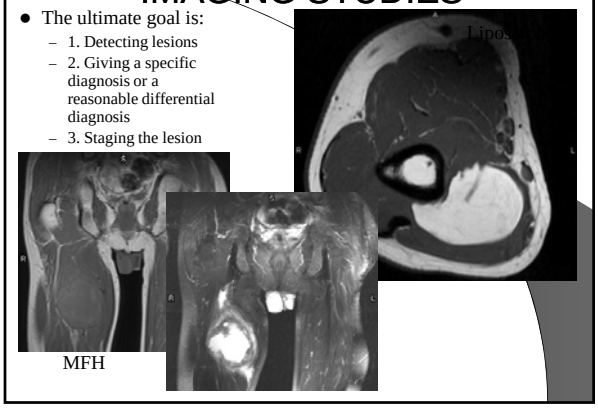




Osteosarcoma, 18M

IMAGING STUDIES

- The ultimate goal is:
  - 1. Detecting lesions
  - 2. Giving a specific diagnosis or a reasonable differential diagnosis
  - 3. Staging the lesion

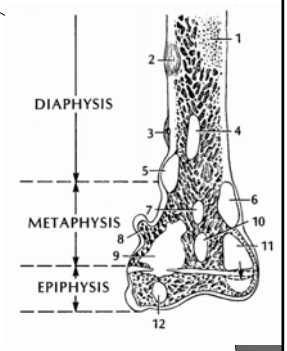


MFH

BONE TUMORS

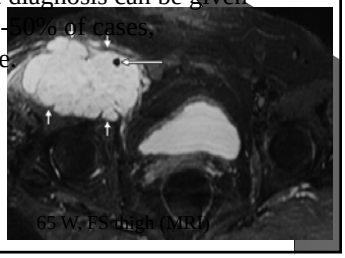
- Conventional radiographs are still important in the diagnosis of bone tumors.
- Many tumors are site-specific.
- Many tumors have a characteristic radiographic appearance.

1. **Ewing sarcoma, lymphoma, myeloma**
2. **Osteofibrous dysplasia, adamantinoma**
3. **Osteoid osteoma**
4. **Fibrous dysplasia**
5. **Chondromyxoid fibroma**
6. **Non-ossifying fibroma**
7. **Bone cyst, osteoblastoma**
8. **Osteochondroma**
9. **Osteosarcoma**
10. **Enchondroma, chondrosarcoma**
11. **Giant-cell tumor**
12. **Chondroblastoma**



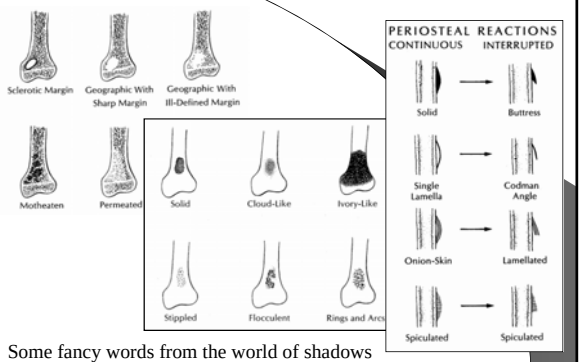
IMAGING STUDIES

- CT and particularly MRI allow detection and and staging by delineating anatomical extent in virtually all cases.
- A relatively specific diagnosis can be given in approximately 25-50% of cases, according to the type.



65 W. FS thigh (MRI)

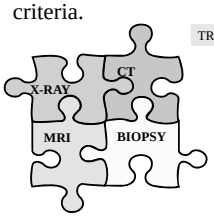
BONE TUMORS

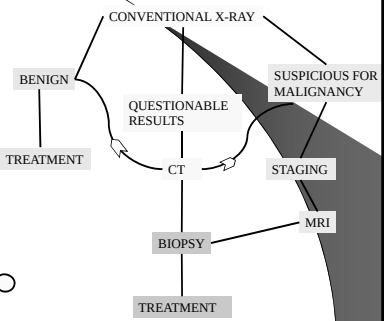


Some fancy words from the world of shadows

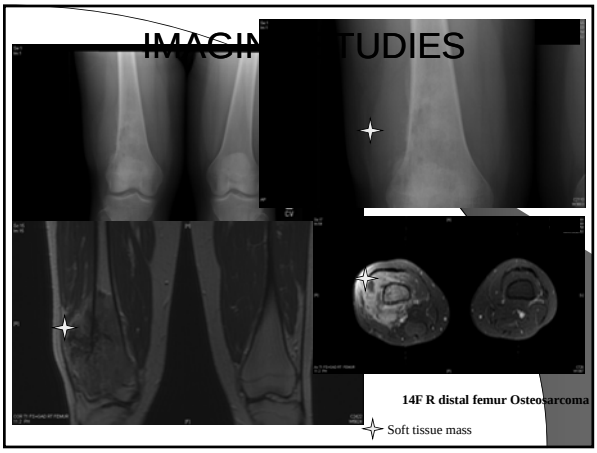
BONE TUMORS

- The diagnosis is based on imaging and histological criteria.





IMAGIN TUDIES



14F R distal femur Osteosarcoma

Soft tissue mass

IMAGING STUDIES

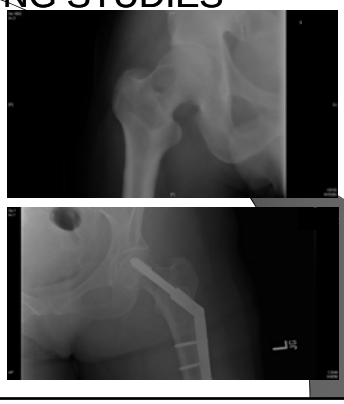
- Although imaging studies may give a reasonably accurate diagnosis on the biological potential of a lesion, there are not many lesions that may be accurately diagnosed by imaging studies alone.
- The biopsy is the gold standard for diagnosis.

TABLE 3–12 SOFT TISSUE MASSES FREQUENTLY DIAGNOSED WITH IMAGING ALONE

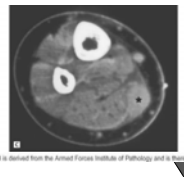
Lipomatous lesions
Angiomatous lesions
Neurogenic tumors
Elastofibroma
Pigmented villonodular synovitis (PVNS)
Synovial chondromatosis
Myositis ossificans
Tumoral calcinosis
Ganglion
Synovial cyst
Giant cell tumor of tendon sheath
Fibromatosis (particularly superficial lesions hand/foot)
Nodular fasciitis
Myxoma
Abscess
Hematoma

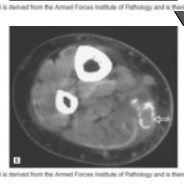
IMAGING STUDIES

- Multiloculated lesions with sclerotic margins in proximal femur:
  - Top 57M
  - Bottom 42F (s/p surgery)



IMAGING STUDIES

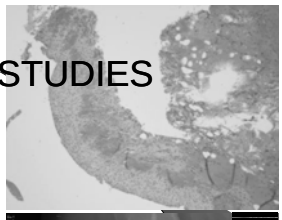


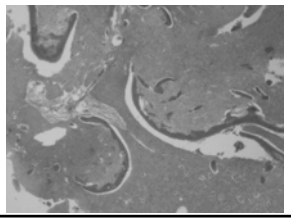


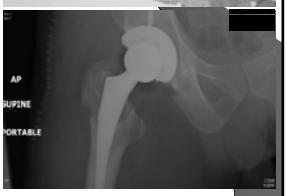
What is this soft tissue lesion?

IMAGING STUDIES

- Top: simple bone cyst.
- Bottom: Fibrous dysplasia.

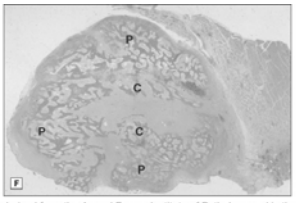






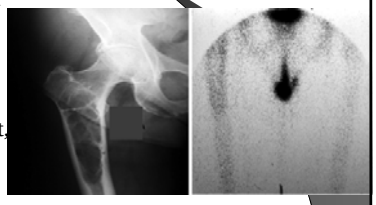
IMAGING STUDIES

- Myositis ossificans.
- Sequential imaging studies at few weeks interval show appearance of reactive shell of bone.
- The histology shows maturing periphery and immature center.



IMAGING STUDIES

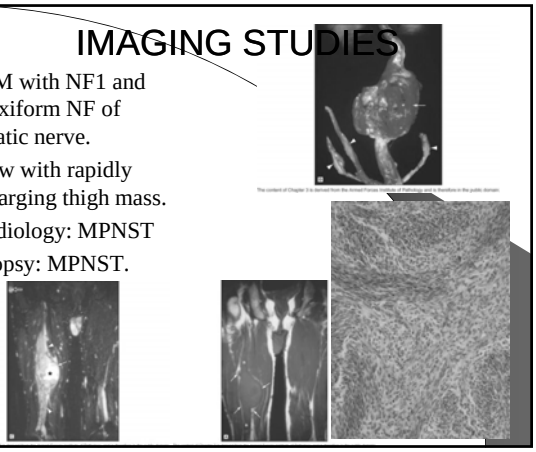
- Proximal femur lytic lesion with negative bone scan.
- Radiological impression: benign lesion (e.g. bone cyst, cystic fibrous dysplasia)
- Diagnosis at biopsy: multiple myeloma.



A word for the wise:
A lesion is benign only after biopsy.

IMAGING STUDIES

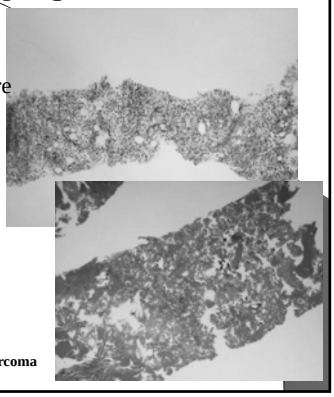
- 42M with NF1 and plexiform NF of sciatic nerve.
- Now with rapidly enlarging thigh mass.
- Radiology: MPNST
- Biopsy: MPNST.



BIOPSY

Metastatic myxoid liposarcoma to liver

- Percutaneous needle core biopsy usually yield adequate tissue for diagnosis.
- There is enough tissue for morphological, IHC & FISH studies.



Osteosarcoma

IMAGING STUDIES

- Conclusion: if it looks malignant probably it is, but you got to prove it.
- The images suggest esophageal cancer with suspected metastasis.
- The lesion turned out to be a neurofibroma.

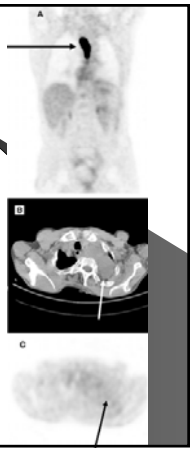
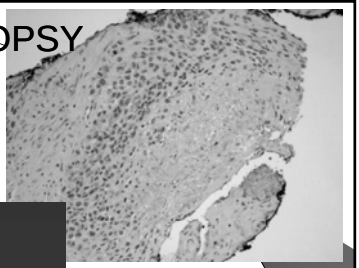
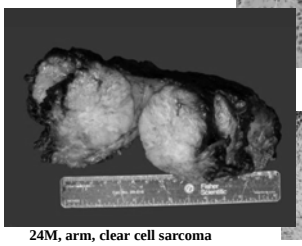


Fig. 1 Coronal image on FDG-PET demonstrating avid FDG uptake by esophageal primary (**a**). Transverse images demonstrating left-sided superior mediastinal mass on CT (**b**) without corresponding FDG uptake on PET (**c**)
Medical Oncology, March 2009

BIOPSY

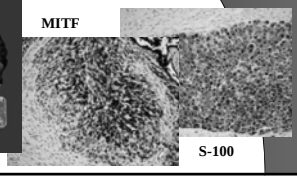
- Core biopsies yield enough material for extensive immunohistochemical stains.





24M, arm, clear cell sarcoma

MITF

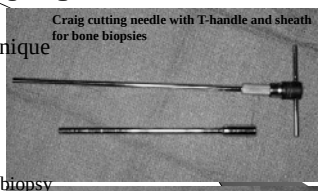


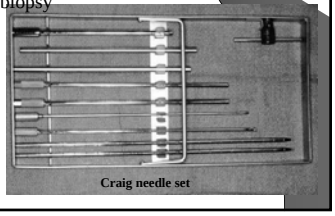
S-100

BIOPSY

- Select least invasive technique that allows diagnosis (including grade):
  - Percutaneous fine needle aspiration.
  - Percutaneous core needle biopsy (blind or image-guided).
  - Incisional biopsy.
  - Excisional biopsy.

Craig cutting needle with T-handle and sheath for bone biopsies

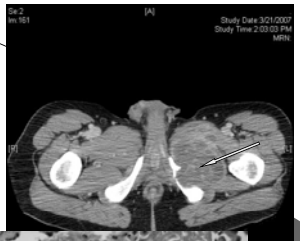


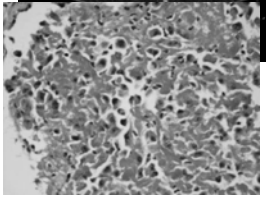


Craig needle set

BIOPSY

- Incisional biopsies are required in many cases.

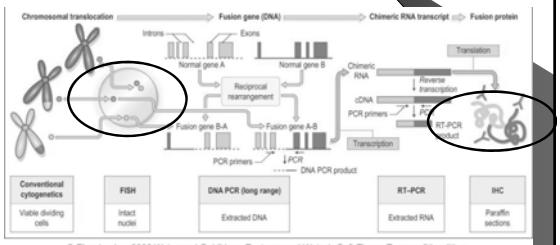




50M, angiosarcoma of ischium.

SPECIAL DIAGNOSTIC STUDIES

- Many sarcomas require additional studies to confirm the diagnosis and, in some cases, to add prognostic information.



GENETICS OF CONNECTIVE TISSUE NEOPLASMS

- The genetic mechanisms involved in carcinogenesis affect three types of cancer genes:
  - 1. Oncogenes (KIT, PDGFRA, MYCN, MDM2, PLAG1, HMGA1) [activation]
  - 2. Tumor suppressor genes (p53, RB1, NF1, INI1) [loss of function]
  - 3. Caretaker genes [loss of function]

GENETICS OF CONNECTIVE TISSUE NEOPLASMS

- Hallmarks of cancer (Hanahan & Weinberg):
  - 1. self-sufficiency in growth signals
  - 2. insensitivity to growth-inhibitory signals
  - 3. evasion of apoptosis
  - 4. limitless replicative potential
  - 5. sustained angiogenesis
  - 6. tissue invasion and metastasis

GENETICS OF CONNECTIVE TISSUE NEOPLASMS

- Numerous cancer-specific genetic alterations have been described, unfortunately almost exclusively for soft tissue neoplasms.
- Some of them (such as translocations, numerical changes, large deletions and gene amplifications) are seen at the cytogenetic level.
- Subtle changes (such as single base pair substitutions, small deletions) require molecular genetic detection.
- Translocations constitute the majority of the specific genetic alterations associated with sarcomas.

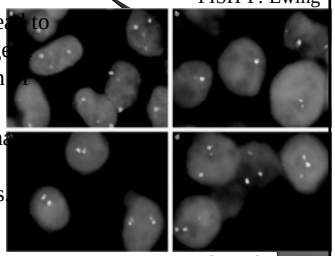
GENETICS OF CONNECTIVE TISSUE NEOPLASMS

- The model of multistep carcinogenesis derived from the study of carcinomas (e.g. adenoma-carcinoma sequence), does not apply to sarcomas.
- Not many "precursor" lesions in sarcomas.

GENETICS OF SOFT TISSUE TUMORS

- Many chromosomal translocations and other genetic rearrangements lead to formation of oncogenic ge fusions or overexpression normal genes.
- Many of these changes ma be used for diagnosis or confirmation of diagnosis

FISH-F: Ewing



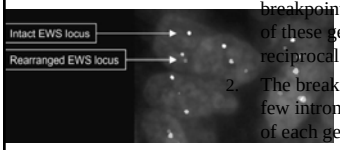
FISH-BA: Ewing

t(11;22)(q24;q12) EWS-FLI1

GENE FUSIONS IN SARCOMAS

- Nonrandom translocations were described first in hematopoietic malignancies.
- Identified in many types of sarcomas and some benign soft tissue tumors.
- Each translocation results in a specific gene fusion.
- Each gene fusion is present in most cases of a specific sarcoma category, and is not present in any other sarcoma type (consistency and specificity).

GENE FUSIONS IN SARCOMAS



FISH with dual color break-apart probe cocktail flanking the EWS breakpoint region at 22q12

1. These translocations disrupt genes located at the chromosomal breakpoints and juxtapose portions of these genes to create two reciprocal chimeric genes.
2. The breaks are confined to one or a few introns within the coding region of each gene.
3. The chimeric genes are transcribed to generate chimeric transcripts.
4. The chimeric transcripts are translated into chimeric proteins.

TABLE 4-1 RECURRENT CHROMOSOMAL TRANSLOCATIONS IN BENIGN AND MALIGNANT SOFT TISSUE TUMORS

Soft tissue tumor	Translocation	Gene fusion	Approximate prevalence*
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14)	*PAX3-FKHR*	65%
	t(1;13)(p36;q14)	*PAX7-FKHR*	15%
Angiomatoid fibrous histiocytoma	t(2;22)(q33;q12)	*EWS-CREB1*	*
	t(12;22)(q13;q12)	*EWS-ATF1*	*
	t(12;16)(q13;p11)	*FUS-ATF1*	*
Alveolar soft part sarcoma	t(X;17)(p11;q25)†	*ASPL-TFE3*	>95%
Clear cell sarcoma	t(12;22)(q13;q12)	*EWS-ATF1*	>90%
	t(2;22)(q33;q12)	*EWS-CREB1*	*
Dermatofibrosarcoma protuberans/giant cell fibroblastoma	t(17;22)(q21;q13)‡	*COL1A1-PDGFB*	>90%
Desmoplastic fibroblastoma	t(2;11)(q31;q12)	Unknown	*
Desmoplastic small round cell tumor	t(11;22)(p13;q12)	*EWS-WT1*	>95%
Epithelioid hemangioendothelioma	t(1;3)(p36.3;q25)	Unknown	*
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22-q31;q12)	*EWS-NR4A3*	75%
	t(9;17)(q22;q11)	*TAF15-NR4A3*	25%
Ewing sarcoma/PNET	t(11;22)(q24;q12)	*EWS-FLI1*	90%
	t(21;22)(q22;q12)	*EWS-ERG*	5%
	t(7;22)(p22;q12)	*EWS-ETV1*	<1%
	t(2;22)(q33;q12)	*EWS-FEV*	<1%
	t(17;22)(q12;q12)	*EWS-E1AF*	<1%
	t(16;21)(p11;q22)	*FUS-ERG*	<1%
Fibromyxoid sarcoma (low-grade)	t(7;16)(q33;p11.2)	*FUS-CREB3L2*	>95%
	t(11;16)(p13;p11.2)	*FUS-CREB3L1*	<5%
Giant cell tumor of tendon sheath	t(1;2)(p13;q37)	*CSF1-COL6A3*	*
Infantile fibrosarcoma	t(12;15)(p13;q26)	*ETV6-NTRK3*	>95%
Inflammatory myofibroblastic tumor	t with 2p23	*ALK* fusions	>50%
Lipoblastoma	t with 8q12	*PLAG1* fusions	*
Lipoma, ordinary	t with 12q15	*HMGA2* fusions	*
	t with 6p21	*HMGA1* rearrangements§	*
Myxoid/round cell liposarcoma	t(12;16)(q13;p11)	*FUS-CHOP*	>95%
	t(12;22)(q13;q11)	*EWS-CHOP*	<5%
Pericytoma	t(7;12)(p22;q13)	*ACTB-GLI*	*
Synovial sarcoma	t(X;18)(p11.2;q11.2)	*SYT-SSX1*	65%
		SYT-SSX2	35%
		SYT-SSX4	<1%

* Insufficient data to estimate prevalence.
† Translocation usually present in unbalanced form as der(X) only (see text for details).
‡ Translocation usually present and amplified as ring chromosome (see text for details).
§ *HMGA1* rearrangements usually do not result in fusion transcripts (see text for details).

GENE FUSIONS IN SARCOMAS

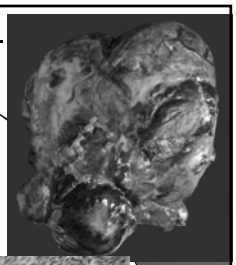
- The novel protein products have significantly altered functional properties.
- In many cases, one or both involved genes are transcription factors, and the chimeric product is a novel transcription factor.

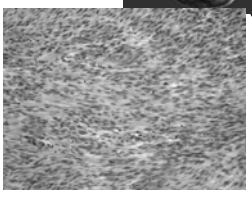
GENE FUSIONS IN SARCOMAS

- These translocations:
  1. represent fundamental genetic steps in the development of these cancers
  2. are useful markers for the diagnosis
  3. may constitute new therapeutic targets

GIST

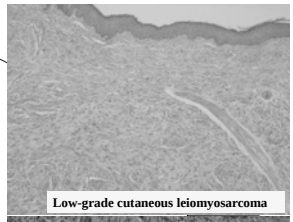
- KIT mutations occur in 80-95% of GISTs (the remaining cases have mutations of PDGFRA, another receptor tyrosine kinase) and lead to ligand-independent phosphorylation and constitutional activation of the KIT signaling pathway to the nucleus.
- In GISTs this mutation is the primary tumorigenic event.
- Imatinib mesylate (Gleevec) is an ATP analogue that binds to KIT and negates the effect of the activating mutation.
- Over 50% of patients with GIST respond to oral administration of Gleevec.
- Gleevec also effective in patients with DFSP (they carry mutation of PDGFRA).



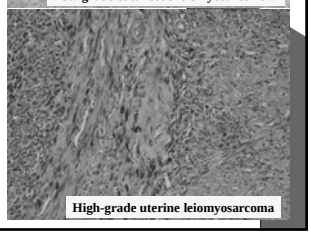


GRADING

- Grading is an arbitrary estimate of the degree of malignancy of a neoplasm (basically an attempt to determine the biological potential of a tumor).
- The purpose of grading is to provide guidance for prognostic prediction and treatment (mainly to determine the need for adjuvant therapy).
- Other independent variables evaluated with grading are tumor size and depth, margins of resection, and clinical situation.



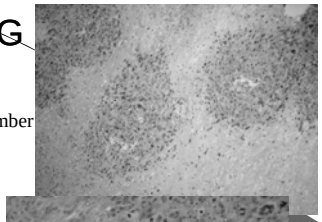
Low-grade cutaneous leiomyosarcoma

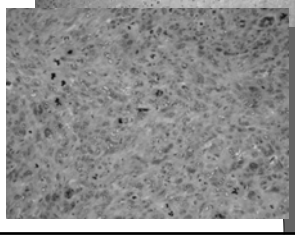


High-grade uterine leiomyosarcoma

GRADING

- Weak points of grading:
  - Subjective elements (number of mitoses, percent of necrosis, tumor differentiation)
  - Sampling
  - Frequent vs. rare tumors



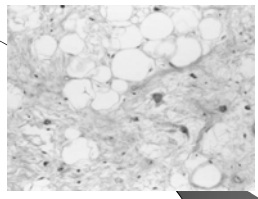


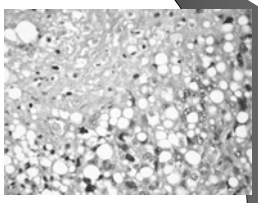
MFH

Well-differentiated liposarcoma

GRADING

- Grading is an element of any current staging system.
- Correct grading requires correct histologic typing of the sarcoma, as demonstrated by the inclusion of "histologic type" as a grading variable.

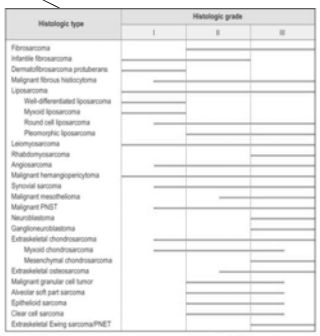




Pleomorphic liposarcoma

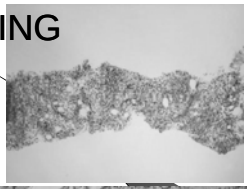
GRADING

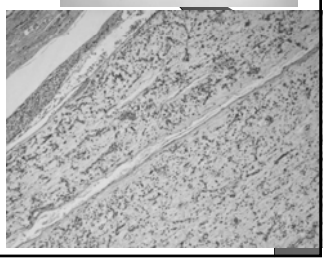
- Any diagnostic entity has a range of malignancy.
- The grade within the overall range depends on the histologic features (cellularity, pleomorphism, mitotic activity, necrosis, etc.)



GRADING

- **Grading applies best to excision specimen because biopsies may be non-representative of the correct grade.**
- Preoperative treatments, such as radiation, chemotherapy, or embolization, can make grading of the resection specimen inapplicable.





GRADING- ST SARCOMAS

GRADING SYSTEM SOFT TISSUE SARCOMAS (FFCC)	
	Score (1-3)
TUMOR DIFFERENTIATION	
well diff	1
defined histogenetic types	2
poorly diff & undef histogenesis	3
MITOTIC COUNT	
0-9/10HPF	1
10-19/HPF	2
>20 HPF	3
TUMOR NECROSIS	
none	0
<50%	1
>50%	2
HISTOLOGIC GRADE	Sum of scores
1	2 or 3
2	4 or 5
3	6, 7 or 8

GRADING-ST SARCOMAS

DIFFERENTIATION SCORE 1
Well differentiated sarcoma (fibro-, lipo-, leiomyo-, chondro-)
Well differentiated MPNST (neurofibroma with malignant transformation)
DIFFERENTIATION SCORE 2
Conventional fibrosarcoma, leiomyosarcoma, angiosarcoma
Conventional MPNST
Myxoid sarcomas (MFH, liposarcoma, chondrosarcoma)
Storiform-pleomorphic MFH
DIFFERENTIATION SCORE 3
Sarcomas of undefined histog. (ASPS, SS,ES,CCS, undiff. Sarc.,malig. rhabdoid tumor)
Ewing family of tumors
Pleomorphic sarcomas (lipo-, leio-)
Round cell and pleomorphic liposarcoma
Rhabdomyosarcoma (except botryoid and spindle cell)
Poorly differentiated angiosarcoma
Triton tumor, epithelioid MPNST
Extraskeletal mesenchymal CS, and osteosarcoma
Giant-cell and inflammatory MFH

STAGING OF ST SARCOMAS

- Staging gives powerful information about survival.

5-yr survival	
Stage	**%**
I	**86**
II	**72**
III	**52**
IV	**10-20**

NEJM 2005; 353: 701-711

STAGING

- The stage is an estimate of the extent or dissemination of a tumor (and in the current systems includes tumor grade).
- Staging is important for planning of treatment and prognostication.
- Clinical data and imaging studies are part of staging process
- (Visceral sarcomas excluded)

BONE SARCOMAS

- Like ST sarcomas, bone sarcomas need to be graded (grading is an important element of the staging and determines if the tumor is stage I or II).
- The TNM system for bone sarcomas follows a 2 tier grading system: low- and high-grade.

STAGING (G-TNM)- ST SARCOMAS

STAGE	GRADE	PRIMARY TUMOR	LYMPH NODES	METASTASIS
I - IV	LOW OR HIGH	T1 (<5 CM) OR T2 (>5 CM)	NEG/POS	ABSENT/PRESENT
IA	LOW	T1a or T1b	NEGATIVE	ABSENT
IB	LOW	T2a or T2b	NEGATIVE	ABSENT
IIA	HIGH	T1a or T1b	NEGATIVE	ABSENT
IIB	HIGH	T2a	NEGATIVE	ABSENT
III	HIGH	T2b	NEGATIVE	ABSENT
IV	ANY	ANY	POSITIVE	ABSENT
	ANY	ANY	POSITIVE OR NEGATIVE	PRESENT

"a" superficial tumors of trunk and extremities (above fascia)
"b" deep tumors of trunk and extremities or intra-abdominal, intra-thoracic or retro-peritoneal

BONE TUMORS

- The staging of bone sarcomas follows the TNM system.

Primary tumor (T)	TX	Primary tumor cannot be assessed
	T0	No evidence of primary tumor
	T1	Tumor less or equal to **8** cm in greatest dimension
	T2	Tumor equal or more than **8** cm in greatest dimension
	T3	**Discontinuous tumors** in the primary bone site
Regional lymph nodes (N)	NX	Regional lymph nodes cannot be assessed
	NO	No regional lymph node metastasis
	N1	Regional lymph node metastasis
Distant metastases (M)	MX	Distant metastasis cannot be assessed
	M0	No distant metastasis
	M1	Distant metastasis:
		M1a: lung
		M1b: other sites

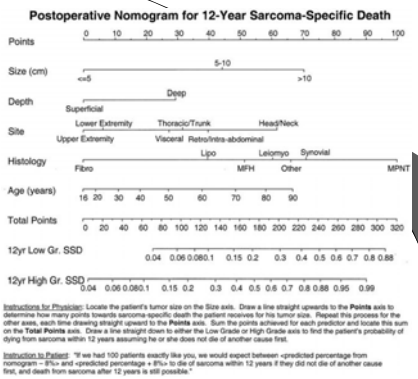
AJCC Cancer Staging Manual, 6th Edition, Springer, New York

BONE TUMORS

Stage IA	T1	N0, NX	M0	Low grade
Stage IB	T2	N0, NX	M0	Low grade
Stage IIA	T1	N0, NX	M0	High grade
Stage IIB	T2	N0, NX	M0	High grade
Stage III	T3	N0, NX	M0	Any grade
Stage IVA	Any T	N0, NX	M1a	Any grade
Stage IVB	Any T	N1	Any M	Any grade
	Any T	Any N	M1b	Any grade

AJCC Cancer Staging Manual, 6th Edition, Springer, New York

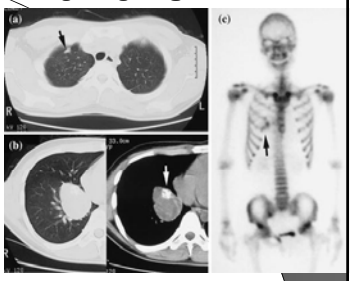
PROGNOSIS



Kattan MW et al. J Clin Oncol 2002; 20: 791-796

BONE TUMORS

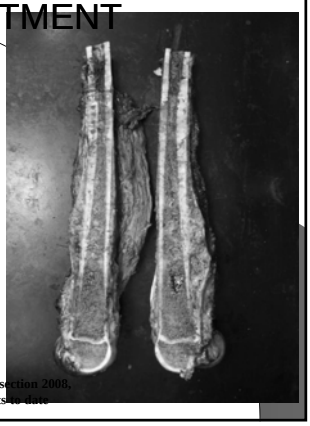
- Stage I: low grade intra-compartmental (risk of metastasis <25%)
- Stage II: high-grade extra-compartmental (risk of metastasis >25%)
- Stage III: any grade, discontinuous tumor in the primary bone site
- Stage IV: any grade, metastatic



18M with OS of pelvis. CT scans show two pulmonary metastatic lesions, **a** a smaller one in the right upper lobe and **b** a larger one in the lower lobe with internal calcification. 99mTc scintigram shows increased uptake in the right lung corresponding to the metastatic lesion (**c**)

TREATMENT

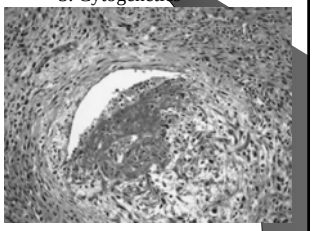
- Surgery and pre- or postoperative external beam radiation treatment in the primary local treatment for most patients with localized disease.
- Adjuvant chemotherapy is usually reserved for patient with high-grade sarcomas.
- Patients with metastatic disease considered for chemotherapy and selected cases may undergo metastasectomy.



Girl with OS distal femur, dx 2007 (@ age 10) , resection 2008, s/p chemo with 100% response, doing fine, no mets to date

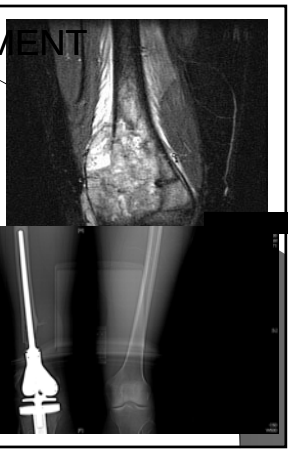
PARAMETERS TO BE INCLUDED IN REPORT OF A SARCOMA

- FINAL REPORT
  - 1. Tumor site, type of excision
  - 2. Depth of the tumor
  - 3. Tumor type and variant
  - 4. Grade (if possible)
  - 5. Tumor size
  - 6. Status of margins & L.N.
  - 7. Percent of necrosis
  - 8. Vascular invasion, if present
- ADDENDUM REPORT(S)
  - 1. Immunohistochemistry
  - 2. Electron microscopy
  - 3. Cytogenetics



TREATMENT

- Currently approximately 90% of patients with localized extremity sarcomas undergo limb-sparing surgery.



31F with OS, 9 years s/p surgery

THAT’S ALL FOLKS!