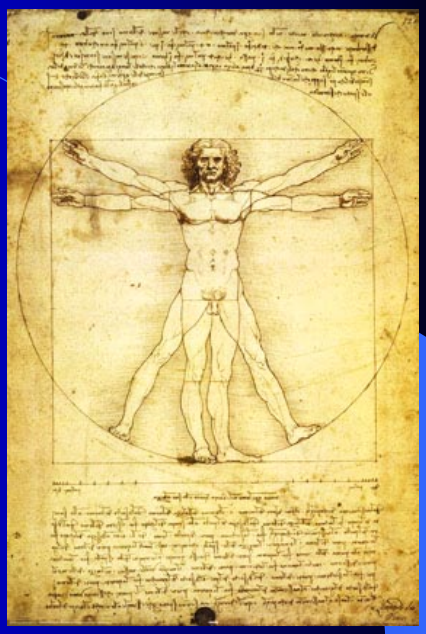
BONE AND SOFT TISSUE TUMORS

- Traditionally bone and soft tissue tumors have been treated separately.
- This separation will be maintained in the following presentation.
- Soft tissue sarcomas will be treated first and the sarcomas of bone will follow.

DEFINITION

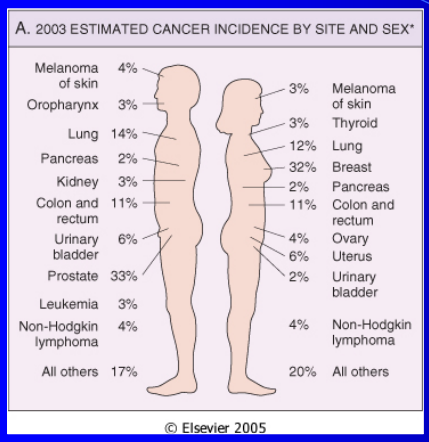


- Soft tissue pathology deals with tumors of the connective tissues.
- The concept of soft tissue is understood broadly to include non-osseous tumors of extremities, trunk wall, retroperitoneum and mediastinum, and head & neck.
- Excluded (with a few exceptions) are organ specific tumors.

EPIDEMIOLOGY

- Sarcomas are rare tumors compared to other malignancies: **8,700** new sarcomas in 2001, with **4,400** deaths.
- The incidence of sarcomas is around **3-4/100,000**.
- Slight male predominance (with some subtypes more common in women).
- Majority of soft tissue tumors affect older adults, but important sub-groups occur predominantly or exclusively in children.
- Incidence of benign soft tissue tumors not known, but probably outnumber malignant tumors **100:1**.

SOFT TISSUE TUMORS



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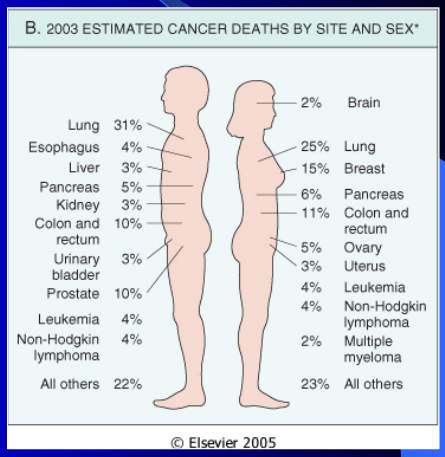


Histological classification of soft tissue tumors


TABLE 1–2 HISTOLOGIC CLASSIFICATION OF SOFT TISSUE TUMORS

Fibroblastic/myofibroblastic tumors
Benign
Nodular fasciitis (including intravascular/cranial)
Proliferative fasciitis/myositis
Organ-associated pseudosarcomatous myofibroblastic proliferations
Ischemic fasciitis
Fibroma of tendon sheath
Pleomorphic fibroma of skin
Nuchal-type fibroma/Gardner-associated fibroma
Elastofibroma
Nasopharyngeal angiofibroma
Keloid
Collagenous fibroma (desmoplastic fibroblastoma)
Fibrous hamartoma of infancy
Infantile digital fibromatosis
Myofibroma/myofibromatosis
Juvenile hyaline fibromatosis
Gingival fibromatosis
Fibromatosis colli
Infantile fibromatosis
Calcifying aponeurotic fibroma
Calcifying fibrous pseudotumor
Intermediate
Adult-type fibromatosis
Superficial (palmar, plantar, penile, knuckle pads)
Deep (extra-abdominal, abdominal, intra-abdominal)
Malignant
Pleomorphic undifferentiated sarcoma/malignant fibrous histiocytoma
Storiform-pleomorphic type
Myxoid type
Giant cell type
Inflammatory type

Lipomatous tumors
Benign
Lipoma
Angiolipoma
Myolipoma
Chondroid lipoma
Spindle cell/pleomorphic lipoma
Lipoblastoma/lipoblastomatosis
Myelolipoma
Hibernoma
Lipomatosis
Intermediate
Atypical lipoma (superficial well-differentiated liposarcoma)
Malignant
Atypical lipomatous tumor/well-differentiated liposarcoma
Lipoma-like
Sclerosing
Spindled
Inflammatory
Myxoid/round cell liposarcoma
Pleomorphic liposarcoma
Dedifferentiated liposarcoma

Smooth muscle tumors and related lesions
Benign
Leiomyoma
Angiomyoma
Intranodal palisaded myofibroblastoma
Mammary myofibroblastoma
Benign genital stromal tumors
Angiomyofibroblastoma
Cellular angiofibroma/angiomyofibroblastoma of male genital tract
Aggressive angiomyxoma
Superficial cervicovaginal myofibroblastoma
Intravenous leiomyomatosis
Leiomyomatosis peritonealis disseminata
Malignant
Leiomyosarcoma

Extragastrointestinal stromal tumors
Benign
Malignant

Skeletal muscle tumors
Benign
Cardiac rhabdomyoma
Adult rhabdomyoma
Fetal rhabdomyoma
Myxoid (classic)
Intermediate (cellular, juvenile)
Genital rhabdomyoma
Malignant
Embryonal rhabdomyosarcoma
Usual type
Botryoid type
Spindle cell type
Alveolar rhabdomyosarcoma
Pleomorphic rhabdomyosarcoma
Sclerosing rhabdomyosarcoma
Other (rhabdoid features, anaplastic features)
Rhabdomyosarcoma with ganglion cells (ectomesenchymoma)

Tumors of blood and lymph vessels
Benign
Papillary endothelial hyperplasia
Hemangioma
Capillary hemangioma
Cavernous hemangioma
Venous hemangioma
Arteriovenous hemangioma
Pyogenic granuloma
Acquired tufted hemangioma
Hobnail hemangioma
Spindle cell hemangioma
Lymphangioma
Lymphomyoma/lymphangiomyomatosis
Angiomatosis
Lymphangiomatosis
Intermediate
Epithelioid hemangioendothelioma
Hobnail hemangioendothelioma (retiform, Dabska-type)
Epithelioid sarcoma-like hemangioendothelioma
Kaposiform hemangioendothelioma
Polymorphous hemangioendothelioma
Malignant
Angiosarcoma
Kaposi sarcoma

Perivascular tumors
Benign
Glomus tumor
Usual type
Glomangioma (glomuvenous malformation)
Glomangiomyoma
Glomangiomatosis
Myopericytoma
Hemangiopericytoma-like tumor of nasal passages

Histological classification of soft tissue tumors

TABLE 1–2 Continued

Malignant
Malignant glomus tumor

Synovial tumors
Benign
Tenosynovial giant cell tumor
Localized type
Diffuse type
Malignant
Malignant tenosynovial giant cell tumor

Mesothelial tumors
Benign
Adenomatoid tumor
Intermediate
Multicystic mesothelioma
Well-differentiated papillary mesothelioma
Malignant
Diffuse mesothelioma
Epithelial type
Sarcomatoid type
Biphasic type

Peripheral nerve sheath tumors and related lesions
Benign
Traumatic neuroma
Mucosal neuroma
Pacinian neuroma
Palisaded encapsulated neuroma
Morton's interdigital neuroma
Nerve sheath ganglion
Neuromuscular hamartoma
Neurofibroma
Usual type (localized)
Diffuse
Plexiform
Epithelioid
Pigmented
Schwannoma
Usual type
Cellular
Plexiform
Degenerated (ancient)
Epithelioid
Neuroblastoma-like
Melanotic schwannoma
Perineurioma
Intraneural
Extraneural
Granular cell tumor
Neurothekeoma
Myxoid type
Cellular type
Ectopic meningioma
Glial heterotopia
Malignant
Malignant peripheral nerve sheath tumor (MPNST)
Usual type
MPNST with rhabdomyoblastic differentiation (malignant Triton tumor)
Glandular MPNST
Epithelioid MPNST
Malignant granular cell tumor
Clear cell sarcoma of tendon and aponeurosis
Malignant melanotic schwannoma
Extraspinal ependymoma

Primitive neuroectodermal tumors and related lesions
Benign
Ganglioneuroma
Pigmented neuroectodermal tumor of infancy (retinal anlage tumor)
Malignant
Neuroblastoma
Ganglioneuroblastoma
Ewing sarcoma/primitive neuroectodermal tumor
Malignant pigmented neuroectodermal tumor of infancy

Paraganglionic tumors (paraganglioma)
Benign
Malignant

Extraskeletal osseous and cartilaginous tumors
Benign
Myositis ossificans
Fibro-osseous pseudotumor of digits
Fibrodysplasia ossificans progressiva
Extraskeletal chondroma/osteochondroma
Extraskeletal osteoma
Malignant
Extraskeletal chondrosarcoma
Well-differentiated chondrosarcoma
Myxoid chondrosarcoma
Mesenchymal chondrosarcoma
Extraskeletal osteosarcoma

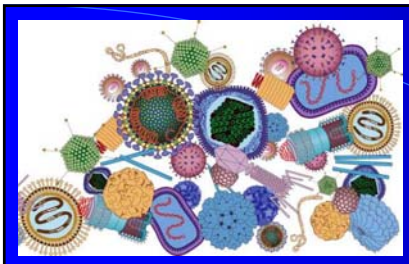
Miscellaneous tumors
Benign
Tumoral calcinosis
Congenital granular cell tumor
Myxoma
Cutaneous
Intramuscular
Juxta-articular myxoma
Ganglion
Amyloid tumor
Intermediate
Ossifying fibromyxoid tumor
Inflammatory myxohyaline tumor
Mixed tumor/myoepithelioma/parachordoma
Pleomorphic hyalinizing angiectatic tumor
Hemangiopericytoma/solitary fibrous tumor/giant cell angiofibroma
Perivascular epithelioid cell family of tumors (PEComa)
Malignant
Synovial sarcoma
Alveolar soft part sarcoma
Epithelioid sarcoma
Desmoplastic small round cell tumor
Malignant extrarenal rhabdoid tumor

ETIOLOGY

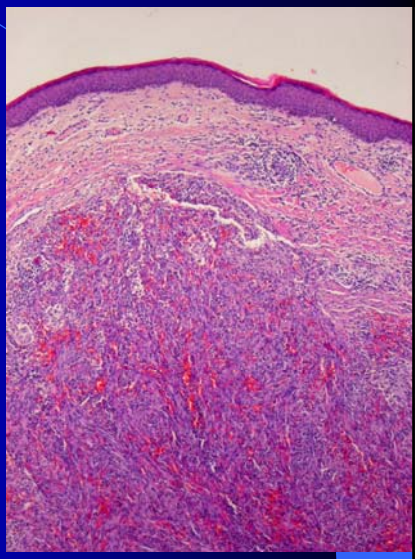
- The etiology of soft tissue sarcomas is poorly understood, and what is known apply only to a small fraction of the group.
- The known etiologic agents are ionizing radiation, oncogenic viruses, and chemicals.
- These agents are able to cause genetic alterations that can lead to tumorigenesis.

ETIOLOGY

- 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).

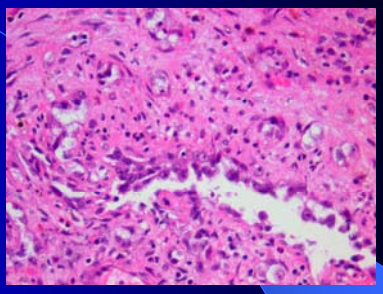


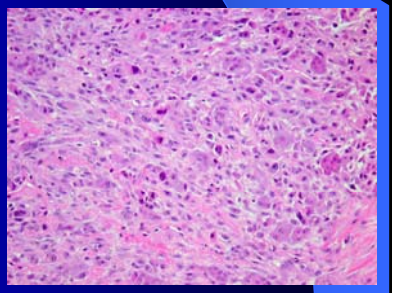
ETIOLOGY



- 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

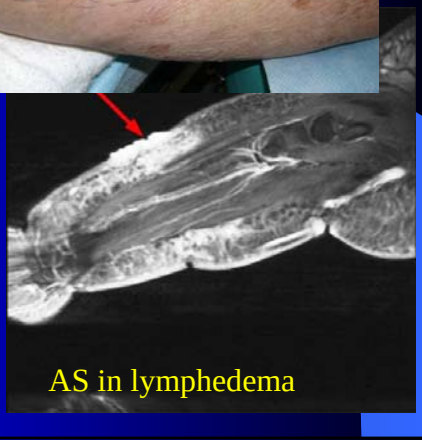




- Herbicides (“agent orange”) and peripheral soft tissue sarcomas
- Retained metal objects (shrapnel, surgical devices) and AS and MFH
- Vinyl chloride, inorganic arsenic, Thorotrast, anabolic steroids linked to AS and MFH.

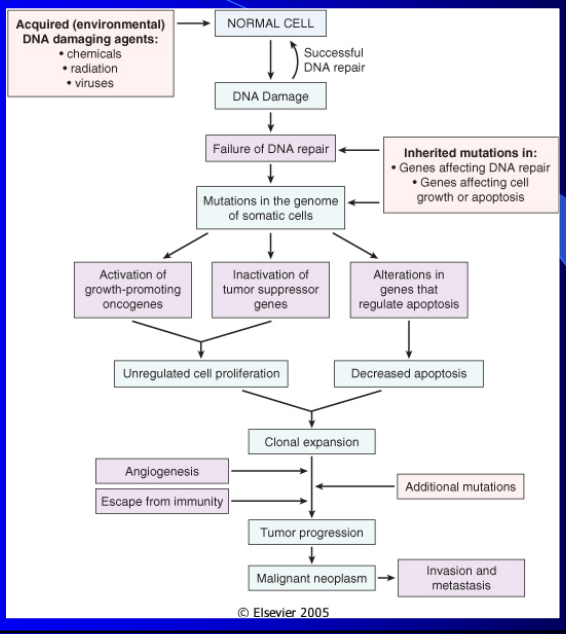
ETIOLOGY

- 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

SOFT TISSUE TUMORS



CONGENITAL SYNDROMES ASSOCIATED WITH BONE AND SOFT TISSUE TUMORS

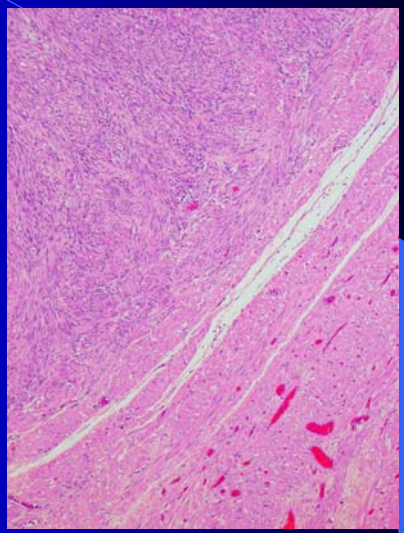
Disorder	Inheritance	Locus	Gene	Tumor
Albright hereditary osteodystrophy	AD	20q13	GNAS1	Soft tissue calcifications and osteomas
Bannayan -Riley- Ruvalcaba syndrome	AD	10q23	PTEN	Lipomas, hemangiomas
Beckwith- Wiedemann syndrome	Sp/AD	11p15	Complex	Embryonal RMS, myxomas, fibromas, hamartomas
Bloom syndrome	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

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

CLASSIFICATION

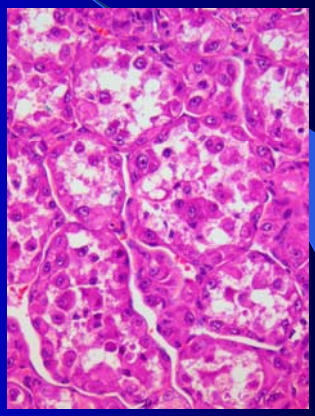
- All tumors are derived from stem cells that are programmed to differentiate into various mature cell types.
- Some of the stem cells probably belong to local, organ-specific pools, as underscored by the fact that many tumors resemble tissues present in the region
- Other involved stem cells may be bone marrow derived.



Vascular leiomyosarcoma

CLASSIFICATION

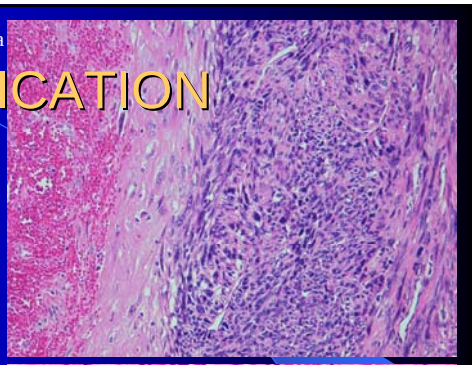
- However, some tumors have no resemblance to normal tissue in the region (metaplastic foci within a tumor, or tumors of different histogenesis from the normal cells of the region)
- Some sarcomas have no normal cell counterparts, probably reflecting an unique genetic makeup.



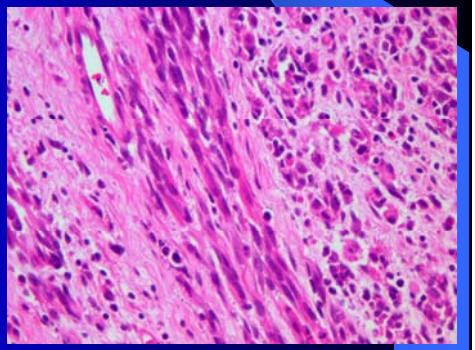
Alveolar soft part sarcoma

Uterine leiomyosarcoma

CLASSIFICATION



- Purpose of classification is to link similar tumors in order to understand their behavior, determine the most appropriate treatment, and investigate their biology.
- Soft tissue tumors are classified according to the cell type they resemble.



Embryonal rhabdomyosarcoma

CLASSIFICATION

- 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.

CLASSIFICATION

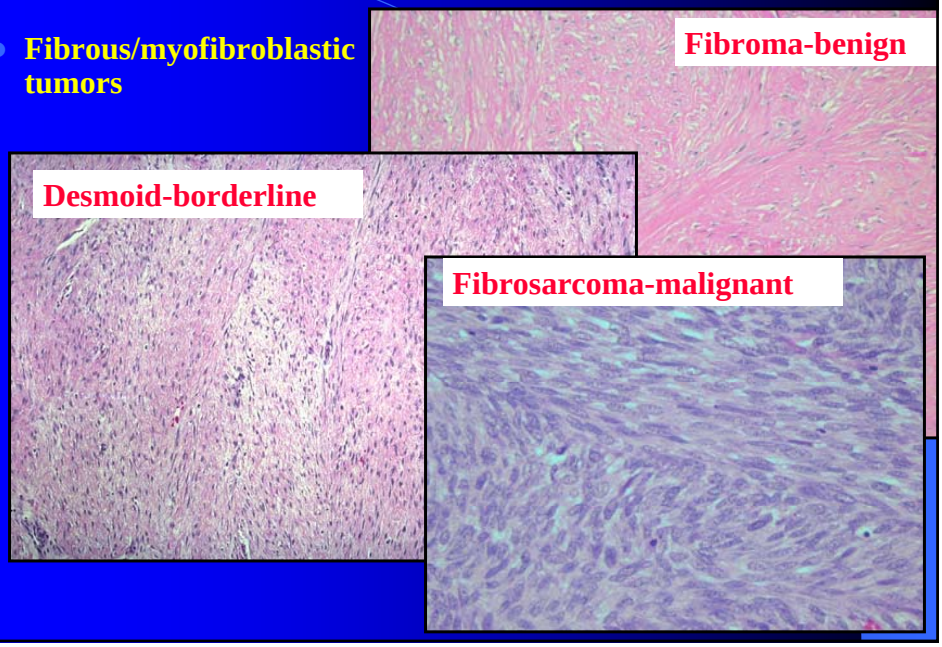
- Tumors are also classified according their biologic potential.
- A three-tiered system is used:
  - **1. Benign**
  - **2. Borderline (intermediate malignant)**
  - **3. Malignant.**

SOFT TISSUE TUMORS

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

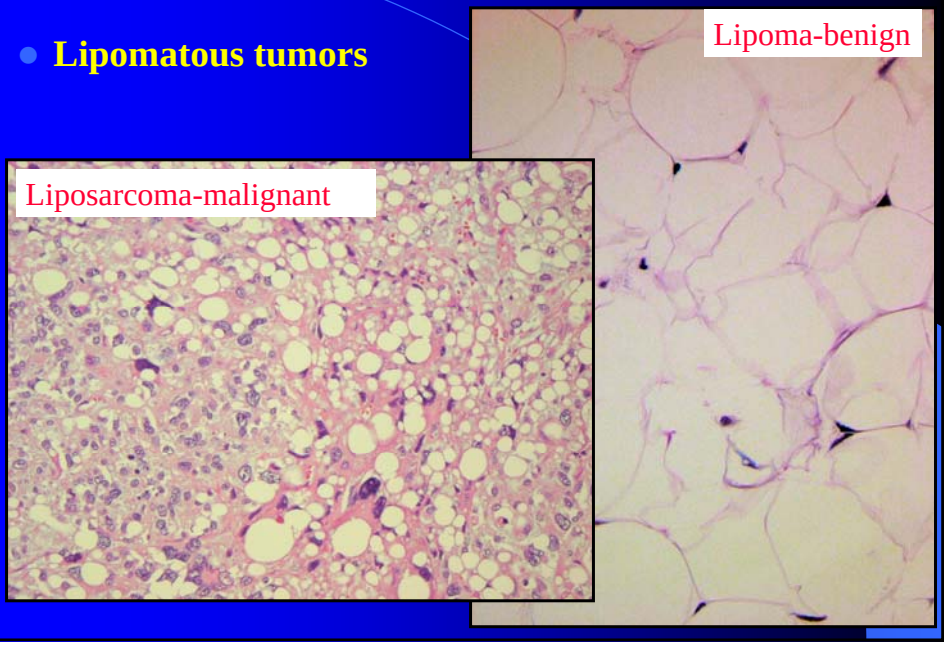
SOFT TISSUE TUMORS

- **Fibrous/myofibroblastic tumors**



SOFT TISSUE TUMORS

- **Lipomatous tumors**

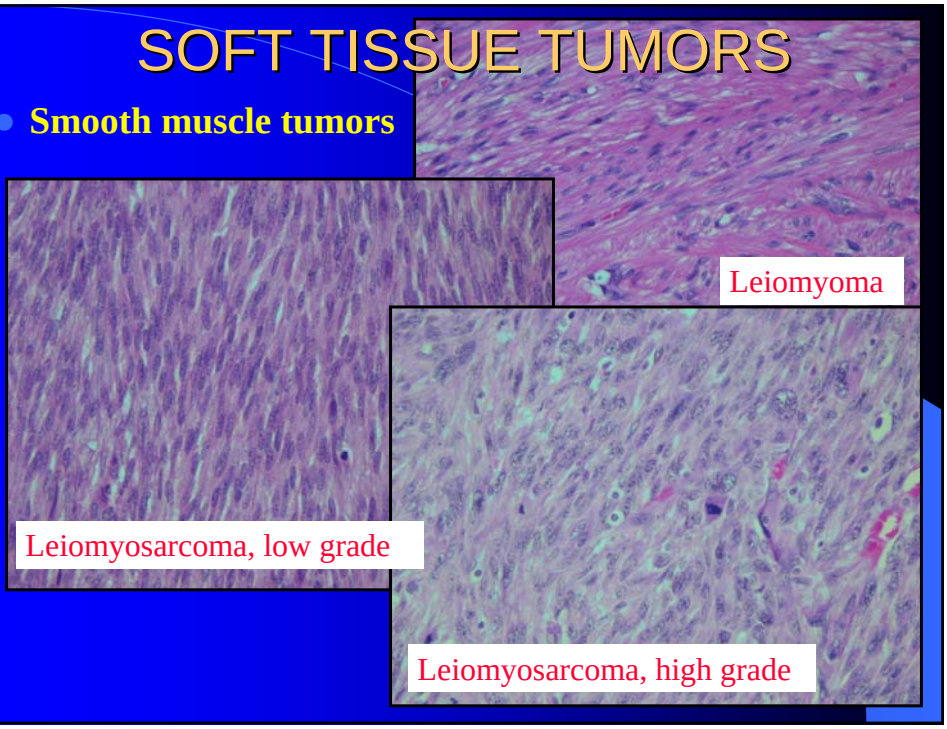


Lipoma-benign

Liposarcoma-malignant

SOFT TISSUE TUMORS

- **Smooth muscle tumors**



Leiomyoma

Leiomyosarcoma, low grade

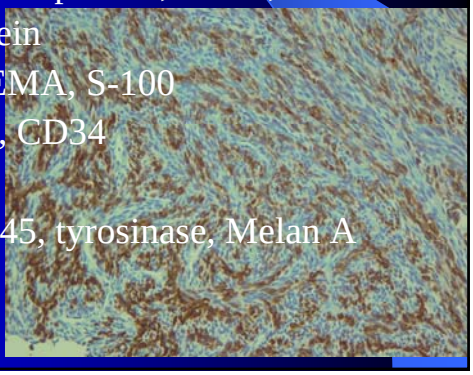
Leiomyosarcoma, high grade

IMMUNOHISTOCHEMISTRY

- Immunohistochemistry is the most practical way to evaluate the presence of certain protein and carbohydrate epitopes on tissue sections.
- Evaluation of cell- or tumor-type specific or cell-cycle related markers may have diagnostic significance.
- Very few markers are specific for one tumor type.
- No cell-cycle marker is able to separate benign and malignant tumors.

IMMUNOHISTOCHEMISTRY

- Myofibroblastic tumors: SMA, HHF35
- Smooth muscle tumors: desmin, SMA, HHF35
- Skeletal muscle tumors: desmin, myogenin, Myo-D1, myoglobin
- Nerve sheath tumors: S-100 protein, CD34, EMA
- Fatty tumors: S-100 protein
- Synovial sarcoma: CK, EMA, S-100
- Epithelioid sarcoma: CK, CD34
- Carcinomas: CK, EMA
- Melanoma: S-100, HMB45, tyrosinase, Melan A



Cam 5.2- synovial sarcoma

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.

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 the histologic type as a grading variable.

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

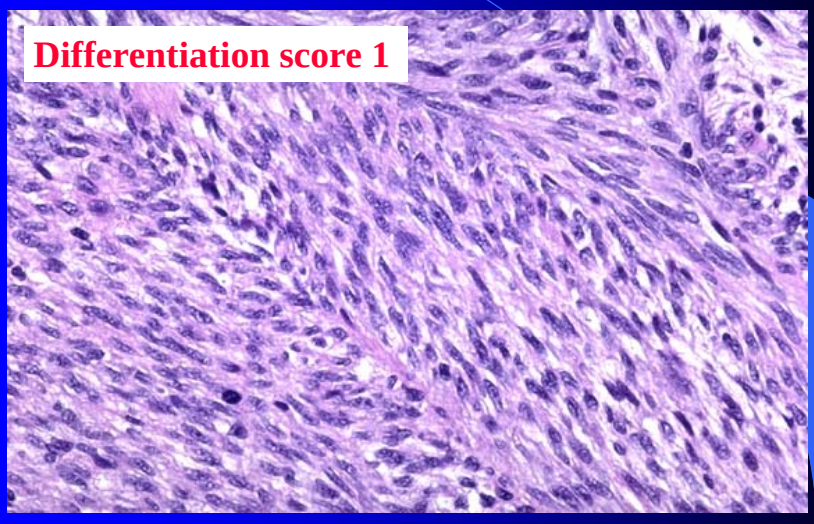
GRADING

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

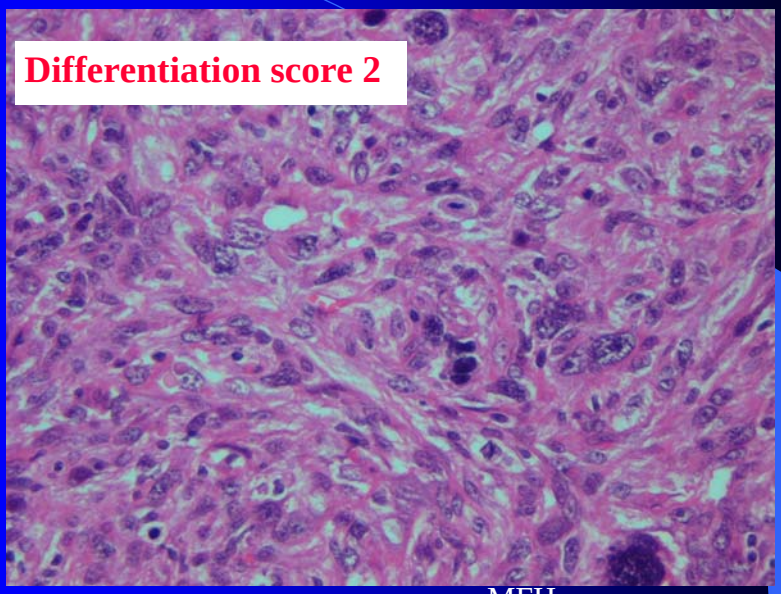
DIFFERENTIATION SCORE 1
Well differentiated sarcoma (fibro-, lipo-, leiomyo-, chondro-)
Well differentiated MPNST (neurofibroma with malignant transformation)
DIFFERENTIATION SCORE 2
Conventional fibrosarcoma, leiomyosarcoma, angiosarcoma
Conventional MPNST
Myxoid sarcomas (MFH, liposarcoma, chondrosarcoma)
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

GRADING



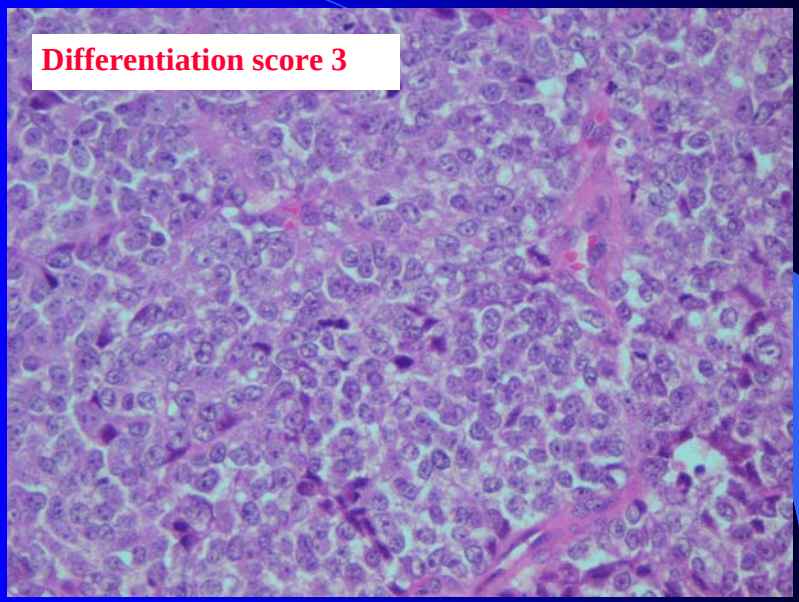
Fibrosarcoma

GRADING



MFH

GRADING



Ewing sarcoma

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)

STAGING (G-TNM)

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

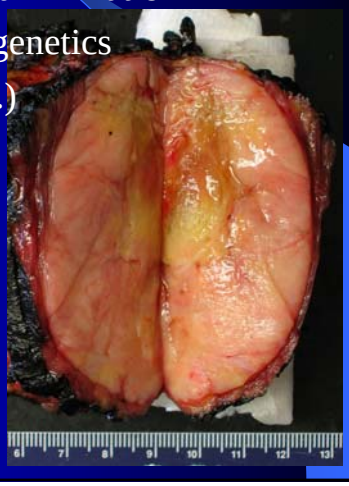
STAGING OF SARCOMAS

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

NEJM 2005; 353: 701-711

SOFT TISSUE SARCOMAS- COMPREHENSIVE ANALYSIS

- Gross examination
- Evaluation of inked margins
- Gross description and tumor measurements
- Photograph
- Sampling of tumor and margins
- Frozen sections for diagnostic or triaging purposes
- Frozen tissue procurement
- Formalin fixation
- Cytogenetics
- (E.M.)

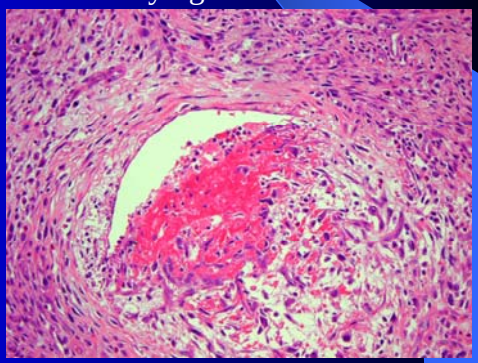


SOFT TISSUE SARCOMAS MARGINS

DESCRIPTION	INTERPRETATION
INTRALESIONAL	The surgical plane of dissection passes through tumor tissue.
MARGINAL	The surgical plane of dissection passes through the pseudocapsule, without microscopic evidence of tumor.
WIDE	The surgical plane of dissection passes outside the reactive zone and through normal tissue.
RADICAL	The surgical margins are all wide and include the entire anatomical compartment(s) involved by the tumor.
CONTAMINATED	A margin obtained by the surgical re-excision of the wound previously found to be microscopically intra-lesional in the same operative procedure.

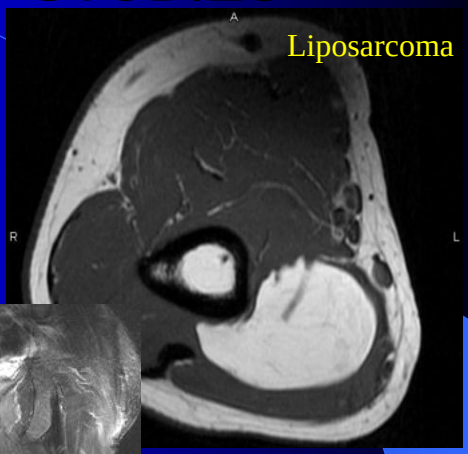
PARAMETERS TO BE INCLUDED IN REPORT OF A SARCOMA

- 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

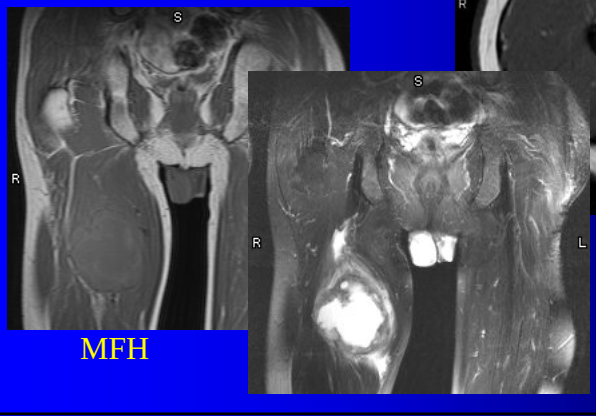


IMAGING STUDIES

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



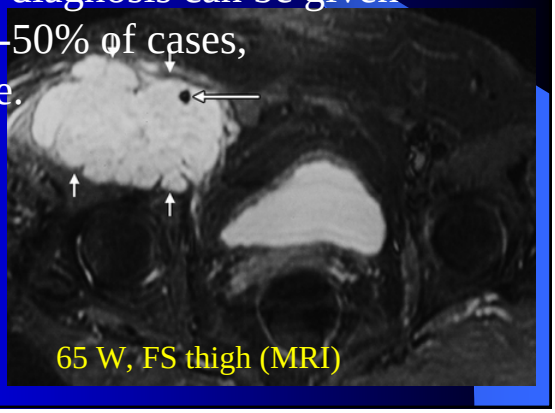
Liposarcoma



MFH

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)

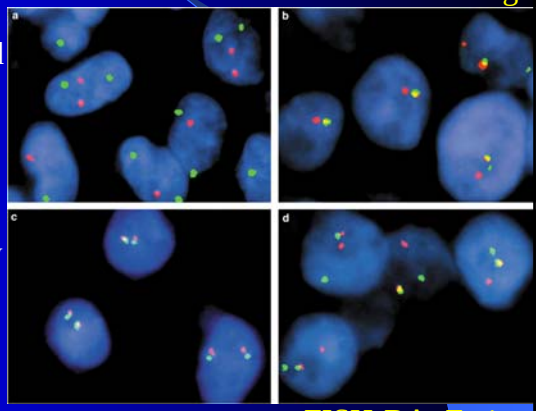
GENETICS OF SOFT TISSUE TUMORS

- Numerous cancer-specific genetic alterations have been described.
- 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.

GENETICS OF SOFT TISSUE TUMORS

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

FISH-F: Ewing



FISH-BA: Ewing

t(11;22)(q24;q12)

GENE FUSIONS IN SARCOMAS

- Nonrandom translocations were described first in hematopoietic malignancies.
- Identified in many types of sarcomas.
- Also identified in 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.
- These genetic events demonstrate consistency and specificity.

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

Soft tissue tumor	Translocation	Gene fusion	Approximate prevalence[1]
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)[2]	*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)[3]	*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-q3;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[4]	*
Myxoid/round cell liposarcoma	t(12;16)(q13;p11)	*FUS-CHOP*	>95%
	t(12;22)(q13;q11)	*EWS-CHOP*	<5%
Pericytoma	t(7;12)(p2;q13)	*ACTB-GLI*	*
Synovial sarcoma	t(X;18)(p11.2;q11.2)	*SYT-SSX1*	65%
		SYT-SSX2	35%
		SYT-SSX4	<1%

[1] Insufficient data to estimate prevalence.
[2] Translocation usually present in unbalanced form as der(X) only (see text for details).
[3] Translocation usually present and amplified as ring chromosome (see text for details).
[4] *HMGA1* rearrangements usually do not result in fusion transcripts (see text for details).

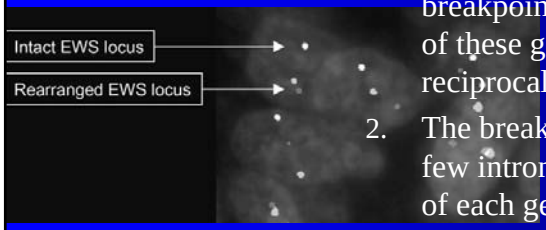
GENE FUSIONS IN SARCOMAS

- 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

GENE FUSIONS IN SARCOMAS

- Investigation of these translocation may:
  1. clarify the molecular etiology of these cancers
  2. help in identifying new markers for diagnosis and monitoring
  3. lead to new therapeutic strategies against tumor-specific markers.

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.

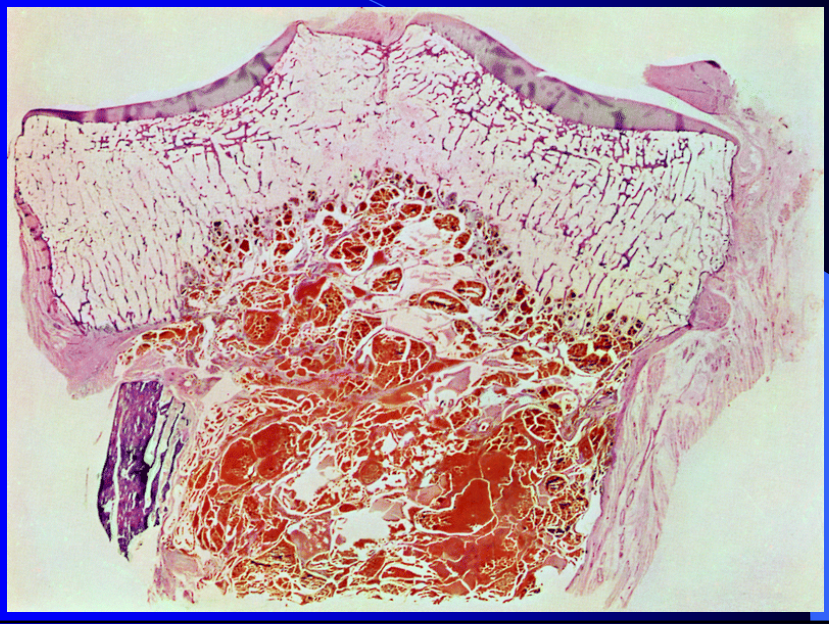
GENE FUSIONS IN SARCOMAS

- 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.

SOFT TISSUE TUMORS SUMMARY

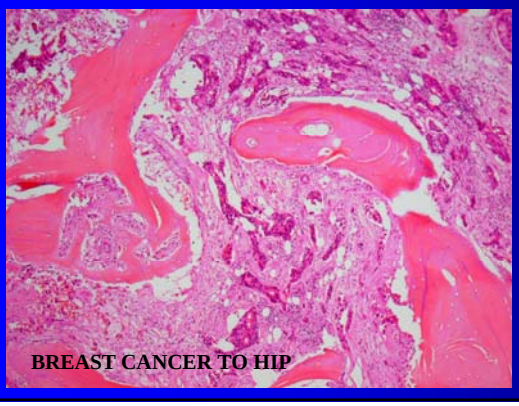
- Tumors of connective tissue.
- Rare (sarcomas: 3-4 cases per 100,000).
- Etiology unclear, with a few exceptions.
- Classified according to tissue they resemble.
- Biologically: benign, borderline or malignant.
- Grading and staging crucial elements to be added to diagnosis.
- Some of the lesions have specific translocations.

BONE TUMORS

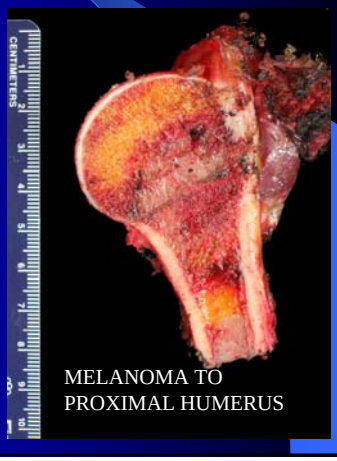


BONE TUMORS

- The majority of tumors involving bone are secondary (or metastatic):
  - secondary (metastases) (95%)
  - primary (5%)



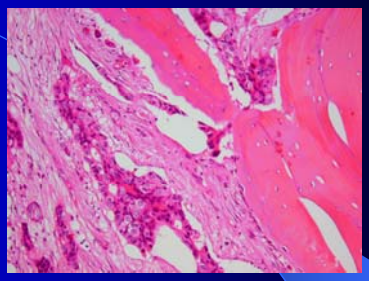
BREAST CANCER TO HIP



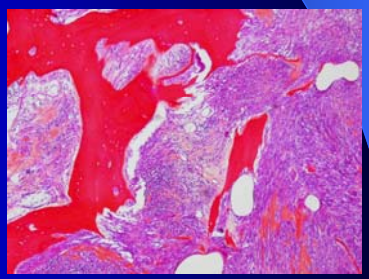
MELANOMA TO PROXIMAL HUMERUS

METASTATIC BONE TUMORS

- Carcinomas are the most common metastatic tumors to bone.
- Other neoplasms may also metastasize to bone (sarcomas, melanomas).



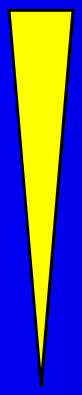
Mammary carcinoma



Uterine leiomyosarcoma

Secondary Tumors of Bone

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



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

BONE TUMORS

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

BONE TUMORS

- In North America and Europe, the incidence rate for bone in males is approximately 0.8 new cases per 100,000 people a year.
- Osteosarcoma is the most common primary malignant tumor of bone (35%), followed by chondrosarcoma (25%) and Ewing sarcoma (16%).
- Chordomas and MFH represent 8 and 5% of the the tumors in the group respectively.

BONE TUMORS

- The majority of bone sarcomas arise de novo.
- Some, however, develop in association with recognizable precursors.

HIGH RISK	Ollier and Maffucci syndrome
	Familial Retinoblastoma syndrome
	Rothmund-Thompson syndrome
MODERATE RISK	Multiple enchondromas
	Polyostotic Paget disease
	Radiation osteitis
LOW RISK	Fibrous dysplasia
	Bone infarct
	Chronic osteomyelitis
	Metallic and polyethylene implants
	Osteogenesis imperfecta
	Giant cell tumor
	Osteoblastoma and Chondroblastoma

WHO CLASSIFICATION OF BONE TUMORS

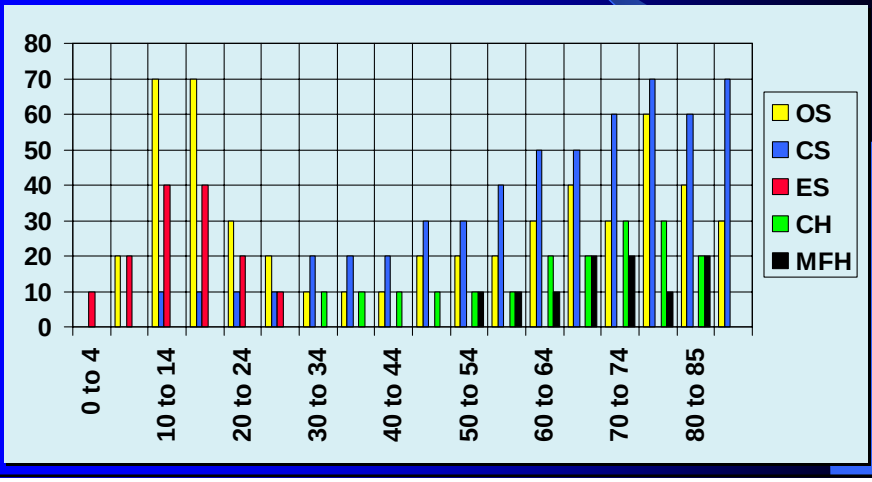
Cartilage tumors	Osteochondroma	
	Chondroma	Enchondroma
		Periosteal chondroma
		Multiple chondromatosis
	Chondroblastoma	
	Chondromyxoid fibroma	
	Chondrosarcoma	Central
		Peripheral
		Dedifferentiated
		Mesenchymal
		Clear cell
Osteogenic tumors	Osteoid osteoma	
	Osteoblastoma	
	Osteosarcoma	Conventional
		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

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

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.

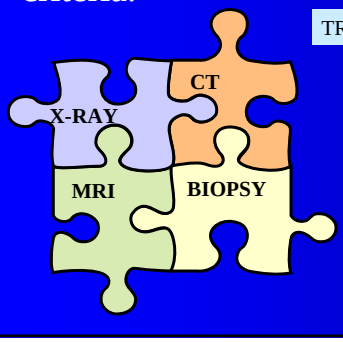


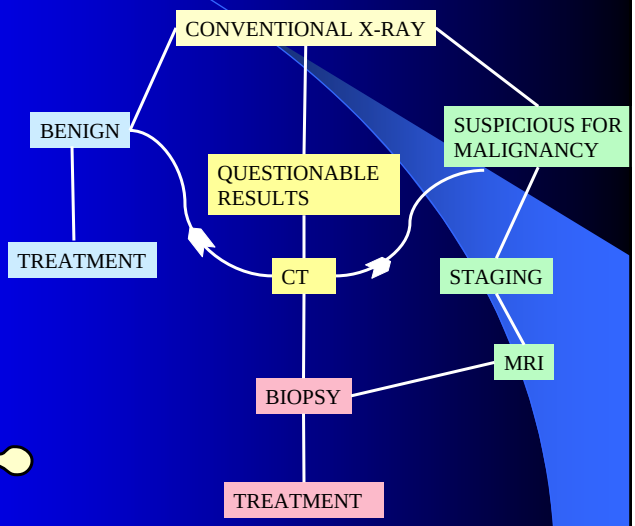
BONE TUMORS

- The clinical presentation of bone tumors is at the beginning non-specific, with pain and swelling presenting first.
- Later, limitation of movement and pathological fracture and general symptoms may occur.
- A long time may elapse until the tumor is diagnosed.

BONE TUMORS BONE TUMORS

- The diagnosis is based on imaging and histological criteria.

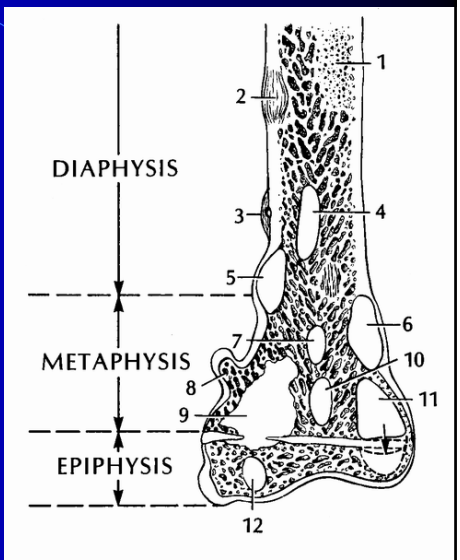




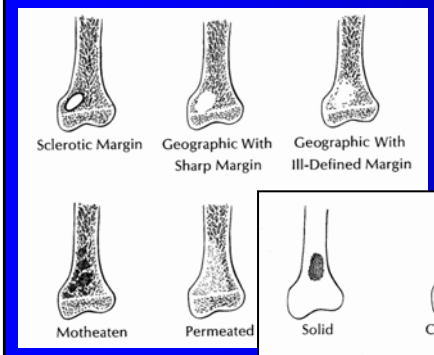
BONE TUMORS

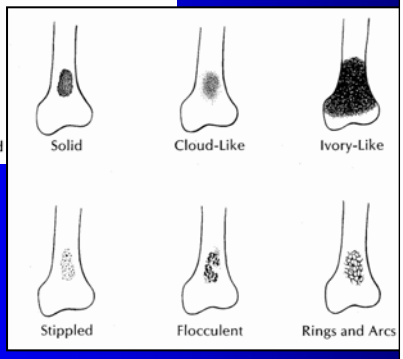
- Conventional radiographs are still important in the diagnosis of bone tumors.
- Many tumors are site-specific.
- Many tumors have a characteristic radiographic appearance.

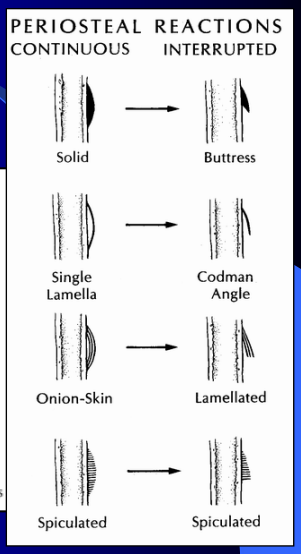
1. **Ewing sarcoma, lymphoma, myeloma**
2. **Osteofibrous dysplasia, adamantinoma**
3. **Osteoid osteoma**
4. **Fibrous dysplasia**
5. **Chondromyxoid fibroma**
6. **Non-ossifying fibroma**
7. **Bone cyst, osteoblastoma**
8. **Osteochondroma**
9. **Osteosarcoma**
10. **Enchondroma, chondrosarcoma**
11.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



BONE TUMORS



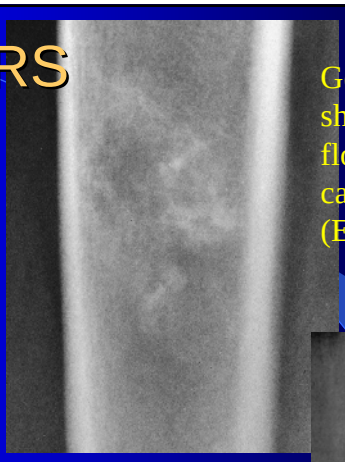




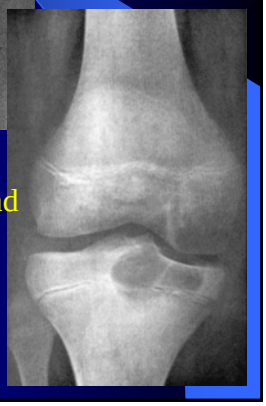
Some fancy words from the world of shadows

BONE TUMORS

- The imaging characteristics of some lesions are diagnostic.
- Even if not clear to the radiologist, the images may help somebody else down the diagnostic chain (e.g. the pathologist)



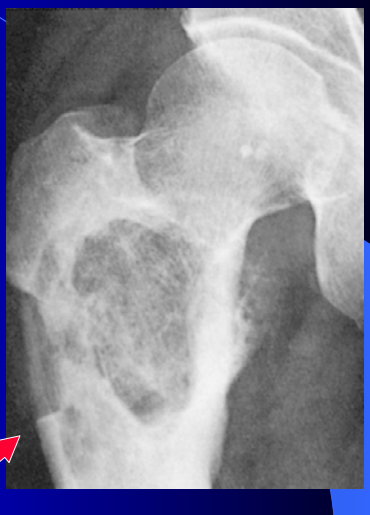
Geographic with sharp margins and flocculent calcifications (Enchondroma)



Sclerotic margin and lytic (Chondroblastoma)

BONE TUMORS

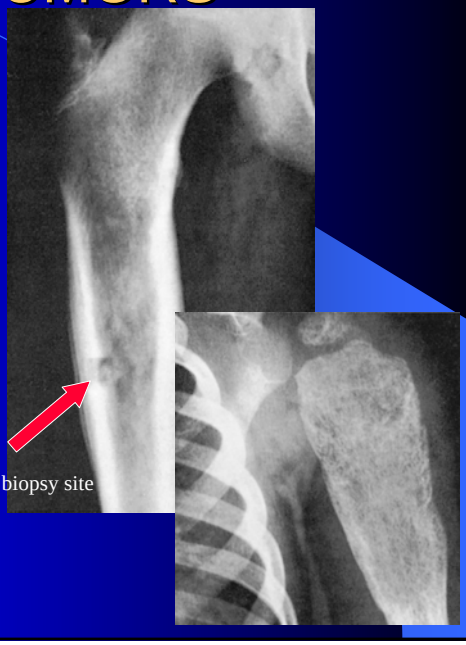
- Geographic with ill defined margins: usually malignant (in this case a primary chondrosarcoma)



Previous biopsy site

BONE TUMORS

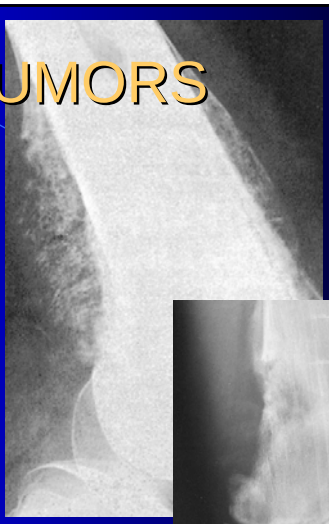
- Moth-eaten and permeated are bad news (unless it's infection)

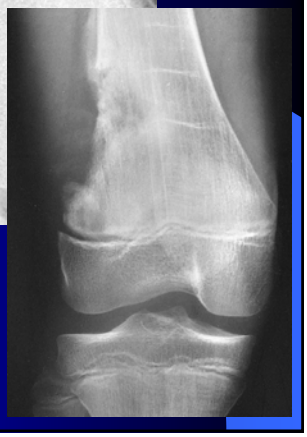


Previous biopsy site

BONE TUMORS

- Periosteal reactions (such as spiculated, Codman's angle, onion skin) are witnesses of cortical destruction and soft tissue extension (usually bad news, unless infective)





BONE TUMORS

- The tumor 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 follows a 2 tier grading system: low- and high-grade.

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

BONE TUMORS

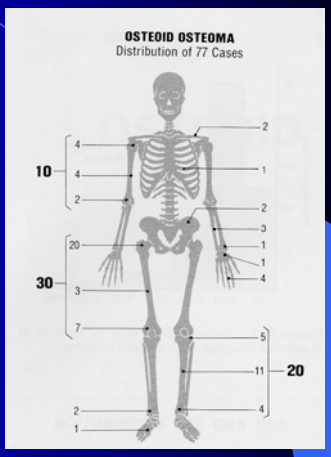
- Stage I: low grade intra-compartmental (risk of metastasis <25%)
- Stage II: high-grade extra-compartmental (risk of metastasis >25%)
- Stage III: any grade, discontinuous tumor in the primary bone site
- Stage IV: any grade, metastatic

BONE-FORMING TUMORS

Osteogenic tumors	**Osteoid osteoma**	
	Osteoblastoma	
	Osteosarcoma	**Conventional**
		Telangiectatic
		Small cell
		Low grade central
		Secondary
		Parosteal
		Periosteal
		High grade surface

OSTEOID OSTEOMA

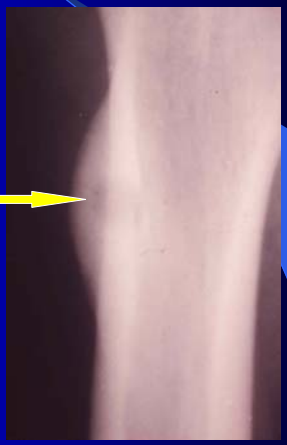
- Benign bone forming tumor.
- Small size, limited growth potential and disproportionate pain.
- Most common in long bones, but every bone may be affected.
- It may be painful on physical examination
- It may be associated with redness of skin and swelling.
- Lesions close to a joint may be associated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



OSTEOID OSTEOMA

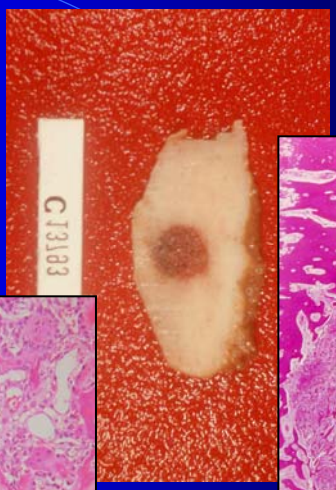
- On plain x-rays the lesion is characterized by dense cortical sclerosis surrounding a radiolucent nidus.
- CT scan best type of imaging study.

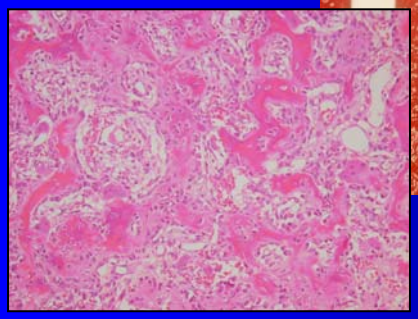
Nidus

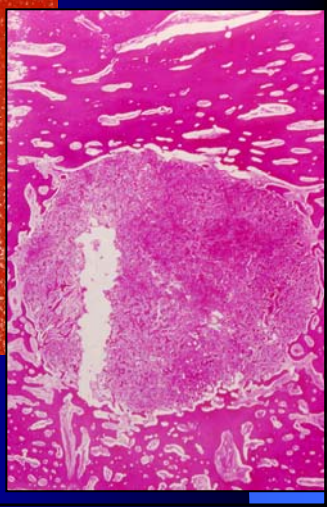


OSTEOID OSTEOMA

- 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.







OSTEOID OSTEOMA

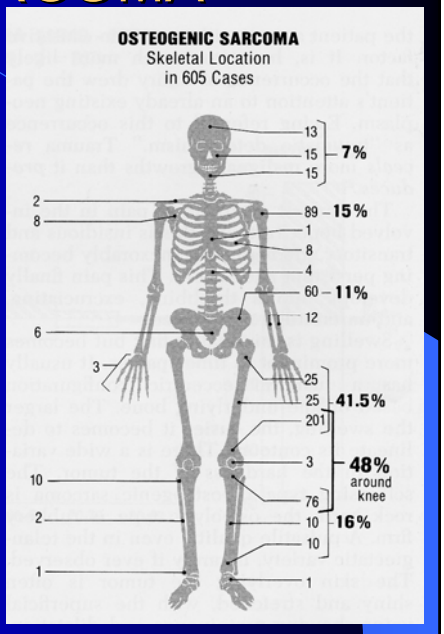
- Near diploid karyotype.
- Two cases with involvement of 22q13 and loss of distal part of 17q.
- Excellent prognosis following local excision (nidus has to be removed completely).

OSTEOSARCOMA

- Malignant primary neoplasm of bone that produces osteoid (osteoid directly produced by the tumor cells).
- Intra-medullary origin (conventional type).
- Rare subtypes.
- Most common, non-hematopoietic tumor of bone (incidence 4-5 per million).

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



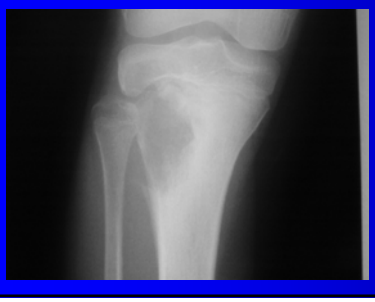
OSTEOSARCOMA

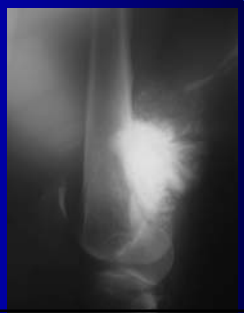
Central

- Low Grade
- High Grade

Surface

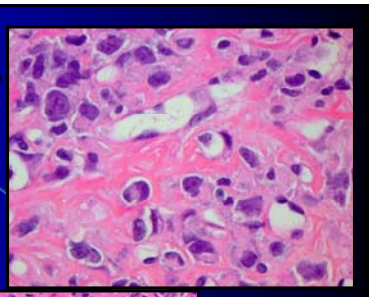
- Low Grade
- High Grade

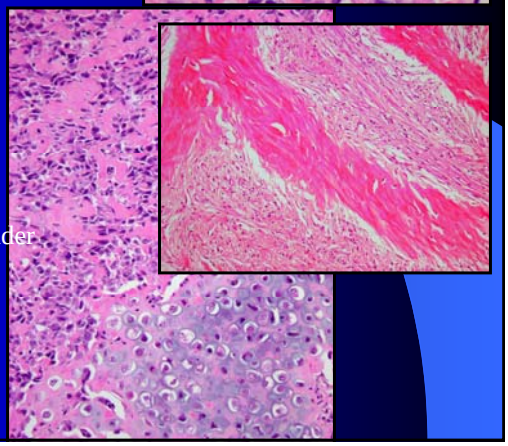




OSTEOSARCOMA

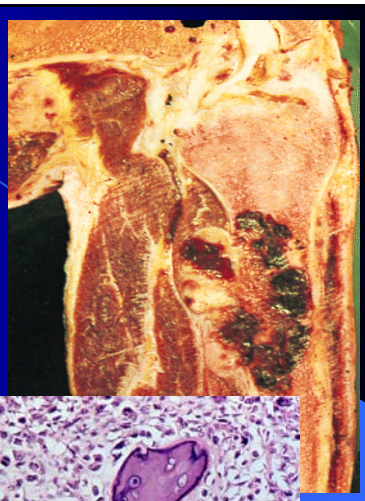
- Conventional:
  - Osteoblastic (50%)
  - Chondroblastic (<25%)
  - Fibroblastic (<1-2 %)
- Telangiectatic (<4%)
- Small cell (1.5%)
- Low grade central (<1%)
- Parosteal (4%)
- Periosteal (<2%)
- High-grade surface (<<1%)
- Secondary (20% of OS in patients older than 40)

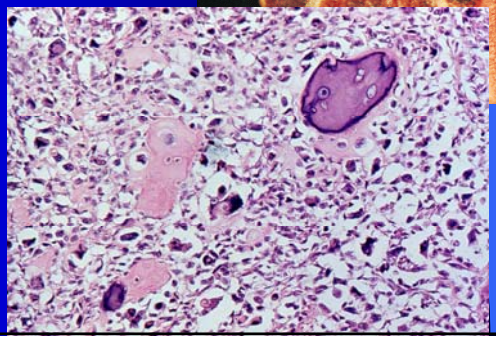




OSTEOSARCOMA

- Anaplastic, pleomorphic tumor.
- Production of osteoid.
- Cartilage and fibrous tissue may also be produced.





OSTEOSARCOMA

- IHC not useful.
- Complex clonal chromosomal aberrations (including numerical and structural alterations).
- Recurrent involvement of 1p11, 13, 1q11-12, 1q21-22, 11p14-15, 14p11-13, 15p11-13, 17p, 19q13.
- Imbalances of +1, -6q, -9, -10, -13 (retinoblastoma gene on chromosome 13) and -17.
- Gains in 3q26, 4q12-13, 5p13-14, 7q31-32, 8q21-23, 12q14-15 (MDM2 and PRIM1), and 17p11-12 (Li-Fraumeni syndrome).
- Over-expression of MET and FOS in >50% of OS, and MYC in <15%.

OSTEOSARCOMA

- Untreated is fatal (aggressive local growth and rapid hematogenous systemic metastasis).
- When treated with surgery alone, survival is limited.
- Age, gender, location, size, stage and laboratory tests traditional prognostic factors.
- The most reliable indicator of survival is the response to preoperative chemotherapy (good prognosis >90% tumor necrosis).
- In good responders survival in 80-90% of cases is nor unusual.
- Bad responders, without change in chemotherapy, die in 80-90% of cases (but with change of regimen long-term survival can be greatly improved).

CARTILAGE-FORMING TUMORS

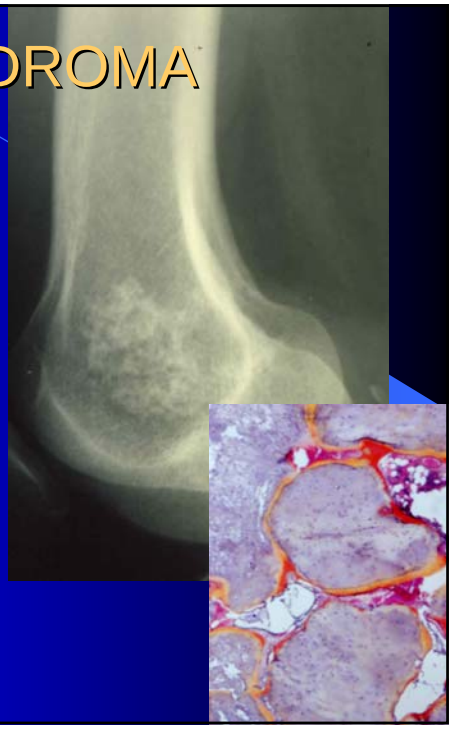
Cartilage tumors	**Osteochondroma**	
	Chondroma	**Enchondroma**
		Periosteal chondroma
		Multiple chondromatosis
	Chondroblastoma	
	Chondromyxoid fibroma	
	Chondrosarcoma	**Central**
		Peripheral
		Dedifferentiated
		Mesenchymal
		Clear cell

ENCHONDROMA

- Benign hyaline cartilage neoplasm of medullary bone.
- Usually single.
- Common (10-25% of all benign bone tumors), but incidence is probably significantly higher.
- Wide age distribution (5-80 years) with most patients between 2nd and 4th decade.
- Most common in hands, followed by long tubular bones. Rare in flat bones.
- Exceedingly rare in craniofacial bones.

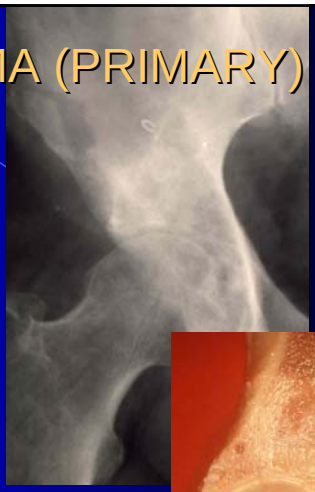
ENCHONDROMA

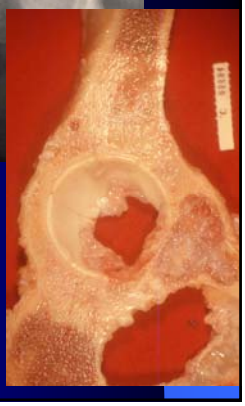
- Swelling of small bones of hands and feet, thinning of cortex and pathological fractures.
- Asymptomatic in long bones.
- Well marginated lesions on imaging; lytic or mineralized.
- Usually in metaphysis, less common in diaphysis, rare in epiphysis.
- Hypocellular, avascular with abundant hyaline cartilage.



CHONDROSARCOMA (PRIMARY)

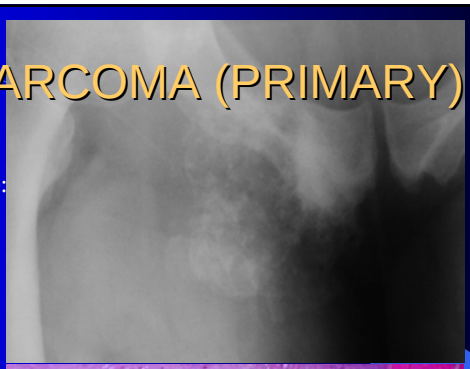
- Malignant neoplasm with pure hyaline cartilage differentiation.
- Primary or conventional chondrosarcoma (90% of CS) arises centrally in a previously normal bone.
- Third most common primary malignancy of bone after myeloma and osteosarcoma.
- Tumor of adulthood (majority of patients >50 years).
- Genetics:
  - Near diploid or pseudo-diploid karyotypes.
  - Simple numerical changes (-X, -Y, +5).
  - Rearrangements of 1p13-p22.

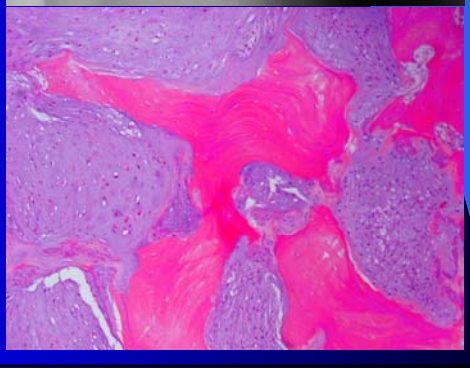




CHONDROSARCOMA (PRIMARY)

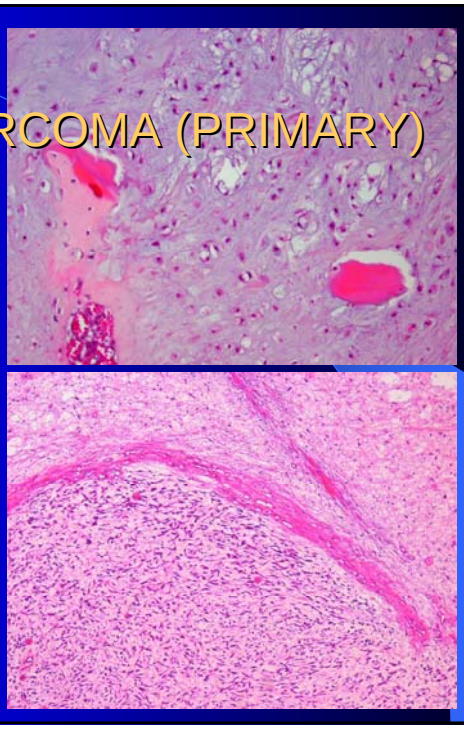
- Most commonly involved sites are: the pelvis, proximal femur and humerus, distal femur and ribs.
- Rare in the fingers (1%).
- Extremely rare in spine and craniofacial bones.
- Local swelling and pain.
- Metaphysis.
- Expansion of bone, thickening of the cortex with possible cortical erosion or destruction.





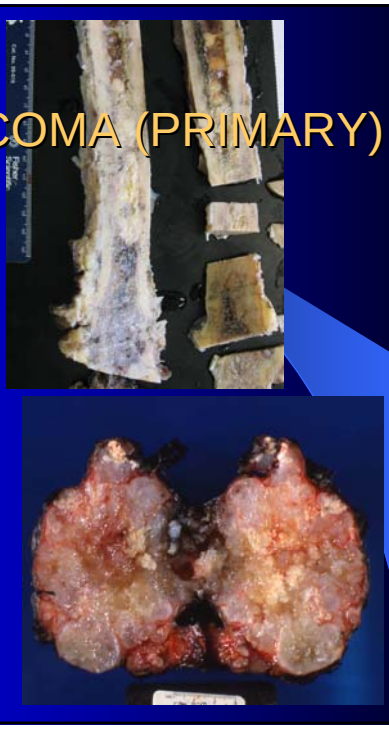
CHONDROSARCOMA (PRIMARY)

- Cut surfaces translucent, blue-gray to white (cartilage), lobular, solid to myxoid areas, cortical erosion and soft tissue extension possible.
- Lobules of cartilage separated by fibrous septa.
- Host lamellar entrapment.
- Three grades:
  - **1. Moderately cellular, oftentimes indistinguishable from enchondroma.**
  - **2. More cellular and atypical with more myxoid matrix.**
  - **3. More cellular,atypical and myxoid than grade 2 lesions. Mitoses are easily detected.**



CHONDROSARCOMA (PRIMARY)

- The histological grade is the most important predictor of local recurrence and metastasis.
- 89% of patients with grade 1 lesions are alive at 5 years.
- Only 53% of patients with grade 2 and 3 lesions are alive at 5 years.
- 10% of recurrent tumors show increase in grade or dedifferentiate.
- Treatment is surgical (chemo and radiation resistant tumors).



Summary of bone sarcomas

- Tumors of connective tissue.
- Very rare (bone sarcomas: 1/10 of soft tissue sarcomas).
- Etiology unclear, with a few exceptions.
- Classified according to tissue they resemble.
- Biologically: benign, borderline or malignant.
- Grading and staging crucial elements to be added to diagnosis.
- No recurrent diagnostic translocation (unless a soft tissue equivalent exists, e.g. Ewing sarcoma).