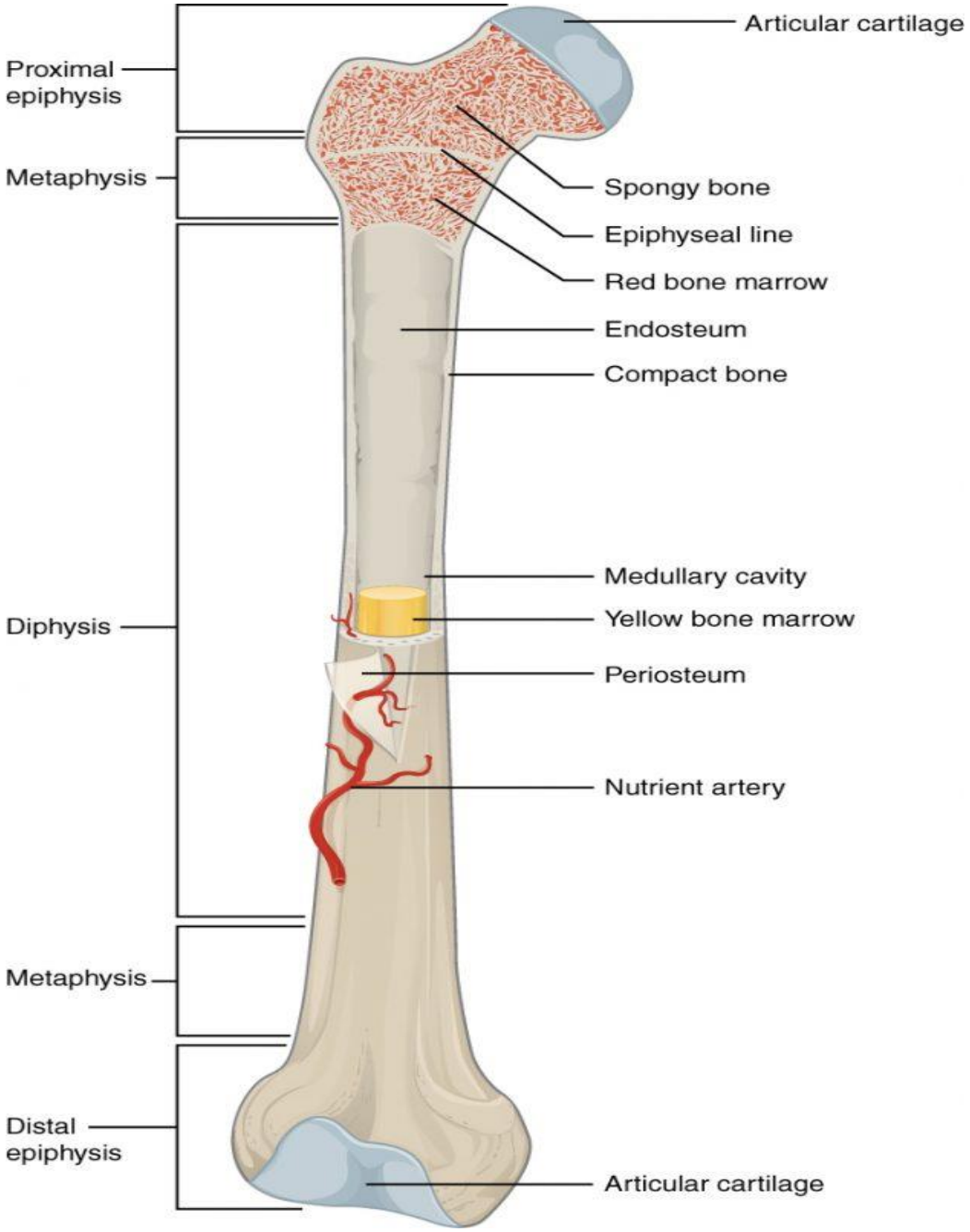
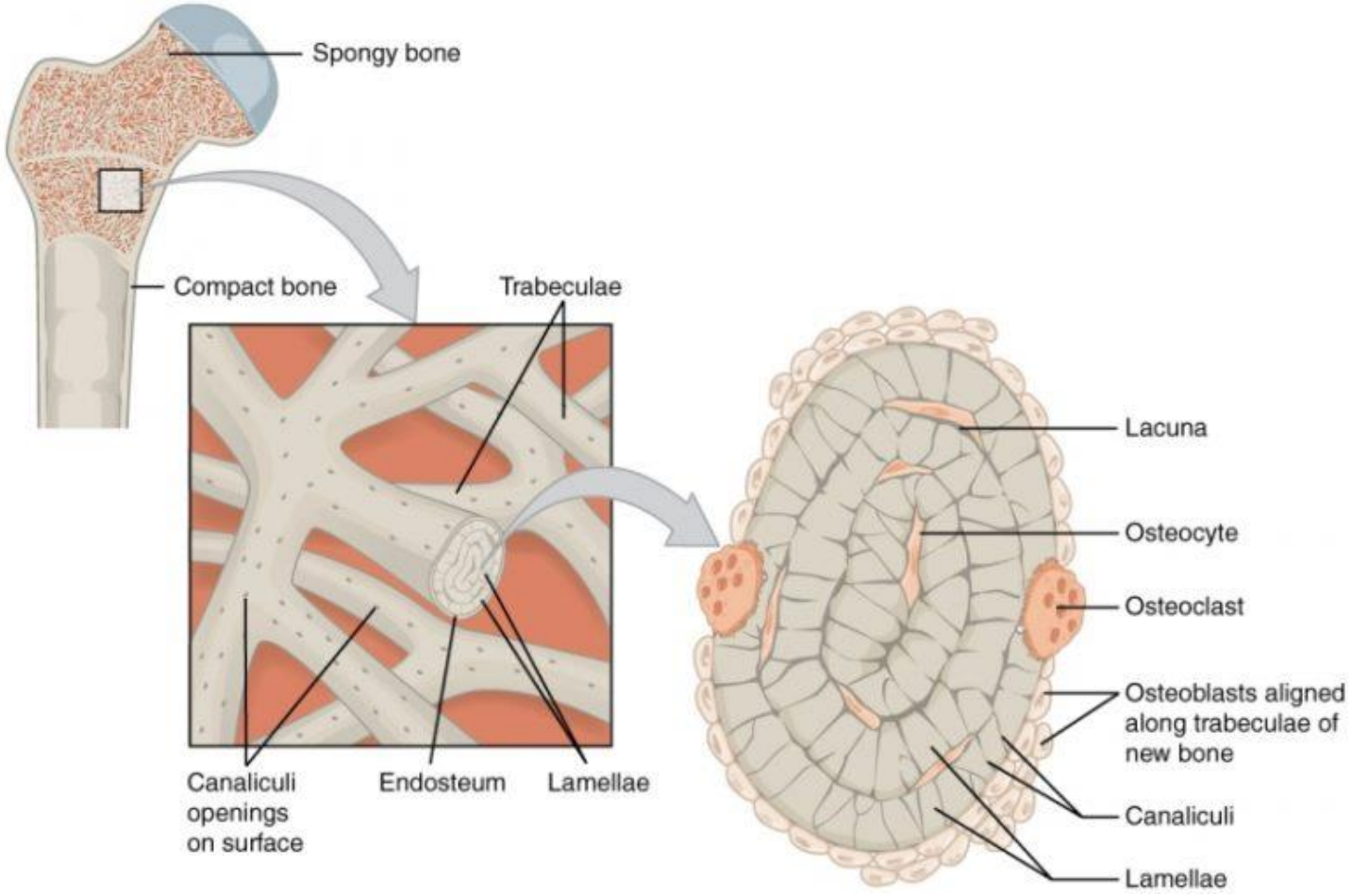
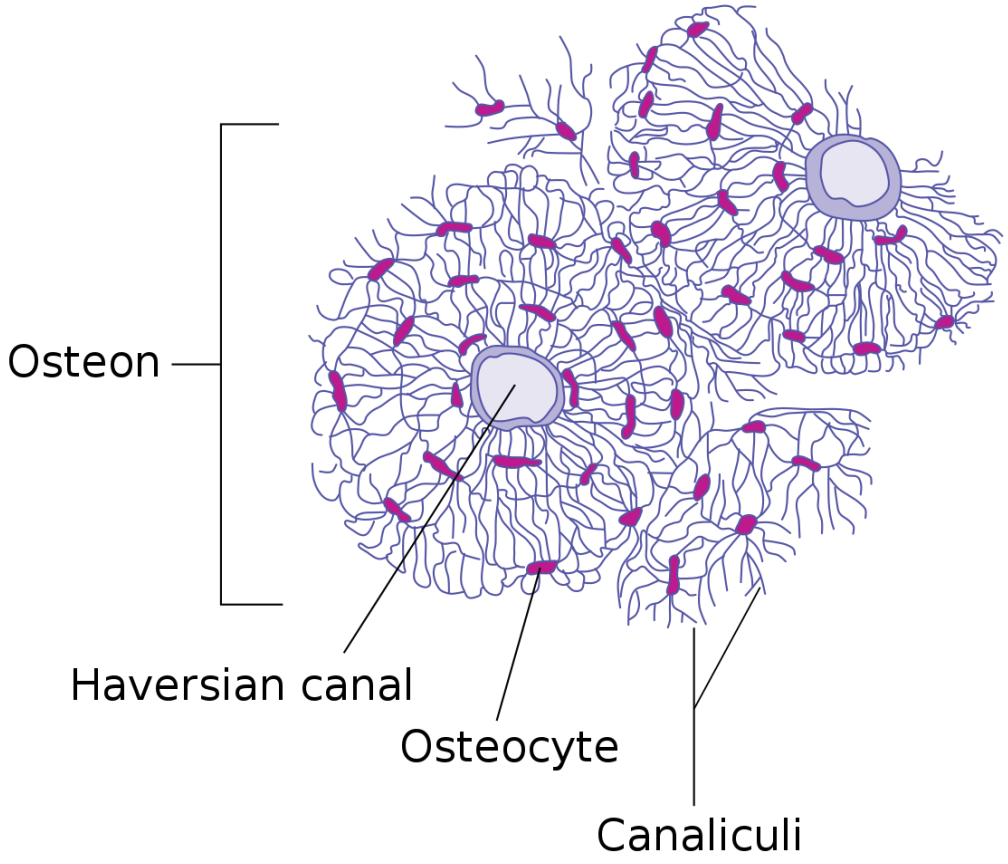
Bone tumours

PROF.DR.KHALID JAVED


Articular cartilage
Proximal epiphysis
Metaphysis
Spongy bone
Epiphyseal line
Red bone marrow
Endosteum
Compact bone
Medullary cavity
Diphysis
Yellow bone marrow
Periosteum
Nutrient artery
Metaphysis
Distal epiphysis
Articular cartilage


Spongy bone
Compact bone
Trabeculae
Canaliculi openings on surface
Endosteum
Lamellae
Lacuna
Osteocyte
Osteoclast
Osteoblasts aligned along trabeculae of new bone
Canaliculi
Lamellae


Osteon
Haversian canal
Osteocyte
Canaliculi

Bone development

- Embryonic mesenchyme ------> osteoprogenitor cells ------> Osteoblasts (specialized non- dividing cells) bone forming cells

- Osteoid :- un-mineralized bone matrix secreted by osteoblasts
  Mainly collagen type I

Osteoblasts also secrete the enzyme alkaline phosphatase

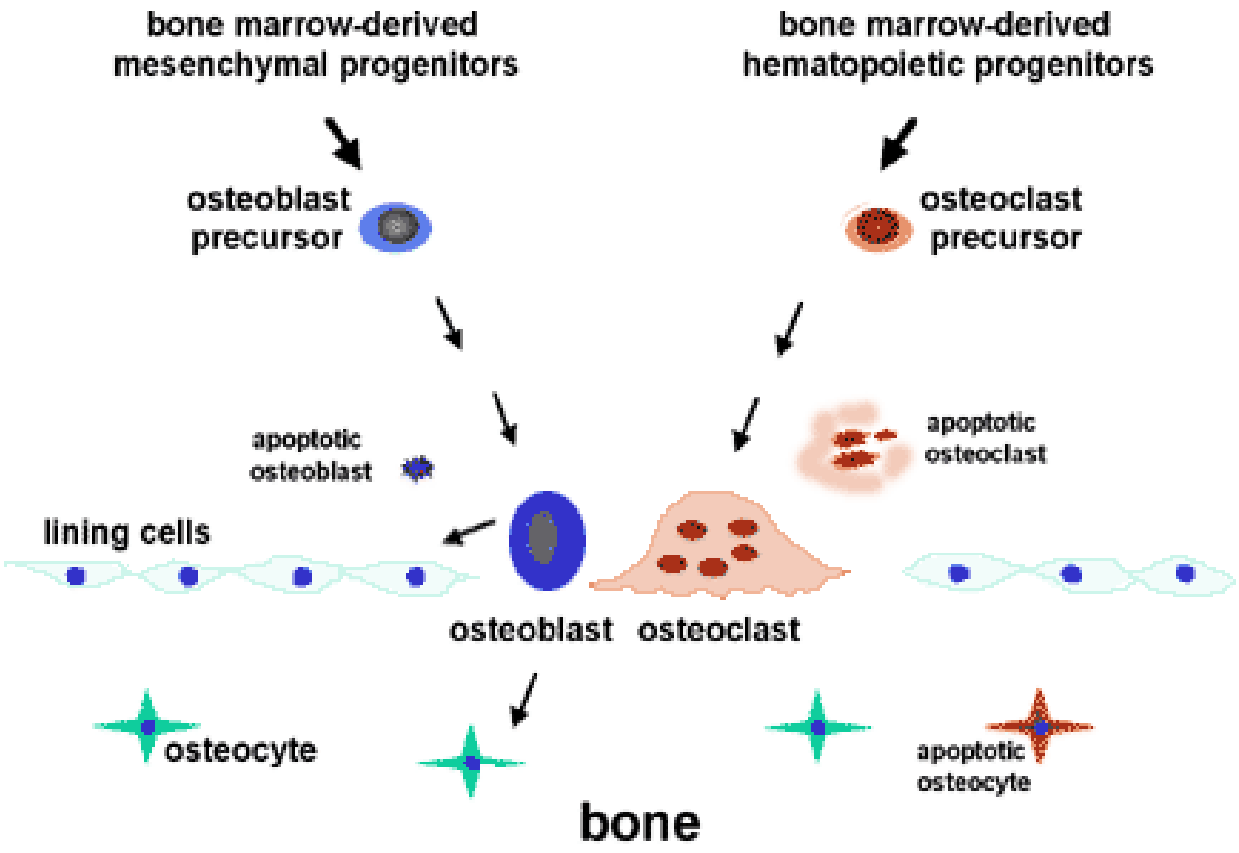
Which brings about the mineralization of the osteoid

Osteoblast morphology

- Cuboidal
- Lined side by side like epithelium
- Growing or bone forming surfaces
- In developing bones/injury/repair
- Basophilic cytoplasm

Osteoclasts

- Resorb the bone.
- Mineral is probably dissolved in the acid environment.
- Probably break down the bone matrix by the release of lysosomal proteases.
- For their action, osteoclasts form sealed compartments next to the bone surface
- Then secrete acids and enzymes which degrade the bone.
- After they finish resorbing bone, undergo apoptosis.


bone marrow-derived
mesenchymal progenitors
bone marrow-derived
hematopoietic progenitors
osteoblast
precursor
osteoclast
precursor
apoptotic
osteoblast
apoptotic
osteoclast
lining cells
osteoblast
osteoclast
osteocyte
apoptotic
osteocyte
bone

Osteocytes

- Bone cells that live inside the bone
- Have long branches which allow them to contact each other as well as the lining cells on the bone surface.
- They sense mechanical strain on the bone and can secrete growth factors to activate the lining cells or stimulate the osteoblasts.

- The osteocytes are thought to direct bone remodeling to accommodate mechanical strain and repair fatigue damage.

Classification of Primary Tumors Involving Bones

Hematopoietic (40%)		**Myeloma**
		Malignant lymphoma
Chondrogenic (22%)	Osteochondroma	Chondrosarcoma
	Chondroma	Dedifferentiated chondrosarcoma
	Chondroblastoma	Mesenchymal chondrosarcoma
	Chondromyxoid fibroma	
Osteogenic (19%)	Osteoid osteoma	Osteosarcoma
	Osteoblastoma	
Unknown origin (10%)	Giant cell tumor	Ewing tumor
		Giant cell tumor
		Adamantinoma

Histiocytic origin	Fibrous histiocytoma	Malignant fibrous histiocytoma
Fibrogenic	Metaphyseal fibrous defect (fibroma)	Desmoplastic fibroma
		Fibrosarcoma
Notochordal		Chordoma
Vascular	Hemangioma	Hemangioendothelioma
		Hemangiopericytoma
Lipogenic	Lipoma	Liposarcoma
Neurogenic	Neurilemmoma	

Primary bone tumors are considerably less common than are bone metastases from other primary sites

Primary bone tumors exhibit

- Great morphologic diversity and clinical behaviors-from benign to aggressively malignant.

Most are classified according to

- The normal cell of origin and apparent pattern of differentiation;

- Overall, matrix-producing and fibrous tumors are the most common,

  and among the benign tumors,
- osteochondroma and fibrous cortical defect occur most frequently.

- Osteosarcoma is the most common primary bone cancer, followed by chondrosarcoma and Ewing sarcoma.

- Benign tumors markedly outnumber their malignant counterparts, particularly before age 40;
- bone tumors in the elderly are much more likely to be malignant.

- Most bone tumors develop during the first several decades of life and have a propensity to originate in the long bones of the extremities.

- Nevertheless, specific tumor types target certain age groups and anatomic sites; such clinical information is often critical for the appropriate diagnosis.

- For instance, most osteosarcomas occur during adolescence, with half arising around the knee, either in the distal femur or proximal tibia.

- In contrast, chondrosarcomas tend to develop during mid- to late adulthood and involve the trunk, limb girdles, and proximal long bones.

- Most bone tumors arise without any prior known cause.

- Nevertheless, genetic syndromes (e.g., Li-Fraumeni and retinoblastoma syndromes) are associated with osteosarcomas,

- as are (rarely) bone infarcts, chronic osteomyelitis, Paget disease, radiation, and metal orthopedic devices.

- In terms of clinical presentations,
- benign lesions are frequently asymptomatic and are detected as incidental findings.
- Others produce pain or a slowly growing mass.
- Occasionally, a sudden pathologic fracture is the first manifestation.
- Radiologic imaging is critical in the evaluation of bone tumors;
- however, biopsy and histologic study are necessary for the final diagnosis.

Benign	Malignant
Osteoma, osteoid osteoma & osteoblastoma osteoblasts (bone forming cells)	osteosarcoma: bone forming cells Sun burst appearance Codman's triangle
Osteochondroma & Chondroma chondrocytes(cartilage forming cells)	chondrosarcoma: cartilagenous Pop corn calcification
Giant cell tumour (osteoclastoma) osteoclasts bone resorptive cells	Ewing sarcoma: Undifferentiated cells t 11:22 Onion skin appearance

Bone-Forming Tumors

The tumor cells in the following neoplasms

all produce bone that is usually woven and variably mineralized

Osteoma

Developmental aberrations or reactive growths rather than true neoplasms.

- Head and neck paranasal sinuses, middle age.
- Usually solitary
- Localized, slowly growing, hard, exophytic
- Multiple lesions are a feature of gardner syndrome,
- Histologically, bland mixture of woven and lamellar bone.
- Local mechanical problems (e.g., Obstruction of a sinus cavity) and cosmetic deformities,
- They are not invasive and do not undergo malignant transformation.

Osteoid Osteoma and Osteoblastoma

- Very similar histologic features.
- The teenage years and 20s, with a male predilection (2 : 1 in osteoid osteomas).
- They are distinguished primarily by their size, site of origin, and their radiographic appearance as well-circumscribed lesions,
- Usually involving the cortex and rarely the medullary cavity.
- The central area of the tumor, termed the *nidus*, is characteristically radiolucent but may become mineralized and sclerotic.

- *Osteoid osteomas* arise most often in the proximal femur and tibia, and are by definition less than 2 cm, whereas
- osteoblastomas are larger.
- Localized pain is an almost universal complaint with osteoid osteomas, and is usually relieved by aspirin.

- *Osteoblastomas* arise most often in the vertebral column; they also cause pain, although it is often more difficult to localize and is not responsive to aspirin.
- Local excision
- Incompletely resected lesions can recur.
- Malignant transformation is rare *unless* the lesion is treated with radiation

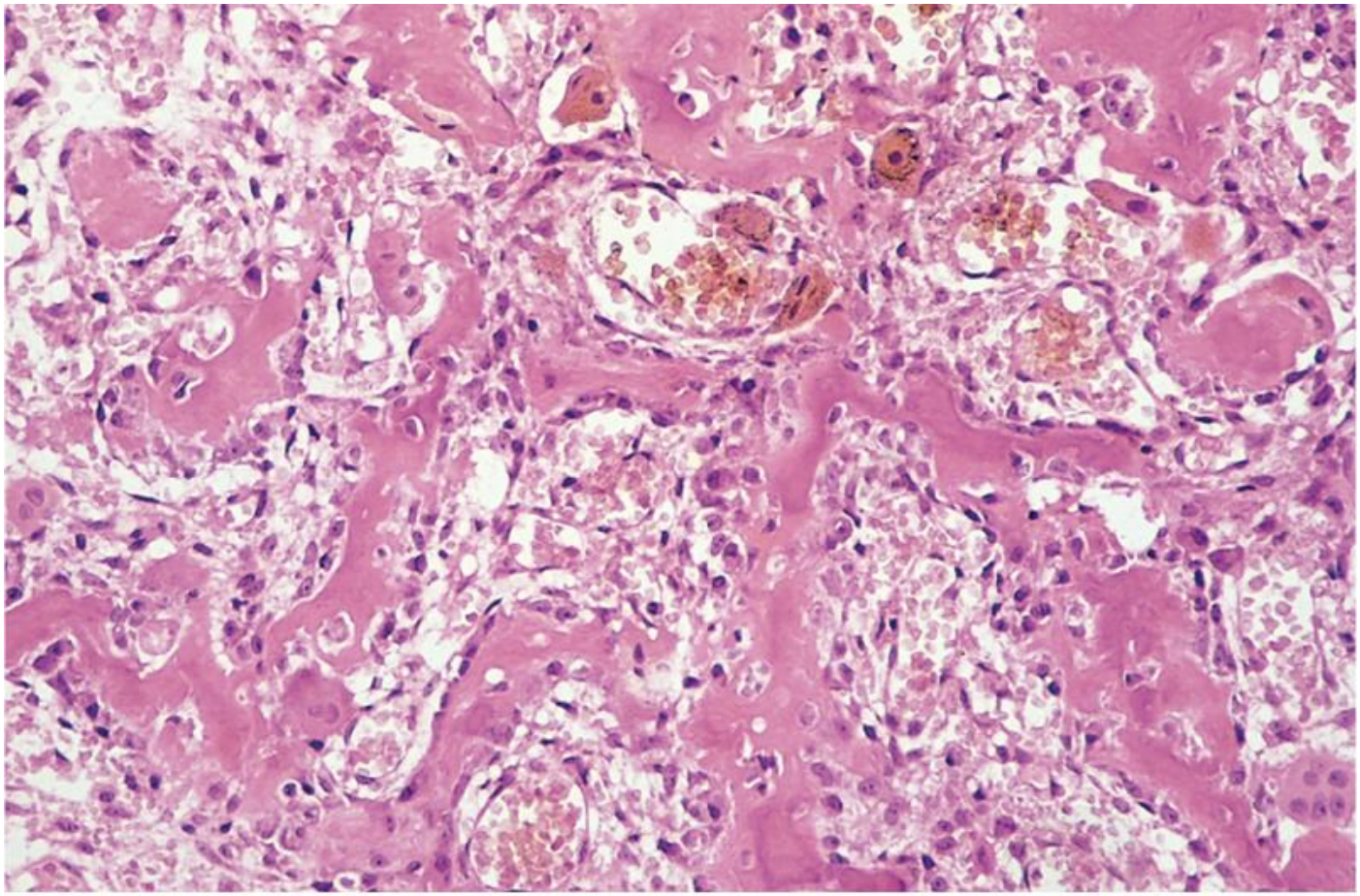
Morphology

- Grossly, both lesions are round-to-oval masses of hemorrhagic gritty tan tissue.

- A rim of sclerotic bone (unusual hardening or thickening of bone) is present at the edge of both types of tumors; more conspicuous in osteoid osteomas.

Osteoid osteoma :-Interlacing trabeculae of woven bone surrounded by osteoblasts

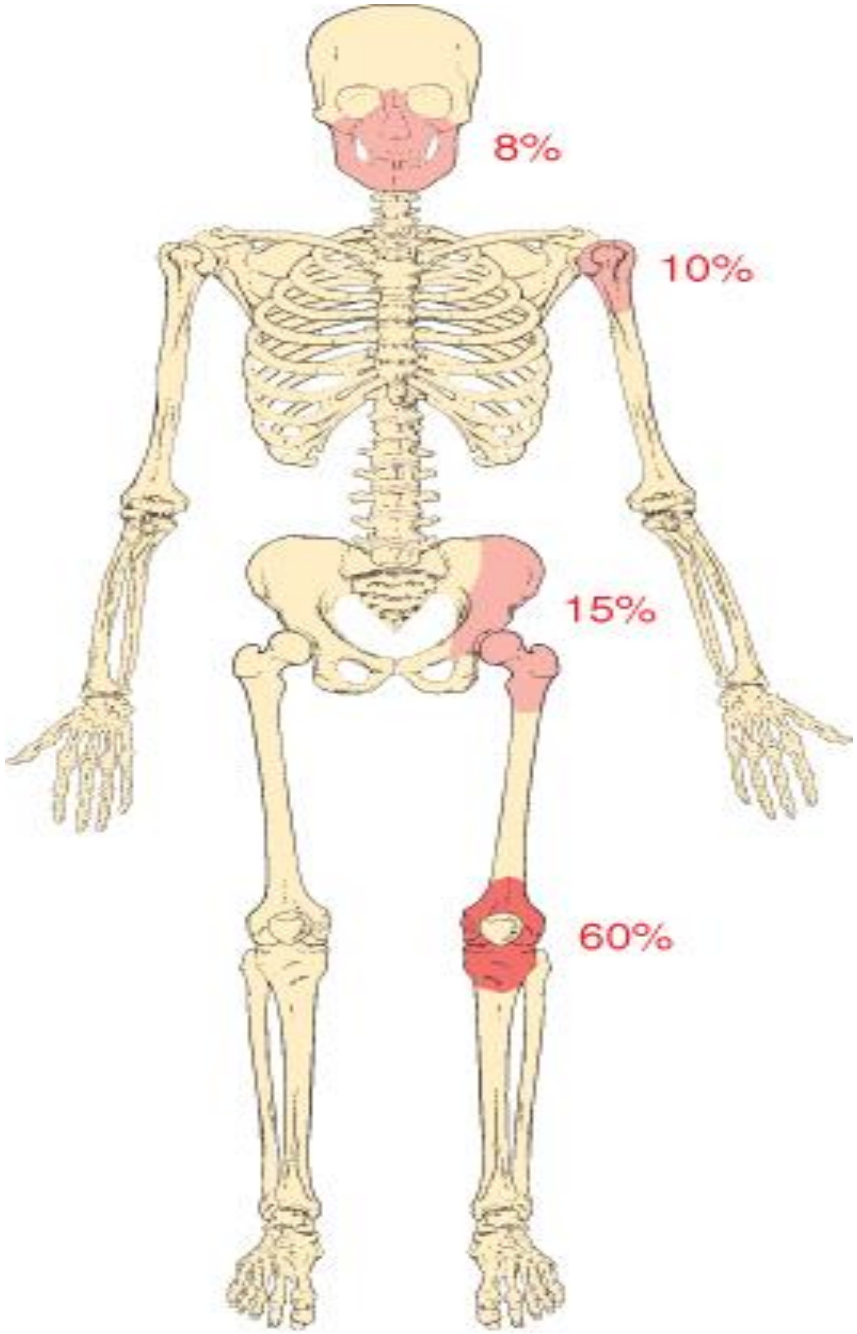
The intervening stroma is loose, vascular connective tissue containing variable numbers of giant cells



OSTEOSARCOMA

- *Bone-producing malignant mesenchymal tumor.*
- Outside of myeloma and lymphoma, osteosarcoma is the most common primary malignant tumor of bone, accounting for approximately 20% of primary bone cancers;
- some 75% of patients are younger than age 20,

- with a second peak occurring in the elderly, usually with other conditions, including Paget disease, bone infarcts, and prior irradiation.



- Men are more commonly affected than women (1.6 : 1).
- Most tumors arise in the metaphyseal region of the long bones of the extremities,
- With almost 60% occurring about the knee, 15% around the hip, 10% at the shoulder, and 8% in the jaw.

Several subtypes of osteosarcoma

- Medullary vs cortical
- Degree of differentiation,
- Solitary vs multicentric,
- Presence of underlying disease, and
- Histologic variants;
- The most common type of osteosarcoma is primary, solitary, intramedullary, and poorly differentiated, producing a predominantly bony matrix

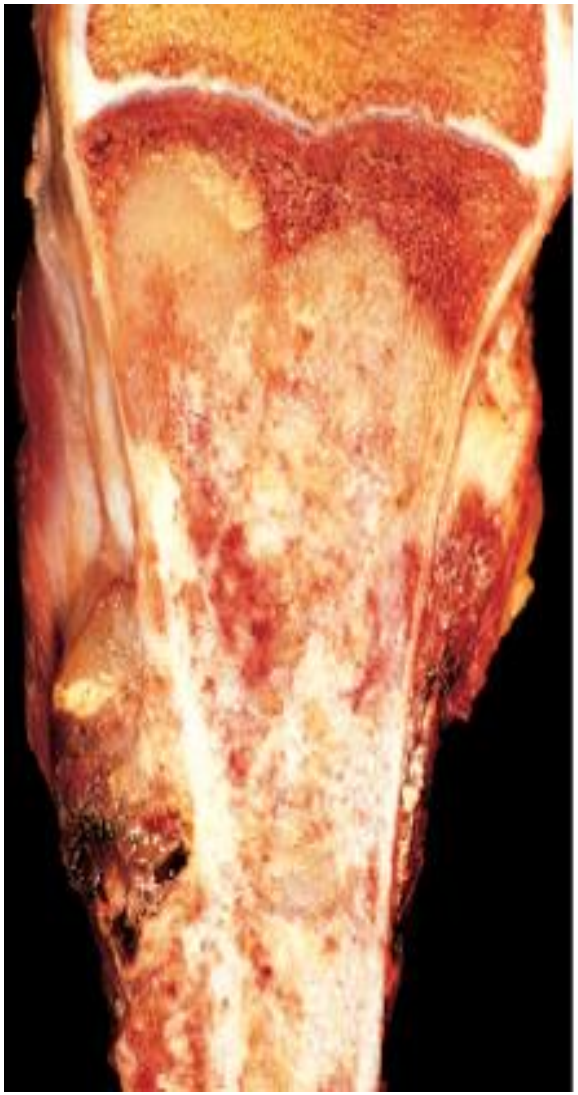
Morphology

- Grossly, osteosarcomas are gritty, gray-white tumors, often exhibiting hemorrhage and cystic degeneration.
- Destroy the surrounding cortices and produce soft tissue masses

- They spread extensively in the medullary canal, infiltrating and replacing the marrow,

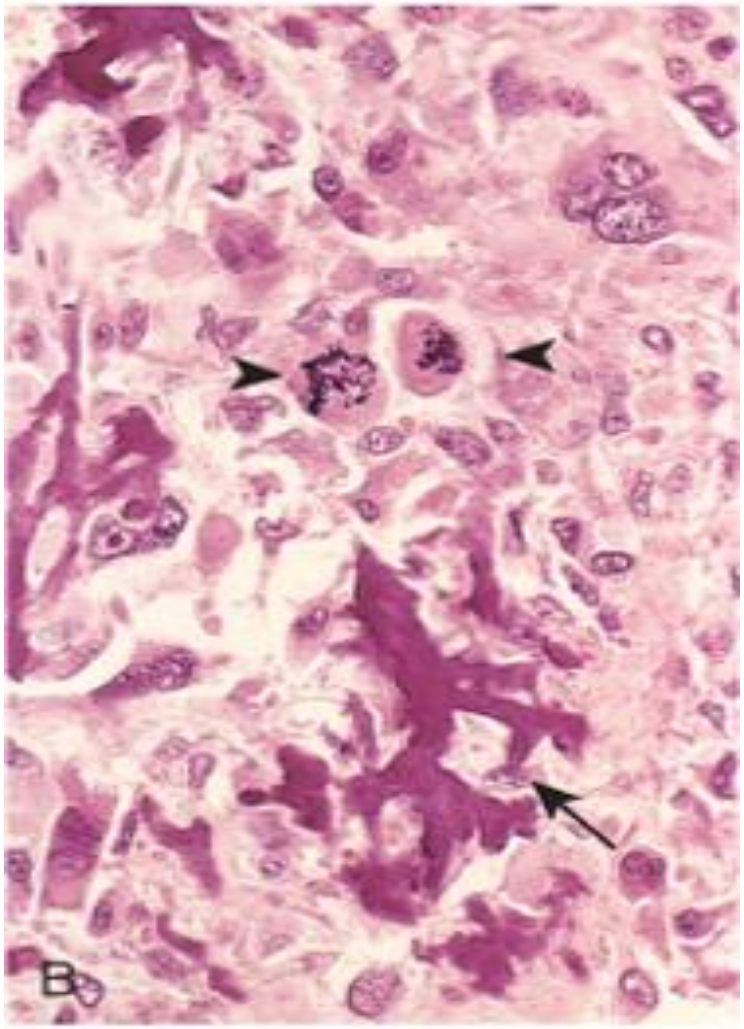
- But only infrequently penetrating the epiphyseal plate or entering the joint space.

Mass involving the upper end of the tibia. The tan-white tumor fills most of the medullary cavity of the metaphysis and proximal diaphysis. It has infiltrated through the cortex, lifted the periosteum, and formed soft tissue masses on both sides of the bone.



- Tumor cells vary in size and shape, and
- frequently have large hyperchromatic nuclei; bizarre tumor giant cells are common, as are mitoses.
- The production of osteoid by malignant cells is essential for diagnosis of osteosarcoma.
- The neoplastic bone is typically coarse and ragged but can also be deposited in broad sheets.
- Cartilage and fibrous tissue can also be present in varying amounts.
- When malignant cartilage is abundant, the tumor is called a chondroblastic osteosarcoma.
- Vascular invasion is common, as is spontaneous tumor necrosis.

Coarse, lacelike pattern of neoplastic bone (*arrow*) produced by anaplastic tumor cells & wildly aberrant mitotic figures



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Pathogenesis

- Several genetic mutations are closely associated with the development of osteosarcoma.
- In particular, RB gene mutations occur in 60% to 70% of sporadic tumors, and
- individuals with hereditary retinoblastomas (due to germ-line mutations in the RB gene) have a thousandfold greater risk of developing osteosarcoma.
- Spontaneous osteosarcomas also frequently exhibit mutations in genes that regulate the cell cycle including p53, cyclins, cyclin-dependent kinases, and kinase inhibitors.
- Many osteosarcomas develop at sites of greatest bone growth.

Clinical Features

- Typically present as painful enlarging masses,
- Although a pathologic fracture can be the first symptom.
- Radiographs usually show a large, destructive, mixed lytic and blastic mass with indistinct infiltrating margins.

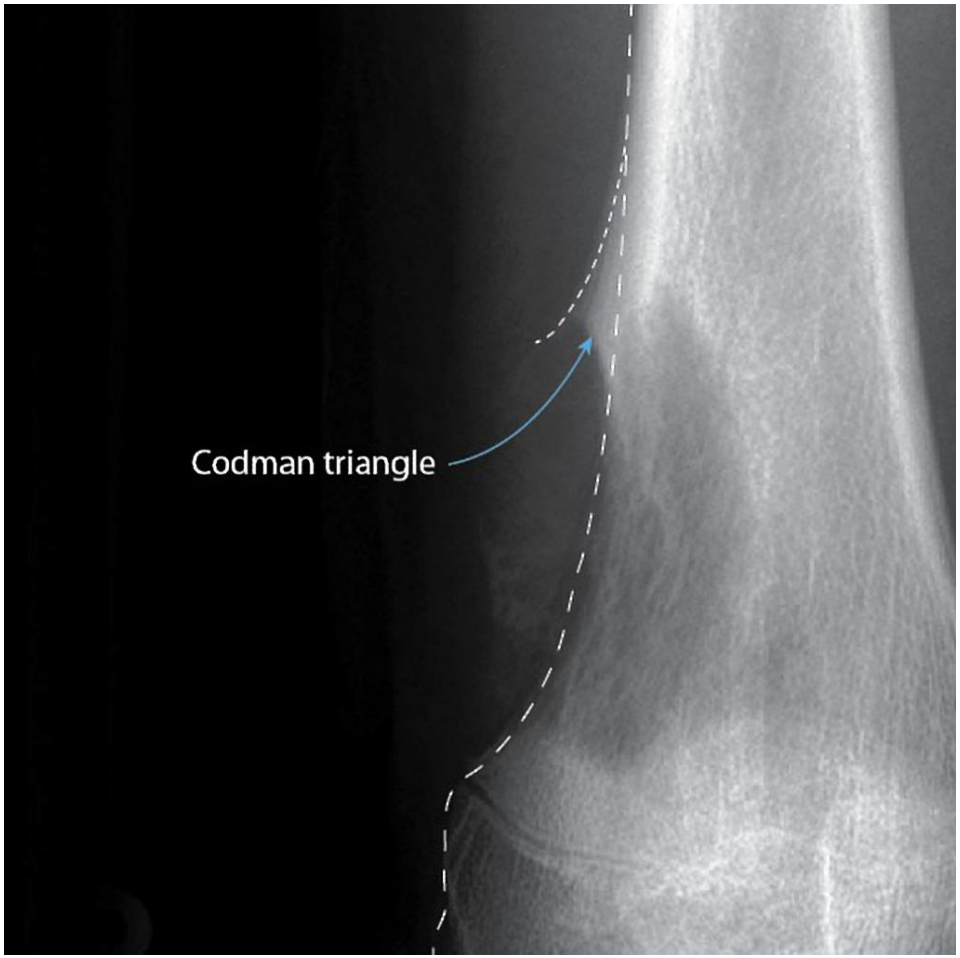
- Osteosarcomas typically spread hematogenously; at the time of diagnosis, approximately 10% to 20% of patients have demonstrable pulmonary metastases.

- The tumor frequently breaks through the cortex and lifts the periosteum, resulting in reactive periosteal bone formation.

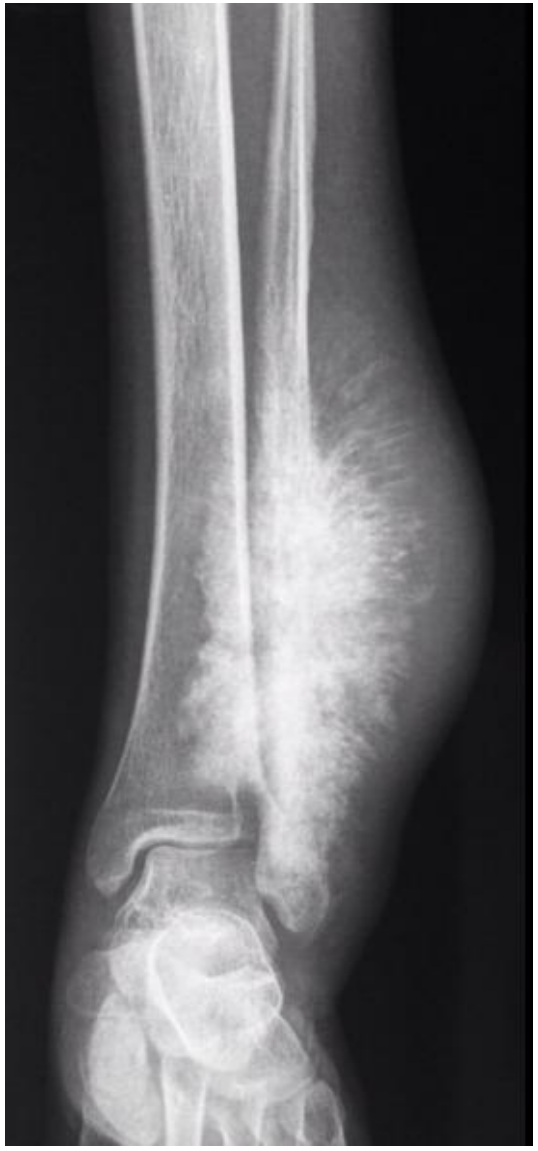
- A triangular shadow on x-ray between the cortex and raised periosteum (Codman triangle) is characteristic of osteosarcomas

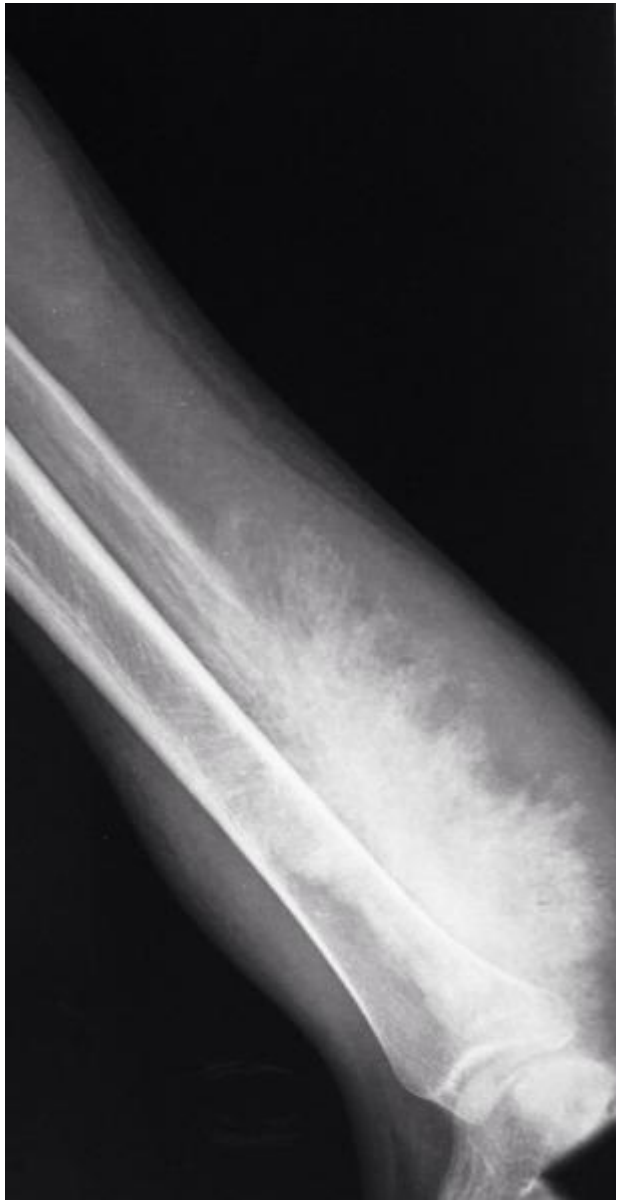
osteosarcoma

Codman triangle is a type of periosteal reaction seen with aggressive bone lesions



The sunburst appearance occurs when the lesion grows too fast and the periosteum does not have enough time to lay down a new layer and instead the Sharpey's fibers stretch out perpendicular to the bone.





- Despite aggressive behavior, standard treatment with chemotherapy and limb-salvage therapy currently yields long-term survivals of 60% to 70%.

- Secondary osteosarcomas occur in an older age group than do primary osteosarcomas.
- They most commonly develop in the setting of Paget disease or previous radiation exposure.
- Secondary osteosarcomas are highly aggressive tumors that do not respond well to therapy.

Osteochondromas
(*exostoses)*

- Common benign cartilage-capped outgrowths attached by a bony stalk to the underlying skeleton.
- Solitary osteochondromas are usually first diagnosed in late adolescence and early adulthood (male-to-female 3 : 1);

- Multiple osteochondromas become apparent during childhood, occurring as *multiple hereditary exostosis*, an autosomal dominant disorder.
- Osteochondromas are true neoplasms and not simple malformations.

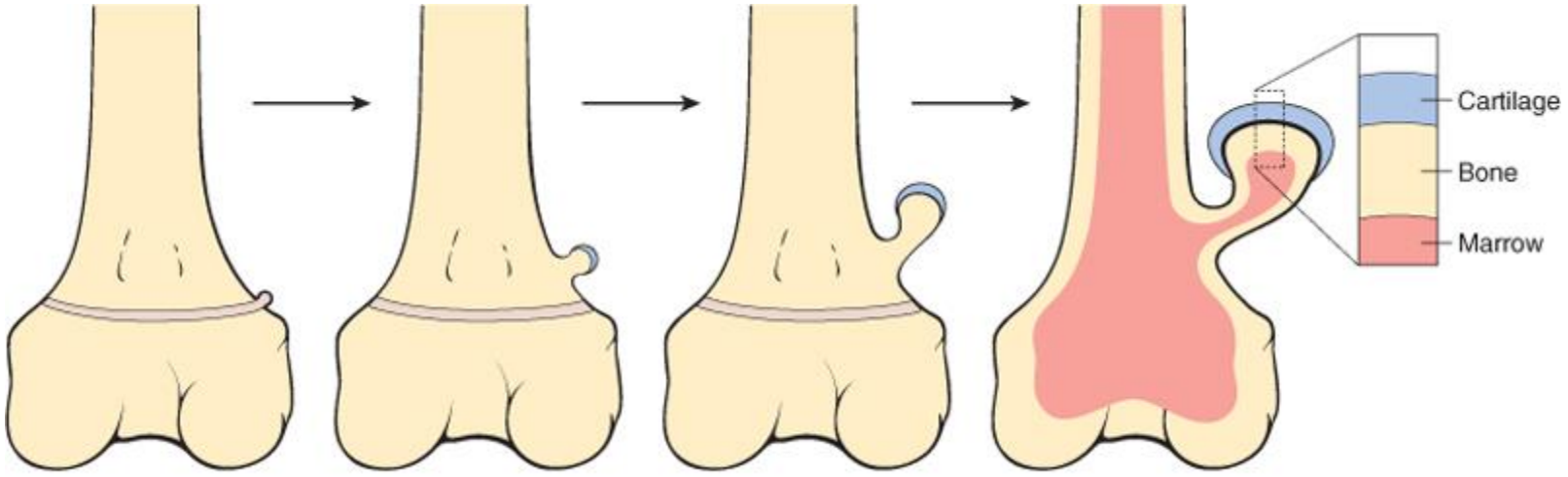
- Develop only in bones of endochondral origin arising at the metaphysis near the growth plate of long tubular bones, especially about the knee;

- They tend to stop growing once the normal growth of the skeleton is completed

- Occasionally they develop from bones of the pelvis, scapula, and ribs, and in these sites are frequently sessile.

- Rarely, exostoses involve the short tubular bones of hands and feet

The development of an osteochondroma, beginning with an outgrowth from the epiphyseal cartilage.



Morphology
vary from 1-20 cm in size.
The cap is benign hyaline cartilage, resembling disorganized growth plate undergoing endochondral ossification.
Newly formed bone forms the inner portion of the head and stalk, with the stalk cortex merging with the cortex of the host bone

- Chondromas are benign tumors of hyaline cartilage.
- Enchondromas when they arise within the medulla
- Juxtacortical chondromas on the bone surface

- Enchondromas are usually diagnosed in persons between ages 20 and 50
- Typically solitary
- Metaphyseal region of tubular bones,
- The favored sites being the short tubular bones of the hands and feet.

- Ollier disease is characterized by multiple chondromas preferentially involving one side of the body, and

- Maffucci syndrome is characterized by multiple chondromas associated with benign soft tissue angiomas.

- Chondromas probably develop from slowly proliferating rests of growth plate cartilage

- Enchondromas are gray-blue, translucent nodules usually smaller than 3 cm.

- Microscopically, there is well-circumscribed hyaline matrix and cytologically benign chondrocytes.
- At the periphery, there is endochondral ossification, while the center frequently calcifies and dies.
- In the hereditary multiple chondromatoses, the islands of cartilage exhibit greater cellularity and atypia, making them difficult to distinguish from chondrosarcoma

Chondrosarcomas

- Variety of tumors sharing the ability to produce neoplastic cartilage;
- They are subclassified according to site (e.G., Intramedullary vs juxtacortical), and
- Histologic variants
- Chondrosarcomas occur roughly half as frequently as osteosarcomas;
- Most patients are age 40 or older,
- Men affected twice as frequently as women.

Morphology

- Conventional chondrosarcomas arise within the medullary cavity
- form an expansile glistening mass that often erodes the cortex
- They exhibit malignant hyaline and myxoid cartilage.
- In myxoid chondrosarcomas, the tumors are viscous and gelatinous, and the matrix oozes from the cut surface.
- Spotty calcifications are typically present, and central necrosis can create cystic spaces.
- The adjacent cortex is thickened or eroded, and
- the tumor grows with broad pushing fronts into marrow spaces and the surrounding soft tissue.

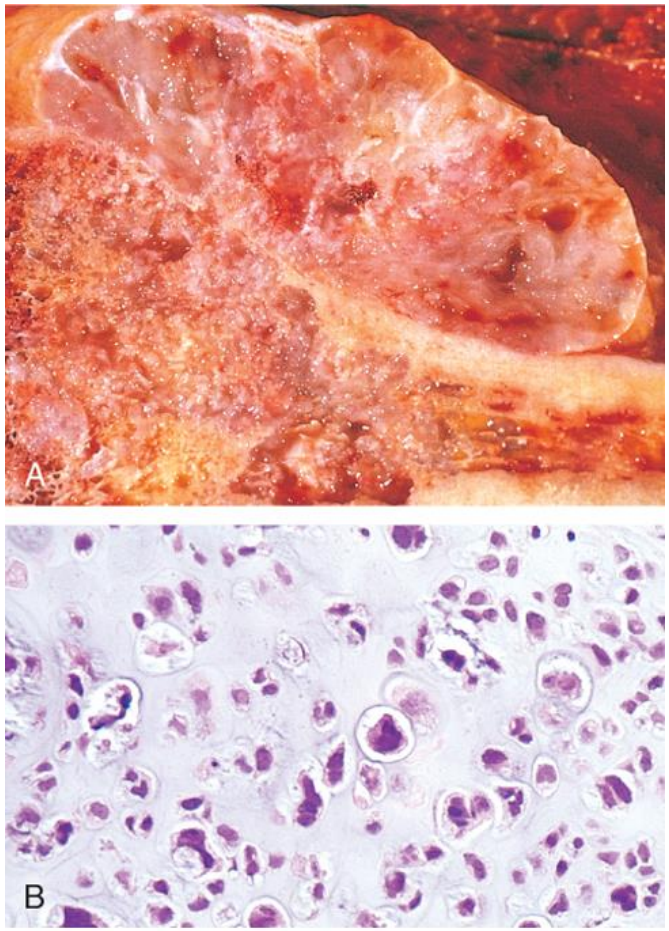
- Tumor grade is determined by cellularity, cytologic atypia, and mitotic activity
- Low-grade tumors resemble normal cartilage.

- Higher grade lesions contain pleomorphic chondrocytes with frequent mitotic figures.

- Multinucleate cells are present with lacunae containing two or more chondrocytes.

- Approximately 10% of patients with conventional low-grade chondrosarcomas have a second high-grade poorly differentiated component (dedifferentiated chondrosarcomas) that include foci of fibro- or osteosarcomas.

- Other histologic variants include clear-cell and mesenchymal chondrosarcomas



Fibrous dysplasia

- Benign tumor
- Localized developmental arrest;
- All components of normal bone are present, but they fail to differentiate into mature structures.
- Fibrous dysplasia occurs as one of three clinical patterns:
- (1) involvement of a single bone (monostotic);
- (2) involvement of multiple bones (polyostotic); and
- (3) polyostotic disease, associated with café au lait skin pigmentations and endocrine abnormalities, especially precocious puberty (Mccune-albright syndrome).

- Monostotic fibrous dysplasia accounts for 70% of cases.
- It usually begins in early adolescence, and ceases with epiphyseal closure; there is no gender predilection.
- In descending order of frequency, ribs, femur, tibia, jawbones, calvaria, and humerus are most commonly affected.
- Lesions are asymptomatic and usually discovered incidentally.

- However, fibrous dysplasia can cause marked enlargement and distortion of bone, so that if the face or skull is involved, disfigurement can occur.

- Polyostotic fibrous dysplasia without endocrine dysfunction accounts for the majority of the remaining cases.
- It presents at a slightly earlier age than the monostotic type and can progress into adulthood.
- In descending order of frequency, femur, skull, tibia, and humerus
- Craniofacial involvement is present in 50% of patients with moderate skeletal involvement, and in 100% of patients with extensive skeletal disease.
- Polyostotic disease tends to involve the shoulder and pelvic girdles, resulting in severe deformities and spontaneous fractures.

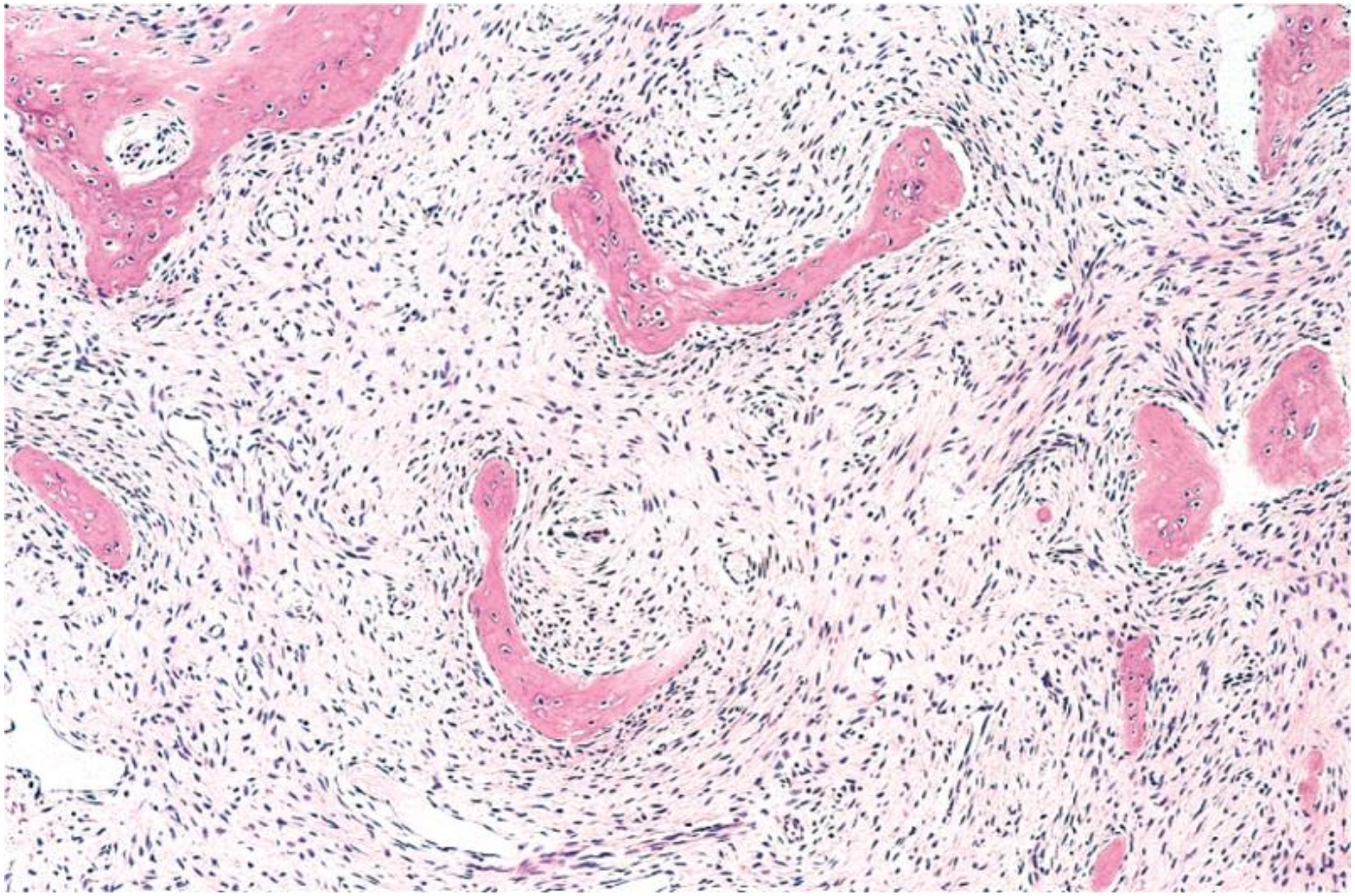
- McCune-Albright syndrome accounts for 3% of all cases.
- The associated endocrinopathies include sexual precocity (girls more often than boys), hyperthyroidism, growth hormone-secreting pituitary adenomas, and primary adrenal hyperplasia.

- The bone lesions are often unilateral, and the skin pigmentation is usually limited to the same side of the body.
- The cutaneous macules are classically large, dark to light brown (café au lait), and irregular

- Grossly, fibrous dysplasia is characterized by well-circumscribed, intramedullary lesions of varying sizes; large masses expand and distort the bone.

- Lesional tissue is tan-white and gritty;

- microscopically, it exhibits curved trabeculae of woven bone (mimicking Chinese characters),
- without osteoblastic rimming, and s
- urrounded by a moderately cellular fibroblastic proliferation



Clinical features

- The natural history depends on the extent of skeletal involvement;
- individuals with monostotic disease usually have minimal symptoms.
- By x-ray, lesions exhibit a characteristic ground-glass appearance with well-defined margins.
- Symptomatic lesions are readily cured by conservative surgery.
- Polyostotic involvement is frequently associated with progressive disease, and more severe skeletal complications (e.g., fractures, long bone deformities, and craniofacial distortion).
- Rarely, polyostotic disease can transform into osteosarcoma, especially following radiotherapy.

Miscellaneous Bone Tumors

Ewing Sarcoma and Primitive Neuroectodermal Tumor

- Primary malignant small round-cell tumors of bone and soft tissue.
- Difficult diagnostic problems because their neoplastic cells resemble those of lymphoma, rhabdomyosarcoma, neuroblastoma, and oat cell carcinoma

- Because they share an identical chromosome translocation, differing only in degree of differentiation.

- PNETs demonstrate neural differentiation whereas Ewing sarcomas are undifferentiated by traditional marker analysis

- These two malignancies account for 6% to 10% of primary malignant bone tumors.
- After osteosarcomas, they are the second most common pediatric bone sarcomas.
- Most patients are 10 to 15 years old, and 80% are younger than age 20.
- Boys are affected slightly more frequently than girls, and
- There is a striking racial predilection; blacks are rarely afflicted.

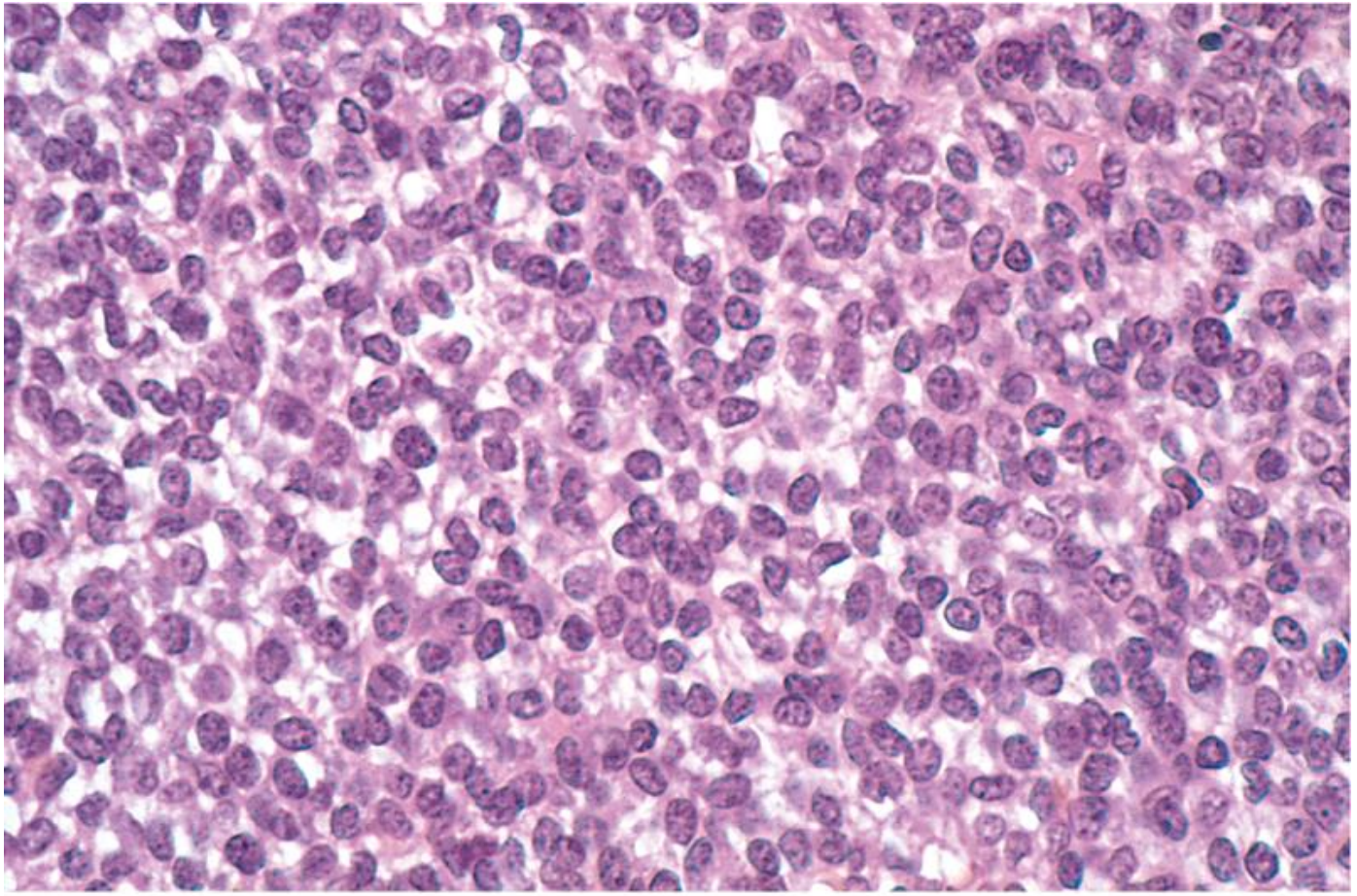
- Translocation that causes fusion of the EWS gene on 22q12 with a member of the ETS family of transcription factors.
- The most common fusion partners are the fl1 gene on 11q24, and the erg gene on 21q22.
- The resulting chimeric protein functions as a constitutively active transcription factor to stimulate cell proliferation.
- Translocations are of diagnostic importance.
- Thus, approximately 95% of patients with Ewing tumor have t(11;22) (q24;q12) or t(21;22) (q22;q12).

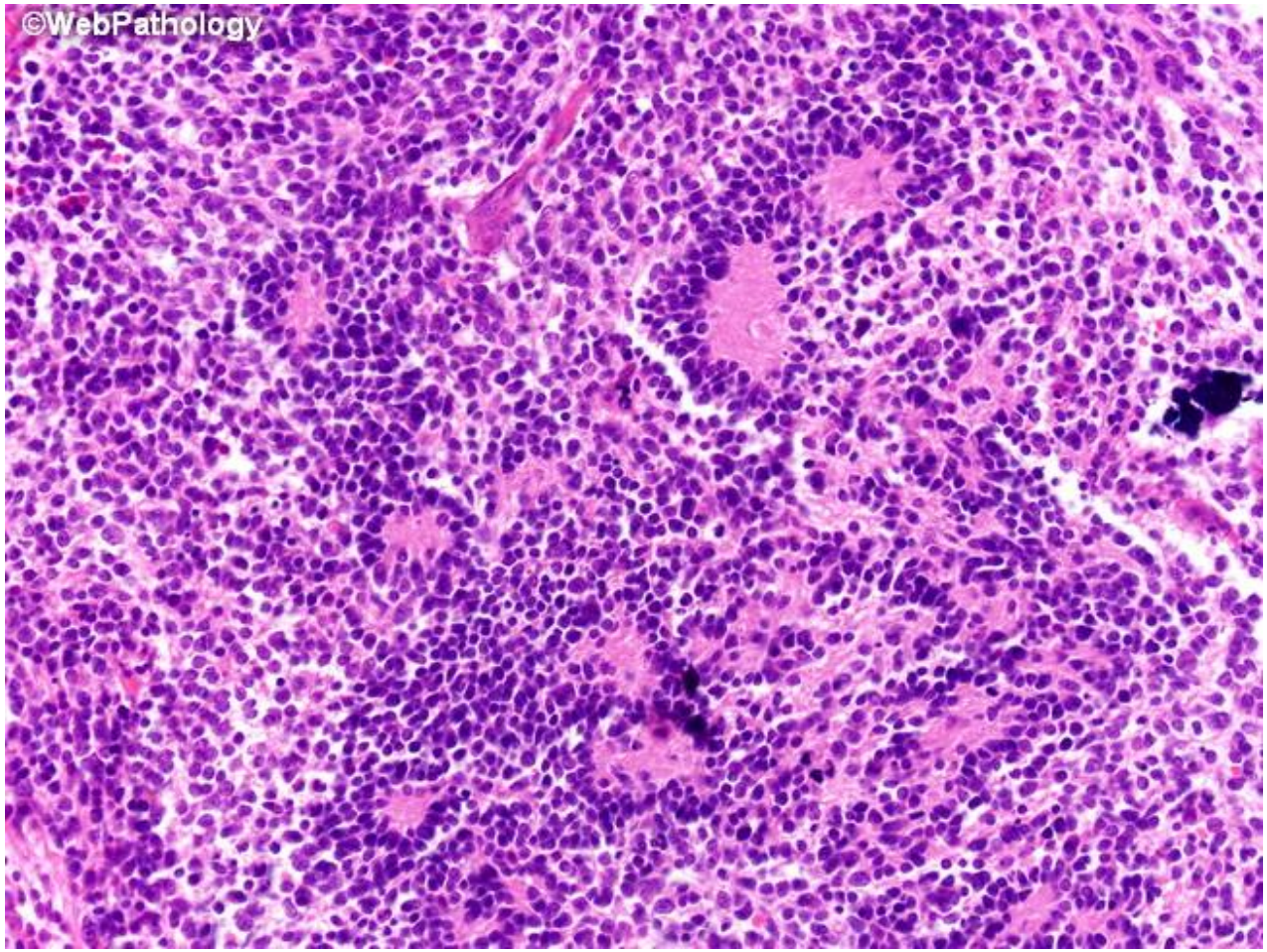
Morphology

- Ewing sarcoma and PNETs arise in the medullary cavity and invade the cortex and periosteum to produce a soft tissue mass.

- The tumor is tan-white, frequently with hemorrhage and necrosis.
- It is composed of sheets of uniform small, round cells that are slightly larger than lymphocytes with few mitoses and little intervening stroma
- The cells have scant glycogen-rich cytoplasm.
- The presence of Homer-Wright rosettes (tumor cells circled about a central fibrillary space) indicates neural differentiation.

Ewing sarcoma. Sheets of small round cells with scant, cleared cytoplasm

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Ewing sarcoma and PNETs

- Typically present as painful enlarging masses in the diaphyses of long tubular bones (especially the femur) and the pelvic flat bones.
- Some patients have systemic signs and symptoms, including fever, elevated erythrocyte sedimentation rate, anemia, and leukocytosis that can mimic infection.

- X-rays show a destructive lytic tumor with infiltrative margins and extension into surrounding soft tissues.
- There is a characteristic periosteal reaction depositing bone in an onionskin fashion

The treatment of Ewing sarcoma and PNET

- Chemotherapy and surgical excision with or without radiation.

- The advent of effective chemotherapy has dramatically improved the prognosis from a dismal 5% to 15% to a 75% 5-year survival;
- At least 50% are long-term cures.

Giant-cell tumors (GCTs)

- Dominated by multinucleated osteoclast-type giant cells, hence the synonym osteoclastoma.

- GCT is relatively uncommon; it is benign but locally aggressive,
- 20s to 40s.

- Current opinion suggests that the giant cell component is likely a reactive macrophage population and the mononuclear cells are neoplastic. The latter show complex cytogenetic abnormalities.

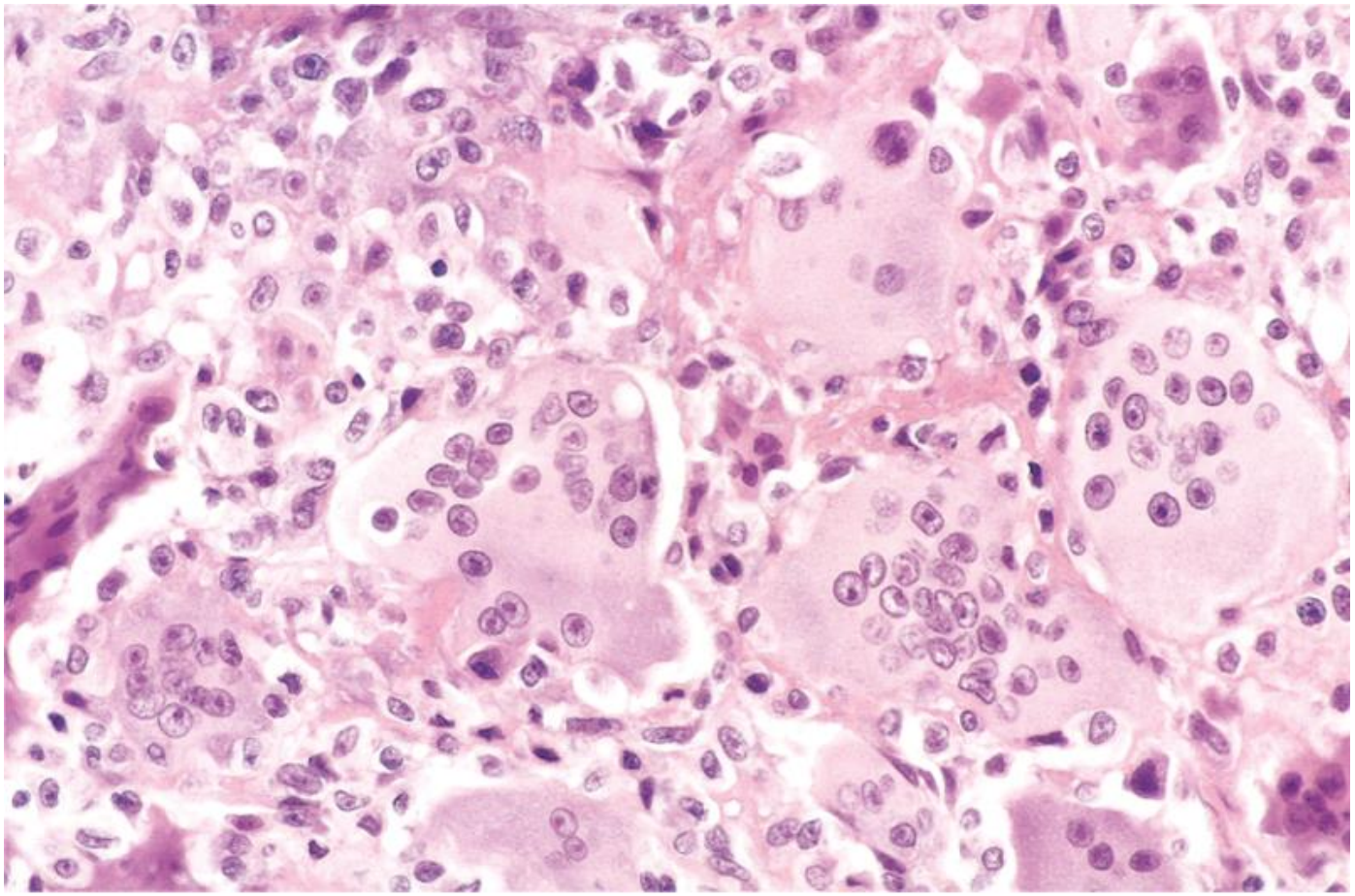
Morphology

- Tumors are large and red-brown with frequent cystic degeneration.

composed of

- Uniform oval mononuclear cells that have indistinct cell membranes and appear to grow in a syncytium. .
- Scattered within this background are numerous osteoclast-type giant cells having 100 or more nuclei that have identical features to those of the mononuclear cells
- Necrosis, hemorrhage, and reactive bone formation are also commonly present.

Benign giant-cell tumor showing abundant multinucleated giant cells and a background of mononuclear cells.



- in adults involve both the epiphyses and the metaphyses, but in
- adolescents they are confined proximally by the growth plate and are limited to the metaphysis.
- The majority of giant cell tumors arise around the knee (distal femur and proximal tibia), but virtually any bone may be involved.
- The location of these tumors in the ends of bones near joints frequently causes patients to complain of arthritic symptoms.
- Occasionally, they present as pathologic fractures.
- Most are solitary; however, multiple or multicentric tumors do occur, especially in the distal extremities.

- Radiographically, giant cell tumors are large, purely lytic, and eccentric, and erode into the subchondral bone plate
- The overlying cortex is frequently destroyed, producing a bulging soft tissue mass delineated by a thin shell of reactive bone.
- Conservative surgery such as curettage is associated with a 40% to 60% recurrence rate.
- Up to 4% metastasize to the lungs.
- The metastatic deposits have the same morphology as the primary tumor.
- Sarcomatous transformation of a giant cell tumor, either de novo or after previous treatment, is a rare event.

Magnetic resonance image of a giant cell tumor that replaces most of the femoral condyle and extends to the subchondral bone plate.