

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

# Bone tumor

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# Introduction

1) Bone forming  
2) Cartilage forming

- Bone tumors are classified according to the normal cell or matrix they produce. Lesions that do not have normal tissue counterparts are grouped according to their clinicopathologic features.
- Benign tumors greatly outnumber their malignant counterparts and occur with greatest frequency within the first three decades of life. In older adults, a bone tumor is more likely to be malignant.

In bone : Metas

# BONE TUMORS

most common tumor:

- Bone tumors are classified into:

- Primary bone tumors → Hemato lymphoid "lymphoma + Multiple lymphoma"
- Secondary bone tumors ( Metastasis)

- Most are classified according to the **normal cell of origin** and **apparent pattern of differentiation**

primary + forming bone  
osteosarcoma

more common

# Primary Bone Tumors

## Bone-Forming tumors

- Osteoid osteoma and osteoblastoma
- Osteosarcoma

## Cartilage-Forming tumors

- Chondroma (Enchondroma)
- Osteochondroma
- Chondrosarcoma

## *Not in Bone non Cartilage* Miscellaneous tumors

- Ewing's sarcoma
- Giant cell tumor of bone

الوئيد لكي بجملة Metas ← هو لاه Giant



الأفهم في المراجعة

والمكانة لهم

Male > Female

Metaphysis

Giant + Ewing

Masses

Category	Behavior	Tumor Type	Common Locations	Age (yr)	Morphology
<b>Cartilage forming</b>	Benign	Osteochondroma	Metaphysis of long bones	10–30	Bony excrescence with cartilage cap
—	—	Chondroma	Small bones of hands and feet	30–50	Circumscribed hyaline cartilage nodule in medulla
—	Malignant	Chondrosarcoma (conventional)	Pelvis, shoulder	40–60	Extends from medulla through cortex into soft tissue, chondrocytes with increased cellularity and atypia
<b>Bone forming</b>	Benign	Osteoid osteoma	Metaphysis of long bones	10–20	Cortical, interlacing microtrabeculae of woven bone
—	—	Osteoblastoma	Vertebral column	10–20	Posterior elements of vertebra, histology similar to osteoid osteoma
—	Malignant	Osteosarcoma	Metaphysis of distal femur, proximal tibia	10–20	Extends from medulla to lift periosteum, malignant cells producing woven bone
<b>Unknown origin</b>	Benign	Giant cell tumor	Epiphysis of long bones	20–40	Destroys medulla and cortex, sheets of osteoclasts
—	—	Aneurysmal bone cyst	Proximal tibia, distal femur, vertebra	10–20	Vertebral body, hemorrhagic spaces separated by cellular, fibrous septae
—	Malignant	Ewing sarcoma	Diaphysis of long bones	10–20	Sheets of primitive small round cells

Adapted from Unni KK, Inwards CY: Dahlin's Bone Tumors, ed 6. Philadelphia, 2010, Lippincott-Williams & Wilkins; by permission of Mayo Foundation.

# • *BONE-FORMING TUMORS*

التحضير  
1313

- Most common Tumor in bone is "lymphoma"
- Most common Tumor in bone out of the cortex "Osteosarcoma"
- Most 2nd common Tumor in bone out of the cortex in Adult "chondrosarcoma"
- Most 2nd common Tumor in bone out of the cortex in children "Ewing sarcoma"

# Osteoid Osteoma and Osteoblastoma

- Osteoid osteoma and osteoblastoma are benign bone producing tumors that have similar histologic features but differ clinically and radiographically
- Osteoid osteomas are, by definition, less than 2 cm in diameter, and are most common in young men. About 50% of cases involve the femur or tibia, where in they typically arise in the cortex. Usually, there is a thick rim of reactive cortical bone that may be the only clue radiographically. Despite their small size, they present with severe nocturnal pain that is relieved by aspirin and other nonsteroidal anti-inflammatory agents. The pain is probably caused by prostaglandin E2 produced by osteoblasts.

	Size	Site	pain relived by Aspirin+ NSAIDs	Treatment
Osteoid Ost.	> 2cm	Metaphysis Femur + Tibia	✓	Radiofrequency
Osteoblastoma	< 2cm	Vertebra	✗	Excision

Same Morphology

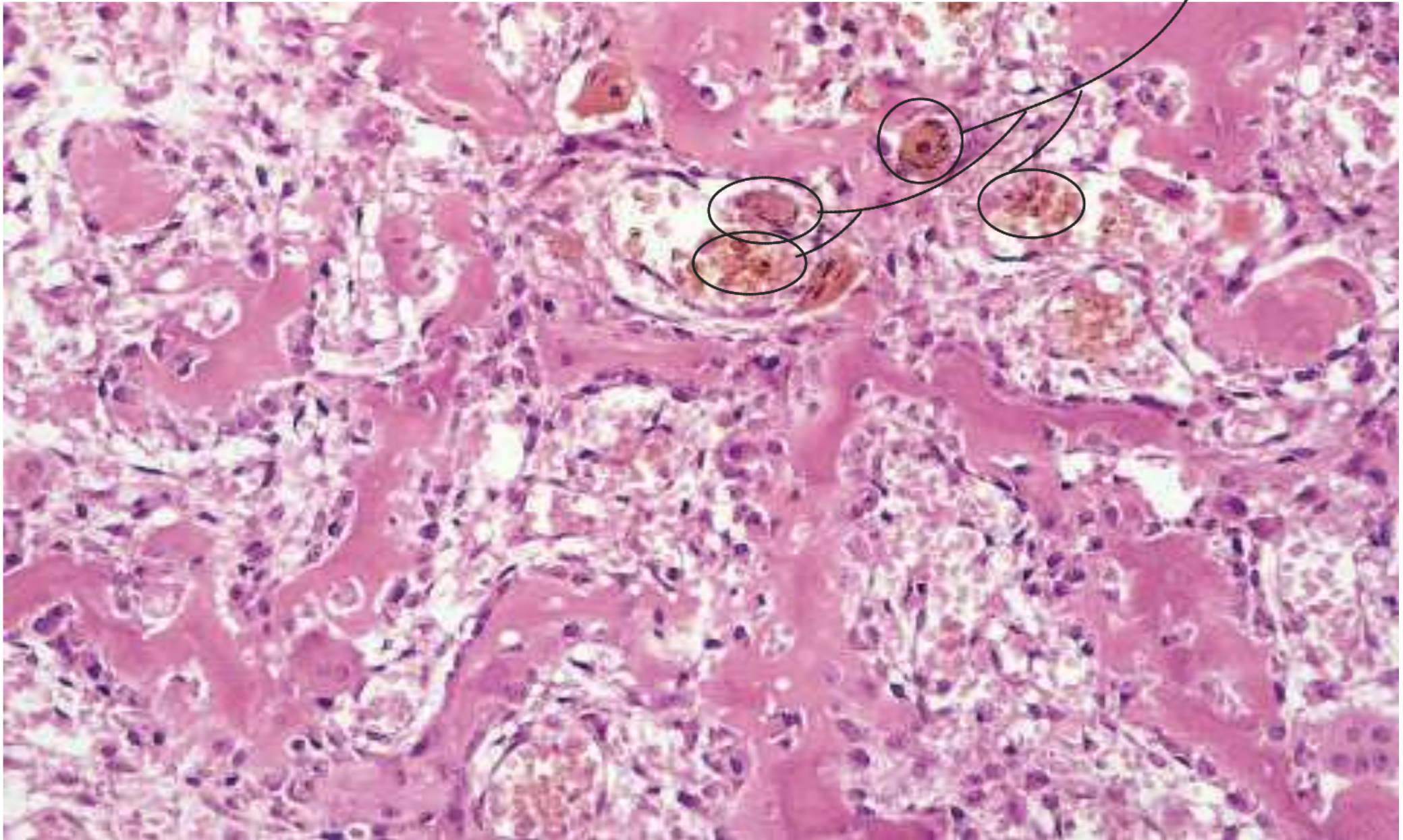
- Osteoblastoma is larger than 2 cm and involves the posterior components of the vertebrae (laminae and pedicles) more frequently. The pain is unresponsive to aspirin, and the tumor usually does not induce a marked bony reaction.
- Osteoid osteoma is frequently treated by radiofrequency ablation, whereas osteoblastoma is usually curetted or excised. Malignant transformation is rare.

- They are well circumscribed and composed of randomly interconnecting delicate trabeculae of woven bone that are prominently rimmed by a single layer of osteoblasts. The stroma surrounding the neoplastic bone consists of loose connective tissue that contains many dilated and congested capillaries. The relatively small size, well defined margins, and benign cytologic features of the neoplastic osteoblasts help distinguish these tumors from osteosarcoma. Osteoid osteomas elicit the formation of a large amount of reactive bone, which encircles the lesion.



Osteoid Ost. + Osteoblastoma "Hence same Morphology"

Blood Vessel



# Osteosarcoma

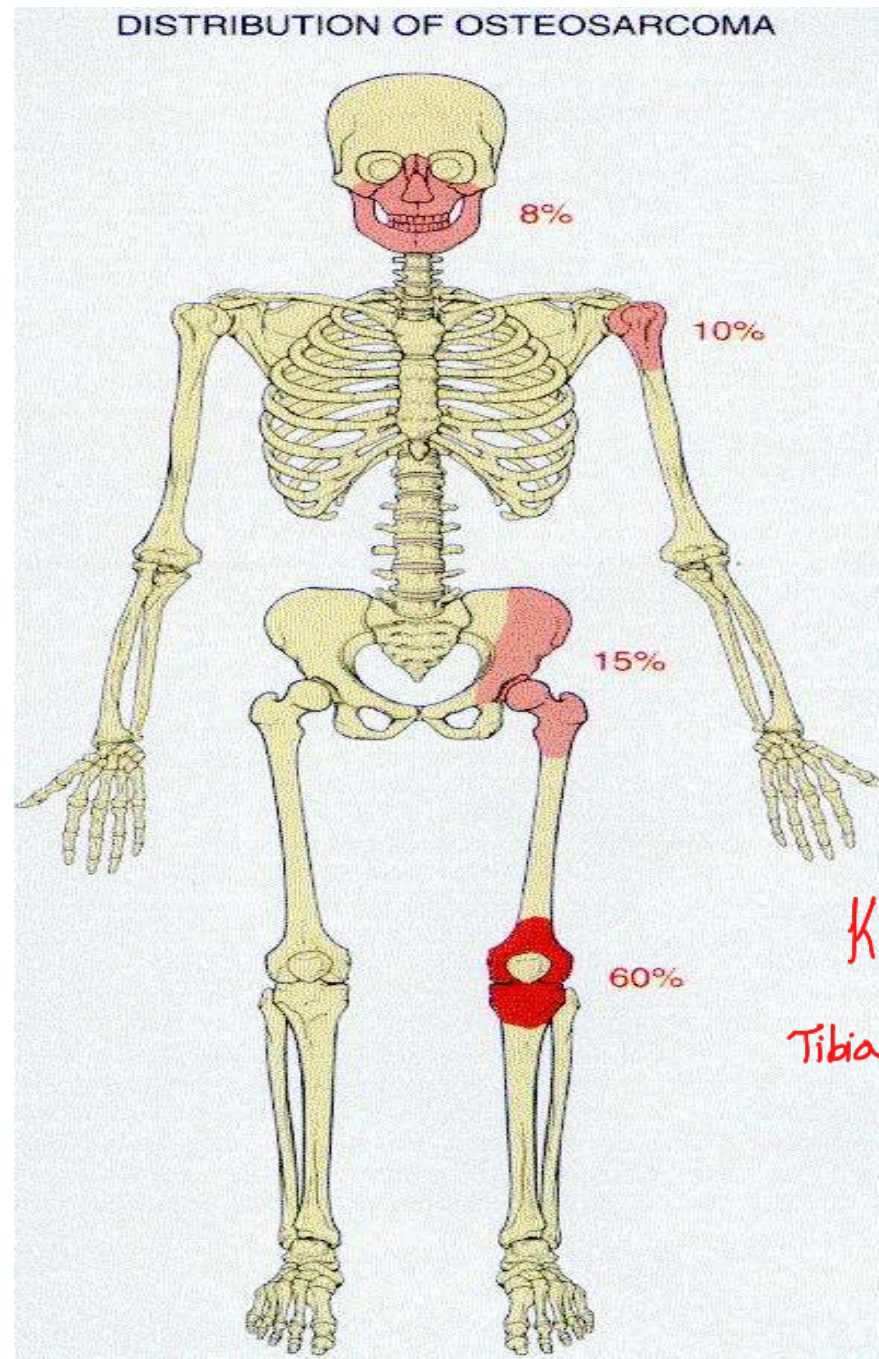
- **Osteosarcoma is a malignant tumor that produces osteoid matrix or mineralized bone.**
- Excluding hematopoietic tumors (myeloma and lymphoma), osteosarcoma is the most common primary malignant tumor of bone.
- Osteosarcoma has a bimodal age distribution; 75% of osteosarcomas occur in persons younger than 20 years of age. The smaller second peak occurs in older adults, who frequently suffer from conditions known to predispose to osteosarcoma, such as Paget disease, bone infarcts, and previous radiation. These are referred to as secondary osteosarcomas.
- Overall, men are more commonly affected than women (~~1.6:1~~).
- The most common sites in adolescents are the metaphyseal regions of the distal femur and proximal tibia.

primary => In young (<20)

secondary => In Old (Adult) with "paget, Infraction, Radiation"



# Osteosarcoma Distribution



الأكثر في الـ Knee  
سواء الـ Tibia or Femur



کلمہ Masses لکن فنا سریع

- Osteosarcomas present as painful, progressively enlarging masses. Sometimes a pathologic fracture is the first indication.
- Radiographs usually show a large, destructive, mixed lytic and sclerotic mass with infiltrative margins. The tumor frequently breaks through the cortex and lifts the periosteum, resulting in reactive subperiosteal bone formation. The triangular shadow between the cortex and raised ends of periosteum, known radiographically as Codman triangle, is indicative of an aggressive tumor, but is not pathognomonic of osteosarcoma.

# Pathogenesis

without  
Details

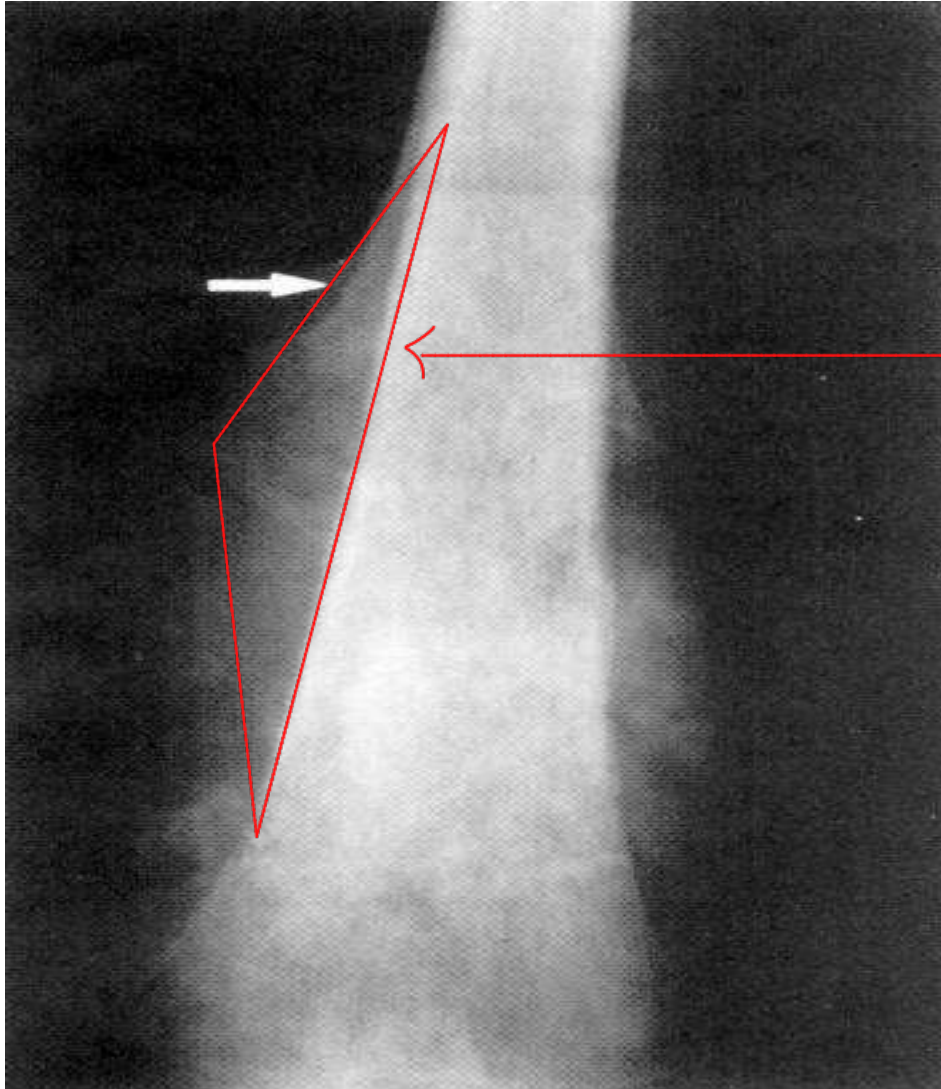
- Approximately 70% of osteosarcomas have acquired genetic abnormalities such as complex structural and numerical chromosomal aberrations.
- 1) • *RB* is a critical negative regulator of the cell cycle. Patients with germline mutations in *RB* have a 1000-fold mutations are present in up to 70% of sporadic osteosarcomas.
- 2) • *TP53* is a gene whose product functions as the guardian of genomic integrity by promoting DNA repair and apoptosis of irreversibly damaged cells. Patients with Li-Fraumeni syndrome, who have germline *TP53* gene mutations, have a greatly elevated incidence of osteosarcoma, and abnormalities that interfere with p53 function are common in sporadic tumors.

المعلم تعرفه  
دون تفاصيله  
apop ...

- 3.) • CDKN2A is inactivated in many osteosarcomas. This gene encodes two tumor suppressors, p16 (a negative regulator of cyclin-dependent kinases) and p14 (which augments p53 function).
- 4.) • MDM2 and CDK4, which are cell cycle regulators that inhibit p53 and RB function, respectively, are overexpressed in many low-grade osteosarcomas

# Osteosarcoma

## Radiograph



Distal femoral osteosarcoma with prominent bone formation extending into the soft tissues. The periosteum, which has been lifted, has laid down a triangular shell of reactive bone known as a Codman triangle

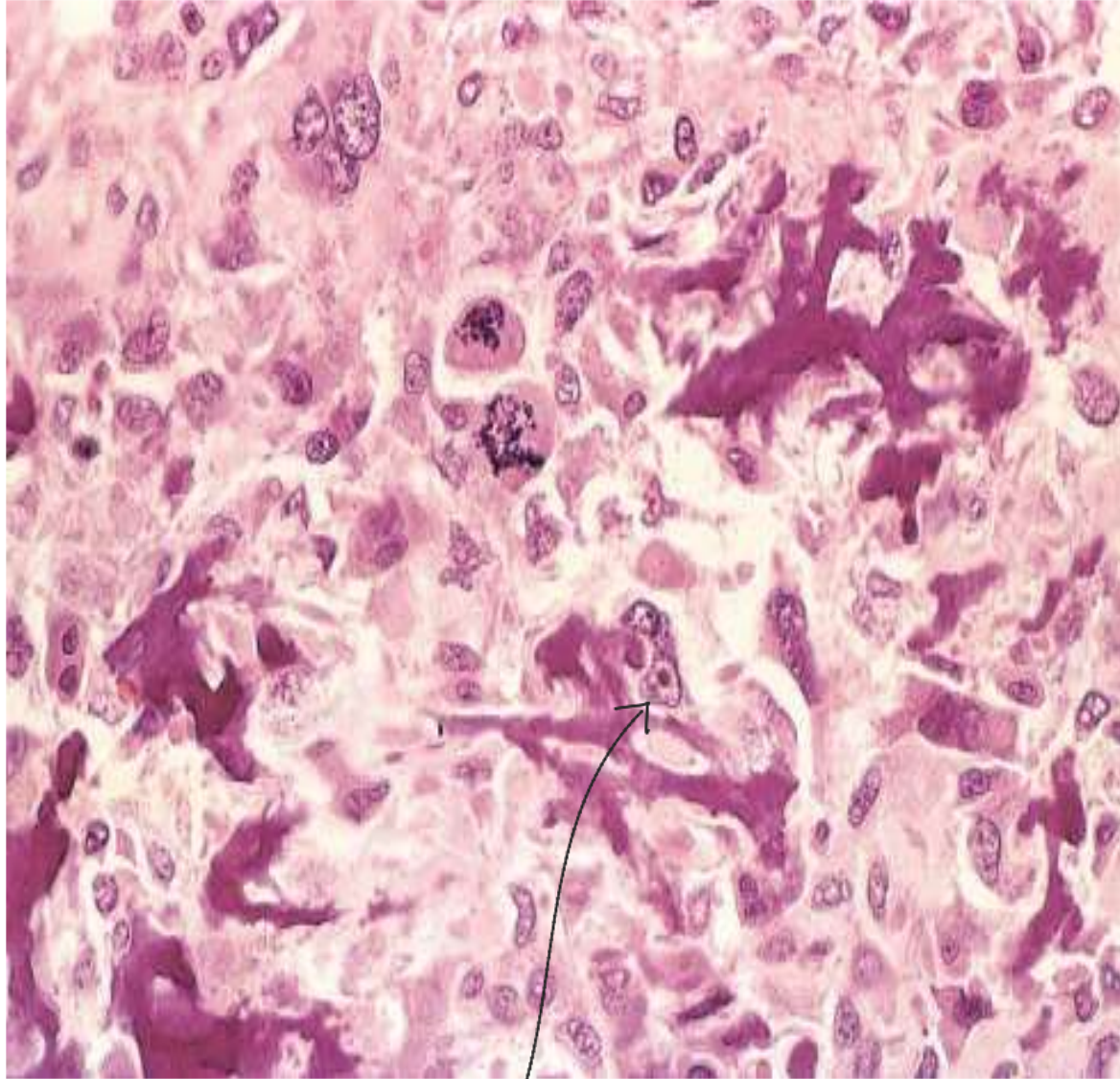
مثلث جيبس



Osteosarcoma of the proximal 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.



# Woven Bone , Osteosarcoma



Fine, lacelike pattern of neoplastic bone produced by anaplastic malignant tumor cells in an osteosarcoma. Note the abnormal mitotic figures.

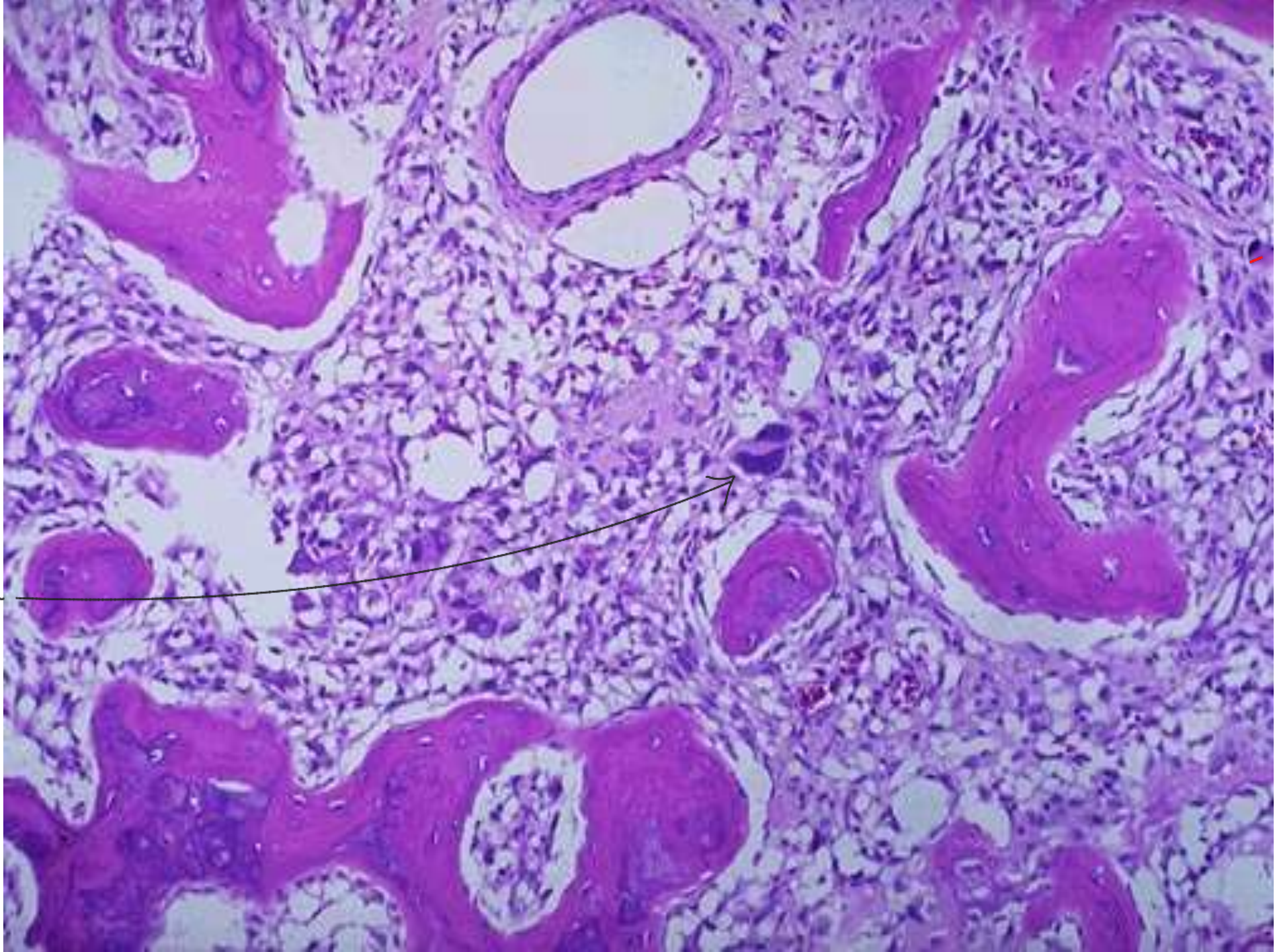
Anaplasia

سکالوم بئسغ



Woven  
Bone  
Osteosarcoma

Anaplasia  
سکالیم بئسغ



*CARTILAGE -  
FORMING TUMORS*



# Osteochondroma

"Osteoid + Cartilage"

Exs-1 gene

أرجل المتصل بالعظم نوعه Hyaline

- These tumors are characterized by the formation of hyaline cartilage.  
Benign cartilaginous tumors are much more common than malignant ones.
- Osteochondroma, known clinically as exostosis, is a benign cartilage-capped tumor that is attached to the underlying skeleton by a bony stalk.
- About 85% are solitary. The remainder are seen as part of the multiple hereditary exostoses syndrome.
- Solitary osteochondromas are usually first diagnosed in late adolescence and early adulthood, but multiple osteochondromas become apparent during childhood.
- Men are affected three times more often than women.

young  
Men > Women

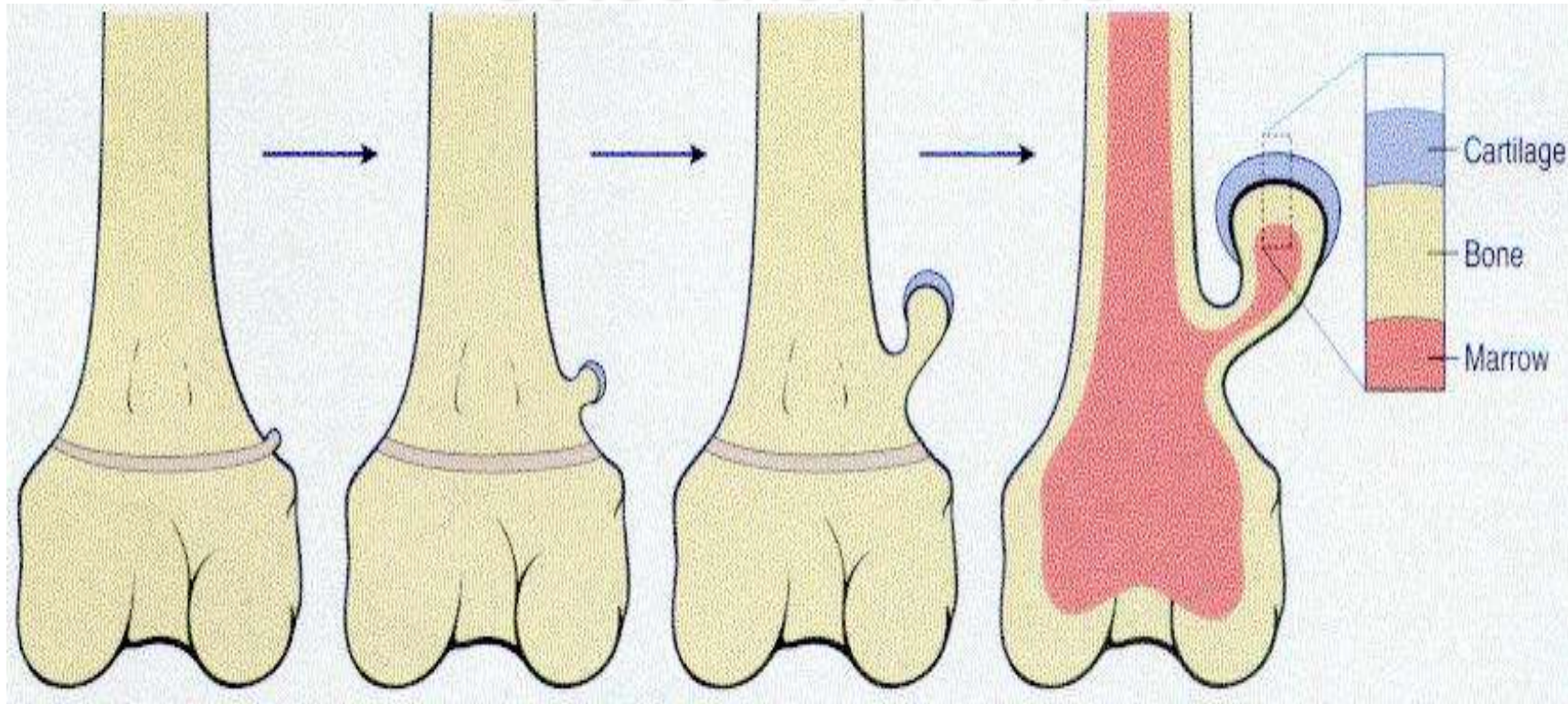
- Osteochondromas develop in bones of endochondral origin and arise from the metaphysis near the growth plate of long tubular bones, especially near the knee.
- They present as slow-growing masses, which can be painful if they impinge on a nerve or if the stalk is fractured. In many cases they are detected incidentally. In multiple hereditary exostoses, the underlying bones may be bowed and shortened, reflecting an associated disturbance in epiphyseal growth.

# Pathogenesis

- Hereditary exostoses are associated with germline loss-of function mutations in either the EXT1 or the EXT2 gene and subsequent loss of the remaining wild-type allele in chondrocytes of the growth plate.
- Reduced expression of *EXT1* or *EXT2* also has been observed in sporadic osteochondromas.

وہاں تک کہ  
→ Chondrosarcoma

# Osteochondroma

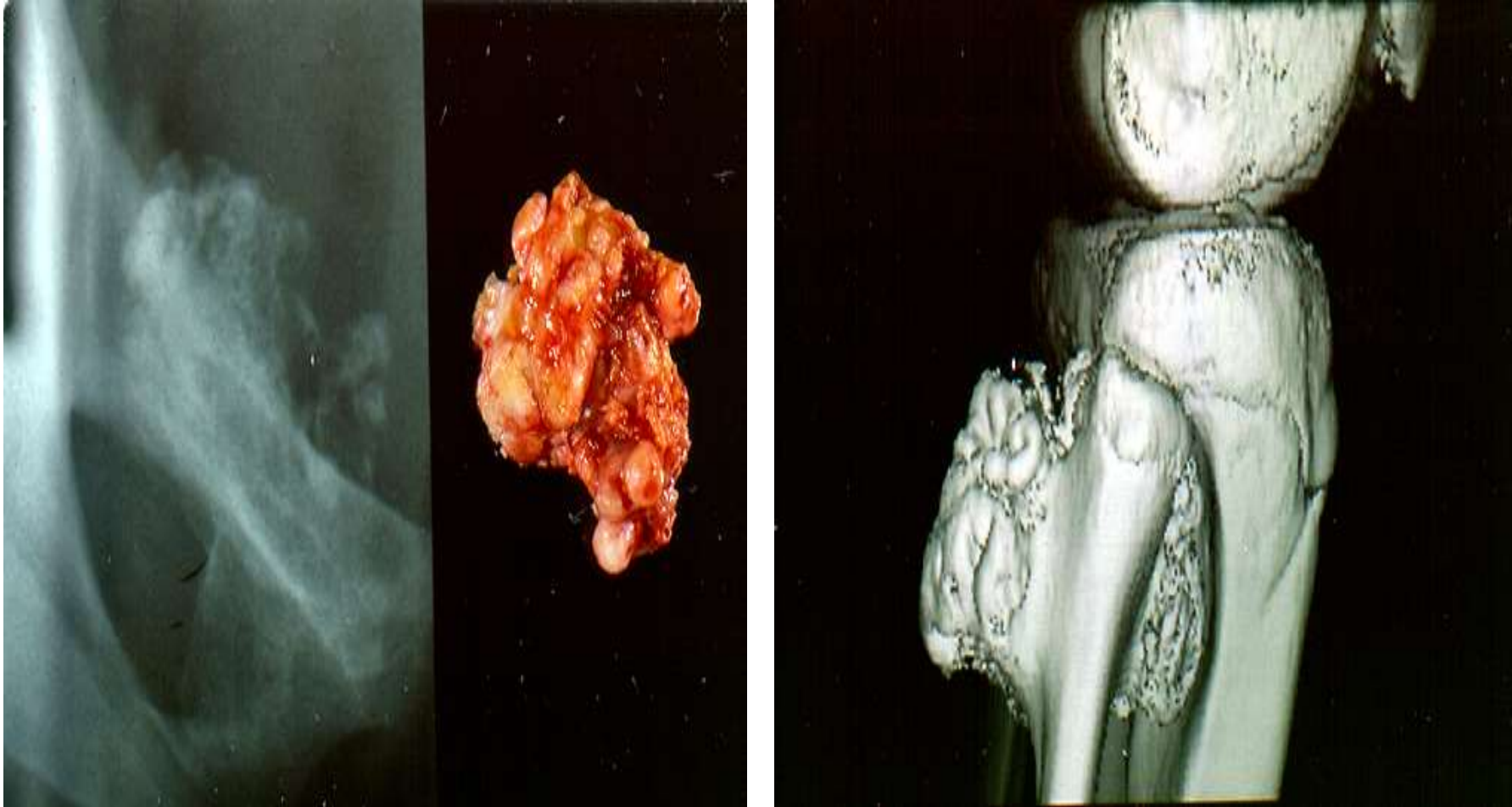


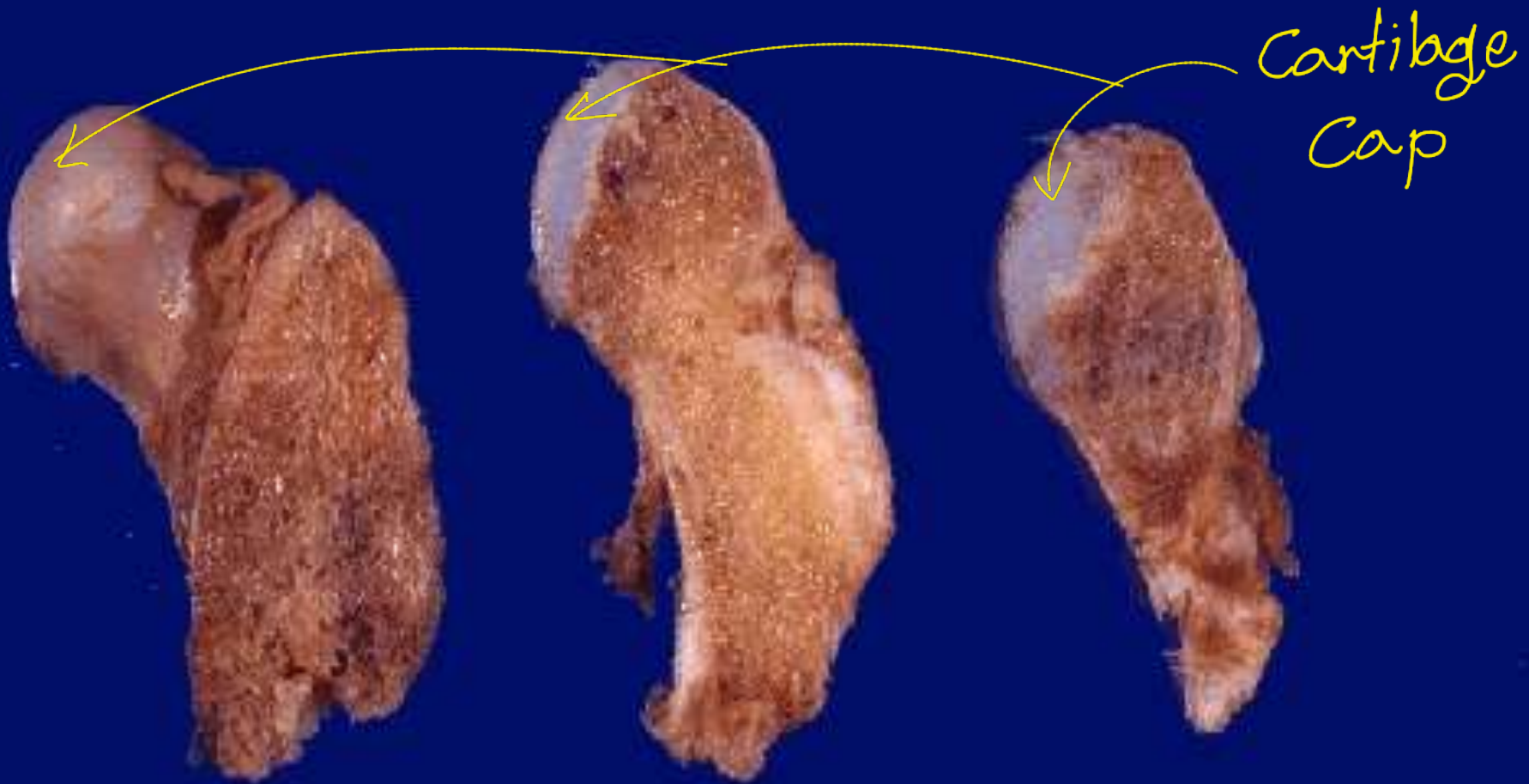
- Osteochondromas are mushroom shaped and range in size from 1 to 20 cm.
- The **outer layer** of the head of the osteochondroma is composed of benign hyaline cartilage varying in thickness
- Newly formed bone forms the **inner portion** of the head and stalk, with the stalk cortex merging with the cortex of the host bone.



# Osteochondroma (exostosis)

Gross





Osteochondroma. Radiograph of an osteochondroma arising from the distal femur. The cartilage cap has the histologic appearance of disorganized growth plate–like cartilage.



# Clinical course

- Osteochondromas usually stop growing at the time of growth plate closure.
- Symptomatic tumors are cured by simple excision.
- Rarely in sporadic cases, but more commonly in those with multiple hereditary exostosis (5%– 20%), osteochondromas progress to chondrosarcoma.



# Chondroma

التي تحدث في

young Age  
Small Bone  
"Hand, fingre"

- **Chondromas are benign tumors of hyaline cartilage that usually occur in bones of endochondral origin.**
- Enchondromas are usually diagnosed in individuals 20 to 50 years of age. Typically, they appear as solitary metaphyseal lesions of the tubular bones of the hands and feet.
- The radiographic features consist of a circumscribed lucency with central irregular calcifications, a sclerotic rim, and an intact cortex.
- *Ollier disease* and *Maffucci syndrome* are disorders characterized by multiple enchondromas (enchondromatosis). Maffucci syndrome also is associated with other rare tumors.

more  
Common

Syndrome  
Multi  
بكونه

اُي شَيءٌ مَرْتَبِعٌ بِ Syndrome  
Multiple يَكُونُ

اَلِي كَلْتَه لِنَد

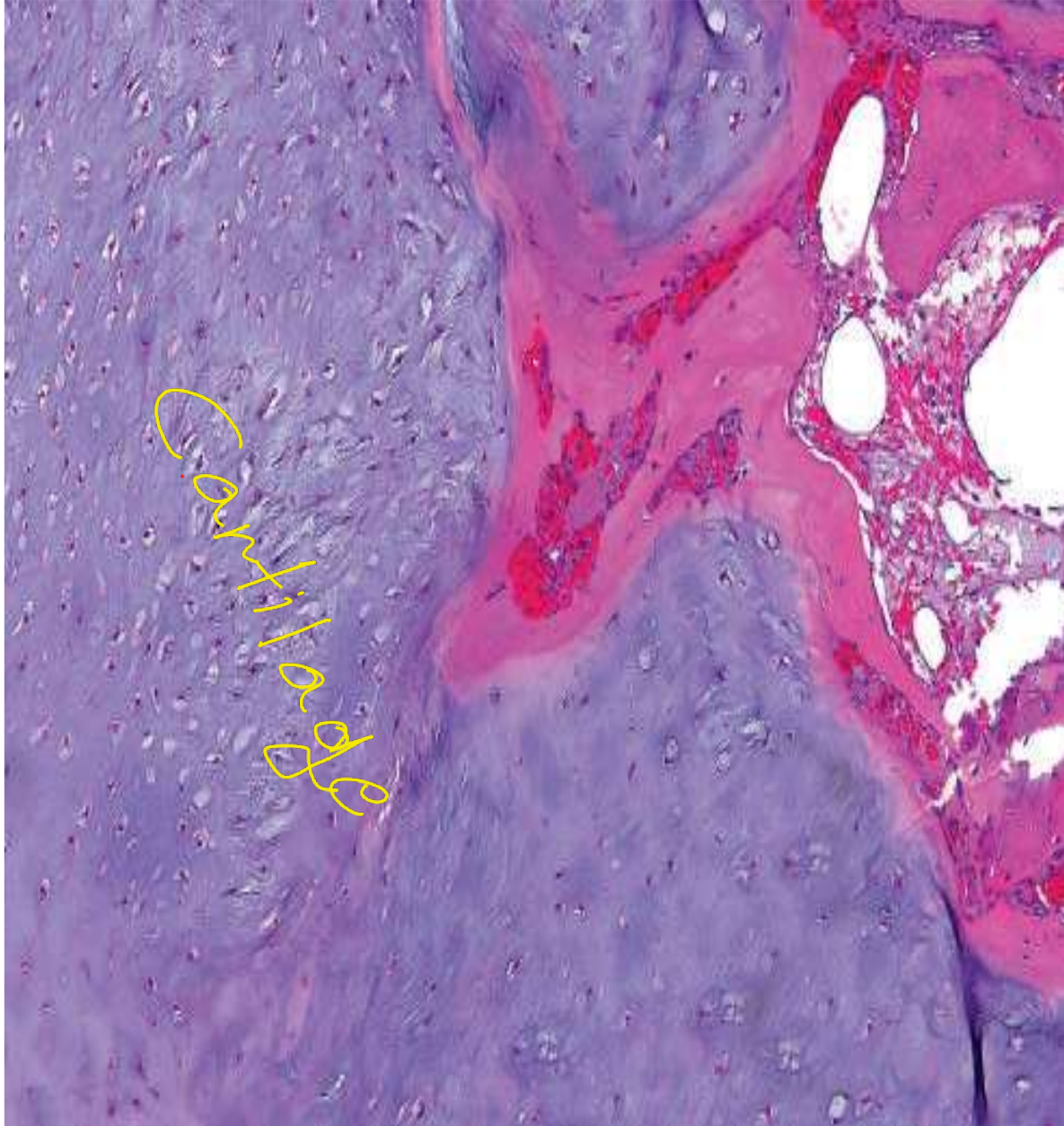
- Most enchondromas of large bones are asymptomatic and are detected incidentally. Occasionally, they are painful and cause pathologic fracture. The tumors in enchondromatosis may be numerous and large, producing severe deformities, especially of the digits.



Enchondroma of the proximal phalanx. The radiolucent nodule of cartilage with central calcification thins but does not penetrate the cortex.

# Pathogenesis

- Heterozygous gain of function mutations in the IDH1 and IDH2 genes, coding for the enzymes isocitrate dehydrogenases, have been identified in the chondrocytes of syndromic and solitary enchondromas.
- Enchondromas are usually smaller than 3 cm and are gray blue and translucent. They are composed of well-circumscribed nodules of hyaline cartilage containing benign chondrocytes. The peripheral portion of the nodules may undergo endochondral ossification, and the center can calcify and infarct. Syndromic enchondromas are sometimes more cellular with more atypia than sporadic enchondromas.



Enchondroma composed of a nodule of hyaline cartilage encased by a thin layer of reactive bone.

# Chondrosarcoma

- **Chondrosarcomas are malignant tumors that produce cartilage.** They are subclassified into conventional (hyaline cartilage-producing), dedifferentiated, clear cell, and mesenchymal types. Approximately 90% of chondrosarcomas are of the conventional type.
- Chondrosarcoma is about half as common as osteosarcoma. Individuals with conventional chondrosarcoma are usually in their 40s or older. These tumors affect men twice as frequently as women.
- The clear cell and especially the mesenchymal variants occur in children and young adults. Chondrosarcomas commonly arise in the axial skeleton, especially the pelvis, shoulder, and ribs.
- Unlike benign enchondroma, the distal extremities are rarely involved. About 15% of conventional chondrosarcomas are secondary, arising from a preexisting enchondroma or osteochondroma.



# Pathogenesis

Mutation  
without Details

- Although chondrosarcomas are genetically heterogeneous, a few reproducible abnormalities have been identified.
- Chondrosarcomas arising in multiple osteochondroma syndrome exhibit mutations in the EXT genes, and both chondromatosis-related and sporadic chondrosarcomas may have IDH1 and IDH2 mutations. Mutation of the collagen COL2A1 gene and silencing of the CDKN2A tumor suppressor gene can also be related to chondrosarcoma

# Clinical Course

- Chondrosarcomas usually present as painful, progressively enlarging masses.
- Tumor grade predicts outcome, which ranges from 80% 5-year survival for Grade 1 tumors to 43% for Grade 3 tumors.
- Grade 1 chondrosarcomas rarely metastasize, whereas 70% of grade 3 tumors spread hematogenously, especially to the lungs. The treatment of conventional chondrosarcoma is wide surgical excision.
- The mesenchymal and dedifferentiated tumors are also excised and are additionally treated with chemotherapy because of their more aggressive clinical course.

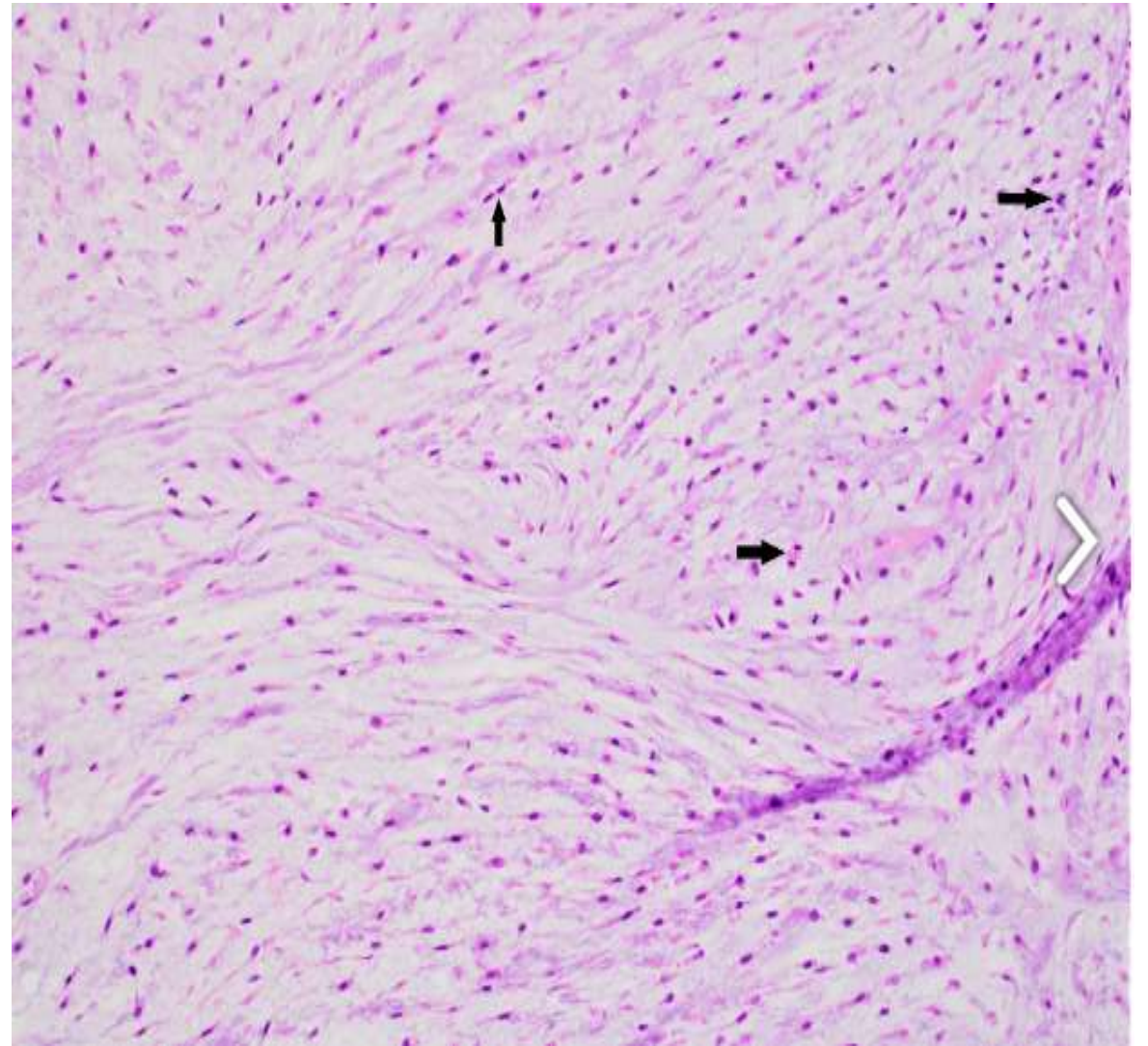
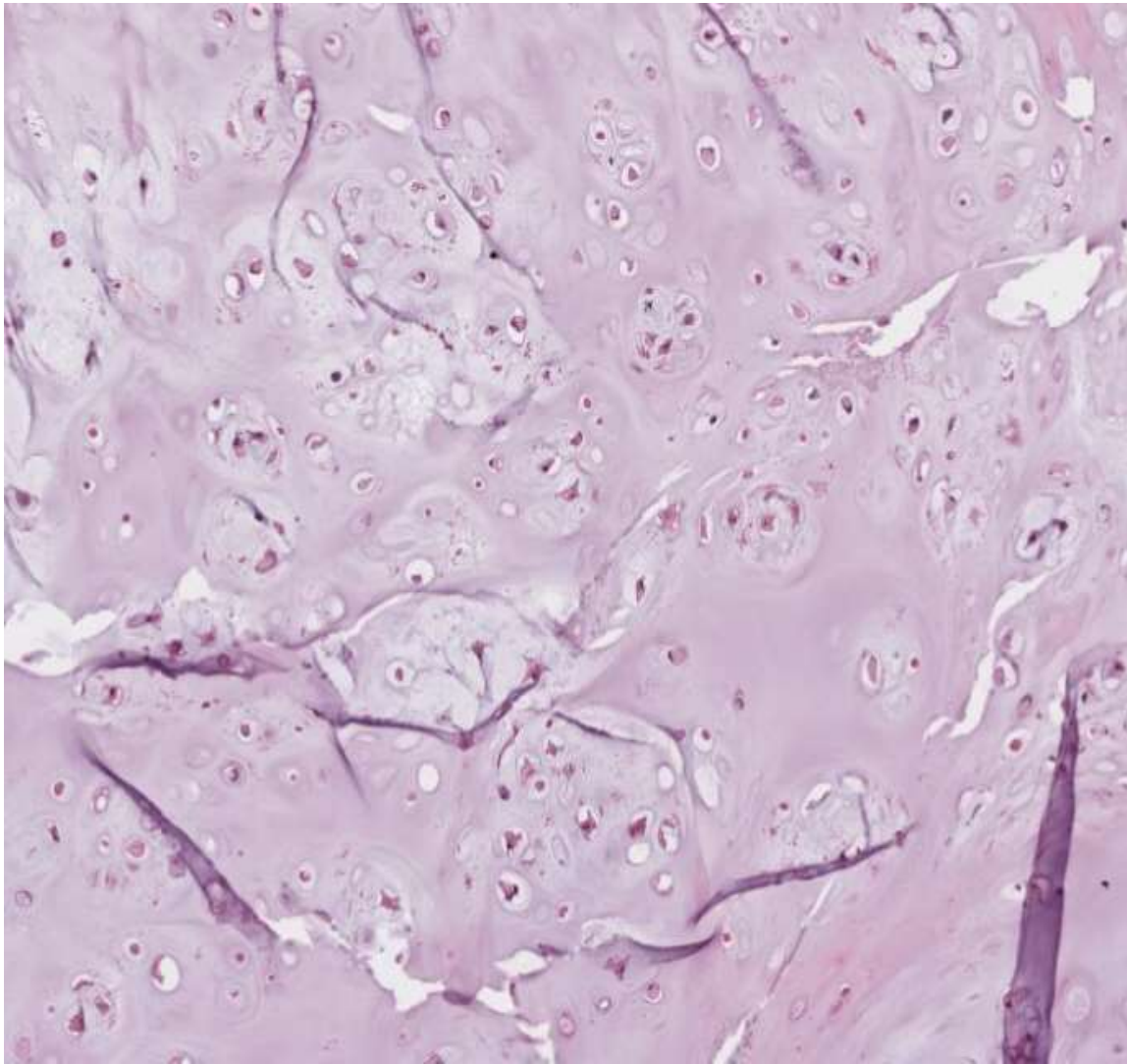


# Morphology

Mass

- **Conventional chondrosarcomas** are large bulky tumors composed of nodules of gray-white, translucent cartilage, along with gelatinous or myxoid areas. **Spotty calcifications** are typically present, and central necrosis may create cystic spaces. The tumor spreads through the cortex into surrounding muscle or fat. Histologically, the cartilage infiltrates the marrow space and entraps normal bony trabeculae. The tumors vary in cellularity, cytologic atypia, and mitotic activity and are assigned a grade from 1 to 3. Grade 1 tumors have relatively low cellularity, and the chondrocytes have plump vesicular nuclei with small nucleoli. By contrast, grade 3 chondrosarcomas are characterized by high cellularity, extreme pleomorphism with bizarre tumor giant cells, and mitoses.

# Conventional

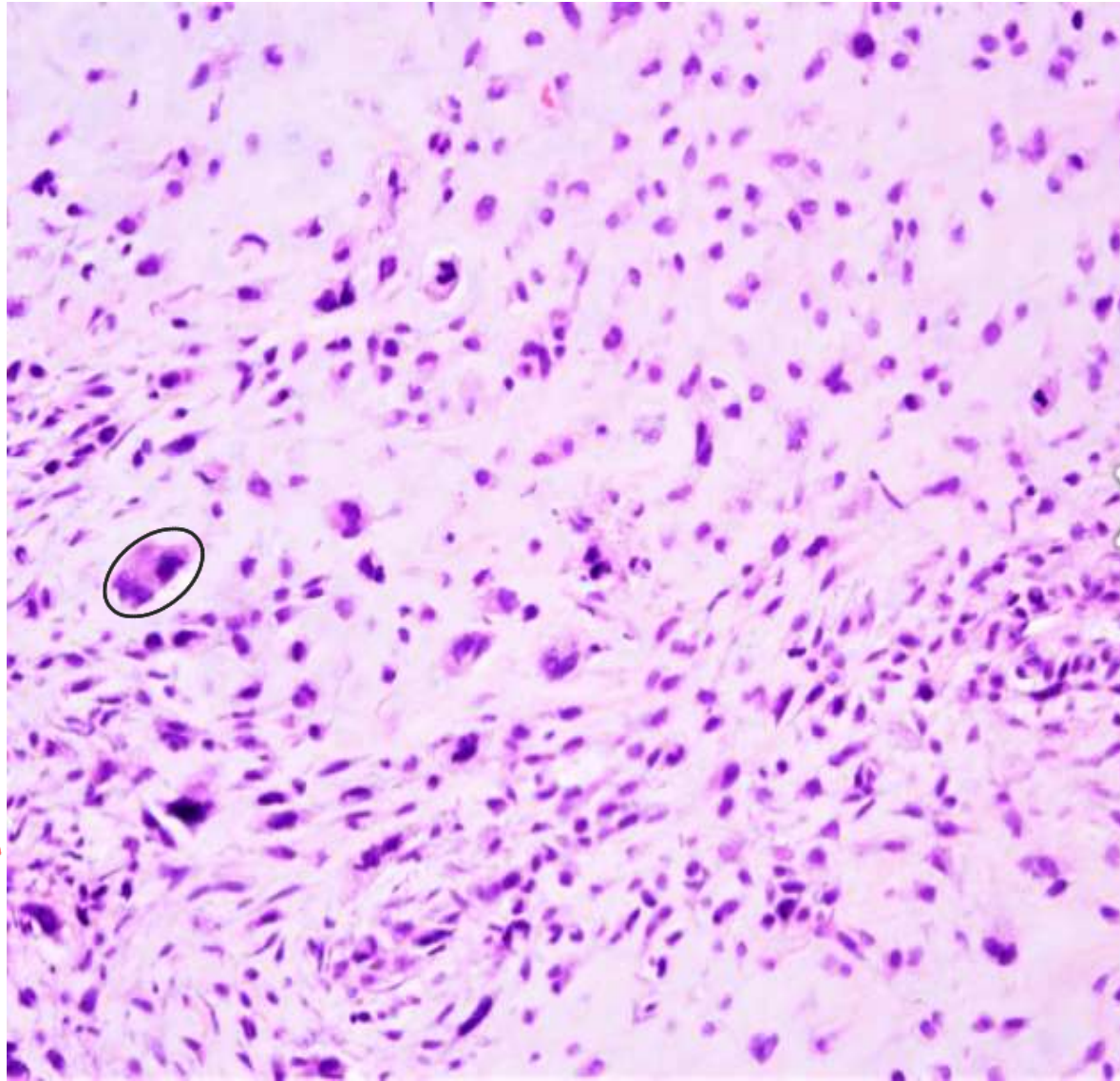


Low Grade

"Chondrosarcoma"

Higher Grade



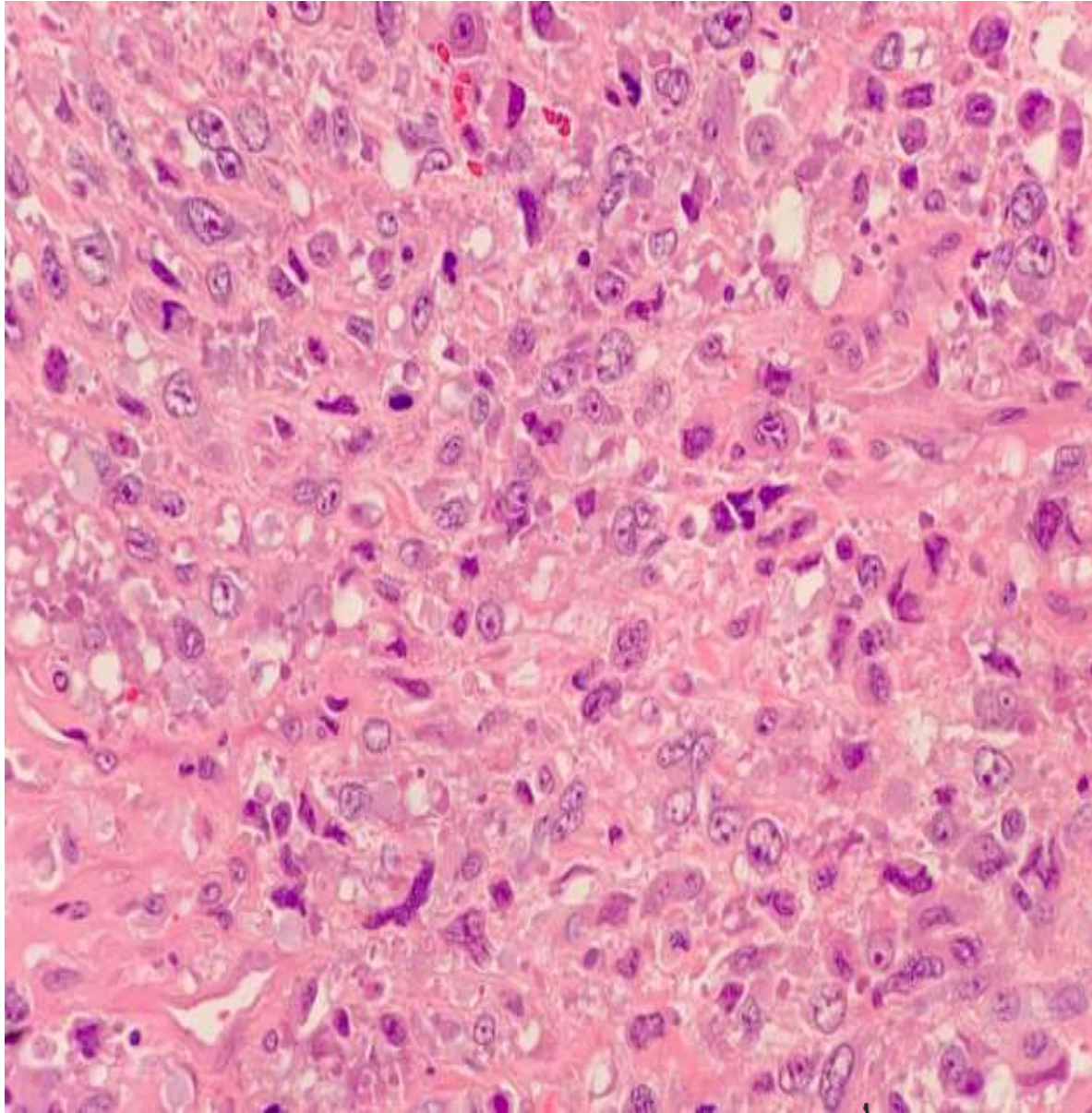


Atypical  
Mitosis

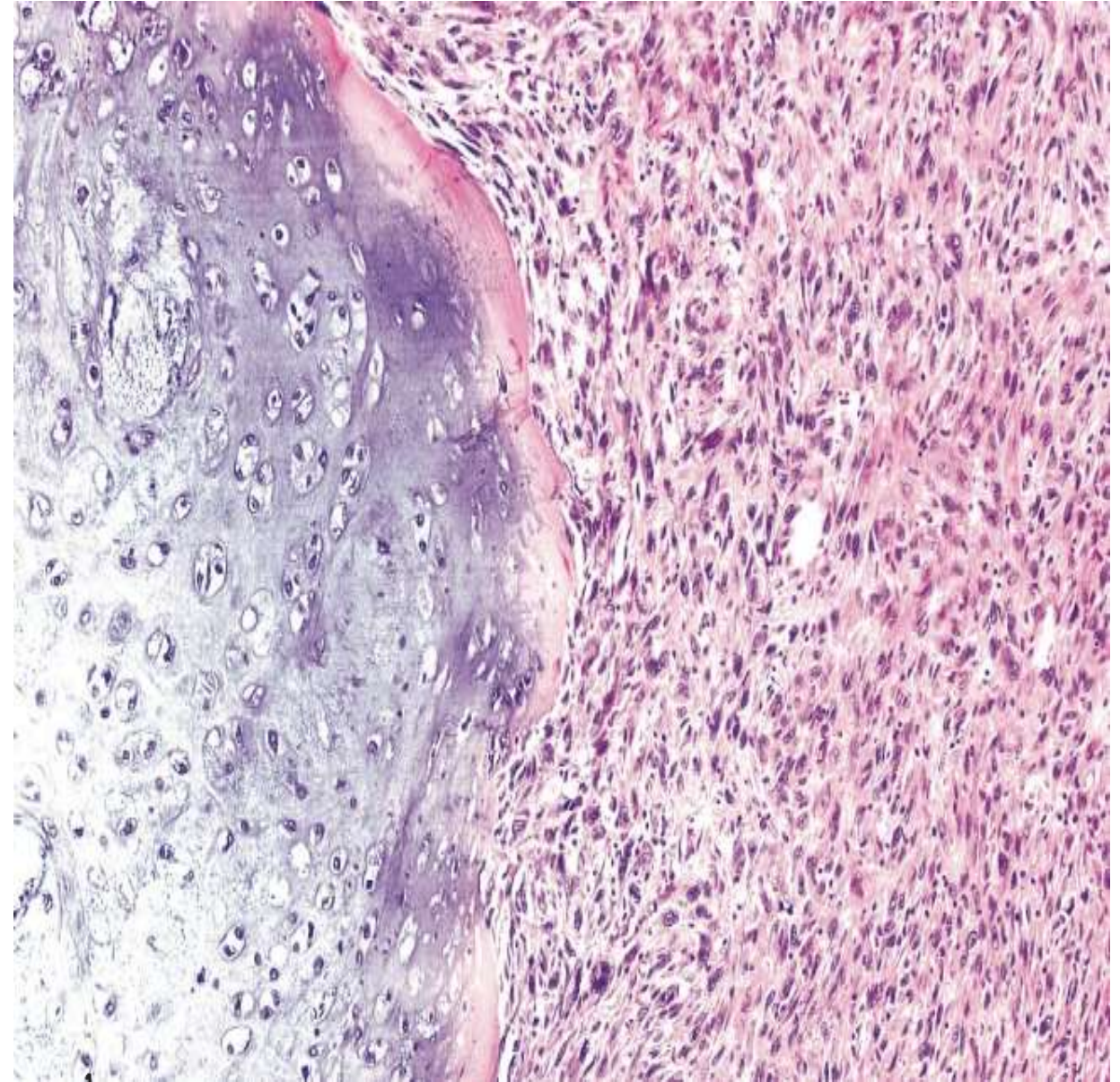
"Higher Grade"

"Chondrosarcoma"





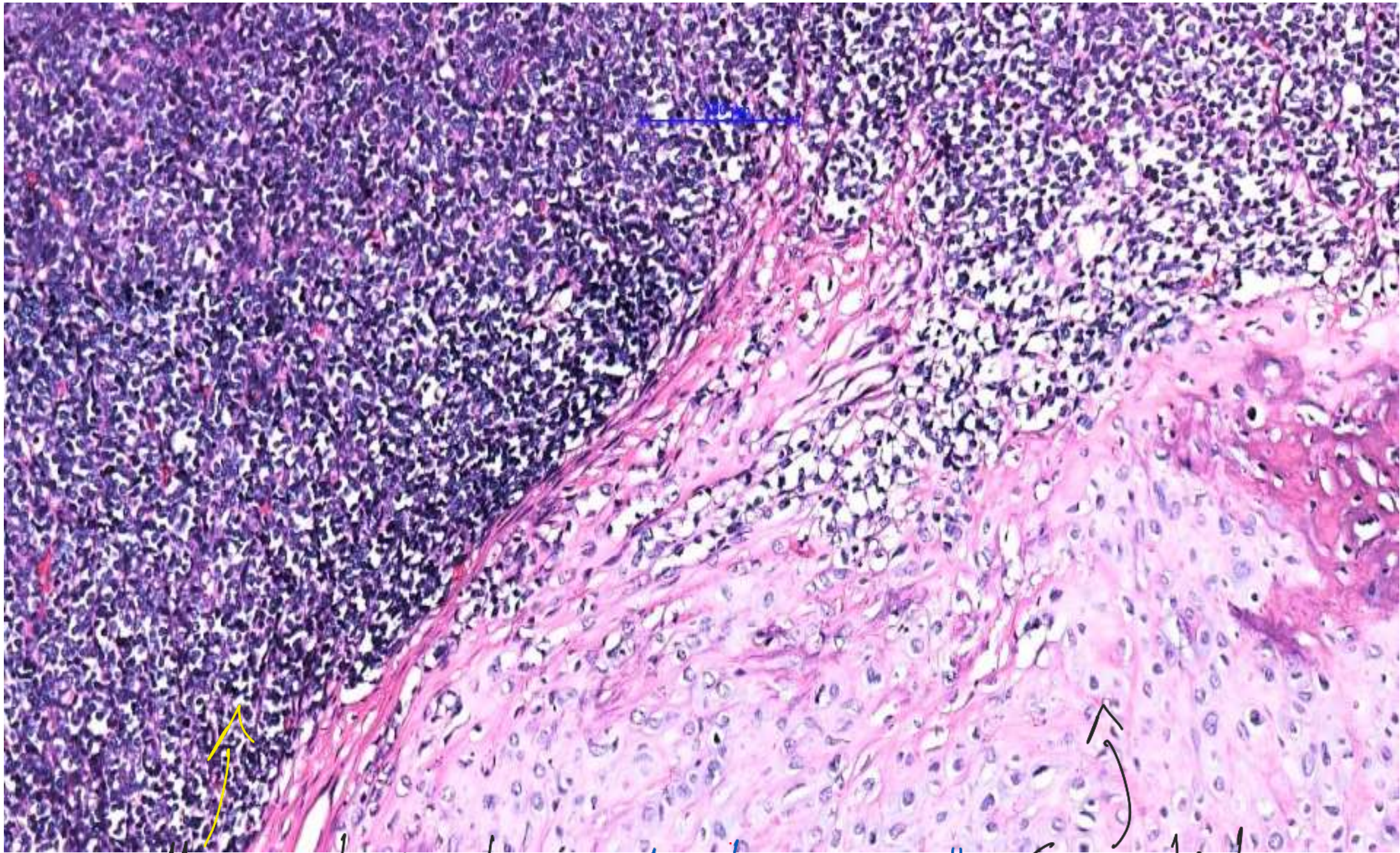
Higher Grade *Conventional*



Dedifferentiate

Chondrosarcoma





Mesenchymal

"chondrosarcoma"

Conventional



# Tumors of Unknown Origin

- Ewing sarcoma is a malignant tumor composed of primitive round cells with varying degrees of neuroectodermal differentiation and a characteristic molecular signature.
- Entities previously classified as primitive neuroectodermal tumor (PNET) and Askin tumor have been unified into the single category of Ewing sarcoma. *↳ Extraskeleton*



- Ewing sarcoma accounts for approximately 10% of primary malignant bone tumors and follows osteosarcoma as the second most common bone sarcoma in children. Of all bone sarcomas, Ewing sarcomas have the youngest average age at presentation (80% are younger than 20 years). Boys are affected slightly more frequently than girls, and there is a predilection for Caucasians.
- The tumors usually arise in the diaphysis of long tubular bones but 20% are extraskeletal. They present as painful enlarging masses, and the affected site is frequently tender, warm, and swollen. Plain radiographs show a destructive lytic tumor with permeative margins that extends into the surrounding soft tissues. The characteristic periosteal reaction produces layers of reactive bone deposited in an *onion-skin* fashion.

اللي كتبتة في ↓

Osteomyelitis زخم العظام

# Pathogenesis

- The vast majority (85%) of Ewing sarcomas contain a balanced (11;22) (q24;q12) translocation generating in-frame fusion of the *EWSR1* gene on chromosome 22 to the *FLI1* gene on chromosome 11.

Molecular

# MORPHOLOGY

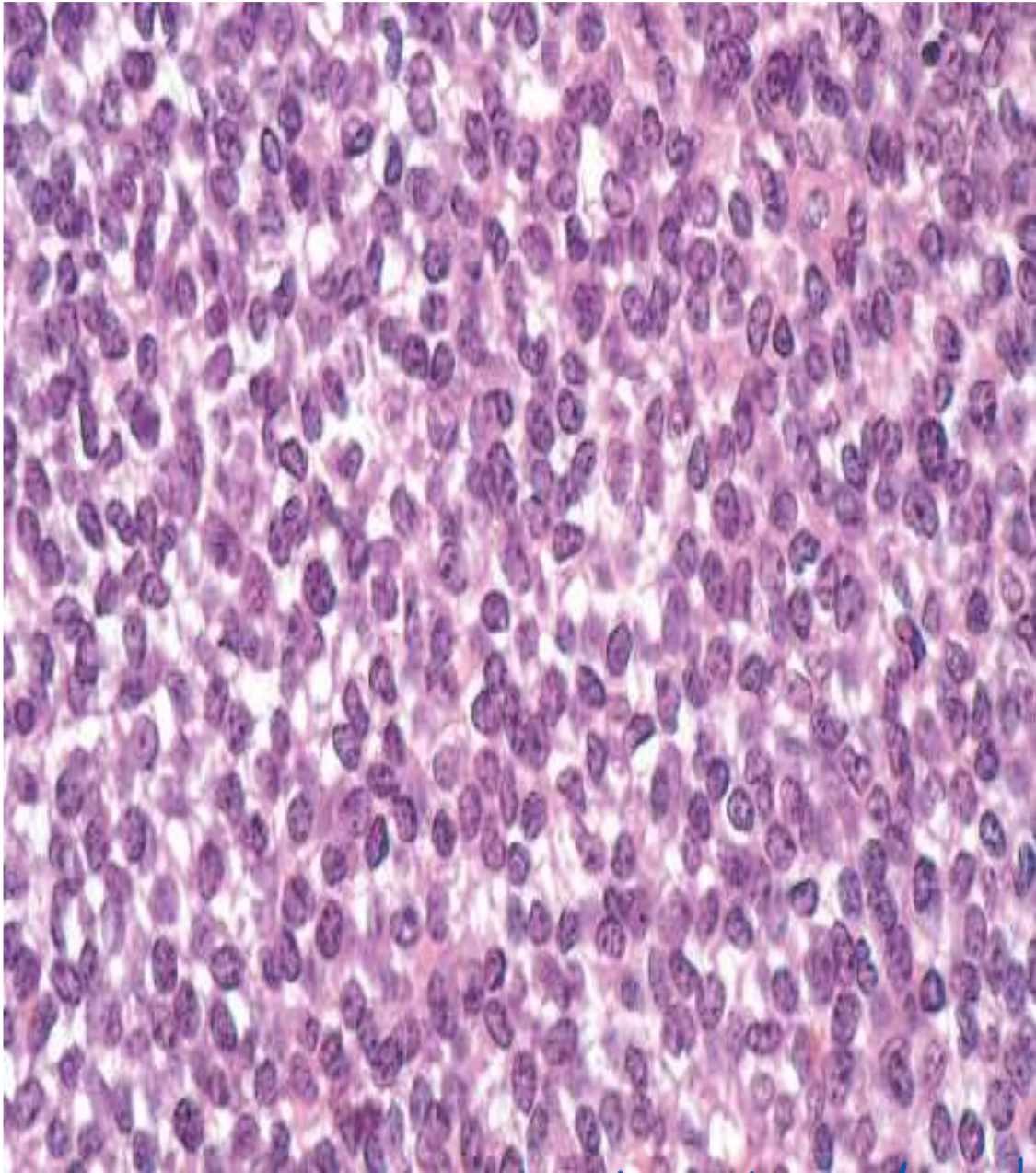
- Arising in the medullary cavity, Ewing sarcoma usually invades the cortex, periosteum, and soft tissue. The tumor is soft, tan white, and frequently contains areas of hemorrhage and necrosis.
- It is one of the small, round blue cell tumors found in children. Like other tumors in this group, Ewing sarcoma is composed of sheets of uniform small, round cells that are slightly larger and more cohesive than lymphocytes, They have scant cytoplasm, which may appear clear because it is rich in glycogen. Homer-Wright rosettes (round groupings of cells with a central fibrillary core) may be present and indicate a greater degree of neuroectodermal differentiation. The tumor cells do not produce bone or cartilage.

→ under 10  
on 20

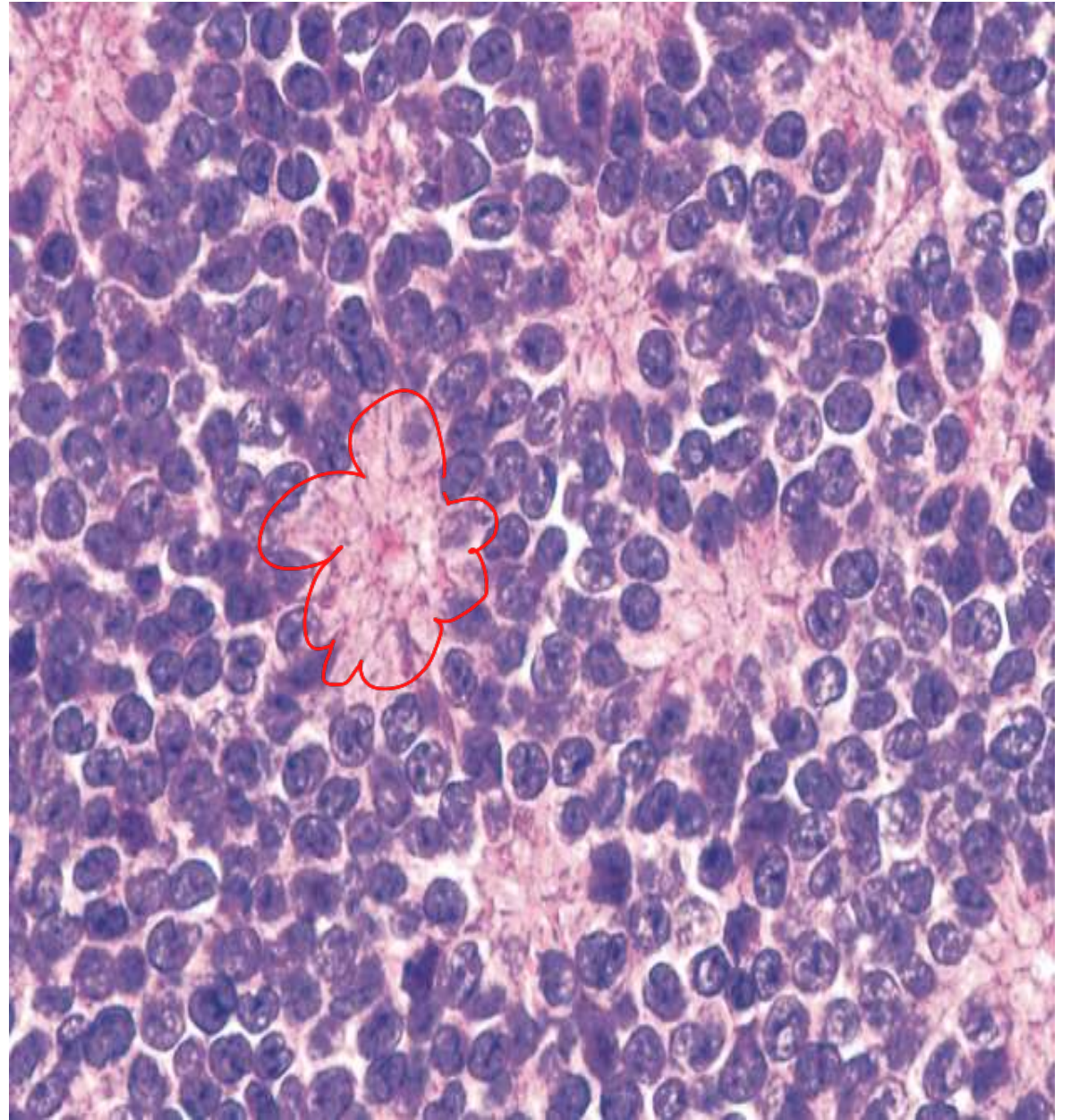
# Clinical Course

- Ewing sarcomas are aggressive malignancies treated with neoadjuvant chemotherapy followed by surgical excision with or without radiation. With chemotherapy, 5-year survival of 75% and long-term cure in 50% of patients is possible.





Ewing Sarcoma "like Mesenchymal"



Ewing Sarcoma Rosette



# Pathogenesis

- Experimental evidence suggests that the neoplastic cells of the giant cell tumor are osteoblast precursors, which represent only a minority of the cells in the tumor.
- The neoplastic cells express high levels of RANKL, which promotes the proliferation and differentiation of normal osteoclast precursors into osteoclasts. The osteoclasts in turn cause localized but highly destructive resorption of bone.

# Giant Cell Tumor

Cell of Origin:  
Osteoclast

- Giant cell tumor is so named because multinucleated giant cells **dominate the histology.**
- It is a locally aggressive neoplasm that almost exclusively affects adults. Giant cell tumors arise in the epiphyses of long bones, most commonly the distal femur and proximal tibia. The typical location of these tumors near joints frequently causes arthritis-like symptoms. Occasionally, they present with pathologic fractures.

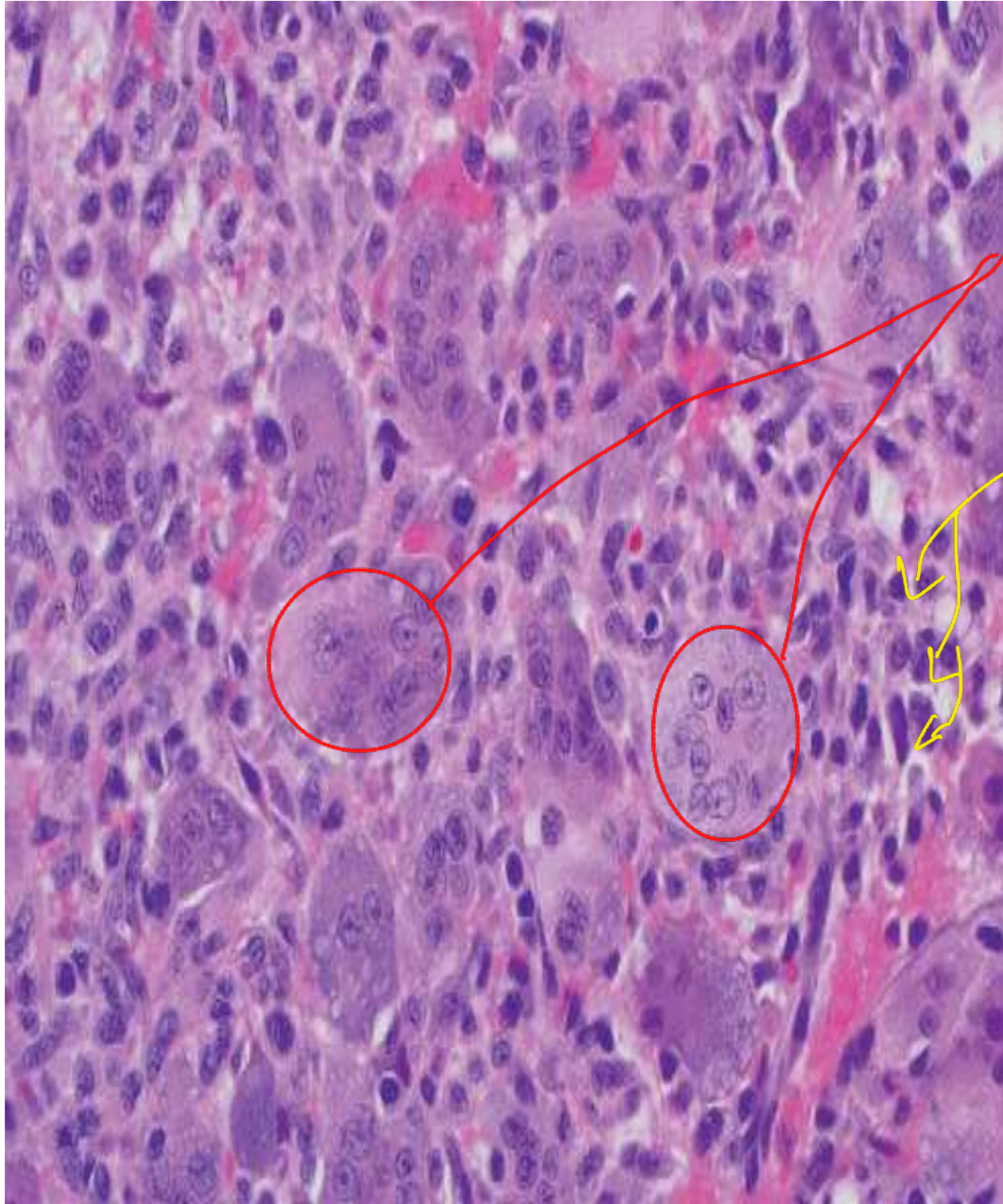
Osteoclast  
then differentiate to  
Osteoblast

# MORPHOLOGY

- Giant cell tumors often destroy the overlying cortex, producing a bulging soft tissue mass delineated by a thin shell of reactive bone. Grossly, they are red-brown masses that frequently undergo cystic degeneration. Microscopically, the tumor conspicuously lacks bone or cartilage, consisting of numerous osteoclast-type giant cells with 100 or more nuclei with uniform, oval mononuclear tumor cells in between.

# Clinical Course

- Giant cell tumors are typically treated with curettage, but 40% to 60% recur locally. Up to 4% of tumors metastasize to the lungs, but these sometimes spontaneously regress and they are seldom fatal. The RANKL inhibitor, Denosumab, has shown promise in treating giant cell tumor.



Giant cell tumor illustrating an abundance of multinucleated giant cells with background mononuclear stromal cells.



# METASTATIC BONE TUMORS

- *Metastatic tumors are the most common malignant tumor of bone.*
- **Pathways of spread:** (1) direct extension, (2) lymphatic or hematogenous dissemination (3) intraspinal seeding (via the Batson plexus of veins).
- **Origin:** Any cancer can spread to bone, but in adults more than 75% of skeletal metastases originate from cancers of the prostate, breast, kidney, and lung. In children, metastases to bone originate from neuroblastoma, Wilms tumor, and rhabdomyosarcoma.
- **The radiologic appearance of metastases:**
- Lytic (bone destroying), purely blastic (bone forming), or mixed

- The presence of bone metastases carries a poor prognosis. Therapeutic options include systemic chemotherapy, radiation, and bisphosphonates. Surgery may be necessary to stabilize pathologic fractures.

Most Common site for Metas is the vertebra



Bone with Metas



Bone  
with  
Metas

Origin  
is not  
primary

في  
Modulla

