PLEASE CLICK ON THE FOLLOWING LINK TO WATCH THE LECTURE ONLINE:-

https://www.youtube.com/watch?v=EivG2a8QlUM&list=PLuBRb5B7fa_eyzMA0u7jajzWugcmiRi5s&index=9

BONE TUMORS

EWING SAROMA AND OSTEOSARCOMA

DR FADI HIYARI

TUMOR

- Definition :

A swelling part of the body , generally without inflammation caused by abnormal growth of tissue may be

a) Benign
b) malignant

BONE TUMORS:

- **Most Common bone tumors are secondaries from other sites**
- **Most common primary bone tumor :**

Multiple myeloma > Osteosarcoma > Chondrosarcoma

- **Most common Radio and Chemo-sensitive bone tumor:** Ewing's Sarcoma > Lymphoma
- **Most common radiation induced bone tumor :** Osteosarcoma > Fibrosarcoma > Malignant fibrous histocytoma

Bone Tumors :

Classification (W.H.O.)

- Bone-forming tumors
- Cartilage forming tumors
- Giant-cell tumour
- Marrow tumors
- Vascular tumors
- Other connective tissue tumors
- Other tumours
- Secondary malignant tumors of bone

Classification by grade -Bone tumors

ORIGIN	BENIGN	LOW GRADE	HIGH GRADE
Bone tumors			
Osteogenic	Osteoid osteoma Osteoblastoma	Parosteal osteosarcoma	• Periosteal osteosarcoma • Intramedullary osteosarcoma
Chondrogenic	Enchondroma Osteochondroma Chondroblastoma Chondromyoid fibroma	Chondrosarcoma	Dedifferentiated chondrosarcoma
Unknown origin	• Giant cell tumor • Histiocytoma	• Adamantinoma	• Ewing's tumor
Fibrogenic	• Nonossifying fibroma	• Desmoplastic fibroma	• Fibrosarcoma
Hematopoietic			• Multiple myeloma • Lymphoma • Leukemia
Vascular	• Hemangioma		• Hemangioendothelioma
Notochordal			• Chordoma
Lipogenic	• Lipoma		

Classification by age – Bone tumors

Age	Benign	Malignant
Infants and childres (0 to 5 years)	Osteomyelitis Osteofibrous dysplasia	Metastatic rhabdomyosarcoma Metastatic rneuroblastoma Leukemia
Young patient (10-40 years)	NOF Osteoid osteoma Giant cell tumor ABC UBC Osteochondroma & MHE Chondroblastoma Fibrous dysplasia Osteomyelitis Eosinophillic granuloma	Osteosarcoma Ewing's Desmoplastic fibroma Leukemia Lymphoma
Older patient (40-80 years)	Enchondroma Bone infarct Bone island Paget's disease Hyperparathyroidism	Metastatic bone disease Myeloma Lyphoma Chondrosarcoma MFH Secondary sarcoma (Paget's, irradiation)

EWING'S SARCOMA :

- First reported by James Ewing in 1921
- Its a small round cell tumor arising in the bones, rarely in soft tissues occur mostly in children and adolescents.
- 2nd most common in patients younger than 25 years (after osteosarcoma)

Ewings family of tumors include:

- **Ewing sarcoma (bone 87%)** worst prognosis.
- **Peripheral PNET 5%** better prognosis.
- **Askin's tumor at chest wall** best prognosis

Etiology:

- Cell of origin in Ewing's Sarcoma unknown, however, thought to be of neuroectodermal origin.

- The most common translocation present in about 90% of Ewing sarcoma cases is t(11,22) , generate and aberrant transcription factor through fusion of EWSR1 gene with FLI1 gene .

- Translocations including t(21:22) with fusion protein EWS-ERG but less common about 10-15% .

Epidemiology:

- Incidence: one per 1 million per year.
- 9% of primary malignancies of bone
- Mostly occur at 5-25 years
- Peak incidence 2nd decade
- SEX: M:F=l.3-1.5:1
- RACE: Caucasians > Asians

SKELETAL DISTRIBUTION:

- **Most common bone: Femur shaft**
- Any bone can be the site
- Lower half > upper half
- Most common diaphysis > metaphysis of long bones.
- upper limb 30%
- Lower limb 45%
- Pelvis 20%
- Spine and ribs 13%
- Skull-face 2%

Clinical presentation:

Symptoms

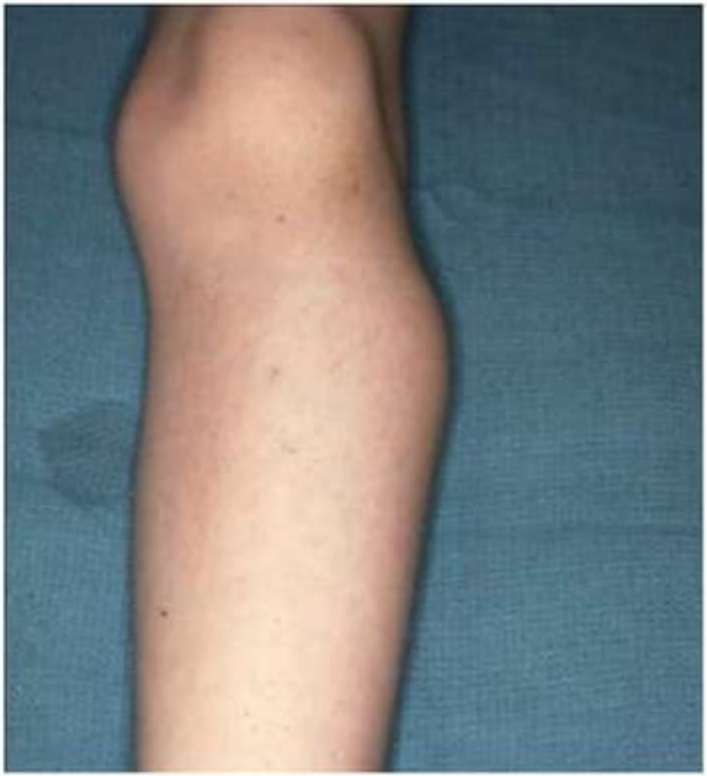
- Local pain- universal complaint- intermittent, mild at first increase in severity with time worse at night
- Pain may be accompanied by paresthesia in pelvic or vertebral tumors
- Swelling- rapidly growing and painful, tense, elastic, hard with local raise of temperature .
- Few cases present with pathological fractures
- Weight loss, fatigue, intermittent pyrexia
- Limitation in movement .
- Conservative treatment of pain can delay the diagnosis for weeks to months

Signs:

- Palpable tender mass with prominent veins
- Fever, erythema and swelling
- Joints and neurological manifestation, joint effusion with limited mobility
- Parathesis ,paralysis and root pain if spine involved

Investigations:

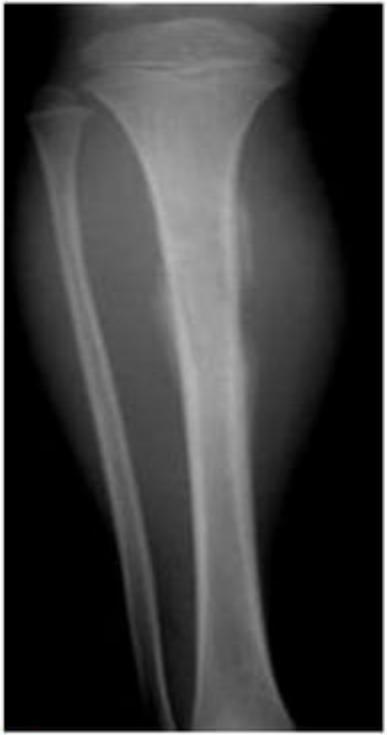
- Hb is reduced (anemia).
- Increased ESR, CRP .
- Leukocytosis

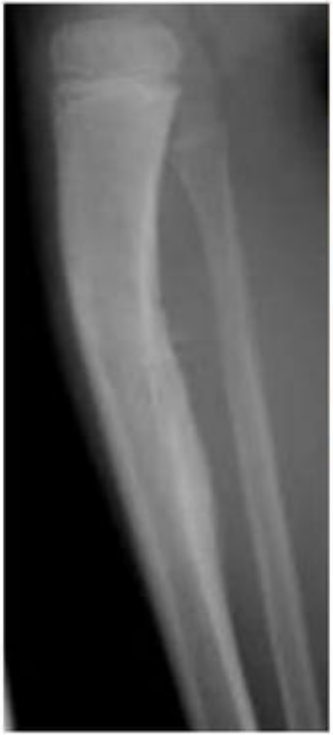


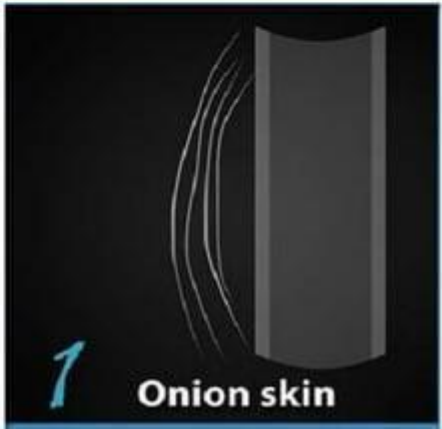
Radiology:

XRAY FINDING :

- Presents as extensive diaphyseal lesion
- At midshaft of the long bone, the cortex displays increased density, extending externally as periosteal new bone, forming multiple thin parallel layers giving **'onion peel appearance .**
- Ewing sarcoma appears as ill defined, **permeative**, focally **moth eaten**, destructive intramedullary lesion accompanied by a periosteal reaction(onion skin)
- Lesion may have both lytic and sclerotic regions
- Extraosseous component is radiolucent with the same density of soft tissue.



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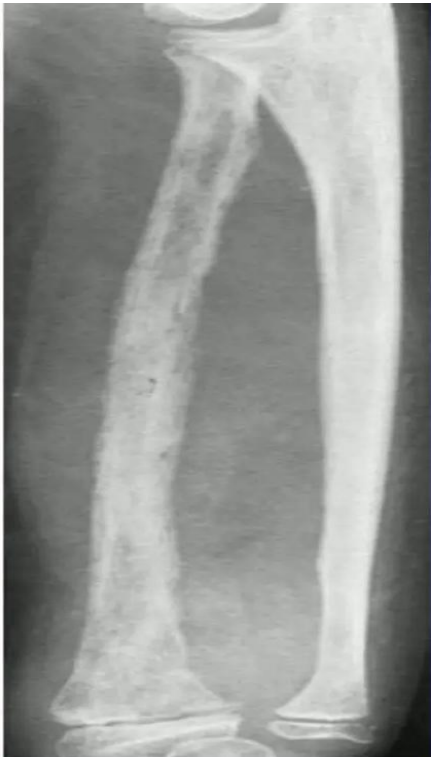
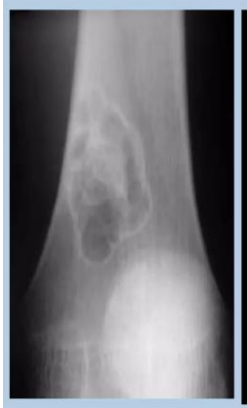
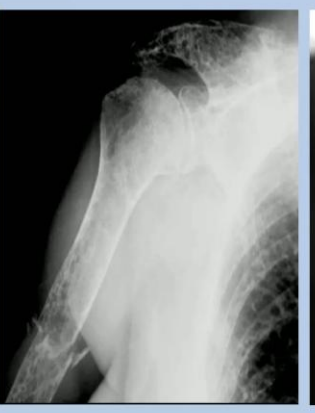
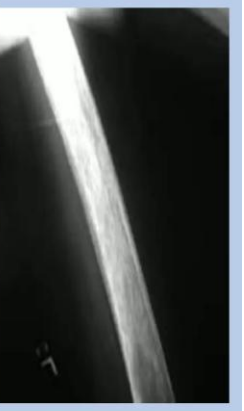
Onion skin



Patterns of Bone Destruction







Geographic

Moth-eaten

Permeative

Radiology:

- **CT SCAN :**
  - Chest CT required at presentation to evaluate for pulmonary metastases
- **MRI SCAN :**
  - Soft tissue , neurovascular and marrow involvement
  - Extent of the tumor for safe resection level
  - Presence of skip metastases
- **BONE SCAN :**

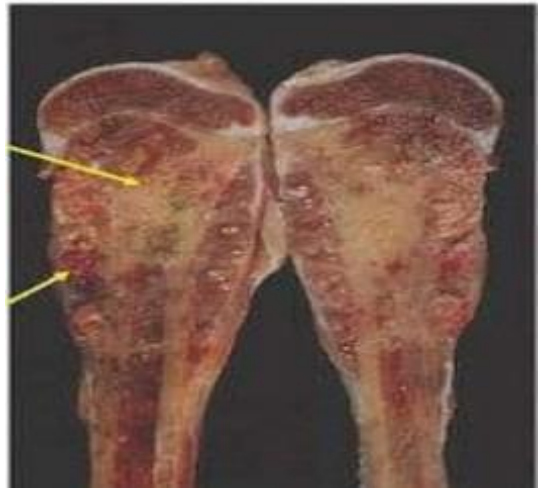
Useful to evaluate the extent of local disease and the presence of bone metastases which shows very hot lesion

Histopathology .

- **Gross appearance** :

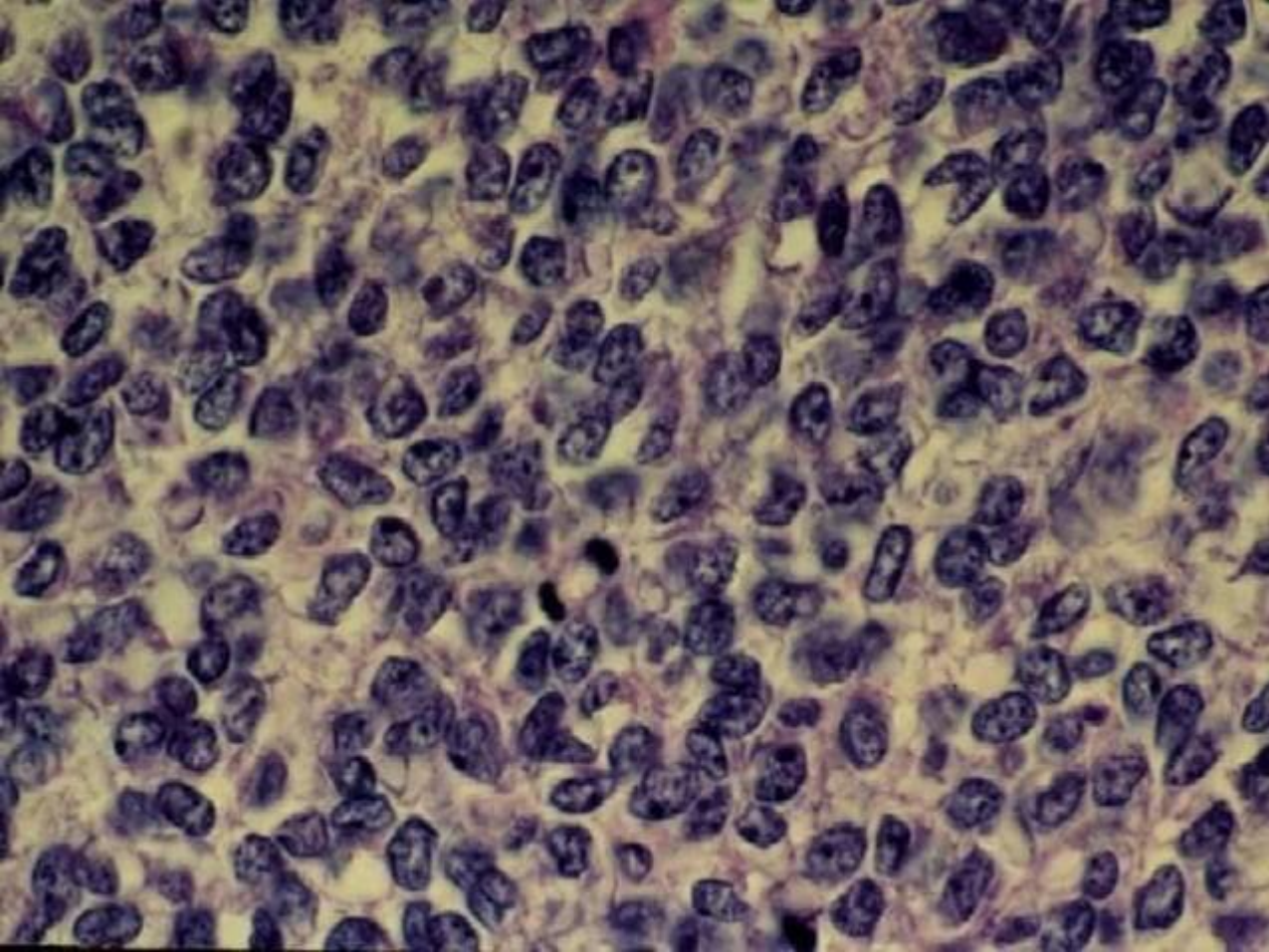
Soft, gray white, occasionally shiny areas of haemorrhage and necrosis

Cortex may be partially or completely destroyed & periosteum may be reflected



Histological features :

- Sheets of monotonous small, round blue cells with indistinct cytoplasm
- Gylcogen granules in the cytoplasm can be seen after periodic acid Schiff (PAS) staining or with electron microscopy .
- PAS – positive granules sensitive to digestion with diastase .



Differential diagnosis :

- Chronic osteomyelitis
- Metastatic neuroblastoma - first 3 years of life, neural filamentous material, elevated urinary catecholamines.
- Lymphosarcoma - larger nuclei and less uniform, lack of intracellular glycogen.
- Reticulum cell sarcoma - PAS negative and reticulin positive(doesn't have glycogen)
- Osteosarcoma

Ewings sarcoma

- Most common in diaphysis
- Very Aggressive
- Onion peel
- More of small round cell
- Soft tissue mass commonly accompanies the lesion.
- Low grade fever .
- Chronic symptoms

Chronic osteomvelitis

- Most comtnon in metaphysis
- Not aggressive
- Moth eaten and osteoporotic and areas of sclerosis
- Shows granulocytes
- Ulceration and sinuses of the skin.
- High grade fever
- Acute onset

Labs test

- Increased WBCs , ESR, CRP
- Increase LDH
- Tissue bx (small round blue cells),
  (high nuclei :cytoplasm ratio) .
- immunostaining :

positive : CD99 , PAS

negative : reticulin (positive lymphoma), neurofilament (positive in neuroblastoma).

- **<u>Bone marrow bx to r/o mets to marrow</u>**

Biopsy:

- FNAC
- Trocar puncture biopsy
- CT guided biopsy
- Open biopsy

Procedure:

- Only vertical incisions are allowed
- Samplings are always taken from the peripheries
- Tissues picked up from periphery
- No post op drain placed

Treatment:

- Goal - make patient free from disease
- Minimize pain and preserve function
- Includes neoadjuvant and adjuvant chemotherapy
- Radiation therapy
- Surgery

Chemotherapy :

- Prior to multi-agent chemotherapy, long term survival was less than 10% now increased to 60%-70%
- Drugs effective are Doxorubicin(DXR), Cyclophosphamide (CPA), Vincristine (VCR), Actinomycin-D (ACT), Ifosfamide (IFM) and Etopside (VP16), G-CSF (granulocyte colony stimulating factor)

Surgery/Radiation :

- Individual basis
- If possible to resect with wide margin resection without irradiation is the treatment of choice
- If surgical margins are uncertain pre operative radiotherapy to be added
- If surgical margins are found inadequate after

Surgery, postoperative radiotherapy may be added

prognosis

Poor prognosis factors :

- Male gender .
- Age more than 15 yrs old .
- Size more than 8 cm .
- Present with mets .
- Poor response to chemotherapy.
- Increase LDH .

osteosarcoma

- Highly malignant tumor of mesenchymal origin.
- Spindle shaped cells that produce osteoid.
- 2nd most common primary malignant bone tumor after Multiple myeloma
- Osteosarcoma most common in patients younger than 25 years
- 15 % of all bx bone tumors
- Most radio resistant bone tumor
- Most radiation induced bone tumor

- **Primary osteosarcoma** :

Arises from the bone in the absence of a benign precursor lesion or treatment

- **Secondary osteosarcoma** :

Arises from a precursor lesion to one that is metastatic from a primary osteosarcoma .

- **Synchronous osteosarcoma** :

lesion that affect multiple bones discovered within 6 months of each other .

- **Metachronous osteosarcoma** :

lesion that affect multiple bones discovered more than 6 months apart.

Epidemiology:

- Incidence :

first peak (adolescents): 7-8 cases per million
second peak (elderly): 4.2 cases per million

- Male: Female-1.5:l(EXCEPT PAROSTEAL VARIETY)
- Peak incidence is in 2^{nd} -3^{rd} decades.
- Primary osteosarcorna (75%) -2^{nd} decades

Bones having the fastest rates of growth have the highest frequency of occurrence.

- Secondary osteosarcoma (25%) -6^{th} decades

usually secondary to underlying conditions such as Paget's disease, extensive bone infarcts, prior osteochondromas/osteoblastomas, and prior radiation

Associated syndromes :

- Hereditary form of retinoblastoma
- Li-Fraumeni syndrome (p53)
- Rothmund-Thomson syndrome (8q24)
- Bloom syndrome
- Paget disease or fibrous dysplasia

SITE

- Around the Knee Joint .(ARISING MAINLY FROM METAPHYSIS ; INTRAMEDULLARY REGION)
- 52% --LOWER END OF FEMUR
- 20%-- UPPER END OF TIBIA
- 9% -- UPPER END OF HUMERUS
- Most common site : DISTAL FEMUR

PREDISPOSING FACTORS :

- **PRIMARY OSTEOSARCOMA** :

- RADIATION
- VIRAL INFECTION : POLYOMA VIRUS / HARVEY VIRUS
- CHEMICALS : BERYLLIUM 20 METHYLCHOLANTHRENE

▶ SECONDARY OSTEOSARCOMA :

PREMALIGNANT LESIOSN SUCH AS

- PAGET'S DISEASE OF BONE , FIBROUS DYSPLASIA
- P53 MUTATION POST RADIATION BONE INFRACTION
- HERIDITORY SURVIVOR OF RETINOBLASTOMA

Osteosarcoma Classification

- Intramedullary (75%)
  - Conventional
    - Osteoblastic (82%)
      - Mixed and Sclerosing
    - Chondroblastic (5%)
    - Fibroblastic (3-4%)
    - MFH-like (3-4%)
    - Osteoblastoma-like (.5%)
    - Giant Cell-rich (.5%)
    - Small-cell (1%)
    - Epithelioid (.5%)
  - Telangiectatic (3%)
  - Well-differentiated (low grade intraosseous; 4%-5%)
- Juxtacortical/Surface (7-10%)
  - Parosteal
  - Periosteal
  - High-grade surface
- Intracortical (.2%)
- Secondary (older population)
  - Pagets (67-90%); Post RT (6-22%); Bone infarct; Fibrous dysplasia; Metallic implant; Osteomyelitis
- OS with specific syndromes
  - Familial; Retinoblastoma; Rothmund-Thomson Syndrome; Multifocal; OI

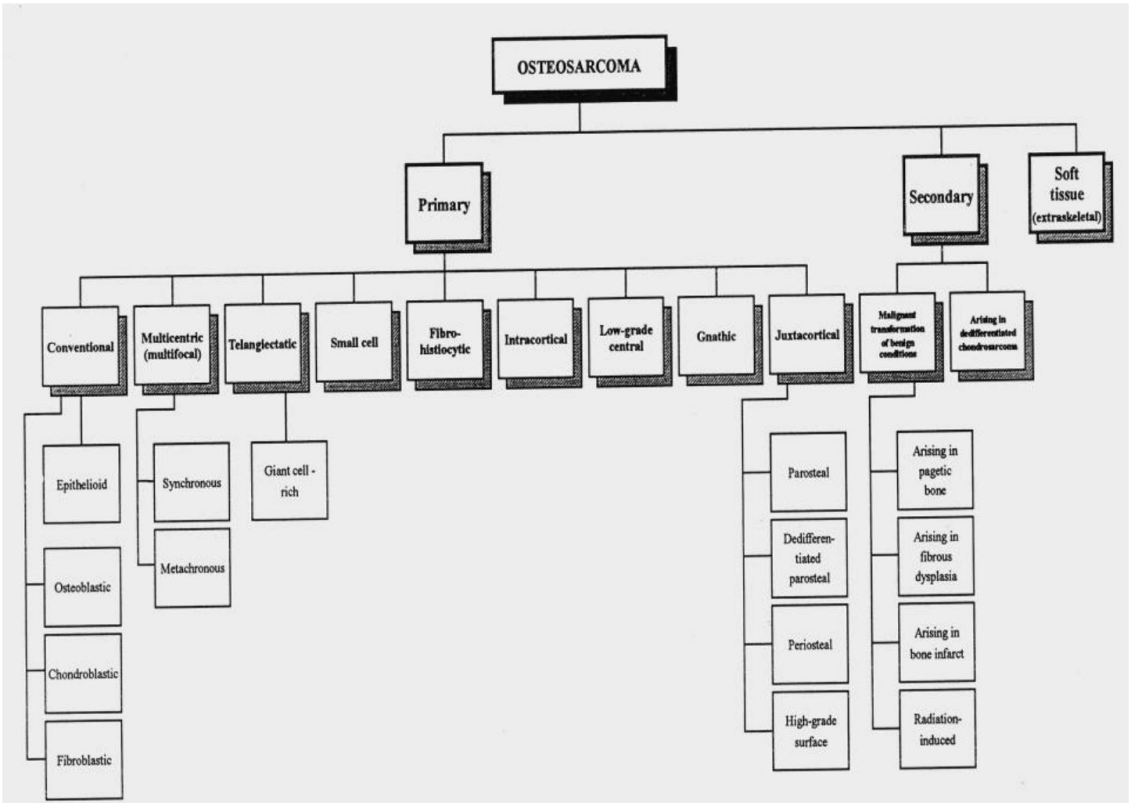


FIG. 55. Osteosarcoma and its subtypes.

PATHOGENISIS :

The tumor arise in the metaphysis where the growth is more active.

The tumor originate beneath the periosteum

After originating tumor may extend in 2 directions

1 towards medulla or 2. towards subperiosteal area

In the medulla the bone trabeculae are destroyed Tumor appear as irregular mass permeating along medullary canal

At first the periosteum offers impenetrable barrier and is only raised off the bone.

On diaphyseal side of tumor the periosteum is often stripped for a short distance

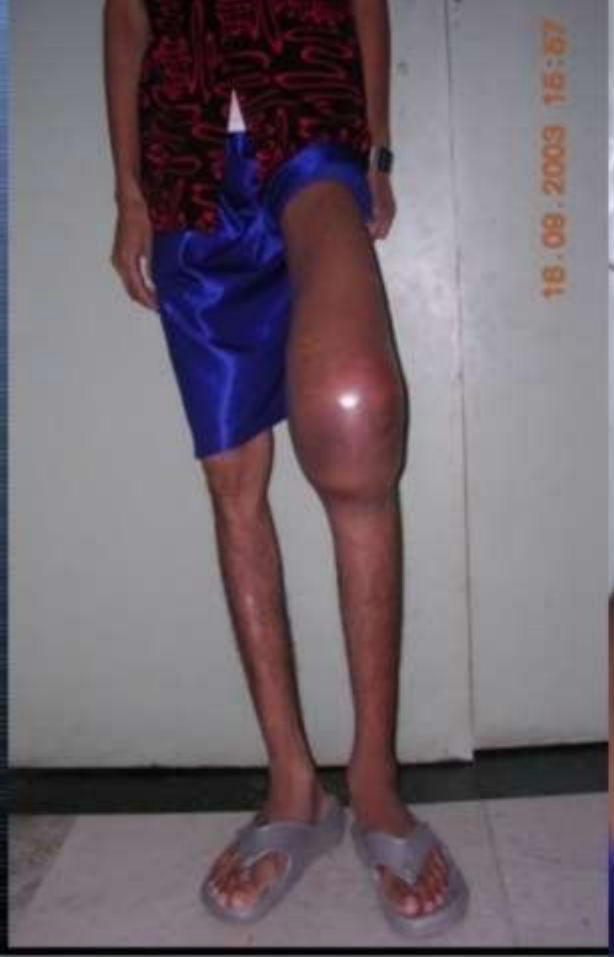
There may be deposition of layers of new bone parallel to shaft Forming 'CODMANS TRIANGLE'

CLINICAL FEATURES:

- PRESENTING FEATURES:
- PAIN(NIGHT PAIN)
- PALPABLE MASS WITH LOCALIZED TENDERNESS
- DECREASED RANGE OF MOTION
- COULD NERVE OR VASCULAR COMPRESSION FROM MASS EFFECT
- MEDIAN TIME OF ONSET OF SYMPTOMS TO DIAGNOSE IS 4 MONTHS .

ASSOCIATED FEATURES :

- EFFUSION & SWELLING OF NEARBY JOINTS
- FEVER (low grade)
- PALLOR & CACHEXIA
- FEATURES ASSOCIATED WITH **PULMONARY METASTASIS**
- PATHOLOGICAL FRACTURES .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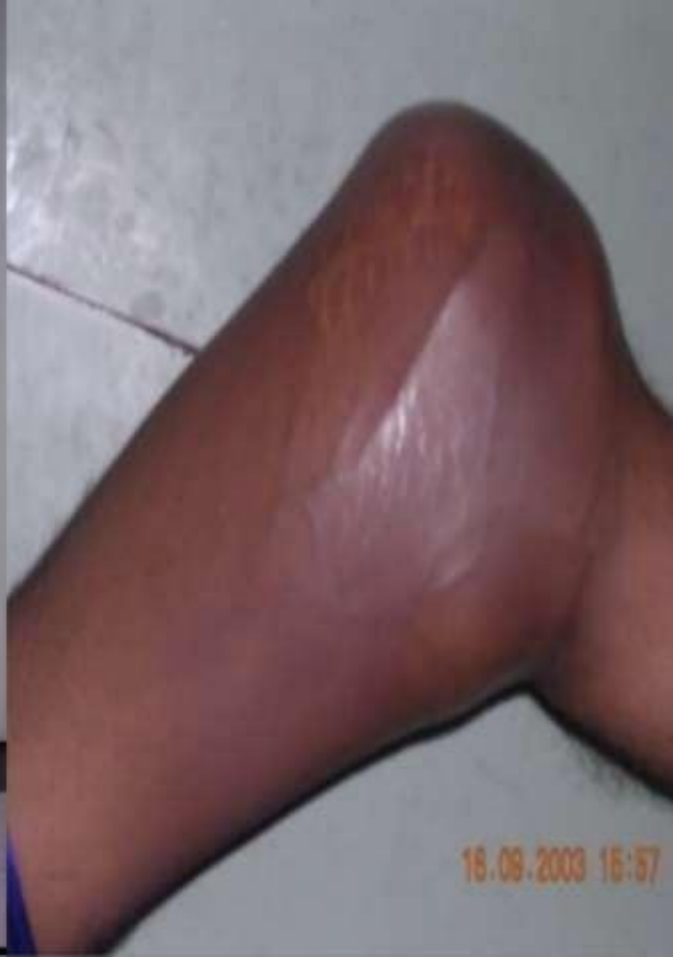
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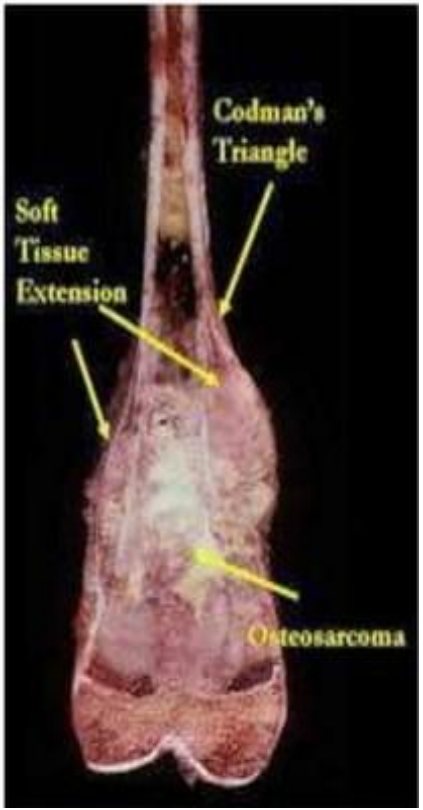
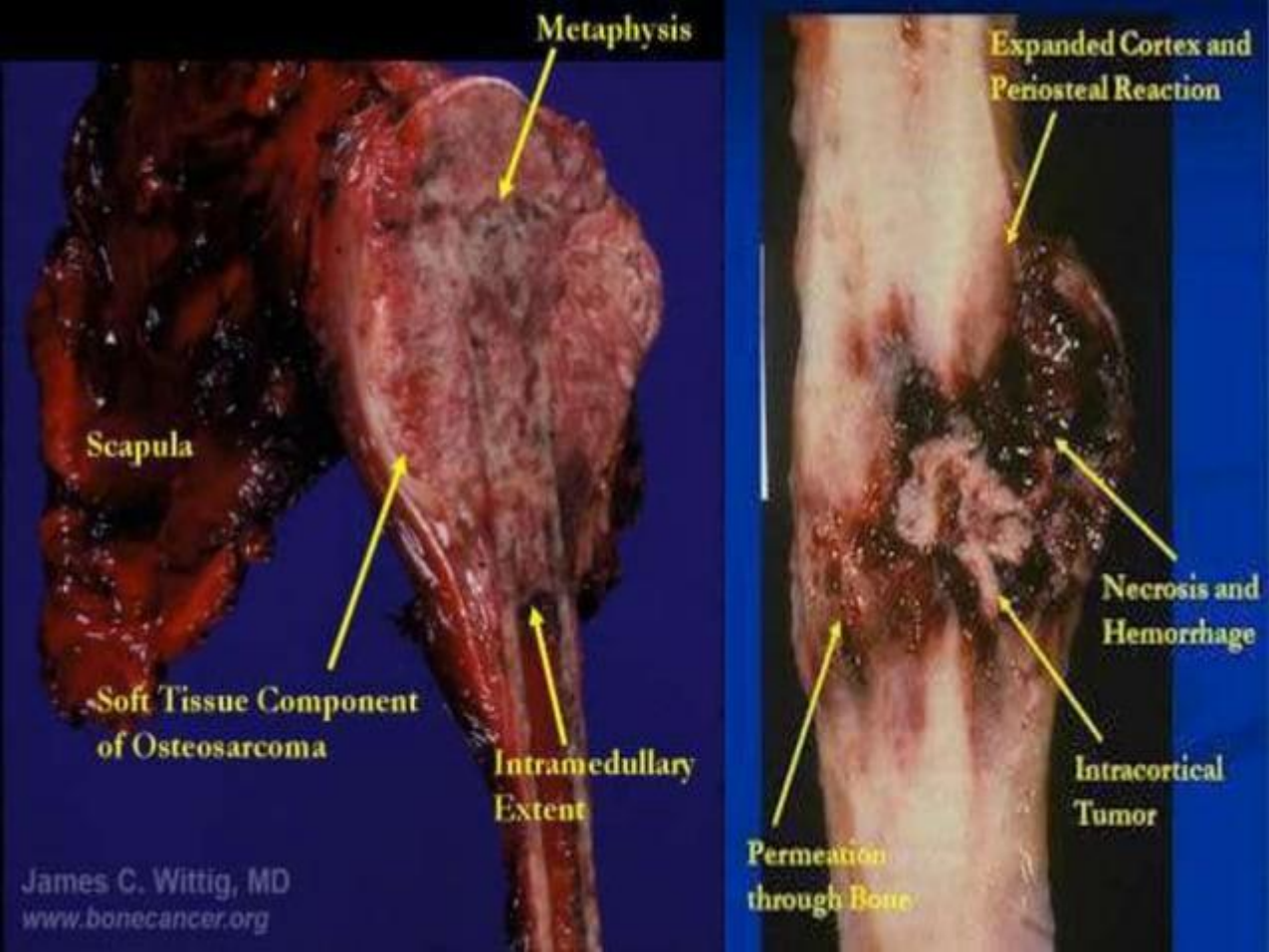
GROSS PATHOLOGY:

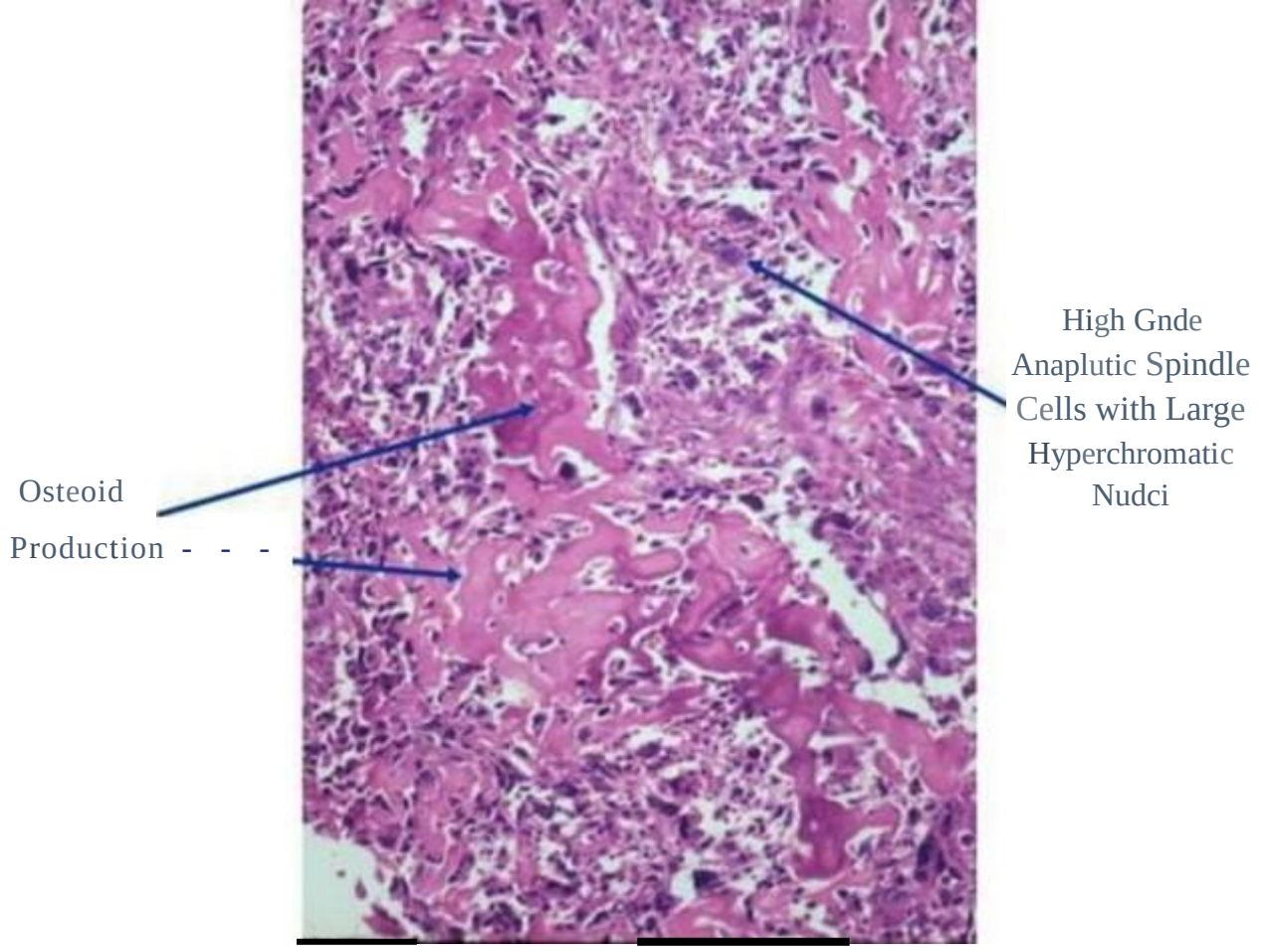
- OS are bulky tumors that are gritty, grayish-white in color.
- Areas of hemorrhage, necrosis and cystic changes.
- Destruction of cortex
- Spread in medullary canal, infiltrating and replacing marrow
- Rarely, they penetrate epiphyseal plate or enter the joint
- There is Reactive periosteal new bone formation

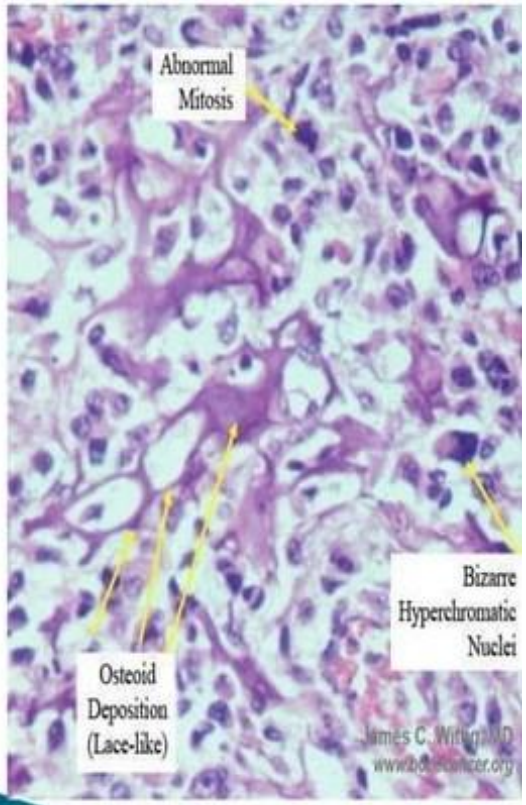



Metaphysis
Scapula
Soft Tissue Component of Osteosarcoma
Intramedullary Extent
James C. Wittig, MD
www.bonecancer.org
Expanded Cortex and Periosteal Reaction
Necrosis and Hemorrhage
Intracortical Tumor
Permeation through Bone

MICROSCOPICALLY :

- High grade spindle cell tumor that produces osteoid matrix.
- Stromal cells show malignant characteristics with atypia, high nuclear-to-cytoplasmic ratio, pleomorphic nuclie and abnormal mitotic figures
- Areas may have mixed histology with different combinations of chondroblastic, osteoblastic, or fibroblastic-looking cells depends on the subtype of osteosarcoma
- Vascular invasion and areas of necrosis common


High Gnde
Anaplutic Spindle
Cells with Large
Hyperchromatic
Nudci
Osteoid
Production - - -



Osteoid in variable amount contain bizarre giant cells or pleomorphic neuclie

Tumor cells may be spindle, oval or round of variable size

25% of OS have osteoclast-Like multinucleated giant cells

Cartilage may be mineralized, immature, myxoid

Differential

- Giant Cell Tumor
- Chondrosarcoma
- Fibrosarcoma
- Aneursymal Bone Cyst
- Ewings sarcoma
- Osteoblastoma
- Metastasis
- Lymphoma
- Osteomyelitis
- Chondroblastoma
- Post traumatic callus

	Osteogenic Sarcoma	Ewing Sarcoma
Presentation	Second decade	Second decade
Race	All	Mostly white
M:F	Slightly greater in males	Slightly greater in males
Predisposition	Retinoblastoma, radiation	None
X-ray	Sclerotic destruction: **"sunburst"**	Lytic with laminar periosteal elevation: **"onion skin"**
Metastases	Lungs, bone	Lungs, bone
Treatment	Chemotherapy, ablative surgery	Radiation and/or surgery
Outcome without metastases at diagnosis	70% cure	60% cure
Outcome with metastases	≤20%	20–30%

RADIOLOGY:

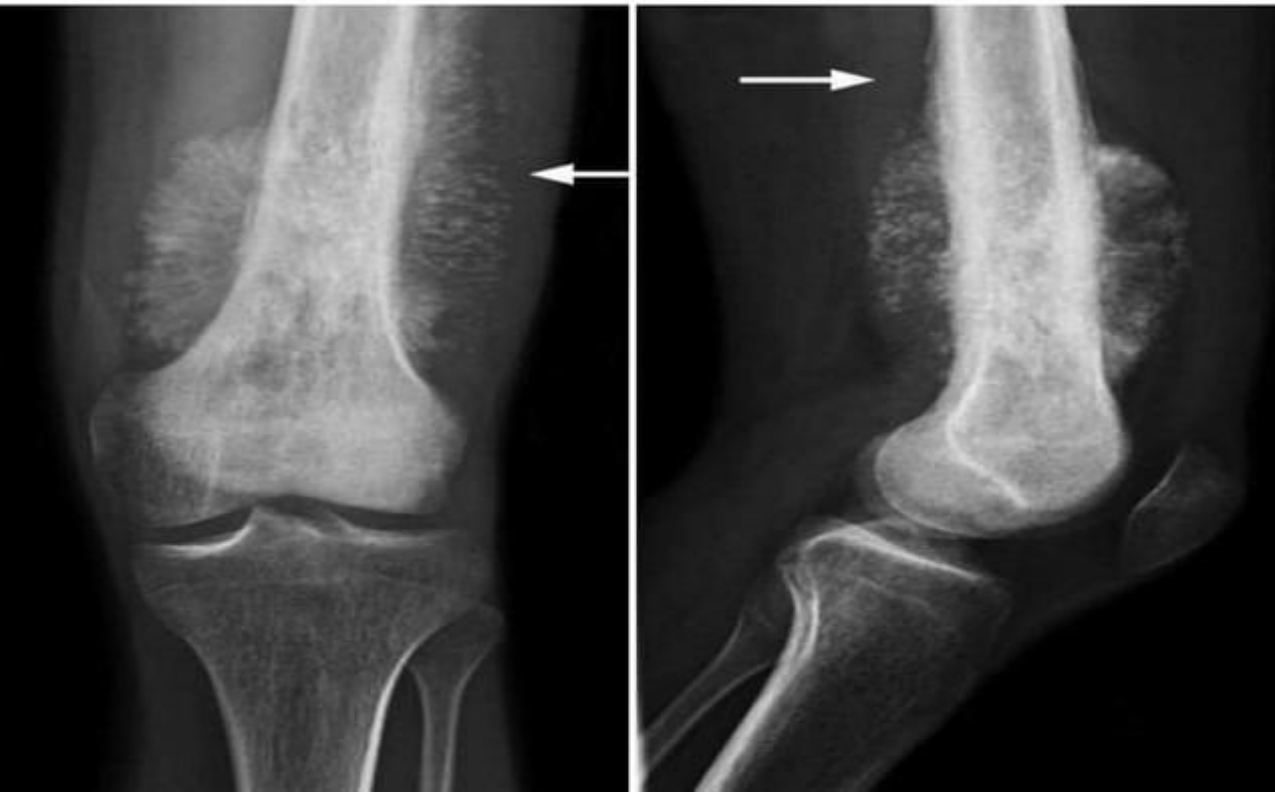
RADIOLOGIC INVESTIGATIONS :

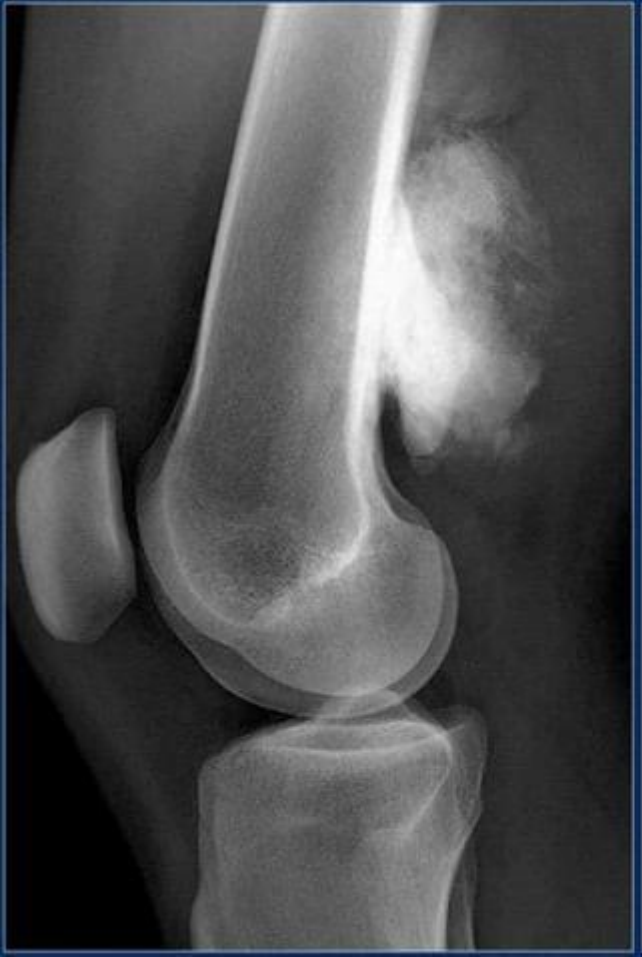
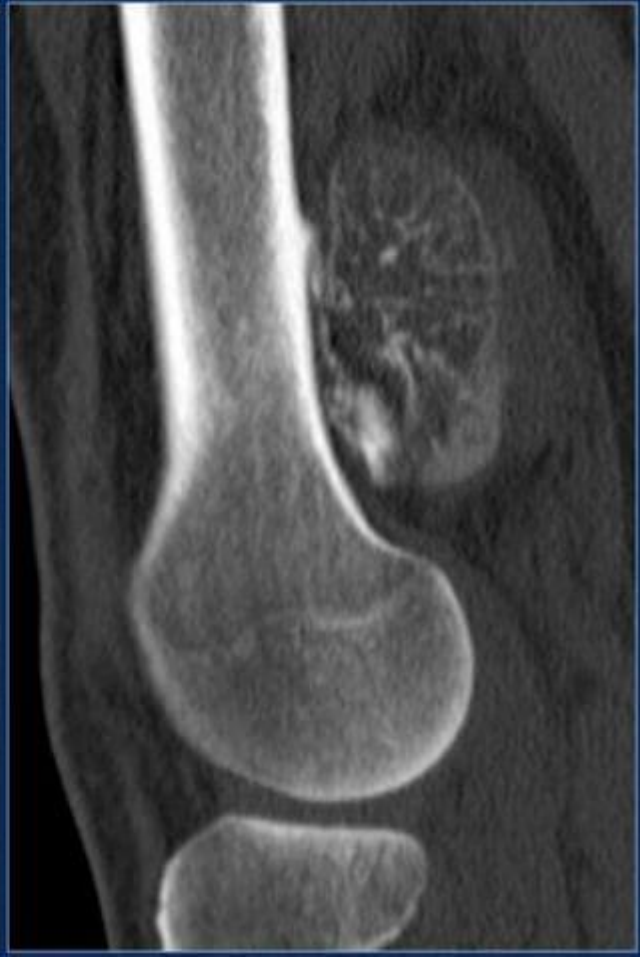
- PLAIN RADIOGRAPH(X-RAY)
- CTSCAN
- MRI SCAN
- BONESCAN
- PET SCAN

X-RAY finding

- Medullary and cortical bony destruction
- Large soft-tissue mass evidenced by soft-tissue shadow
- Periosteal reaction (Codman's triangle)
- Characteristic blastic lesion
- Pattern of matrix mineralization "sunburst" or "hair-on-end"
- Usually mixed blastic and lytic but may be purely blastic or purely lytic
- Ossification (mineralized osteoid) usually detectable in tumor/bone or soft tissue mass

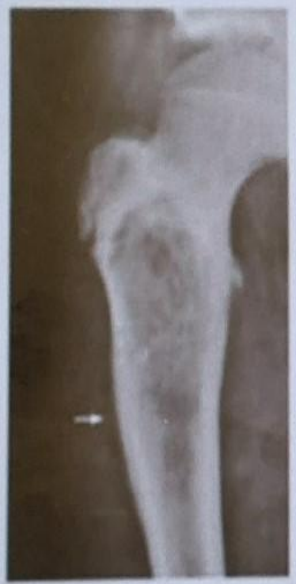
SUN BURST APPEARANCE :



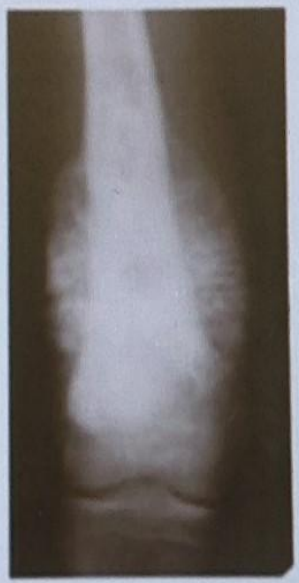



Periosteal Reactions

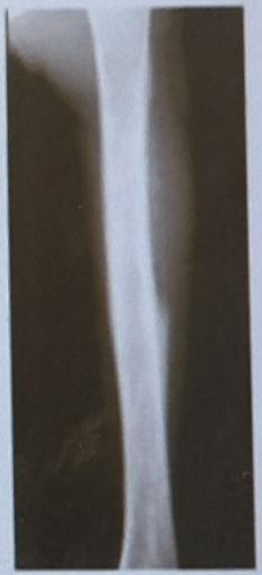
Solid
Eg: Post traumatic, HPOA



Lamellated
Eg: Ewings, Osteomyelitis



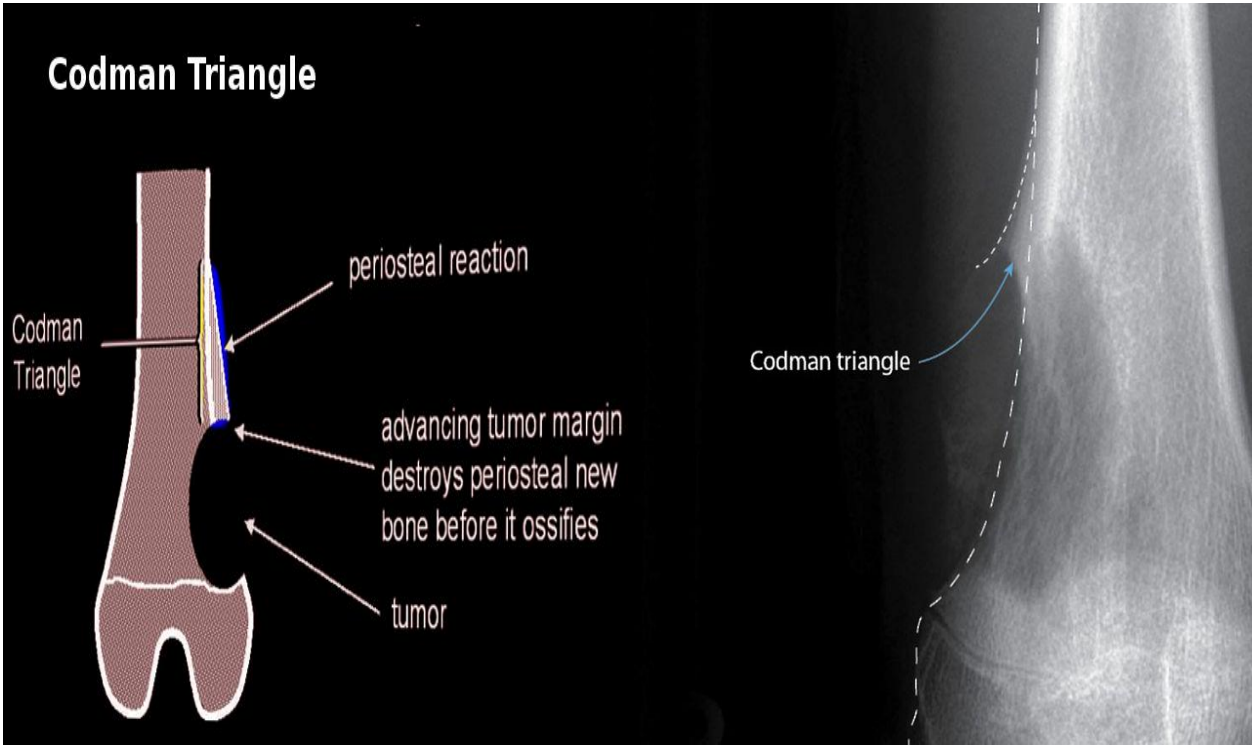
Sunburst
Eg: Osteosarcoma, Ewings sarcoma



Codman's Triangle
Eg: Osteosarcoma, Ewings sarcoma

Less malignant → More malignant

CODMAN'S TRIANLGE :

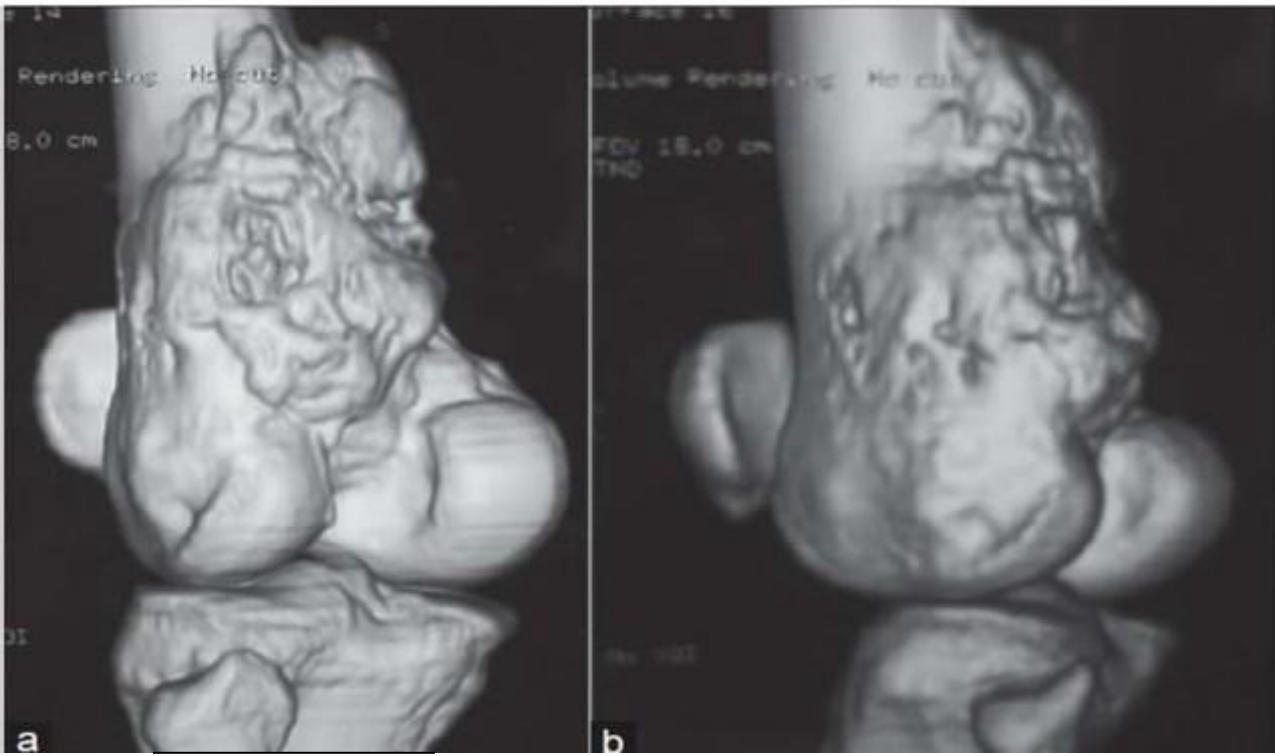


RADIOLOGY FINDING

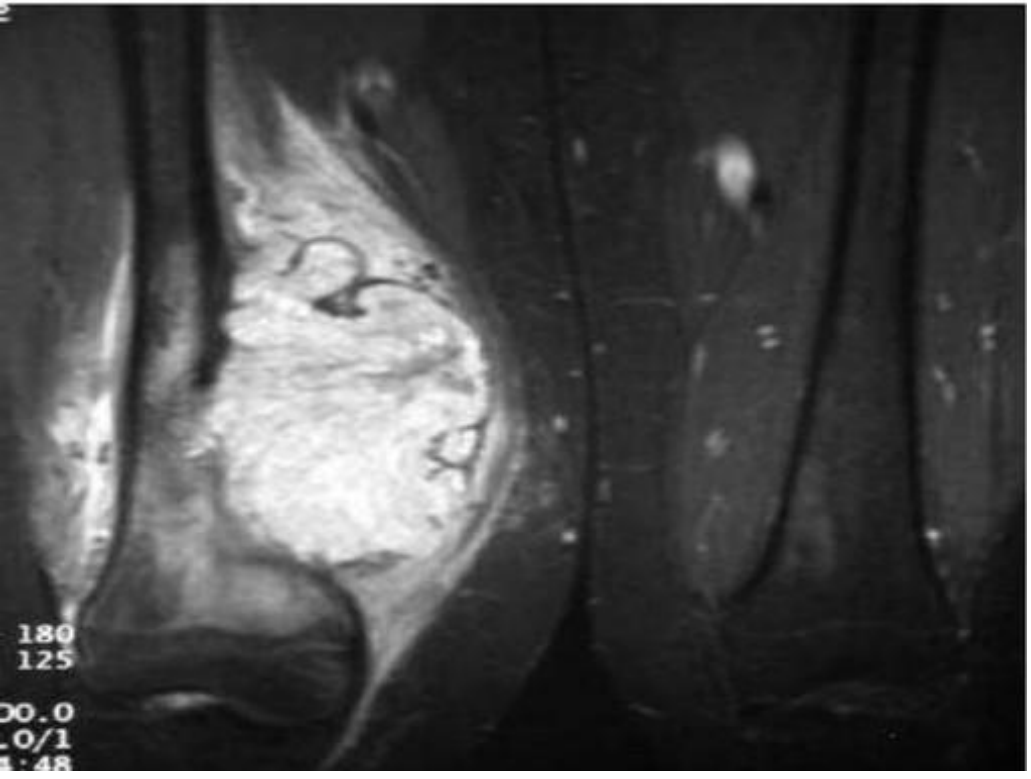
- **CT SCAN :**
  - Chest CT required at presentation to evaluate for pulmonary metastases
  - CT of extremity may help detect subtle mineralization
- **MRI SCAN :**
  - Soft tissue and neurovascular involvement
  - Extent of the tumor for safe resection level
  - Presence of skip metastases
- **BONE SCAN :**

Useful to evaluate the extent of local disease and the presence of bone metastases

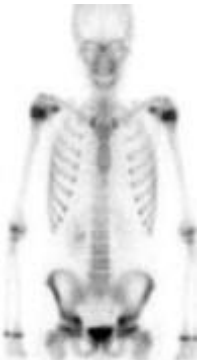
CT IMAGES OF OS :

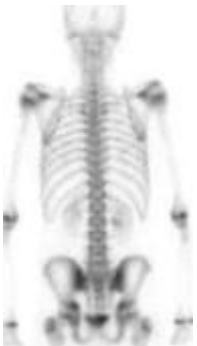


MRI IMAGES OF OS :



BONE SCAN IMAGES :





Laboratory studies :

- Full blood count, ESR, CRP.
- LDH (elevated level is associated with poor prognosis)
- ALP (highly osteogenic)
- Platelet count
- Electrolyte levels
- Liver function tests
- Renal function tests
- Urinalysis

Biopsy:

- FNAC
- Trocar puncture biopsy
- CT guided biopsy
- Open biopsy

Procedure:

- Only vertical incisions are allowed
- Samplings are always taken from the peripheries
- Tissues picked up from periphery
- No post op drain placed

CHEMOTHERAPY:

- Introduction of systemic chemotherapy has dramatically improved survival rates.

- Before the routine use of chemotherapy treatment was immediate wide or radical amputation

CHEMOTHERAPY AGENTS:

- Methotrexate with leucovorin (folinic acid)
- Doxorubicin (Adriamycin)
- Cisplatin or carboplatin
- Etoposide
- If osfamide
- Cyclophosphamide
- Actinon1ycin D (dactinomycin)
- Bleomycin

- NEO-ADJUVANT CHEMOTHERAPY:

CT ADMINISTERED BEFORE THE SURGICAL RESECTION OF PRIMARY TUMOUR

- ADJUVANT CHEMOTHERAPY:

CT ADMINISTERED POSTOPERATIVELY TO TREAT PRESUMED MICRO-METASTASIS

TREATMENT

- Current standard of care

SURGERY:

► SURGERY IS THE MAINSTAY OF THERAPY :

- LIMB SACRIFICING SURGERY OR
- LIMB SALVAGING SURGERY

CHOICE BETWEEN LIMB SALVAGE SURGERY AND AMPUTATION MUST BE MADE ON THE BASIS OF THE EXPECTATIONS AND DESIRES OF THE INDIVIDUAL PATIENT AND THE FAMILY

RADIOTHERAPY:

- Radiation therapy has no major role in osteosarcoma

- Radiation therapy may be useful in some cases where the tumor cannot be completely removed by surgery.

E.g. in pelvic bones or in the bones of the face.

- Megavoltage (upto 6000-8000 rads)

POOR PROGNOSIS :

- Tumor size>10 cm
- Tumor volume > 10 cm
- Elevated alkaline phosphatase
- Positive surgical margins
- Local recurrence
- Synchronous metastases
- Prior manipulative therapy

Thank you