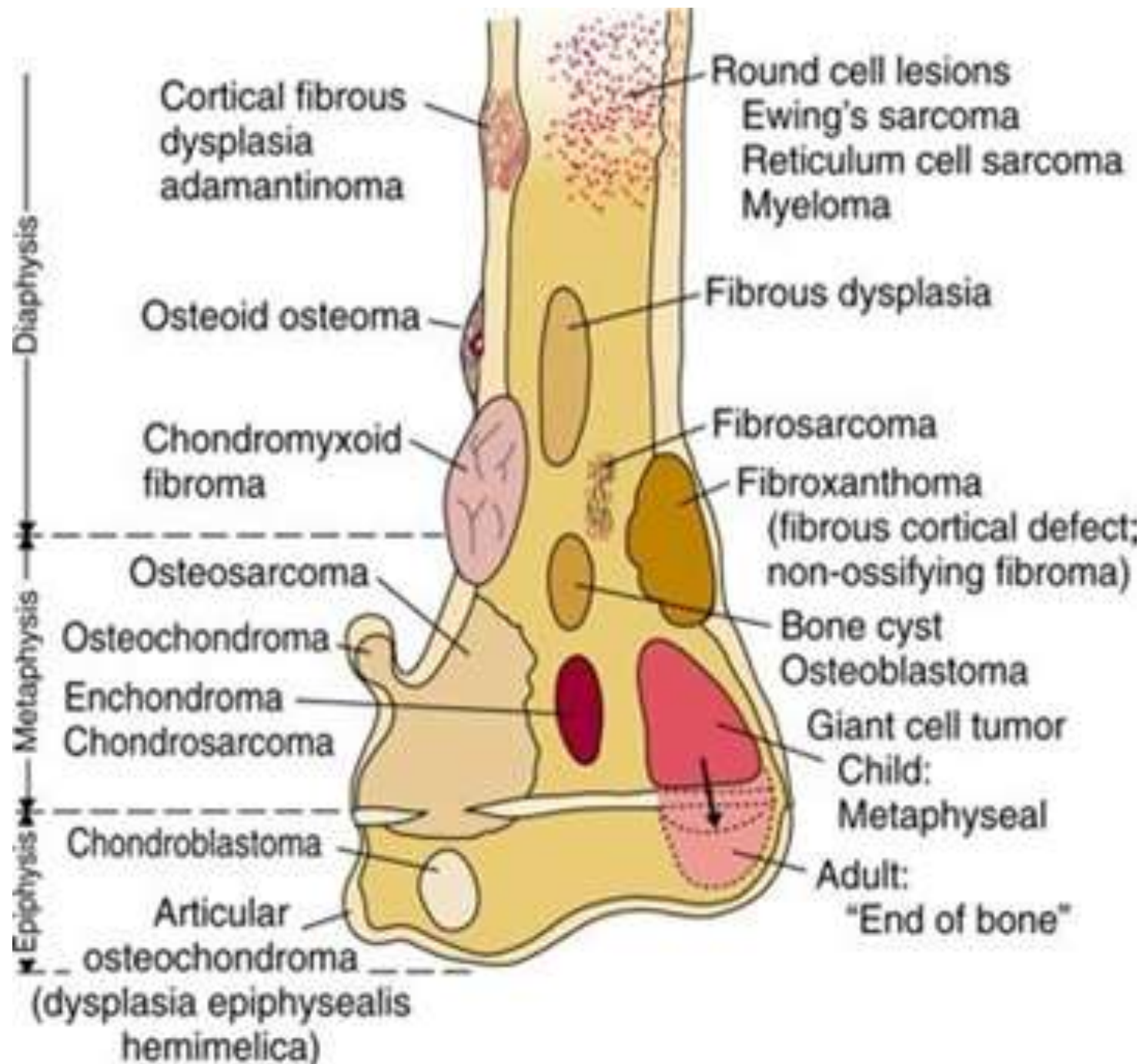


EWINGS SARCOMA

DR.PRINCE.M.PAUL

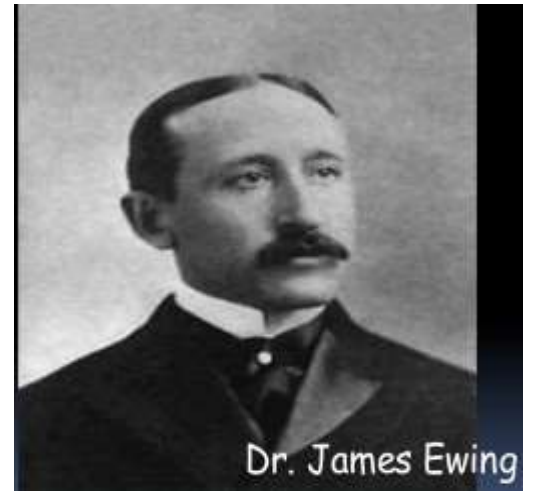
MBBS,MD,D.ORTHO,DNB(ORTHO),MNAMS

CONSULTANT,ORTHOPAEDICS



Introduction

- ▶ Identified in 1921 by James Ewing
- ▶ 2nd most common bone tumor in children
- ▶ Ewing's Sarcoma Family of tumors:
 - Ewing's sarcoma (Bone –87%)
 - Extraosseous Ewing's sarcoma (8%)
 - Peripheral PNET(5%)
 - Askin's tumor

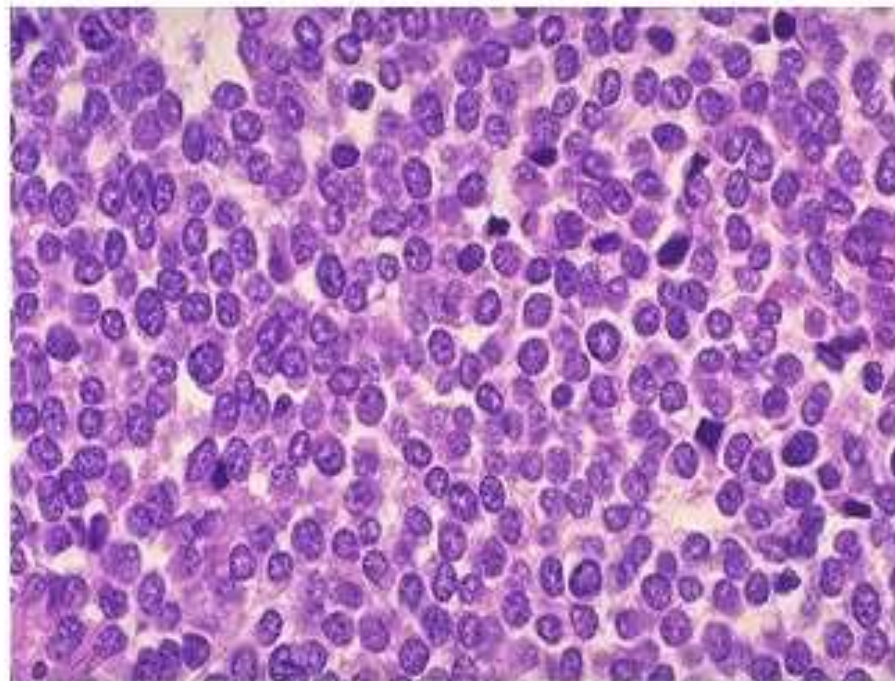


Epidemiology

- Involvement of the head and neck in Ewing's sarcoma is very unusual, accounting for approximately 1% to 4% of cases.
- Males are affected somewhat more commonly than females; the ratio is 3:2.
- Unlike osteosarcoma, Ewing's sarcoma has a predilection for whites; blacks and Asians are uncommonly affected.

Pathology

- ▶ One of many 'small round blue cell' tumors seen in pediatrics
- ▶ Poorly differentiated tumor
- ▶ Unknown origin, Thought to be of neural crest progenitor cells origin



ROUND CELL NEOPLASM

Heterogeneous group of neoplasms are characterised by the sheets of poorly differentiated cells:

- Small (similar to lymphocyte in size)
- Round (round nuclei and scanty cytoplasm)
- Blue (blue staining due to high nuclear/cytoplasmic ratios)

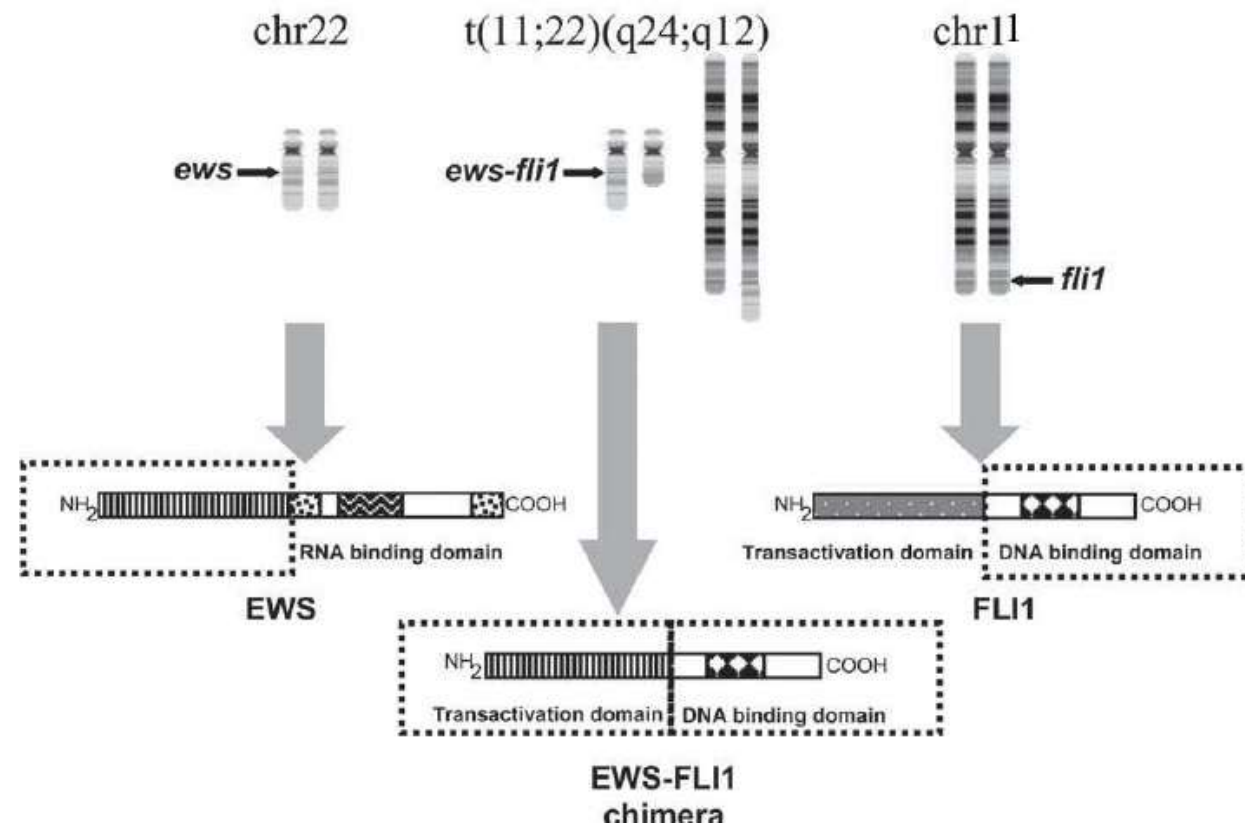
OSSEO ARTICULAR TUMORS IN THIS CATEGORY

- Ewings sarcoma/Primitive neuroectodermal tumour(ES/PNET)
- Hematopoietic malignancies
- Plasma cell neoplasms
- Small cell osteosarcoma
- Mesenchymal chondrosarcoma
- Poorly differentiated small cell synovial sarcoma
- Rhabdomyosarcoma(embryonal and alveolar subtypes)

Cytogenetics

- ▶ Consistent cytogenetic abnormality, $t(11;22)(q24;q12)$ present in 90-95%
 - resultant fusion gene is EWS/FLI-1
- ▶ Also seen:
 - $t(21;22)(q22;q12) \rightarrow$ 5-10%
EWS/ERG
 - $t(7;22)$ and $t(17;22) \rightarrow$ the remainder
EWS/ETV1 and EWS/E1AF respectively
 - $t(1;16)(q21;q13)$
present along with $t(11;22)$
- ▶ The c-myc protooncogene is frequently expressed in Ewing's.
- ▶ CD 99 (MIC2)

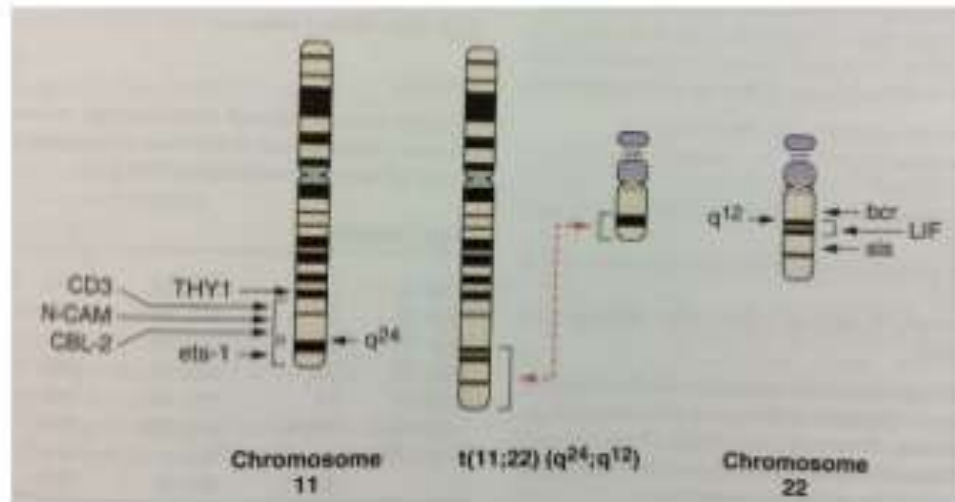
- 80 to 90% have a translocation of chromosomes 11 and 22 or 21 and 22



TYPES

- Extraskkeletal (soft tissue) ES
- Periosteal
- Atypical (large cell)
- cells are more pleomorphic
- Multifocal

*All are characterised by recurrent
chromosomal translocation involving
11 & 22 (85%) & 21 & 22 (15%)*



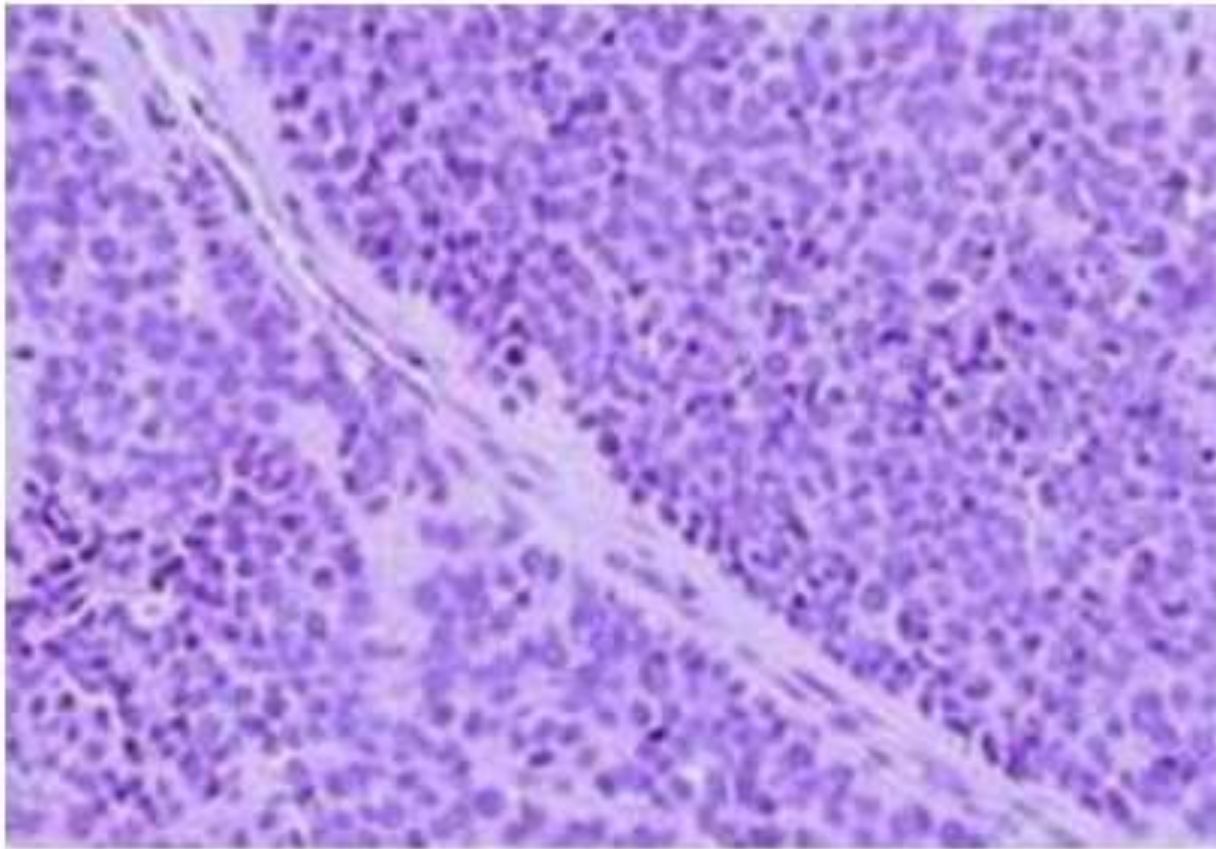
GROSS

- Whitish gray soft tissue arising from marrow spaces
- Necrotic and haemorrhagic areas
- Elevated perforated periosteum
- NOT ENCAPSULATED, invades surrounding muscle mass.
- Moist & glistening
- Resembles pus (mistaken for Osteomyelitis)



HISTOPATHOLOGY

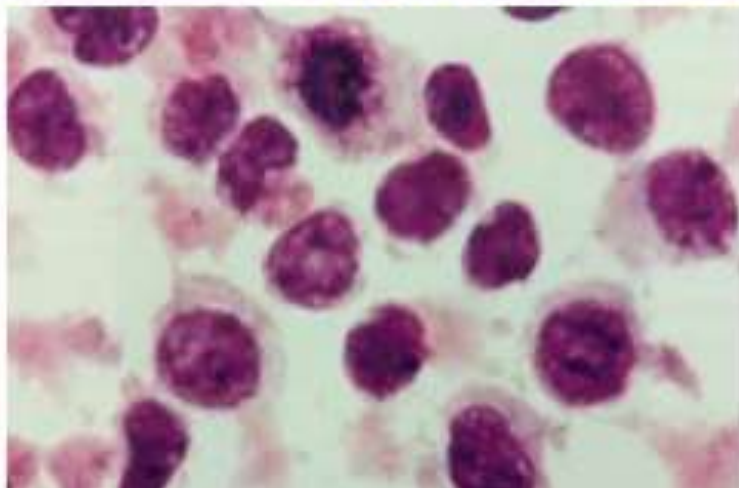
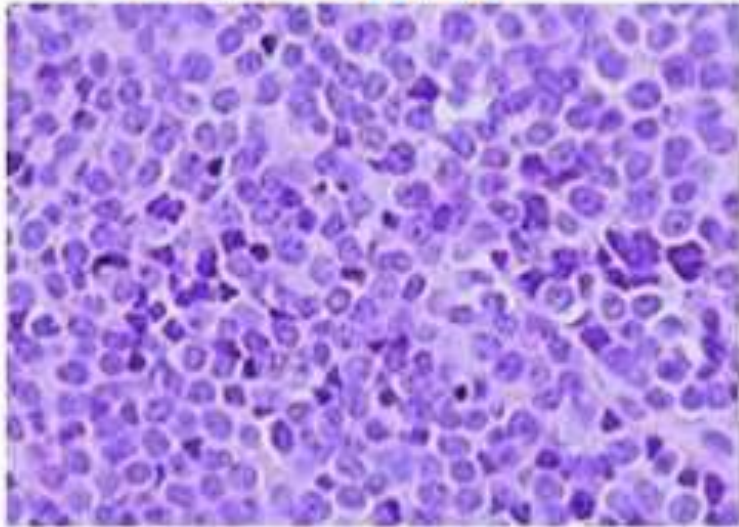
Low power



**Small round cell tumor with little intercellular stroma
Between the areas of highly cellular tumor, fibrous strands
compartmentalise the tumor**

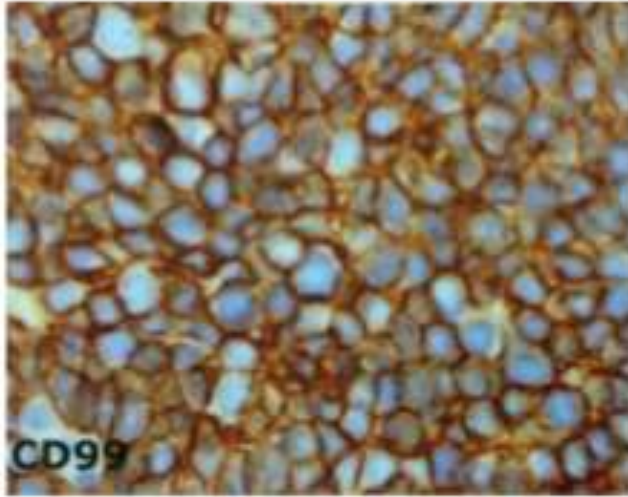
HISTOPATHOLOGY

HIGH POWER



- Cells are uniform and round to oval
- Cytoplasm is scanty & lacy
- Nuclei are round to oval, have a delicate, finely dispersed chromatin
- Nucleoli are inconspicuous
- Mitotic figures rare

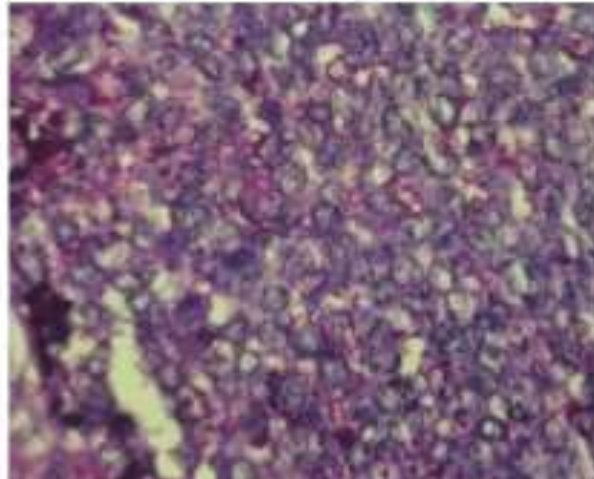
HISTOPATHOLOGY



IHC. Lymphoid markers CD99
strong positivity in short bones of
hand



Reticulin is poor
No evidence of Matrix



Glycogen identifiable in
cytoplasm - PAS Stain...

- Occasional rosette or pseudorosette formation

Should be distinguished from

➤ Neuroblastoma

➤ Rhabdomyoma

➤ NHL

CLINICAL FEATURES

most common 2nd decade

- **5 - 25yrs.** (90% below 20)
- Highest frequency **5-15yrs**
- Mean age - **13yrs.**
- Male predominance – **3:2**
- Localised, painful, tender mass
- Systemic symp. – fever, malaise, weight loss
 - mistaken for OM
 - dissemination of tumor
- May metastasize to other bones

- ▶ Pain & swelling of affected area
- ▶ May also have systemic symptoms:
 - Fever
 - Anemia
 - Weight loss
 - Elevated WBC & ESR,LDH
- ▶ Longest lag time in diagnosis for any pediatric solid tumor (mean of 146 days)
- ▶ Pathological fracture



LOCATION

- **UPPER LIMB:** 13%

- **LOWER LIMB:** 45%

femur most common

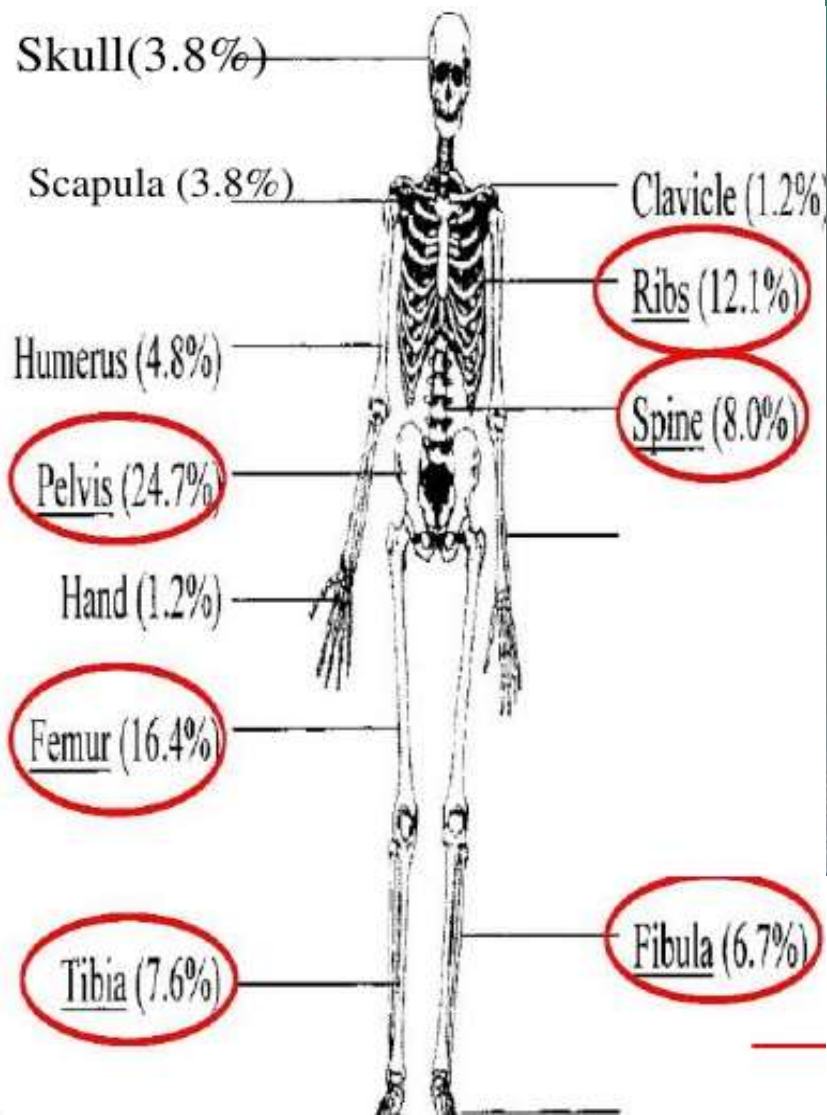


Table 30-1 Sites of Ewing Sarcoma in the Intergroup Ewing Sarcoma Study

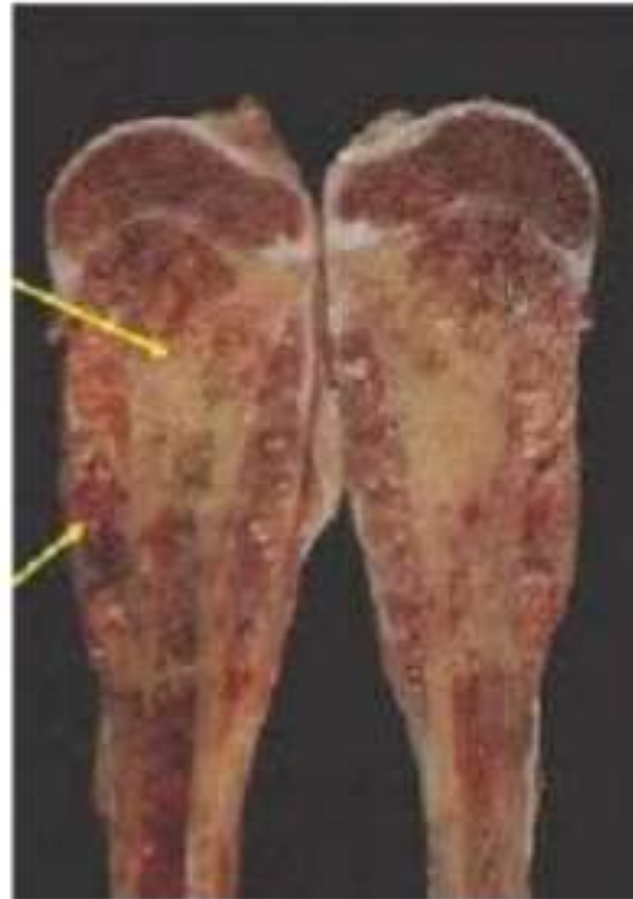
Primary Site	Frequency of Occurrence (%)
Pelvis	20.5
Ilium	12.5
Sacrum	3.3
Ischium	1.7
Pubis	3.0
Lower Extremity	45.6
Femur	20.8
Fibula	12.2
Tibia	10.6
Foot	2.0
Upper Extremity	12.9
Humerus	10.6
Forearm	2.0
Hand	0.3
Axial Skeleton, Ribs	11.8
Skull	2.3

From Kissane JM, Askin FB, Foulkes M, et al: Ewing's sarcoma of bone: clinicopathologic aspects of 303 cases from the Intergroup Ewing's Sarcoma Study, *Hum Pathol* 14:773, 1983.

LOCATION IN LONG BONES

*almost always
metaphyseal or
diaphyseal*

- metadiaphysis: 44%
- mid-diaphysis: 33%
- metaphysis: 15%
- epiphysis: 1-2%



Routes of spread

- ▶ direct extension into adjacent bone or soft tissue.
- ▶ Metastases generally spread through bloodstream
- ▶ 25% present with metastatic disease
 - Lungs (38%)
 - Bone (31%)
 - Bone Marrow (11%)
- ▶ **Nearly all pts. have micromets at diagnosis, so all Need chemo.**

Table 9-1 Staging System of the Musculoskeletal Tumor Society (Enneking System)

Stage	Grade, Tumor Size, and Metastasis Status	Description
IA	G ₁ T ₁ M ₀	Low grade Intracompartmental No metastases
IB	G ₁ T ₂ M ₀	Low grade Extracompartmental No metastases
IIA	G ₂ T ₁ M ₀	High grade Intracompartmental No metastases
IIB	G ₂ T ₂ M ₀	High grade Extracompartmental No metastases
IIIA	G _{1/2} T ₁ M ₁	Any grade Intracompartmental With metastases
IIIB	G _{1/2} T ₂ M ₁	Any grade Extracompartmental With metastases

Table 9-2 American Joint Committee on Cancer Staging System for Primary Malignant Tumors of Bone for Those Tumors Diagnosed on or after January 1, 2003

Stage	Tumor	Lymph Node	Metastases	Grade
IA	T1	N0	M0	G1 or G2
IB	T2	N0	M0	G1 or G2
IIA	T1	N0	M0	G3 or G4
IIB	T2	N0	M0	G3 or G4
III	T3	N0	M0	Any G
IVA	Any T	N0	M1a	Any G
IVB	Any T	N1	Any M	Any G
	Any T	Any N	M1b	Any G

DIAGNOSIS

- ESR is usually elevated
- Alkaline Phosphatase - normal (OS - elevated)
- Plain X Ray
- CT
- MRI
- Bone Scan
- PET Scan
- Biopsy - Wide Bore Needle Aspiration
 - Open (incisional) biopsy

	Primary	Staging
History & Physical Examination		
<i>Histo-pathology</i>	-Biopsy -Genetics -IHC	-Bone Marrow
<i>Imaging</i>	-X-ray -CT scan -MRI	-CT Thorax -Bone scan -PET scan
<i>Lab Test</i>	- Renal – RFT - Cardiac – 2D-ECHO	

► Laboratory tests:

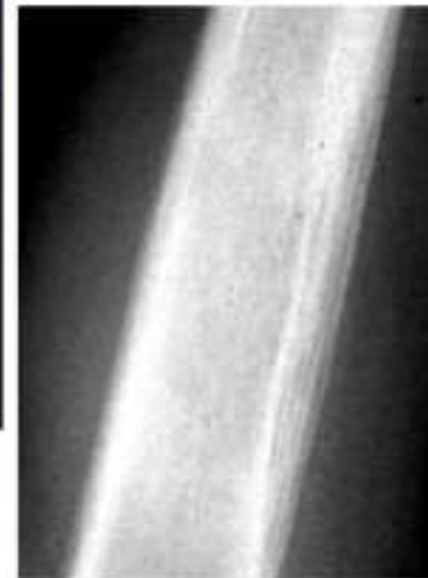
- CBC, Alkaline phosphatase, liver/kidney function tests,
- LDH:
 - useful as gauge of tumor burden
 - Falls with effective therapy and rises with disease recurrence

Biopsy

- ▶ Confirmation of diagnosis:
 - biopsy and histopathologic examination
 - core needle / open Inx biopsy
 - Cytogenetics and IHC

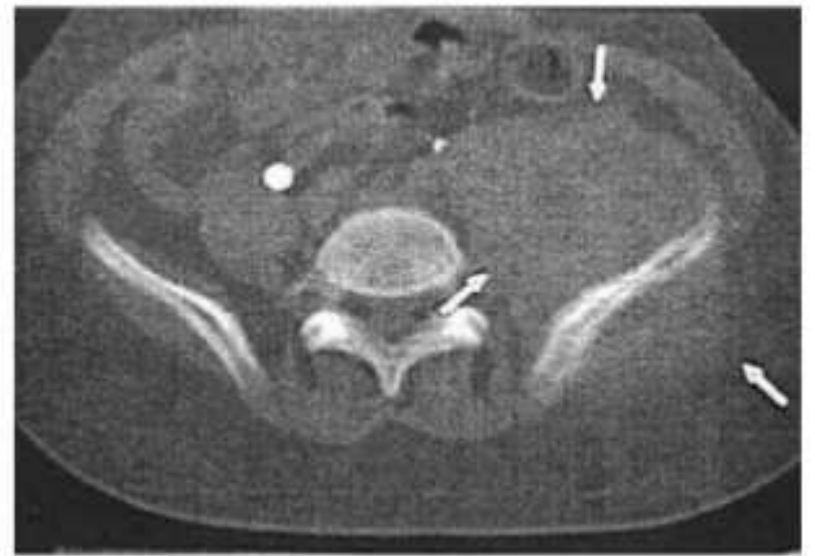
PLAIN RADIOGRAPH

- The lesion is **poorly defined**
- **Permeative** or moth-eaten type of bone destruction
- Aggressive **periosteal** response
 - onion peel*
 - codman triangle*
 - sunburst appearance*
- Large **soft-tissue mass**
- Occasionally, the bone lesion itself is almost imperceptible, with the soft-tissue mass being the only prominent feature



CT SCAN

- reveals pattern of bone destruction
- provides information about the medullary extension
- delineates extraosseous involvement



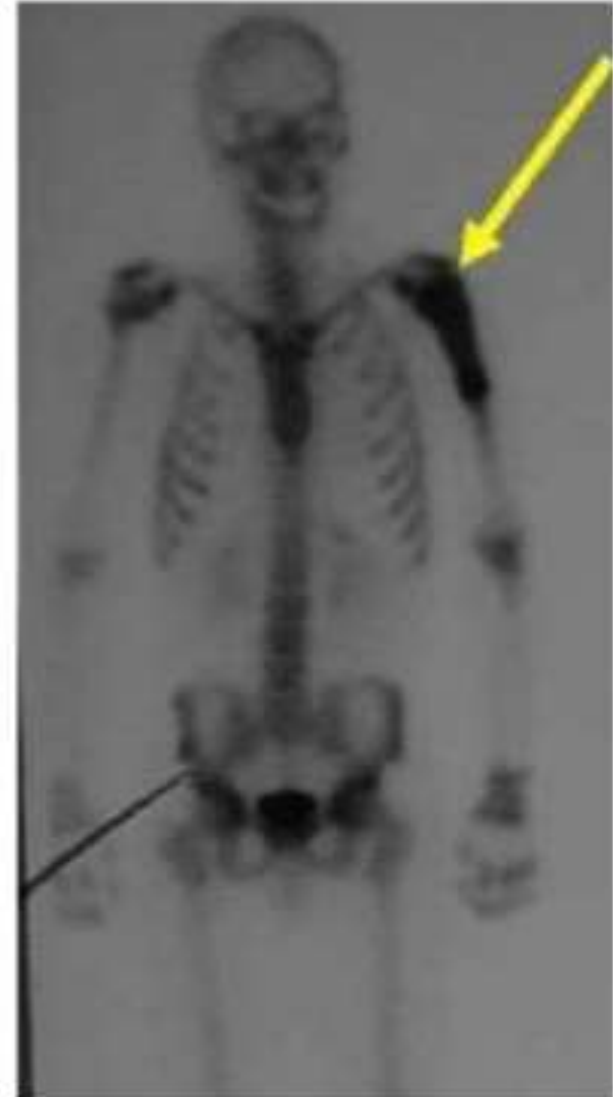
MRI

- Demonstrates the extent of intraosseous and extraosseous involvement of tumor (staging of tumor can be done)
- Effectively reveals extension through the epiphy. plate.
- T1-weighted images - intermediate to low signal intensity, which becomes bright on T2 weighting.
- Hypocellular areas & areas of necrosis - lesser intensity



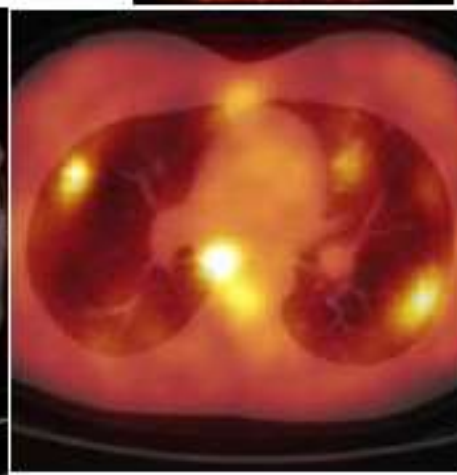
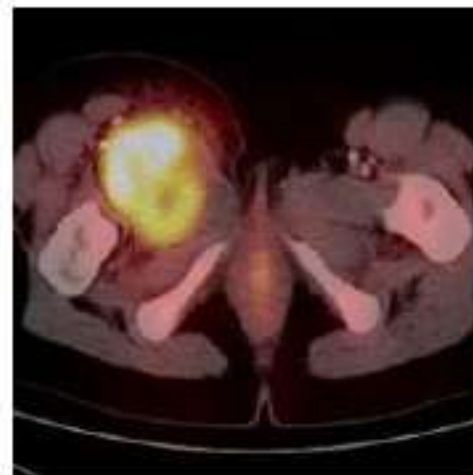
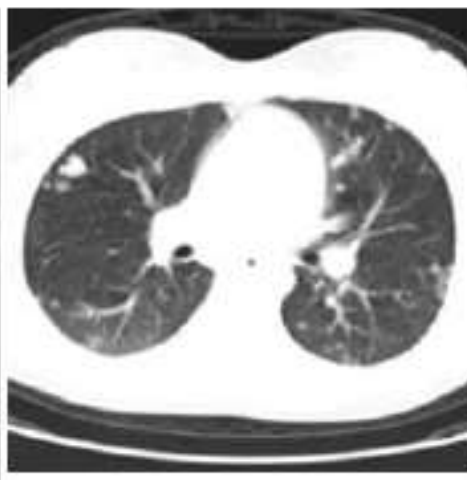
RADIOISOTOPE BONE SCAN

- **Technetium-99m** methylene diphosphonate (^{99m}Tc -MDP) - **Increased uptake** in areas of bone destruction
- **Gallium-67**-citrate - **Soft tissue extension**
- Scintigraphy – nonspecific but reliable in identifying metastatic lesions
- **Metastases** may be present in up to 30% of cases at time of diagnosis (mostly to **bones & lungs**)

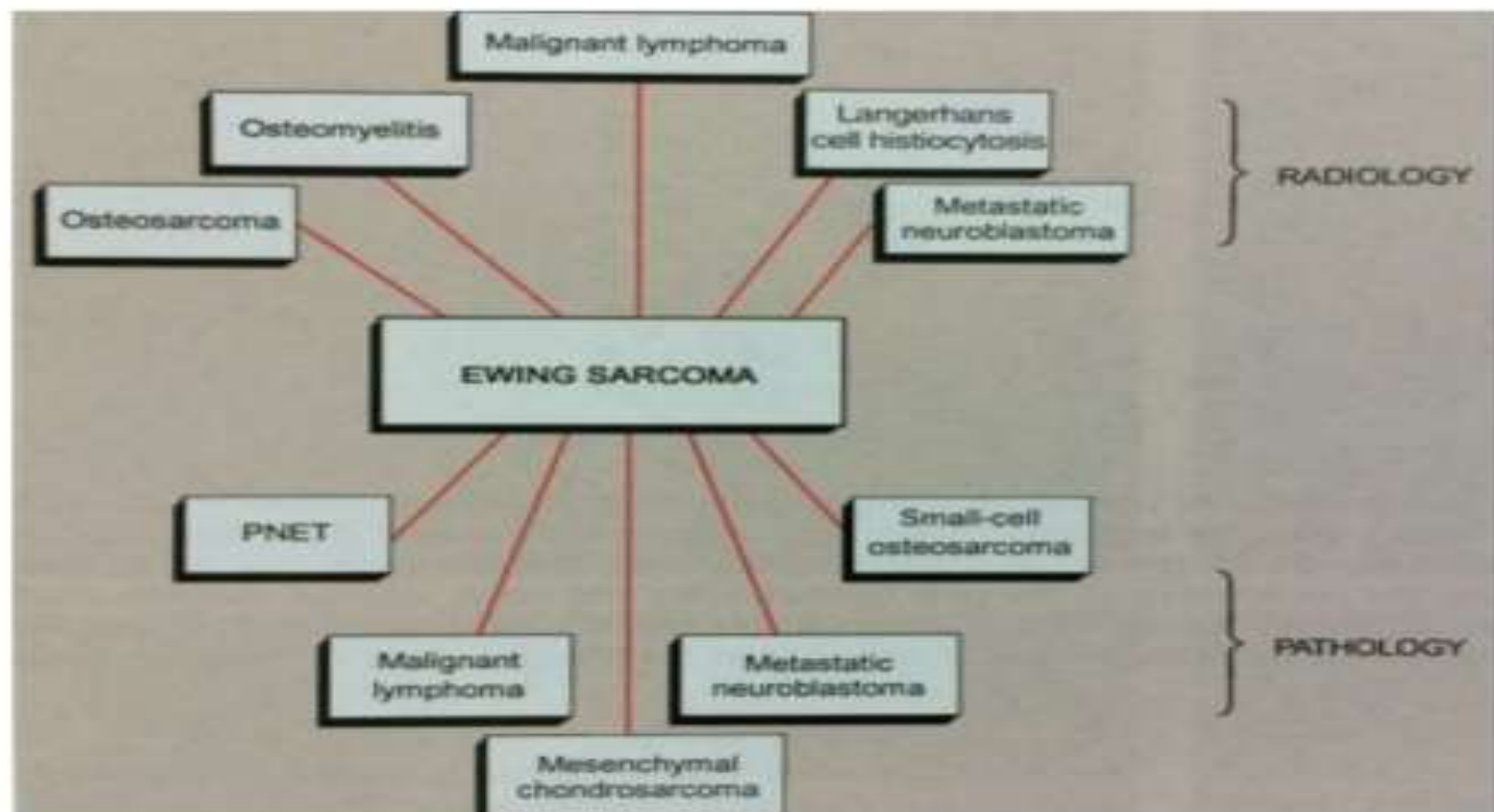


PET/PET- CT Scan

- ▶ newer technique
- ▶ Under evaluation to detect
 - local and distal extent,
 - Predictor of outcome and recurrence



DIFFERENTIAL DIAGNOSIS



TREATMENT

CHEMOTHERAPY



Chemotherapy

► First Line therapy:

- VAC/IE
 - Vincristine 2.0 mg/m² on D1
 - Adriamycin 75 mg/m² on D1
 - Cyclophosphamide 1.2 gm/m² on D1
 - Ifosphamide 1.8 gm/m² on D1-5
 - Etoposide 100 mg/m² on D1-5
- **Substitute adriamycin with dactinomycin (1.2 mg/m² on D1) after 375 mg/m²
- VAI (Vincristine, Adriamycin, Ifosphamide)
- VIDE (Vincristine, ifosphamide, Doxorubicin, Etoposide)

Second line therapy (relapse and refractory disease)

- ▶ Cyclophosphamide (250 mg/m²) and topotecan (0.75 mg/m²) D1-D5
- ▶ Temozolomide and irinotecan
- ▶ Ifosfamide and etoposide
- ▶ Ifosfamide, etoposide and carboplatin
- ▶ Docetaxel and gemcitabine

Role of Surgery

- ▶ Development of Innovative Surgical Techniques:
Limb preservation & Structural bone function preservation
 - ▶ Chemo - cytoreduction makes resection possible
 - ▶ Local failure rates with RT in historical series :
9 - 25% *
 - ▶ Concern over second malignancies
- ▶ Surgical Indications
 - Expendable bone (fibula, rib, clavicle)
 - Bone defect able to be reconstructed with modest loss of function
 - May consider amputation if considerable growth remaining
 - After pre-op RT
 - ▶ Limb-salvage surgery is preferred.
 - ▶ Curative surgery requires wide local excision and negative margin
 - Bony margins of at least 1 cm, with a 2 to 5 cm margin recommend.
 - Soft tissue at least 5mm in fat or muscle , with 2mm through fascial planes.

RADIOTHERAPY

PRINCIPLES

- to sterilise tumor compartment before surgery
- potentially reduce the risk of dissemination during surgery
- **It is a Radioresponsive Tumor**
- RT in combination with Chemotherapy achieve local control but complete surgery when feasible is the first choice of local control

PROGNOSIS

Poor prognostic factors:

- Age >17ys
- Large size tumor > 8cm
- Metastases
- Pelvic & Sacral tumors
- Fever, Leucocytosis & Raised ESR at presentation
- <90% necrosis after Chemo
- Extraosseous soft tissue extension
- Postradiation medullary tumor
- ***Small bones(strong CD99⁺ve) – better prognosis***