26th Annual General Pediatric Review & Self-Assessment

Nicklaus Children's Hospital

ONCOLOGY

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Disclosure of Relevant Relationship

Dr. Khatib has not had (in the past 24 months) any relevant conflicts of interest or relevant financial relationship with the manufacturers of products or services that will be discussed in this CME activity or in his presentation.

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Cancer in Children

- Fourth leading cause of death 1-19 yrs
- 15,700 new cases each year
- Yearly incidence 1.5/ 10000 children <15 yrs
- 3000 deaths from childhood cancer each year in the U.S.

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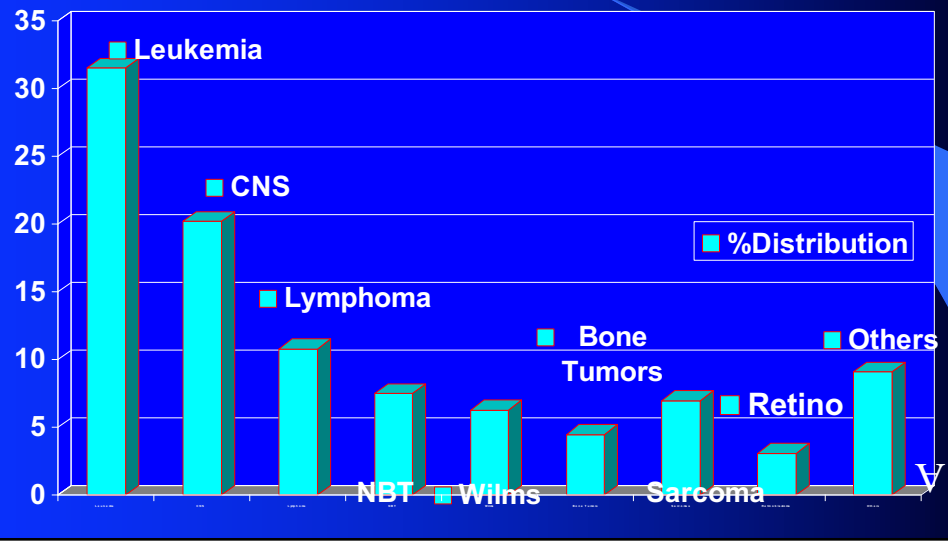
Distribution of Childhood Cancers



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Selected Hereditary Cancer Syndromes That Manifest in Childhood

Cancer Syndrome	Gene
Retinoblastoma	*RB1*
Wilms tumor	*WT1*, others
Familial adenomatous polyposis	*APC*
Multiple endocrine neoplasia type 2	*RET*
Li-Fraumeni	*TP53*
Von Hippel-Lindau	*VHL*
Nevoid basal cell carcinoma	*PTC*

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Acute Lymphocytic Leukemia

- Presenting signs:
  - Fever, bone pain, arthritis, pallor, petechiae, bruising
  - lymphadenopathy, hepatosplenomegaly
- Peak Age : 3-6 years
- Labs
  - CBC normal or cytopenias or high WBC
  - High LDH or Uric acid
  - CXR -CSF

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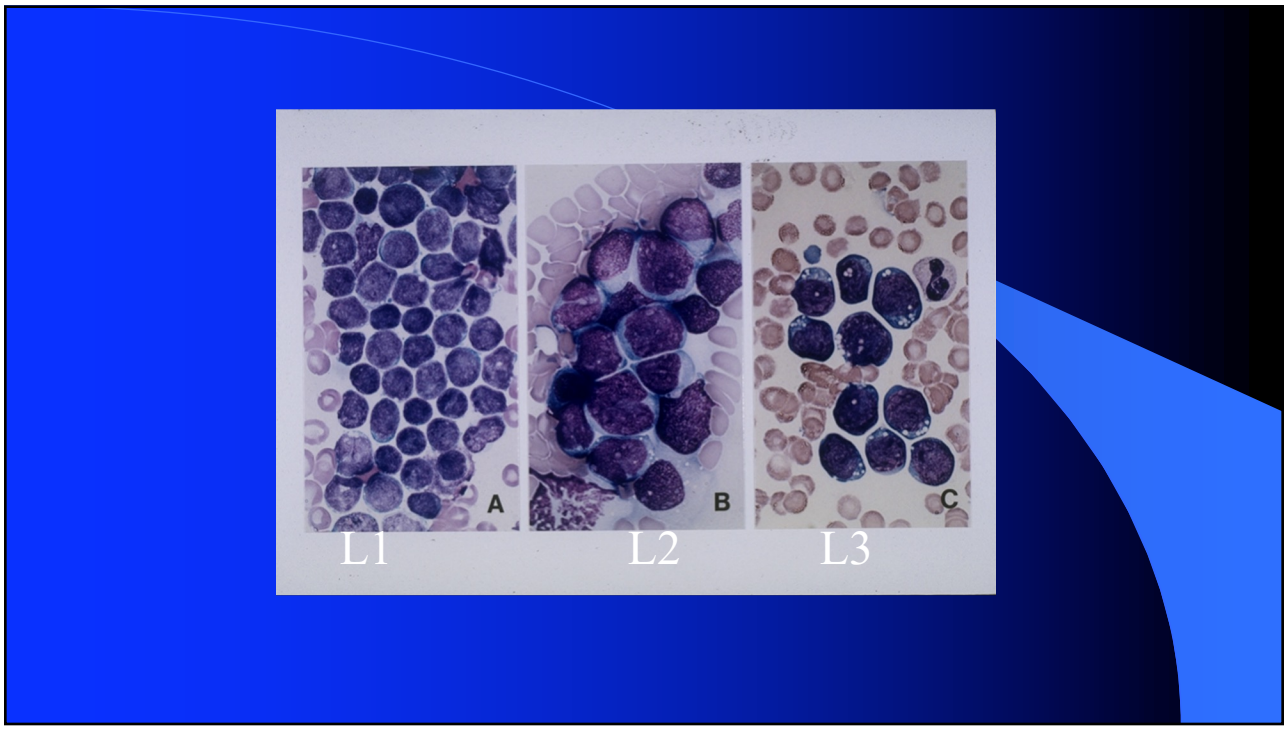

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Acute Lymphocytic Leukemia

- Prognosis
  - Better for low WBC count, pre-B type (non-T)
  - DNA index > 1.16 (Hyperdiploid) better
  - t(9,22) Ph+ worse
- Treatment
  - Induction: Prednisone, Vincristine, Asparaginase
  - Consolidation/maintenance: 6MP + methotrexate
  - trimethoprim/sulfa: PCP/PJP prophylaxis

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ALL- Chicken Pox

- High risk of disseminated fulminant disease in susceptible patients on chemotherapy (Prednisone)
- If previously had chicken pox or the vaccine and IgG titer positive: **Reassure**
- **Exposure:** > 1/2 hour in same room with a child who has active vesicles or who develops rash within 2 days of exposure
- VZIG or IVIG within 72 hours if seronegative
- If rash develops: IV acyclovir, CXR, LFT's

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Lymphomas

- **Hodgkin's Lymphoma**
  - Fever, night sweats, weight loss, lymphadenopathy, mediastinal mass, spleen, marrow involvement
- **Non-Hodgkin's Lymphoma**
  - Burkitt's: jaw, ileocecal, marrow. B-cell
  - Lymphoblastic: Mediastinal mass, T-cell leukemia
  - Large cell lymphoma: LN's, bone, lung, skin

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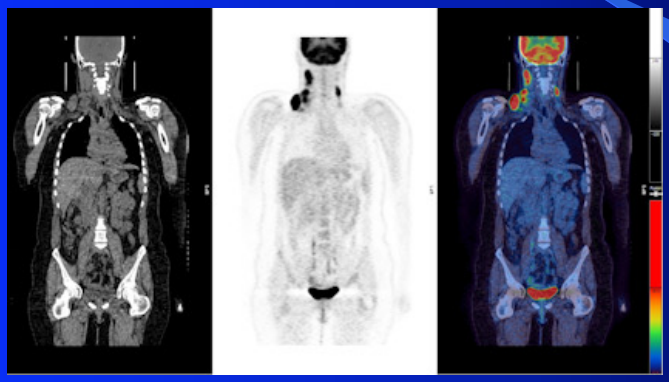
PET CT in Hodgkin's Lymphoma



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CNS Tumors In Children
Most common solid tumor in children

Supratentorial astrocytoma	15-25%
Cerebellar astrocytoma	10-20%
Medulloblastoma	10-20%
High grade glioma	10-15%
Brain stem glioma	10-20%
Ependymoma	5-10%
Craniopharyngioma	6-9%
Pineal tumors	0.5-2%

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Risk Factors for Brain Tumors

- ***GENETIC***
  - Phacomatoses: NF-1, NF-2, Tuberous sclerosis, von Hippel Lindau
  - Li-Fraumeni syndrome: p53 gene mutation
  - Turcot syndrome: APC gene
  - Random events
- **Environmental**
  - Ionizing radiation:
    - In utero,
    - cranial XRT in ALL
  - Electromagnetic fields
    - Conflicting data
  - Immunosuppressive agents
  - Toxic chemicals

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Clinical Presentation
Neurologic Deficits

Supratentorial
- Headache
- Seizures
- Hemiparesis
- Hyper-reflexia
- Clonus

Infratentorial
- Headache +vomiting (hydrocephalus)
- Ataxia
- Dysmetria
- Cranial nerve V-IX dysfunction

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Clinical Presentation

- Lethargy
- Declining academic performance
- Personality changes, irritability
- Anorexia
- Developmental delay
- Macrocephaly
- “setting sun” eyes

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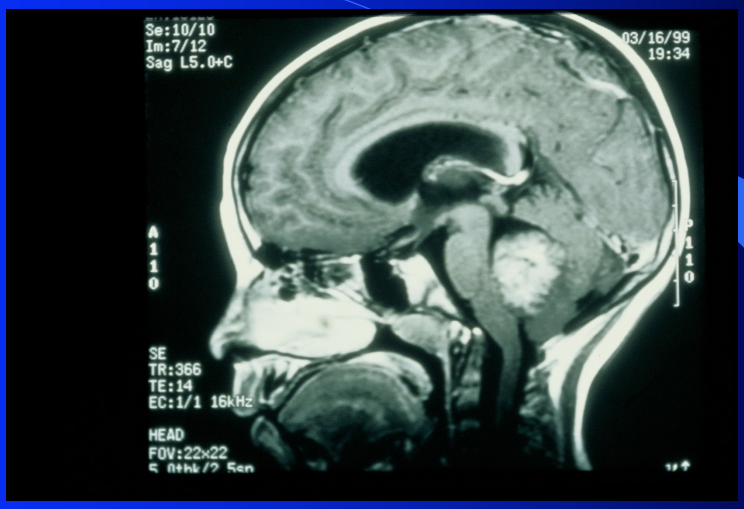

MEDULLOBLASTOMA

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Medulloblastoma

- Primitive neuroectodermal tumor of posterior fossa
- 25% of childhood CNS tumors
- 40% of posterior fossa tumors
- Arises from neuroepithelial roof of 4th ventricle
- Peak incidence: 1-4yrs of age

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Medulloblastoma- Treatment

- Complete surgical resection
- Craniospinal radiotherapy with Boost to posterior fossa to 5400 cGy
- Chemotherapy cisplatin/vincristine/etoposide/cytoxan or ccnu
- 5- year survival 60-70% for high risk
  80-90% for average risk
- Multiple subtypes

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Wilms' Tumor

- Nephroblastoma
- Most common kidney tumor in childhood
- 6% of childhood malignancies
- 7.5 cases per million children yearly
- Peak age at diagnosis 2-3 years

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Wilms'- Presentation

- Abdominal or flank mass
- Hematuria
- Pain, fever, malaise
- Hypertension

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Wilms' Tumor Genetics

- Most cases are sporadic
- Rarely familial- autosomal dominant (1%)
- WT1 gene on chromosome 11 short arm
  deleted or inactivated
- Associated congenital anomalies:
  aniridia, hemihypertrophy, GU anomalies
  NF-1, Beckwith-Weidemann syndrome

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Genetic Heterogeneity in Wilms Tumor Syndromes

Locus	Syndrome
WT1 gene at 11p13	Denys-Drash
11p13 region	WAGR
11p15 region	Beckwith-Wiedemann
Xq26	Simpson-Golabi-Behmel
17q12-21	Familial Wilms
19q13	Familial Wilms

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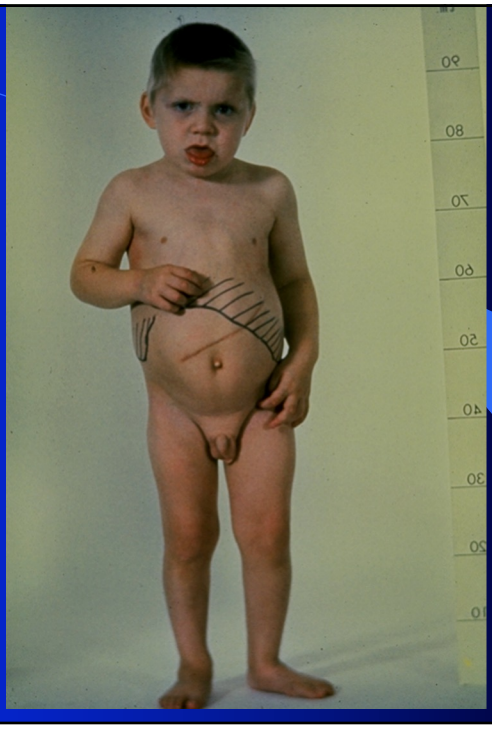
BECKWITH-WEIDEMAN SYNDROME



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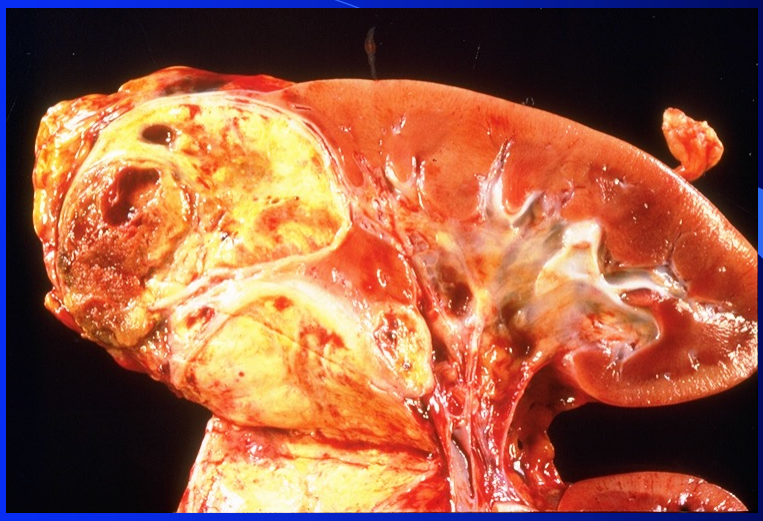

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Diagnostic Evaluation- Wilms'

- History and physical exam
- Abdominal ultrasound
- Chest X-ray with oblique views
- CT or MRI scan of abdomen
- CT scan of chest
- CBC, BUN, Cr, LFT's
- Urinalysis

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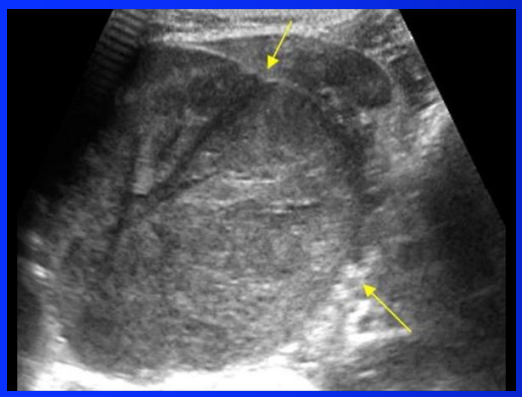
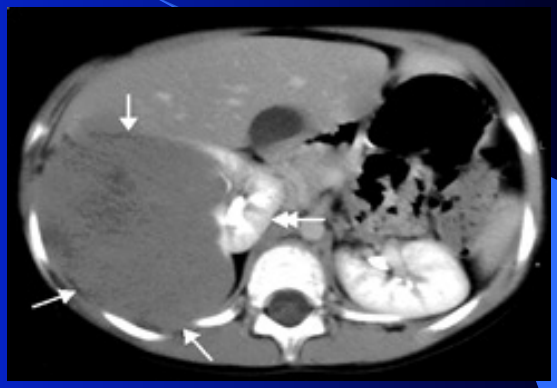
Wilms Tumor





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Staging of Wilms' Tumor

- **STAGE I**: Tumor limited to kidney and completely resected.
- **STAGE II**: Tumor extends beyond kidney and completely excised. (e.g..... through renal capsule, or into renal vein)
- **STAGE III**: Residual tumor confined to abdomen:

  Incomplete resection, lymph node involvement, peritoneal implants, tumor spillage beyond flank
- **STAGE IV**: Metastasis to lungs, liver, brain, or bone
- **STAGE V**: Bilateral renal involvement.

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Wilms'- Histology

- Favorable

  Blastemal- Stromal- Epithelial elements
- Unfavorable or anaplastic

  Rapidly dividing, large nuclei, mitoses
- Nephroblastomatosis

  small blastemic clusters- pre-malignant?
- Clear cell sarcoma
- Rhabdoid Tumor

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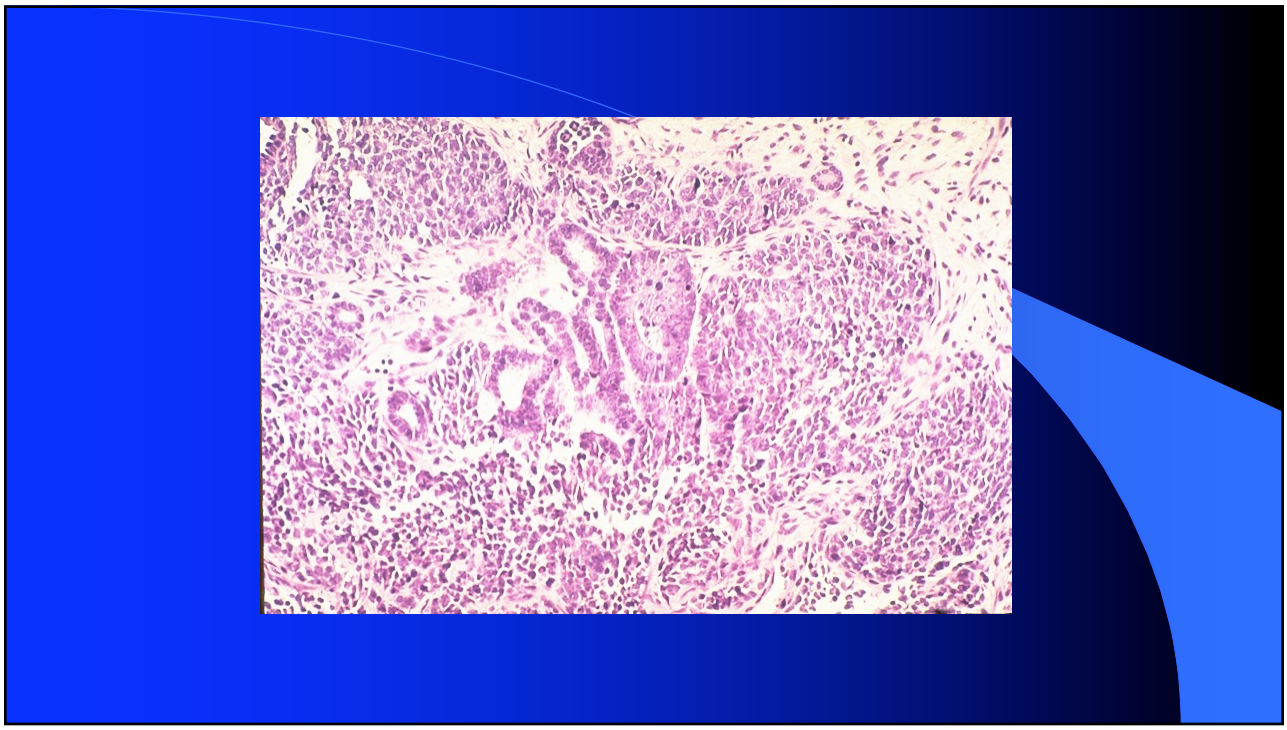

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Treatment of Wilms' Tumor

- **SURGERY**

  Attempt complete removal, Biopsy lymph nodes, Inspect other kidney, Stage and histology

- **CHEMOTHERAPY**

  Post-operative vs. pre-operative

  Vincristine + Actinomycin

  Adriamycin, Ifosfamide, VP-16

- **RADIOTHERAPY**

  Stages III and IV only

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Bilateral Wilms'

- Synchronous 4-7%
  Metachronous 1-2%
- Approach: Biopsy or partial resection
  Chemotherapy
  +/- Radiation
  Second look surgery
- Survival: 87%

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Late Effects- Wilms'

- Single kidney: contact sports, renal disease
- Radiation:
  - scoliosis
  - soft tissue under-development
  - thyroid function
  - 2nd malignancy: sarcoma, AML, breast, thyroid, skin
- Chemotherapy: Cardiac (anthracycline)

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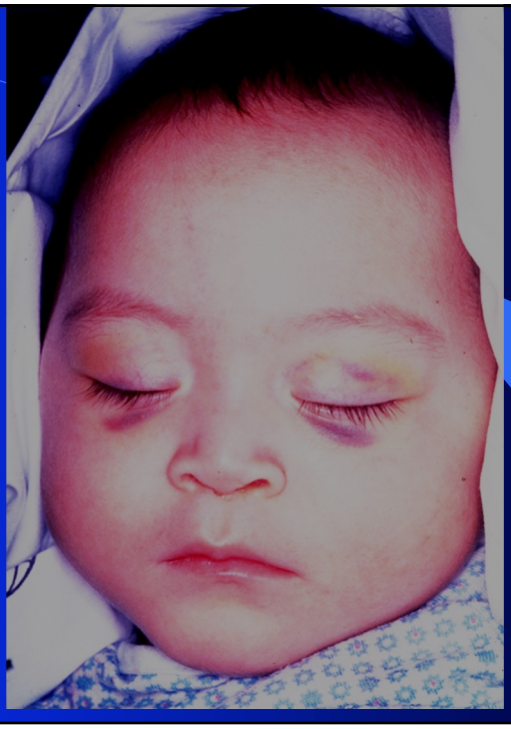
NEUROBLASTOMA

ORBITAL BONE METS



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NEUROBLASTOMA

- Tumor of neural crest origin
  sympathetic nervous system
- 2nd most common solid tumor in children
- Most common in 1st year of life
- 7-9.6 cases per million children yearly=500
- Spontaneous regression or
  maturation to ganglioneuroma possible

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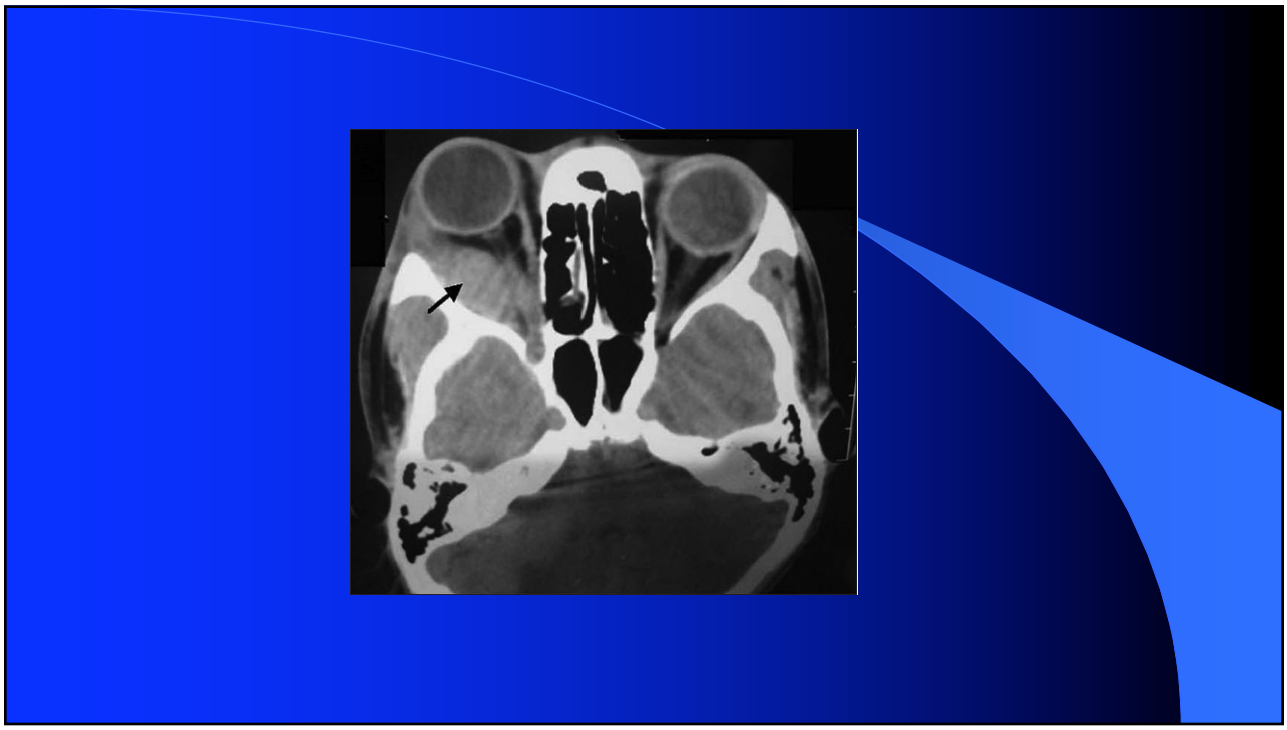

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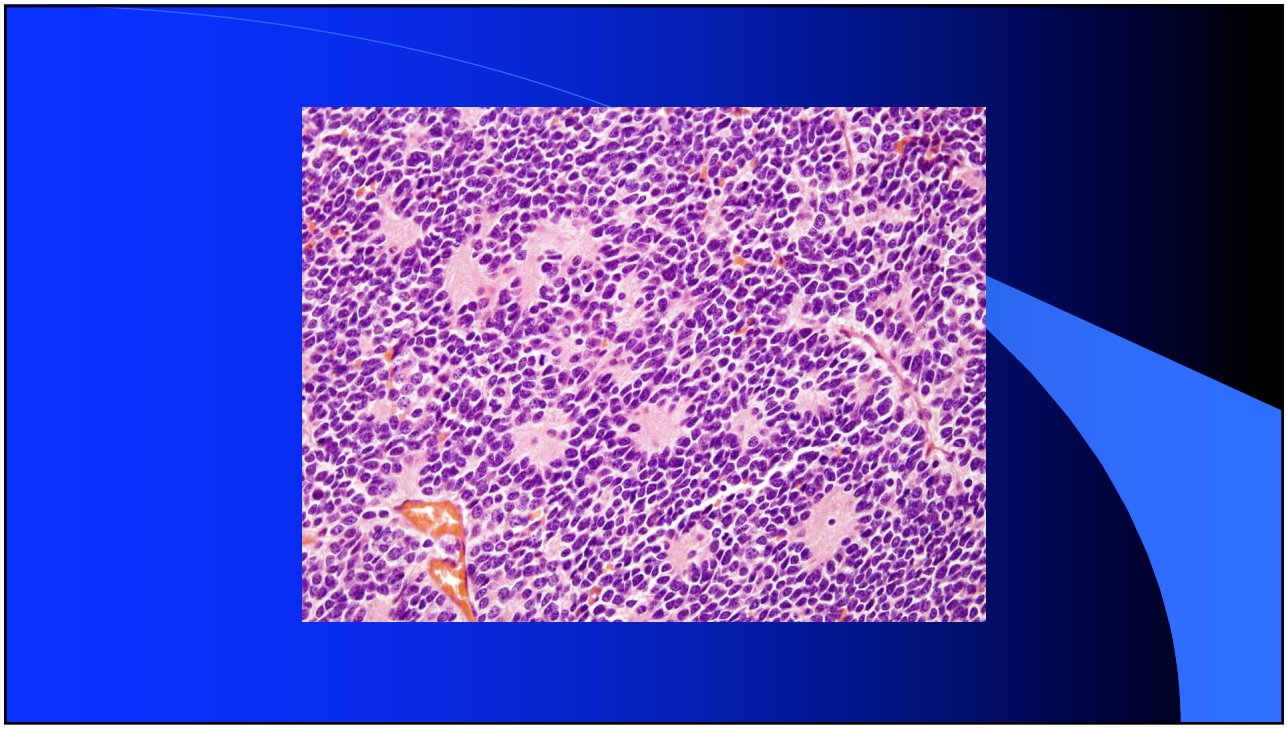

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NBT- Pathology

- "Small Blue Round Cell" Tumor

  -Dense nests of cells separated by fibrillar bundles with hemorrhage, necrosis, calcification, and rosettes.

  -Ganglion cells, nerve bundles, and schwann cells present in mature form.

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NBT-Biology

- Rare genetic predisposition- ALK gene
- N-myc oncogene amplification- Chr. 2
- Deletion of short arm of chromosome 1
- DNA index or ploidy

$$\frac{\text{DNA CONTENT OF TUMOR}}{\text{NORMAL DNA CONTENT}} \geq 1.0$$

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Neuroblastoma in Infants

- A distinct biologic entity with good prognosis.
- Age < 18 months
- Hyperdiploid (DNA index >1.0)
- N-myc not amplified

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Neuroblastoma

- Primary sites
  Abdomen: adrenal 40%
  paraspinal ganglia 25%
  Thorax: paraspinal ganglia 15%
  Neck 5%
  Pelvis 5%
- Metastatic disease 60-70% at diagnosis

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NBT- Presentation

- Abdominal mass
- Respiratory symptoms
- Superior vena cava syndrome
- Horner's syndrome
- Vascular compression/edema lower extremity
- Spinal cord compression
- Bone marrow infiltration: anemia, thrombocytopenia, pain
- Sphenoid bone mets: ecchymosis of eyelids, proptosis
- Subcutaneous nodules
- Ataxia/ opsoclonus-myoclonus syndrome
- Intractable diarrhea- vasoactive intestinal polypeptide
- Hypertension

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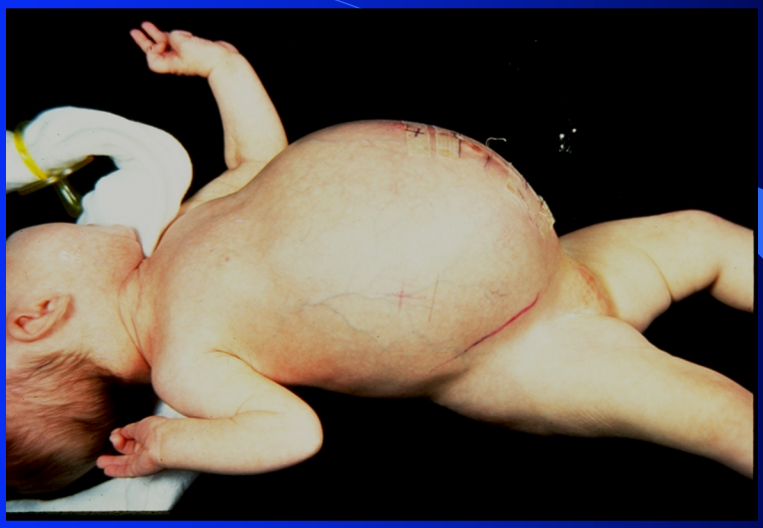

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NBT- Diagnosis

- Suspect neuroblastoma!
- Urine catecholamine metabolites elevated in 90% of children- VMA and HVA
- Nonspecific markers: NSE, ferritin, GD2
- Bone marrow aspirate and biopsy
- Radiologic work-up

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Radiologic Evaluation-NBT

- CT scan of primary
- CT scan of abdomen
- Skeletal survey including CXR
- MRI for paraspinal/intraspinal disease
- Metaiodobenzylguanidine scan (^{123}I-MIBG)
- PET CT

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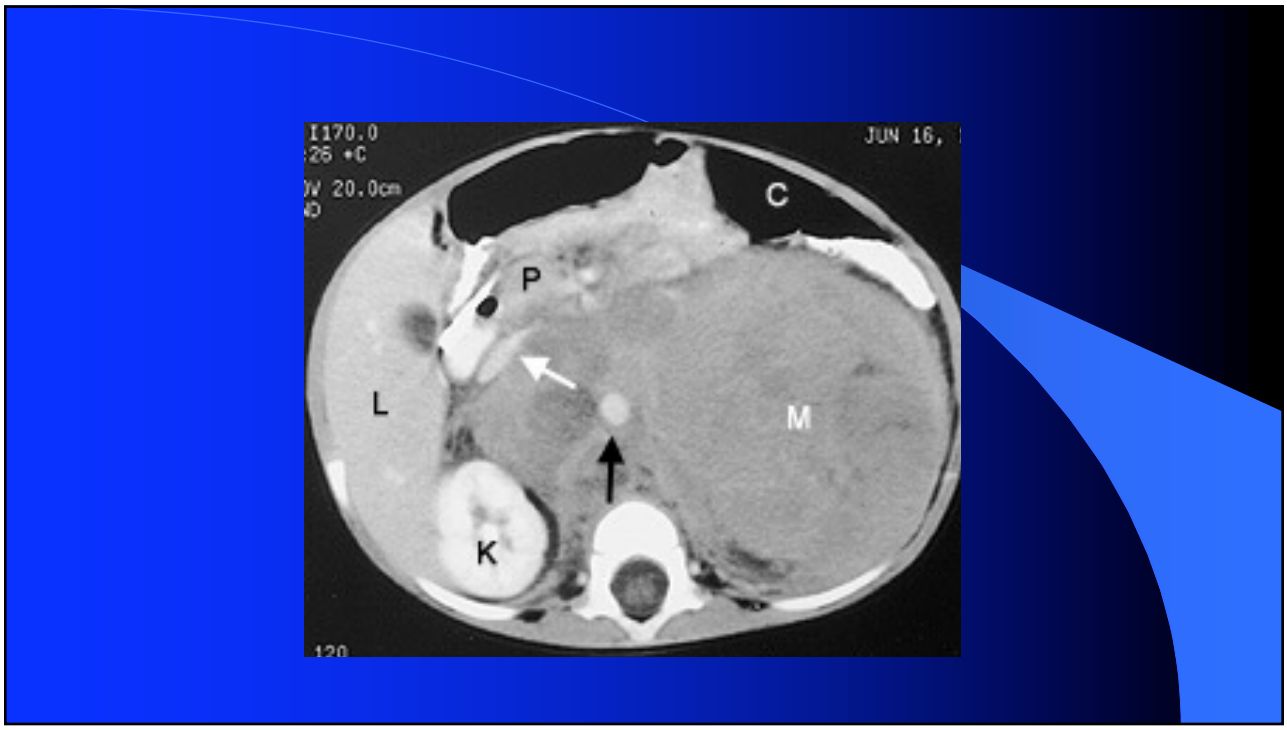

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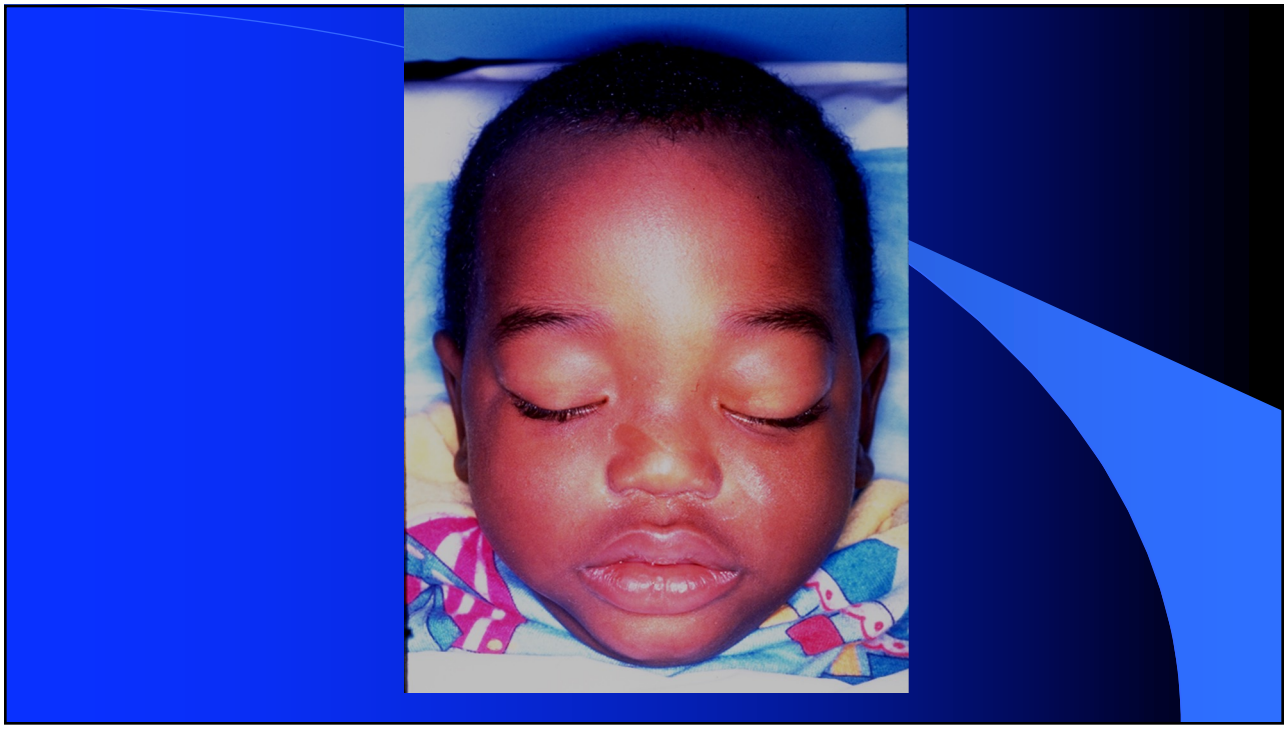

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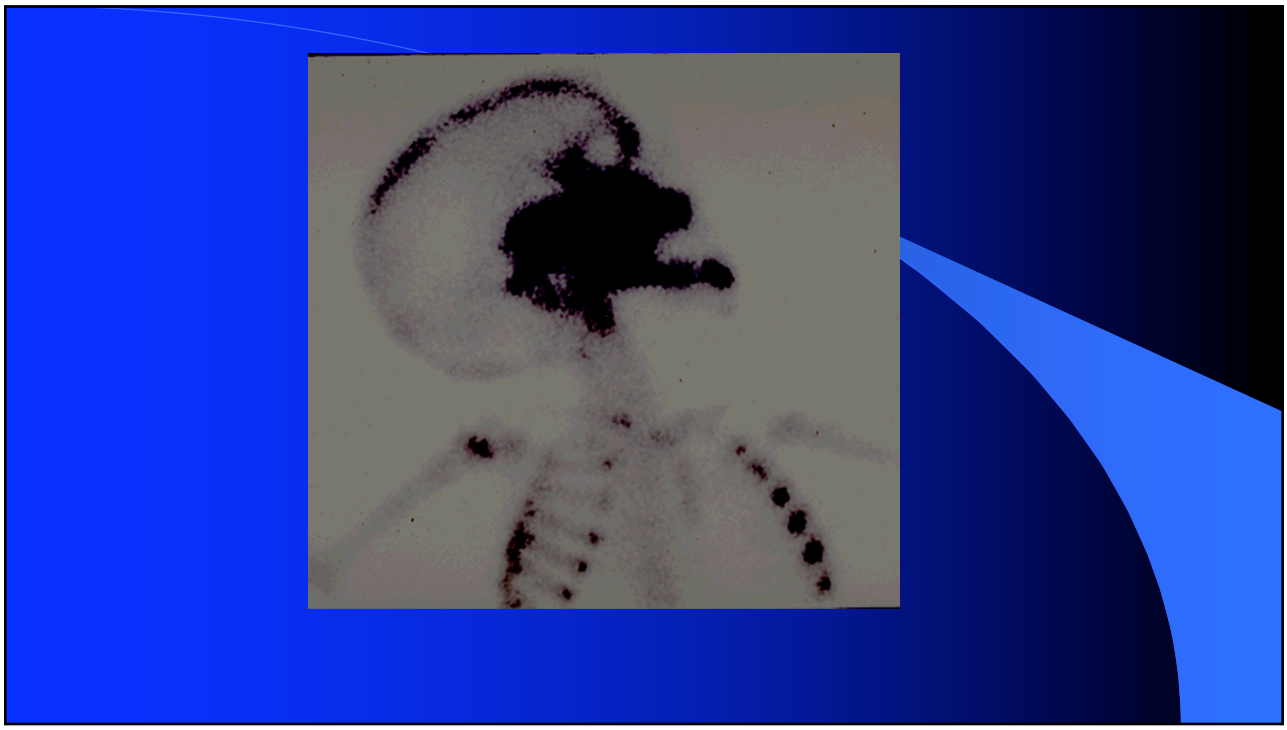

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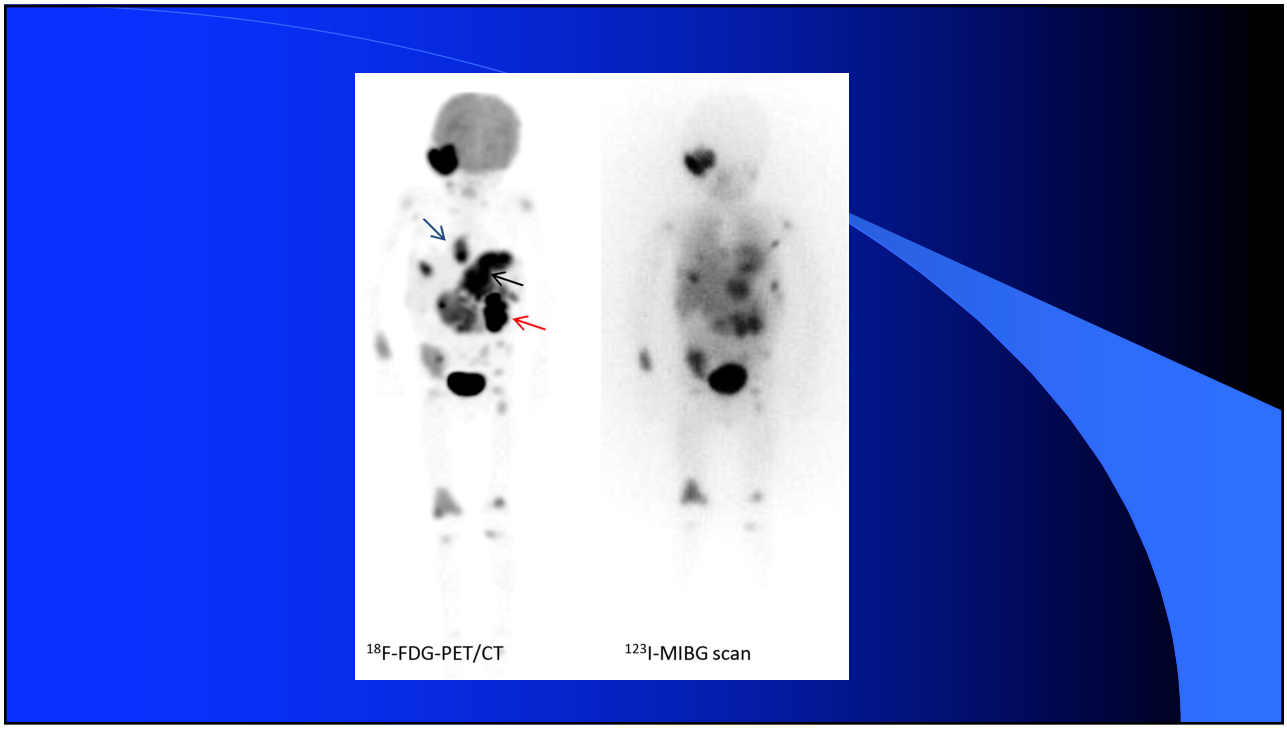

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Neuroblastoma-Staging

Evans- POG- ***International Staging System***

- **Stage 1**. Localized tumor confined to the area of origin- ***complete excision***, +/- microscopic residual, no positive nodes.
- **Stage 2**.

  2A) Unilateral tumor ***incompletely*** excised, negative nodes

  2B) Unilateral tumor with ***positive ipsilateral nodes***, +/- gross excision, negative contralateral nodes

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NBT-Staging

- **Stage 3:** Tumor infiltrating across midline or presence of ***contralateral*** lymph nodes.
- **Stage 4:** Dissemination to distant lymph nodes, bone, bone marrow, or liver
- **Stage 4S:** Localized primary as in stages 1 or 2 with liver, skin, +/- bone marrow disease. No lymph nodes, no bone disease.

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International Neuroblastoma Risk Group Staging System (INRGSS)

Stage	
L1	Localized disease without image-defined risk factors
L2	Localized disease with image-defined risk factors
M	Metastatic disease
MS	Metastatic disease "special" where MS is equivalent to stage 4S

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Treatment - NBT

- Low risk (<18 months)

  Stage 1,2, 4S: No therapy, Surgery only
  Stage 3, 4: Cyclo/Adria +/- Cisplatin/VP-16

- High risk (>12 mo.., N-myc amplified)

  Intensive chemotherapy- add Ifosfamide, Carbo
  Radiation therapy
  Bone marrow or stem cell rescue
  Immunotherapy/MIBG
  2nd look surgery

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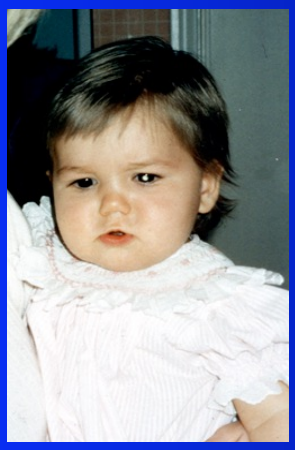
Retinoblastoma



- 1 in 18,000 live births
- 80% diagnosed before age 3-4 yr.
- 20-30% bilateral
- 90% sporadic (i.e.... no family history)
- 40% are related to a germline mutation in Rb gene

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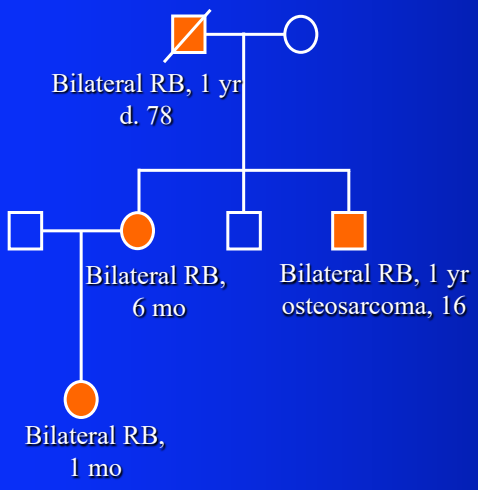
Genetic Features of Heritable Retinoblastoma



- Autosomal dominant transmission
- *RB1* gene on chr 13 (first tumor suppressor gene discovered)
- Penetrance >90%
- Prototype for Knudson's "two-hit" hypothesis

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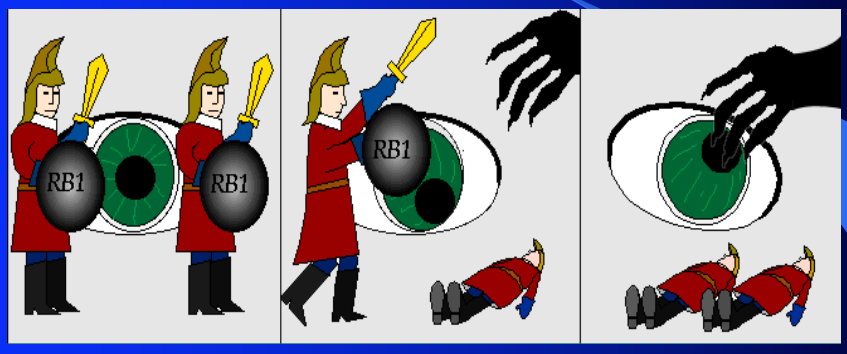
Knudson's "Two-Hit" Model for Retinoblastoma



Normal
2 intact copies

Predisposed
1 intact copy
1 mutation

Affected
Loss of both copies

Modified from *Time*, Oct. 27, 1986

ASCO

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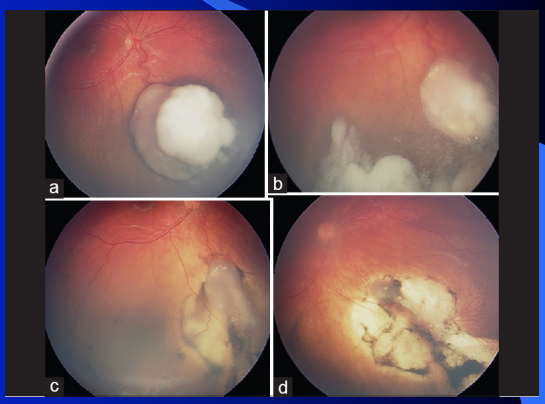
Retinoblastoma

- ***PRESENTATION***

LEUKOCORIA
STRABISMUS
PUPIL/IRIS ABNORMALITIES



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Retinoblastoma

- ***PATTERN OF SPREAD***

Extension into orbit -scleral emissary veins
Invasion of optic nerve
Subarachnoid spread into CSF
Bone, brain, or bone marrow
Pineal gland tumor

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Retinoblastoma

- ***TREATMENT***
  - Surgery-Laser- Cryotherapy
  - Radiotherapy- avoided
  - Chemotherapy
    - Systemic
    - Intra-arterial
    - Intra-vitreous

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Soft Tissue Sarcomas

- Highly aggressive malignancies
- Originate from primitive mesenchymal cells:

  fibrous tissue, adipose, blood and lymphatics

  fasciae, synovial structures

  smooth and striated muscles

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Rhabdomyosarcoma

- Arises from rhabdomyoblasts
- 5-8% of childhood cancers
- 4 per million children yearly
- Slight male preponderance
- Associated with familial cancer syndrome

  Li-Fraumeni - (p53 mutation)

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Clinical Presentation- RMS

- ***Orbit***: proptosis, eyelid swelling, blindness
- ***Paranasal sinuses***: nasal obstruction, sinusitis, epistaxis, nasal speech
- ***Base of skull***: cranial nerve palsy, headache, vomiting, diplopia
- ***Oropharynx***: dysphagia
- ***Middle ear:*** chronic otitis, facial palsy, hearing loss

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RMS- Clinical Presentation

- ***Extremity***: palpable mass, lymph node enlargement.
- ***Retroperitoneal***: abdominal pain, weakness, parasthesia (lumbosacral plexus)
- ***Vaginal***: bleeding, protruding polypoid mass
- ***Bladder/prostate***: urinary retention, hematuria
- ***Paratesticular***: scrotal mass (non-tender)
- Metastasis: bone pain, cytopenias

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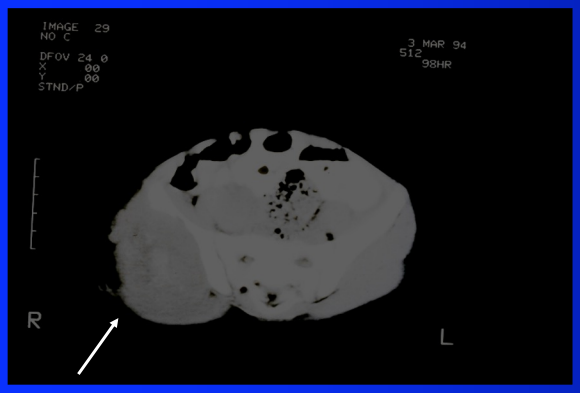

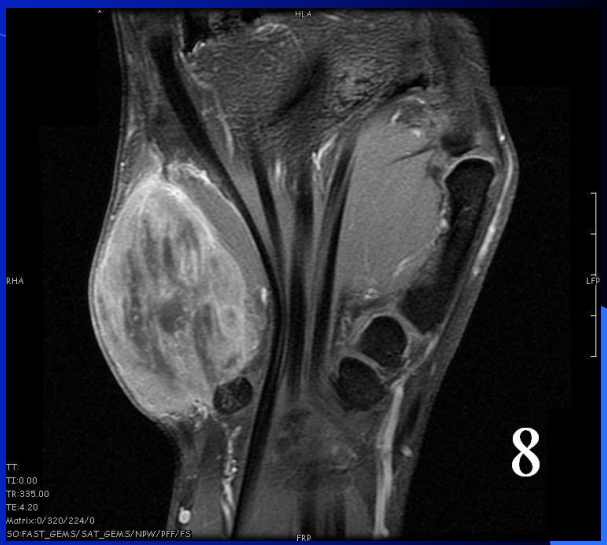

ALVEOLAR RHABDOMYOSARCOMA

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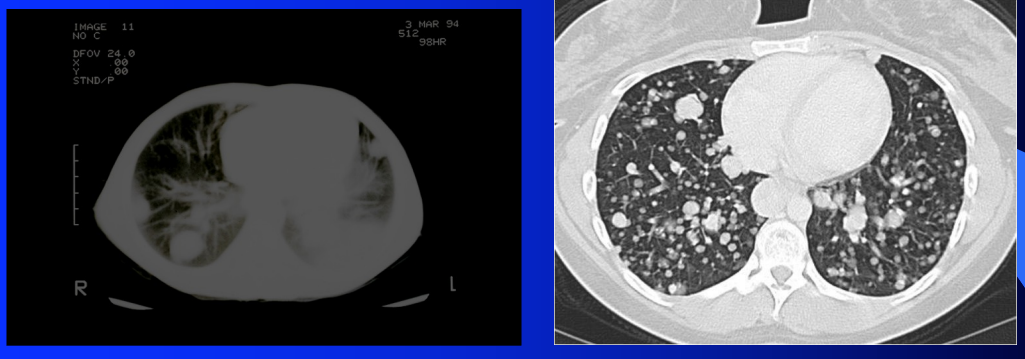

CHEST CT WITH LUNG METASTASIS

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Diagnostic Evaluation-RMS

- History+ physical
- CBC, liver- kidney function, U/A
- CT/MRI primary tumor
- CXR, CT chest
- CT abdomen /pelvis (lymph nodes)
- Bone scan/PET CT
- Bone marrow aspirate + biopsy
- CSF cytology (parameningeal tumors)

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Approach to a Patient With Rhabdomyosarcoma

Biopsy

↓

Attempt complete resection with free margins

↓

Staging work-up

↓

Chemotherapy +/- Radiation

↓

2nd look surgery

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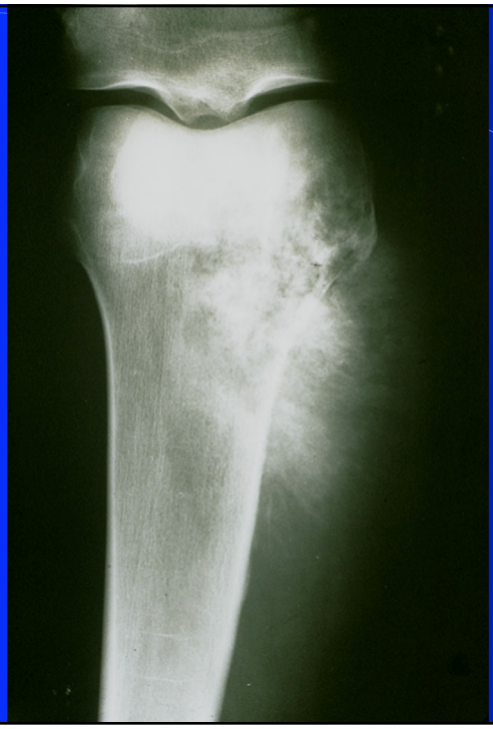

OSTEOSARCOMA

SUNBURST APPEARANCE

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OSTEOSARCOMA

- Epidemiology
- Etiology + Genetics
  - retinoblastoma gene
  - p53 gene
  - growth spurt
  - radiation induced

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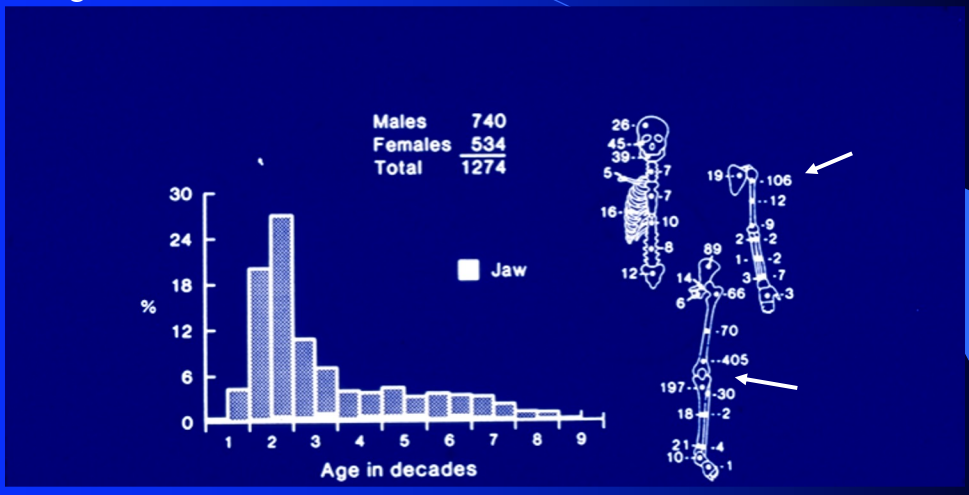
Age, Sex and Skeletal distribution of Osteosarcoma (Dahlin-Mayo Clinic)



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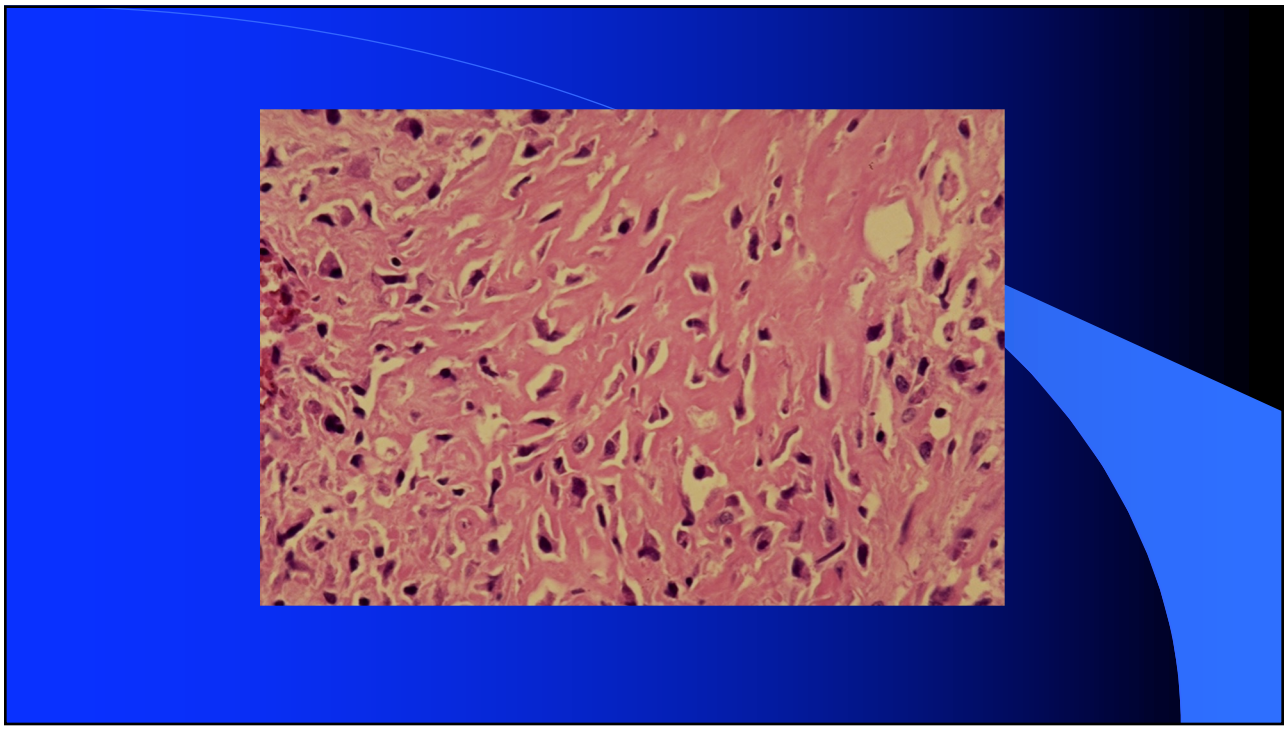

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Osteosarcoma

- Most common malignant bone tumor
- Distal femur most common then proximal tibia and humerus (growth plates)
- Sunburst appearance on X-ray
- Metastasis to lungs+bones (CT chest,PET scan)
- Treatment with chemotherapy: cisplatinum, doxorubicin and methotrexate and surgery ; (limb-salvage or amputation)

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Osteosarcoma- Clinical Presentation

- Bone pain
- Swelling

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Osteosarcoma- Treatment

- Surgery
- Adjuvant chemotherapy (post-op)
- Pre-surgical chemotherapy
  - Histologic evaluation
- Biologic response modifiers (BCG-MTP-PE- CAR-T cells)

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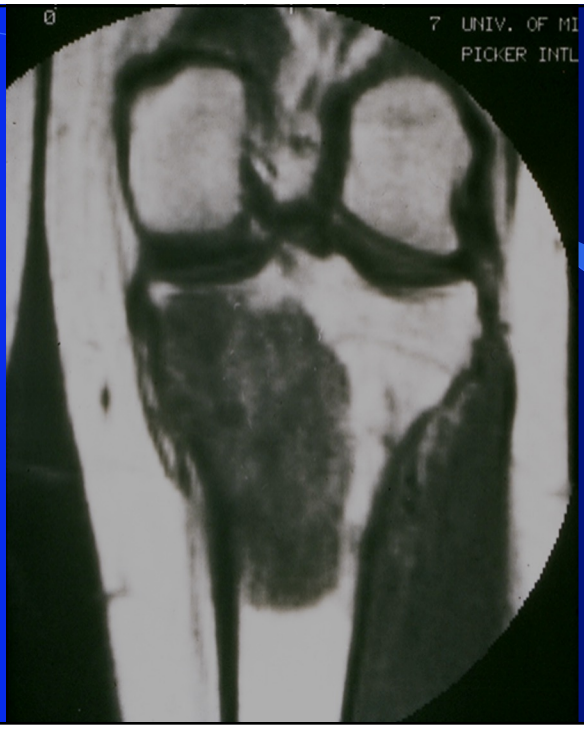
Osteosarcoma- Surgery

- Amputation
- Limb Salvage
  - **AUTOLOGOUS GRAFT**
  - **VASCULARIZED GRAFT**
  - **ALLOGRAFT**
  - **ENDOPROSTHESES**
  - **EXCISION**

75



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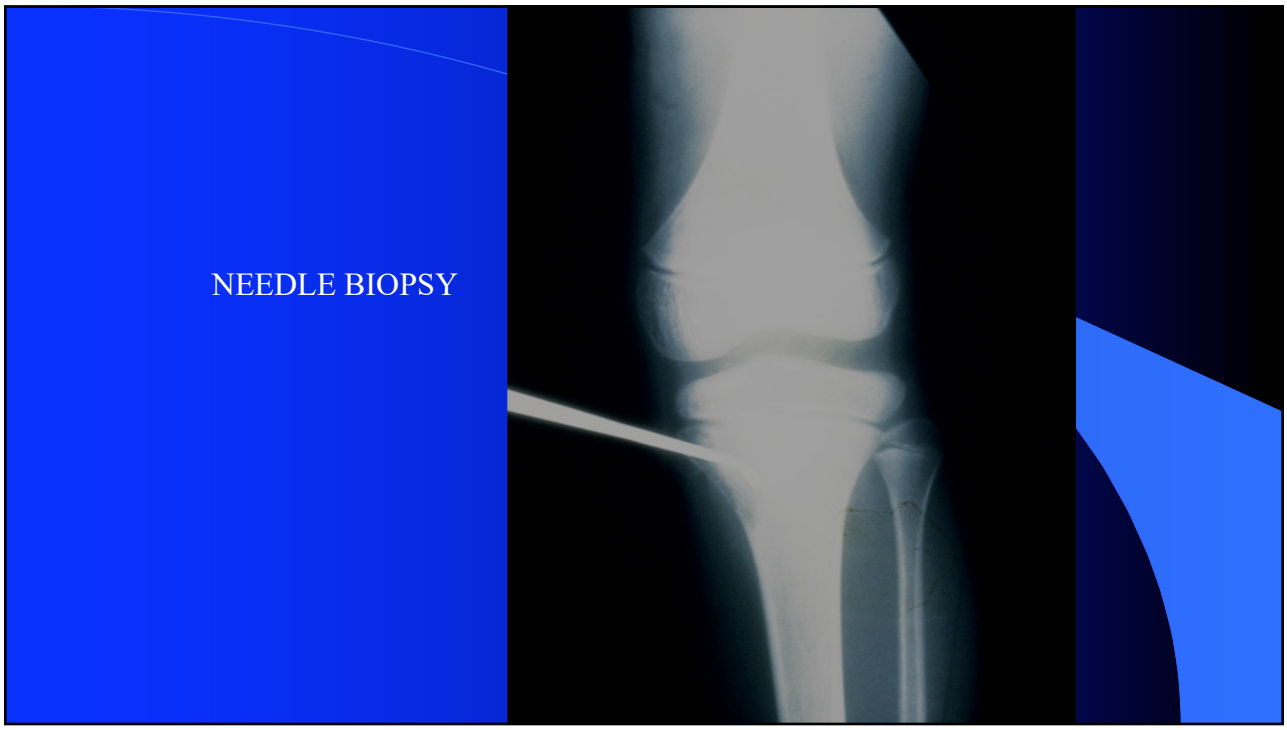

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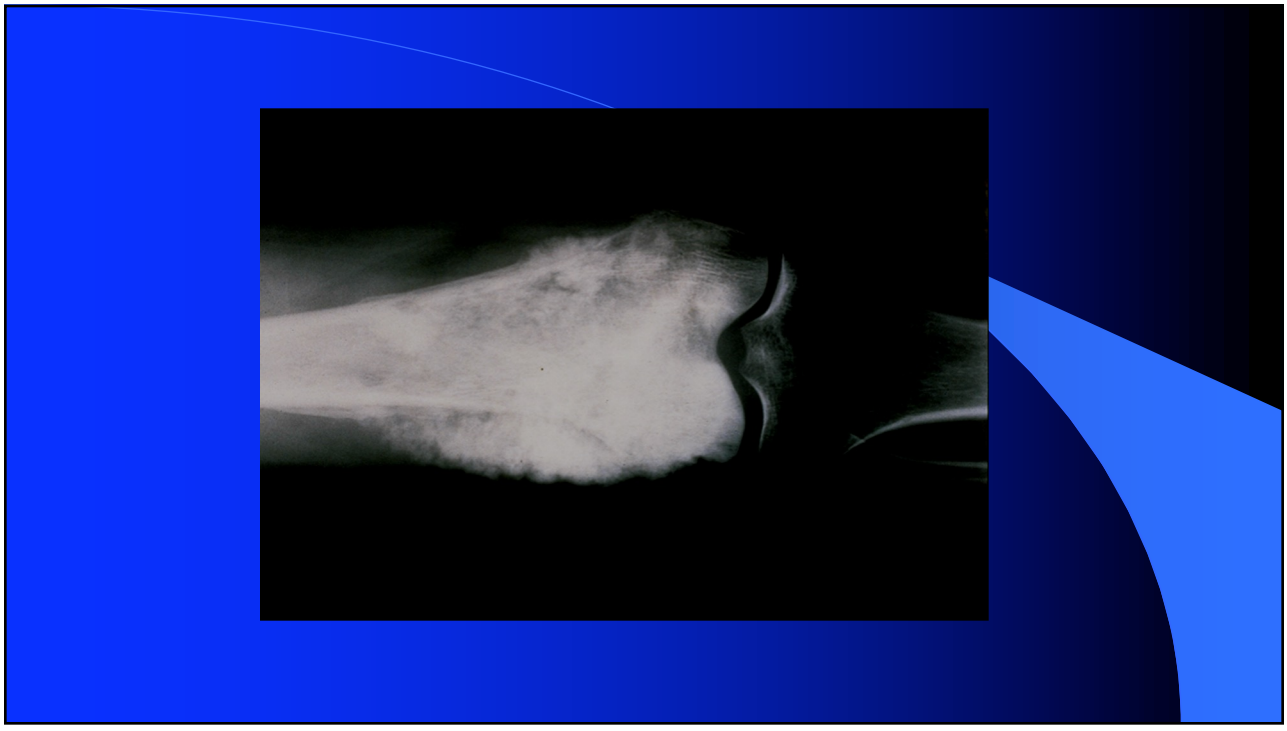

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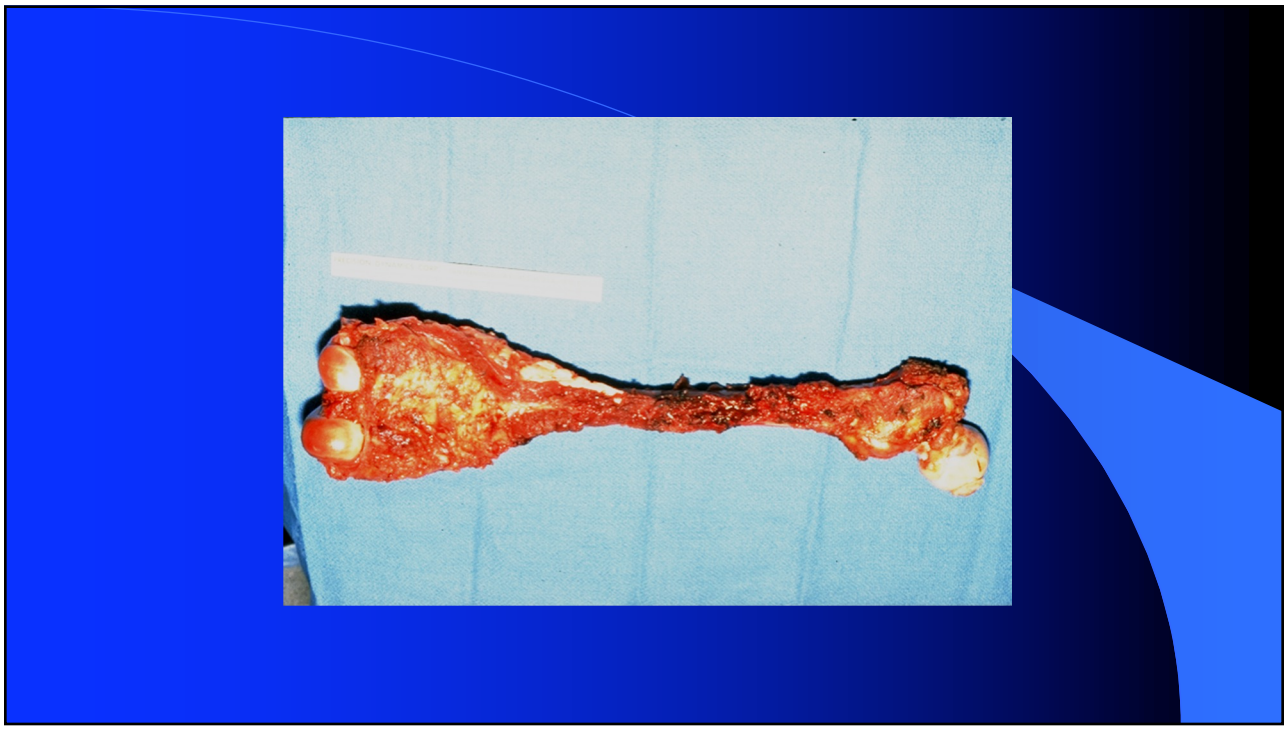


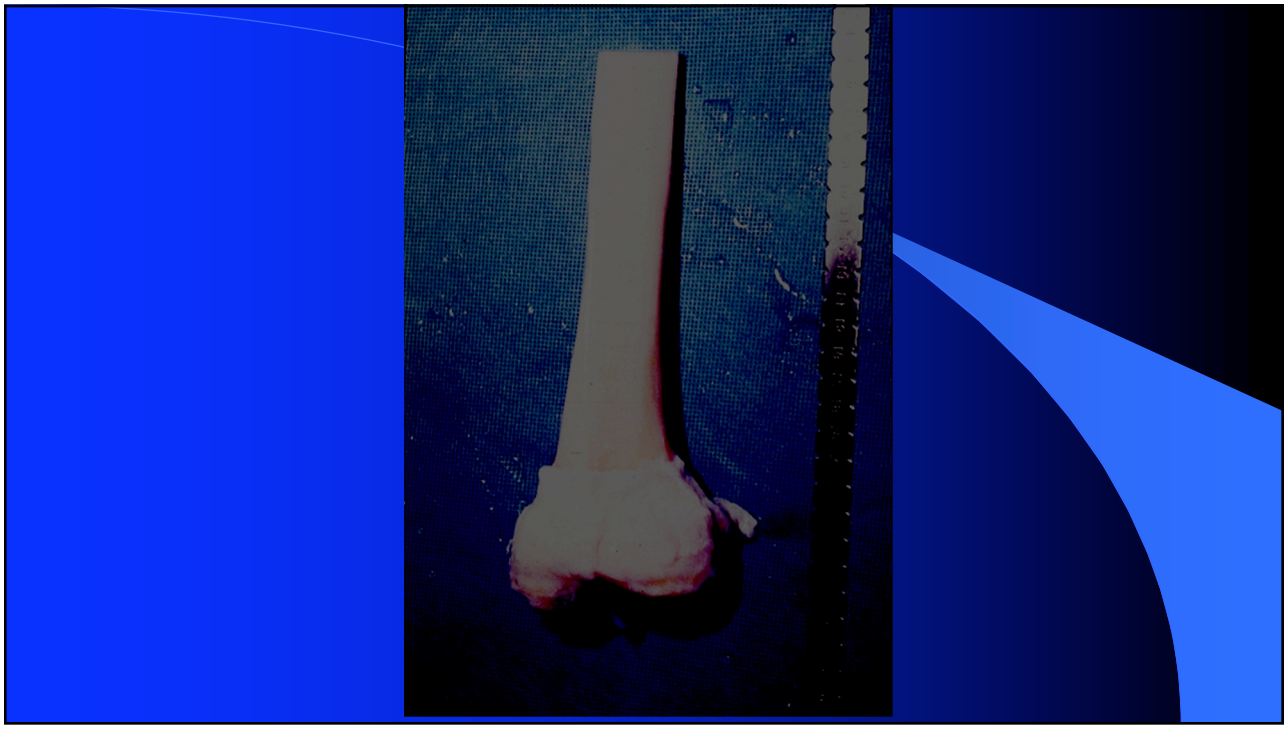
79

80

Osteosarcoma- Chemo

- Chemotherapy for local and disseminated disease control.
- Methotrexate, Cisplatinum, Doxorubicin pre- and post-operatively for 8-12 months
- Improves survival to ~ 75%
- Ifosfamide, carboplatin, etoposide (ICE) for relapses or non-responders

81



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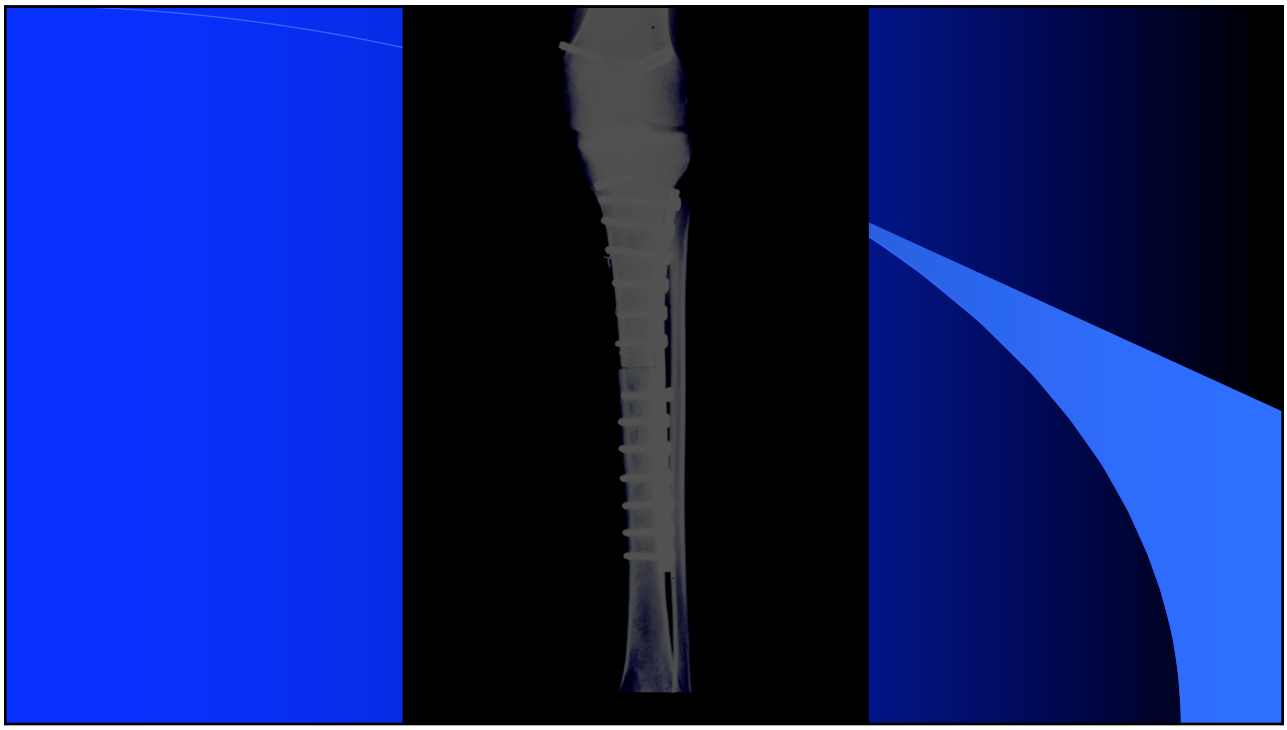

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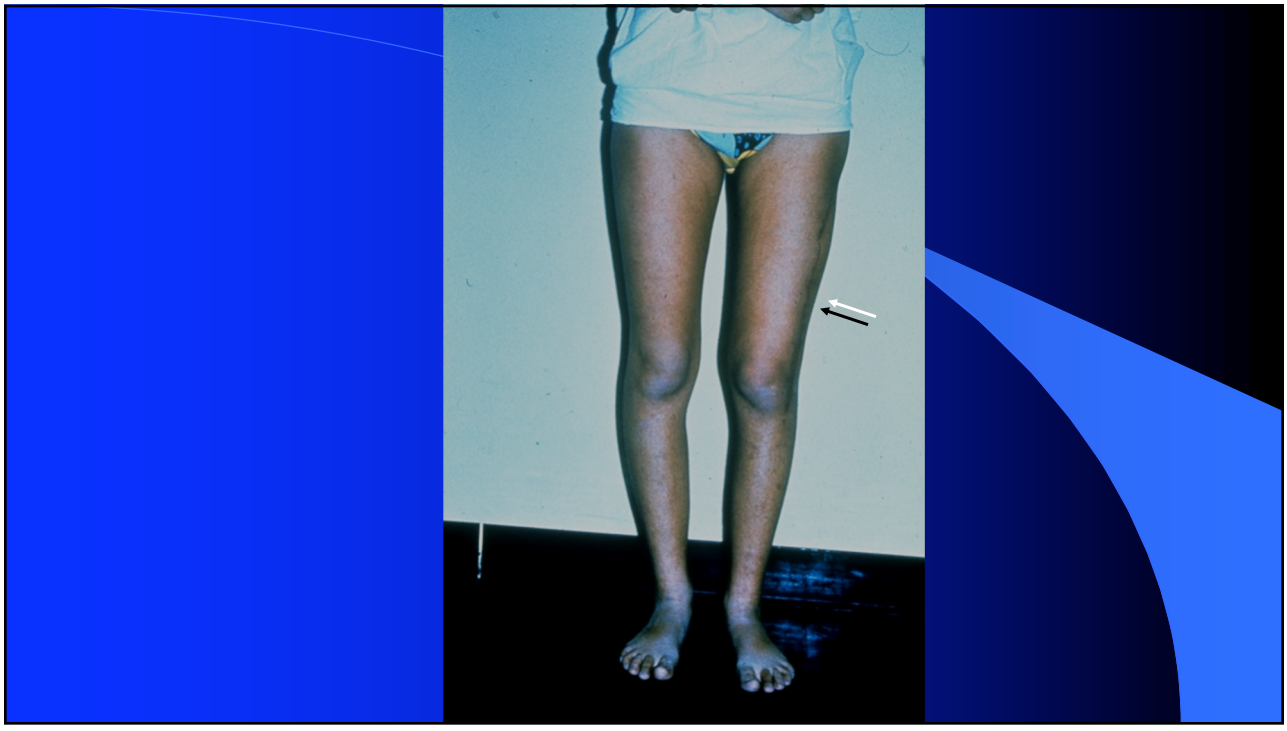

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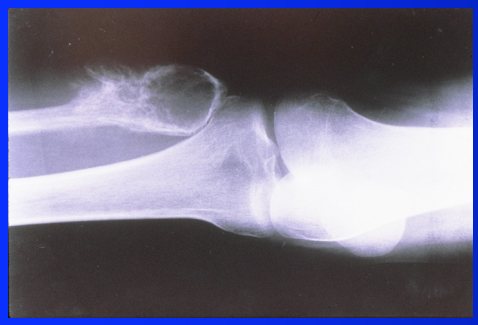
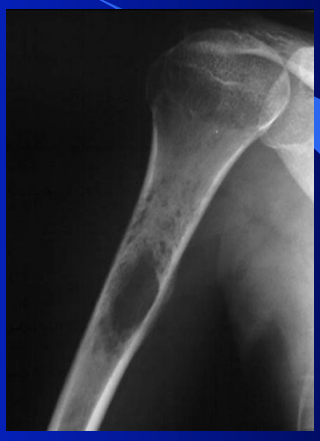
Ewing Sarcoma

- Malignant small blue round cell tumor of bone or soft tissue. Any bone can be involved.
- Onion skin appearance on X-ray
- Bone pain, fever, high LDH
- PAS stain+, Mic-2, CD-99, t(11;22), FISH
- Lung, bone , and bone marrow mets
- Chemotherapy VAC, surgery, +/- radiation

85





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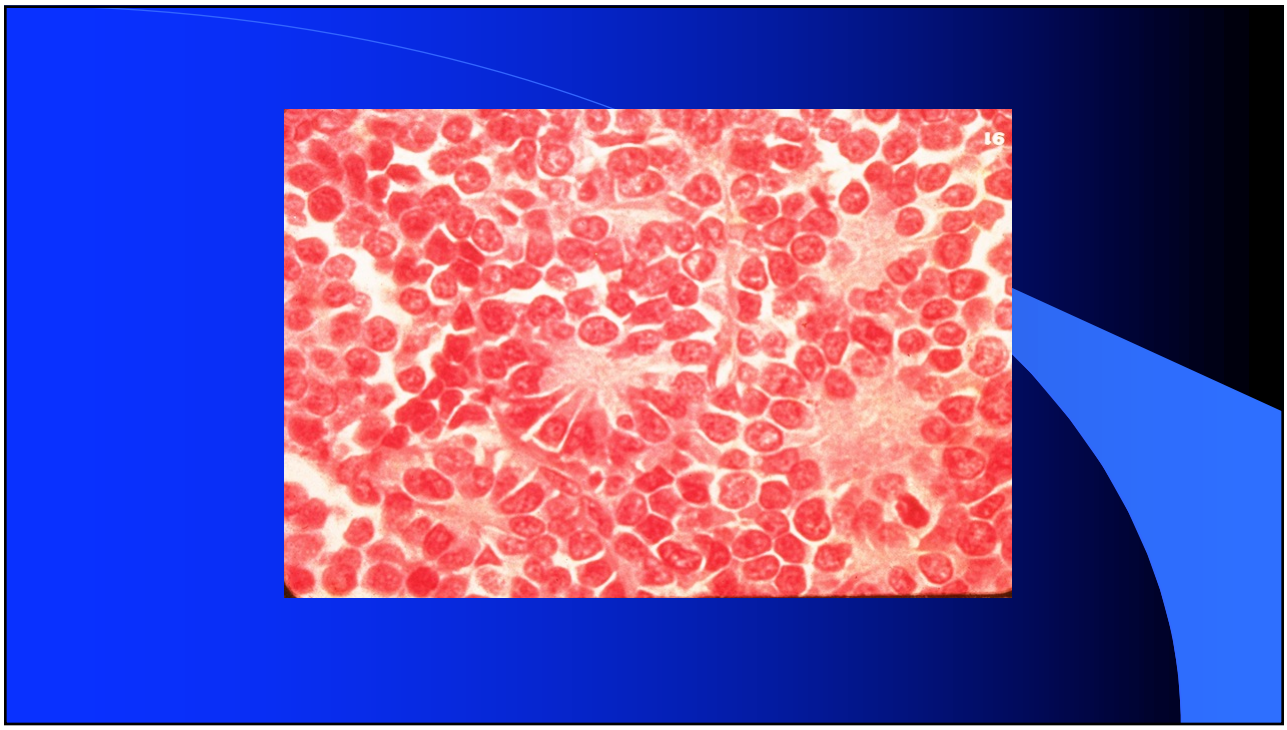

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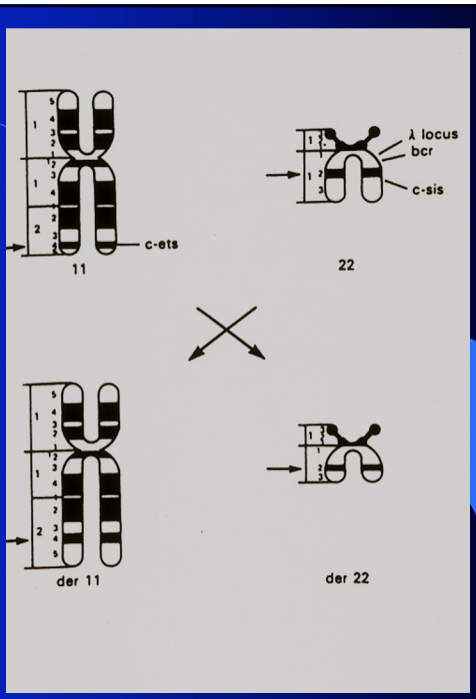
EWINGS / PNET
CHROMOSOMAL ANALYSIS

t (11;22) (q24;q12)

EWS/FLI1 fusion



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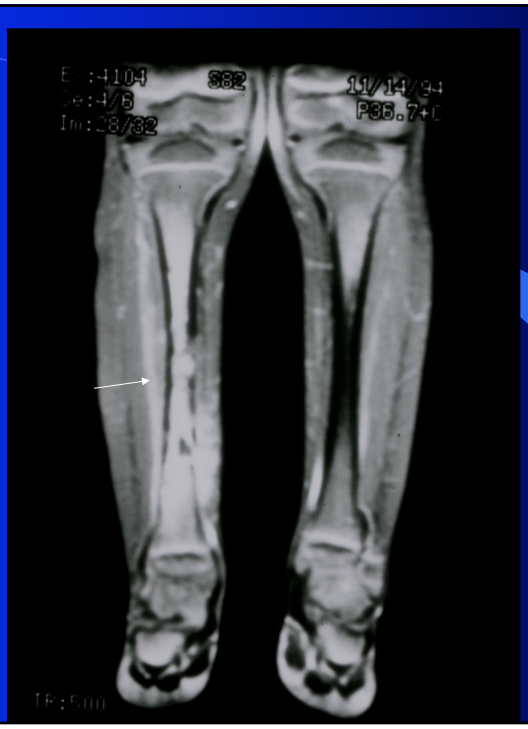
EWING SARCOMA



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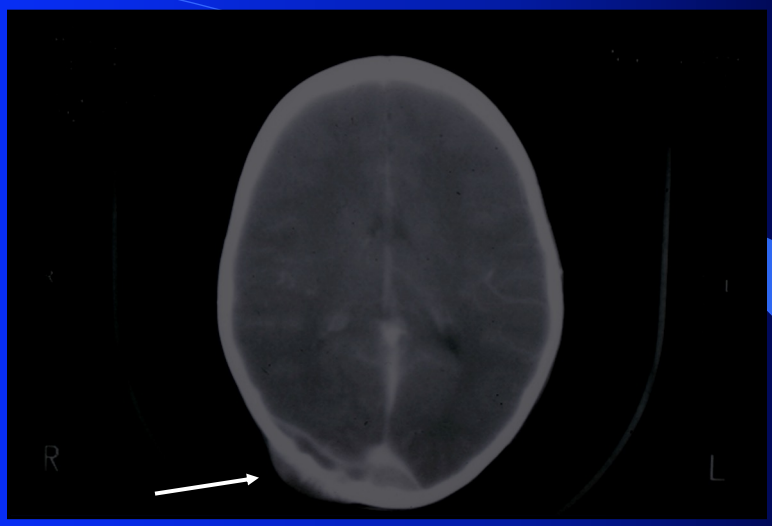

EWING SARCOMA – SKULL METASTASIS

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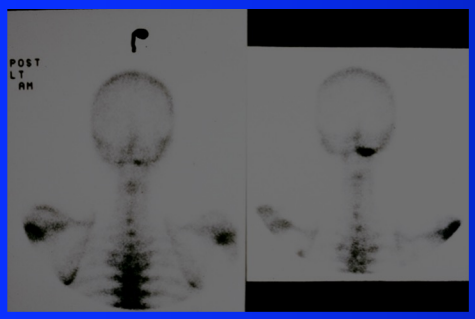
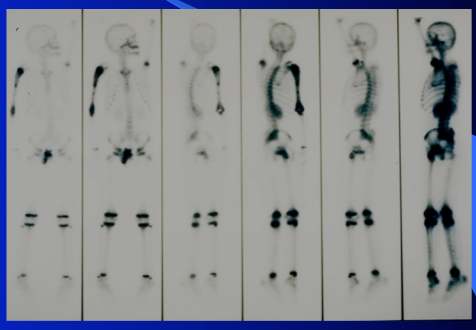


BONE SCAN- SKULL METASTASIS



Humerus Lesion

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Langerhan Cell Histiocytosis

- LCH affects patients from neonates to adults. The age at onset varies according to the variety of LCH.
- Unifocal
  - Localized eosinophilic granuloma occurs mostly frequently in those aged 5-15 years.
- Multi-focal
  - The chronic multifocal form, including Hand-Schüller-Christian syndrome, has a peak of onset in children aged 2-10 years.
- Multi-system
  - Letterer-Siwe disease occurs predominantly in children younger than 2 years.

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LCH

- Classic Triad of Hand-Schüller-Christian syndrome
  - **Lytic bone lesions (esp. Skull defects)**
  - **Diabetes Insipidus**
  - **Exophthalmos**
- Oral Changes
  - **Gum swelling and necrosis**
  - **Extrusion of teeth**
- Rash
  - Papular, seborrheic or petechial rash
  - Minute xanthomatous Nodules
  - Raised yellow to brown lesions in neck and axilla
- Growth retardation
- Developmental delay
- Lung changes- honeycomb appearance

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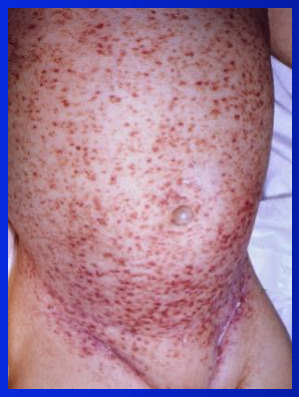
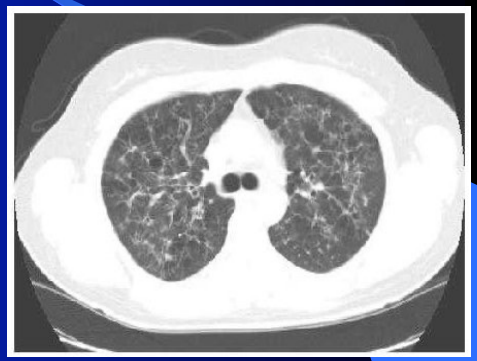
Histiocytosis





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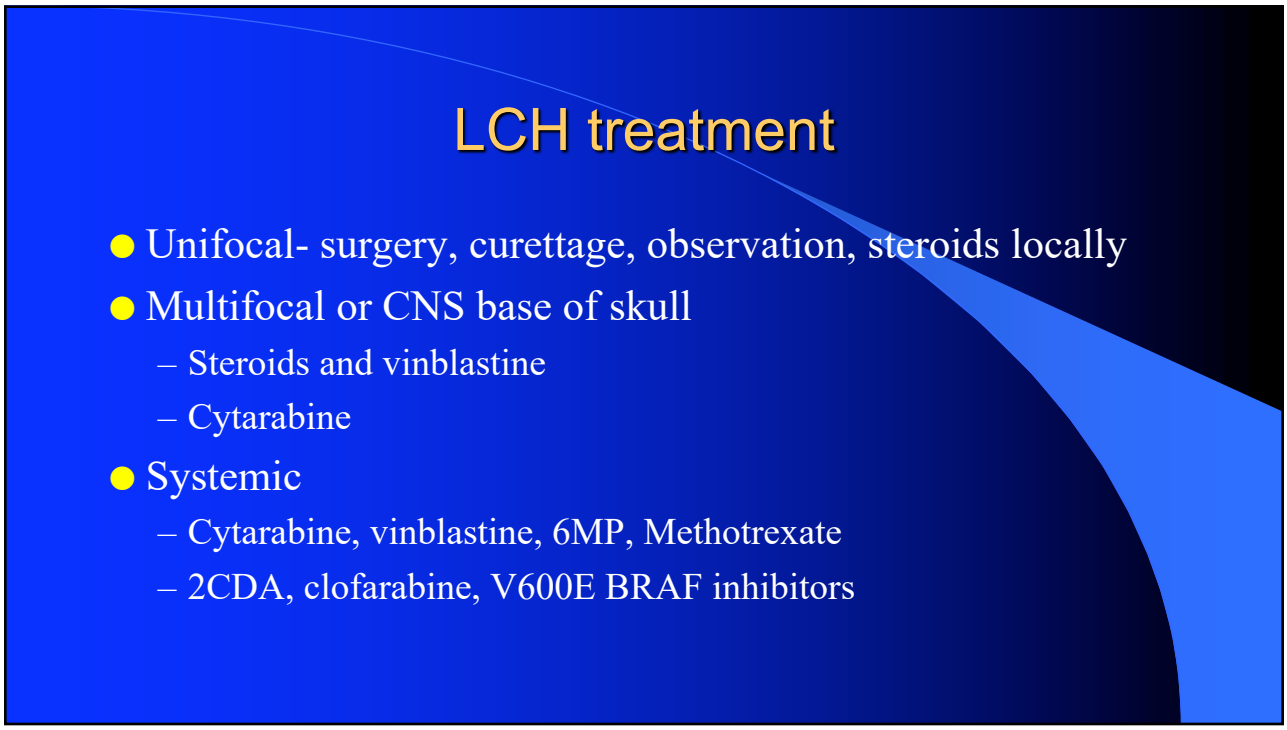
LCH treatment
Unifocal- surgery, curettage, observation, steroids locally
Multifocal or CNS base of skull
– Steroids and vinblastine
– Cytarabine
Systemic
– Cytarabine, vinblastine, 6MP, Methotrexate
– 2CDA, clofarabine, V600E BRAF inhibitors

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