Paediatric Malignancies

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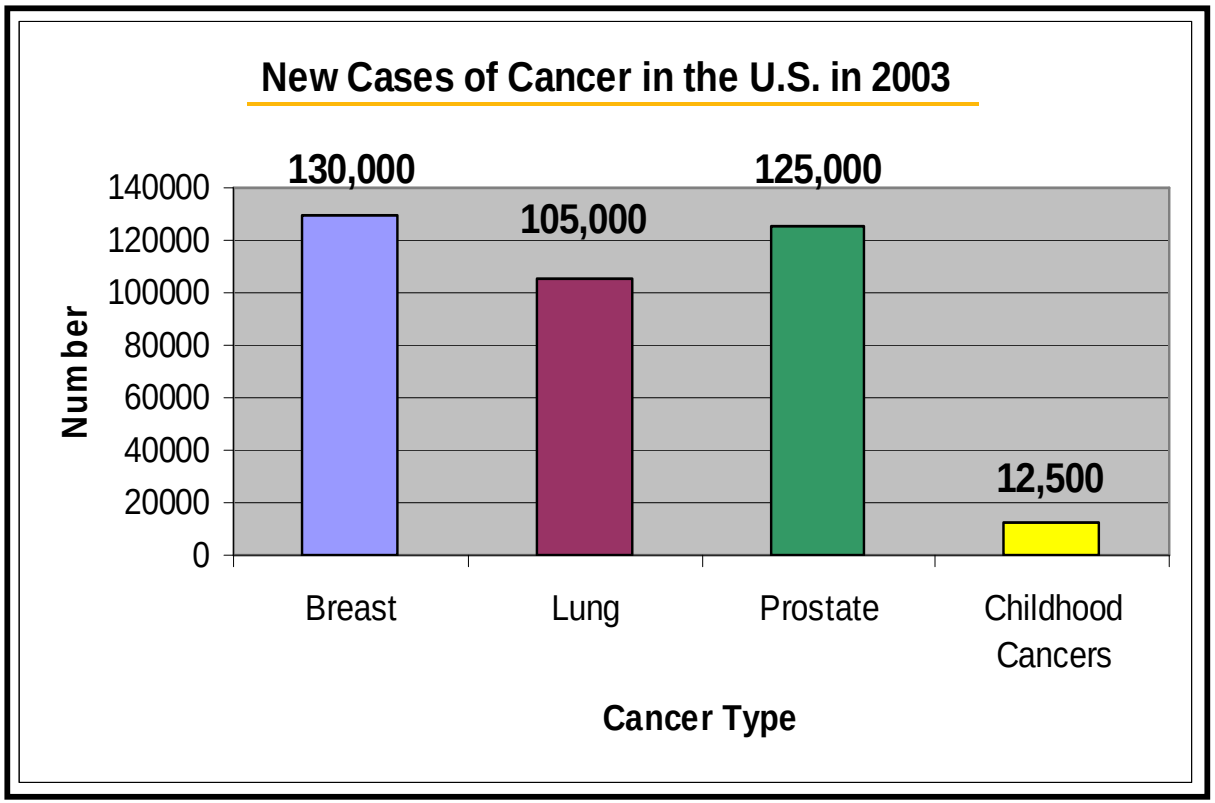
First Take Home point

- Childhood Cancer is a rare disease…



BUT…

- **One in every 330 Americans develops cancer before age 20.**

- **1 in 750 20-year-olds alive in the U.S. today is a survivor of childhood cancer.**

More Statistics

* **Over 3,000 children die from cancer yearly in the U.S.**
  - More than from AIDS, asthma, diabetes, and cystic fibrosis combined

Earlier diagnosis and referral can impact outcome

PNG Picture

TABLE 1

DIAGNOSIS OF CHILDREN WITH CANCER AT PORT MORESBY GENERAL HOSPITAL

Diagnosis	Number (%)
Lymphoma	19 (30)
Burkitt's	11 (17)
Non-Hodgkin's	6 (9)
Hodgkin's	2 (3)
Leukaemia	19 (30)
Acute myeloblastic	11 (17)
Acute lymphoblastic	4 (6)
Chronic myelocytic	4 (6)
CNS tumours	5 (8)
Neuroblastoma	5 (8)
Retinoblastoma	6 (9)
Wilm's tumour	5 (8)
Rhabdomyosarcoma	2 (3)
Ewing's sarcoma	1 (2)
Phaeochromocytoma	1 (2)
Craniopharyngioma	1 (2)
Total	64

CNS = central nervous system

Kiromat et al 2002; PNG Med J

Outcome of Cancer Treatment in PNG

OUTCOME BY DIAGNOSIS IN CANCER PATIENTS TREATED IN PORT MORESBY GENERAL HOSPITAL

Diagnosis	No	Treated	Remission	On treatment	Died	Lost
Wilm's tumour	5	5	2	0	3	0
Burkitt's lymphoma	11	10	3	0	6	2
Retinoblastoma	6	6	0	0	5	1
CNS tumours	5	0	0	0	5	0
Phaeochromocytoma	1	0	0	0	1	0
Craniopharyngioma	1	0	0	0	1	0
Rhabdomyosarcoma	2	2	0	0	1	1
Ewing's sarcoma	1	1	0	0	1	0
Neuroblastoma	5	3	0	0	4	1
Non-Hodgkin's lymphoma	5	4	0	0	4	1
Hodgkin's lymphoma	1	1	1	0	0	0
ALL	4	2	1	0	3	0
AML	11	0	0	0	11	0
CML	4	4	0	2	2	0
Total	62	38	7	2	47	6

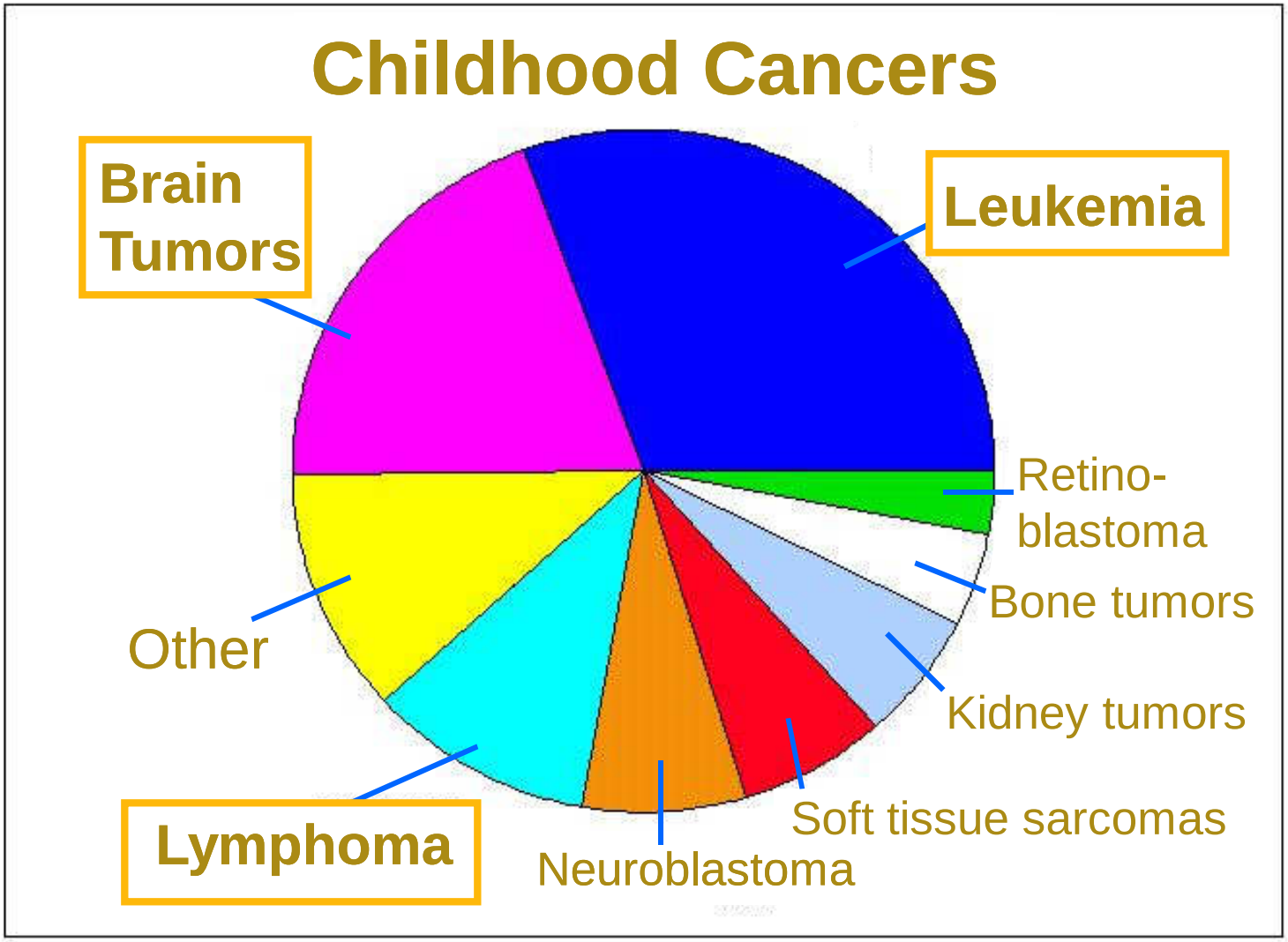
CNS = central nervous system
ALL = acute lymphoblastic leukaemia
AML = acute myeloblastic leukaemia
CML = chronic myelocytic leukaemia

76% mortality & 11% remission

Kiromat et al 2002; PNG Med J

Second Take Home points…

- Leukemia is the most common childhood cancer
- Brain tumors are second most common
- Lymphomas are the third most common
- Then solid tumors outside the CNS
  - Neuroblastoma - neural crest derived
  - Wilms - renal tumors and syndromes
  - Bone tumors
  - Rhabdomyosarcoma - soft tissue sarcomas


Childhood Cancers
Brain Tumors
Leukemia
Retino-blastoma
Bone tumors
Kidney tumors
Soft tissue sarcomas
Neuroblastoma
Lymphoma
Other

Pediatric Malignancies

- 1% of all cancers
- Involves tissues of:

  CNS, bone, muscle, endothelial tissue
- Grows in a short period of time

Causes

- Genetic alteration
- Environmental influences
- Metastasic disease seen in 80%

Response to Treatment

- Very responsive to chemotherapy
- More than 60% cure rate
- Cure rate in PNG - ? <20%.

Classification of Tumors

- Embryonal tumor arises from embryonic tissue
- Lymphomas = lymphatic tissue
- Leukemias = blood
- Sarcoma = seen in bone, cartilage, nerve and fat

Cardinal Signs of Cancer

- Unusual mass or swelling
- Unexplained paleness and loss of energy
- Spontaneous bruising
- Prolonged, unexplained fever
- Headaches in morning
- Sudden eye or vision changes
- Excessive – rapid weight loss.

Diagnostic Tests

- X-ray
- Skeletal survey
- CT scan
- Ultrasound
- MRI
- Bone marrow aspiration

Biopsy

- Identify cell to determine type of treatment

Treatment Modalities

- Determined by:
  - Type of cancer
  - Location
  - Extent of disease

Malignant Tumours

- Cancers in infants & childhood differ biologically & histologically from their counterparts occurring in adults.
- 1-2% of all malignant tumours occur in childhood.
- Leukaemia is the leading cause of death in US in children 4 -14 years of age.
- In children 4 -14 years age, malignant disease accounts for 9% of all deaths, behind accidents.
- **However, benign tumours more commoner.**

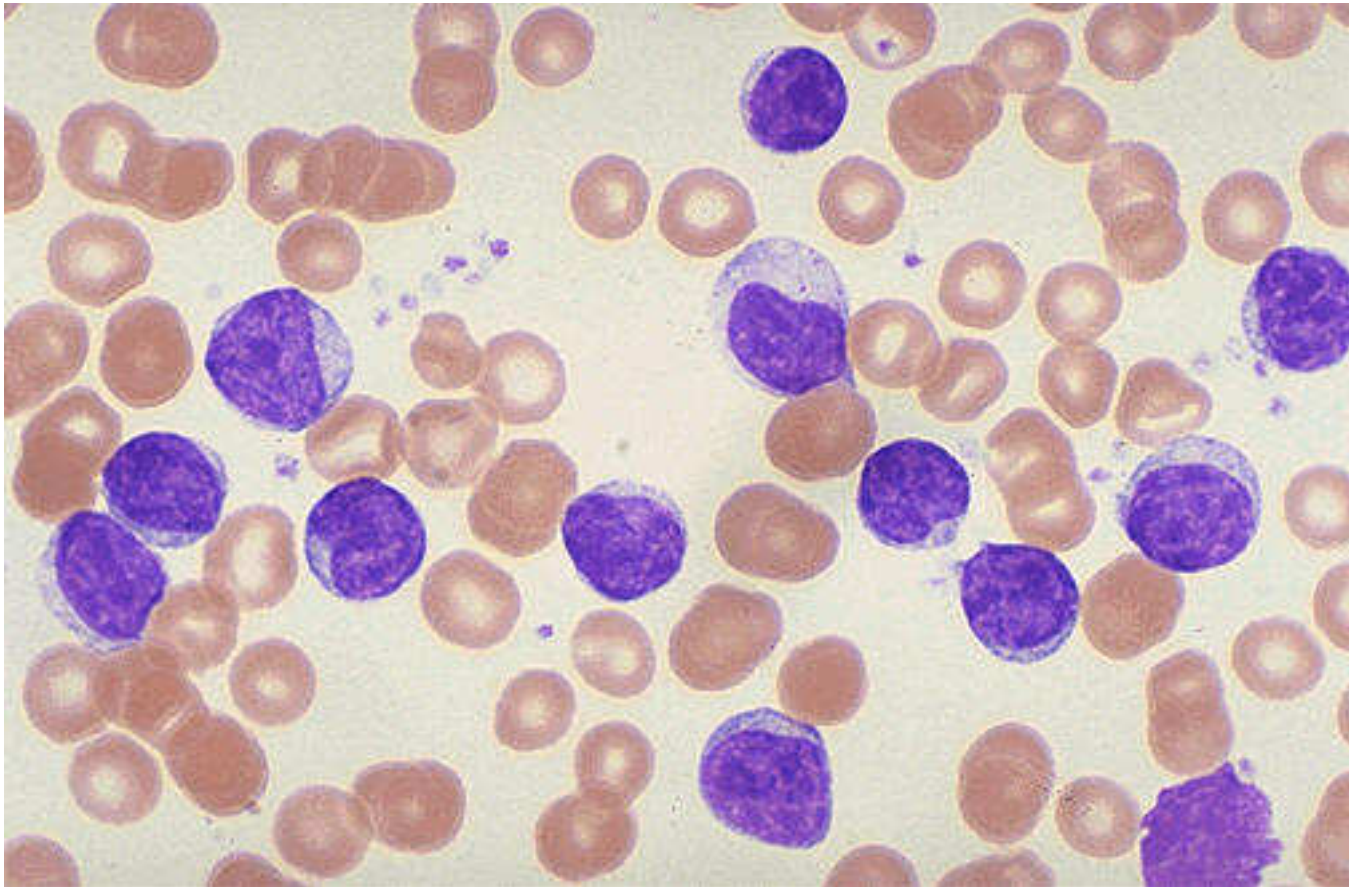
Common Malignant Neoplasm in Childhood

0 – 4 Years	5-9 Years	10-14 Years
Leukemia	Leukemia	Hepatocarcinoma
Retinoblastoma	Retinoblastoma	Soft tissue sarcoma
Neuroblastoma	Neuroblastoma	Osteogenic sarcoma
Wilm's tumour	Hepatocarcinoma	Thyroid carcinoma
Hepatoblastoma	Soft tissue sarcoma	Hodgkin disease
Soft tissue sarcoma (esp. Rhabdomyosarcoma)	CNS tumours	
Teratomas & CNS tumours	Ewing sarcoma & Lymphoma	

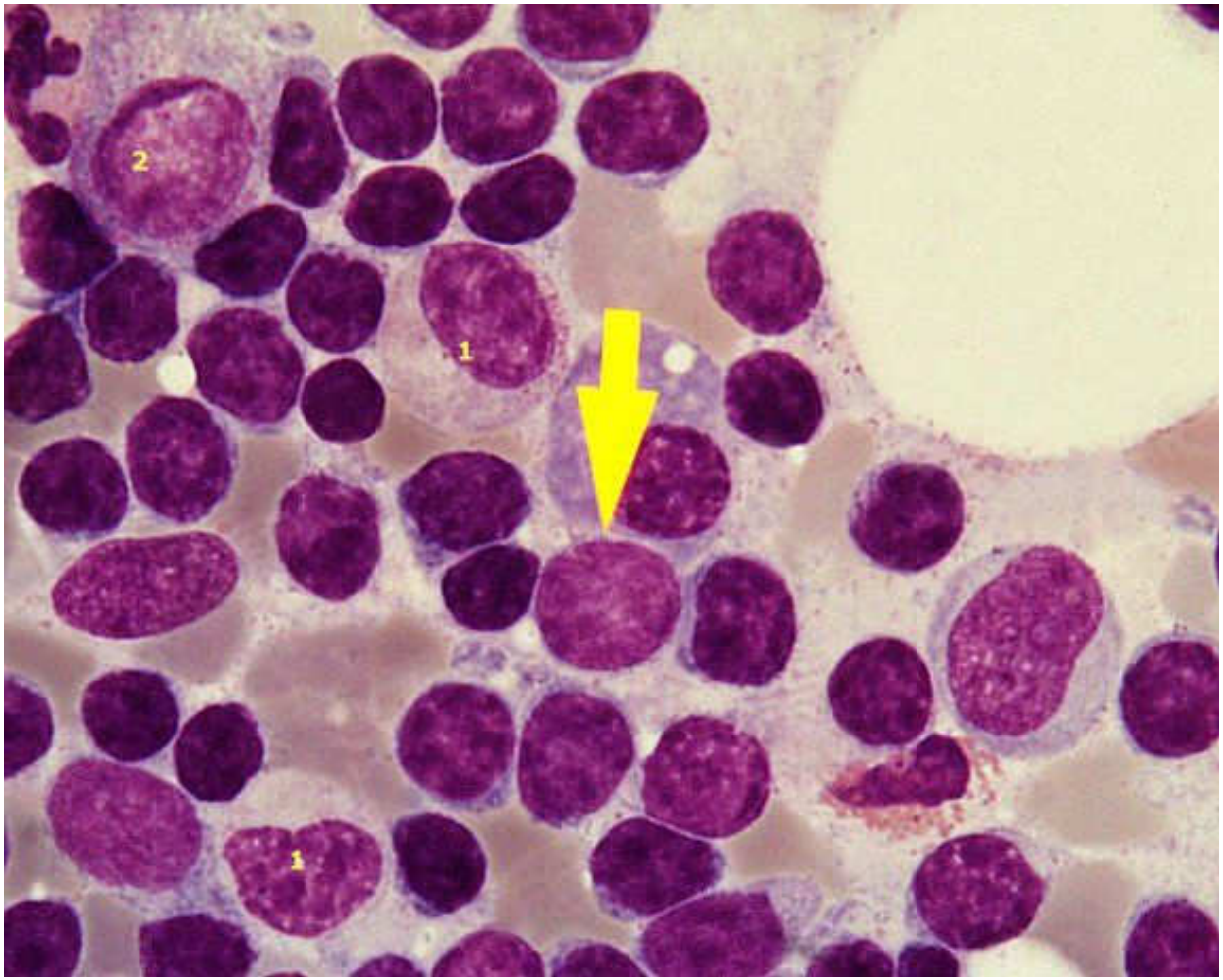
Leukaemia alone accounts for more deaths in children young than 15 years of age than all other tumors collectively.

Leukemias

Peripheral smear show lymphoBLASTS

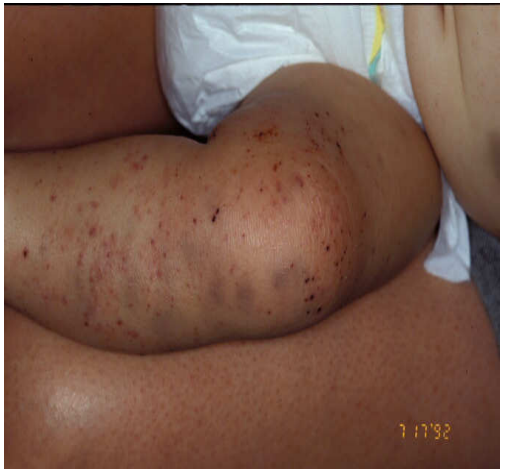


Bone marrow



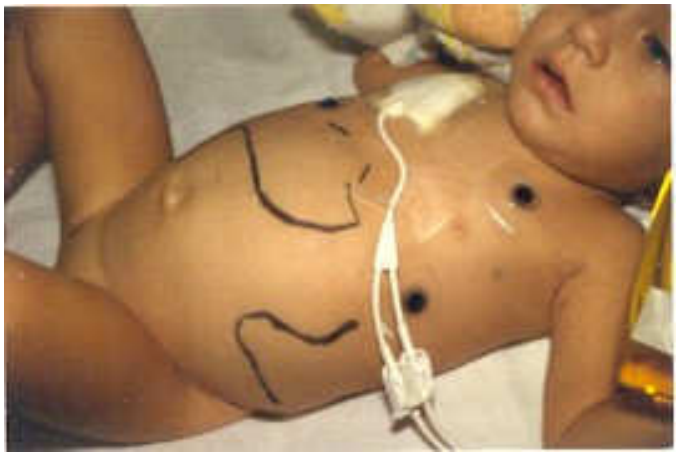
Leukemia: Signs and Symptoms

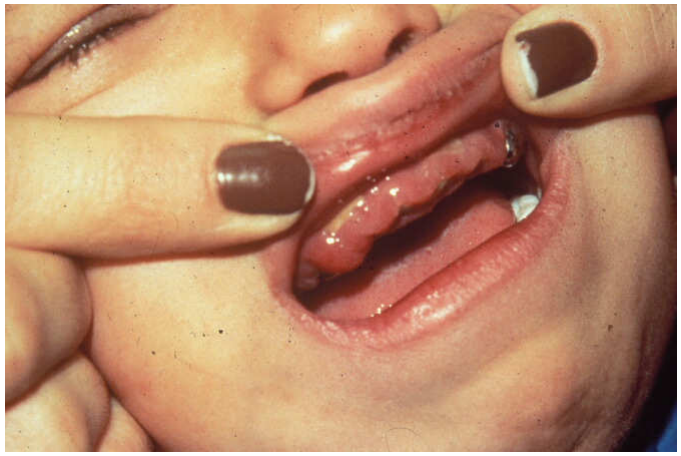
- **Bone marrow infiltration**
  - **Anemia**
    - Pallor, lethargy
    - Dyspnea, ↑murmur
  - **↓ Platelets**
    - Bleeding, petechiae, purpura
  - **Neutropenia**
    - Fevers and infections
  - **Bone pain**
    - Limp, ↓ walking, irritability



Leukemia: Signs and Symptoms

- **Extramedullary spread**
  - Lymphadenopathy
  - Hepatosplenomegaly
  - Orthopnea, cough
    - mediastinal mass
    - tracheal compression
  - Facial nerve palsy
  - Testicular enlargement
  - Skin lesions
  - Gingival hypertrophy
- **Fever of malignancy**





Monoblastic leukemia

CBC and Differential

Very helpful in the diagnosis ALL

↑**WBC** - 50%; nl or ↓WBC – 50%

+ blasts on smear in 80%

≥ **2 Cytopenias** - 95%

↓ Hgb - 80% ↓ Plts – 90%

↓ % Neutrophils – 90%

1 Cytopenia - 4%

Normal CBC and diff – 1%

Bone Marrow Biopsy for confirmation

CNS Tumors

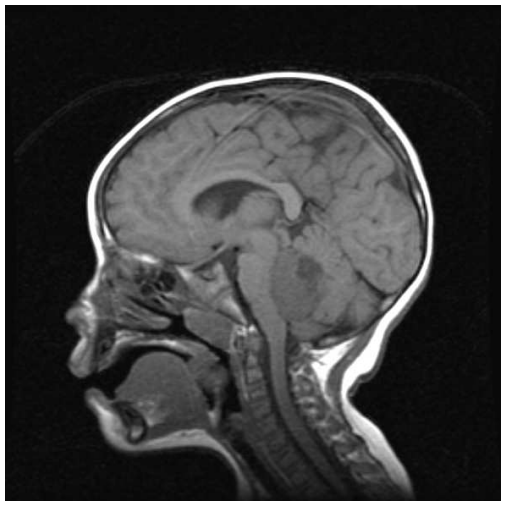
Brain Tumors of Childhood

Heterogeneous

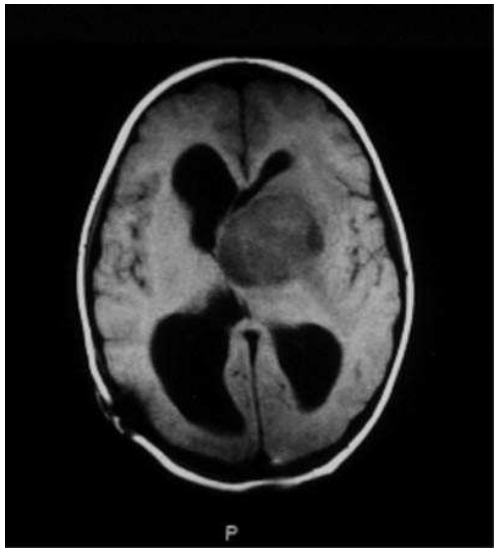
* Cell of origin:
  glial, neural, other, combination
* Location:
  - posterior fossa: 50%
  - supratentorial: 50%
* Clinical presentation:
  - **location**
  - **age**

Brain Tumors of Childhood

- **Infratentorial**
  50%
  esp < 6 y/o



- **Supratentorial**
  50%
  esp > 8 y/o



Nonlocalizing Signs of Brain Tumors

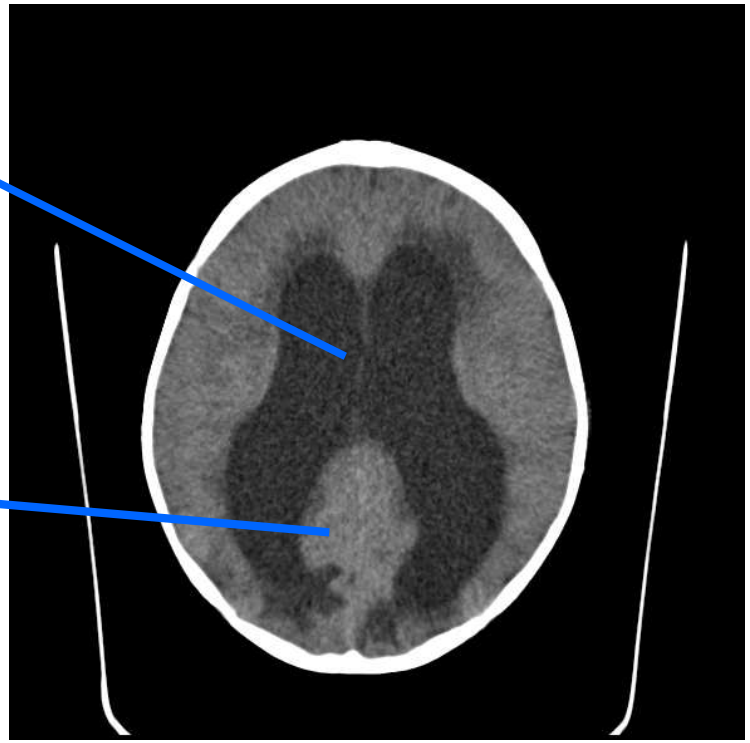
Increased intracranial pressure (ICP)

Obstructed CSF flow and hydrocephalus

Child is often asymptomatic until critical threshold reached

Medulloblastoma

Can grow very large before detection



Increased Intracranial Pressure (ICP)

- **Headaches, progressively worsening**
- **Vomiting (morning)**
- **Irritability**
- **Papilledema**
  - **rare < 2 y/o - head can expand**
- **"Double vision" with 6th nerve palsy**
- **Head tilt**
- **Bulging fontanel (infant)**

In a young child with ? brain tumor:
Measure head circumference and observe gait

Supratentorial Tumors

Signs depend on location and age

like in adults; in addition:

Younger child:

Developmental delay or loss of milestones

Older child:

Deteriorating school performance

Personality changes

Endocrinopathies:

DI, hypothyroidism, precocious puberty

Neuroblastoma & Ganglioneuroma

- Pathogenesis: N-myc gene (a proto-oncogene) amplification. The number of copies is related to the aggressiveness of the tumor.
- Catecholamine producing tumor thus urinary catecholamines and metabolites are same has pheochromocytoma.
- Hypertension is a common feature.
- 40% originates in the adrenal medulla and presents as a large abdominal mass. Rest occur along sympathetic chain – paraveterbral region of abdomen 25% & posterior mediasternum 15%.
- Occasionally converts to a more differentiated form termed ganglioneuroma (benign form) and reflects reduction in number of copies of N-myc gene products.

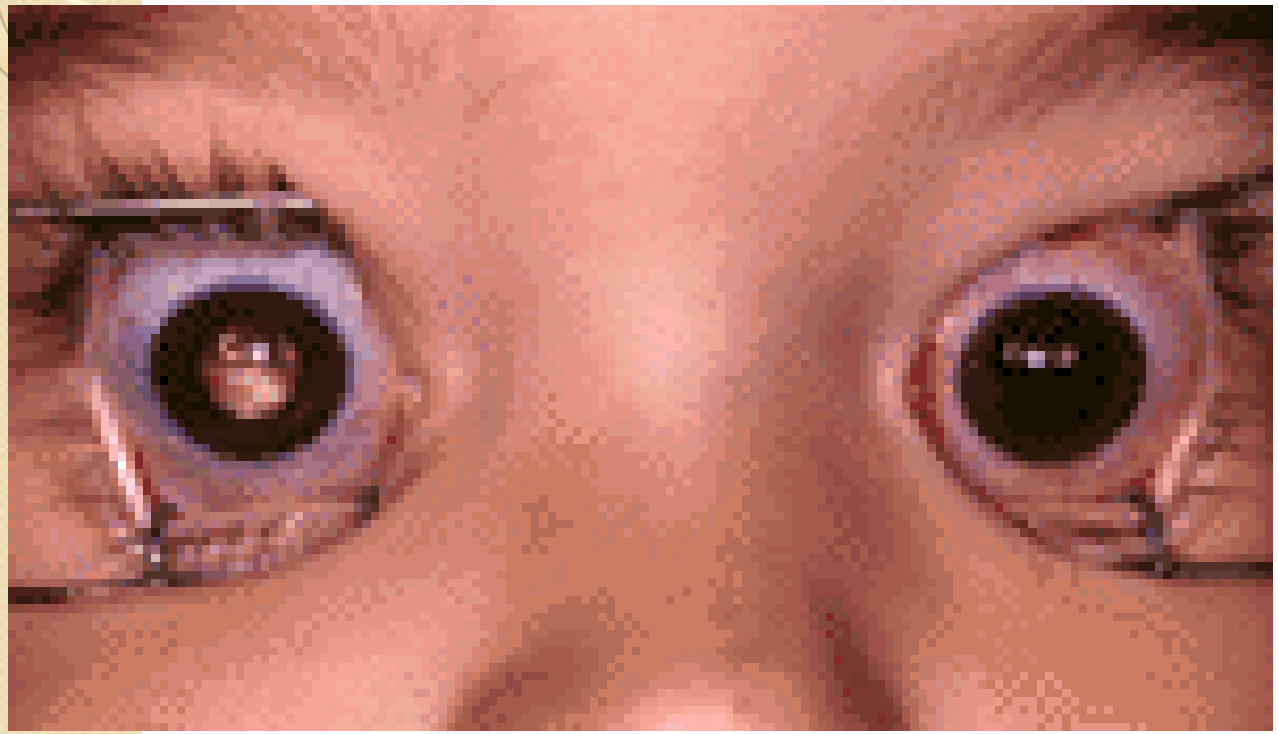
Retinoblastoma

- Intraocular / Embryonic tumor
- 1 in 16,000
- + family history
- High incidence of malignancies

Retinoblastoma

- Malignant retinal tumor
- Sporadic in 60% of cases; unilateral & monocentric in origin
- Familial in 40% of cases; bilateral & multicentric in origin
- Pathogenesis: homozygous deletion of the Rb gene, a tumor suppressor gene (chromosome 13 at band q14).

Retinoblastoma



Pupil reflex

"Cat Eyes"

http://www.djo.harvard.edu/meei/PI/RB/RB.html

Retinoblastoma

http://homepage.idx.com.au/muznsam/

Lymphomas

Lymphoma

- Generally classified into Hodgkin lymphoma and Non-Hodgkin lymphoma
- Affects children between 4-9 yrs of age.
- Clinical cure is possible with aggressive therapy.
- Reed-Sternberg cells are the defining characteristic feature. Severity of the disease is directly proportional to the number or RS cells.

Non-Hodgkin lymphoma

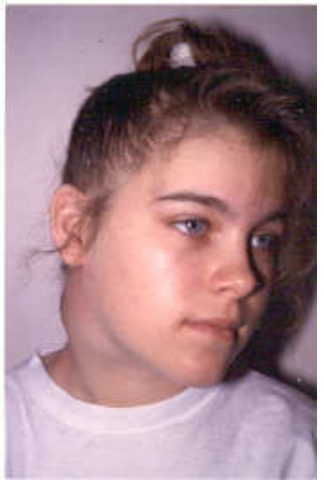
- Heterogeneous group of lymph node neoplasm originating from B & T lymphocyte.
- Sites: lymph node, BM, spleen or extra-nodal tissue (e.g. GIT – MALT).
- Multiple lymph nodes (migratory nature of lymphocytes). Contrast this with Hodgkin lymphoma.
- Burkitt lymphoma is common in children.

.

Childhood Lymphomas

- **Signs and Symptoms depend on:**
  - Lymphoma subtype
    - Hodgkin's Disease (HD)
    - Nonhodgkin's Lymphoma (NHL)
      - **Burkitt's**
      - **Lymphoblastic**
      - **Anaplastic Large Cell**

Presentation of Hodgkin's Disease



- **Age:** adolescents >> young child
- Painless lymphadenopathy
  - Progresses over weeks → months
- **Location**
  - **Cervical/supraclavicular ↑ LNS**
    - unilateral or bilateral
  - **Mediastinum ± hilum**

95%

  - LNs below diaphragm and spleen
  - Liver, lung, bone marrow

Presentation of Hodgkin's Disease

- Systemic symptoms
  - **Fevers**
  - **Night sweats**
  - **Weight loss**
  - Pruritus

} **"B" symptoms** 25%

- Superior Mediastinal Syndrome (SMS)
  - Orthopnea, SOB, stridor, hypoxia
    - Tracheal
    - Bronchial
    - Cardiac

} compression

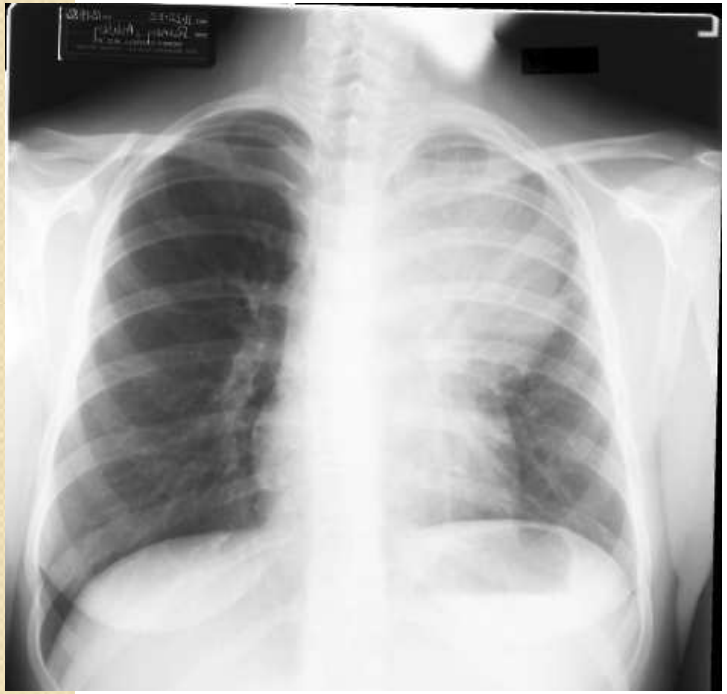
= Oncologic Emergency

What is the Test to get?

HD in 16 y/o girl

↑ left cervical LNs, 40 # wt loss

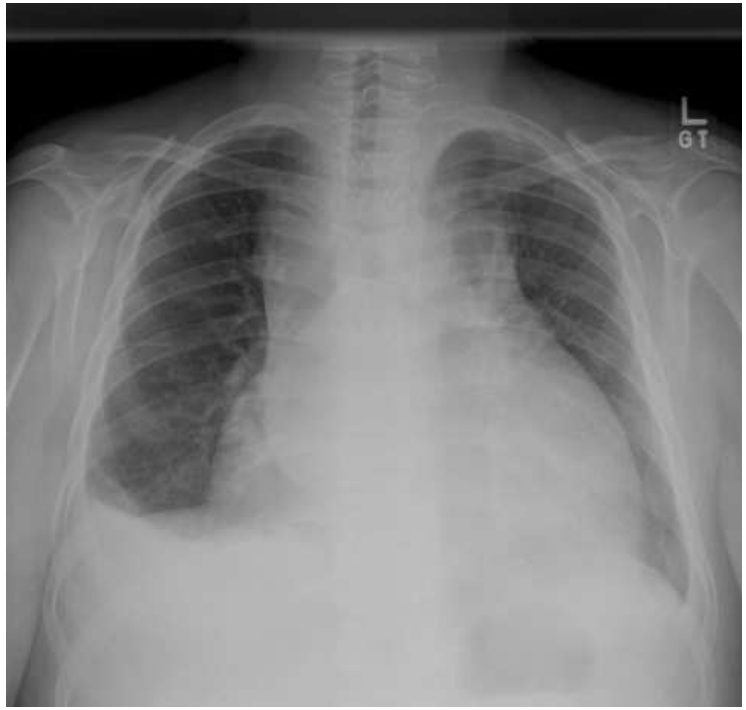
cough, no orthopnea



HD in 9 y/o boy

cough, fever, night sweats

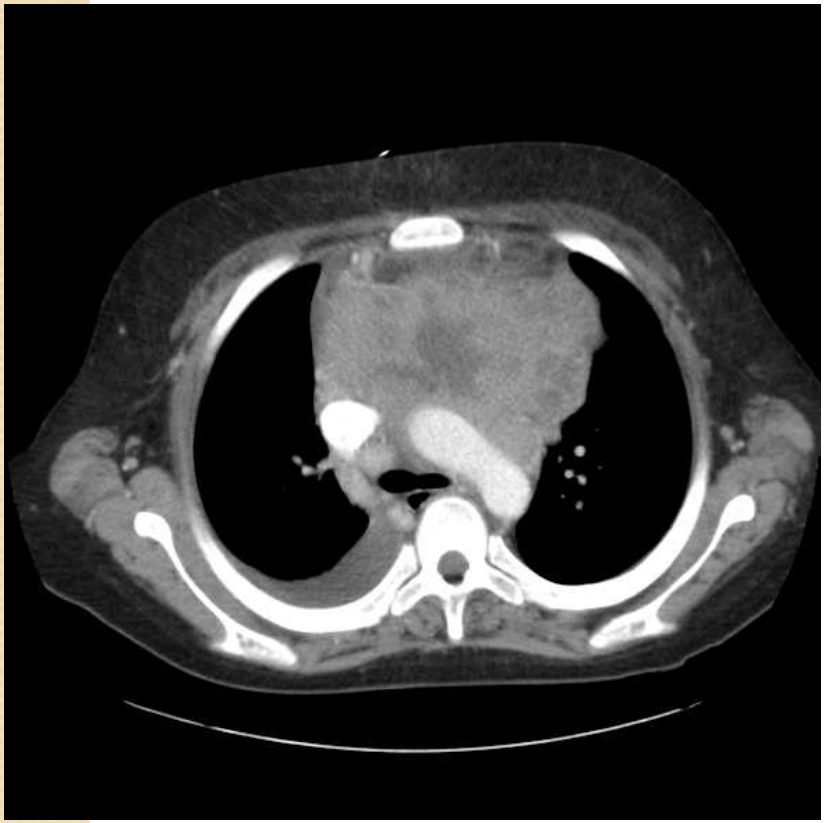
Pruritus shins, + orthopnea



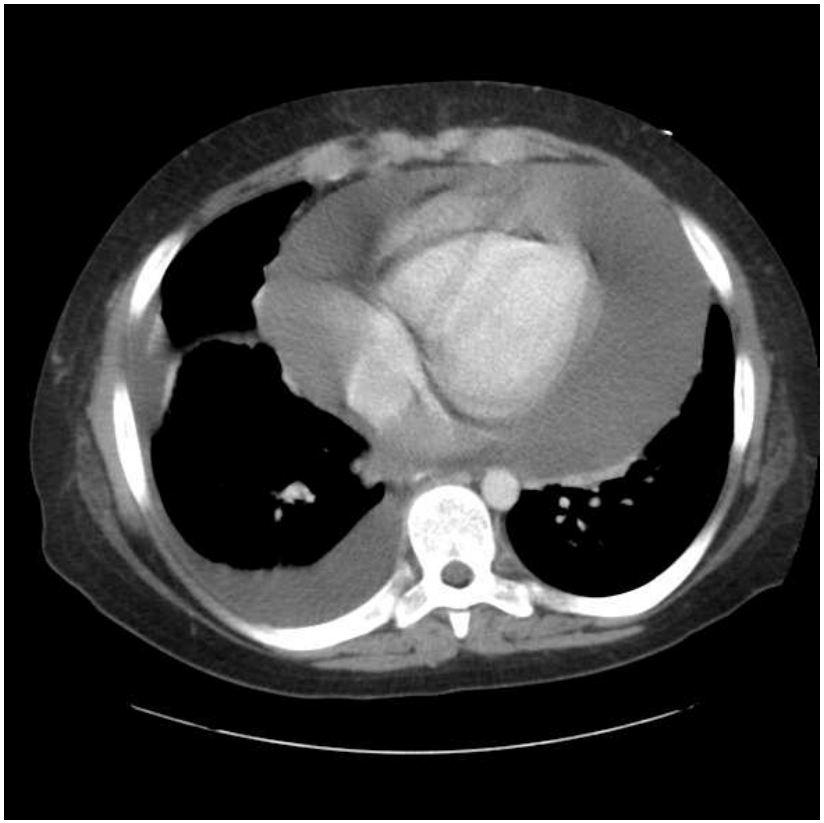
Superior Mediastinal Syndrome (SMS)

= Oncologic Emergency

HD – 9 y/o CT scan with SMS



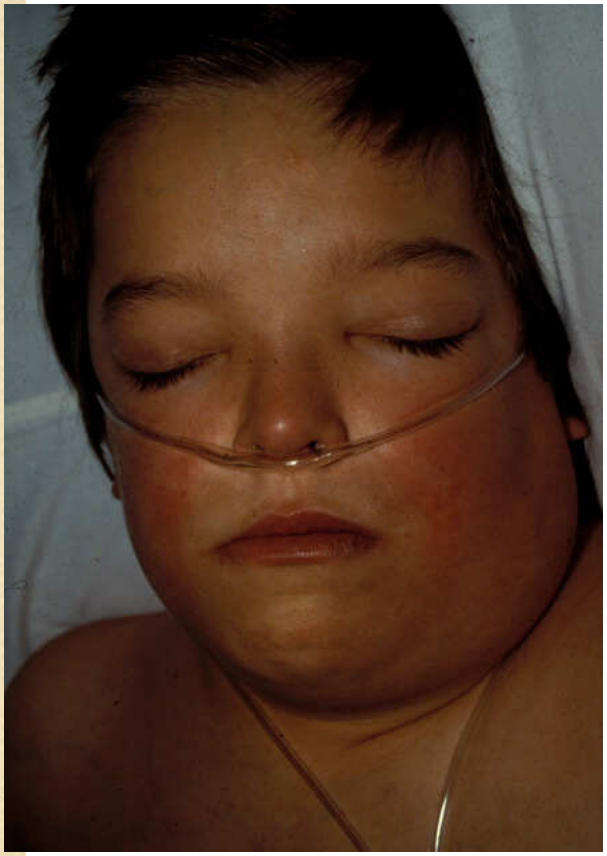
Ant. mediastinal mass compressing trachea; Pleural effusion

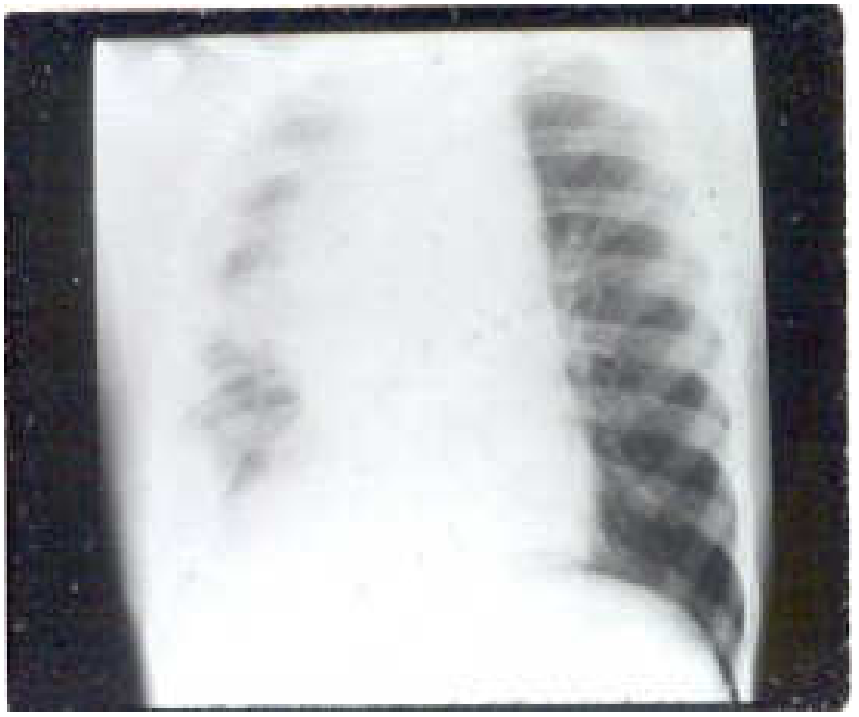


Pericardial effusion with tamponade

Superior Vena Cava (SVC) Syndrome in 10 y/o with **Lymphoblastic Lymphoma**

Facial swelling, plethora, cyanosis, □ neck veins



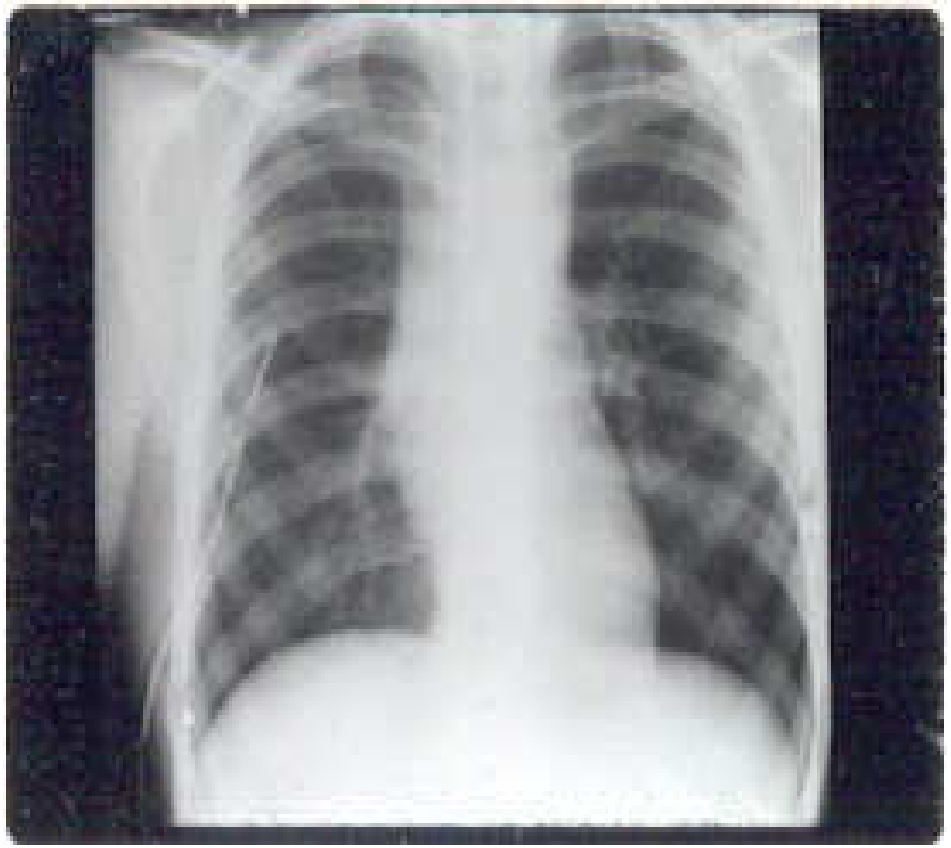


Mediastinal mass: tracheal and SVC compression

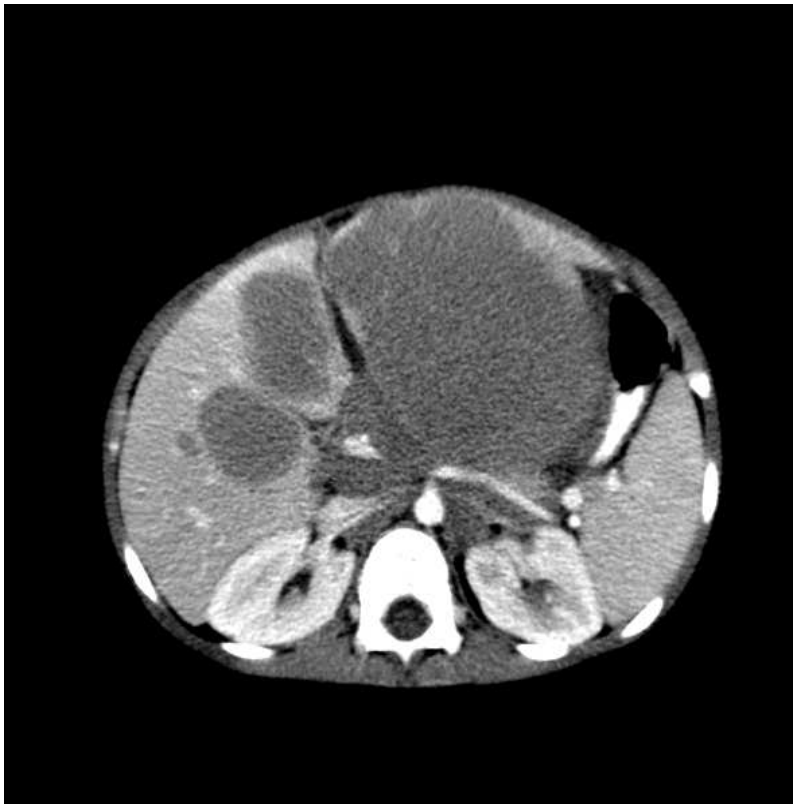
Lymphoblastic Lymphoma (T-cell, thymus)

Same boy 1 week after initial treatment

- **rapid onset**
- **rapid response**



Burkitt's Lymphoma



- **B-cell origin**
- **> 5 y/o**
- **Abdominal mass**
  - Large mass + ☐ LNs
  - Cecum or appendix
- **Nasopharynx**
- **Tumor lysis syndrome**
  - ☐ Uric acid, phosphorus, creatinine
  - Treatment can precipitate renal failure

= Oncologic Emergency

Tests

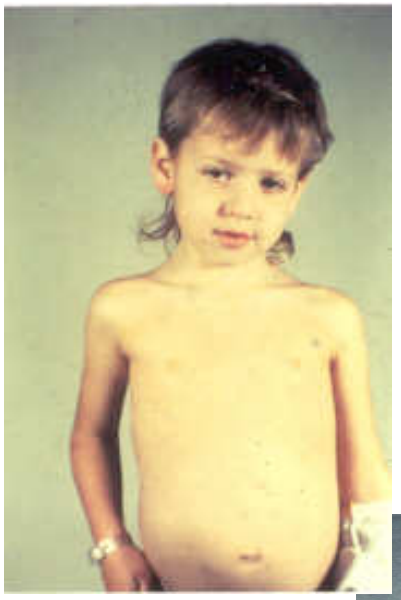
- FBC
- FNAC
- Lymph node biospy

Other Abdominal Tumors

Malignant Abdominal Masses

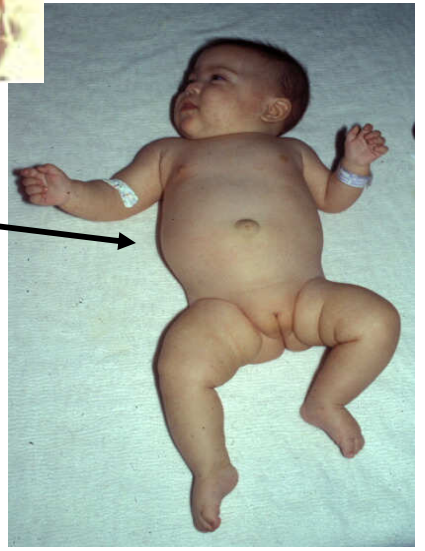
Most common:

- **Burkitt's lymphoma**
- **Neuroblastoma**
- **Wilms Tumor**



Other:

- Hepatoblastoma
- Rhabdomyosarcoma
  - –pelvic
- Ovarian germ cell tumors
  - – pelvic

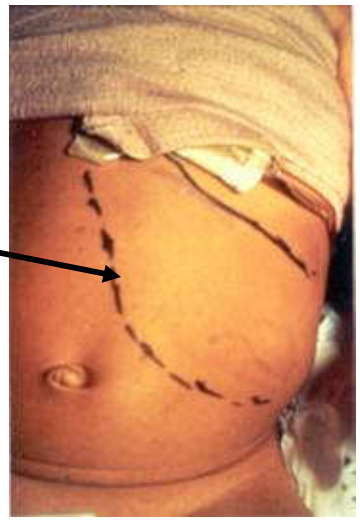


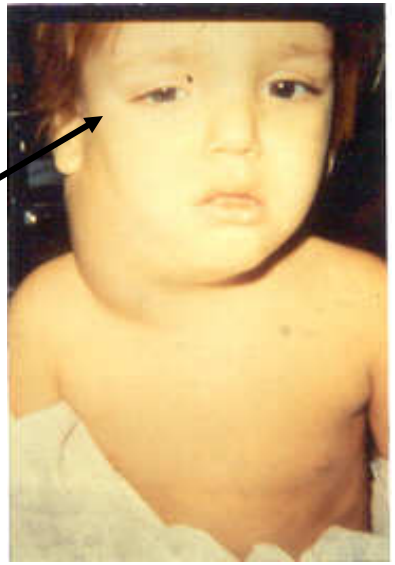
Neuroblastoma

- **Age**
  - 90% < 5 y/o; 50% < 2 y/o
  - Occasional USG detection *in utero*
- **Location:** any neural crest tissue
  - Adrenal
  - Paraspinal sympathetic tissue
    - Cervical, Thoracic, Pelvic
- **Often metastatic at diagnosis**
  - Bone and/or bone marrow
    - > 1 y/o: 70%

Neuroblastoma: Signs and Symptoms

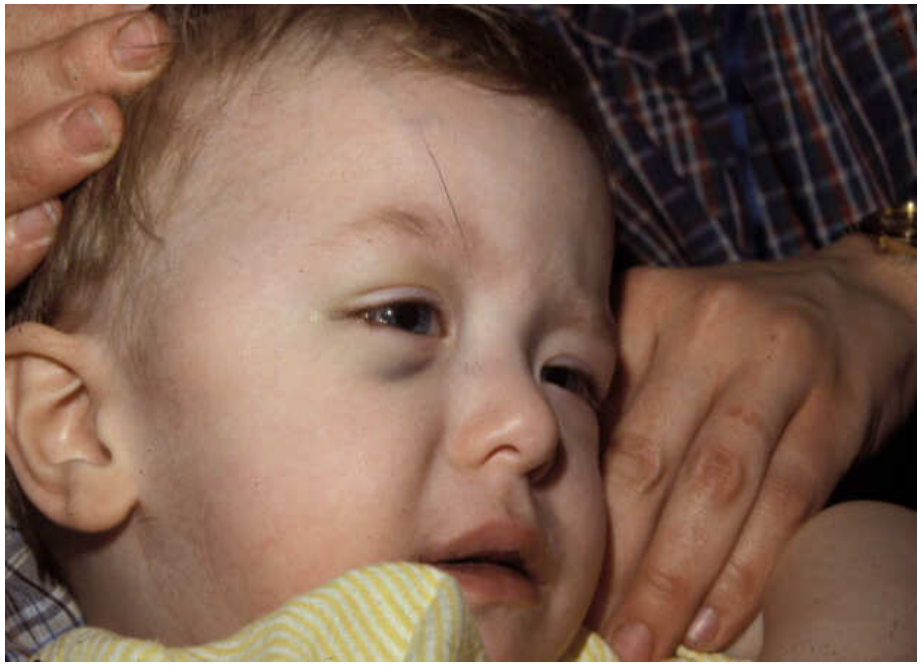
- **Abdominal mass**
  - Often crosses midline
- **Lower extremity weakness**
  - Spinal cord compression
    - Thoracic
    - abdominal
- **Cervical, high thoracic mass**
  - Horner's syndrome
    - Miosis, ptosis, anhydrosis



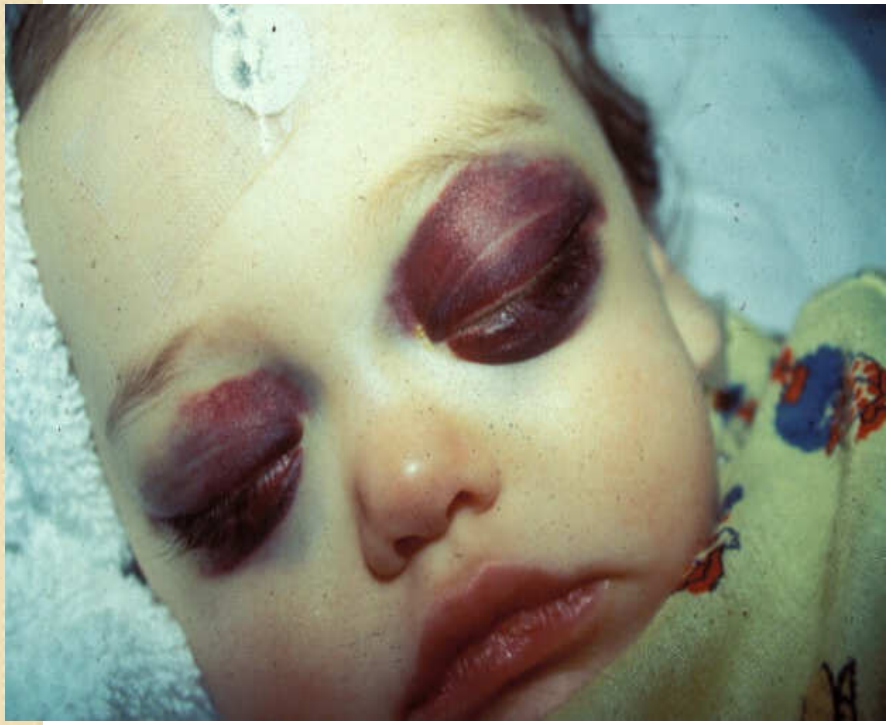


Neuroblastoma: Signs and Symptoms

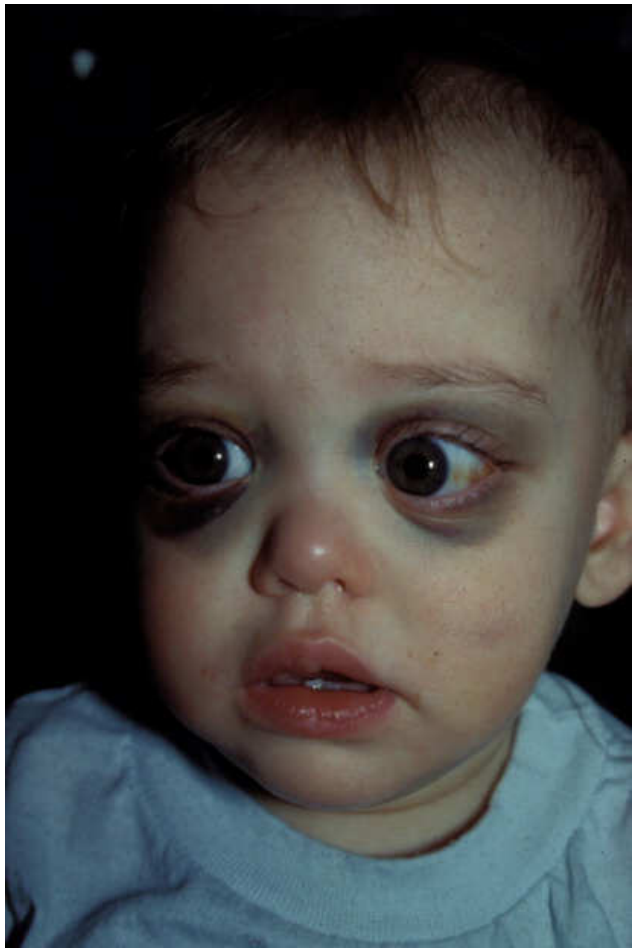
- Signs of metastatic disease
  - Irritability
  - Weight loss
  - Bone pain
  - Fever
  - Proptosis
  - Bone lesions
  - Periorbital ecchymoses



More Periorbital Ecchymoses of Neuroblastoma



13 months old at diagnosis



1 month into therapy

Neuroblastoma: Signs and Symptoms

- **Paraneoplastic syndromes**
  - Watery diarrhea – Vasoactive Intestinal Peptide
  - Opsoclonus-myoclonus, cerebellar ataxia
    - Cross-reacting antibodies
- **↑ Urinary catecholamines**
  - VMA/HVA – 85%
- **↑ BP** – 25%
  - Renal compression
  - Catecholamine secretion

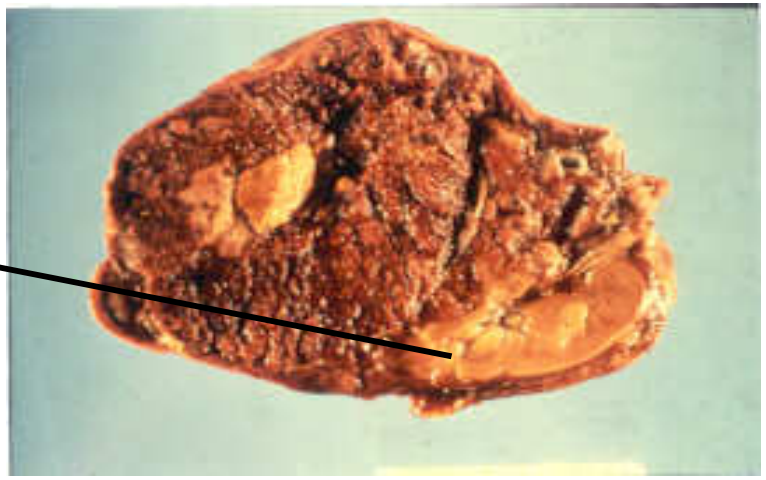


TABLE 10-11 -- Prognostic Factors in Neuroblastomas

Variable	Favorable	Unfavorable
Stage *	Stage 1, 2A, 2B, 4S	Stage 3, 4
Age *	≤ 1 year	>1 year
Histology *		
••Evidence of schwannian stroma and gangliocytic differentiation [a]	Present	Absent
••Mitotic rate [b]	Low	High
••Mitosis-karyorrhexis index [c]	≤200/5000 cells	>200/5000 cells
••Intratumoral calcification	Present	Absent
DNA ploidy *	Hyperdiploid or near-triploid	Diploid, near-diploid, or near-tetraploid
N-myc *	Not amplified	Amplified
Chromosome 17q Gain	Absent	Present
Chromosome 1p Loss	Absent	Present
Trk-A Expression	Present	Absent
Telomerase Expression	Low or absent	Highly expressed
MRP Expression	Absent	Present
CD44 Expression	Present	Absent
Serum Biochemical Markers		
••Ferritin	Normal	Elevated
••Lactate Dehydrogenase	≤1500 U/mL	> 1500 U/mL

Trk-A, tyrosine kinase receptor A; *MRP*, multidrug resistance-associated protein.

*Corresponds to the most commonly used parameters in clinical practice for assessment of prognosis and risk stratification.

[a] It is not only the presence but also the *amount* of schwannian stroma that confers the designation of a favorable histology. At least *50% or more schwannian stroma* is required before a neoplasm can be classified as ganglioneuroblastoma or ganglioneuroma.

[b] Mitotic rate is classified as *low* (≤10 mitoses/10 high power fields) or *high* (>10 mitoses/10 high power fields).

[c] Mitotic karyorrhexis index (MKI) is defined as the number of mitotic or karyorrhectic cells per 5000 tumor cells in random foci.

Ref: Robins Pathological Basis of Diseases, 7th Ed

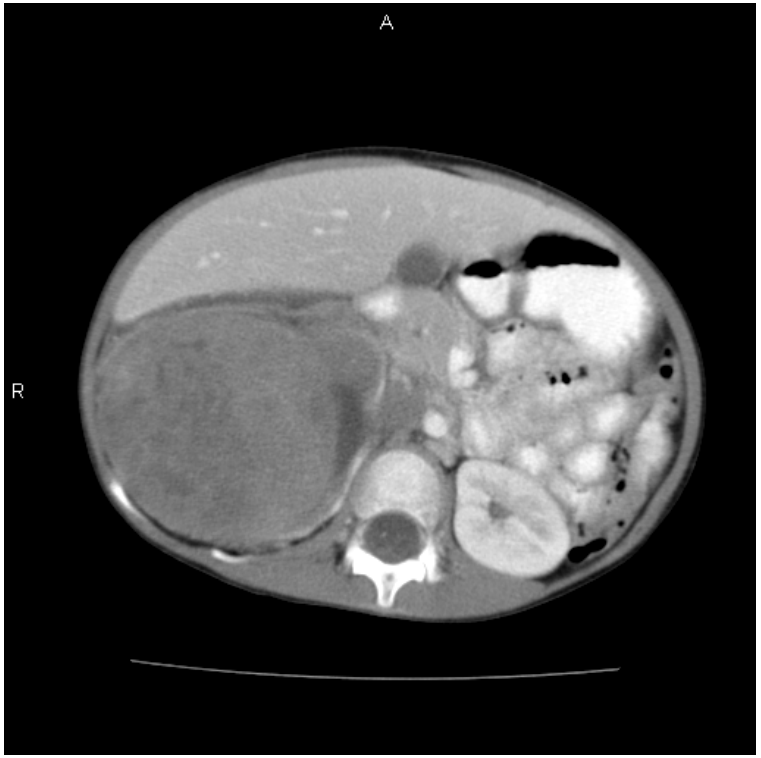
Wilms Tumor (Nephroblastoma)

- Common tumor in children.
- Malignant tumor originating from renal (metanephric) blastema (nephrons); One of two embryological structures giving rise to kidneys. Other being ureteric bud (collecting ducts).
- Peaks between 1-4 yrs.
- 5 year survival rate of 90% (surgery & chemotherapy).
- Commonly presents as an abdominal mass (can be mistaken for enlarged spleen)
- Pathogenesis: deletions of WT-1 & WT-2 genes on the short arm of chromosome 11. These are tumor suppressor genes.

Wilms tumor: Signs and Symptoms

- **Abdominal mass**
  - Often <u>asymptomatic</u>
    - Healthy appearing

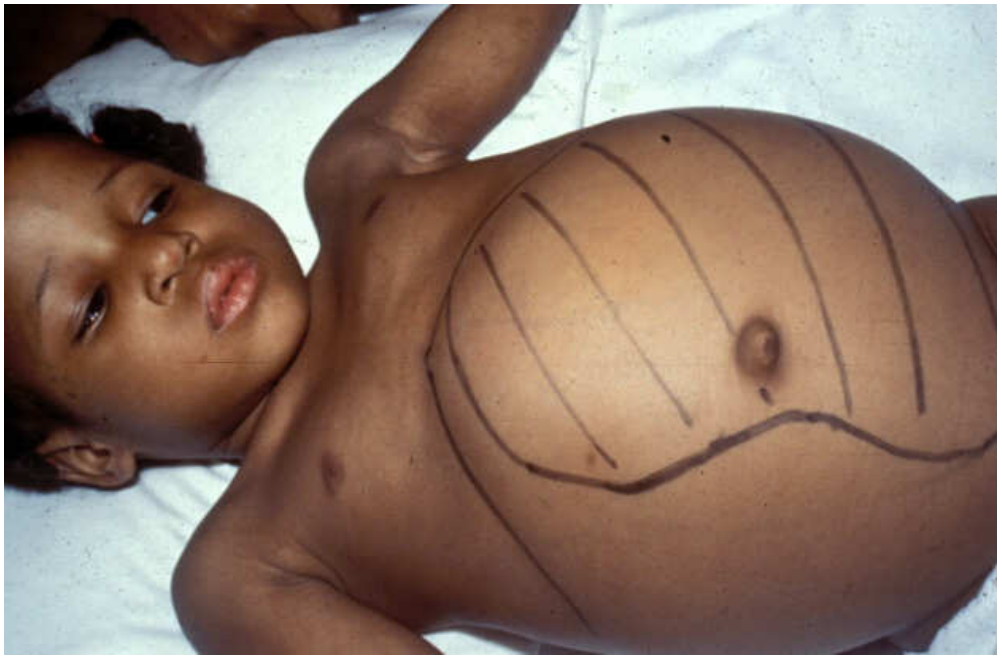
2 days before dx



Encapsulated mass

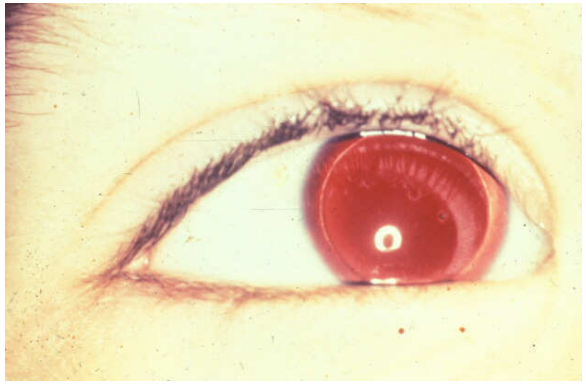
Wilms tumor: Signs and Symptoms

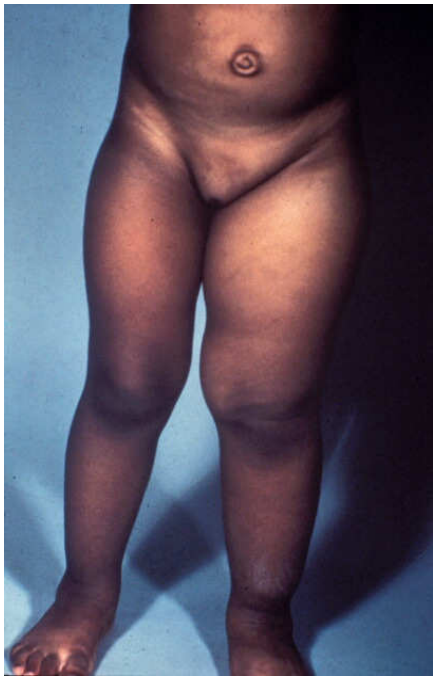
Mass enlarges toward pelvis



Signs and Symptoms of Wilms tumor

- **Associated anomalies, syndromes** – 15%
  - Hemihypertrophy
  - Aniridia

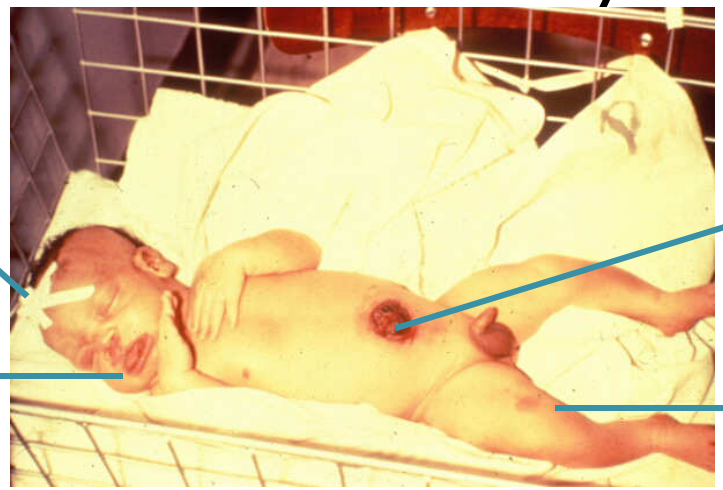




  - WAGR syndrome
    - Wilms, aniridia,
      ambiguous genitalia, retardation

Signs and Symptoms of Wilms tumor

- **More anomalies, syndromes**
  - GU anomalies
  - Denys-Drash syndrome
    - GU anomalies and renal failure
  - Beckwith-Wiedemann syndrome



Bone tumors

Bone Tumors in Childhood

- **Age** – Adolescents > younger children
- Signs and symptoms
  - **Bone pain**, ☐ palpable mass, ☐ ☐ motion
    - Often hx of sports injury (coincidental)

Osteogenic Sarcoma

Metaphyses of long bones:

Distal femur

Proximal tibia

Proximal humerus

Pelvis

Ewing Sarcoma

All bones:

Long: diaphyses

Flat

Pelvis

Skull

Ribs

Ewing Sarcoma

- Tumor of flat bones
  - Pelvis, chest, vertebrae
- Rare in children under 5 years
- 75% diagnosed by age 20

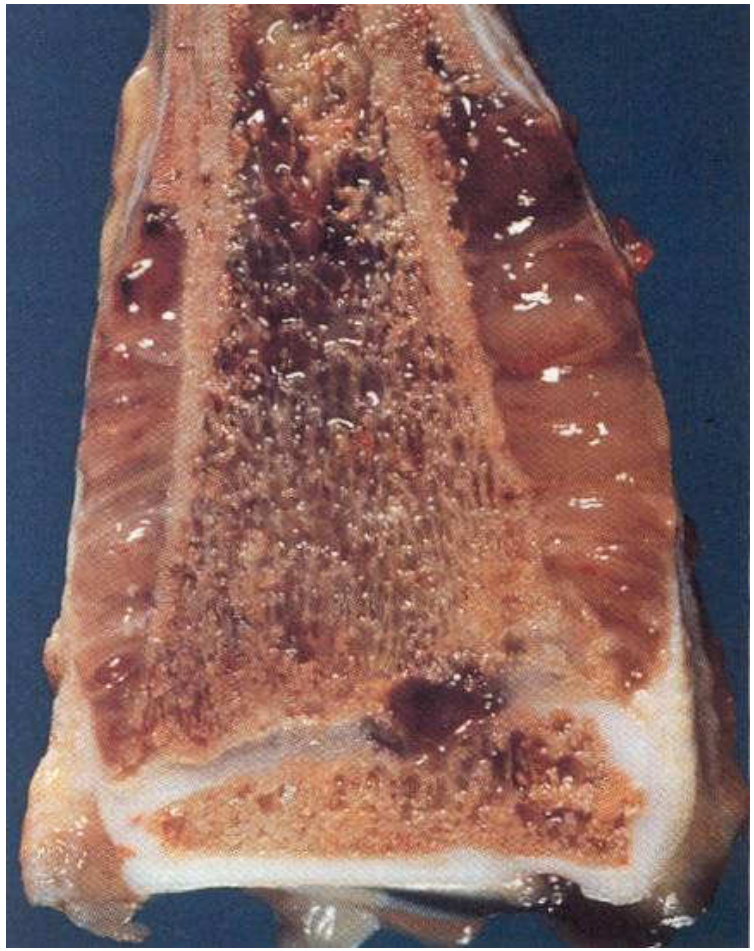
Ewing Sarcoma

- Presents between 5-20 but peaks in boys younger than 15 yrs.
- Histology resembles malignant lymphoma
- Site: diaphysis of long bones, ribs, pelvis and scapula.
- Highly malignant with early metastasis.
- Can mimic osteomyelitis in early stages.
- Tumor extends from medulla through to cortical bone and into subperiosteal space – "onion skin" appearance on x-ray.
- 5 year survival rate of 60% (surgery & chemotherapy).

Ewing Sarcoma

Ewing Sarcoma Tumor

Ewing Sarcoma at distal end of the tibia. tumor extends into the soft tissue.



Anderson's Pathology

Osteogenic Sarcoma

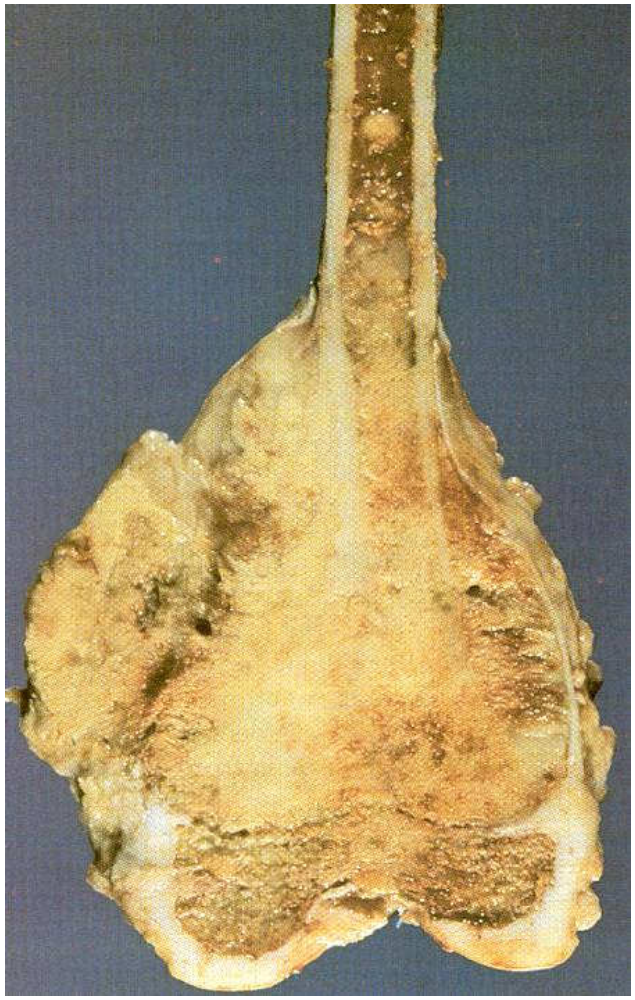
- Malignant tumor of bone
- 400 new cases each year
- Peak incidence is in the second decade of life, when adolescents are gaining vertical height rapidly.
- Approximately 20% have metastases at diagnosis
- **High rate of metastasis to lungs**

Osteogenic Sarcoma

- Affects ages 10-20 yrs of age.
- Show a predilection for metaphyses of long bones. 60% affects knee.
- X-ray shows "sunburst pattern" & "Codman triangle". Signs of elevation of periosteum due to subperiosteal new bone formation.
- Surgical & chemotherapy can achieve 60% 5 year survival rate.
- Early metastasis to lungs, liver & brain.
- Can be mistaken for osteomyelitis.
- Can occur following surgical cure of retinoblatoma presumable due to loss of Rb suppressor gene locus on chromosome 13.

Osteosarcoma Tumor

Femur has a large mass involving the metaphysis of bone. Tumor has destroyed the cortex.



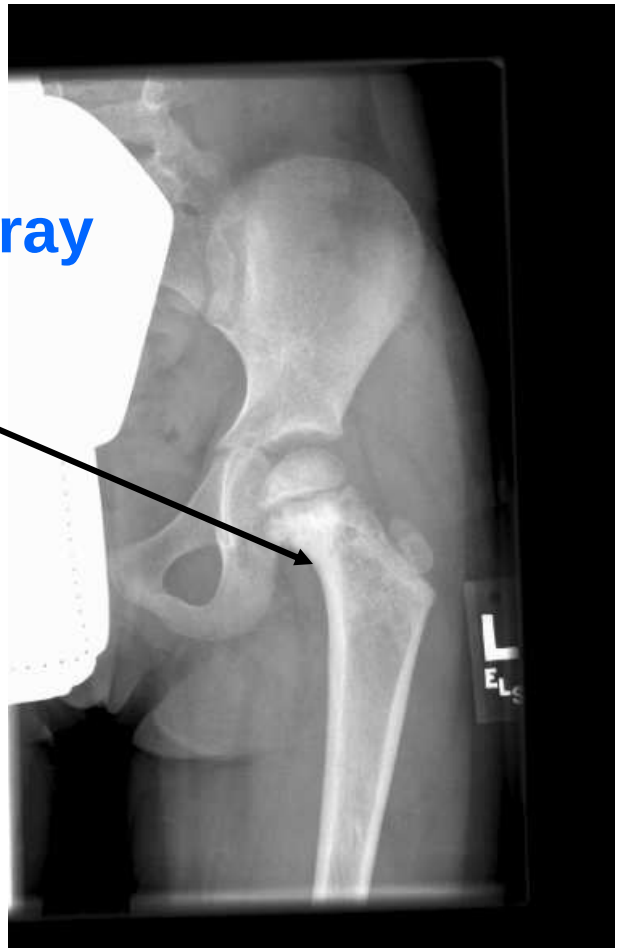
Anderson's Pathology

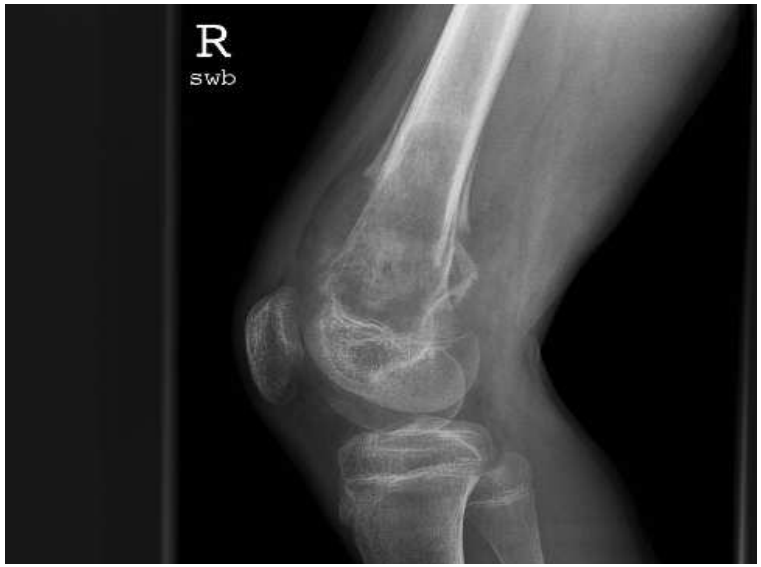
Presentation of Bone Tumors

Plain X-Rays are usually abnormal

Classic X-ray of Ewing:

Moth-eaten lytic lesion





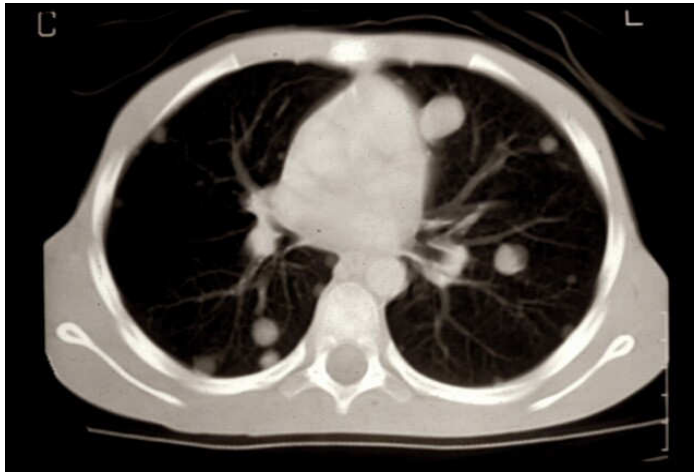
Classic X-ray of O.S.:

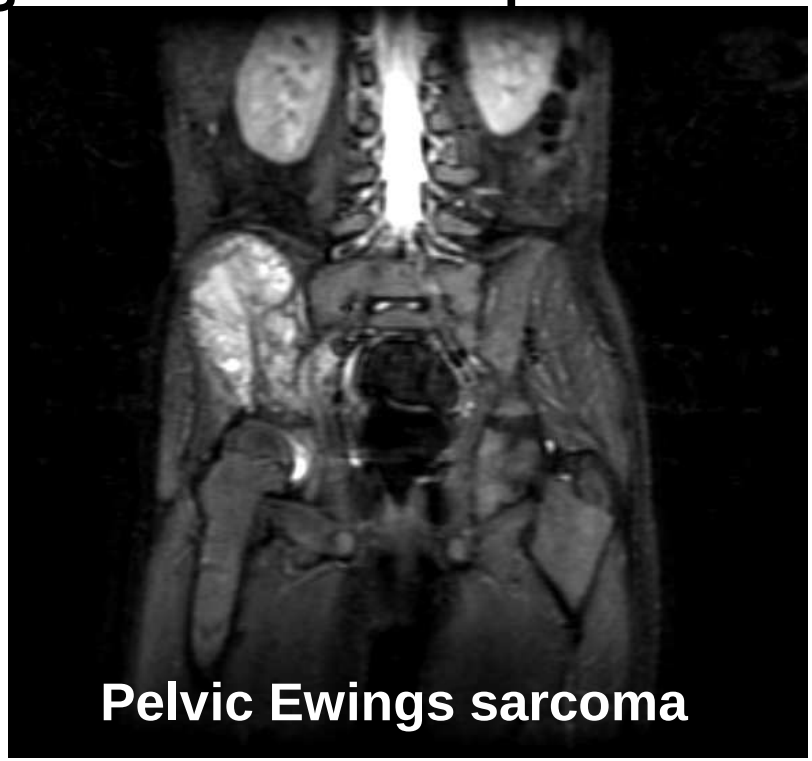
“Sunburst pattern”
Periosteal reaction
Soft tissue mass + calcium

Presentation of Bone Tumors

Further radiographic evaluation may help with differential diagnosis of bone pain

- Bone scan
- MRI
- Chest CT scan
  - Metastases 20%





Pelvic Ewings sarcoma

Soft tissue sarcomas

Presentation of Soft Tissue Sarcomas

- **Rhabdomyosarcoma – most common**
- **Age**
  - Birth to > 20 y/o
  - 70% < 10 y/o
- **Sites**
  - Head and neck – 40%
  - Genitourinary – 20%
  - Extremities – 20%
  - Trunk – 10%
  - Retroperitoneal – 10%

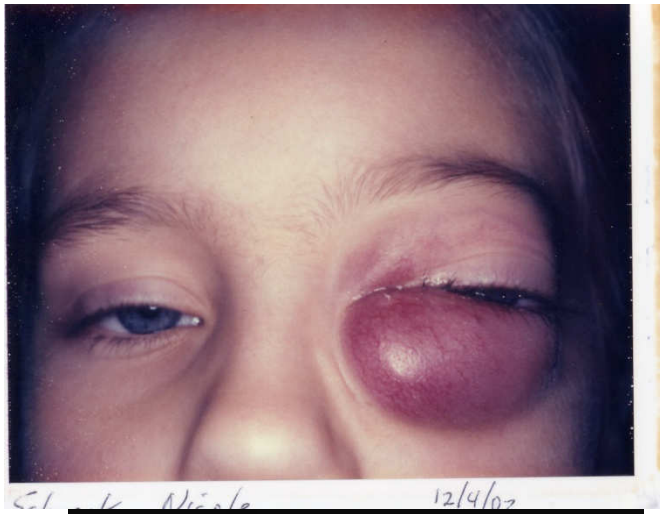
Signs and symptoms depend on age and site

Rhabdomyosarcomas: Signs and Symptoms

Head and neck

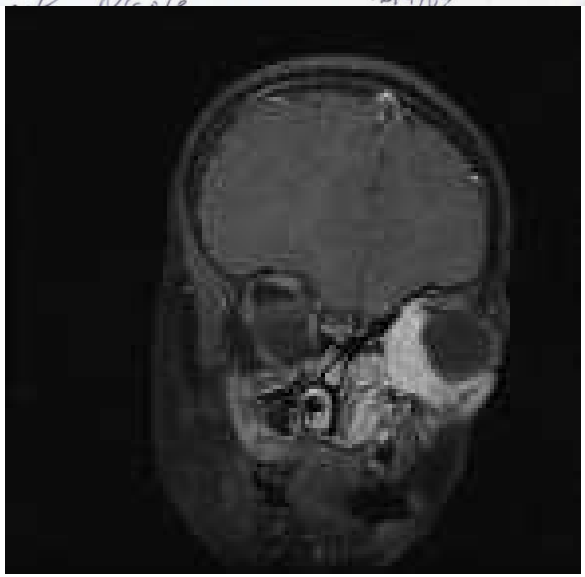
Orbit

- Proptosis
- Periorbital swelling



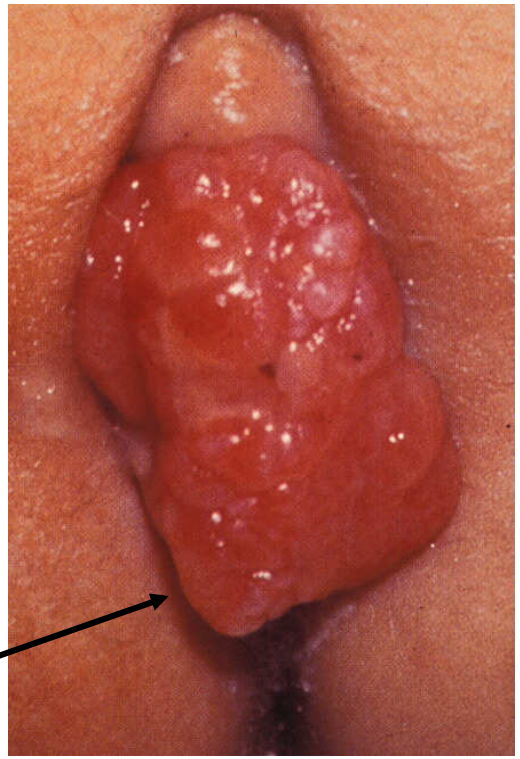
Parameningeal

- Cranial nerve palsies
- Hearing loss
- Chronic aural or sinus drainage



Rhabdomyosarcomas: Signs and Symptoms

- Genitourinary
  - **Bladder and prostate**
    - Hematuria
    - Urinary obstruction
  - **Paratesticular**
    - Painless mass - ↑ testicle
  - **Vagina and uterus**
    - Abdominal mass
    - Vaginal mass
    - Vaginal bleeding or discharge

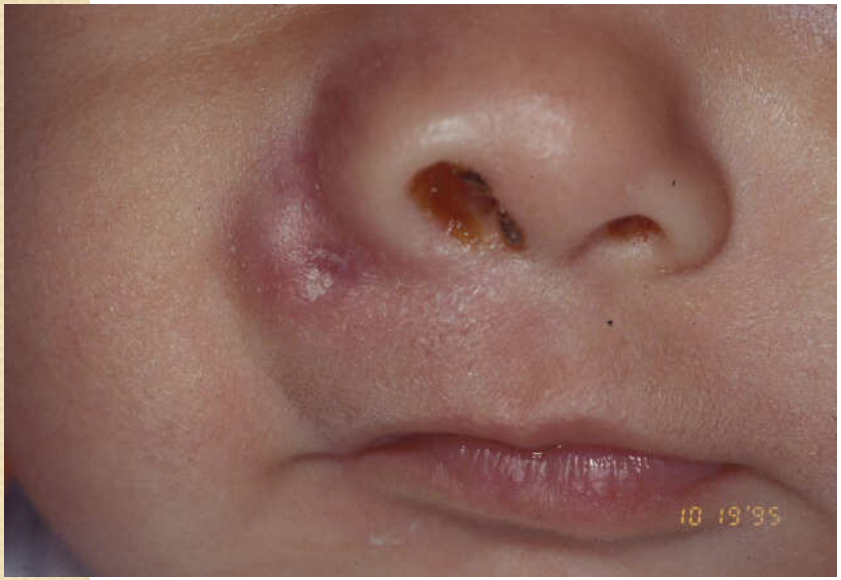


Botryoid: grape-like

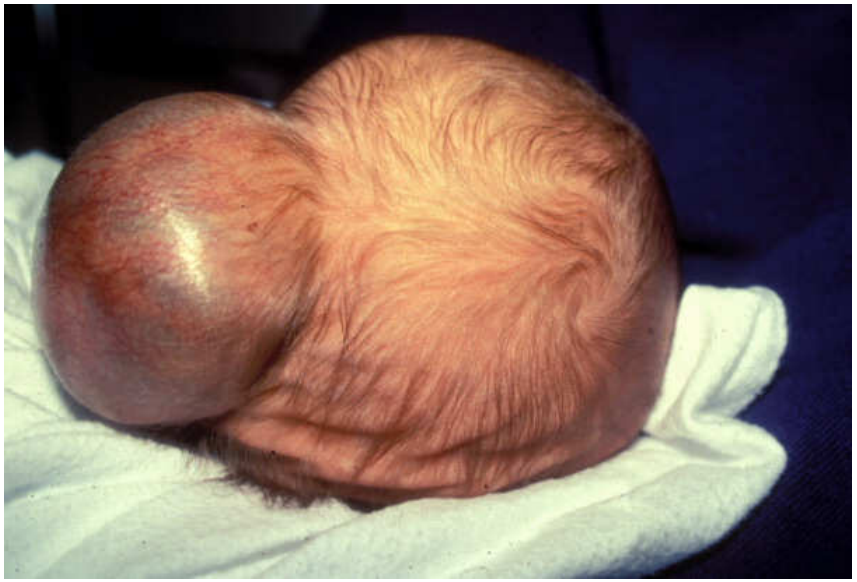
Rhabdomyosarcoma – other sites

Can show up at any site and any age

6 week old



Newborn



Concluding Remarks

Over 70% of children diagnosed with cancer will be cured of their disease.

- **1 in every 1000 young adults alive in the U.S. today is a survivor of childhood cancer.**

- **Children should be followed throughout adulthood for potential late effects of therapy and second malignancies.**

END

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Link below:

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