Common Pediatric Oncological Diseases

Prof. Abdulrahman Alsultan

Objectives

- Knowledge of childhood cancer epidemiology
- Knowledge of clinical manifestations, diagnostic approach, treatment overview, and prognosis of common childhood cancers.

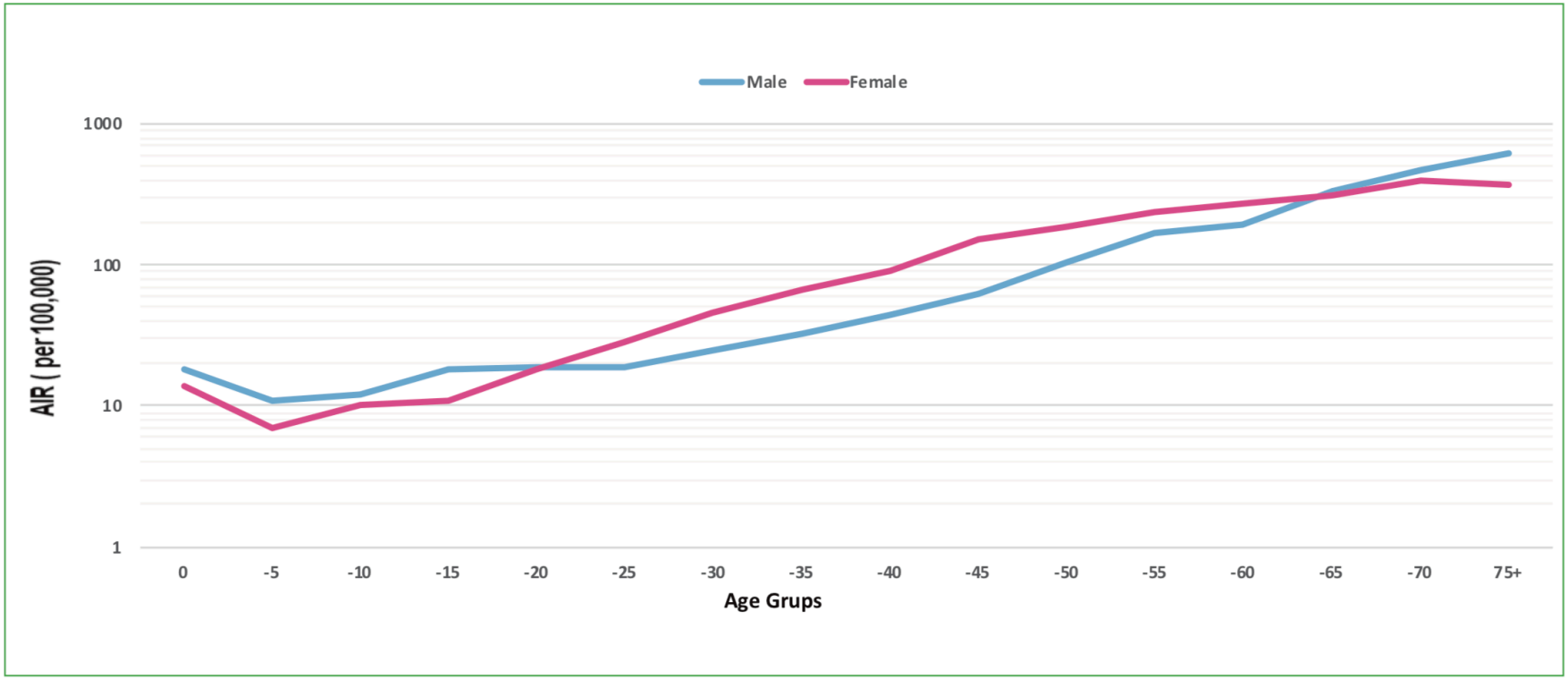
When to suspect childhood cancer

Epidemiology

- Childhood cancer is rare
- Cancer incidence in among US children aged 0-14 years was 16.7/100,000 in 2012-2016 (SEER data).
- Cancer is the second leading cause of death in children (ACCIDENTS are number one)

Epidemiology- Saudi Arabia

Figure 2.2: Age-Specific Incidence Rate (AIR) for all cancers among Saudis, 2015



National Health Information Center Saudi Cancer Registry

Epidemiology- Saudi Arabia

Table 2.7.3: Top ten cancers reported among Saudi Adults by gender, 2015

Male	5036	%
Colorectal	808	16.0
NHL	437	8.7
Prostate	340	6.7
Lung	323	6.4
Liver	266	5.3
Leukaemia	262	5.2
Hodgkin's lymphoma	226	4.5
Thyroid	224	4.4
Bladder	192	3.8
Stomach	184	3.7

Female	6275	%
Breast	1978	31.5
Thyroid	785	12.5
Colorectal	655	10.4
Corpus Uteri	403	6.4
NHL	303	4.8
Ovary	208	3.3
Leukaemia	185	2.9
Hodgkin's lymphoma	144	2.3
Stomach	131	2.1
Cervix Uteri	102	1.6

National Health Information Center Saudi Cancer Registry

Epidemiology- Saudi Arabia

Table 2.8.2: Top ten cancers among Saudi Children, 2015

Site	No.	%
Leukaemia	255	35.0
Brain, CNS	89	12.2
NHL	89	12.2
Hodgkin's lymphoma	66	9.1
Kidney	43	5.9
Bone	32	4.4
Adrenal gland	28	3.8
Eye	26	3.6
Connective,Soft tissue	23	3.2
Ovary	12	1.6

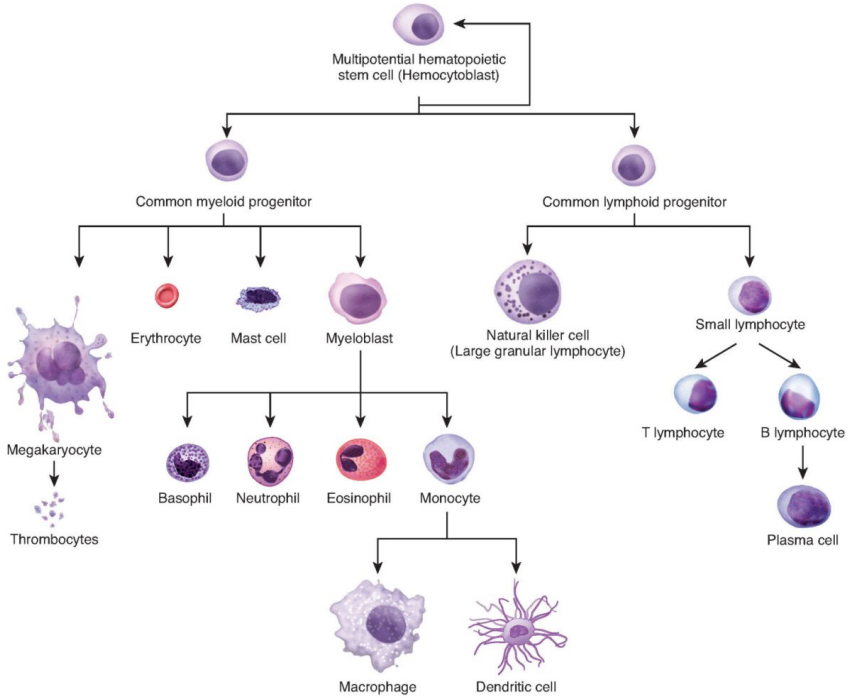
National Health Information Center Saudi Cancer Registry

Causes of Childhood Cancer

- Mostly unknown.
- Genetic predisposition: e.g.
  - Down syndrome
  - Neurofibromatosis
  - Fanconi anemia
  - Li-Fraumeni syndrome (germline *P53* mutation)
- Environmental factors:
  - Ionizing radiation or radiotherapy
  - Chemotherapy.
  - ? Infectious etiology
  - ? Chemical exposures e.g. pesticides, benzene

Leukemia

- Types:
  - Acute lymphoblastic leukemia (ALL)
  - Acute myelogenous leukemia (AML)
  - Chronic myelogenous (CML)



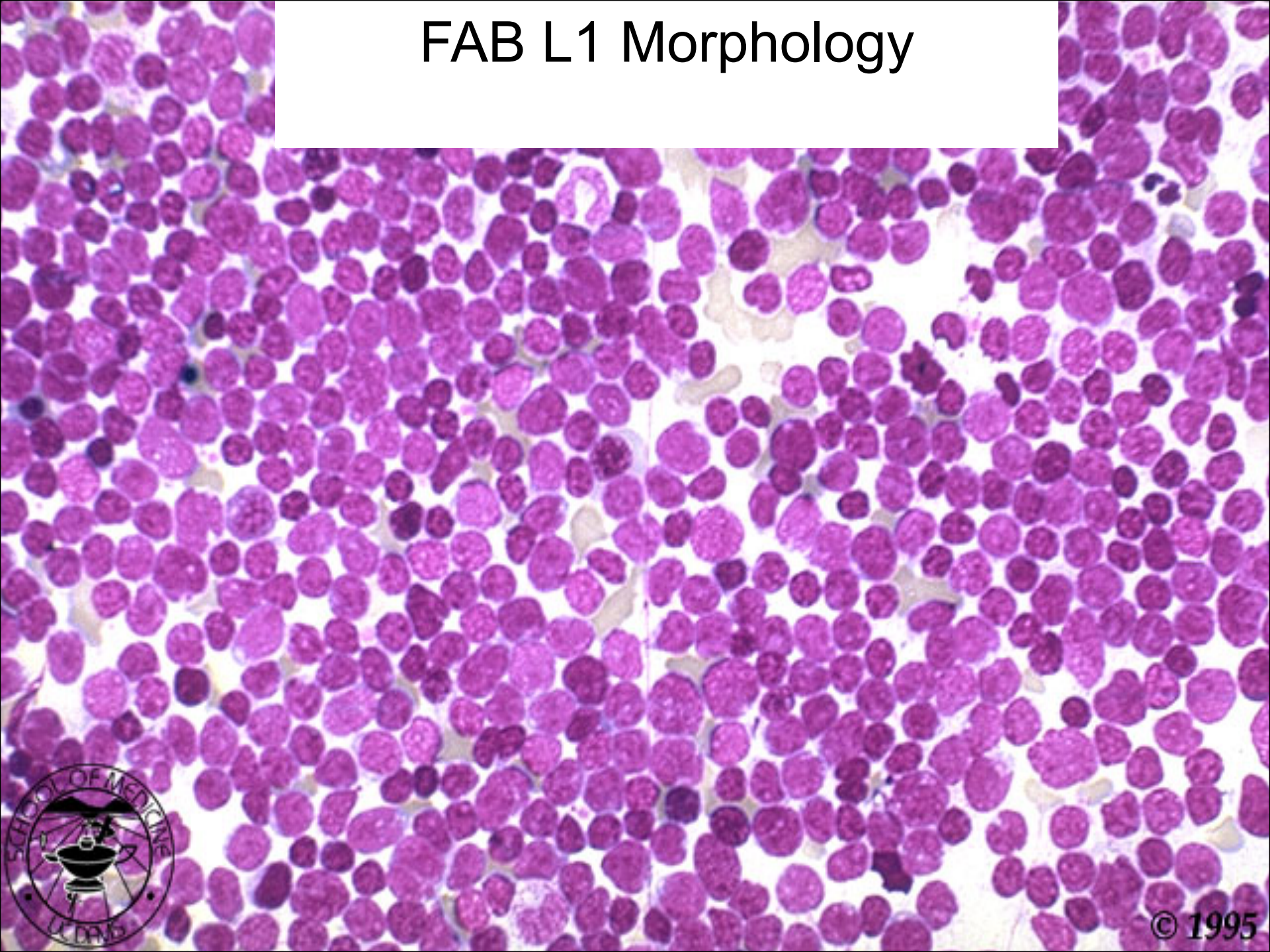
Leukemia

- Symptoms:
  - Lethargy
  - Fever/Infection
  - Bone/Joint pain
  - Bleeding
  - Anorexia
  - Abdominal pain
  - CNS signs
- Signs:
  - Pallor
  - Hepatosplenomegaly
  - Petechiae/Purpura
  - Lymphadenopathy.
  - Testicular involvement

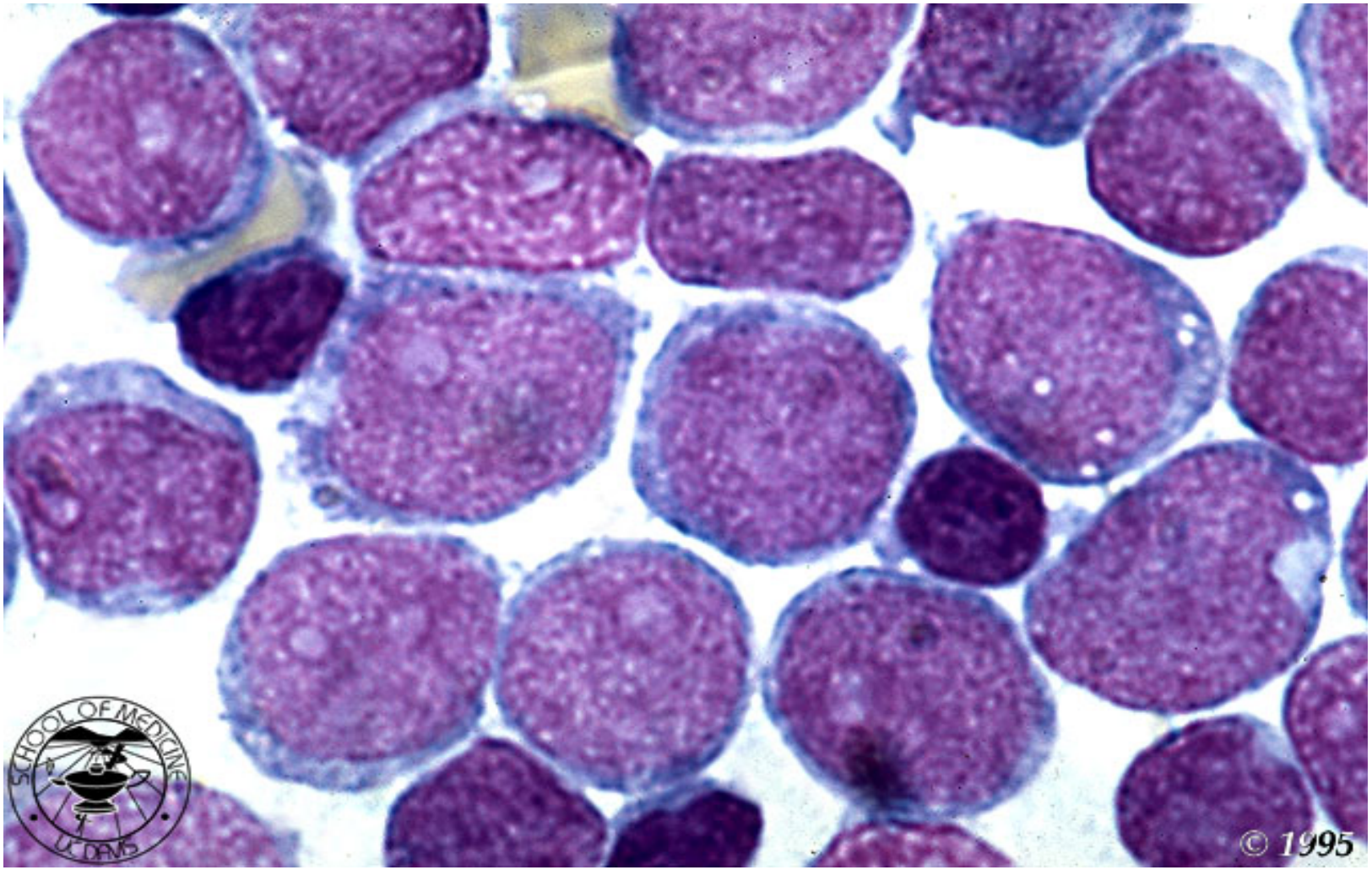
Leukemia

- Workup:
  - CBC and differential
  - LFT, electrolytes (K, Ph), uric acid, LDH
  - CxR
  - Bone marrow study:
    - Morphology
    - Flow cytometry
    - Molecular studies e.g. BCR-ABL
    - Cytogenetics e.g. t (9;22)
  - Lumbar puncture

FAB L1 Morphology



Acute Myelogenous Leukemia



FAB M1

Flow Cytometry

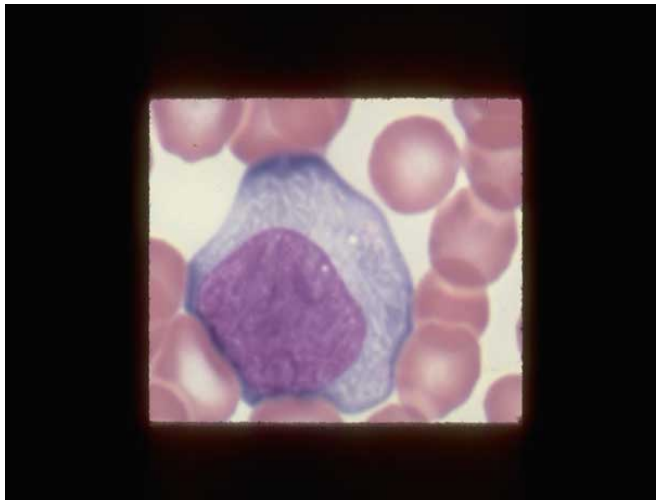
- B-ALL
  - CD10, CD19, CD20, CD22, CD79a, HLA-DR, CD34 & TdT
- T-ALL
  - CD2, CD3, CD5, CD7, CD1a, TdT
- AML
  - CD13, CD15, CD33, CD117, MPO, HLA-DR, CD34

Prognostic Factors in ALL

- NCI Risk Grouping
  - Std Risk: Age 1-9 yr and WBC <50,000/μl
  - High Risk: Age <1 or ≥ 10 yr and/or WBC ≥ 50k
- Immunophenotype
- Cytogenetics
- Response to induction therapy
- CNS disease

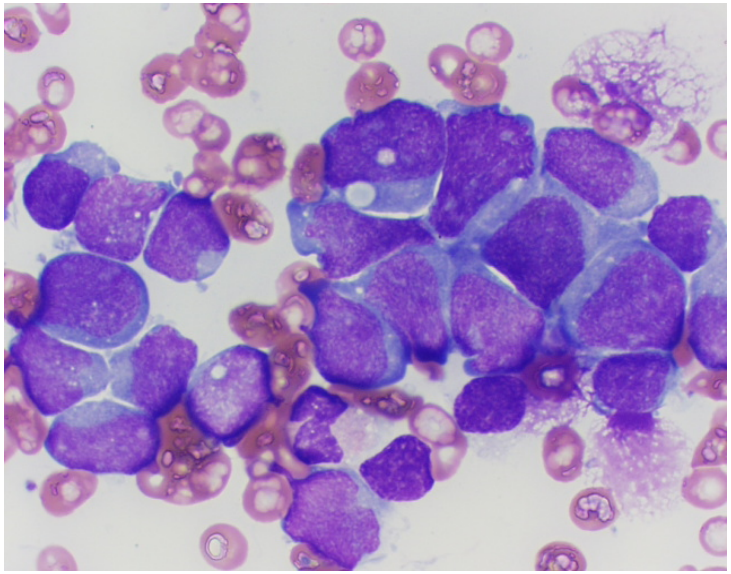
Leukemia

- Differential diagnosis:
  - Non-malignant:
    - Infectious mononucleosis
    - JRA
    - ITP
    - Aplastic anemia
    - Pertusis



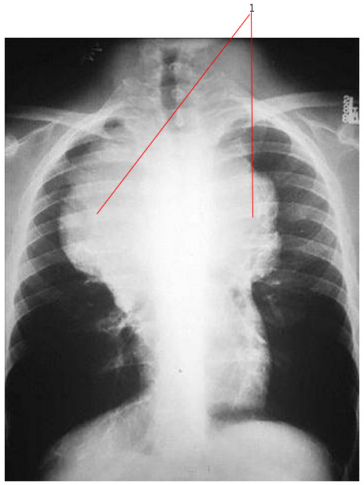
Leukemia

- Differential diagnosis:
  - Malignant:
    - Lymphoma (BM blasts < 20%)
    - Neuroblastoma
    - Rhabdomyosarcoma

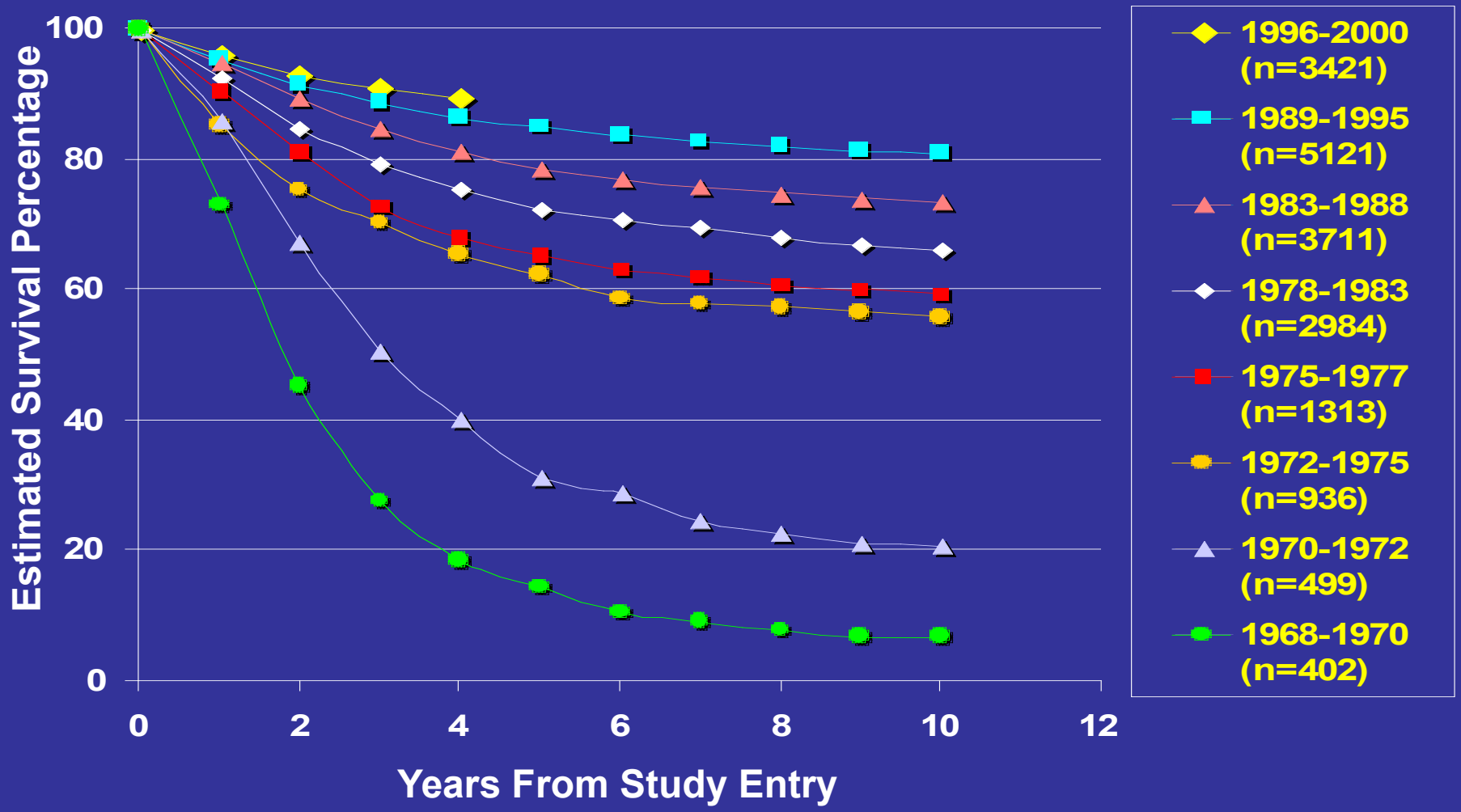


Leukemia

- Treatment:
  - Supportive care:
    - Tumor lysis syndrome (high uric acid/K/Ph)
    - Hyperleukocytosis
    - Superior vena cava syndrome
    - Infections
  - **Chemotherapy**
  - Cranial radiation if CNS positive
  - Hematopoietic stem cell transplant (rarely)



Improved Survival in Childhood ALL



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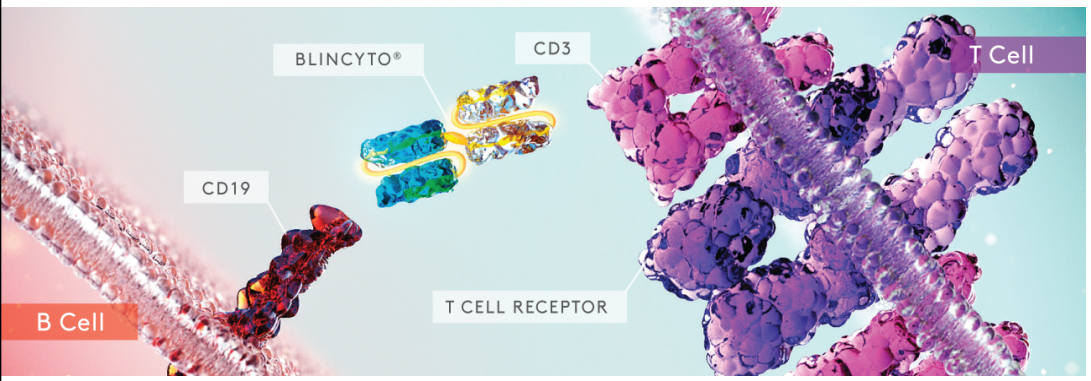
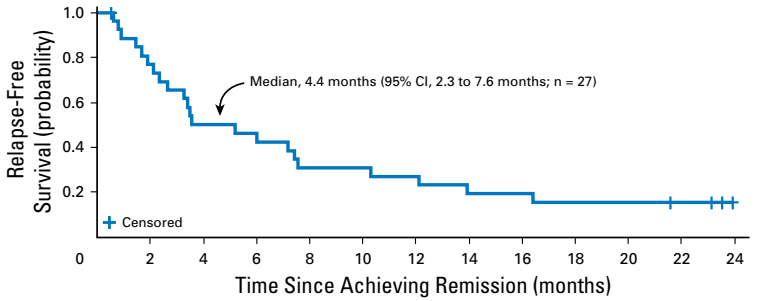
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

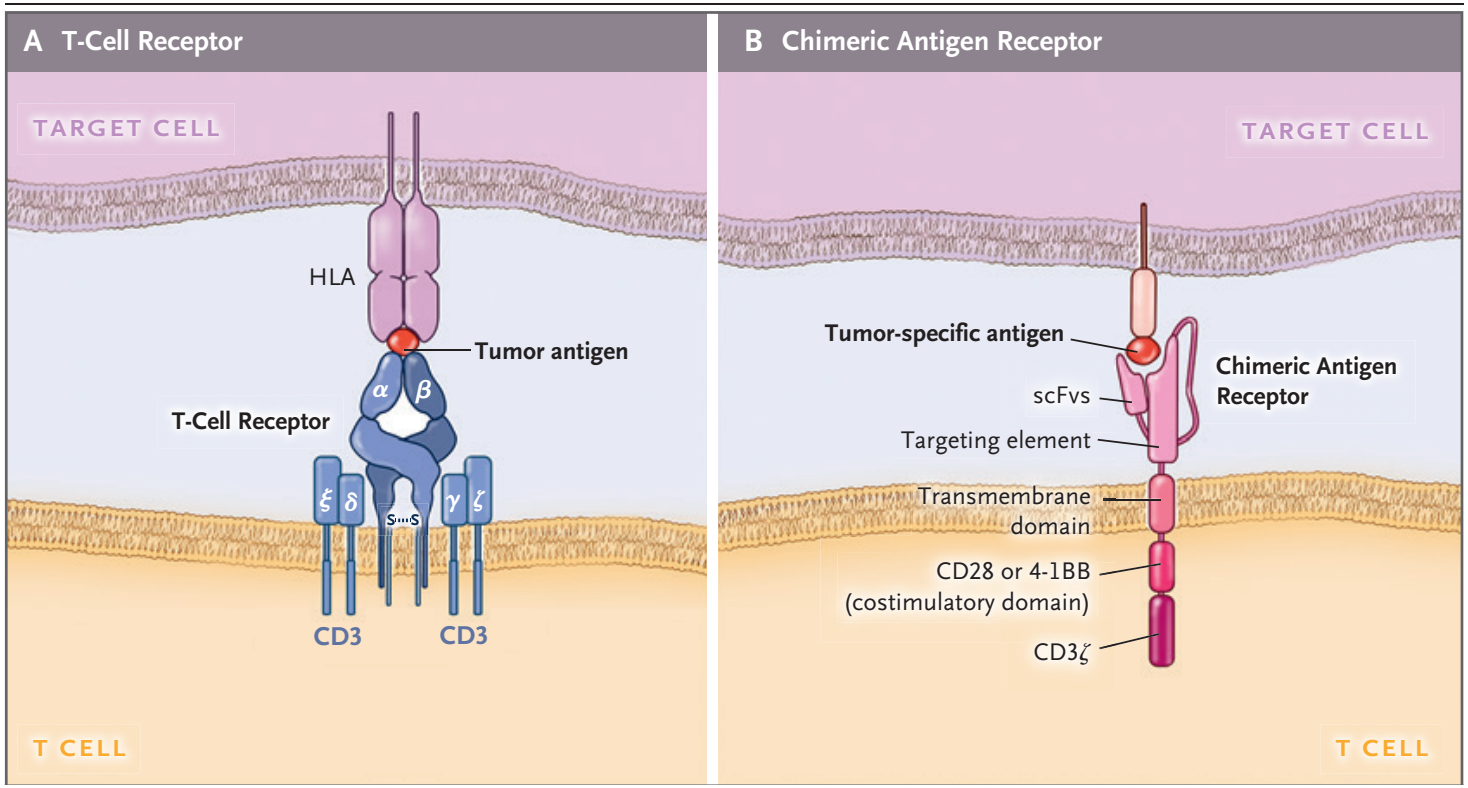
Phase I/Phase II Study of Blinatumomab in Pediatric Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia

Arend von Stackelberg, Franco Locatelli, Gerhard Zugmaier, Rupert Handgretinger, Tanya M. Trippett, Carmelo Rizzari, Peter Bader, Maureen M. O'Brien, Benoît Brethon, Deepa Bhojwani, Paul Gerhardt Schlegel, Arndt Borkhardt, Susan R. Rheingold, Todd Michael Cooper, Christian M. Zwaan, Phillip Barnette, Chiara Messina, Gérard Michel, Steven G. DuBois, Kuolung Hu, Min Zhu, James A. Whitlock, and Lia Gore

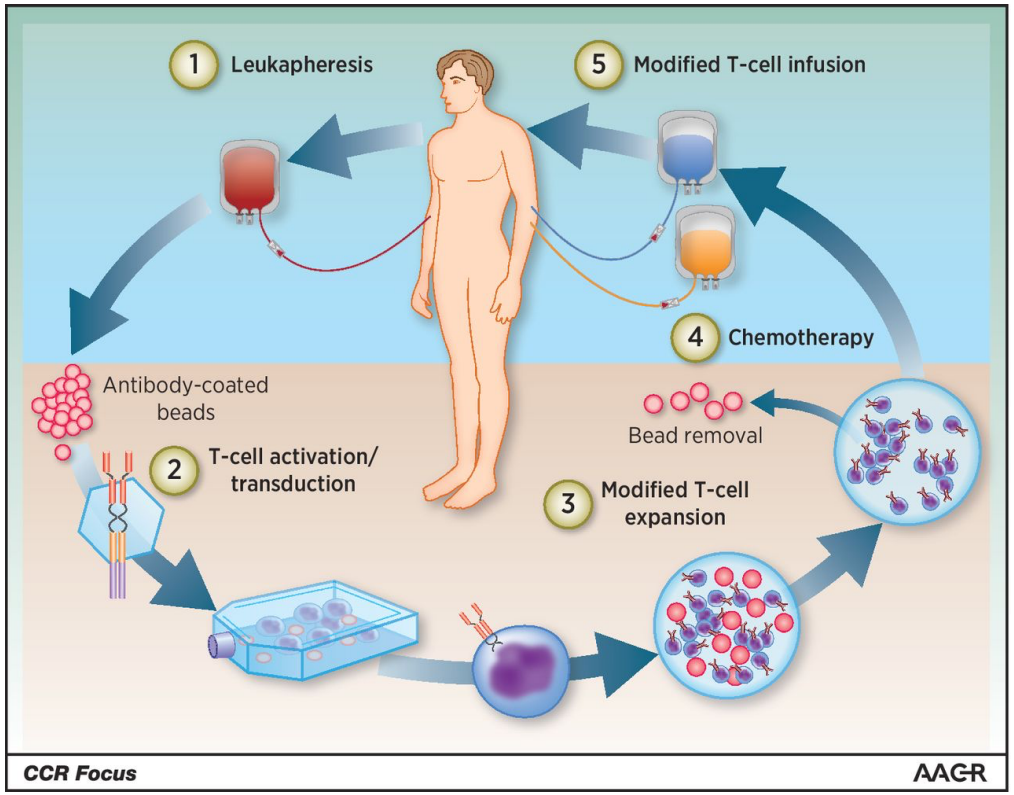




Chimeric Antigen Receptor Therapy (CAR T-cell)



CAR T-cell therapy



1. Peripheral blood mononuclear cells are collected from the patient using a large-volume leukapheresis procedure.
2. The cells are then transferred to a GMP manufacturing facility for T cell engineering and expansion. Patient T cells are then incubated with CAR-encoding viral vectors, which enter the T cells and introduce CAR gene RNA. CAR RNA is then reverse-transcribed into DNA, which recombines into the T cell genome, resulting in permanent CAR gene incorporation.
3. Transformed T cells undergo ex vivo expansion for multiple days, resulting in a product that is ~ 90% CD3+ T cells.
4. The cells are transferred back to the center for infusion after chemo depletion.

CAR T-cell therapy

In Girl's Last Hope, Altered Immune Cells Beat Leukemia

By **DENISE GRADY** DEC. 9, 2012

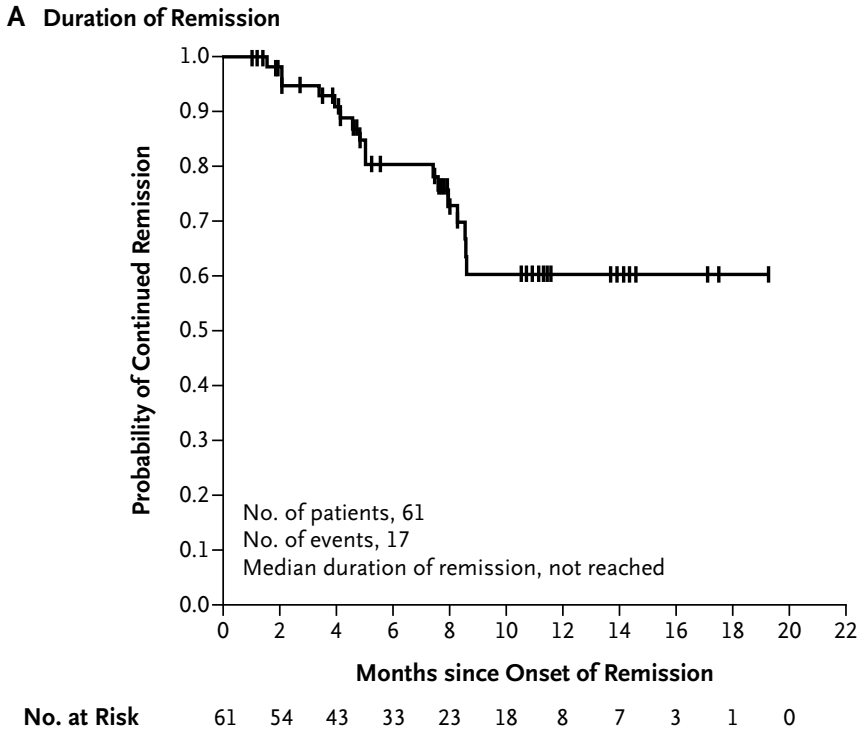
Emma Whitehead, with her mother, Kari. Last spring, Emma was near death from acute lymphoblastic leukemia but is now in remission after an experimental treatment at the Children's Hospital of Philadelphia. Jeff Swensen for The New York Times

RELATED COVERAGE

An Experimental Treatment for Leukemia
DEC. 9, 2012

Immune System, Loaded With Remade T-cells, Vanquishes Cancer SEPT. 12, 2011

CAR T-cell therapy



Brain tumors

- 2nd most common cancers in children
- Most common solid neoplasms
- 60-70% 5 year survival

Brain tumors

- Clinical presentation:
  - General and non-localizing symptoms

    (e.g. headache, vomiting, behavioral changes, learning problems, weight loss/gain)

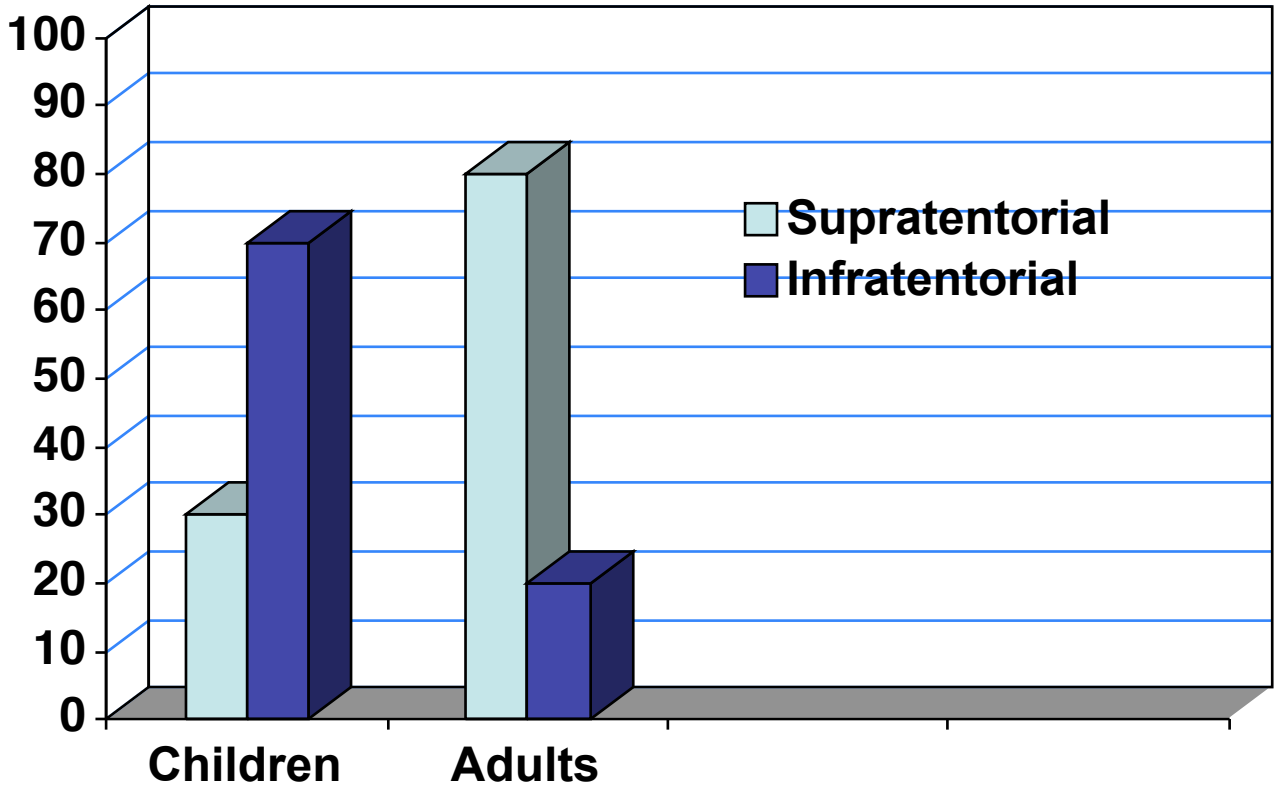
  - Increased intracranial pressure

    (e.g. irritability, vomiting, bulging fontanelle, papilledema, parinaud syndrome)

  - Localizing signs

    (depend on tumor location e.g. ataxia)

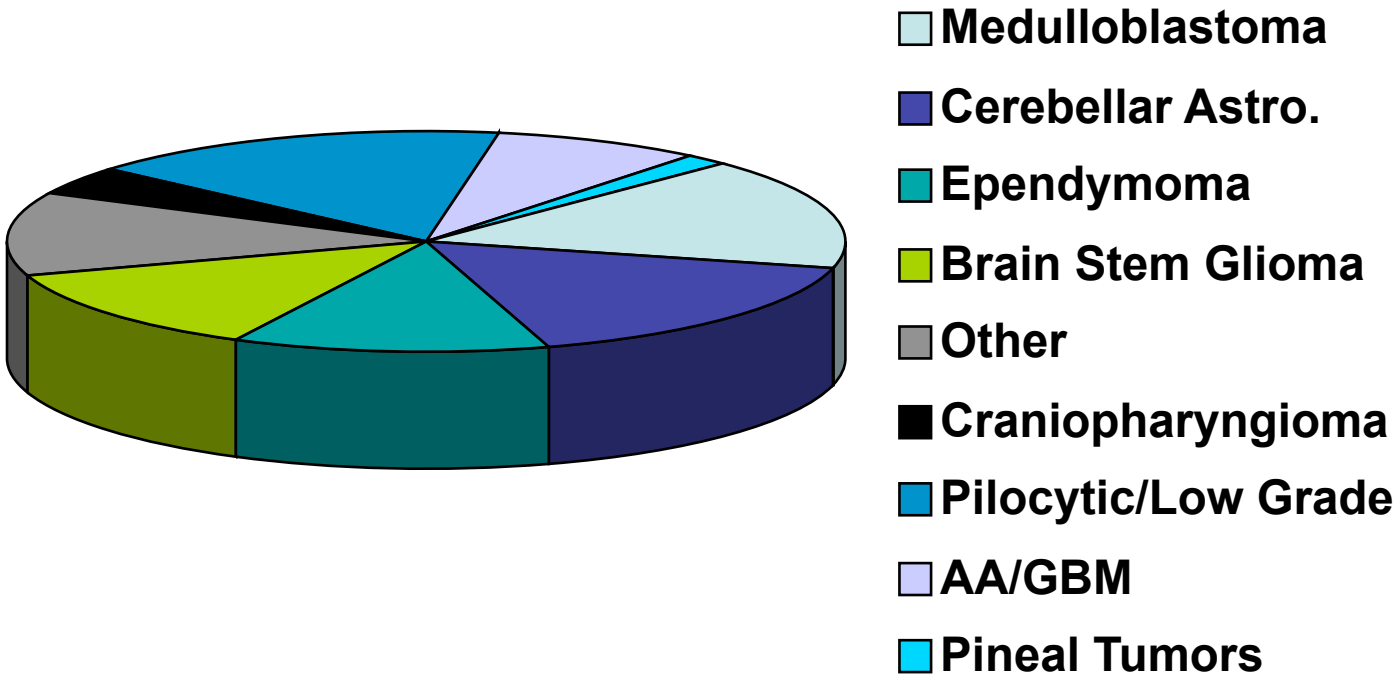
Brain Tumors: Distribution



Brain tumors

- Workup:
  - Brain MRI/Spine
  - CSF cytopathology
  - Surgical biopsy
  - CSF tumor markers (B-HCG/AFP) if germ cell tumor is suspected

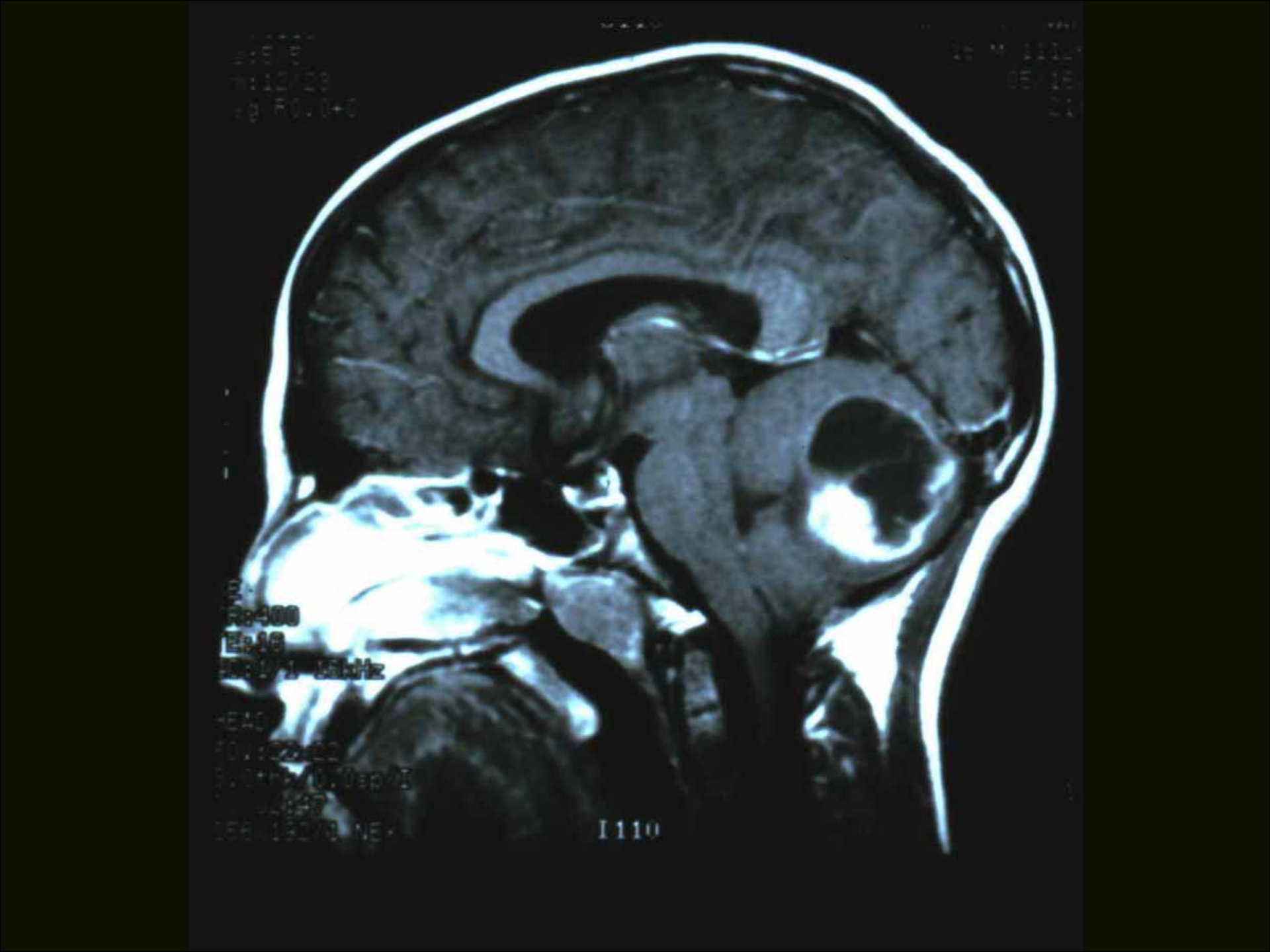
Pediatric Brain Tumors: Distribution



Astrocytoma (Glioma)

- Low grade: good prognosis
  - WHO grade I (juvenile pilocytic astrocytoma)
  - WHO grade II (diffuse fibrillary astrocytoma)

- High grade: v. poor prognosis
  - WHO grade III (anaplastic astrocytoma)
  - WHO grade IV (Glioblastoma multiforme)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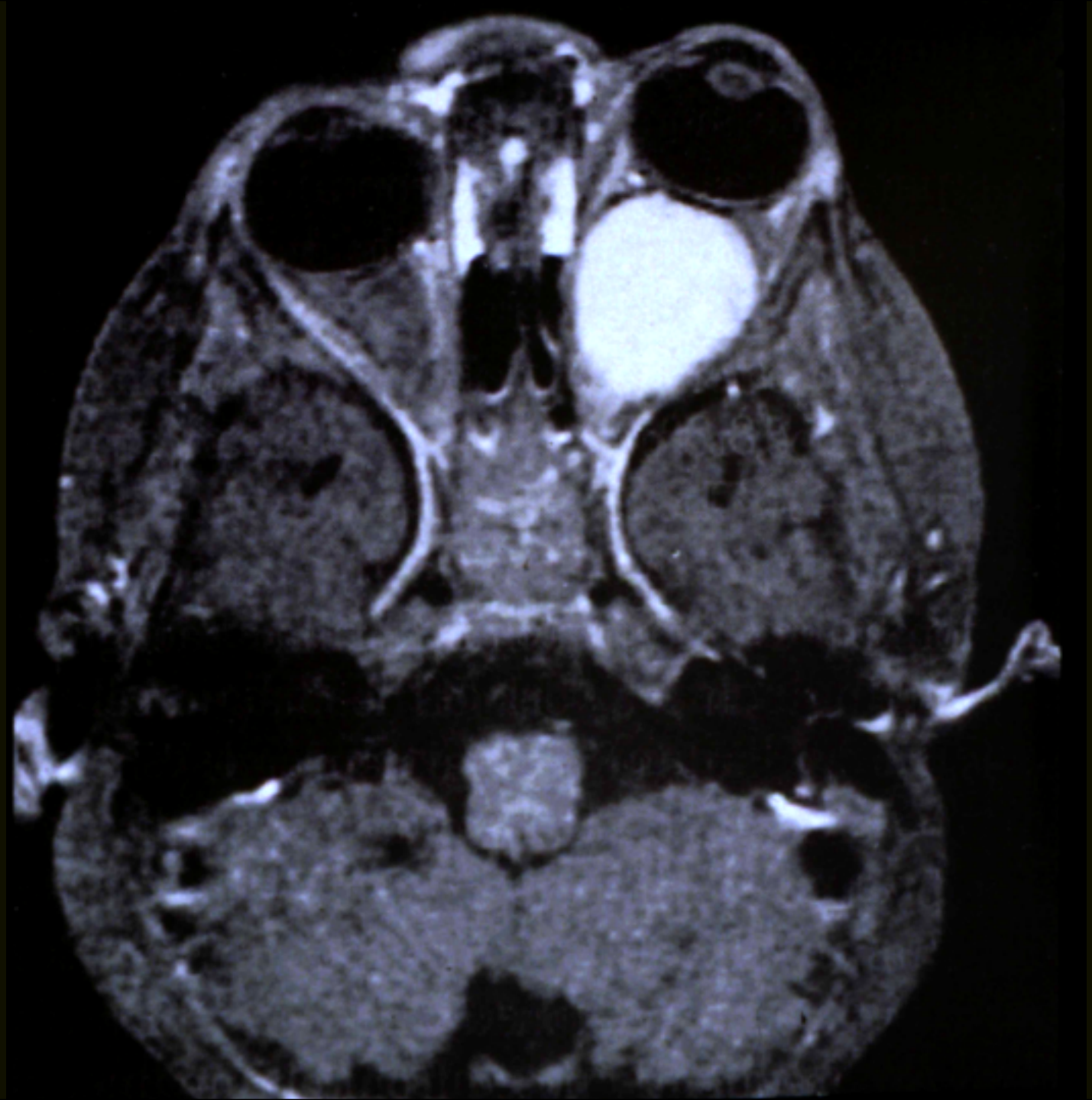
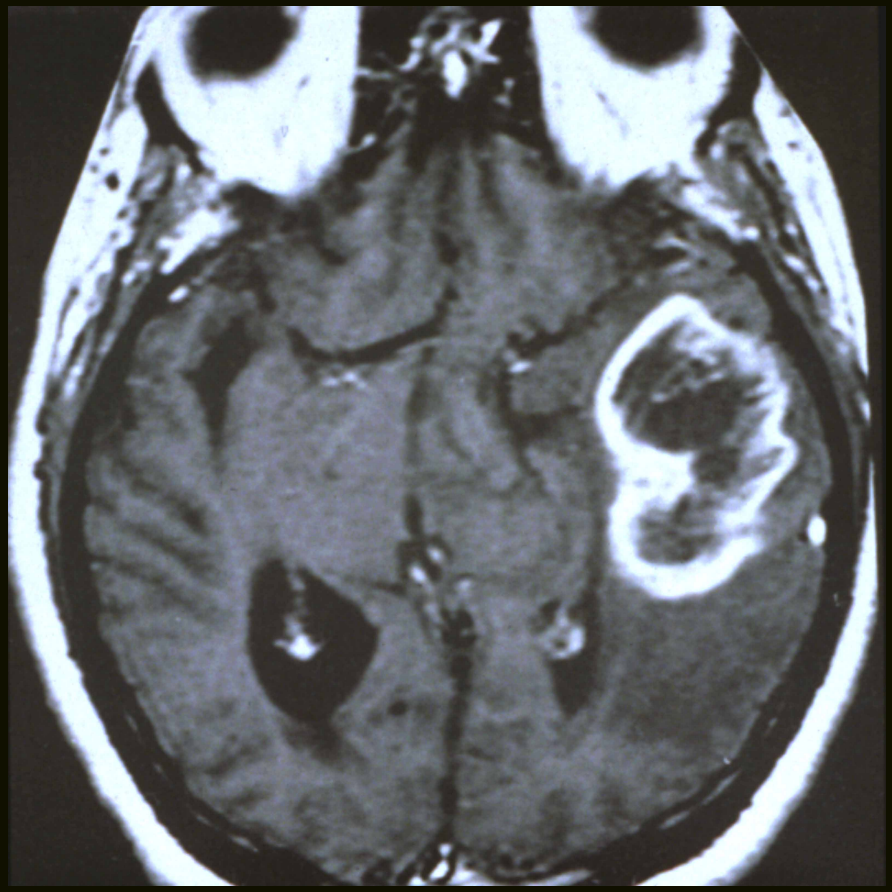
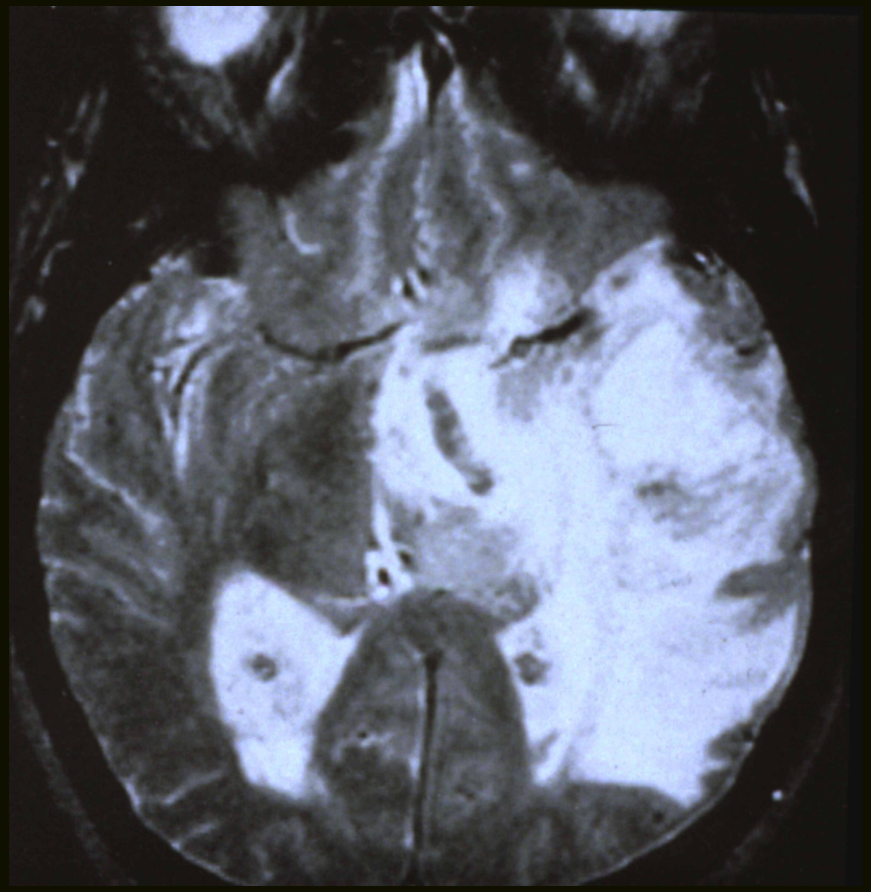
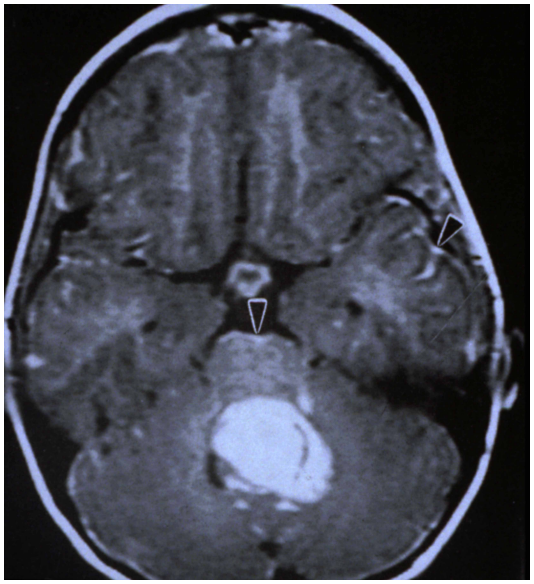






Medulloblastoma

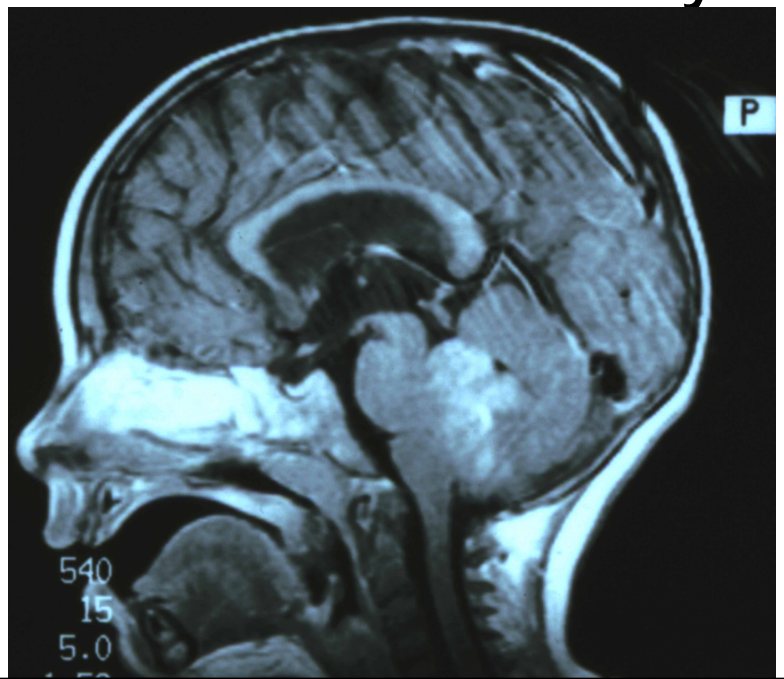


- Location: posterior fossa (PNET).
- Staging: M0= non-metastatic
  M1= mets to CSF
  M2= mets within brain
  M3= mets to spinal cord
  M4= mets outside brain.
- Prognosis: 85% survival (non metastatic)
  50% survival (metastatic)

Ependymoma

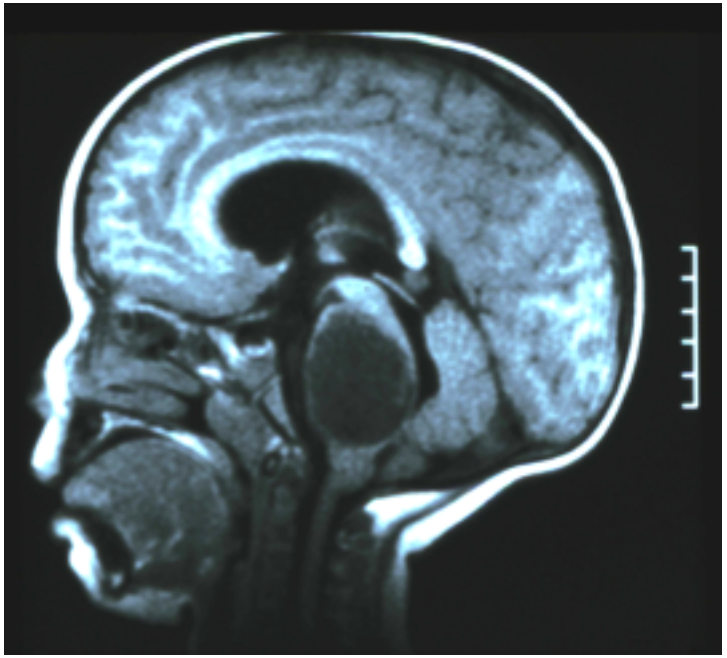
- Site: ventricular lining
- Prognosis: 50-60% if fully resected

  0-10% if not fully resected



Brain stem glioma

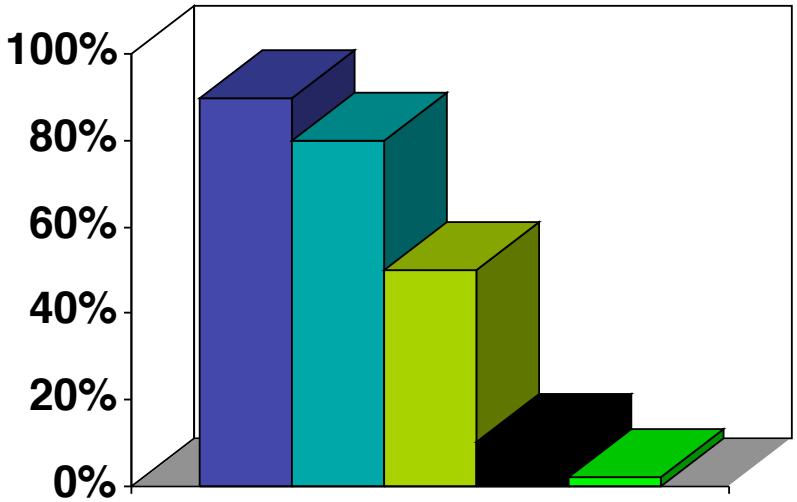
- Diffuse pontine glioma:
  - Aggressive in 6-18 months after radiation



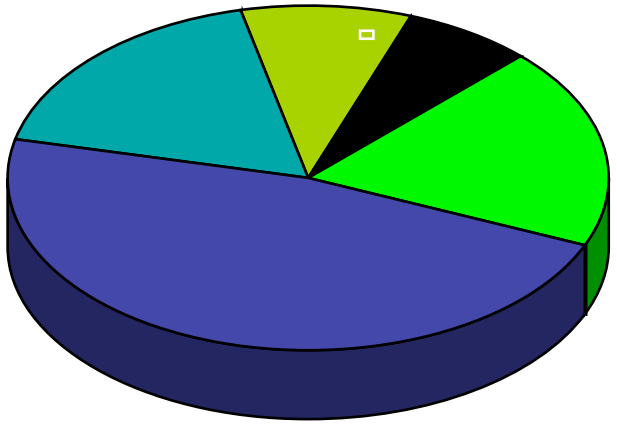
Brain tumors

- Treatment:
  - Surgery
    - Needed for diagnosis in most cases (exceptions: BSG, GCT)
    - Gross total resection is the ideal
    - Supportive measures e.g. shunts,
  - Radiotherapy
  - Chemotherapy
    - Used as adjuvant therapy in most cases
    - Particularly efficacious in GCT and medulloblastoma
    - In < 3 y/o children to avoid radiation (High dose chemotherapy followed by autologus stem cell transplant)

Pediatric Brain Tumors: Survival/Frequency

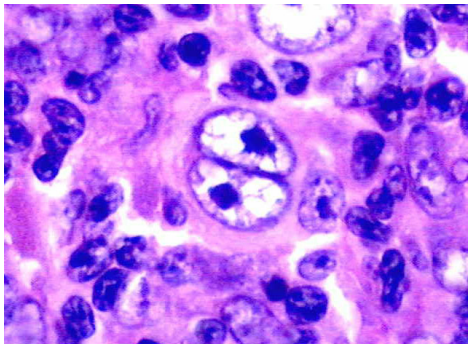


Low Grade/Pilocytic
Medulloblastoma (standard risk)
Ependymoma
Glioblastoma Multiforme
Brain Stem Glioma



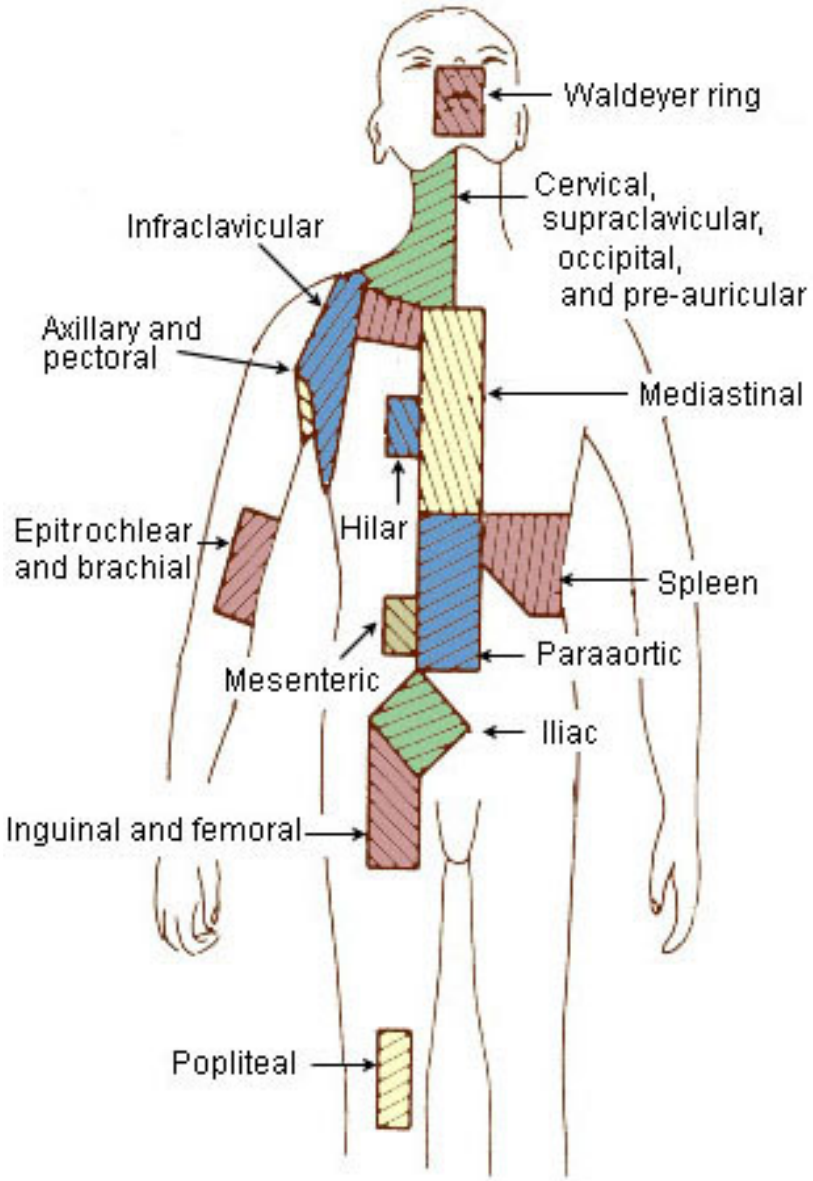
Hodgkin Lymphoma

- Bimodal – Mid-20's and after 50 yr..
  - Rarely < 5 yr



- Classical Hodgkin Lymphoma (cHL)
  - Nodular sclerosis (NS)
    - Most common histology in children/adolescents
    - 80% of cases 10-19yr
  - Mixed Cellularity (MC)
    - more common in < 10yr
    - Majority are EBV(+)
  - Lymphocyte –Deplete
    - Rare in children, more common in HIV –infected patients
  - Lymphocyte-rich

Hodgkin Disease



Hodgkin Disease

Ann Arbor Staging

- ***Stage I –*** single site/nodal region of involvement
- ***Stage II*** – 2 or more sites/nodal regions on same side of diaphragm
- ***Stage III*** – Sites/nodal regions involved on both sides of diaphragm
- ***Stage IV –*** diffuse or disseminated involvement in one or more extralymphatic organs
- ***(E)*** – designation for extralymphatic involvement in any stage
- ***(S) -*** splenic involvement

Hodgkin Disease

- “A” – no associated symptoms
- “B”
  - Fever (>38^{o} C) usually > 3 consecutive days
  - Unexplained weight loss of 10% - preceding 6 months
  - “Drenching” night sweats
- “X” – bulky disease
  - mediastinum $\geq$ 1/3 intrathoracic diameter
  - > 10 cm other nodal site
- “E” – extranodal involvement
- Pruritus
- Alcohol-induced pain
- Autoimmune disorders e.g. ITP

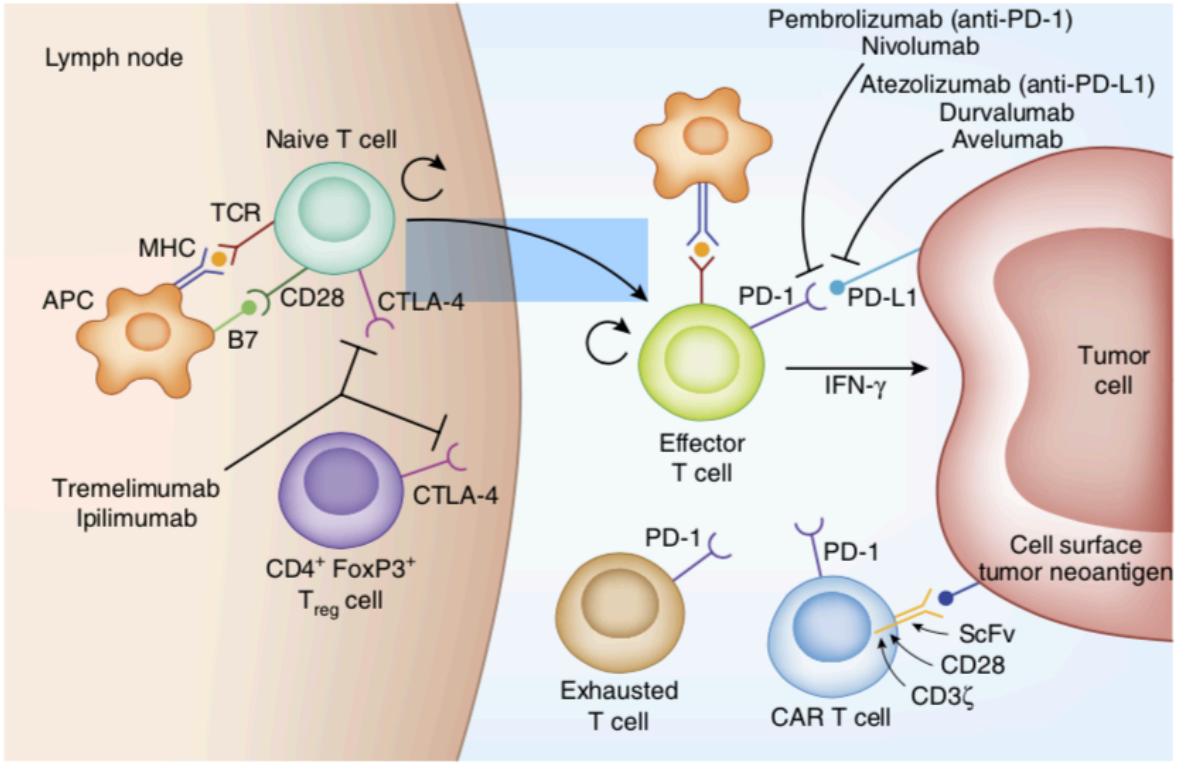
Lymphoma

- Workup:
  - Labs
    - CBC
    - ESR/CRP
    - Renal and hepatic function
    - LDH and uric acid
  - Lymph node biopsy
  - CT neck, chest, abdomen, pelvis
  - Bone marrow biopsy (Bilateral biopsies)
  - PET scan

Hodgkin Disease

- Treatment:
  - 90-95% of all children/adolescence with HD can be cured
  - Multi-agent chemotherapy given in short, pulsed cycles of chemotherapy.
    - Radiation – involved field (15 – 25 Gy)
  - Goal is now to minimize late effects

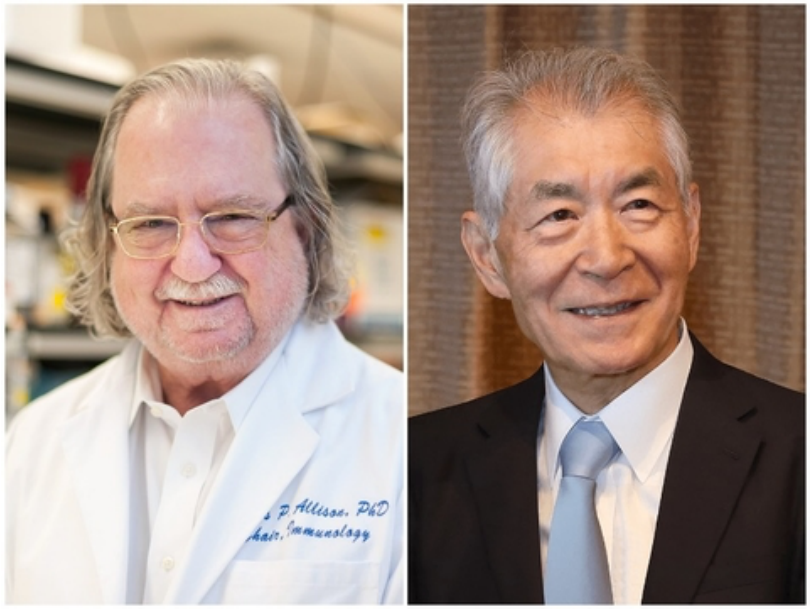
Immune Tolerance in Cancer



Both PD-1/PD-L1 and CTLA-4 create a checkpoint on the immune system to maintain self-tolerance and prevent autoimmune disorders in normal cells. However, this leads to immune evasion in cancer.

June et. al. Nat. Med. 23, 540–547 (2017)

Unleashing the Immune System to Conquer Cancer



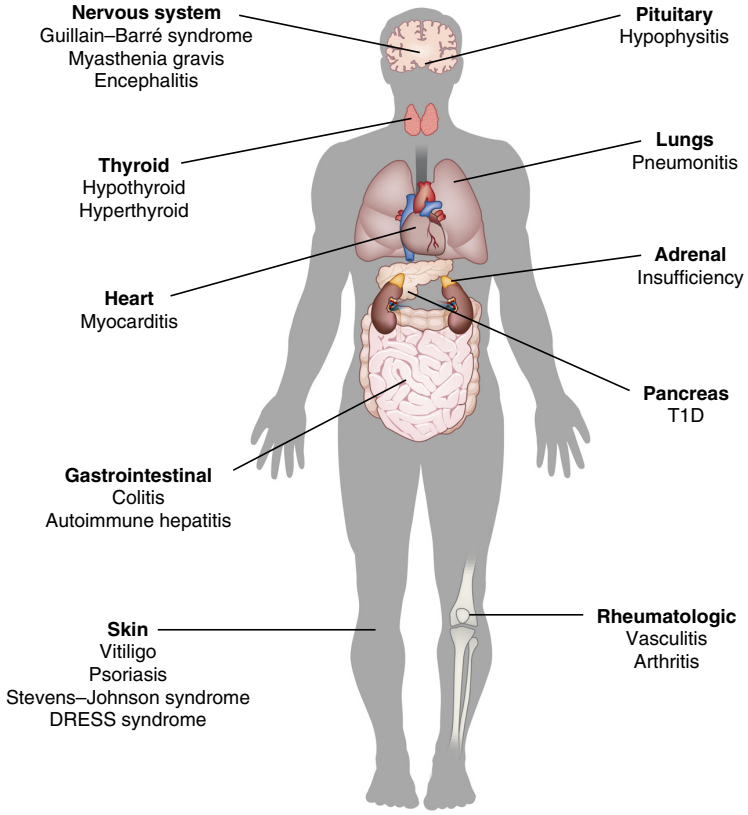
The Nobel Prize in Physiology or Medicine 2018 was awarded to both James P. Allison from the United States and Tasuku Honjo from Japan for "for their discovery of cancer therapy by inhibition of negative immune regulation" which is related to their work on PD-1 and CTLA-4

Approved Indications of checkpoint inhibitors

Table 1: FDA approved indications for checkpoint inhibitors as of December 2018

Cancer type	Ipilimumab	Pembrolizumab	Nivolumab	Cemiplimab-rwlc	Atezolizumab	Durvalumab	Avelumab
Advanced melanoma	p	p	p				
Recurrent/metastatic head and neck squamous cell carcinoma		p	p				
Metastatic non-small cell lung cancer		p	p		p	p	
Refractory/relapsed classical Hodgkin lymphoma		p	p				
Advanced/metastatic urothelial carcinoma		p	p		p	p	p
Advanced/metastatic solid tumor with microsatellite instability/ mismatch repair deficiency		p					
Advanced/metastatic gastric cancer		p	p				
Recurrent/metastatic cervical cancer		p	p				
Refractory/relapsed primary mediastinal large B-cell lymphoma		p	p				
Hepatocellular carcinoma previously treated with sorafenib		p	p				
Advanced renal cell carcinoma	p		p				
Advanced/metastatic colon cancer with microsatellite instability/ mismatch repair deficiency	p		p				
Advanced/metastatic cutaneous squamous cell carcinoma				p			
Metastatic merkel cell carcinoma		p					p

Autoimmunity is a major side effect of Checkpoint inhibitors

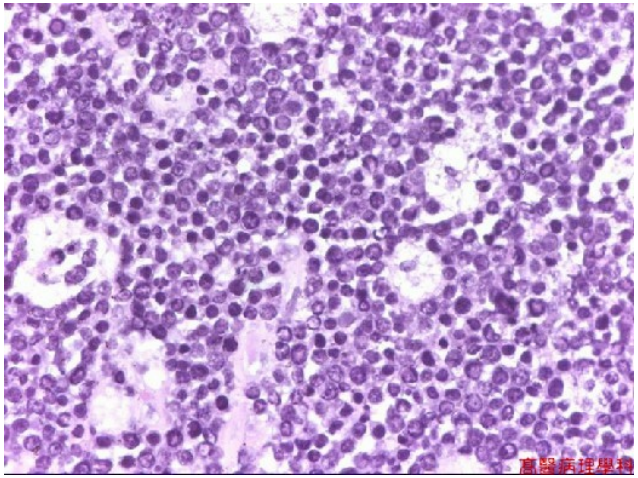


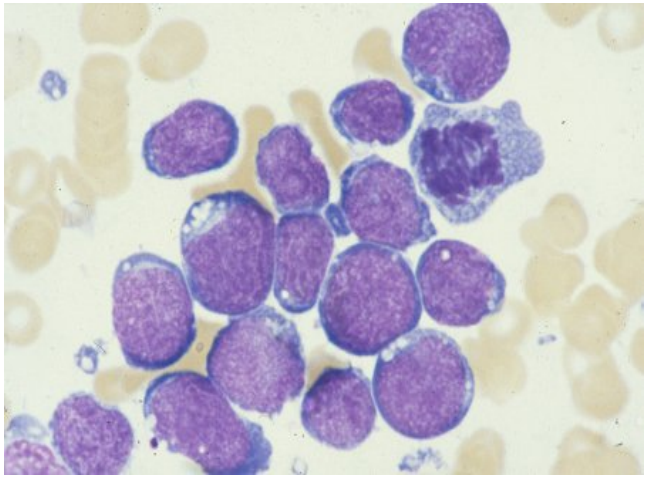
June et. al. Nat. Med. 23, 540–547 (2017)

Non-Hodgkin Lymphoma

- No peak in incidence
- Immunodeficiency (10-100x increased risk over general population)
  - Inherited or Acquired (HIV, post-transplant)
  - Often EBV associated
  - NHL in < 3 years of age – suspect immunodeficiency
- Environmental Exposures
  - Insecticides/pesticides – adult NHL only
  - Viruses – EBV (endemic malaria regions and Burkitt lymphoma and immunodeficiency)

Burkitt Lymphoma





- Mature B-cell (TdT-), CD10(+/-), CD19(+), CD20(+), sIg (+)
- *C-MYC (+)*
- Burkitt leukemia (B-ALL) (20% of cases)
  - treated same as lymphoma
- Abdominal disease most common presentation
- Head & neck second most common site
- Extranodal disease very common
- Very rapidly growing ($t_{1/2}$ = 18-24 hr)

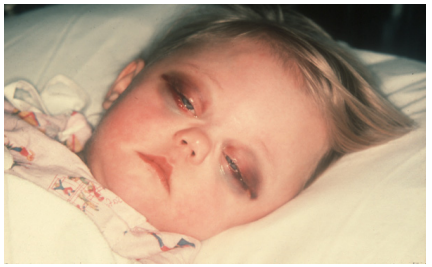
T. Gross

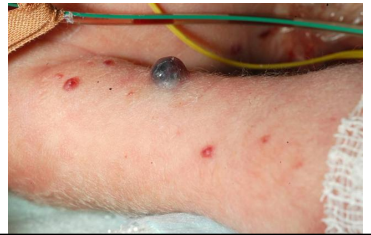
Treatment

- **Potential Complications:**
  - **Superior vena cava syndrome**
    - Sx: Cough, dyspnea, orthopnea, dysphagia, wheezing, hoarseness, facial edema, chest pain.
    - Treatment
      - Tissue diagnosis if possible
      - Emergency XRT +/- steroids
  - **Tumor lysis syndrome**
- **Treatment: Chemotherapy**

Neuroblastoma

- Second most common solid neoplasm in childhood
- Originates from neural crest tissue (sympathetic nerve pathway)
- Median age of diagnosis is 22 months
- > 95% of cases are diagnosed before 10 years of age
- Clinical Presentation:
  - Asymptomatic mass (e.g. abdomen or chest)
  - Horner's Syndrome
  - Spinal Cord Compression (medical emergency)
  - "Racoon eyes"
  - Hepatomegaly
  - Systemic symptoms (hypertension,intractable diarrhea (VIP), opsoclonus/myoclonus)
  - Bone pain
  - Skin lesions





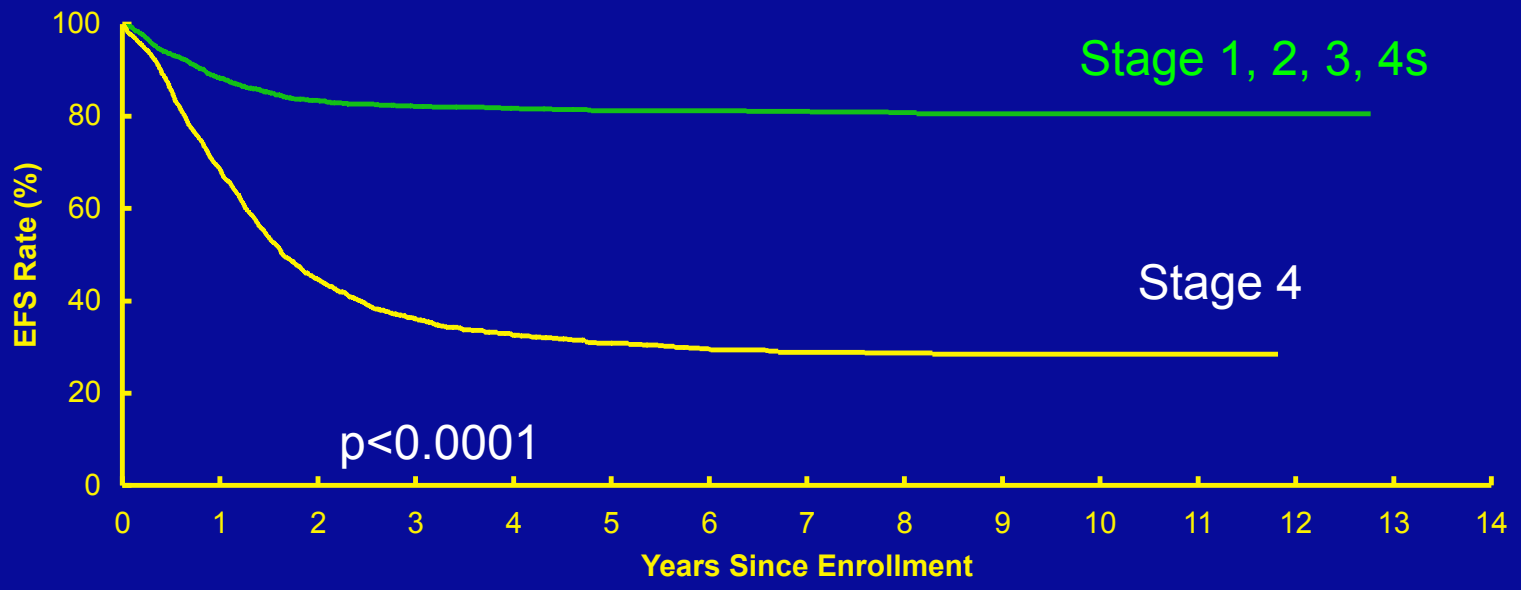
Neuroblastoma

- Workup:
  - Urine catecholamine levels (VMA/HVA)
  - Imaging (CT/MRI, CxR, MIBG)
  - Biopsy: MYCN
  - Bone marrow
  - Bone scan

Event-Free Survival by INSS Stage Cooperative Group Studies (CCG,POG,COG)

London W.B. COG Statistics and Data Center

1986-2001 (n=3,432)



Neuroblastoma

- Treatment:
  - Low risk: Surgery +/- chemotherapy
  - Intermediate risk: surgery + chemotherapy
  - High risk: Challenging

    (High dose chemo/ autologus stem cell transplant + surgery + radiation+immunotherapy)

- Screening:
  - Urine VMA/HVA measured in infants e.g. Japan
  - Increased rates of diagnosis but NO decrease in mortality
  - Spontaneous remission

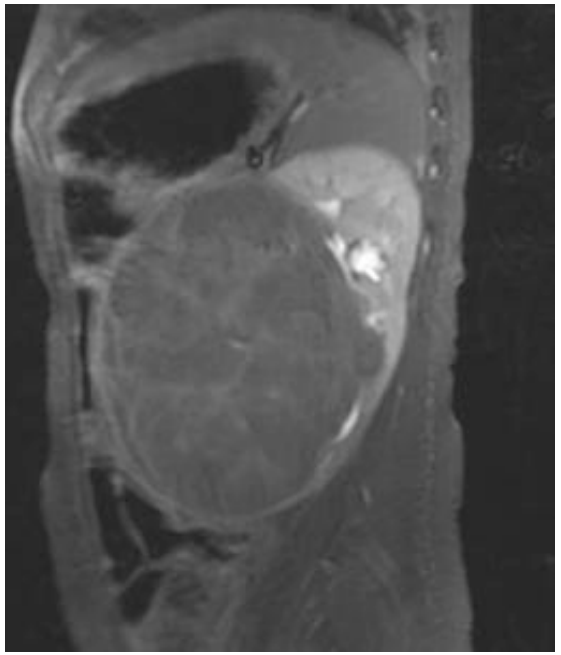
Wilms tumor

- Most common primary malignant renal tumor of childhood
- 5-10% of patients have bilateral tumors
- Median age at presentation:
  - Unilateral tumors: 44 months
  - Bilateral tumors: 31 months
- Clincial features:
  - Asymptomatic upper abdominal mass
  - Abdominal pain (20-30%)
  - Fever (20-30%)
  - Anemia
  - Hematuria (20-30%)
  - Hypertension (25%)

Wilms tumor

- Associated anomalies:
  - WAGR syndrome (wilms tumor, aniridia, genitourinary malformation, mental retardation)
  - Hemihypertrophy and Beckwith-Wiedemann syndrome

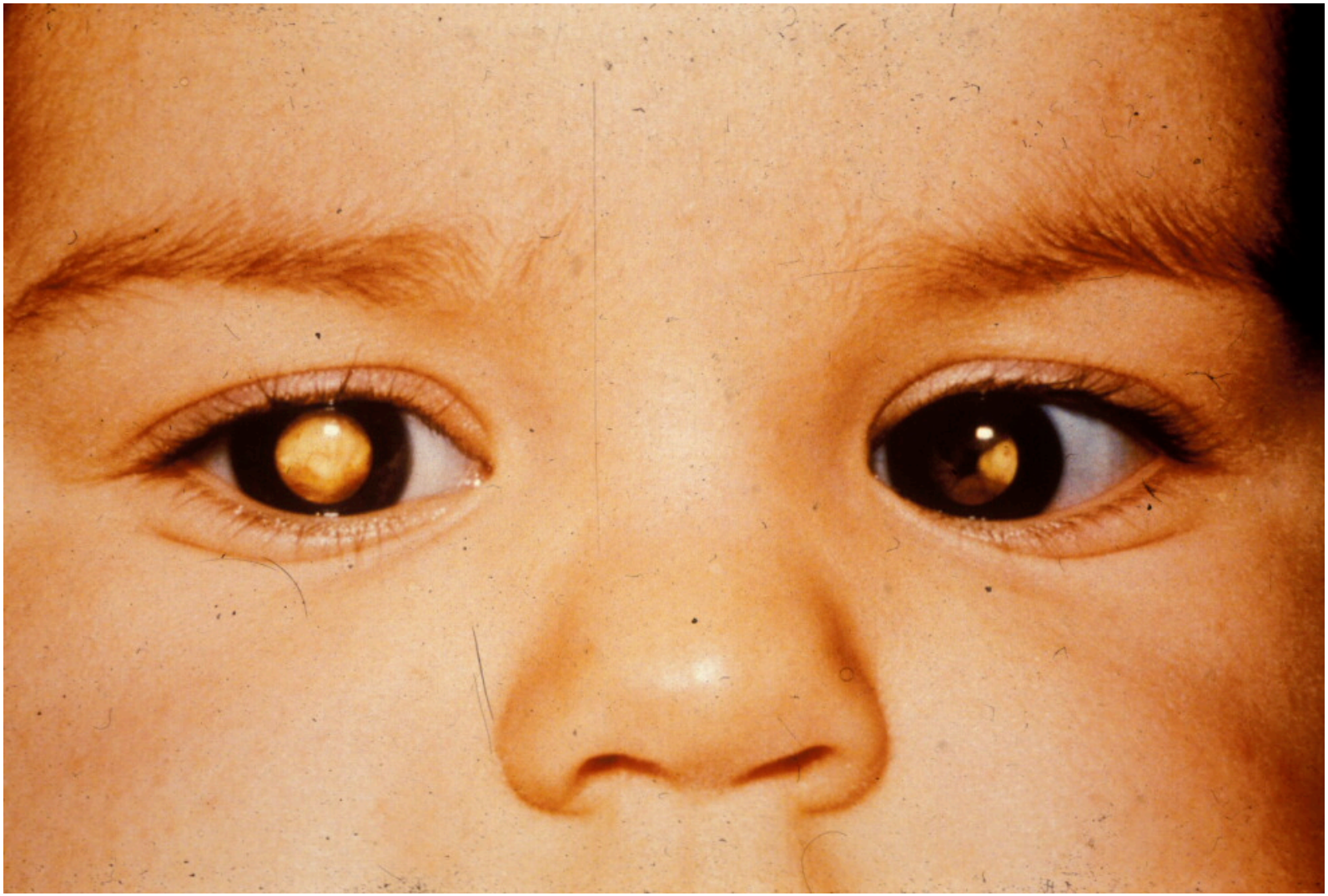
- Workup:
  - CBC, renal and liver functions
  - CT abdomen
  - CxR/CT chest

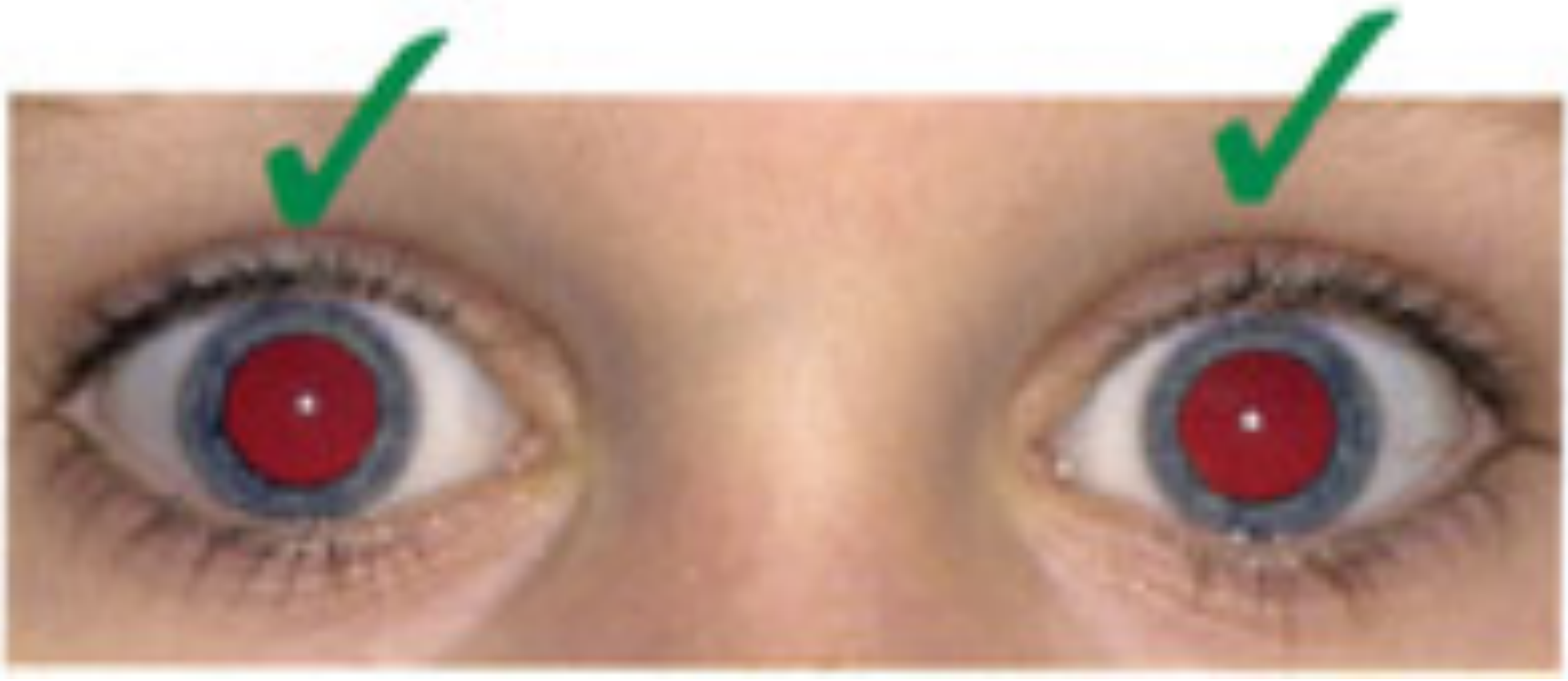


Wilms tumor

- Prognostic Factors:
  - Stage
  - Histology (anaplasia=unfavorable histology)
  - Tumors cytogenetics

- Treatment:
  - Surgery
  - Chemotherapy
  - Radiotherapy





Retinoblastoma

- US: 300 new cases/year
- Non-hereditary, unilateral:
  - 60-75% of cases
  - 2-3 yrs of age
- Hereditary, bilateral:
  - Germline mutation of *RB1*
  - 25-40% of cases
  - 6-18 months of age

- Workup:
  - Examination under anesthesia
  - MRI orbit and brain
  - Bone scan, BM, and CSF in advanced disease

- Treatment:
  - Priorities: Cure > eye salvage > vision preservation
  - +/- adjuvant chemotherapy +/- Radiotherapy +/- focal therapy +/- Enucleation