Childhood tumors

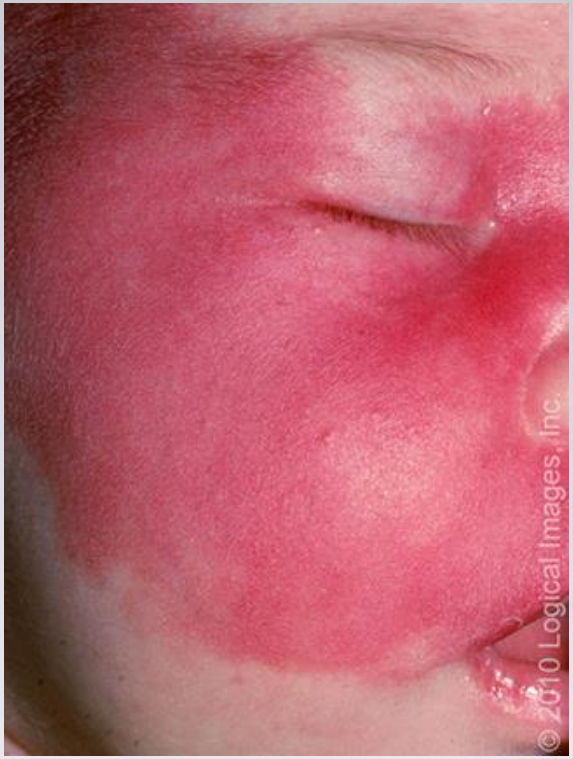
Judit Halász MD, PhD

18/10/2017

Benign tumors and tumor-like lesions

1. Hemangiomas:

- most common tumors in infancy
- located in the skin (face, scalp)
- Flat, large (port-wine stains)

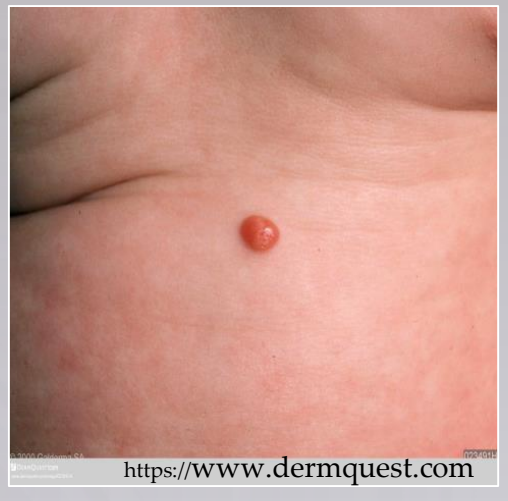


2. Lymphatic tumors:

- lymphangiomas (benign tumor)
- Lymphangiectasis (dilations of lymph channels**)**

3. Fibrous tumors:

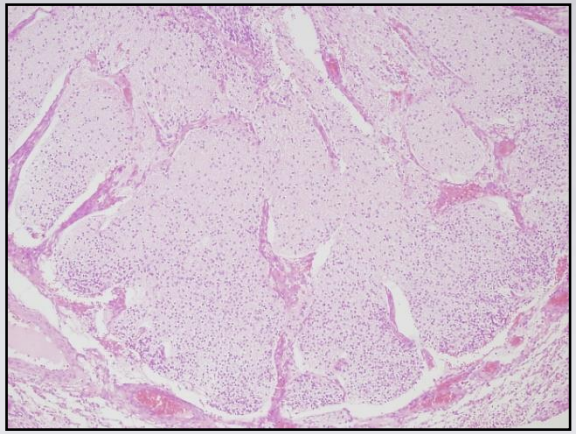
- myofibromatosis (most commonly benign soliter lesions)

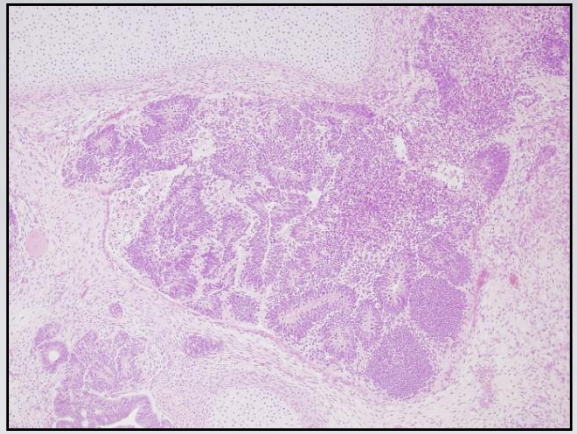


https://www.dermquest.com

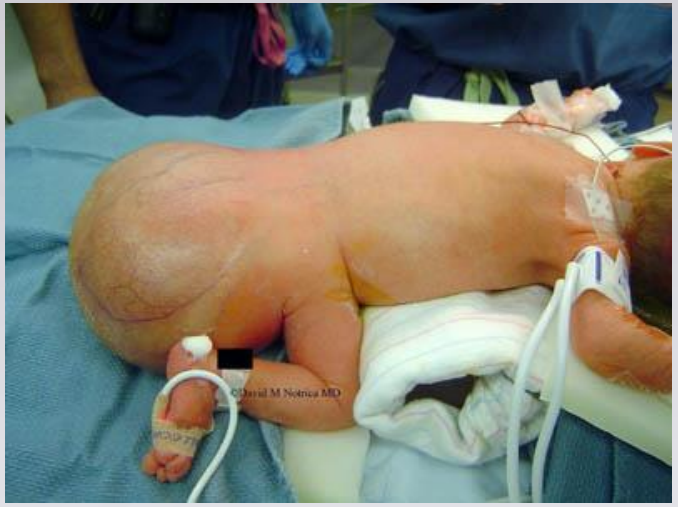
4. **Teratomas:**

- benign, cytic or solid malignant (immature) lesions
- in infancy and childhood most commonly sacrococcigeal
- testicular, ovarial, mediastinal, retroperitoneal
- 75 % are benign (mature tissue elements)
- 12 % are malignant (immature tissue elements)





mature tissue Neurotubules = immature tissue



http://www.phoenixchildrens.org/medical-specialties/pediatric-surgery/tumors/sacrococcygeal-teratoma

Distribution of Pediatric Malignancies in Hungary (2007)

1. **Leukemias (ALL 22 %, AML 4 %, CML 1 %)**
2. Brain tumors (25 %)
3. Lymphomas (NHL 7 %, HL 7 %)
4. Neuroblastoma (9 %)
5. Soft tissue tumors (6 %)
6. Wilms tumor (5 %)
7. Osteosarcoma (4 %)
8. Ewing sarcoma (4 %)
9. Retinoblastoma (2 %)
10. Germ cell tumors (2 %)
11. Pleuropulmonary blastoma
12. Liver tumors (1 %)

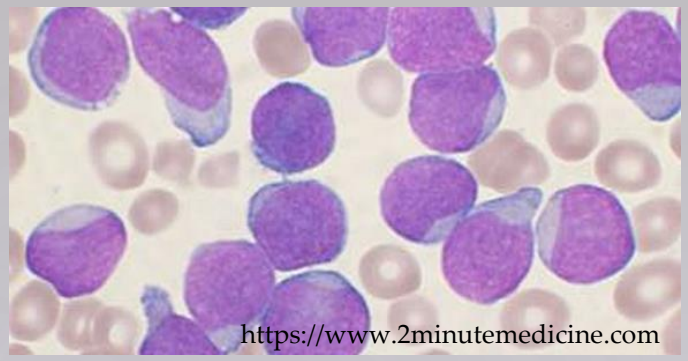
Hungarian National Registry of Pediatric Malignancies

Age distribution of malignant childhood neoplasms

0 to 4 years	5 to 9 years	10 to 14 years
Leukemia	Leukemia	
Retinoblastoma	Retinoblastoma	
Neuroblastoma	Neuroblastoma	
Hepatoblastoma	Hepatocellular carcinoma	Hepatoellular carcinoma
Soft tissue sarcomas (Rhabdomyosarcoma)	Soft tissue sarcoma	Soft tissue sarcomas
Central nervous system	Central nervous system	
Teratomas	Ewing sarcoma	
Wilms tumor	Lymphoma	
		Osteogenic sarcoma
		Thyroid carcinoma
		Hodgkin disease

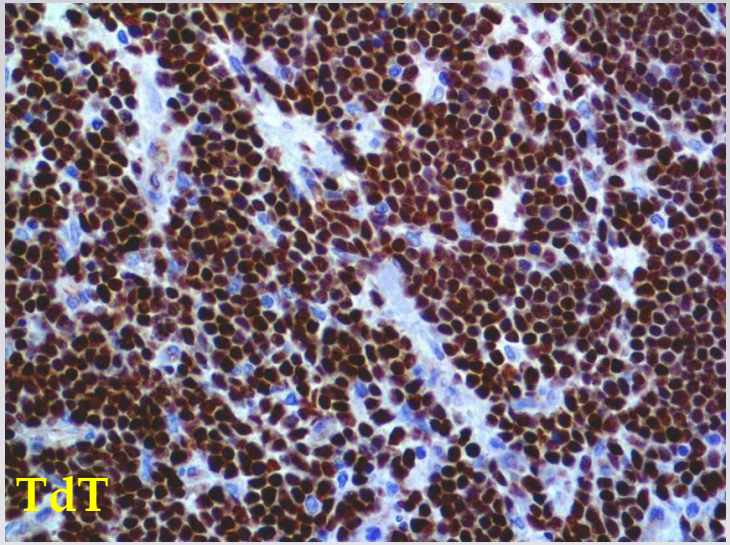
Kumar, Kotran, Robbins: Basic Pathology

LEUKEMIAS


https://www.2minutemedicine.com

1. Acut lyphoblastic leukemia/lymphoma

- precursor B (pre-B) or T (pre-T) **lymphoblasts**
- 85 % of ALLs are **pre-B tumors**
- typically manifest **as a childhood acut leukemias** with extensive bone marrow and variable periferal blood involvement
- the less common **pre-T cell ALLs tend to be present in adolescent** males as lymphomas, often with thymic involvement



www.biosb.com

1. **Pre-B cells expressing TdT (terminal deoxytransferase=DNA polymersae)**
2. **Lacking surface Ig**
3. **No azurophilic granules (AML) in the cytoplasm**
4. **TEL1 and AML1 genes rearrangent, t(12;21)**
5. **t (14;22) Philadelphia chromosome-like ALL with worse prognosis**

2. Acute myelogenous leukemia:

- most commonly 15 to 39 years

- 20 % of childhood leukemias

- **undifferentiated myeloblasts** with early myeloid differentiation

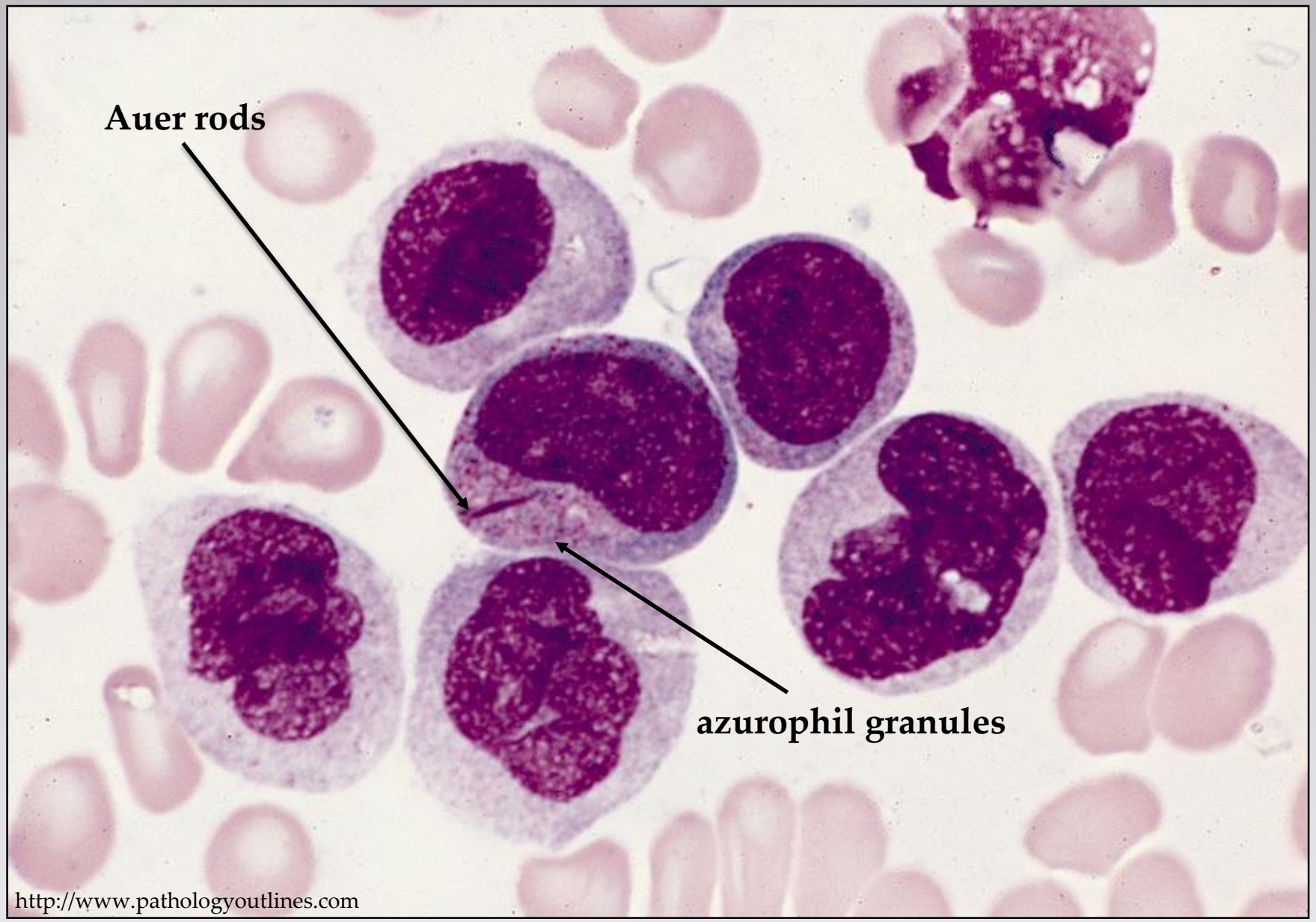
- neoplastic myeloid precursor cells accumulate in the marrow and **suppress remaining normal hematopoetic progenitor cells** by phisical replacement

- failure of normal hematopoesis results in anaemia, neutropenia and thrombocyto-penia

A. French-American-British **(FAB)** classification system was used from 1976 to 2001, divided AML into M0-M7 (*Br J Haematol 1976;33:451*)

B. WHO classification (2001 and revised in 2008) requires **minimium of 20% of blasts in bone marrow or blood to diagnose AML** (was 30 % under FAB), which eliminates myelodysplastic category of "refractory anemia with excess blasts in transformation" (*Blood 2002;100:2292*).

C. WHO classification also separates out AML "with recurrent genetic abnormalities", which have distinct clinical features


Auer rods
azurophil granules
http://www.pathologyoutlines.com

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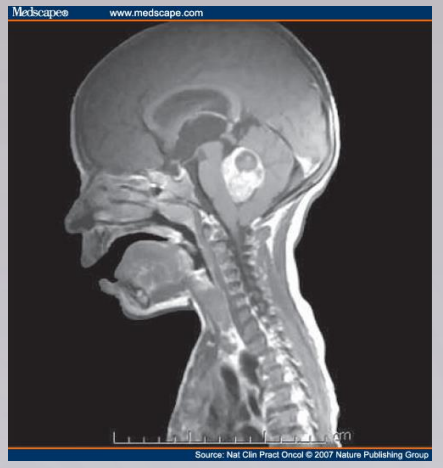
Hungarian National Registry of Pediatric Malignancies

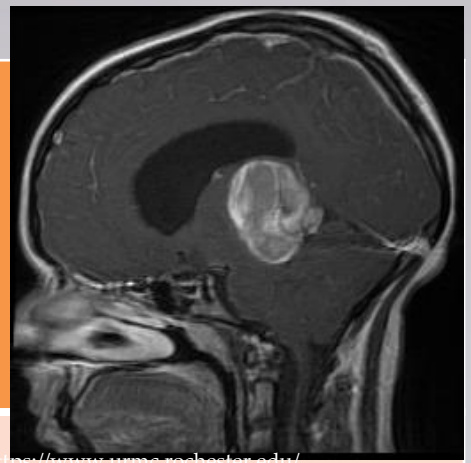
Malignant tumors of central nervous system



- Primary malignant CNS tumors are the **second** most common childhood malignancies
- CNS tumors account for approximately **20 %** of all childhood malignancies
- approximately 1/3 to 1/2 are located in the **posterior fossa**
- **CLASSIFICATION** — Two main classification systems are used to categorize childhood CNS tumors:
- World Health Organization (**WHO**) classification is based on tumor histology and molecular parameters.
- International Classification of Childhood Cancer (**ICCC**) is based on the primary tumor site and morphology.

GLIOMAS - classified as tumors of neuroepithelial tissue, derived from the glial cells (astrocytes, oligodendrocytes, ependymal cells)

1. ASTROCYTOMAS



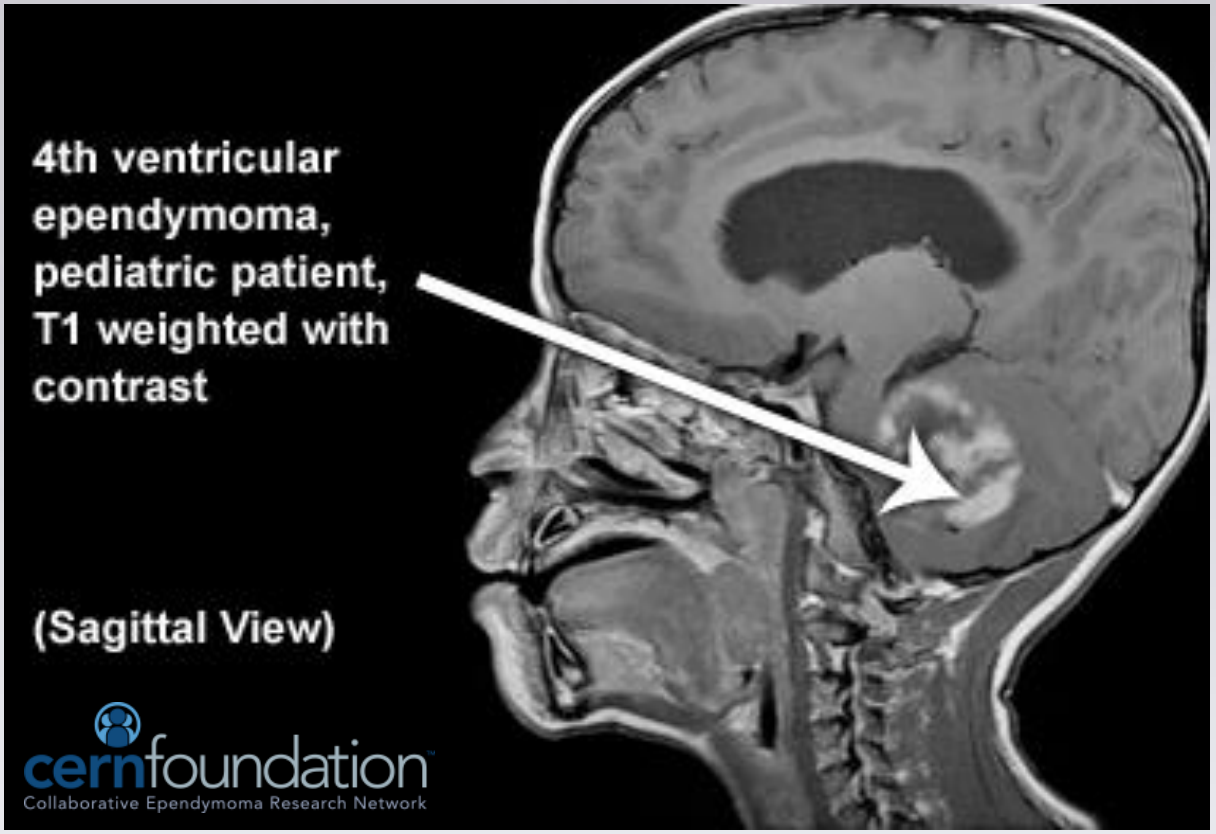
Low grade astrocytomas (largest group): pilocytic astrocytomas (most common), diffuse astrocytomas, oligodendroglial tumors and gangliogliomas.

High grade malignant astrocytomas: anaplastic gliomas, diffuse intrinsic pontine glioma and glioblastoma.

Highly malignant and agressive tumors with extremely poor prognosis.

2. EPENDYMOMAS

Derived from **primitive glia**. 10 % of intracranial tumors, 60 % located in the posterior fossa or within the fourth ventricle, 40 to 60 % of the spinal cord tumors.



Embrional tumors	Medulloblastoma, primitive neuroectodermal tumors, atypical teratoid rhabdoid tumors
Tumors of sellar region	Pituitary tumors
Neuronal and mixed neuronal-glial tumors	Gangliomas, gangliocytomas, dysplastic gangliocytoma of cerebellum, cerebellar liponeurocytomas, central neurocytomas and glomus tumor.
Tumors of cranial and paraspinal nerves	Schwannomas, neurofibromas, and malignant peripheral nerve sheat tumors.
Germ cell tumors	Germinoma, embryonal carcinoma, yolk sac tumor, choriocarcinoma, and teratoma.
Meningiomas	Arise from the arachnoidal cap cell in the arachnoid membrane having varying degrees of malignancy.
Lymphomas	Rare
Unclassified tumors	Hemangiomas, unspecified neoplasm

Epidemiology of central nervous system tumors in children
Ching Lau, MD, PhD
Wan-Yee Teo, MBBS, FAAP, MRCPCH (UK), PhD
Section Editor
David G Poplack, MD
Deputy Editor
Carrie Armsby, MD, MPH

MEDULLOBLASTOMA

- highly cellular tumors presumed to **arise from neuronal precursors in the cerebellum** (stem cells located in the subependymal matrix and the **external granular layer (EGL) of the cerebellum**).

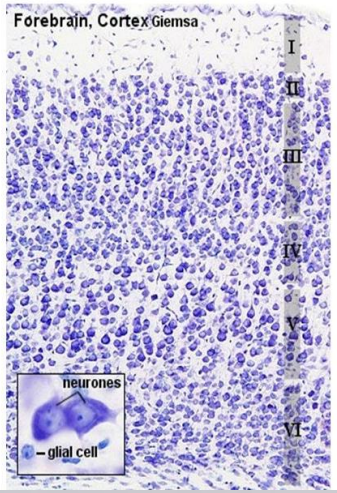
- In about 5 % of cases, medulloblastomas have been associated with **inherited disorders:**

- The **Gorlin syndrome** (**nevoid basal cell carcinoma** syndrome) is due to the mutations in the patched-1 (PTCH1) gene, which is a key component in the **sonic hedgehog (SHH)** pathway. SHH is produced by Purkinje cells and stimulates growth and migration of granule neuron precursor cells.

- In **Turcot syndrome** medulloblastomas are seen in conjuction with **colonic polyposis**. This syndrome is associated with mutation in the pathway.

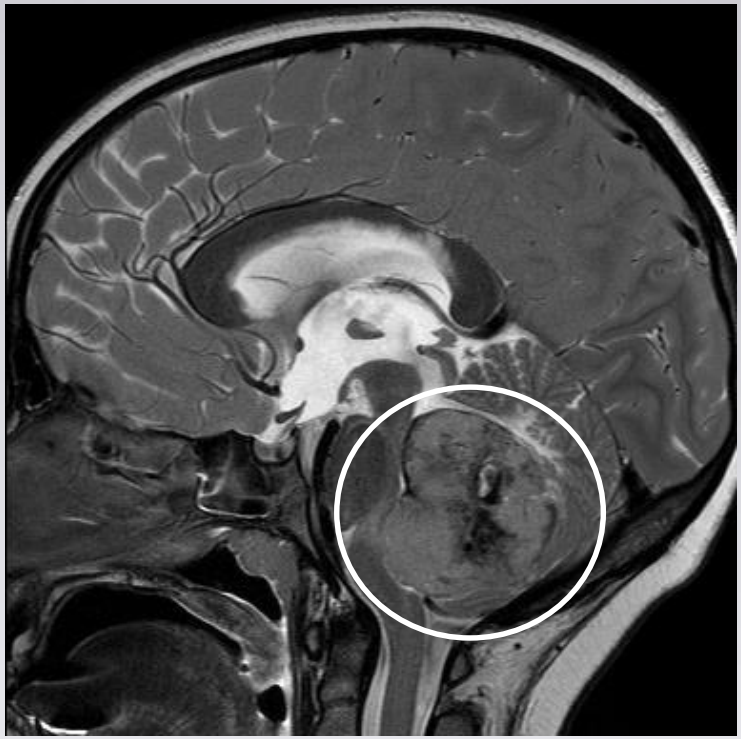
- 4 molecular subgroups of medulloblastoma have been identified having divergent tumor cell histology, genetics, clinical behavior, and patient outcomes: **SHH, WNT, GROUP 3**, and **GROUP 4**

1)molecular layer
2)external granular layer
3)pyramidal layer
4)internal granular layer
5)ganglionic layer
6)multiform layer

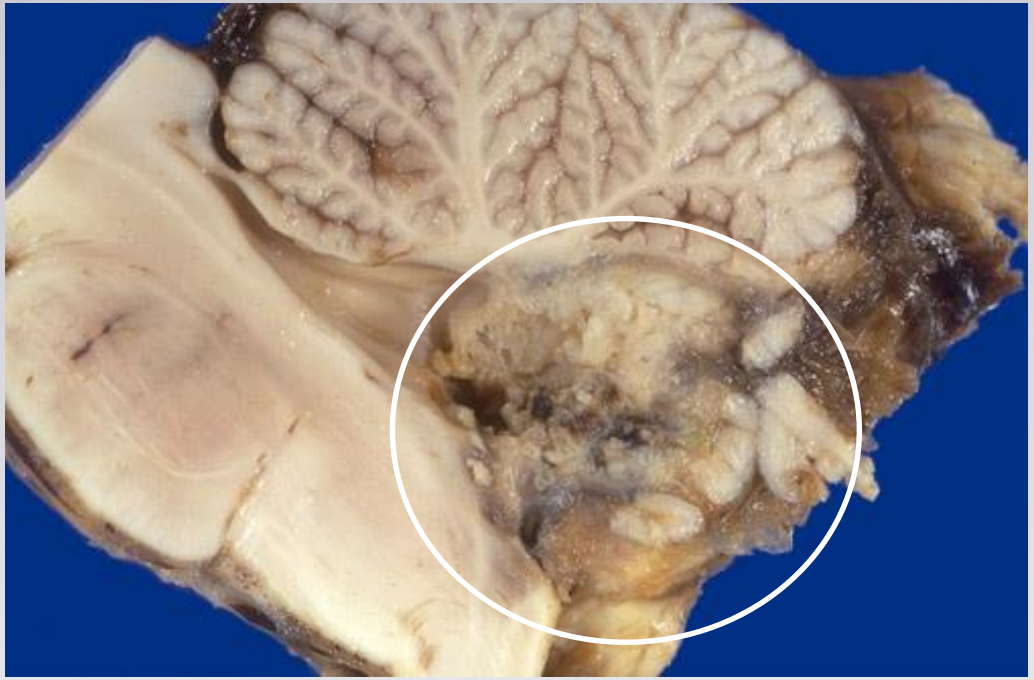


Kharkhov National Medical University, Department of histology, cytology and embryology

- Cerebellum and dorsal brain, posterior vermis, and roof of the fourth ventricle
- Nausea, vomiting, headache
- Distroy the brain tissue, leptomeningeal dissemination
- Low level of glucose and tumor cells in CSF
- Extracranial metastases are rare
- Operation, chemotherapy, intrathecal chemotherapy, radiotherapy



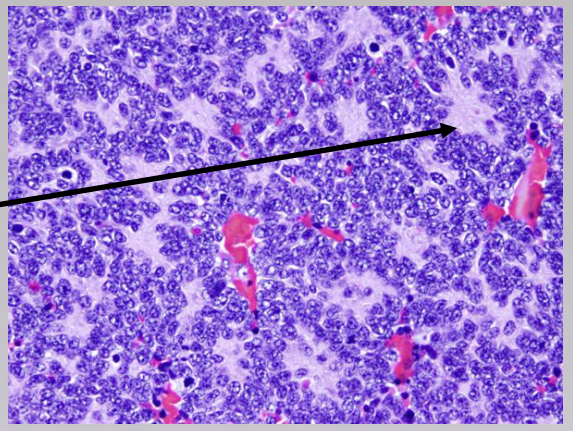
http://neuropathology-web.org



Pathology Learning Resources
Duke University Medical School

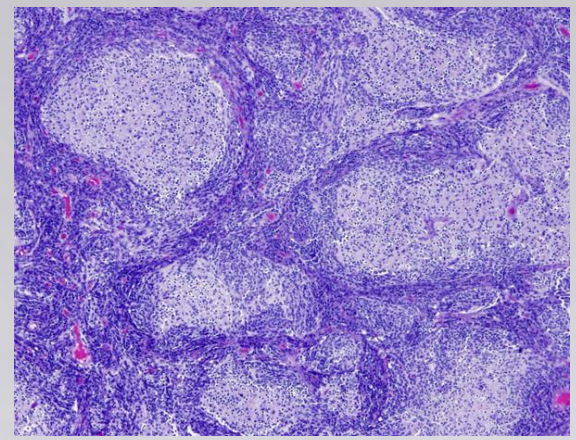
- **Classic medulloblastoma:**

Small blue round cell tumor
Syncytial arrangement of densely packed undifferentiated cells (embryonal cells)
Mitosis with apoptotic bodies
Homer-Wright rosettes



- **Desmoplastic/nodular medulloblastoma:**

Densely packed, undifferentiated cells with hyperchromatic and pleomorphic nuclei which produce dense intercellular reticulin fiber network with nodular reticulin free zones

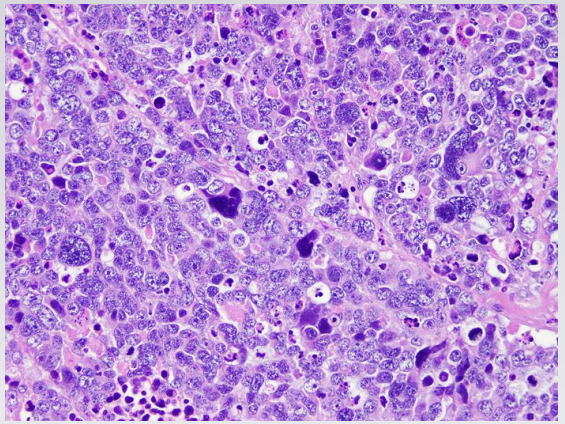


- **Medulloblastoma with extensive nodularity:**

Expanded lobular architecture as reticulin free nodular zones are enlarged and rich in neuropil-like tissue

- **Large cell / anaplastic medulloblastoma:**

Anaplasia with marked nuclear pleomorphism, high mitotic count and apoptotic counts
Nuclear molding and cell wrapping
(Pathol Res Pract 2016;212:965)



Molecular pathway	WNT	SHH	Group 3	Group 4
Genes	Beta-catenin mutation, APC, monosomy 6, TP53	PTCH1 deletion! SUFU deletion, MYCN amplification, TP53 mutant/wilde	MYCN amplification, isochromosome 17q	MYCN amplification, isochromosome 17q
Clinical profile	Older children and adults, good prognosis	Infants, children, and adults, intmediate prognosis	Infants, children, poor prognosis	Older children, adults, most common form, intermedate prognosis
Tumor location	IV ventricule, infiltration of dorsal brainsterm	Cerebellar hemispheres	Cerebellum NOS	Cerebellum NOS
Histology	Classic	D/N, LCA	Classic, LCA	Classic, LCA
Cells of origine	Precursor around the IV ventricule	EGL	EGL	Unknown
Tumor syndrome	Tucrot	Gorlin	None	None

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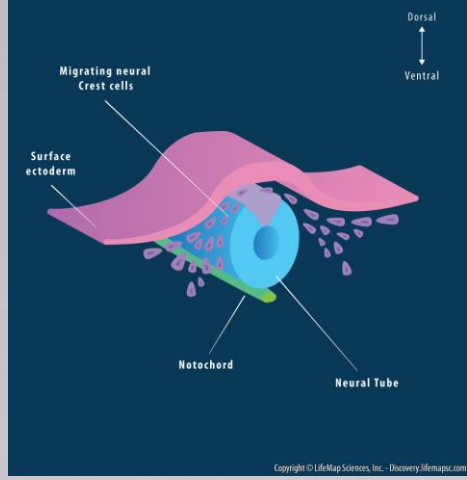
Hungarian National Registry of Pediatric Malignancies

NEUROBLASTOMA



- a spectrum of **neuroblastic tumors** (including neuroblastomas, ganglioneuroblastomas, and ganglioneuromas)
- arise from **primitive sympathetic ganglion cells** originated from the neural crest during the fetal development (adrenal medulla, sympathetic nervous system)
- by contrast, pheochromocytomas and paragangliomas arise from a different type of cell (chromaffin cells)
- 3rd most common childhood cancer (leukemias, brain tumors)
- most commom **extracranial** solid malignant tumor during the first two years of life
- most common cancer among infants younger than 12 months
- slightly more common among boys and white infants

Risk factors (maternal and infant)

- **opiate compsuption**
- **folate deficiency**
- **toxic exposures**
- **congenital abnormalities**
- **size of gestational age**
- **gestational diabetes**

Risk factors (genetic)

- **Turner syndrome**
- **Hirsprung disease**
- **Neurofibromatosis 1**

Familial cases (1-2 %)

Signs and symptoms and sites

- abdominal pain
- abdominal mass
- diarrhoea, obstipation (catecholamines (CA) production: dopamin, HVA, WMA in urine/blood)
- pain and weakness
- ophtalmic involvement: Horner syndrome (ptosis, miosis, enophtalmus), proptosis and opsoclonus
- hypertension (CA, renal artery obstruction)

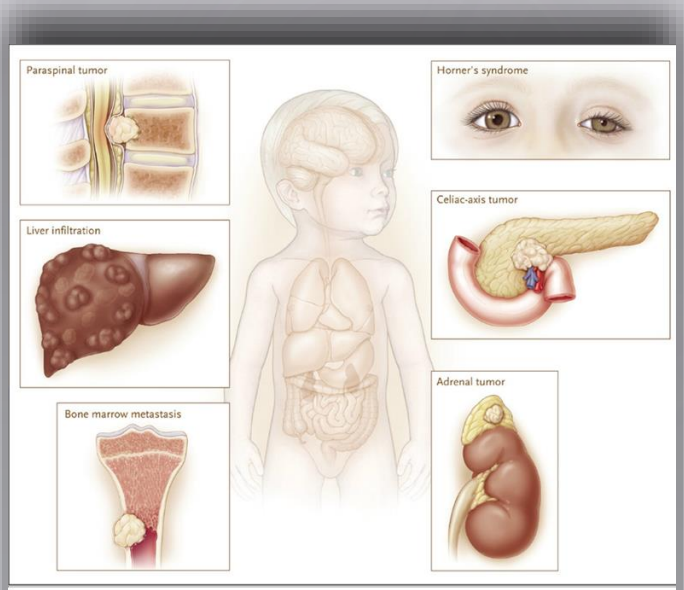


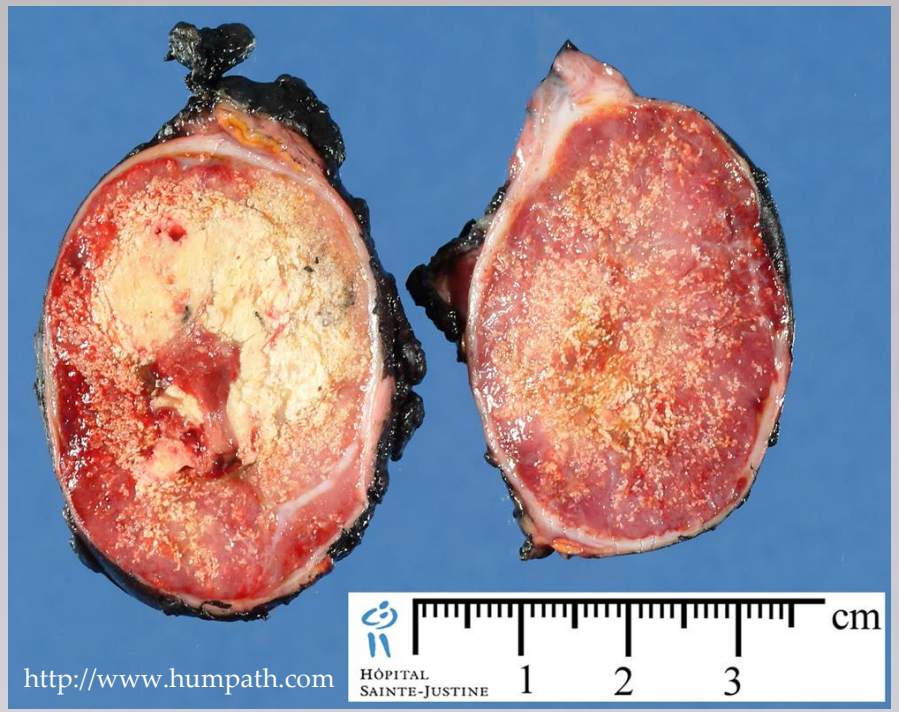
Figure 2. **Possible Locations of Neuroblastoma Tumors.** Neuroblastoma tumors begin in the adrenal gland, then may metastasize throughout the body to the liver, spine, orbits, intestines and bone. Slide adapted from (Maris, 2010, New England Journal of Medicine)

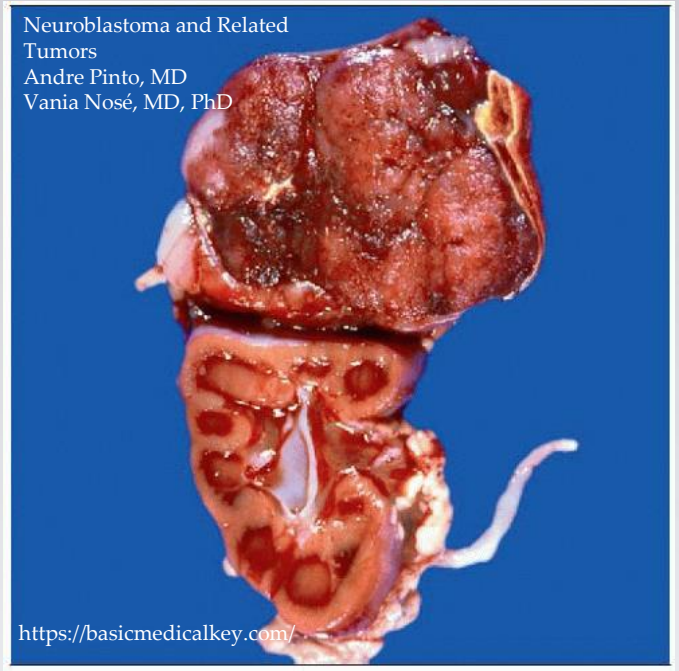
Sites:

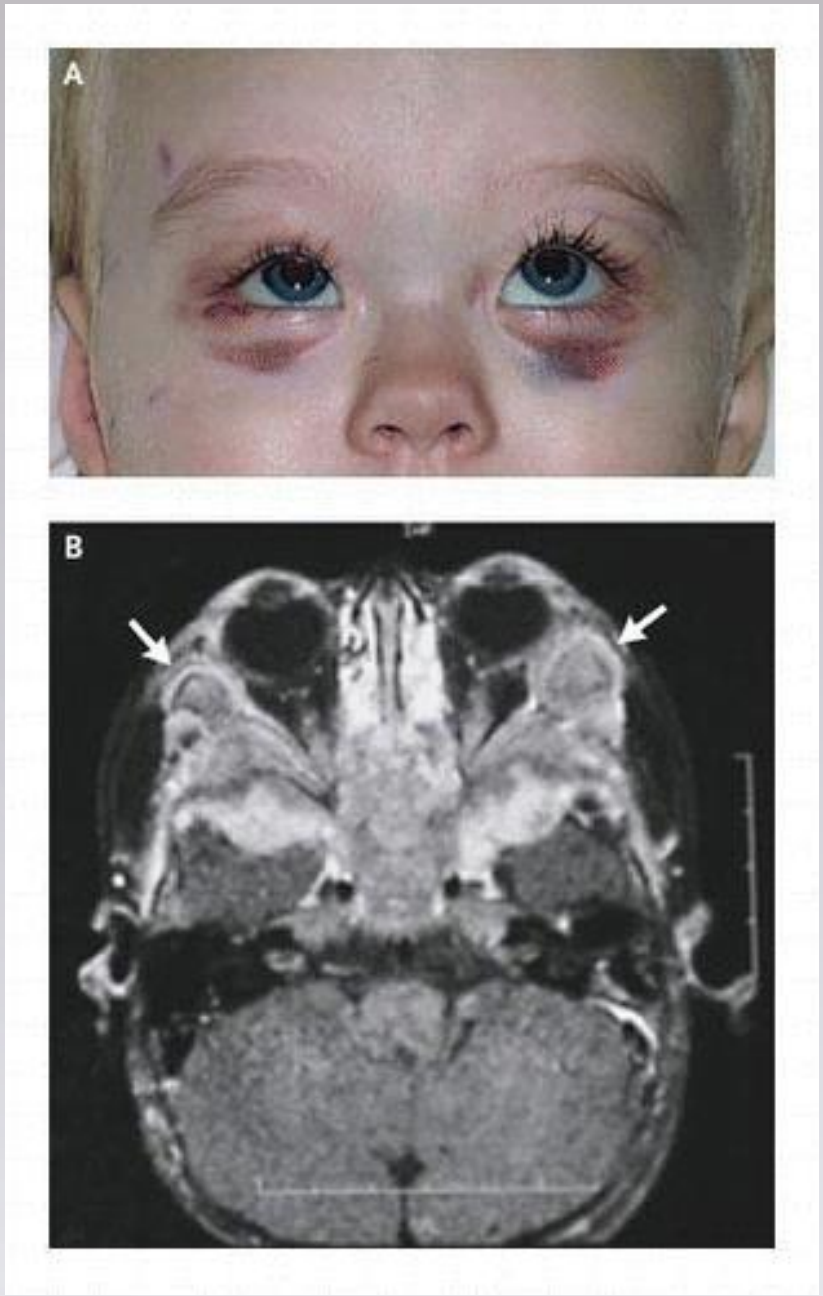
- **Suprarenal glands (medulla)**
- **Retroperitoneum**
- **Mediastinum**
- **Paravertebral region**
- **Sympathetic nervous system**

Metastases:

- **Bones**
- **Orbital region**
- **Liver**
- **Lung**
- **Lymph nodes**







Raccoon Eyes and Neuroblastoma
Robert Timmerman, M.D.
N Engl J Med 2003; 349:e4July 24, 2003DOI: 10.1056/ENEJMicm020675

Prognostic factors

- **Age:** infants **< 1 year** = excellent prognosis (most cases are in stage I or stage II) **(seems to be lost in children over the age of two)**
- **Ploidy** of the tumor cells correlates with outcome: **hyperdiploid or near-triploid** tumors occuring in infants have a particularly good prognosis
- **Deletion** of the distal short arm of **chromosome 1** (1p) in the region of band p36 is the most common cytogenetic abnormality (70-80%) having worse prognosis.
- **Amplification** of **N-myc oncogene** having a worse prognosis.
- **Differentation and regression (Trk A receptor):** high levels of expression of Trka A gene are associated a favorable outcome (lacking N-myc amplification)
- **Preserved** lenght of telomeres (poor prognosis)

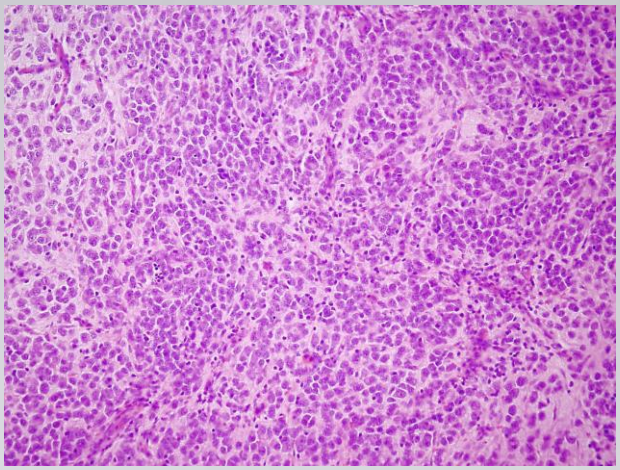
HISTOLOGY OF NEUROBLASTOMA

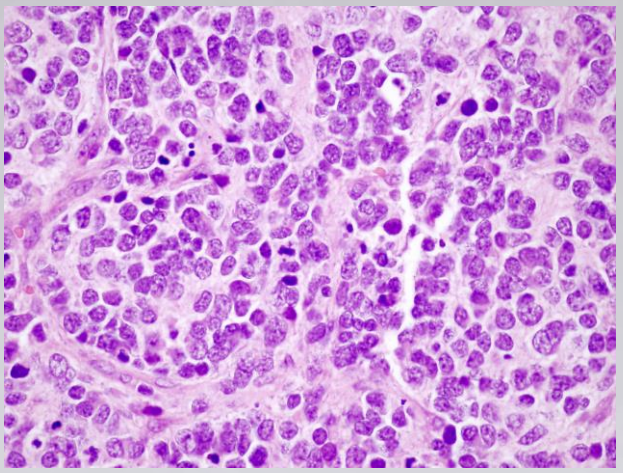
The International Neuroblastoma Pathology Classification classifies tumors of neuroblastic origin.

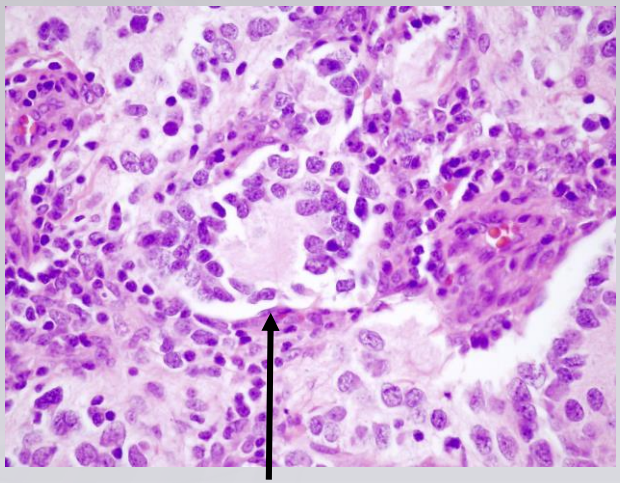
1. Neuroblastoma

neuroblasts, no Schwannian (stromal cells) = **stroma poor tumors**

undifferentiared, poorly differentiated and differentiating forms







Homer-Wright pseudorosette

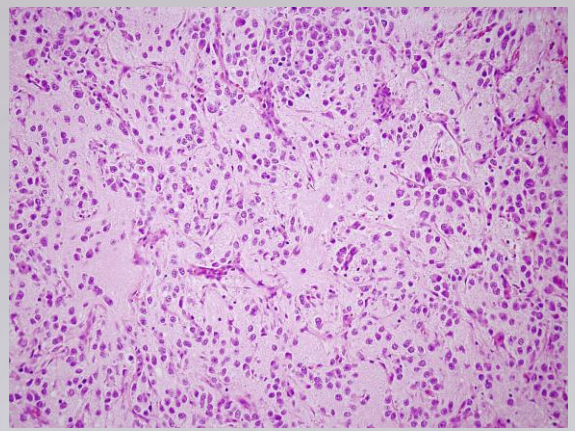
Diff.diagnoses:

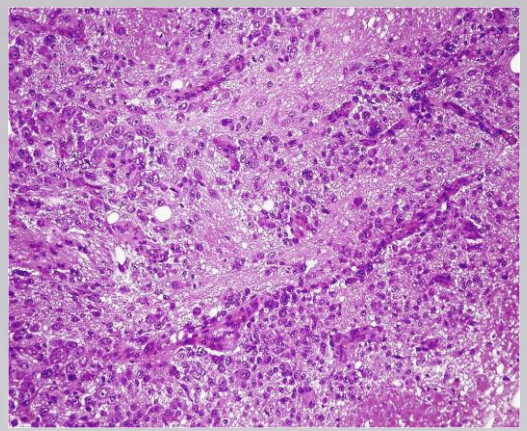
small round blue cell tumors: lymphoma, Ewing/PNET, undifferentiated soft tissue sarcomas, small cell osteosarcoma, desmoplastic chondrosarcoma

NSE, S-100 , synaptophysin and chromogranin can help

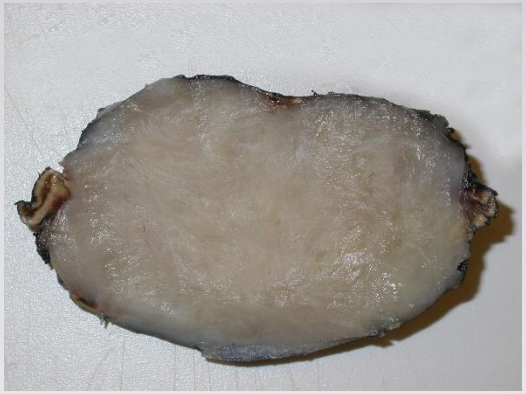
2. Ganglioneuroblastoma (mature ganglion cells and neuroblasts)

"Intermixed-stroma rich" or "stroma rich" (Schwannian cells)

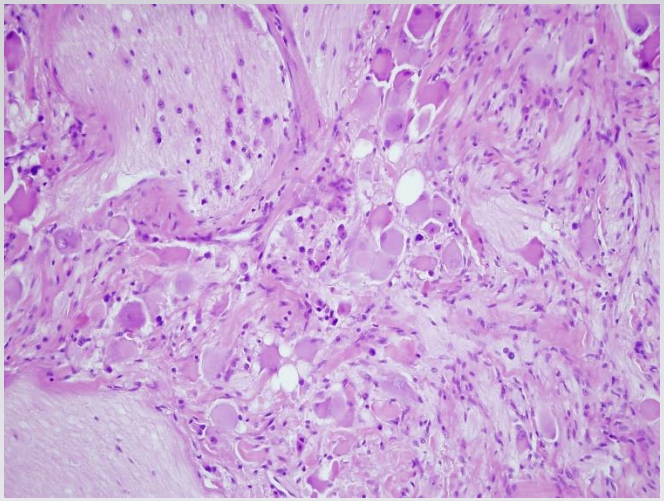




3. Ganglioneuroma (Schwannian cell dominant)



Spontanous regression!!



Mature ganglion cells and nerves

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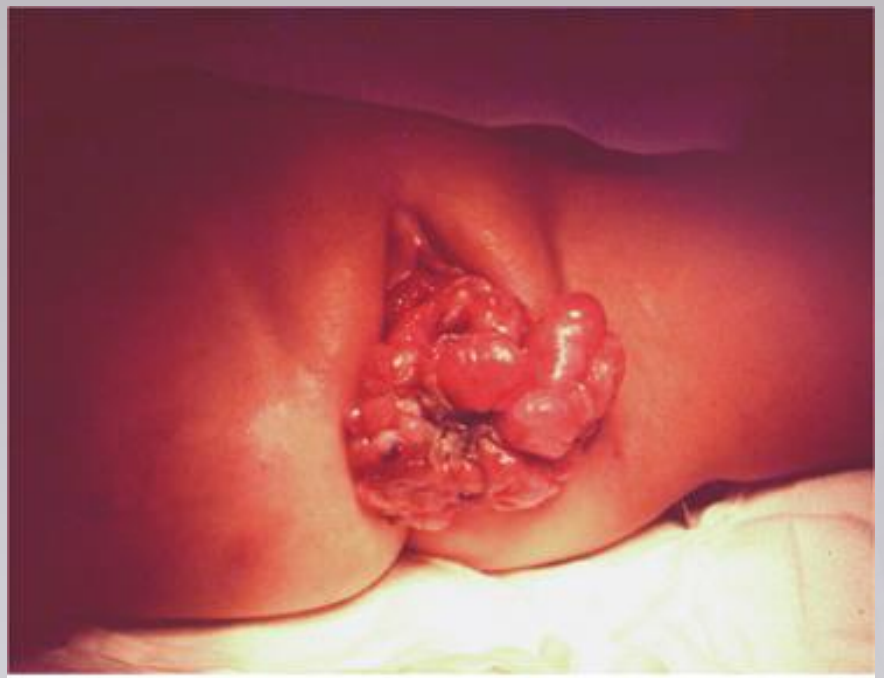
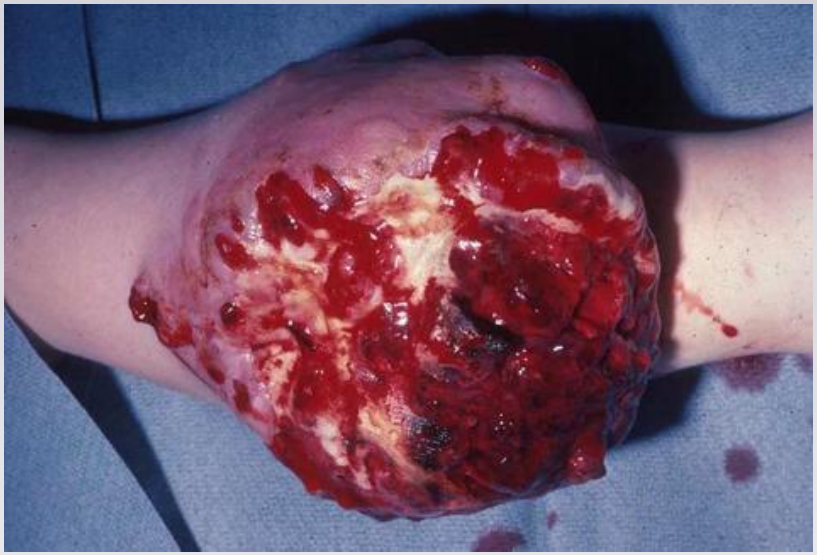
RHABDOMYOSARCOMA

- More commonly in children younger than six years of age, small male predominance
- **head and neck** RMS are more common in younger children (the orbit), they are almost always of the **embryonal type**
- nearly 80 % of **genitourinary** tract RMS **are embryonal**
- **botryoid variant** (sarcoma botryoides), a unique form of embryonal RMS arising within the **wall of the bladder or vagina**, is seen almost exclusively in infants (vaginal bleeding, bulky tumorous mass)
- **extremity** tumors more commonly in adolescents and are frequently **alveolar type**
- the etiology and specific risk factors for RMS are not known
- most cases of RMS appear to be sporadic, but the disease has been associated with familial syndromes such as neurofibromatosis, the Li-Fraumeni, **Beckwith-Wiedemann**, and **Costello syndromes**

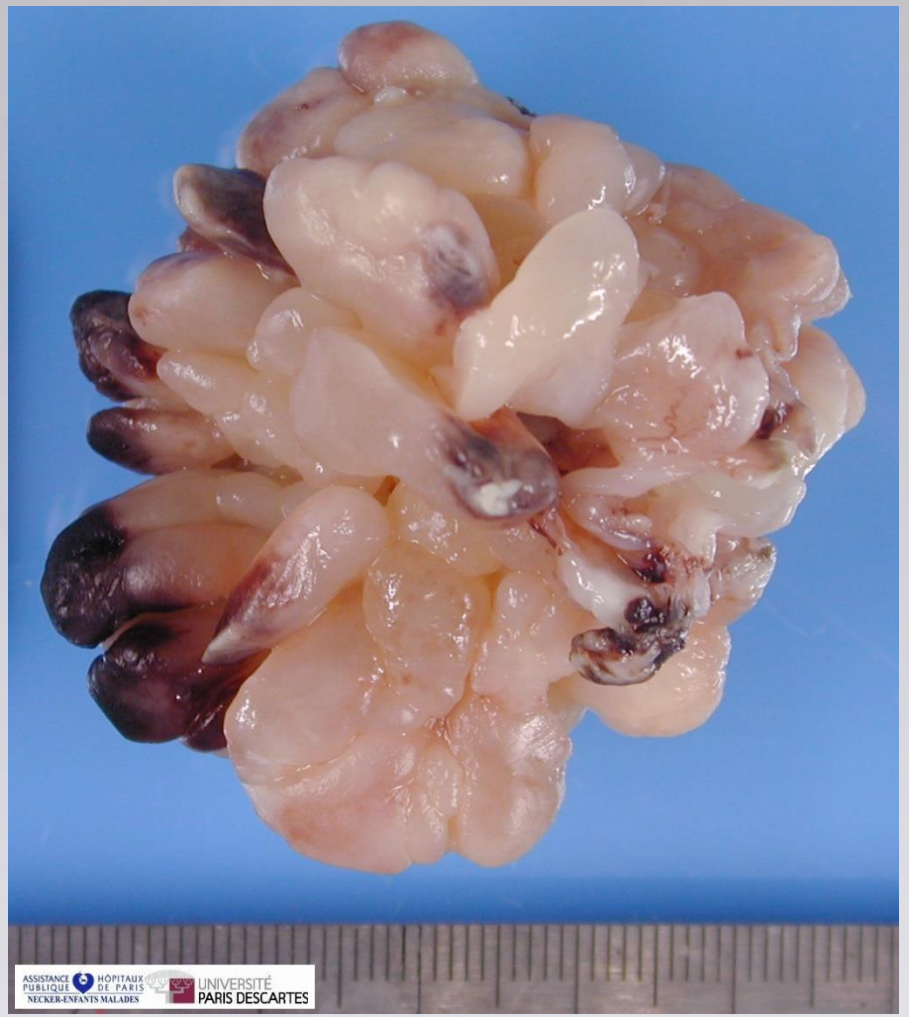


Fuente: Barbara L. Hoffman, John O. Schorge, Joseph I. Schaffer, Lisa M. Halvorson, Karen D. Bradshaw, F. Gary Cunningham: *Ginecología de Williams*, 2e: www.accessmedicina.com



www.cancerwall.com

Grape-like structure



Histology:

1. Embryonal RMS:

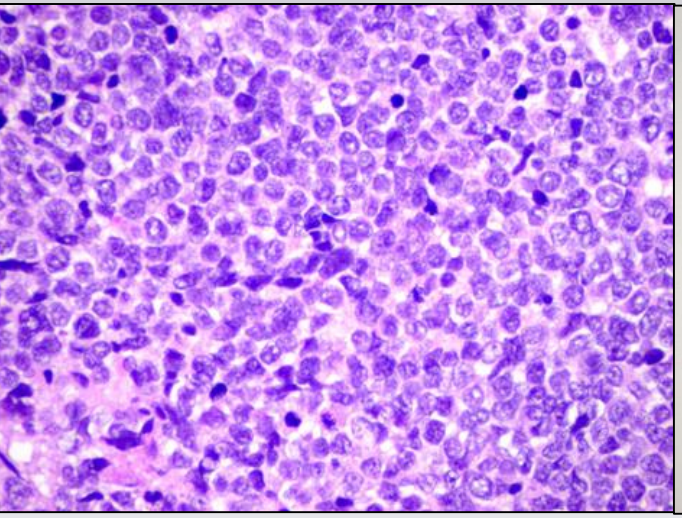
- composed of typical rhabdomyoblasts
- no alveolar arrangement

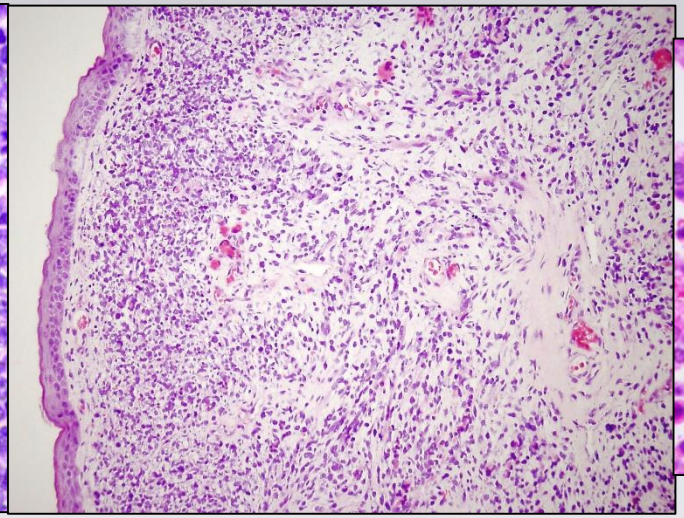
2. Botryoid variant

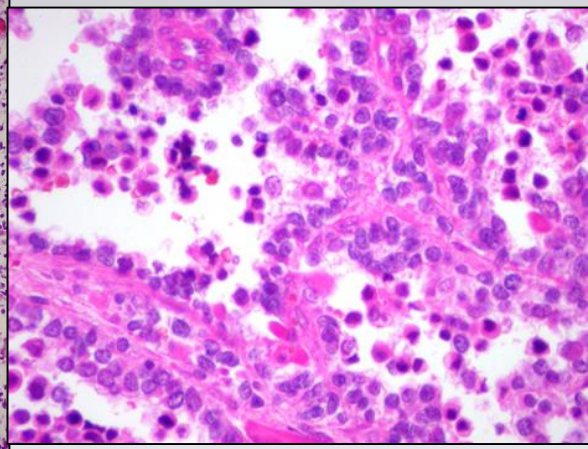
- grape-like appearance
- epithelial surface, and subepithelial dense aggregates of rhabdomyoblasts (the so-called "cambium" layer)

3. Alveolar type:

- predominant (>50 percent) alveolar component
- characteristic translocations t(1;13) or t(2;13)







4. Anaplastic type: undifferentiated

Alveolar RMS and chromosome translocations:

- More commonly, chromosome **2 and 13, t(2;13)(q35;q14)** fuses the **PAX3 gene** (transcription regulator in early neuromuscular development) with the FKHR **(FOXO1) gene** (transcription factor).

- second, less common translocation, **t(1;13)(p36;q14),** fuses a different gene, the **PAX7** with **FOXO1** (better prognosis)

- **Detection of transcriptions: Real-Time PCR (RT-PCR), FISH (with FOXO1 probe)**

Fusion negative cases (45 %): similar to embryonal type – favorable outcome

Embryonal type geneteic alterations:

- **loss of heterozygosity** (LOH) at the 11p15 locus

Common and variant gene fusions predict distinct clinical phenotypes in rhabdomyosarcoma.
Kelly KM, Womer RB, Sorensen PH, Xiong QB, Barr FG
J Clin Oncol. 1997;15(5):1831.

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10. Germ cell tumors (2 %)
11. Pleuropulmonary blastoma
12. Liver tumors (1 %)

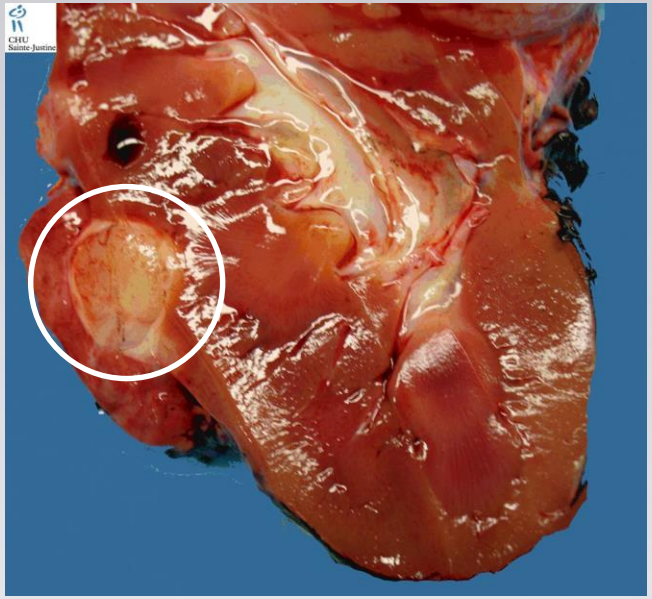
Hungarian National Registry of Pediatric Malignancies

WILMS TUMOR

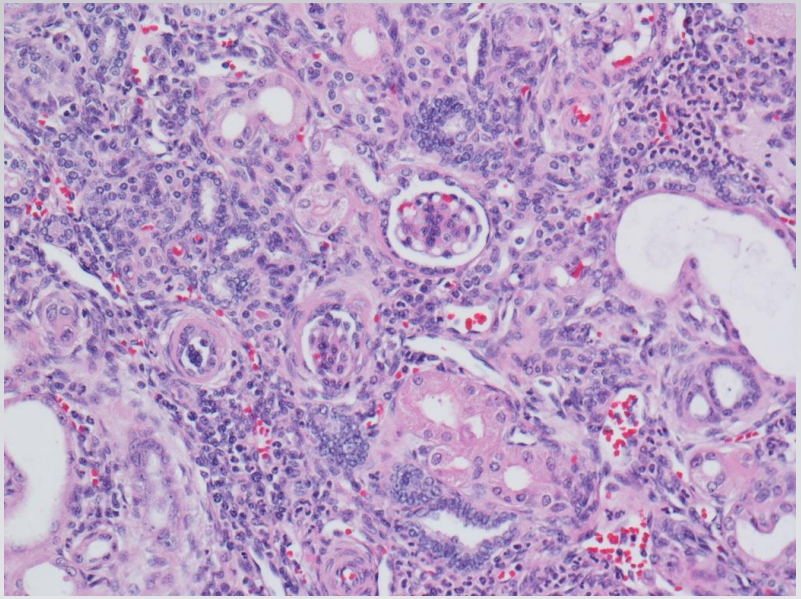
- **prolifetating metanephric blastema** without normal tubular and glomerulal differentiation

- arise from foci of **persistent metanephric cells** referred to as **nephrogenic rests** or nephroblastomatosis

- **Nephrogenic rests** normally occur in 1 percent of newborn kidneys and regress early in childhood. In contrast, they are present in 35 percent of kidneys with unilateral Wilms tumor and almost 100 percent of kidneys with bilateral disease.



Mandolin Ziadie, M.D.
2003-2016, PathologyOutlines.com, Inc.



Mandolin Ziadie, M.D.
2003-2016, PathologyOutlines.com, Inc.

- loss of function, mutations of a number of **tumor suppressor and transcription genes:** WT1,TP53, FWT1, FWT2, 11p15.5

1. WT1 gene is located on chromosome 11p13:

gene product is expressed in the developing kidney, testis, and ovary
play a role in the development and differentiation of genitourinary tissues

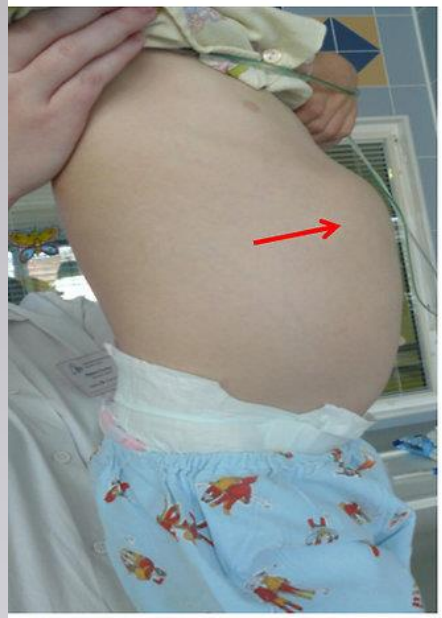
WT1 associated congenital syndromes:

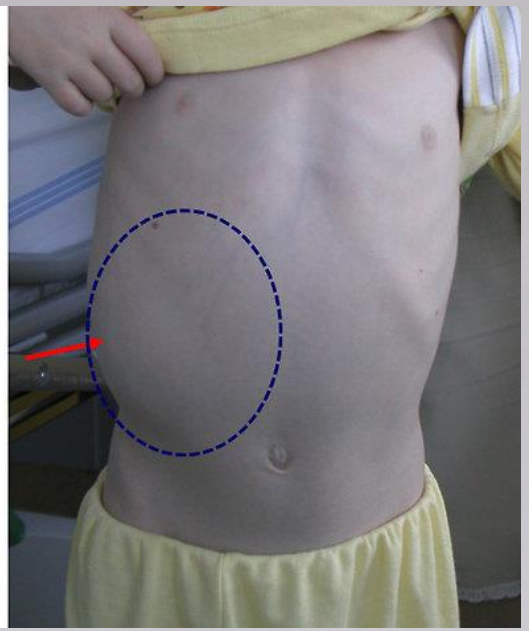
- **WAGR** syndrome (**W**ilms, **A**nridia, **G**enitourinary abnormalities, mental **R**etardation
- **Denys-Drash** syndrome: progressive renal disease, male pseudohermaphroditism, and Wilms tumor

2. WT2 gene (11p15.5) mutation:

- **Beckwith-Wiedemann syndrome:** macrosomia, macroglossia, omphalocele, prominent eyes, ear creases, large kidneys, pancreatic hyperplasia, and **hemihypertrophy**

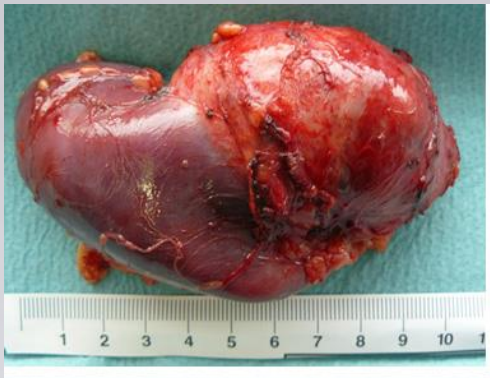
3. TP53 mutation: anaplastic Wilms tumor: abnormal mitotic figures

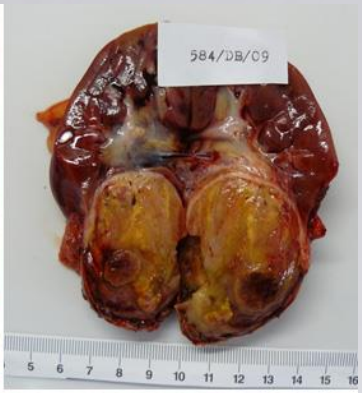


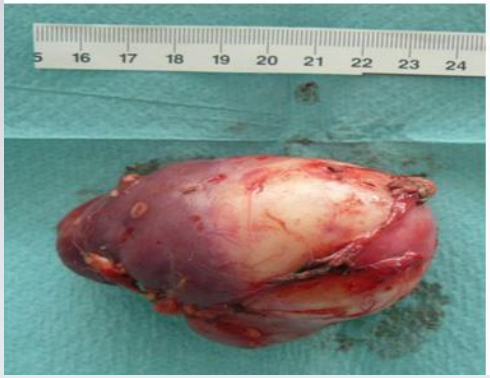


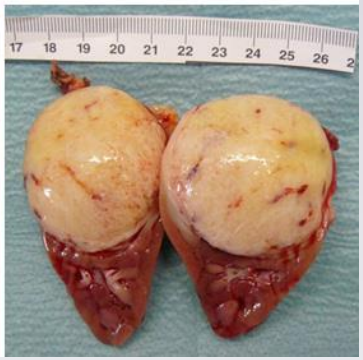
Typical symptoms are:

- an **abnormally large abdomen**
- abdominal pain
- fever
- nausea and vomiting
- blood in the urine (in about 20% of cases)
- high blood pressure in some cases
- metastases: lung







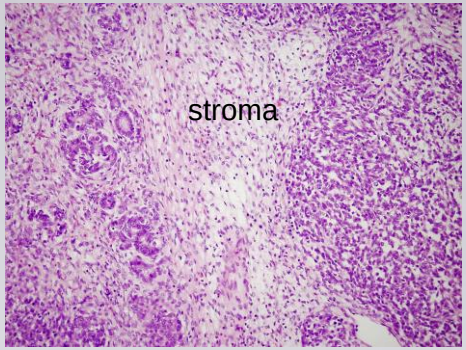


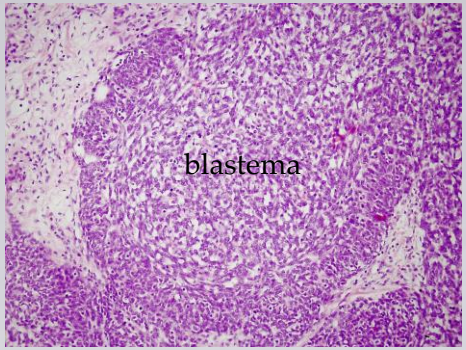
Viera Bajčiová, MD, PhD
http://telemedicina.med.muni.cz

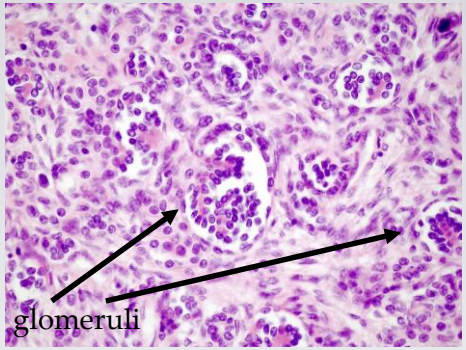
Histology:

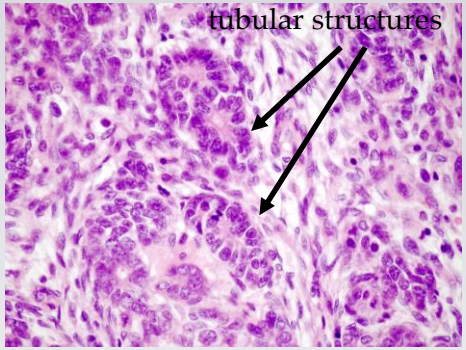
- the **classic favorable histology shows** three components/cell types:

- **Blastemal cells** – Undifferentiated cells
- **Stromal cells** – Immature spindle cells and heterologous skeletal muscle, cartilage, osteoid, or fat
- **Epithelial cells** – Glomeruli and tubules

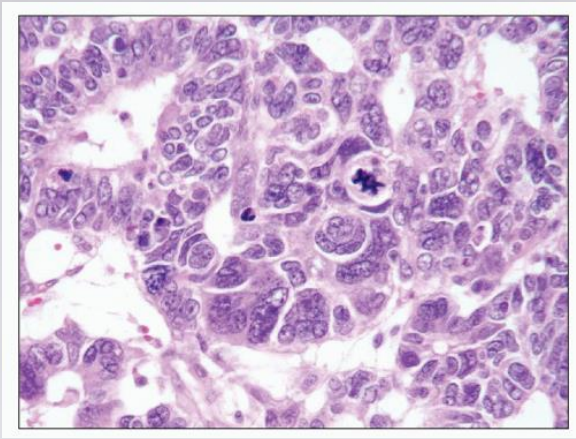








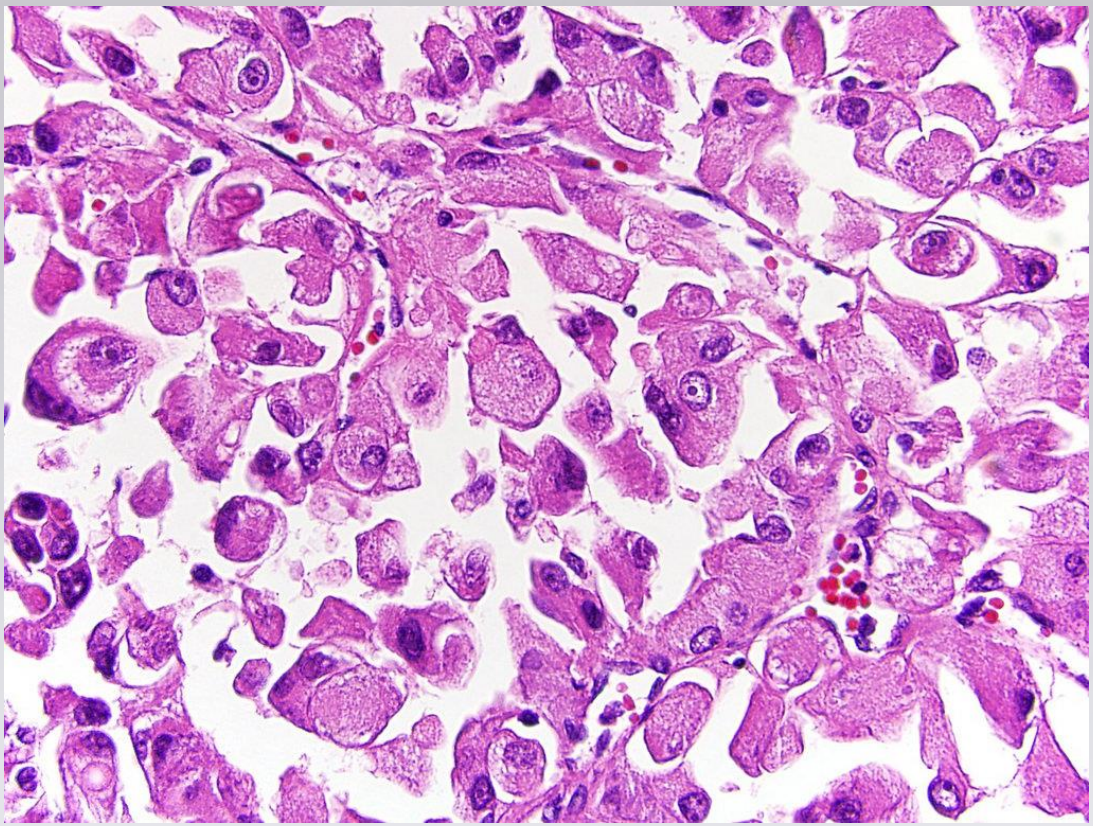
Anaplasia: multipolar mitotic figures - poor outcome



https://abdominalkey.com/renal-neoplasms/

Other childhood malignant renal tumors

Clear cell sarcoma (bone metastases)
Rhabdoid tumor of the kidney: very poor prognosis
Congenital mesoblastic nephroma: hypertension (renin)
Renal cell carcinoma (rare)



rhabdomyoblast-like tumor cells

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Hungarian National Registry of Pediatric Malignancies

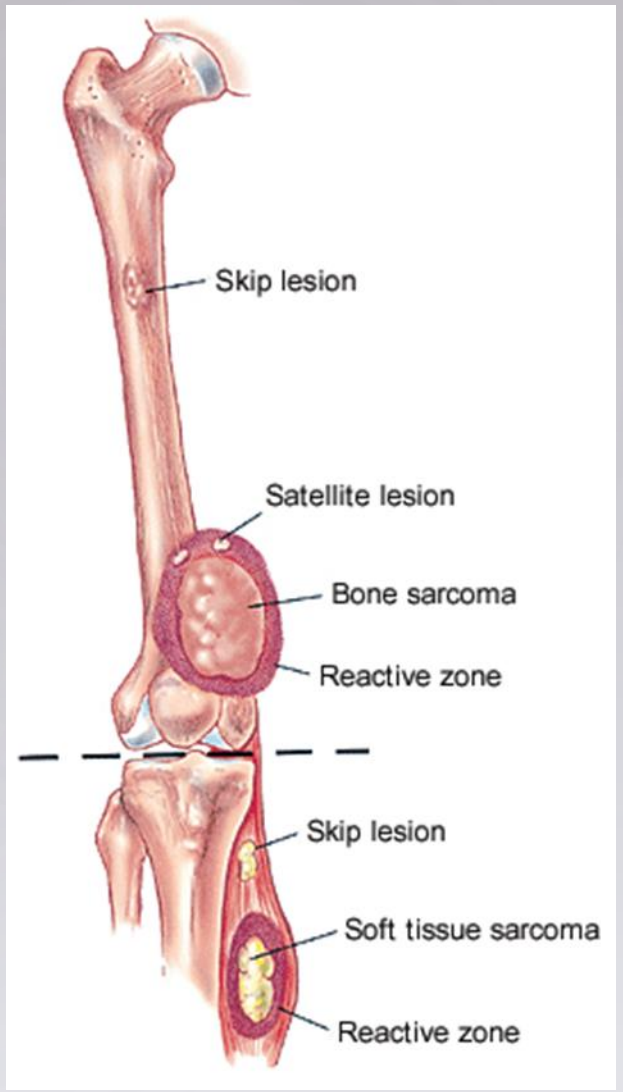
OSTEOSARCOMA

- aggressive malignant neoplasm arising from primitive transformed cells of **mesenchymal origin** that exhibit **osteoblastic** differentiation and produce **malignant** osteoid

- most common histological form of **primary bone cancer**

- **metaphyseal region of tubular long bones:** **femur**, **tibia**, and **humerus**. About 8% of all cases occur in the skull and jaw, and another 8% in the pelvis

- **Metastases:** lung, promixal joints (skip metastases)



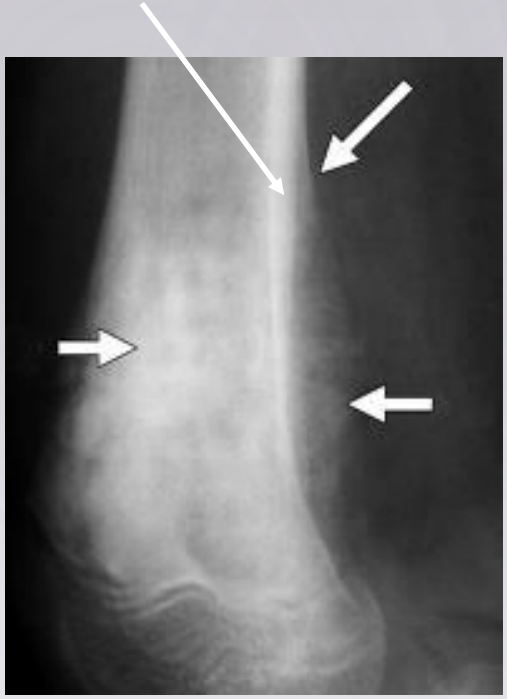
Osteosarcoma: A Multidisciplinary Approach to Diagnosis and Treatment JAMES C. WITTIG, M.D., JACOB BICKELS, M.D., DENNIS PRIEBAT, M.D., JAMES JELINEK, M.D., KRISTEN KELLAR-GRANEY, BARRY SHMOOKLER, M.D., and MARTIN M. MALAWER, M.D., Washington Cancer Institute, Washington Hospital Center, Washington, D.C.

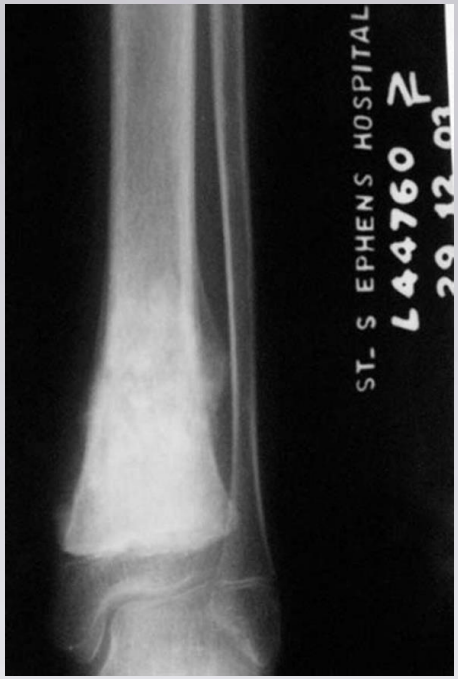
Pathology

- The tumor may be localized at the end of the **long bone** **(metaphyseal region)**.
- Most often it affects the **proximal end of tibia or humerus, or distal end of femur.**
- The tumor **is solid, hard, irregular** (**"moth-eaten" or "sun-burst" appearance on X-ray)**

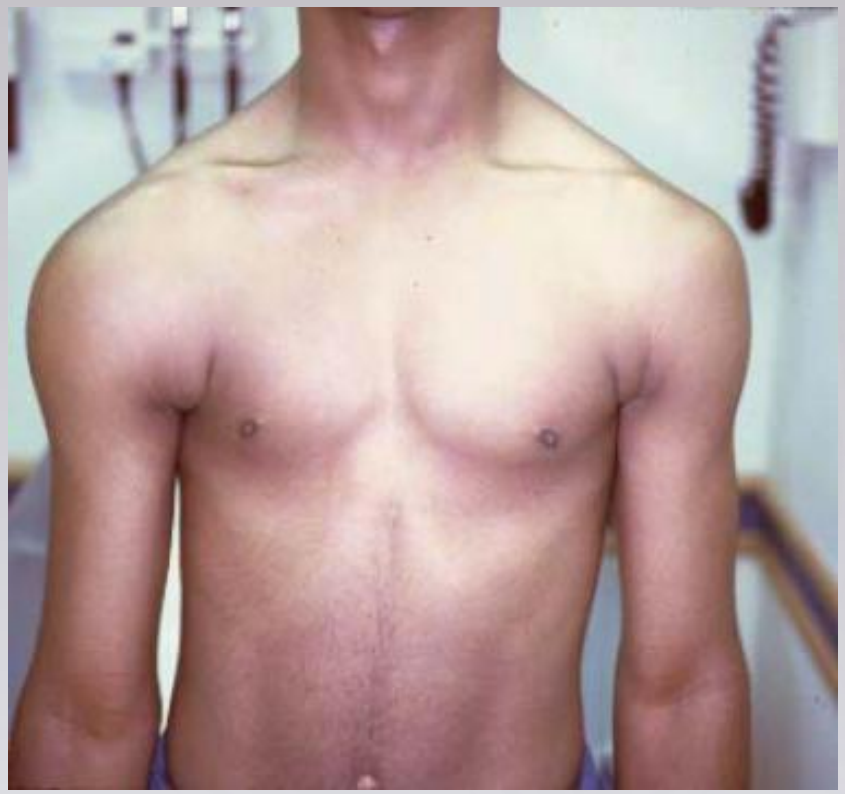
  Elevation of periosteum due to the tumorous-mass (new bone formation)

  (Codman's triangle)





Chondroblastic Osteosarcoma of the Lower Tibia: A case report
by J. Terrence Jose Jerome, MBBS, DNB (Ortho)1 , MNAMS (Ortho), Mathew Varghese, M.S. (Ortho)2 , Balu Sankaran, FRCS (C), FAMS3
The Foot and Ankle Online Journal 3 (2): 1



http://emedicine.medscape.com

Osteosarcoma Clinical Presentation
Charles T Mehlman, DO, MPH; Chief Editor: Harris Gellman, MD 2016

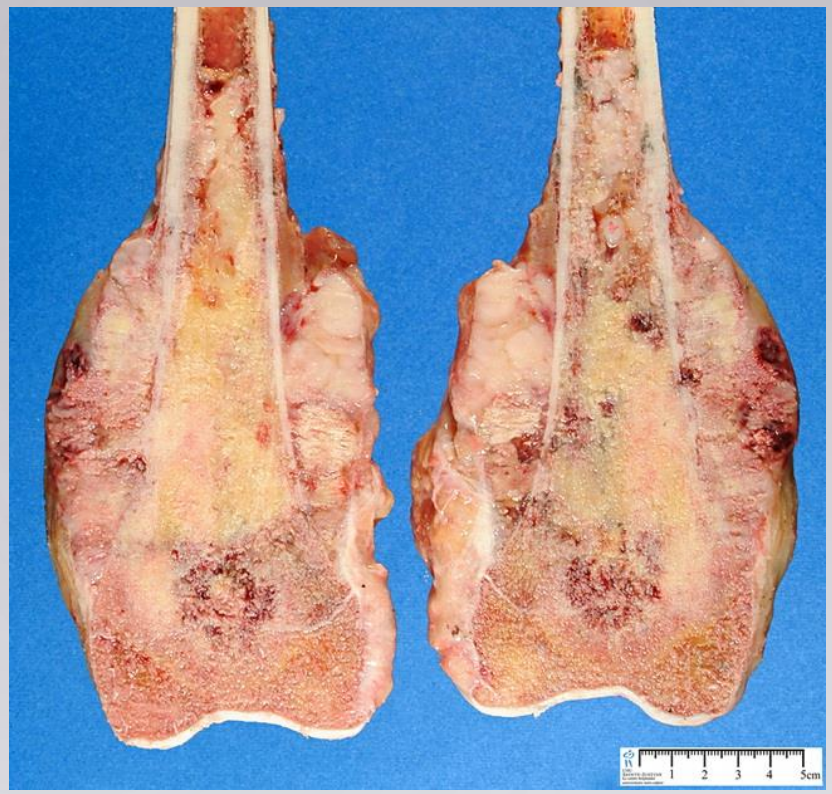
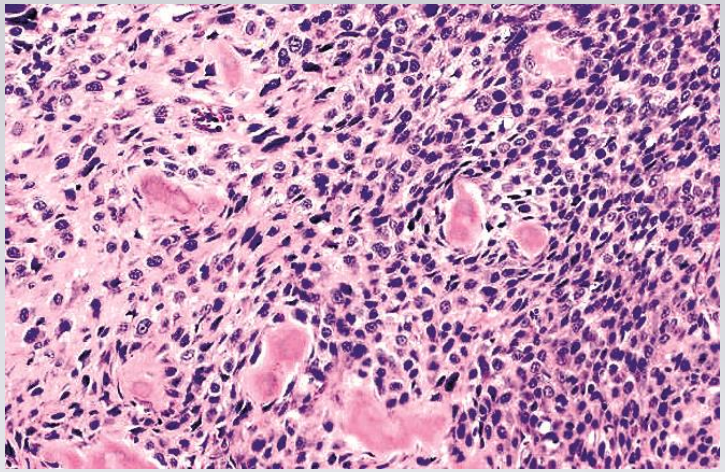


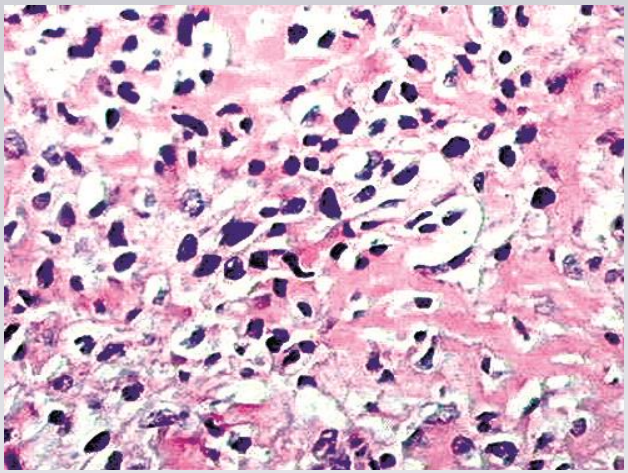
Image courtesy of Dr. Jean-Christophe Fournet, Paris, France; humpath.com

Histology:

- The characteristic feature of osteosarcoma is presence of **osteoid** (bone formation) (amorphous, eosinophilic/pink) within the tumor.
- anaplastic tumor cells (some are giant, **osteoclast-like giant cells)**
- numerous **atypical mitoses**
- tumor cells are included in the **osteoid matrix**



Nat Pernick, M.D.



Dr. Mark R. Wick

Genetic predisposition

- **deletion** of chromosome 13q14 inactivates the **retinoblastoma gene** is associated with a high risk of osteosarcoma development.
- **Bone dysplasias**, including Paget's disease, fibrous dysplasia, enchondromatosis, and hereditary multiple exostoses, increase the risk of osteosarcoma.
- **Li–Fraumeni syndrome** (germline **TP53** mutation) is a predisposing factor for osteosarcoma development.
- **Rothmund–Thomson syndrome** (i.e. autosomal recessive association of congenital bone defects, hair and skin dysplasias, hypogonadism, and cataracts) is associated with increased risk of this disease.

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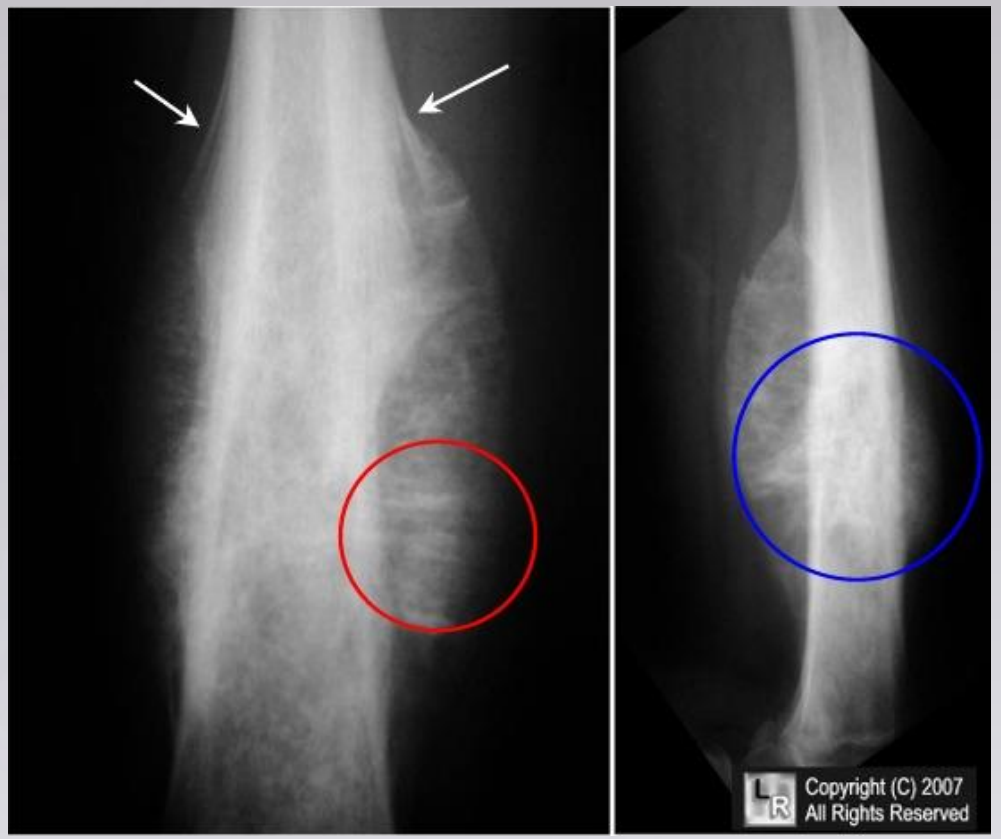
EWING SARCOMA/PNET

- **ES** was described by **James Ewing** in **1921** as an undifferentiated tumor involving the **diaphysis of long bones** that, in contrast to osteosarcoma
- A family of Ewing sarcoma
- **Bone marrow** of any bones and soft tissues, most commonly in the flat and long bones
- Second most common malignant bone tumor after osteosarcoma
- Not associated with specific familial or congenital syndromes
- Specific environmental exposures have **not been identified as risk factors**
- **Neuroectodermal origin:** tumor cells likely derive from the neural crest
- **Alternative theory:** originated from the mesenchymal progenitor or stem cells in the bone marrow
- Range from the **classic Ewing sarcoma**, **atypical ES** and **PNET**

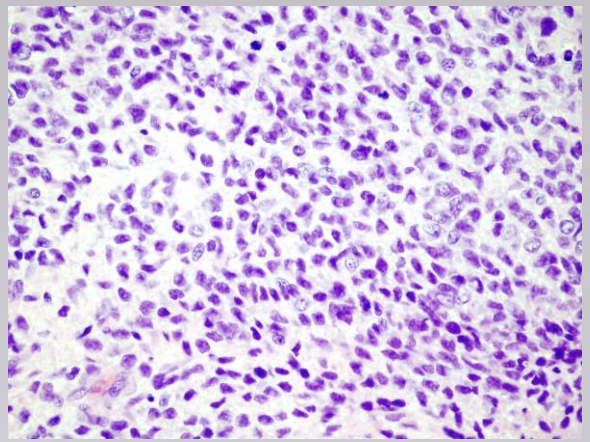
Mosby's Medical Dictionary, 9th edition. © 2009, Elsevier

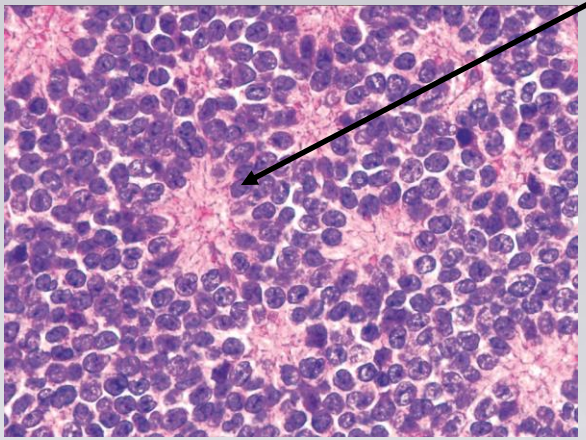
Codman's triangle



http://learningradiology.com/index.htm

Histology:





www.pathologyoutlines.com

Classic Ewing sarcoma

- primitive tumor cells lacking neural differentiation
- small, roud, hyperchromatic nuclei
- rosettes or pseudorosettes

Atypical Ewing sarcoma

- more pleomorphic
- higher mitotic rate
- neural differentiation is absent

Peripheral PNET

- similar histological picture

Diff. diagnoses: lymphomas, rhabdomyosarcoma, desmoplastic small round cell tumor, neuroblastoma, small cell osteosarcoma, desmoplastic chondrosarcoma, undifferentiated synovial sarcoma

Metastases: lung, bone marrow, bones

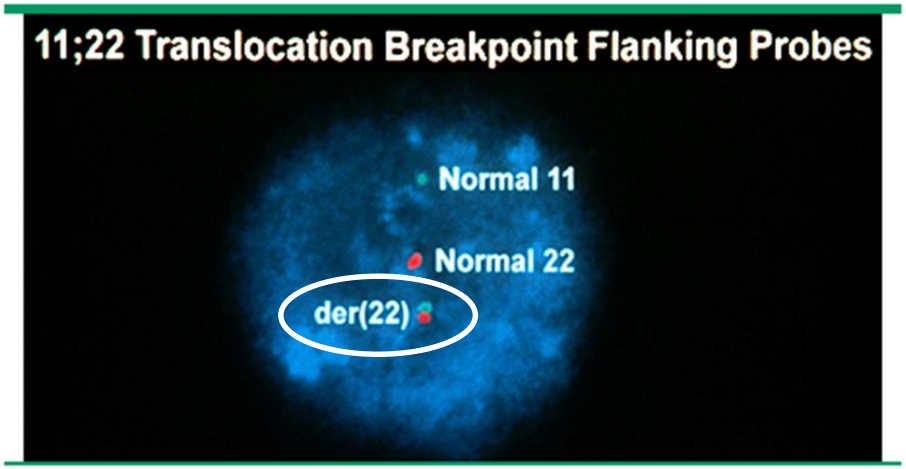
Molecular genetics:

EWSR1: 22q12, encodes EWS protein (RNA binding protein)

recurrent chromosomal translocation: t(11;22)(q24;q12)

- **EWSR1-FLI1: t(11,22), FLI1 is a transcription factor**
- **EWSR1-ERG: t(21,22)**

Typical chromosomal translocation seen in Ewing sarcoma



Fluorescence in situ hybridization (FISH) study demonstrating the (11;22)(q24;q12) translocation [der(22)] found in Ewing sarcoma and primitive peripheral neuroectodermal tumors (PNET).

Courtesy of Andrew L Rosenberg, MD.

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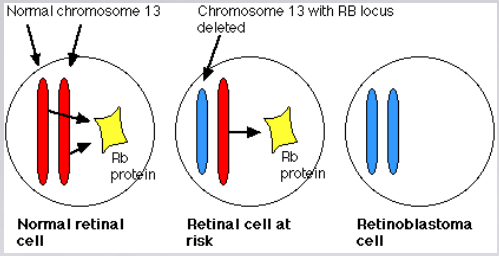
RETINOBLASTOMA

- Retinoblastoma is the most common primary **intraocular malignancy** of childhood and accounts for 10 to 15 percent of cancers within the first year of life.
- The majority of cases are diagnosed in children younger than two years of age.
- Approximately **one-third of cases are bilateral.**
- Children who have a family history of retinoblastoma or a personal or family history of 13q deletion have an increased risk of developing retinoblastoma.
- Typically presents **leukocoria (white pupillary reflex), or strabismus**



http://www.biology-pages.info

- Mutational inactivation of **two alleles of RB tumorsuppressor gene (13q14)** encoding the mutant Rb protein (restrict the ability to progress from G1 phase to S phase.

Typical case of the **"two-hit" modell** (Knudson, 1971)
RB gene was the first described tumor suppressor gene.

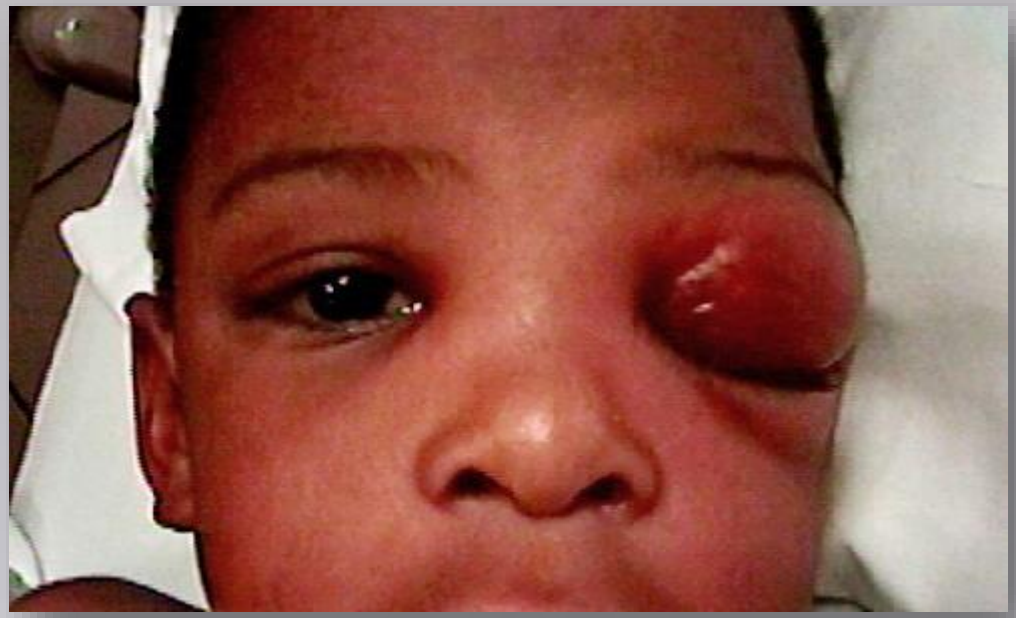
Zélia M. Corrêa, MD, PhD; and Jesse L. Berry, MD

- Leukocoria (white pupilla reflex)
- Strabismus, nystagmus, and red eye
- Ocular inflammation, orbital cellulitis, vitreous haemorrhage
- Fill the eye, destroy the globe
- Metastases spread via the optic nerve to the CNS (subarachnoid space, CF)
- Distant metastases: lung, bone, liver, brain, and lymphatic dissemination (eyelid)

Morphologically: solitary or multifocal
well-circumscribed
pink in color, with dilated feeding blood vessels

1. Exophitic
2. Endophitic
3. Diffuse infiltrating

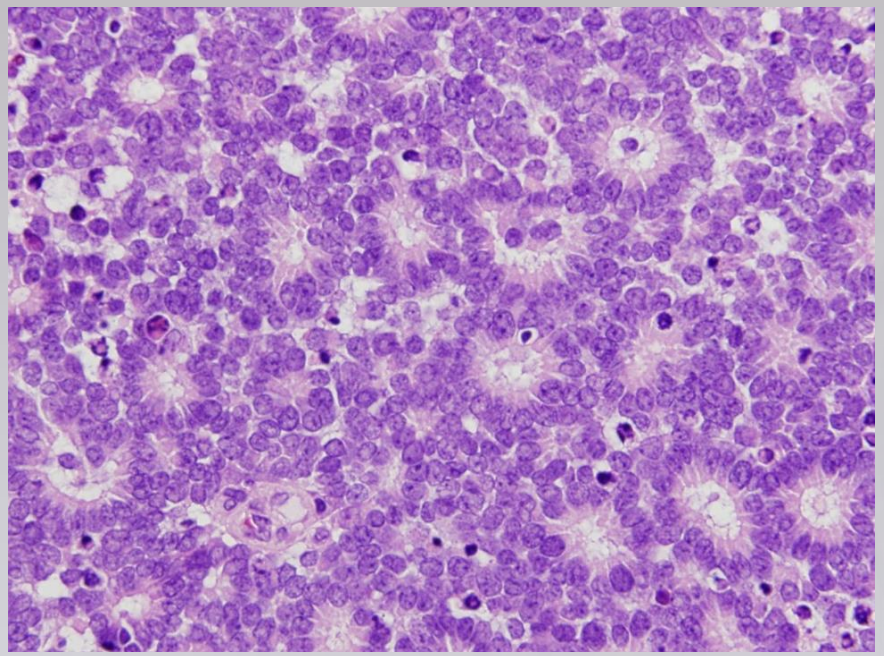
Trilateral retinoblastoma: unilateral or bilaterral tumor with intracranial PNET



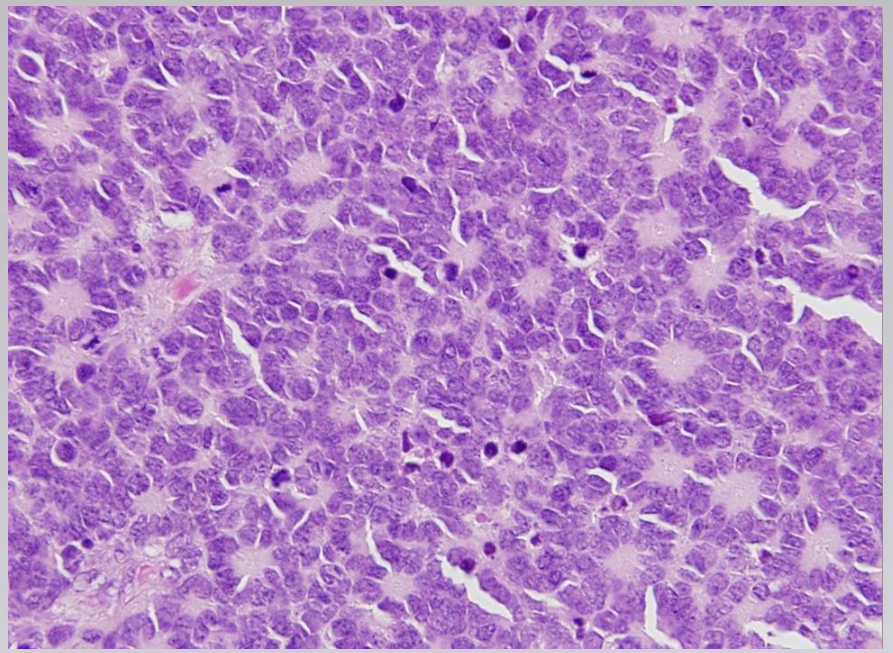
Orbital cellulitis

Phtisis bulbi

Bilateral Retinoblastoma Presenting with Unilateral Phthisis.
Maka E, Csákány B, **Tóth J**.
J Pediatr Ophthalmol Strabismus. 2009 Nov 27. doi: 10.3928/01913913-20091118-06.



Flexner-Wintersteiner rosettes with real lumens



Homer-Wright rosettes

diagnosis of retinoblastoma can usually be made based on the dilated indirect ophthalmoscopic examination

imaging studies (US, MRI)

pathology is not necessary to confirm the diagnosis and biopsy is contraindicated because of the risk of tumor seeding

Hereditary cases (40 %)	**Germline mutation of RB1 gene locus** is present in **all cells** in the body, the second "hit" occuring later in development of the retineal cells. Mostly bilateral.
Nonhereditary cases (60 %)	Both allelic mutations arise **spontaneously** in **a single somatic cell of the retina.** In a small proportion of retinoblastomas high level of **MYCN amplification** also can be detected without RB1 gene mutation (early age and undifferantiated tumor cells)

Retinoblastoma
Zélia M. Corrêa, MD, PhD; and Jesse L. Berry, MD
American Academy of Ophthalmology APR 28, 2016

Retinoblastoma: Clinical presentation, evaluation, and diagnosis
Paul L Kaufman, MD,Jonathan Kim, MD,Jesse L Berry, MD,Section Editors,Evelyn A Paysse, MD
Alberto S Pappo, MD
Deputy Editor Carrie Armsby, MD, MP

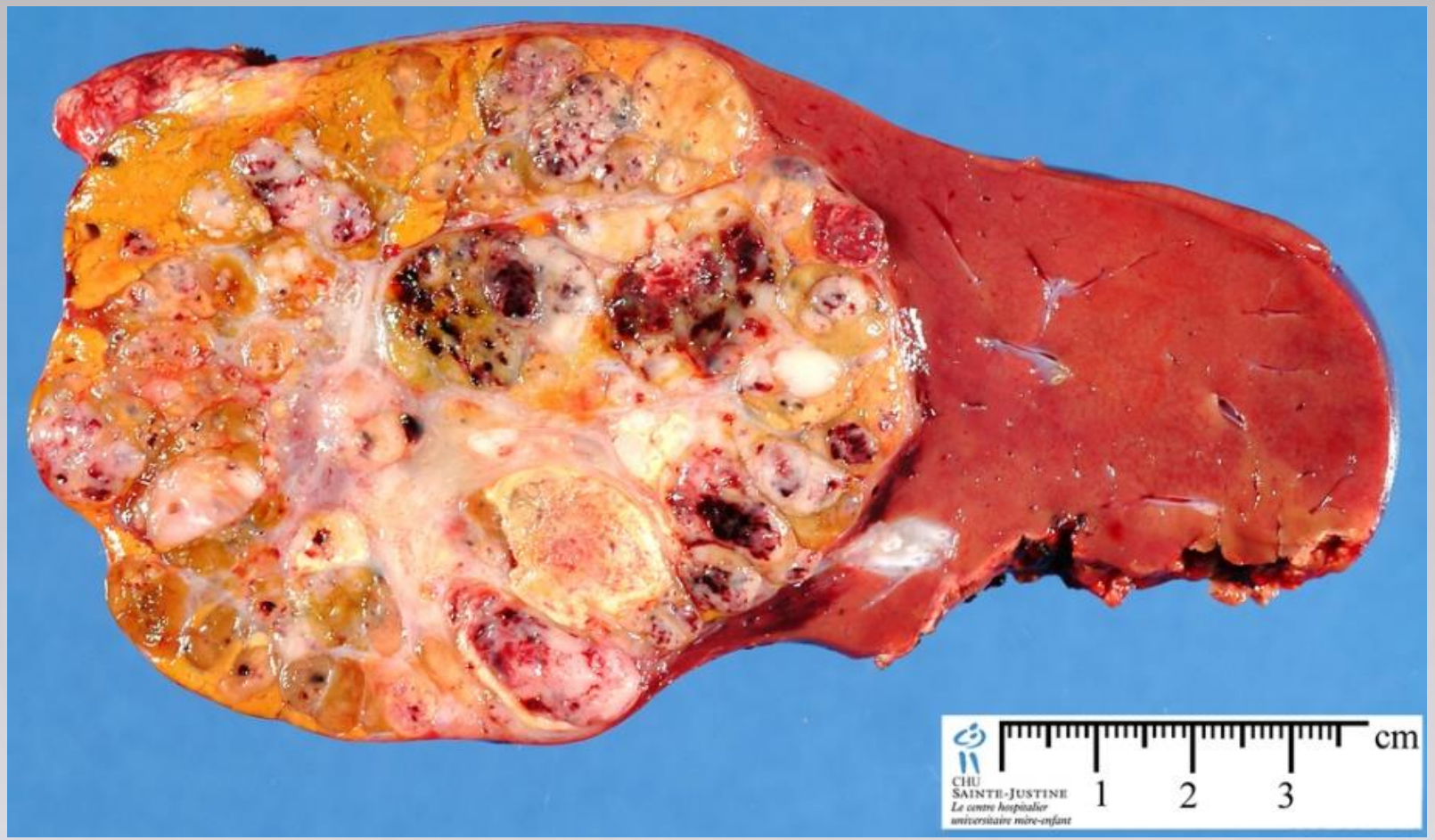
Distribution of Pediatric Malignancies in Hungary (2007)

1. Leukemias (ALL 22 %, AML 4 %, CML 1 %)
2. Brain tumors (25 %)
3. Lymphomas (NHL 7 %, HL 7 %)
4. Neuroblastoma (9 %)
5. Soft tissue tumors (6 %)
6. Wilms tumor (5 %)
7. Osteosarcoma (4 %)
8. Ewing sarcoma (4 %)
9. Retinoblastoma (2 %)
10. Germ cell tumors (2 %)
11. Pleuropulmonary blastoma
12. **Liver tumors (1 %)**

Hungarian National Registry of Pediatric Malignancies

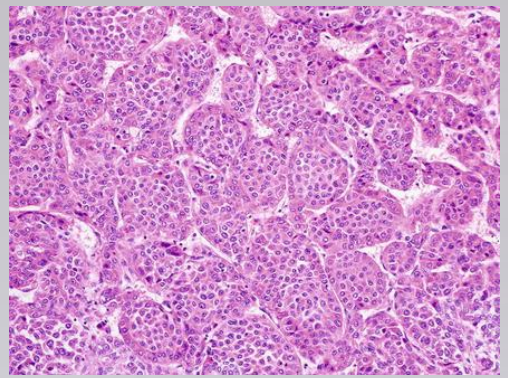
HEPATOBLASTOMA

- most common primary hepatic malignancy in early childhood
- more commonly in first two years of life
- hepatoblastoma in boys is twice
- **arise from primitive cells (stem cells) in the liver** with potential to differentiate along several lines
- **Beckwith Wiedmann syndrome**, trisomy 18, trisomy 21, Acardia syndrome, Li-Fraumeni syndrome, Goldenhar syndrome, type 1a glycogen storage disease (von Gierke disease), and **familial adenomatous polyposis are associated with HB**
- Serum alpha-fetoprotein (AFP) levels are markedly elevated
- Cirrhosis and other risks factors are absent in patients with hepatoblastoma



- Large, haemorrhagic, and necrotic tumorous mass (more commonly in the right lobe)
- Encapsulated, nodular, **rupture (peritoneal dissemination)**
- Elevated abdomen, pain, fever, general symptoms

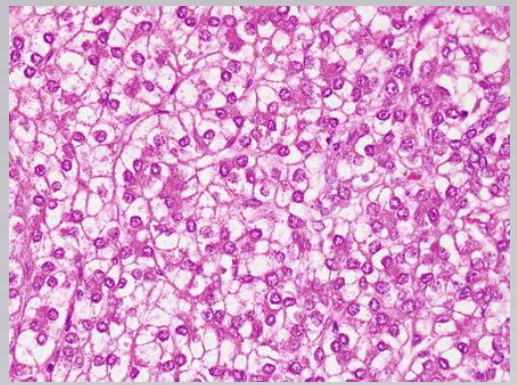
Histology: hepatoblastoma mimics the developing fetal and embryonal liver

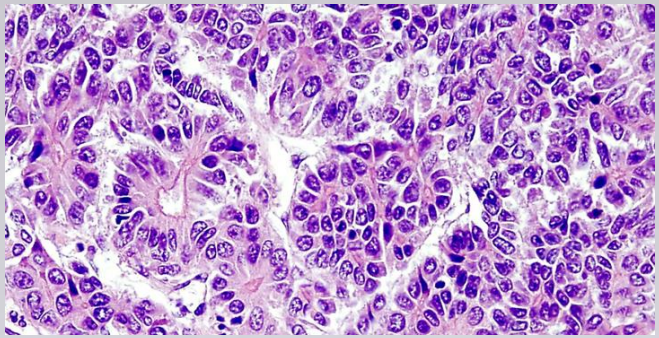


https://abdominalkey.com/malignant-pediatric-liver-tumors/

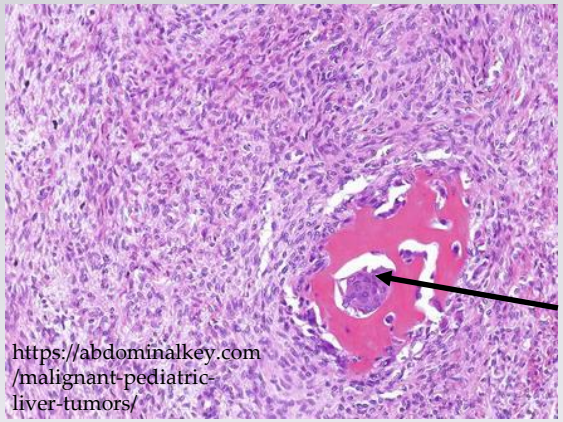
Pure epithelial (epithelial elements)

- **Fetal (clear cell: glycogene, lipid)**
- **Embryonal**
- **Macrotrabecular**
- **Small cell undifferetntiated**





Mixed: (epithelial and mesenchymal elements)

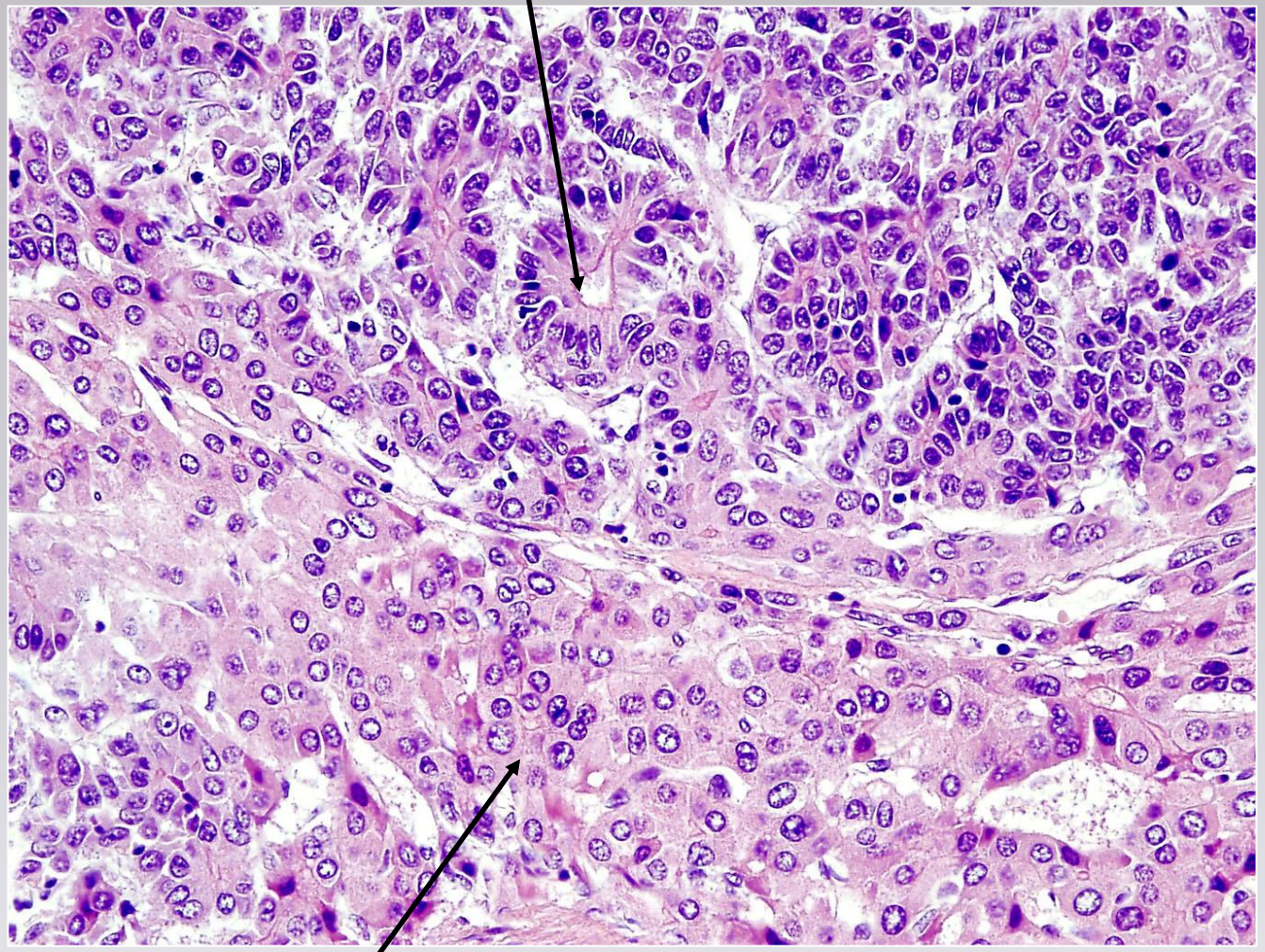


https://abdominalkey.com/malignant-pediatric-liver-tumors/

osteoid

Pure fetal type of hepatoblastomas have a favorable outcome!

Embryonal type of tumor cells (rosettes, primitive tumor cells)



Fetal type of tumor cells (resemble the liver cells)

TAKE HOME MESSAGE!

- The childhood malignancies are rare, BUT **you always have to think about it!!!!**

WHEN?

- Pain (more than 2 weeks), fever with no sign of infection, elevated abdomen, headache and vomiting (no sign of gastroenteritis), strabism, swelling of any part of extremities, do not find any causes of symptoms etc.

Recognation IN TIME, applying the modern chemotherapies, and surgical removement of solid tumors save lifes.

- **Sandvich therapy: chemotherapy+operation+chemo/irradiation**

Thank you for your attention!