Pediatric brain tumors

Done by : Toleen Nezam Jaber

Introduction

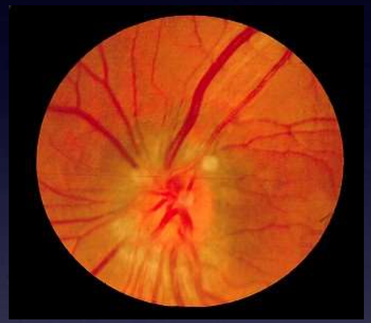
- Second most common malignancy in childhood
- Overall mortality 30% and highest morbidity of all malignancies
- Comparatively good prognosis as opposed to adult brain tumors.
- Males > females especially in medulloblastoma and ependymomas
- 5% familial and hereditary

Disorder	Associated brainTumors	Comment
Neurofibromatosis 1	optic glioma, acoustic neuroma, astrocytoma, meningioma	Autosomal dominant- tumor suppressor gene NF1
Neurofibromatosis 2	Acoustic neuroma , meningioma	Autosomal dominant- tumor suppressor gene NF1
Tuberous sclerosis	Subependymal nodules, subependymal giantcell astro.	Autosomal dominant
Von hipple landau	Hemangioblastoma of cerebellum	Autosomal dominant
Familial polyposis syndrome (turcot’s)	Medulloblastoma, glioblastoma multiforme, anaplastic astrocytoma	Autosomal dominant

Pediatric brain tumors warning signs

- Headache (most common manifestation) - in infants who can’t articulate the source this presents as irritability . Usually early morning headache that is relieved by vomiting
  Nausea and vomiting - posterior fossa tumors are more likely to cause it imaging if presistent vomiting upon awakening
- Ataxia and gait abnormality - Initial cerebellar dysfunction may be insidious with clumsiness, worsening handwriting, changes in speech, or difficulty in motor skills such as running or hopping
- Seizures
- Cranial nerve palsies Cranial neuropathies, such as diplopia, nystagmus, inability to adduct the eye during attempted lateral gaze, facial palsy, drooling, and difficulties with swallowing, suggest underlying brainstem pathology. Younger children may not be able to complain of diplopia. Instead, they may squint, cover one eye with their hand, or tilt their head to one side.

- Impaired vision Vision impairment may be due to cranial neuropathy (eg, diplopia) from a brainstem lesion, increased ICP leading to papilledema, or a lesion along the optic pathway that courses from the occipital pole of the cerebral cortex through the optic chiasm to the retina



- papilledema refers to bilateral optic disc swelling
  that is due to ICP

- Torticollis Sudden-onset nontraumatic torticollis should therefore raise a suspicion of spinal cord tumor or posterior fossa tumor

- Macrocephaly most common presenting sign in infants

- Developmental delay and behavioral changes

- Indications for Neuroimaging :
  1- headache imaging if : wakes a child from sleep , early morning, associated with confusion/ disorientation and if < 4Y/O
  2 persistent vomiting upon wakening
  3new onset seizure other than simple febrile seizure or depressed consciousness
  4visual findings : papilledema, optic atrophy, new onset nystagmus, reduced acquity not due to refractive errors, paralytic squint, nystagmus
  5motor : regression in motor skills, focal motor weakness, abnormal gait and coordination, bell’s palsy with no improvement in 4 weeks, swallowing difficulties without apparent cause.

Manifestations based on site

- Supratentorial tumors
  - focal neurological signs (motor, sensory, language)
  - seizures
  - reflex asymmetry
  - in infants may present with premature hand preference (< 18 months)
  -raised ICP (pappiloedema, nausea and vomiting, headache)

- Infratentorial
  - raised ICP (pappiloedema, nausea and vomiting, headache)
  - torticollis
  - blurred vision, nystagmus, diplopia

- Brainstem
  - gaze palsy
  - CN palsy
  - upper motor neurone deficits (hemiparesis, hyperreflexia, clonus)

- Suprasellar/third ventricle
  - neuroendocrine deficits precede neurooptha lmologic symptoms by 2 years (obesity, abnormal linear growth ,precocious/delayed puberty,hypothyroidism)
  -diencephalic syndrome
  (failure to thrive, emaciation, inappropriate happy affect)

- Pineal
  Parinaud syndrome (upward gaze paresis , pseudo- argyll Roberston pupils, nystagmus to convergence or retraction)

Based on Age

Signs and symptoms associated with central nervous system tumors in children

Infants and young children (<4 years)	All children (including older children and adolescents)
Macrocephaly (41%)	Headaches (33%)
Nausea and vomiting (30%)	Nausea and vomiting (32%)
Irritability (24%)	Abnormal gait or coordination (27%)
Lethargy (21%)	Seizures (13%)
Abnormal gait or coordination (19%)	Papilledema (13%)
Weight loss/poor growth (14%)	Unspecified symptoms of elevated ICP (10%)
Bulging fontanelle and/or splayed sutures (13%)	Squint/strabismus (7%)
Seizures (10%)	Behavior changes and/or declining school performance (7%)
Papilledema (10%)	Macrocephaly (7%)
Headache (10%)	Cranial nerve palsies (7%)
Unspecified focal neurologic signs (10%)	Lethargy/fatigue (6%)
Unspecified symptoms of elevated ICP (9%)	Abnormal eye movements (6%)
Focal motor weakness (7%)	Hemiplegia (6%)
Head tilt/torticollis (7%)	Altered level of consciousness (5%)
Altered level of consciousness (7%)	Weight loss (5%)
Squint/strabismus (6%)	Unspecified visual or eye abnormalities (5%)
Abnormal eye movements (6%)	
Developmental delay or loss of milestones (5%)	
Hemiplegia (5%)	

ICP: intracranial pressure.

1. *Wilne SH, Dineen RA, Dommett RM, et al. Identifying brain tumours in children and young adults. BMJ 2013; 347:f5844.*
2. *Wilne S, Collier J, Kennedy C, et al. Presentation of childhood CNS tumours: a systematic review and meta-analysis. Lancet Oncol 2007; 8:685.*

Diagnosis

- Complete history and physical examination (including ophthalmic)
- Neuroimaging (MRI -+ gadolinium). MRI is the investigation of choice followed by CT
- Midline and suprasellar/ optic chiasm/ pituitary region should undergo neuroendocrine dysfunction evaluation
- Serum and CSF measuring for beta-HCG and alpha-FP for germ cell tumors
- Lumbar puncture for cytology in tumors with propensity to spread to leptomeninges (remember to delay lumbar puncture till after surgery or shunt in case of hydrocephalus, supratentorial midline shift or infratentorial tumors to avoid herniation)
- Histology :Children in whom neuroimaging confirms the presence of a mass should be referred to a pediatric neurosurgeon for further evaluation. Postsurgical therapy, which may include radiation and/or chemotherapy, is dependent upon the histologic diagnosis

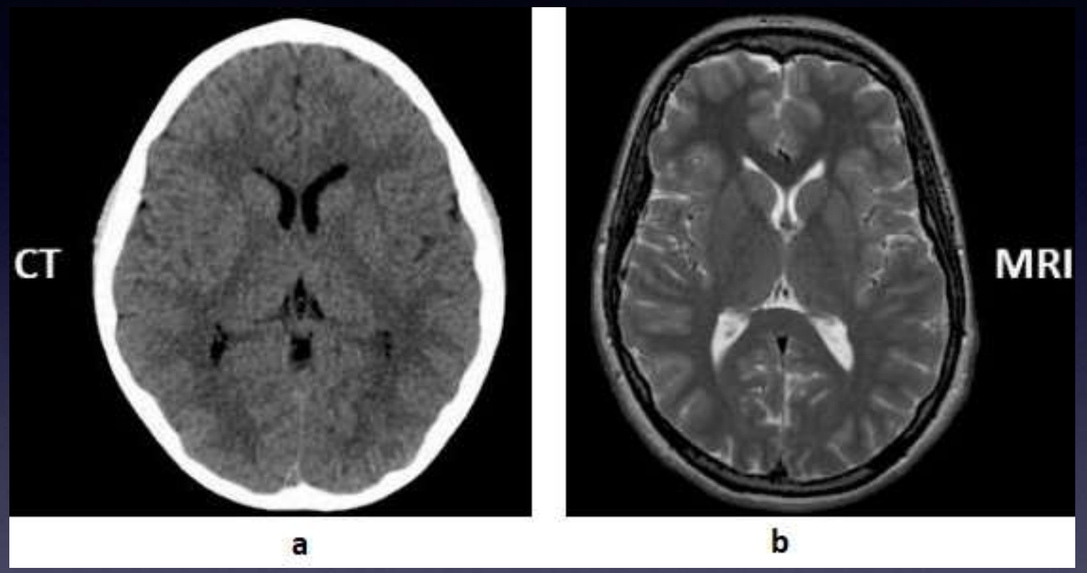
- NEUROIMAGING 1- MRI
  -MRI is the best Neuroimaging modality for brain tumors Compared with CT, it provides more detailed images of parenchymal lesions
  -Gadolinium-enhanced MRI can also provide information that may indicate a specific tumor type
  -MRI is also used to stage tumors that have a predilection for leptomeningeal spread.
  -Magnetic resonance spectroscopy, a supplementation to traditional MRI, can differentiate locally infiltrative brain tumors from other intracranial lesions by detecting the presence of specific metabolic signals (eg, N-acetylaspartate, choline, and lactate) that are present in brain tumor tissue.

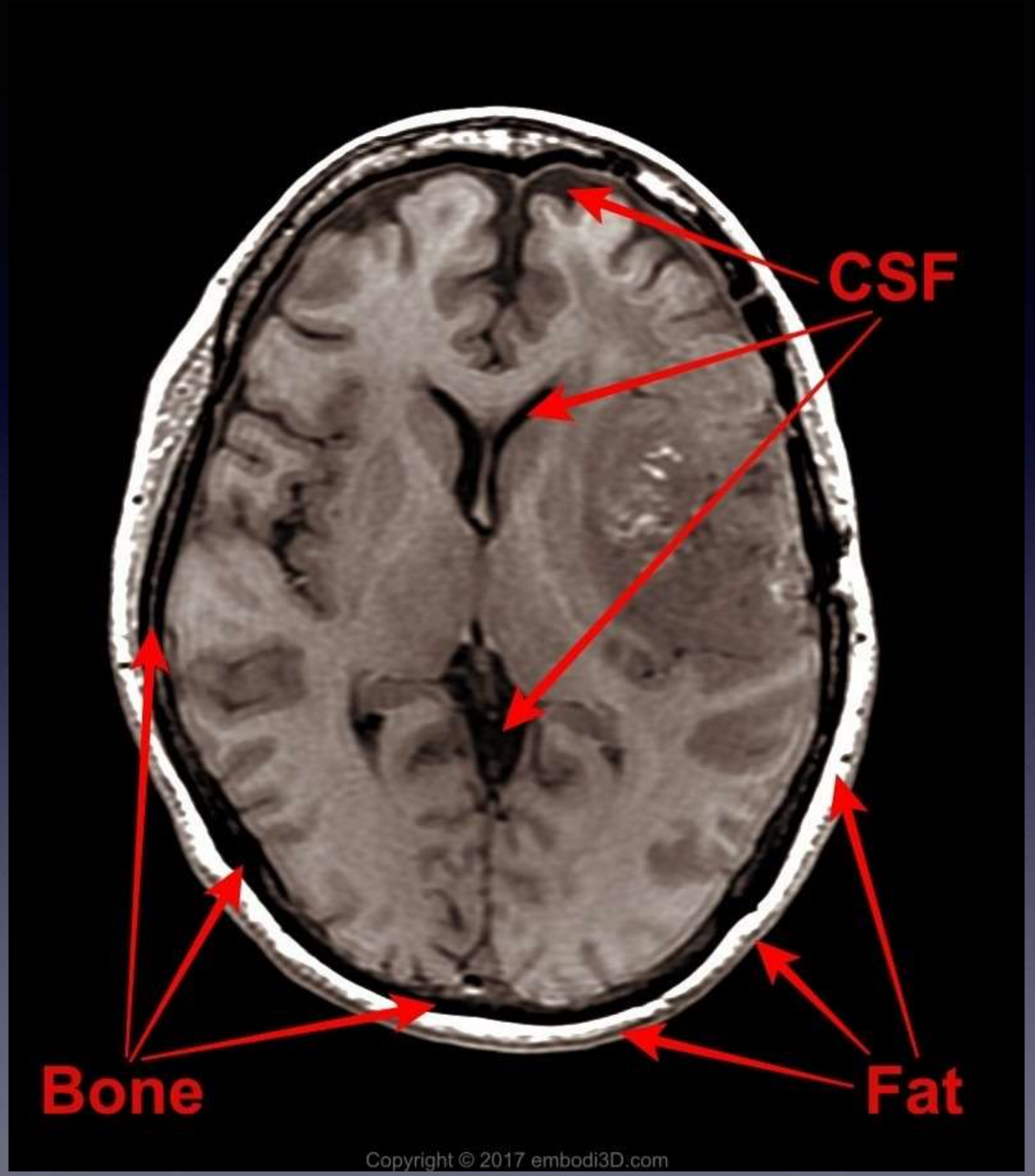
- 2- CT
  CT is often the first imaging study performed because it is more widely available, has a shorter required study time, and usually does not require sedation CT is the preferred initial study in an emergent situation with a medically unstable child in whom elevated intracranial pressure (ICP) is suspected. However, it is important to note that a normal CT study does not completely exclude the possibility of a brain lesion.

- Positron emission tomography scan
  Positron emission tomography (PET) scans are not routinely used at all centers as part of standard work-up for brain tumors, but they can provide useful information to supplement those from MRI scans. PET scans utilize a positron-emitting radionuclide isotope coupled with a sugar (eg, fluorodeoxyglucose) to differentiate malignant lesions with a high metabolic rate from more benign lesions and surrounding tissue with a lower metabolic rate

How to differentiate MRI from CT

- In MRI :
  bone is black
  fat and Water is white
  you can’t see what the patient is laying on
  skin and subcutaneous fat on scalp is white



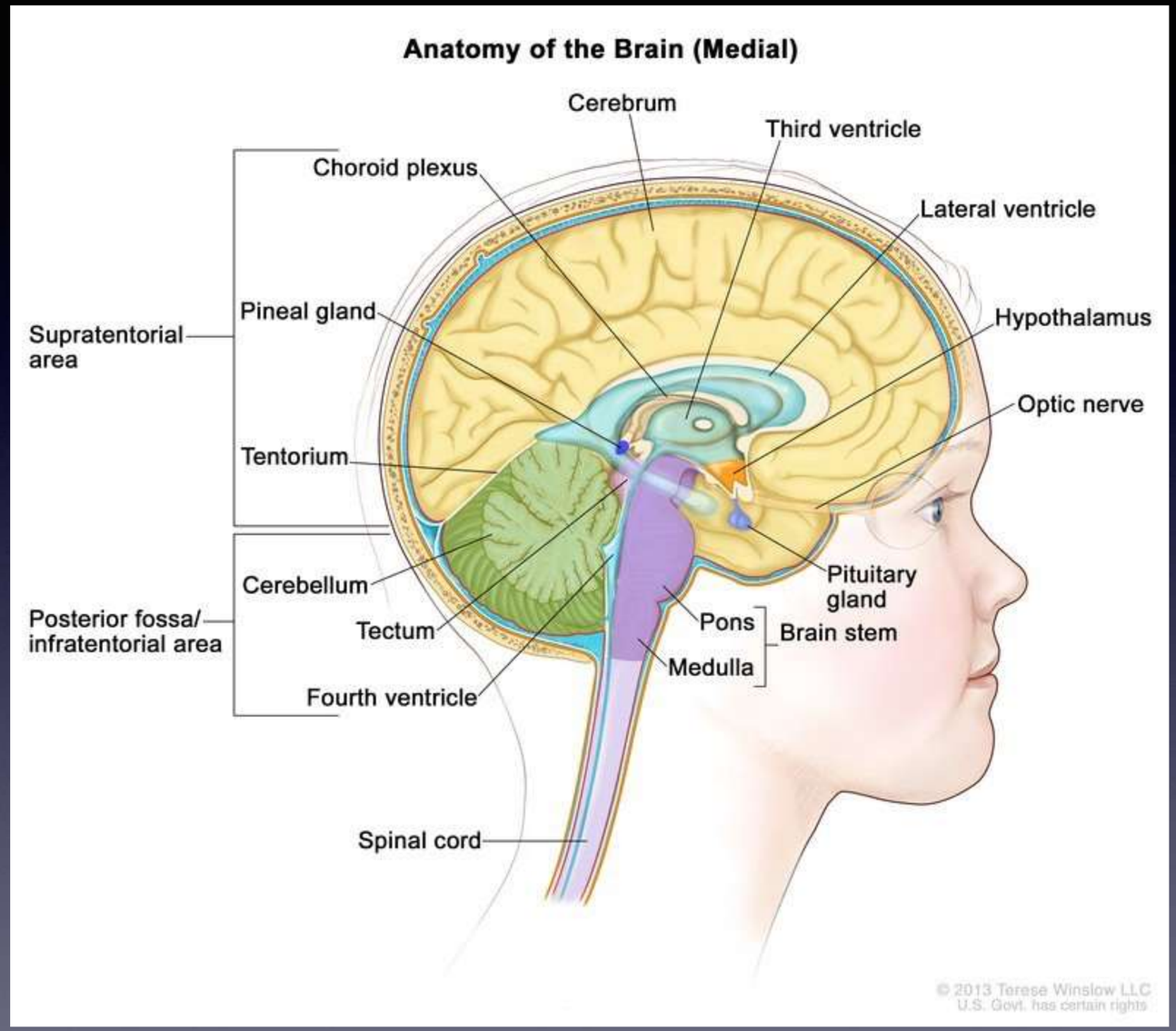

CSF
Bone
Fat
Copyright © 2017 embodi3D.com

Classification

- Based on location
- Based on histology
- WHO grading of brain tumors

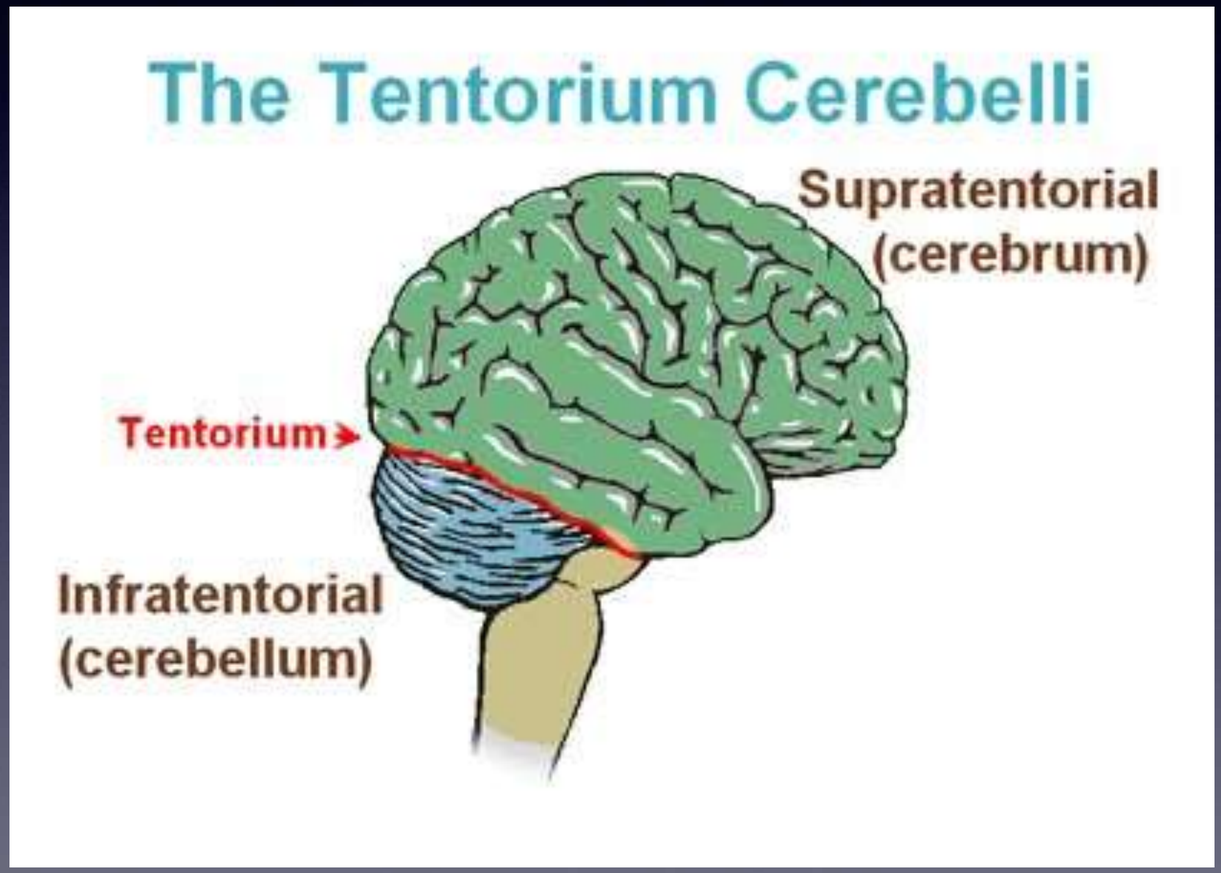
Based on site

Most common :
supratentorial < 1 year.
(Teratomas and choroid plexus)
Infratentorial 1-10 years
(Medulloblastoma and juvenile Astrocytoma)
Supratentorial > 10 years



Supratentorial

- Astrocytoma
- Ependymoma
- Gliomas
- PNET
- Choroid plexus
- Germ cell
- Meningiomas



Infratentorial

- Medulloblastoma (PNET)
- Astrocytoma
- Brain stem glioma

WHO grading

- Grade 1 : slow growing non malignant long survival
- Grade 2 : slow growing but recur and may be malignant or non malignant
- Grade 3 : malignant and often recur
- Grade 4 : reproduce rapidly, very aggressive

Based on histology

- Most common
  0-14 years : pilocystic astrocytoma, medulloblastoma, PNET.
  15-19 years : pilocytic astrocytoma, pituitary tumors

- Note : grade of each subtype is indicated between the brackets in the following slide

- Astrocytoma
  - pilocystic astrocytoma (1) - fibrillary infiltrating low grade astrocytoma (2)
  - anaplastic astrocytoma (3) -glioblastoma multiforme (4)

- Ependymal
  - ependymoma (2) most common - anaplastic ependymoma (3) - myxopapillary (1)

- Choroid plexus
  - choroid plexus papilloma (1) -choroid plexus carcinoma (3)

- Embryonal tumors (all are grade 4)
  -medulloblastoma -supratentorial PNET. -ependymoblastoma -medulloepithelioblastoma. - atypical teratoid/rhabdoid tumor

- Pineal parenchymal

- Craniopharyngioma (1)

- Germ cell tumors

- Brain stem tumors

- Metastatic tumors

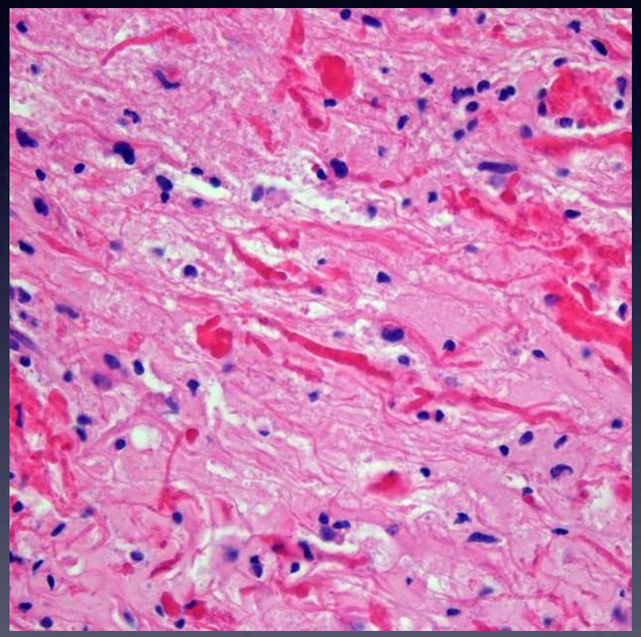
Astrocytoma

- Cell of origin : glial cells
- Most common site : cerebellum (67%) if in optic chiasm NF1
- MRI : well circumscribed contrast enhancing nodule in the wall of a cystic mass
- Grossly : Most are soft grey and discrete

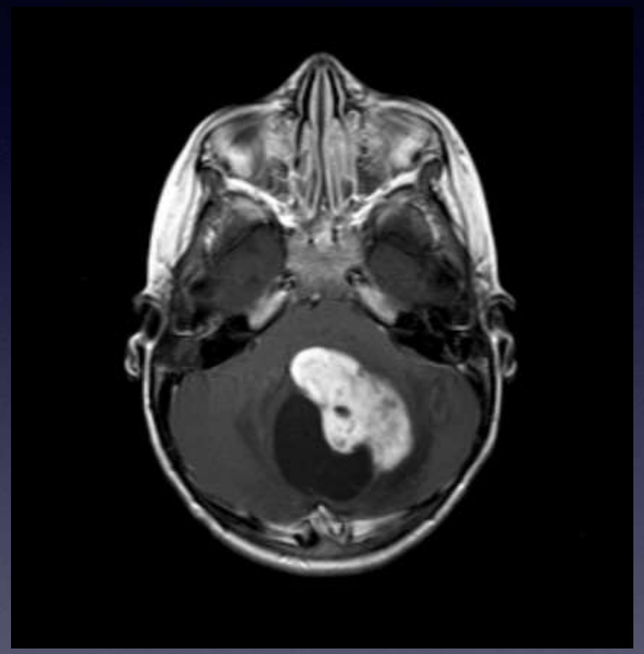
Pilocytic astrocytoma

- Rarely invasive and rarely malignant transformation long survival is the rule
- Histopathology biphasic : a- compacted bipolar cells with Rosenthal fibers b- loose multipolar cells with cystic granules
- bad prognostic factors : supratentorial , high mitoses, late radiotherapy.

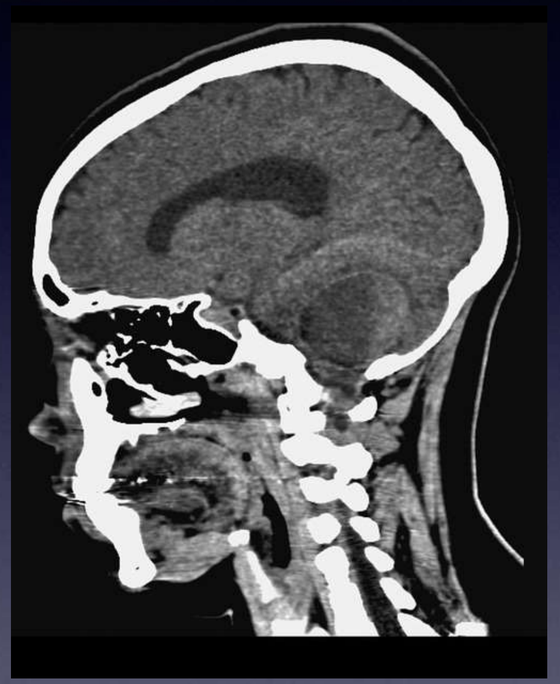
PA



Rosenthal fibers

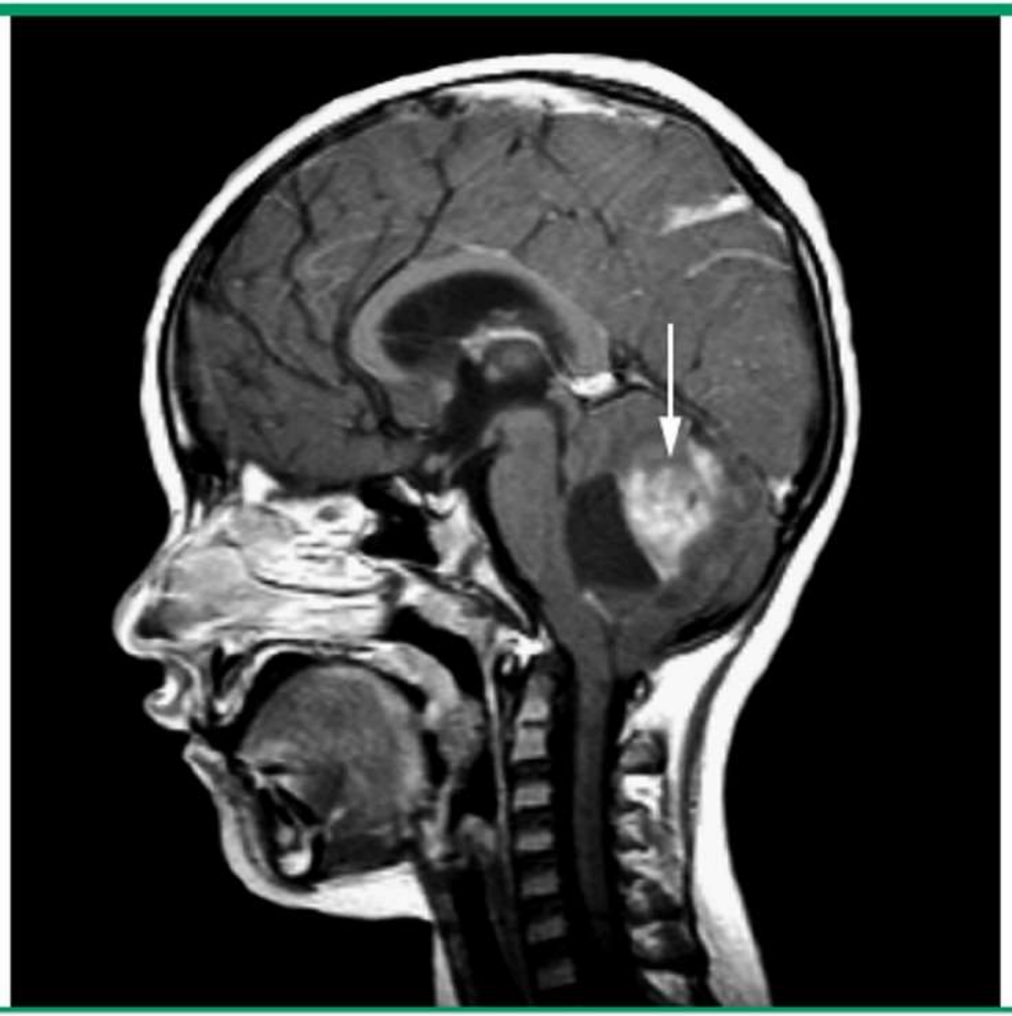


Axial MRI t1 with contrast



Sagittal ct non contrast

Magnetic resonance image of pilocytic astrocytoma



Sagittal T1 post-contrast MRI of a pilocytic astrocytoma (large cystic mass with a mural nodule [arrow]) in the posterior fossa.

MRI: magnetic resonance imaging.

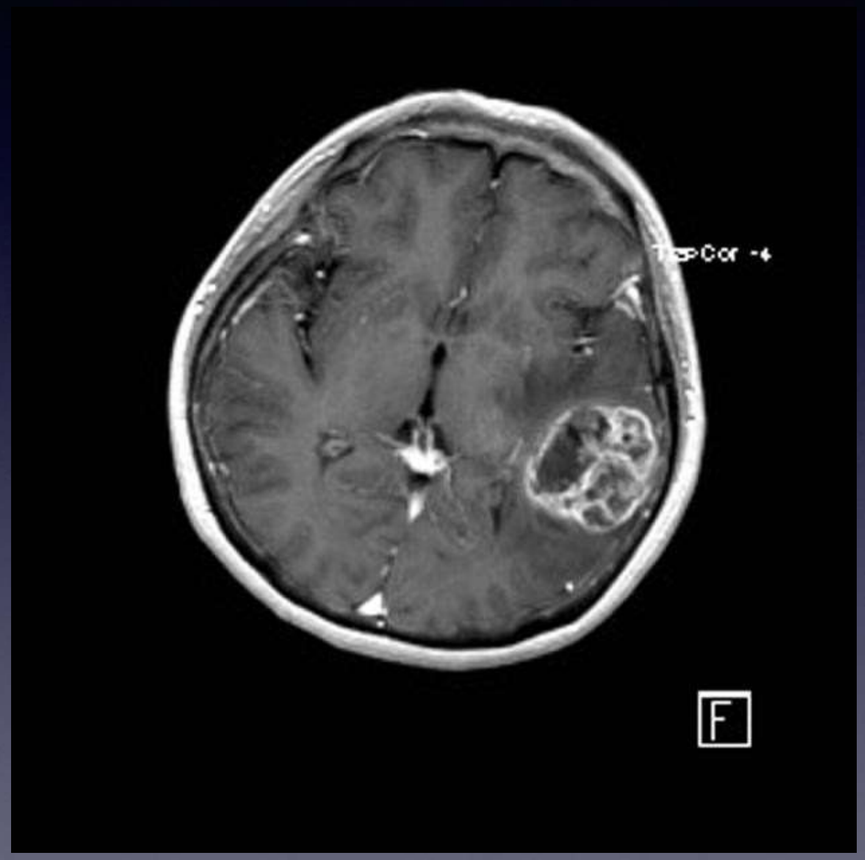
Polymyxoid astrocytoma

- Usually 10 months of age
- Hypothalamic and thalamic region
- Grossly :solid and gelatinous
- IHC : GFAP, s100, synaptophysin
- More aggressive than pilocystic

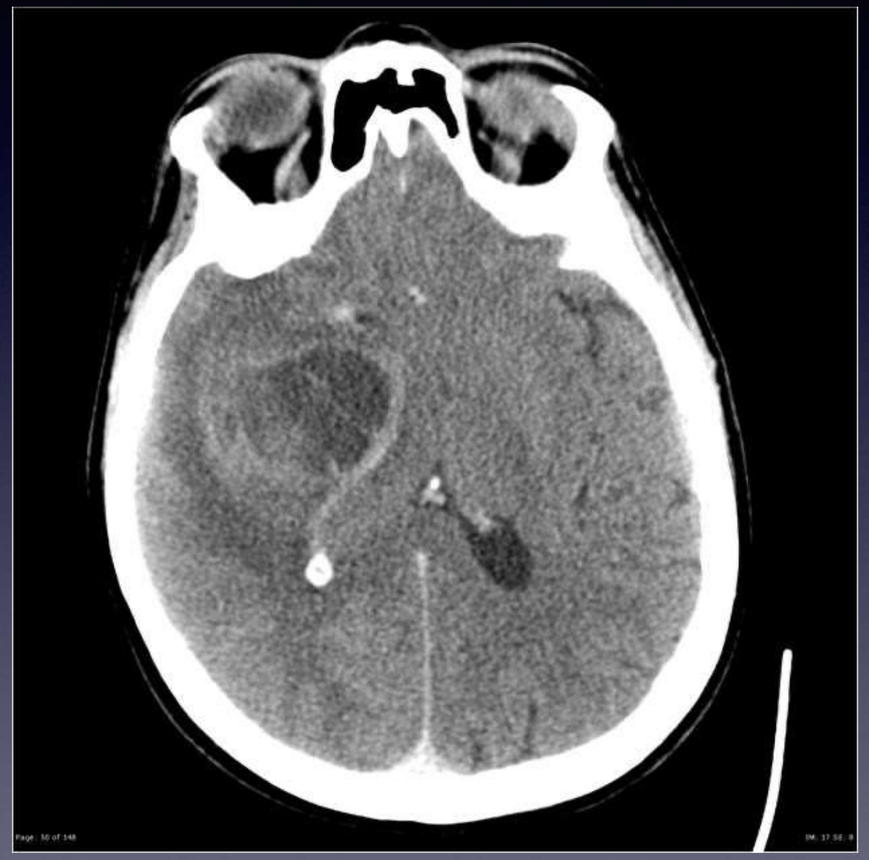
Glioblastoma multiforme

- Most common adult primary intracranial neoplasm, rare in pediatrics
- They can spread to the contralateral hemisphere
- Most common site : subcortical white matter and deep grey matter
- Grossly : poorly marginated, necrotic mass
- IHC : GFAP, S100, EGFR

GBM

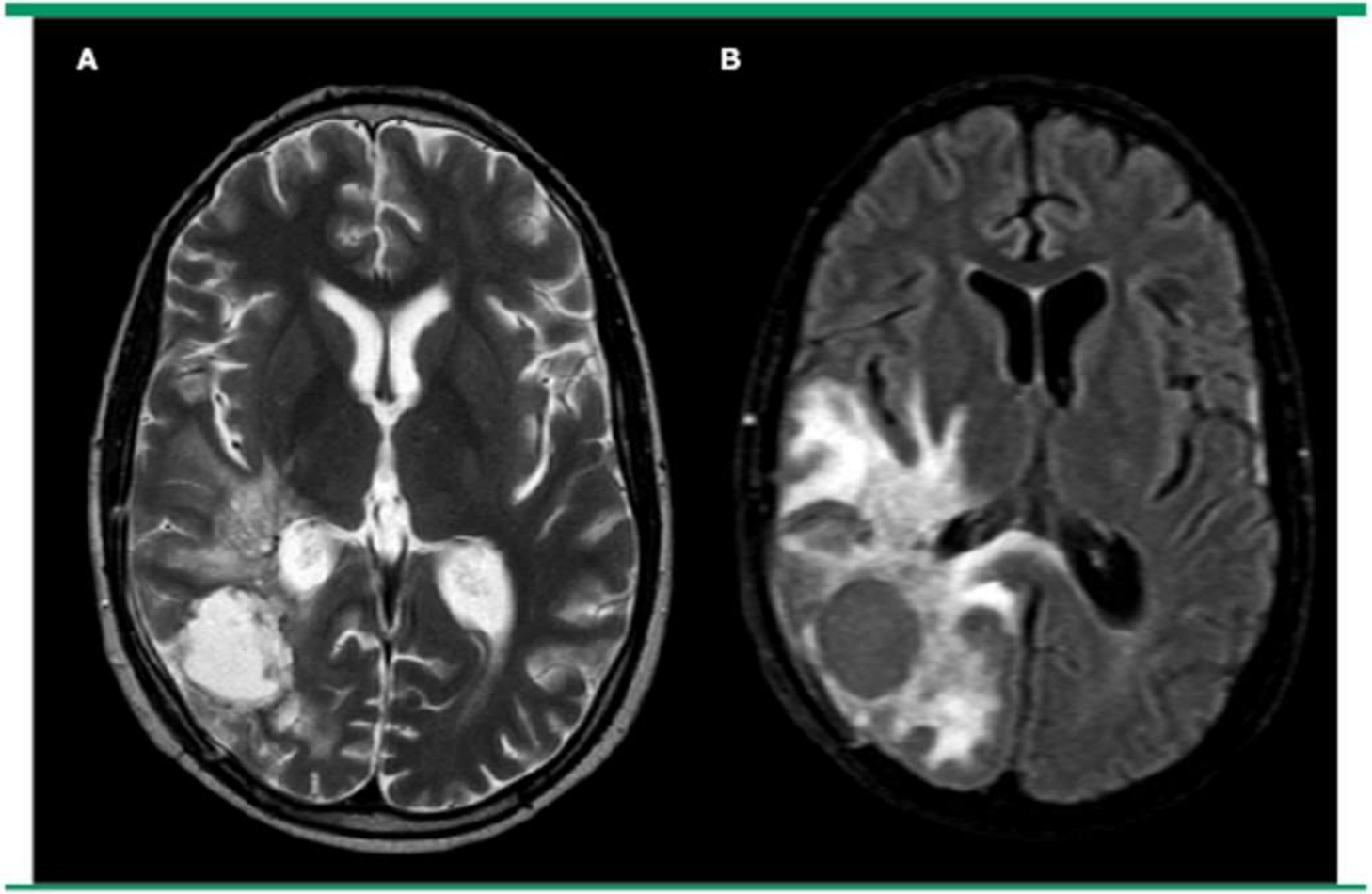


Axial T1 with contrast



Axial CT with contrast

Magnetic resonance image of a glioblastoma



(A) The T2 axial image of this glioblastoma multiforme shows a heterogeneous infiltrating mass that fills large portions of the right temporal and parietal lobes.

(B) The axial flair image of this lesion shows the extensive edema and midline shift that have resulted from the mass.

Treatment of astrocytomas

- Surgery is the number one modality
- In benign lesions if total resection alone 80-100% survival
- If subtotal followup the patient may go for a second surgery or radiotherapy
- In malignant always follow resection with radiotherapy

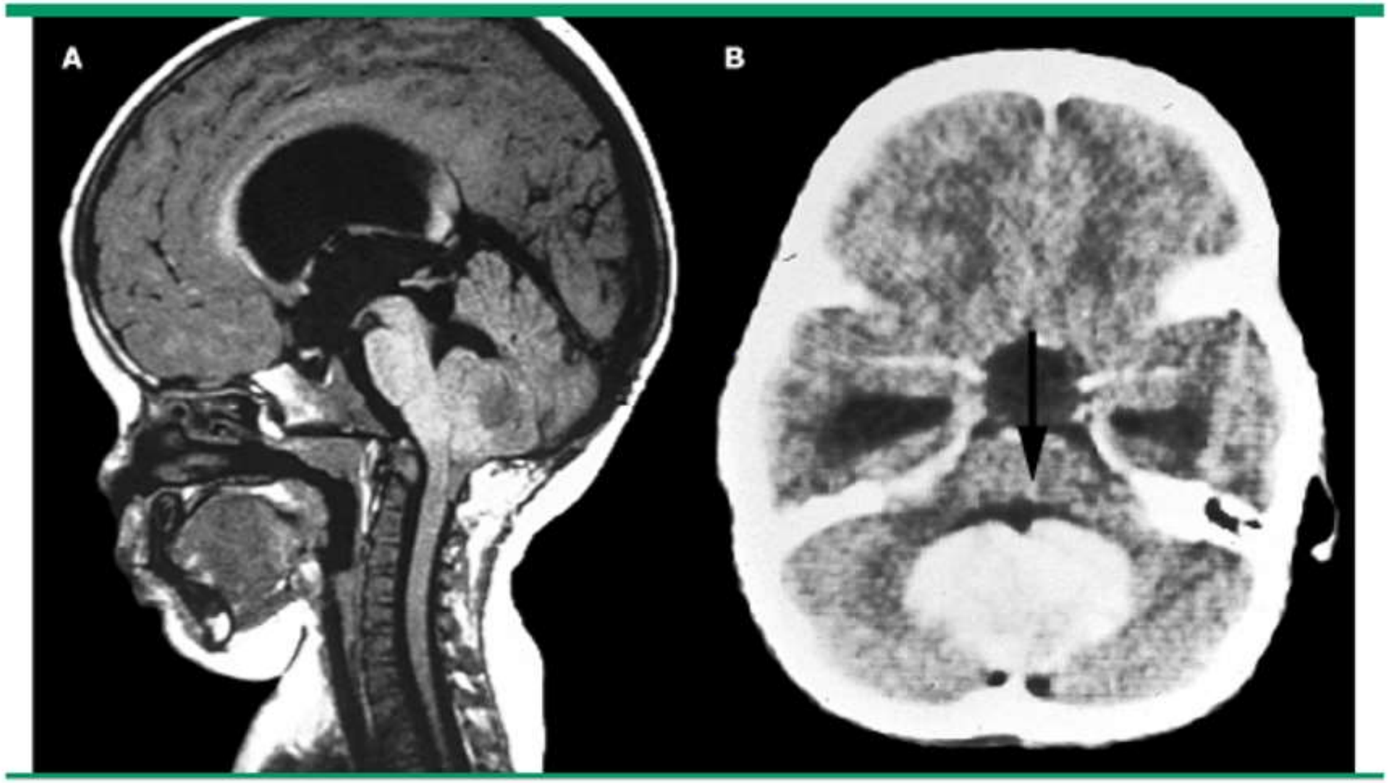
Embryonal tumors

- Most common malignant tumor in pediatrics all subtypes are WHO Grade 4
- Medulloblastoma is the second most common tumor

Medulloblastoma

- 25% Of childhood tumors
- Most common tumor to metastasize extra-cranially
- Site : cerebellum, vermis.
- Age: 5-7 years
- RF : turcot, gorlin, JC virus, SV 40
- Grossly : cystic change, calcifications
- Histology : monomorphic sheets of round small blue cells. Homer wright pseudorosettes. variants : desmoplastic, extensive nodularity (better), large cell (poor)
- IHC : synaptophysin

Magnetic resonance imaging and computed tomography scans of a medulloblastoma in a child



(A) MRI sagittal image of a posterior fossa mass causing compression and dilatation of the third and lateral ventricles.
(B) CT with contrast: Axial image that demonstrates a large posterior fossa mass causing compression of the fourth ventricle (arrow) and dilation of the temporal horns.

MRI: magnetic resonance image; CT: computed tomography.

- Radiology :
  MRI : t1 : hypointense, 90% enhance with Gd
  Ct : usually hyperdense with cysts and necrosis

- Four molecular subtypes :
  WNT , SHH, group 3 (common, both children &infants) , group 4 (most common in children)

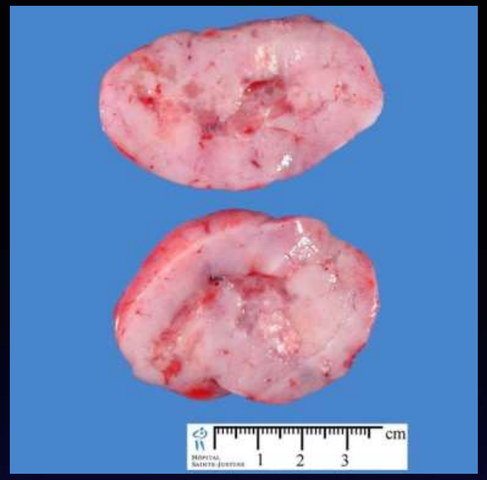
Treatment and prognosis

- Prognosis 60-75% overall
  M0 + good resection = 85%. M1 = 38%. residual = 56%
  WNT (very good) SHH (infants good other intermediate) group 3 (poor) group 4 (intermediate)

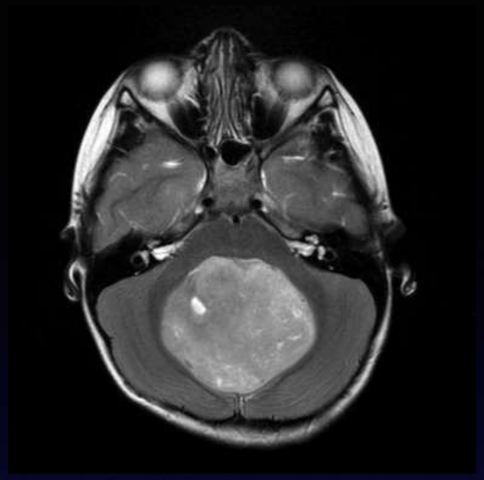
- Treatment (adjunct to surgery) depends on both age and risk
  1- < 3 years : high dose chemo + peripheral stem cell reinfusion
  2- >3 years + low risk : low dose craniospinal radiation + chemo
  3- >3 years + high risk : high dose craniospinal radiation + chemo

- Why avoid radiation as much as possible. ?
  mental retardation, neuroendocrine dysfunction and secondary tumor risk as well as risk of microcephaly in < 3 years

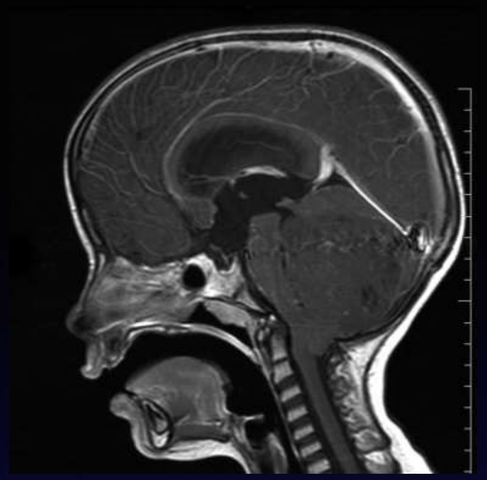
- High risk groups :
  < 3 years
  residual mass > 1.5
  distant mets
  large cell type
  loss of ch 17p, CMYC, NMYC amplification



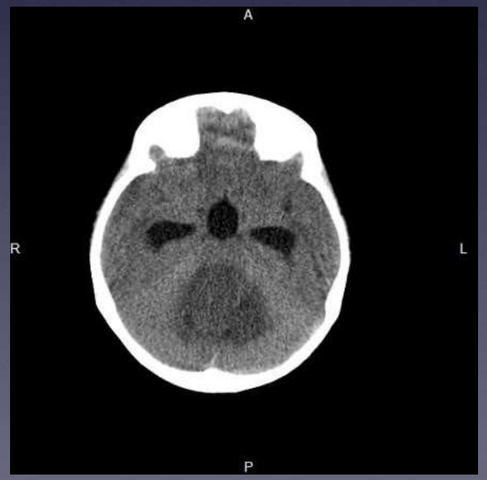
Gross pathology



Axial T2



Sagittal T1

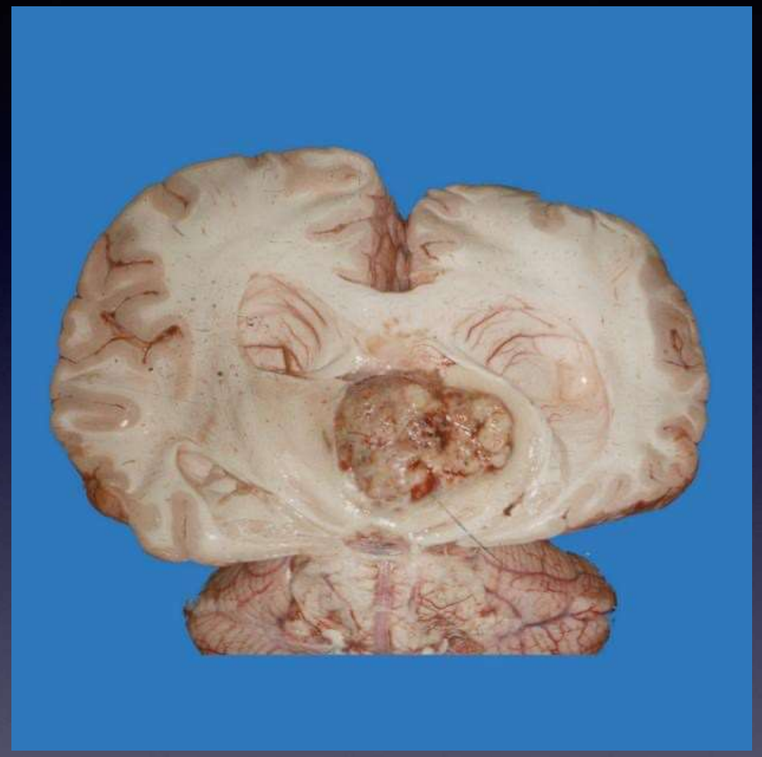


Axial CT non contrast

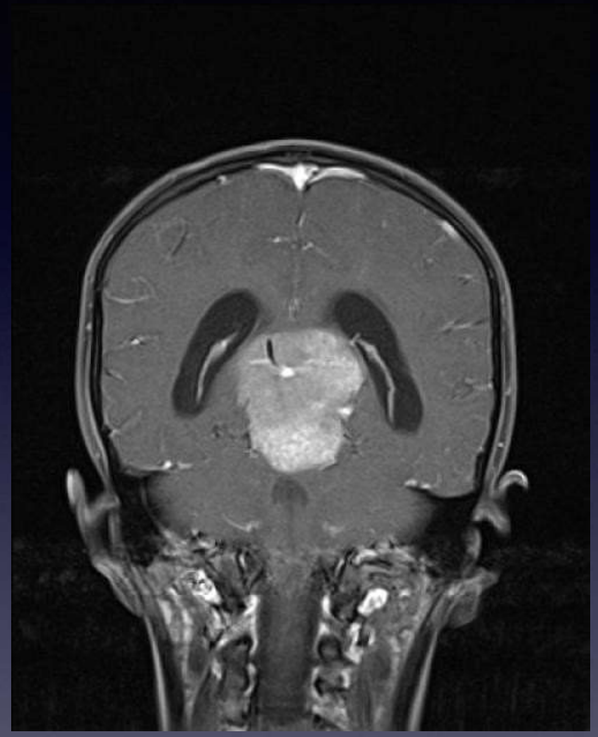
Supratentorial PNET

- Small blue round cells arise in cerebral hemisphere and are aggressive
- Contrast enhancement is the rule
- Grossly large well dermacted cystic and calcified
- Pineoblastoma (most common) may present as Parinaud syndrome
  ependymoblastoma
  medulloepithelioma

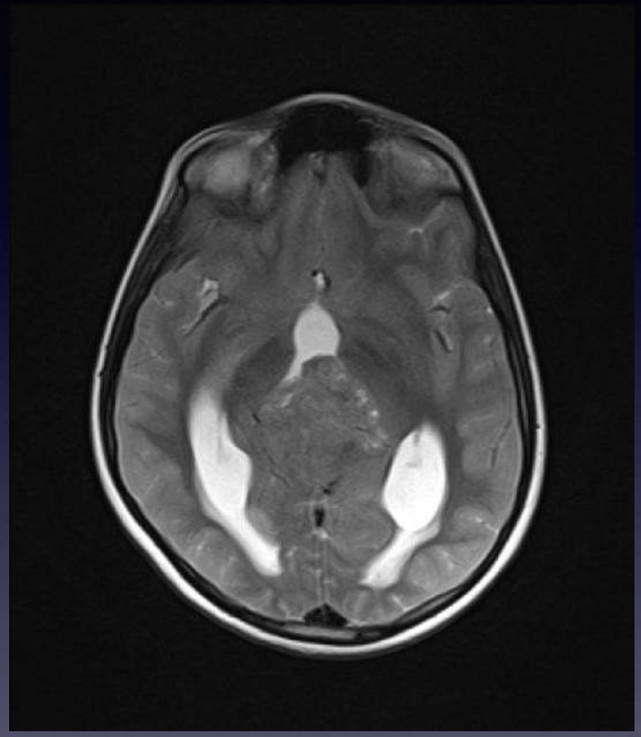
Pineoblastoma



Grossly



Coronal t1 with contrast



Axial t2

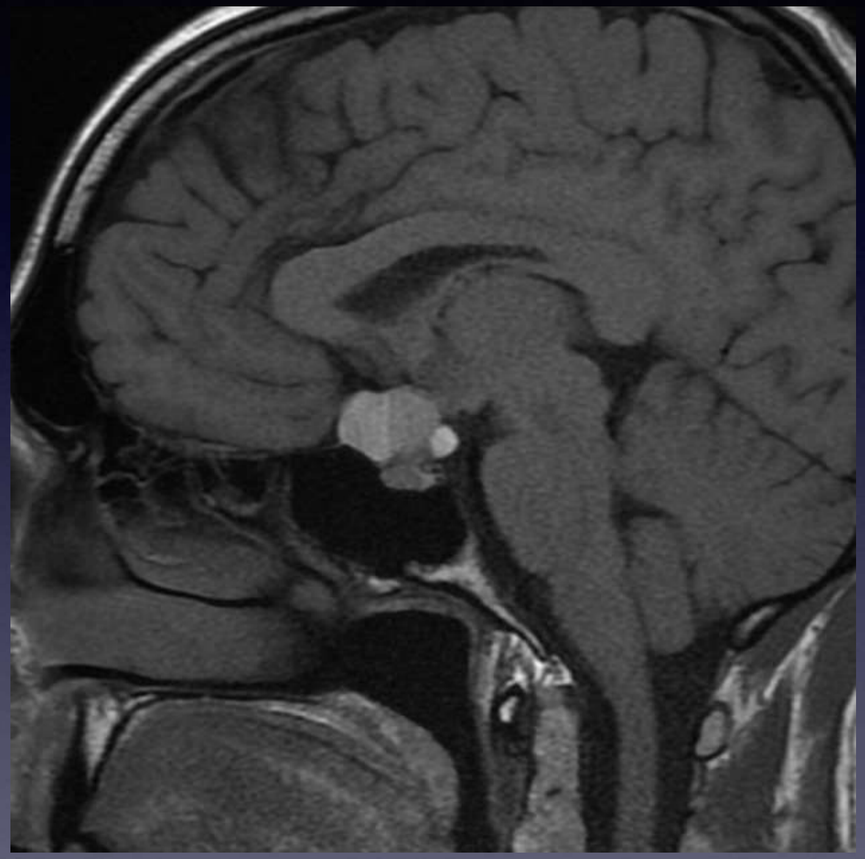
- Pineoblastoma are associated with hereditary neuroblastoma on MRI they are usually > 4 cm and evidence of invasion is present
- Multimodal treatment but the prognosis is poor 5YS 15%

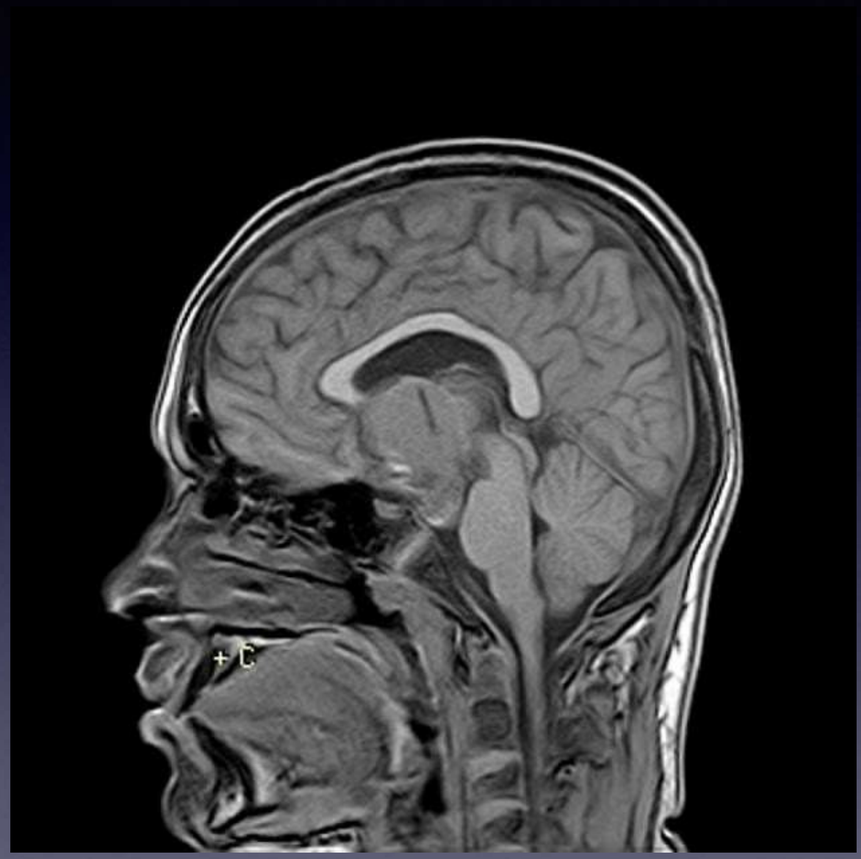
Malignancies in pineal area

- Pineoblastoma 2nd most common
- Germ cell most common
  children 10-12 years
  insidious the first symptom being poorschool performance. And behavioral changes
  tumor markers : beta-HCG and alpha-FP

Craniopharyngeoma

- Benign WHO 1 tumors usually arising in sellar and suprasellar region
- S/s : visual in 20 % of. Children preceded by endocrinological short stature, growth failure, delayed puberty and diabetes insipidus.
- Derived from rathke’s cleft





Sagittal T1

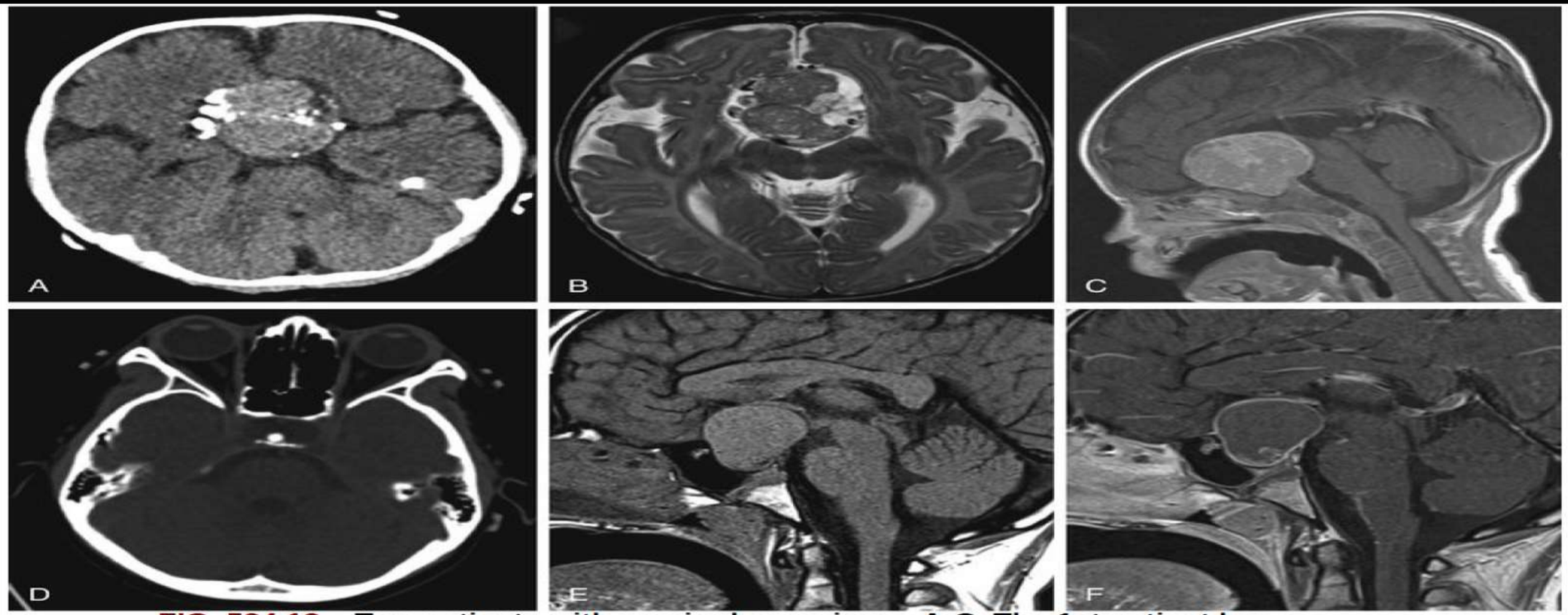


FIG. 524.12 Two patients with craniopharyngioma. A-C, The 1st patient has a predominantly solid sellar-suprasellar mass with internal calcifications, which are seen best on the axial CT image (A). The mass is predominantly T2 isointense to hypointense and there are few T2 hyperintense cystic components along the left aspect of the mass (B). The solid components show enhancement (C). D-F, The 2nd patient has a predominantly cystic sellar-suprasellar mass with internal calcification (D), intrinsic T1 hyperintensity of the cyst contents (E), and a thin rim of postcontrast enhancement (F). Both lesions result in posterior and superior displacement of the optic chiasm. (From Seeburg DP, Dremmen MHG, Huisman TAGM: Imaging of the sella and parasellar region in the pediatric population, Neuroimag Clin N Am 27:99–121, 2017, Fig 2, p 103.)

Metastatic tumors

- Uncommon in children
- Leukemia, lymphoma, osteogenic sarcoma, rhabdomyosarcoma, Ewing sarcoma.

NEUROBLASTOMA & WILMS TUMOR

Neuroblastoma

- Neuroblastoma is derived from **neural crest cells that form** the adrenal medulla and the sympathetic nervous system .
- Most cases occur in young children.
- Neuroblastoma may rarely (1-2% of cases) be hereditary.
- In sporadic cases, several somatic genetic mutations have been identified, with *MYCN amplification being* the most common.
- **it is the most common extracranial solid tumor of childhood and the most common malignancy in infancy.**
- The median age at diagnosis is 17 months.

Clinical presentation

- The most common presentation is **abdominal pain or mass**. The mass is often palpated in the abdomen or flank and is hard and nontender , and can cross the midline .
- It can occur anywhere along the sympathetic nervous system

The **adrenal gland** is the most common primary site (40%), followed by abdominal (25 %), thoracic (15 %), cervical (5%), and pelvic sympathetic ganglia (5 %) .

- Children with localized disease are often asymptomatic at diagnosis, whereas children with metastases often appear ill and have systemic complaints such as fever, weight loss, and pain.

Abdominal tumors presentation

- Abdominal tumors can present with **abdominal pain or fullness, abdominal mass,** hypertension.
- The mass is **typically, but not always, non-tender, fixed, firm and cross the midline .** Such masses may also be detected initially using abdominal ultrasonography .

Thoracic , cervical and paraspinal T.

- **1/Thoracic tumors ;** may be **detected incidentally** on radiographs

  -Can cause **tracheal deviation** or narrowing with resultant stridor
- **2/cervical masses** may be associated with a **Horner syndrome** (ptosis, miosis, and anhidrosis)
- - Large thoracic tumors, usually associated with mechanical obstruction, may cause **the superior vena cava syndrome**
- **3/ Paraspinal tumors** may invade through the neural foramina and cause spinal cord compression which can cause Localized back pain, weakness .

Paraneoplastic syndromes

- **paraneoplastic syndromes;**
- including secretory diarrhea from paraneoplastic production of vasoactive intestinal polypeptide [VIP]
- profuse sweating
- **Opsomyoclonus** (rapid, dancing eye movements, rhythmic jerking (myoclonus) involving limbs or trunk, and/or ataxia.)
- **Metastasis** : both lymphatic and hematogenous routes

1/**bones and bone marrow** can cause pain/limb ,blood count abnormalities, and fever .

2/periorbital mets; ecchymosis and proptosis

3/skin mets ; skin nodules with blueberry muffin apperance

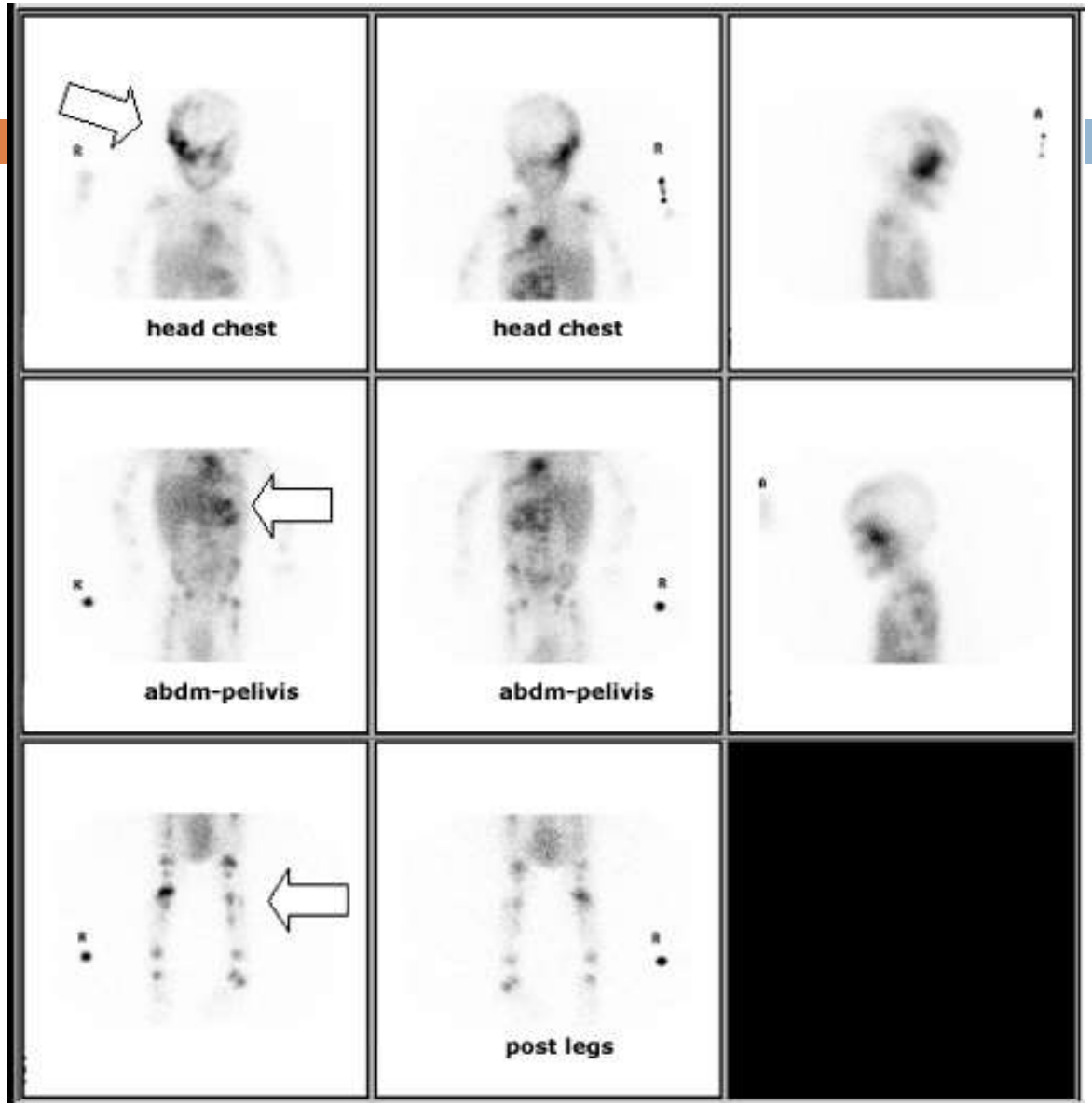
4/liver mets ; hepatomeagly

LABORATORY/IMAGING STUDIES

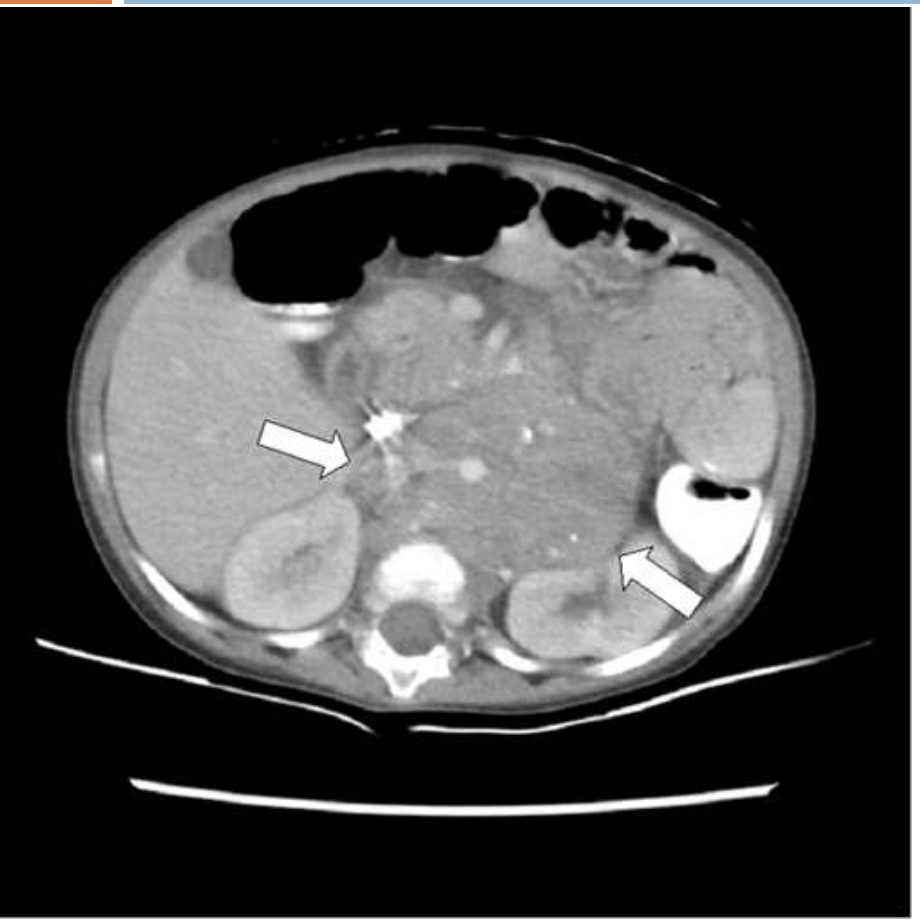
- CBC
- X-ray: Calcification within abdominal
- urinary catecholamines: About 90% of neuroblastomas produce catecholamines (**Vanillylmandelic acid; Homovanillic acid**)
- Definitive diagnosis of neuroblastoma requires tissue biopsy
- A computed tomography (CT) scan of the chest, abdomen, and pelvis;
- Metaiodobenzylguanidine "MIBG" scan;
- bilateral bone marrow aspiration and biopsies;

MIBG scan

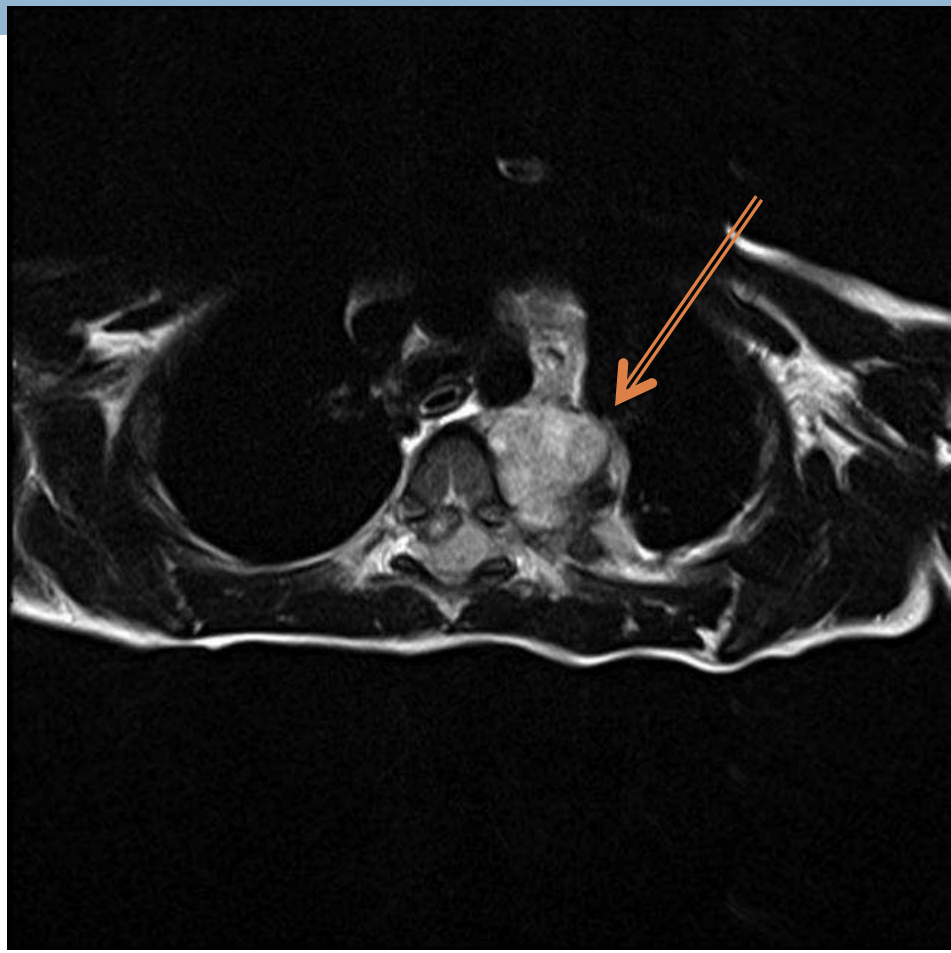
- Metaiodobenzylguanidine
- • Chemical analog of norepinephrine
- • Diagnosis of pheochromocytoma & neuroblastoma
- • Concentrated in sympathetic tissues
- • Labeled with radioactive iodine (I131)
- • Will concentrate in tumors and emit radiation
- • Special note: thyroid gland must be protected
- • Simultaneous administration of potassium iodide
- • Non-radioactive iodine
- • Will be taken up by thyroid instead



Multiple neuroblastoma metastases
MIBG scan



Neuroblastoma arising from the adrenal gland ct scan



MRI axial t2

Differential Diagnosis

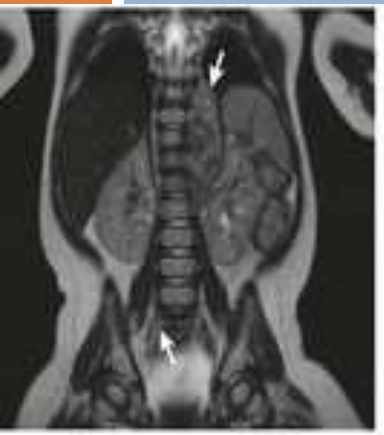
- Wilms tumor
- Leukemia: if there is bone marrow mets.
- Child abuse: in presence of peri-orbital ecchymosis

Treatment:

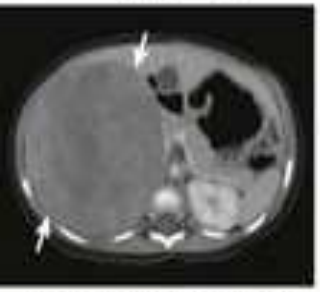
- Chemotherapy +/- surgical resection +/- radiotherapy

Treatment

- Children with very **low– or low-risk** tumors who undergo a **gross total resection** require no further therapy.
- Patients with **intermediate risk** disease are usually treated **with surgery and 4-8 cycles of chemotherapy**.
- In patients with **high-risk disease, combination chemotherapy** is given after confirmation of the diagnosis.
- The aggressive chemotherapy and radiation therapies currently used to treat high-risk neuroblastoma may result in **complications** such as ototoxicity, nephrotoxicity, growth problems, and second malignancies.

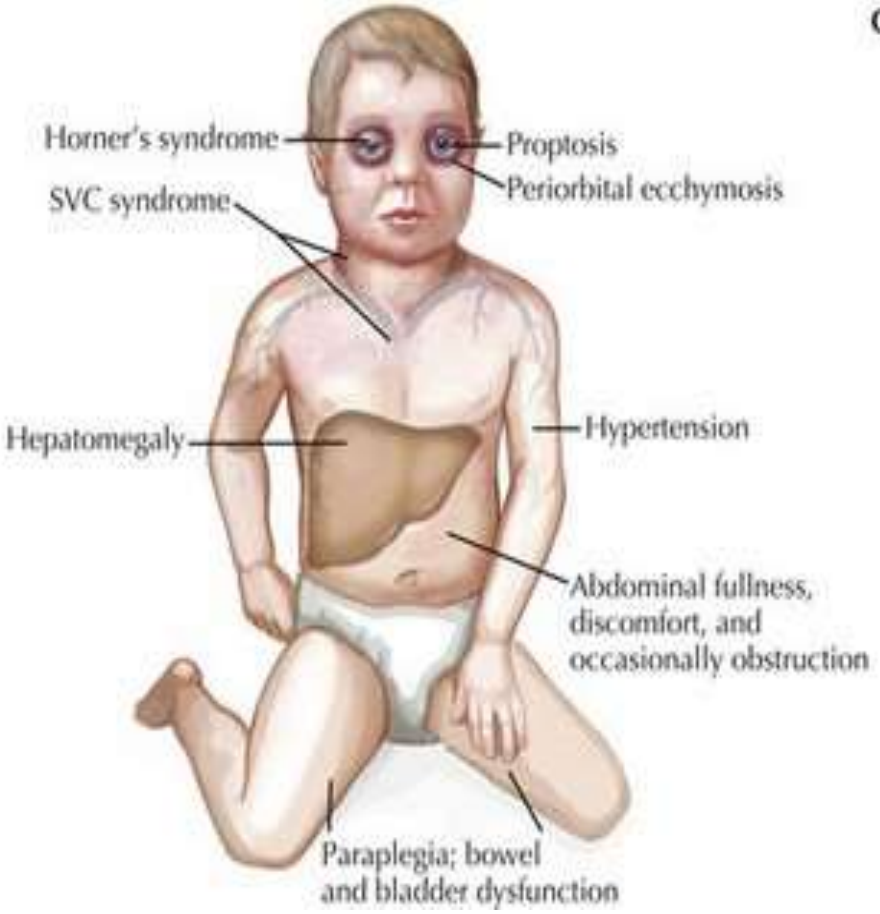


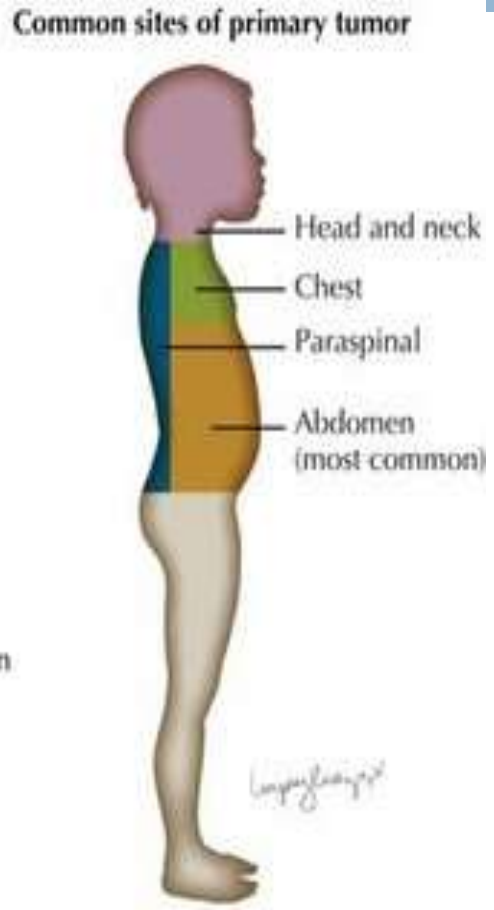
MR image, paraspinal tumor



CT, abdominal tumor

Radiology images courtesy of Lisa States, MD Children's Hospital of Philadelphia





Wilms Tumor

- **Wilms tumor is thought to arise from primitive, metanephric** blastema, the precursor of a normal kidney.
- Wilms tumor is the most common malignant renal tumor of childhood
- *75%* of cases occur in children younger than *5* , the mean age at diagnosis is 3 to 3.5 years of age .
- approximately 15-20% of sporadic tumors have *WT1 mutations or deletions.*
- Certain syndromes including **Beckwith-Wiedemann** and **WAGR** are at increased risk of developing the disease.
- It can be bilateral in 5% of cases .

- **- WAGR**
  WT1
  Wilms Tumor
  Aniridia
  genitourinary anomalies
  (eg, cryptorchidism, ambiguous genitalia)
  Retardation

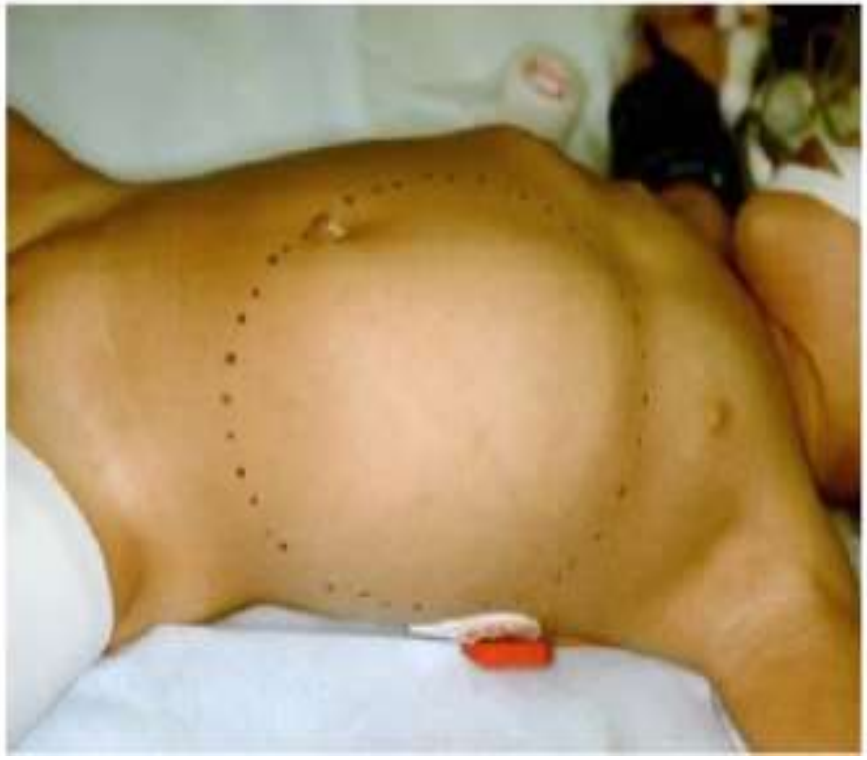
-Beckwith Wiedemann
WT2
Hemihypertrophy
Mcroglossia
Visceromegaly

Clinical menifstation

- Mostly present with **abdominal mass** (smooth , firm and less likely to cross the midline)
- associated symptoms may include
- **abdominal pain** (often mistaken for constipation)
- **Hematuria**
- **Hypertension** (secondary to pressure on renal artery or increased secretion of renin by tumor)
- **Non specific** ; fever, anorexia , weight loss and constipation .
- Symptoms of associated congenital anomalies if present (15%)

LABORATORY/IMAGING STUDIES

- An abdominal **ultrasound or computed tomography (CT)** scan can usually distinguish an intrarenal mass from a mass arising from the adrenal gland (most commonly neuroblastoma)
- The diagnostic work-up includes a complete blood count, urinalysis, liver and renal function studies, as well as a CT scan of the chest, abdomen, and pelvis to assess for metastatic involvement (pulmonary involvement is the most common metastatic site).
- The diagnosis is confirmed by **histological examination** of the tumor.



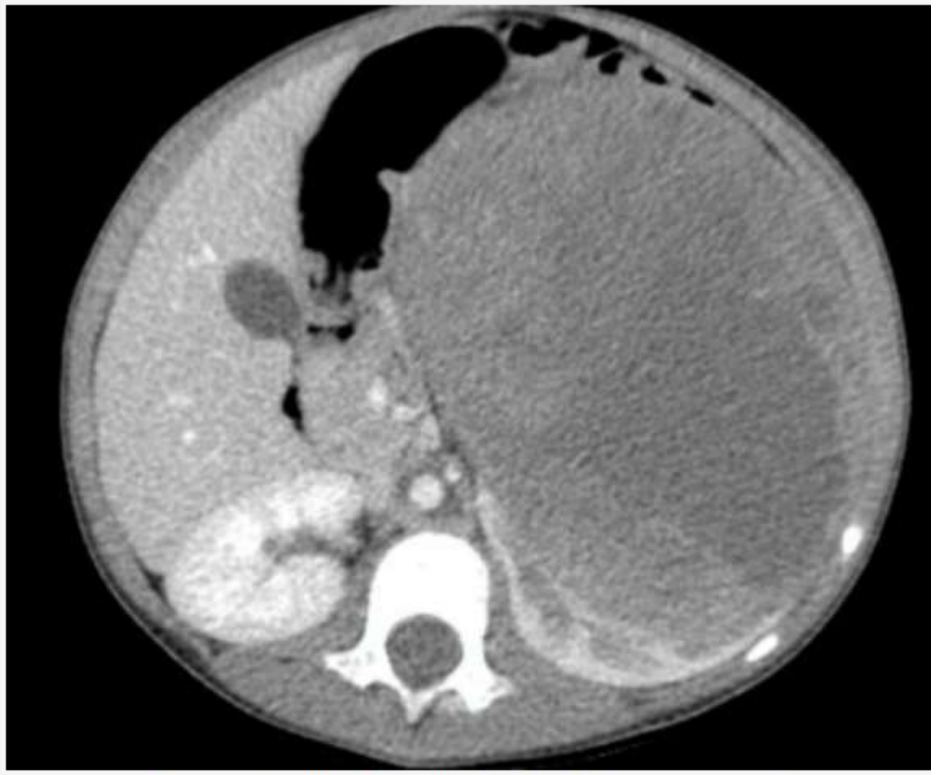


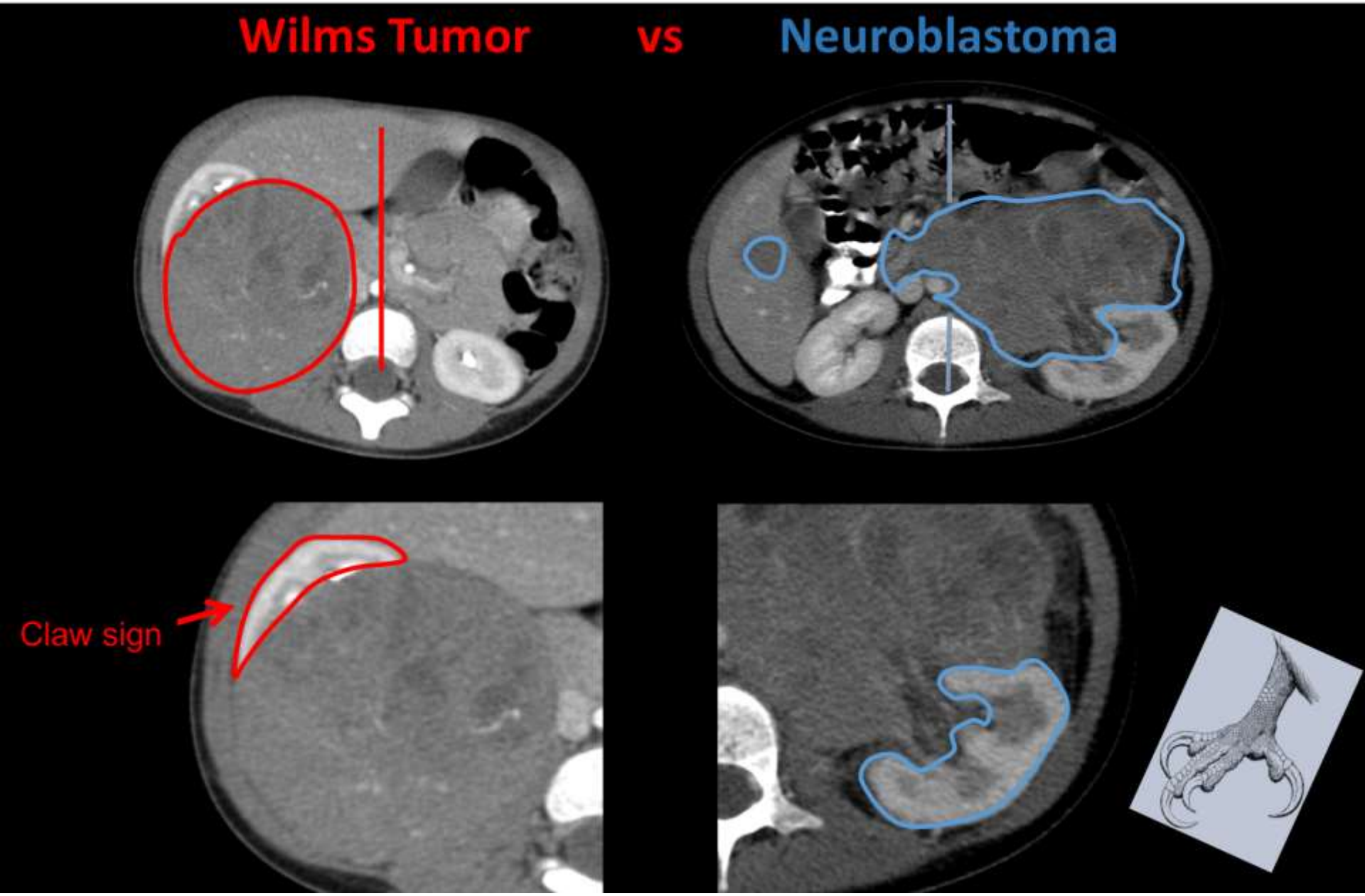
Figure 15.9B Axial CT of the abdomen revealing a very large mass.

Axial abdominal ct scan

Treatment: neoadjuvant chemotherapy followed by nephrectomy and then adjuvant chemotherapy

Prognosis : excellent >90% overall cure rate .

Comparsion	Neuroblastoma	Wilms tumor
Age	Younger age group <2yr	Slightly older <5 yr , median age 3 years
Associations	Ass. With **Opsomyoclonus**	**Beckwith-Wiedemann** and **WAGR**
Constitutional symptoms	More common	Less common
origin	Mostly adrenal gland	Intrarenal
Abdominal mass	non-tender, fixed, and firm And may cross the midline	smooth , firm and less likely to cross the midline
Tumor margins	Poorly marginated	Well circumscribed mass , claw sign
Vessel involvement	Encases vascular structures but does not invade them	Can invade vasculture with extension into renal vein /ivc
Metastasis	Bone and bone marrow	Lungs

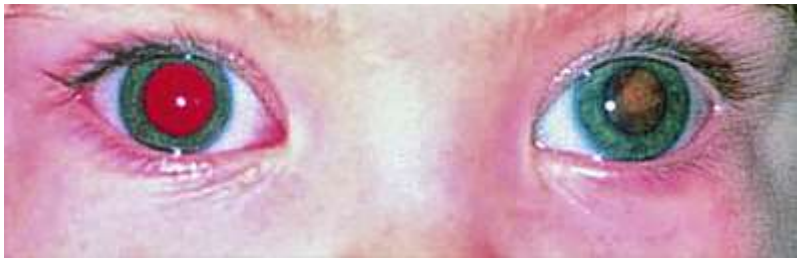

Wilms Tumor
vs
Neuroblastoma
Claw sign

Retinoblastoma

- Retinoblastoma **is the most common primary intraocular malignancy of childhood**
- accounts for 10 to 15 % of cancers that occur within the first year of life.
- Retinoblastoma typically presents as **leukocoria** in a child **under the age of three years.**
- Retinoblastoma occurs in heritable (due to germline mutations) and nonheritable forms (due to somatic mutations)
- Germline mutations in the retinoblastoma (RB1) gene are present in approximately 40 % of cases, predominantly in bilateral disease.

- **Clinical features** — Retinoblastoma typically presents as leukocoria (picture 1) and strabismus (picture 2) ,nystagmus, and a red inflamed eye.
- Diagnosis ; ophthalmoscope , early diagnosis is cruical .

Picture 1



Picture 2
Exotropia plus slightly enlarged corneal diameter and loss of red reflex in left eye.

SARCOMAS

RECALL

- Sarcomas are divided into soft tissue sarcomas and bone cancers. Soft tissue sarcomas arise primarily from the connective tissues of the body, such as muscle tissue, fibrous tissue, and adipose tissue. **Rhabdomyosarcoma** (RMS), the most common soft tissue sarcoma in children, is derived from mesenchymal cells of muscle lineage. Less common soft tissue sarcomas include fibrosarcoma, synovial sarcoma, and extraosseous Ewing sarcoma. The most common malignant bone cancers in children are **osteosarcoma** and **Ewing sarcoma**. Osteosarcomas derive from primitive bone-forming mesenchymal stem cells. Ewing sarcomas are thought to be of neural crest cell origin.

ETIOLOGY

- The cause is unknown for most children diagnosed with sarcoma, although a few observations have been made regarding risks. Individuals with:

 - Li-Fraumeni syndrome (associated with a germline p53 mutation)

 - neurofibromatosis (associated with NF1 mutations) have an increased risk of soft tissue sarcomas.

- There is a 500-fold increased risk for osteosarcoma for individuals with hereditary retinoblastoma.
- Prior treatment for childhood cancer with radiation therapy or chemotherapy (specifically alkylating agents), or both, increases the risk for osteosarcoma as a second malignancy.

Rhabdomyosarcoma

EPIDEMIOLOGY

- The incidence of **RMS** peaks in children 2-6 years old and again in adolescents. The early peak is associated with tumors in the genitourinary region, head, and neck; the later peak is associated with tumors in the extremities, trunk, and male genitourinary tract.
- Boys are affected 1.5 times more often than girls.

CLINICAL MANIFESTATIONS

- The clinical presentation of RMS varies, depending on the site of origin, subsequent mass effect, and presence of metastatic disease.

-Periorbital swelling, proptosis, and limitation of extraocular motion may be seen with an orbital tumor. (20%)

-Nasal mass, chronic otitis media, ear discharge, dysphagia, neck mass, and cranial nerve involvement may be noted with tumors in other head and neck sites. (30%)

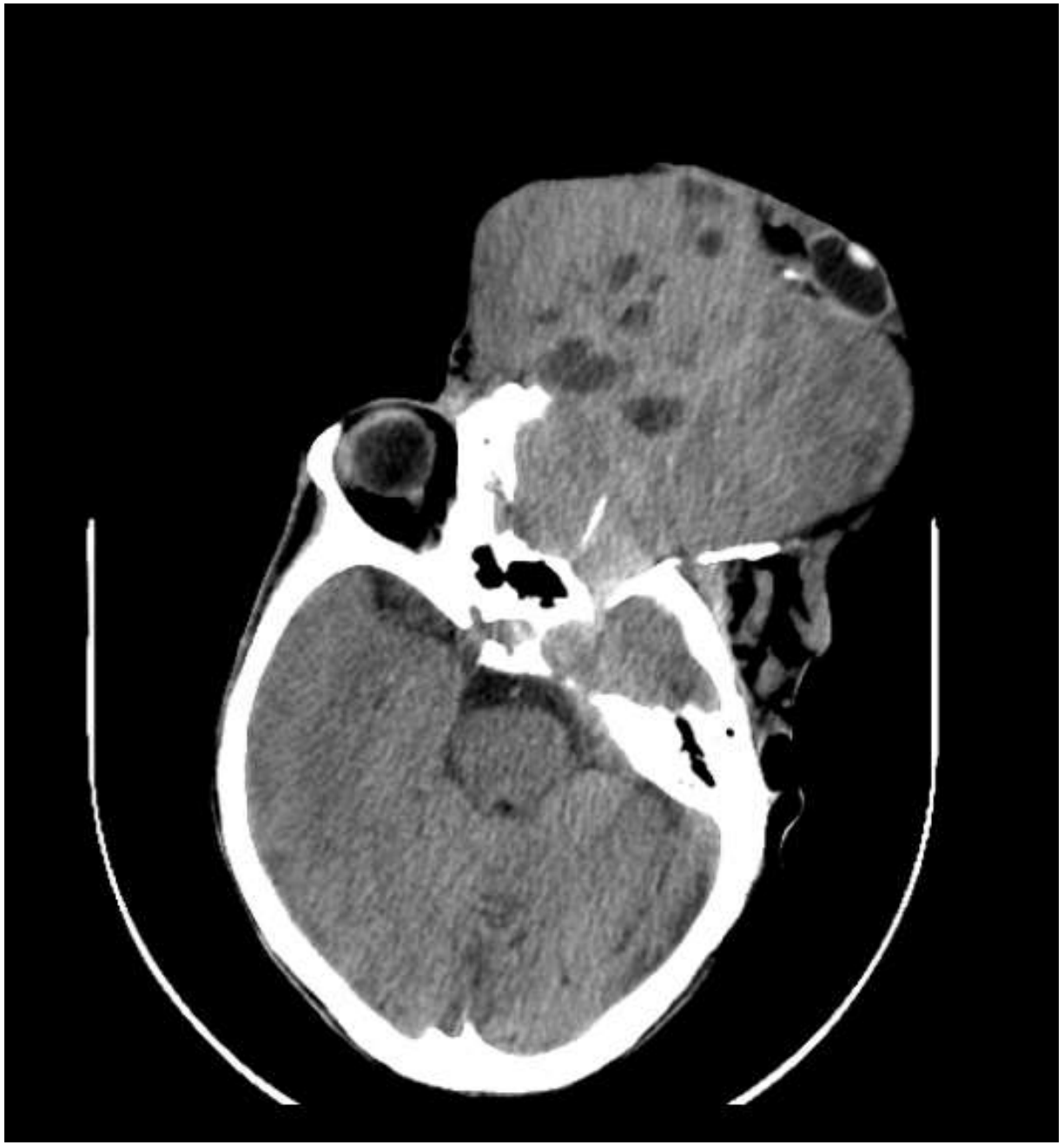
-Urethral or vaginal masses, paratesticular swelling, hematuria, and urinary frequency or retention may be noted with tumors in the genitourinary tract. (25%)

-Trunk or extremity lesions tend to present as rapidly growing masses that may or may not be painful. (15%)

-If there is metastatic disease to bone or bone marrow, limb pain and evidence of marrow failure may be present.

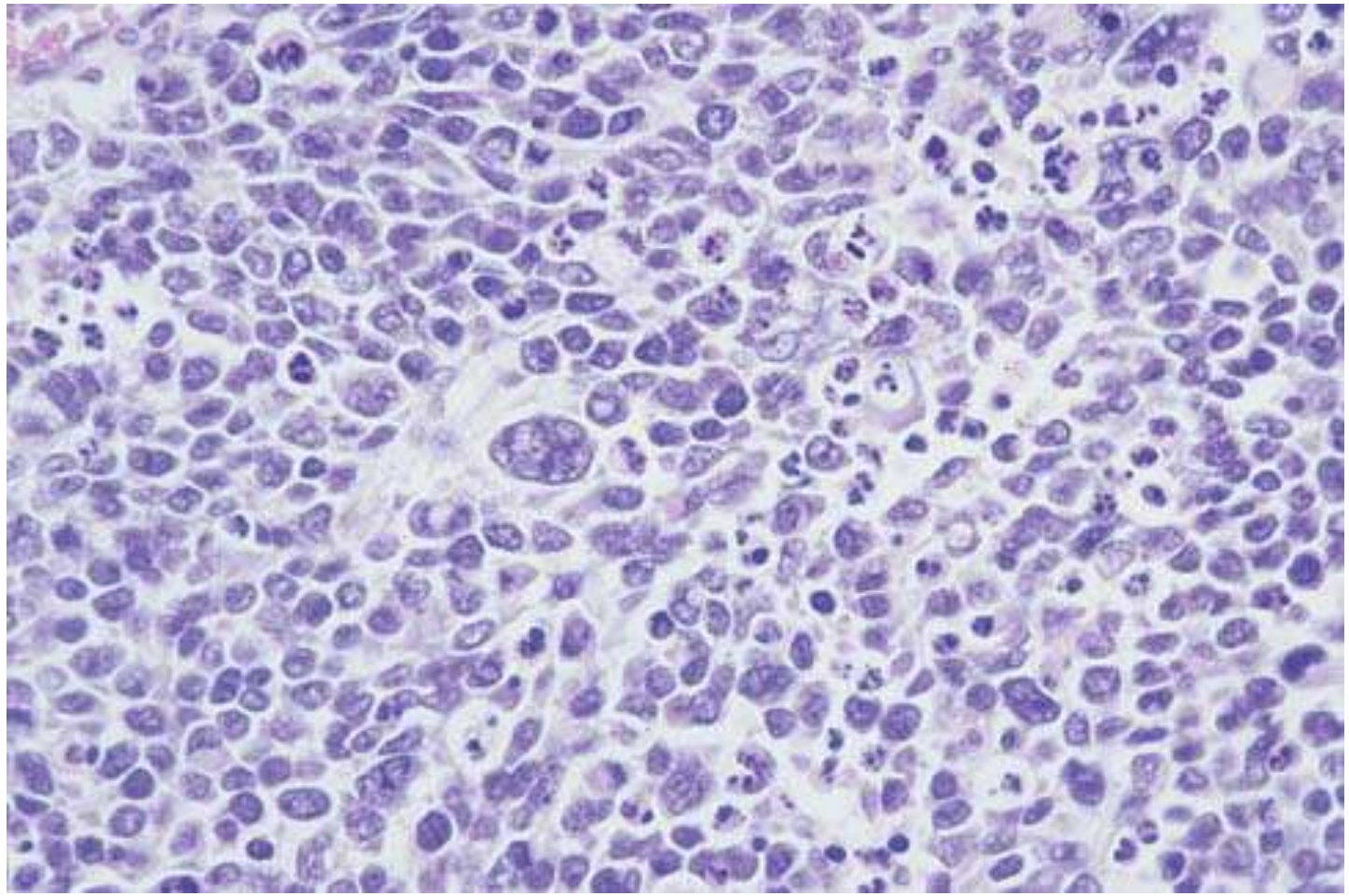
LABORATORY/IMAGING STUDIES

- Tissue biopsy is needed for a definitive diagnosis of sarcoma.
- Immunohistochemical staining for muscle-specific proteins, such as actin and myosin, helps confirm the diagnosis of RMS.
- Metastatic evaluation for patients with RMS should include PET scan (when available), CT, and bilateral bone marrow aspiration/biopsy.
- A lumbar puncture is required in patients with a parameningeal primary site due to the risk of direct extension into the central nervous system (CNS).



CT without contrast

There's huge mass with necrotic and calcified lesions inside, expanding left orbit, with the displacement of left oculus bulbus to anterior. The mass is involving into paranasal sinuses and nasal cavity. Destruction is seen in frontal and maxillary bone.



small, round, blue cell tumors

Immunostains are positive for desmin, myosin and vimentin

Two major histological variants exist for RMS: embryonal and alveolar.
-The embryonal 60% (ERMS; embryonal RMS) histological variant is most common in younger children with head, neck, and genitourinary primary tumors.
-The alveolar 20% (ARMS; alveolar RMS) histological variant occurs in older patients and is seen most commonly in trunk and extremity tumors.

DIFFERENTIAL DIAGNOSIS

- The differential diagnosis for RMS depends on the location of the tumor.
- Tumors of the trunk and extremities often present as a painless mass and may initially be thought to be benign tumors.
- Head and neck RMS may be misdiagnosed as allergies, orbital cellulitis, or chronic infection of ears or sinuses.
- The differential diagnosis for intraabdominal RMS includes other abdominal malignancies, such as Wilms tumor and neuroblastoma.

TREATMENT

- Treatment of RMS is currently based on a staging system that incorporates a number of diagnostic features including primary site, histological subtype, stage (local, regional or metastatic involvement), and surgical grouping (the ability or inability to achieve a gross total resection prior to chemotherapy/radiation).
- Multimodal therapy approach (Surgical resection, chemotherapy and radiation)
- The most common chemotherapy agents used in RMS are vincristine, dactinomycin, and cyclophosphamide.
- Radiation is administered to the primary tumor when surgical resection is incomplete or would be morbid. It may also be administered to involved regional nodal sites, and sometimes to distant metastatic sites.

OSTEOSARCOMA

EPIDEMIOLOGY

- **Osteosarcoma** most commonly affects adolescents; the peak incidence occurs during the period of maximum growth velocity.

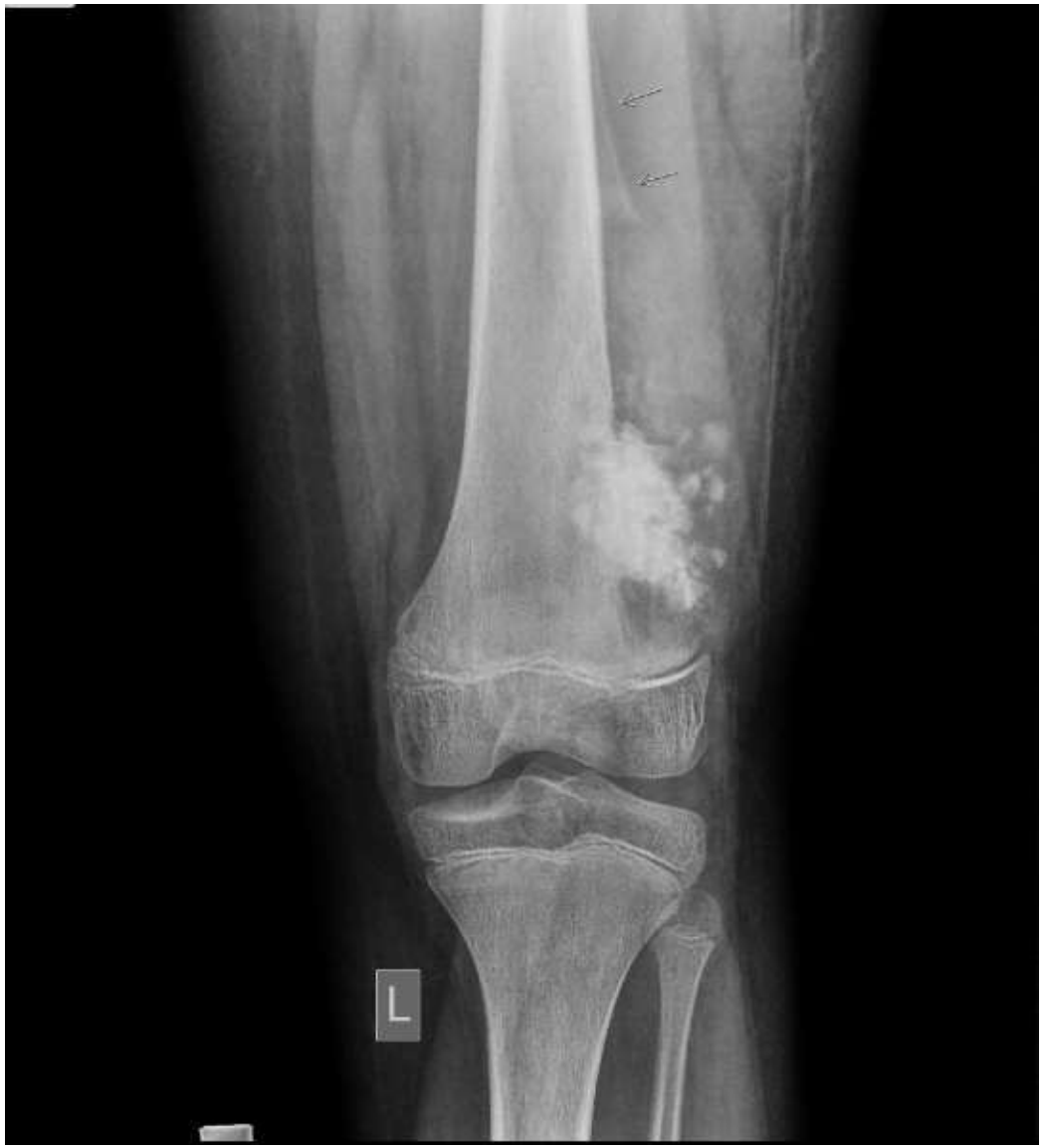
CLINICAL MANIFESTATIONS

- Osteosarcoma is often located at the epiphysis or metaphysis of long bones that are associated with maximum growth velocity (distal femur, proximal tibia, proximal humerus), but any bone may be involved.
- It presents with pain and may be associated with a palpable mass. Because the pain and swelling often are initially thought to be related to trauma, radiographs of the affected region are frequently obtained; the radiographs usually reveal a lytic lesion, sometimes associated with calcification in the soft tissue surrounding the lesion.
- Although 75-80% of patients with osteosarcoma have apparently localized disease at diagnosis, most patients are believed to have micrometastatic disease as well.

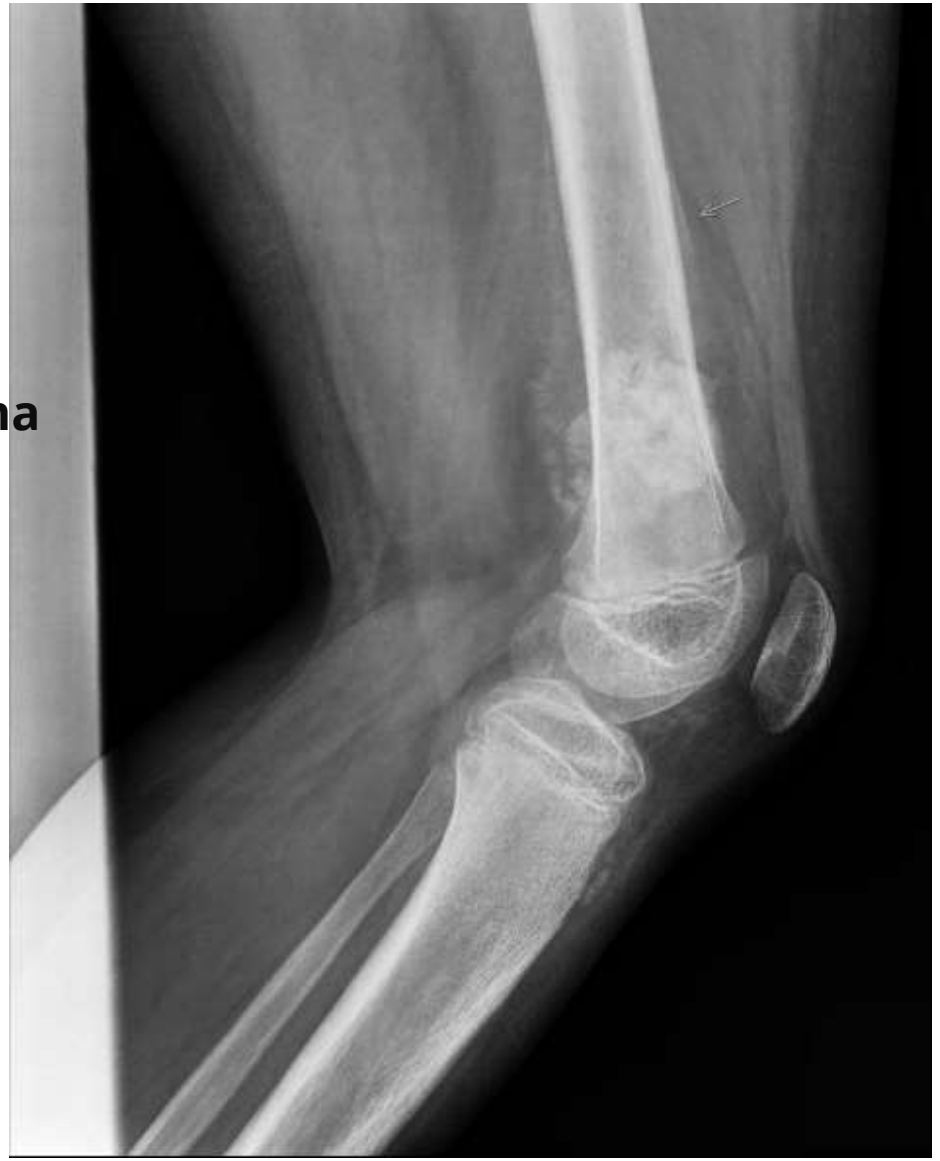
LABORATORY/IMAGING STUDIES

- Tissue biopsy
- The diagnosis of osteosarcoma is established with the presence of osteoid and immunohistochemical analysis of the biopsy material.
- The extent of the primary tumor should be delineated carefully with MRI before starting chemotherapy to determine surgical resection options. Osteosarcoma tends to metastasize to the lungs, most commonly, and rarely to other bones.
- Metastatic evaluation includes a chest CT scan and a bone scan (or PET scan).

Case: 12 year old male, complaining of painful mass in the lower part of left femur.

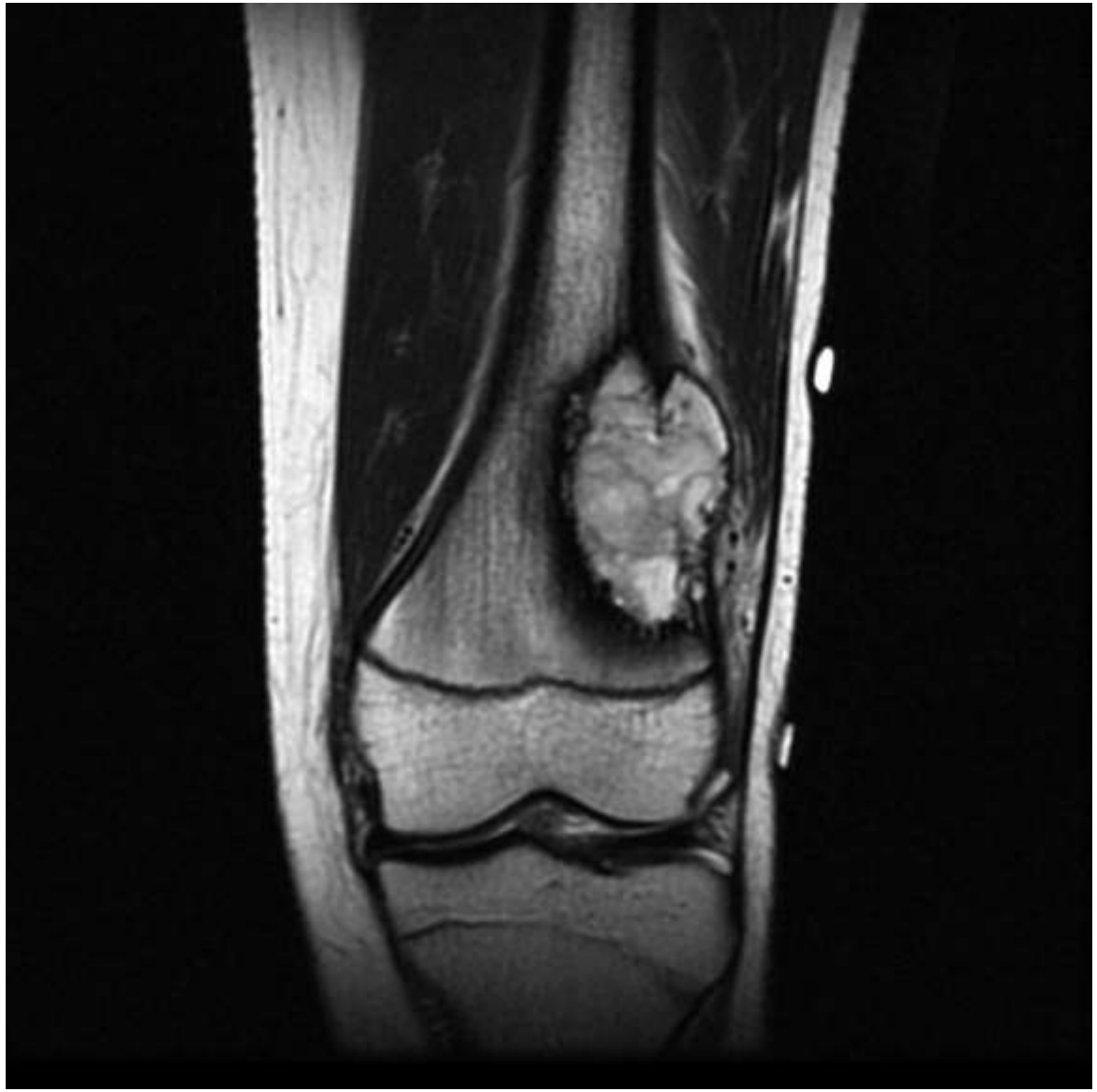


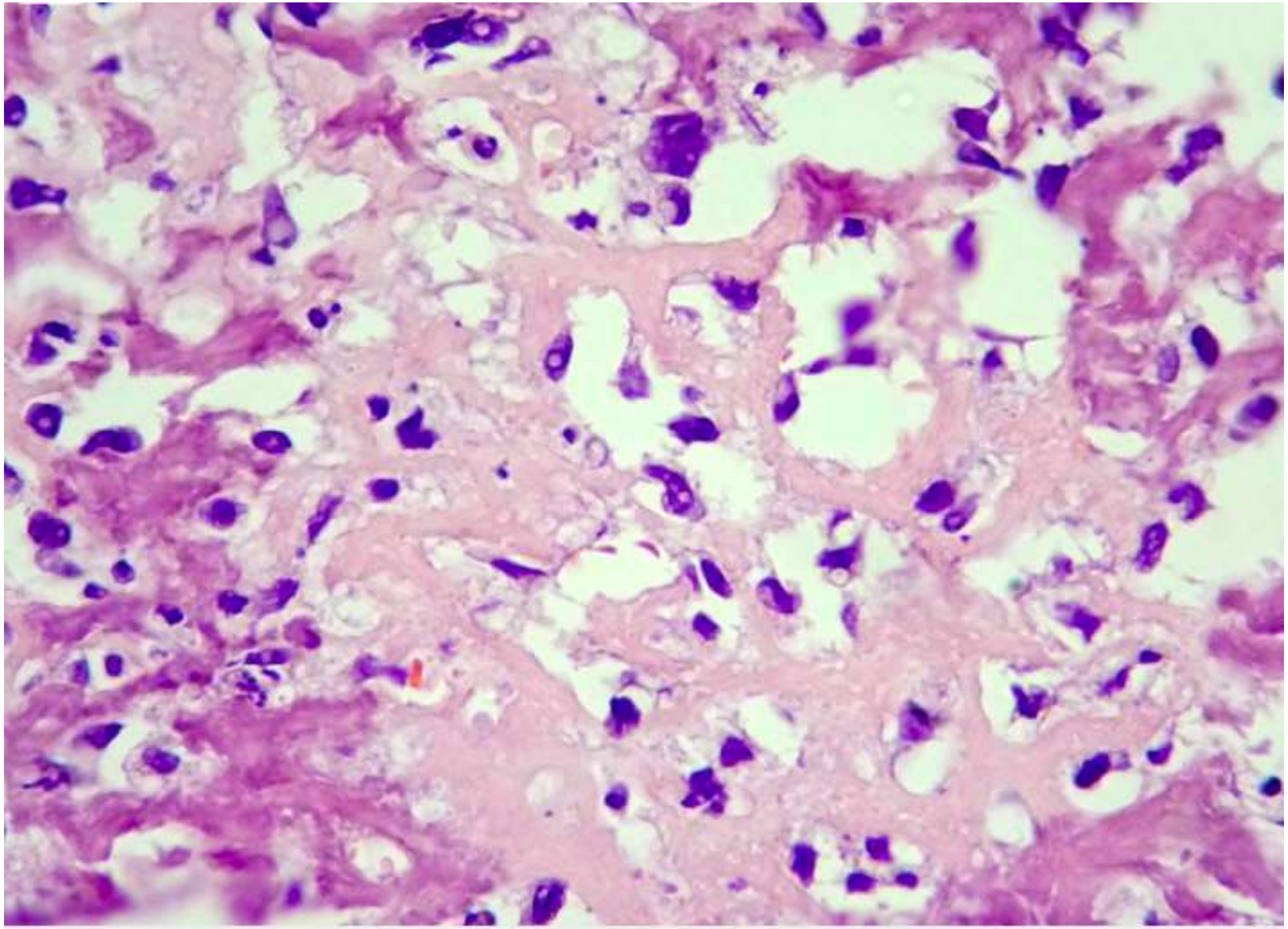
Osteosarcoma
X ray



There is a bone tumor with wide zone of transition, matrix ossification and aggressive periosteal reaction (Codman triangle - arrow), at the distal of left femur.

MRI





Osteoblastic osteosarcoma: Malignant cells producing osteoid (dense, pink, amorphous intercellular material) is the histological hallmark of osteosarcoma.

DIFFERENTIAL DIAGNOSIS

- Children with osteogenic sarcoma are often initially believed to have pain and swelling related to trauma.

TREATMENT

- The current treatment of osteosarcoma involves neoadjuvant chemotherapy, surgical resection of the primary tumor, followed by adjuvant chemotherapy. The most common chemotherapy agents used for osteosarcoma are high-dose methotrexate, doxorubicin, and cisplatin. Radiation therapy is ineffective for osteosarcoma, although it is sometimes used for palliative intent to treat pain.

EWING SARCOMA

EPIDEMIOLOGY

- The incidence of **Ewing sarcoma** peaks between ages 10 and 20 years but may occur at any age.
- Ewing sarcoma primarily affects whites; it rarely occurs in African American children or Asian children.

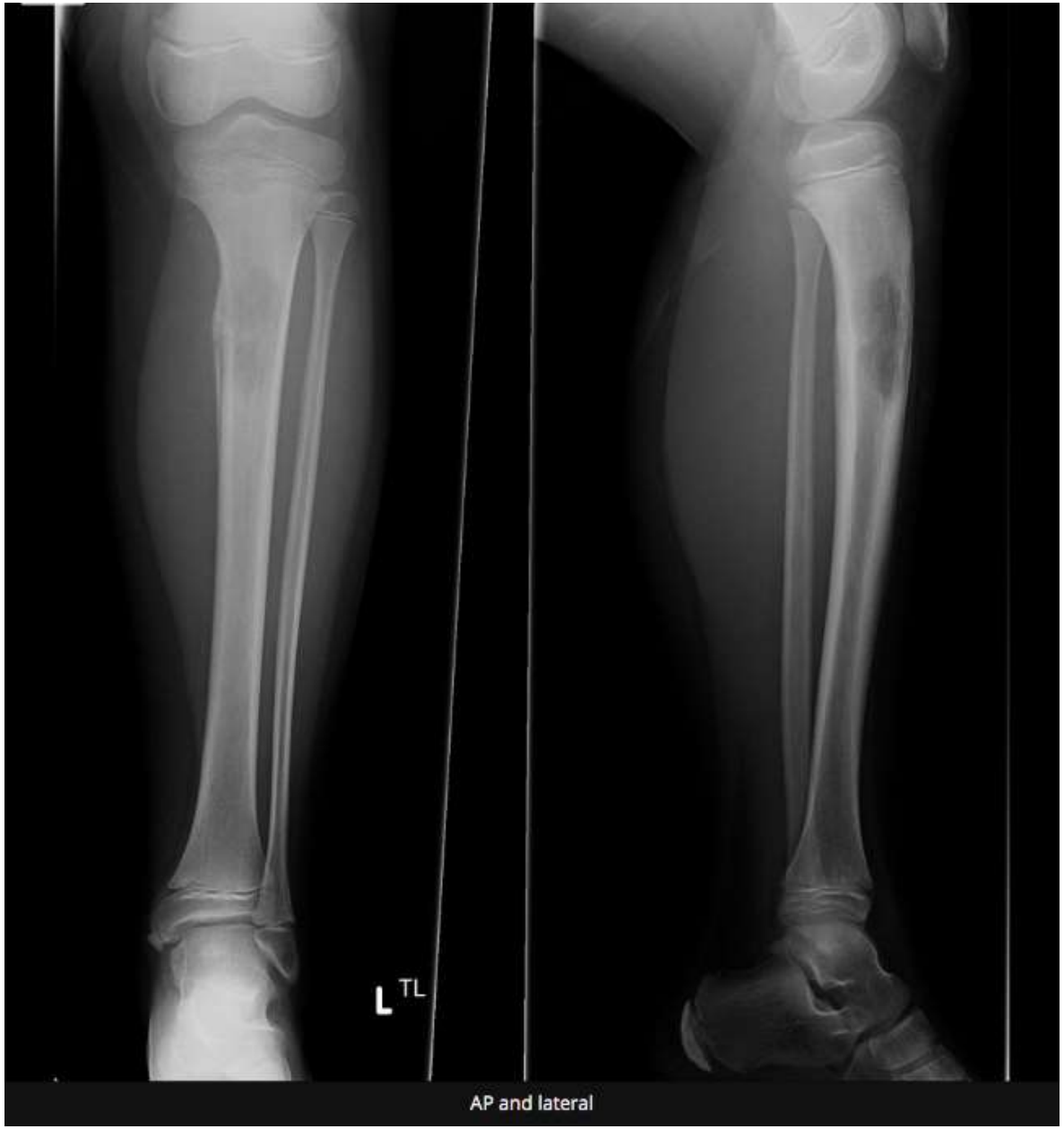
CLINICAL MANIFESTATIONS

- Although Ewing sarcoma can occur in almost any bone in the body, the femur and pelvis are the most common sites. In addition to local pain and swelling, clinical manifestations may include constitutional symptoms such as fever, fatigue, and weight loss.

LABORATORY/IMAGING STUDIES

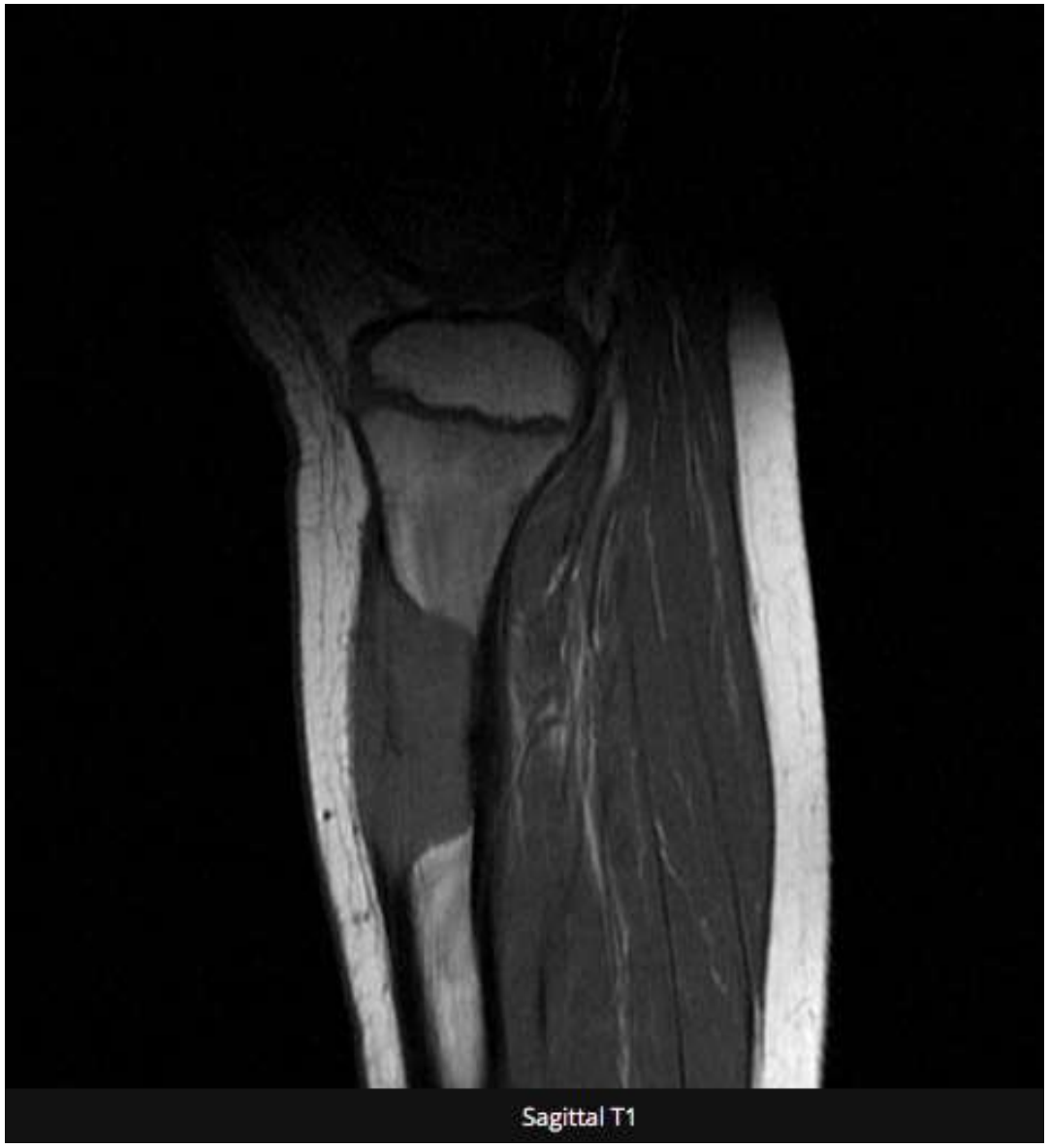
- Tissue biopsy
- The diagnosis of Ewing sarcoma is established with immunohistochemical analysis along with cytogenetic and molecular diagnostic studies of the biopsy material.
- MRI of the primary lesion should be performed to delineate extent of the lesion and any associated soft tissue mass.
- Metastatic evaluation involves a PET scan (when available), chest CT scan, and bilateral bone marrow aspiration/biopsy.

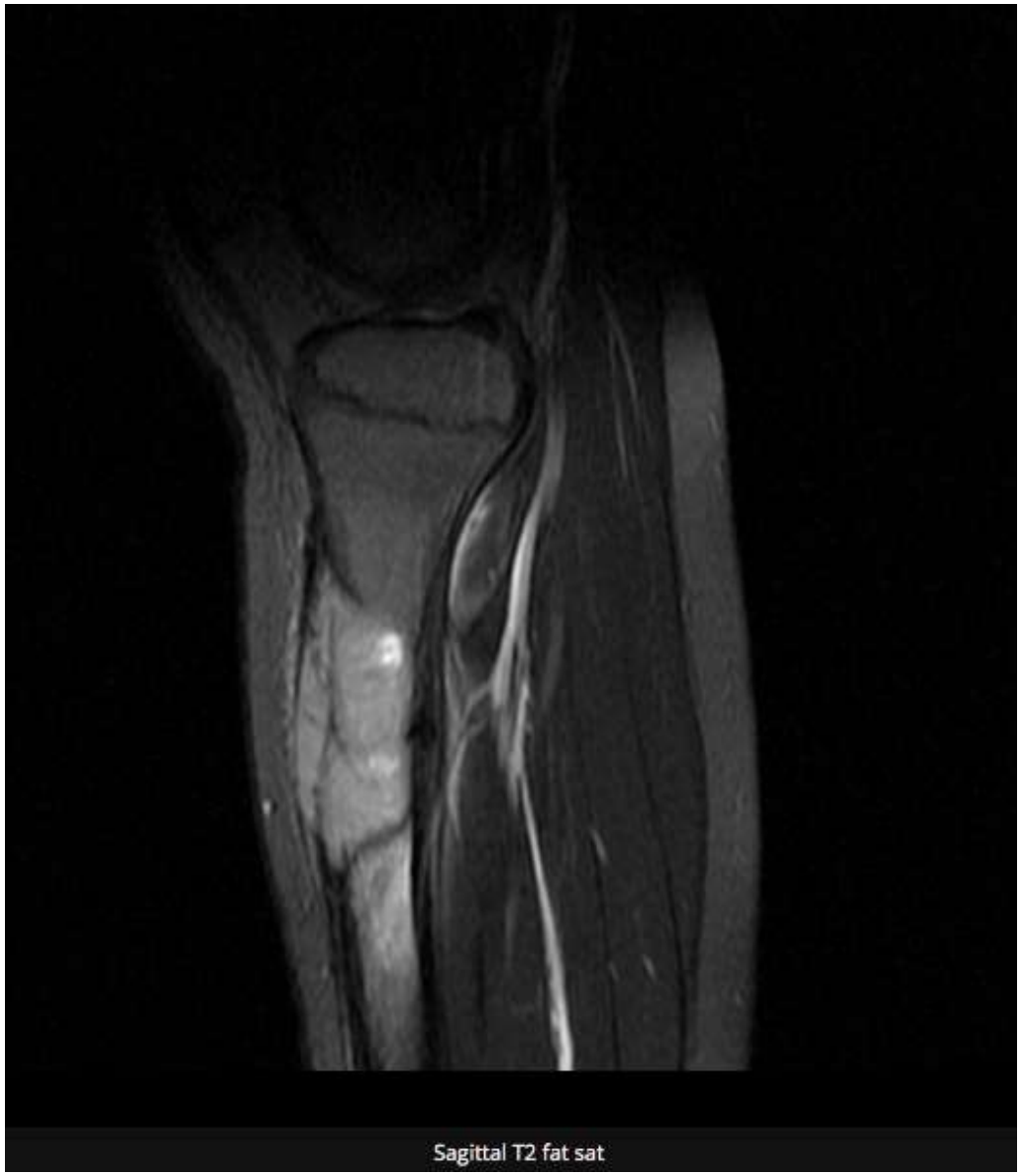
Case: 9 year old male, complaining of atraumatic leg pain.



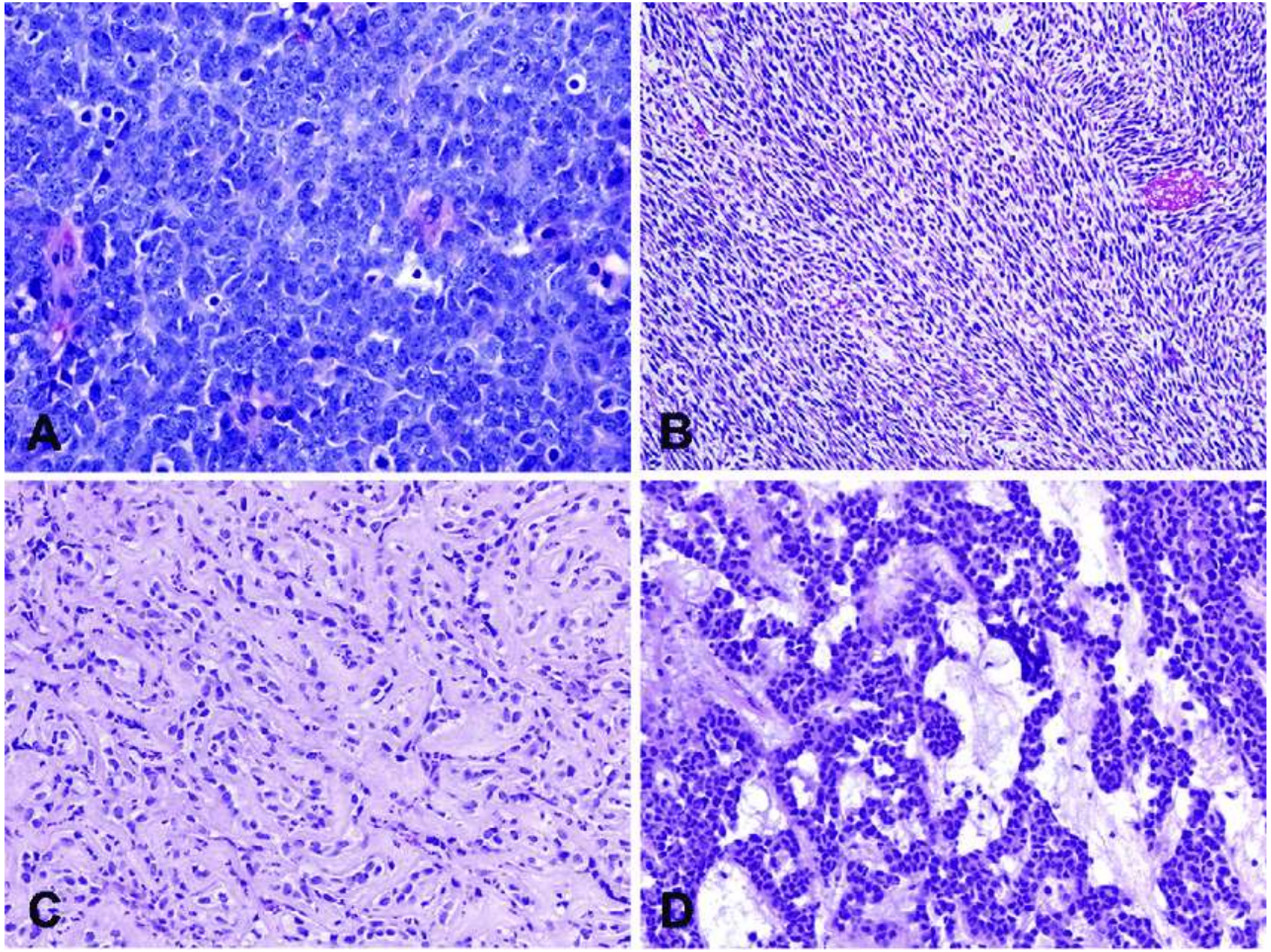
Ewing sarcoma X ray

There is a lucent lesion located centrally within the proximal tibial diaphysis. It demonstrates a relatively narrow but indistinct zone of transition. Periosteal reaction is seen involving the medial aspect of the tibia.





The cylindrical lesion demonstrates intrinsic low T1 and high T2 signal. It extends through the anteromedial tibial cortex with destruction of the bone. Periosteal elevation is also seen anteromedially. There is diffuse contrast enhancement and enhancement of a soft tissue component



small, round, blue cell tumors

DIFFERENTIAL DIAGNOSIS

- Patients with Ewing sarcoma may be misdiagnosed as having osteomyelitis.

TREATMENT

- The treatment for Ewing sarcoma is similar to osteosarcoma and requires neoadjuvant chemotherapy, local control measures, followed by adjuvant chemotherapy. The most common chemotherapy agents used for Ewing sarcoma are vincristine, doxorubicin, and cyclophosphamide in combination with ifosfamide and etoposide.
- In contrast to osteosarcoma, Ewing sarcoma is radiation sensitive, and radiation therapy is administered to patients where the primary tumor cannot be safely resected as well as for metastatic sites.

SARCOMA COMPLICATIONS

- In addition to potential late effects from chemotherapy, children with sarcomas may have complications related to local control of the tumor:

-If the local disease is controlled with surgery, the long-term sequelae may include loss of limb or limitation of function.

-If local control is accomplished with radiation therapy, the late effects depend on the dose of radiation given, the extent of the radiated site, and the development of the child at the time of radiation therapy.

SARCOMA PROGNOSIS

- For all children with sarcoma, presence or absence of metastatic disease at presentation is the most important prognostic factor. The outlook remains poor for patients who have distant metastases from Ewing sarcoma, RMS, or osteosarcoma.
- Patients with localized RMS in favorable sites have an excellent prognosis when treated with surgery followed by chemotherapy. In patients with osteosarcoma, the amount of tumor necrosis after preoperative chemotherapy is prognostic*

HEPATOBLASTOMA

EPIDEMIOLOGY

- Hepatoblastoma (HBL) is the most common primary liver tumor in children, although it is a comparatively uncommon pediatric solid tumor.
- It is usually diagnosed during the first 3 years of life.
- There is a slight male preponderance with a M:F ratio of up to 3:2
- There may also be predilection towards the right lobe of the liver.

ETIOLOGY

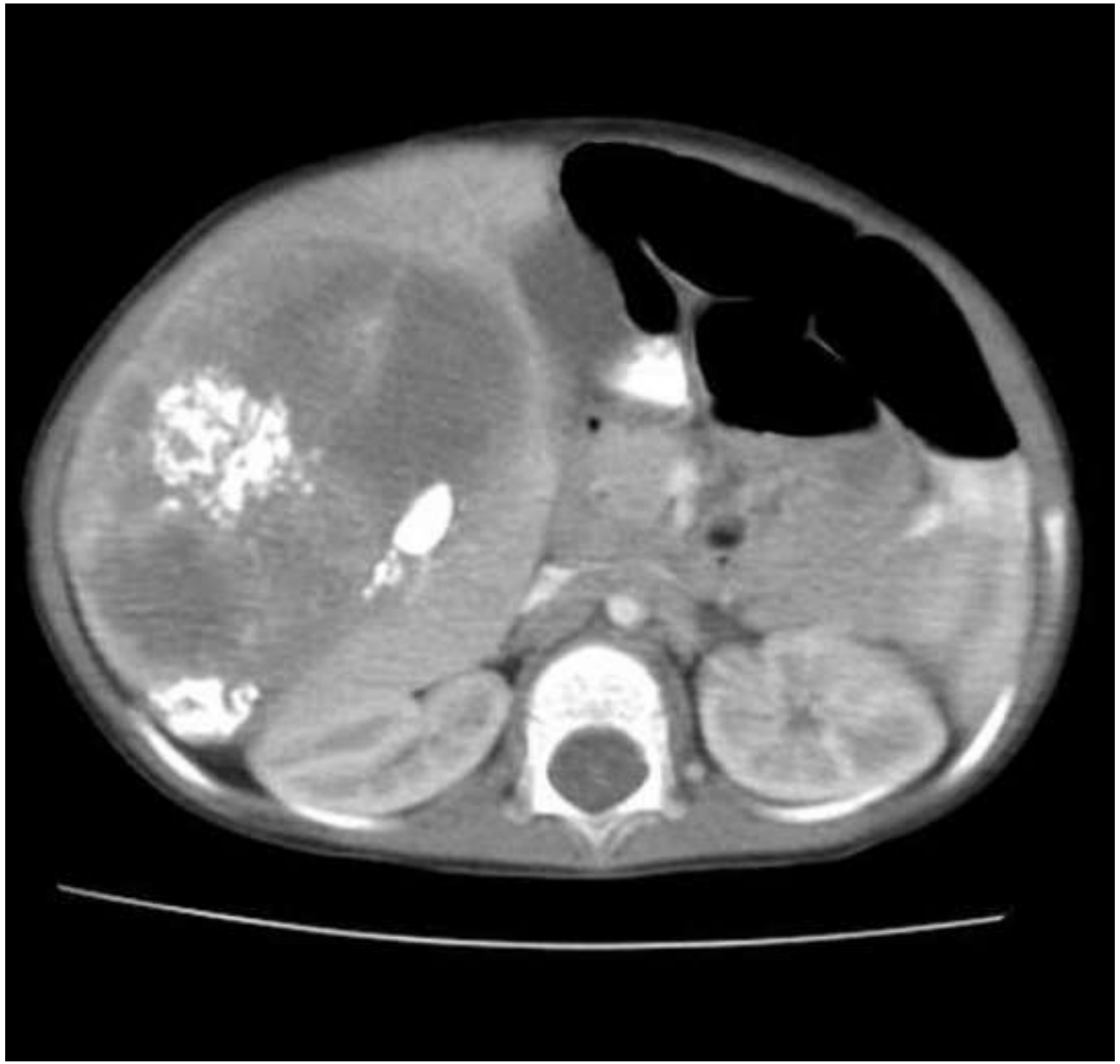
- Most HBLs are sporadic, but some are associated with constitutional genetic abnormalities and malformations, such as the Beckwith-Wiedemann syndrome and familial adenomatous polyposis.
- Extremely premature babies with a birth weight of less than 1 kilo have been reported to have a greatly increased risk of developing HBL.

CLINICAL MANIFESTATIONS

- The most common sign is abdominal distension or abdominal mass. Some children present with abdominal discomfort, generalized fatigue, and loss of appetite, due to tumor distension or secondary anemia.
- Children with a ruptured tumor usually present with vomiting, symptoms of peritoneal irritation, and severe anemia.
- Rare cases manifest precocious puberty/virilization due to β-human chorionic gonadotropin (hCG) secretion by the tumor.

LABORATORY/IMAGING STUDIES

- Serum alpha-fetoprotein (AFP) is the most important clinical marker for HBL, and remains the key clinical marker of malignant change, response to the treatment, and relapse.
- Abdominal ultrasonography usually reveals a large mass in liver, sometimes with satellite lesions and areas of hemorrhage within the tumor.
- The most useful diagnostic modality is multiphase computed tomography (CT) or magnetic resonance imaging (MRI).
- Histological diagnosis of a tumor specimen is essential, although some investigators believe that biopsy may not be necessary for young children (6 months to 3 years) with a very high AFP level.

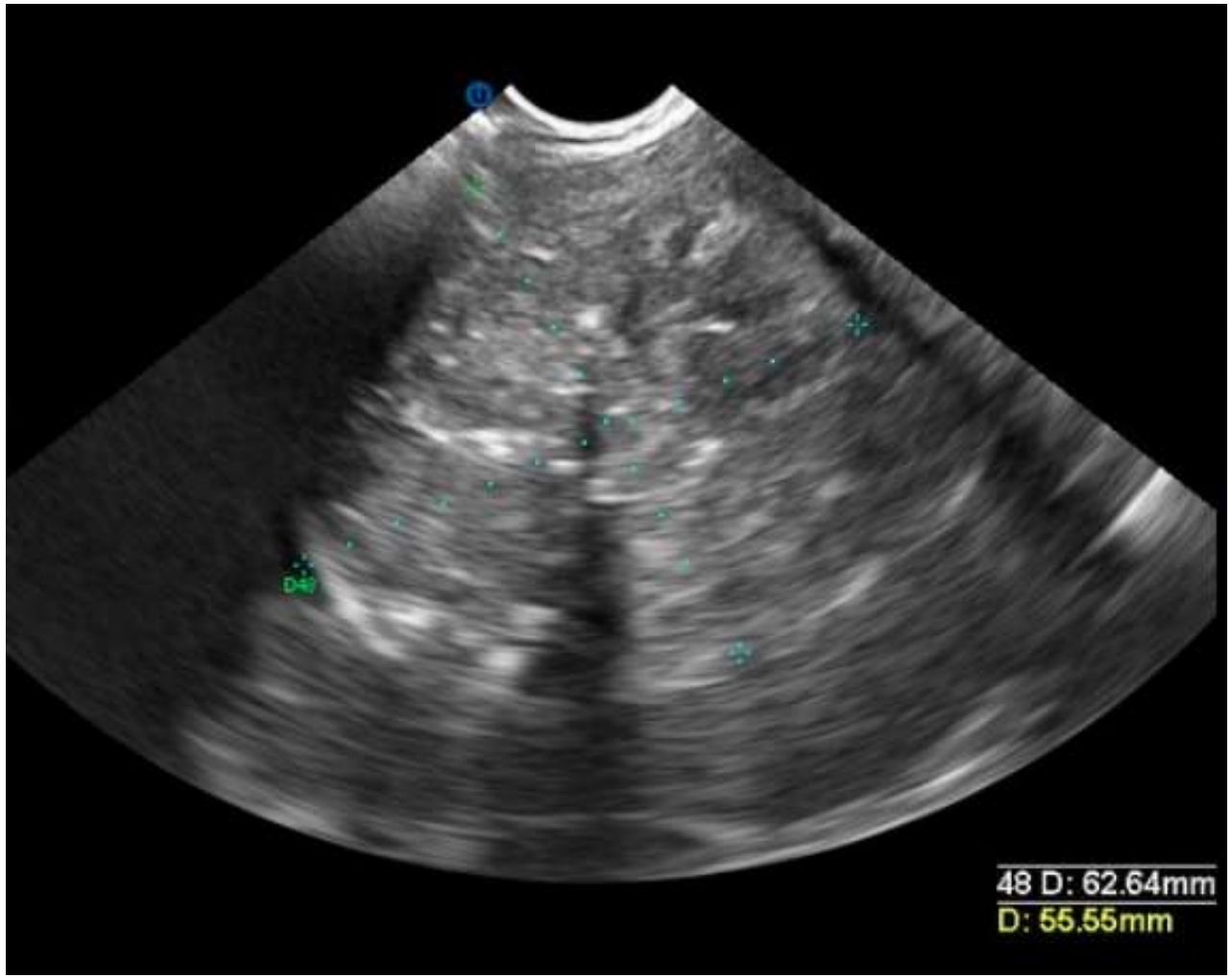


CT with contrast

Large lobulated hypodense mass with scattered calcification in the posterior segments of the right lobe of the liver.

The mass demonstrates minute heterogeneous enhancement.

US



Coronal view of the right lobe of the liver shows a large, lobulated, inhomogeneous mass with hyperechoic as well as hypoechoic areas, containing scattered calcification with distal acoustic shadowing.

TREATMENT

- Complete surgical resection plus liver transplantation and chemotherapy.

Thank you!

Natalie Tareq