ONCOLOGY (BRAIN - GENERAL)

- ≈ 1/3 brain tumors can be called BENIGN (mainly extra-axial tumors - meningiomas, acoustic neuromas).
- tumor mass of 30-60 g (3-6 × 10^{10} cells) usually produces ***neurologic symptoms***.
- brain cancer is ***lethal*** when tumor + edema reaches **100 g** (vs. ≈ 1000 g in systemic cancers).
- immune system per se can kill only ≈ 0.0001 g, or 1 × 10^{5} glioma cells.

CLINICAL FEATURES

Systemic symptoms (malaise, weight loss, anorexia, fever) suggests metastatic rather than primary brain tumor!

Significant overlap between brain tumor headache and **migraine** or **tension-type headache**.

No pattern is diagnostic of brain tumor!

Seizures

- most common with *SLOWLY GROWING* tumors affecting *cortex* (esp. meningiomas, oligodendrogliomas, low-grade gliomas).

PERFORMANCE SCALES

KARNOFSKY performance scale - objective measurement of ***functional ability***:

100 – Normal (no evidence of disease)
90 – Minor symptoms (able to carry on normal activity)
80 – Some symptoms (normal activity with effort)
70 – Unable to carry on normal activity (cares for self) - *justifies aggressive therapy*!
20 – Active supportive treatment needed (very sick)
10 – Moribund

WHO performance scale

Grade	Definition
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work, office work
2	Ambulatory and capable of all self care, but unable to carry out ay work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair
5	Dead

EPIDEMIOLOGY

- 1-2% of all cancers.
- 13% of all cancer deaths.
- 6th most common cancer in **adults**.
- after leukemia, 2nd most common cancer in **children** [20% pediatric tumors]!
- two peaks of incidence:
  small peak in childhood (predominance of *embryonal CNS neoplasms* and relative absence of gliomas) → much higher peak in 60-80 years (predominance of supratentorial *gliomas*)
- men ≥ women (except meningiomas ← women : men = 2:1).
- well-documented **environmental risk factor** (Israeli study) - **ionizing radiation** (e.g. given for treatment of tinea capitis) - increases risk for meningiomas almost 10 times and for gliomas 2.5 times.
- ***Epstein-Barr virus*** evidence in primary CNS lymphoma tissue

HEREDITARY SYNDROMES

Up to date - see here >>

- make only < 5% of all primary CNS tumors cases:

Syndrome	Gene	Nervous Tumor	Other tumors
Neurofibromatosis type 1 (von Recklinghausen's disease)	NF1 (17q11)	**Neurofibroma**, **malignant peripheral nerve sheath tumor (MPNST)**, meningioma, **optic nerve glioma**, (low-grade) astrocytoma	Iris hamartomas, osseous lesions, pheochromocytoma, leukemia

Neurofibromatosis type 2	NF2 (22q12)	**Bilateral vestibular schwannoma**, peripheral **schwannoma**, **meningiomas**, astrocytoma, meningioangiomatosis, spinal ependymoma, glial hamartias, cerebral calcification	Posterior lens opacities, retinal hamartoma
von Hippel–Lindau syndrome	VHL (3p25)	**Hemangioblastoma**	Retinal hemangioblastoma, **renal cell carcinoma**, pheochromocytoma, visceral cysts
Tuberous sclerosis	TSC1 (9q34), TSC2 (16p13)	**Subependymal giant cell astrocytoma (SEGA)** Hamartomas - cortical tubers and subependymal nodules	Cardiac rhabdomyoma, adenomatous polyps of small intestine, cysts of lung and kidney, renal angiomyolipoma, lymphangioleiomyomatosis, cutaneous angiofibroma, subungual fibroma
Li-Fraumeni syndrome	p53 (17p13)	various malignant **gliomas**, PNET (**medulloblastoma**)	Breast carcinoma, bone and soft tissue sarcoma, adrenocortical carcinoma, leukemia
Multiple endocrine neoplasia 1	not known	**pituitary** adenomas, malignant **schwannoma**	
Retinoblastoma	Rb (13q14)	retinoblastoma, **pinealoblastoma**	
Turcot syndrome	APC (5q21), hMLH1 (3p21), hPSM2 (7p22)	**GBM**, **medulloblastoma**	Colorectal polyps
Werner's syndrome	WRN (8p12)	**meningioma**	
Cowden disease (multiple hamartoma syndrome)	PTEN (10q23)*	Dysplastic gangliocytoma of cerebellum (**Lhermitte-Duclos**), megalencephaly	Hamartomas of skin, GI tract, gingival fibromatosis, multiple trichilemmoma, thyroid neoplasms, breast carcinoma
GORLIN syndrome (nevoid basal cell carcinoma syndrome)	PTCH (9q31)**	**Medulloblastoma** (in ≈ 5% mutation carriers)	• autosomal dominant - nevoid basal cell carcinoma, jaw keratocysts, skeletal abnormalities, ovarian fibromas, ectopic calcifications, palmar and plantar pits

*s. MMAC1 (mutated in multiple advanced cancers 1)
** human analog of "patched" gene of *Drosophila*

Most common scenario - *patient inherits one mutant (inactive) copy of tumor-suppressor gene* and thus carries so-called germline mutation in every cell, which is unveiled when second copy of tumor-suppressor gene is inactivated (either by mutation or by loss of portion of chromosome).

WHO CLASSIFICATION

see Onc1 >>

- diagnoses should consist of a histopathological name followed by the genetic features; e.g.:
  Diffuse astrocytoma, IDH-mutant
  Medulloblastoma, WNT-activated
  Oligodendroglioma, IDH-mutant and 1p/19q-codeleted
  Glioblastoma, IDH-wildtype

WHO 2021 GRADES

CNS WHO Grades of Selected Types	
Astrocytoma, IDH-mutant	2, 3, 4
Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted	2, 3
Glioblastoma, IDH-wildtype	4
Diffuse astrocytoma, *MYB*- or *MYBL1*-altered	1
Polymorphous low-grade neuroepithelial tumor of the young	1
Diffuse hemispheric glioma, H3 G34-mutant	4
Pleomorphic xanthoastrocytoma	2, 3
Multinodular and vacuolating neuronal tumor	1
Supratentorial ependymoma[a]	2, 3
Posterior fossa ependymoma[a]	2, 3
Myxopapillary ependymoma	2
Meningioma	1, 2, 3
Solitary fibrous tumor	1, 2, 3

FREQUENCIES

Most common primary CNS tumors in **adults**:

1. Glioblastoma (50-60%)
2. Meningioma
3. Astrocytoma
4. Pituitary adenoma, Vestibular schwannoma

Most common primary CNS tumors in **children**:

1. Medulloblastoma (10-30%) - propensity to dissemination via CSF! exquisitely radio & chemosensitive
2. Astrocytoma (esp. cerebellar pilocytic astrocytoma) (20%)
3. Glioblastoma (20%)
4. Ependymoma, Craniopharyngioma

Most common primary CNS tumors in **children (< 2 yrs)**:

1. Medulloblastoma
2. Ependymoma
3. Low-grade gliomas (esp. midline pilocytic astrocytomas)

Childhood cancers:

1) leukemias
2) CNS tumors
3) lymphomas
4) neuroblastomas

LOCATION

– adults 70% supratentorial
– children (2-12 yrs) 70% infratentorial

– infants (< 2 yrs) and adolescents (> 12 yrs) 50/50%

Age	Posterior Fossa	Meninges
Adulthood	Metastases, hemangioblastoma	Meningioma, CN8 schwannoma, metastases, lymphoma
Childhood	Medulloblastoma!!!, ependymoma, cerebellar pilocytic astrocytomas, brain stem astrocytoma, choroid plexus tumor	Leukemia, lymphoma

Intraventricular tumors – see here >>

Sellar and parasellar tumor – see here >>

CP angle tumor – see here >>

Tumors that spread **via CSF**:

HIGH-GRADE GLIOMAS (10-25%)
MEDULLOBLASTOMAS (10-20%)
EPENDYMOMAS (12%)
CHOROID PLEXUS CARCINOMAS
OLIGODENDROGLIOMAS (1%)
PINEAL GERMINOMAS (rare), *PINEOBLASTOMAS*!!!

Tumors that tend to bleed – see here >>

DIAGNOSIS

IMAGING

Oral boards:
Do physical exam + labs (do not jump to imaging!)
Spend money – ask for MRI!!!!!
Before ordering "with contrast" – check for creatinine, contrast allergy

T1 - well-demarcated area of ***low density***.

T1 with gadolinium - most precise way to image brain tumor!

T2 - ***brightness*** in more extensive region (signal of *surrounding brain edema*);

- tumors that are ***hypointense*** on T2:
  METASTATIC MELANOMA (paramagnetic properties of melanin)
  DERMOID
  COLLOID CYSTS
  INTRATUMORAL HEMORRHAGE
- *MENINGIOMAS* are usually ***isointense*** on all image sequences!!!

DW-MRI – some tumors show **diffusion restriction**! (due to hypercellularity and proteinaceous stroma)

Epidermoid cyst has ***diffusion restriction*** (bright on DWI, dark on ADC)
vs. arachnoid cyst (normal DWI)

Abscess, stroke, lymphoma (high cellularity), radiation necrosis have ***diffusion restriction*** vs. gliomas and metastases do not restrict diffusion!

PW-MRI:

- markedly increased rCBV - excess vascularization (growth of high-grade tumors);
- increased rCBV - low-grade tumors;
- decreased rCBV - vasogenic edema or radiation necrosis.

Contrast enhancement is sign of malignancy! Exceptions exist:

Tumors that **enhance strongly**: **benign** tumors (meningiomas, CN schwannomas, pilocytic astrocytoma, pituitary adenoma), **malignant** tumors (high-grade gliomas, metastases, lymphoma)

- ***degree of enhancement homogeneity*** varies - more benign lesions tend to be more homogeneous.
- pituitary adenomas always enhance less than normal pituitary gland!

Beware of benign conditions that enhance: tumefactive MS*, lymphocytic hypophysitis, sarcoid, subacute stroke, subacute ICH, abscess, toxoplasmosis
Always can biopsy if in doubt!
*periventricular WHITE matter and incomplete ring enhancement is classic

Tumors that show **no enhancement**: low-grade gliomas (astro, oligo), epidermoids

- tumors that tend to calcify (usually benign):

Oligodendrogliomas (90%), **meningiomas**, **craniopharyngioma**, ependymomas, choroid plexus tumors, teratoma, chordoma, central neurocytoma.

- **edema** surrounding small neoplasm suggests rapidly growing malignant tumor (exception – MENINGIOMA - benign slow-growing tumor that can produce profound edema and contrast enhancement).

N.B. for tumors with *propensity for leptomeningeal spread* (*MEDULLOBLASTOMAS*, *EPENDYMOMAS*, *CHOROID PLEXUS CARCINOMAS*, malignant *PINEAL REGION TUMORS*), spinal MRI must be done!; vice versa - detection of **extramedullary, intradural spinal tumor** → immediate brain MRI.

Cyst + mural nodule see Onc1 >>

- most hypervascular tumors - *CHOROID PLEXUS PAPILLOMAS*, *HEMANGIOBLASTOMAS*

MRS see Onc1 >>

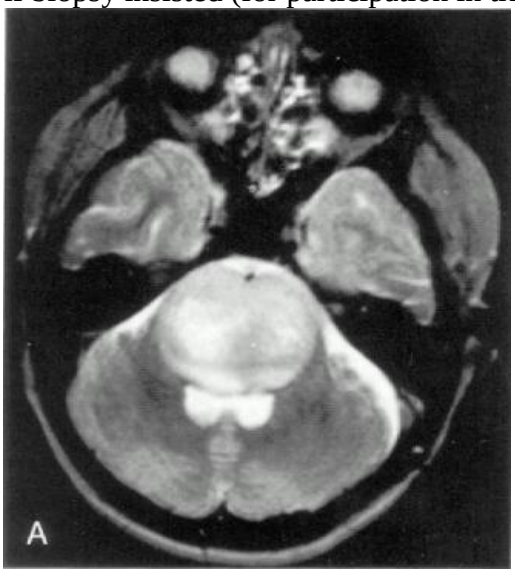
Tumor – lots of membranes (choline) and anaerobic metabolism (lactate)
Stroke – everything is down except anaerobic metabolism (lactate↑)
Necrosis – everything is down except dead lipids↑
Abscess – atypical peaks
MS - normal

Brain and skull mts image review protocol:

parenchymal - gadolinium MPRAGE, FLAIR (not all mts enhance so FLAIR is even more sensitive, esp. for small mts)
calvarial - DWI (bright areas in the skull; vs. bone marrow abnormalities - will be diffuse signal along entire skull)

PATHOLOGY

- **BIOPSY**: most **primary brain tumors** are verified histologically (either resection surgery or biopsy for unresectable cases*), but 80% **metastatic tumors** are diagnosed & treated empirically (if biopsy is available from extra-CNS locations).
  *biopsy is not indicated in *OPTIC GLIOMAS* and *DIFFUSE BRAIN STEM GLIOMAS* (unless exophytic component exists - even then, biopsy cannot always be obtained);
  - biopsy is not required for diffuse intrinsic pontine gliomas (diagnosis can be made by MRI alone; histologic findings do not influence treatment);
  - if biopsy insisted (for participation in trials) – via middle cerebellar peduncle.



- stereotactic biopsy usually provides enough tissue to *make diagnosis* of glioma but may not provide enough to *grade tumor* (most informative specimen is one taken from ***area of contrast enhancement***).

Small, blue, round cell tumors of childhood:

1) neuroblastoma
2) PNET, medulloblastoma
3) non-Hodgkin lymphoma
4) Ewing sarcoma
5) undifferentiated soft tissue sarcoma (rhabdomyosarcoma).

Stains	*Neuroblastoma*	*Lymphoma*	*Ewing's sarcoma*	*Rhabdomyosarcoma*	*Primitive neuroectodermal tumor*
Neurofilament	+	-	±	-	-
Synaptophysin	+	-	-	-	-
Neuron-specific enolase (NSE)	+	-	-*	-*	+
β_2-microglobulin	-	-	-	-	+

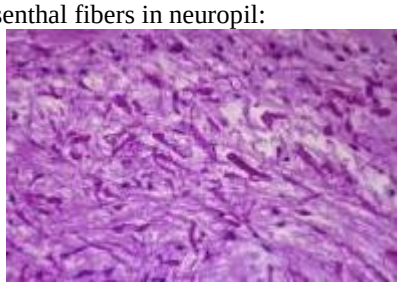
Leukocyte common antigen (T-200 protein)	-	+	-	-	-
Vimentin	-	±	+	+	+
Myoglobin	-	-	-	+	-
Myosin	-	-	-	+	-
Actin	-	-	-	+	-
Desmin	-	-	-	+	-

*extraosseous Ewing's sarcoma, variants of Ewing's sarcoma and rhabdomyosarcoma stain for NSE.

Rosenthal fibers are characteristic feature of:

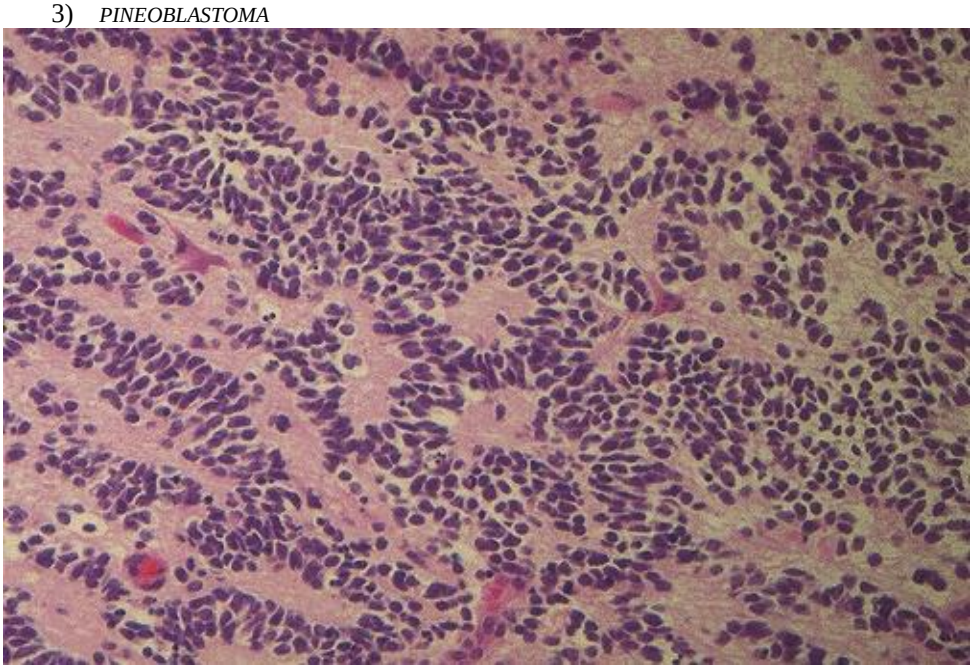
1) *JUVENILE PILOCYTIC ASTROCYTOMAS*
2) *CRANIOPHARYNGIOMAS*
3) around *EPENDYMOMAS*
4) *ALEXANDER DISEASE* (Rosenthal fibers radiate from vessels)

Rosenthal fibers in neuropil:



Homer-Wright rosettes:

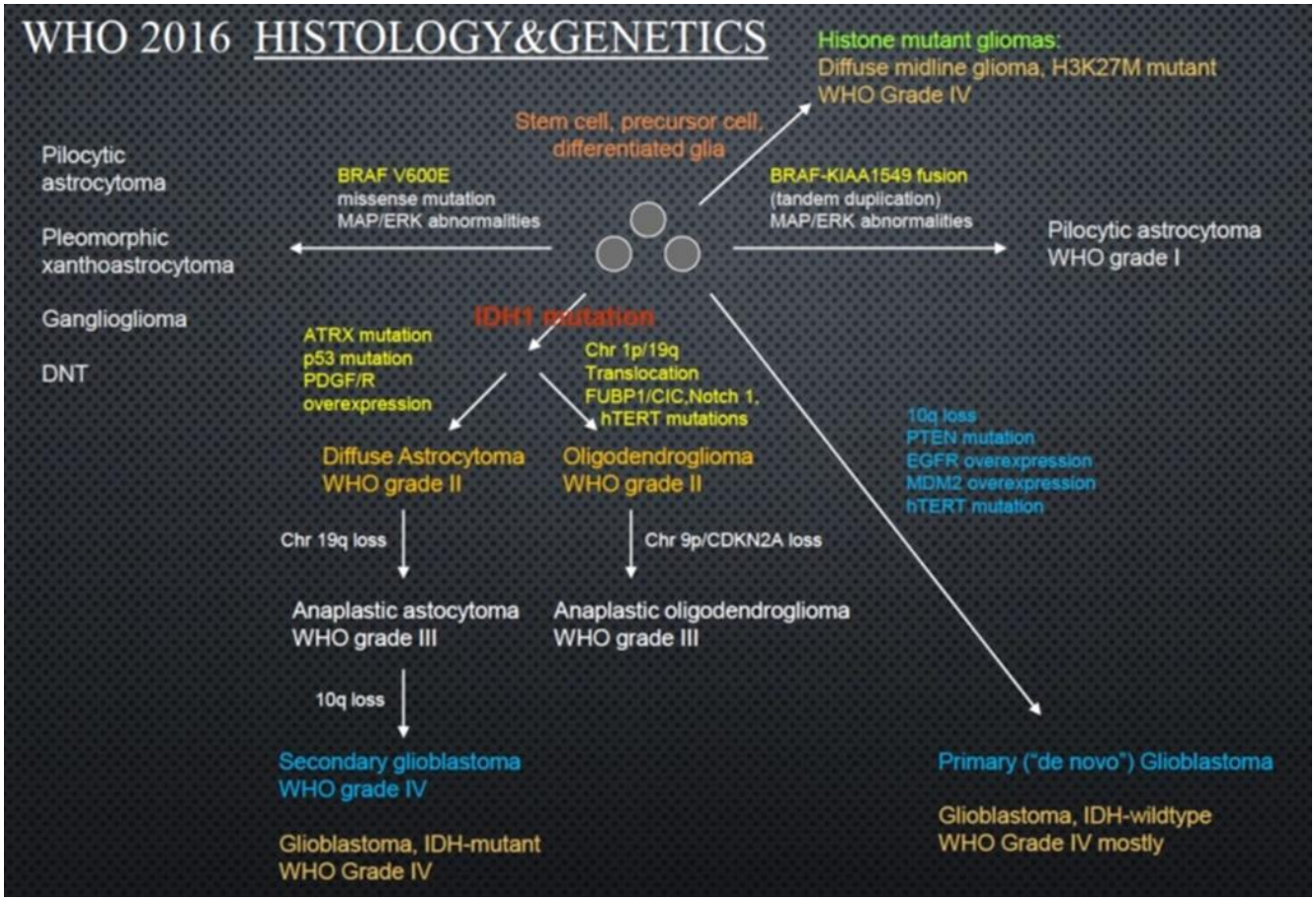
1) *MEDULLOBLASTOMA*
2) *NEUROBLASTOMA*
3) *PINEOBLASTOMA*



IMMUNOHISTOCHEMISTRY TUMOR MARKERS / STAINS / GENETICS

See p. Onc1 >>

While tumors are monoclonal in origin (i.e. they originate from single cell), as they grow they progress through ***series of genomic changes*** that permit evolution to more and more malignant stages.



MEDICAL TREATMENT

Mention tumor board (but never go to tumor board without staging!)

- start **DEXAMETHASONE** promptly (+ omeprazole, insulin sliding scale) if mass effect / edema is symptomatic!

  Brain edema type in tumors is VASOGENIC

- in instances of extreme intracranial pressure, speed and action of dexamethasone are not sufficient → add MANNITOL.

SURGERY

Oncology medications (e.g. in metastatic disease) to stop before surgery (impaired wound healing!)
BEVACIZUMAB (Avastin®) - ≥ 4 weeks prior and ≥ 4 weeks after surgery
PANITUMUMAB (Vectibix®) – same as Avastin
LENVATINIB (Lenvima®) - ≥ 1 week prior and ≥ 2 weeks after surgery + until adequate wound healing
SUNITINIB
SORAFENIB

- markedly elevated AFP and β-hCG (pathognomonic for *GERM CELL TUMORS*) → trial chemotherapy or radiotherapy without tissue biopsy (germinomas → radio; nongerminomatous germ cell tumors → chemo)

Intracranial tumors ***compressing optic apparatus*** during pregnancy:

a) no visual deterioration → treat conservatively
b) visual deterioration in 1st or 2nd trimester → neurosurgical procedure without delay
c) visual deterioration in 3rd trimester → urgent C-section → neurosurgical intervention

Biopsy nonoperative tumors! (check germ cell tumor markers, CFS cytology pre-biopsy, esp. in peds)

Preop:

1) preop embolization (not for ethmoidal feeders!) vs intraop feeder localization and early control
2) 2 units of blood
3) monitoring – use heavily but have a reason for it*
4) 5-ALA
5) navigation
6) Keppra, dex, abx, mannitol
7) preop EVD (e.g. posterior fossa tumor with HCP) or prep for Frazer burhole
8) postop EVD (esp. if intraventricular bleed – protect foramen of Monroe with cotton balls)

*e.g. anterior frontal tumor – risk of SMA – if plegic postop but MEP was OK then motor will recover

CSF DIVERSION

a) when there is a high risk of postop CSF leak (e.g. before trans-sphenoidal resection with tumor invading diaphragma sellae) → **lumbar drain**
b) tumors causing hydrocephalus (esp. posterior fossa) – low threshold to put **EVD** (drain at > 15) or at least prep for Frazer burhole.

EMBOLIZATION

Preoperative embolization is for very vascular benign tumors – usually skull base meningiomas!

- goal – to decrease intraoperative blood loss – use small particles.
- beware dangerous anastomoses!

Embolization is not for *ethmoidal feeders* – need to catheterize ophthalmic artery → risk of blindness!

INTRAOP

- MANNITOL (1 g/kg) + **hyperventilation** (P_{CO2} 25-30 mmHg) for definitive ICP reduction in preparation for dural opening and brain retraction.
  - in some cases, it is worth placing lumbar drain to drain CSF – causes further brain relaxation.
  - open CSF cisterns early!
- DEXAMETHASONE (10 mg IV) before manipulating nervous tissue.
- AED if cortex will be violated or significant retraction of lobes is expected.

Attempt **surgical resection** in all cases (except multiple metastases*, brainstem gliomas, optic gliomas, CNS lymphoma**)

*__SRS__ / **whole-brain radiation therapy (WBRT)** – current mainstay of palliation

**systemic METHOTREXATE > whole-brain radiation therapy (WBRT)

Always send for **frozen pathology** – to confirm preoperative diagnosis!

When possible, circumferential disconnection and tumor delivery *en bloc* is ideal - minimized blood loss, best navigation accuracy!
Cover opening into ventricle!
N.B. most common cause of postoperative hematoma is **residual tumor**!
— ***Surgicel*** may give delayed postoperative MRI enhancement!!!

- **tack-up stitches** are used to prevent epidural hematoma!

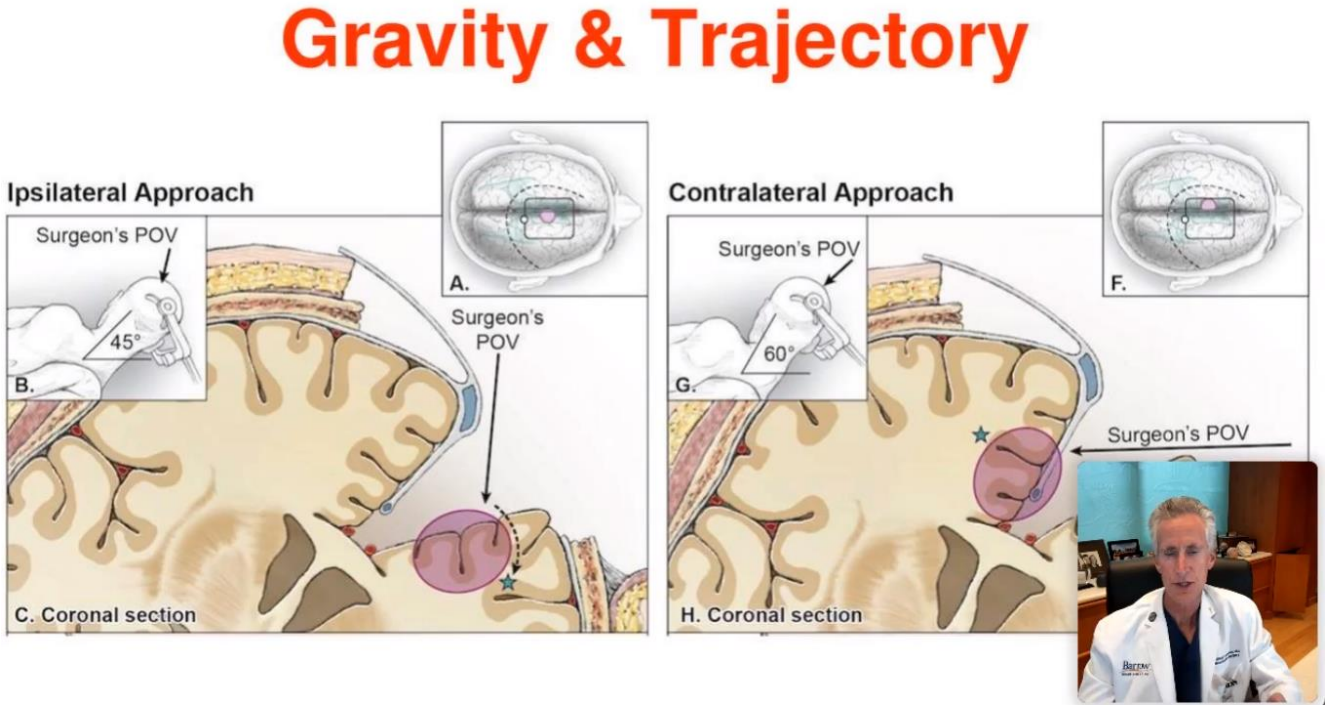
OPERATIVE CORRIDOR

1. **Transcortical**

2. **Sulcal / fissure approach** to limit cortical manipulation (need to access large lesions deep in brain may make this too confining).
   No gyrus should be entered, unless it is involved in tumor.
   Longer but safer pathways through sulci and fissures minimize **cortical** retraction and preserve **white matter tracts**!

3. Via **ventricles** endoscopically (only if HCP is present)

- handheld retractors are less traumatic (retraction injury) – so called ***dynamic retraction***.
- ***gravity retraction*** – explained by Dr. Lawton – sometimes counterintuitive gravity retraction gives better access and view:



4. As lesion's depth advances, operative **working angles** become more important than simple **extent of exposure**

LATERAL VENTRICLE

See p. O340 >>

Summary:

Relatively high risk for mortality and neurological morbidity.

- large size, difficult-to-reach deep location, high vascularity (feeding ***choroidal vessels*** are ***reached late*** in resection) + neighboring vital diencephalic and brainstem structures

Benign tumors – present late with HCP, mass effect

- small asymptomatic bening tumors may be observed.

PREOPERATIVE TESTING

1) thorough **MRI analysis** - benign tumors *involving deep structures* (deep veins, ventricular walls, fornices, thalamus, or basal ganglia) → **subtotal resection**
2) **feeding vessels** + tumor vascularity
3) **venous anatomy** (esp. thalamostriate veins) – what are main drainage pathways (there are no reliable principles to determine which veins can be safely sacrificed!) - vital diencephalic structures have minimal venous collaterals!

   One of septal veins may be safely sacrificed vs. **thalamostriate** and **internal cerebral veins** are indispensable!!!
4) functionality of overlying cortex
5) neuropsychological
6) *3rd ventricular tumors* – **endocrinologic** and **neuro-ophthalmologic**
7) *4th ventricular tumors* – **ENT** eval for lower cranial nerves

PREPARATION IN OR

- routine preop **EVD** for ventricular tumors and conditions with HCP – stretched white matter tracts are more susceptible to injury from operative manipulation or retraction
- may be **vascular**! (preop **angiography & embolization!!!!** – true for all intraventricular tumors) – key issue is ***early vascular feeder control**** ***– only then may proceed with piecemeal resection!***

  *e.g. atrium tumors:

  Right side – approach transtemporally (to get to feeders)

  Left side – superior parietal lobule approach

  - if intraventricular bleed – protect foramen of Monroe and rest of ventricles with cotton balls and leave EVD postop.
  - before closure – pristine hemostasis (not bipolar on ventricular walls but patient irrigation)
- always **monitoring** (MEP, SSEP, BAER)! – decline in signal → briskly debulking acutely expanding intralesional hemorrhagic mass, or CSF drainage.
- always **navigation**! (add US to compensate for shifts after CSF drainage)

APPROACH

Some transgression of normal brain is necessary to reach these deep lesions - selection of operative corridor plays important role in the final outcome!

Only two major choices:

A. **Transcortical** - parasagittal veins are not a concern, tedious interhemispheric arachnoid dissection is not required, but projection fibers in the frontal lobe are disrupted + ↑risk of postop seizures
B. **Transcallosal** - access only to frontal horn and body + 3rd ventricle!

Lesion Location	**Suggested Approaches**
Frontal horn	Anterior interhemispheric **transcallosal** **Transcortical** (via middle frontal gyrus)
Body	Anterior lesions - same as frontal horn.

	Posterior lesions: Posterior interhemispheric **transcallosal** **Transcortical** (via superior parietal lobule)
Atrium or trigone	*Ipsilateral* interhemispheric **transcortical** (via cingulate/precuneus) *Contralateral* interhemispheric **transcortical** (via falx → precuneus) **Transcortical** (via paramedian/superior parietal lobule) ***Trans-sulcal*** (intraparietal sulcus)
Temporal horn	**Transcortical** (anterior temporal neocortical resection) **Transcortical** (via middle temporal gyrus) ***Trans-sulcal*** (via occipitotemporal sulcus) **Transcortical** (via inferior parietal lobule) **Transsylvian**
Occipital horn	Posterior interhemispheric **transcortical** **Transcortical** (occipital neocortical resection) Lesions around calcar avis - ***supracerebellar transtentorial transparahippocampal***

- crani - SSS is often unroofed for access to midline lateral ventricular lesions
- use Vycor / BrainPath retractors (connect to Greenberg frame) / Greenberg retractors.
- narrow operative corridors can be extended using endoscopic-assisted microsurgery.
- after resection:
  - fenestration of septum pellucidum and lamina terminalis (in select cases) may obviate a need for postoperative shunt
  - generous irrigation of the ventricular system
  - do not leave behind even smallest pieces of hemostatic material (i.e., SURGICEL or Gelfoam powder) → risk of acute postoperative HCP.
  - replace CSF with warm irrigation to prevent hemispheric collapse → SDH.

POSTOPERATIVE

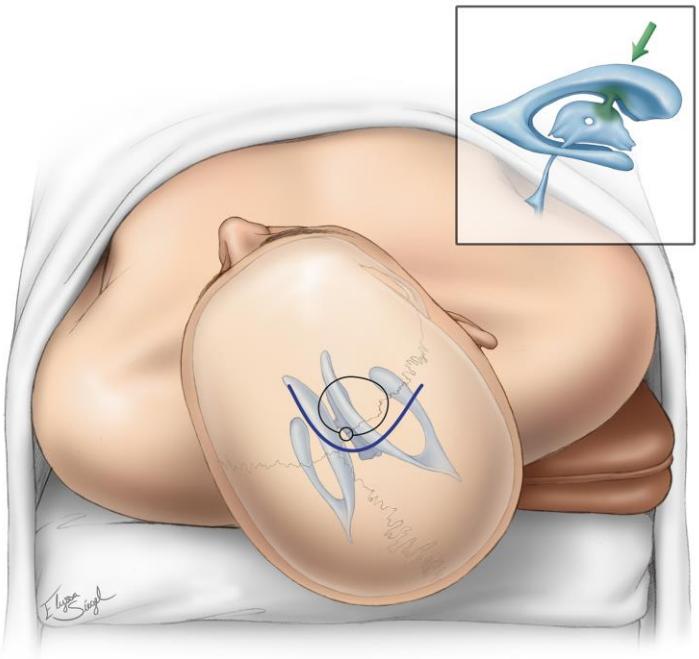
- in select patients, **EVD** should be left (10-15 cmH2O) to monitor ICP and drain intraventricular debris.
- 33% patients require **permanent CSF diversion** despite gross total resection.

FRONTAL HORN, BODY

MIDDLE FRONTAL GYRUS APPROACH

– if HCP exist

- at level of coronal suture (3.5 cm from midline, 1 cm anterior to coronal suture) → direct approach to frontal horn and foramen of Monro.
- significant speech problems may occur even when Broca's area is undisturbed.



INTERHEMISPHERIC TRANSCALLOSAL APPROACH

See p. Op340 >>

Complications

- **disconnection of hemispheres**: mutism (decreased speech spontaneity), akinesia, apathy, unilateral weakness (leg > arm), incontinence, forced grasping, fixed gaze, disinhibition, right-left confusion.
  Crossed dominance (hemisphere controlling the dominant hand is contralateral to the hemisphere controlling speech and language - Wada test prior to transcallosal surgery) is a contraindication → writing and speech deficits postoperatively
  – result of cerebral injury during *early childhood* → cortical functional reorganization.
  – especially with more posterior callosotomy (splenium) - increasing risks of cognitive dysfunction.
  – several studies have suggested that interhemispheric transfer should be preserved as long as the splenium is intact.
- **leg motor cortex injury** – venous infarction or retraction injury.
- **short term memory deficits** – from fornix manipulation

TEMPORAL HORN

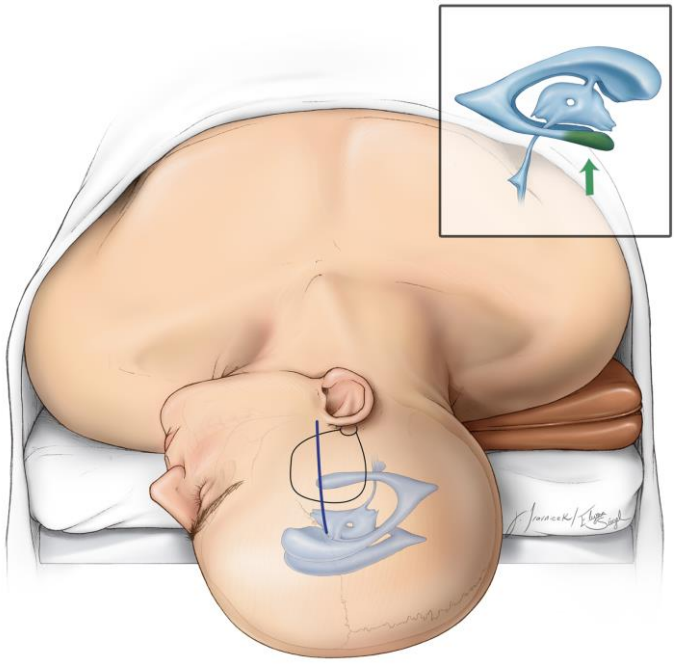
- temporal approaches provide early access to **anterior choroidal artery** but poor visualization of **posterior choroidal vessels** (until lesion is almost completely resected).
- temporal horn is 3.5 cm from temporal tip.

Safest temporal corticotomy is ANTERIOR INFERIOR TEMPORAL GYRUS (middle temporal gyrus might be OK on nondominant side; speech cortex in dominant hemisphere H: cortical stimulation).

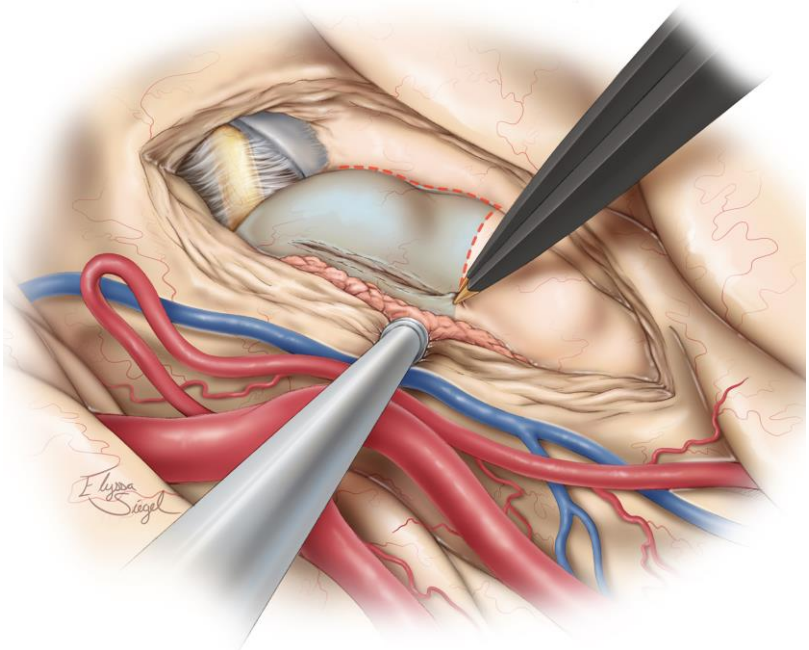
Access to temporal horn:

A. **Transcortical** (anterior temporal neocortical resection ≈ 2.5–3 cm is well tolerated in dominant and nondominant hemispheres) – for lesions anterior to plane of cerebral peduncle; oblique working angle can reach even midportion of temporal horn!
B. **Transcortical** (via middle temporal gyrus) – high-risk of damage to speech cortex* in dominant hemisphere (H: awake cortical stimulation!); in nondominant hemisphere it is acceptable route!

*despite small corticotomy, by time resection is complete more extensive retraction injury to cortices is inflicted



C. ***Trans-sulcal*** (via occipitotemporal sulcus) – for posterior lesions; risk – visual field deficits – Dr. Cohen-Gadol avoids this approach!
D. **Transcortical** (via inferior parietal lobule)
E. **Transsylvian –** only limited indication: resection of small dominant amygdala / anterior hippocampal lesions without transgression of dominant neocortex; cannot reach midsection of temporal horn:



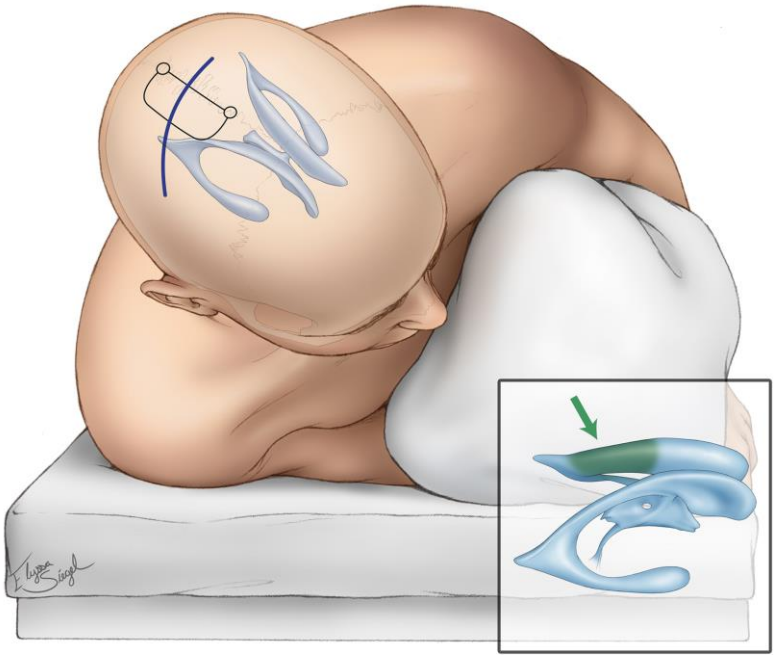
(see CN3 anteriorly)

ATRIUM / TRIGONE

A. **Transcortical** (via paramedian/superior parietal lobule) - most commonly used approach; use of 2-cm retractor blade without tension - avoid significant retraction; angular gyrus → alexia, acalculia and apraxia (dominant hemisphere), visual-spatial processing problems, homonymous hemianopia and hemineglect

Variant - ***Trans-sulcal*** (intraparietal sulcus)

B. *Contralateral* **interhemispheric transcortical** (via falx → precuneus) – Dr. Cohen-Gadol preference!



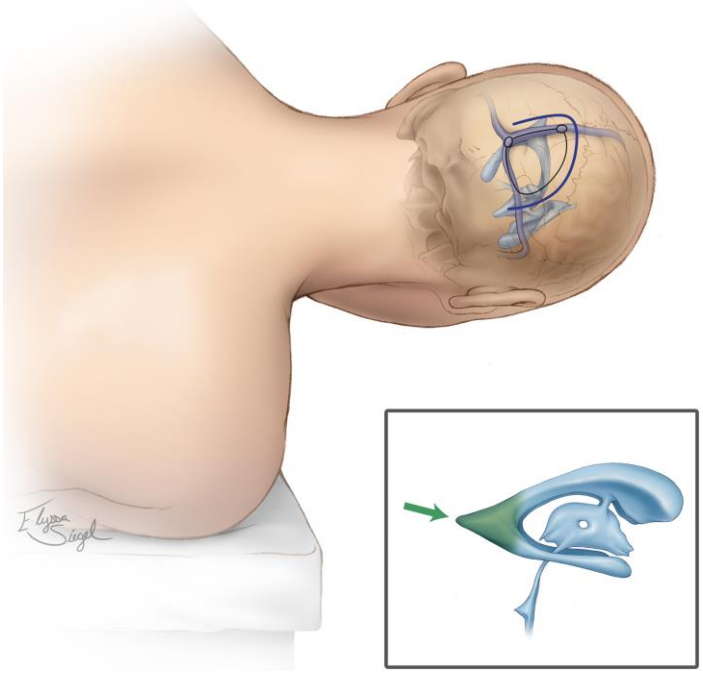
C. *Ipsilateral* **interhemispheric transcortical** (via cingulate/precuneus)

- incisions contraindicated in **dominant hemisphere** (→ speech deficits).
- vascular supply is away from surgeon's line of vision.

OCCIPITAL HORN

- **main problem -** early access to choroidal vessels – prepare for ***blood loss***.

A. Posterior interhemispheric **transcortical** (there are no bridging veins at occipital pole) → permanent loss of homonymous visual field (acceptable, if present preoperatively):



B. **Transcortical** (occipital neocortical resection) → permanent loss of homonymous visual field (acceptable, if present preoperatively)
C. Lesions around calcar avis - ***supracerebellar transtentorial transparahippocampal***

THIRD VENTRICLE

See p. O340 >>

Summary

POSTERIOR FOSSA

Preop

- place EVD in OR prior to craniotomy (esp. if HCP) - frontally prior to positioning or occipitally once positioned (or at least prep for occipital Frazer bur hole).
- preop panspine MRI (drop mts?, esp. if tumors that seed via CSF) – may need sedation (thus, may need EVD).
- advise patients pre-op of the likelihood of need for G-tube and tracheostomy (may be temporary) if tumors invade brainstem.

Always open and drain CSF from cisterna magna!!!!

Postop

- avoid hypertension – risk of bleeding into posterior fossa!
- if significant manipulation of brain stem, should remain intubated for first postoperative night and be extubated once lower cranial nerve function has been assessed by ENT, speech.

CP ANGLE

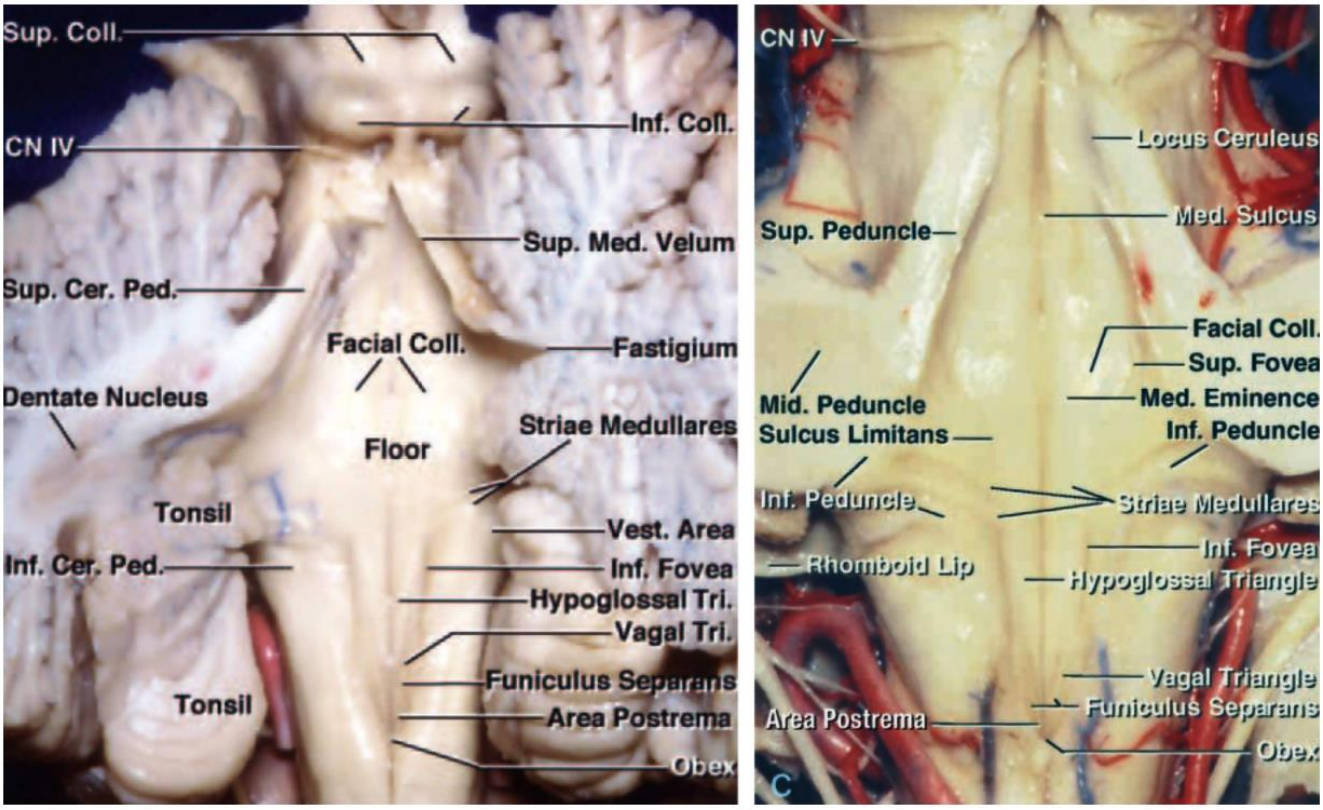
Preop audiogram!
50/50 rule (> 50 dB pure tone audiogram / < 50% speech discrimination = nonserviceable hearing)

See Case P4 >>

4TH VENTRICLE

- open cisterna magna (by opening arachnoid).
- **mark floor of 4th ventricle** – by advancing Telfa / cut finger of glove into 4th ventricle from below (start between cerebellar tonsils) – or will fail Oral Boards!

Manipulation of floor - high risk of diplopia, facial weakness, swallowing and ventilatory dysfunction (→ gastrostomy and tracheostomy):



Invasion of the ventricular floor by the tumor - plan a subtotal radical resection (avoid any temptation during surgery to manipulate the tumor that invades the floor).

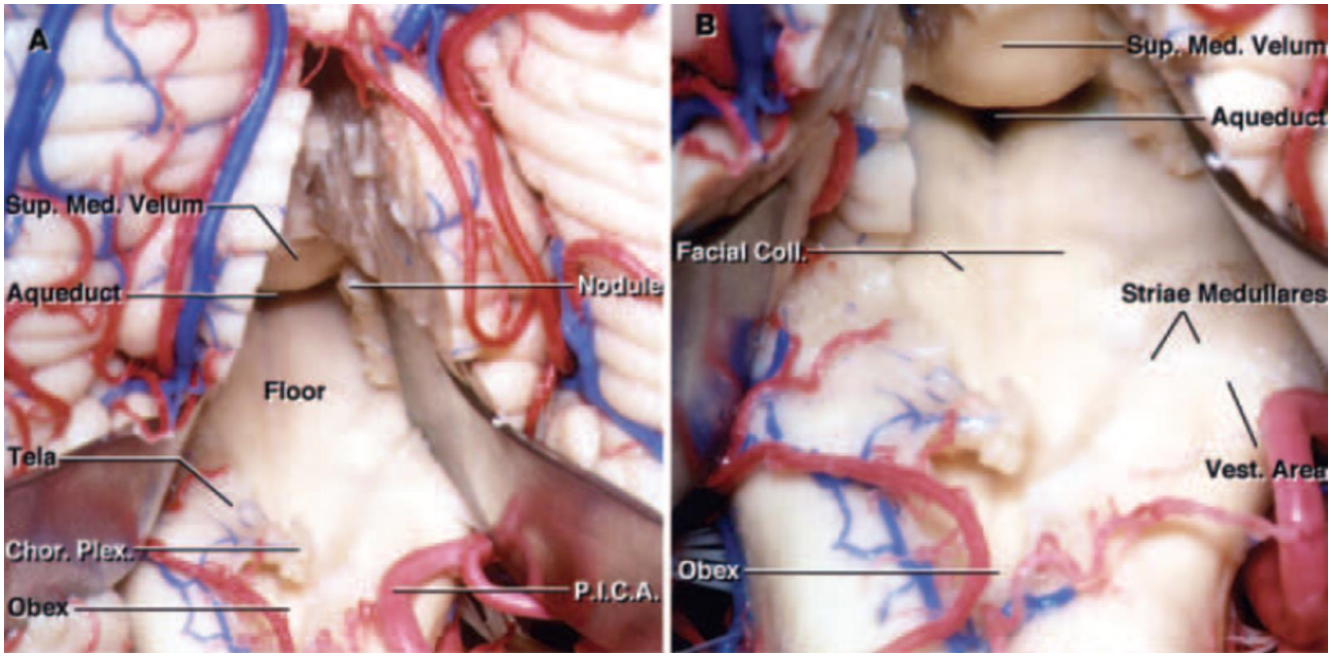
PICAs may be encased by the tumor (esp. if having a repeat operation) - plan a subtotal resection.

Lesions within brainstem parenchyma → placement of **defibrillator pads** before surgery!

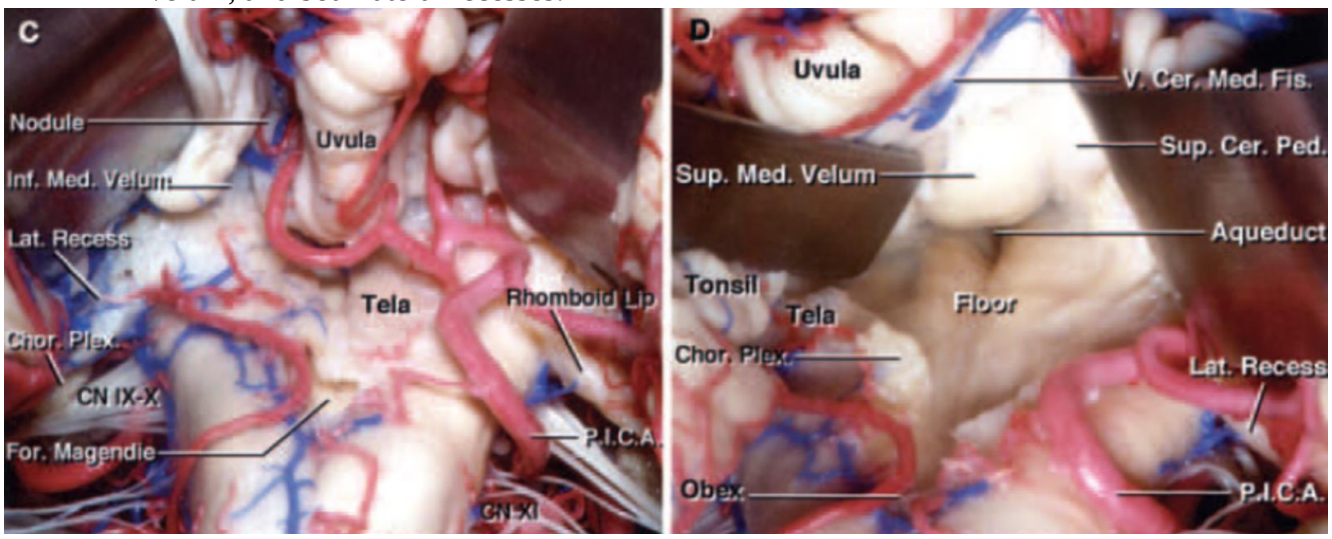
Intense nausea - surgery near the floor of the fourth ventricle (standing order for antiemetics).

Two main approaches to the fourth ventricle (after standard midline suboccipital craniotomy as for Chiari)

A. **Transvermian approach** - splitting inferior 1/3 of vermis in midline, two halves are retracted to opposite sides.
   - indication: large midline lesions that occupy rostral 4th ventricle and do not extend into lateral recesses.
   - split the vermis to the smallest extent possible (usually up to the fastigium, but not into the superior medullary velum - superior exposure is limited)
   - risk of caudal vermian split syndrome (truncal ataxia, dysequilibrium, oscillation of head and trunk, nystagmus), cerebellar mutism (esp. pediatric patients); injury to dentate nucleus (more severe dysequilibrium)



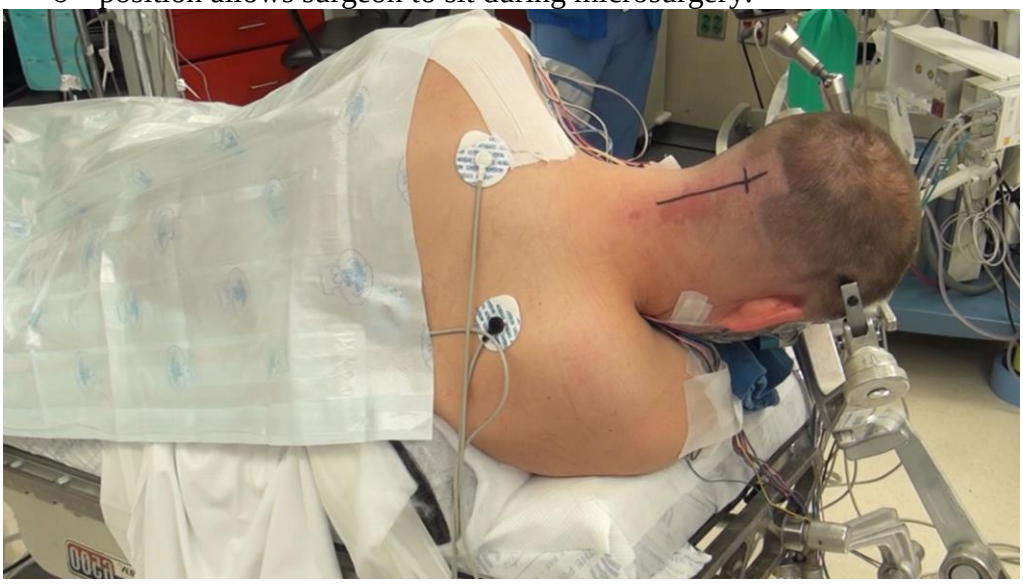
B. **Telovelar approach** (preferred!!!) - exposes 4th ventricle through the cerebello-medullary fissure (between tonsil and brainstem) without incising vermis or cerebellar hemisphere.
   - uses natural planes - no functioning nerve tissue is harmed - reduced risk of cerebellar mutism.
   - tonsils have been retracted superolaterally to expose tela choroidea, inferior medullary velum, and both lateral recesses:



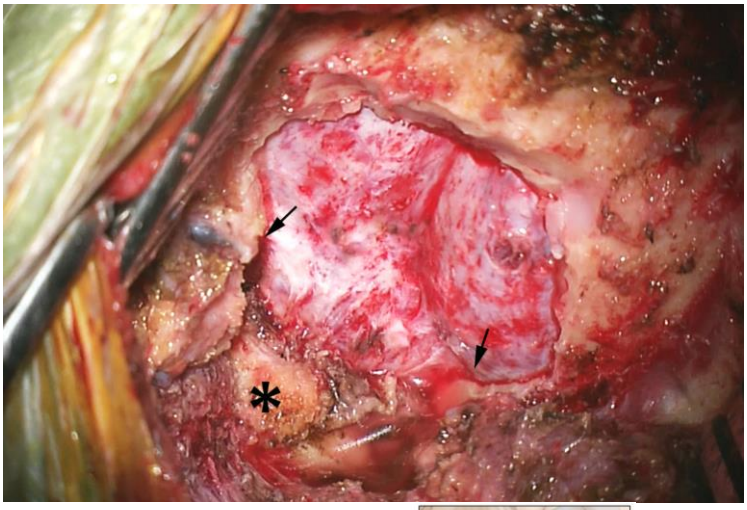
   - indication: lesions within the foramen of Luschka
     - rostral intraventricular exposure can be achieved by inferior-to-superior working angles through a **C1 laminectomy** – i.e. generous ventricular exposure from obex to aqueduct.
   - **floor of 4th ventricle is protected by sliding a cottonoid up along the floor**
   - CONS: narrower corridor than with a widely split vermis; limited access to deep or large tumors involving the rostral third of the 4th ventricle; limited access to contralateral floor of the 4th ventricle (TVA can be done bilaterally to circumvent this limitation).

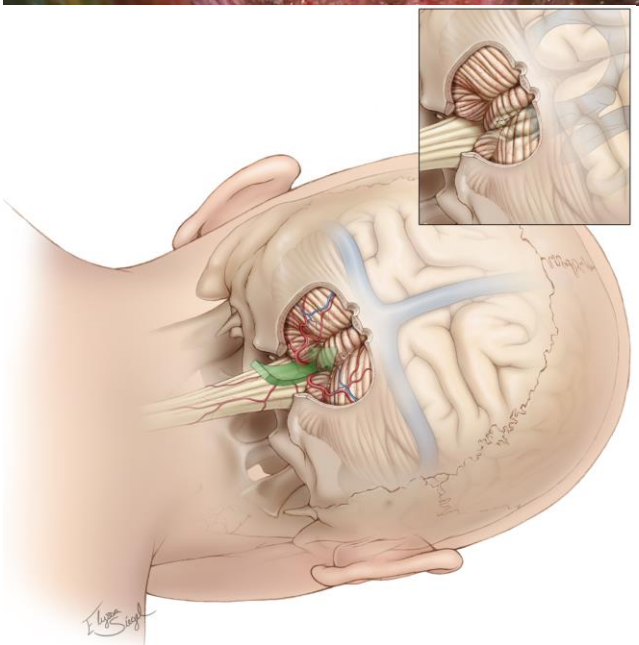
Technique
   - patient is in **modified park-bench position** with head flexed and turned toward floor:
     - linear incision.
     - short horizontal line marks the location of the transverse sinuses.

- patient's shoulder is mobilized inferiorly and anteriorly - increases the surgeon's working space within the suboccipital area.
- lateral position uses gravity retraction and the blood runs out.
- position allows surgeon to sit during microsurgery.

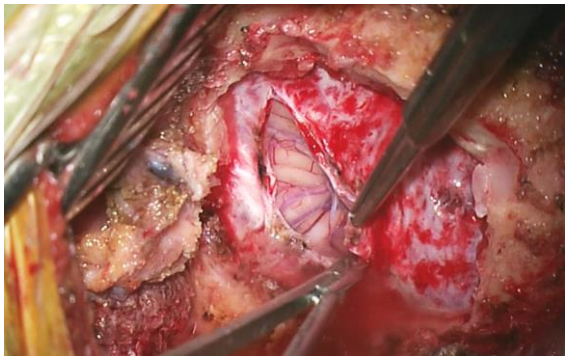


— burr holes are placed on either side of keel; posterior arch is generously removed (arrows); patent occipital sinus may cause brisk bleeding; C1 laminae (*) are not removed in this case.

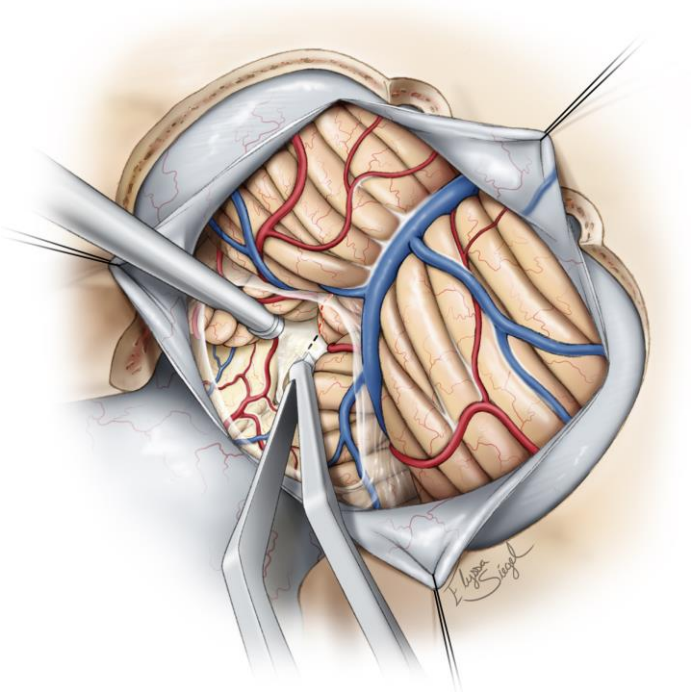




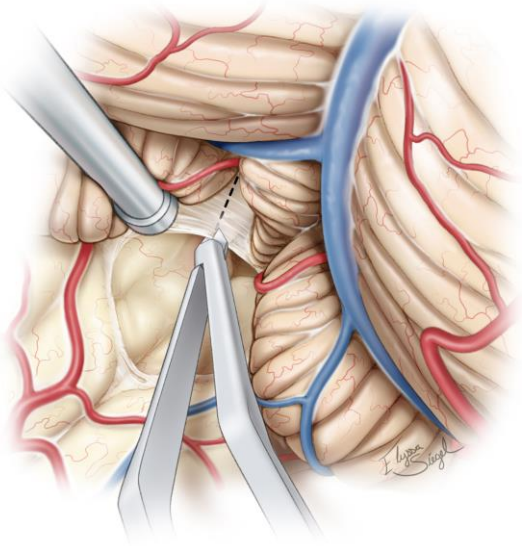
- dura is incised in a curvilinear fashion and tacked up superiorly



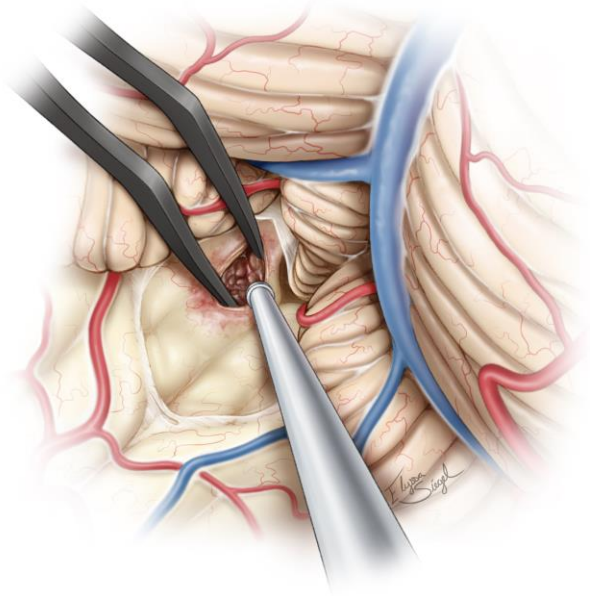
- dissection plane between medial edge of **tonsil** and adjacent edge of **uvula** → tonsil is retracted superolaterally and uvula is retracted superomedially to expose ***tela choroidea and inferior medullary velum***:
  - microscissors are used to prevent blunt dissection and protect the PICA branches.
  - minor transection of vermis (red hashed line) may be occasionally necessary



- tela choroidea and inferior medullary velum are coagulated and divided:



- microsurgical resection (cavernous malformation or intraventricular tumor) using mapping strategies:



INSULA

- in the past, insular gliomas were traditionally managed conservatively and debulking surgery was performed only in patients with neurologic deficits secondary to significant mass effect or edema.
- advances in microsurgical and mapping strategies improved safety of resection and have expanded indications for patients without preoperative dense neurological deficits.

  N.B. high-grade gliomas are still treated conservatively (unless located along the lateral aspect of the nondominant insula in a young highly functional patient)
- **fMRI + MEG + DTI + intraoperative navigation and awake mapping*** - guide in creating safe transcortical corridors to achieve adequate exposure in large tumors.

  *language, motor function (in posteromedial deep margins of the tumor intimately associated with the internal capsule) – operation is long and patient get tired after 4 hours (some experts, thus, operate asleep – esp. anxious patients, nondominant side)

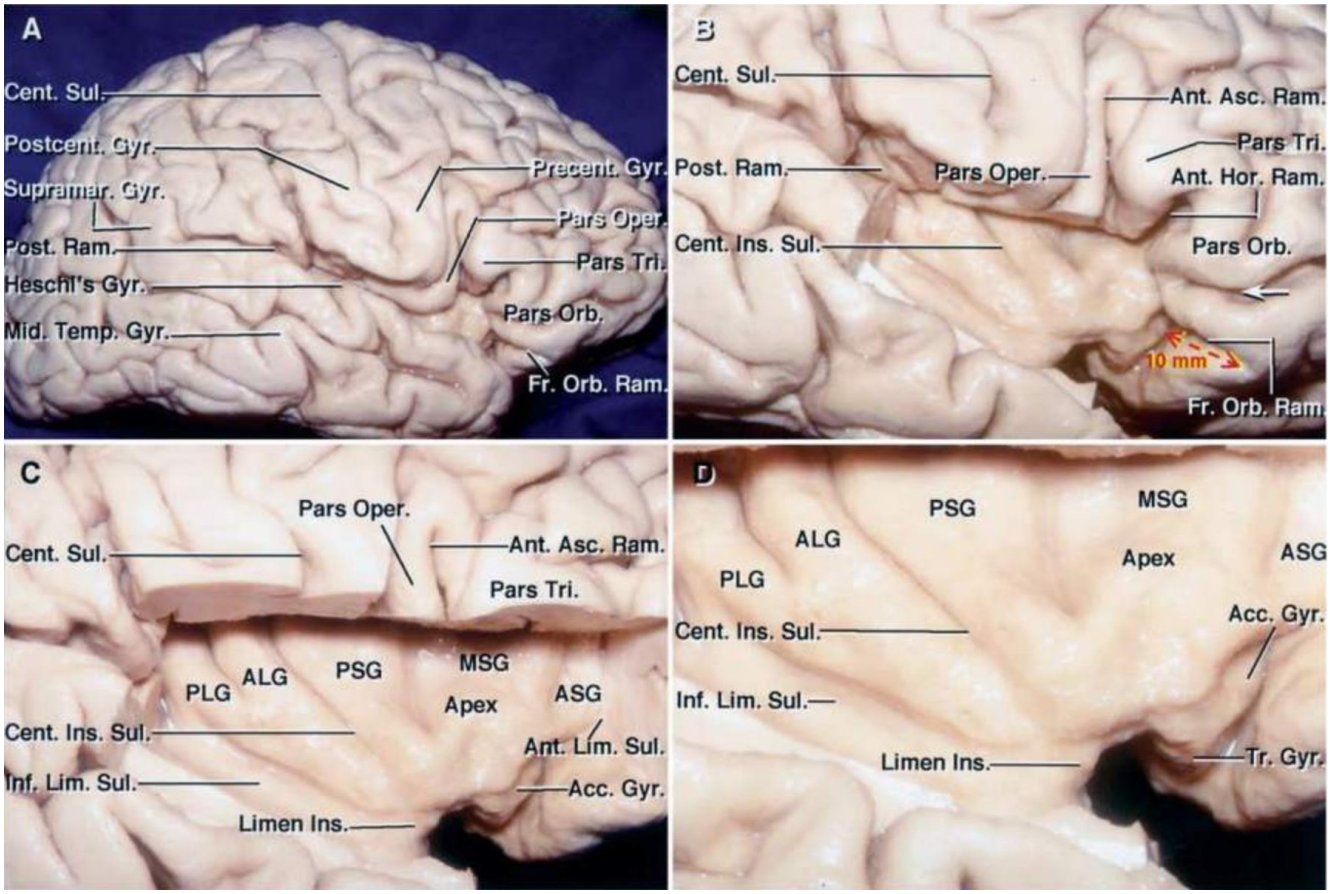
  Left insular tumors – awake
  Right insular tumors – awake or asleep mapping

N.B. there is ***significant functional plasticity in insula*** - allows to compensate and recover over time after aggressive insular resection, as long as the essential language and motor areas identified by intraoperative cortical and subcortical stimulation mapping were preserved.

- transsylvian operative corridor alone is not adequate for moderate to large size lesions - most common causes of subtotal resection! H: combined trans-Sylvian and transcortical (transopercular) approach.

ANATOMY

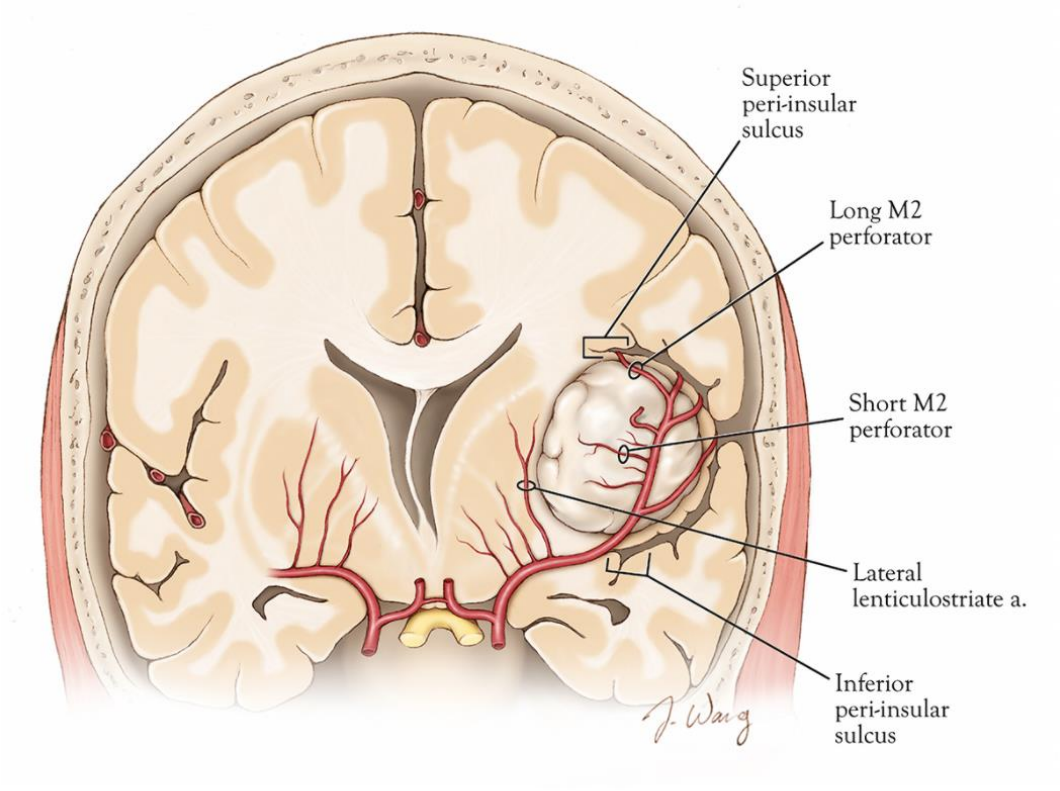
- insula is a pyramid, and its apex is the most lateral and superficial point of the structure, located 9-16 mm from the cortical surface; insular apex is beneath the anterior Sylvian point, just inferior to the vertex of the *pars triangularis* (anterior Sylvian point is the most generous portion of the Sylvian cistern where the Sylvian split can begin):

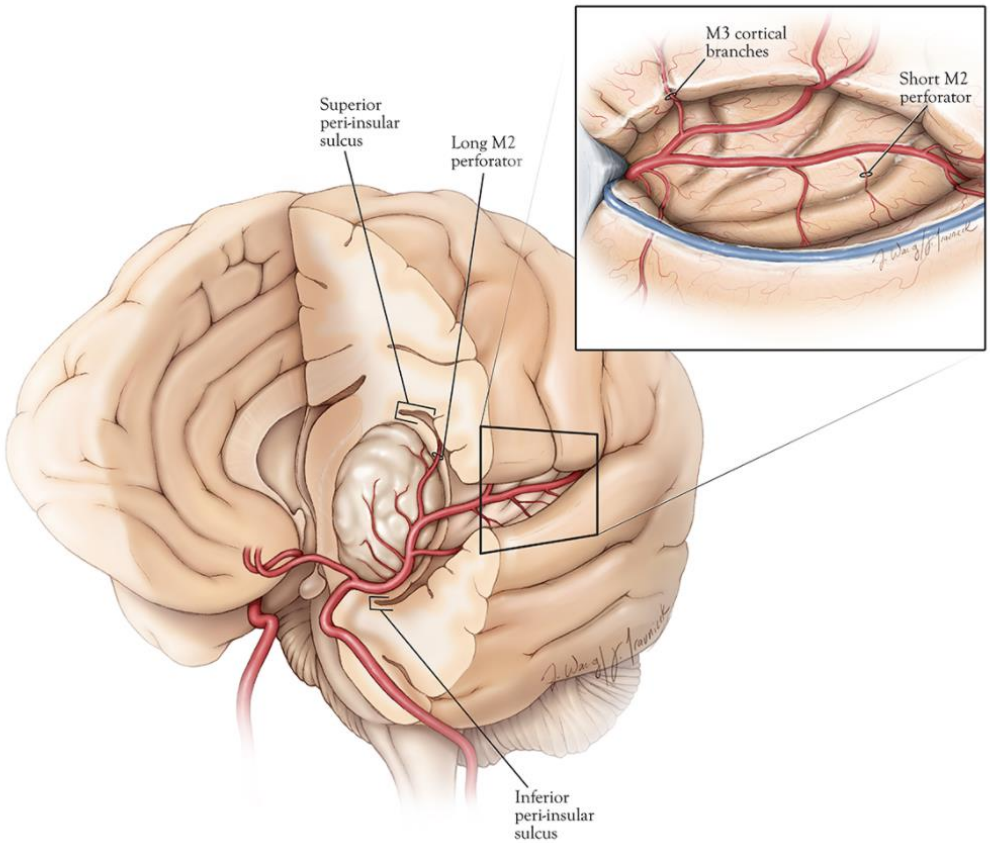


- insular stem is the anterobasal portion of the insula located in the depth of the proximal Sylvian fissure; limen insula is located within the insular stem.

SURGICAL ANATOMY

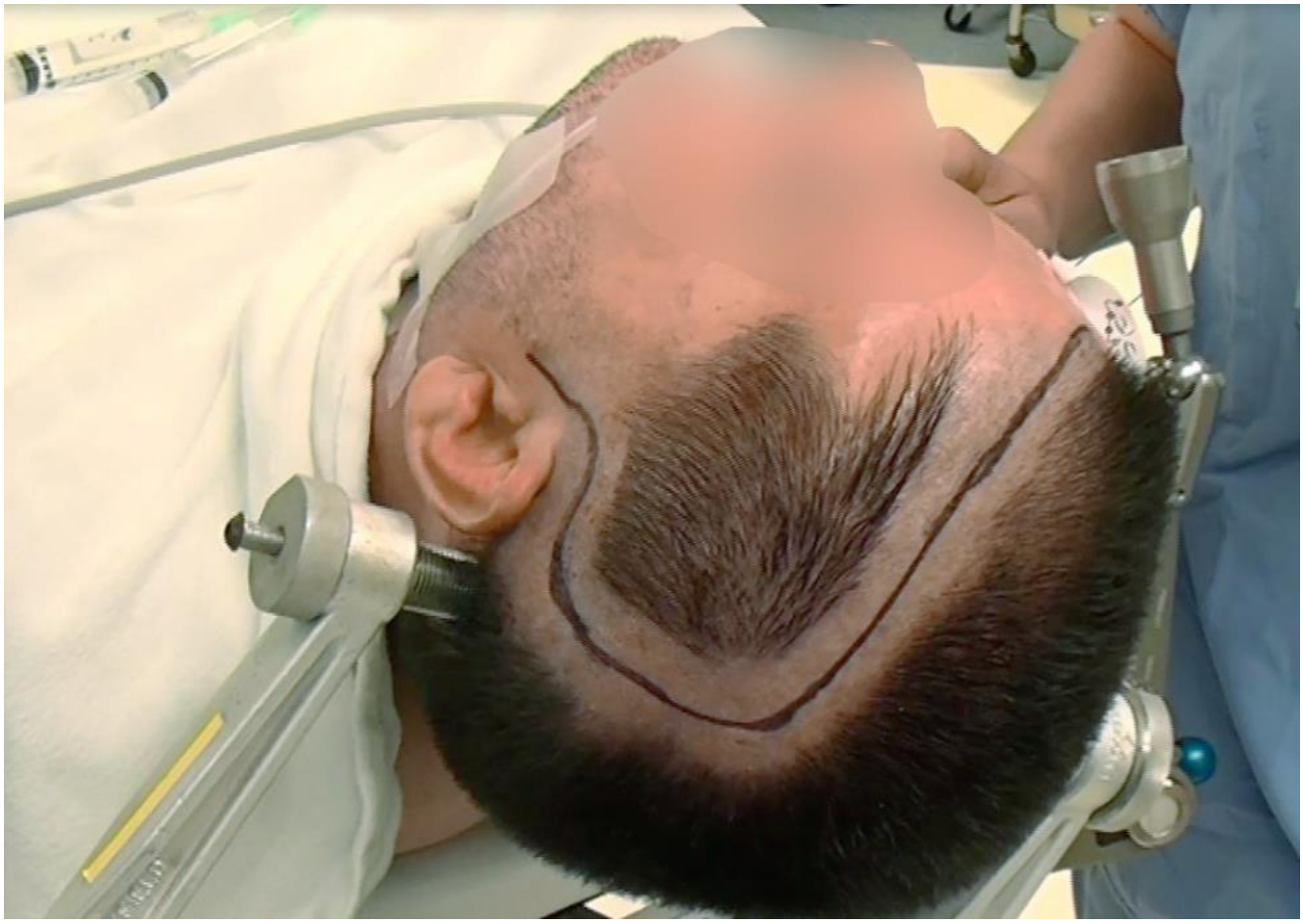
- **lateral lenticulostriate arteries** determine the most medial extent of resection (some recommend a preoperative DSA to more precisely localize these important perforators; others state that intraoperative inspection often exposes these fine vessels enough)
- short M2 perforators supply the tumor.
- long M2 perforators supply corona radiata (especially the ones travelling toward the central sulcus) and must be preserved.
- superior and inferior peri-insular sulci represent the lateral superior and inferior anatomic margins of the resection - their exposure ensures adequate Sylvian fissure split so that residual tumor does not hide within the blind spots of the operator.



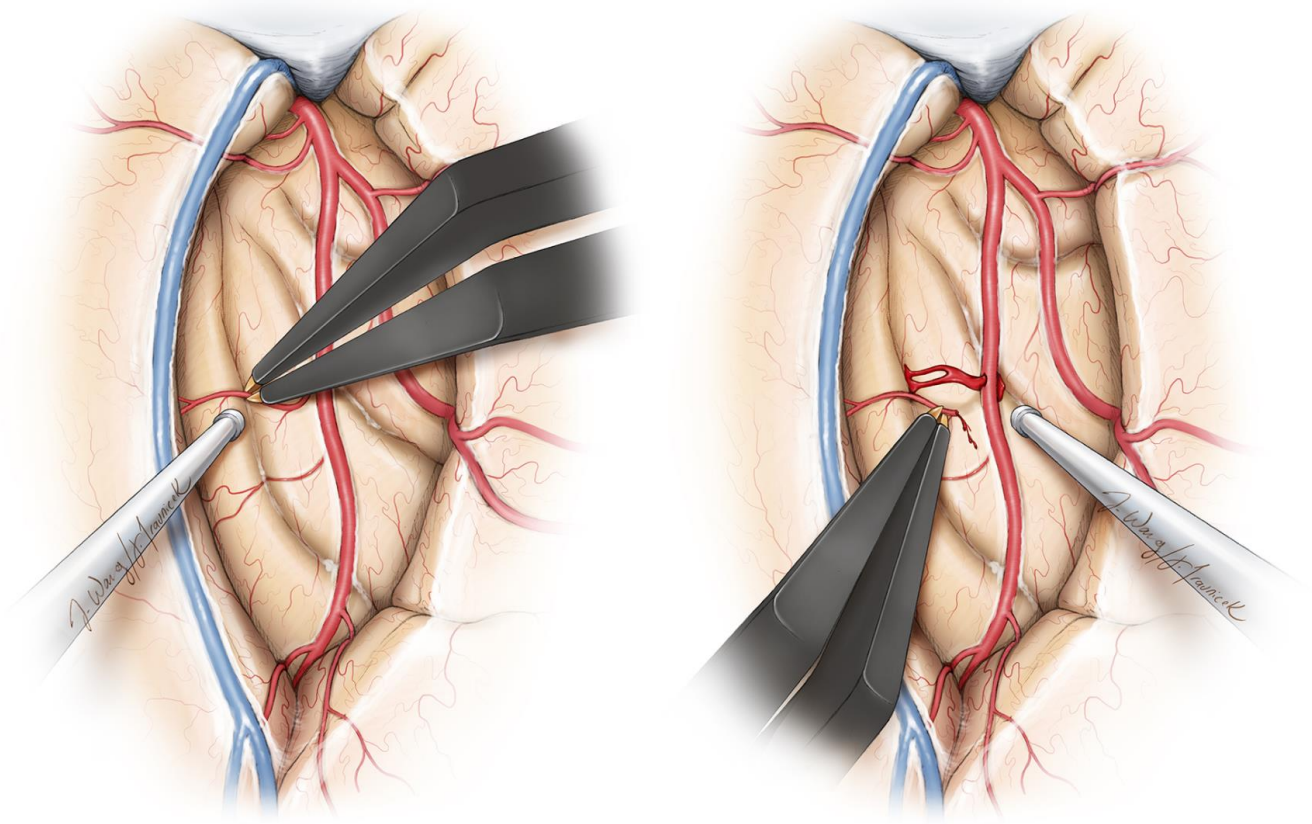


- insula receives most of its vascular supply from short perforating vessels originating from M2 and M3 segments - these short perforators, often engulfed by the superficial aspects of the tumor, can be safely coagulated and cut during subpial resection, effectively devascularizing the tumor.
- M2 segments also give rise to long perforating branches that travel posteriorly and superiorly on the insula and supply the corona radiata (→ hemiparesis).

SURGERY

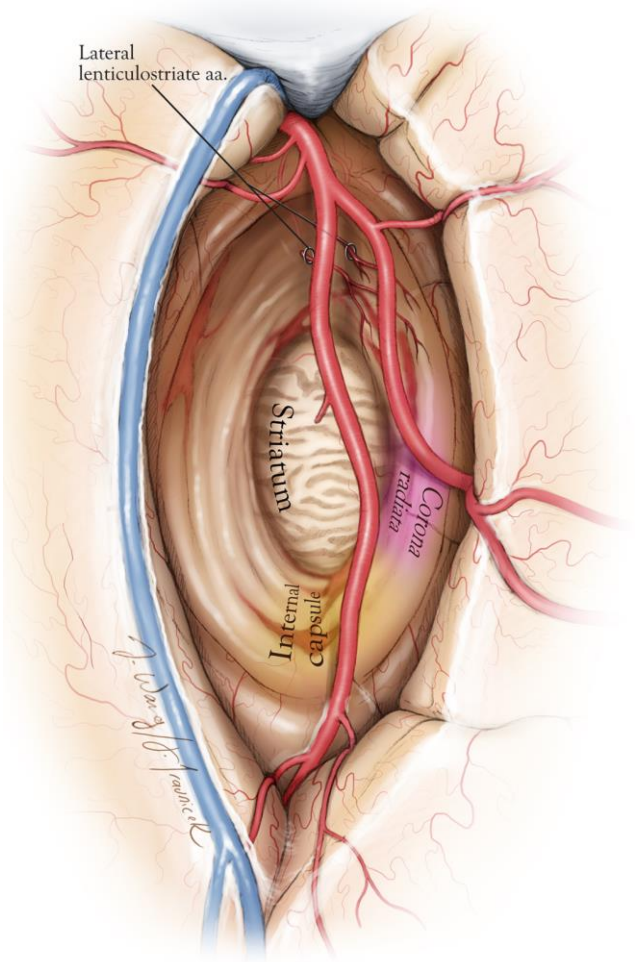


- patient is moderately sedated during the craniotomy and **Sylvian fissure dissection** (until superior and inferior peri-insular sulci identified, and the lateral portion of the tumor through the transsylvian route removed) → awaken.
- M2 perforators on insular cortex must be thoroughly coagulated and sharply cut to mobilize M2 and avoid injury to the parent vessel via their avulsion.
    - avulsion of parent vessel can result in its severe spasm and even occlusion; H: small piece of thrombin soaked cotton and gentle tamponade by the patient operator will stop the bleeding; papaverine-soaked Gelfoam pledgets can relieve the spasm in the M2-M3 branches.



- several pial incisions are made on insular cortex between M2 branches, thus creating several working windows/channels for conservative subpial (intracapsular) tumor debulking (CUSA might be too risky – use only bipolar and suction):
- patient is awaken for subcortical mapping and frequent neurologic exams - to guide removal of the **posterior and superior poles** of the tumor - corona radiata and posterior limb of internal capsule.

  Remember, **anterior and medial borders** of the cavity are defined by the lateral lenticulostriate arteries and striatum (characteristic nutmeg appearance)



- **additional corticotomy*** (in the negatively mapped!!!) in frontal and temporal opercula allow further uncovering and exposure of poles of the tumor; **anterior temporal lobectomy** (if tumor extends there) may improve exposure
  *combined trans-Sylvian and transcortical (transopercular) approach

POSTOP

- seizure prophylaxis!!!
- it is not uncommon that some patients develop deficits 24 to 48 hours after surgery, especially language deficits for dominant-side surgery; delayed deficits will recover within 2-4 weeks.

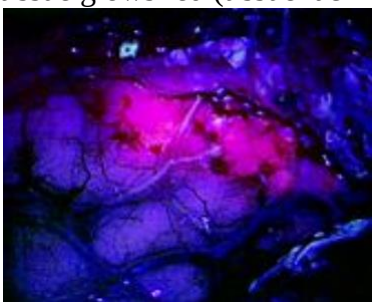
ADJUNCTS

5-ALA (GLEOLAN, AMINOLEVULINIC ACID)

A must for suspected high-grade (grade 3-4) glioma surgery!
Fluorescence rates

100% high-grade glioma
20% of low-grade gliomas - even if MRI-nonenhancing!!!!
77-94% of meningiomas (grade I-III)
80% of ependymomas
43% of PNETs
40% of gangliogliomas
25% of medulloblastomas
15% of pilocytic astrocytomas

- 5-ALA is metabolized to protoporphyrin IX (part of the heme biosynthesis pathway) - tumor-specific accumulation of **fluorescent protoporphyrin IX**. N.B. essentially nontoxic!
  - PPV 99%, NPV only 37%
  - necrotic tissue will not fluoresce.
  - microscope focal point – no more than 30 cm (fluorescence energy declines by the 4th power of the focal distance)
  - at 20 mins of exposure to light, photobleaching / fluorescence decay starts H: completing conventional resection under normal light, → turn blue laser light on - tumor tissue glows red (tissue lacking PpIX appears blue):



- **contraindication**: *porphyrias*.
- 20 mg/kg (patient > 75 kg needs two vials) PO 3 hours prior to anesthesia.
- max fluorescence time is 5-8 hours, thus, experts recommend administer 6 hours before resection.

1. Photosensitivity
   - reduce exposure to sunlight or room lights for 48 hours postoperatively (place wristband on the patient indicating the time when this 48-hr period will end).
   - dim and / or turn OR lights away from the patient until fully draped.
2. No liver failure cases reported (but LFTs may become elevated up to 10-fold in 11-15% of patients in a first week, and return to normal at 6 weeks).

iMRI

5-ALA and iMRI work synergistically!

be aware of ***thin rim enhancement along the surface of the resection cavity*** artifact *caused by surgeon's mechanical disruption to BBB*; also **gadolinium subarachnoid accumulation** (esp. due to bleeding in hypervascular tumors or resumed resection after IV gadolinium)

TUMOR RESECTION

Goal - resection of ***maximal amount*** of tumor consistent with ***functional preservation***

- 70% tumor resection is a minimum and 5 mL residual tumor volume is a maximum to statistically significantly improve survival and recurrence in GBM!

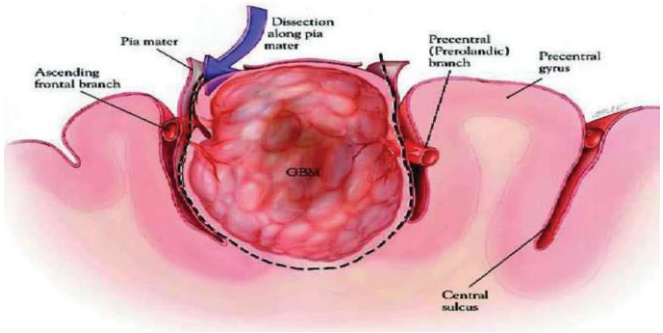
  Chaichana KL et al. Establishing percent resection and residual volume thresholds affecting survival and recurrence for patients with newly diagnosed intracranial glioblastoma. Neuro Oncol. 2014 Jan;16(1):113-22. doi: 10.1093/neuonc/not137. Epub 2013 Nov 26.

Pediatric tumor:
Ependymoma – aim for GTR
Medulloblastoma, Astrocytoma – aim for near-total resection (no need for GTR at expense of complications)
Pilocytic astrocytoma – curative even with incomplete resection (resect recurrences)
Craniopharyngioma – aim for GTR or subtotal+XRT
Nonoperative tumors – 1) diffuse **pontine** glioma* 2) optic pathway glioma** 3) germ cell tumors

*vs. **midbrain tectum**, **medulla** (esp. focal or exophytic) → surgery
**except optic nerve in already blind eye

Early **access to blood supply** – **obtain proximal control** (e.g. choroidal vessels in choroid plexus papillomas).
N.B. resist temptation to pull the tumor en bloc – there could be a critical vessel attached to tumor base (where you cannot see and can be avulsed); also tumor base can be attached to dural sinus wall, etc
H: CUSA, piecemeal resections (will result in **bleeding**, and many times this cannot be avoided), *CO_2 laser*.

- persistent bleeding may be due to residual tumor!!!
- **intraventricular bleeding** → protect foramen of Monro with cotton square*
  *if foramen of Monro cannot be cleared of obstruction, open window in septum pellucidum (almost routinely), leave EVD
- attempts of perilesional (en bloc) resection for high-grade gliomas without central debulking:



- cerebellum - split hemispheric pia horizontally (parallel to widened folia)
  CEREBELLAR MUTISM (anatomic origin - *deep cerebellar nuclei*) - one of most commonly cited complications

Finish surgery after hemostasis achieved!

POSTOPERATIVELY

- subQ heparin immediately postop or on POD1; but **postoperative hematoma** is the most frequent cause of death

Contrast MRI within 48 hours - to evaluate resection success (later, prominent enhancement of neovascularized reactive gliosis develops)

- look at **DWI and ADC** - if there is adjacent stroke it will start enhancing (as natural evolution) 3-4 weeks later and radiologist will call it as "tumor progression".
- for tumors with *propensity for leptomeningeal spread* (*MEDULLOBLASTOMAS*, *EPENDYMOMAS*, *CHOROID PLEXUS CARCINOMAS*, certain *PINEAL GERMINOMAS*) - ***baseline*** spinal MRI *prior to surgery* (to avoid postoperative artifacts); first ***postoperative*** spinal MRI - *at least 2 weeks after surgery*; if equivocal → repeat after 1-2 weeks (artifacts secondary to surgery regress while drop metastasis remain stable or increase); then yearly during first 24 months.
- residual or recurrent contrast enhancement ≥ 3 months after surgery suggests ***recurrence***.

N.B. true *tumor progression* (persistent contrast enhancement) cannot be confirmed prior to **3 months**!

Continue **anticonvulsants** for at least 7 days (few recommend - 1 year).

Continue DEXAMETHASONE for at least 5 days;

- speed of weaning depends on:
  - postop new deficits

- amount of edema on postop FLAIR MRI

- indications for steroid maintenance:
  1) large volume of tumor remains, large edema ← check on postop MRI
  2) unexpected (likely from edema) new / worsening postoperative deficits
  3) tumor in brainstem or spinal cord
  4) steroid dependence

Posterior fossa tumors:

- place EVD in OR prior to craniotomy (or at least prep for occipital Frazer bur hole)
- if surgery entails significant manipulation of brain stem, patient should remain intubated for first postoperative night and be extubated carefully once lower cranial nerve function has been assessed by ENT, speech.
- important to avoid hypertension immediately postop – risk of bleeding into posterior fossa!

RADIOTHERAPY

For lesions < 4 cm – **radiosurgery**

IMRT – local field with narrow margins except:

Target volume	Tumor types
larger margins	*ASTROCYTOMAS* (T2 + 2 cm margin), *OLIGODENDROGLIOMAS* (T2 + 2-3 cm margin)
whole brain	*LYMPHOMA*, *METASTASES*
entire CNS (craniospinal axis)	*PRIMITIVE NEUROECTODERMAL TUMORS* (incl. *MEDULLOBLASTOMA*), *NEUROBLASTOMA*, *GERM CELL TUMORS*, *PINEOBLASTOMA*, *CHOROID PLEXUS CARCINOMA*, some *EPENDYMOMAS* (infratentorial or high-grade with documented *leptomeningeal dissemination*)

Total dose depends on tumor histopathology and on CNS tolerance (depends on age):
see p. Rx11 >>

For children < 3 yrs (age by which myelinization is thought to be complete), try to delay radiotherapy or use reduced doses (as compensation use chemotherapy);
in *MEDULLOBLASTOMA* radiotherapy is so effective that is used in children despite its adverse consequences!

- start **corticosteroids** before radiotherapy (dose can be tapered relatively early, and often discontinued after 1-2 weeks).

Radiosensitive tumors:
1) *MEDULLOBLASTOMAS*
2) *GERM CELL TUMORS*
3) *CNS LYMPHOMAS*
4) certain *METASTASES* (small-cell lung tumor, germ-cell tumors, hematological)

Radioresistant tumors: *MENINGIOMAS*, *ACOUSTIC NEUROMAS*, *CRANIOPHARYNGIOMAS*, certain *METASTASES* (melanoma, sarcoma, renal-cell carcinoma)

PSEUDOPROGRESSION VS. PROGRESSION

- transient radiologic deterioration (enhancement volume↑, FLAIR signal↑) after chemoradiotherapy (14-30% GBMs, 5-24% metastases) mimicking progression:
  a) if **GBM had MGMT methylation** – it is likely a sign of response – resolves after additional cycles of adjuvant TMZ (i.e. pseudoprogression).
  b) if **GBM had unmethylated MGMT** – it is more likely a true progression – time to change adjuvant protocol.
  c) in **brain metastases treated with monoclonal antibodies** – antibodies elicit inflammatory reaction with local increase in BBB permeability
- can be differentiated by:
  a) **RANO criteria** - membrane turnover, cell density, and vascularity are increased in glioblastoma: see >>
     ^{1}H-MRS - increased membrane turnover (high Cho/Cr and Cho/NAA ratios)
     DW-MRI - increased cellularity (low ADC)
     PW-MRI - high vascularity (high CBV)
  b) **iRANO (immunotherapy response assessment for neuro-oncology) criteria** - modification of RANO criteria to address the challenges of novel immunotherapy (vs. routine Stupp protocol) for high-grade gliomas.
     - key differences from RANO:
       1) new enhancing lesion outside the main radiation field are encountered in immunotherapy and therefore do not automatically denote progressive disease in iRANO.
       2) onset of immunotherapy effect can be delayed - iRANO requires a repeat scan (3 months later) to confirm disease progression
     - progressive disease can be diagnosed in the setting of immunotherapy in the following scenarios:
       a) significant clinical deterioration (not attributable to other non-tumor causes and not due to steroid decrease)
       b) > 6 months of immunotherapy – same as RANO imaging criteria
       c) ≤ 6 months of immunotherapy - requires a second scan confirming further progressive disease 3 months after the initial scan showing features of progressive disease (during this interval, immunotherapy can continue* if toxicity is minimal)

**do not give steroids* – will defeat purpose of immunotherapy!!!*

RADIATION NECROSIS

Manifests 6-24 months after radiotherapy, lasts 18 months

Diagnosis – **MRI** (gadolinium – TRAM, PW; repeat MRI at short intervals), **MRS**, **PET** → **biopsy**
Treatment – observation, vit. E, steroids, anticoagulation, hyperbaric oxygenation, bevacizumab (Avastin), LITT ablation, surgical debulking.

CHEMOTHERAPY

- must have ability to cross BBB! (esp. for peripheral areas of tumor in which BBB is relatively intact).

Chemotherapy - adjunctive for highly aggressive and infiltrating neoplasms.

Most chemosensitive tumors:
1) *PRIMARY CNS LYMPHOMA* – most sensitive!
2) *MEDULLOBLASTOMAS*
3) *GERM CELL TUMORS*
4) *OLIGODENDROGLIOMA* – most sensitive of gliomas.

PCV combination (PROCARBAZINE, LOMUSTINE (CCNU), VINCRISTINE) - unusually beneficial against *OLIGOS*

Avoid corticosteroids during chemotherapy! – corticosteroids close BBB

TEMOZOLOMIDE (Temodar®) – oral **prodrug** → DNA alkylation

- 35% crosses BBB.
- rapidly eliminated ($T_{1/2} \approx 1.8$ hr).
- VALPROIC ACID decreases clearance of temozolomide by ≈ 5%.
- inactivation of MGMT gene in tumor tissue by methylation is the strongest predictor for outcome and benefit of temozolomide
- side effects:
  1) **N&V** (H: premedicate with ZOFRAN)
  2) **myelosuppression** (prior to dosing, must have absolute neutrophil count (ANC) > 1.5 and platelet count > 100)
  3) **infection** (DAPSONE prophylaxis against *Pneumocystis carinii pneumonia* is required for all patients on Temodar!)

Stupp protocol – standard of care for GBM (start 2-5 weeks postop)

6 weeks of combination treatment:

radiotherapy 60 Gy in 30 fractions are delivered for a total of 6 weeks, to target volume defined as contrast-enhancing lesion + 2–3 cm margin

PLUS

TEMOZOLOMIDE (75 mg / m^2 of body-surface area / day, 7 days per week from first to last day of radiotherapy, i.e. for 42 days

↓

6 months of chemo:

6 cycles of TEMOZOLOMIDE (150–200 mg / m^2 of body-surface area / day for 5 days during each 28-day cycle

CARMUSTINE (BCNU) - most effective and most frequently used drug for *MALIGNANT ASTROCYTOMAS*.

- special form - **Gliadel®** implanted biodegradable polymer wafer (polifeprosan 20 with carmustine) - *slow release* (over 2-3 wk) of carmustine in cavity.
- dura must be closed water tight (may place overlay DuraGuard) or will lead to wound breakdown.

BEVACIZUMAB (Avastin®) - anti-VEGF monoclonal antibody.

- FDA approved for recurrent GBM.
- VEGF is a ***vascular permeability factor***! - anti-VEGF therapy decreases tumor enhancement on imaging!!!
- adverse effects:
  1) fatal *GI perforation* (0.3-3%)
  2) most worried adverse effect – *intracranial hemorrhages*; also other types of bleeding (hemoptysis, GI bleeding, hematemesis, epistaxis, and vaginal bleeding)
  3) *wound healing complications* - withhold Avastin for at least 28 days prior and 28 days after surgery and until the wound is fully healed; T½ 30-60 days
  4) *arterial thromboembolic events*
  5) *venous thromboembolism*
  6) *renal injury and proteinuria*
  7) posterior reversible encephalopathy syndrome (PRES)
  8) CHF
- use effective ***contraception*** during treatment with Avastin and for 6 months after the last dose.

TREATMENT ACCORDING TO TUMOR TYPE

- see here >>

PROGNOSIS

Favorable prognostic variables:

1) lower ***tumor grade*** – most important!
2) young ***age*** (< 45 yr) – second most important!
3) better ***clinical status*** (Karnofsky performance index)
4) little or no ***residual tumor*** after initial resection (prognosis is worse for midline tumors - aggressive resections are difficult).
5) certain ***genetic characteristics***; e.g. IDH-mutant gliomas

Median survival (after gross total resection):
LOW-GRADE ASTROCYTOMAS ≈ 90 mos
ANAPLASTIC ASTROCYTOMA ≈ 75 months
GLIOBLASTOMA MULTIFORME ≈ 14 months with surgery alone, 40 mos with surgery + radiotherapy (< 5% survive 5 years)

Memorial Sloan Kettering recursive partitioning analysis (RPA) classes:

class 1 (patients < 50 yr old)
class 2 (patients ≥ 50 yr old with KPS ≥ 70)
class 3 (patients > 50 yr old + KPS < 70)

NEUROLOGICAL PARANEOPLASTIC SYNDROMES

- immunological "remote" effects of systemic cancer affecting nervous system.

- antigens shared by neurons and tumor cells (i.e. antibodies also confer some degree of antitumor effect).
- some patients have easily controlled neoplasms but die of neurologic disorder!

Esp. small cell carcinoma of lung **anti-Hu** antibodies against all neuron nuclei → encephalitis, neuropathy
anti-Yo = antibodies against Purkinje cells (subacute cerebellar degeneration) – associated with gynecologic cancer.
N.B. if no underlying malignancy is found but anti-Yo is present in woman, prophylactic total hysterectomy/bilateral salpingo-oophorectomy is recommended!

Treatment

1. Treatment of primary cancer - removal of antigen source.
2. Specific treatment (e.g. 3,4-DIAMINOPYRIDINE for Lambert-Eaton syndrome)
3. Immunosuppressive therapy (may be difficult with concurrent chemotherapy) – corticosteroids, IVIG, plasma exchange.

ONCOLOGY (BRAIN – TUMOR TYPES)

PEDIATRIC TUMORS

CNS tumors are the most common solid tumors in children and they cause more deaths than any other childhood malignancy!

1. **Embryonal tumors** (grade 4) - most common group:
   - primitive histologic appearance, where tumor cells resemble CNS tissues early in human development ("small round blue cell" appearance + elevated proliferative rate)
     1) **Medulloblastomas** (most common type) - arise in posterior fossa
     2) **Atypical teratoid/rhabdoid tumor (AR/RT)** - often originate outside of the posterior fossa
     3) **Embryonal tumor with multilayered rosettes (ETMR)** – has gone by many other names over the years

2. **Pediatric-type diffuse low-grade gliomas** – see p. Onc10 >>

3. **Pediatric-type diffuse high-grade gliomas** – see p. Onc10 >>
   - have different driving molecular alterations than in adults; e.g. large number of pediatric high grade gliomas are driven by mutations in histone genes.

4. **Glioneuronal tumors** (grade 1):
   - **Desmoplastic infantile astrocytoma, desmoplastic infantile ganglioglioma**
   - **Ganglioglioma**
   - **Dysembryoplastic neuroepithelial tumors (DNT)**
   - **Diffuse leptomeningeal glioneuronal tumors**

5. **Ependymomas**

6. **Choroid plexus tumors**

METASTASES

≈ 5-10 times more common than **primary CNS tumors**!
- brain metastases occur in ***20-33% of patients who die of systemic cancer***
- 15% systemic cancers present with neurologic symptoms! (esp. lung cancers) (*direct* or *paraneoplastic*).

Sources (virtually any tumor but prostate is unlikely):

Lung (35-50%), esp. *small-cell carcinomas* (20% lung cancers)
Breast (13-20%)
Melanoma (16%)
Colorectum (9%)
Kidney (8%)
Unknown source (10%)

Prostate – rarely (vs. spine)

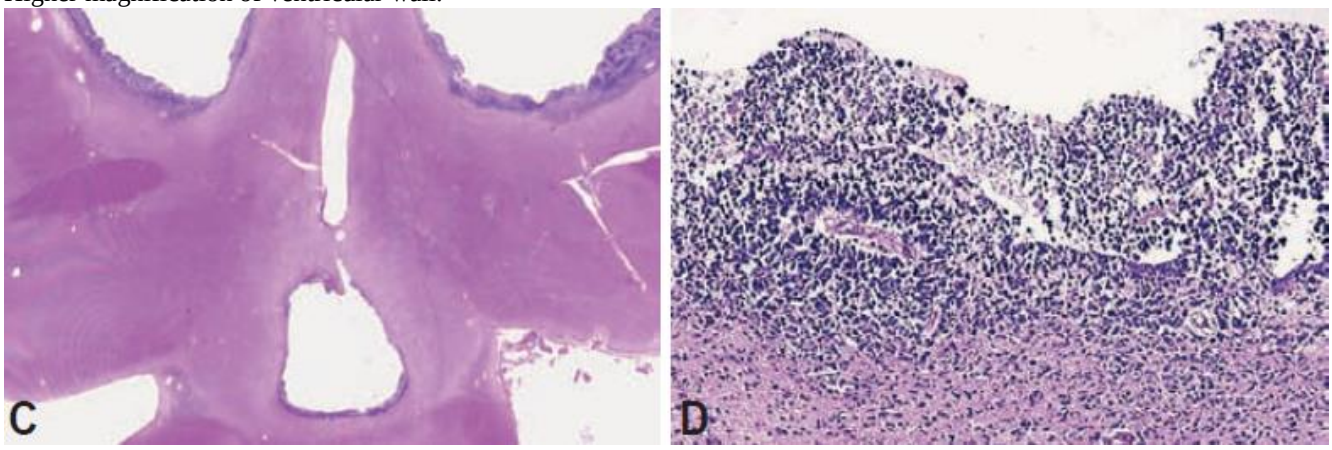
Propensity to spread to brain: lung > renal > melanoma

Melanoma is tumor type most prone to spread to brain!
- similar ***embryologic origins***

N.B. in **childhood**, most common metastatic tumors are:
leukemia > lymphomas > osteogenic sarcomas > rhabdomyosarcomas > Ewing sarcoma

- metastases prefer anatomical arterial "watershed areas" and gray matter-white matter junction
- proliferation higher than in primary neoplasm.

C, **D** Extensive spread of small cell lung carcinoma cells along the walls of both lateral ventricles and the third ventricle. **D** Higher magnification of ventricular wall.

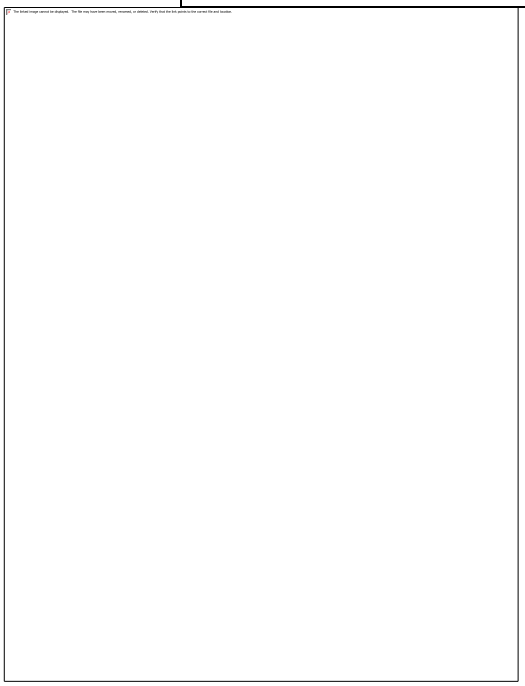


Clinic:
Headache (42-50%) and **seizures*** (15-40%) are most common presenting symptoms!

- **leptomeningeal** metastasis - *cranial nerve dysfunction and radiculopathy*, HCP

Diagnosis

Brain and skull mts image review protocol:
parenchymal - gadolinium MPRAGE, FLAIR (not all mts enhance so FLAIR is even more sensitive, esp. for small mts)
calvarial - DWI (bright areas in the skull; vs. bone marrow abnormalities - will be diffuse signal along entire skull)



- **calcification** is unusual.
- **circumscribed** well-demarcated, approximately spherical lesions at **gray-white matter junction**
- significant vasogenic **white matter edema** (out of proportion to lesion size)
    - in majority cases **edema** is substantial (for unclear reasons, some metastases produce almost no edema).

- some metastases *hemorrhage* spontaneously (esp. melanoma, renal cell carcinoma, choriocarcinoma).
- some enhance ***brightly and solidly*** (esp. small lesions), others are in ***ring configuration*** (esp. large lesions - core of necrosis).

  N.B. administration of 3 times usual dose of gadolinium is more sensitive than standard protocol for detection of brain metastases!

N.B. 8-10% of patients with systemic primary tumor and intracranial lesion(s), actually have primary CNS tumors (not metastases) – look for cortical infiltration and variable enhancement pattern ← help to suspect primary CNS tumor (→ biopsy)

PET

- value of **fluoro-deoxyglucose** PET is highly questionable based on the physiologically high levels of glucose metabolism in healthy brain parenchyma - FDG PET has poor sensitivity (27%) for mts detection.

CSF

- cytological examination in **leptomeningeal** metastases reveals malignant cells in initial CSF sample in 50% vs 90% when CSF sampling is repeated in adequate volumes (10 mL).

Specific markers:

- CEA, PSA, CA125, CA153, AFP, HCG, LDH.
- *anti-Yo antibody* in cerebellar degeneration;
- *anti-Hu antibody* in limbic encephalopathy;
- *anti-Ri antibody* in opsoclonus and ataxia.

1. **Skin and thyroid examination**
2. **Chest-abdomen-pelvis CT**
3. **Whole-body FDG PET**

- if primary tumor is not quickly revealed by careful evaluation, pathologic diagnosis of single brain tumor needs to be disclosed by resection or, if unresectable, by biopsy.

  N.B. always insist on biopsy of extracranial tumor (if known) – brain lesion may be radiosensitive!

For *incidentally* discovered brain metastasis *without significant mass effect or edema*, withholding steroids & antiepileptics is appropriate.

CNS Systematic Review and Evidence-Based Guidelines for the Treatment of Adults With Metastatic Brain Tumors (2019)

Brain metastases with symptoms related to mass effect

Level 3 recommendation: corticosteroids are recommended to provide temporary relief of symptoms related to *increased ICP and edema*:

mild symptoms - starting dose of 4-8 mg/d of dexamethasone
moderate to severe symptoms - 16 mg/d of dexamethasone

Level 3 recommendation: DEXAMETHASONE is the drug choice (minimal mineralocorticoid effect).

Level 3 recommendation: steroids should be tapered as rapidly as possible but no faster than clinically tolerated.

Level 3 recommendation: prophylactic AEDs are not recommended if did not undergo surgical resection.

Level 3 recommendation: postcraniotomy AED use is not recommended.

If needs anticoagulation: therapeutic anticoagulation does not increase the risk of intracranial hemorrhage

Indications for surgical resection (metastasectomy) - in patient with good performance status:

a) solitary metastasis > 3 cm (i.e. no other sites of metastasis exist in body) – class 1 evidence; for < 3 cm → radiosurgery
b) life-threatening strategically located metastasis - steroid-resistant neurological symptoms despite other multiple cerebral metastases (symptomatic lesion is resected, for remaining lesions → radiotherapy)
c) need for tissue diagnosis

Oligometastases – bit controversial but be aggressive surgically* (even if it involves multiple craniotomies during the same setting – remove all possible lesions [even small ones – use intraop US to localize] through each craniotomy). *historical hesitance was due to poor prognosis in brain mts (now it is different – modern systemic therapy!)

Requirements for surgical resection:

1) limited and/or controlled **systemic disease**; i.e. most patients succumb to systemic cancer rather than intracranial lesion – may mask benefit of surgery
2) **Karnofsky score** > 70 (functions independently, spends < 50% time in bed)
3) lesion in noneloquent area

Most important factor for decision making – status of **extracranial disease**!

- in many studies reporting the cause of death, systemic causes of death trump neurological causes of death.

Contraindications to surgery:

1) radiosensitive tumor (e.g. small-cell lung cancer metastasis – WBRT even for solitary mts)
2) life expectancy < 3 months (WBRT indicated)
3) multiple lesions, leptomeningeal disease

Patchell RA et al. "*A randomized trial of surgery in the treatment of single metastases to the brain*". N Engl J Med 1990; 322:494-500.

Prospective randomized trial:

a) surgical removal followed by radiotherapy (surgical group) – 25 patients
b) needle biopsy and radiotherapy (radiation group) – 23 patients

Results:

- **recurrence** at the site of the original metastasis was less frequent in the surgical group (20% vs. 52%)
- **survival** was significantly longer in the surgical group (40 vs. 15 weeks)

Resection for metastases (metastasectomy) – see p. Op340 >>

Postop – SRS at 2-3 weeks (incision healed, resection cavity is smallest) - radiotherapy always after resection (any modality is good but justify use of it):

(most sensitive - *small cell lung cancer*, *seminomas*, *hematologic* malignancies)
(melanoma, sarcoma and renal-cell carcinoma are not sensitive at all)

a) **whole-brain radiation therapy (WBRT) ± hippocampus-sparing** – 30 Gy in 10 fractions over 2 weeks) – for older patients, for irregular resection cavity

WBRT as primary treatment - multiple mts (> 4-10), pathology – small cell lung, leptomeningeal disease

b) **SRS** – for nice resection cavity, **< 4 mts** (modern paradigm shift: SRS even for multiple mts! – volume becomes more important than a number – best for < 10 mL). Local control > 85-90% - why to operate? (surgery gives tissue + relieves mass effect quickly)

Current standard - ***do not include a brain margin*** (some centers include 1-2 mm of margin only to compensate for system inaccuracy).

Adding WBRT after SRS – no difference in OS

Dose – depends on tumor size:

If can, use 24 Gy (unless close to brainstem or optic structures)

Maximum tolerated dose (MTD) of single session SRS:

Tumor size	MTD (Gy, Tumor Margin)
< 2 cm	24
2 – 3 cm	18
3 – 4 cm	15 – so **better fractionate*** (e.g. 8 Gy x 3)

*esp. if proximity to brainstem, optic nerves

- most tumors that metastasize to brain are not chemosensitive!
  (most sensitive - *small cell lung cancer* and *seminomas*)

> Combining radiotherapies (WBRT + SRS or SRS + WBRT*) improves CNS control but does not improve survival.

* for patients with > 4 brain metastases, the addition of WBRT to SRS is not recommended unless metastases' cumulative volume is high (> 7 cc), number (> 15), size, or location does not make them amenable to local therapy (surgical resection or SRS).

RADIATION THERAPY ONCOLOGY GROUP (RTOG) classes for predicting outcome in brain metastases after whole brain radiotherapy – **this is historical**!!!

Class	Karnofsky score	Systemic Disease	Median Survival (months) with WBRT	Adding SRS boost to WBRT
1 (age ≤ 65 yrs)	≥ 70	Controlled primary disease, no extracranial metastases	7.1 (13.5 for single metastasis, 6.0 for multiple metastases)	16.1
2 (age > 65 yrs)	≥ 70	Not group 1 or 3	4.2 (8.1 for single metastasis, 4.1 for multiple metastases)	10.3
3	< 70		2.3	8.7

LASER (LITT)

- Dr. Danish – do not use LITT upfront, always do SRS first (vs. recurrent glioma – prefers LITT first and then SRS for LITT failure).

RECURRENCE AFTER SRS

a) **LITT**
b) **repeat SRS** is another option although local control rate is lower (e.g. tumor control rate was 53.5% by In-Young Kim et al. 2018) than after primary SRS.

FOLLOW UP

MRI every 2–3 months for one year, then every 3-4 months (less frequent beyond 2 years if both are present – no relapse before 2 years and total tumor volume < 5 mL)

- predictors of intracranial failure beyond 2 yr:
  failure before 2 yr (HR = 2.2, 95% CI: 1.2-4.3, P = .01)
  total tumor volume ≥ 5 cc (HR= 2.3, 95% CI: 1.2-4.3, P = .01)

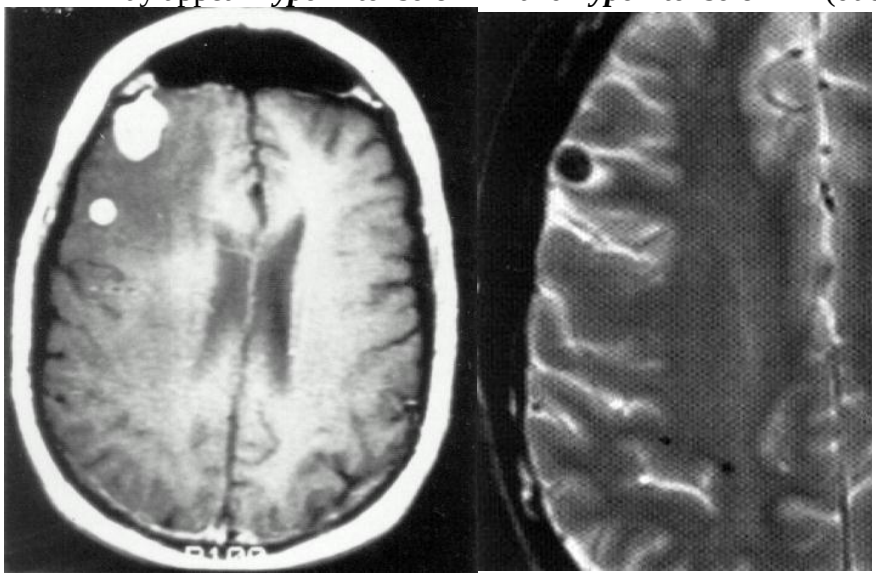
MELANOMA

Melanoma that metastasizes to CNS is incurable

Melanoma is tumor type most prone to spread to brain!
And does so with multiple brain metastases

- unique tendency to hemorrhage!
- *PRIMARY INTRACRANIAL MELANOMA* can arise from meninges.

  - may appear ***hyperintense*** on **T1** and ***hypointense*** on **T2** (due to melanin).



1-3 lesions: surgical removal / SRS ± whole brain radiation
Multiple metastases: whole brain radiation

CNS Guidelines for Metastatic Brain Tumors (2019)
There is ***insufficient evidence*** to make recommendations regarding BRAF inhibitors (BRAFi) DABRAFENIB and VEMURAFENIB for brain metastases due to **melanoma**

LUNG CANCER, SMALL CELL

Treatment is whole brain radiation (even for single symptomatic metastasis)
Newer trend – SRS + chemotherapy – tumor tends to shrink very rapidly; WBRT reserved for failures.

Small cell – used to be nonop; now if solitary symptomatic – may resect; lower threshold (than other mts) for WBRT

BREAST CANCER

CNS Guidelines for Metastatic Brain Tumors (2019)
Level 3 recommendation: WBRT + temozolomide is recommended for triple negative breast cancer.

Triple-negative breast cancer - negative for estrogen receptors, progesterone receptors, and excess HER2 protein - growth of the cancer is not fueled by estrogen and progesterone, or HER2 protein – limited hormonal treatment and targeted therapy → worse prognosis

See O1 case >>

NEOPLASTIC MENINGITIS / LEPTOMENINGEAL CARCINOMATOSIS

NM - proliferation of neoplastic cells in ***subarachnoid space***.

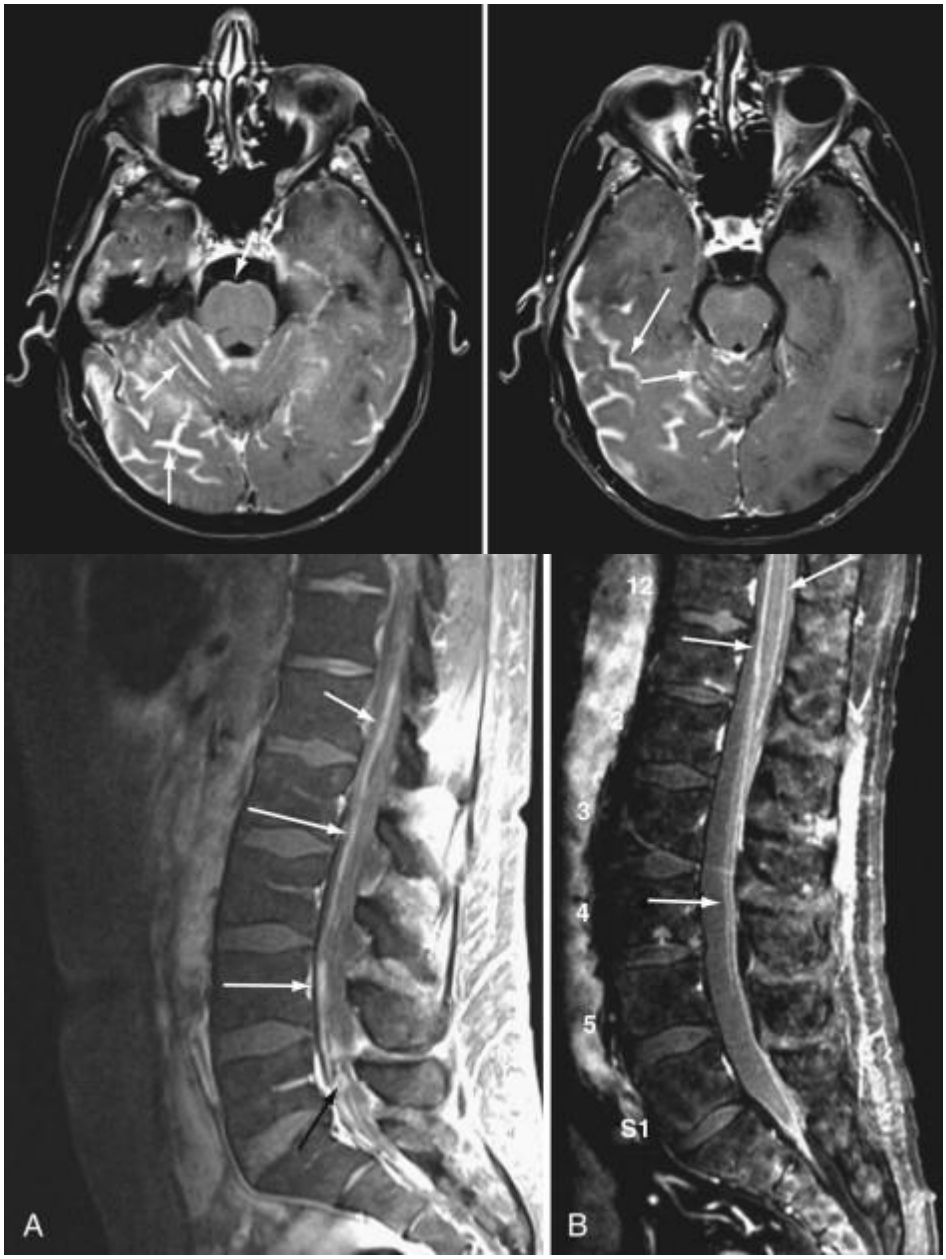
1. Any **systemic solid tumor**; Most patients have *breast cancer* – best prognosis!
2. **Hematologic malignancies**
3. **CNS tumors** (direct meningeal seeding via CSF) → *LEPTOMENINGEAL GLIOMATOSIS*.

Clinically - subacute meningitis (but afebrile with preserved consciousness):

1. MENINGEAL IRRITATION: **nuchal rigidity** (< 20% patients), **back pain**
2. CSF FLOW OBSTRUCTION → **ICP↑**, **hydrocephalus**.
3. LOCAL TUMOR INFILTRATION → **multiple cranial nerve palsies** (94%), **radiculopathies**, **myelopathy;** occlusion of blood vessels (as they cross subarachnoid) → **microinfarcts**

MULTIFOCAL neurological symptoms!
Classical vignette: **CN3 palsy + foot drop**

Marked enhancement of leptomeninges and nerve roots - patchy finely nodular or linear.



Periodic **CSF examinations** - most useful test!!! malignant cells in CSF + ↑protein ± ↓glucose
Normal CSF does not exclude diagnosis!

15% *false-negatives* after 3 high-volume (> 10 mL) LPs (5% after 6 LPs) → **meningeal biopsy**

Treatment:

- **craniospinal radiotherapy** for bulky / symptomatic deposits.
  ↓
- **intrathecal chemotherapy** (studies show that IT treatment provides no differences in outcome): METHOTREXATE* > CYTARABINE > THIOTEPA
  - CSF-flow study is recommended for all patients at initiation of intrathecal chemotherapy; if obstruction is noted → defer therapy (whole neuraxis radiotherapy is reasonable alternative).
- *fixed focal neurologic deficits* (e.g. cranial-nerve palsies) do not improve, but *encephalopathies* can improve dramatically with treatment.

*toxicity of intrathecal or high-dose systemic methotrexate is increased after whole-brain RT - *necrotizing leukoencephalopathy*
(H: administer MTX before RT)

Prognosis - average survival time – 3.5-6 months (except - **breast cancer** - 11-25% alive at 1 year, 6% - at 2 years)

Exception - *LEUKEMIC / LYMPHOMATOUS MENINGITIS* (esp. ALL) - can be eradicated completely from CNS!

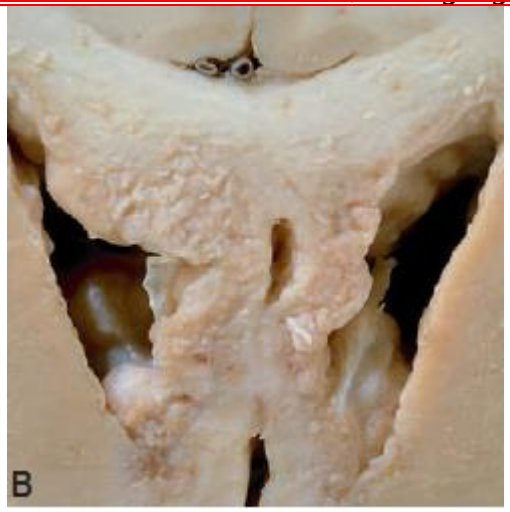
PRIMARY CNS LYMPHOMA

- extranodal non-Hodgkin lymphoma (90% - high-grade *diffuse large **B-cell** lymphoma*)

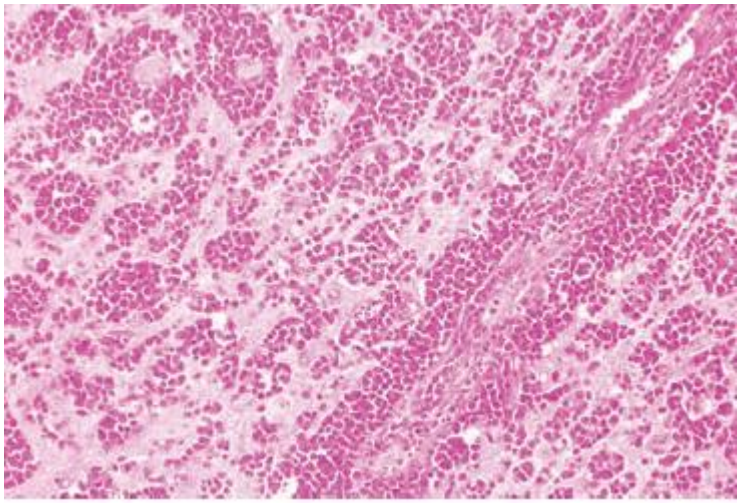
- associated with ***immunodeficiency states***; in AIDS all patients express Epstein-Barr virus-related genome; prior to HAART, incidence in AIDS patients was 3600-fold higher than in general population.

  N.B. immunosuppressed patients are at risk for both ***primary CNS lymphomas*** and ***CNS infections*** (such as *toxoplasmosis* or *cryptococcosis*) - patients treated empirically with antibiotics should undergo prompt biopsy if lesions are not responding to therapy.
- multiple lesions in 25% cases (easily mistaken for metastases).
- typically *remains confined to CNS*

  N.B. *if lymphoma is also found outside of CNS* → diagnosis is *non-Hodgkin lymphoma metastatic to CNS* (occurs preferentially in *meninges*)
- ***periventricular white matter***, ***basal ganglia***, ***corpus callosum***:



- ***predilection for blood vessels*** (lymphoid clustering around small cerebral vessels) – angiocentricity – differentiate form viral infections!!!



- NEUROLYMPHOMATOSIS (rare) - lymphoma restricted to **nerves** (axonal and/or demyelinating neuropathy).
- **LYMPHOMATOSIS CEREBRI** - diffusely infiltrating forms.
- *frontal lobe* is most frequently involved region → ***neurocognitive changes***
- binocular vitreous involvement! **ophthalmologic examination** - for all patients.
  cellular infiltrates in vitreous on slit-lamp examination → vitrectomy (may establish diagnosis – no need for brain biopsy).
- **lumbar puncture** - unequivocally *positive CSF cytology* eliminates need for brain biopsy!
- hyperdense on noncontrast CT; smoothly rounded homogeneous ***subependymal or intraventricular prominent contrast enhancement (“light bulb”)***:

  – ring enhancement is common in AIDS due to central necrosis.
  – ***diffusion restriction*** – rather unique among tumors (other tumors do not restrict)

For *AIDS patients*, most difficult problem – differentiate ring-enhancing lesions between PCNSL and Toxoplasma – frequently coexist!

  – positive *Toxoplasma serology*, presence of *multiple lesions* favors toxoplasmosis:

1) **SPECT** / **PET** – hypometabolic toxoplasmosis and hypermetabolic PCNSL;
2) **trial with antitoxoplasmosis antibiotics** for 1 week (absence of response → stereotactic **biopsy**)

If above is not helpful → **MRS, SPECT**

N.B. no patient should be treated without definitive cytologic proof of diagnosis:

a) vitrectomy
b) positive CSF cytology (use flow cytometry; for HIV-infected check for syphilis, cryptococcal antigen)
c) stereotactic brain biopsy

N.B. hold off on steroids – do emergency biopsy!

- ***until diagnosis confirmation, corticosteroids should be withheld*** (unless herniation is imminent) (biopsy following steroid administration often yields normal, necrotic, or nondiagnostic tissue) - steroid-treated lesions may disappear within hours!
  Nonneoplastic contrast-enhancing processes (e.g. MS, sarcoidosis) can also resolve with steroids! - steroid-induced resolution of intracranial mass does not establish diagnosis of PCNSL

Treatment (rule out systemic disease – chest-abdomen-pelvis CT)

- *most radiosensitive & chemosensitive CNS tumor*

Surgery has only diagnostic role (biopsy)!
Even partial resection is associated with worse survival.
Modern paradigm - resection is recommended for large, compressive lesions in fit patients

High-dose ***systemic*** METHOTREXATE - most successful treatment strategy!
– for *LEPTOMENINGEAL LYMPHOMA*, ***intrathecal*** drug is needed.

Avoid corticosteroids during chemotherapy!

Avoid METHOTREXATE following radiotherapy – XRT opens BBB → ↑risk of treatment-related necrotizing leukoencephalopathy

N.B. steroid-induced remission is short-lived and is not definitive treatment!

Whole-brain radiation therapy (WBRT) 40-45 Gy in 20-25 daily treatments - best second-line treatment:
a) adjuvant only if MTX fails
b) mainstay of treatment in ***immunocompromised patients***

- 5-year survival only 15-30% (used to be 3-4% similar to *GBM*)

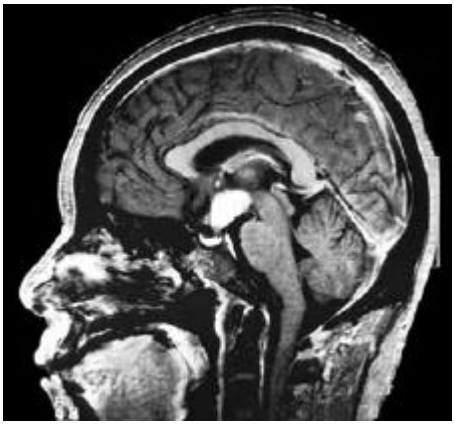
HISTIOCYTIC TUMORS

- masses composed of histiocytes (not microglia!)

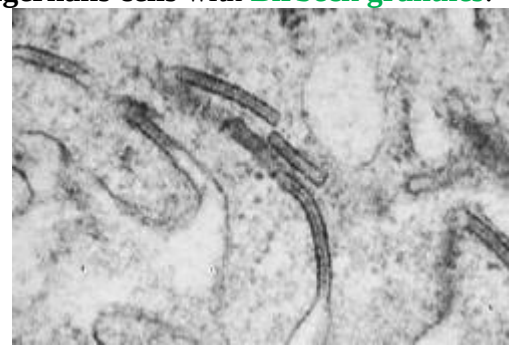
- in most patients, there is no defect in immunologic integrity and clinical course is benign (malignancy extremely rare).
- commonly associated with histologically ***identical extracranial lesions***.

LANGERHANS CELL HISTIOCYTOSIS

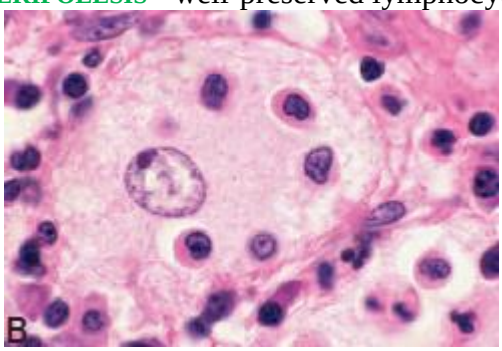
- most common form (2/3 of cases) - eosinophilic granuloma - solitary bone (osteolytic) lesion of skull or spine - may spontaneously recover or requires minimal treatment, e.g. surgical resection.
- in brain principal involvement is hypothalamus and posterior pituitary → diabetes insipidus (25%).



- **multisystemic disease with organ dysfunction** may resist systemic chemotherapy (mortality rate reaches 20%).
- **CD68** – differentiates histiocytosis from lymphoma.
- **Langerhans cells** with **Birbeck granules**:



- **EMPERIPOLESIS** - well-preserved lymphocytes and plasma cells within cytoplasm of histiocyte**:**



MENINGIOMA

- benign extra-axial neoplasm of arachnoidal cells in arachnoidal cap (component of arachnoidal villi in dura)

- 13-26% of all primary intracranial neoplasms; 30% in Africa!
- at autopsy, 2.3% people have undiagnosed asymptomatic meningiomas.
- male-to-**female** ratio = 1:2 (1.4-2.8)
- 60% of sporadic meningiomas - *loss of NF-2 gene* (22q12).
- radiation → 4-fold increased risk for multiple meningiomas 19-36 years later (dose-related).

WHO Classification of Meningiomas:

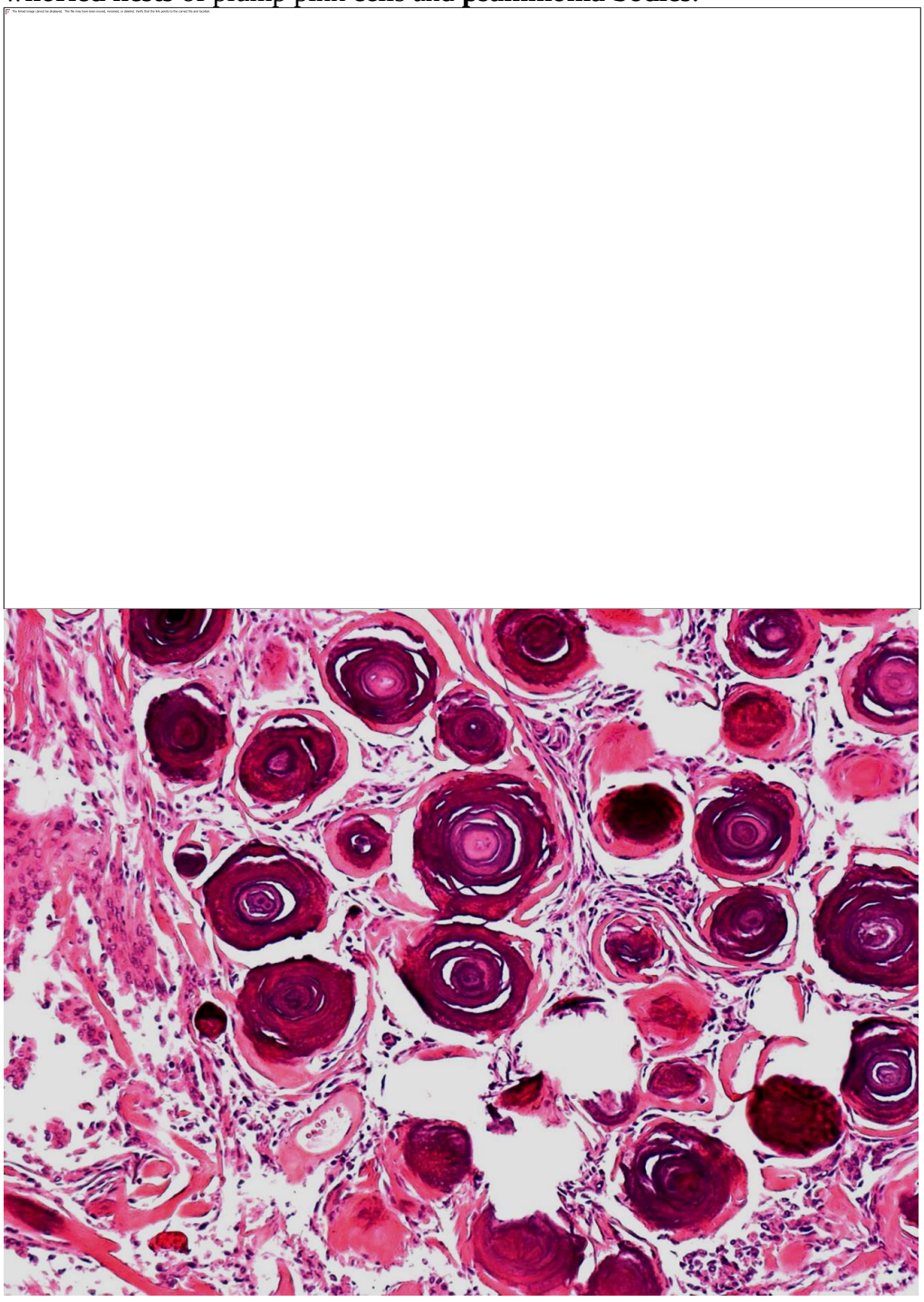
Grade
Grade I - **(benign) meningioma** (90-94%)
Grade II - **atypical meningioma** (5-7%) ≥ 4 mitoses per 10 high-power fields
Grade III - **anaplastic meningioma** (1-5%) ≥ 20 mitoses per 10 high-power fields

Papillary meningioma – grade **III**

- true brain invasion upgrades to grade II (even if histology is benign).

N.B. tumor type that closely resembles meningioma is *HEMANGIOPERICYTOMA*

- with worsening grade, meningiomas lose progesterone receptors and start expressing estrogen receptors
- somatostatin receptors present 100% (esp. SSTR2).
- **whorled nests** of plump pink cells and **psammoma bodies**:



Clinic

"Foramen Magnum Syndrome" - collection of peculiar clinical findings (CANDES):

1. Neck / suboccipital pain
2. CN11 palsy
3. Atrophy of hand intrinsic muscles
4. Cape distribution of sensory loss
5. Dysesthesia of hands (numbness, tingling, and cold sensation)

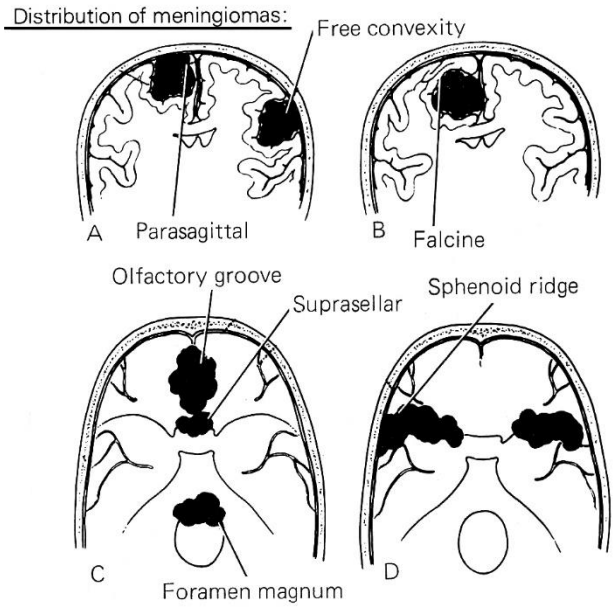
6. Stereoanesthesia.

+ spastic weakness in all 4 limbs (begins in ipsilateral arm, progresses to ipsilateral leg, and then moves to opposite leg and arm) – **rotatory paralysis**

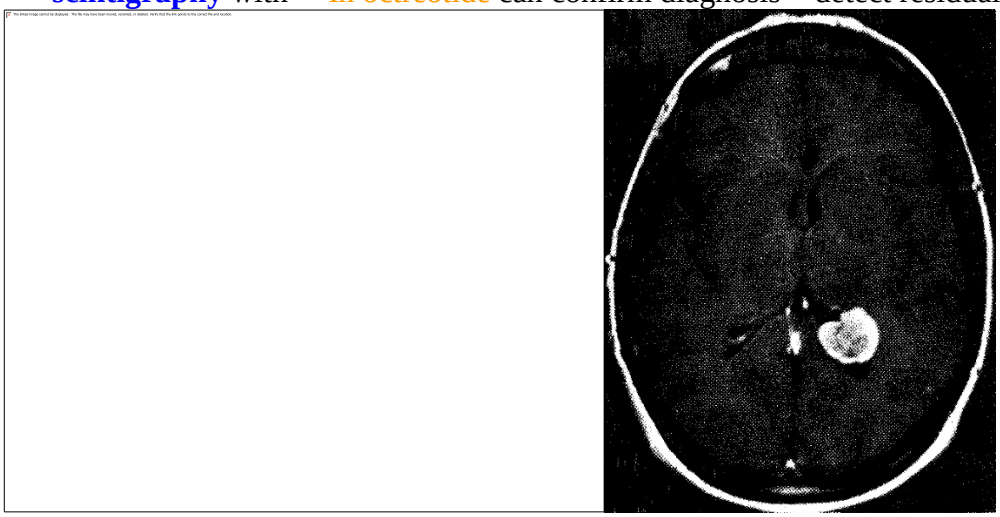
Diagnosis - **MRI** – isointense on all MRI sequences to cortex

- dural-based ("dural tail") extraaxial tumor with well-defined borders
- enhances homogeneously and intensely

  MENINGIOMA of optic nerve - "tram-track" sign
- ***calcification*** (small punctate) (10-20%).
- can ***invade skull bones*** → *hyperostosis*; sometimes causes reactive *hyperostosis* without invasion! (imaging is insufficient to predict bone invasion!!!)
- edema may be massive (risk of seizures).
- 2% ***intraventricular*** (75% in left occipital horn).



- **angiography** "mother-in-law" blush!
- **scintigraphy** with ^{111}In octreotide can confirm diagnosis + detect residual or recurrent tumor



Differential

1. Dural metastasis
2. Dural lymphoma
3. Dural histiocytoma

TREATMENT

- newly diagnosed meningioma - **wait-and-see** approach when clinical conditions allow it; surgical removal is still considered the treatment of choice.
- resection is indicated for:
    a) symptomatic, mass effect
    b) fast growing tumors

- *small asymptomatic tumors* are best left for **observation** (esp. for elderly patients, esp. if calcified) - repeat MR in 3-6 months (growth only few mm excludes major mimickers – metastasis, lymphomas).
    - some may "burn out" and cease growing.
    - growth > 2 mm / year – indication for surgery.

- chemoresistant, radioresistant.

PRINCIPLES IN MENINGIOMA RESECTION

See p. Op340 >>

Table 21-25 Simpson grading system for removal of meningiomas[212]

Grade	Degree of removal
I	macroscopically complete removal with excision of dural attachment and abnormal bone (including sinus resection when involved)
II	macroscopically complete with endothermy coagulation (Bovie, or laser) of dural attachment
III	macroscopically complete without resection or coagulation of dural attachment or of its extradural extensions (e.g. hyperostotic bone)
IV	partial removal leaving tumor in situ
V	simple decompression (± biopsy)

Degree of Resection	Recurrence rate
Complete resection with dural margin	9%
Complete resection with coagulation of dura	19 %
Complete resection (no treatment of dura)	29 %
Partial removal leaving tumor *in situ*	40 %
Decompression	NA

LOCATIONS

Parasagittal meningiomas frequently involve **sagittal sinus** - middle and posterior thirds, if involved but patent (DSA is gold standard over MRV), cannot be sacrificed; therefore, total resection of these tumors is often impossible! (SRS vs wait until tumor completely occludes SSS)
See p. Op340 >>

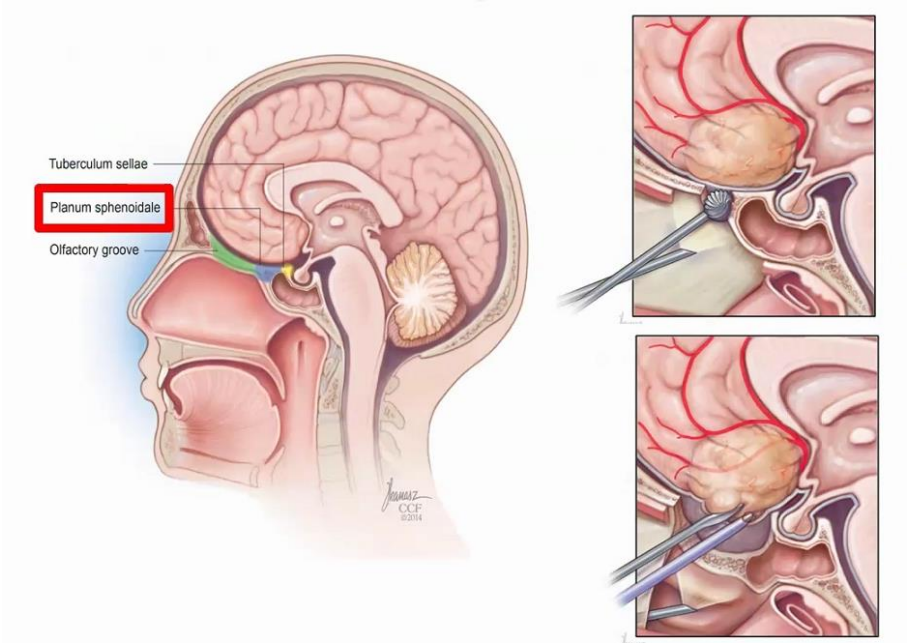
Skull base: using bipolar / Penfield #1, disconnect tumor at base from dura (disconnects blood supply).

Anterior Skull Base Meningiomas
See p. Op340 >>
Preop – evaluate olfaction and vision!

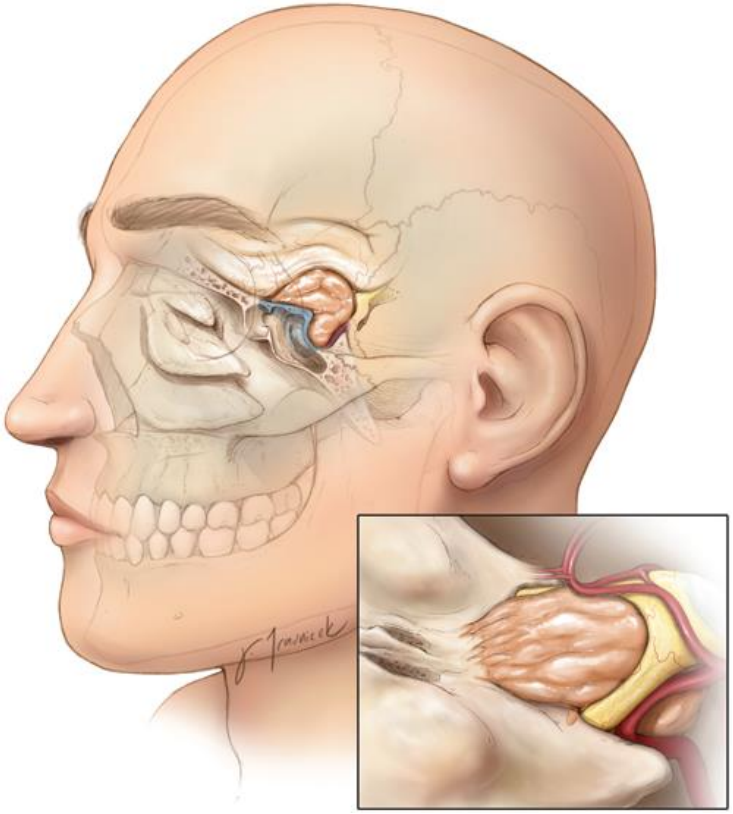
A. **Endoscopic (transnasal)** for small tumors with no optic canal invasion, no kissing carotids – early tumor devascularization, no retraction on brain, but anosmia, high-flow CSF leak (nasoseptal flap is a must).
B. **(Unilateral) Subfrontal vs interhemispheric craniotomy** (up to removing supraorbital rim – to minimize frontal retraction) - 50% preserves smell - bulbs and tracts are often displaced laterally.

Anterior → posterior:

1. Olfactory groove tumors – fed by ***ethmoidal arteries*** (branches of ophthalmic – do not attempt to embolize – risk of blindness!), push optic chiasm inferiorly.
2. Planum sphenoidale tumors
3. Tuberculum sellae / anterior clinoid tumors – push optic chiasm superiorly, recommend clinoidectomy for all!



Meningioma of the tuberculum sellae: extent of bone removal is highlighted in blue.
Inset: typical planum attachment, optical canal invasion, and displacement of the optic apparatus and surrounding vasculature:



Sphenoid wing meningioma see p. Op340 >>

1) outer-third tumors - if insinuates in sylvian tissue, adherence to sylvian veins - surgical cure is not possible.
2) middle-third tumors - cure is likely.

3) inner-third tumors - compress optic nerve, encase ICA and MCA, grow into cavernous sinus and optic canal - complete resection is not possible.

- need pterional to OZ craniotomy
- devascularize extradurally.
- tumor capsule incision at where tumor comes to surface → debulk → dissect away from vessels.
- careful when bipolarizing dura on temporal floor – trigeminal ganglion.

Tentorial and torcular meningioma see p. Op340 >>

- grow in infratentorial and supratentorial compartments
- ***anterolateral (AL) incisural meningioma***: pterional, subtemporal / retrosig approaches.
- ***posteromedial (PM) incisural meningioma***: occipital or supracerebellar infratentorial approaches.
- major supply - Bernasconi-Cassinari artery, artery of Davidoff & Schechter - should be coagulated thoroughly before one attempts to remove tumor.

Cavernous Sinus Meningioma

— **Asymptomatic** - observe.
— **Symptomatic** in otherwise healthy - resect by trained neurosurgeon.

- avoid injuring cranial nerves or carotid artery.

Cerebellopontine angle meningioma

- facial nerve
  - in acoustic neuromas, nerve lies anterosuperiorly to tumor - encountered late in surgery.
  - in CPA meningiomas, nerve may lie along posterior tumor edge.
- **SRS** is good alternative or adjuvant to surgery.

Clival and petroclival meningioma

- partial resection does not translate into any benefit and only renders further surgeries more difficult

a) anterior petrosal (Kawase) approach
b) posterior petrosal approaches
c) far lateral approach

ADJUVANT XRT

WHO grade I - no adjuvant therapy after resection even if subtotal (if not surgical candidate – primary XRT).
WHO grade III - adjuvant fractionated radiotherapy regardless of the extent of resection.
WHO grade II - optimal postoperative management depends on surgical resection extent:

a) after ***gross total resection***, EBRT appears not to affect progression-free survival and overall survival - observation is indicated (except patients > 55 yo do better with XRT) vs. IMRT
b) after ***subtotal resection***, EBRT or SRS improves tumor control and delays progression.

Indications for XRT (clinical benefit in many case series):

a) ADJUVANT therapy - for grade II-III / recurrent grade I tumors → IMRT

RTOG 0539: phase II study

Risk Group	Grade	Surgery/Recurrence	
Low	I	GTR (Simpson I-III)	Observation
	I	STR (Simpson IV-V)	
Intermediate	I	Recurrent	54 Gy to GTV + 1 cm (0.5 cm at natural barriers)
	II	GTR	
High	II	Recurrent or STR	54 Gy to GTV + 2 cm →60 Gy to GTV + 1 cm
	III	Any	

*GTV includes tumor bed and any residual nodular enhancement

Atypical meningioma post GTR: IMRT 54 Gy in 30fx with 1 cm margin (SRS/SRT is mostly from retrospective study).

Anaplastic meningioma (or STR or recurrent atypical): IMRT 60 Gy in 30fx with 2 CM margin is standard care (SRS is not commonly used)

If SRS is used - margin is 1-2 mm

b) PRIMARY treatment – when surgery is not feasible: elderly patients, skull base, parasaggital, some unresectable tumors; used less frequently in convexity or optic nerve sheath tumors → SRS
   - SRS as PRIMARY treatment - equivalent to a Simpson grade I resection
   - **15** Gy to 50% isodose line with GK (80% with LINAC) (atypical meningioma - include up to 1 cm of brain margin)
   - meningiomas tend to swell a lot after SRS

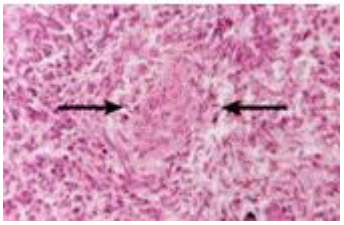
Prognosis - can be cured surgically
Significant predictors of poor outcome:
1) mitotic index > 6 (tumors with proliferation indices > 5% have ≈ 100% recurrence)
2) WHO 3
3) progesterone receptor score of 0 (i.e. absence of receptors)

Follow-up schedule (Dr. JD Day):
- annually for 5 years, then q2yrs for 3 yrs, then q3-5 yrs indefinitely.
- atypical meningiomas - q6mos for 5 yrs, then annually indefinitely.
- skull base meningiomas - annually indefinitely (to detect the recurrence while still small and good for SRS or else repeat surgery complication rate is much higher).

See O5 case >>

ASTROCYTOMA

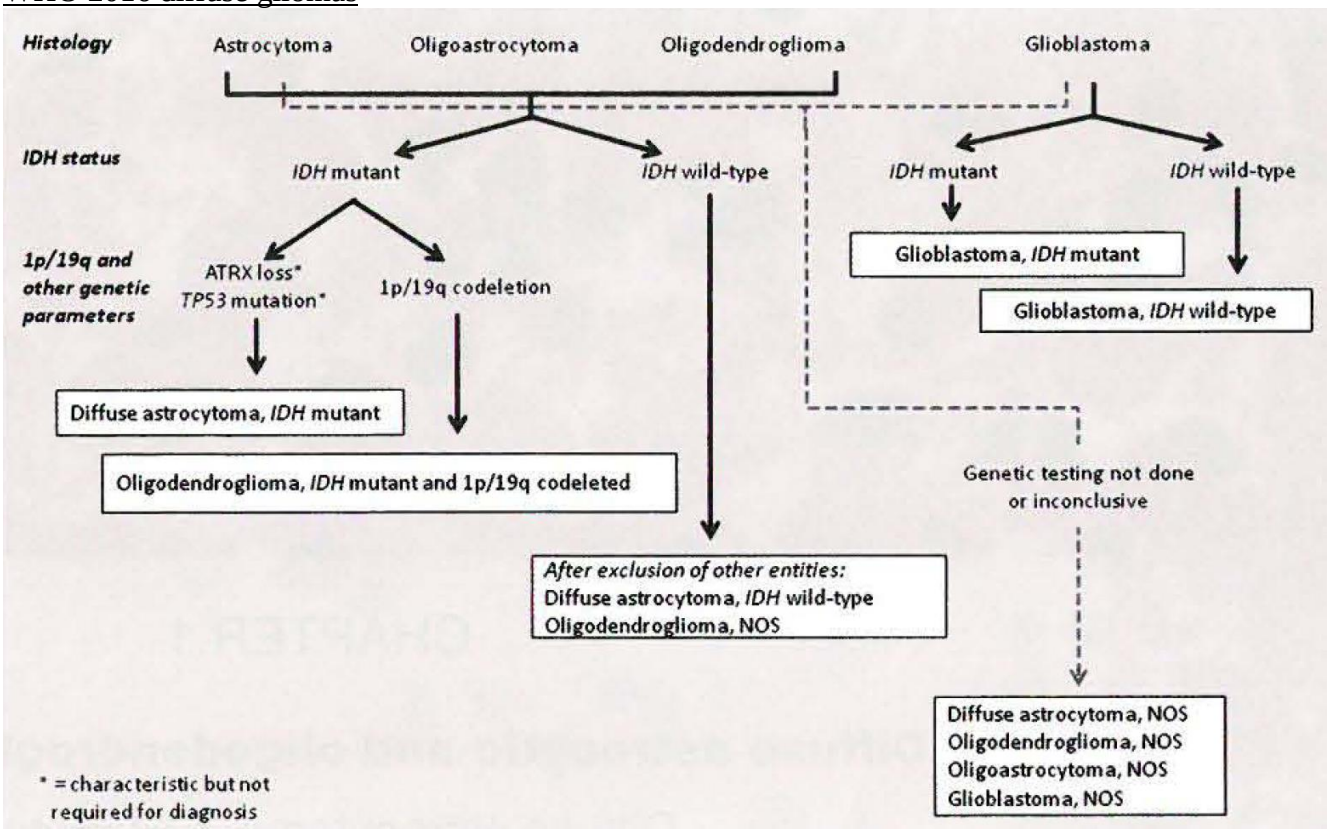
Most common (60%) primary CNS tumors in adults (second most common in children)!
4 histologic criteria - appearance in a predictable sequence:
1) nuclear atypia
2) mitoses (grade III)
3) endothelial proliferation (grade IV) - multi layering of endothelium (rather than simple hypervascularity or increased number of vessels); if proliferation is extreme, tuft forms ball-like structure - **glomeruloid body**:



4) necrosis

GLIOBLASTOMA MULTIFORME - endothelial proliferation and/or necrosis

WHO 2016 diffuse gliomas



Virtually every growth factor known to stimulate cell division has been identified as aberrantly expressed in GBM cell lines!
EGFR gene is most frequently amplified ***oncogene*** in astrocytic tumors!
CDKN2A gene is most frequently altered ***tumor suppressor gene*** in GBM!

LOW GRADE

Grade 1 (pilocytic astrocytoma, SEGA) are curable with **gross total resection** and do not need further therapy;

- if resection subtotal & tumor regrows → **radiotherapy**.

Grade 2 (oligo, diffuse astrocytoma, oligo-astrocytoma [diagnosis acceptable only if molecular markers N/A], PXA) are mostly incurable.

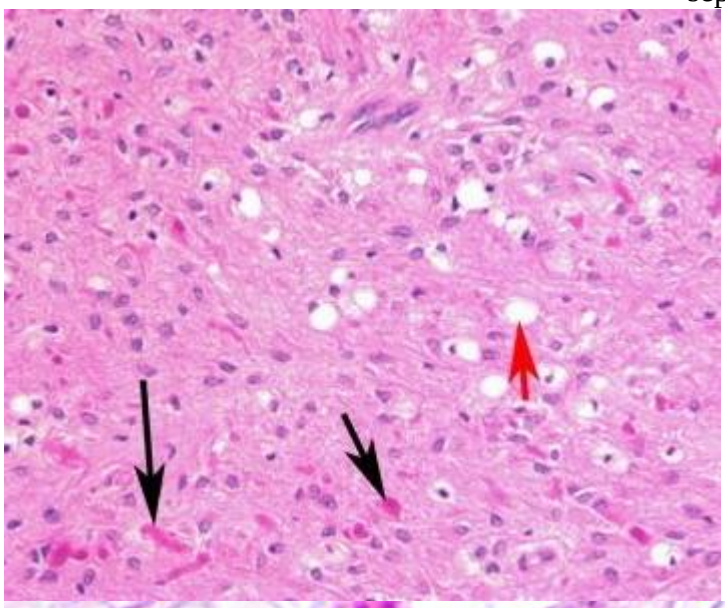
N.B. modern approach – maximal safe resection; if unlikely to resect > 50% of tumor then biopsy is warranted instead

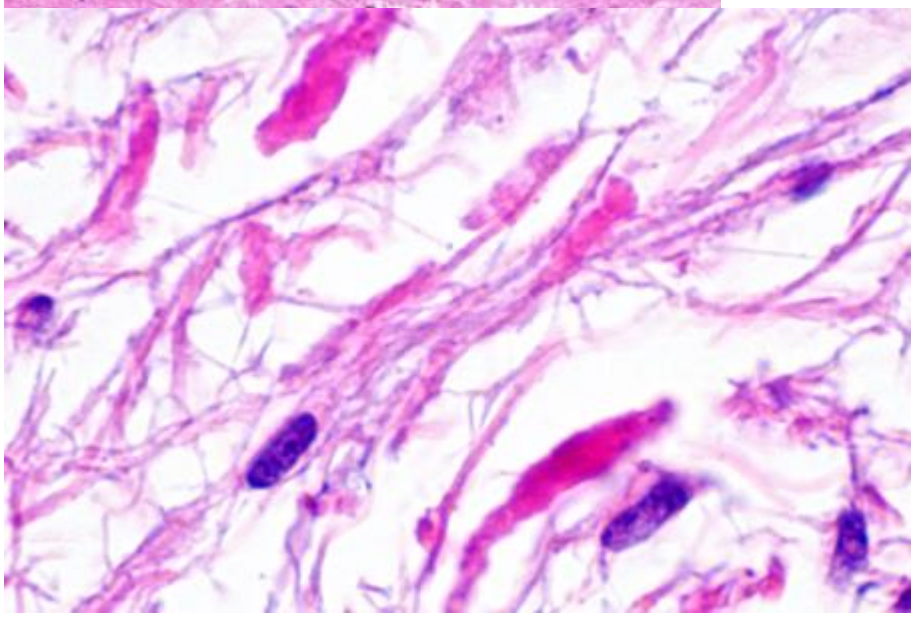
- completely **resected** grade 2 diffuse gliomas (astro, oligo) → **annual MRI** (i.e. hold off on adjuvant therapy, esp. in < 40 yo, oligo) vs. other experts add **radiotherapy*** **± chemotherapy** (esp. for > 40 yo or incompletely resected or IDH-wildtype)
  *Lower dose immediate (or delayed – for recurrence) radiotherapy (45–50.4 Gy)
- recurrence – **surgery** → **chemo** Temodar (for astro, oligo), PCV (for oligo).

PILOCYTIC ASTROCYTOMA (WHO grade 1; ***cerebellum of children***) - only astrocytoma which is **localized**, all other tumors are **infiltrative**

1) mature-appearing astrocytes
2) Ki67 < 1% - very slow growing!
3) macrocysts* + microcysts**
4) fibrillary astrocytes (with long, thin "hairlike" processes)
5) Rosenthal's fibers (elongated eosinophilic mass – modified process of astrocyte)

*e.g. cyst in cerebellum with enhancing mural nodule
** separates tumor from glial reaction

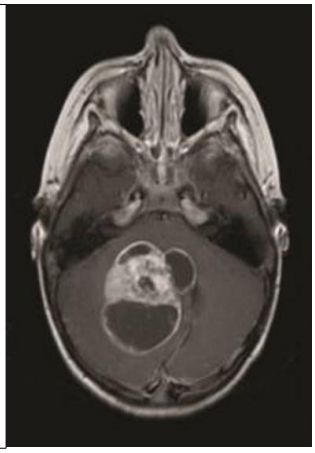




Bilateral optic nerve (esp. intraorbital optic nerve*) pilocytic astrocytoma is pathognomonic for NF-1! *vs. optic chiasm (worse prognosis) in non-NF1 cases

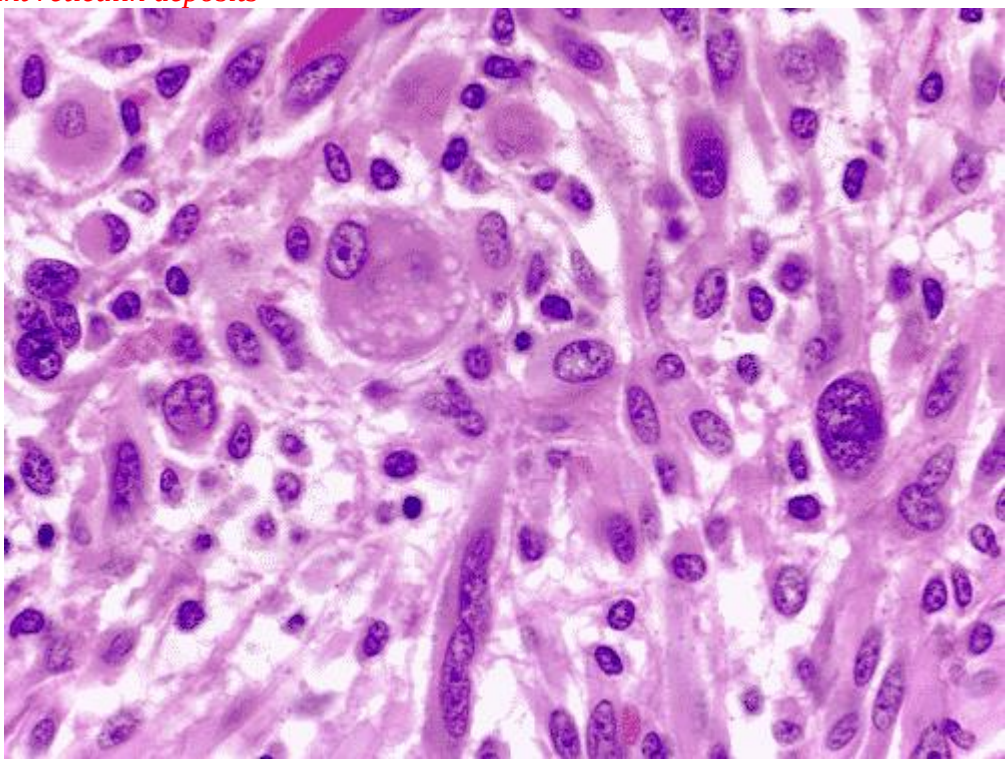
N.B. in **NF**, prognosis is similar (or better) to **non-NF patients** (but NF patients have ↑ risk of other tumors).

- most common glioma in children and adolescents.
- intensely enhancing (grade 1 !!!).



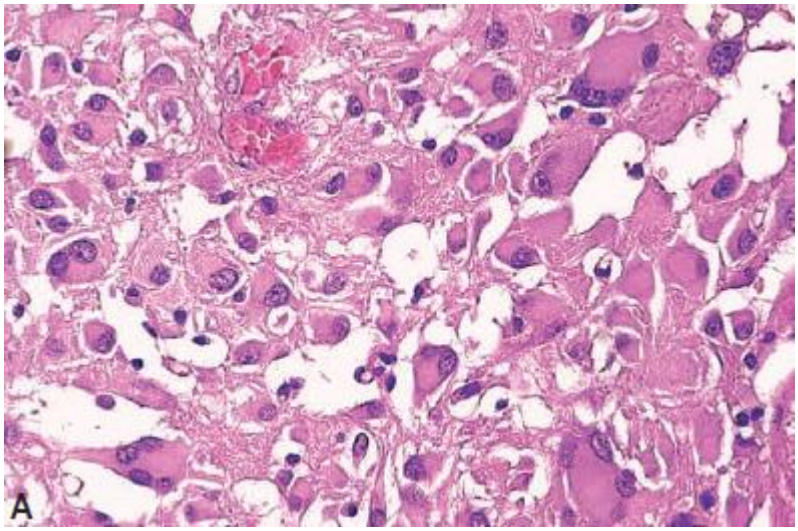
PLEOMORPHIC XANTHOASTROCYTOMA (grade 1 → WHO 2021 grade 2); may be as cyst with nodule:

1) astrocytic *pleomorphism*
2) *lipidized* giant cells.
3) *abundant reticulin deposits*



- BRAF V600E mutation!!!! (plus, no IDH mutation)
- intensely enhancing

SUBEPENDYMAL GIANT-CELL ASTROCYTOMA (SEGA) (WHO grade 1; unique to ***tuberous sclerosis***; lateral wall of 3rd ventricle) - *giant, multinucleated globoid cells*.



- imaging – marked contrast enhancement.
- treatment – surgery / mTOR inhibitors (everolimus).

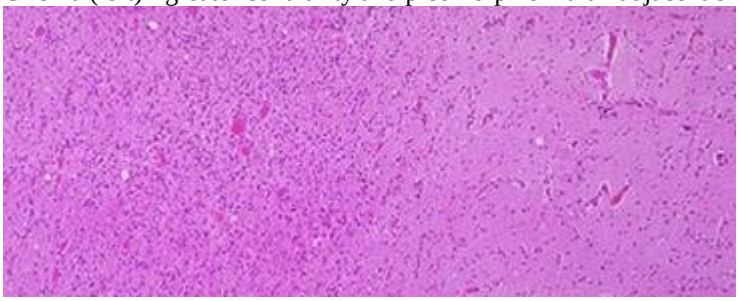
DIFFUSE (formerly - LOW-GRADE) ASTROCYTOMA (WHO grade 2) - slight hypercellularity, uniform cells (resemble mature)

Normal astrocytes show no H&E-stainable cytoplasm that is distinct from the background neuropil. **Reactive astrocytes** are defined by enlarged nuclei and the presence of stainable, defined cytoplasm, culminating in the **gemistocyte**, which has a mass of eosinophilic cytoplasm, often an eccentric nucleus, and cytoplasm that extends into fine processes

- **gemistocytic astrocyte** - hypertrophic reactive astrocyte with eosinophilic greatly swollen cytoplasm (abundant glial fibrils) and eccentric nucleus; *> 20% gemistocytes* → course similar to *ANAPLASTIC ASTROCYTOMA*

"Gemistocytes are bad"

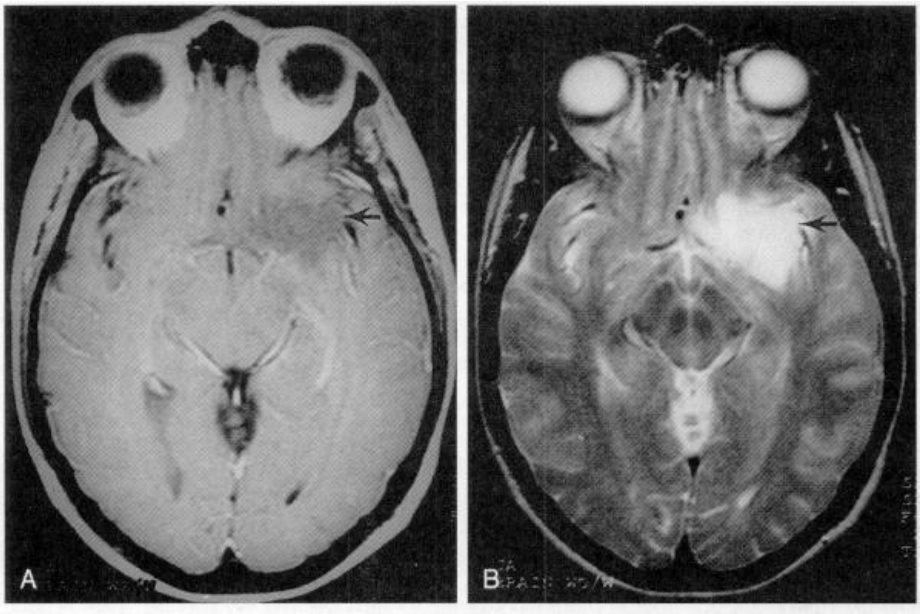
Glioma (left) - greater cellularity and pleomorphism than adjacent brain (right), margin is not distinct:



No *LOW-GRADE ASTROCYTOMAS* after age 45

N.B. diffuse astrocytoma, IDH-wildtype is an uncommon diagnosis

DIFFUSE LOW-GRADE ASTROCYTOMAS do not enhance (best MRI sequence – **FLAIR**)! Contrast enhancement is sign of malignancy!



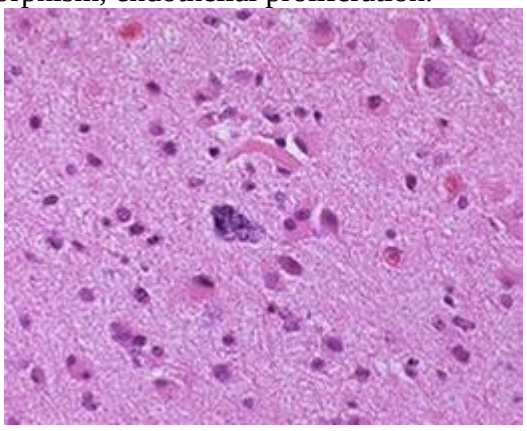
Treatment – **surgery**; if incompletely resected → local field (1-2 cm margin) **irradiation**.

- *recurrence* → tumor resection → chemotherapy.

N.B. completely resected grade 2 diffuse gliomas (astro, oligo) – watch and wait (i.e. hold off on adjuvant therapy)

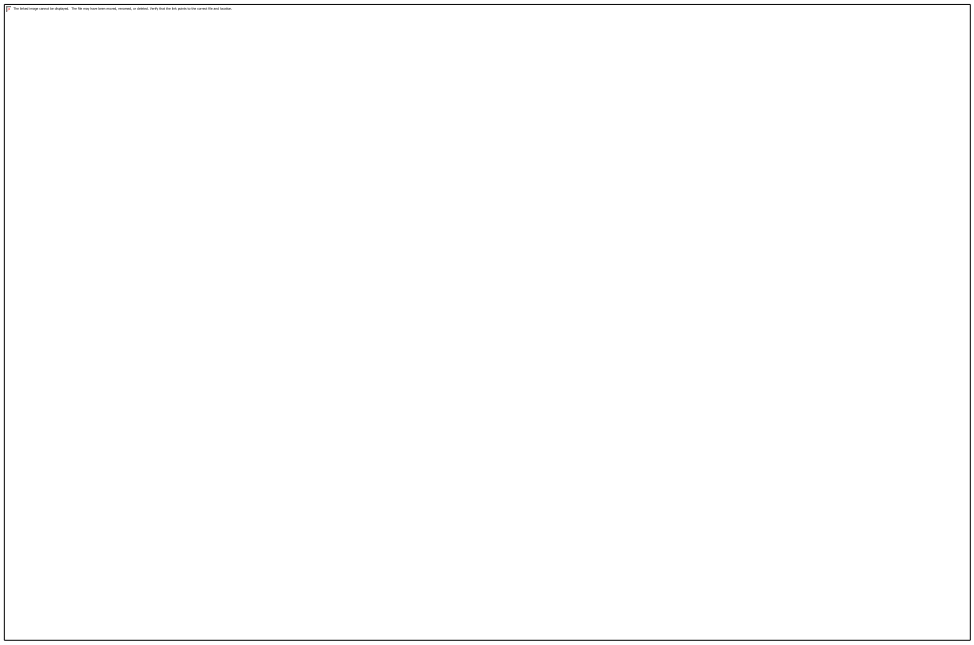
HIGH GRADE

ANAPLASTIC ASTROCYTOMA (WHO grade 3) - moderate hypercellularity, increased mitoses, anaplasia, nuclear pleomorphism, endothelial proliferation.



GLIOBLASTOMA (WHO grade 4) - marked cellularity, high proliferation indices, anaplasia, foci of necrosis (!!!) accompanied by pseudopalisading (tumor cells crowded along edges of necrotic region).

N.B. necrosis is no longer a requirement for grade 4 (but if present confirms grade 4)



Primary (de novo), type 2 *glioblastoma* typically found in older patients with short clinical history; prognosis is worse!

- spread across corpus callosum.
- *GLIOBLASTOMAS* with p53 mutation are *secondary glioblastomas* (type 1) - occur in younger patients whose tumors have progressed from lower grade astrocytoma.

90% GBMs are primary; 10% - secondary

- IDH1 mutation (means ≥ grade 2 tumor)
  - ***first most common mutation*** to occur in gliomas
  - significantly better prognosis (survival improved 3-fold)
  - mostly in young patients with secondary GBM

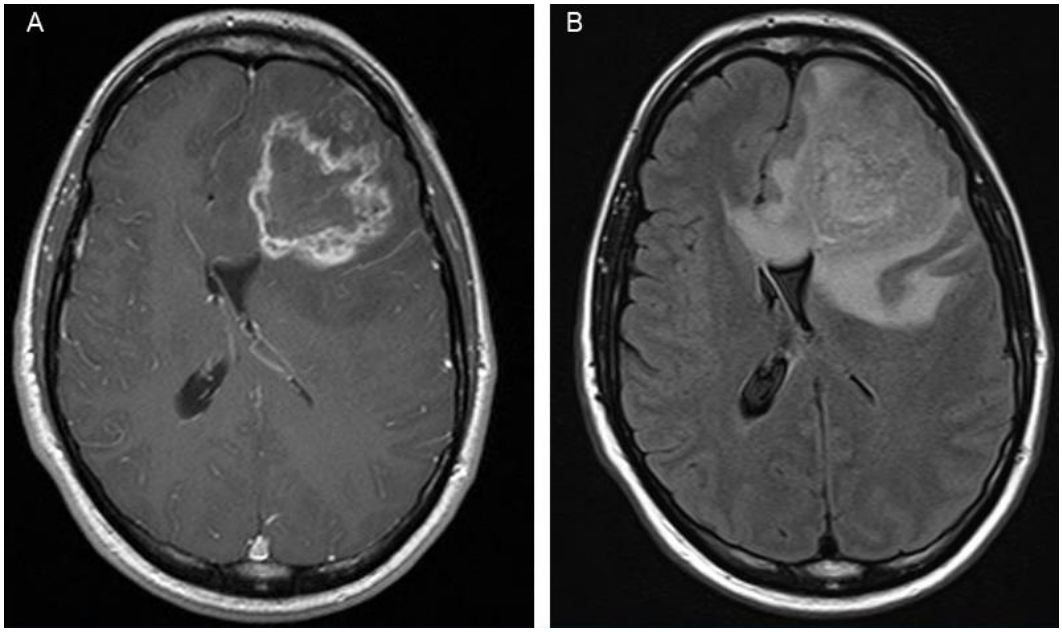
WHO 2021: GBM with IDH mutation is called *astrocytoma, IDH-mutant, grade 4*
WHO 2021: GBM without IDH mutation is called *glioblastoma, IDH-wildtype*

N.B. in WHO 2021, term "glioblastoma" is reserved only for IDH-wildtype grade 4 astrocytomas! (i.e. glioblastoma = worst of the worst)

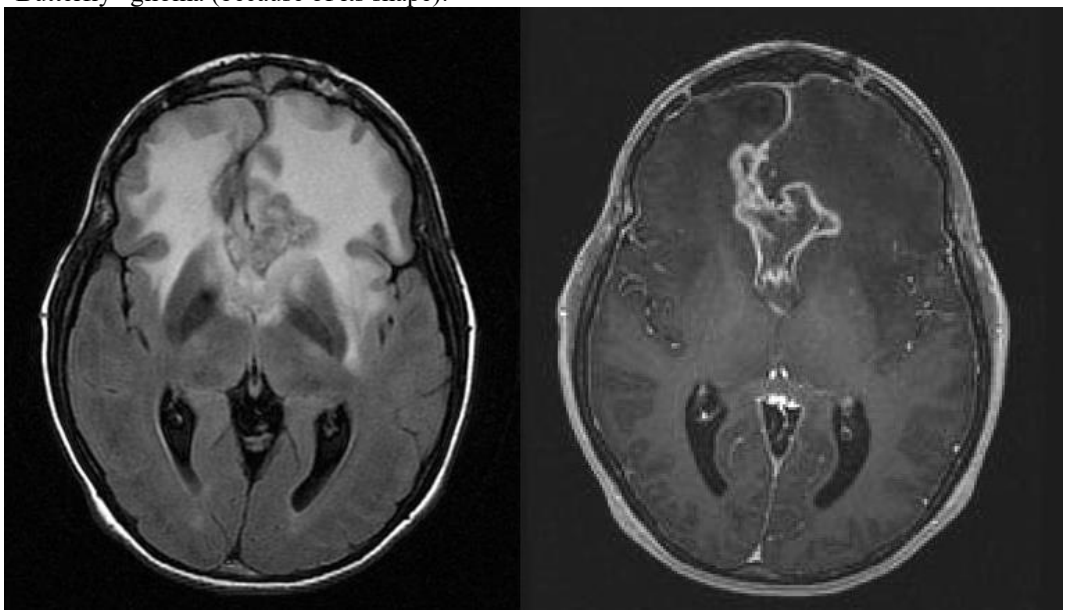
- EGFR gene amplification = GBM or tumor (even if otherwise looks like low grade) will behave as GBM.
- WHO 2021: IDH-wildtype diffuse astrocytic tumors in adults, presence at least one (TERT promoter mutation / EGFR gene amplification / combined gain of entire chromosome 7 & loss of entire chromosome 10 [+7/−10]) - sufficient to assign grade 4.

<u>Diagnosis</u>

- enhance heterogeneously in irregular ring configuration, surrounding edema:



"Butterfly" glioma (because of its shape):



TREATMENT

Multidisciplinary team

- cornerstone of therapy is **surgery**: maximal possible resection (**debulking**) → STUPP protocol (start at ≥ 2 weeks postop): local field **irradiation** (60 Gy; 2-3 cm margin) + **chemotherapy** (TMZ). see Stupp protocol >>
- *recurrence* → tumor resection / LITT / SRS → chemotherapy.
- chemotherapy: (*GBM is chemoresistant*)
  - oral TEMOZOLOMIDE - standard of care for newly diagnosed GBM; given during and for 6 months following radiotherapy; GBM with **methylated MGMT gene promoter** is more likely to respond.
  - intravenous CARMUSTINE (incl. implantable Gliadel® wafers)
  - LOMUSTINE + PROCARBAZINE + VINCRISTINE
  - BEVACIZUMAB (anti-VEGF antibody) - FDA approved for recurrent GBM.

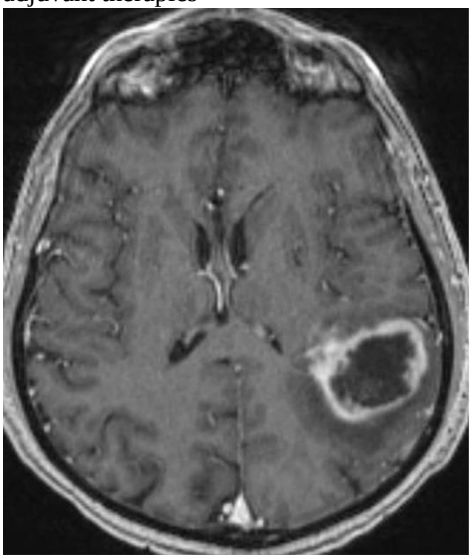
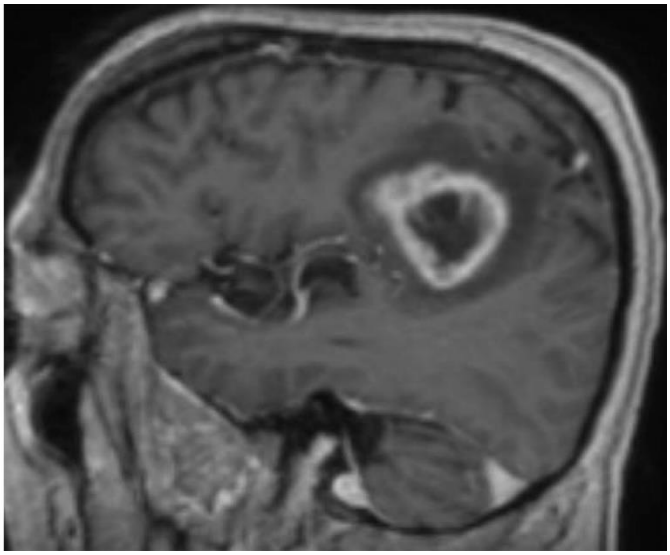
anti-VEGF is standard of care for recurrent GBM

For patients > 70 yo with non-methylated MGMT, do just XRT (no TMZ)

Nonoperative HGGs (→ noninvasive tests vs. biopsy → adjuvant treatment)

poor KPS
multifocal / thalamic / corpus callosum / deep insular tumor
N.B. surgery has no role in diffuse intrinsic **pontine*** tumors!
*vs. **midbrain**, **medulla** (esp. focal or exophytic) → surgery
HGGs infiltrating eloquent regions frequently leads to postop worsening of neurologic function (despite anatomical preservation of these cortices and tracts) - survival time is too short to recover from "temporary" neurologic deficits!
If *gross total resection is not anticipated*, high risk of postop hemorrhage!

Angular gyrus area HGG - despite awake mapping, real risk of permanent speech dysfunction – better biopsy → adjuvant therapies

N.B. SRS is not recommended for **newly*** **diagnosed** GBM!

*vs. **recurrent** GBM (SRS is an option)

Recurrence (repeat *radiation has no clear role*) → **re-resection*** (may leave GammaTile Cesium-131 or carmustine Gliadel® wafers inside cavity**) / **LITT** / **SRS** → **chemotherapy** (Avastin or Temodar), tumor treatment fields Optune helmet

*make sure KPS is good + no bevacizumab within 4 weeks of surgery
**make sure no connection to ventricles!

MULTIFOCAL / MULTICENTRIC GLIOBLASTOMA

Glioblastoma with multiple localizations (mGBM):

a) **multifocal** - enhancing lesions present a connection visible on FLAIR
b) **multicentric** (rare) - absence of a clear dissemination pathway on MRI

Remove dominant lesion (old dogma – only biopsy)
EOR may positively influence survival in mGBM.
Surgical resection can be a reasonable option when performance and access to adjuvant treatment can be preserved.

FOLLOW UP POSTOP

Low-grade astrocytomas
MRIs: at 3 mos postop → q6 mos x 2 → annually.

- may do MRI without contrast (e.g. if patient is allergic to gadolinium) – if see recurrence (FLAIR signal, diffusion restriction), then add gadolinium.

High-grade astrocytomas

MD Anderson protocol:

During chemotherapy - MRIs q2 months.

After completion of chemotherapy - MRIs q2 months for 1 yr → q3 months for 1 year → q4 months for 1 year → q6 months indefinitely.

N.B. look for pseudoprogression vs. true progression (pMRI, TRAM, MRS, and other protocols)

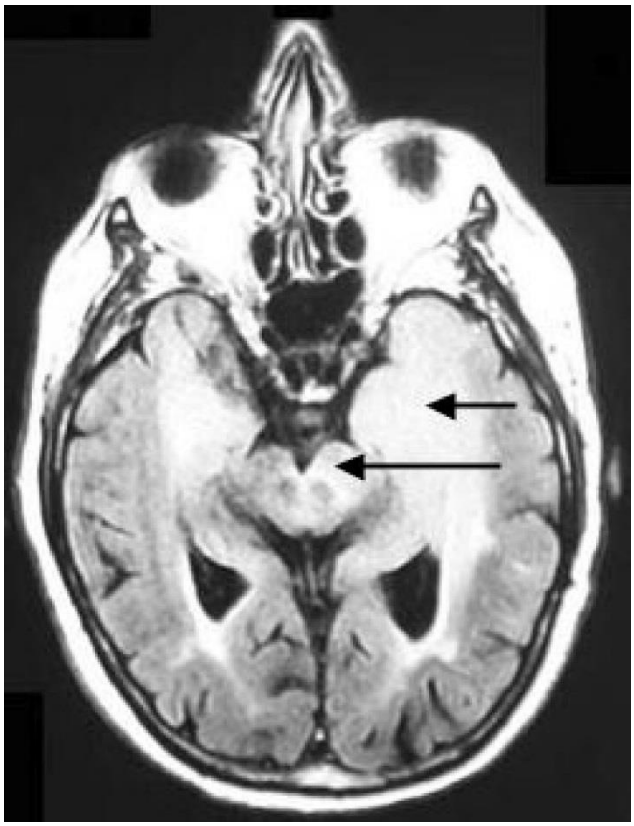
See O3 case >>
See O4 case >>

GLIOMATOSIS CEREBRI

- diffuse white matter spread of glioma (grade 2 to 4) - entire brain infiltrated with tumor cells.

- it is no longer a separate entity in WHO 2016, rather being considered a growth pattern found in many gliomas, including IDH-mutant astrocytic and oligodendroglial tumors as well as IDH-wild-type glioblastomas.
- clinical syndrome - dementia, personality change, seizures.
- **MRI** - increased FLAIR/T_2 signal in diffuse areas of white matter and cortex; tumor is infiltrative (no enhancing mass!); contrast enhancement is later phenomenon.
- **biopsy** - tumor from low grade to glioblastoma.
- treatment - whole-brain radiotherapy (50 Gy) + chemotherapy (TMZ).
- very poor prognosis

FLAIR MRI:



BRAINSTEM GLIOMAS

- prognosis is highly variable:

1. Focal tectal – most commonly *LOW-GRADE ASTROCYTOMAS*; **best prognosis** (median survival > 50 months).

2. Diffuse intrinsic pontine (80% of all brain stem tumors); **worst prognosis** (median survival < 12 months) – most commonly *ANAPLASTIC ASTROCYTOMAS* producing diffuse infiltration in pons → extending throughout brainstem → spinal cord and cerebellum; exophytic growth is seen in 2/3 cases.

3. Focal cervicomedullary – most commonly *LOW-GRADE ASTROCYTOMAS*.

Predominantly tumors of childhood!

- risk factor – ***neurofibromatosis***.

Diagnosis:

- **MRI** - expansile, infiltrative process (enlarged brainstem).
- **tissue confirmation** is frequently not feasible (unless exophytic component exists - even then, biopsy cannot always be obtained);
  - biopsy is not required for diffuse intrinsic pontine gliomas (diagnosis can be made by MRI alone; histologic findings do not influence treatment).
  - biopsy for tectal gliomas is reserved for progressive symptomatic cases - can be done endoscopically, e.g. during ETV.

Treatment

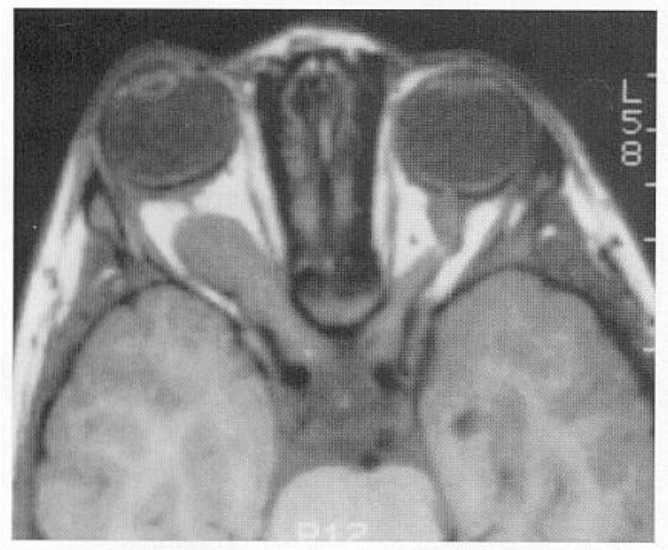
N.B. surgery has no role in diffuse intrinsic **pontine** tumors (short clinical history, nonenhancing; if features are different → biopsy; if biopsy insisted (for participation in trials) – via middle cerebellar peduncle)

Adults with tectal or cervicomedullary tumor, or with *mild symptoms of long duration* → observation; ↑symptoms / radiographic progression (esp. appearance of aggressive features such as enhancement) → **shunting** (ETV or VPS), (endoscopic) **biopsy** → **radiotherapy** or endoscopic **resection**

- **surgery** is most appropriate for benign *focal*, *dorsal exophytic*, *cystic* tumors; most suitable locations - cervicomedullary and tectal; some experts say that open surgery for tectal gliomas is obsolete (vs. endoscopic resection).
- chemotherapy efficacy has not been proved - cannot be recommended! (may benefit in some recurrences).

OPTIC GLIOMAS

Marked expansion of right optic nerve (NF-1):



Differential diagnosis – *MENINGIOMA* ("tram-track" sign - enhancement of nerve–optic sheath periphery).

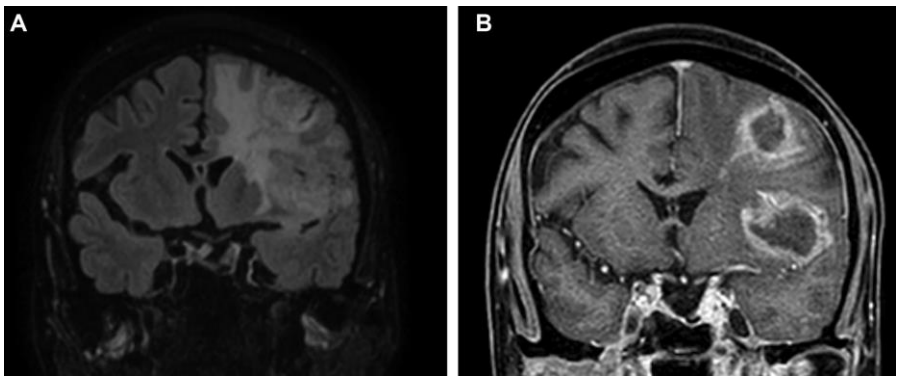
Treatment

- optic nerve gliomas:
    a) no severe symptoms → **observation**.
    b) proptosis, progressing visual decline → **radiotherapy**.
    c) if eye is already blind (unilateral tumor of ***optic nerve***) → **resection** (prevents recurrence or extension through chiasm).
        – transcranial approach.
        – complete resection of tumor-infiltrated nerve from chiasm to globe (sparing globe for cosmetic effect).
- chiasmatic / hypothalamic gliomas → **radiotherapy** (45-55 Gy in daily 1.8-Gy fractions).
  N.B. resection of chiasm with resultant blindness is never indicated!

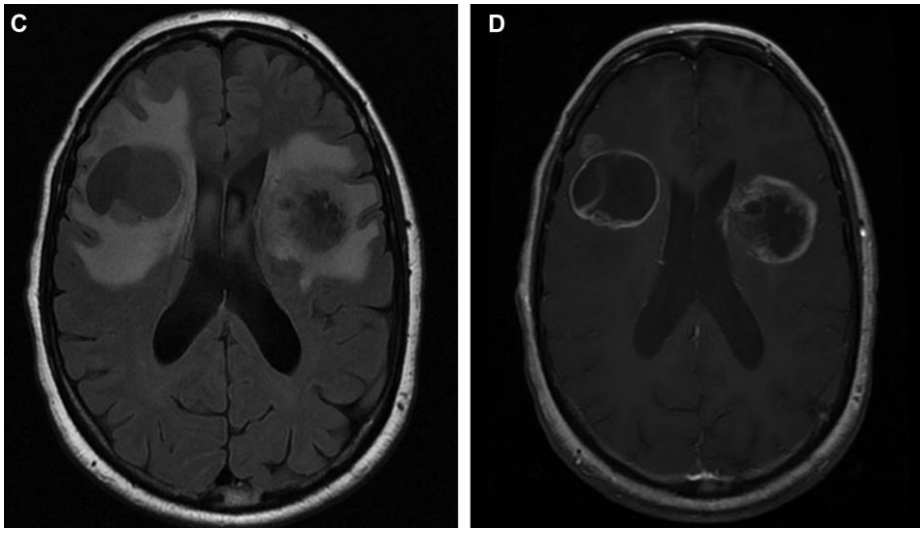
GLIOBLASTOMA WITH MULTIPLE LOCALIZATIONS (MGBM)

a) **multifocal** - enhancing lesions present a connection visible on FLAIR
b) **multicentric** (rare) - absence of a clear dissemination pathway on MRI

Multifocal:



Multicentric:



Role for Surgical Resection

Filippo Friso. Is There a Role for Surgical Resection of Multifocal Glioblastoma? A Retrospective Analysis of 100 Patients. Neurosurgery 89:1042–1051, 2021

Incidence of mGBM was 16%

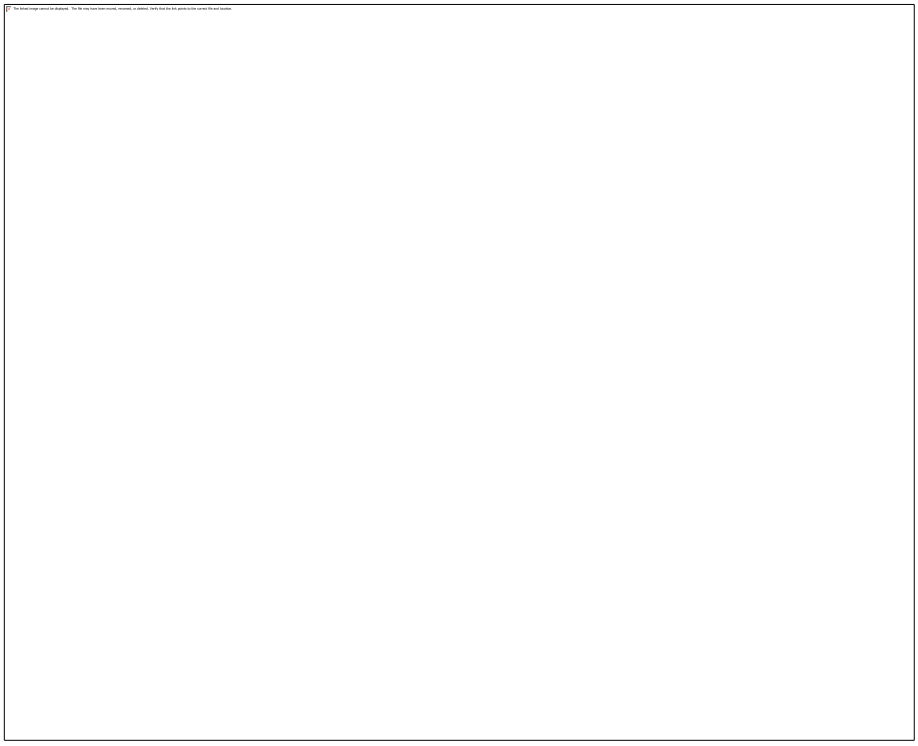
- 100 patients underwent:
  - 15% **GTR** (no enhancing residual) → median OS 17 mos
  - 14% **STR** (< 30% residual) → median OS 11 mos
  - 32% **PR** (> 30% residual) → median OS 7 mos
  - 39% **biopsy** (> 75% residual) → median OS 5 mos

EOR may positively influence survival in mGBM.
Surgical resection can be a reasonable option when performance and access to adjuvant treatment can be preserved.

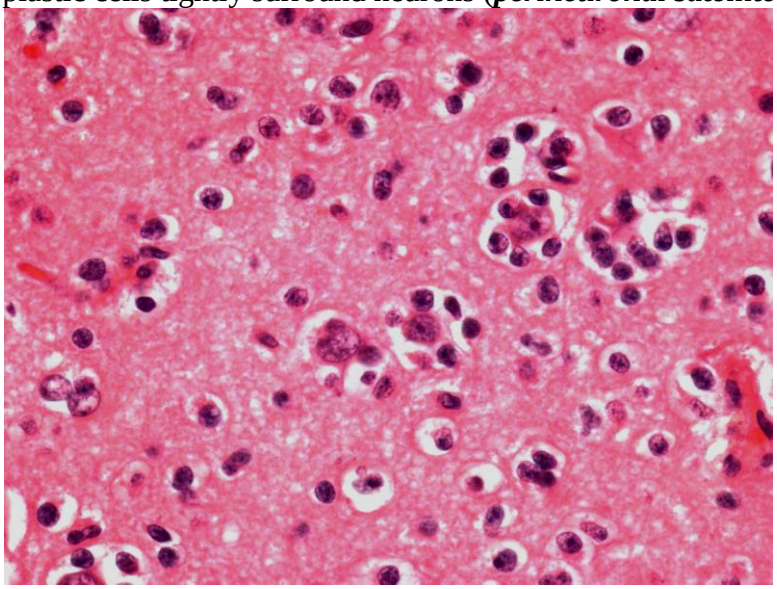
OLIGODENDROGLIOMAS

- definitive diagnosis (a must mutations!) - IDH1/2 mutation + 1p19q co-deletion
  - if histology looks like oligo, but IDH-wild type – call astrocytoma!
- most "benign" of gliomas – never grade 4 (but infiltrative nature - *surgical cure remains unlikely*)!

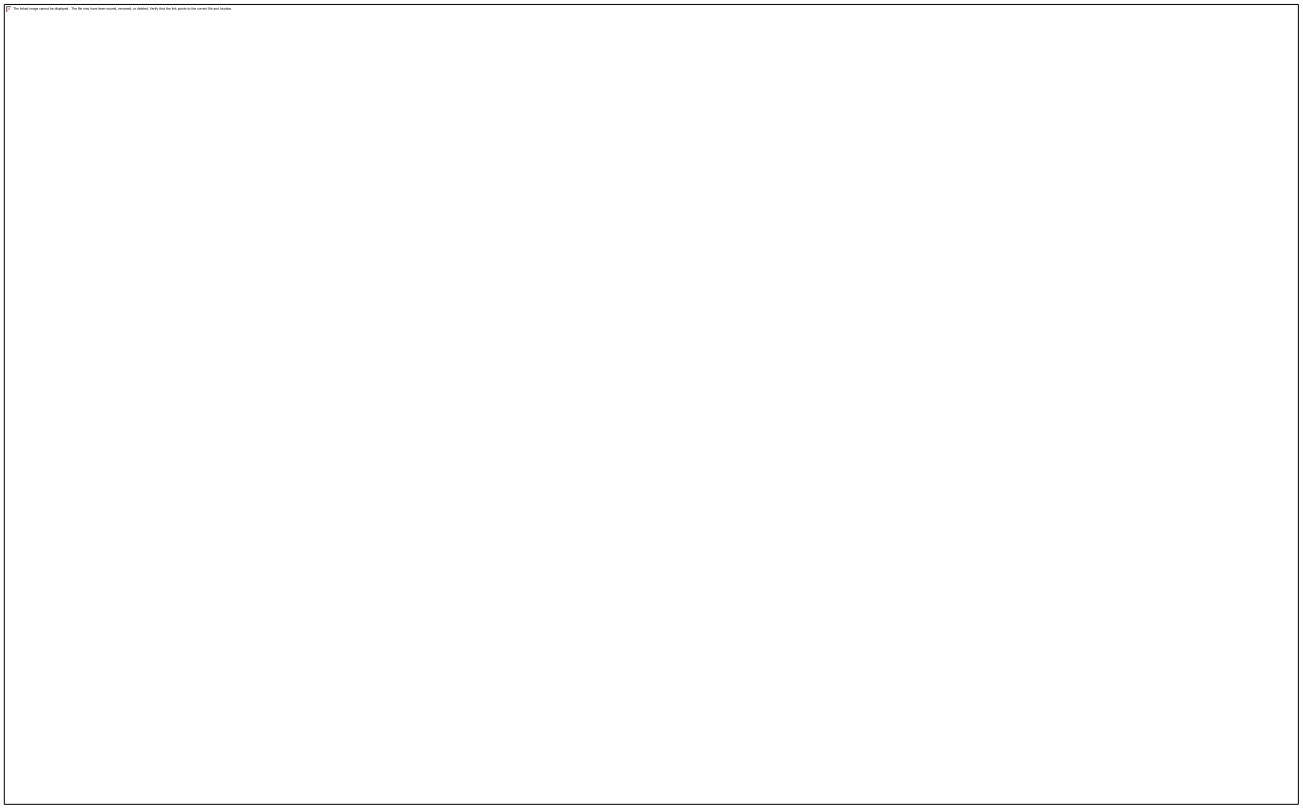
  Seizures, **hemorrhage**, and **calcifications** are more common with oligodendrogliomas than other gliomas!
- very cellular - monotonous “fried egg” cells + branching *network of anastomosing capillaries* (*“chicken-wire”*): (≈ *CENTRAL NEUROCYTOMA*)



- neoplastic cells tightly surround neurons (***perineuronal satellitosis***):



- 90% have **calcifications** (micro, macro); do not enhance (unless anaplastic):



- treatment:
  Observation ÷ aggressive multimodal treatment
- completely resected, esp. < 40 yo → **serial MRI**.
- *surgical cure remains unlikely*! anaplastic / recurrence / incomplete removal → **radiotherapy**.
- most sensitive to chemotherapy of all gliomas!!! – for anaplastic, recurrences
  esp. **PCV combination** (**PROCARBAZINE**, **LOMUSTINE**, **VINCRISTINE**) - unusually beneficial against *OLIGOS*.
- prognosis - much better than for *ASTROCYTOMAS*!
  1. **Oligodendroglioma** (grade II) ≈ 80%; median survival 6-10 yrs.
  2. **Anaplastic oligodendroglioma** (grade III) ≈ 20%; median survival 2-4 yrs.
     combined loss of 1p/19q is significant predictor of longer survival (100% response to chemotherapy).

  N.B. late progression of disease is common (5-year survival time used to indicate "cure" in other cancers is not relevant for oligodendrogliomas).

OLIGOASTROCYTOMAS

- some tumors are truly mixed (both cell types arise from common precursor - *oligodendrocyte type-2 astrocyte, s. O2A cell*).

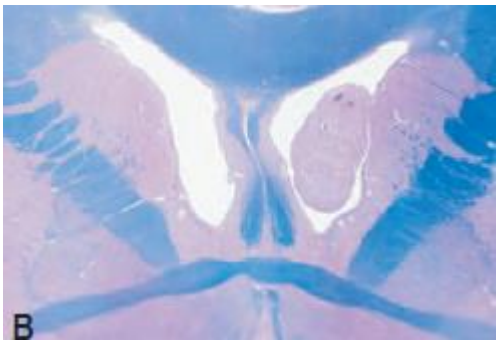
EPENDYMOMA

Pediatric 4th ventricle tumor → obstructive hydrocephalus ± brain stem compression

WHO 2021

1. **Supratentorial** ependymoma
2. **Posterior fossa** ependymoma
3. **Spinal** ependymoma

4. **Myxopapillary** ependymoma (WHO 2016 grade I → now WNO 2021 grade 2; young adult low-grade tumors in ***conus medullaris, cauda equina*** and ***filum terminale***)
5. **Subependymoma** (WHO 2016 grade I) - features of both **ependymoma** and **astrocytoma** – tumor attached to ventricular wall:

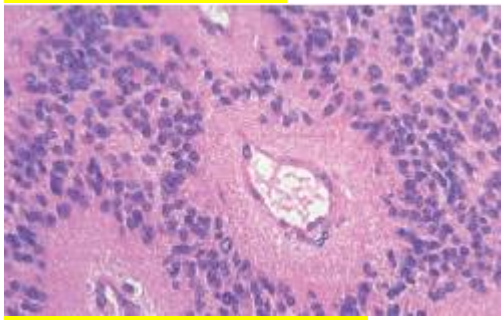


WHO 2016

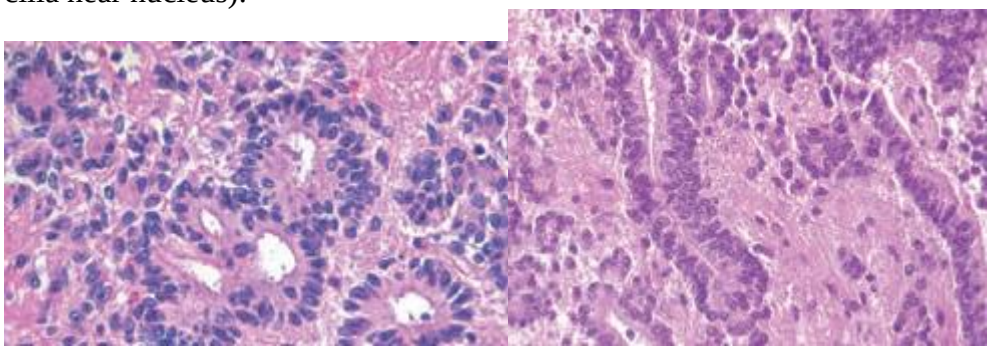
1. **Ependymoma** (WHO grade II)
2. **Anaplastic ependymoma** (WHO grade III)

- now pathologist can choose to assign either CNS WHO grade 2 or grade 3 (former anaplastic ependymoma) to an ependymoma, according to its histopathological features.

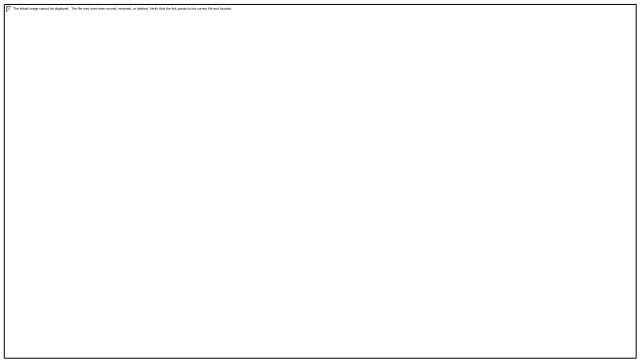
- 100% IDH-1 negative.
- 2/3 are located in posterior fossa
- most frequent (56-70%) intramedullary spine tumors
- not invasive (displaces brain parenchyma)
- do not proliferate rapidly – slow growing
- 90% do not metastasize; only ≈ 12% spread via CSF (esp. high-grade posterior fossa tumors) – **"drop metastases"** – do spinal MRI!
- acellular, fibrillary eosinophilic halo surrounding **blood vessel** (PERIVASCULAR PSEUDOROSETTES):



- EPENDYMAL ROSETTES - ependymal cells radially aligned about **central lumen** with long, delicate processes (cilia) extending into lumen; cells contain **BLEPHAROPLASTS** (basal bodies of cilia near nucleus):



MRI - discrete, heterogeneous mass with variable enhancement**; add spinal MRI!!!**



Treatment

- avoid EVD (often possible) → upward herniation
- **resection** via midline suboccipital craniectomy
  Gross total resection may not be possible when invasion of the floor is extensive, or when tumor extends through the foramen of Luschka (bradycardia may prevent GTR – place *pacing electrodes* on anterior chest preop!)
  N.B. most relapses are local! - *inability to eradicate primary tumor* remains single most important factor leading to treatment failure!
  - advise patients pre-op of the likelihood of need for G-tube and tracheostomy (may be temporary).
  - **postoperative MRI** within 72 hours of surgery - unexpected residual lesion → ***second-look surgery*** (vs. residual medulloblastoma – treat with chemoradio).
  - 2 weeks postop, **perform LP** - 10 cc of CSF for cytology: any number of malignant cells by definition there are drop mets; if negative, it is not as helpful (sensitivity is not high).
    - CSF from an EVD is not as sensitive as LP.
- standard postoperative LOCAL (1-2 cm margin, 50-55 Gy) **radiotherapy** substantially improves survival (modern trend – even for kids < 3 yo; adults with GTR may be observed postop).
  - aggressive *anaplastic features* or *residual tumor* → whole-brain radiation.
  - documented *leptomeningeal dissemination* → craniospinal axis radiation.

In summary, majority need postop radiation (at least, tumor bed in posterior fossa)
Chemotherapy has no role currently!

Prognosis

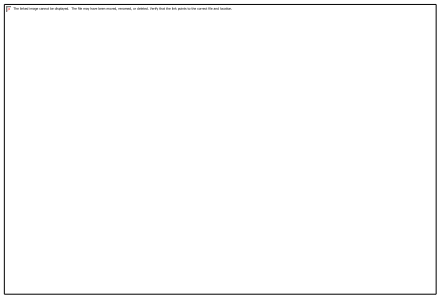
- extent of tumor resection is most important prognostic factor + *younger patient*, worse prognosis!
- prognosis is worse than medulloblastoma (later - exquisite sensitivity to adjuvant therapy).

RELA fusion-positive ependymoma; in WHO 2021 it is called **ZFTA fusion-positive ependymoma** - majority of supratentorial ependymomas in childhood - worst prognosis of all molecular subtypes.

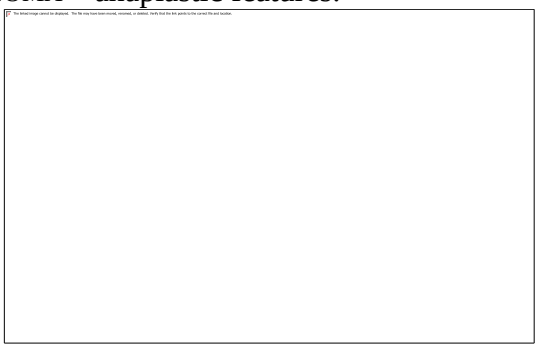
CHOROID PLEXUS PAPILLOMA

Lateral ventricles of **children**! (4^{th} ventricle in **adults**)

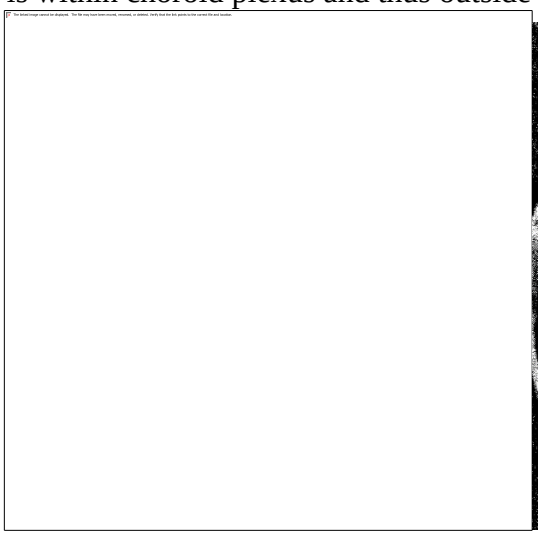
- often pedunculated
- does not invade brain parenchyma
- histologically ≈ normal; except epithelium is more flattened than normal

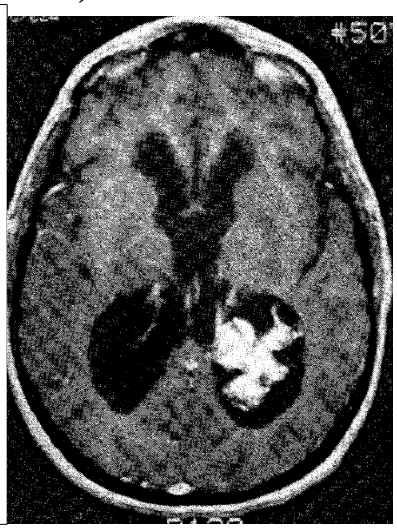


CARCINOMA – anaplastic features:



- occasionally may spread via CSF (more common with CARCINOMA)
- increased CSF secretion by tumor cells (up to 4 times of normal) → HCP
- imaging (craniospinal!) - lobulated, 'cauliflower-like' mass with *marked contrast enhancement* (papilloma is within choroid plexus and thus outside BBB):





- ***punctate*** **calcifications*** (20%)

  *vs. *global calcification* - more indicative of CARCINOMA!

High incidence of surgical cure! (60% still need VPS postop); subtotal resection / carcinoma → chemo / radio

Extremely **vascular**! (preop **angiography & embolization!!!!** – true for all intraventricular tumors)

- determination of **tumor stalk** location is crucial – dictates surgical approach! (interhemispheric vs transcortical)

EMBRYONAL TUMORS

PNET, MEDULLOBLASTOMA

- very malignant (WHO grade 4) *EMBRYONAL TUMORS*

- 75% in children < 15 years
- genetic syndromes (geneticist consultation!) *Turcot syndrome, Li-Fraumeni syndrome, Gorlin syndrome, blue rubber-bleb nevus syndrome, Rubinstein-Taybi syndrome*
- with H&E staining, it appears as blue tumor.

- dense cellularity – cords of primitive **small "blue" cells** ("Indian files") with ↑↑↑**mitotic index** and ↑↑↑ **nuclear-cytoplasmic ratio** (i.e. minimal perceptible cytoplasm).
- Homer-Wright rosettes - pseudorosettes - circular arrangement of tumor cells around area of fibrillarity (tangled eosinophilic cytoplasmic [neuritic] processes; no lumen or vessel);
  - evidence of ***neuroblastic*** differentiation
  - found in MEDULLOBLASTOMA (20% cases), PNET, NEUROBLASTOMA (15-50%)

- propensity to dissemination via CSF (one of most feared complications of *MEDULLOBLASTOMA*!!!) – opaque subarachnoid space with granular appearance ("*sugar coating*") → ***spinal drop metastases***!!!
- 5% patients have systemic metastases (esp. to long bones - 80%), esp. **large cell medulloblastoma** – worst prognosis!

SUPRATENTORIAL (OR BRAINSTEM) (4%) - PRIMITIVE NEUROECTODERMAL TUMOR.
Term "PNET" was eliminated in WHO 2016 classification

INFRATENTORIAL (i.e. CEREBELLAR) (96%) - MEDULLOBLASTOMA; most common (20-30%) childhood brain tumor!!! (75% in cerebellar vermis)

- loss of 17p (30-40% *MEDULLOBLASTOMAS*)

WHO 2021 CLASSIFICATION

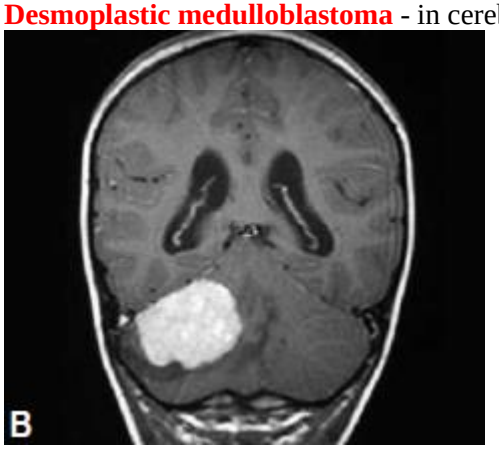
1. Medulloblastoma, WNT-activated
2. Medulloblastoma, SHH-activated and TP53-wildtype
3. Medulloblastoma, SHH-activated and TP53-mutant
4. Medulloblastoma, non-WNT/non-SHH

Diagnosis

High risk of CSF-borne metastases - **preop MRI of craniospinal axis**
(postop blood may give artefacts)

- hyperdense on plain CT
- homogeneous *enhancement*; no calcifications:

Desmoplastic medulloblastoma - in cerebellar hemisphere of adults:



Differential - *EPENDYMOMA, CHOROID PLEXUS PAPILLOMA* - commonly contain **calcifications**.
MEDULLOBLASTOMA – **DWI restricts**

Treatment:

Resection (debulking) of > 75% tumor mass is considered "gross total resection"

- within 2 days postop MRI; for persistent lesion → may effectively treat with **chemoradio** (vs. ependymoma – second-look surgery is a must).
- one of most commonly cited complications after surgery is **CEREBELLAR MUTISM**, s. **POSTERIOR FOSSA SYNDROME** (anatomic origin - *deep cerebellar nuclei*): apathy, minimal-to-absent speech, pseudobulbar emotional lability, refusal to initiate movement, cerebellar dysfunction, hemiparesis, swallowing apraxia;
  - become apparent 12-48 hours after surgery.
  - usually resolving completely. within 6 months.
- 2 weeks after surgery, do ***CSF cytology***.
- radiotherapy is so effective that is used even in children < 3 yrs.

Exquisitely radiosensitive tumor!

- platinum-based chemotherapy (followed by BMT).

One of most chemosensitive tumors!

DEXAMETHASONE is very effective - can even alleviate hydrocephalus by reopening CSF pathways in posterior fossa!

Prognosis

- by genetic category:

MYC-amplified group 3 - worst prognosis.
SHH and group 4 - intermediate prognosis.
Wingless (WNT) - prognostically most favorable (but almost only type that bleeds spontaneously)

N.B. different adjuvant treatments based on molecular category!

- prognosis due to exquisite sensitivity to adjuvant therapy is better than of ependymoma.
- **COLLIN law** – all ***tumors relapse*** at period = age at diagnosis + 9 months.
- 5-year survival: 60–70%.

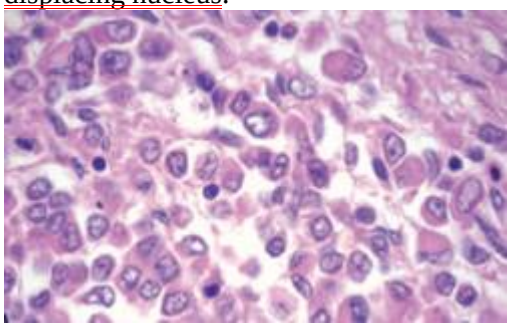
ATYPICAL TERATOID/RHABDOID TUMOR (WHO GRADE 4)

AT/RT ± Bilateral renal malignant rhabdoid tumors

"Nasty CP angle tumor in kids"

"CP angle tumor in ≤ 3 yo kid is AT/RT until proven otherwise" (20% cases)

- **age < 5 (mostly < 2) yrs**
- **inactivation of INI1 gene** in 100% cases.
- blood / tissue is tested for *SMARCB1* and *SMARCA4* mutations.
- Ki-67/MIB-1 labelling indices > 50%, focally up to 100%
- **rhabdoid cells** - vesicular chromatin, prominent nucleoli, eosinophilic globular cytoplasmic inclusions displacing nucleus:



Rhabdoid = rod-shaped

- can stain for anything (muscle markers, etc)
- prognosis is poor – attempt resection (likely subtotal) → participation in trials of chemotherapy with stem cell rescue (delay XRT until > 3 yo).

TUMORS OF NEURAL CREST CELLS (NEURON TUMORS)

NEURONAL TUMORS:

PNS – from primordial (embryonal) neural crest cells (pluripotent sympathetic cells - ultimately populate sympathetic chain and adrenal medulla)

1. *PHEOCHROMOCYTOMA* – if in adrenals
2. Sympathoblastomas (s. neurocristopathies) - spectrum of maturation and dedifferentiation:

   GANGLIONEUROMA (S. GANGLIOMA) – benign (from **well-differentiated ganglia cells**)

   GANGLIONEUROBLASTOMA - moderately differentiated

   NEUROBLASTOMA - malignant (from **postganglionic sympathetic undifferentiated neuroblasts**)

CNS (has "-cytoma" in name):

GANGLIOCYTOMA (S. CENTRAL GANGLIONEUROMA) – benign

CENTRAL NEUROCYTOMA – benign (from **well-differentiated neurons**)

NEURONAL + GLIAL TUMORS:

PNS:

CNS:

GANGLIOGLIOMA – benign or malignant (← ANAPLASTIC GANGLIOGLIOMA)

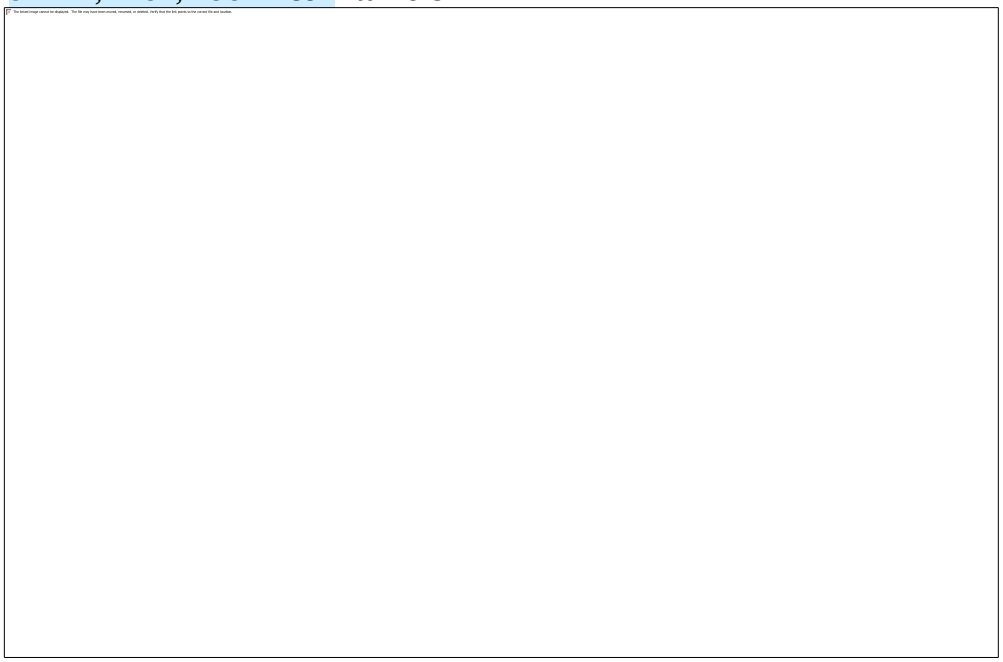
GANGLIOGLIOMAS are most common tumor cause of pediatric seizures

DYSEMBRYOPLASTIC NEUROEPITHELIAL TUMOR (DNET) - benign (extremely slow-growing)

NEUROBLASTOMA

- highly undifferentiated embryonal malignancy from postganglionic sympathetic neuroblasts.

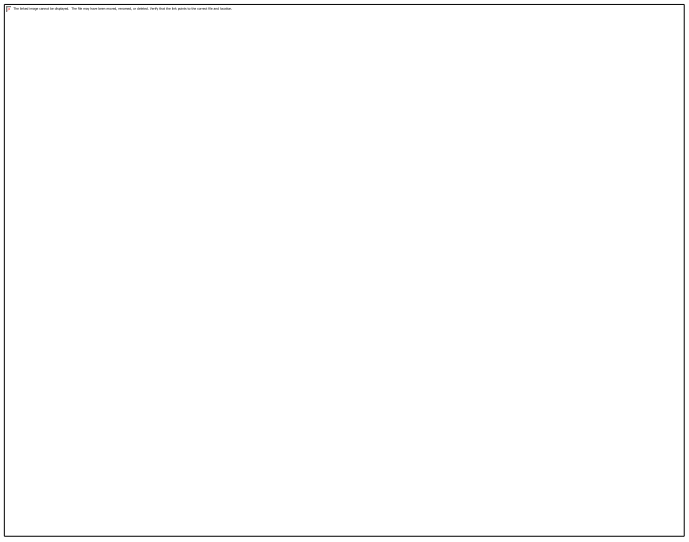
- anywhere *along sympathetic nervous system;*
  60-70% in abdominal retroperitoneum (adrenal medulla, paraspinal ganglia)
  15-20% posterior mediastinum (sympathetic trunk, aortic body)
  5% pelvic (organ of Zuckerkandl)
  3-5% cervical (carotid body)
  2% intracranial (e.g. olfactory bulb & olfactory mucosa - so called *ESTHESIONEUROBLASTOMAS*)
  1% primary tumor cannot be found.
- one of the "SMALL, BLUE, ROUND cell" tumors



Small, blue, round cell tumors of childhood:

1) neuroblastoma
2) primitive neuroectodermal tumors (incl. medulloblastoma)
3) non-Hodgkin lymphoma
4) Ewing sarcoma
5) undifferentiated soft tissue sarcoma (rhabdomyosarcoma).

- Homer-Wright rosettes – same as in medulloblastoma see >>



- N-*myc* oncogene amplification (20-25% cases; in 2p; high metastatic potential); 1p deletion (70-80%).
- most common malignancy during **infancy**! rare after age 10 years!
- great mimicker - myriad clinical presentations: mass effect, catecholamine secretion (> 90% tumors), metastases (> 50% patients) → local effects, constitutional malaise:

  HUTCHINSON syndrome - widespread metastasis to ***bone*** (bone is most common site of mts): bone ***pain*** → ***limping*** and pathologic fractures.

  PEPPER syndrome - overwhelming metastasis to ***liver*** → intra-abdominal pressure↑ → ***respiratory compromise***.

  "blueberry muffin" babies - ***subcutaneous*** metastases - nontender, bluish subcutaneous nodules; when provoked, nodules become intensely red and subsequently blanch.

  metastases to ***orbits*** → ***periorbital ecchymosis*** ("raccoon eyes" - can mimic child abuse), ***proptosis***

  VIP secretion → ***paraneoplastic*** **VERNER-MORRISON syndrome**: intractable secretory diarrhea.
- *spontaneous regression* is common!!!
- Dx: in urine HVA↑, VMA↑; serum dopamine or norepinephrine↑; MIBG **scintigraphy** (if negative → **bone scintigraphy)**; **MRI**; **biopsy** - neurofilaments, synaptophysin, and neuron-specific enolase (NSE)**; bone marrow** sampling!!!
- Rx:

  low-stages (stages 1-2) – surgery

  NEUROBLASTOMA does not require specific anesthetic protocol (vs. *PHEOCHROMOCYTOMA*).

  Documented spontaneous rate of resolution!!! (surgical capsule can be violated, leaving residual tumor, and good outcome still might be achieved)

  - neuroblastoma in ***paraspinal ganglia*** may invade through neural foramina (*"dumbbell" tumor*) → *spinal cord compression*.

  H: emergency chemotherapy (laminectomy reserved for patients who do not respond!)

  Complications are lower for delayed or second-look procedures, after tumor shrinkage by chemotherapy.

  advanced stages – chemotherapy

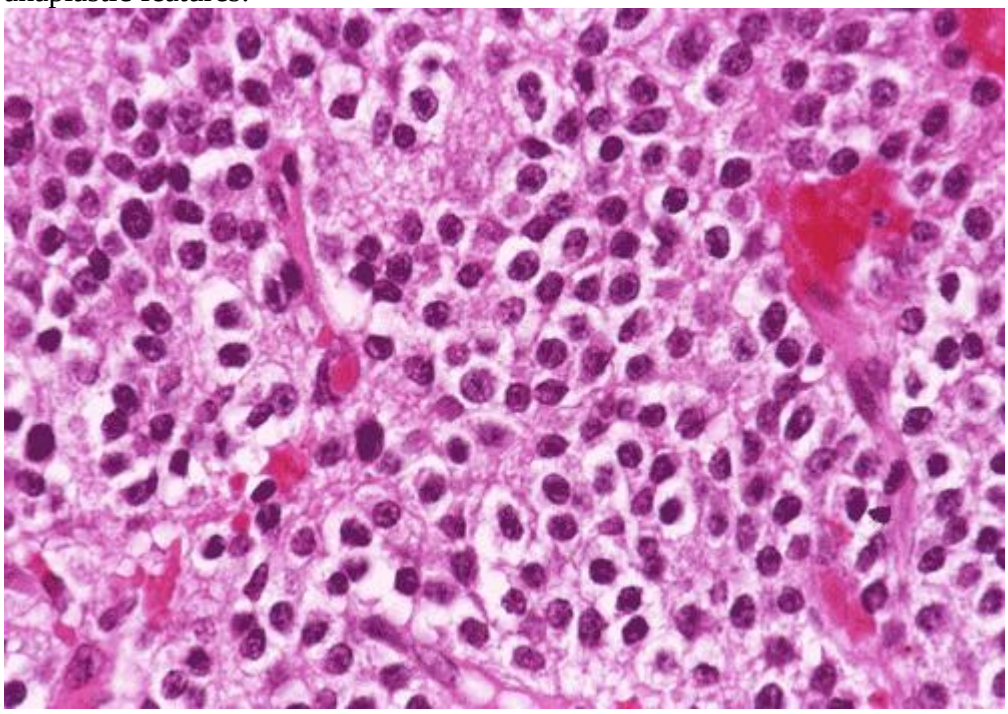
  Surgery is contraindicated for **high-stage** neuroblastoma!
- **AGE** is most significant prognosticator – **INFANTS (< 1 YR)** have better prognosis

  N.B. neonatal screening has no benefit on mortality and morbidity!!!

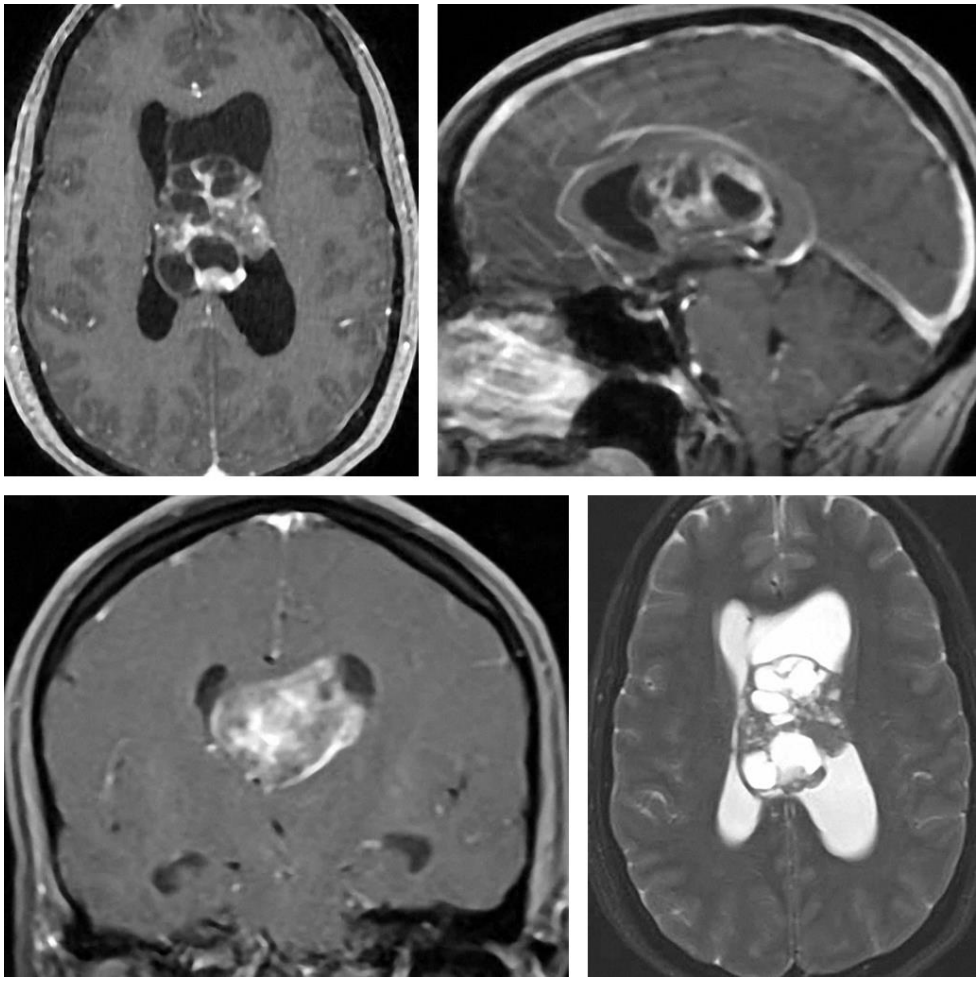
(CENTRAL) NEUROCYTOMA

- ***benign*** tumor of **young adults** - slowly growing well-differentiated neurons.

- ≈ *OLIGODENDROGLIOMA* - monomorphic small cells with evenly spaced, round, uniform nuclei, no anaplastic features:



- commonest lateral ventricular mass in young adults – grow from septum pellucidum - frontal horns and bodies → obstruction of foramen of Monro.
- **CT** - calcification and small cysts, obstructive hydrocephalus.
- **MRI** - isodense intraventricular mass, variable cyst formation and **contrast enhancement**.



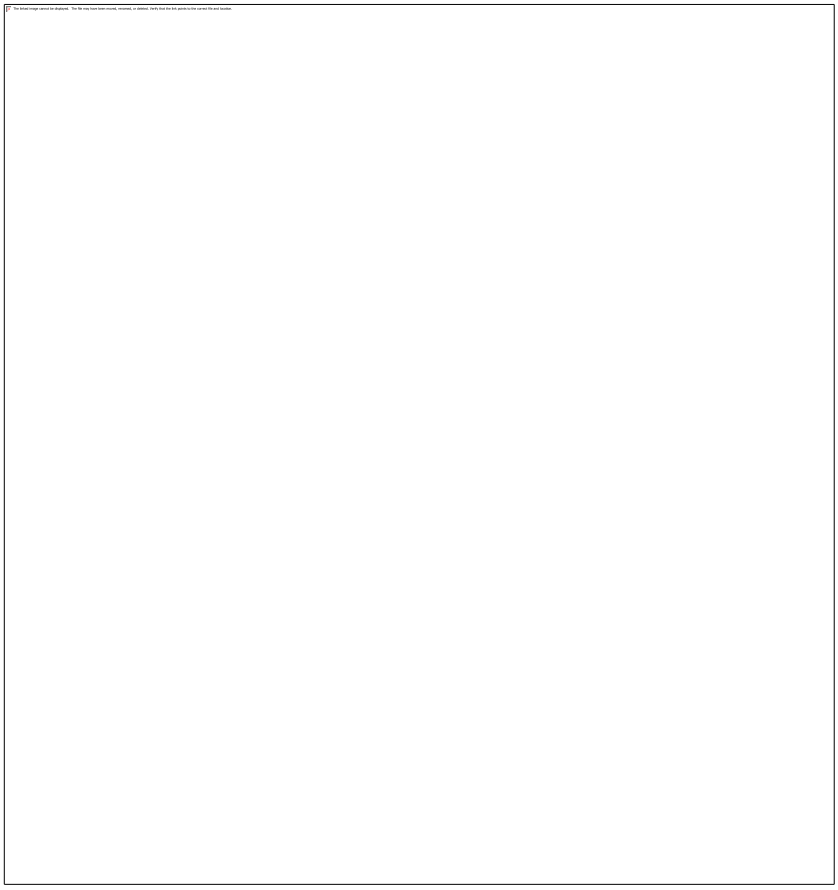
- **resection** is often curative.

DYSEMBRYOPLASTIC NEUROEPITHELIAL TUMOR (DNET)

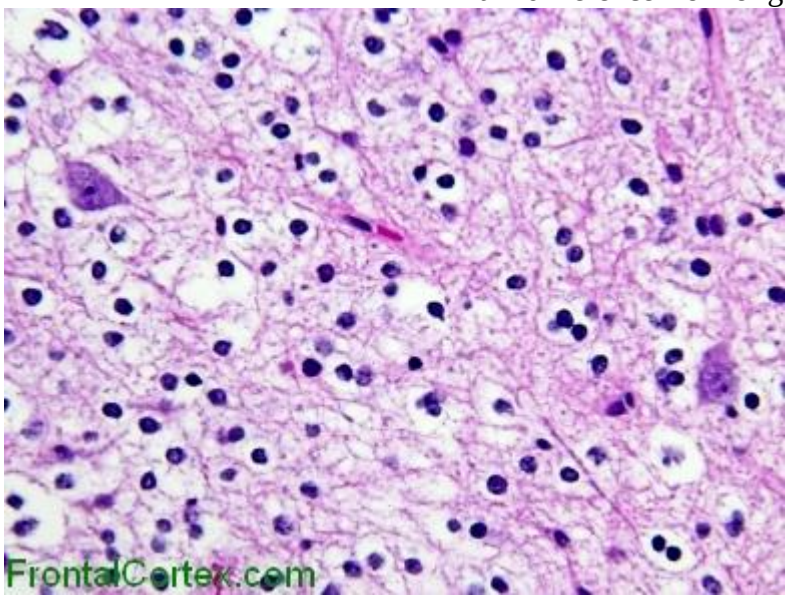
- extremely slow-growing benign mixed glial-neuronal tumor.

- ages 3-35 years.
- ***intracortical*** nodular-cystic neoplasm → *megagyrus*
- 2/3 in temporal cortex, 1/3 in frontal cortex.
- frequent association with dysplastic cortex

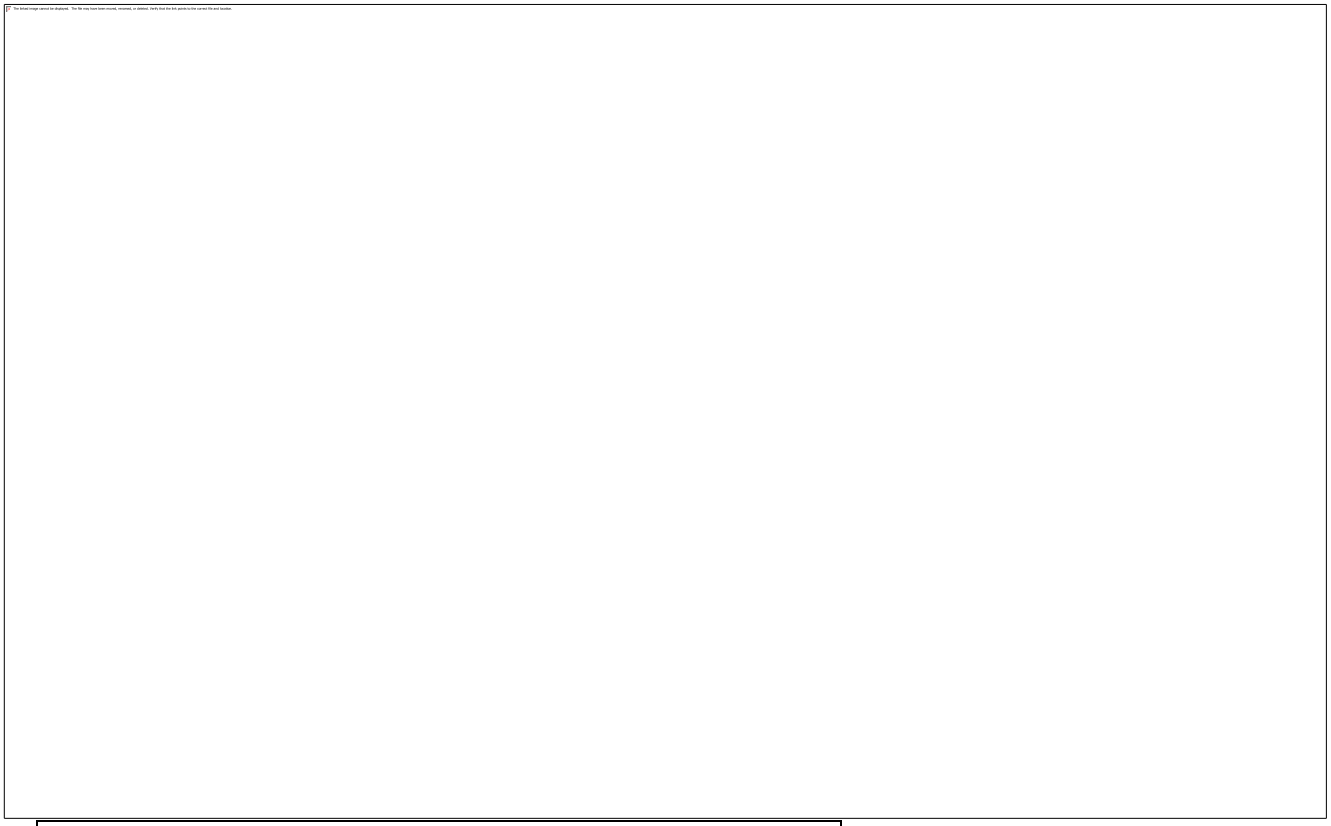
  DNET and cortical dysplasia often go together!



- well-differentiated "normal neurons floating in pool of mucopolysaccharide-rich fluid" and surrounded (but NOT tightly*) by neoplastic oligodendroglial-like cells:
  *main difference from oligodendroglioma (perineural satellitosis)



- ***intractable partial seizures*** + no neurological deficits
- MRI ≈ *LOW-GRADE ASTROCYTOMA*:



Vignette: kid with seizures + bubbly lesion in temporal lobe

- treatment – only surgery!

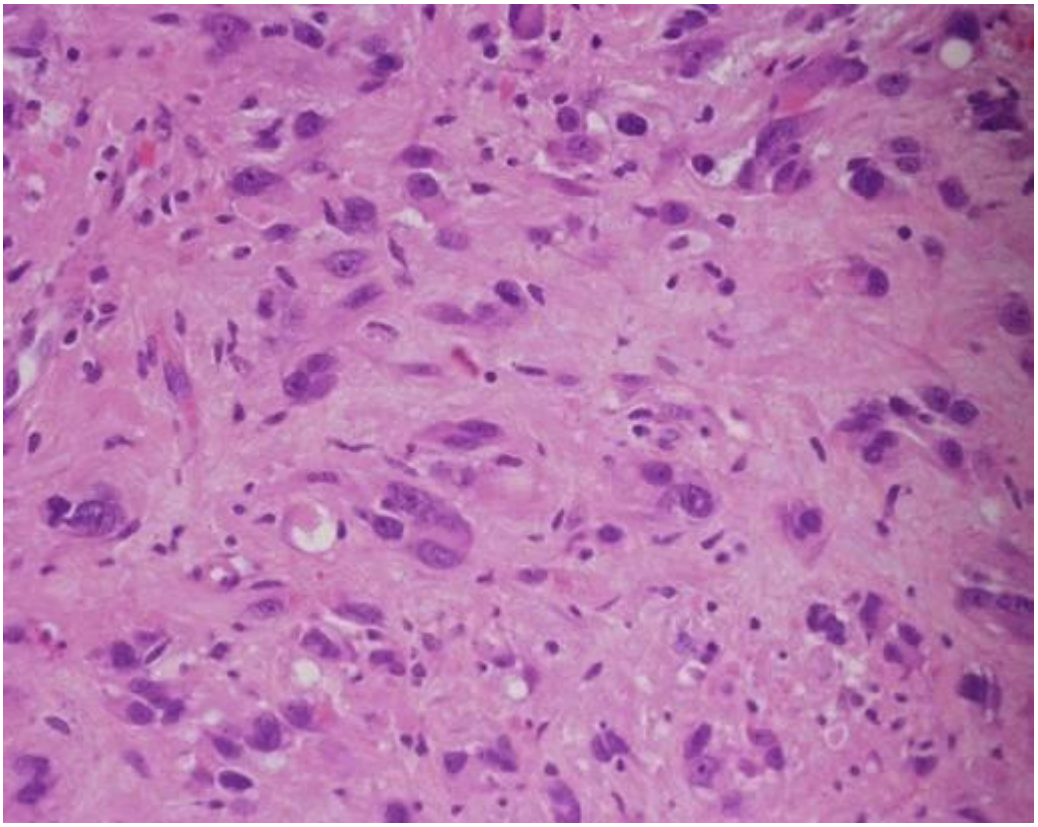
GANGLIOGLIOMA

- rare benign slowly growing **CNS** tumors:

GANGLIOGLIOMA (95%) - astrocytic + neuronal components.

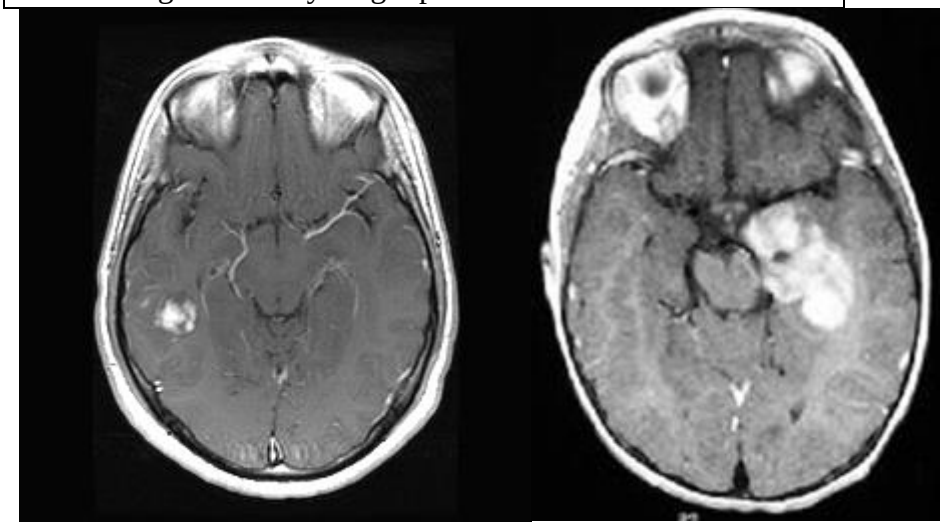
GANGLIOCYTOMA (5%) - only neuronal component.

- biphasic: neoplastic mature ganglion cells* + neoplastic glial cells
  *large *binucleated* ***neurons*** (important diagnostic feature!!!):



- clinically – as DNET; MRI:

Solid, ± cystic, ± enhancing tumor in temporal lobe with no surrounding edema in younger patient with intractable seizures

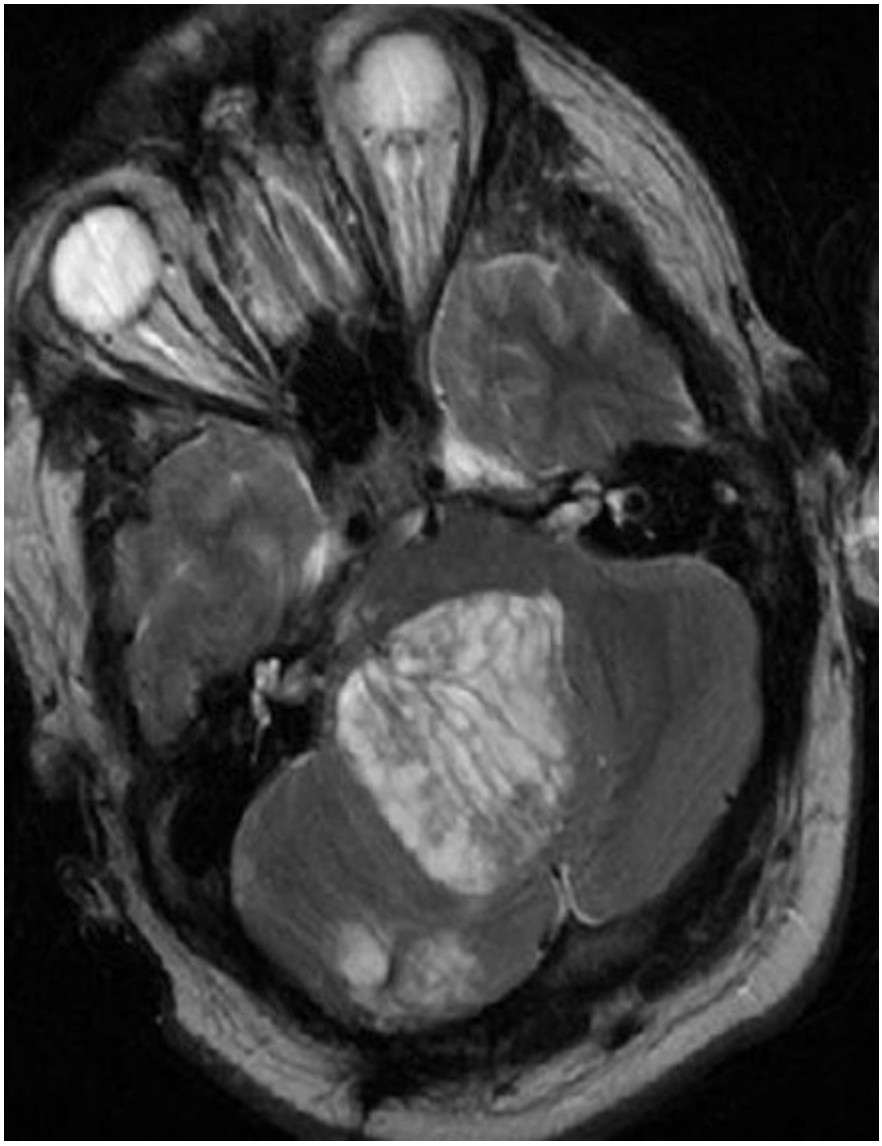


- **resection** (may have good prognosis even when untreated).

Lhermitte-Duclos disease (s. dysplastic gangliocytoma of cerebellum)

- rare, benign, slowly growing tumor of cerebellum, sometimes considered as hamartoma.

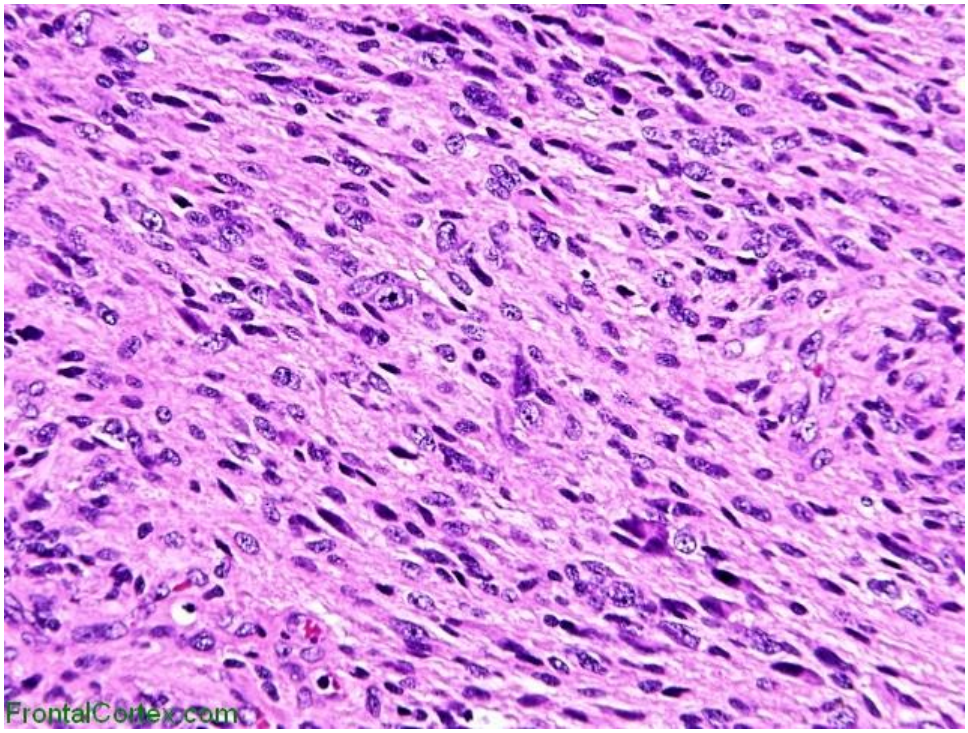
- pathognomonic for **COWDEN syndrome** (mutations of PTEN gene)
- histology: diffuse hypertrophy of stratum granulosum of cerebellum
- MRI - LINEAR STRIATIONS, no enhancement:



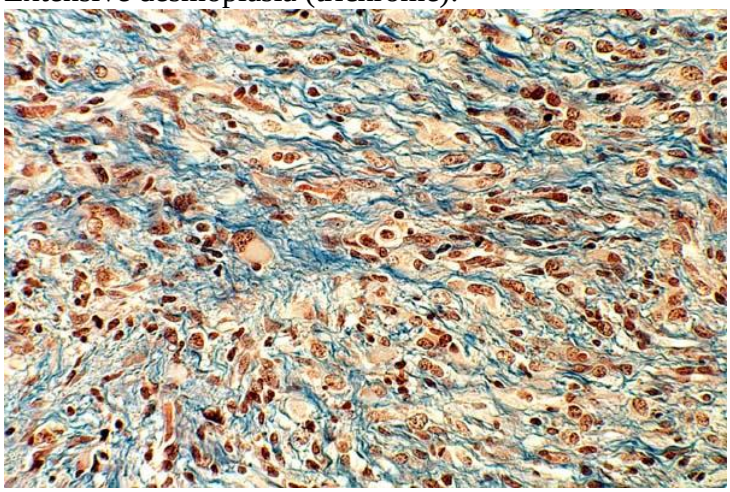
- treatment:
  asymptomatic → observe
  symptomatic → debulking (complete removal is not needed)

Desmoplastic Infantile Ganglioglioma and Astrocytoma (DIG/DIA) WHO grade I

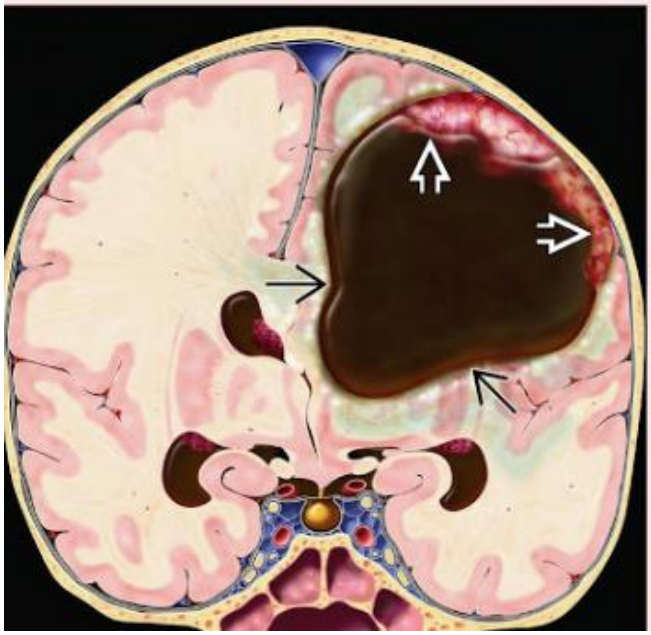
- rare (< 0.1% of CNS tumors) supratentorial tumors of infancy (most < 1 year).
- large, cystic with enhancing mural nodule
- prominent desmoplasia with neoplastic ***glial*** (DIA) or ***glioneuronal*** component (DIG).
- *Infant with rapidly progressive macrocephaly and seizures*
- treatment: gross total resection; chemotherapy if infiltrative or progressive.
- prognosis is excellent (but multiple cerebrospinal metastases have been reported).

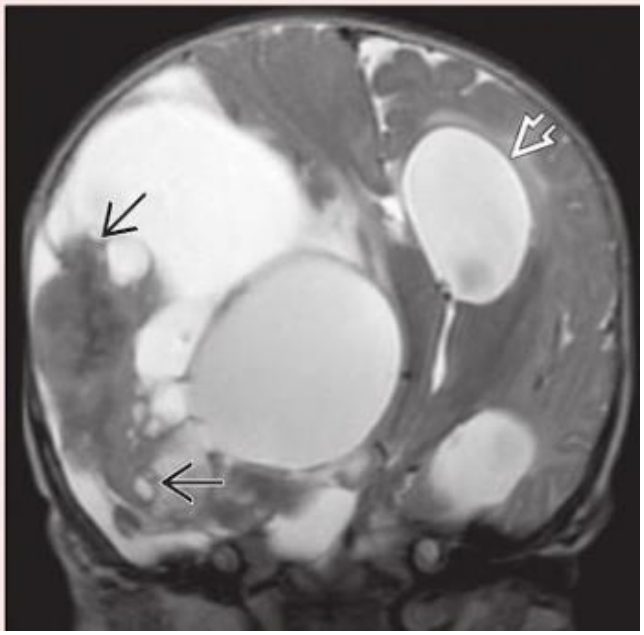


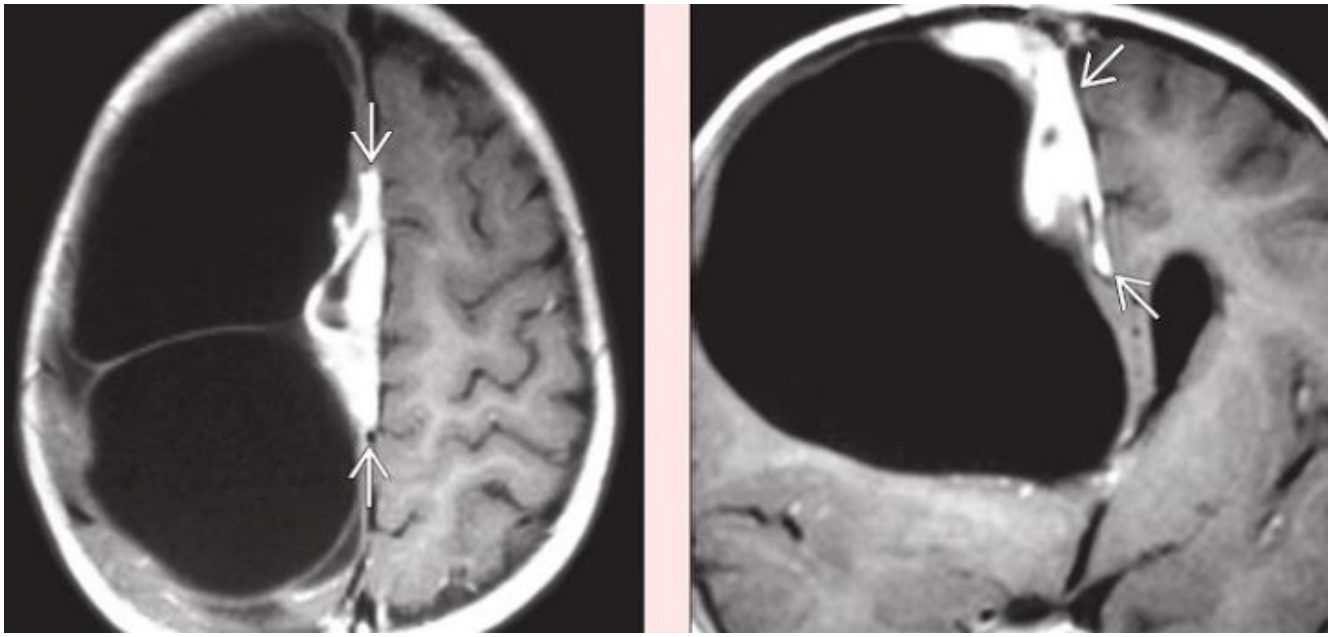
Extensive desmoplasia (trichrome):



- large cystic and solid mass (enhancing):





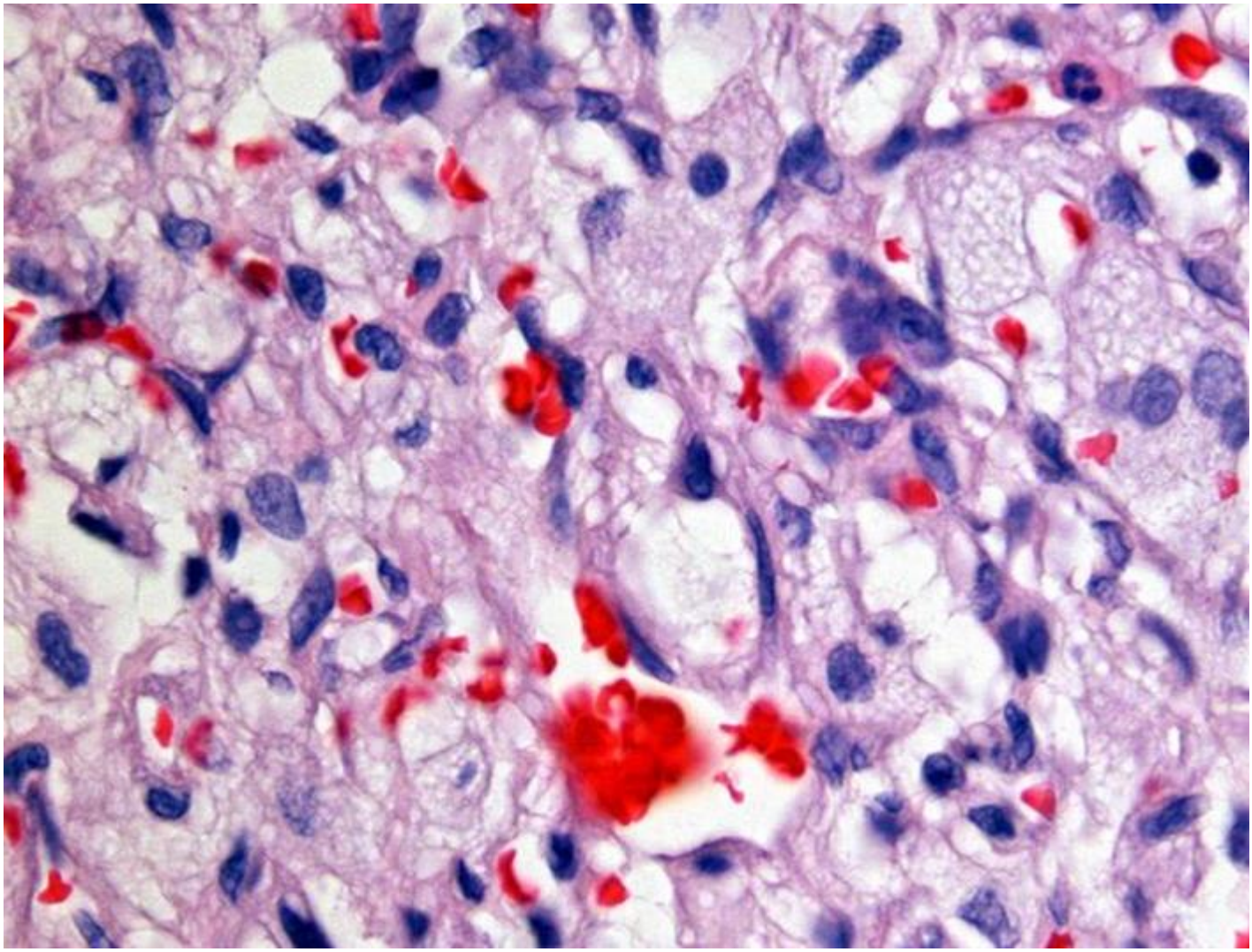


- treatment: gross total resection
- despite large size and poorly differentiated cells, prognosis is excellent (but multiple cerebrospinal metastases have been reported).

VASCULAR TUMORS

HEMANGIOBLASTOMA

- cherry-red in color (highly-vascular - *may simulate AVM*!!!).
- histology - primitive vascular channels; neoplastic ***stromal cells*** with multiple vacuoles and granular eosinophilic cytoplasm (”bubbly cytoplasm” - can be mistaken for *XANTHOCHROMIC ASTROCYTOMAS*)



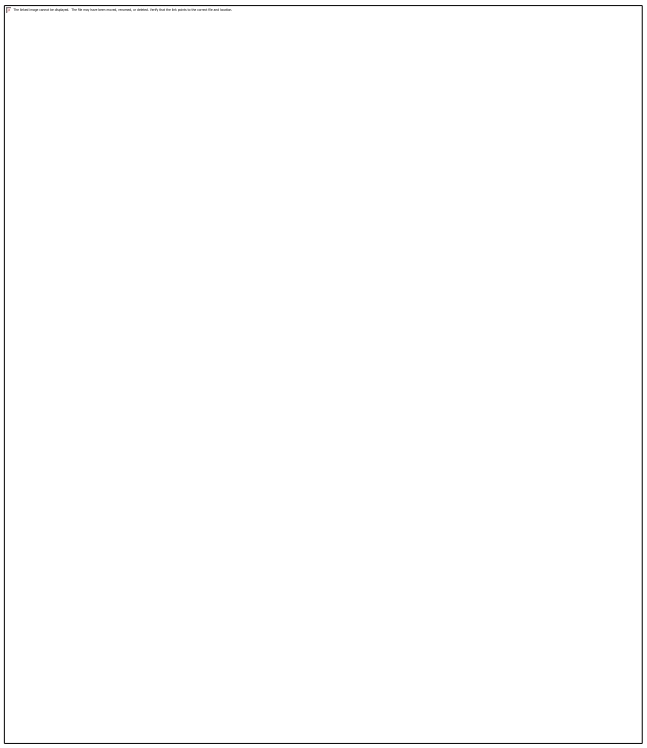
- complete neural axis imaging - very intense enhancement!
- *intensely enhancing* **mass** OR *intensely enhancing* mural **nodule** + *nonenhancing wall* **cyst**
  *vs. cystic metastases (have enhancing wall)
- not invasive
- no calcification
- subarachnoid dissemination is extremely rare, tumor enlarges extremely slowly.
- ***brachyury protein*** - present in majority of hemangioblastomas (helps to differentiate from clear cell renal cell carcinoma metastases in von Hippel-Lindau syndrome).
- ***asymptomatic*** → **observe**.
- tumor ***enlargement*** or ***symptomatic*** → (***embolization*** for enlarged feeding arteries and draining veins →) **surgery**

  N.B. *all patients must be screened** *for PHEOCHROMOCYTOMAS* preop (may cause perioperative hypertensive crisis induced by anesthetic or analgesic agents)
  → pheo resection first (if unable, then α-blockade → β-blockade preop)
  *CT, plasma [metanephrine] and [normetanephrine]
- target - **mural nodule** (otherwise, cyst will recur); ***no need to resect capsule*** if it is nonenhancing on MRI (5-ALA may aid in visual localization of small hemangioblastomas within cyst wall).
- identify ***feeding vessels*** → coagulate and cut (arterial feeders prior to draining veins!)
- ***coagulate tumor surface*** (to shrink the tumor) with wide bipolar → ***dissect tumor circumferentially*** by careful devascularizing blood supply
  - do not remove in piecemeal fashion - significant bleeding may ensue
  - HGBs with attachment to floor of 4th ventricle may be hazardous to remove (cardio-respiratory complications).
- for unresectable - BEVACIZUMAB, ***embolization***, ***radiotherapy***

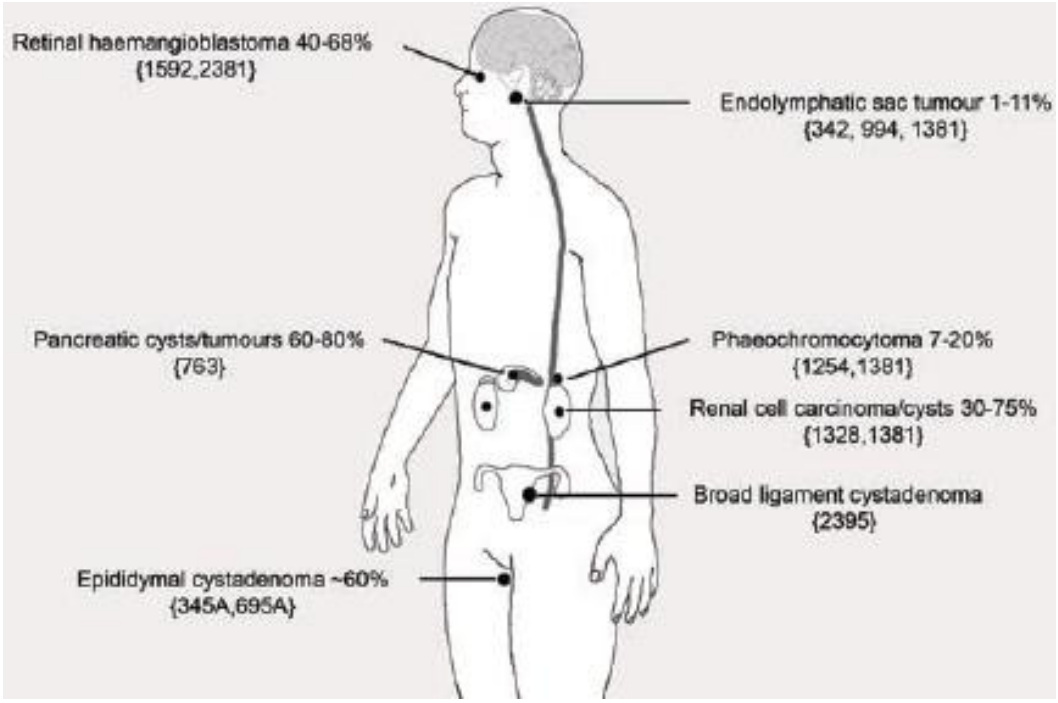
20-25% hemangioblastomas are part of **von HIPPEL-LINDAU (VHL) disease** – **AD** deletion of VHL (tumor suppressor gene on 3p) → constitutive overexpression of **VEGF**

1) retinal angiomatosis (*von Hippel's disease*)
2) multiple (vs. in sporadic cases – solitary) cerebellar hemangioblastomas (*Lindau's syndrome*) – benign, produce erythropoietin-like substances → asymptomatic ***polycythemia***.

(most common *primary adult intraaxial posterior fossa tumor*)



3) various visceral tumors; **pheochromocytoma**; renal carcinoma is most common cause of death!



- life expectancy 40–50 years.
- ***screen all family members***:
  1) germline VHL mutations
  2) *retinal examination*; retinal angioma is indication for MRI

Positive family members → early lifetime screening by MRI (start at age > 10 years).

- if surgery is not indicated:
  - BELZUTIFAN (Welireg) – *hypoxia-inducible factor inhibitor* - for **RCC**, **hemangioblastomas**, **pancreatic neuroendocrine tumors**.
  - for advanced **RCC** (do not work for **hemangioblastoma**) - ***tyrosine kinase inhibitors***: PAZOPANIB (Votrient), SUNITINIB (Sutent)

SOLITARY FIBROUS TUMOR (HEMANGIOPERICYTOMA)

- rare ***dural*** tumor from perivascular pericytes
- very vascular.
- STAT6 immunohistochemistry
- histo mimics meningioma & hemangioblastoma but far more aggressive, may metastasize.
- imaging - lobulated (vs. meningioma - spherical) dural based mass, no calcification, no hyperostosis, multiple flow voids (high vascularity).
- treatment – **surgery** → **radiotherapy** and/or **chemotherapy**.

PITUITARY / (PARA)SELLAR TUMORS

NEUROHYPOPHYSIS is rare site of neoplasia:

1) *INFUNDIBULOMAS* are rare variants of *PILOCYTIC ASTROCYTOMAS*.
2) *GRANULAR CELL TUMORS* (*MYOBLASTOMAS*, *CHORISTOMAS*) are rare tumors with uncertain cell origin.

DIFFERENTIAL DIAGNOSIS

1. **Tumors**:
   1) pituitary adenoma, pituitary carcinoma, craniopharyngioma
   2) meningioma, metastatic tumors*
   3) cranial nerves - optic glioma, CN5 schwannoma
   4) bone - chordoma, chondrosarcoma
   5) lipoma, epidermoid, dermoid, teratoma, germ cell tumors (← treated with radiation)

   *most commonly involve pituitary stalk

   H: surgery with *histological diagnosis*.

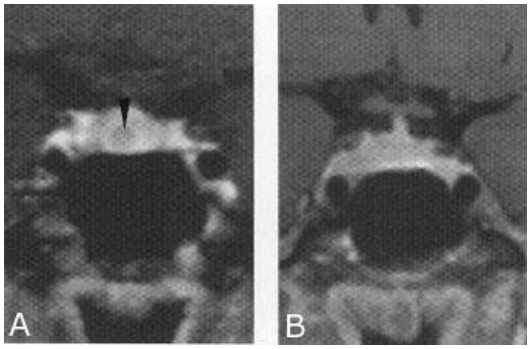
2. **Not tumors**: hemorrhage, carotid aneurysm, empty sella, Rathke's cleft cyst, tuber cinereum hamartoma, granulomas (e.g. tuberculosis, neurosarcoid, eosinophilic), lymphocytic hypophysitis.

   H: *neuroradiological imaging*, possibly *biopsy*.

Dual-energy CT (utilizes high-frequency cycling of high/low voltages to improve the quality) - can discriminate between ***pituitary adenomas*** and ***meningiomas*** with a sensitivity of 90.9% and specificity of 100%.

Pituitary MRI protocol - 1-mm thick ***coronal*** T1 through pituitary gland w/wo GADOLINIUM.

- add *fat-saturated T1* - eliminates high signal from fat in clivus and clinoid processes (could be mistaken for enhancement).
- *dynamic T1*
  A) scan at 90 s following injection of gadolinium reveals microadenoma (*arrowhead*).
  B) after 4 min enhancement is similar to rest of gland.

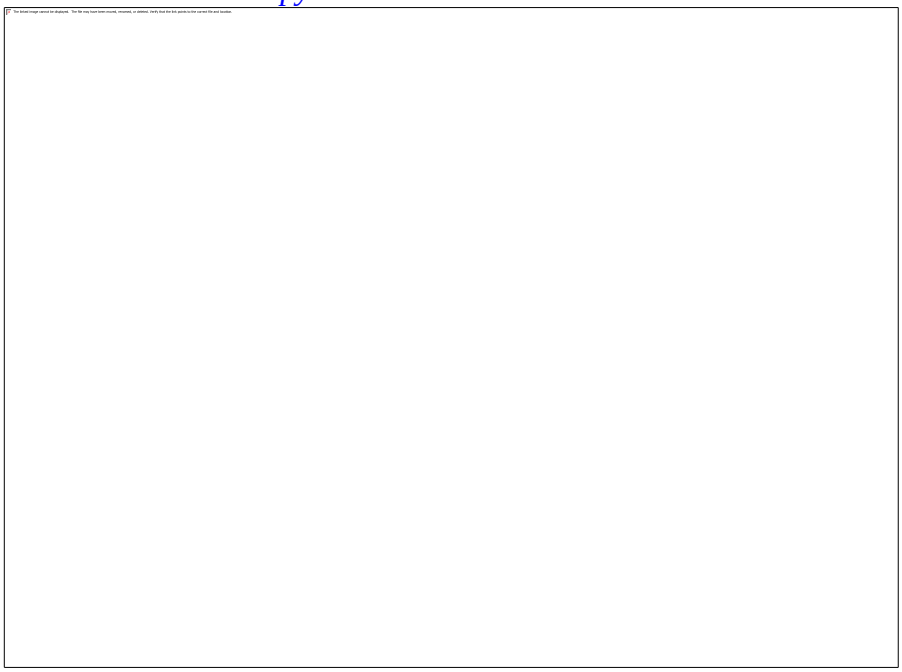


PITUITARY ADENOMA

< 1 cm – **MICROADENOMAS**

> 1 cm – **MACROADENOMAS**.

- **no mitotic activity**
- routine staining is meaningless - difficult to dif from normal tissue; *immunohistochemical* staining and *electronmicroscopy* are essential



- nuclei with *"salt and pepper" chromatin* (s. endocrine chromatin).
- frequency of secretion: prolactin* > GH > ACTH > gonadotropins > TSH
  *↑[prolactin] < 200 may be due to stalk compression
- diabetes insipidus is more common in *CRANIOPHARYNGIOMAS*
- **headache** due to stretching of diaphragma sellae
- *crossing fibers* in ***optic chiasm*** (superior bitemporal quadrantanopia → full **bitemporal hemianopia**); any type of visual field deficit is possible (even monocular) – formal quantitative visual field testing is important in all cases!!!
- prefixed and postfixed chiasm – 10% each.
- lateral extension into **cavernous sinus** → **ophthalmoplegias**, postganglionic Horner.

Diagnosis

- most important endocrine tests – 5 axes:
  1) prolactin
  2) TSH&fT4
  3) IGF-I
  4) fasting morning cortisol & ACTH

5) LSH, FSH, testosterone / estradiol
   - **inferior petrosal sinus sampling** is used to localize tumors not seen radiographically (e.g. many ACTH-secreting microadenomas are < 5 mm).
   - be aware of **hook effect** - false negatives or inaccurately low results – ask for dilution!

- 10% of *asymptomatic individuals* have focally abnormal pituitary areas on contrast MRI! - great care with nonfunctional **MICROADENOMAS** diagnosis on MRI basis!
  N.B. adenomas always *hypodense* - enhance *later* and *lesser* than normal pituitary tissue!
  Never have calcifications! (look at CT – if calcium is present, it is craniopharyngioma)?
- biopsy - indicated if nonoperative etiology is suspected on imaging (e.g. germinoma, hypophysitis).

Rx:

- prolactin-secreting **MICROADENOMA** **or even macroadenoma** (galactorrhea in XX, impotence in XY) → dopamine agonists (e.g. **BROMOCRIPTINE**, **CABERGOLINE**).
  - **CSF rhinorrhea** – following favorable response to initiation of dopamine agonist.
- other secreting adenomas → **total surgical resection***
  N.B. *GH hypersecretion* and *ACTH hypersecretion* are clear indications for surgery, even when mass is not important.
  ACTH hypersecretion → **KETOCONAZOLE**, **PASIREOTIDE**
  GH hypersecretion → **OCTREOTIDE**, **PEGVISOMANT** (GH receptor antagonist)
- **MACROADENOMA** → **subtotal surgical debulking** → curative adjuvant **radiation therapy***
- incidental asymptomatic adenomas – periodic endocrine examinations, visual field examinations, MRI - onset of symptoms or MRI growth → treatment.
  *radiation therapy is less effective in controlling endocrine hypersecretion (success 50%) than adenoma growth (success 100%)

PITUITARY SURGERY

- adenomas lack discrete capsule, but presence of ***pseudocapsule*** facilitates surgical separation.
- no imaging technique can perfectly visualize the *medial cavernous sinus wall*
- Make sure you are not operating on undiagnosed prolactinoma! (even with hemianopia!)
  Considerations for surgery in prolactinomas:
  cystic prolactinomas may not respond as well to medical therapy and require cyst decompression
  skull base erosion - tumor regression by medical treatment may induce CSF leakage
- Make sure visual changes are documented!
  N.B. antisecretory medications can lead tumors to be more fibrotic - challenging to remove during microsurgery; H: stop medications 4-6 weeks preop!

Patients with **Cushing's** disease - optimize cardiopulmonary status.
Patients with **acromegaly** - special preparations for endotracheal intubation

TRANSSPHENOIDAL APPROACH – gold standard for pituitary adenoma.

- possible for fairly large medial suprasellar extensions, as long as tumor is soft (usual case) and can drop into sella with progressive resection (alternatively: follow postop MRI – when remaining tumor falls down → second look surgery)

Think that sella-sphenoid sinus is "pelvis" and tumor is "baby" – look at MRI if baby can be delivered vaginally (transsphenoidal) or needs C-section (subfrontal)

Guidelines on the Management of Patients with Nonfunctioning Pituitary Adenomas (CNS 2016)
Level III recommendation: Transsphenoidal microsurgery or endoscopic resection is recommended.

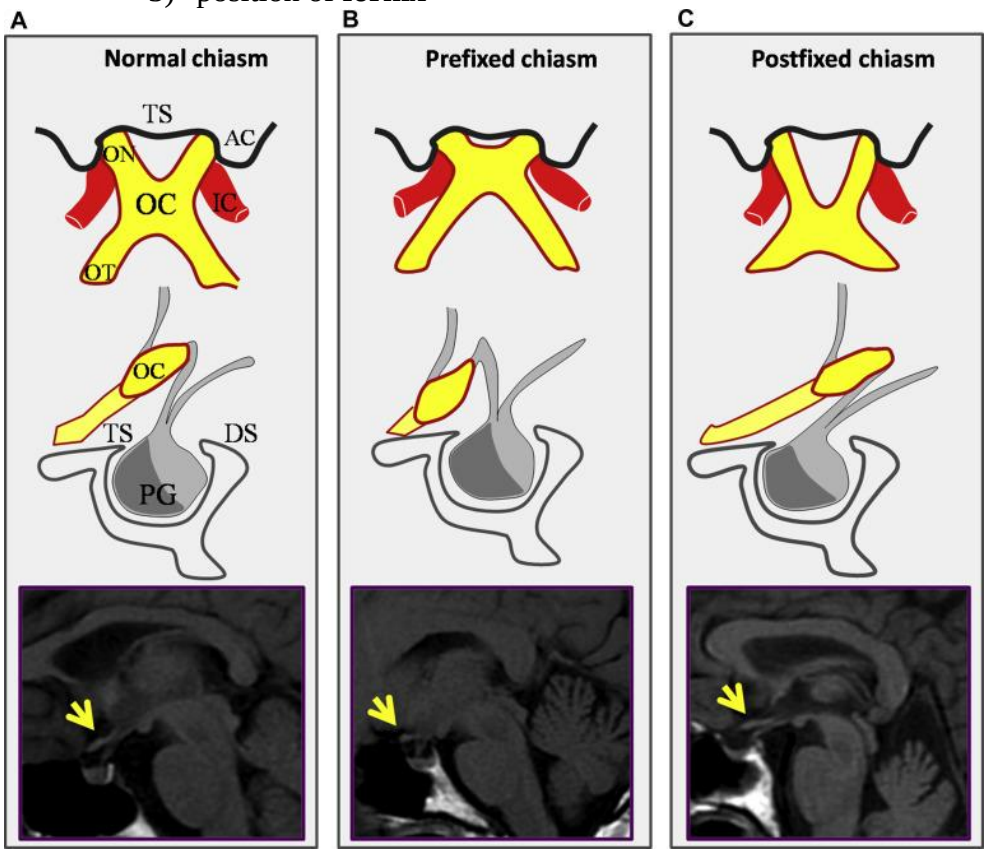
Insufficient evidence to recommend perioperative CSF diversion to prevent postop CSF leak.

If sella is not enlarged, transsphenoidal approach is contraindicated!
If tumor will be difficult to deliver transsphenoidally, think about alternative approaches:

A. *ENDOSCOPIC TRANSNASAL* through anterior cranial fossa – for smaller tumors

B. *CRANIOTOMY*: rarely needed!
   1. Subfrontal
      N.B. only by subfrontal approach one can visualize *both* optic nerves and carotid arteries!
      If chiasm is prefixed (severely limited view of tumor mass) - resect tuberculum sellae and open sphenoid sinus
   2. Interhemispheric
   3. Pterional - for ***parasellar tumors***
   4. Subtemporal - for ***parasellar tumors***

- when choosing craniotomy approach, consider the following:
  1) position of **chiasm** (esp. is it prefixed)
  2) position of **AComA-ACA complex**; AComA perforators (go superiorly from AComA) are very friable!
  3) position of **fornix**



  a) chiasm directly above pituitary (80%).
  b) **prefixed** - chiasm anteriorly to pituitary – above *tuberculum sellae* (9%)
  c) **postfixed** - chiasm behind pituitary – above *dorsum sellae* (11%).

IMAGING

1. **CT** - ***nasal septum*** deviation, ***intra-sphenoid septum*** where septum leads (e.g. carotid – better not to remove such septum)
2. **MRI**
3. **CTA** – if **circle of Willis** is *incomplete* (cannot sacrifice carotid), **position of carotids**! (look for "*kissing*" carotids)

SURGERY

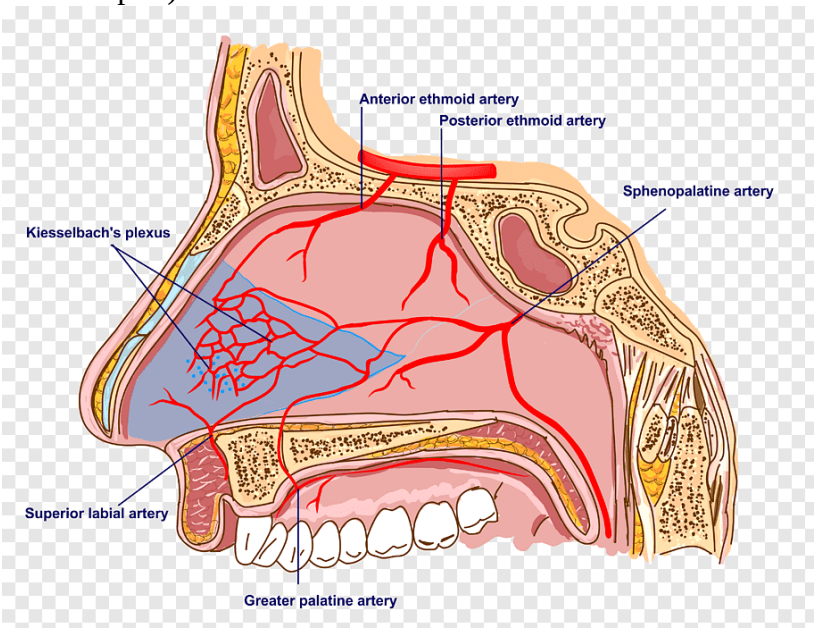
neck in extended sniffing position
navigation (most common cause of subtotal tumor removal is inadequate bony exposure!)

- nose and oropharynx with Betadine solution.
- pack nose with OXYMETAZOLINE* / PHENYLEPHRINE solution pledgets. *e.g. Afrin®
- prepping abdomen for **fat graft harvesting**

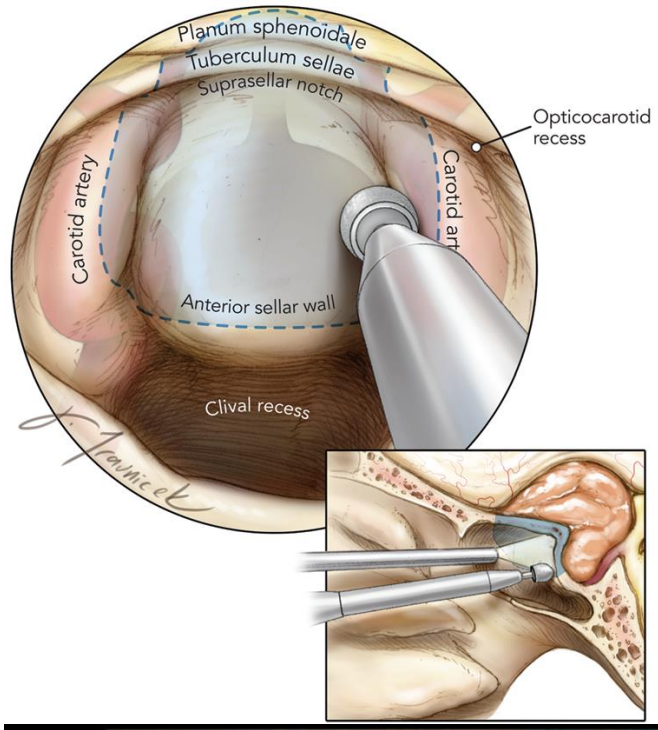
Insufficient evidence to recommend perioperative CSF diversion (LD) to prevent postop CSF leak.
place LD preop if tumor goes above sella – may inject saline through lumbar drain to push tumor into sella

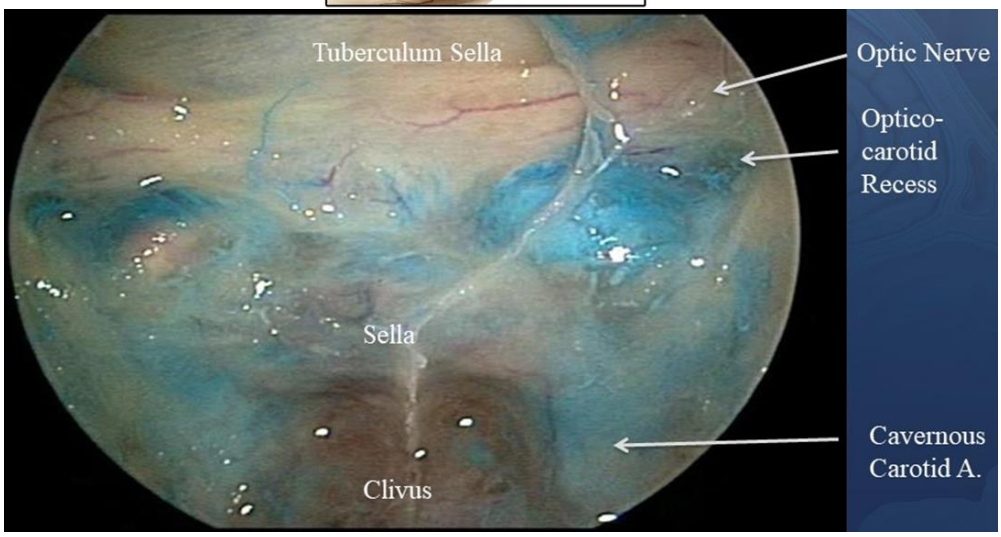
Sublabial-Septal approach

- maxillary gingiva and anterior inferior nasal septum (through lip skin) infiltrated with 1% lidocaine with epinephrine 1:100,000.
- **lip** mucosa incision from canine-to-canine (few mm from gingival fold - enough of mucosal cuff for repair)

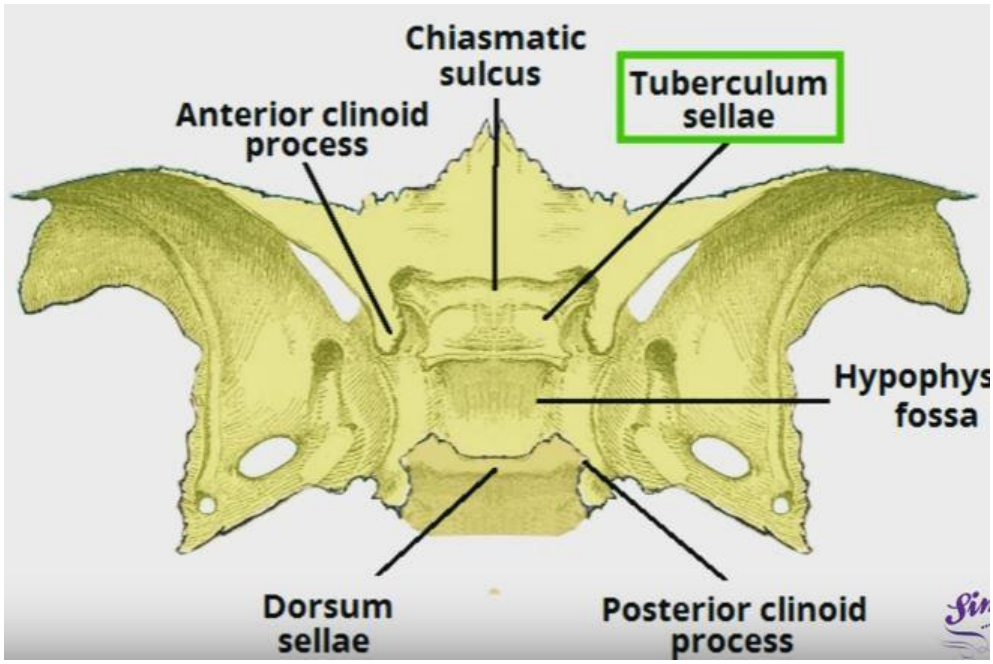


- elevate nasal mucosa on both sides of nasal floor (hard palate) staying on bone with Freer dissector / Penfield # 1 → elevate mucosa from right side of cartilaginous septum with Penfield #2 (its blunt edge helps to not perforate mucosa) → inferior portion of cartilaginous septum is detached from maxillary spine using # 15-blade / Freer and reflected to the side → elevate mucosa from bony septum back to the vomer.
- Hardy retractor is inserted.
- bony septum is removed with pituitary rongeur / Jansen-Middleton Septum Forceps (save large bone pieces for implantation on sella floor)
- sphenoid sinus is entered at rostrum and ostia using osteotome/chisel.
- once inside sphenoid sinus, ***mucosa is removed*** (beware dehisced bone and exposed carotid!); if left in place - risk of mucocele (esp. if naso-septal flap is used)
- MICROSCOPE is brought into field.
- open sella from inferior intercavernous sinus to superior one and from one cavernous sinus to contralateral one - "4 blues"





TUMOR REMOVAL



- sella is opened using chisel → removed laterally to cavernous sinus area using 2 mm Kerrison / Stryker Sonopet drill.

Dura opening

- dura is cauterized using suction Bovie cautery and opened using # 11 blade (X or + -shaped incision).

  N.B. use **navigation** and **Doppler** to check for carotids!
  N.B. use **25G needle** puncture before using # 11 blade!

- some experts warn - diagonal incisions should be avoided - risk of injury to ICA (esp. at upper aspect of sella); thus, ***make the vertical incision first*** (horizontal incision may result in the tumor decompression and descent of the arachnoid superiorly, which may be inadvertently opened with a subsequent vertical cut).
- **bleeding from lateral margins** is likely from cavernous sinus (H: thrombin-soaked Gelfoam packing, HOB elevation – but risk of air embolism!!!)

Tumor dissection and debulking

- **microadenomas**: transverse or vertical incision is made in the gland, and blunt dissection is then performed around the normal-appearing tissue to search for the tumor.

Three types of dissection:

PSEUDOCAPSULE – tumor squeezed normal collagen reticulum of pituitary gland;
PSEUDOCAPSULE is very tough – can retract on it during dissection

1. **EXTRA-CAPSULAR** – avoid it as you are doing hypophysectomy of normal gland!
2. **INTRA-CAPSULAR** – traditional way when tumor is removed in piecemeal fashion using various ring curettes and pituitary forceps – messy, leaving tumor behind.
3. **PSEUDO-CAPSULAR** – dissecting along PSEUDOCAPSULE plane – removing tumor en masse;
   - possible for **microadenomas** and **macroadenomas** (may debulk center first); not possible for tumors *invading cavernous sinus*
   - need very wide exposure – must see "4 blues"
   - find normal gland then follow where it interfaces with tumor pseudocapsule
   - find plane with Rhoton # 3 dissector – goes easy inside capsule plane.

Macroadenomas:

- ***sella is emptied*** with ring curettes – start at **inferior** sella, then go **lateral**, last is **center** of tumor –diaphragm shows up when tumor is removed

- if diaphragma sellae starts sinking into the field → drain 50 mL of CSF from lumbar drain.
- 100% alcohol soaked pledgets may be placed into sella cavity for a few minutes (but only if no CSF leak).
- no reason to send for frozen pathology (but Dr. Broaddus does)!

Suprasellar extension

A. **Visualizing superior aspect of tumor**:
   a) intraop MRI
   b) 30 and 45 degree endoscopes
   c) 90 degree US probe

Level III Recommendation: iMRI can improve gross total resection, but is associated with an increased false-positive rate → removing normal tissue and is thus not recommended.

B. **Pushing tumor down**:
   a) ***Valsalva*** (does not work if there is CSF leak) + ***compress bilateral jugulars*** for 30 seconds = "Valsalva on steroids"
   b) ***insufflating*** subarachnoid space with 1-3 mL preservative-free saline ***via lumbar drain***.
   c) ***removal of more of superior bone*** (beware optic chiasm and nerves – use navigation with segmented bone and optic apparatus).

Cavernous sinus invasion

- almost impossible to remove (causes CN deficits – mostly permanent), however, master experts do it safely.
- if tumor soft – remove as much tumor in cavernous sinus as can be easily removed; if tumor firm – it's OK to leave some tumor in cavernous sinus to avoid cranial neuropathy (residual → SRS).

CLOSURE

- if there is *CSF leak* and no lumbar drain, lower head of the table to drain some CSF and then elevate it to stop CSF leak; then place nasoseptal flap and LD postop (if still leak → re-explore: repack sella and potentially sphenoid sinus; rule out HCP as cause of peristent CSF leak).
- ***sella maybe packed*** with:
  a) Dr. Broaddus technique: DuraGen to cover sellar floor → bone → another layer of DuraGen → DuraSeal spray
  b) Dr. Cohen-Gadol technique: small pieces of adipose tissue wrapped in Surgicel → reconstruct sellar floor with small sheet of prosthesis.

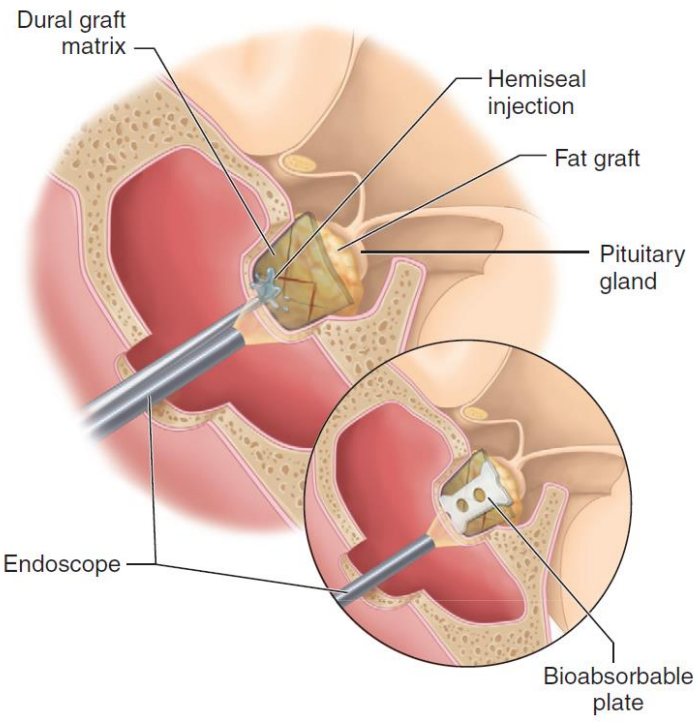
  N.B. sphenoid sinus itself is not packed with fat! (case report of blindness from too big of fat graft jammed into sella – do not overpack, some materials may swell!)

  N.B. any placement of intracranial fat will obscure postoperative imaging of residual tumor! (Dr. Caldwell: fat gets absorbed and allows perfect MRI follow ups compared to using titanium mesh or Medpor)
- **bone** (e.g. nasal septum) fragment is placed intradurally to close entrance into sella followed by → **nasoseptal flap**** (optional; mandatory if there is CSF leak) → **DuraSeal*** spray (through Angiocath threaded through ring of curette).

  *some experts do not use it

  **make sure mucosal surface is outside (else will form mucocele)
- gingiva is closed using interrupted inverted 4-0 chromic gut.
- **Merocel packs** (lubricated with bacitracin ointment)

Guidelines on the Management of Patients with Nonfunctioning Pituitary Adenomas (CNS 2016): ***insufficient evidence*** to recommend specific dural closure techniques.



CAROTID INJURY

N.B. brisk bleeding can occur with a breach in McConnell's capsular arteries, which arise from the cavernous carotid that often supply vascularized sellar tumors.

Prevention:

1) **Review imaging** - MRI with contrast, CT (intrasphenoidal septation leads to carotid canal – avoid cutting burrs)
2) **Preop carotid occlusion test**.
3) **Neuronavigation**.
4) **Doppler probe** then cut dura away from carotid; may also try to aspirate with **25G needle** before cutting dura.
5) **ICG angiography** (microscope or endoscope with filter) – shows major vessels.
6) Avoid traction on tumor

Treatment: Abandon the rest of tumor resection!

1) alert anesthesia - **call for blood** and **start resuscitation** (maintain slight HTN – to promote perfusion)
    - anesthesiologist may **compress carotid in the neck**; at extreme – ADENOSINE bolus IV to allow for carotid inspection and targeted patching.
2) **large bore suction**
    - try to **bipolar** if it is a small wall laceration or side branch avulsion.
3) **pack** tightly (Gelfoam wrapped in Surgicel; best thromboplastic material – muscle*, then fat) to stop bleeding (do not occlude carotid!) - often times, there is no need for high pressure!
    *have thigh prepped or cut piece of tongue (last resort, but tongue is right there)
    - place endoscope in opposite nare and apply pressure with cottonoid
4) keep **intubated** with tight **BP control** → **CTA** (other experts say transport straight to DSA: stenting, sacrifice; vs need surgical bypass)
    N.B. delayed pseudoaneurysm formation! – presents with profuse nose bleed; treatment: coiling + pipeline stent.
5) if still bleeding → **angiography**:
    a) **covered ICA stent**: Jostent – very stiff and difficult to navigate; load with Aspirin and Plavix in OR.
    b) **ICA coiling** (patient may wake up asymptomatic; if TIAs → ECA-ICA bypass)
    Look at CTA (if available) – if *circle of Willis is incomplete* – cannot sacrifice carotid!

OPTIC APPARATUS INJURY

Etiology Risk factors – previous surgery / SRS

1) traction on tumor
2) devascularization / vasospasm
3) optic chiasm prolapse into empty sella
4) excessive packing of sella
5) sella hematoma
6) optic canal fracture (aggressive opening of self-retaining speculum)

Treatment: decompressing hematoma or orbital fracture, BP augmentation

POSTOP

- **nasal packs** for 3 days; concomitantly abx (to prevent toxic shock syndrome – analogy with vaginal tampons) - Ancef / Keflex / Clindamycin, saline nasal spray every 2-3 hours while awake, phenylephrine nasal spray q6h PRN epistaxis
    - some experts prescribe AUGMENTIN for 14 days.

- HYDROCORTISONE taper per endocrinology recs / rapidly if BP is OK: 100 mg q8h → 50 mg q8h → 25 mg q12h → 15-20 mg + 5-10 mg (discharge on this dose)
  Level III Recommendations: perioperative corticosteroid supplementation is recommended for NFPA patients with **preoperative** or immediate **postoperative** (day 2) hypocortisolemia.
  i.e. not for patients with normal adrenal function
- olfactory dysfunction (anosmia, sinusitis, empty nose syndrome).
  Empty nose syndrome – from excessive resection of intranasal components (nasal dryness, pain, lack of ability to sense breathing); H: nasal sprays, ENT reconstruction.
- cavernous sinus inflammation (from tumor resection, sella packing, fracture, hematoma, residual tumor, infection) – delayed oculomotor palsy; LP to rule out infection → short course of steroids.
- meningitis (2.0%)
- visual deterioration (2.0%)

CSF leak (4.7%)

- **prevention**: HOB 30-45 all the time, no straws, no nose blowing, no straining, no sneezing with closed mouth for 1-2 weeks.
  - if has **lumbar drain** – keep it clamped until nasal packs are out.
- **signs** may be subtle: postnasal drip, orthostatic headache.
- **diagnosis**: beta2-transferrin, CT (pneumocephalus); to localize leak - inject through LD: Omnipaque (→ CT myelogram) or fluorescein (→ endoscopy)
- **treatment**:
  - HOB up
  - drain LD at 10 cc/hr
  - Diamox
  - surgical repair
  - shunting

Diabetes insipidus

- **monitor**: strict Is and Os, BMP and urine spec gravity QID and PRN.
- **diagnosis**:
  1) urinary output > 300 cc/hr x2 consecutive hours or > 250 cc/hr x3 hrs
  2) urine spec gravity < 1.005
  3) Na persistently > 145
- **treatment**:
  1) patient must have easy access to drinking water to auto-cope with high urinary output
  2) if patient cannot keep I&Os even H: DDAVP 1 mcg q12h IV PRN as it may be transient; Dr. Sahni gives DDAVP liberally; if DDAVP required for > 5 days, transition to scheduled 0.5 mcg q12hr subQ and then intranasal if ENT clears for that - permanent diabetes insipidus appears in 0.1% (microadenomas) or 1-5% (macroadenomas).

"**Triphasic response**":

phase 1: injury to pituitary reduces ADH levels for 4–5 days → DI

phase 2: cell death liberates ADH for 4–5 days → transient normalization or SIADH-like water retention (NB: if inadvertently continuing vasopressin - significant hemodilution and renal shutdown; avoid central pontine myelinolysis by correcting back < 10 mEq/L/24 hrs)

phase 3: absent ADH secretion → DI

F/U

- **MRI** with fat suppression at 3 months; then annually for 10 years – so recurrence can be detected early and, while small, can be treated with radiation, thus, avoiding redo surgery.

- ophthalmologic follow-up after surgical / radiation therapy
- close monitoring of hormonal status (at least thyroid and adrenal function) at frequent intervals (at 3 and 6 mo, and yearly thereafter); life-long for acromegaly (sudden jump in IGF-I → MRI) and after XRT (hypopituitarism may develop after years).

RADIOTHERAPY

- for growing residuals / recurrence, cavernous sinus invasion

A. **Radiosurgery** – enough ≥ 1 mm from optic apparatus. Tumor margin dose 12-16 Gy for ***nonfunctioning***, double (30-35 Gy) for ***functioning***.

B. **Stereotactic fractionated** – can radiate even if tumor contacts chiasm (outcomes similar to SRS but latency is longer with more frequent hypopituitarism!).

General rule: radiotherapy is indicated when surgery is not an option.

- BROMOCRIPTINE, OCTREOTIDE may confer relative radioresistance – stop these agents 4-6 weeks prior to SRS and restart 1 week after SRS.
- 4% risk for permanent cranial neuropathy with SRS
- *Time to endocrinologic remission is 12-144 months*
- with SRS, only 38-60% tumors demonstrate shrinkage postop – SRS is not good for decompression.
- no dose limits to carotid artery (but avoid hotspots > 25 Gy on it).

See O2 case >>

Pituitary Carcinomas

- extremely rare!
- diagnosis confirmation needs ***distant metastases***.

HYPOPHYSITIS

Main forms:

1. Lymphocytic - the most common form!
   - autoimmune inflammation of the pituitary stalk with **T-lymphocytic infiltrate**;
   - primarily in late pregnancy or early postpartum period

2. Granulomatous - second most common form: more aggressive

3. Xanthomatous

4. Plasmacytic - part of **IgG4-related disease** (look for other CNS manifestation of IgG4-related disease - ***idiopathic hypertrophic pachymeningitis***) - infiltration with **IgG4-secreting plasma cells**; prompt response to oral steroids.

CLINICAL FEATURES

1. **Mass effect**.
2. Anterior **panhypopituitarism** +/- **diabetes insipidus** (50% patients) - hormone deficiencies out of proportion to radiographic findings.

DIAGNOSIS

- response to **steroids** is nonspecific (can also occur in other conditions).
- radiology: symmetric enlargement, bright enhancement, sella not remodeled
  - in adenoma, should see ***posteriorly compressed brightly enhancing normal pituitary*** (if not, suspect hypophysitis).
- diagnosis generally requires **biopsy**

TREATMENT

- natural course unknown.
- it is unclear whether **immune suppressing medications** improve pituitary function outcomes compared to supportive therapy.
- if mass effect is significant, **pituitary debulking** (rather than GTR) is feasible.

EMPTY SELLA SYNDROME

- arachnoid herniation through incomplete diaphragma sellae (sella enlargement with gland flattened on sellar floor)

- typical patient - female (> 80%), obese (75%), hypertensive (30%) with benign intracranial hypertension (10%) and CSF rhinorrhea (10%).
- no specific therapy is needed (but hypopituitarism may be present)

PITUITARY APOPLEXY

- hemorrhage or acute ischemia of pituitary gland (esp. **MACROADENOMAS**; rarely into normal hypophysis) → *hypothalamic*, *chiasmal*, *cavernous sinus*, *brainstem* compression - can be *lethal*!

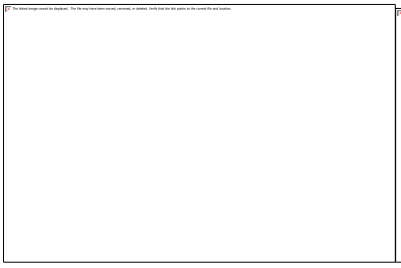
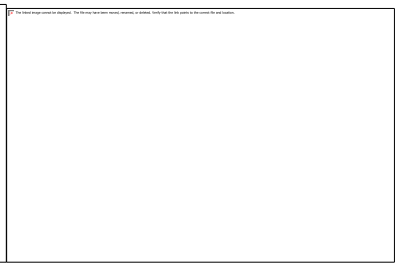
- pituitary apoplexy is only pituitary cause of *papilledema!*
- sudden-onset:
  A) **meningeal irritation** - severe headache (87%), nausea-vomiting, stiff neck, fever.
  B) **eye signs** - partial ophthalmoplegia, rapidly progressive visual loss.
  C) varying degrees of **acute panhypopituitarism** (73%) (e.g. vascular collapse ← deficient ACTH)
  D) **altered consciousness** (13%) ← hypothalamic compression.
- stable case: IV **fluids** + IV **high-dose steroid replacement**!
  Indications for **emergency trans-sphenoidal decompression**:
  a) rapidly deteriorating vision
  b) progression to coma!!!

CRANIOPHARYNGIOMA

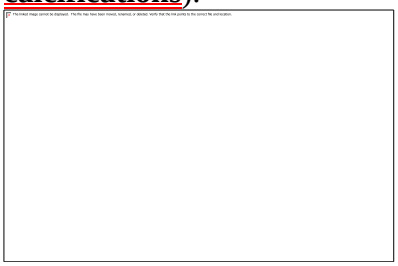
- **histologically benign** (grade 1 - do not undergo malignant degeneration) pediatric extra-axial tumor of Rathke's pouch stomodeal epithelium

- **solid** and **cystic** components (***machinery oil*** with floating *cholesterol crystals*); cyst rupture → intense sterile chemical meningitis.
- *intrasellar + suprasellar (70%); only suprasellar (20%), purely intrasellar (10%).*
- stimulate ***significant glial response*** (with profuse numbers of eosinophilic **Rosenthal fibers**)
- two main **histological types** - distinct tumor types in WHO 2021:

  1) **ADAMANTINOMATOUS form** (*children*; **embryogenetic** origin) - resembles enamel pulp of developing teeth; hallmark - areas of compactly arranged plump anuclear keratinocytes with keratin nodules ("wet" keratin, 80-90% are **calcified**)

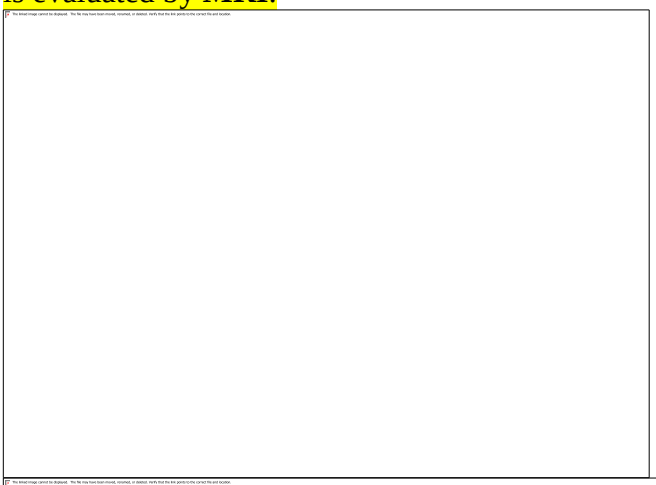
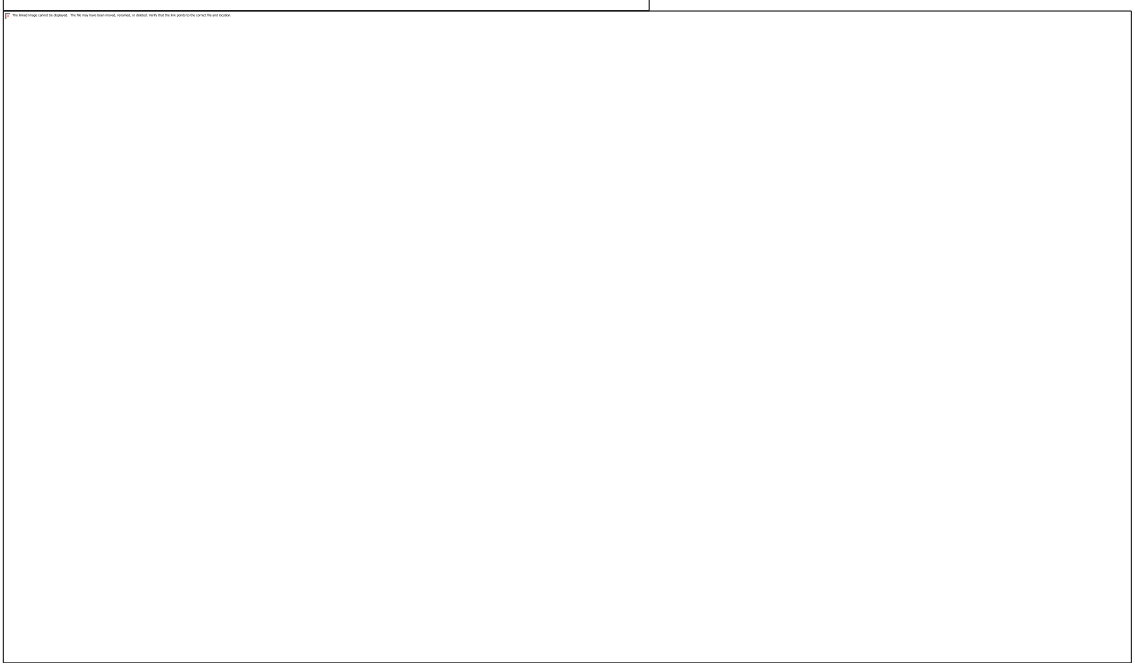



2) **SQUAMOUS PAPILLARY form** (*adults*; **metaplastic** origin, BRAF V600 mutation) – only simple squamous epithelium (no complex heterogeneous architecture, **no calcifications**):



- ***do not expand sella***
- **solid portions** and **capsule** show contrast enhancement.

  CT is enough for *diagnosis* (calcifications), but *tumor extension* (e.g. hypothalamus invasion) is evaluated by **MRI**.

- may have **malignant clinical course** (location + adherence to critical structures with difficult removal + ability to recur)

- because of slow growth, *papilledema* is less common than *optic pallor*.

TREATMENT

Old asymptomatic patient → **observation**
Else - surgery for cyst decompression and removal of accessible tumor;
Preop endocrine eval (same as for pituitary adenomas!)

- **total resection** may be attempted: all tumors should be **aspirated** (even if they appear solid radiographically) → tumor gradually mobilized (using modern microsurgical techniques, 90% success rate); if successful – no further treatment is required, just serial **neuroradiological follow-up**
- tight adherence to surrounding tissue (*optic apparatus*, *anterior cerebral artery*, or *hypothalamus*) - complete resection hazardous → observation / radiotherapy.

N.B. multiple comparisons strongly suggest that patients treated with **subtotal resection + irradiation** have **less neuroendocrine dysfunction and fewer neurologic deficits** than those who have had aggressive attempts at complete resection (hypothalamic injury!!! → ***neuropsychological deficits***)

- 11.5 Gy marginal dose SRS - only benign tumor that can completely disappear after SRS!!!
- large solitary *cysts* → treatment with intracavitary **radiocolloids** or BLEOMYCIN
  - if *radiocolloid leaks* → moyamoya-like disease!

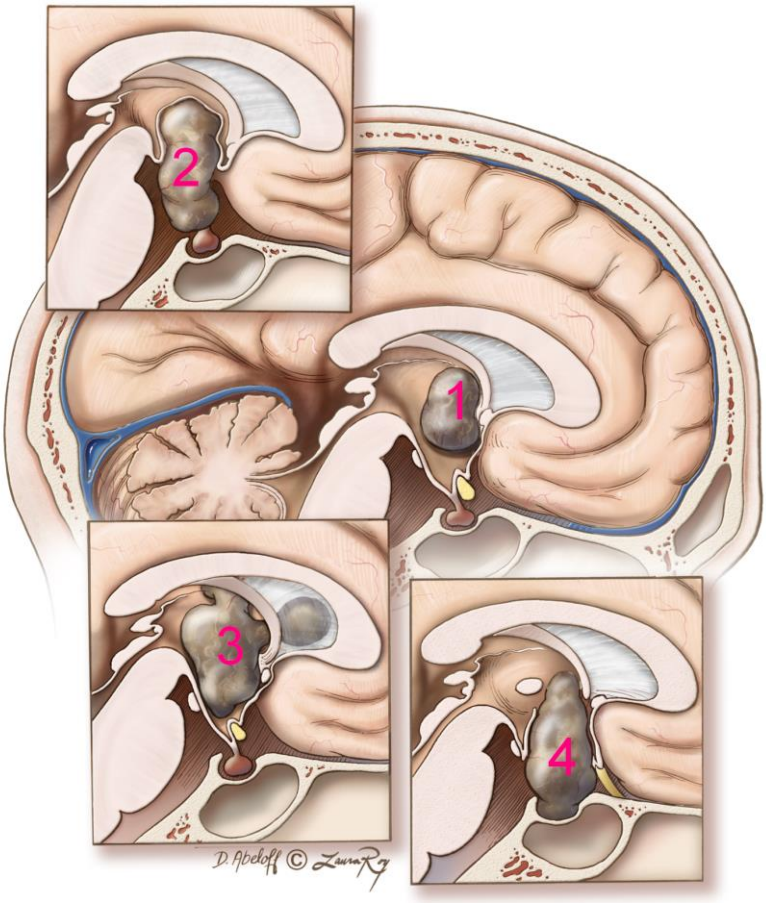
- preoperative ***steroids*** are strongly recommended in all patients → postop hydrocortisone + dex
- ***fluid and electrolyte balance*** should be monitored closely (DI, SIADH, cerebral salt wasting are common in postoperative period!).

Approach:

a) endoscopic endonasal (EES) – preferred
b) open
c) stereotactic cyst aspiration – palliative for purely cystic tumors

floor of the third ventricle (important factor in approach selection):
affected → endoscopic endonasal
intact → translamina terminalis or transcallosal
retrochiasmatic craniopharyngioma - no safe and effective transcranial corridor (H: readily exposed via endoscopic transnasal trajectory)

1 (intraventricular craniopharyngioma) → transcallosal.
2 (tumor with **engulfment of the pituitary stalk** – stalk salvage impossible) → endoscopic transnasal transtuberculum.
3 (multicompartment) → transcallosal.
4 (fills the sella) → endoscopic transnasal expanded transsellar.



a) tumors *located primarily in sella* can be removed **transsphenoidally** (if sella is not enlarged, transsphenoidal approach needs expansion – to drill off tuberculum); *large cysts that enter sella* can be drained and resected transsphenoidally (or leave stent into sphenoid sinus, assuming no CSF aspirated)

b) **subfrontal** approach - for lesions that lie *anterior to optic chiasm* (tissue behind chiasm can be mobilized by dissecting through lamina terminalis – needs significant frontal lobe retraction (free arachnoid adhesions to olfactory tracts and bulbs)

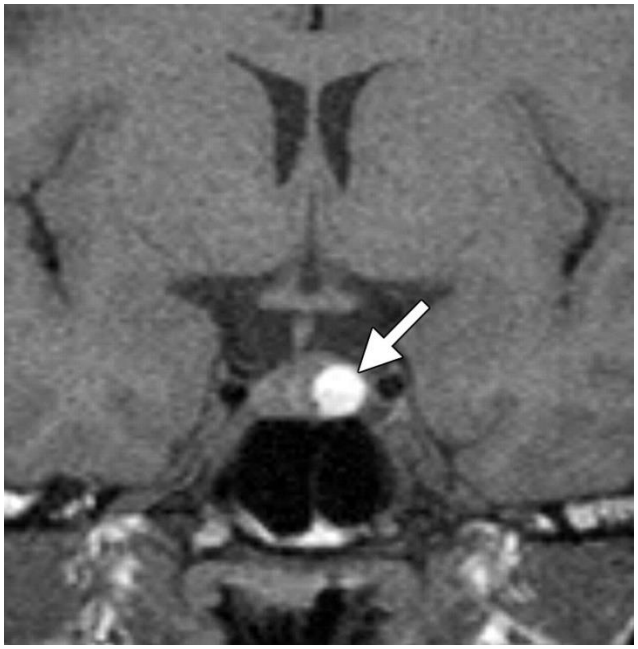
c) **pterional** approach (large frontotemporal flap up to OZ) - for lesions *extending onto dorsum sella or into temporal fossa*.

d) *tumors limited to 3rd ventricle* can be approached through corpus callosum (**interhemispheric**).

Neuropsychological deficits represent major limiting factor of independent social functioning because 1) patients often can overcome minor neurological deficits and 2) hormone-replacing therapies are widely available. Psychosocial impairment correlates directly with degree of hypothalamic injury sustained at time of surgery!

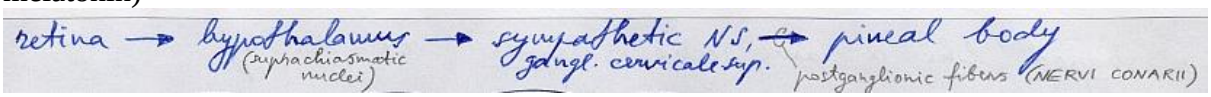
RATHKE CLEFT CYST

- common benign remnant of Rathke cleft.
- small intracystic nodules with high signal intensity at T1 and low signal intensity at T2 are characteristic feature:



PINEAL TUMORS

PINEALOCYTE - pineal parenchymal cell (specialized photoendocrine neuron); receives direct innervation by peripheral sympathetic nervous fibers (signals from retina)! (serotonin → melatonin)



Pineal area is outside BBB!

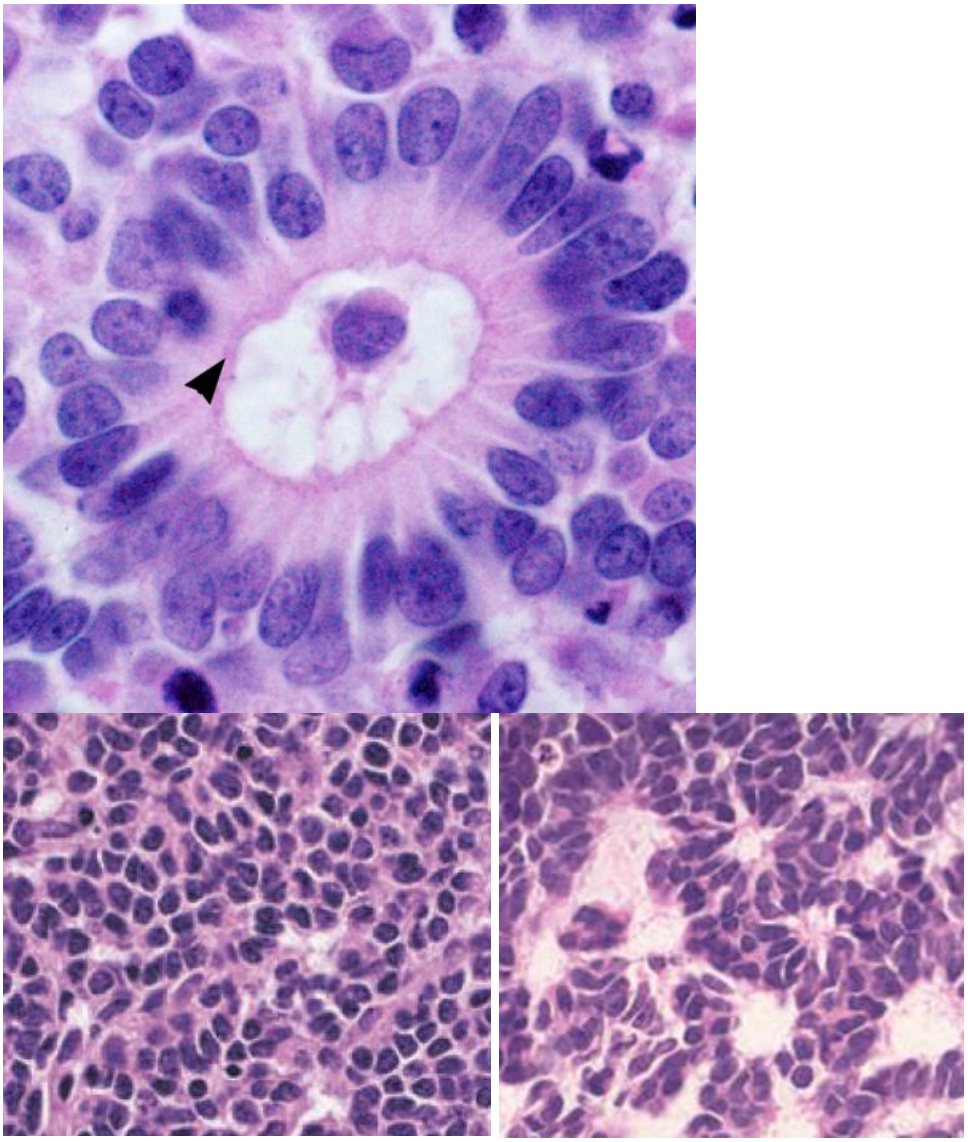
Pineal region has greatest variety of tumor types among CNS!

PINEAL REGION TUMOR is preferred general term.

- term PINEALOMA was originally used by Krabbe but is now obsolete.

1. Germ cell tumors (40-65%)
2. Glial cell tumors (15-25%)
3. Miscellaneous tumors and cysts
4. Pineal parenchymal tumors (17%):

1) **PINEOBLASTOMA** (WHO grade 4) (50%) – undifferentiated (primitive) highly malignant embryonal tumor in younger patients;
   - **poorly demarcated** - *propensity to seed subarachnoid space*
   - diffuse (patternless) dense growth of small primitive cells only interrupted by occasional **Homer-Wright rosettes** (≈ PNET in pineal gland) >>
   - less common are **Flexner-Wintersteiner rosettes** (differentiation toward *RETINOBLASTOMA* - ciliary 9 + 0 configuration similar to that of retinal photoreceptor; found in some cases of familial bilateral retinoblastoma - with RB1 gene abnormalities "TRILATERAL RETINOBLASTOMA"):



- tx: surgery → radiation ± chemotherapy; spinal irradiation *only for documented seeding*

2) **PINEOCYTOMA** (WHO grade I) – in adults.
   - tx: surgery

DIAGNOSTIC WORKUP

N.B. pineal calcification in child < 7 yrs is suggestive of neoplasm (normal pineal gland does not calcify at this age)

1. Imaging (MRI, MRV)

2. Send serum and CSF tumor markers + CSF cytology – to rule out germ cell tumors

   Absence of AFP or β-hCG does not rule out mixed germ cell tumor! – wait for frozen sections on biopsy before proceeding with tumor resection!

   placental alkaline phosphatase (PLAP) – useful only on immunohistochemical slides (i.e. not useful as CSF marker)

3. Biopsy

4. *Treat hydrocephalus prior to biopsy or resection*!
   ETV (endoscopic third ventriculostomy)* is better than ventriculoperitoneal shunt (peritoneal seeding is rare, but well-documented, complication!)

*may add biopsy with flexible endoscope

Biopsy is recommended whenever possible! (except in markedly elevated AFP and β-hCG)

A) preliminary part of **SURGICAL RESECTION**
B) **ENDOSCOPIC** (ETV first!)
   a) use ETV bur hole and flexible endoscope to go through foramen of Monroe posteriorly
   b) use separate more frontal bur hole and rigid endoscope
C) **STEREOTACTIC BIOPSY** – for known primary systemic tumors, multiple lesions, poor surgical candidates, brainstem invasion – ***laterosuperior trajectory***
   a) ***anterior*** (precoronal entry point - through thalamus)
   b) ***posterior*** (entry point near parieto-occipital junction - through sensory cortex)

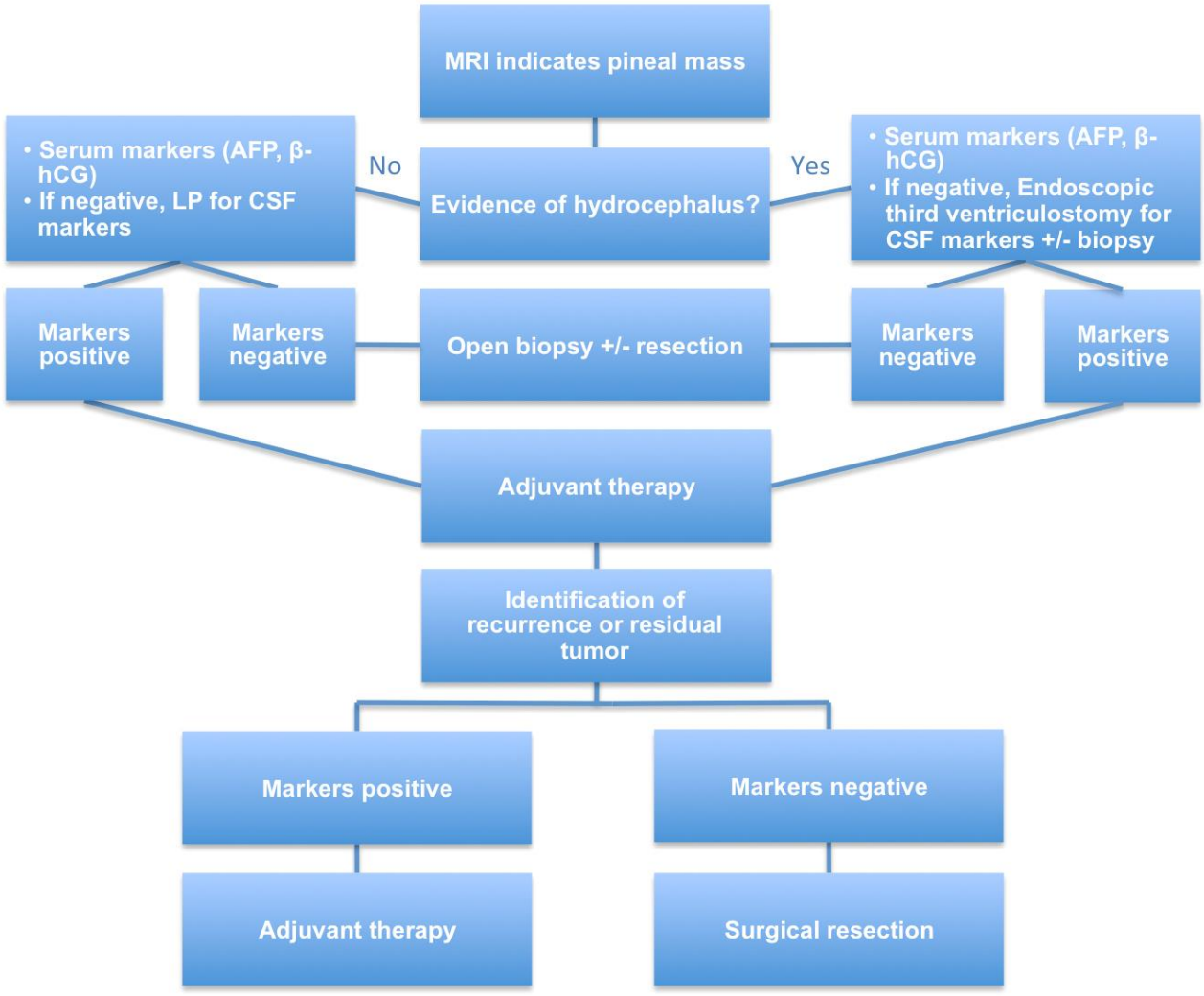
Main principle of pineal region tumors - rule out a nonoperative germ cell tumor (serum tumor markers → CSF tumor markers + cytology* → biopsy**)

*CSF cytology is rarely diagnostic, but the presence of malignant cells can obviate biopsy

****endoscopic biopsy** as part of ETV (if HCP present) or **stereotactic biopsy** or **open biopsy** (most reliable!) as first stage of resection

LP only if no HCP (otherwise, get CSF during ETV)!

N.B. most experts go for gross total resection for all symptomatic cases (with negative tumor markers) and do open biopsy!



SURGERY

Treat hydrocephalus prior to biopsy or resection! (e.g. ETV)

Except for well-encapsulated teratomas, *few pineal region tumors are amenable to complete resection*! Open resection remains preferable to endoscopic approach.

- blood supply of these tumors is from branches of the medial and lateral posterior choroidal arteries

Infratentorial-supracerebellar approach (the best approach in 80% of cases – either *sitting or prone position-concorde*) - with posterior surface of tumor exposed, central portion of capsule is cauterized and opened → debulked (suction, cautery, tumor forceps, CUSA) → as tumor is decompressed, capsule can be separated from surrounding thalamus

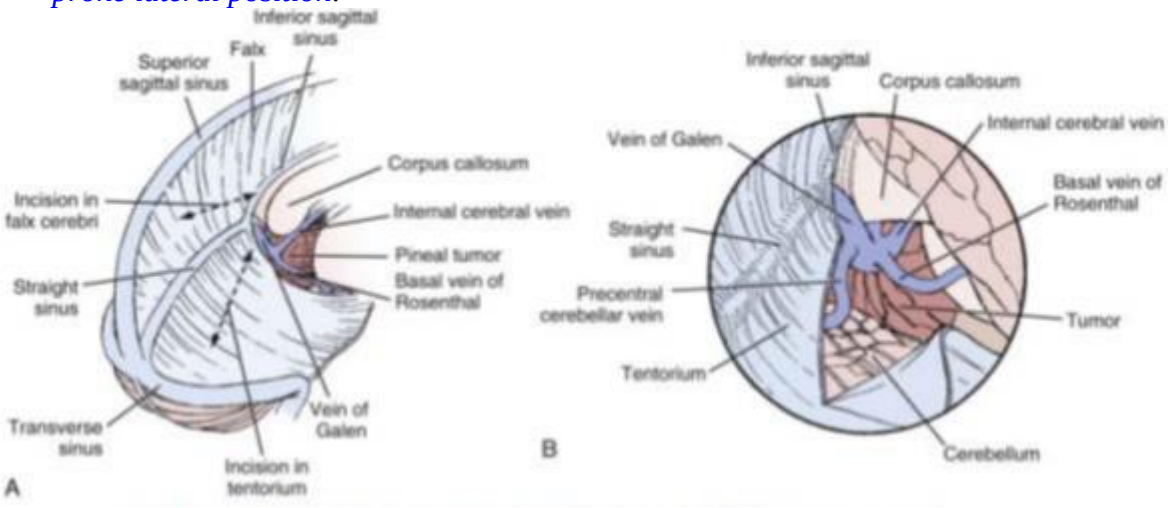
- most of vessels along wall of capsule are choroidal vessels and need not be preserved.
- dissection continues until third ventricle is encountered (can reach up to foramen of Monroe with long instruments)
- then retracting tumor superiorly and dissecting it bluntly off brainstem under direct vision
- finally, tumor is removed superiorly after separating attachments along velum interpositum and deep venous system

Densely adherent tumors necessitate subtotal resection to preserve deep venous structures and brainstem pial planes!

Supratentorial approaches preferred for large tumors:

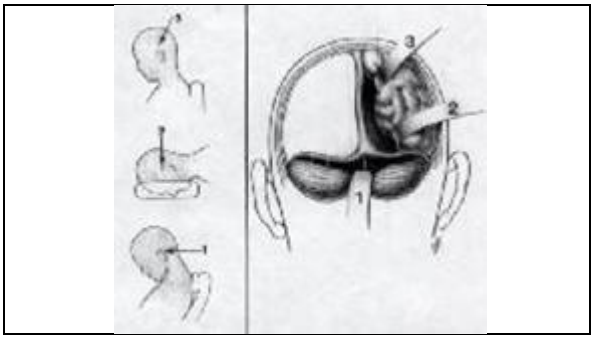
a) **parietal-interhemispheric-transcallosal approach** - paramedian trajectory between falx and right parietal lobe, with partial resection of corpus callosum; in *sitting or prone position* (unlikely that sufficient exposure can be achieved without sacrificing at least one bridging vein, although sacrifice of > 1 should be avoided; same with deep veins); posterior openings in splenium have been performed routinely without deficits.

b) **occipital-transtentorial approach** - requires retraction of occipital lobe (lack of bridging veins near occipital pole!; risk for hemianopia) and division of tentorium; perform in *three-quarter prone lateral position*.



c) **transcortical transventricular approach** through right lateral ventricle – only for tumors that extend into lateral ventricle

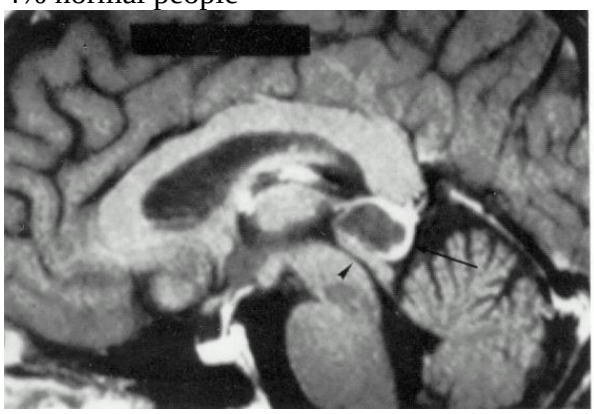
1 - supracerebellar-infratentorial approach. 2 - occipital-transtentorial approach. 3 - parietal-interhemispheric approach.



- preop – **MRV, spinal MRI** (perform before and > 2 weeks* after surgery)
  blood clots or operative debris can sometimes mimic spinal metastasis (H: serial images before instituting spinal irradiation) - incidence of spinal seeding is low, and prophylactic spinal irradiation is not recommended unless there is clear radiographic evidence of metastasis
  *exception - highly malignant PINEOBLASTOMAS
- pineal parenchymal tumors displace deep venous system superiorly - infratentorial-supracerebellar approach
  vs. MENINGIOMAS (arising from velum interpositum) or CORPUS CALLOSUM TUMORS - displace deep venous system ventrally - choose supratentorial approach.
- **tumor markers**, if present preoperatively, should be measured in postoperative period to serve as baseline.
- can recur locally / distally as late as 5 yrs after diagnosis! – regular MRI follow-up

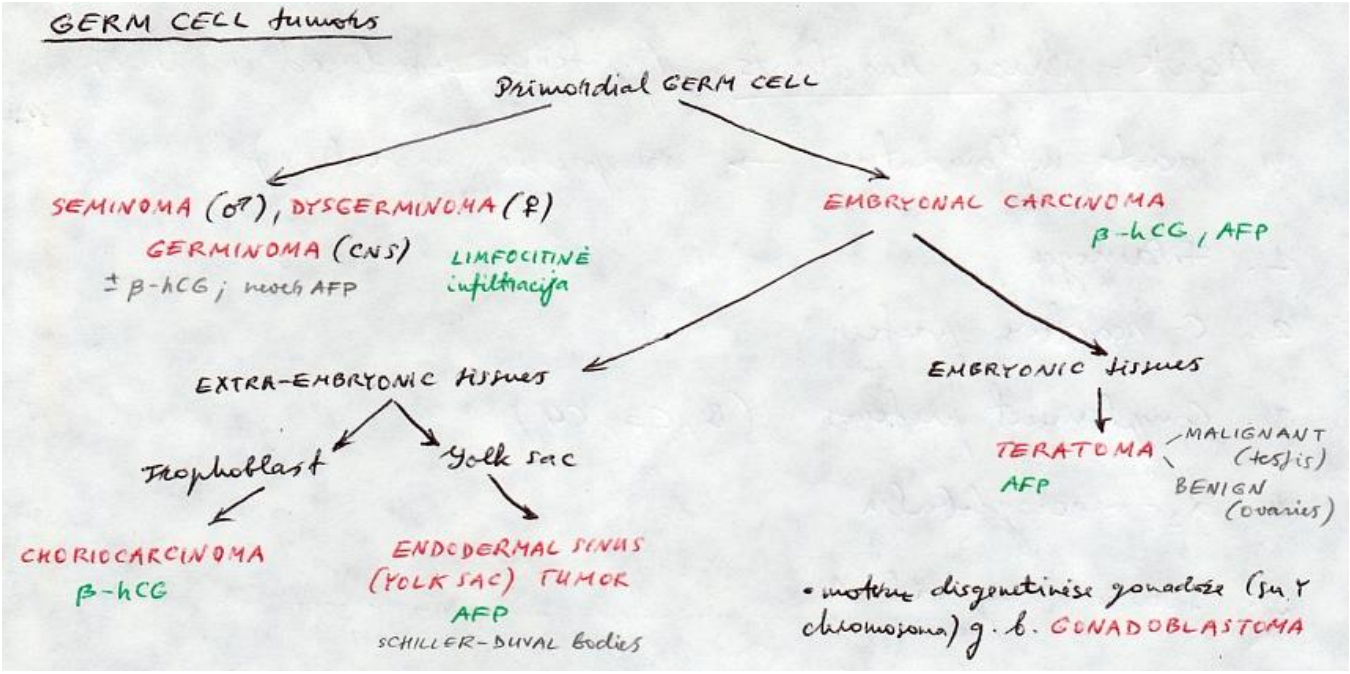
BENIGN PINEAL CYSTS

- 4% normal people



- static asymptomatic **anatomic variant** - does not require treatment but ensure with **follow up MRI** that lesion is not growing → hydrocephalus (if > 2 cm).

GERM CELLS



see also p. 2626 (germ cell tumors in ovaries) >>
see also p. 2611 (germ cell tumors in testicles) >>

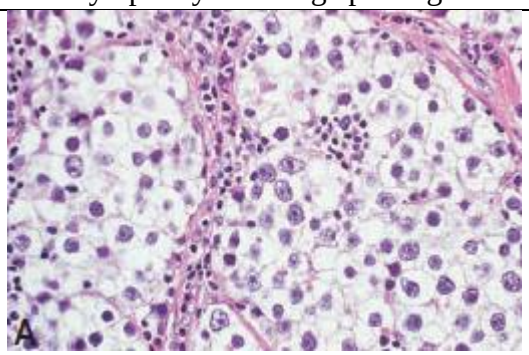
Malignant (except mature teratomas)!!!
Germinomas secrete placental alkaline phosphatase (PLAP), LDH, CEA!!!

Most patients - childhood or adolescence

- most prevalent in far-east Asia
- found primarily in midline, esp. **pineal** (55%) and **suprasellar**
  most prevalent neoplasms of pineal region in children!
- histologically indistinguishable from those found *extracranially*

A. **GERMINOMA (S. INTRACRANIAL SEMINOMA)** (60-70% of all germ cell tumors) - intermediate degree of malignancy; pathognomonic *"two-cell" appearance*:

mature dark lymphocytes + large pale* germinoma cells



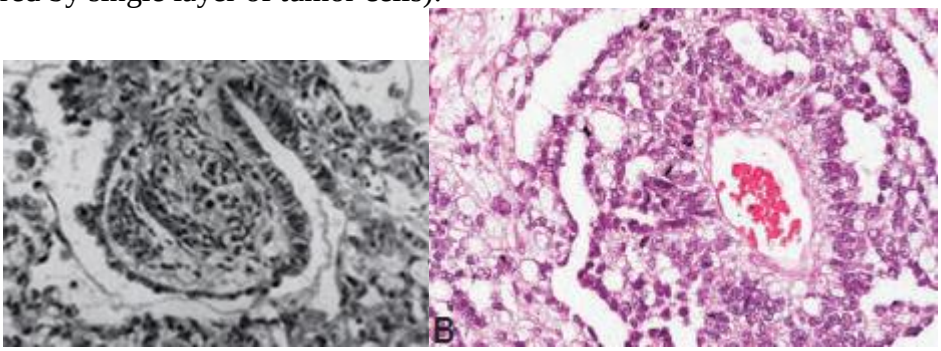
*lipids in cytoplasm

B. **NONGERMINOMATOUS germ cell tumors**:

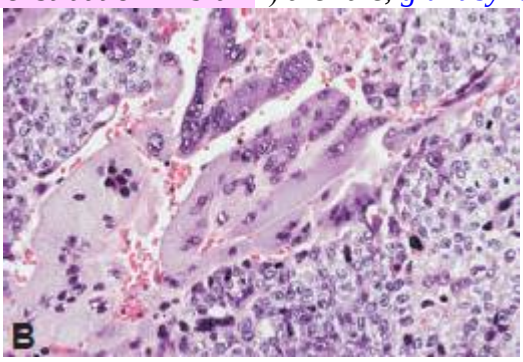
1) **EMBRYONAL CELL CARCINOMA*** (5%) - least differentiated and most malignant
   - may exceptionally replicate structure of early embryo - "**embryoid bodies**" (germ discs and miniature amniotic cavities).

2) **TERATOMA** (18%); contain fat!!!!!
   mature teratoma - mixture of "adult-type" tissues derived from all 3 germinal layers (may form **FETUS-IN-FETU**); does not secrete AFP!!!!
   vs. DERMOID – only ectoderm & mesoderm; EPIDERMOID – only ectoderm
   immature teratoma (s. teratoid); may secrete AFP!!!!

3) **YOLK SAC TUMOR (s. endodermal sinus tumor)***; contains **Schiller-Duval bodies** (pathognomonic glomeruloid structure - tumor cell–lined space with invaginated vascular pedicle covered by single layer of tumor cells):



4) **CHORIOCARCINOMA*** (5%) - **vascular channels**, **blood lakes** and extensive ***hemorrhagic necrosis*** ("menstruation in brain") are rule; *giant syncytiotrophoblastic cells*:



*highly malignant

Clinic

May cause **pseudoprecocious*** **puberty**:

**pseudo* because hypothalamic-gonadal axis is not mature

a) tumor secretion of hCG [properties of LH] → testosterone production by neoplastic syncytiotrophoblasts in boys.
b) tumor expression of cytochrome P450 aromatase → conversion of C19 steroids to estrogens → precocious puberty in girls.

Diagnosis

- **MRI** is largely nonspecific - **solid** masses, prominent homogenous contrast **enhancement**
- presurgical assessment and F/U after treatment: **AFP** + **ß-HCG** + **PLAP** + **CEA** in serum and CSF:

Tumor	AFP	β-hCG
*pure germinoma**		
mixed germinoma with syncytiotrophoblastic giant cells		+
mature teratomas		
immature teratomas	±	
endodermal sinus tumors	+	
choriocarcinomas		+
embryonal cell carcinomas	+	+

**GERMINOMAS* also secrete lactic dehydrogenase (LDH) isoenzyme and placental alkaline phosphatase (PLAP) – but useful only on immunohistochemical slides; some use also for follow up in serum! *GERMINOMAS* may also secrete CEA

- **biopsy** - recommended whenever possible! (except in markedly elevated AFP and β-hCG – check before biopsy!)

Treatment (SRS has no role)

GERMINOMAS – **radiation** - among most radiosensitive tumors (chemotherapy is not required)

NONGERMINOMATOUS GERM CELL TUMORS – **chemotherapy** → restaging → radiation: local vs. craniospinal

mature teratomas – cured with surgery alone

- markedly elevated AFP and β-hCG (pathognomonic for *GERM CELL TUMORS*) → trial chemotherapy or radiotherapy without tissue biopsy!

Prognosis:

MATURE TERATOMAS > *GERMINOMAS* (excellent prognosis; > 90% 5-yr survival) > *PINEAL CELL TUMORS* > *NONGERMINOMATOUS GERM CELL TUMORS* (patients rarely survive beyond 2 years)

GASTRULATION INCLUSION CYSTS

EPIDERMOID, DERMOID, RATHKE CLEFT CYST, COLLOID CYST, NEURENTERIC CYSTS

- benign **EXTRA-AXIAL** dysraphic malformations (inclusion cysts) at GASTRULATION stage

DERMOID AND EPIDERMOID CYSTS, DERMAL SINUS TRACTS – surface ectoderm malformation.

NEURENTERIC CYSTS, RATHKE CLEFT CYSTS, COLLOID CYSTS – all the same just different location – endodermal malformation.

Any infant with dermal sinus tract → neuroradiological evaluation!

EPIDERMOIDS have outer **connective tissue capsule** and are lined with **stratified squamous epithelium** (i.e. composed of *ectodermal* remnants); most commonly **lateral** (CP angle; dif. CHOLESTEATOMA); may have macroscopic "keratin pearls" in wall (histo – cell nuclei among keratin); may be **acquired** from LP without stylet.

DERMOIDS have outer **connective tissue capsule** and are lined with **stratified squamous epithelium**, which also contains hair follicles, sebaceous and sweat glands (i.e. composed of *ectodermal* and *mesodermal* remnants); in **midline** (esp. posterior fossa, cauda equina)

NEURENTERIC CYSTS - *endodermal* malformation; **ventral**

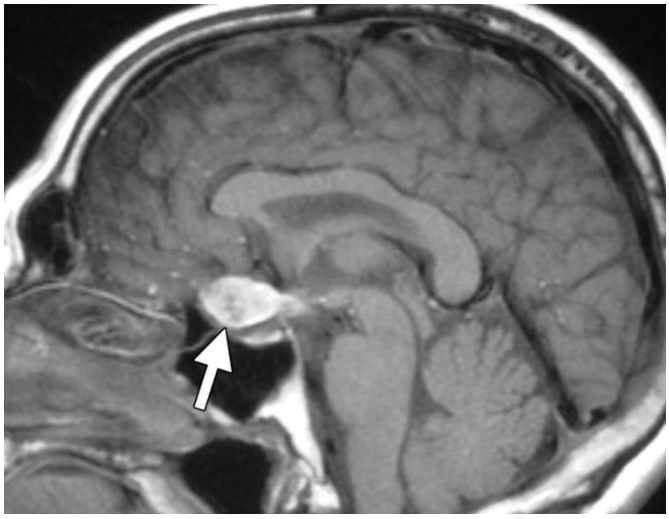
vs. *TERATOMAS* - composed of *ectoderm*, *mesoderm*, and *endoderm*

(EPI)DERMOID

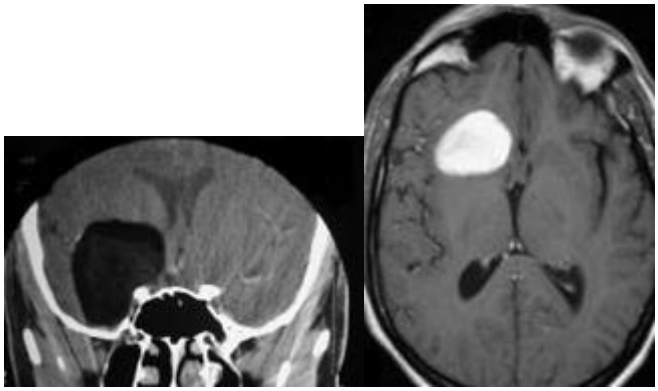
- benign inclusion cysts (not true neoplasms!) composed of **ectodermal elements** secondary to congenital or posttraumatic epidermal or dermal inclusions.
- *EPIDERMOIDS* 4-10 times more frequent than *DERMOIDS*
- clinically – **insidious mass effect** (dermoids grow faster [than epidermoids] → manifest earlier).
- *expand slowly over many years* - central accumulation of epithelial debris and glandular secretions – predictable ***linear growth*** (vs. tumors – ***grow exponentially*** due to cell multiplication).
- *EPIDERMOIDS* > *DERMOIDS* may stain positive for **CA19-9** (tumor marker for pancreatic cancer)
- **CT** – hypodense (fat)
- **MRI** - no enhancement, no edema!!!; diffusion restriction on DWI (vs. arachnoid cysts – no diffusion restriction)

EPIDERMOID - similar to CSF – hypointense on T1 and hyperintense on T2 (epidermoid has diffusion restriction vs arachnoid cyst)
DERMOID - similar to fat – hyperintense on both T1 and T2 – unique tumor.

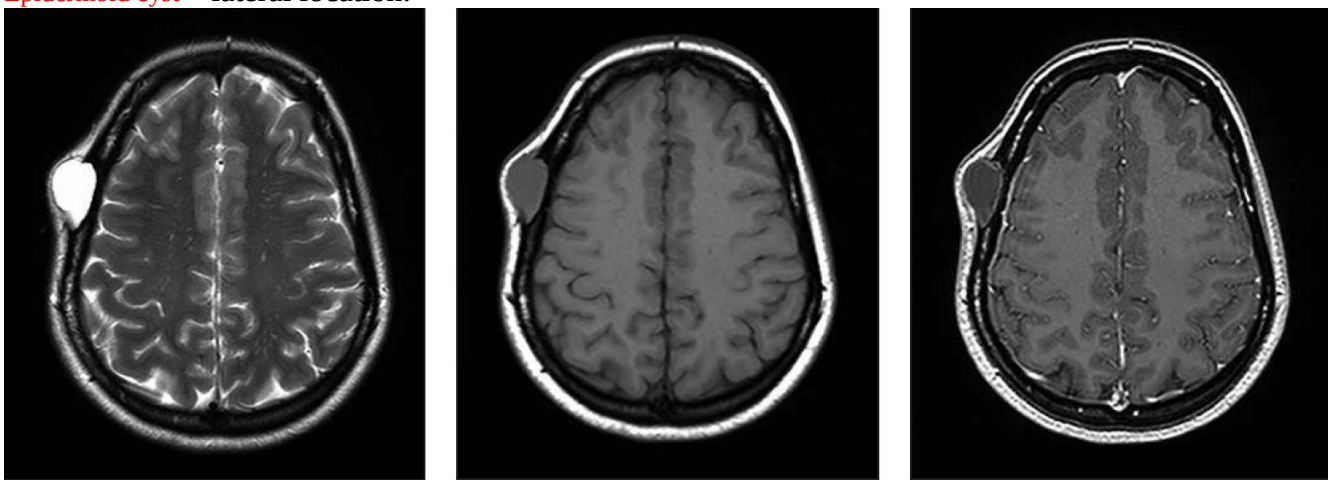
- *cyst rupture and spillage* → acute chemical meningitis or increased ICP (maybe fatal):



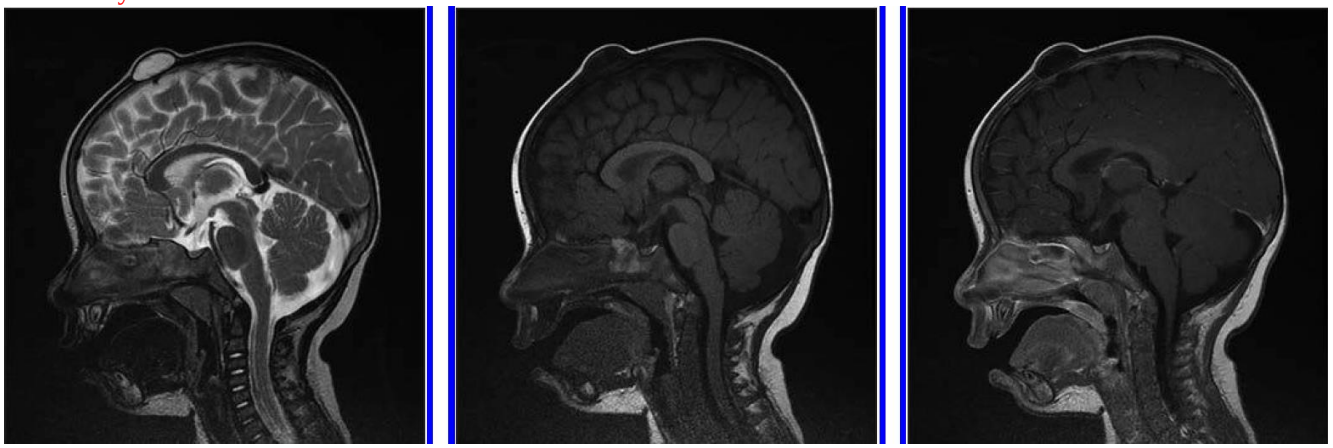
Dermoid:



Epidermoid cyst – lateral location:



Dermoid cyst – midline location:



- treatment - complete **excision**
  - avoid spilling of contents → chemical meningitis; prophylaxis – irrigation with dexamethasone solution intraop + 2 weeks of DEXAMETHASONE.
  - fragments of capsule adherent to important structures are left to avoid neural or vascular injury.

COLLOID CYSTS

- congenital benign cyst in 3rd ventricle → postural intermittent obstructive hydrocephalus with paroxysmal headache, N/V, AMS associated with changing head position (*up to sudden death*)
  - short-term memory deficits due to fornix stretching!

- **CT** - 66% hyperdense and 33% isodense.
- **MRI** - all depends on cyst contents; dif – basilar tip aneurysm!

Strategy:
a) small cyst, normal ventricles, few or no symptoms → **observation** with serial MRIs.
b) large cyst & hydrocephalus → **surgery**:

- **endoscopic / transcortical approach** – only if enough hydrocephalus is present (best for large hydrocephalus); risk of *venous bleeding* on the other side – do septostomy early, leave EVD! risk of *fornix* stretch; risk of *seizures* via transcortical routes. see p. Op340 >>
- **transcallosal approach** (best for small hydrocephalus) see p. Op340 >>
- **subfrontal lamina terminalis approach**

Endoscopic – least invasive, but less likely complete resection; can be used only on cysts that can be aspirated
Open – more complications.

N.B. prevention of sudden death is not indication for surgery in asymptomatic patients with small cysts and no hydrocephalus!

- cysts > 10 mm associated with increased risk of hydrocephalus.
- headaches, in absence of hydrocephalus, is *not* indication for intervention!
  - explain to patient that cyst stretches fornix - look for preoperative short memory deficits – those may worsen postop if even unilateral fornix is further violated surgically.

  - shrink choroid plexus over foramen with gentle bipolar coagulation
  - cyst is **punctured** and contents are **aspirated** → **careful circumdissection** → completely remove (leave portion of cyst behind if it is attached to thalamostriate or internal cerebral veins).
    - *septal vein* may be disconnected from *thalamostriate vein* to expand transforaminal corridor via a small anterior transchoroidal dissection - obviates excessive manipulation of fornix.
- do not leave **EVD** as procedure is usually pristine (vs. if required preoperative EVD, it is left in ventricle and weaned off postoperatively).

Hydrocephalus may develop despite cyst removal; H: periodic CT.

NEURENTERIC CYSTS

Neurenteric canal – normal embryologic transitory communication between neural tube ECTODERM, NOTOCHORDAL canal, and gut ENDODERM; canal persistence → **VENTRAL EXTRA-AXIAL** paravertebral neurenteric cyst(s) or fistula(s).

- almost pathognomonically associated with vertebral anomalies or diastematomyelia.

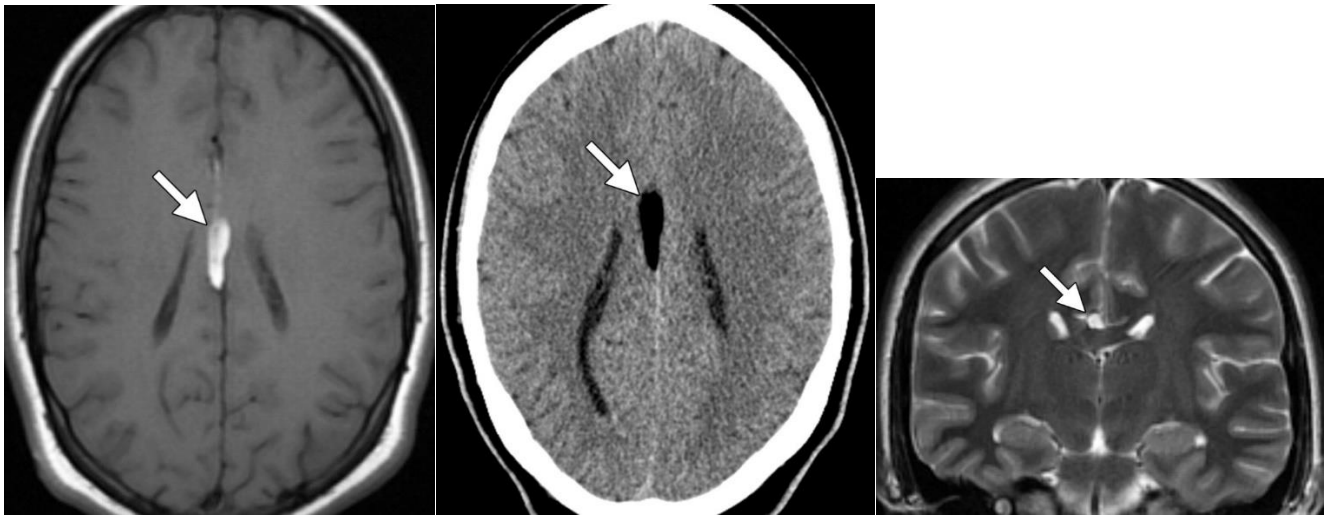
- **mucin-containing cells** (PAS stain)
- persistent fistulas (between enteric structures and these cysts within CNS) → recurrent aseptic meningitis.
- **MRI** - often parallel signal intensity of CSF.
- treatment - **complete resection** (vs. cyst aspiration, marsupialization, or cyst-subarachnoid shunt - in difficult cases).

ARACHNOID CYSTS

- ***anywhere on brain surface***.
- contain fluid identical to CSF - **no diffusion restriction**, never calcify!
- almost all occur in relation to arachnoid cistern (exception: intrasellar - only one that is extradural).
- middle fossa cysts are notorious for hemorrhage due to tearing of bridging veins.
- *asymptomatic* - single follow-up imaging in 6–8 months is adequate to rule-out any increase in size (children need to be followed until adulthood).
- surgery in ***symptomatic***:
  a) cyst **aspiration** – high rate of recurrence.
  b) cyst **fenestration** – best treatment!
  c) cyst **shunting** – second best treatment; into peritoneum, use a low pressure valve.
  d) cyst **excision** - significant *morbidity and mortality* (may be due to abrupt decompression)

  Suprasellar cysts (endocrinopathies tend to persist even after successful treatment of suprasellar cysts):
  a) endoscopic / percutaneous **ventriculo-cystostomy** - procedure of choice.
  b) subfrontal or transcallosal **cystectomy** - dangerous and ineffective.
  N.B. simple VPS promotes cyst growth!

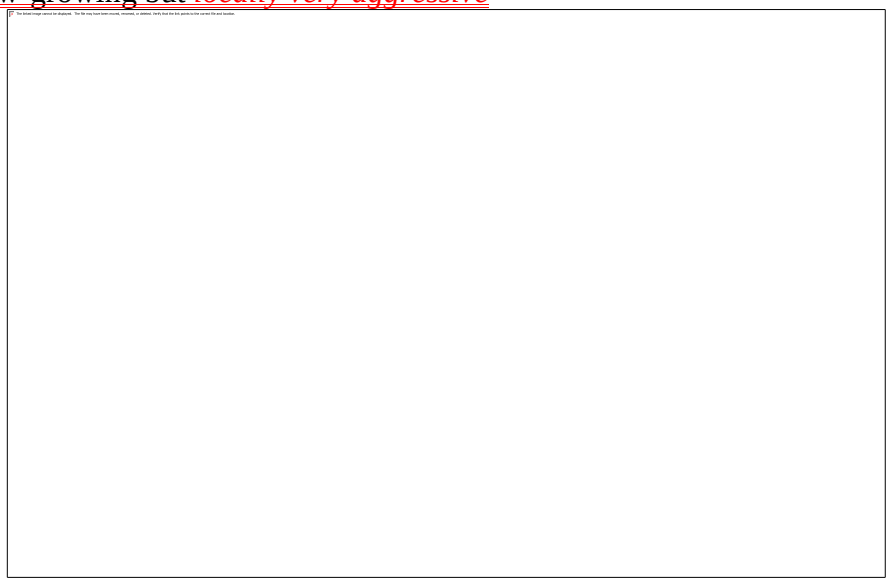
LIPOMA



CHORDOMA

- extradural malignant tumor of ectopic notochordal remnants (i.e. embryonal tumor).
- midline along axial skeleton: **sacrum > clivus > vertebrae.**
- uniform large ***physaliphorous cells*** ["bubble carrying"] – numerous VACUOLES in cytoplasm.
- abundant ***mucinous matrix***

- slow-growing but *locally very aggressive*

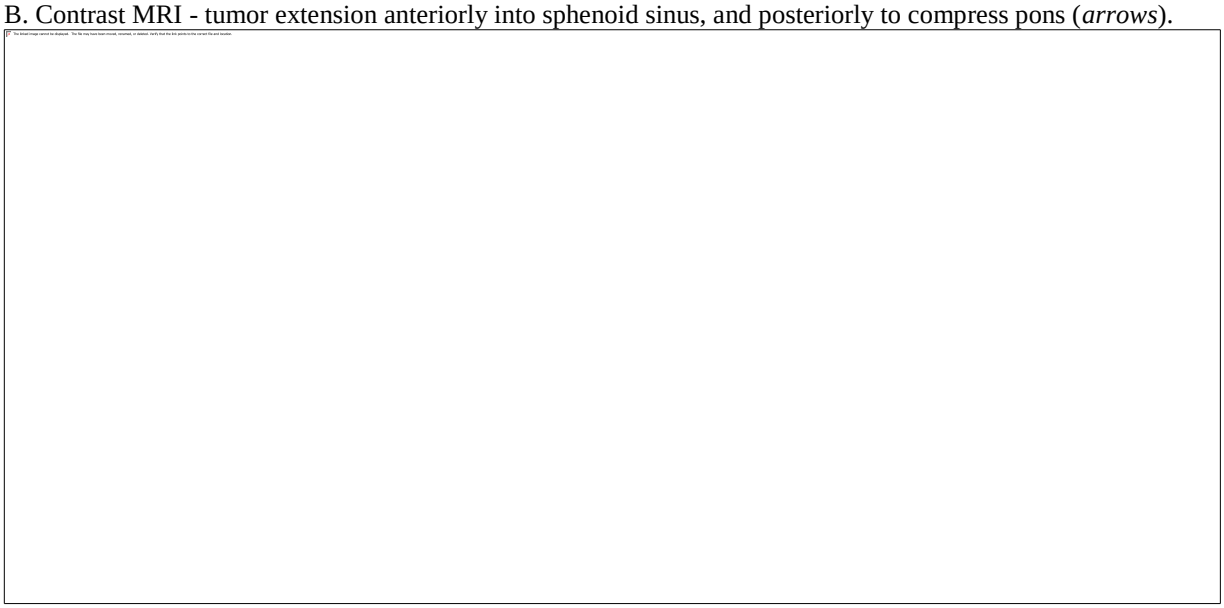


Brachyury gene - early mutational event in chordoma evolution.

- differentiates chordoma from chondrosarcoma.
- gives poor prognosis – progression-free survival 5 mos (vs. 13 mos in absence of Brachyury mutation).

CT – extra-axial hypodense area with significant erosion (of clivus, vertebrae, or sacrum) displacing brain stem or other structures; **calcification** (87%); variable enhancement.

Clival chordoma:
A. T2-MRI - chordoma of clivus (*arrows*).
B. Contrast MRI - tumor extension anteriorly into sphenoid sinus, and posteriorly to compress pons (*arrows*).



Surgical resection (*complete excision is difficult at best*) → **radiotherapy** with **proton** beams

- high rate of *multiple local recurrences*
- many experts mandate FNA biopsy all suspected chordomas (→ preop proton beam), others are afraid of biopsy tract seeding!

Tumors showing good results with **chemotherapy**

1. **Osteosarcoma** - cisplatin, ifosfamide, bleomycin, actinomycin D, and alfa-interferon
2. **Chordoma** - tyrosine kinase inhibitors

Approach for surgery:

a. **upper clivus** tumor - *transseptal, transsphenoidal*.

b. **lateralized upper clival** or **lateralized midclival** tumor - through *sphenoethmoidectomy* (± maxillectomy).
c. **midline midclival** or **lower clivus** tumor - *transoral*.

Ecchordosis physaliphora - small, well-circumscribed, gelatinous masses adherent to brainstem.
- although composed of notochordal remnants, seldom (if ever) progresses into *CHORDOMA*.
- found in ≈ 2% autopsies!

SKULL TUMORS

- 20% are **benign** and 80% - **malignant**.
  - most common benign - osteoma and hemangioma.
  - most common malignancy – osteosarcoma.
- *malignant transformation* (to osteosarcoma, chondrosarcoma, or fibrosarcoma) - in 2% *PAGET DISEASE* and 0.5% *FIBROUS DYSPLASIA* cases.

DIAGNOSIS

Plain X-ray / CT

There is enough overlap of features to prevent any systematic means of determining etiology of all or even most radiographic skull lucencies.

a) radiolucent (osteolytic) – most tumors (benign and malignant)
b) radiopaque (osteoblastic) – *OSTEOMA*, *OSSIFYING FIBROMA*, *INTRAOSSEOUS MENINGIOMA*, sclerotic form of *FIBROUS DYSPLASIA*, later stages of *PAGET DISEASE*, some *METASTASES* (e.g. prostate, breast, bladder, hypernephroma).

Malignant tumors – single large or multiple lesions, irregular poorly defined borders, no periosteal reaction (no sclerosis).
Benign tumors – single, small, grossly round / oval lesion, with peripheral sclerosis, intralesional calcifications, peripheral bone vascularity.

Some helpful features for lytic lesions:
1. **Multiplicity** - presence of ≥ 6 lesions = metastases (> 50% cases are from breast), myeloma, Langerhans cell histiocytosis
2. **Diffuse / extensive**: fibrous dysplasia, Paget disease
3. **Origin** (intradiploic, full thickness, inner or outer table only):
   a) most vault lesions originate intradiploically, so limitation to this space may merely signify early recognition of lesion.
   b) expansion of diploë with bulging of tables = benign lesion.
   c) full thickness lesions affecting both tables congruently = malignancy.
4. **Edges**:
   a) smooth edges, whether regular, distinct, or indistinct: no predictive value.
   b) irregular margins (especially ragged undermined edges): osteomyelitis or malignancy.
   c) sharply demarcated, full thickness punched out defects: suggest myeloma.
5. Circumferential sclerosis suggests benignity.
6. Peripheral vascular channels: highly suggestive of benign lesions (seen in ≈ 66% of venous lakes and ≈ 50% of hemangiomas)
7. **Pattern within lucency**:
   a) hemangiomas - honeycomb or trabecular or sunburst pattern

b) fibrous dysplasia - well-defined islands of bone, grossly mottled appearance with randomly arranged cystic and dense areas.

8. **Pain**: Langerhans cell histiocytosis.
9. **Location** on cranial vault (high vs. low): poor correlation with benign vs. malignant lesions
   - lesion LOCATION is of little differential diagnostic value, but certain tendencies exist.

MRI – because skull lesions may have an intracranial component.
- hypointense on T1, hyperintense on T2.
- some degree of contrast enhancement is common.

Brain and skull mts image review protocol: **parenchymal** - gadolinium MPRAGE, FLAIR (not all mts enhance so FLAIR is even more sensitive, esp. for small mts) **calvarial** - DWI (bright areas in the skull; vs. bone marrow abnormalities - will be diffuse signal along entire skull)

Nuclear bone scan - helpful adjunctive test for specific lesions.
- "hot" area of increased radioisotope uptake (*OSTEOMAS*, *OSSIFYING FIBROMAS*, *OSTEOBLASTOMAS*, all *malignant tumors*).

Biopsy - paramount importance! (esp. for questionable skull lesions).
- if bone has not been destroyed – use Craig needle.

Arteriography - high vascularity (tumors of *vascular origin*, *MULTIPLE MYELOMA*); not helpful in diagnosis of other tumors.

Solitary lesion in kids – dermoid vs. Langerhans-cell histiocytosis – usually, solitary lesions need resection; if high-risk (air sinus, orbit involvement) – adjuvant therapy
Preop work-up:
1) skeletal survey
2) LFTs

TREATMENT

A. Observation
B. Biopsy
C. Resection
D. Medical treatment

Malignant - surgery is treatment of choice for cure (except *MULTIPLE MYELOMA* → chemo)
- if other means cannot control tumor expansion, surgery is still option in metastatic disease (esp. for solitary lesions)
- **complete en bloc resection** is preferred (with extensive margins for *malignant tumors*).
- preoperative embolization is recommended for *ANGIOSARCOMAS*
- unresectable lesions → curettage, SRS.
- **SRS** is primary treatment for metastases, secondary *OSTEOSARCOMA* (esp. in elderly patients), *MULTIPLE MYELOMA* (if chemotherapy fails).
- tumors showing good results with **chemotherapy**
  - **Osteosarcoma** - cisplatin, ifosfamide, bleomycin, actinomycin D, and alfa-interferon
  - **Chordoma** - tyrosine kinase inhibitors

No treatment is required for asymptomatic **benign** lesions unless diagnostic concerns exist!

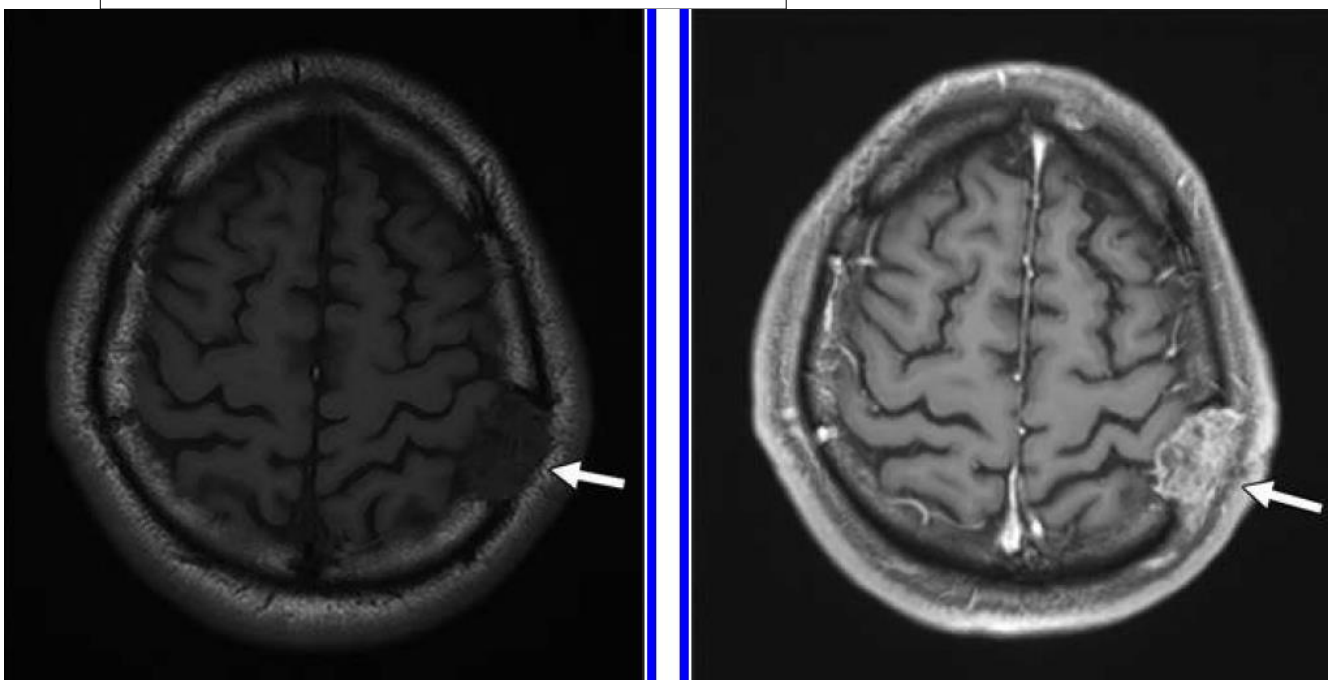
- pain control - aspirin or NSAIDs.
- surgery - for symptomatic relief, cosmetic reasons, or cranial nerve decompression.

MULTIPLE MYELOMA, *PLASMACYTOMA* – see "Intro (neuro - oncology - spine, nerves).pdf"

METASTASES (skull is common site!); dura is effective barrier - *brain invasion is rare*

- **osteoblastic** mts - breast, prostate, bladder, hypernephroma.

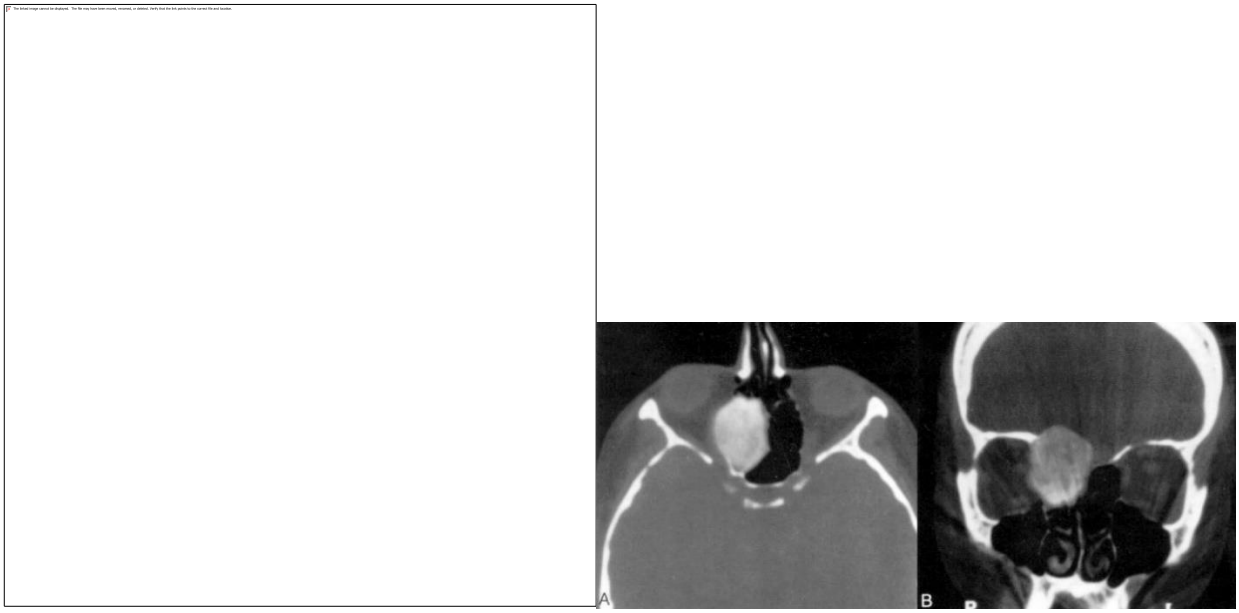
HEMANGIOMA - classic *"sunburst"* or *"spoke wheel" pattern*



Surgical resection with preop embolization.
Radiotherapy stops tumor progression but cannot reduce tumor volume.

FIBROUS DYSPLASIA – developmental anomaly (not true neoplasm); most are asymptomatic vs. progressive deformity; *"ground glass"* - skull lucency with patches of increased density.

- disease of osteoblasts (vs. Paget disease – of osteoclasts)
- most commonly presents in the teens or 20s - lesions grow during childhood and usually do not progress beyond puberty.
- most are asymptomatic.



Typical slow progression does not justify prophylactic surgery
Symptomatic patients:
1) bisphosphonate therapy
2) surgical decompression - curettage, bone allografting, stabilization.

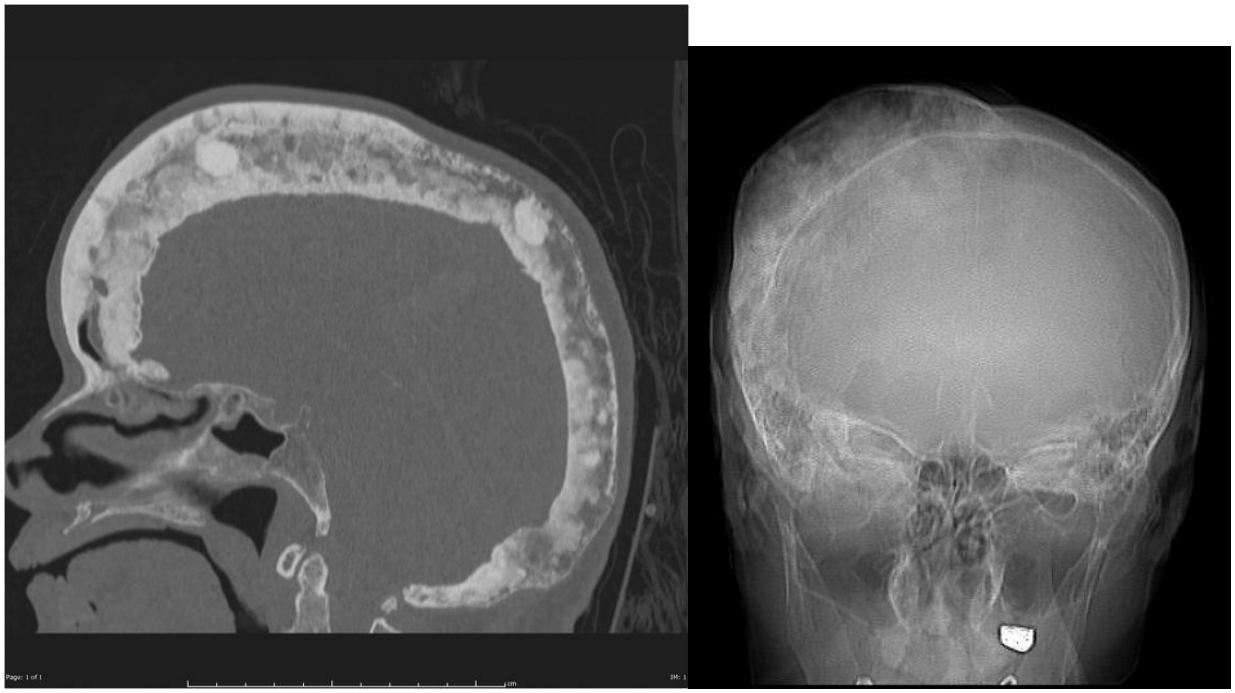
PAGET DISEASE – chronic disease of osteoclasts - excessive abnormal bone remodeling → expanded bone with a coarsened trabecular pattern.

N.B. can be confused with fibrous dysplasia, but occurs in older age! (patients are older than in fibrous dysplasia)

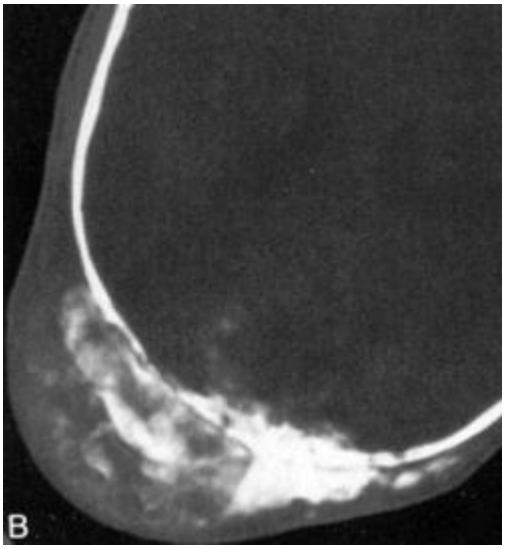
- 75% are asymptomatic; others – pain with deformities (historically, *changing hat size* was a giveaway), compression
  - may cause cranial nerve compression (e.g. hearing loss), vascular compression, basilar impression
- AlkPhos↑ (but normal [Ca] and [phosphate]), urine hydroxyproline↑
- positive **bone scan** - highly sensitive but not specific

  Lincoln sign: diffuse mandibular uptake forming a bearded appearance
- imaging – lytic and sclerotic areas.
- treatment is medical – **bisphosphonates** (!!!), CALCITONIN, NSAIDs.
- malignant degeneration (1% = secondary osteosarcoma) / deformations (esp. spine) → surgery (profuse bleeding!!!)

Widening of diploic space, typical "cotton wool" appearance (mixed lytic and sclerotic lesions) and over-riding enlarged frontal bone (**Tam o' Shanter hat sign**):



OSTEOSARCOMA (second most frequent malignant skull tumor after multiple myeloma); *sun-ray picture*:



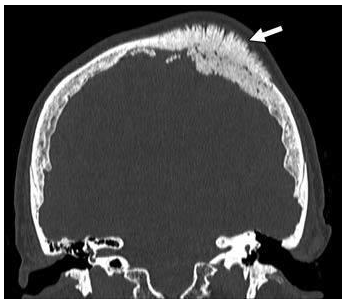
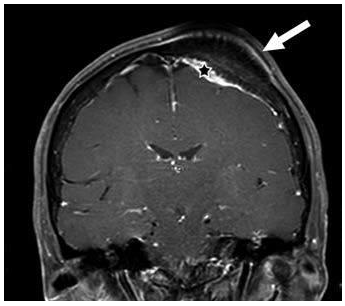
CHONDROSARCOMA (third most common malignant skull tumor)

EWING SARCOMA - typical *onion skin appearance* (laminated periosteal changes); uniform, densely packed small cells.

OSTEOID OSTEOMA - nocturnal local tenderness relieved by NSAIDs.
OSTEOMA – no oncological indications for treatment.

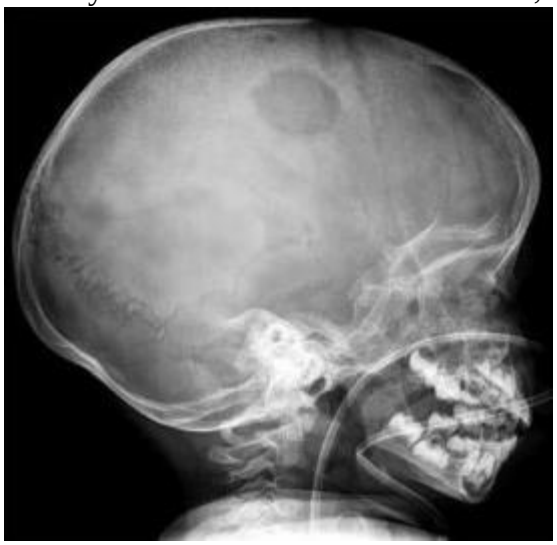
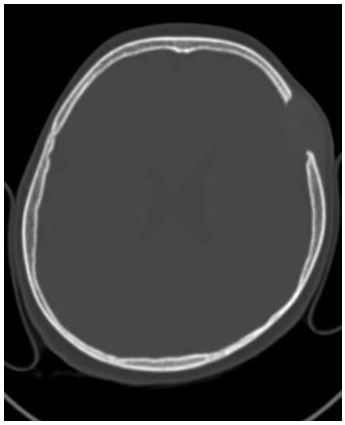
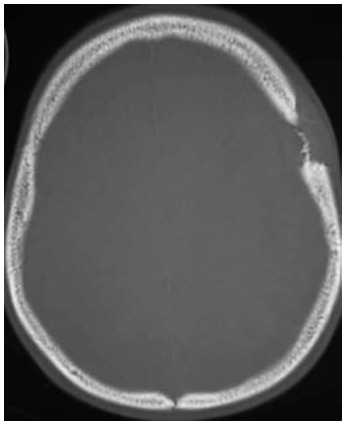
Hyperostosis frontalis interna - asymptomatic symmetric hyperostosis of inner table of frontal bone - common incidental finding in women > 40 yrs.

Intra-osseus meningioma

LANGERHANS HISTIOCYTOSIS

multisystemic abnormal proliferation of Langerhans cells in various tissues.
most common in children 6-10 years old
asymptomatic or painful.
Osteolytic lesion without sclerotic border, with well-defined contours

Treatment

Single lesions → surveillance or systemic corticosteroids.
Diffuse or aggressive forms - surgical excision, radiotherapy, chemotherapy.