CENTRAL NERVOUS SYSTEM TUMORS(3)

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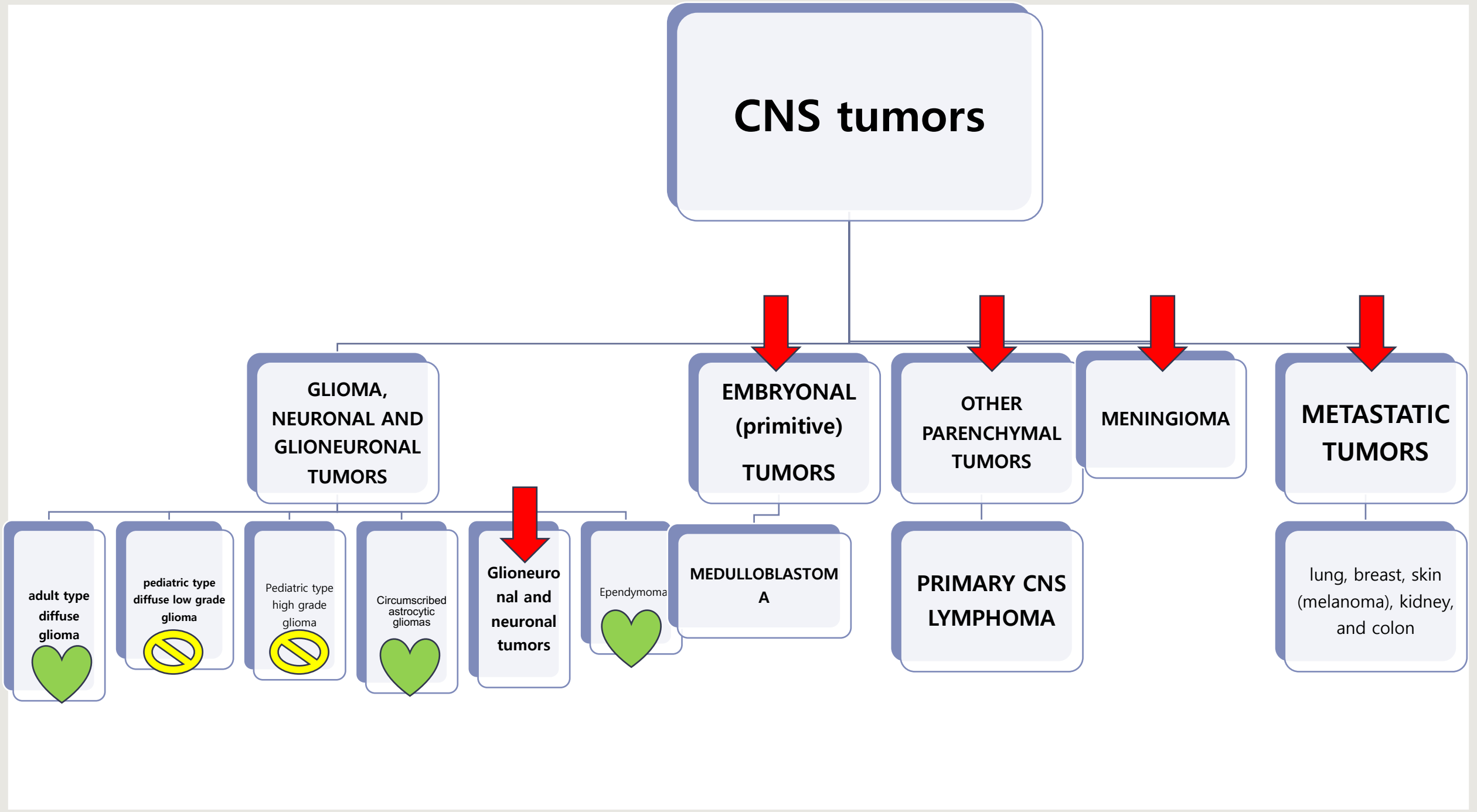

CNS tumors
GLIOMA, NEURONAL AND GLIONEURONAL TUMORS
EMBRYONAL (primitive) TUMORS
OTHER PARENCHYMAL TUMORS
MENINGIOMA
METASTATIC TUMORS
adult type diffuse glioma
pediatric type diffuse low grade glioma
Pediatric type high grade glioma
Circumscribed astrocytic gliomas
Glioneuronal and neuronal tumors
Ependymoma
MEDULLOBLASTOMA
PRIMARY CNS LYMPHOMA
lung, breast, skin (melanoma), kidney, and colon

Neuronal Tumors

- **less** frequent than gliomas
- composed of cells with **neuronal characteristics and express neuronal markers**, such as synaptophysin, neurofilaments, and NeuN
- **lower-grade** lesions
- often present with **seizures**.

1- Gangliogliomas, WHO grade 1:

- **children and young adults.**
- **Slow growing tumor**
- composed of a mixture of **neoplastic ganglion and glial cells,** EGBs >RF
- most commonly in the **temporal lobe.**
- 20-50% have mutations in BRAF gene

2-Dysembryoplastic neuroepithelial tumor (DNT), WHO grade 1:

- **Rare**
- **children and young adults**
- **Slow growing tumor**
- **Present with seizure**
- most commonly in the **superficial temporal lobe.**

Embryonal (Primitive) Neoplasms

- Primitive or undifferentiated small round cell tumor of neuroectodermal origin resembling normal progenitor cells in the developing CNS.

- The most common CNS embryonal tumor is **Medulloblastoma** accounting for 20% of pediatric brain tumors

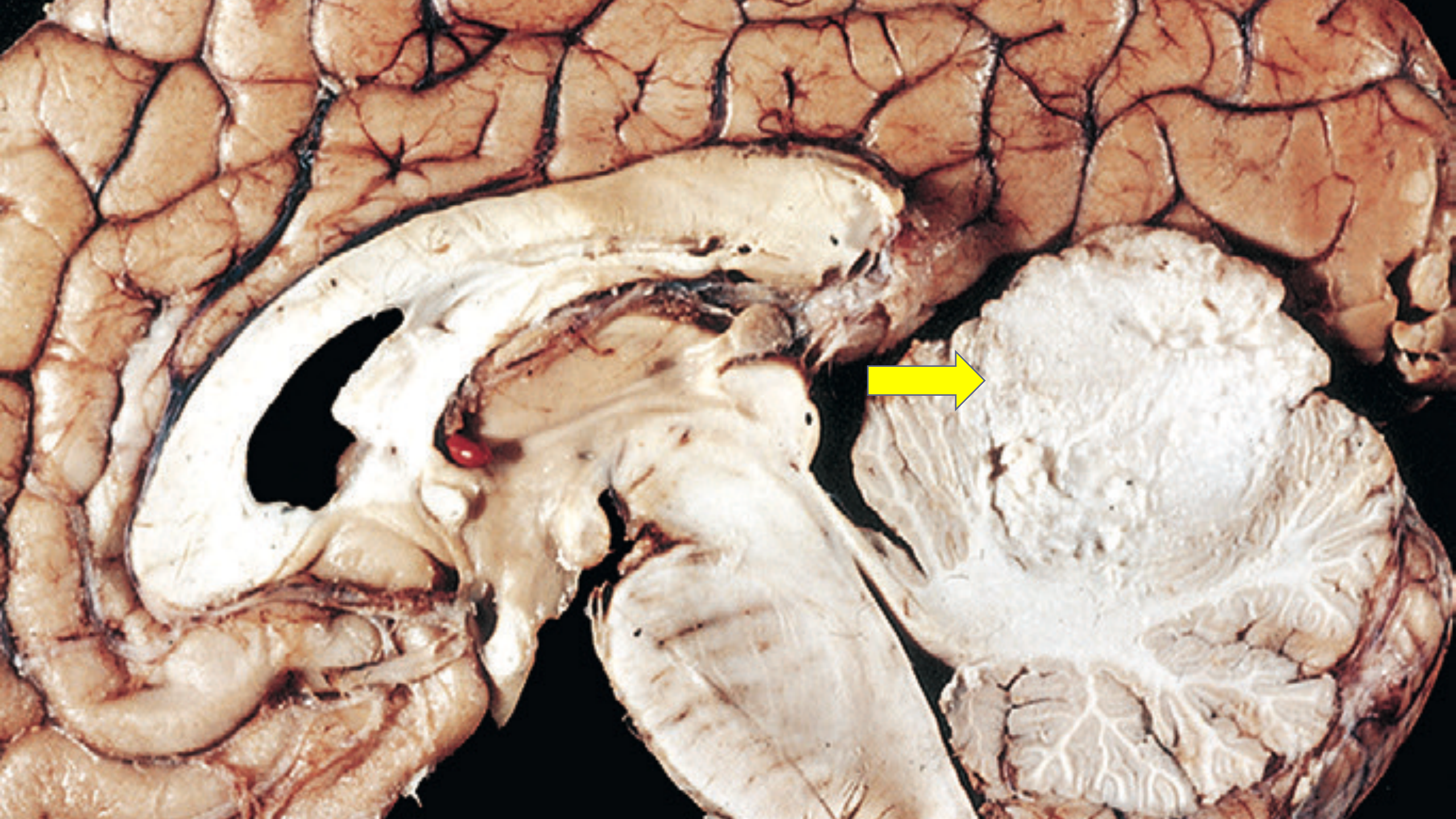
Medulloblastoma

- predominantly in **children**
- mainly in **cerebellum**
- **All are highly malignant, WHO grade 4**
- **radiosensitive**.
- the prognosis for untreated patients is **dismal**
- **5-year survival rate may be as high as 75% w**ith total excision,chemotherapy, and irradiation

Macroscopic:

- In children (midline) while in adults (lateral)
- well circumscribed (often)
- may extend to the cerebellar surface and involve the Leptomeninges

- **complication:**
  - Medulloblastomas have tendency to spread to the subarachnoid space
    → Dissemination through the CSF



Morphology:

- Very Cellular

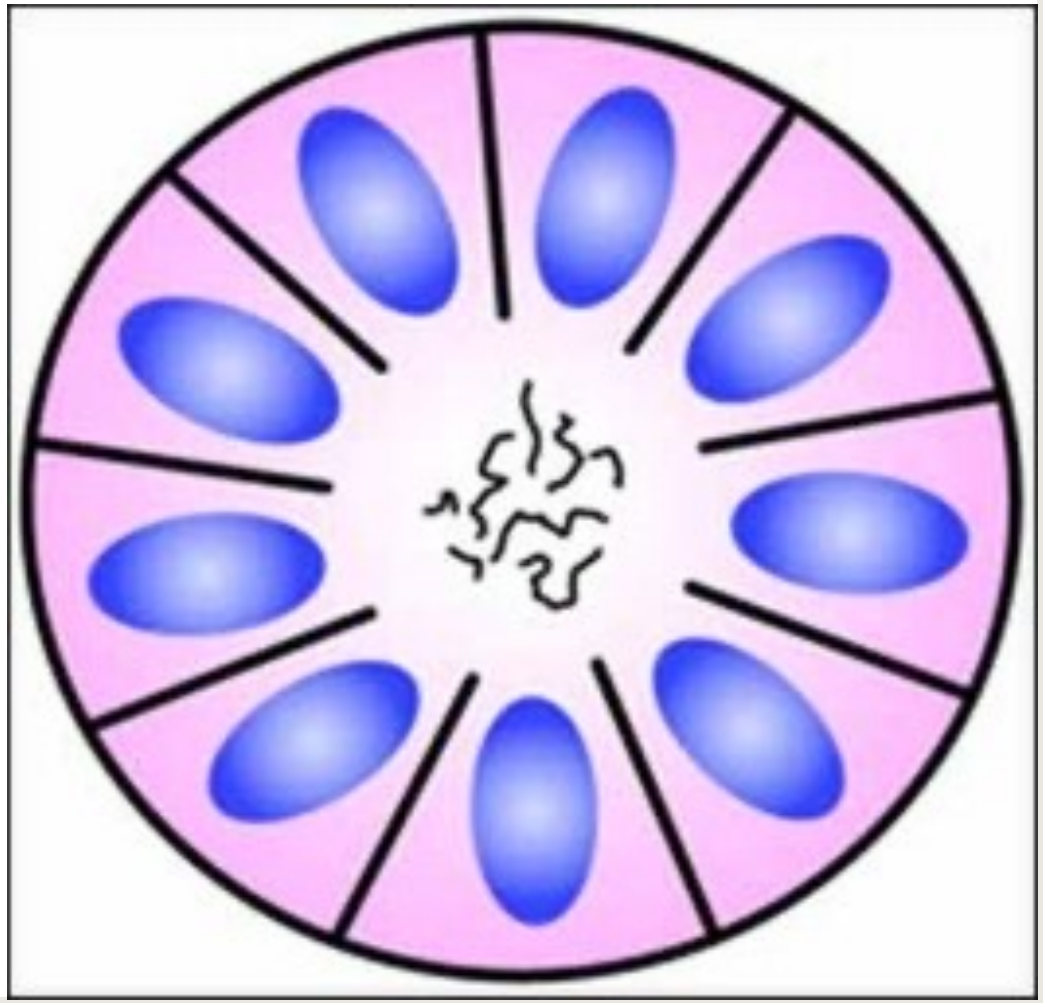
- sheets of small primitive cells (“small blue”), Each cell with little cytoplasm and hyperchromatic elongated or crescent-shaped nuclei

- mitoses are abundant.

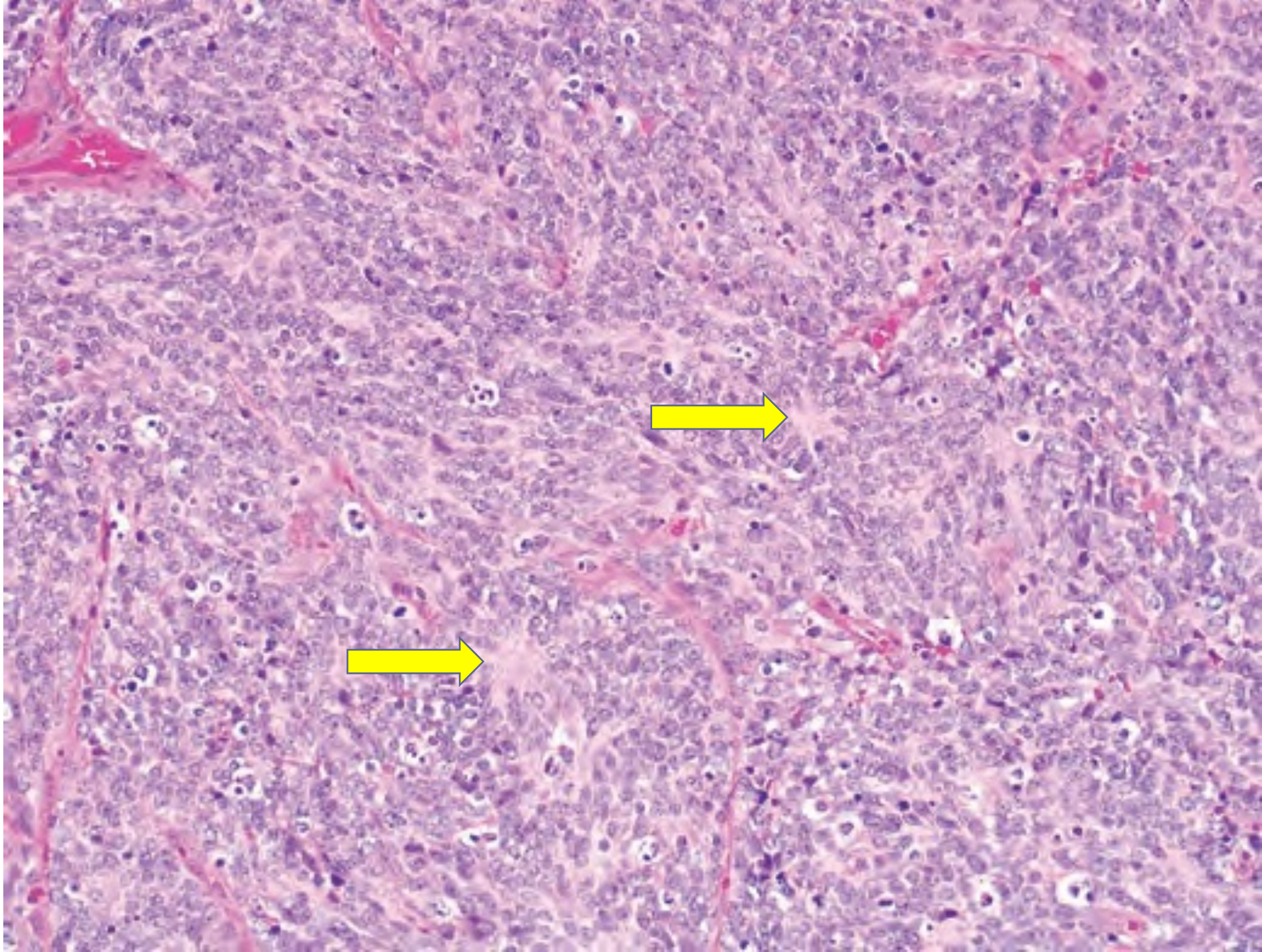
- often express neuronal markers such as synaptophysin, expression of glial markers (GFAP) is less common.

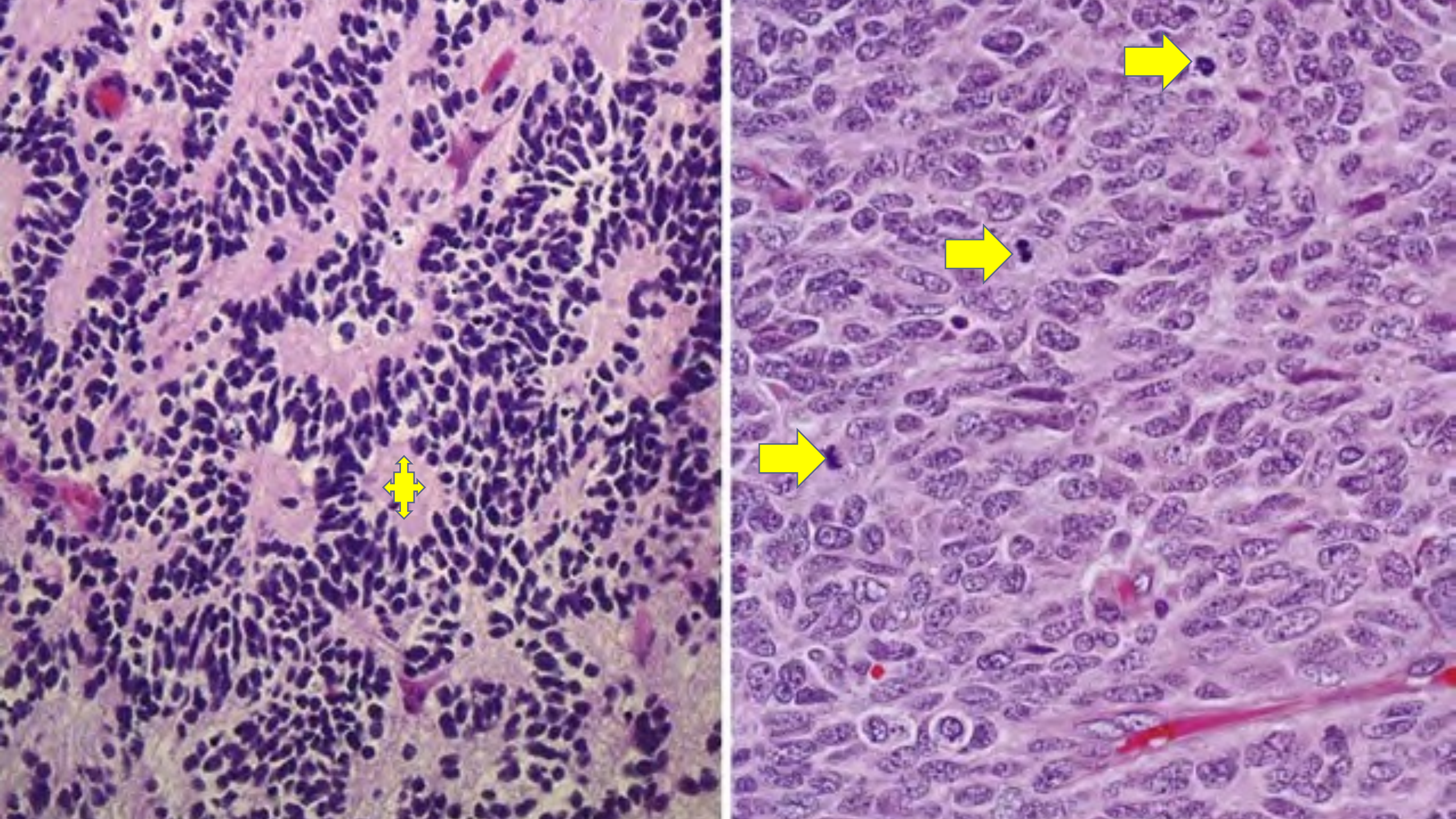
Morphology:

- **Homer Wright Rosettes:**
  - primitive tumor cells surrounding central neuropil (delicate pink material formed by neuronal processes).
  - Represents focal neuronal differentiation
  - Not specific; seen also in neuroblastoma and pineablastoma



Sheets of primitive small blue cells that form Homer Wright rosettes with central neuropil (arrows).





Oncogenic pathways in Medulloblastoma:

- **Wnt pathway activation**: associated with gain of function mutations in the gene for **β-catenin**; have the **most favorable prognosis** of all the genetic subtypes.

- **MYC overexpression**: due to **MYC amplification**; these tumors have the **poorest prognosis.**

- **Hedgehog pathway activation(gain of function):** associated with loss of function mutations in **PTCH1** (a negative regulator of the Hedgehog); these tumors have an **intermediate prognosis**, but the concomitant presence of ***P53* mutation** confers a **very poor prognosis.**

- Medulloblastomas are classified according to **molecular characteristics** in addition to **histopathological features into:**

- Medulloblastoma, WNT activated
- Medulloblastoma, SHH activated and P53 wildtype
- Medulloblastoma, SHH activated and P53 mutant
- Medulloblastoma, non-WNT/non-SHH, group 3
- Medulloblastoma, non-WNT/non-SHH, group 4

Table 8.01 Medulloblastoma subtypes characterized by combined genetic and histological parameters

Genetic profile	Histology	Prognosis
Medulloblastoma, WNT-activated	Classic	Low-risk tumour; classic morphology found in almost all WNT-activated tumours
	Large cell / anaplastic (very rare)	Tumour of uncertain clinicopathological significance
Medulloblastoma, SHH-activated, TP53-mutant	Classic	Uncommon high-risk tumour
	Large cell / anaplastic	High-risk tumour; prevalent in children aged 7-17 years
	Desmoplastic/nodular (very rare)	Tumour of uncertain clinicopathological significance
Medulloblastoma, SHH-activated, TP53-wildtype	Classic	Standard-risk tumour
	Large cell / anaplastic	Tumour of uncertain clinicopathological significance
	Desmoplastic/nodular	Low-risk tumour in infants; prevalent in infants and adults
	Extensive nodularity	Low-risk tumour of infancy
Medulloblastoma, non-WNT/non-SHH, group 3	Classic	Standard-risk tumour
	Large cell / anaplastic	High-risk tumour
Medulloblastoma, non-WNT/non-SHH, group 4	Classic	Standard-risk tumour; classic morphology found in almost all group 4 tumours
	Large cell / anaplastic (rare)	Tumour of uncertain clinicopathological significance

Meningiomas, WHO grades 1-3

- tumors that arise from meningothelial cells of the arachnoid matter and usually attached to the dura

- **Age at presentation:** adults (women>men)

- **Location: any of the external surfaces of the brain, spinal cord, within the ventricular system, from the stromal arachnoid cells in the choroid plexus.**

- **Presentation:** Most common headache, seizures, weakness (depends on location)

- **Prognosis:** determined by the lesion size and location, surgical accessibility, and histologic grade.

- Most meningiomas are easily separable from the underlying brain but some tumors are infiltrative (associated with increased risk of recurrence)

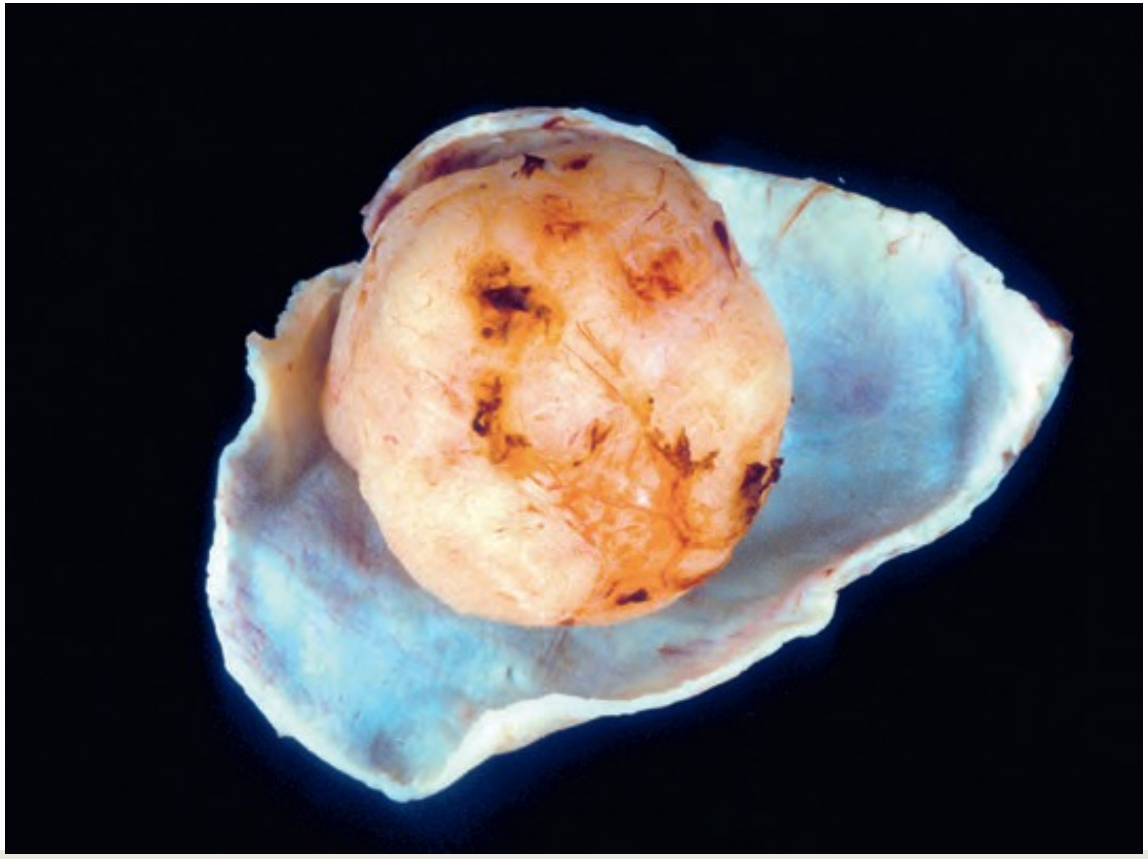
- Meningiomas express **progesterone receptors** and may grow more rapidly during pregnancy, & regress after delivery.

Pathogenesis

- The most common cytogenetic abnormality is loss of chromosome 22, especially the long arm (22q). The deletions include the region that harbors the NF2 gene.
- Of sporadic meningiomas, 50% to 60% harbor mutations in the NF2 gene
- In meningiomas without NF2 mutations, mutations occur in other genes.
- Multiple meningiomas + 8th nerve schwannoma + Ependymomas of the cervical spinal cord → common in the setting of NF2.

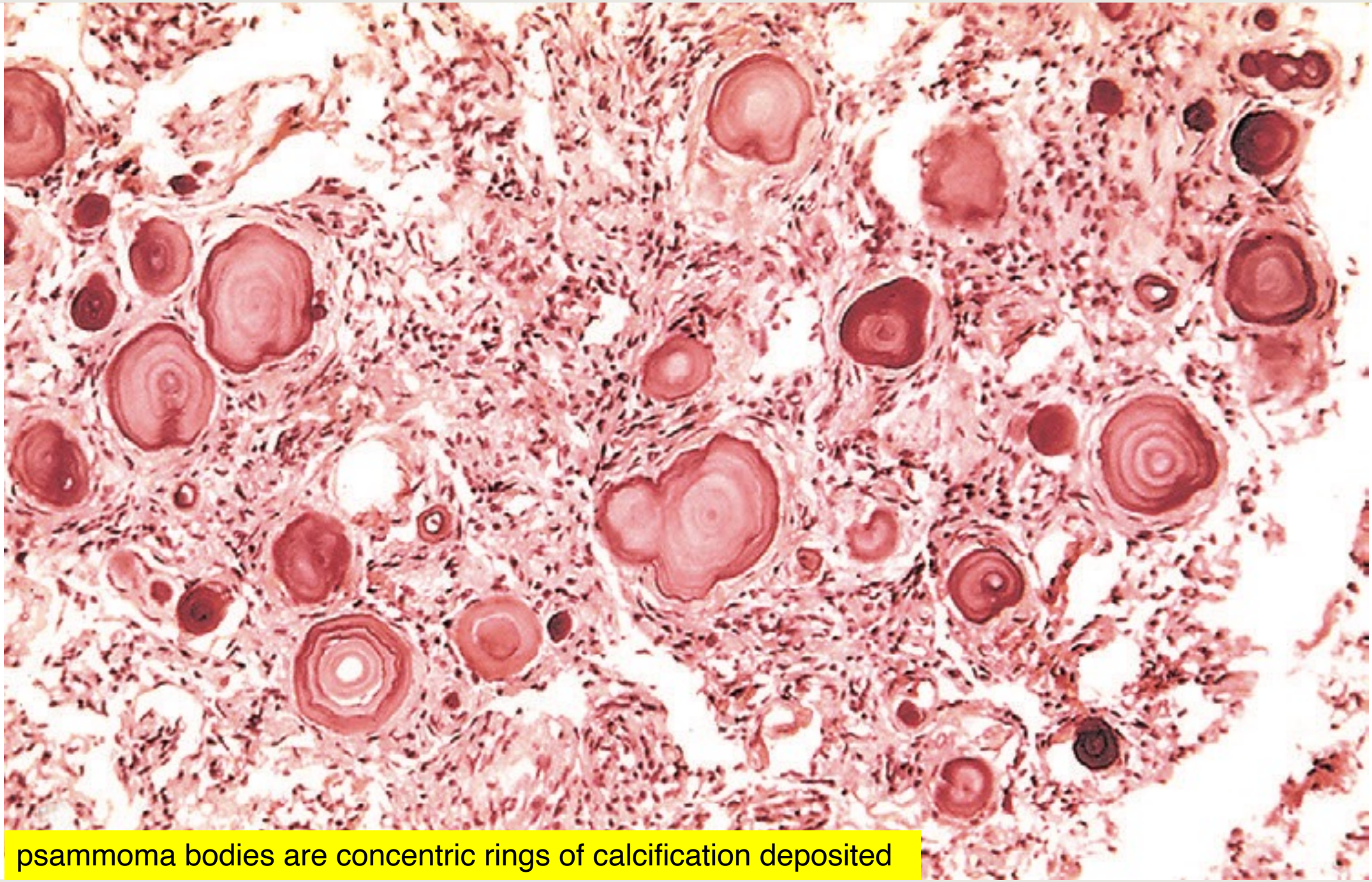
Macroscopic:

- rubbery, rounded, or bosselated dural masses that compress underlying brain
- Mostly separable from underlying brain, but some tumors are infiltrative



Meningiomas (WHO grade 1):

- well-defined dura-based masses that may compress the brain but do not typically invade it +/- overlying bone extension.
- Epithelioid cells arranged in whorly (syncytial)pattern +/- psammoma bodies
- Many histologic subtype, with no prognostic difference, including:
  - meningothelial (most common)→clusters of epithelioid cells with fuzzy or indiscernible cell membranes
  - Other patterns include fibrous, transitional, angiomatous, microcystic, lymphoplasmacytic rich, metaplastic, secretory and psammomatous



psammoma bodies are concentric rings of calcification deposited

MENINGIOMAS, WHO grade 2

- recurrence and aggressive local growth (may require radiation & surgery)

1- 4 to 19 mitoses/10 HPF; or

2- (3 out of 5): increased cellularity, small cells with a high N/C ratio, prominent nucleoli, patternless growth, or necrosis; **or**

3- **clear cell** or **chordoid subtypes of meningioma; or**

4- unequivocal brain invasion

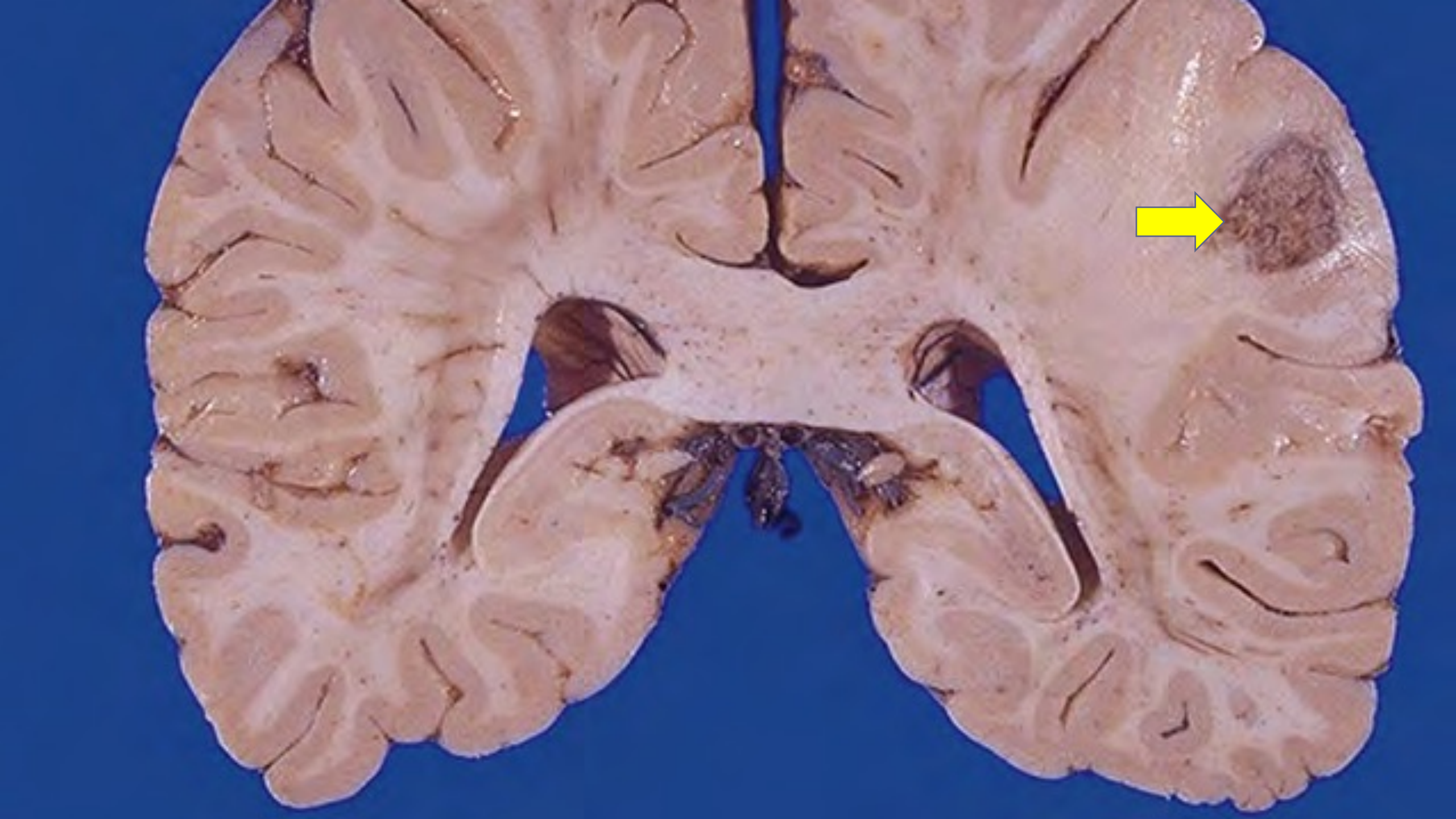
MENINGIOMAS, WHO grade 3:

- Rare, highly aggressive, resemble a high-grade sarcoma or carcinoma or melanoma morphologically.

1. **≥20 mitoses/ 10HPF;** or
2. Frank anaplasia (sarcoma, carcinoma or melanoma like); or
3. TERT promotor mutation; or
4. Homozygous deletion of CDKN2A/B ; or
5. **Papillary;** or **rhabdoid meningioma.**

Metastatic Tumors:

- >50% of intracranial tumors.
- mostly **carcinomas**
- The most common primary sites are **lung, breast, skin (melanoma), kidney, and colon (**80% of cases).
- **sharply demarcated masses**, often at the grey-white matter junction, and elicit local edema and reactive gliosis



OTHER PARENCHYMAL TUMORS

Primary Central Nervous System Lymphoma:

- **the most common CNS neoplasm in immunosuppressed individuals**

- In non-immunosuppressed populations, the frequency increases after 60 years of age.

- aggressive disease , poor response to chemotherapy (especially if compared with comparable histology that occur at non-CNS site)

- The most common type: **diffuse large B-cell lymphomas**

- **Primary brain lymphoma:**

  - Multifocal

  - involvement outside of the CNS (in lymph nodes or BM) is a rare and late complication.

  - relatively **well defined** as compared with glial neoplasms but not as discrete as metastases.

Familial Tumor Syndromes

- inherited syndromes caused by mutations in tumor suppressor genes and associated with increased risk of neoplasms
- tumors of the nervous system make a prominent aspect of some of these syndromes, including:
  - ✓ **Tuberous Sclerosis**
  - ✓ **Von Hippel-Lindau Disease**

Tuberous Sclerosis

- autosomal dominant syndrome
- 1 in 6000 births
- characterized by:
  - **development of hamartomas and benign neoplasms involving the brain and other tissues**
  - **Extracerebral lesions**:
    - renal angiomyolipomas, retinal glial hamartomas, pulmonary lymphangioleiomyomatosis, and cardiac rhabdomyomas develop during childhood and adolescence.

Cysts at various sites, including the liver, kidneys, and pancreas.

- **Cutaneous lesions:**
  - Angiofibromas
  - localized leathery thickenings (shagreen patches)
  - hypopigmented areas (ash-leaf patches)
  - subungual fibromas.

CNS hamartomas

- Hamartomas within the CNS take the form of **cortical tubers and subependymal nodules**
  - **Cortical tubers** are epileptogenic, and surgical resection can be beneficial.
  - **subependymal giant cell astrocytoma (SEGA):** benign neoplasm develops from the subependymal nodules

Subependymal giant cell astrocytomas (SEGA)

- Incidence: 1 in 5000 to 10000 live births

- benign neoplasms that appear to develop from the hamartomatous nodules near the foramen of Monro.

- Clinically: obstructive hydrocephalus that require surgical intervention and therapy with an mTOR inhibitor

Pathogenesis:

- tuberous sclerosis gene 1 (TSC1) on chromosome 9q34 and encodes a protein known as **hamartin**

- tuberous sclerosis gene 2 (TSC2) on chromosome 16p13.3 and encodes **tuberin** and considered the most commonly mutated gene.

- Hamartin and tuberin form a dimeric complex → inhibits the kinase mTOR.

Pathogenesis:

- kinase mTOR:
  - a key regulator of protein synthesis
  - “ senses” the cell nutrient status and regulate the cellular metabolism.
  - mTOR controls cell size
- Mutations in TSC1 or TSC2 disrupt this control and lead to increased and unregulated mTOR activity → voluminous cytoplasm.

Von Hippel-Lindau Disease:

- autosomal dominant disease
- 1 in 30,000 to 40,000.
- **Associated with:**
  - hemangioblastomas of the CNS

    - in the cerebellum and retina, brainstem, spinal cord and nerve roots.
  - cysts in pancreas, liver, and kidneys
  - Increased risk of renal cell carcinomas
  - pheochromocytomas

Hemangioblastomas

- highly vascular neoplasms consists of:
  - numerous thin-walled vessels
  - intervening neoplastic cells with vacuolated, lipid-rich cytoplasm.

- The neoplastic cells express inhibin (useful diagnostic marker).


thank you