CENTRAL NERVOUS SYTEM TUMORS(2)

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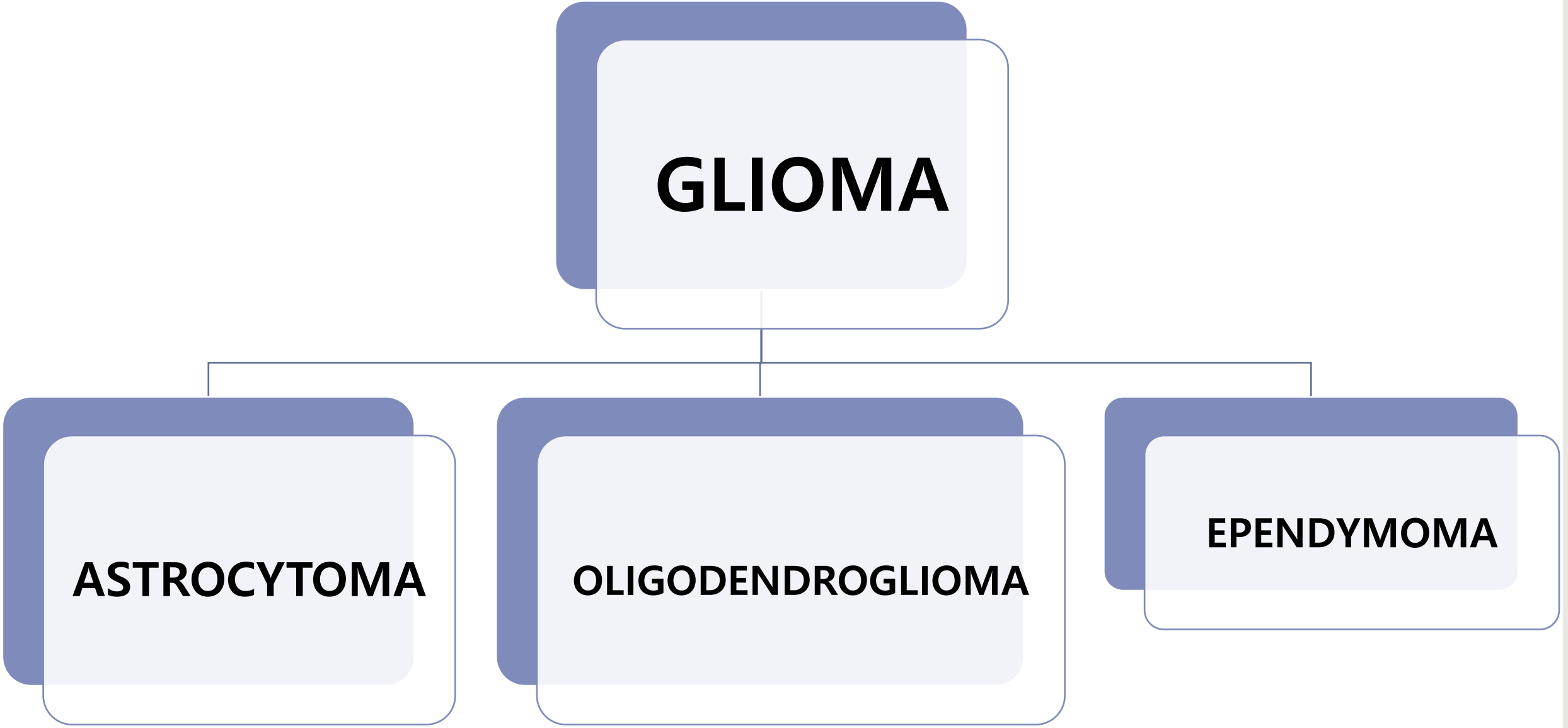
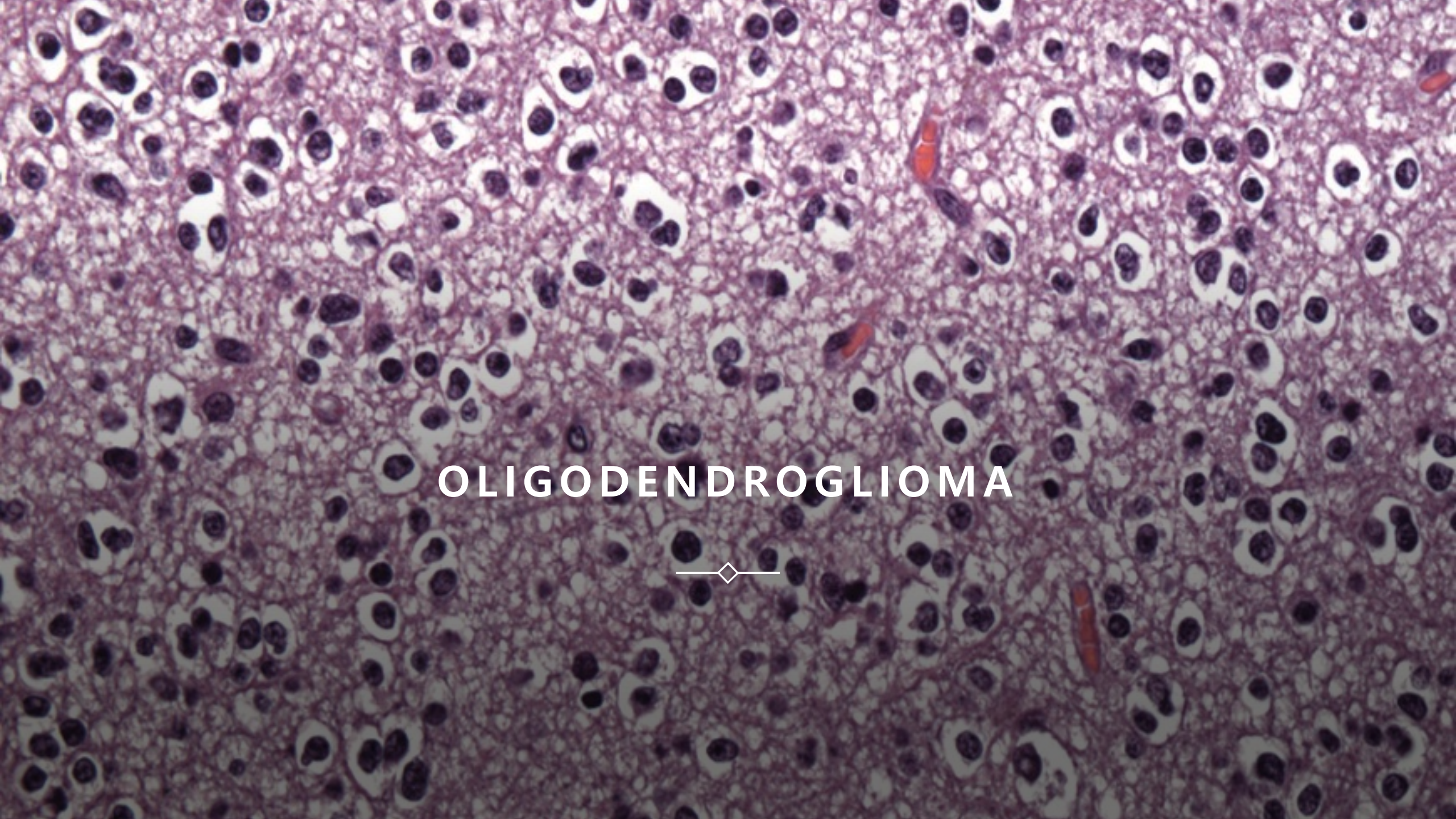
Dermatopathologist & Neuropathologist


GLIOMA
ASTROCYTOMA
OLIGODENDROGLIOMA
EPENDYMOMA



OLIGODENDROGLIOMA

Oligodendroglioma

- Accounts for 5-15% of gliomas

- **Age at diagnosis:** 40-50.

- **Location:** mostly in the cerebral hemispheres, mainly in the frontal or temporal lobes, white matter.

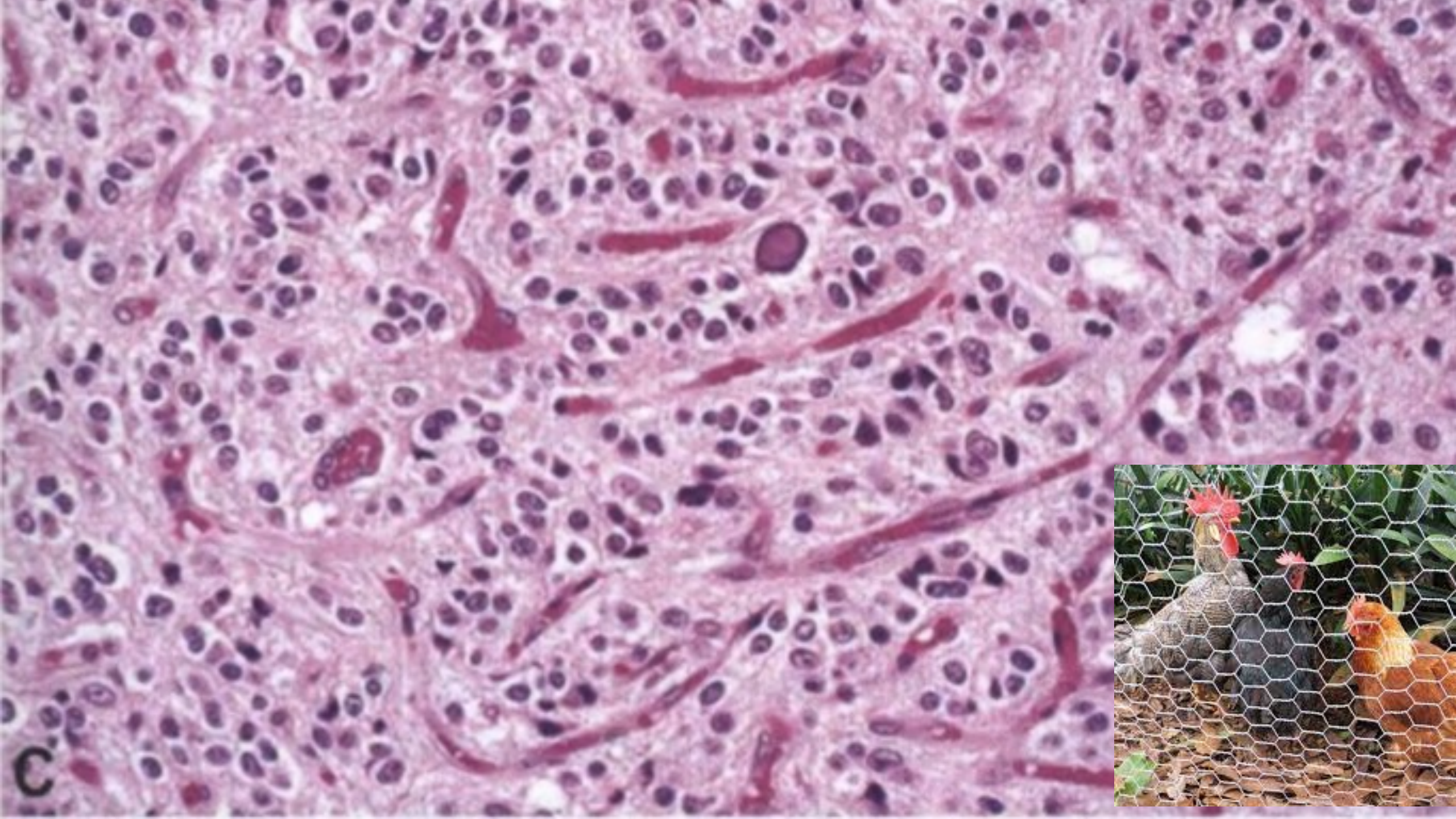
- **The presence of IDH mutation and 1p & 19q codeletion is diagnostic for oliogodendroglioma**

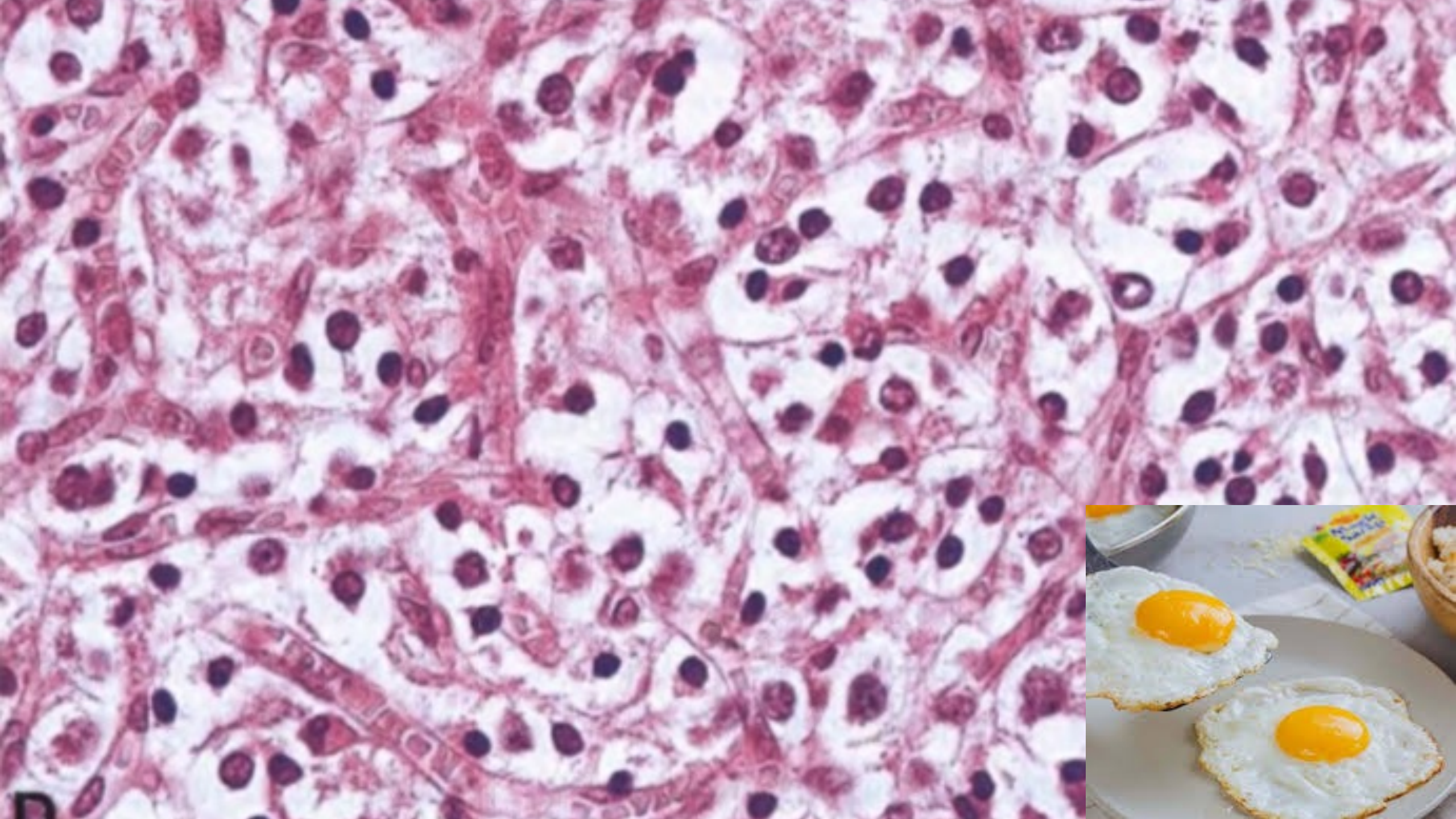
- **Treatment and prognosis:**
- The combination of surgery, chemotherapy, and radiotherapy yields an average survival of:
  - 10-20 years for WHO grade 2.
  - 5-10 years for WHO grade 3.
- **Grade 3 is more aggressive than grade 2 oligodendroglioma**
- **NO grade 1 OR 4 oligodendroglioma**
- **Better prognosis than astrocytoma of the same grade!**

Oligodendroglioma ,WHO grade 2:

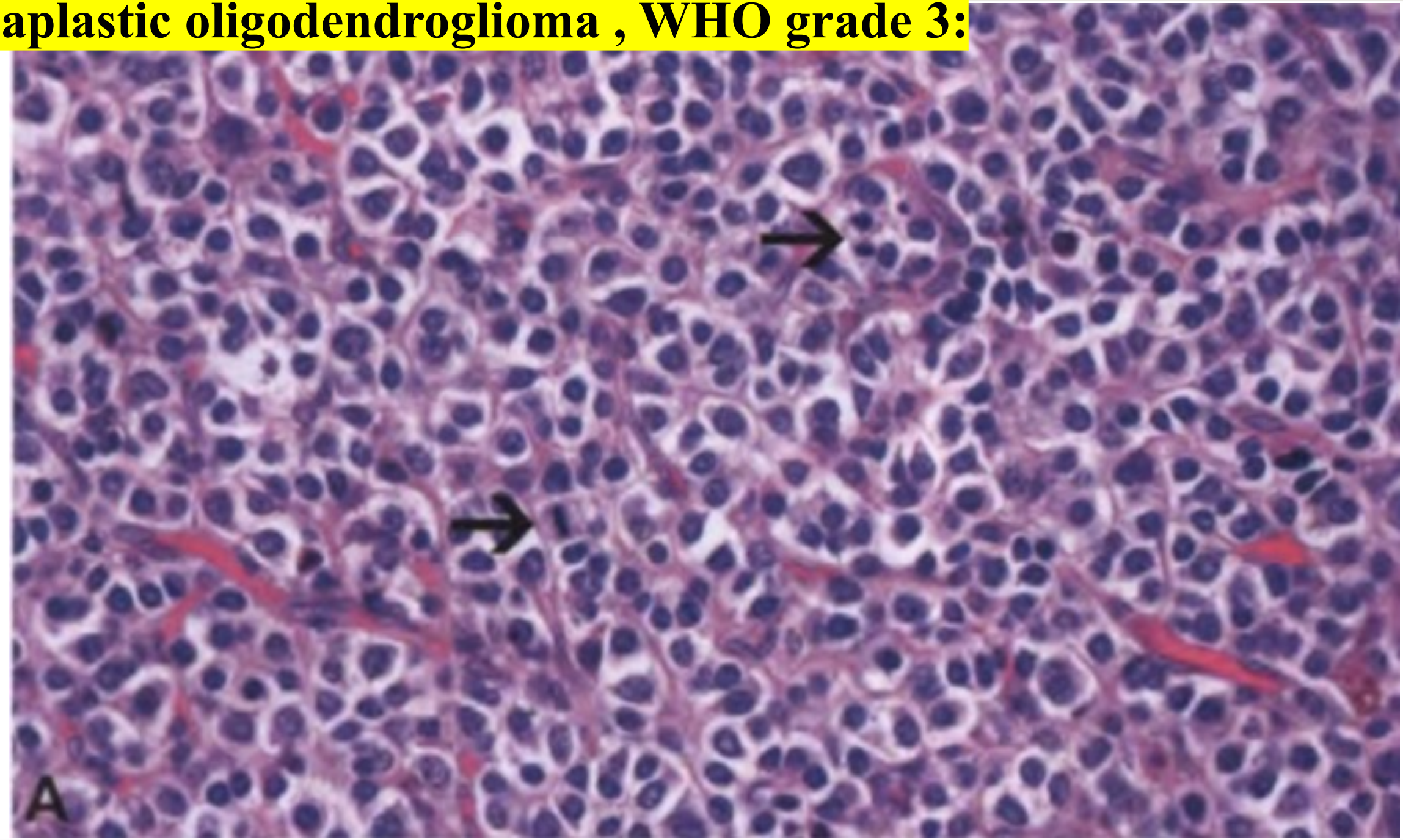
- infiltrative tumors
- +/- cysts, focal hemorrhage, and calcification.

- sheets of regular cells with spherical nuclei containing finely granular chromatin
- The nuclei are surrounded by a clear halo of cytoplasm (fried-egg appearance).
- delicate network of anastomosing capillaries “chicken-wire”
- Calcification in 90% of tumors.
- Mitotic activity usually is **low.**
- **No** spontaneous necrosis
- **No** microvascular proliferation





Anaplastic oligodendroglioma , WHO grade 3:



IDHm 1p/19q-codel Oligodendrogliomas, grades 2-3

Essential diagnostic criteria for oligodendroglioma, IDH-mutant and 1p/19q-codeleted, WHO grade 2
A diffuse glioma
WITH
an IDH1 codon 132 or IDH2 codon 172 missense mutation*
AND
combined whole arm deletions of 1p and 19q
AND
absence of histological features of anaplasia

Essential diagnostic criteria for oligodendroglioma, IDH-mutant and 1p/19q-codeleted, WHO grade 3
A diffuse glioma
WITH
an IDH1 codon 132 or IDH2 codon 172 missense mutation*
AND
combined whole arm deletions of 1p and 19q
AND
histological features of anaplasia, including brisk mitotic activity and/or pathological microvascular proliferation with or without necrosis
AND/OR
homozygous *CDKN2A* deletion**

UPDATE

Essential:

A diffusely infiltrating glioma

AND

IDH1 codon 132 or *IDH2* codon 172 missense mutation[a]

AND

Combined whole-arm deletions of 1p and 19q

Desirable:

DNA methylome profile of oligodendroglioma, IDH-mutant and 1p/19q-codeleted

Retained nuclear expression of ATRX

TERT promoter mutation

Traditional Histologic Grading

+

CDKN2A-HD can be used for CNS WHO grade 3

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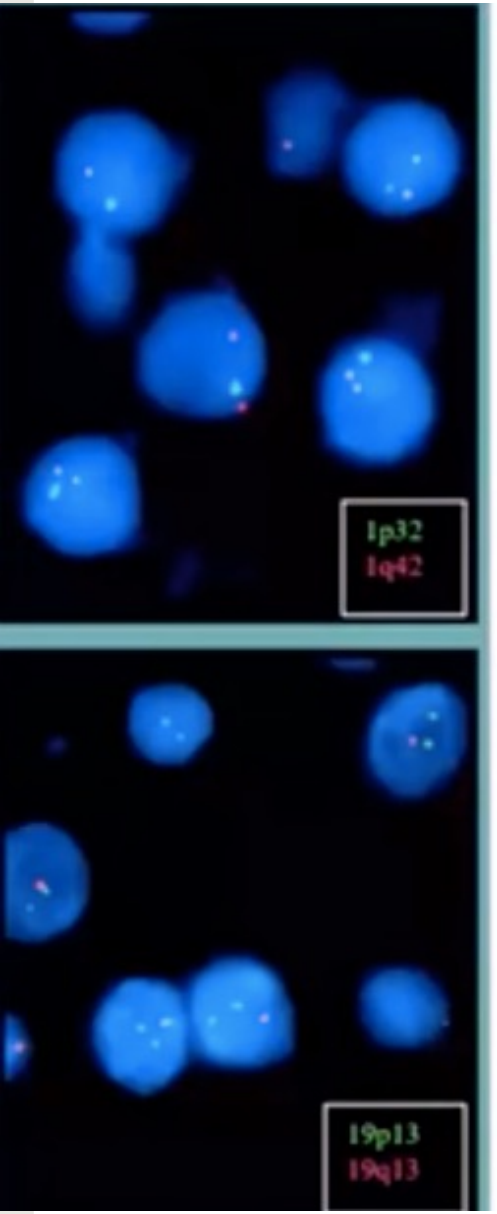

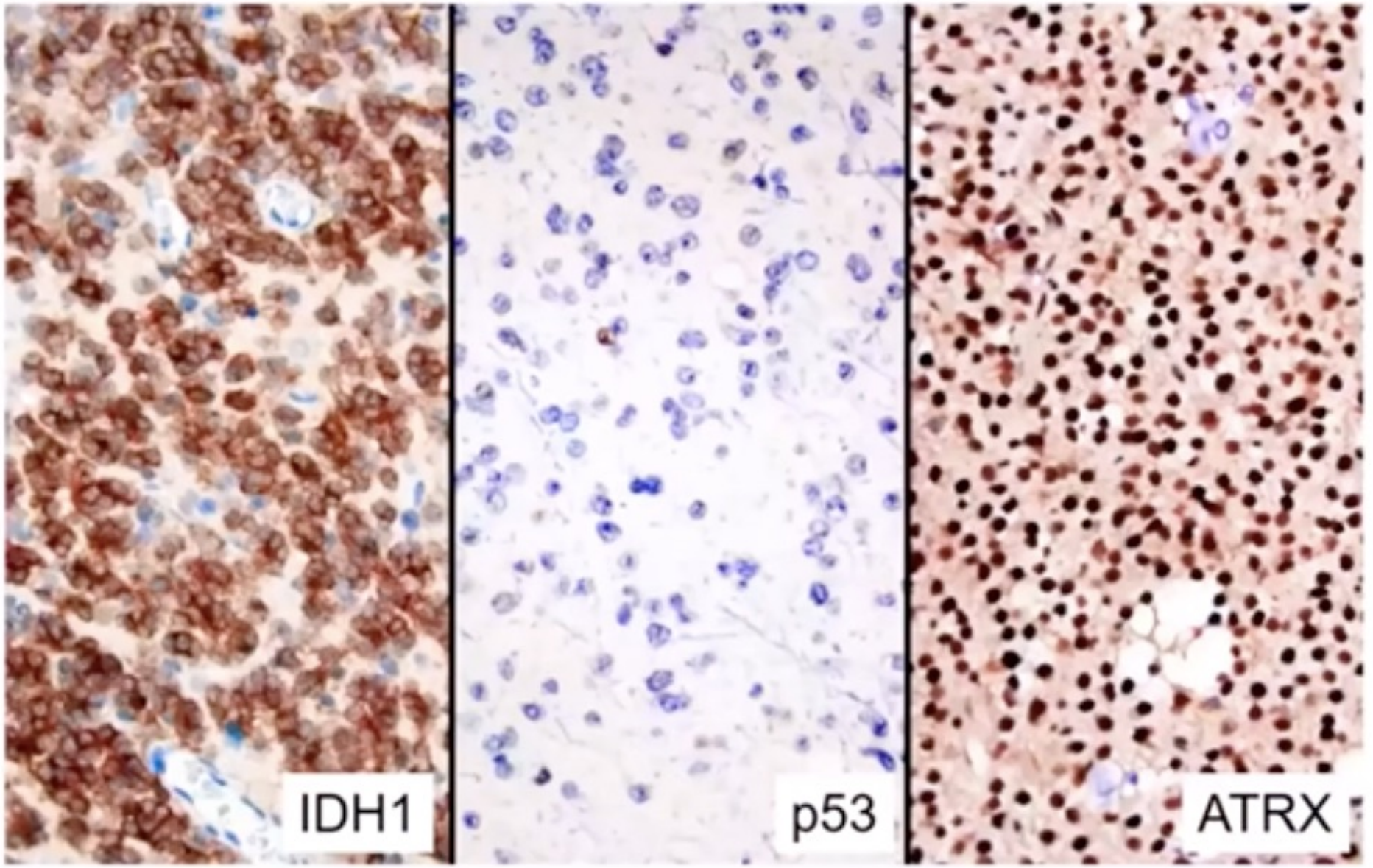

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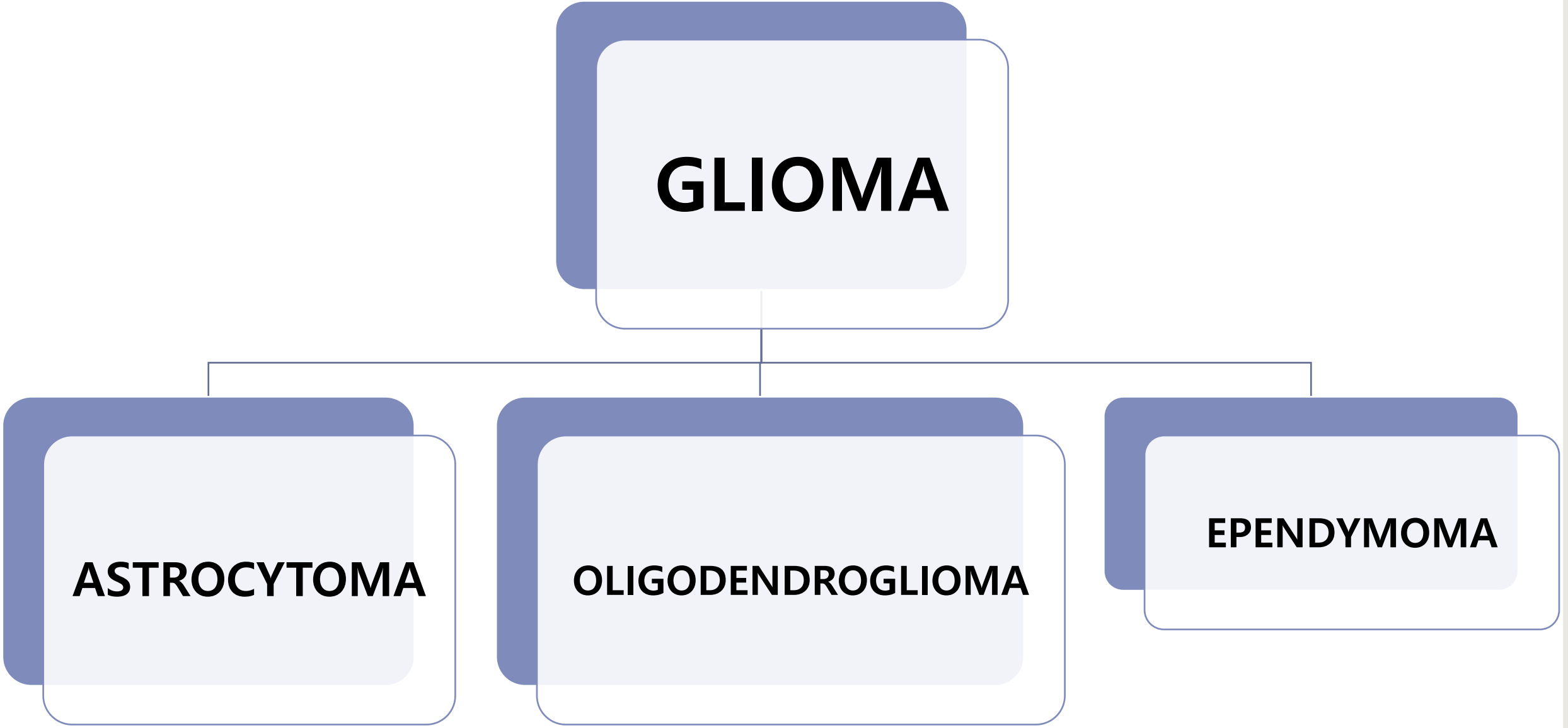
GLIOMA
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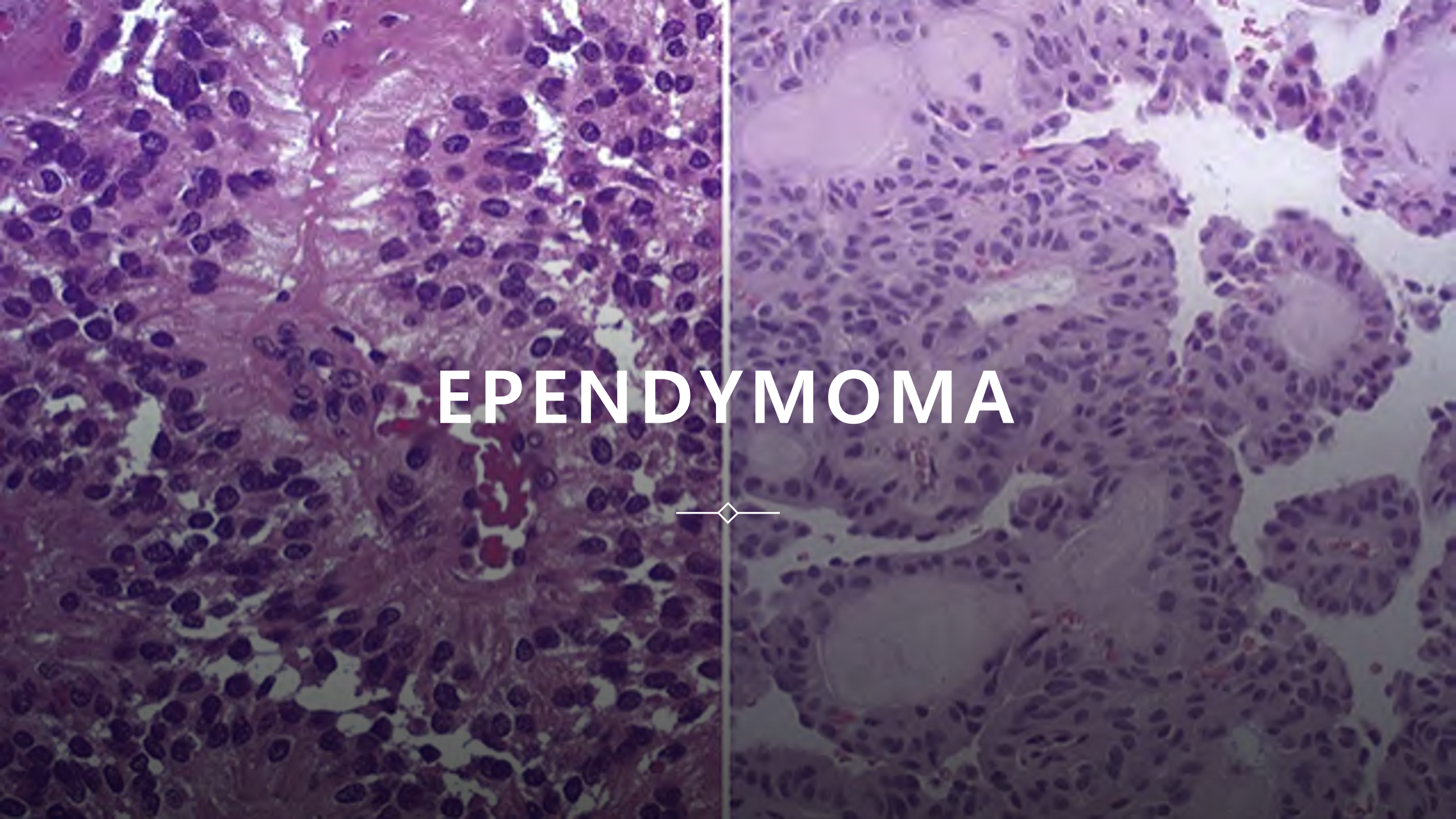


EPENDYMOMA

Ependymoma:

- circumscribed glioma, Mostly arise next to the ependyma- lined ventricular system, including the central canal of the spinal cord.
- **Location: posterior fossa (60%), supratentorial (30%), spinal (10%)**
- **Age:**
  - In the first 2 decades of life; near **the 4th ventricle (post. Fossa)**
  - In adults; the **spinal cord and supratentorial ependymomas occur with almost equal frequency**
- The clinical outcome for completely resected supratentorial and spinal ependymomas is better than for those in the posterior fossa.

Morphology:

- A composed of uniform small cells with round to oval nuclei and granular chromatin in a fibrillary matrix and characterized by:
  - **Rosette formation:**
    - **Ependymal rosettes:** diagnostic hallmark of ependymoma (25%)
    - **perivascular pseudorosettes:** not specific for ependymoma.

- low cell density and a low mitotic count.
- Cilia and microvilli are seen on ultrastructural examination.

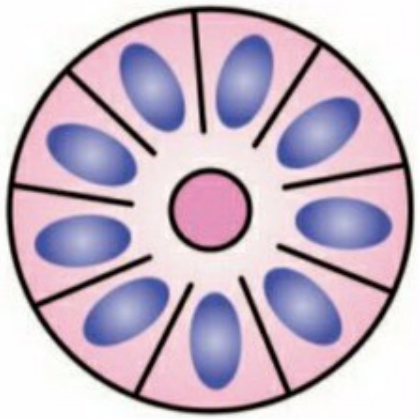
Ependymal rosettes:

- tumor cells arranged around central canal or lumen that resemble the embryologic ependymal canal, with long, delicate processes extending into a lumen.

Perivascular pseudorosettes:

- composed of tumor cells radially arranged around vessels with an intervening anucleated zone containing thin ependymal processes.

Ependymal rosettes



perivascular pseudorosettes

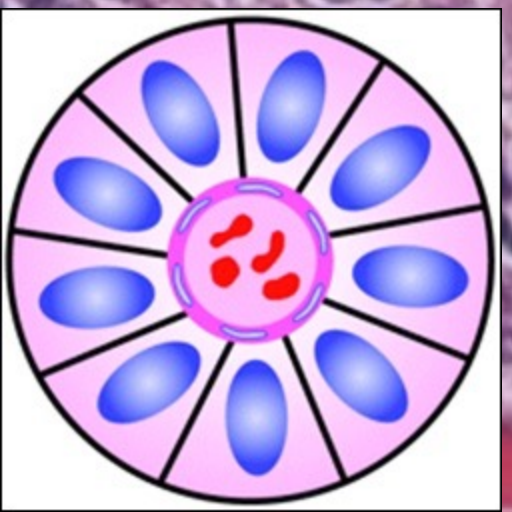


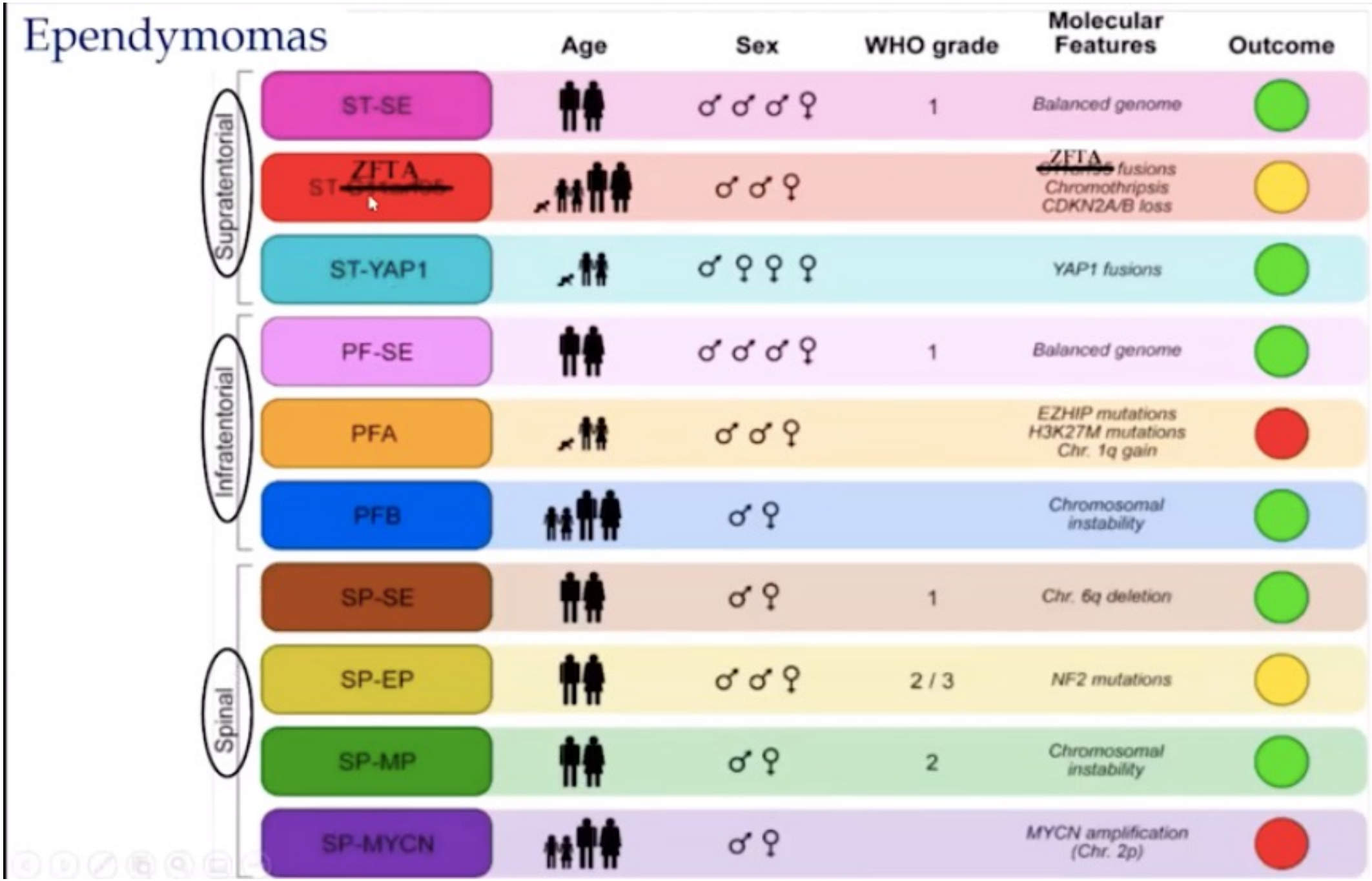
Table 1. Recommended ependymal tumor types

Tumor type	WHO grade
Supratentorial ependymoma, ~~*C11orf95*~~ ZFTA fusion-positive	
Supratentorial ependymoma, *YAP1* fusion-positive	
Supratentorial ependymoma	Grade 2/ 3
Posterior fossa ependymoma, Group PFA	
Posterior fossa ependymoma, Group PFB	
Posterior fossa ependymoma	Grade 2/ 3
Spinal ependymoma, *MYCN*-amplified	
Spinal ependymoma	Grade 2/ 3
Myxopapillary ependymoma	Grade 2
Subependymoma	Grade 1

Sufficient data are currently unavailable for a WHO grade to be assigned to molecularly defined ependymomas.

UPDATE

Ependymomas



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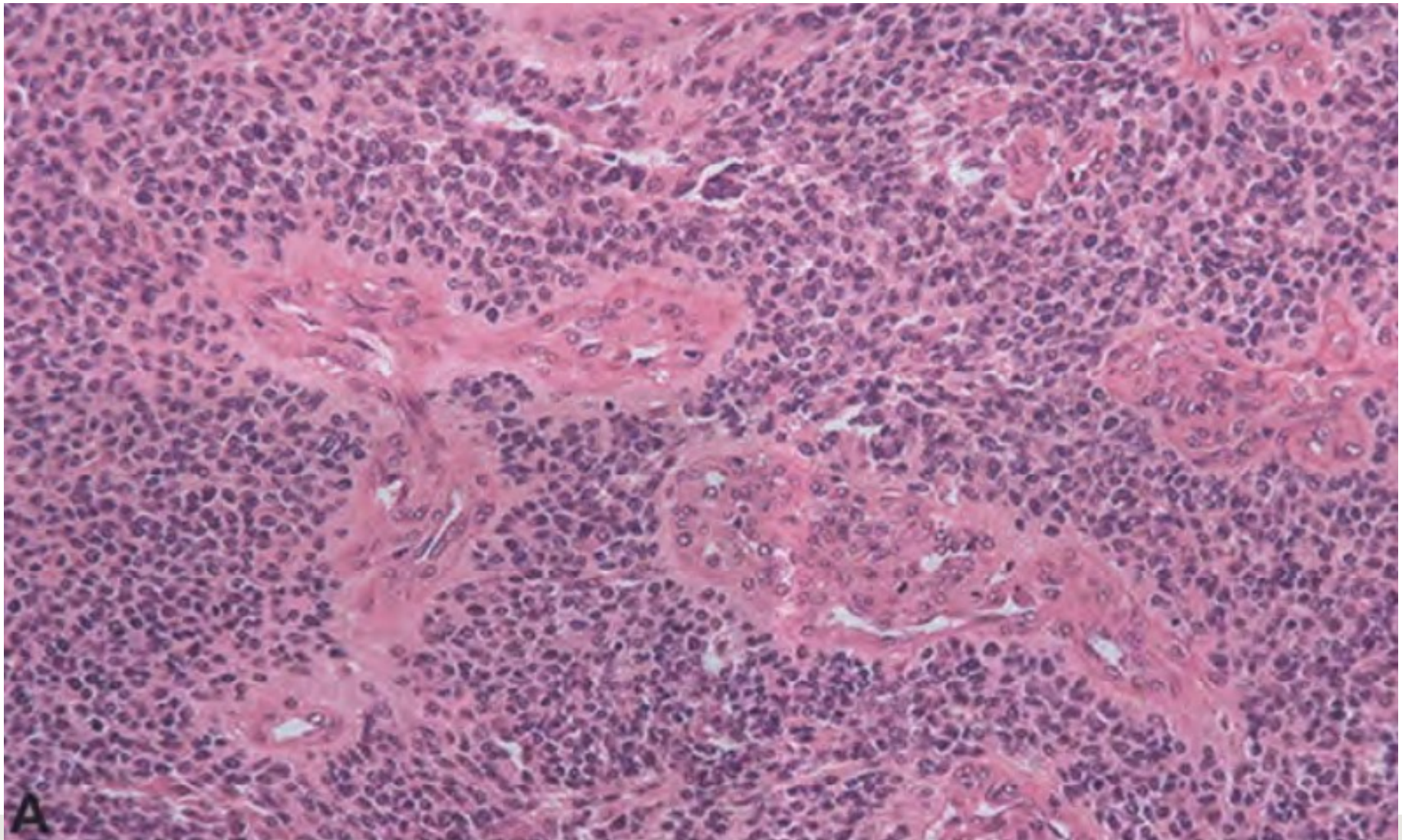
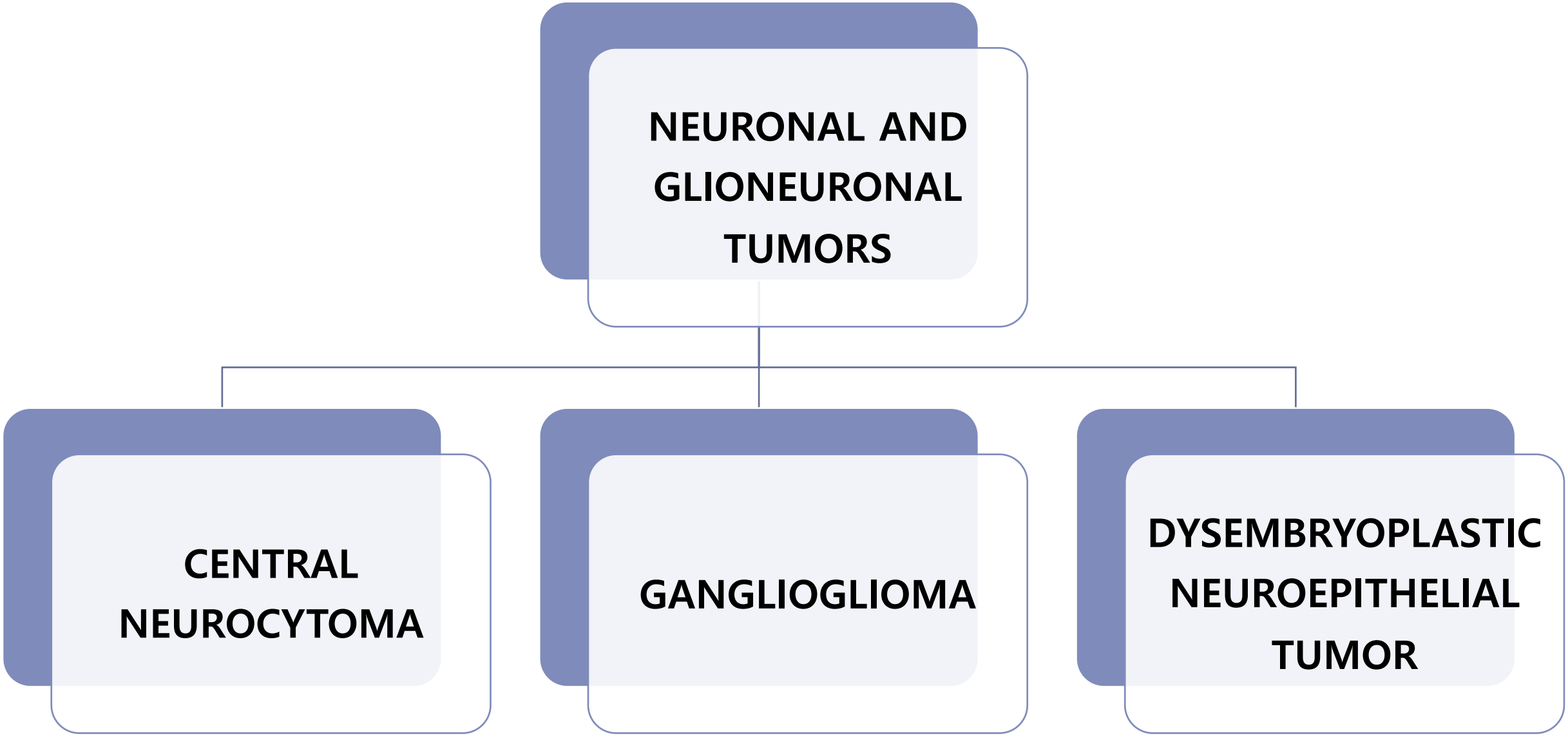
- **Anaplastic ependymomas:** increased cell density, high mitotic rates, necrosis, microvascular proliferation, and less evident ependymal differentiation.




NEURONAL AND GLIONEURONAL TUMORS
CENTRAL NEUROCYTOMA
GANGLIOGLIOMA
DYSEMBRYOPLASTIC NEUROEPITHELIAL TUMOR

Neuronal Tumors

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

- **Central neurocytoma, WHO grade 2:** low-grade **neuronal tumor** within and adjacent to the **lateral ventricle(s) and/or the third ventricle** affecting **young adults**

- **Gangliogliomas, WHO grade 1:** Well differentiated **glioneuronal tumor** affecting **children and young adults.** composed of a mixture of **neoplastic ganglion and glial cells**, most commonly in the **temporal lobe.**

- **Dysembryoplastic neuroepithelial tumor (DNT), WHO grade 1:low-grade glioneuronal tumor** affecting the cerebral cortex of **children and young adults** most commonly in the **superficial temporal lobe.**

Embryonal (Primitive) Neoplasms

- Primitive small round cell tumor of neuroectodermal origin resembling normal progenitor cells in the developing CNS.
- **Medulloblastoma:**
  - The most common CNS embryonal tumor
  - 20% of pediatric brain tumors

Medulloblastoma, WHO grade 4:

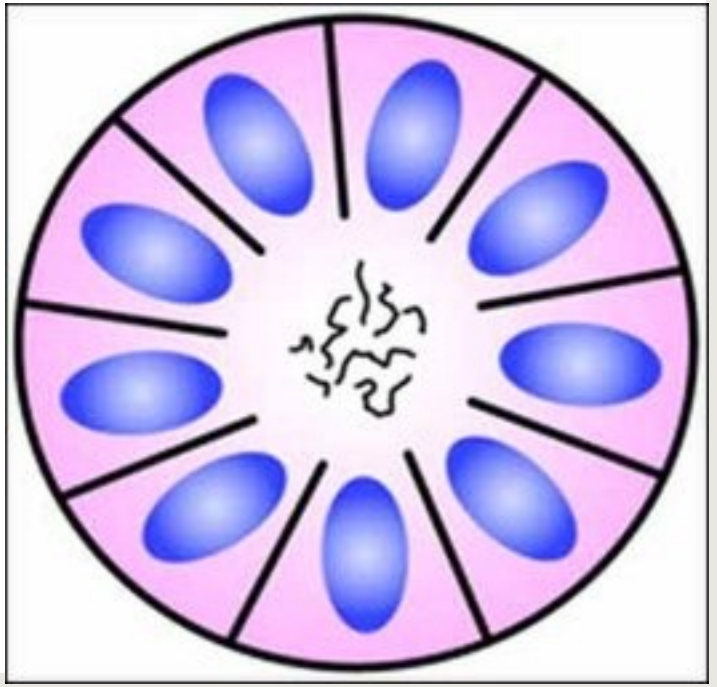
- predominantly in **children**
- mainly in **cerebellum**
- **All are highly malignant, WHO grade 4**
- the prognosis for untreated patients is **dismal**
- **radiosensitive**.
- With total excision, chemotherapy, and irradiation, the 5-year survival rate may be as high as 75%.

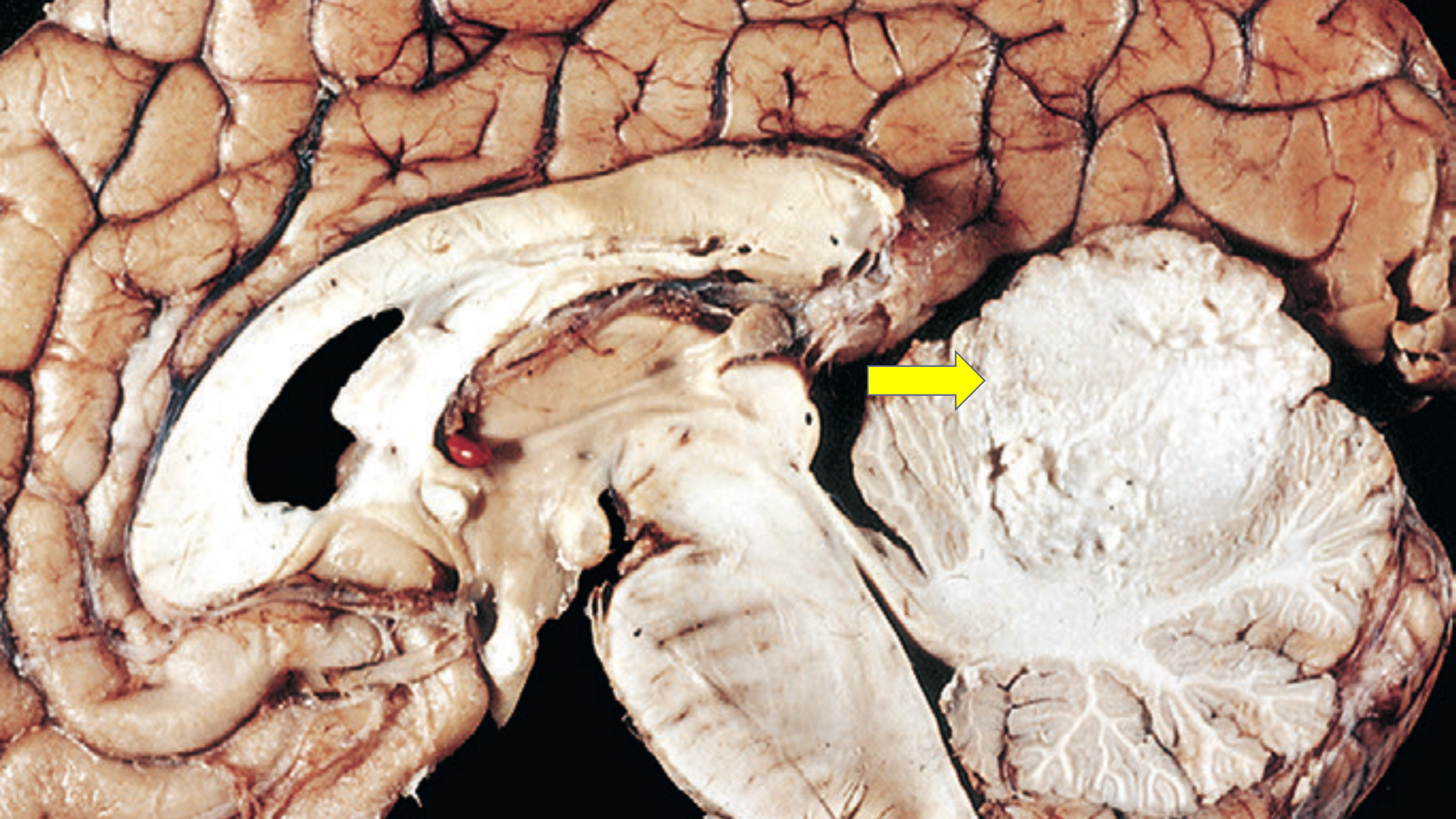
Morphology:

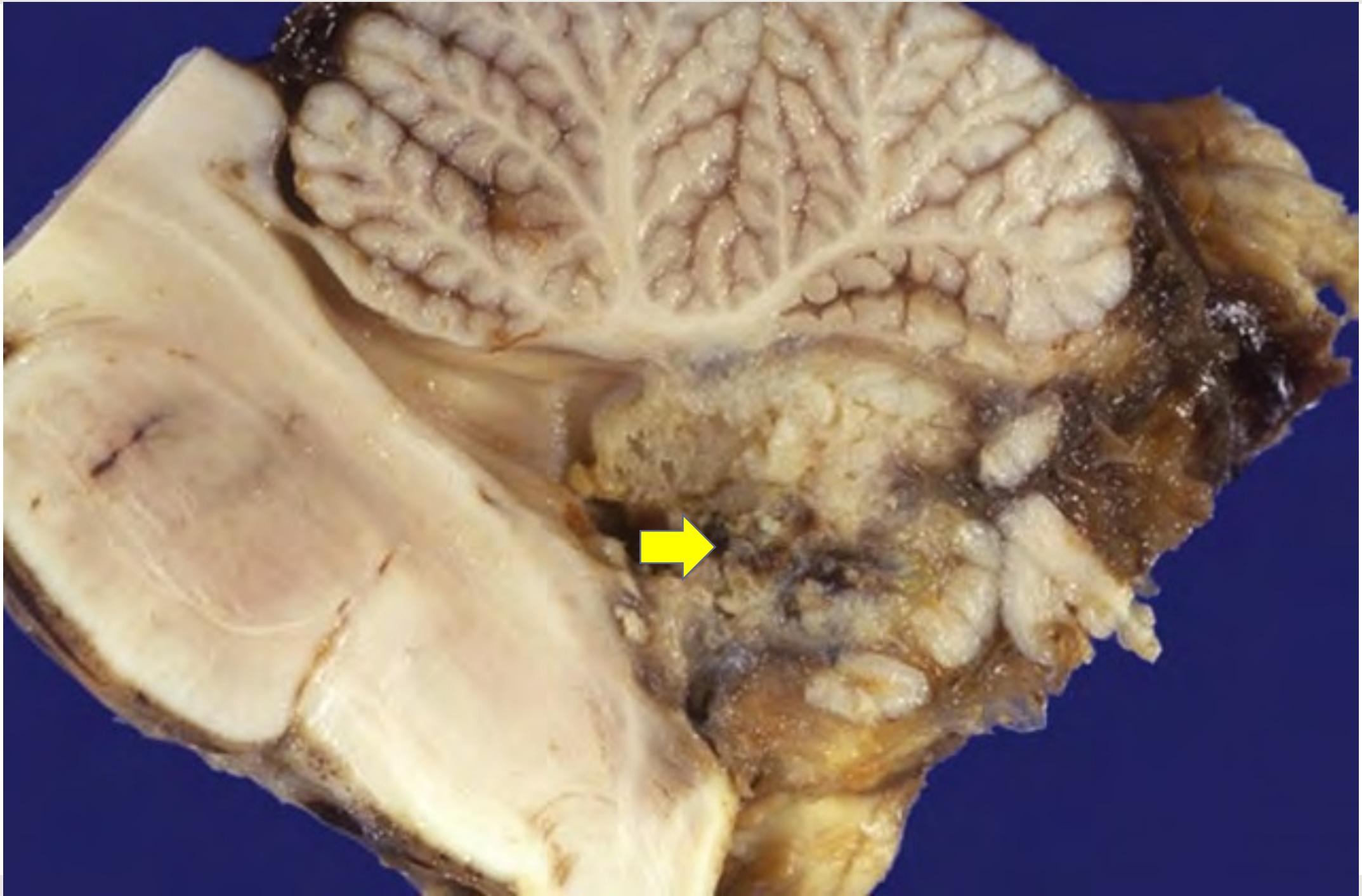
- densely cellular, with sheets of anaplastic (“small blue”) cells with little cytoplasm and hyperchromatic nuclei
- mitoses are abundant.
- **Homer Wright Rosettes:**
  - primitive tumor cells surrounding central neuropil

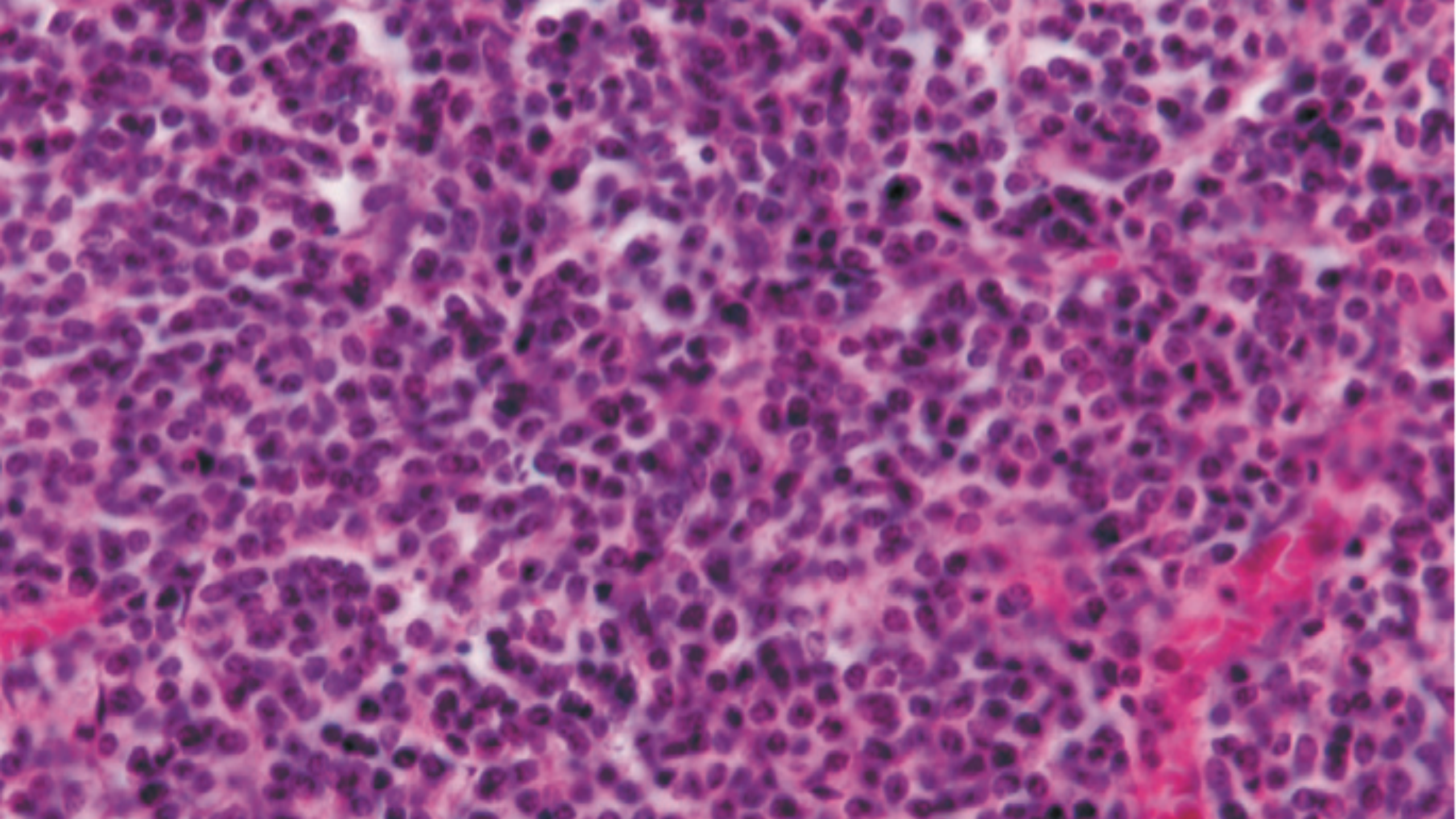
(delicate pink material formed by neuronal processes).

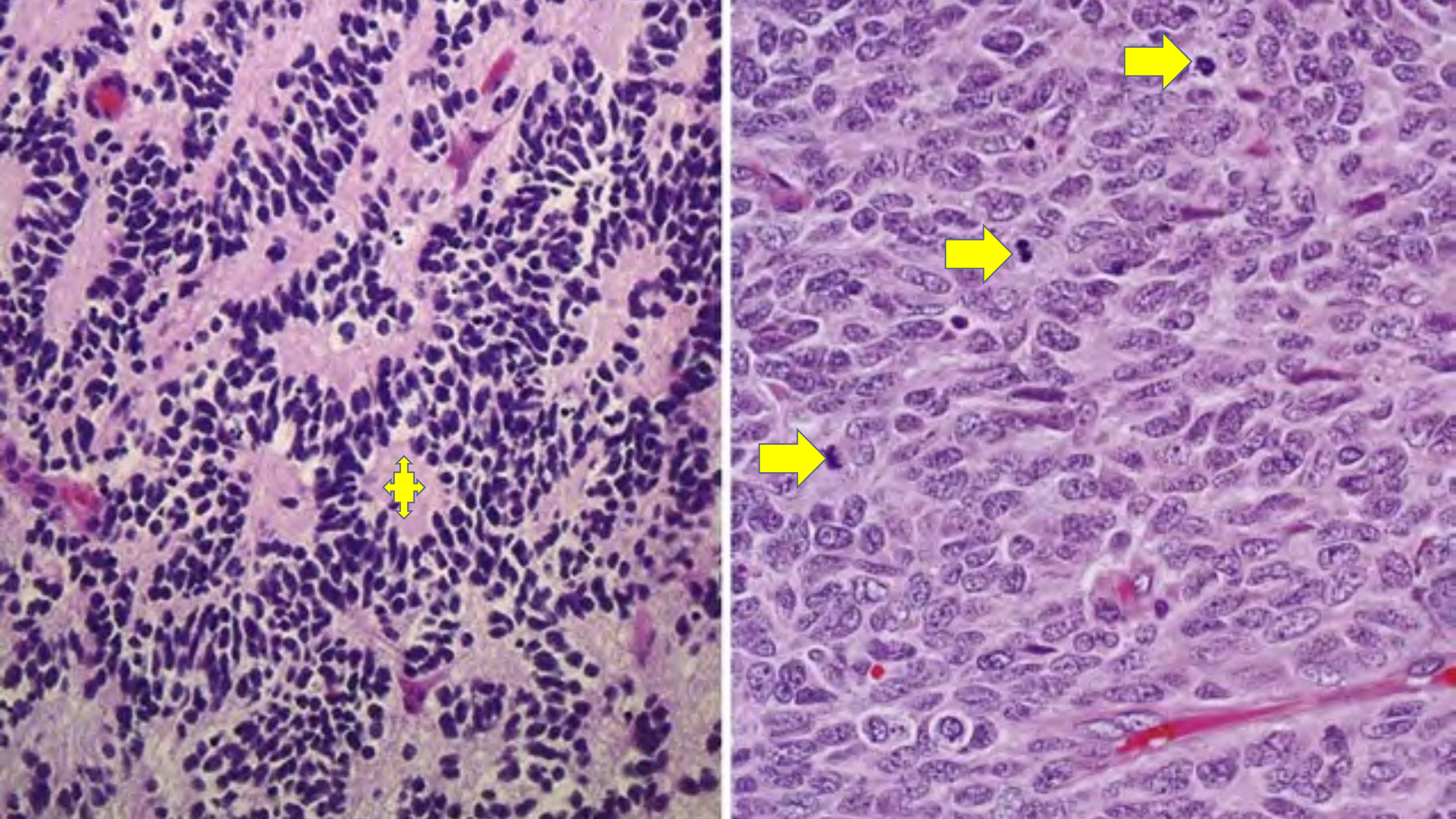
  - Represents focal neuronal differentiation
  - seen also in neuroblastomas











Pathogenesis

- medulloblastomas are classified according to **molecular characteristics** in addition to **histopathological features**.

- **Clinical trials** are ongoing that seek to tailor therapy targeted to **molecular alterations**, with the **goal of avoiding radiation therapy when possible.**

Oncogenic pathways in Medulloblastoma:

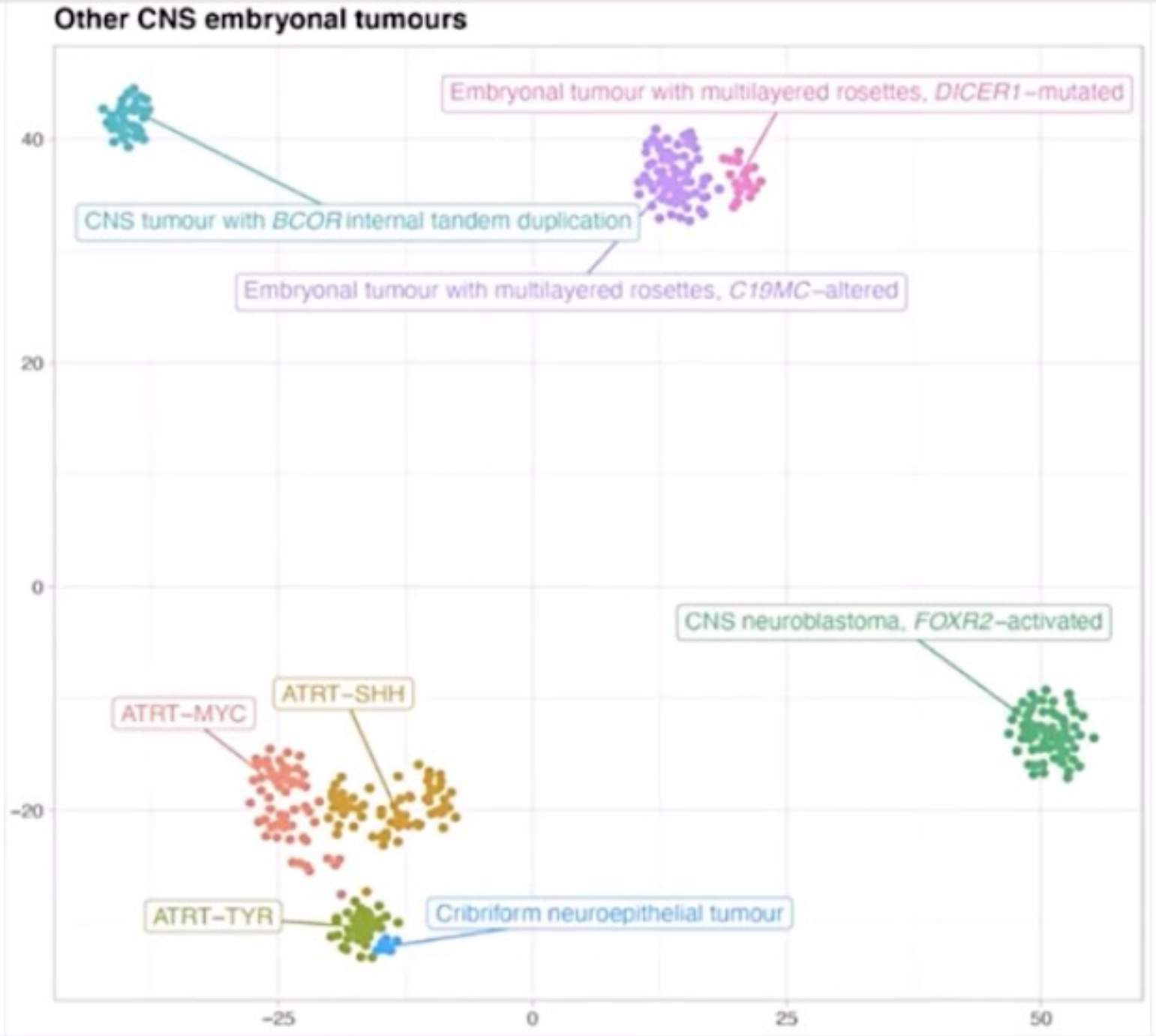
- **Wnt pathway activation**: associated with gain of function mutations in the gene for **β-catenin**; have the **most favorable prognosis** of all of the genetic subtypes.

- **Hedgehog pathway activation:** 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.**

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

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


Other CNS embryonal tumours
Embryonal tumour with multilayered rosettes, DICER1–mutated
CNS tumour with BCOR internal tandem duplication
Embryonal tumour with multilayered rosettes, C19MC–altered
CNS neuroblastoma, FOXR2–activated
ATRT–SHH
ATRT–MYC
ATRT–TYR
Cribriform neuroepithelial tumour
40
20
0
−20
−25
0
25
50

UPDATE

OTHER PARENCHYMAL TUMORS

Primary Central Nervous System Lymphoma:

- **aggressive disease , poor response** to **chemotherapy**.
- most common type: **diffuse large B-cell lymphomas**
- it is the **most common CNS neoplasm in immunosuppressed individuals**
- Presentation:
  - multiple tumor nodules within the brain parenchyma,
  - relatively **well defined** as compared with glial neoplasms
  - not as discrete as metastases.
- lymphoma originating outside the CNS rarely spreads to the brain parenchyma

Germ Cell Tumors

- Can be **primary or metastatic**
- **Primary brain germ cell tumors:**
  - **Locations:** along the **midline**, most commonly in the **pineal and the suprasellar** regions.
  - 90% during the **first 2 decades of life**.
  - The most common primary CNS germ cell tumor is **germinoma**, closely resembles testicular seminoma.

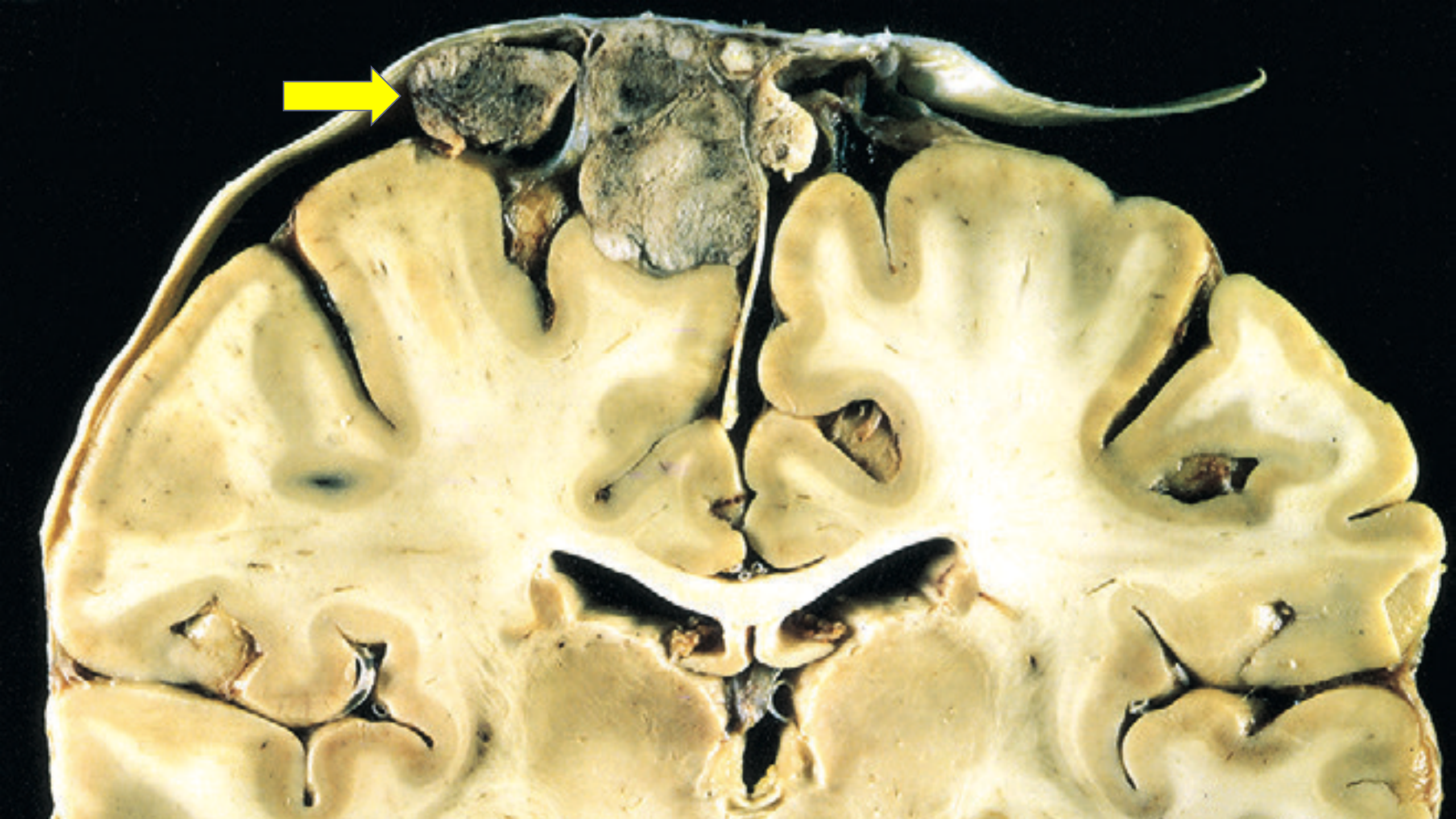
Meningiomas

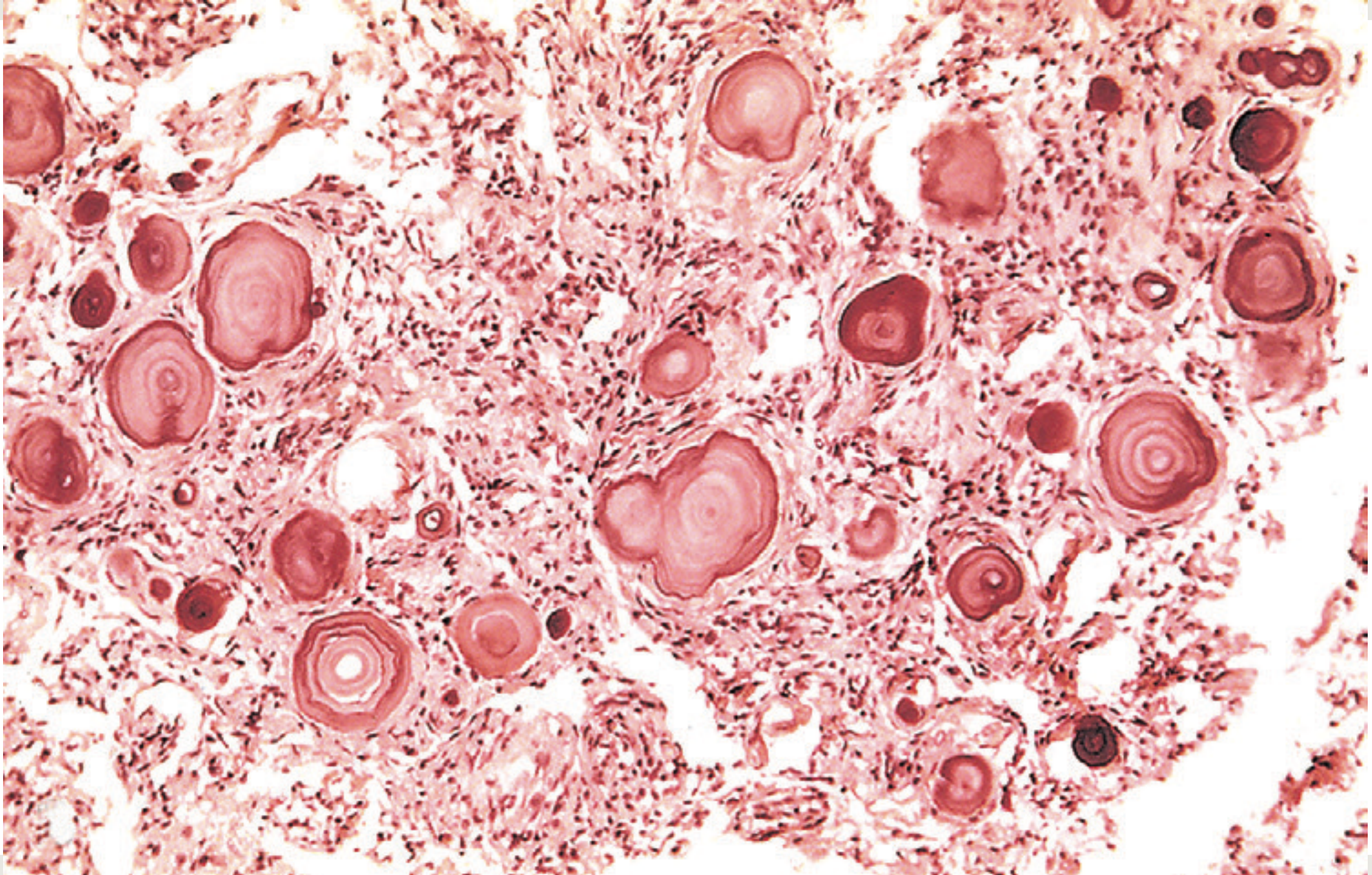
- tumors that arise from meningothelial cells of the arachnoid matter
- **Age at presentation:** adults (women>men)
- **Location: intracranial, intraspinal or orbital** attached to the dura.
- **Presentation:** Most common headache, seizures, weakness (depends on location)

- Mostly separable from underlying brain, but some tumors are infiltrative, a feature associated with an increased risk for recurrence.
- **Prognosis:** determined by the lesion size and location, surgical accessibility, and histologic grade.

➢ **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





ATYPICAL MENINGIOMAS

- **WHO grade 2**
- recurrence and aggressive local growth and may require radiation therapy + surgery.

1- 4 ≥ mitoses/10HPF; 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**

ANAPLASTIC MENINGIOMAS

- **WHO grade 3 (malignant)**
- highly aggressive, resemble a high-grade sarcoma or carcinoma morphologically.

1. **>20 mitoses/ 10HPF;** or
2. **Papillary;** or **rhabdoid meningioma.**

Meningiomas

Essential diagnostic criteria
Classic histopathologic features matching at least one of the meningioma subtypes
OR
Suggestive histopathologic features combined with biallelic inactivation of NF2 or other classic drivers of conventional meningioma (*TRAF7, AKT1, KLF4, SMO, PIK3CA*), clear cell meningioma (*SMARCE1*), rhabdoid meningioma (*BAP1*)
OR
Suggestive histopathologic features combined with one of the defined DNA methylation classes of meningioma

Desirable diagnostic criteria
Dural or meningeal localization
EMA immunoreactivity
Strong and diffuse SSTR2A immunoreactivity
Classic copy number alterations of *NF2*-mutant meningioma, such as monosomy 22/22q in lower grade meningiomas, with additional losses of 1p, 6, 10q, 14q, and/or 18 in higher grade meningiomas

UPDATE

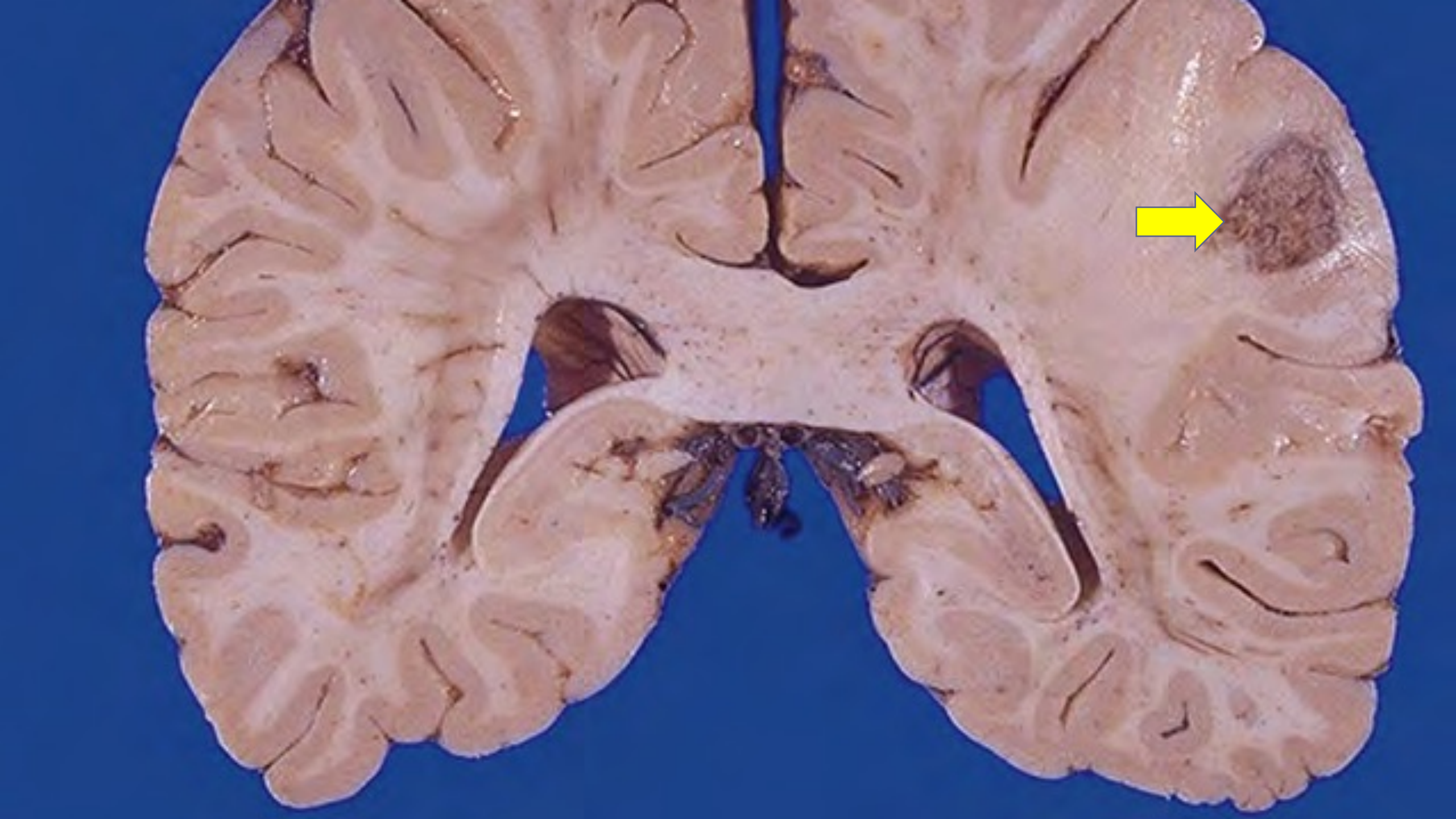
MENINGIOMA GRADING (WHO 2021)

- Atypical (WHO grade 2) (~20%)
  - High mitotic index (≥4/10 HPF)
  - At least 3 of 5 “soft criteria”: sheeting, spontaneous necrosis, macronucleoli, small cells, hypercellularity
  - Brain Invasion (not as clear in o/w benign)
- Anaplastic (Malignant) (WHO grade 3) (~1-2%)
  - Excessive mitotic index (≥20/10 HPF)
  - Frank anaplasia = sarcoma, carcinoma, or melanoma-like
  - TERT promoter mutation
  - CDKN2A homozygous deletion

UPDATE

Metastatic Tumors:

- mostly **carcinomas**
- 25-50% of intracranial tumors.
- The most common primary sites are **lung, breast, skin (melanoma), kidney, and gastrointestinal tract (**80% of cases).
- **sharply demarcated masses**, often at the grey-white matter junction, and elicit local edema
- The boundary between tumor and brain parenchyma is sharp at the microscopic level as well, with surrounding reactive gliosis.




thank you