بسم الله الرحمن الرحيم

DOPAMINE SCIENTIFIC TEAM

Central Nervous System Tumors (Pt.2)

FINAL | Lecture 2

﴿ إِنِّي تَوَكَّلْتُ عَلَى اللَّهِ رَبِّي وَرَبِّكُمْ ۚ مَّا مِن دَابَّةٍ إِلَّا هُوَ آخِذٌ بِنَاصِيَتِهَا ۚ إِنَّ رَبِّي عَلَىٰ صِرَاطٍ مُّسْتَقِيمٍ ﴾

Done by: Mahmoud Aljunaidi

PATHOLOGY

رحلة اليقين مع سورة يس

بِسۡمِ ٱللَّهِ ٱلرَّحۡمَٰنِ ٱلرَّحِيمِ

وَلَقَدۡ أَضَلَّ مِنكُمۡ جِبِلّٗا كَثِيرًاۖ أَفَلَمۡ تَكُونُواْ تَعۡقِلُونَ ٦٢

هَٰذِهِۦ جَهَنَّمُ ٱلَّتِي كُنتُمۡ تُوعَدُونَ ٦٣ ٱصۡلَوۡهَا ٱلۡيَوۡمَ بِمَا كُنتُمۡ تَكۡفُرُونَ ٦٤

{أَضَلَّ مِنْكُمْ جِبِلًّا كَثِيرًا} أي: خلقا كثيرا. {أَفَلَمْ تَكُونُوا تَعْقِلُونَ} أي: فلا كان لكم عقل يأمركم بموالاة ربكم ووليكم الحق، ويزجركم عن اتخاذ أعدى الأعداء لكم وليا، فلو كان لكم عقل صحيح لما فعلتم ذلك. فإذا أطعتم الشيطان، وعاديتم الرحمن، وكذبتم بلقائه، ووردتم القيامة دار الجزاء، وحق عليكم القول بالعذاب فـ {هَذِهِ جَهَنَّمُ الَّتِي كُنْتُمْ تُوعَدُونَ} وتكذبون بها، فانظروا إليها عيانا، فهناك تنزعج منهم القلوب، وتزوغ الأبصار، ويحصل الفزع الأكبر. ثم يكمل ذلك، بأن يؤمر بهم إلى النار، ويقال لهم: {اصْلَوْهَا الْيَوْمَ بِمَا كُنْتُمْ تَكْفُرُونَ} أي: ادخلوها على وجه تصلاكم، ويحيط بكم حرها، ويبلغ منكم كل مبلغ، بسبب كفركم بآيات الله، وتكذيبكم لرسل الله.

Central Nervous System Tumors (2)

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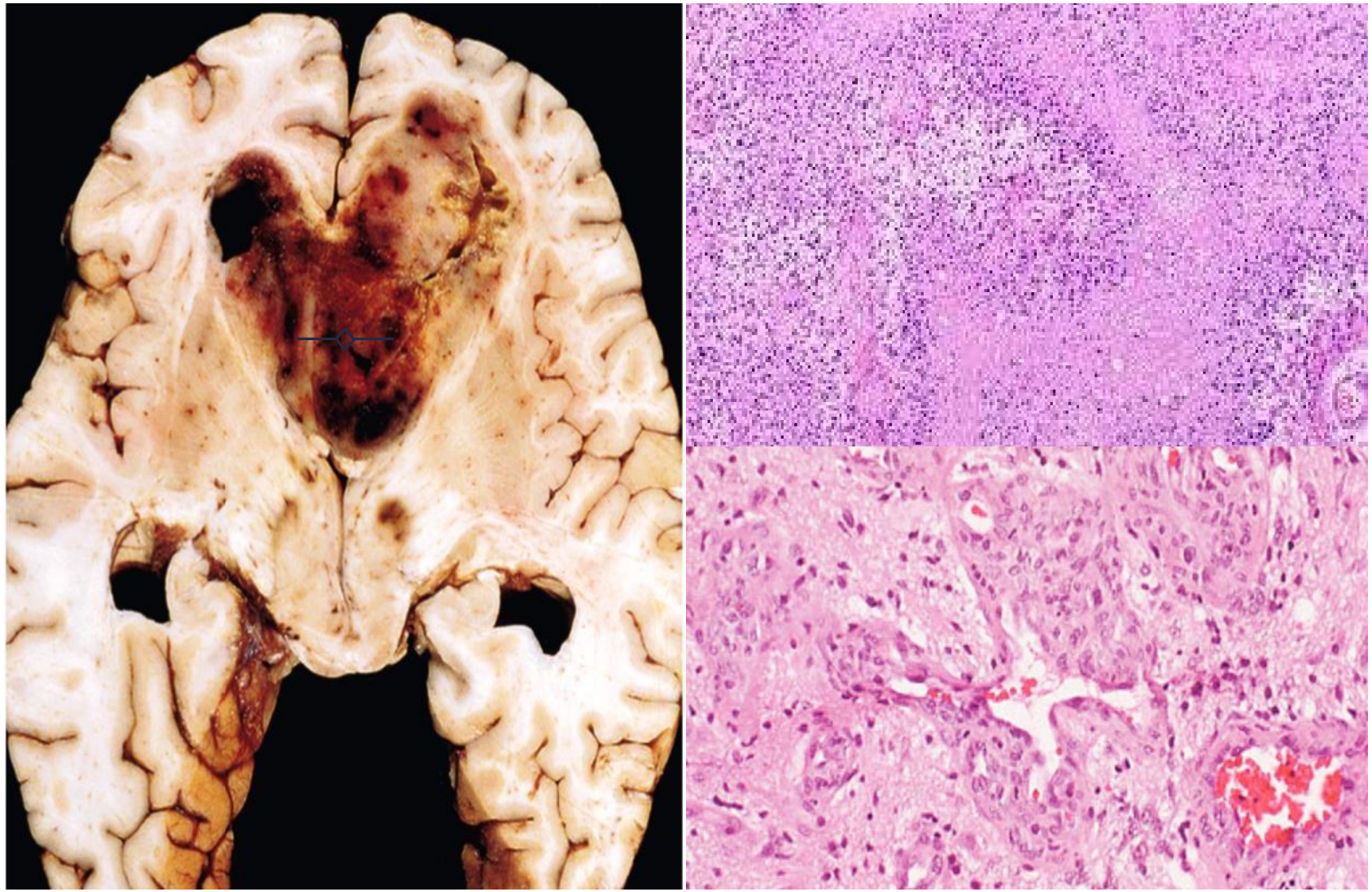
Remember: The Characteristic features of CNS tumors

1. No premalignant Stage.
2. Metastasis is rare.
3. Prognosis depends on: Location and Growth pattern, but **NOT** the STAGE (no staging of CNS tumors).

Glioblastomas, IDH-wild-type, grade 4



Definition

❖ It's a **Diffuse glioma,** an infiltrative tumor that extends beyond its grossly visible margins, making it difficult to distinguish the tumor boundary from the surrounding normal brain tissue.

❖ As the name implies, this tumor is **IDH-wildtype** and **H3 wildtype**, which can be proven/detected by **molecular testing**.

❖ Also, this tumor has **one or more** of the following histologic or genetic features:

- **Microvascular proliferation.**
- **Palisading Necrosis.**
- **TERT** (Telomerase Reverse Transcriptase) promotor **mutation.**
- **EGFR** gene **amplification.**
- **Combined gain** of entire **chromosome 7** and **loss** of entire chromosome **10** [+7 / -10].

✓ In diffuse gliomas that are both IDH-wild type and H3-wild type, the presence of any one of the five defining features is sufficient to classify the tumor as glioblastoma, IDH-wild type (WHO grade 4). In other words, **even a single qualifying feature is enough** to make this diagnosis when both IDH and H3 mutations are absent.

Glioblastomas, IDH-wild-type:

- **The most common malignant glioma** (50% of all primary malignant brain tumors in adults).
- **Always grade 4** (no lower grade precursor); bad prognosis.
  - Generally, grade 4 presents with marked cellular atypia, increased mitotic activity, areas of necrosis, and microvascular proliferation.
- Despite treatment with surgery, chemotherapy, and radiotherapy, **their prognosis remains poorer than that of all other tumor grades.** Also, it has worse prognosis than astrocytoma, IDH-mutant (grade 4), making it more aggressive than this type of astrocytoma.
- **Age**: 6th-8th decades of life (>50).
- **Site**: it can affect any area in the **cerebral hemispheres**, with the most common being the temporal, parietal, frontal lobes, basal ganglia and thalamus.

Course and Prognosis

❖ **Clinically:**

- Rapid progression, due to the high proliferative activity, involving larger areas of the brain.
  - **Butterfly glioma:** Rapid infiltration of the corpus callosum with **growth to the contralateral** hemisphere leading to **bilateral symmetrical lesion**, for example, affecting both frontal lobes along with the corpus callosum leading to a **butterfly shaped glioma.**
- Symptoms depend on the site, for example this tumor can obstruct the **ventricular system**, leading to increased intracranial pressure with symptoms such as **nausea**, **vomiting**, and **headache**. It may also create an **epileptogenic focus**, resulting in **Seizures**. Additionally, patients can develop focal **neurocognitive impairment** depending on the region of the brain involved.

❖ **Prognosis:**

- **Very Poor** (even with resection, chemotherapy and radiotherapy).
- The median survival is only about **15-18 months.**

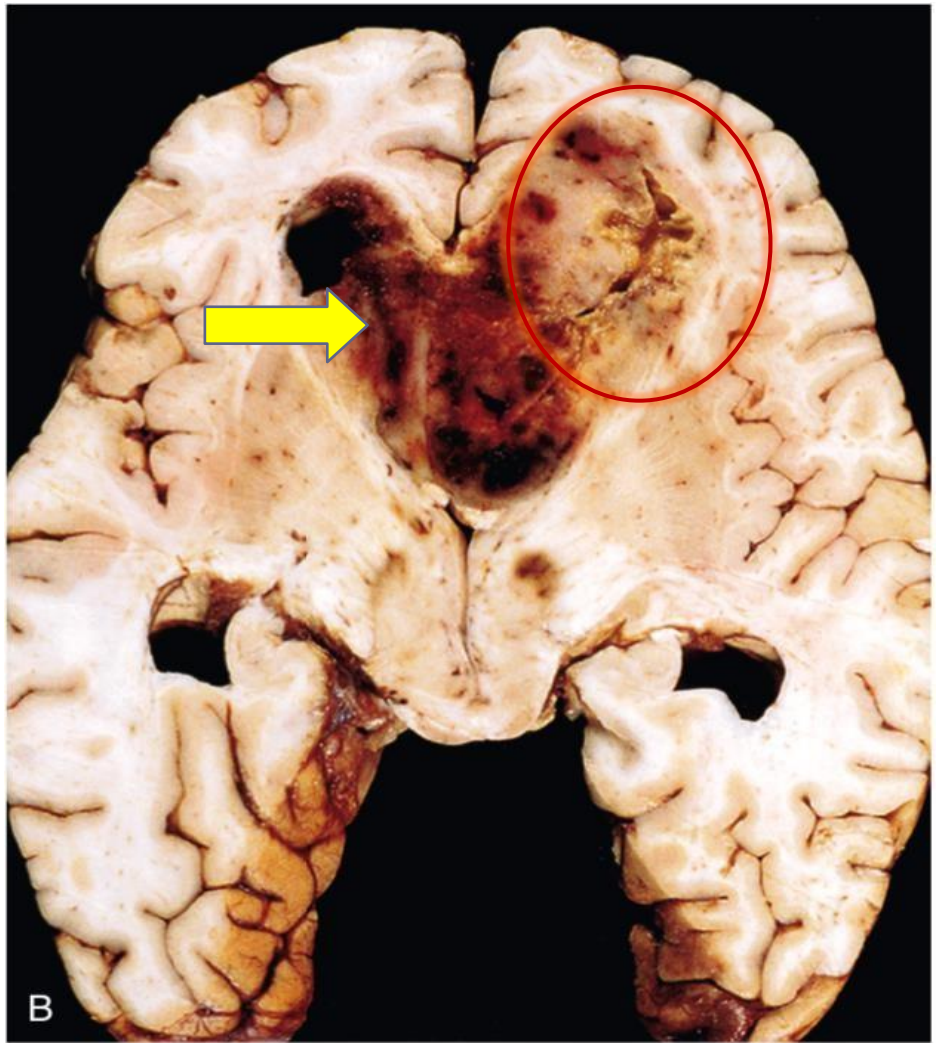
The Glioblastoma Redefinition

- As discussed previously, the classification of CNS tumors arose from clinical observations made by neuropathologists and neurosurgeons. They noted that patients diagnosed with glioblastoma could have very different outcomes: one patient might survive only around 15 months with a typical pattern of deterioration, while another could live for several years.
- These differences led to molecular studies, which revealed that what was once considered a single entity consists of biologically distinct tumors. **It became clear that glioblastoma is defined as IDH-wild type, and that specific molecular mutations or characteristic histologic features follow a particular pattern in these tumors.**

Morphology

Macroscopic

- Variation in the gross appearance of the tumor from region to region is characteristic, and was called **glioblastoma multiforme**, due to shape variation:
  - Some areas are **firm and white** (no necrosis, nor hemorrhage), others are **soft and yellow** (due to tissue necrosis), others show cystic degeneration and hemorrhage.
- In this image it's a **butterfly glioma**, involving both sides and corpus callosum, with sharp boundaries not clearly visible. It shows an area of hemorrhage (**yellow arrow**), necrosis and cystic degeneration (red circle).
- **The surrounding area may be involved and appear as firm and white.**



Morphology

Microscopic

- Similar to astrocytoma, IDH-mutant, grade 4 with:
  1. **High cellularity** (cellular tumor).
  2. **Prominent** nuclear **atypia**.
  3. Brisk **mitotic activity.**
  4. **And** one of the five criteria (mentioned previously):
     - **Necrosis**:

       Irregular zones of necrosis surrounded by dense accumulations of tumor cells arranged in a "pseudopalisading" pattern, where the cells line up along both sides of the necrotic zone (**palisading necrosis**).
     - **Or Microvascular proliferation:**

       The presence of abnormal vessels with walls composed >2 layers of vascular wall cells, instead of the normal one layer.
     - **Or One of the 3 molecular mutations.** (Next Slide)

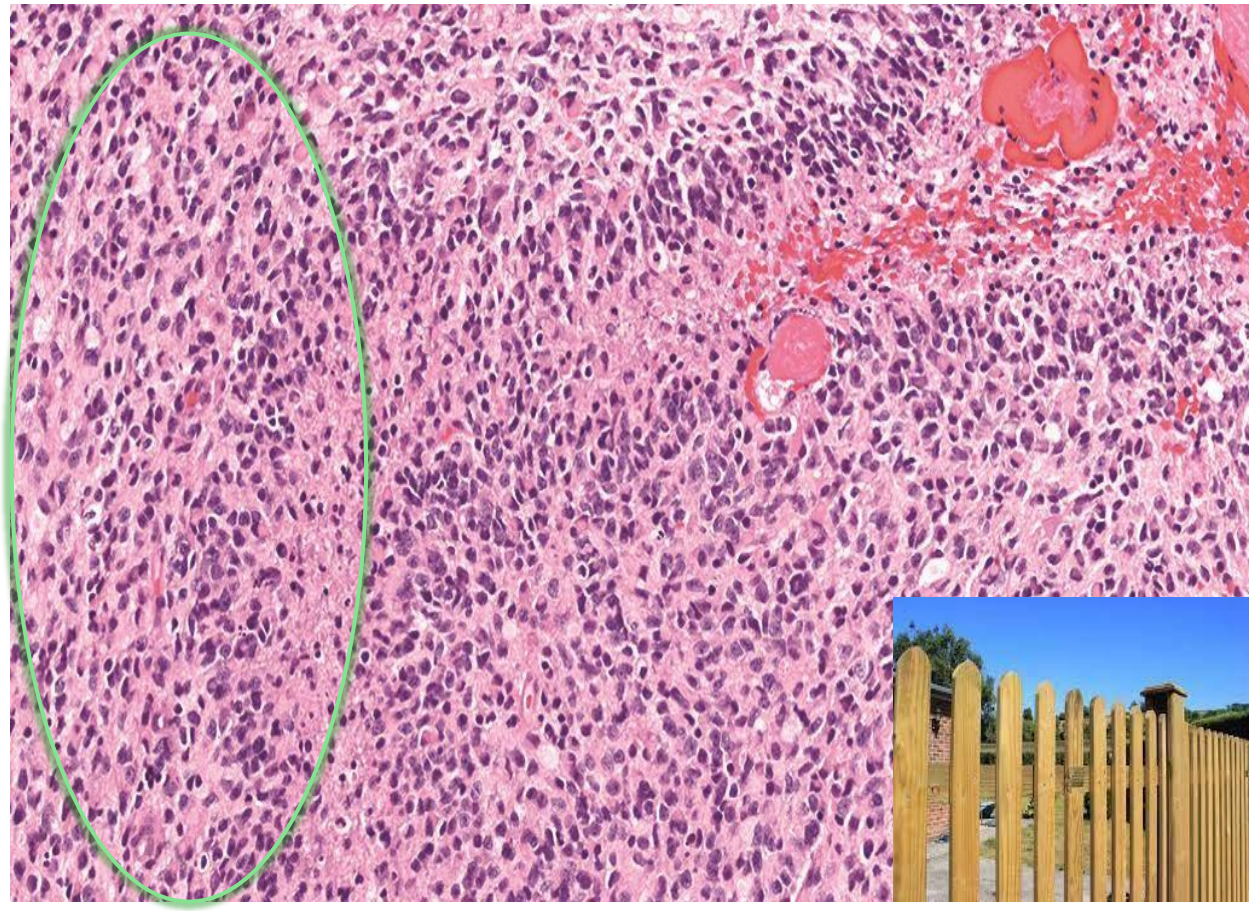
Molecular Markers in Glioblastoma Diagnosis

- The presence of **any of** the following Molecular features **(even in the absence of necrosis or microvascular proliferation)** lead to the **designation of glioblastoma**, IDH wildtype, grade 4:
  - The presence of **TERT** promotor **mutation.**
  - **EGFR** gene **amplification.**
  - **+7/-10** chromosome copy number changes

Morphology

Microscopic

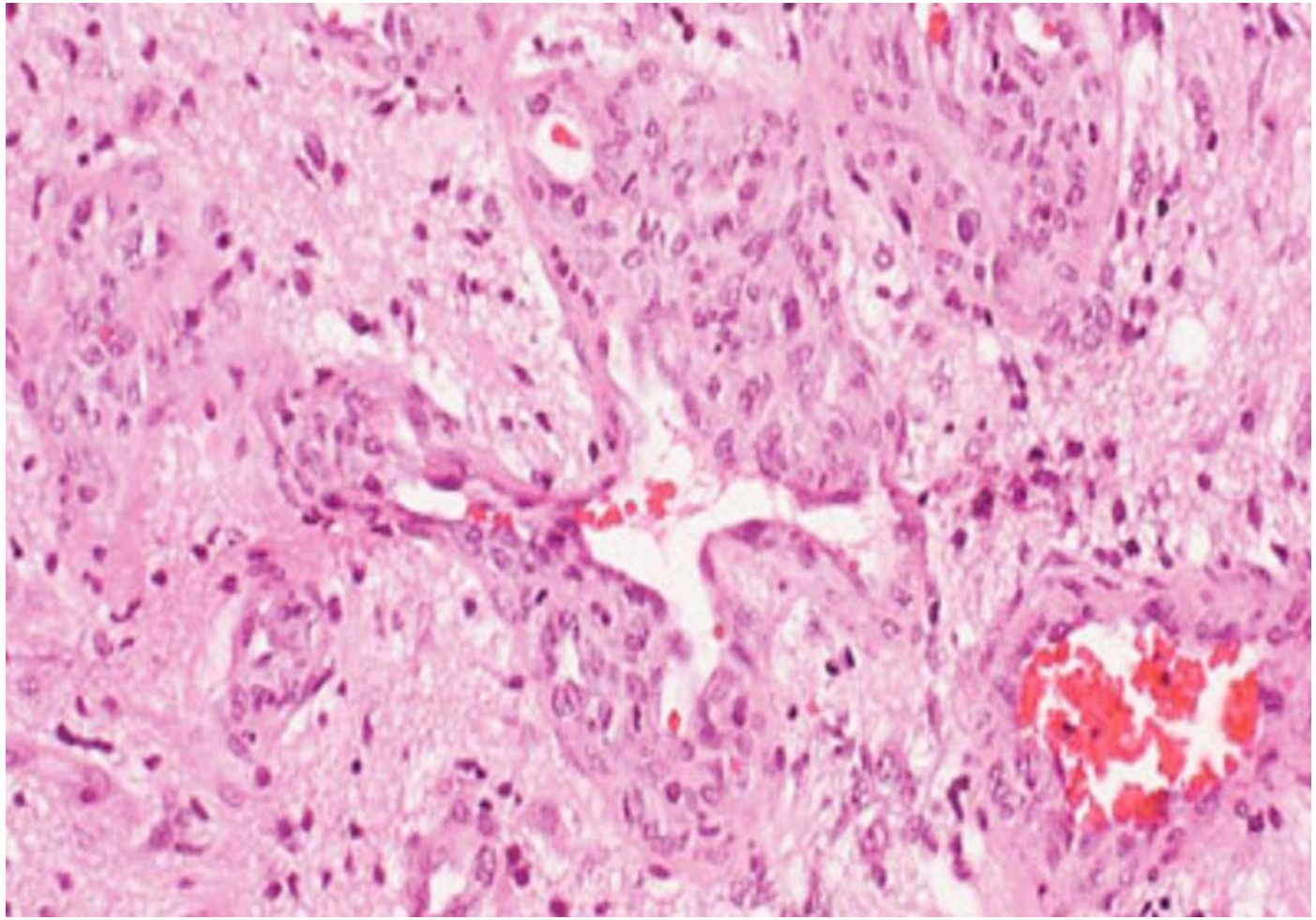
- This figure demonstrates the key histologic features of glioblastoma, IDH-wild type.
- There is a **marked increase in cellularity (Green oval)** evident by the high density of dark-staining nuclei compared to normal white matter. These nuclei are **hyperchromatic** and show **significant variation** in size and shape, indicating pronounced **pleomorphism and cellular atypia.**
- In addition, mitotic figures and apoptosis can be observed.
  - The presence of necrosis, together with cellular atypia and brisk mitotic activity, is sufficient to support a diagnosis of glioblastoma in the appropriate molecular context (IDH-wild type and H3-wild type).
- A characteristic feature seen here is **pseudopalisading necrosis**, in the center (the curved structure). where necrotic areas appear as pink, friable zones surrounded on both sides by densely packed tumor cells arranged in a layered pattern (زي السور).
  - Although not entirely specific, this finding strongly supports the diagnosis.



Morphology

Microscopic

- Another important feature is **microvascular proliferation.**
- Here, the blood vessel appears abnormal, with irregular lumen and wall composed of at least 3 layers of proliferating endothelial cells.
- **The presence of two or more layers is sufficient to define this feature.**

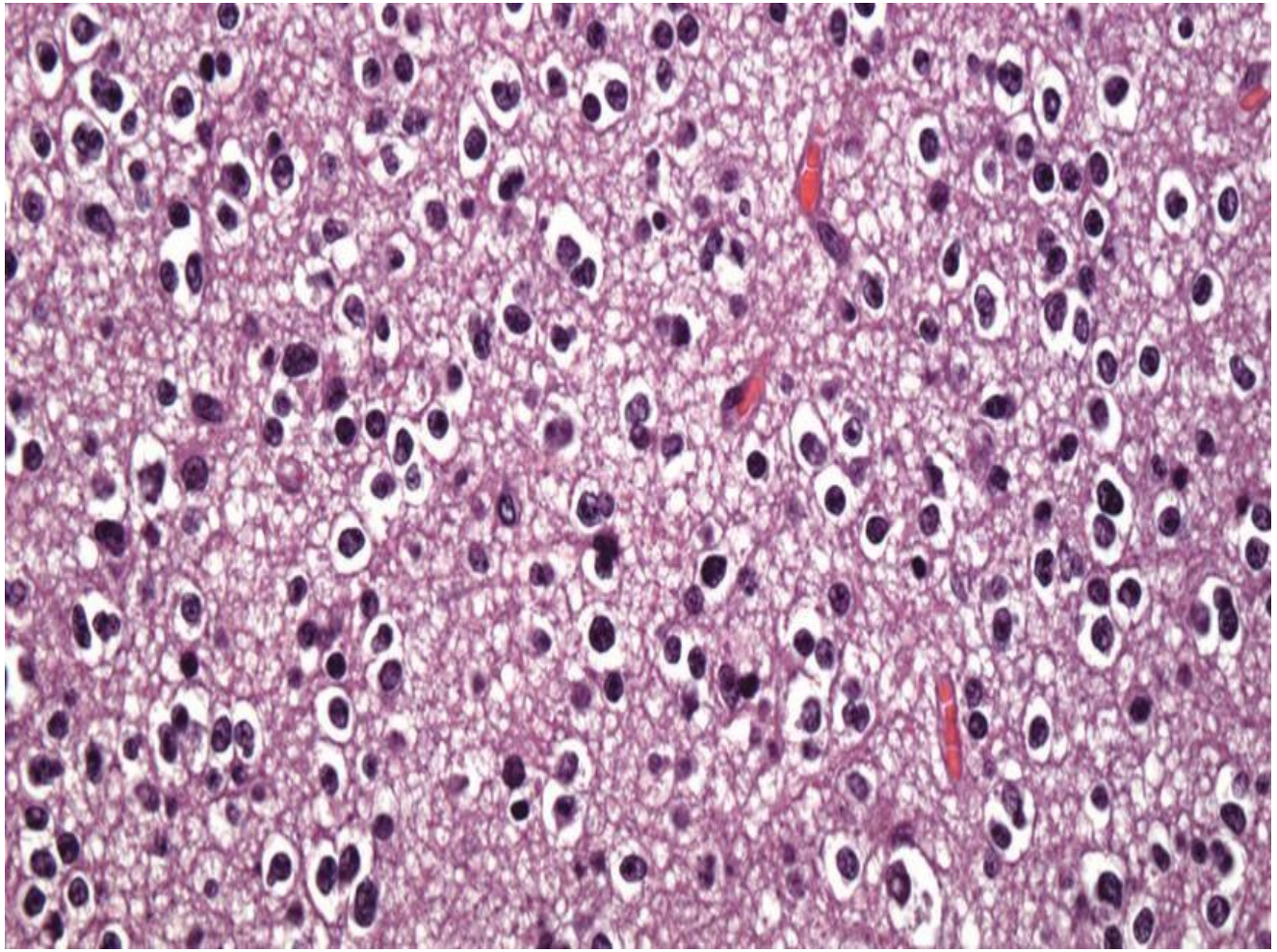


Manual of basic neuropathology, 5th rdition

Morphology

Microscopic; Oligodendroglioma, IDH-Mutant, and 1p/19q-codeleted.

- The third adult-type diffuse glioma is oligodendroglioma, IDH-mutant with 1p/19q co-deletion.
- This tumor is characterized by activation of a **telomerase-dependent process**, and it does not carry **p53** or **ATRX** mutations, as these are mutually exclusive.



Oligodendroglioma, IDH-mutant and 1p/19q-codeleted

- Definition: A **diffusely infiltrating**, **slow-growing glioma** with IDH1 or IDH2 **mutation** and **codeletion** of chromosomal arms 1p and 19q.
- One of the common gliomas: 5-15% of gliomas.
- **Age at diagnosis:** 40-50 yrs.
- **Location**: This tumor prefers the white matter and mostly appears in the cerebral hemispheres, mainly in the **frontal** or **temporal** lobes, white matter.

Prognosis and Grading of Oligodendroglioma

❖The combination of surgery, chemotherapy, and radiotherapy yields an average survival of:

- 10-20 years for WHO grade 2, while for grade 2 astrocytoma it's more than 10 years.
- 5-10 years for WHO grade 3.

✓ Grade 3 is **more aggressive** than grade 2 oligodendroglioma.

- **When corrected for tumor grade** (for example, grade 2 vs grade 2)**, oligodendrogliomas (CNS WHO grade 2,3) have best prognosis among diffuse glial tumors.**

➢**NO grade 1 OR 4 oligodendroglioma.**

Morphology

Micro/Macro-scopic

❖Macroscopic:

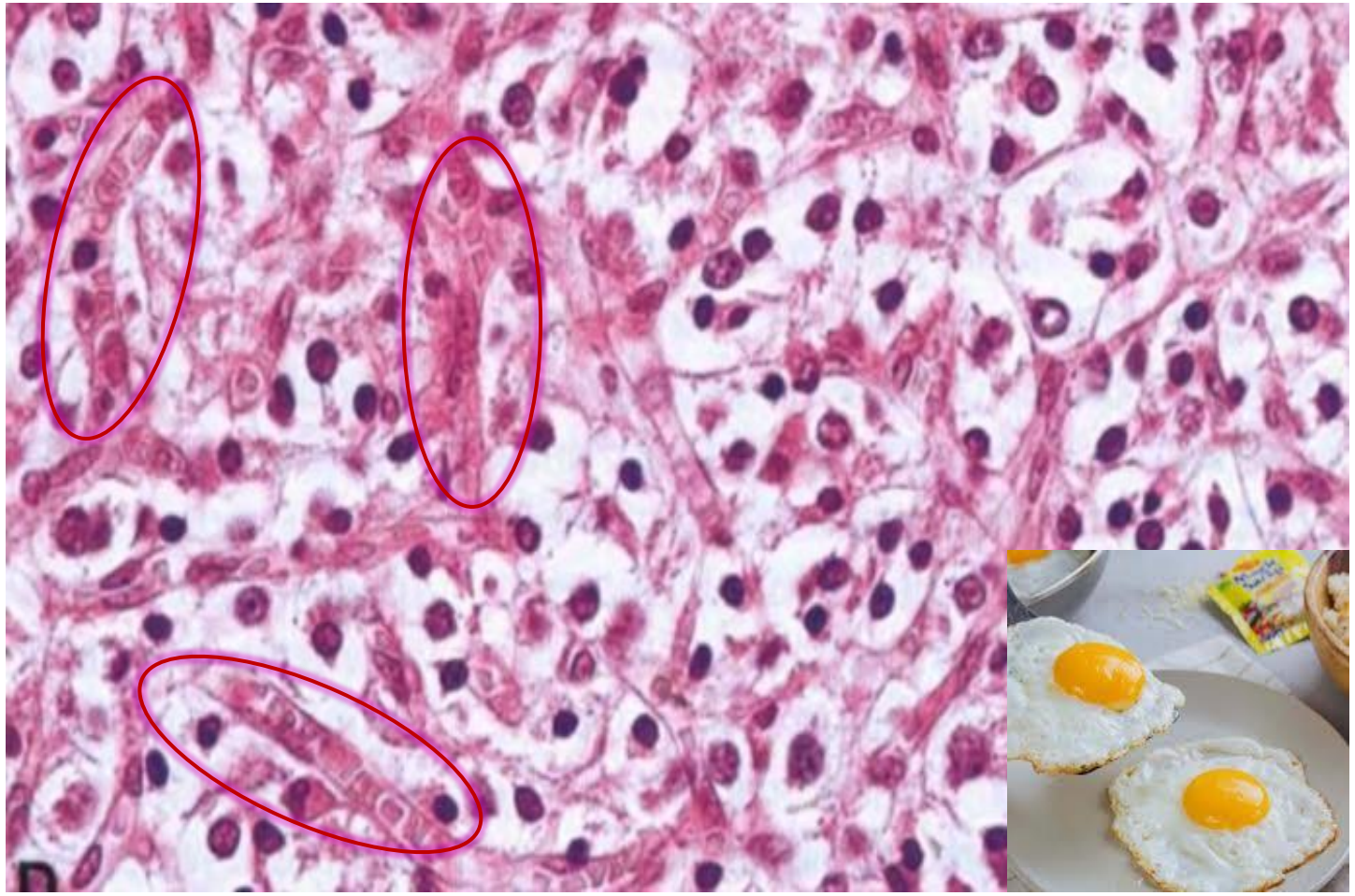
- **Infiltrative tumors** with blurring of grey matter-white matter boundary, difficult to fully excise due to their diffuse infiltration beyond visible margins.
- With or without (+/-) gelatinous gray mass, cysts, focal hemorrhage, and **calcification** that can also be seen both microscopically (it's the most classic example of CNS tumors with calcification).

❖Microscopic:

- Sheets of regular uniform cells **resembling oligodendrocytes**.
- Spherical nuclei containing finely granular chromatin (**salt and pepper**).
- The nuclei are surrounded by a clear halo of cytoplasm → **fried-egg appearance.**
- The proliferation of the regular uniform cells is presented in a background of Delicate network of **"chicken-wire"-like** anastomosing capillaries.

Morphology
Microscopic; Fried-egg Appearance.

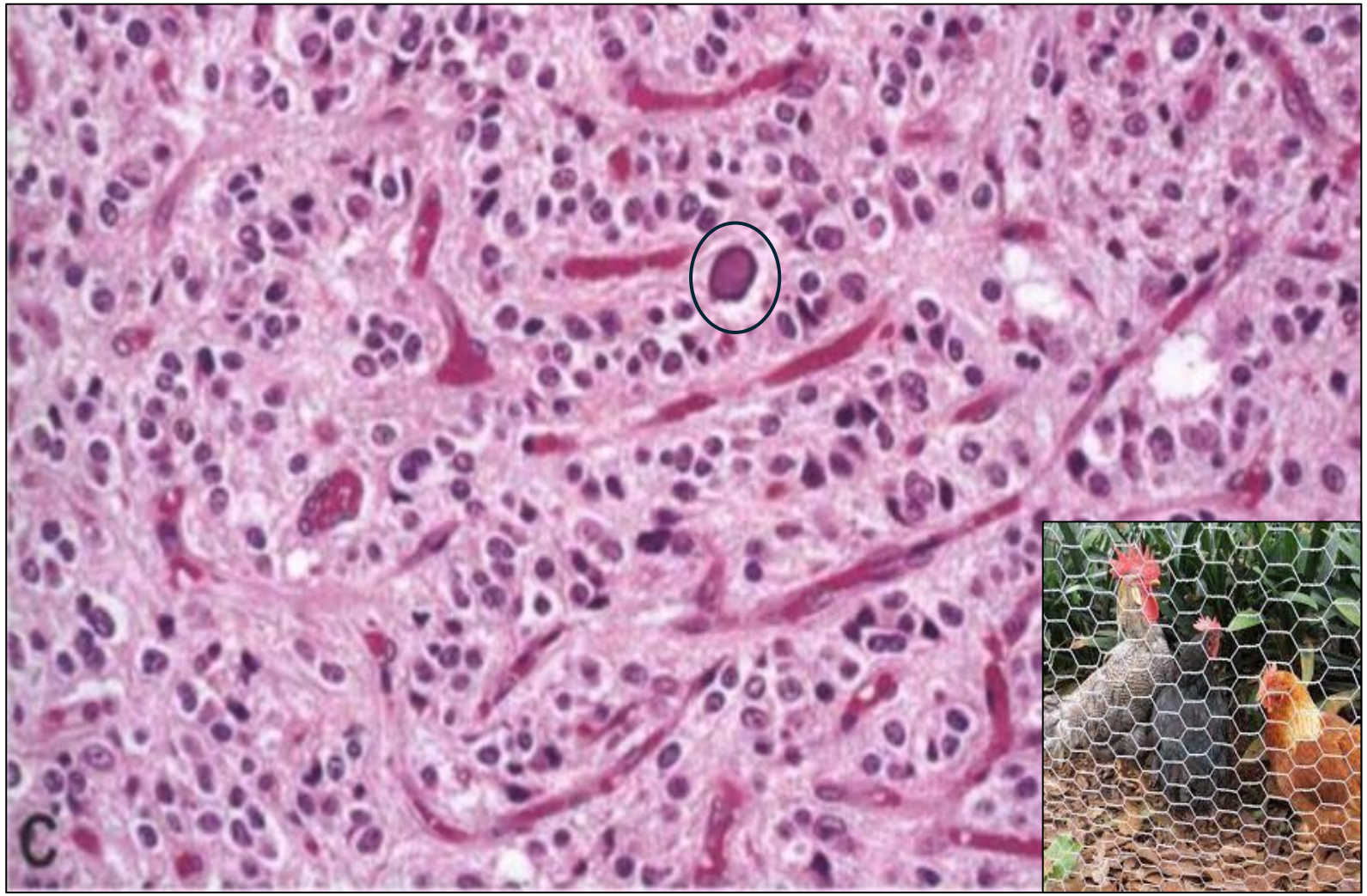
- Here, we see the proliferation of uniform, regular cells with round spherical nuclei where the chromatin appears finely granulated (**salt and pepper appearance**). Each cell has a clear perinuclear halos (**fried-egg appearance**), and proliferation within a delicate capillary network giving a **"chicken wire" pattern (pink oval)**.
- Analogy: The nucleus is the yolk, and the perinuclear halo resembles the egg-white.



Morphology

Microscopic; (Chicken-wire)-like anastomosing capillaries.

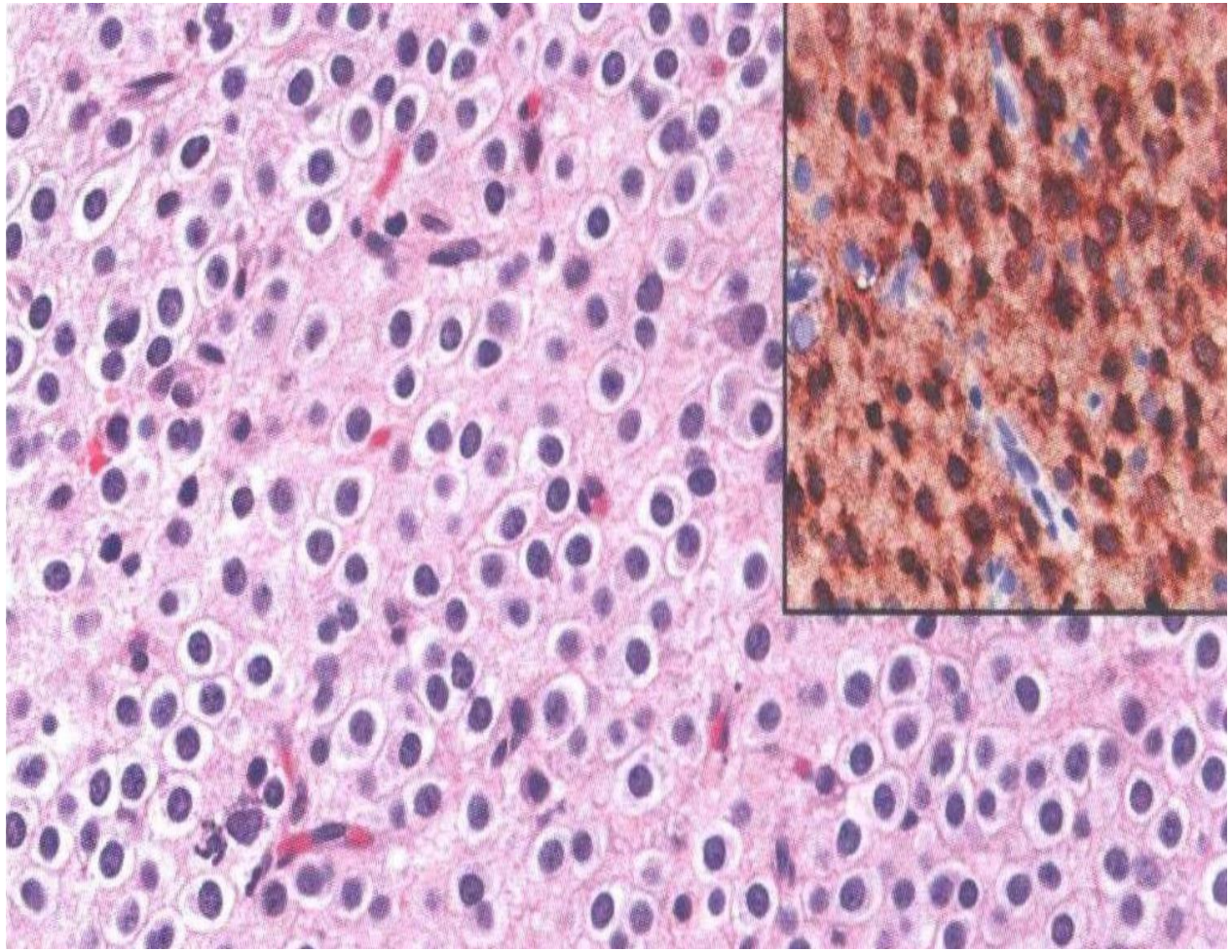
Same as before, but here focal of **calcification** can be seen.
(Black circle).



Morphology

Microscopic

- Notice how uniform the cells are, with their fried-egg appearance.
- In the section on the right, the same tumor is stained with an IDH1 immunostain, which highlights the cytoplasm in **brown**, confirming the presence of the IDH1 mutation **(positive)**.



Histological Features of WHO Grade 2 Oligodendroglioma

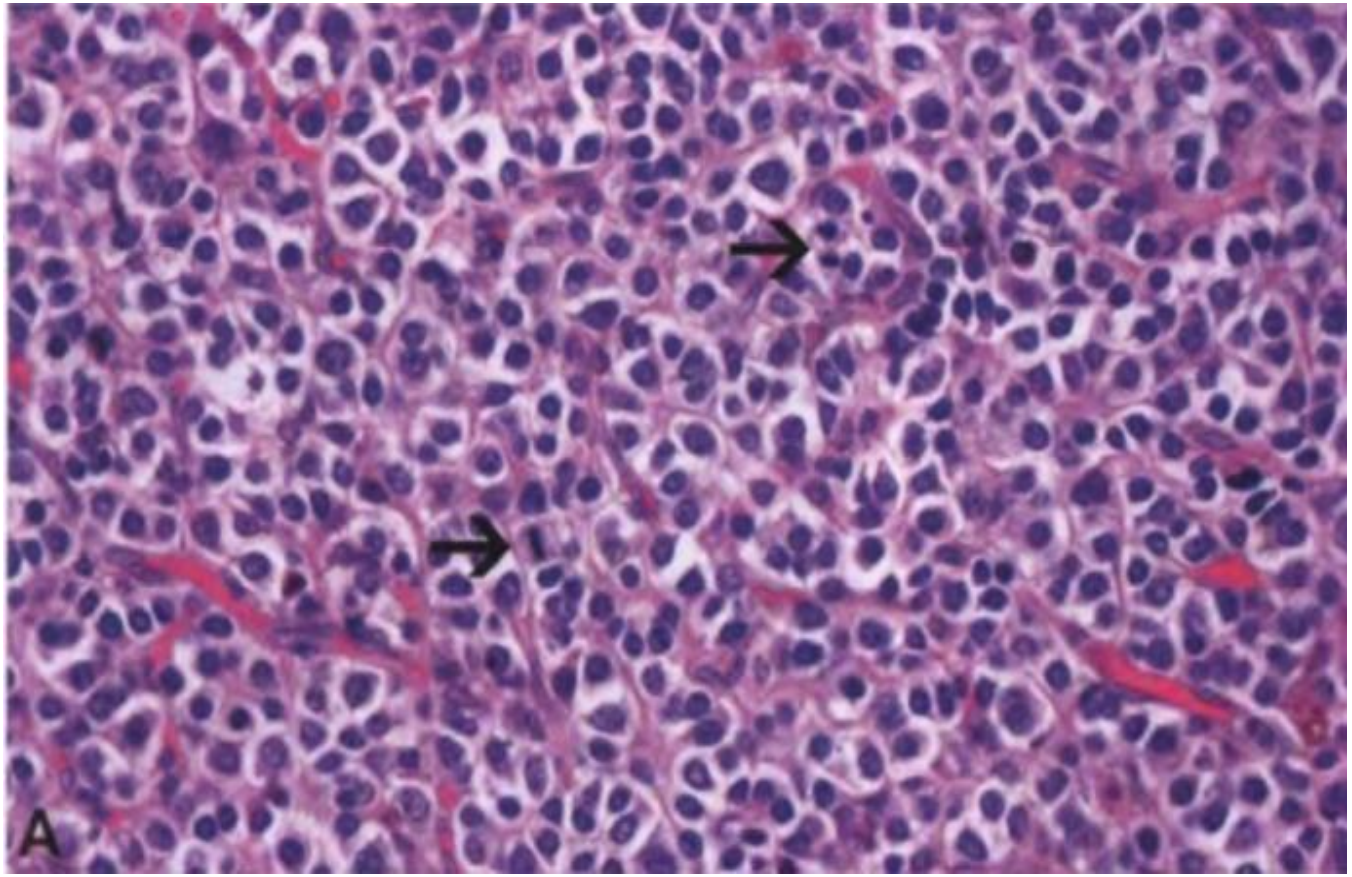
- **Calcification** up to 90% of cases.

- **Mitotic activity** usually is absent or low **(Ki67<5%).**
  - When examining Ki67, an immunohistochemical marker that highlights cells actively in the cell cycle regardless of visible mitosis, its labeling index is typically **below 5%** in grade 2 oligodendrogliomas.
- **No spontaneous necrosis.**

- **No microvascular proliferation.**

oligodendroglioma , IDH-mutant, & 1p/19q-codeleted, WHO grade 3

Compared to grade 2, grade 3 tumors demonstrate **increased cellularity**, **hyperchromatic nuclei**, brisk mitotic activity **(black arrows)** – (≥ 6 mitoses per 10 high-power fields or KI67 >10%), and/or microvascular proliferation, or homozygous CDKN2A deletion. These histologic or molecular features are sufficient to upgrade the tumor to grade 3.



Things in gray are discussed later, but I felt the need to add them here.

oligodendroglioma , IDH-mutant, & 1p/19q-codeleted, WHO grade 3

- Defined as: An IDH-mutant and 1p/19q-codeleted oligodendroglioma with focal or diffuse histological features of anaplasia (in particular, **pathological microvascular proliferation and/or brisk mitotic activity with or without necrosis)** or one of the molecular features discussed later.
- Microvascular proliferation and brisk mitotic activity **are stronger than the necrosis** in oligodendroglioma.
  - So, it's enough to have an increase in the mitotic activity (brisk mitotic activity) or pathologic microvascular proliferation to call it grade 3 oligodendroglioma.
- **Brisk mitotic activity:** High level of cell division. Specifically, if six or more mitoses are observed per high-power field, the activity is considered brisk. Alternatively, using Ki67 staining, a labeling index above 10% also indicates brisk mitotic activity in the tumor.

IDH-mutant 1p/19q codeleted oligodendrogliomas, grades 2-3

❖ A table comparing both grades:

- Both are diffuse gliomas.
- Both must have IDH mutation.
- Both must have 1p/19q codeletion.
- In grade 2 there are absence of histological features of anaplasia.
- In grade 3, **only one** of these is sufficient for the **upgrade of grade 2 to grade 3:**
  1. Microvascular proliferation.
  2. Brisk mitotic activity.
  3. **Homozygous deletion of cyclin dependent kinase N2A** (CDKN2A).

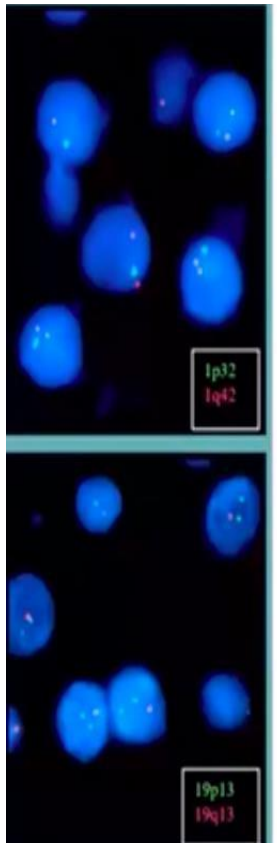
Essential diagnostic criteria for oligodendroglioma, IDH-mutant and 1p/19q-codeleted, WHO grade 2	Essential diagnostic criteria for oligodendroglioma, IDH-mutant and 1p/19q-codeleted, WHO grade 3
A diffuse glioma	A diffuse glioma
WITH	WITH
an IDH1 codon 132 or IDH2 codon 172 missense mutation*	an IDH1 codon 132 or IDH2 codon 172 missense mutation*
AND	AND
combined whole arm deletions of 1p and 19q	combined whole arm deletions of 1p and 19q
AND	AND
absence of histological features of anaplasia	histological features of anaplasia, including brisk mitotic activity and/or pathological microvascular proliferation with or without necrosis
	AND/OR
	homozygous *CDKN2A* deletion**

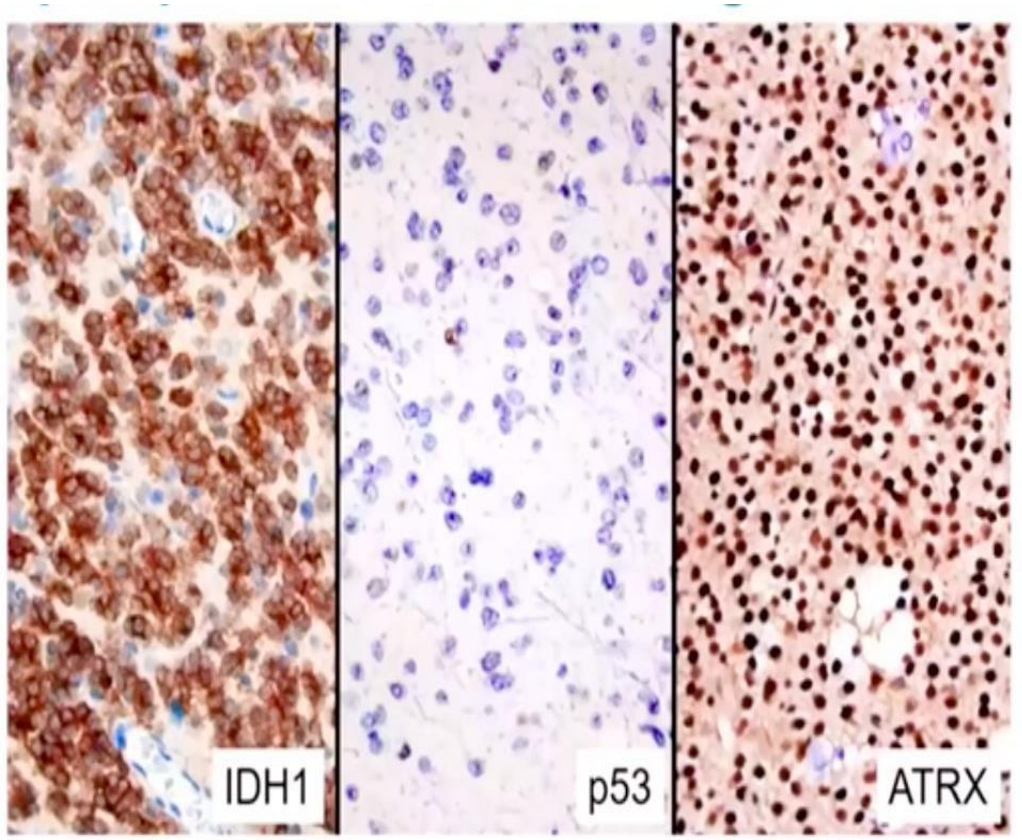
Everything mentioned about the table has been written, in case if inability to read the table

Typical Findings of Oligodendrogliomas

- Using FISH, a co-deletion of 1p/19q can be identified. Just know this, we are not required to read FISH results.
- IDH1 is expected to be mutated, detectable either by immunohistochemistry or IDH sequencing. Here, using immunostains, the cytoplasm of IDH1-mutant cells appears **brown**.
- p53 and ATRX, in contrast, remain wild-type (**p53** shows a **negative** result, while **ATRX** is preserved and **positive**).

➢ **This pattern differs from astrocytomas, where IDH mutation is shared but p53 and ATRX show opposite expressions.**



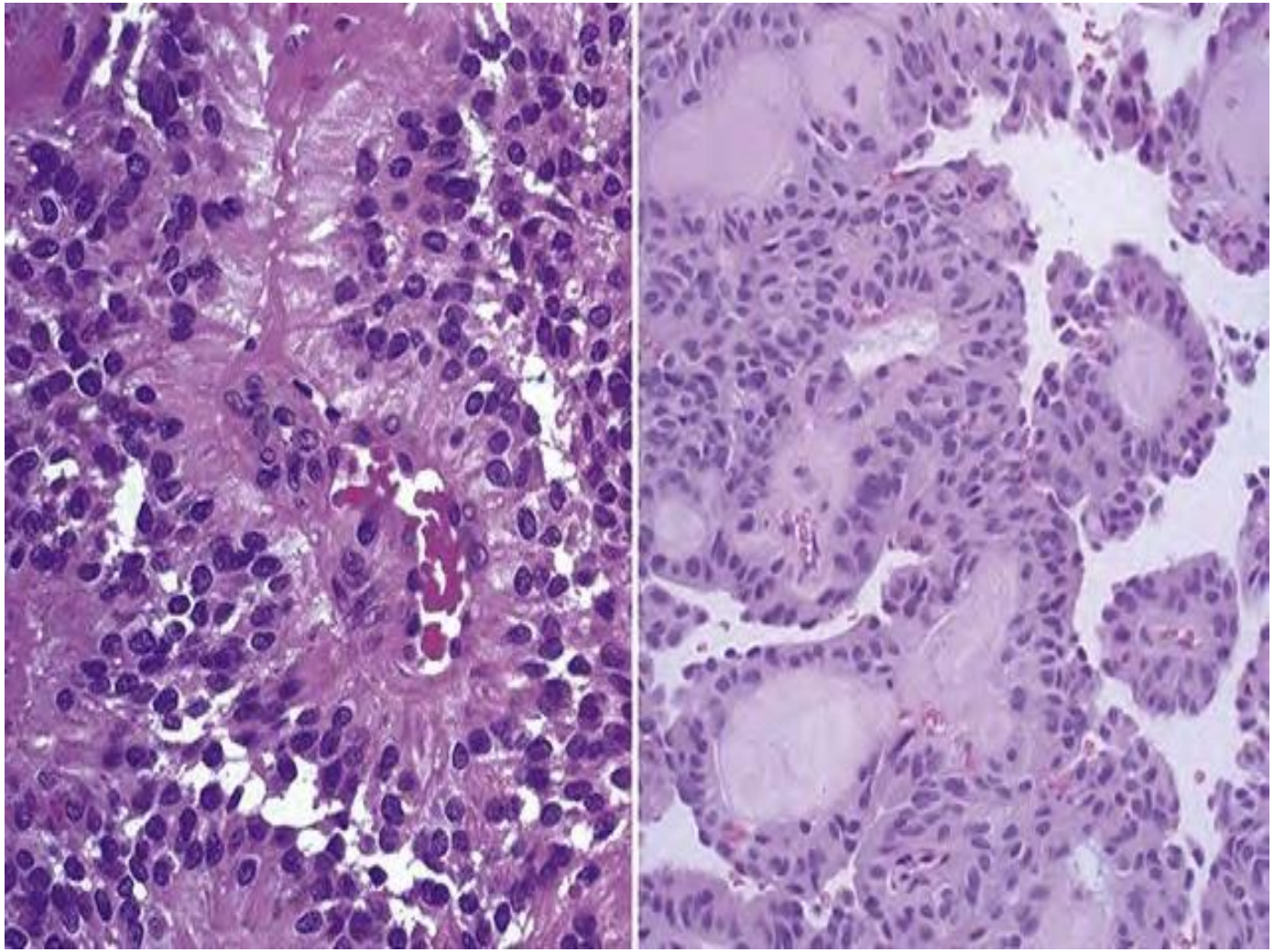


UPDATE

FISH: Fluorescence In Situ Hybridization.

EPENDYMOMA, WHO 2&3

- Ependymoma, which is another glial tumor affecting adults and the pediatric age group.
- It is located in the middle between tumors.
- It can be WHO grade 2 or 3.



EPENDYMOMA

❖ **Definition:**

- Glioma, Mostly arise next to the **ependyma-lined ventricular system**, including the central canal of the spinal cord.

❖ **Location:**

- **Posterior fossa**: near the 4th ventricle, accounting for 5-10% of brain tumors in the first two decades of life.
- **Supratentorial**.
- **Spinal**: the **most common** location in adults and in patients with **neurofibromatosis type 2** NF2 (one of the familial tumor syndromes).

EPENDYMOMA

❖ **Age:**

- In the first 2 decades of life; near **the 4th ventricle (post. Fossa)** accounting for 5-10% of primary brain tumors in this age group.
- 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,** because the tumor located in posterior fossa is near vital (more critical) areas of the brain and is not easily resected**.**

Ependymoma, WHO grade 2, microscopic features:

- Similar to ependymal cells; Uniform small cells with round to oval nuclei and granular chromatin in a fibrillary background.
- **Low cellularity.**
- **Low mitotic count.**
- No necrosis or microvascular proliferation MVP.
- **Cilia and microvilli** are seen on ultrastructural examination, but the utilization of this feature to diagnose ependymomas, seeing cilia and microvilli on microscopes, **decreased** because of how valuable and small brain tissue samples are.

Ependymoma WHO grade 2, Morphology:

- Tumor cells may form glandlike structures (rosettes) by arranging themselves around a center → **Rosette formation,** and the name of the rosette depends on the contents of the rosette**:**
  1. **Ependymal rosettes**:
     Diagnostic hallmark of ependymoma (25%), **specific for ependymoma.**
  2. **Perivascular pseudorosettes**:
     Not specific for ependymoma (seen in glioblastoma and medulloblastoma), a form of differentiation.

- **So, this feature can be both specific and nonspecific.**

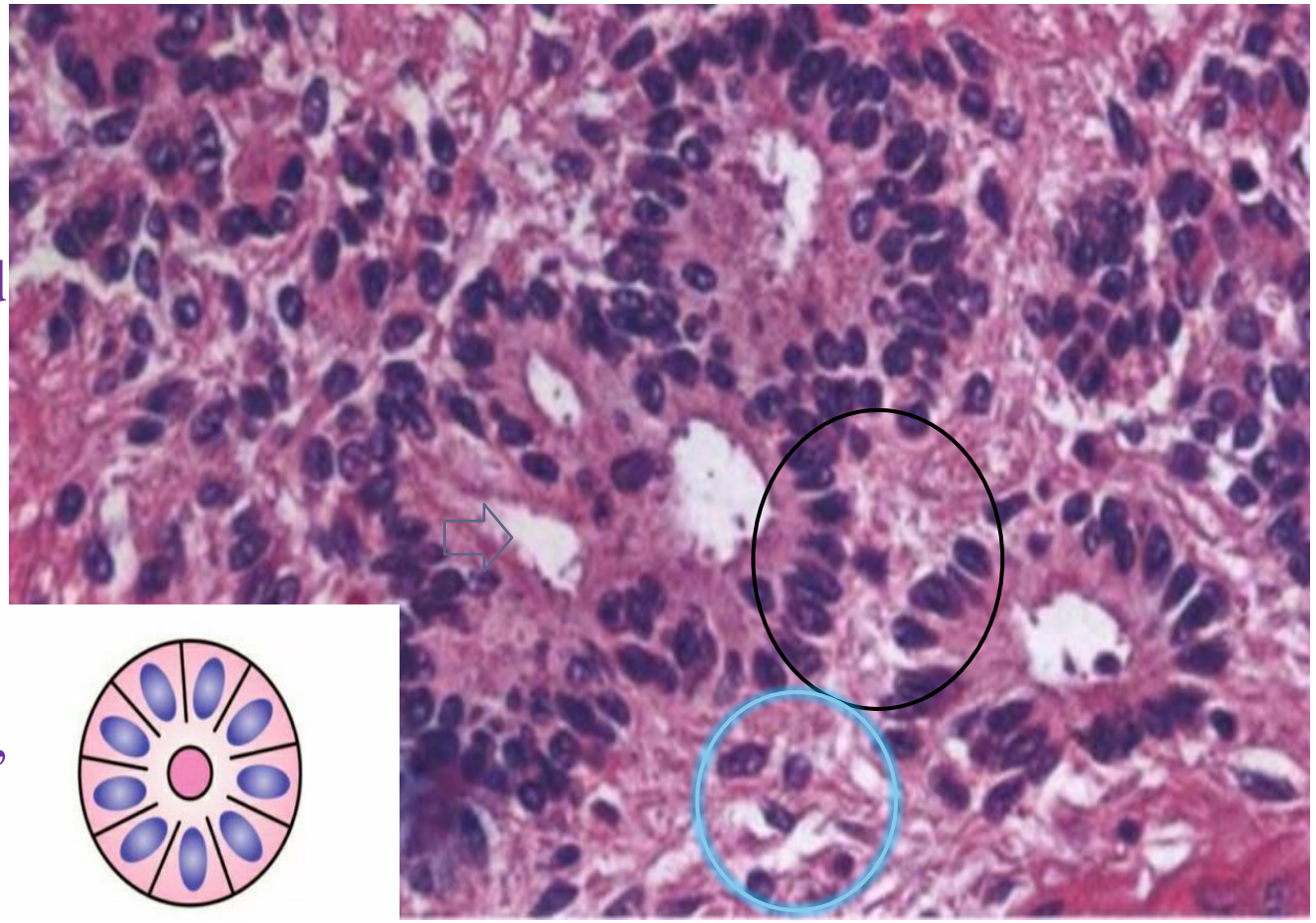
Rosette formation

1. **Ependymal rosettes:**
   - Tumor cells arranged around **central canal or lumen** that resemble the embryologic ependymal canal, with long, delicate processes extending into a lumen.

2. **Perivascular pseudorosettes:**
   - Tumor cells radially arranged around vessels.
   - Called "pseudo" because the **central structure is not formed by the tumor itself,** but instead represents a native, non-neoplastic element (blood vessel).

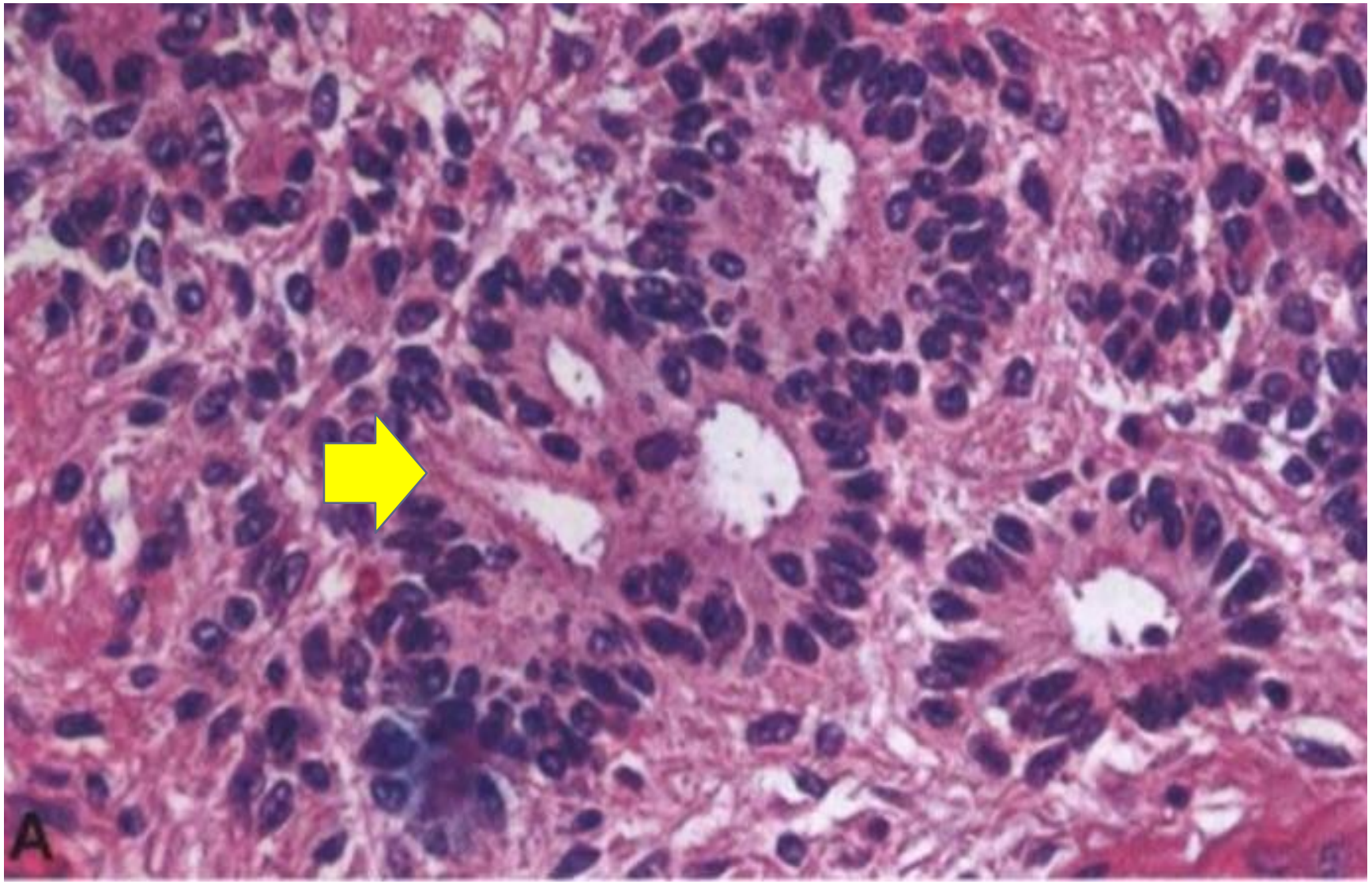
Ependymal rosettes:

- This histologic section shows the features of ependymoma.
- In the **black circle** we have **glial proliferation** with **fibrillary background** (feathery pink-red background).
- One can see rounded, slightly elongated uniform nuclei, with finely granular chromatin (Teal circle).
- Some of the cells arrange themselves in a circle around a **real lumen** (central canal), this is what is called **ependymal rosette.**
- **When seen in the section, ependymoma is the diagnosis.**



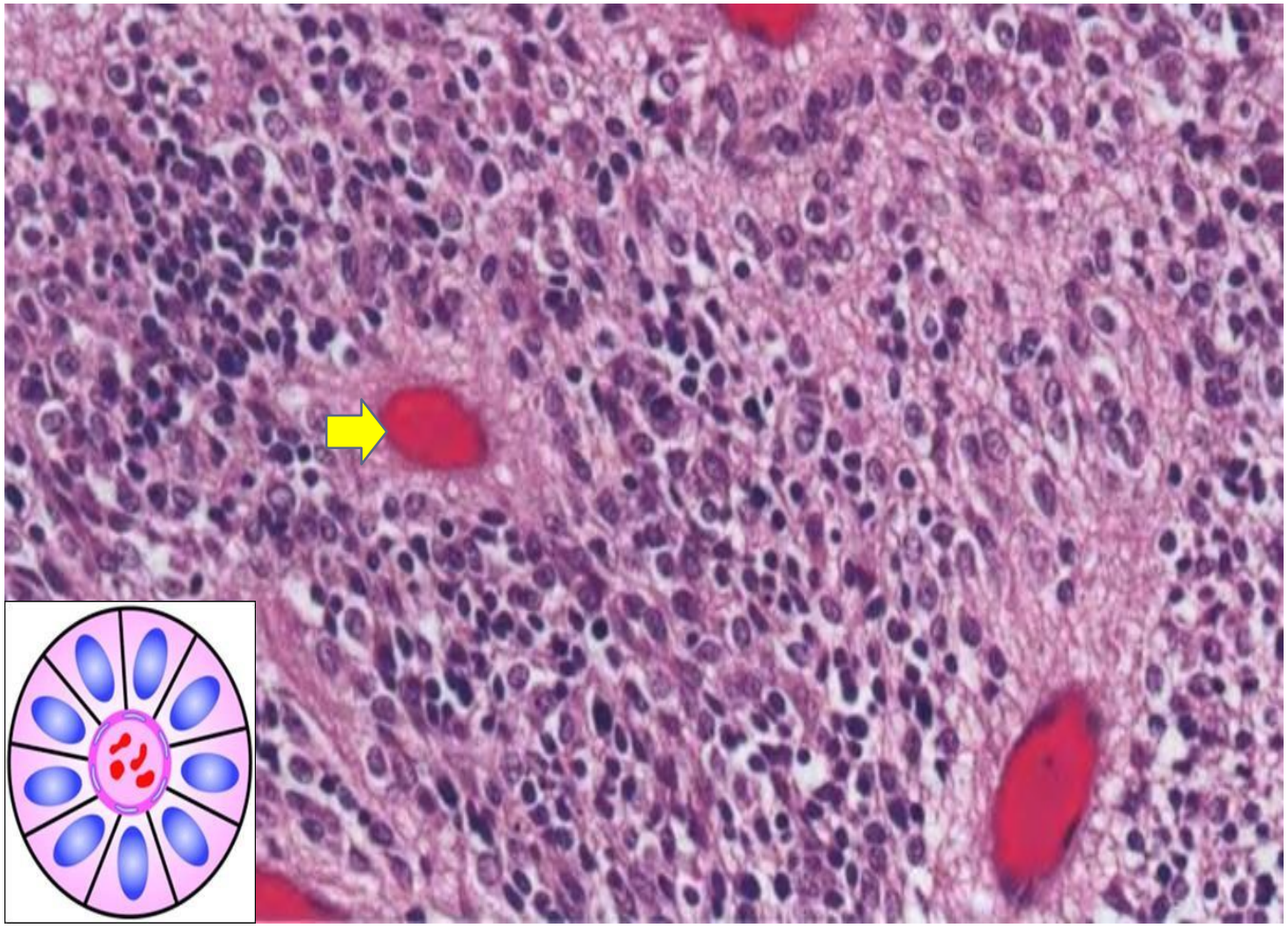
Ependymal rosettes:

The same here, ependymal rosettes are seen in the center.



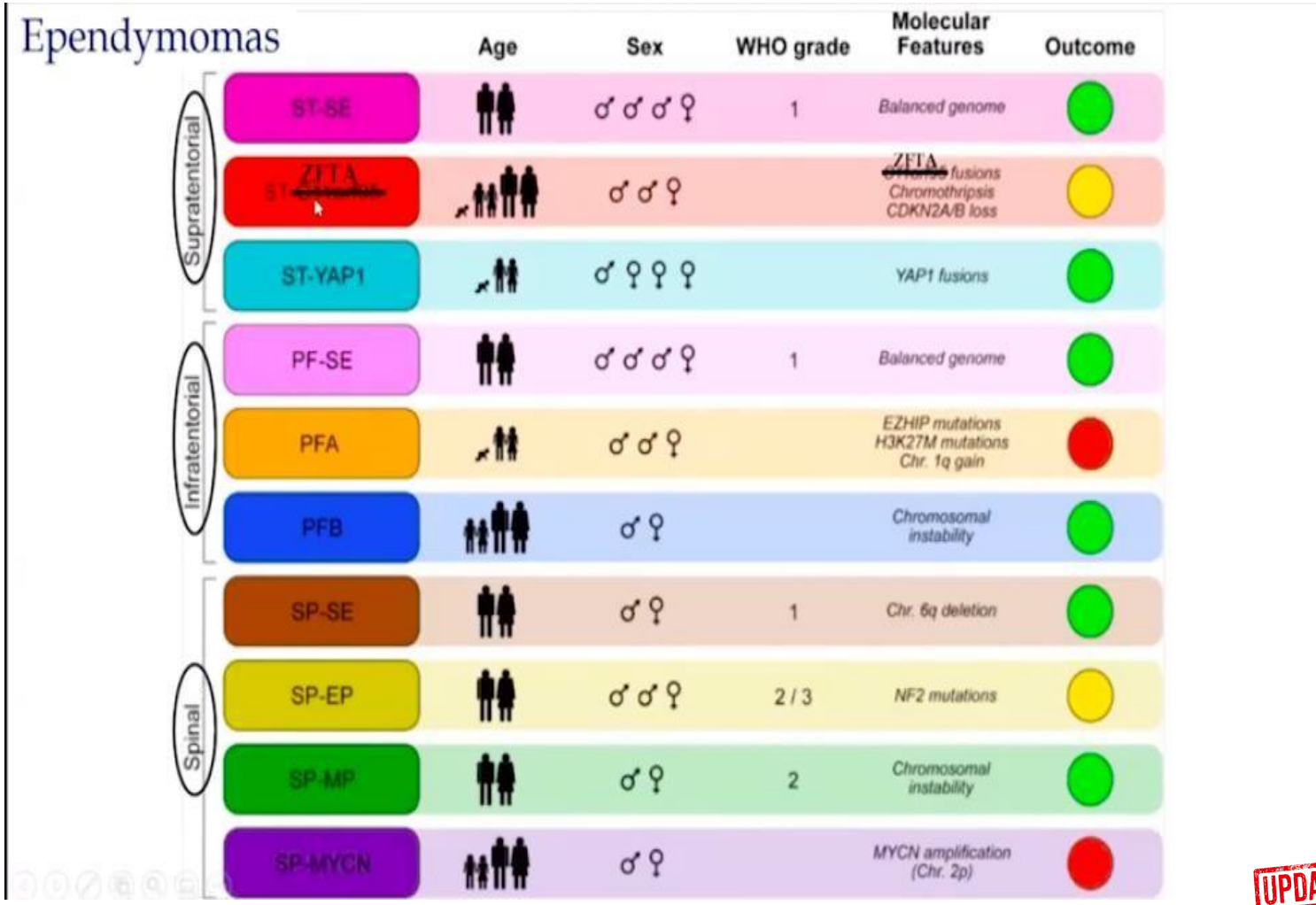
Perivascular Pseudorosettes

- Tumor cells are same, but they here arrange themselves around a **blood vessel** (yellow arrow) instead of a real lumen/ central canal.
- **Nonspecific but reflects a sort of differentiation.**



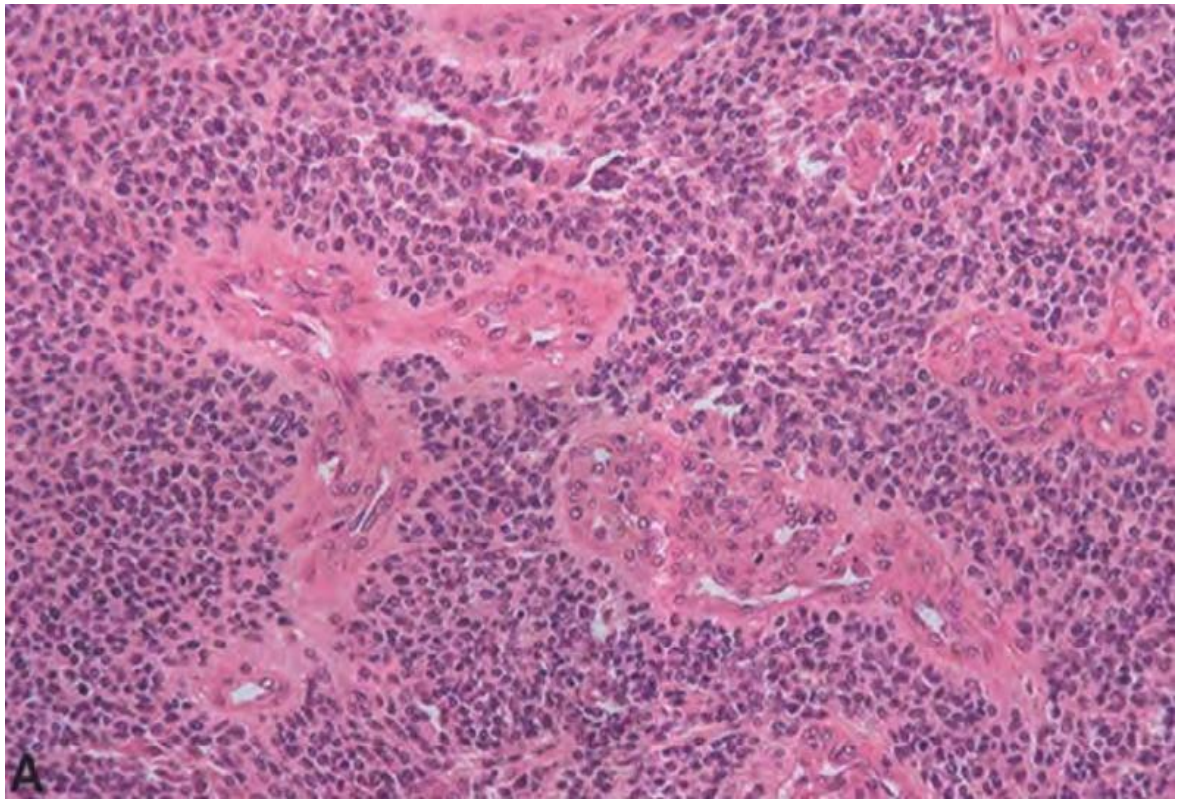
EPENDYMOMA

- Since the advent of molecular biology, ependymomas have been classified into 10 distinct types, each defined by a **unique genetic profile.**
- These genetic differences influence the tumor's typical location and clinical behavior.
- Prognosis also varies by type, with some showing better outcomes (green) and others worse (red).
- It's important to understand that, despite similar appearances under the microscope, ependymomas are not all the same (clinical outcomes can range widely).

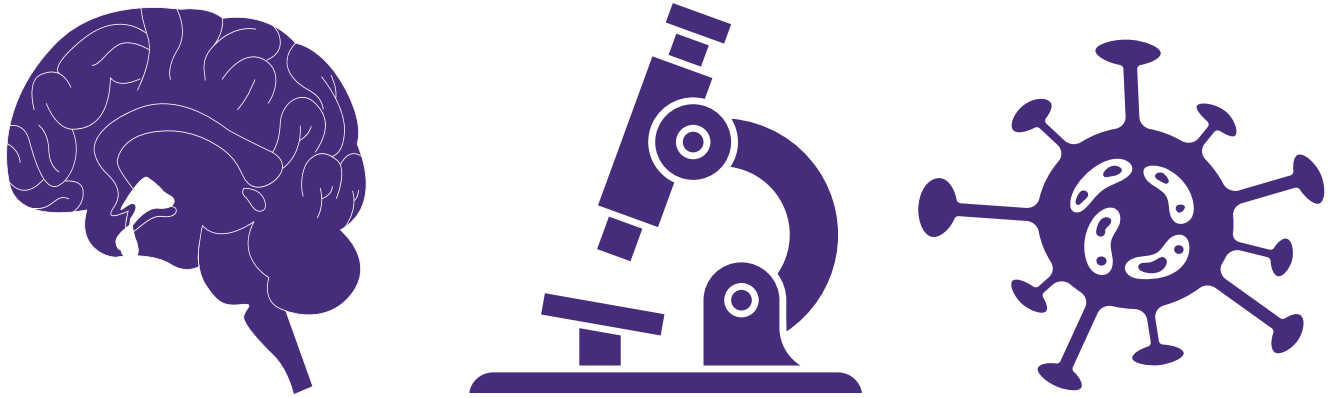


Anaplastic ependymomas, WHO grade 3:

- Show more cellularity, more cytologic atypia, and **less evident ependymal differentiation**, thus anaplastic.
- Brisk mitotic rates, and microvascular proliferation **carry more prognostic impact** than necrosis and atypia.




thank you



PATHOLOGY QUIZ LECTURE 2

External Resources

رسالة من الفريق العلمي

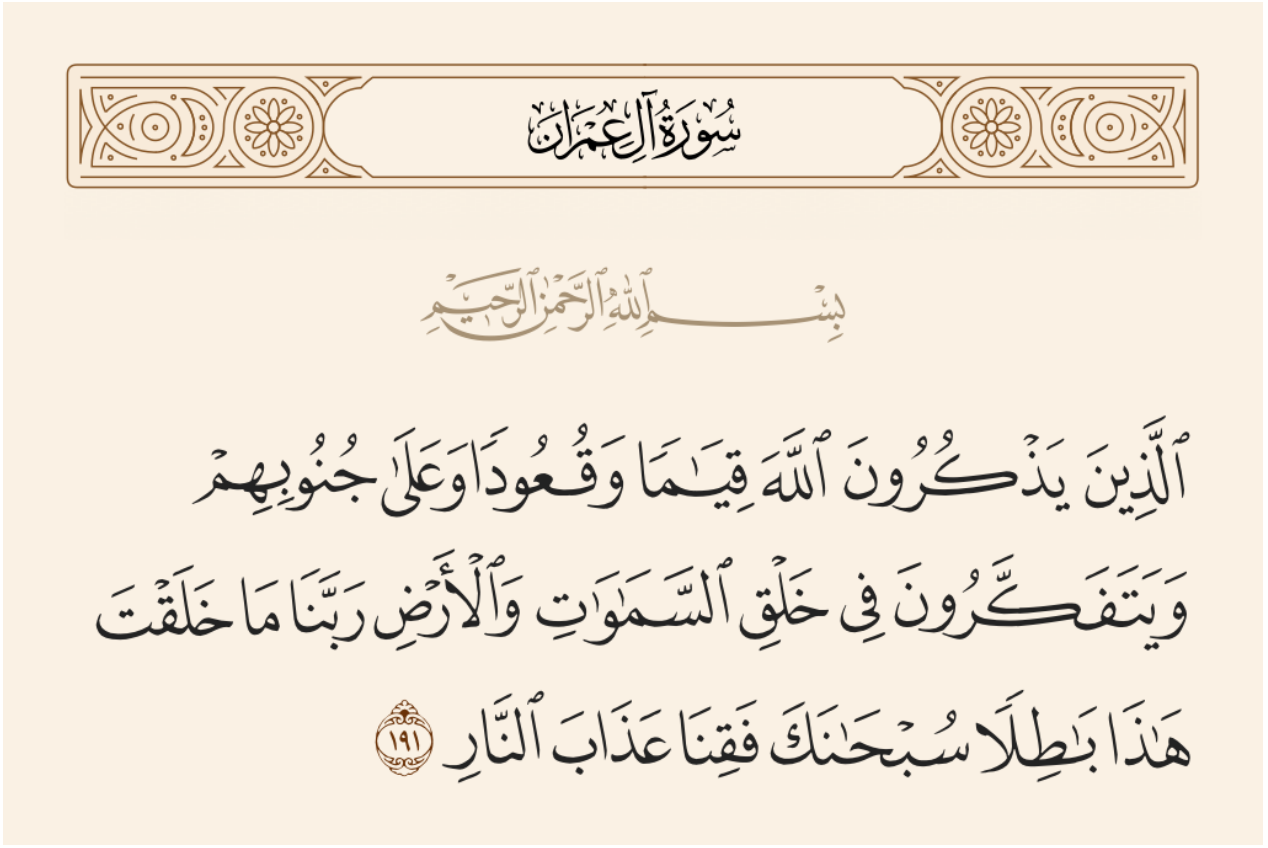
References as cited:

1. WHO Book 2021

Additional sources:

1. Glioblastoma, IDHm, Grade 4, **Medical Centric Podcast** on Yt: [Link]

اللهم إن عمر عطية في ذمتك وحبل جوارك، فقِه من فتنة القبر وعذاب النار،
أنت أهل الوفاء والحق، فاغفر له وارحمه إنك أنت الغفور الرحيم.



Scan the QR code or click it for FEEDBACK

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			