بسم الله الرحمن الرحيم

DOPAMINE SCIENTIFIC TEAM

CNS Tumors (Pt.1)

FINAL | Lecture 1

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

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PATHOLOGY

رحلة اليقين مع سورة يس

بِسْمِ ٱللَّهِ ٱلرَّحْمَٰنِ ٱلرَّحِيمِ

وَٱمْتَٰزُواْ ٱلْيَوْمَ أَيُّهَا ٱلْمُجْرِمُونَ (٥٩) ۞أَلَمْ أَعْهَدْ إِلَيْكُمْ يَٰبَنِيٓ ءَادَمَ أَن لَّا تَعْبُدُواْ ٱلشَّيْطَٰنَۖ إِنَّهُۥ لَكُمْ عَدُوٌّ مُّبِينٌ (٦٠) وَأَنِ ٱعْبُدُونِي هَٰذَا صِرَٰطٌ مُّسْتَقِيمٌ (٦١)

{ وَٱمْتَٰزُواْ ٱلْيَوْمَ أَيُّهَا ٱلْمُجْرِمُونَ } ويقال للكفار في ذلك اليوم: تميَّزوا عن المؤمنين، وانفصلوا عنهم.

{أَلَمْ أَعْهَدْ إِلَيْكُمْ يَٰبَنِيٓ ءَادَمَ أَن لَّا تَعْبُدُواْ ٱلشَّيْطَٰنَۖ إِنَّهُۥ لَكُمْ عَدُوٌّ مُّبِينٌ} ويقول الله لهم توبيخًا وتذكيرًا: ألم أوصكم على ألسنة رسلي أن لا تعبدوا الشيطان ولا تطيعوه؟ إنه لكم عدو ظاهر العداوة. { وَأَنِ ٱعْبُدُونِي هَٰذَا صِرَٰطٌ مُّسْتَقِيمٌ } وأمرتكم بعبادتي وحدي، فعبادتي وطاعتي ومعصية الشيطان هي الدين القويم الموصل لمرضاتي وجنَّاتي.

وَقُل رَّبِّ أَدْخِلْنِي مُدْخَلَ صِدْقٍ وَأَخْرِجْنِي مُخْرَجَ صِدْقٍ وَاجْعَل لِّي مِن لَّدُنكَ سُلْطَانًا نَّصِيرًا

CENTRAL NERVOUS SYSTEM TUMORS(1)

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A note to consider beforehand

- The classification of CNS tumors, names of the tumors, and diagnostic techniques are constantly changing. Therefore, we will only be focusing on the key concepts that are in the slides since Robin's might still have some outdated information.

CNS TUMORS:

- may arise from the **cells of the coverings called meningothelial cells** (meningiomas), **the brain cells** (gliomas, neuronal, and glioneuronal tumors), or **other CNS cell populations** (primary CNS lymphoma, germ cell tumors), or they may originate elsewhere in the body (**metastases**).

- Can involve the **brain or spinal cord**

https://answers.childrenshospital.org/spinal-cord-injury/

EPIDEMIOLOGY:

They have unique characteristics that set them apart from any other neoplastic conditions.

- **INCIDENCE**: They are not common
  - The annual incidence of CNS tumors in the U.S →
    - 24 /100,000 for intracranial tumors, 1/3 of those are malignant
    - 1-2/100,000 for intraspinal tumors Even more rare

They make up 20% of pediatric tumors

- **Metastases are more common than primary brain tumors.**

- ✓ There are 3 characteristic features that differentiate CNS tumors from other types of tumors.

Characteristic features of CNS tumors:

1. **No Premalignant stage: no** in situ lesions.
   Other tumors do have a premalignant stage; for example, squamous dysplasia is a precursor for squamous cell carcinoma, atypical adenomatous hyperplasia is a precursor for adenocarcinoma, and tubular adenoma is a precursor for colon cancer.
2. **Metastasis is rare!**
   1. Even the most highly malignant gliomas **rarely spread** outside of the CNS.
   2. but the brain is **not comparably protected** against the spread of distant tumors.

Characteristic features of CNS tumors:

- ✓ More than 50% of intracranial tumors are metastatic in origin, such as lung cancer, breast cancer, melanomas, kidney tumors, and colon cancer, they're all associated with metastasis to the brain. However, it is **rare** for a primary CNS tumor to spread to other body parts.
- ✓ Remember that the TNM staging system classifies cancer based on three criteria: **T**umor size, **N**ode involvement, and **M**etastasis. Meanwhile, primary brain tumors don't have lymph node metastases nor distant metastases. Therefore, **TNM staging isn't used for brain tumors**, and there are other prognostic factors that determine the management plan and the outcomes.

Characteristic features of CNS tumors:

3. Growth pattern (infiltrative or not) and tumor location strongly influence the prognosis:

- Even low-grade lesions may infiltrate large regions of the brain, leading to serious clinical deficits, inability to be resected, and poor prognosis.
- The anatomic site of the neoplasm can influence outcome independent of tumor type or grade due to local effects

Prognosis in the CNS tumors is highly influenced by:

1. The growth pattern indicates whether the tumor is circumscribed or infiltrating to adjacent tissues. Infiltrative tumors are more susceptible to recurrence and poorer outcomes or neurological deficits because they can't be surgically excised, since the junction between the normal and the abnormal tissues is vague. Unlike circumscribed tumors that have clear boundaries, better prognosis, and less neurological deficits.

The junction between normal and abnormal tissue is vague not only grossly but also microscopically. Tumor cells can travel several centimeters away from the main mass, infiltrating between normal tissue. Because of this infiltrative nature, distinguishing the boundaries of such tumors is challenging not only for surgeons but also for neuropathologists.

2. The tumor location is the single most important prognostic factor, regardless of its histologic features or grade. The significance of the location shows in:

- Minimal pressure of a low-grade tumor that is located in the medulla beside the cardiovascular or respiratory centers can be lethal.
- Many **signs, symptoms** and neurological manifestations depend on the location of the tumor in the brain. A tumor near the optic chiasma has different consequences from the same type of tumor but in the temporal lobe.
- It dictates whether the tumor is **reachable for excision**.
- Location can guide the **differential diagnosis**, as certain tumors tend to develop in specific regions. For example, paraventricular tumors in adults are often meningiomas, while posterior fossa tumors in children are commonly medulloblastoma or pilocytic astrocytoma.

So the location determines the signs and symptoms, outcome and management plan (is it resectable or not), and the differential diagnoses.

In neuropathology, tumors are like real estate, the location is almost everything!

LOCATION
LOCATION
LOCATION
LOCATION
LOCATION

Histologic grading of CNS tumors

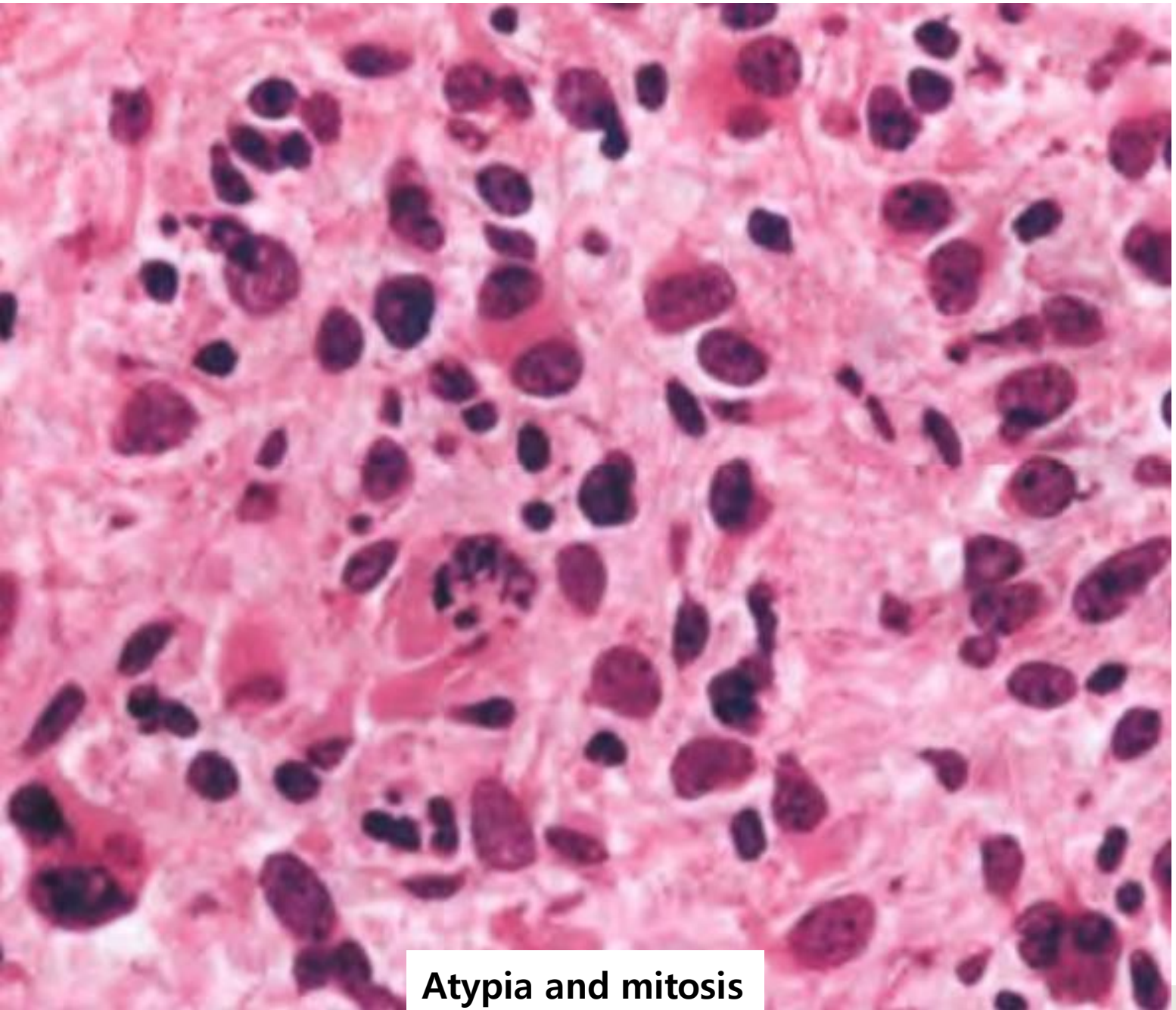
- WHO released in 2021 the blue book for the classification of CNS tumors according to certain histologic and molecular findings that includes **grading from grade 1 to grade 4** rather than the usual TNM staging, these histologic criteria include:

1. **Atypia** (different from what is throught to be normal) such as Hyperchromasia, nuclear enlargement, pleomorphism, bizarre atypical cells, multinucleation, or binucleation, etc.
2. **Mitosis**
3. **Microvascular proliferation:** the presence of abnormally shaped blood vessels that are lined by two or more layers of cells (normal vessels are lined by one layer of endothelium). Notice the star-shaped vessel in the red circle.
4. **Necrosis**

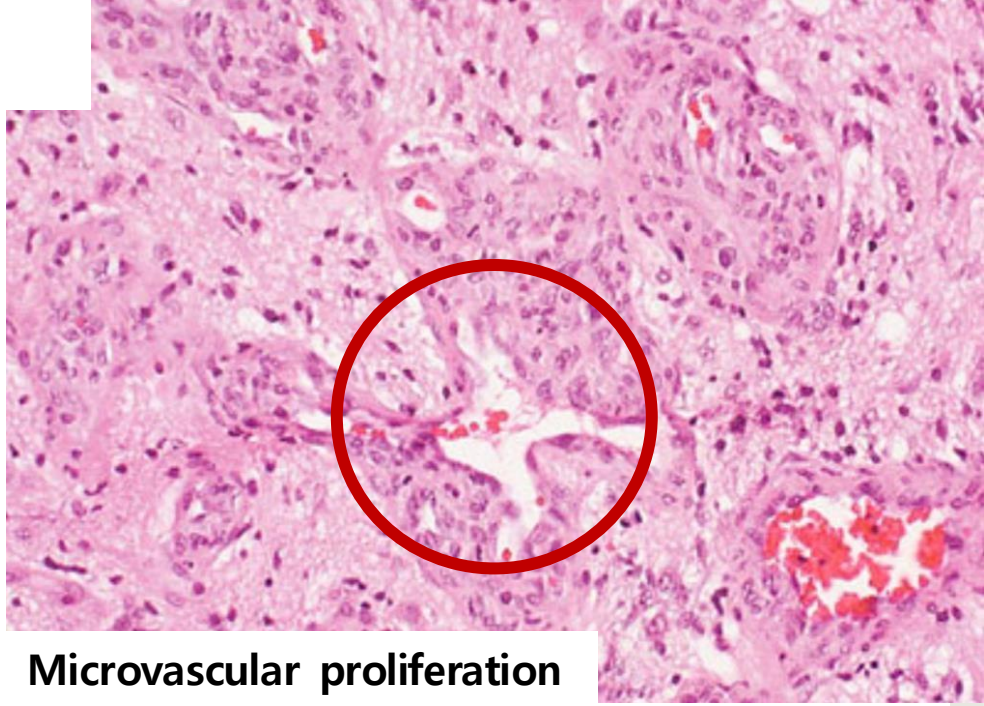
+ molecular findings

- Each type of cancer has its own features but these are the general characteristics of each grade.

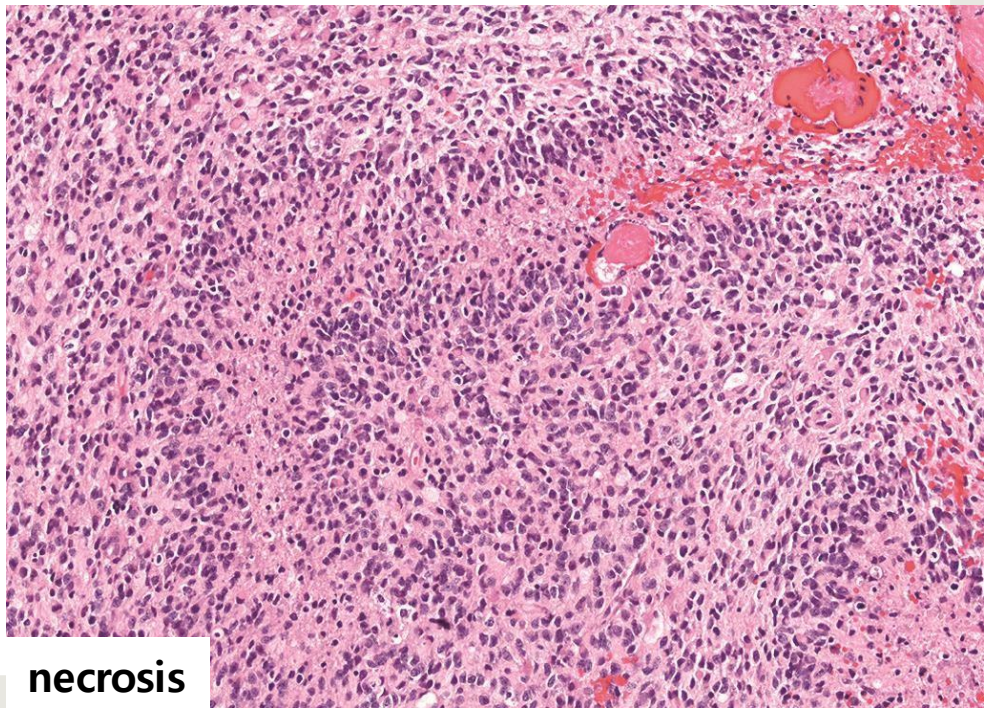
The histologic grading of CNS tumors depends on:



Atypia and mitosis



Microvascular proliferation



necrosis

Histologic grading of CNS tumors

Grade 1 lesions:

- low proliferative activity rare mitosis
- Can be cured after surgical resection alone. Most of them are circumscribed

Examples: pilocytic astrocytoma (PA), subependymal giant cell astrocytoma (SEGA), choroid plexus papilloma, myxopapillary ependymoma

Grade 2 lesions:

- low proliferative activity
- usually **infiltrative** and often recur
- Some grade II entities tend to progress to higher grades of malignancy.

To grade III

Examples: astrocytoma, IDH- mutant, grade 2

oligodendroglioma, IDH- mutant and 1p/19q-codeleted, grade 2

Histologic grading of CNS tumors

grade 3 lesions:

- clear histological evidence of malignancy (nuclear atypia and Higher proliferative activity (mitosis)).
- In most settings, patients receive radiation and/or chemotherapy.

No vascular proliferation or necrosis

Radiotherapy ± Chemotherapy

Examples:

astrocytoma, IDH- mutant, grade 3

oligodendroglioma, IDH- mutant and 1p/19q-codeleted, grade 3.

✓ Notice that the naming system of brain tumors includes the phenotype, genotype, and the grade.

Example:
Phenotype: oligodendroglioma
Genotype: IDH- mutant and 1p/19q-codeleted
Grade: 3

Histologic grading of CNS tumors

grade 4 lesions (high grade):

- cytologically malignant, mitotically active, rapid proliferation, necrosis- prone neoplasms Prominent cytological atypia
- associated with rapid pre- and postoperative disease evolution and fatal outcome.
- Widespread infiltration of surrounding tissue and a risk of craniospinal dissemination.

examples: Glioblastoma, IDH-wildtype, medulloblastoma, pineoblastoma, and most embryonal neoplasms like Atypical teratoid rhabdoid tumor (ATRT)

Histologic grading of CNS tumors

Not for memorization
We refer to this table from the WHO book in order to grade and predict the behavior of each tumor.

WHO grades of select CNS tumours	
Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	II
Anaplastic astrocytoma, IDH-mutant	III
Glioblastoma, IDH-wildtype	IV
Glioblastoma, IDH-mutant	IV
Diffuse midline glioma, H3 K27M-mutant	IV
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	II
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	III
Other astrocytic tumours	
Pilocytic astrocytoma	I
Subependymal giant cell astrocytoma	I
Pleomorphic xanthoastrocytoma	II
Anaplastic pleomorphic xanthoastrocytoma	III
Ependymal tumours	
Subependymoma	I
Myxopapillary ependymoma	I
Ependymoma	II
Ependymoma, *RELA* fusion-positive	II or III
Anaplastic ependymoma	III
Other gliomas	
Angiocentric glioma	I
Chordoid glioma of third ventricle	II
Choroid plexus tumours	
Choroid plexus papilloma	I
Atypical choroid plexus papilloma	II
Choroid plexus carcinoma	III
Neuronal and mixed neuronal-glial tumours	
Dysembryoplastic neuroepithelial tumour	I
Gangliocytoma	I
Ganglioglioma	I
Anaplastic ganglioglioma	III
Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)	I
Desmoplastic infantile astrocytoma and ganglioglioma	I
Papillary glioneuronal tumour	I
Rosette-forming glioneuronal tumour	I
Central neurocytoma	II
Extraventricular neurocytoma	II
Cerebellar liponeurocytoma	II
Tumours of the pineal region	I
Pineocytoma	II or III
Pineal parenchymal tumour of intermediate differentiation	
Pineoblastoma	IV
Papillary tumour of the pineal region	II or III
Embryonal tumours	
Medulloblastoma (all subtypes)	IV
Embryonal tumour with multilayered rosettes, C19MC-altered	IV
Medulloepithelioma	IV
CNS embryonal tumour, NOS	IV
Atypical teratoid/rhabdoid tumour	IV
CNS embryonal tumour with rhabdoid features	IV
Tumours of the cranial and paraspinal nerves	
Schwannoma	I
Neurofibroma	I
Perineurioma	I
Malignant peripheral nerve sheath tumour (MPNST) I	I, III or IV
Meningiomas	
Meningioma	I
Atypical meningioma	II
Anaplastic (malignant) meningioma	III
Mesenchymal, non-meningothelial tumours	
Solitary fibrous tumour / haemangiopericytoma	I, II or III
Haemangioblastoma	I
Tumours of the sellar region	I
Craniopharyngioma	I
Granular cell tumour	I
Pituicytoma	I
Spindle cell oncocytoma	I

Pediatric CNS tumors:

- 20% of all pediatric tumors.
- Childhood CNS tumors differ from those in adults in:

1. **Location:**
   - 2/3 infratentorial in kids (posterior fossa)
   - 2/3 supratentorial in adults (cerebral hemispheres above tentorium)

2. **Mutation profile & histologic subtype:**
   - Kids: medulloblastoma, pilocytic astrocytoma, ependymoma
   - Adults: glioblastoma, metastases, meningiomas, diffuse gliomas constitute most gliomas in adults (including astrocytomas and oligodendrogliomas).

Each age group have different types of tumors more commonly occurring in them. For example, for kids if you see a case of posterior fossa tumor your first thought wouldn't be metastasis since it's rare in children.

Classification of CNS tumors

- According to The 2016 WHO classification of brain tumors, the tumors are classified based on:

combined phenotype-genotype (integrated diagnoses):

1) **phenotype**: the histologic features and microscopic similarities with what's thought to be their cell of origin (based on the light microscopic appearance, the immunohistochemical expression of proteins, and the electron microscopic assessment of ultrastructural features).

2) **genotype**: tumor genetic profile and molecular studies

- The 2016 classification helped **improving treatment protocols and predicting prognosis.**

Classification of CNS tumors

- ✓Before 2016, the classification depended solely on the **phenotype** of the tumor, which means how the tumor looks like microscopically and how much the observed cells resemble the original cells, using the light microscope and electron microscope. Afterwards, the ability to study the **genetic profile** of each tumor was developed, and many advances happened in molecular pathology, so a lot of changes in the categorization had to be done based on the phenotype-genotype to establish more precise diagnoses and tailored management plans.

genetic alterations in gliomas: The main 3

1- **Mutations in isocitrate dehydrogenase (IDH) genes:**

- observed as an early event in gliomagenesis
- Seen in all cases of diffuse astrocytomas and oligodendrogliomas
- Gain of function Mutation affection IDH1 codon 132 or IDH2 codon 172.
- The most frequent is IDH1 R132H mutation (83-91%) of IDH mutant gliomas
- IDH2 mutation: R172K is the most frequent IDH2 mutation (2nd most common)

- ✓ Can be detected by immunohistochemical stains and molecular studies:
  - IDH1-R132H immune stain
  - IDH sequencing for IDH1 codon 132 and IDH2 codon 172

- ✓ Gain of function mutation→ lead to increased production of 2-hydroxyglutarate (oncometabolite)→interferes with the activity of several enzymes that regulate gene expression→ DNA hypermethylation & maintaining the cells in stem cell-like physiological states→ self- renewal and tumorigenesis

There is an immunohistochemical stain capable of only detecting the IDH1-R132H mutation. So, an individual that has an IDH1-R132H mutation will test positive using this stain. Result usually is out in less than 24hr, which is preferred over IDH sequencing that takes a month.

If the patient tests negative (no IDH1-R132H mutation), then perform an IDH sequencing (genomic profile and molecular studies).

IDH1-R132H mutation -> has both an immunohistochemical stain and IDH sequencing.

IDH2 mutation -> only has IDH sequencing.

p=short arm, q=long arm

2-whole arm Co-deletion of 1p and 19q chromosomal segments:

Whole arm co-deletion of BOTH 1p AND 19q, one is not sufficient.

- Diagnostic of oligodendrogliomas in the presence of IDH mutation.

1p/19q co-deletion + IDH mutation = diagnosis is oligodendrogliomas regardless of histology.

- The vast majority of IDH mutant and 1p/19q co-deleted oligodendroglioma →carry TERT promotor hotspot mutations
- **TERT promotor hotspot mutations**: telomerase stabilization, cellular immortalization and proliferation

TERT = Telomerase Reverse Transcriptase

Telomerase is an enzyme responsible for the lengthening of telomeres by adding repetitive DNA sequences to their ends. It is composed of a protein component and a catalytic subunit. The catalytic subunit, which is essential for the enzyme's activation, is known as TERT.

When TERT becomes activated (such as in the presence of IDH mutation and 1p/19q co-deletion), telomerase activity is upregulated, leading to continuous addition of telomeric DNA repeats. This results in stabilization and persistent activation of telomerase, allowing cells to maintain telomere length. Consequently, the cells acquire the ability to proliferate indefinitely, effectively becoming immortal.

3- ATRX and P53 loss of function mutation:

- Both occur in IDH mutant astrocytomas **not oligodendrogliomas.**
- **ATRX mutation** induces abnormal telomeres maintenance mechanism known as **"alternative lengthening of telomeres"**
- **ATRX mutation is Mutual exclusive with the activating promoter mutation of the TERT gene (1p/19q codeletion)**
- **P53 mutation:** enable tumor cell survival
  - ATRX → associated with genomic instability → induces P53 dependent cell death→ mutation in P53 helps these cells to survive.

Both 1p/19q co-deletion and ATRX mutation lead to telomere lengthening, but through different mechanisms. In tumors with 1p/19q co-deletion (classically seen in oligodendroglioma), telomere maintenance is telomerase-dependent. In contrast, tumors with ATRX mutation (commonly seen in astrocytoma) use a telomerase-independent mechanism for telomere lengthening.
These two mechanisms are mutually exclusive, meaning that a tumor will utilize only one pathway. Therefore, if a tumor has an ATRX mutation, it will not have a 1p/19q co-deletion, and vice versa.

p53 is a tumor suppressor gene that plays a critical role in regulating the cell cycle and inducing apoptosis in response to DNA damage.
In cells with an ATRX mutation, there is an attempt to activate p53 in response to genomic instability. However, ATRX-mutant tumors are commonly associated with loss of p53 function. As a result, the cell cycle is not properly arrested, and apoptosis is not effectively induced. This allows the cell to continue proliferating and surviving despite the presence of DNA damage.

Gliomas

WHO 2016

2.1: Diffuse astrocytic and oligodendroglial tumours

- 2.1.1: Introduction
- 2.1.2: Diffuse astrocytoma, IDH-mutant
  - 2.1.2.1: Gemistocytic astrocytoma, IDH-mutant
- 2.1.3: Diffuse astrocytoma, IDH-wildtype
- 2.1.4: Diffuse astrocytoma, NOS
- 2.1.5: Anaplastic astrocytoma, IDH-mutant
- 2.1.6: Anaplastic astrocytoma, IDH-wildtype
- 2.1.7: Anaplastic astrocytoma, NOS
- 2.1.8: Glioblastoma, IDH-wildtype
  - 2.1.8.1: Giant cell glioblastoma
  - 2.1.8.2: Gliosarcoma
  - 2.1.8.3: Epithelioid glioblastoma
- 2.1.9: Glioblastoma, IDH-mutant
- 2.1.10: Glioblastoma, NOS
- 2.1.11: Diffuse midline glioma, H3 K27M mutant
- 2.2.1: Oligodendroglioma, IDH-mutant and 1p/19q-codeleted
- 2.2.2: Oligodendroglioma, NOS
- 2.2.3: Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codel
- 2.2.4: Anaplastic oligodendroglioma, NOS
- 2.2.5: Oligoastrocytoma, NOS
- 2.2.6: Anaplastic oligoastrocytoma, NOS

2.3: Other astrocytic tumours

- 2.3.1: Pilocytic astrocytoma
  - 2.3.1.1: Pilomyxoid astrocytoma
- 2.3.2: Subependymal giant cell astrocytoma
- 2.3.3: Pleomorphic xanthoastrocytoma

Based on genotype and phenotype

Gliomas, Glioneuronal and Neuronal Tumours

WHO 2021

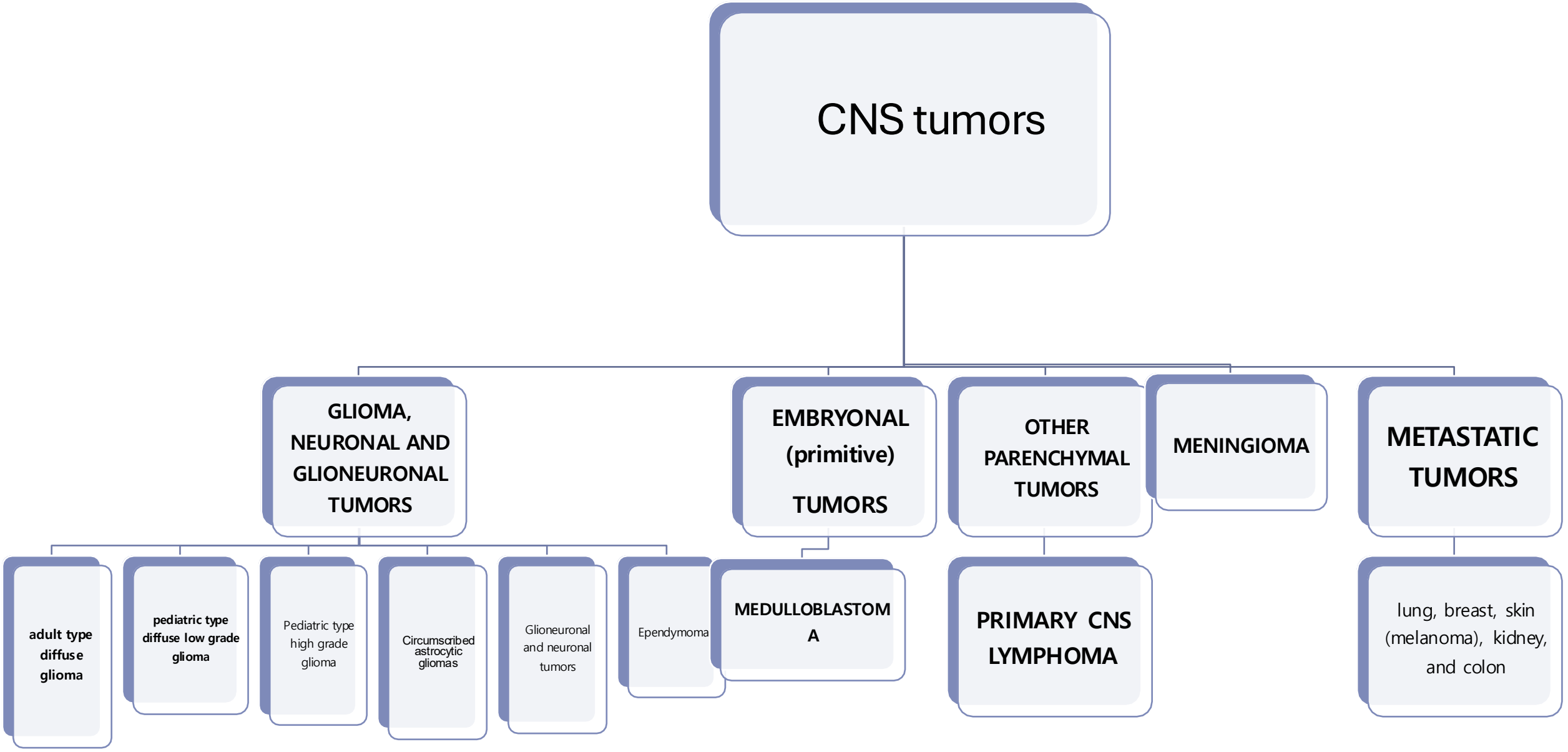
- 2.0.0.1: Introduction to gliomas, glioneuronal tumours, and neuronal tumours

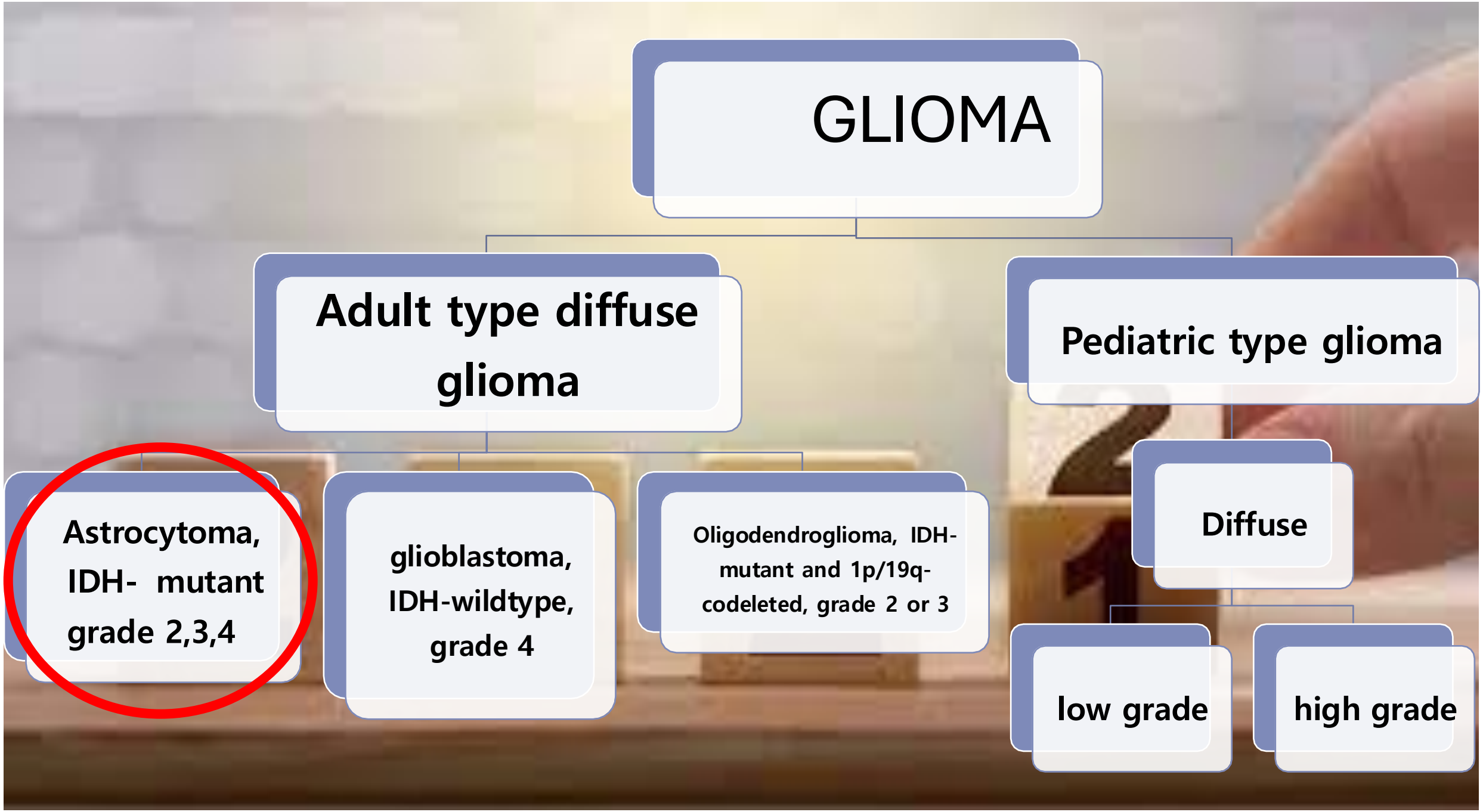
2.1: Gliomas, Glioneuronal and Neuronal Tumours

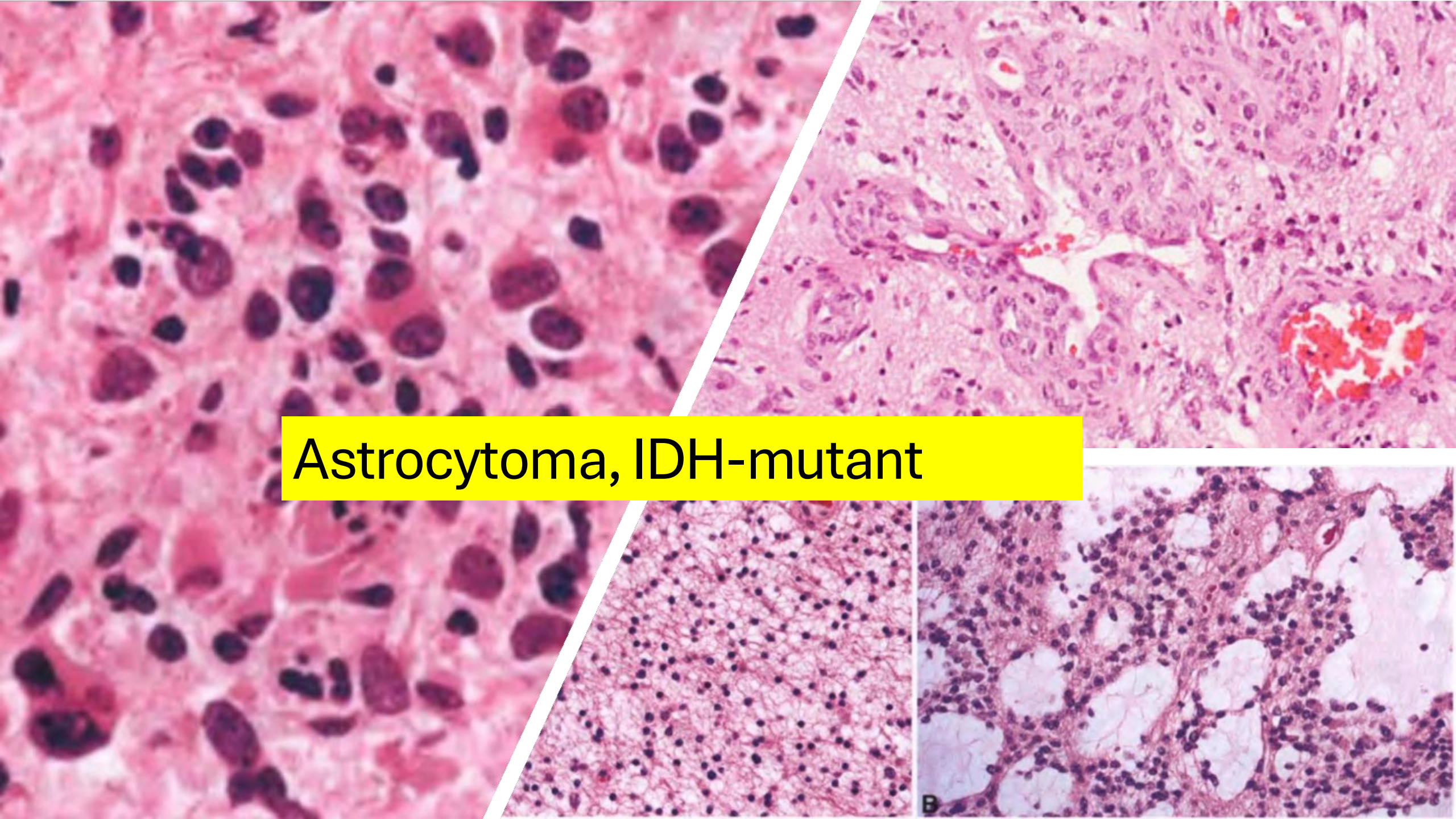
Listen to the doc explanation for this side:
28:33

- Adult-type diffuse gliomas
  - 2.1.1.1: Astrocytoma, IDH-mutant
  - 2.1.1.2: Oligodendroglioma, IDH-mutant and 1p/19q-codeleted
  - 2.1.1.3: Glioblastoma, IDH-wildtype
- Paediatric-type diffuse low-grade gliomas
  - 2.1.4.1: Diffuse astrocytoma, MYB or MYBL1-altered
  - 2.1.4.2: Angiocentric glioma
  - 2.1.3.5: Polymorphous low-grade neuroepithelial tumour of the young
  - 2.1.5.1: Diffuse low-grade glioma, MAPK pathway-altered
- 2.1.2: Paediatric-type diffuse high grade gliomas
  - 2.1.2.1: Diffuse midline glioma, H3 K27-altered
  - 2.1.2.2: Diffuse hemispheric glioma, H3 G34-mutant
  - 2.1.2.3: Diffuse paediatric-type high grade glioma, H3 wildtype and IDH wild type
  - ~~2.1.2.4: Diffuse midline glioma, EGFR mutant (formerly Bithalamic glioma, EGFR mutant)~~
  - 2.1.2.4: Infant-type hemispheric glioma
- 2.1.3: Circumscribed astrocytic gliomas
  - 2.1.3.1: Pilocytic astrocytoma
  - 2.1.3.2: High-grade astrocytoma with piloid features
  - 2.1.3.3: Pleomorphic xanthoastrocytoma
  - 2.2.0.4: Subependymal giant cell astrocytoma
  - 2.2.0.1: Chordoid glioma
  - 2.2.0.2: Astroblastoma, MN1-altered
- 2.1.4: Glioneuronal and neuronal tumours
  - 2.1.3.7: Ganglioglioma
  - 2.1.3.9: Desmoplastic infantile ganglioglioma / Desmoplastic infantile astrocytoma
  - 2.1.3.10: Dysembryoplastic neuroepithelial tumour
  - 2.2.0.3: Diffuse glioneuronal tumour with oligodendroglioma-like features and nuclear clusters
  - 2.2.0.5: Papillary glioneuronal tumour

Lots of entities were removed or added based on advanced molecular profiling


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


GLIOMA
Adult type diffuse glioma
Pediatric type glioma
Astrocytoma, IDH- mutant grade 2,3,4
glioblastoma, IDH-wildtype, grade 4
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted, grade 2 or 3
Diffuse
low grade
high grade


Astrocytoma, IDH-mutant
B

Definition:

Phenotype: It Is a diffusely infiltrating glioma so it is difficult to point out it's margin in gross examination. Microscopically, neoplastic cells can be found a few cm away from the main mass. Therefore, recurrence is common and surgical resection alone is insufficient.

Genotype (All three must happen):

- IDH1 or less frequently IDH2 mutation.
- Inactivating mutation in TP53 and/or ATRX
- absence of 1p/19q codeletion

Remember, they are mutually exclusive.

- **Age at diagnosis:** 40–60 year old (middle age to adult).
- **Location:** cerebral hemispheres +/- cerebellum, brainstem, or spinal cord.
- **Presentation:** As we already know, symptoms depend on **location**
  - Tumor can be epileptogenic so causes seizures, headaches, and focal neurologic deficits related to the anatomic site of involvement such as nausea and vomiting related to increased intracranial pressure.
  - Clinically: static for years (patient is stable) or Progressive.
- **The prognosis gets poorer as the grade increases**

- **On the basis of histologic and molecular features of astrocytomas, IDH- mutant are stratified into three groups:**
  - **astrocytomas, IDH- mutant,** grade 2, median survival is >10 years.
  - **astrocytomas, IDH- mutant** grade 3, median survival is 5-10 years
  - **astrocytomas, IDH- mutant** grade 4, median survival is 3 years.

The higher the grade, the worse the median survival. So, grade is crucial in predicting the outcome and treatment plan of the patient.

- **NO grade 1 astrocytoma, IDH- mutant, because by convention grade 1 implies benign behavior and all diffuse gliomas are considered malignant**

Morphology, macroscopic:

Grade 2 &3:

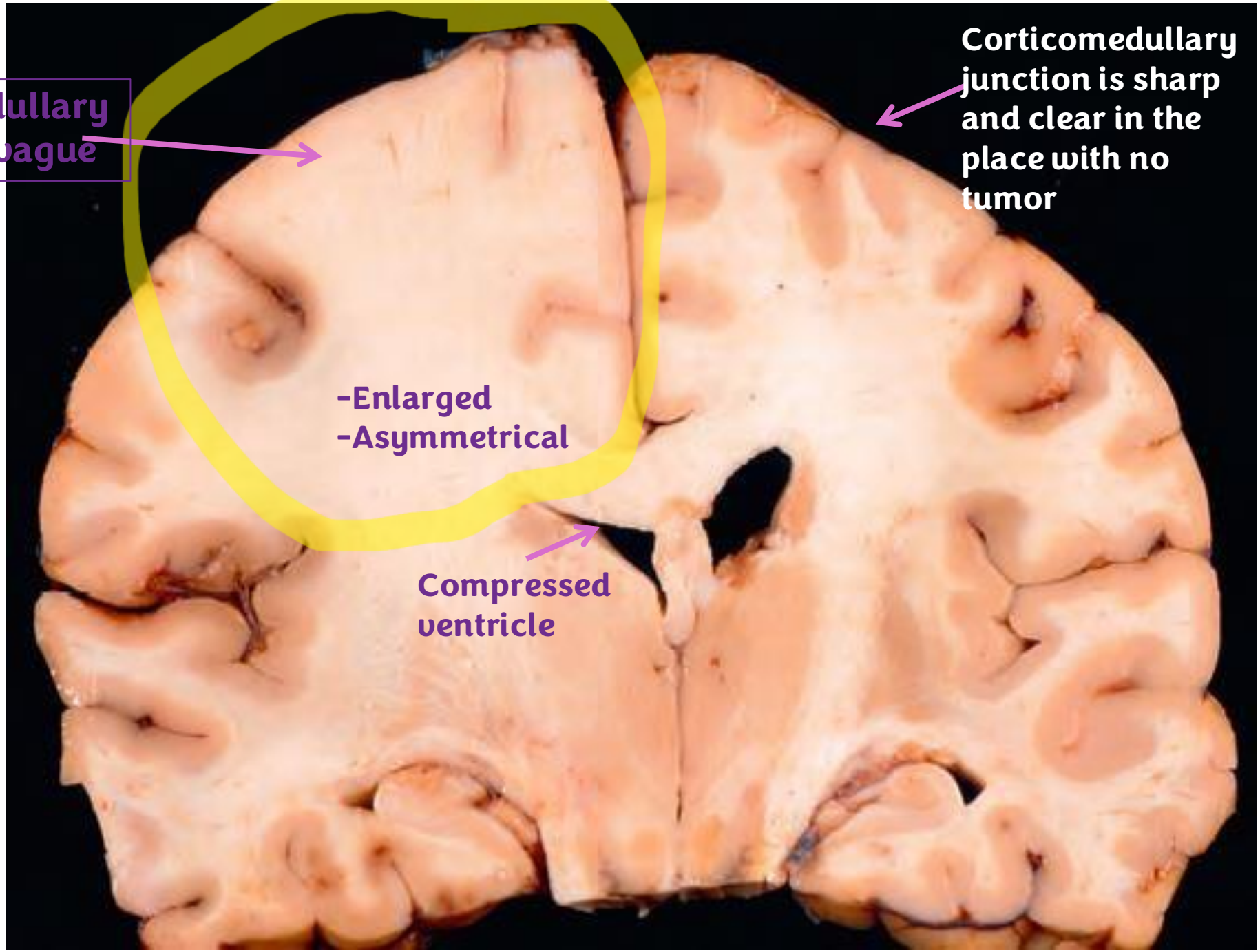
- poorly defined, infiltrative tumors
- expand and distort the invaded brain
- **NO** discrete mass, Infiltration beyond the grossly evident margins.

Grade 4:

- poorly defined, infiltrative tumors
- **lacks large** areas of central necrosis and hemorrhage seen in IDH-wild-type GBM

Necrosis and hemorrhage can be observed, but way less than grade 4 glioblastoma.

Corticomedullary junction is vague



This is a coronal section of the brain.

The area marked with yellow has an astrocytoma, IDH-mutant, grade 2 tumor.

Remember it's poorly defined and infiltrative, so tumor can still be found outside the yellow region.

Diffuse astrocytoma, IDH- mutant, WHO grade 2, Microscopic:

- The transition between neoplastic and normal tissue is **indistinct**
- tumor cells infiltrate normal tissue many centimeters from the main lesion.

How to decide if the area has a tumor?

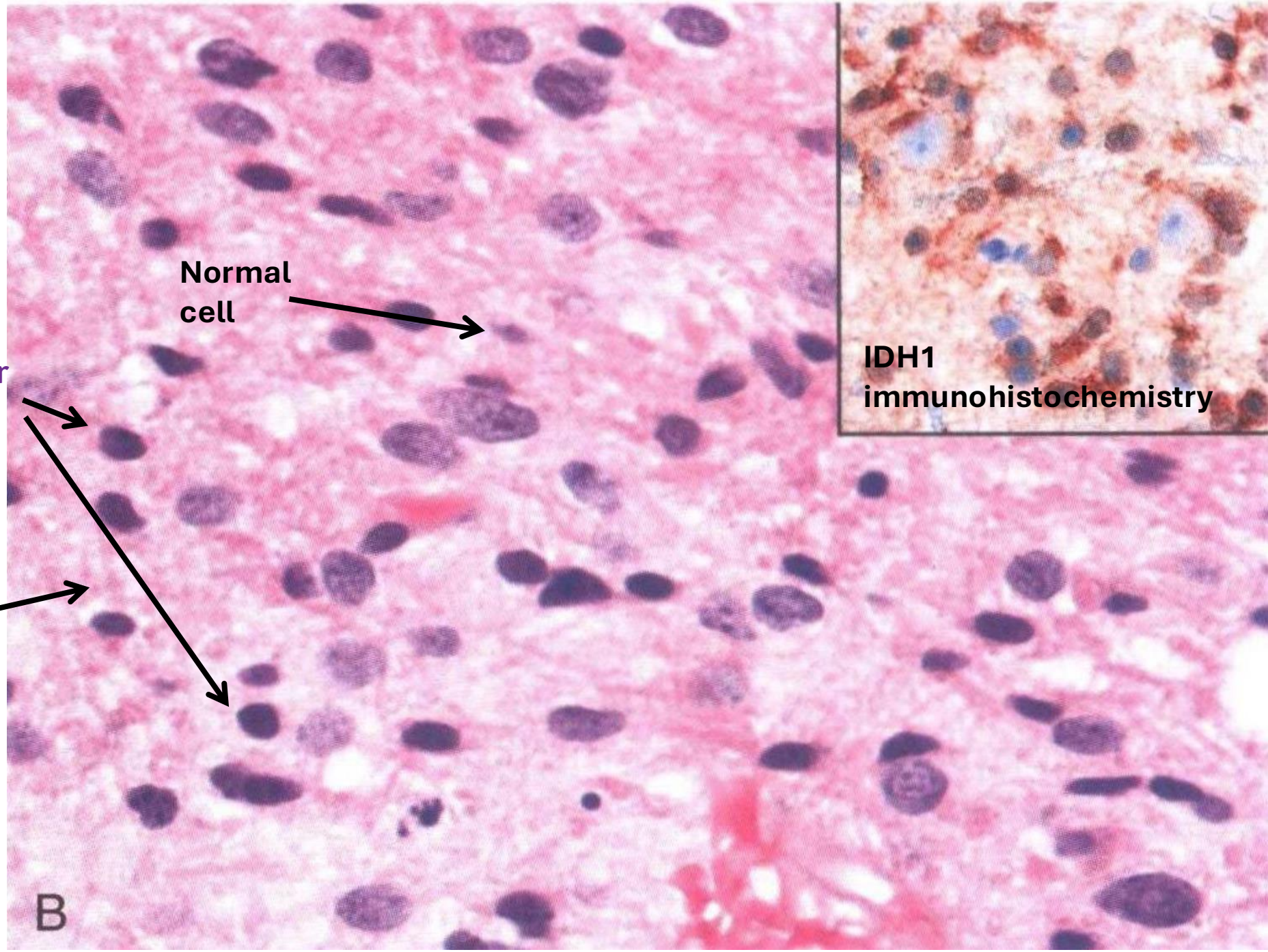
- **Hypercellular** (compared to normal white matter): **mild to moderate** increase in the number of glial cell nuclei. Not sufficient alone to decide, since it can just be gliosis (reactive process that increased their number).
- **Cytologic atypia**:
  - mild
  - enlarged, elongated or irregular hyperchromatic nuclei (these features are very important to distinguish between normal tissue and tumor, since tumor can look like normal tissue)
  - No prominent atypia

+ Tumor cells are located in a **fibrillary background** made of a network of fine astrocytic cell processes

- **NO or rare** Mitotic activity (maybe one)
- **NO** necrosis
- **NO** microvascular proliferation

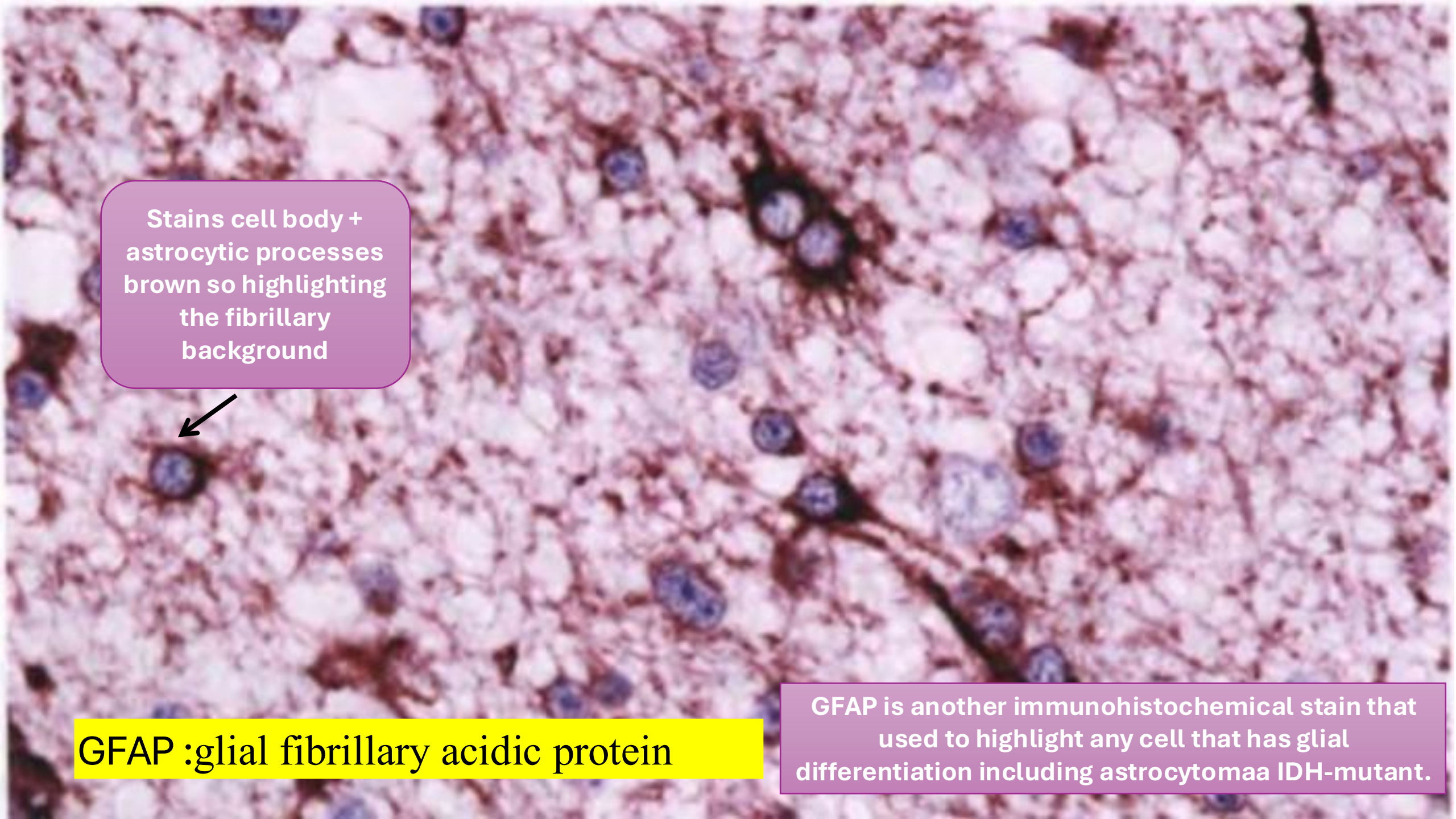
Enlarged irregular nuclei embedded within fibrillar matrix of the brain

Inset: IDH1 immune stain is positive in tumor cells, stains cytoplasm of tumor cells brown.



Fibrillary background made of a network of fine astrocytic cell processes

Tumor cells embedded in normal tissue background. Notice: no necrosis, mitosis, or microvascular proliferation.

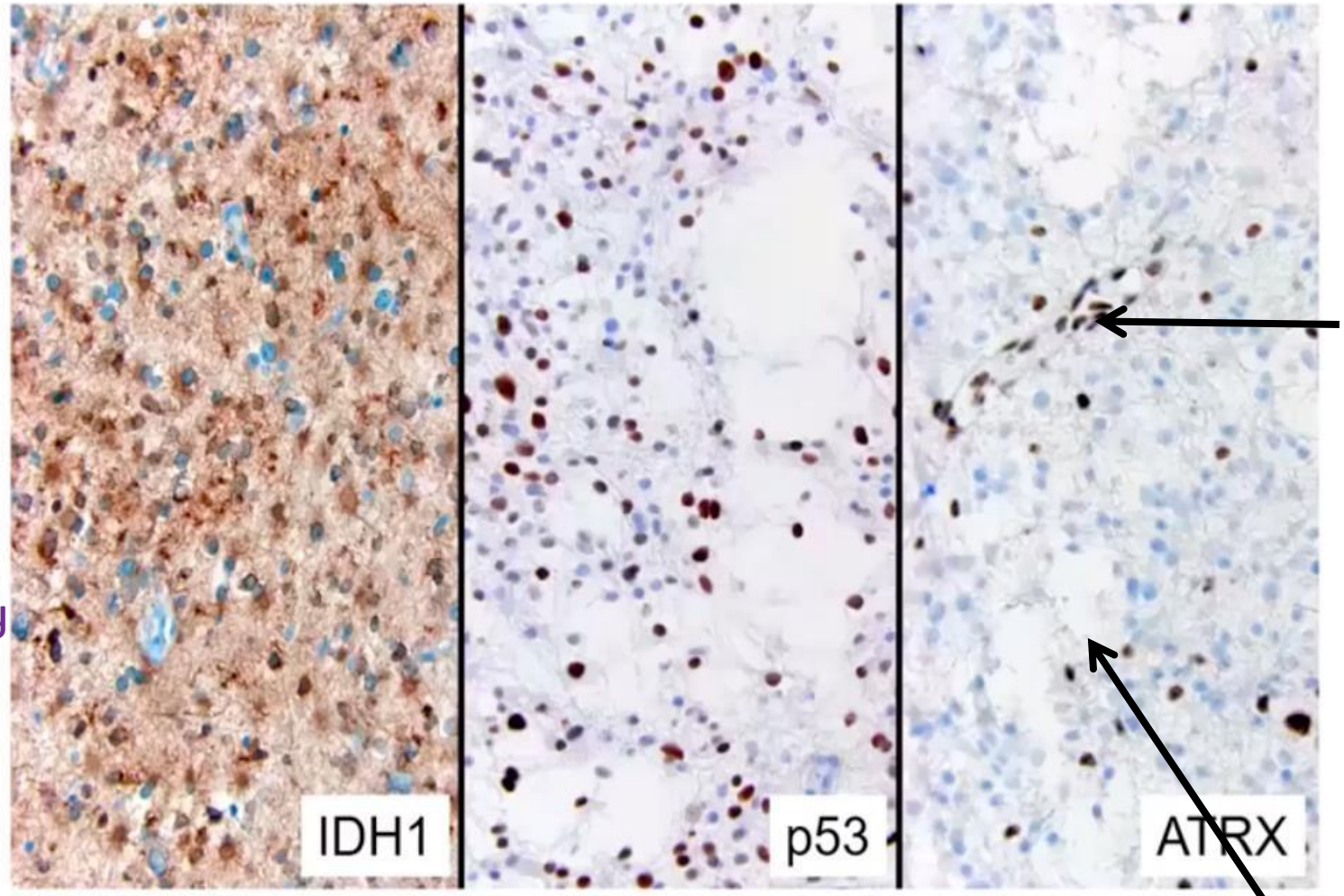

Stains cell body + astrocytic processes brown so highlighting the fibrillary background
GFAP :glial fibrillary acidic protein
GFAP is another immunohistochemical stain that used to highlight any cell that has glial differentiation including astrocytomaa IDH-mutant.

Astrocytoma, IDH-mutant, CNS WHO grades 2-4

Very important since this is typical of all **IDH-mutant astrocytoma** regardless of grade.

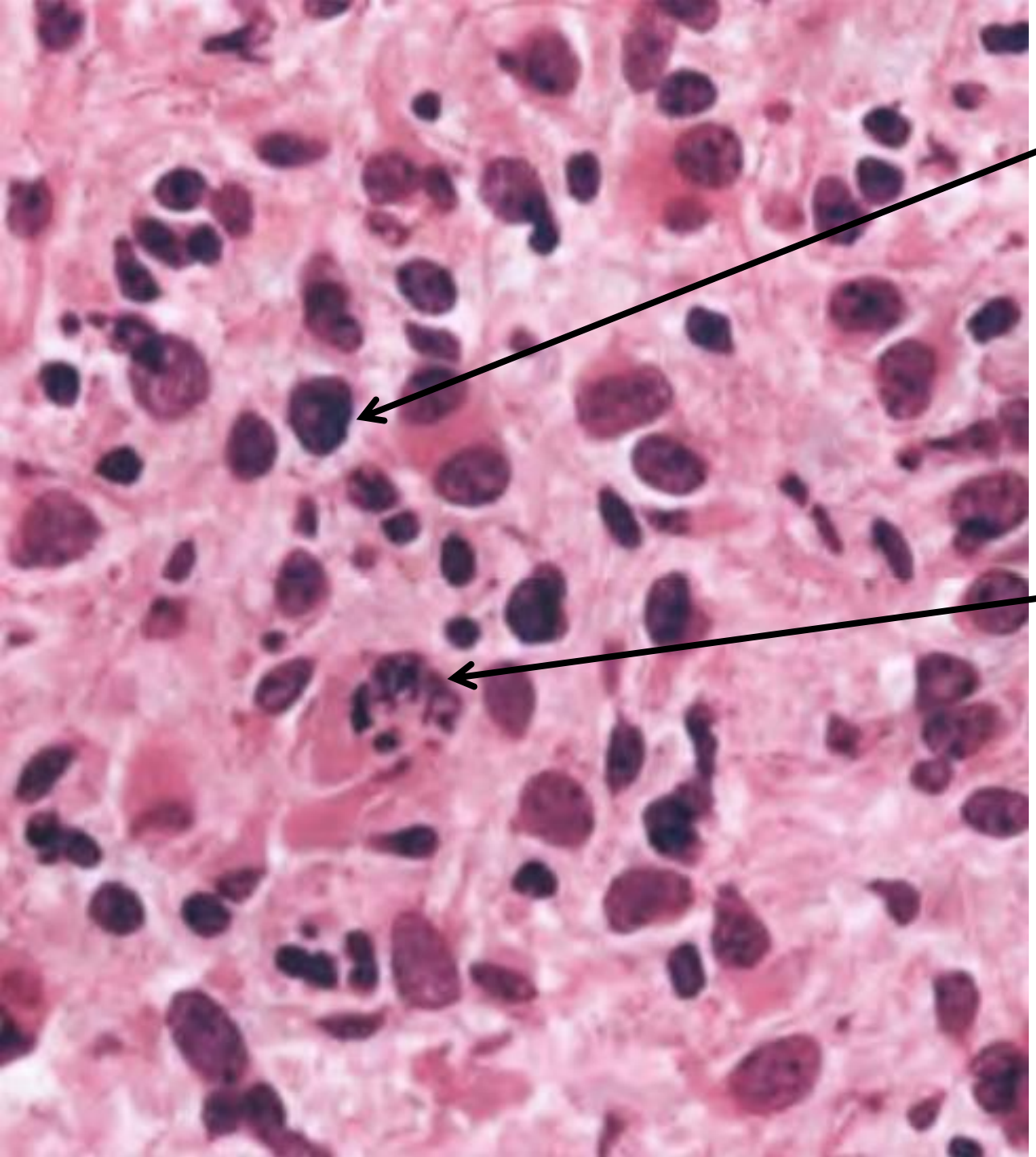
(1) Must be positive for IDH1 mutation in immunohistochemical stain, or IDH sequencing if immunohistochemistry isn't available or was negative.

(2) Must have P53 mutation, seen by its increased expression in tumor cells staining their nuclei with brown (positive).



These brown pigments are within normal blood vessels and cells, their nuclei stained brown due to normal ATRX.

(3) Tumor cells must be ATRX mutant.
In normal tissue, ATRX is preserved, so shows a brown pigment.
When mutated, the brown pigment is lost indicating it's absence (negative).



Hyperchromatic glial cells, irregular nuclei, more atypia, and cellularity.

Astrocytoma, IDH-mutant, grade 3:

- More densely cellular
- More nuclear pleomorphism
- mitotic figures are **present**
- **NO** necrosis
- **NO** microvascular proliferation

Astrocytoma, IDH-mutant, grade 4:

Same features as grade 3 but in addition to **at least one** of the three below:

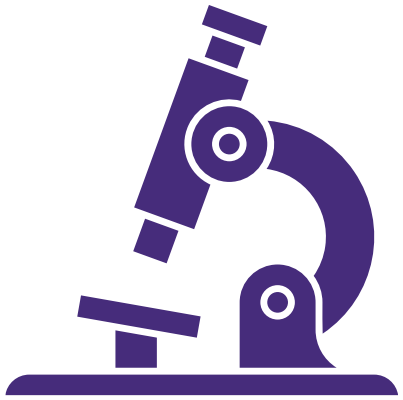
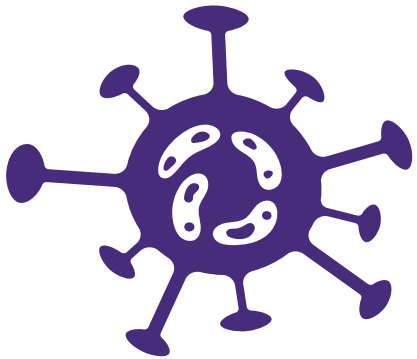
- Microvascular proliferation
- Necrosis
- Presence of homozygous deletion of CDKN2A &/or CDKN2B

- Same as grade 3 with Microvascular proliferation and/or necrosis

- The presence of homozygous deletion of CDKN2A &/or CDKN2B
  → **astrocytomas, IDH- mutant, grade 4 (EVEN IF THE HISTOLOGY SUGGESTS A LOWER GRADE).**

Very important because the prognosis is different, and the median survival for these patients is 3 years.


thank you

PATHOLOGY QUIZ LECTURE 1

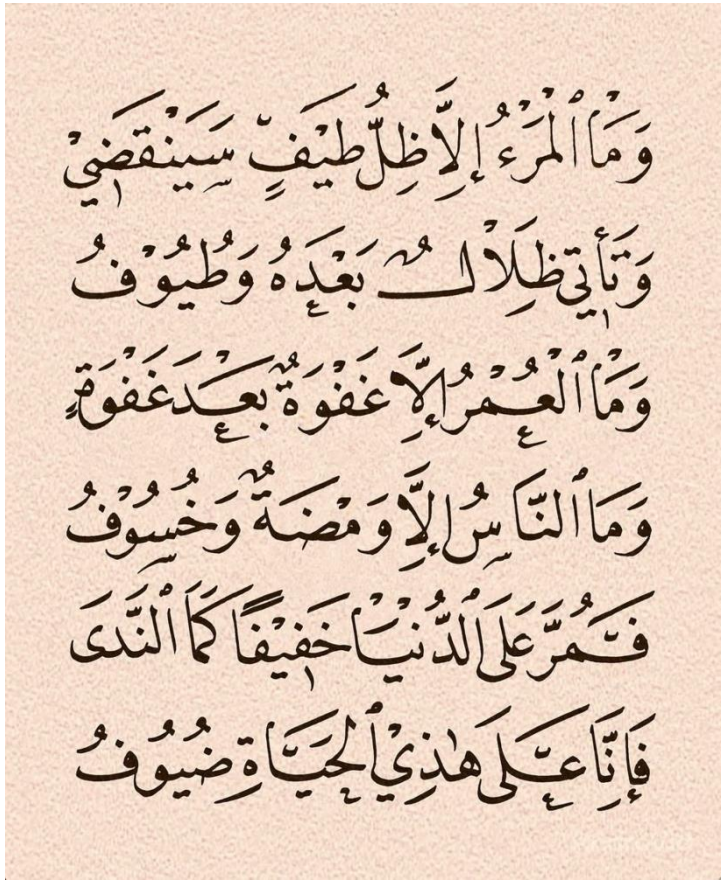
External Resources

رسالة من الفريق العلمي

Additional sources:

1. Highly recommended

اللهم إن عمر عطية وروضة ضياء في ذمتك وحبل جوارك، فقِهما من فتنة القبر وعذاب النار، أنت أهل الوفاء والحق، فاغفر لهما وارحمهما 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			