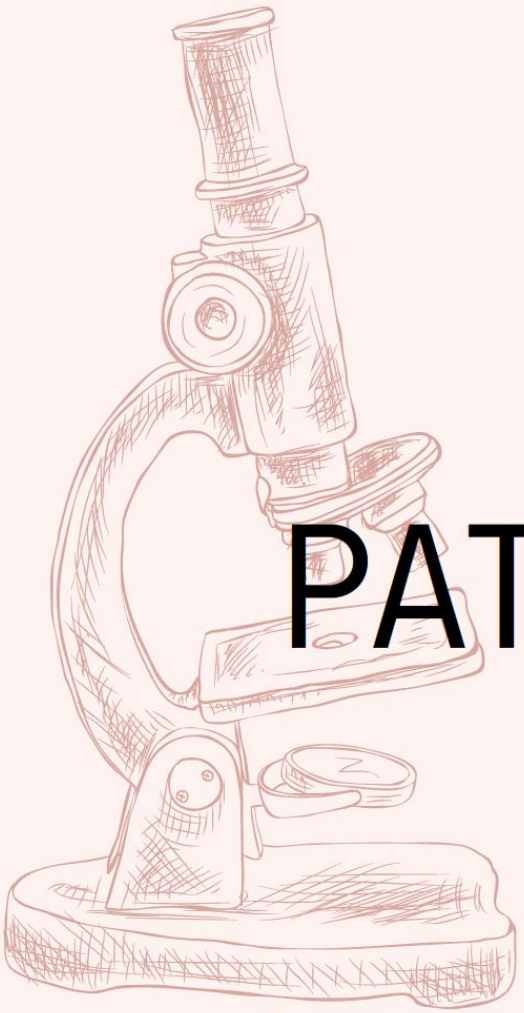
Sheet No. 4



PATHOLOGY

Central Nervous System

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بسم الله الرحمن الرحيم

Note : Anything in *blue italic* is extra for further clarification

INTRODUCTION:

CNS tumors can involve the brain or spinal cord, and are divided into:

1- Primary CNS tumors (account for about 50 to 75% of CNS tumors):

- CNS tumors arise more commonly from the cells of CNS themselves (primary)

May arise from:
- The cells of the coverings (meningiomas)
- The brain cells (gliomas, neuronal tumors)
- Other CNS cell populations (primary CNS lymphoma, germ cell tumors)

2- Secondary (metastatic) CNS tumors (account for about 25 to 50% of CNS tumors):

- They originate elsewhere in the body (metastases).
  - Brain is a common site for metastasis, where tumors travel from any site of origin to the CNS.

EPIDEMIOLOGY:

- **INCIDENCE:**
  - The annual incidence of CNS tumors →
    - 10 - 17/100,000 for intracranial tumors.
    - 1-2/100,000 for intraspinal tumors (much less common).

- **50-75% are primary tumors, and the rest are metastatic (secondary).**

Why CNS tumors are unique?

CHARACTERISTIC FEATURES OF CNS TUMORS:

CNS tumors are not that common, but they are very important and have unique characteristic features that distinguish them from any other neoplastic process.

1- NO premalignant or in situ stages.

- No precancerous or premalignant stage for CNS tumors, this is different from other tumors such as lung adenocarcinoma that can be preceded by atypical adenomatous hyperplasia, and Squamous cell carcinoma that can be preceded by squamous dysplasia.

2- Metastasis is rare! → TNM staging system cannot be used to determine the prognosis of the patient.

- Even the most highly malignant gliomas are confined to the CNS and **rarely spread** outside it.
- but the brain is **not comparably protected** against the spread of distant tumors as it is a common site for metastasis.

TNM staging system is used to determine the prognosis for other tumors in the body:

- T ----> size of tumor.

- N---- > lymph node metastasis.

- M ----> distant metastasis.

This isn't applicable in CNS tumors because metastasis is rare.

3- Growth pattern (infiltrative or not) and tumor location are the most important determinants of the prognosis:

- **Growth pattern (infiltrative/diffuse or circumscribed):**

Even low-grade lesions may infiltrate large regions of the brain, leading to serious clinical deficits, inability to be resected and poor prognosis.

Same meaning

Tumors in the CNS are described either circumscribed or infiltrative/diffused:

- Infiltrative tumor →invade beyond the grossly evident margin (poorly circumscribed), does not form a distinct mass so it **cannot be surgically removed**, and has a greater chance of recurrence.
- Circumscribed tumor→can be **completely removed surgically** and will cause less neurological deficits (no infiltration for adjacent structures).

That's why the outcome and the management plan such as undergoing surgical excision of a tumor is determined by its growth pattern.

➢ Tumor location (the most important factor!)

The anatomic site of the neoplasm can influence outcome independent of histologic type or grade. Some tumors can be lethal only because they are present in critical locations. Even the most benign tumor if it is located near vital center it can lead to death, and maybe a very aggressive stage 4 tumor located in a non-critical location will have better prognosis and less neurological deficits.

- Example: Meningioma grade 1 (benign and circumscribed) that involves the posterior fossa near the vital centers in the medulla. If this tumor causes pressure on the cardiorespiratory center, this will result in cardiorespiratory arrest, and can be lethal regardless of the grade and the classification, so it's not about the grade and the type of the tumor its about the anatomic site.

Why the location is almost everything?

- The location is going to determine the **neurologic deficit** that is associated with the presence of this tumor.

- And can determine the ability for this tumor to be completely **surgically** resected.

- And it is going to guide your **diagnosis** of the histological type of the tumor because certain tumors tend to happen in certain locations.

CNS tumors are much like real estate! Location is almost everything.

Examples: -

- pilocytic astrocytoma and medulloblastoma tend to occur in the posterior fossa.
- ependymoma and central neurocytoma tend to occur intraventricularly.

***Age: The prognosis of CNS tumors also depends on age as they are classified into adult tumors and pediatric tumors.** (More details are on page 7)

Certain tumors tend to happen in pediatric age group, and other tend to happen in adults.

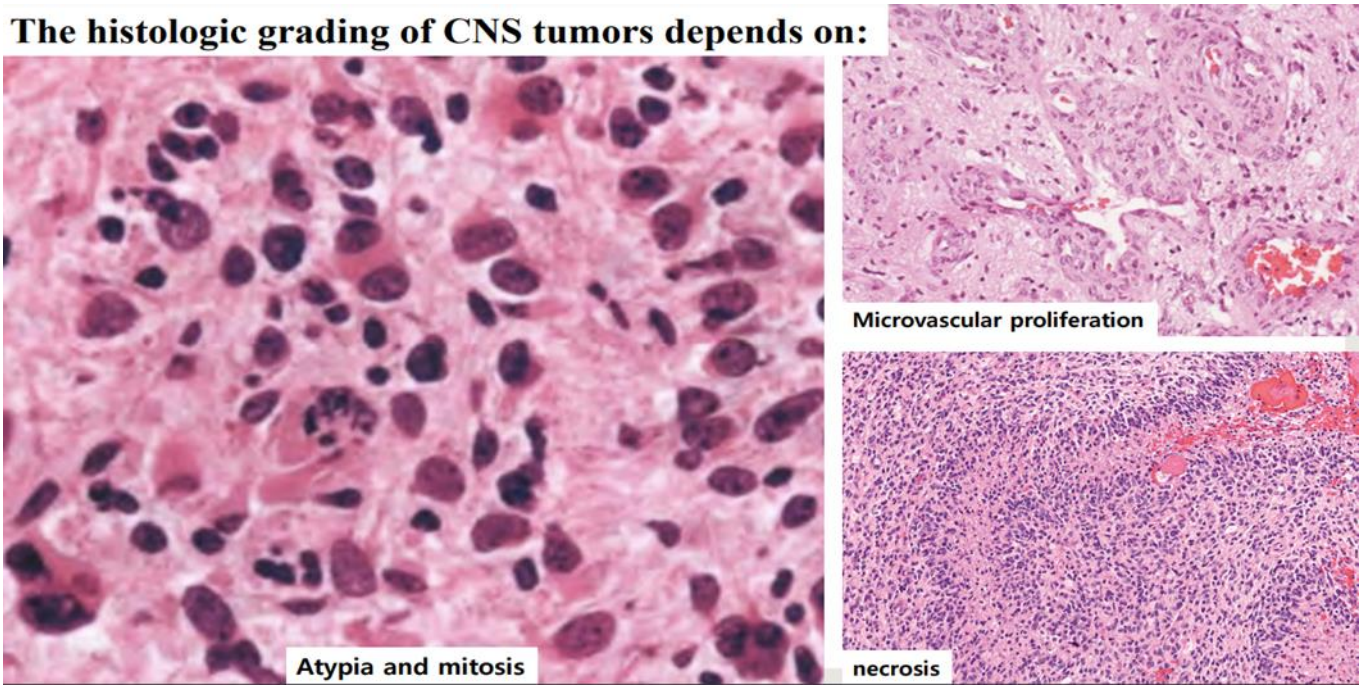
اللهم صلّ على سيدنا محمد

HISTOLOGIC GRADING OF CNS TUMORS:

We cannot use TNM staging system to determine the prognosis of these tumors, and the main 2 determinants of prognosis are growth pattern and tumor location, BUT also ***GRADING*** is a determinant for the prognosis and outcome of a tumor→ So CNS tumors are graded into 4 grades according to certain histologic features.

The histologic grading of CNS tumors depends on these features:

1- Cellularity
2- Atypia
3- Mitosis
4- Microvascular proliferation
5- Necrosis



Histologic grading of CNS tumors (CNS tumors are classified into 4 types):

Grade	Features (In general)	Examples
Grade 1 lesions (benign)	**- Low proliferative activity (very low or almost no mitotic activity and low cellularity).** **- Can be cured after complete surgical resection alone (circumscribed).**	Pilocytic astrocytoma (PA), subependymal giant cell astrocytoma (SEGA), choroid plexus papilloma, myxopapillary ependymoma which is a type of ependymoma that happens in the filum terminale.
Grade 2 lesions (low grade)	**- low proliferative activity (but higher cellularity than grade 1).** **- usually infiltrative and often recur.** **- Some grade II entities tend to progress to higher grades of malignancy.**	Diffuse astrocytoma, oligodendroglioma, central neurocytoma, some types of ependymoma
Grade 3 lesions (anaplastic)	**- clear histological evidence of malignancy (increase cellularity, nuclear atypia, and Higher proliferative activity (evident mitotic activity)). *Each tumor type has a cut point for the number of mitotic divisions that convert it from grade 2 to 3.** **- In most settings, patients receive radiation and/or chemotherapy (surgical excision is not enough).** ***Atypia (focal or diffused) starts to appear in this grade (grade 3).**	Anaplastic astrocytoma, anaplastic oligodendroglioma
Grade 4 lesions (high grade)	**- Cytologically highly malignant, mitotically active, rapid proliferation, necrosis-prone neoplasms, microvascular proliferation, and cytologic atypia (pleomorphism, hyperchromasia, and maybe bizarre cells).** **- Associated with rapid pre- and postoperative disease evolution and fatal outcome.** **Widespread infiltration of surrounding tissue and a risk of craniospinal dissemination (CSF spread).**	Glioblastoma (GBM), medulloblastoma, pineoblastoma, and most embryonal neoplasms

NOT REQUIRED

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, 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

*WHO grades of CNS tumors: each tumor has a certain grade according to WHO. Examples:

Pilocytic astrocytoma→ grade **1**

Central neurocytoma→grade 2

Anaplastic pleomorphic Xanthoastrocytoma (PXA)→grade 3

Pediatric CNS tumors:

- **20% of all pediatric tumors→1/5th of pediatric tumors are CNS tumors (quite common).**
- **Childhood CNS tumors differ from those in adults in:**

1- Clinical features
2- Molecular pathways
3- Location:

- 2/3 infratentorial in kids (posterior fossa).
- 2/3 supratentorial in adults (cerebral hemispheres above tentorium cerebelli).

4-Histologic type:

Certain histologic types tend to happen in pediatric age group, and other tend to happen in adults.

- **Kids:** medulloblastoma, pilocytic astrocytoma, ependymoma
- **Adults:** glioblastoma, metastases, primary CNS lymphomas, meningiomas, diffuse gliomas constitute most gliomas in adults (including diffuse astrocytomas and oligodendrogliomas).

*The presence of common histologic types of tumors in children does not mean that it is impossible for them to occur in adults and vice versa, but rather it means that in most cases (i.e. the common scenario) they will affect children, and therefore we put them on the top of the differential diagnosis list when diagnosing a child with CNS tumor.

Now let's go in a journey through the years in order to overview the CNS tumors' classification over years..

It had been long time since **1979** when the first WHO book for the classification of CNS tumors (1st edition) was released. It was the reference for neurosurgeons, neuropathologists and neuroradiologists worldwide.

The 2nd was published in **1997**, 3rd in **2000**, and 4th in **2007** in which Robbins -our reference textbook- depends on.

For nearly a century, the classification of brain tumors has been done according to their microscopic similarities with what's thought to be their cell of origin/ phenotype, based on:

1. light microscopic appearance
2. immunohistochemical expression of proteins
3. electron microscopic assessment of ultrastructural feature

And hence the names were produced (astro, oligo, ependymoma and so on..)

The **2000 and 2007** WHO classifications were based on the described classification and unfortunately your pathology textbook is outdated.

↓

From 2007 to 2016, a huge change in the classification took place…

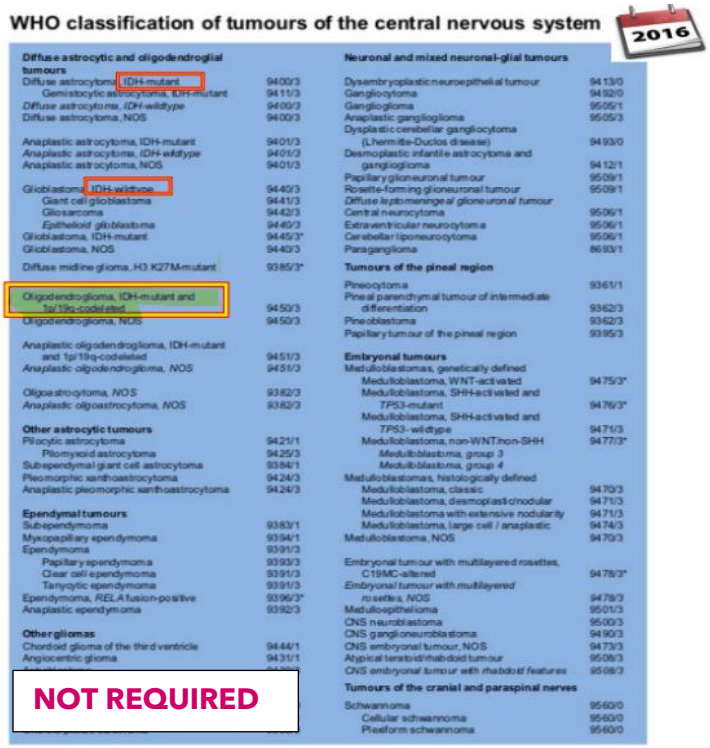
↓

The **2016** classification breaks with this nearly century-old tradition and incorporates well-established molecular parameters into the classification which includes diagnostic categories that depend on genotype. This classification implemented the combined phenotypic-genotypic diagnostics based on histologic features & tumor genetic profile (integrated diagnoses).

➔ This classification helped improving treatment protocols and predicting prognosis.

↓

Moving **from 2016 to 2021** , the 5th edition was released, implementing a huge change based on the advanced knowledge in the molecular classification of CNS tumors.



As you can see, the 2016 classification includes both the phenotype/ the name and the genotype/ mutation

And this is the INTEGRATED /combined classification.

Examples:

diffused astrocytoma→IDH mutant

Oligodendroglioma→IDH mutant and 1p/19q deleted.

Genetic alterations in gliomas:

1- Mutations in isocitrate dehydrogenase (IDH) genes (the most important):

- Observed as an **early event** in gliomagenesis.
- Seen in astrocytomas and oligodendrogliomas (**there is no diagnosis for these 2 tumors without IDH mutation).**
- 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 (this is the one used for immune stain).
- Other rare mutations: R132C, R132G, R132S, & R132L
- IDH2 mutation: R172K is the most frequent IDH2 mutation.

How IDH mutations are detected?

1- By immunohistochemical stains:
Only IDH1 has immune stain→ IDH1-R132H immune stain (cytoplasmic stain).

2- By molecular studies (direct way but expensive and take time):
For both IDH1 and IDH2→ IDH sequencing for IDH1 codon 132 and IDH2 codon 172

If the tumor is IDH1 Negative, the only solution here is to sequence for IDH1 and IDH2 by molecular tests.

Gain of function mutation (NOT loss 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→ eventually will cause self- renewal and tumorigenesis.**

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

- Diagnostic of oligodendrogliomas in the presence of IDH mutation.

  ➔ So this tumor by definition needs histology, IDH mutation and co-deletion to diagnose it, without anyone of them it's not oligodendroglioma.

- The vast majority of IDH mutant and 1p/19q co-deleted oligodendroglioma carry TERT promotor hotspot mutations

p= short arm

q= long arm

TERT promotor hotspot mutations: telomerase stabilization, cellular immortalization and proliferation

What does TERT stand for?

Telomerase reverse transcriptase (abbreviated to TERT, or hTERT in humans) is a catalytic subunit of the enzyme telomerase, which, together with the telomerase RNA component (TERC), comprises the most important unit of the telomerase complex.

3- ATRX and P53 loss of function mutation:

- Both occur in IDH mutant astrocytomas

- **ATRX mutation**:
  ➔ Induces abnormal telomeres maintenance mechanism known as "alternative lengthening of telomeres"
  ➔ It is Mutual exclusive with the activating promoter mutation of the TERT gene (1p/19q codeletion).

  -mutual exclusive means → cannot coexist at the same time

  So if the presence of ATRX mutation was proved → it is IDH astrocytoma NOT oligodendroglioma (because oligodendroglioma exhibits TERT promoter mutation)

- **P53 mutation**:
  ➔ Enable tumor cell survival

- ATRX → associated with genomic instability → the cells are not stable→ induces P53 (tumor suppressor gene) dependent cell death BUT the mutation in P53 (which is a loss of function) helps these cells to survive. That's why when there's ATRX mutation, there's is also P53 mutation that coexists with.

ATRX is a chromatin remodeling protein. ATRX mutations are widely distributed in glioma, and correlate with alternative lengthening of telomeres (ALT) development, but they also affect other cellular functions related to epigenetic regulation

4- Other genetic alterations:

- include mutations that lead to

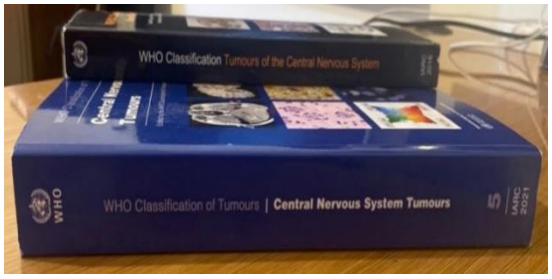
  ➔ Overexpression of the EGF receptor (EGFR) and other receptor tyrosine kinases
  ➔ Disable p53 or RB

-The epidermal growth factor receptor protein (EGFR) is involved in cell signaling pathways that control cell division and survival.

RB (retinoblastoma) is a tumor suppressor with important chromatin regulatory functions that affect genomic stability..

Going back to WHO classification of CNS tumors…

A new textbook in **2022** which shows lots of updates was released, and as you can see from the picture below, which compares between the 5th edition (twice the size) and the revised 4th one.



22 New Entities

- Diffuse astrocytoma, *MYB* or *MYBL1*-altered
- Polymorphous low-grade neuroepithelial tumor of the young
- Diffuse low-grade glioma, MAPK pathway-altered
- Diffuse hemispheric glioma, H3.3 G34-mutant

7 Gliomas

- Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype
- Infant-type hemispheric glioma
- High-grade astrocytoma with piloid features (Methylation only dx)
- Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters (provisional entity)
- Myxoid glioneuronal tumor

3 Glioneuronal

- Multinodular and vacuolating neuronal tumor
- Supratentorial ependymoma, *YAP1* fusion-positive
- Posterior fossa ependymoma, PFA
- Posterior fossa ependymoma, PFB

4 Ependymomas

- Spinal ependymoma, *MYCN*-amplified
- Cribriform neuroepithelial tumor (provisional entity)
- CNS neuroblastoma, *FOXR2*-activated
- CNS tumor with *BCOR* internal tandem duplication

4 Embryonal

- Desmoplastic myxoid tumor, *SMARCB1*-mutant
- Angiomatoid fibrous histiocytoma / Intracranial myxoid mesenchymal tumor
- CIC-rearranged sarcoma
- Primary intracranial sarcoma, *DICER1*-mutant

3 Sarcom

- Pituitary blastoma

1 Pituitary

NOT REQUIRED

In the new book, we have about 22 new entities that were introduced based on the advances of molecular testing.

One of these entities for example, high grade astrocytoma with piloid features can be diagnosed only by DNA methylation profiling.

So this confirms that Molecular parameters became the base of classification of these tumors; because some of them cannot be diagnosed without molecular testing

Also, 13 entities were edited by the means of terminology

13 with Revised Terminology

- Astrocytoma, IDH-mutant
- Diffuse midline glioma, H3 K27-altered
- Chordoid glioma
- Astroblastoma, MN1-altered ZFTA
- Supratentorial ependymoma, ~~C11orf95~~ fusion-positive
- Embryonal tumor with multilayered rosettes
- Malignant melanotic nerve sheath tumor
- Solitary fibrous tumor
- Mesenchymal chondrosarcoma (formerly a subtype)
- Adamantinomatous craniopharyngioma (formerly a subtype)
- Papillary craniopharyngioma (formerly a subtype)
- Pituicytoma, granular cell tumor of the sellar region, and spindle cell oncocytoma (grouped
- Pituitary adenoma / PitNET

NOT REQUIRED

Look at the difference between 016 and 021 classification… what's important for you to know is that 021 made it easier for understanding.

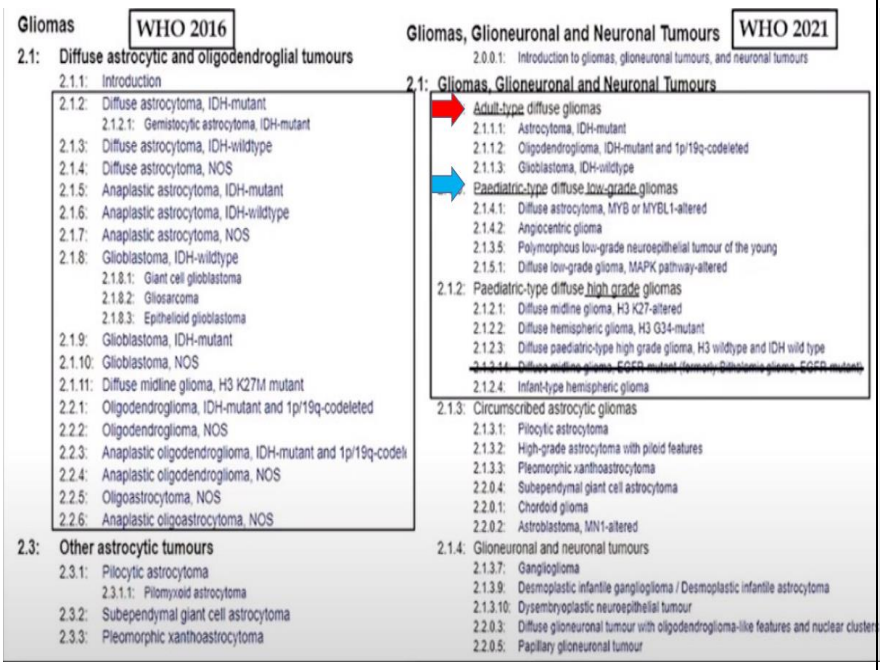
Firstly, tumors were divided based on **infiltration** to:

1. Diffuse/ infiltrative
2. Circumscribed

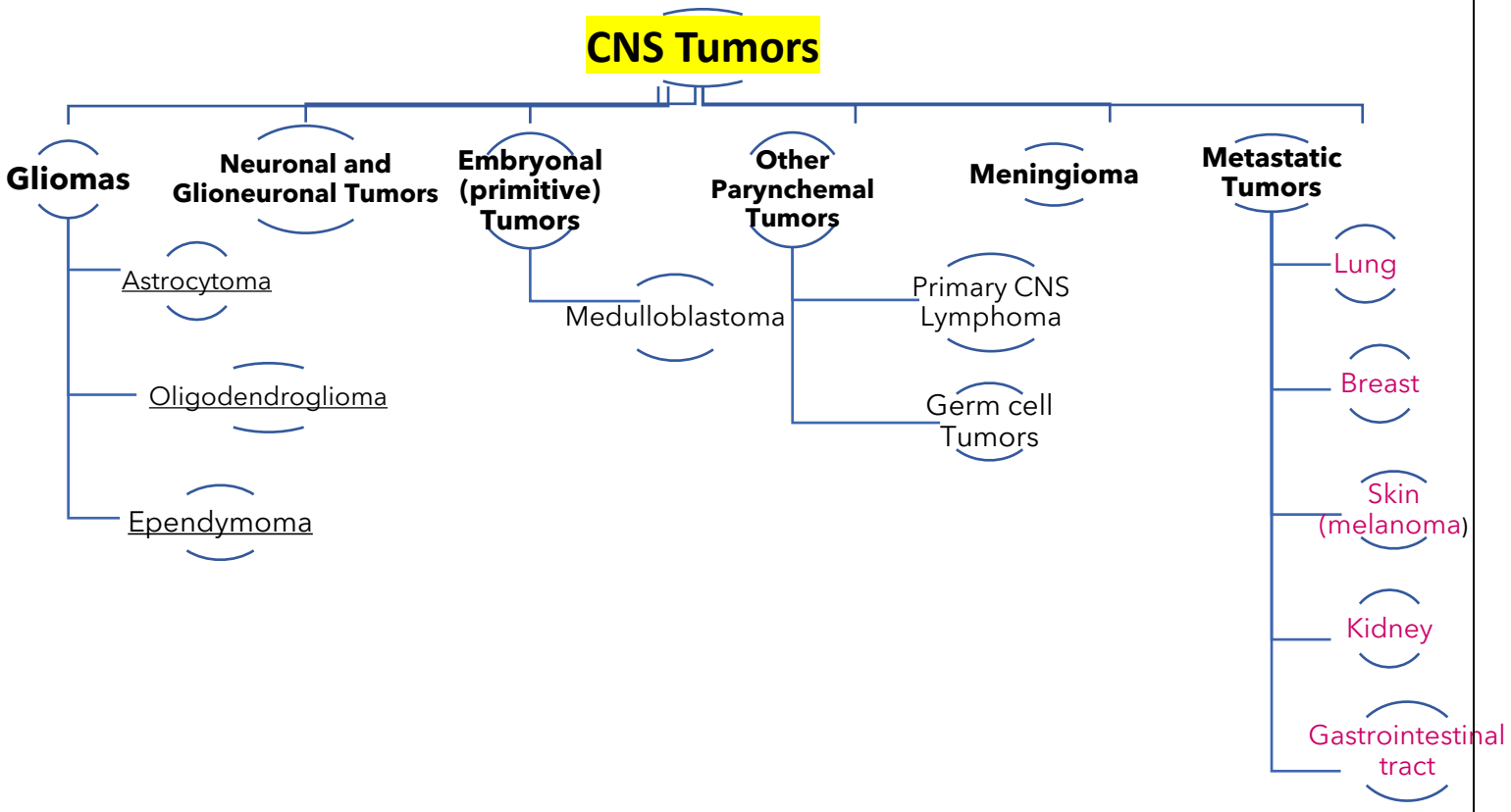
Then, the diffuse gliomas were further subdivided to:

1. Adult-type
2. Pediatric-type

(Why? We said before that there's difference between adult-type and pediatric-type in the molecular background, location and histologic features)



Now, let's go back to our textbook Robbins classification of CNS tumors:



Lets start with the MOST COMMON GLIOMA...

Astrocytoma

Classified based on their infiltrative potential.

Diffuse/ infiltrating

- Grade 2-4
- Poorly circumscribed
- Tend to infiltrate beyond the grossly evident margins
- Associated with more neurologic deficits
- Complete surgical excision is not always available so recurrence is higher

Circumscribed

- Grade 1 or 2 (low grade)
- Well circumscribed
- Low or nearly no infiltration
- Less neurologic deficits
- Surgical excision is more possible

E.g;

1. **Pilocytic astrocytoma (PA)**
2. **Subependymal giant cell astrocytoma (SEGA)**
3. **pleomorphic xanthoastrocytoma (PXA)**

Diffuse Astrocytoma

• 80% of primary brain tumors in adults.

• Age at diagnosis: 40–60 year old.

Location: cerebral hemispheres +/- cerebellum, brainstem, or spinal cord (less common locations).

• Presentation→ depends mainly on location

1. **Seizures**, sudden onset is a common presentation for most brain tumors.
2. **Headaches**; due to increase in intracranial pressure for example
3. **Focal neurologic deficits** related to the anatomic site of involvement.

• Static for years

or

• Progressive: such as rapid clinical deterioration, due to the appearance of higher-grade component and more rapid tumor growth (these tumors can suddenly be converted to more aggressive tumors specially grade 3 tumors which will lead to sudden deterioration).

Astrocytoma

Stratified into 3 groups based on histologic features.

Diffuse Astrocytoma

- Grade 2
- Mean survival is > 5 years

Anaplastic Astrocytoma

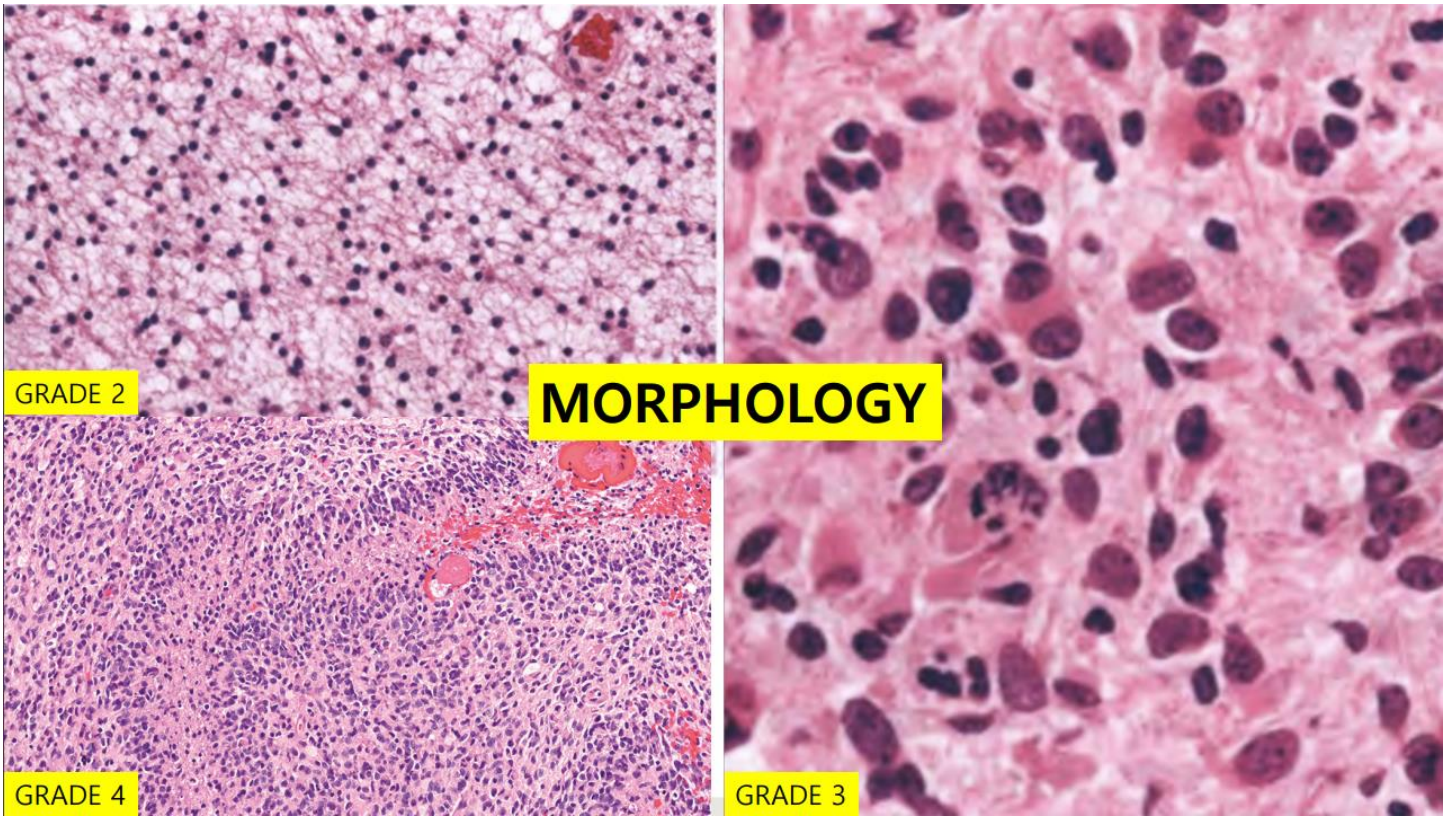
- Grade 3
- Mean survival is 2-3 years

Glioblastoma

- Grade 4
- Mean survival is 15 months (maximum 18 months)

Keep in mind that..

- The prognosis gets poorer as the grade increases
- NO grade 1 diffuse astrocytoma→ because most grade 1 tumors are benign and well circumscribed but astrocytomas are malignant by definition and graded from 2 to 4.



Question:

Which of the following is true?

A- The TNM staging system is applicable for CNS tumors

B- microvascular proliferation is not a histological feature for grading of CNS tumors

C- There are some rare types of oligodendroglioma that don’t have the IDH mutations

D- nuclear Atypia is a characteristic feature of Anaplastic grade 3 lesions

E- two-thirds of the tumors in pediatrics are supratentorial

Answer : D

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