# CNS Tumors

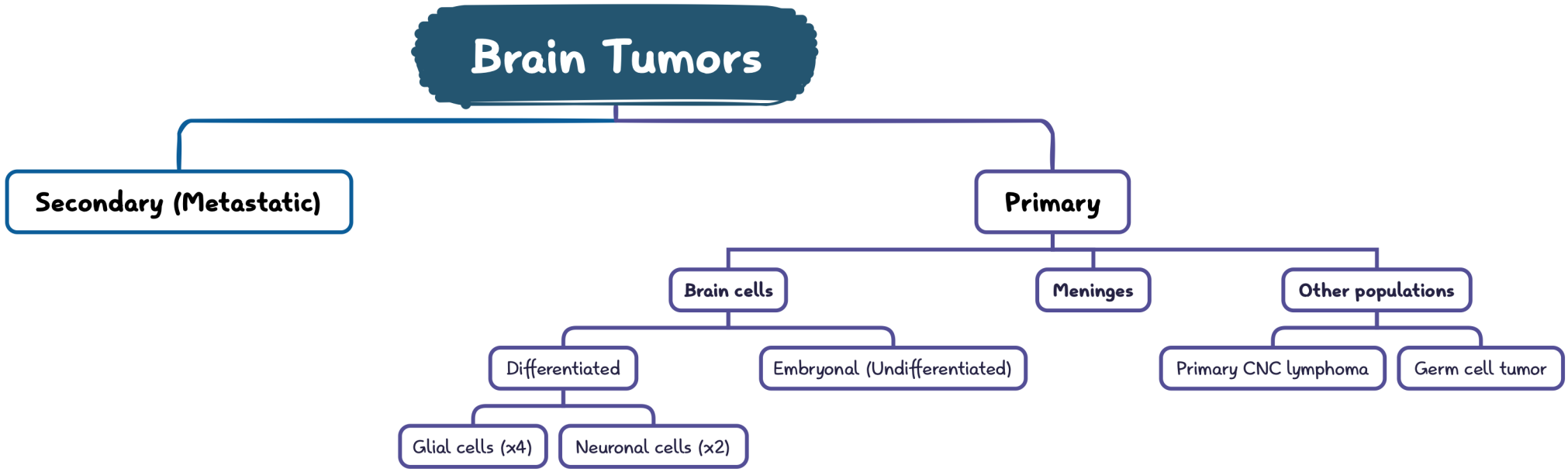
* Characteristics:

1) NO premalignant stage. 2) Rare metastasis 3) Prognosis depends on: location and growth patterns

- growth pattern: **(A): circumscribed (B): infiltrative**

* Grading system: depends on: **(1): mitosis** **(2): atypia** **(3): microvascular proliferation (MVP)** **(4): necrosis**

| Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|
| - Benign<br>- ↓ Proliferative<br>- Circumscribed **A** | - ↓ Proliferative<br>- can infiltrate and recur **B**<br>- progess to grades 3 and 4 | - infiltrative **B**<br>- ↑ Proliferative (**1**)<br>- Atypia (**2**)<br>- Tx: radio + chemo | - Malignant<br>- infiltrative **B**<br>- mitosis (**1**) - atypia (**2**)<br>- mvp (**3**) - necrosis (**4**) |



# GLIAL CELL TUMORS:

| Type | Genotype | Locations | Clinical | Grades | Survival / prognosis | Macroscopic | Microscopic = phenotype |
|---|---|---|---|---|---|---|---|
| **Astrocytoma**<br>(40-60 yrs old) | 1) **IDH** mutation (IDH1>IDH2)<br><br>2) **TP53 +- ATRX**<br><br>3) for grade (4): **CDNK2 (A+B)** | - Mainly cerebral hemisphere +- any cns area | - static vs progressive<br>- seizures<br>- headache<br>- focal neuro deficits (location) | - no grade (1)<br>- grade (2):<br>(B, mild 2 (not prominent), Nuclei: hypercelluar (increase in no), enlarged, elongated, or irregular hyperchromatic)<br>Fine astrocyte processes: **Fibrillary background**<br>- grade (3):<br>(B, 1, nuclear polymorphism)<br>- grade (4):<br>(B, 1, 2, 3, 4) | >10 yrs<br><br>5-10 yrs<br><br>3 yrs | **- grades (2+3):** Poorly identified, infiltration beyond grossly evident margins, no discrete mass<br>**- grade (4):** Similar to before + areas of necrosis **4** and hemorrhage but not large like in IDH-wild GBM (glioblastoma) | Diffusely infiltrating glioma = **B** "Malignant"<br>- Blurred boundaries between involved and non-involved areas |
| **Glioblastoma**<br>(60s-80s)<br>(most malignant glioma)<br>(50% of all 1° malignant brain tumors) | NO IDH<br>NO H3<br>+ at least one of these:<br>1) **TERT** promotor mutation<br><br>2) **EGFR** gene amplification<br><br>3) **[+7 / -10]**: combined gain of entire chromosome 7 and loss of entire chr.10 | - Cerebral hemispheres (frontal, temporal, parietal)<br>- Thalamus<br>- Basal ganglia<br><br>- rapid infiltration to the CC with growth to the contralateral hemisphere = **Bilateral symmetrical lesion** (Butterfly) | - seizures<br>- cognitive impairment<br>- nausea and vomiting<br>- headache | - no grades (1),(2),(3)<br>- grade (4):<br>(B, 1, 2, 3, 4) | 15-18 months!!<br>Very poor prognosis even with resection, chemo and radio | - variations between regions (**multiform**):may be<br>- firm and white<br>- soft and yellow (necrosis)<br>- with hemorrhage<br>- with cystic degeneration | (similar to grade 4 astrocytoma (IDH mutant))<br>- brisk **1**<br>- prominent nuclear atypia **2**<br>- **3** abnormal vessel walls with 2 or more layers<br>- irregular **4** surrounded by dense accumulation of tumor cells = **Palisading necrosis** متل سور من الخلايا |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Oligodendroglioma**<br>(40-50 yrs old)<br>(5-15%) | 1) **IDH** (1or2)<br><br>2) **[1p/ 19q] codeletion**<br><br>3) for grade (3): Homozygous **CDK2A** deletion<br><br>= IDH mutant, 1p/19q codeleted | - Mostly in cerebral hemispheres (<u>frontal</u> and <u>temporal</u> lobe white matters) 🤍 | | - no grade (1)<br>- grade (2):<br>(B, low 1 or absent: Ki67<5%)<br>- grade (3):<br>Anaplasia (focal or diffuse)<br>(B, brisk 1and/or 3)<br>(with or without 4)<br>(Ki67>10%,<br>- no grade (4) | <u>10-20 yrs</u><br><br><u>5-10 yrs</u><br><br>Through the combination of surgery + chemo + radio<br><br>**The best among all diffuse glial tumors** | - infiltrative with <u>blurring</u> of grey + white matters boundary<br>- <u>gelatinous</u> gray mass, cysts, focal <u>hemorrhage</u> and <u>calcification</u> | - sheets of **<u>REGULAR UNIFORM</u>** cells resembling oligo.<br>**<u>Nuclei:</u>**<br>- spherical nuclei with granular chromatin (**salt & paper**) 🧂<br>- surrounded by a clear halo of cytoplasm **(fried-egg)** 🍳<br>- anastomosing capillaries **(chicken-wire)** 🐔<br>- calcification in 90% |
| **Ependymoma**<br>(1st two decades + adults) | 10 subtypes each with specific genotype | - Posterior fossa, near the 4th ventricle (5-10% of tumors in the first 2 decades)<br><br>- Supratentorial<br><br>- Spinal cord: the most common in <u>ADULTS</u> and <u>NF2</u> pts (neurofibromatosis)<br><br>Post.fossa tumors have poor prognosis | | - no grade (1)<br>- grade (2):<br>(low 1, low cellularity)<br>(uniform, small, round/oval nuclei, granular chromatin in a fibrillary background)<br>(ultrastructural exam.: cilia and microvilli)<br>- grade (3): "ANAPLASTIC"<br>(brisk 1, 3 (more prognostic impact than necrosis, atypia))<br>(less differentiation = less rosettes) | Tumor cells may form glandlike structures (rosettes) → Rosette formation: 🎯<br>**- Ependymal rosettes:** diagnostic hallmark of ependymoma (25%)<br>**- Perivascular pseudorosettes:** not specific for ependymoma (seen in <u>glioblastoma</u> and <u>medulloblastoma</u>)<br><br>Ependymal rosettes:<br>- tumor cells arranged around central canal or lumen that resemble the embryologic ependymal canal, with long, delicate processes extending into a lumen.<br>Perivascular pseudorosettes:<br>• tumor cells radially arranged around vessels.<br>• Called "pseudo" because the central structure is not formed by the tumor itself, but instead represents a native, non-neoplastic element | | |

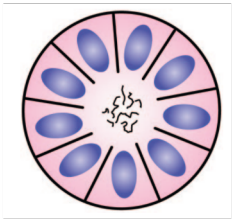
# NEURONAL TUMORS:

- Less frequent than glial
- Have neuronal characteristics and express **neuronal markers**: synaptophysin, neurofilaments and NerN
- **Lower grades** (1 and 2)
- Present with **seizures**

| | | | | |
|---|---|---|---|---|
| **Gangliogliomas** grade (1) | Children and young adults  | Slow growing tumor  | Temporal lobe | From its name: **mix** of neoplastic ganglion and glial cells<br>20-50% have **BRAF** gene mutation (IDH wild) |
| **Dysembryoblastic neuroepithelial tumor DNT** grade (1) | | | Superficial Temporal lobe | Rare |

# EMRYONAL (PRIMITIVE) NEOPLASMS:

- Primitive (undifferentiated) small round cell tumor
- Origin: **neuro-ectoderm** (resembling progenitor cells of the developing CNS)
- Most common type: **Medulloblastoma** 20% of pediatric brain tumors !!!
- Radiosensitive



| Type | Locations | Grades | Survival | Microscopic |
|---|---|---|---|---|
| **Medulloblastoma**<br>(predominantly in **children**)<br>(20% of pediatric brain tumors) | - Mainly in the **Cerebellum**<br>(children): it the midline (vermis)<br>(adults): lateral parts<br>- may extend to the cerebellar surface<br>- can involve leptomeninges<br>- Disseminate through the **subarachnoid** space:<br>1) CSF spread<br>2) Drop metastasis along the spinal cord | - no grade (1),(2),(3)<br>- grade (4):<br>(A!!!,1)<br>Often well circumscribed (small and round) | - **untreated:** dismal prognosis قاتل<br><br>**- with** total escision + chemo + irradiation:<br>5 yrs up to 75% | • Very Cellular<br>• Sheets of small primitive cells ("small blue"), with↓cytoplasm and ↑ hyperchromatic elongated or crescent shaped nuclei<br>• Mitoses are abundant.<br>• Often can show:<br>- Neuronal diff. and express markers such as synaptophysin<br>- Glial diff. (less common) and express glial markers (GFAP)<br>• **Homer Wright Rosettes:** (pseudo)<br>- Represents focal neuronal differentiation<br>- Primitive tumor cells surrounding **central neuropil** (delicate pink material formed by **neuronal processes**).<br>- Not specific: seen also in neuroblastoma and pineablastoma |

# MENINGIOMAS:

- Meningothelial cells of the **Arachnoid matter** – attached to the dura

| | |
|---|---|
| **Genotype** | **Most common**: Loss of chromosome 22, especially **22q** (long arm) (region of **NF2** gene)<br>- 50–60% of SPORADIC meningiomas have **NF2 mutations**<br>- May be **multiple** in **NF2** (with 8th nerve schwannoma or glial tumors)<br>Grade (3) may have others |
| **Location** | - Any external surface of brain - Spinal cord -Within **ventricular system** (from **stromal arachnoid cells** in choroid plexus) |
| **Clinical** | - Adults (more common in **women**)<br>- **Symptoms:** Headache, seizures, weakness (location-dependent)<br>- May grow faster during **pregnancy** 🤰 (express **progesterone receptors**), regress after delivery |
| **Grades** | Grade 1**:** A<br>• (well-defined), dura-based masses, compress the brain but do not typically invade it +/- overlying bone extension.<br>• **Epithelioid cells** arranged in whorly (syncytial) pattern لافين حولين بعض +/- **psammoma bodies** (calcification)<br>Many histologic **subtypes** with no prognostic difference (e.g., meningothelial (most common, fuzzy cell mem), metaplastic, microcystic, fibrous, transitional, angiomatous, , lymphoplasmacyte rich, , secretory and psammomatou)<br><br>Grade 2 (Atypical): B<br>• Recurrence, aggressive local growth<br>• Requires radiation/surgery<br>• Criteria: 4–19 **mitosis**/10 HPF (1) OR 3/5 of the following: ↑ cellularity, small cells with ↑N/C ratio, prominent nucleoli, patternless growth, **necrosis** (4); OR Clear cell/chordoid **subtype**; OR unequivocal brain invasion<br><br>Grade 3 (Anaplastic): B<br>• Rare, highly aggressive<br>• Resemble high-grade **sarcoma**, **carcinoma**, or **melanoma**<br>• Criteria: >20 **mitosis**/10 HPF (1), or frank (large) anaplasia, or **TERT** mutation, or **CDKN2 (A/B)** deletion, or papillary/rhabdoid **subtypes** |

| | |
|---|---|
| **Prognosis** | Depend on:<br>Tumor size, Location, Surgical accessibility, and Histologic grade: Grade 2 and 3 = **higher risk of recurrence** and **poorer outcomes** |
| **Macroscopic** | - **Rubbery**, rounded, or **bosselated** dural masses<br>- Usually compress but do not invade brain<br>- **Mostly separable**, but some are infiltrative (↑ recurrence risk)<br>- May extend into **overlying bone** in (Grade 1) |

## PRIMARY CNS LYPHOMA:

1- The most common CNS neoplasm **in immunosuppressed individuals**
 - In non-immunosuppressed populations, the frequency increases after **60 years of age.**
2- **Aggressive** disease, poor response to Chemotherapy (especially if compared with comparable histology that occur at non-CNS site)
3- The most common type: **Diffuse large B-cell** lymphomas!!
4- Primary brain lymphoma: **Multifocal**
5- Involvement outside of the CNS (in lymph nodes or BM) is a rare and late complication !!
6- Relatively **well defined** as compared with glial neoplasms but not as discrete as metastases.

## METASTATIC TUMORS:

- **>50%** of intracranial tumors
- mostly **carcinomas** ☹ "Malignant"
- The most common **primary sites:** 1) lung, 2) breast, 3) skin (melanoma), 4) kidney, and 5) colon (80% of cases).
- Sharply demarcated masses, often at the **grey-white matter junction**, and elicit local edema and **reactive gliosis**
- The boundary between tumor and brain parenchyma is **sharp** at the microscopic level with surrounding reactive gliosis

يعني الحدود تبعتها واضحة كتيير ومفصولة عن خلايا الدماغ وحوليها gliosis

# FAMILIAL TUMOR SYNDROME:

• Inherited syndromes caused by mutations in **tumor suppressor genes** and associated with increased risk of neoplasms

• Tumors of the nervous system make a **prominent** aspect of some of these syndromes,

including:

✓ Tuberous Sclerosis

✓ Von Hippel-Lindau Disease