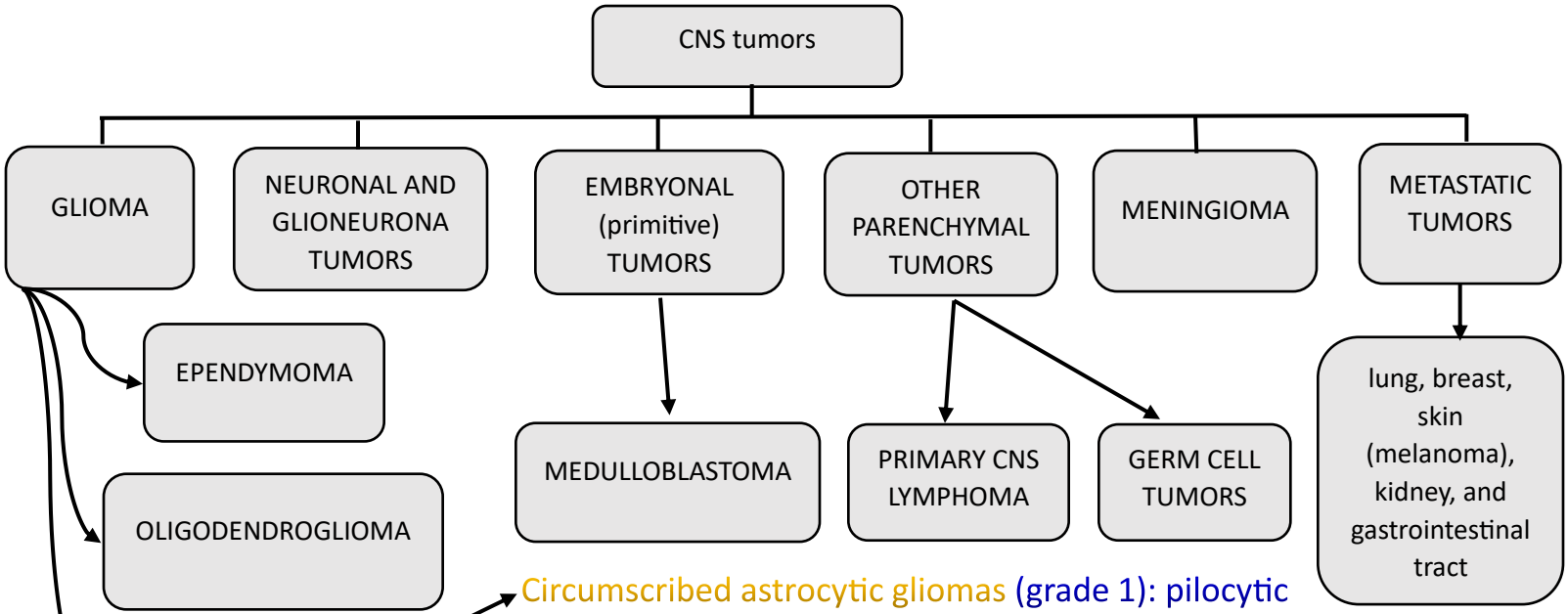
CENTRAL NERVOUS SYSTEM TUMORS

- Tumors that involve the brain or the spinal cord.
- Can be primary(most commonly) or metastatic(rare) in origin → we don't use TNM staging system because metastasis is rare.
- No precancerous, premalignant or in situ stage.

Tumors → Infiltrative: do not form a discrete mass/ surgical excision will be difficult/ high probability of recurrence.
↓
Circumscribed: amenable for complete surgical excision/ less neurologic deficit.



Circumscribed astrocytic gliomas (grade 1): pilocytic astrocytoma(PA), subependymal giant cell astrocytoma (SEGA), pleomorphic xanthoastrocytoma (PXA)

Diffuse (infiltrating) astrocytoma (grade 2-4):

Presentation:
seizures, headaches, and 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.

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

- The prognosis gets poorer as the grade increases:

▶ NO grade 1 diffuse astrocytoma.
▶ Grade 2 (diffuse astrocytoma), mean survival is > 5 years.
▶ Grade 3 (anaplastic astrocytoma), mean survival is 2-3 years
▶ Grade 4 (glioblastoma), mean survival is 15 months.

- The histologic grading of CNS tumors depends on:

1. Cellularity and atypia.
2. Mitosis.
3. Microvascular proliferation.
4. Necrosis.

	Grade 1 lesions (benign)	Grade 2 lesions (low grade)	Grade 3 lesions (anaplastic)	Grade 4 lesions (high grade)
Characteristic	• Circumscribed. • low proliferative activity. • Low cellularity. • Can be cured after surgical resection alone.	• Infiltrative & recur. • low proliferative activity. • Higher cellularity. • Tend to progress to higher grades of malignancy.	• clear histological evidence of malignancy (nuclear atypia and Higher proliferative activity (mitosis)). • Patients receive radiation and/or chemotherapy.	• cytologically malignant, mitotically active, rapid proliferation, necrosis-prone neoplasms. • associated with rapid pre- and postoperative disease evolution and fatal outcome. • Widespread infiltration of surrounding tissue and a risk of craniospinal dissemination (CSF spread).
Examples	pilocytic astrocytoma (PA), subependymal giant cell astrocytoma (SEGA), choroid plexus papilloma, myxopapillary ependymoma	Diffuse astrocytoma, oligodendroglioma, neurocytoma, some types of ependymoma	Anaplastic astrocytoma, anaplastic oligodendroglioma	Glioblastoma, medulloblastoma, pineoblastoma, and most embryonal neoplasms

• 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/ location (most important factor) of the neoplasm can influence outcome independent of histologic type or grade.

• If the tumor present in :

- Posterior fossa ⟶ pilocytic astrocytoma or medulloblastoma.
- Intraventricular location ⟶ central neurocytoma or ependymoma.

Pediatric CNS tumors		
	Kids	Adults
Location	2/3 infratentorial (posterior fossa)	2/3 supratentorial (cerebral hemispheres above tentorium)
histologic type	medulloblastoma, pilocytic astrocytoma, ependymoma	glioblastoma, metastases, meningiomas, diffuse gliomas constitute most gliomas in adults(including diffuse astrocytomas and oligodendrogliomas).

Genetic alterations in gliomas

1) Mutations in isocitrate dehydrogenase (IDH) genes:

- observed as an early event in gliomagenesis.
- Seen in astrocytomas and oligodendrogliomas.
- There is a gain of function not loss of function.
- The most frequent IDH1 mutation: R132H mutation.
- The most frequent IDH2 mutation: R172K mutation.

► 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.

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

- Diagnostic of oligodendrogliomas in the presence of IDH mutation(without them there is no diagnosis for oligodendroglioma).
- The vast majority of IDH mutant and 1p/19q codeleted oligodendroglioma ➔carry TERT promotor hotspot mutations:
  telomerase stabilization, cellular immortalization and proliferation

3) ATRX and P53 loss of function mutation:

- Both occur in IDH mutant astrocytomas.
- P53 mutation: enable tumor cell survival
- ATRX mutation → induces abnormal telomeres maintenance mechanism known as "alternative lengthening of telomeres"
  Mutual exclusive with the activating promoter mutation of the TERT gene (1p/19q codeletion) >>> Any tumor have ATRX mutation , it is impossible to have a TERT mutation so no 1p/19q codeletion
  Associated with genomic instability ➔ induces P53 dependent cell death ➔ mutation in P53 helps these cells to survive.

4) Mutations that lead to overexpression of the EGF receptor, receptor tyrosine kinases or disable p53 or RB.