Tumors of the Central Nervous System

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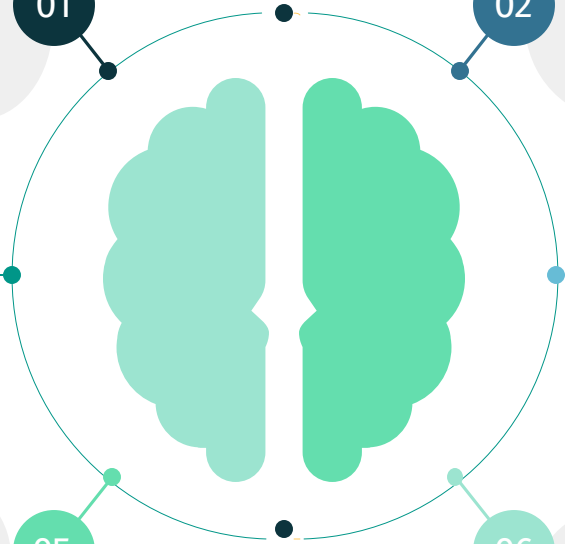
Central nervous system tumors

According to the 2016 MoH Cancer Incidence Report CNS tumors are the 10th most common cancer in jordan

But the 2nd most common cancer among Jordaian childen (20% of all pediatric tumors)

CNS tumors include intracranial and intraspinal tumors.

Unique features of the Nervous system tumors



01

Metastasis

More common than primary brain tumor, which rarely metastasize

02

Anatomical location

Influence outcome *independent* of histologic classification due to local effects.

03

Precursors

No morphologically evident premalignant or in situ stages like carcinomas.

04

Pattern

Tumors with low grade histologic features can infiltrate widly → serious clinical deficits

05

In Children

~70% of CNS tumors arise in posterior fossa

06

In adults

~70% of CNS tumors arise above the tentorium.

WHO Classification of Tumors of the CNS

01

WHO Classification of Tumors series are authoritative reference books for the histological & molecular classification of tumors.

02

Classification of tumors of the CNS has been based on the concept of “histogenesis” & **Grading** on the basis of histologic criteria to predict tumors behavior.

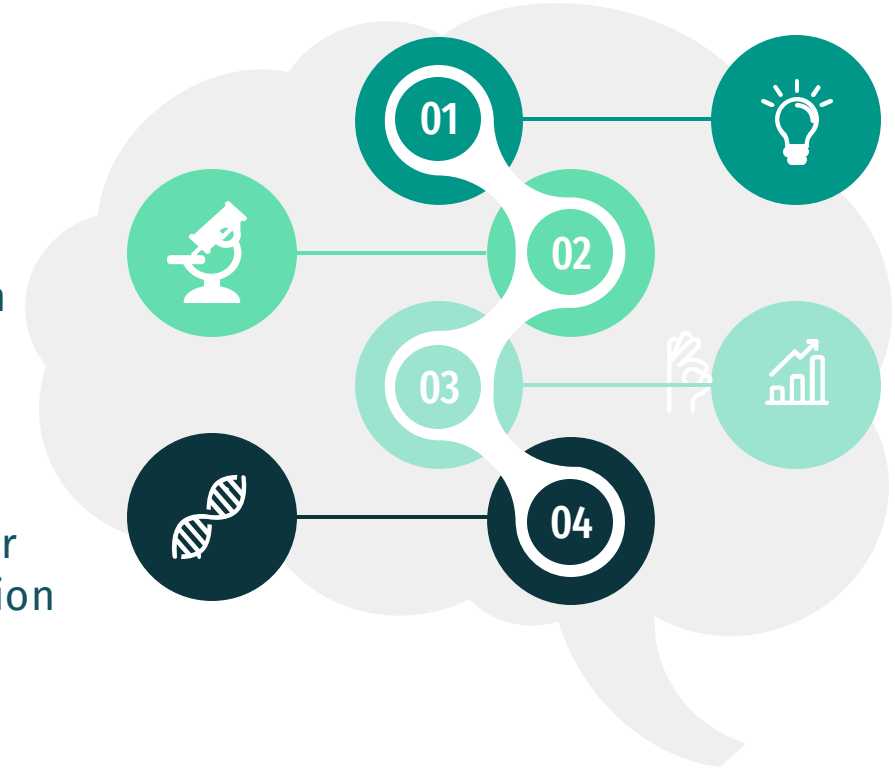
03

2000 & 2007 classifications considered histological features and genetic changes that underlie the tumorigenesis. (Genetics were **supplementary** information)

04

The 2016 CNS WHO presents major restructuring of the diffuse gliomas, medulloblastomas & other embryonal tumors, defining tumors by both histology & molecular features

2016 WHO Classification of Tumors of the CNS



Integrated diagnosis (incorporating all tissue-based information)

Histologic classification

WHO grade

Molecular Information

Main histologic category (cell of origin)

01 **Gliomas**: long been classified as astrocytomas, oligodendrogliomas, and ependymomas

02 **Neuronal tumors**: composed of cells with neuronal characteristics

03 **Embryonal (Primitive) neoplasms:** have “small round cell” appearance reminiscent of normal progenitor cells in the developing CNS.

04 **Others**: Lymphoma, meningioma, germ cell tumors, metastasis

Gliomas

01

The most common primary tumor of the brain

02

They arise from a progenitor cell(not mature) that differentiates down one of the cellular lineages.

03

Many subtypes typically occur in certain anatomic regions, with characteristic age distribution & clinical course.

Gliomas

- Highlights of WHO 2021 classification is the incorporation of molecular features, specifically IDH gene mutations and deletion on chromosomes segments 1p/19q
- Simplified classification of adult type diffuse gliomas into 3 groups:

1. Astrocytoma, IDH mutant, WHO grade 2 - 4
2. Glioblastoma, IDH wildtype, WHO grade 4
3. Oligodendroglioma, IDH mutant and 1p / 19q co-deleted, WHO grade 2 - 3

#Localized astrocytomas; **of which the most common are <u>the pilocytic astrocytomas.</u>**

Isocitrate Dehydrogenase Mutations/IDH1 and IDH2

2007

TUMOURS OF NEUROEPITHELIAL TISSUE

Astrocytic tumours	
Pilocytic astrocytoma	9421/1[1]
Pilomyxoid astrocytoma	*9425/3**
Subependymal giant cell astrocytoma	9384/1
Pleomorphic xanthoastrocytoma	9424/3
Diffuse astrocytoma	9400/3
Fibrillary astrocytoma	9420/3
Gemistocytic astrocytoma	9411/3
Protoplasmic astrocytoma	9410/3
Anaplastic astrocytoma	9401/3
Glioblastoma	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Gliomatosis cerebri	9381/3
Oligodendroglial tumours	
Oligodendroglioma	9450/3
Anaplastic oligodendroglioma	9451/3
Oligoastrocytic tumours	
Oligoastrocytoma	9382/3
Anaplastic oligoastrocytoma	9382/3

2016

Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	9400/3
Gemistocytic astrocytoma, IDH-mutant	9411/3
Diffuse astrocytoma, IDH-wildtype	*9400/3*
Diffuse astrocytoma, NOS	9400/3
Anaplastic astrocytoma, IDH-mutant	9401/3
Anaplastic astrocytoma, IDH-wildtype	*9401/3*
Anaplastic astrocytoma, NOS	9401/3
Glioblastoma, IDH-wildtype	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Epithelioid glioblastoma	*9440/3*
Glioblastoma, IDH-mutant	9445/3*
Glioblastoma, NOS	9440/3
Diffuse midline glioma, H3 K27M–mutant	9385/3*
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9450/3
Oligodendroglioma, NOS	9450/3
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9451/3
Anaplastic oligodendroglioma, NOS	*9451/3*

Isocitrate Dehydrogenase Mutations/IDH1 and IDH2

01

Where?

Astrocytoma, glioblastoma and oligodendrogliomas

02

Function

lead to increased production of 2-hydroxyglutarate→ interferes with the activity of several enzymes that regulate gene expression

03

Importance

In diagnosis & prognosis (significantly better prognosis than tumor with IDH-wild type)

04

Testing

Immunohistochemistry for IDH1
DNA sequencing for IDH1 and IDH2

Astrocytoma, IDH mutant, WHO grade 2 - 4

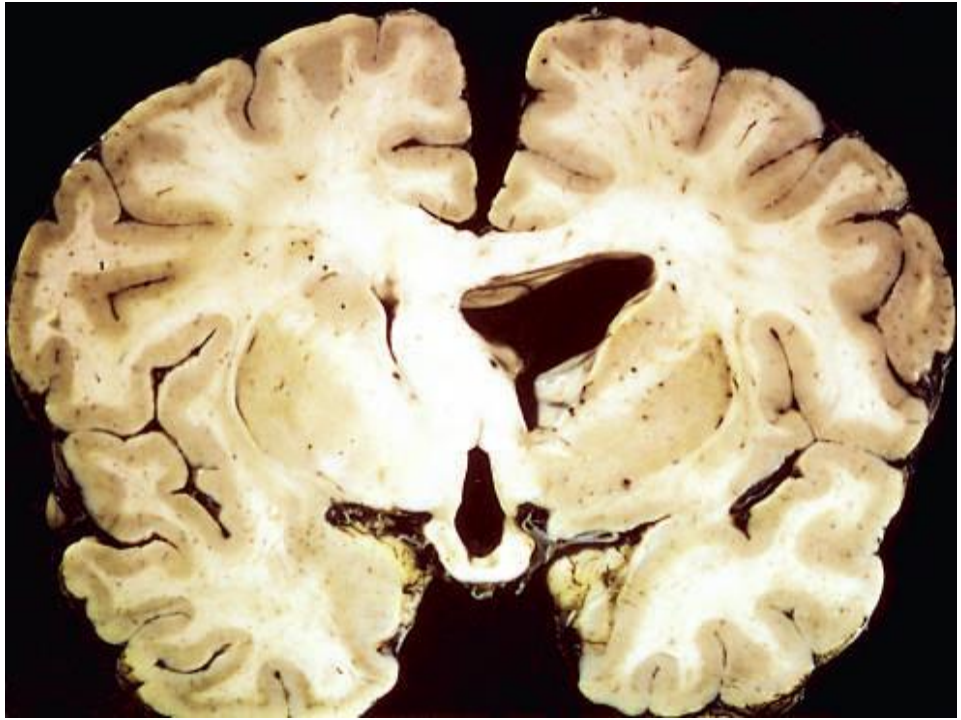
- Arise from astrocytes
- Most frequent in 30s-50s.
- Usually found in the cerebral hemispheres.
- Signs & symptoms: seizures, headaches, & focal neurologic deficits related to the anatomic site of involvement.

Astrocytoma, IDH mutant, WHO grade 2 - 4

- **On the basis of histologic and molecular features, they are stratified into three groups (WHO grade).**
- No WHO grade 1 for infiltrating astrocytomas.
- These grade correlates well with the clinical course & outcome (prognosis).
- Pathogenesis: - As the name indicate, driver mutations in isocitrate dehydrogenase (IDH) gene 1 or, less frequently IDH2.
  - Inactivating mutation in p53 and ATRX genes

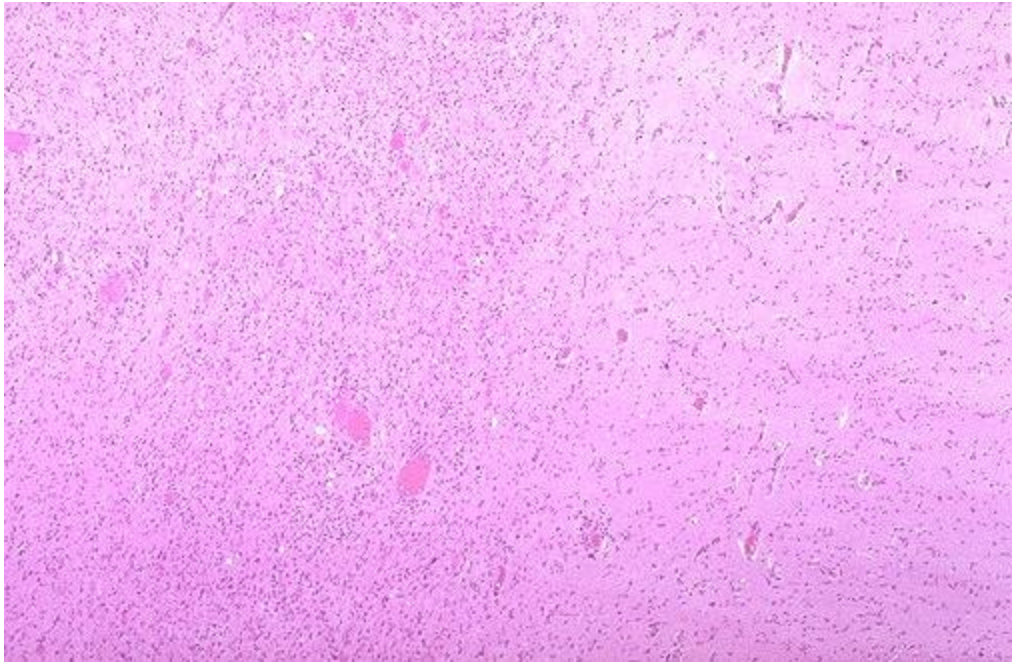
WHO grade II and III

- Poorly defined, gray, infiltrative (beyond grossly evident margins) tumors that expand & distort the invaded brain **without** forming a discrete mass.

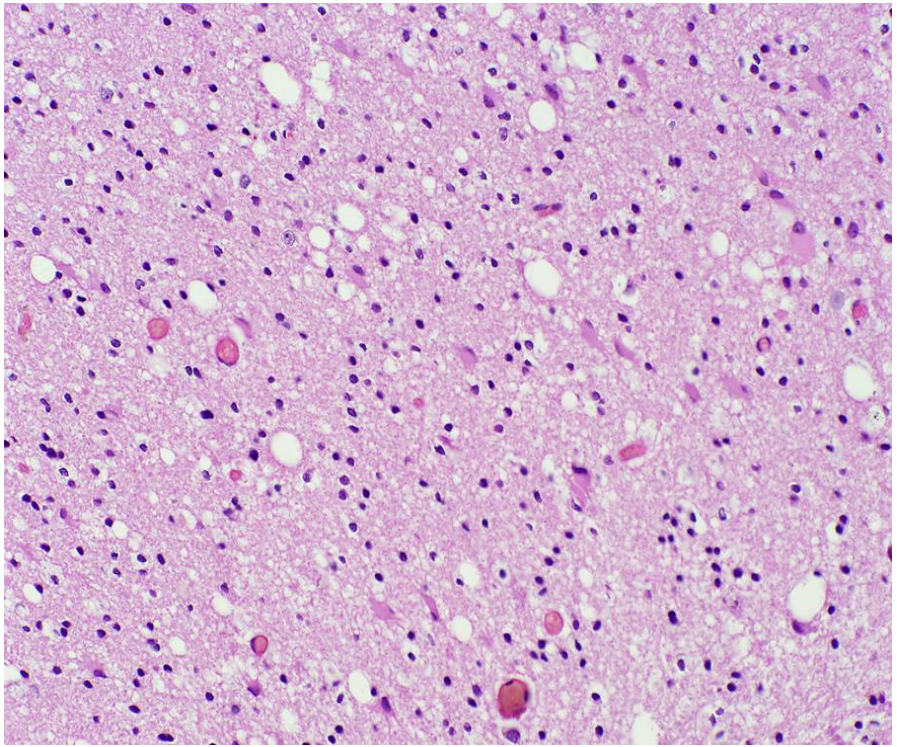


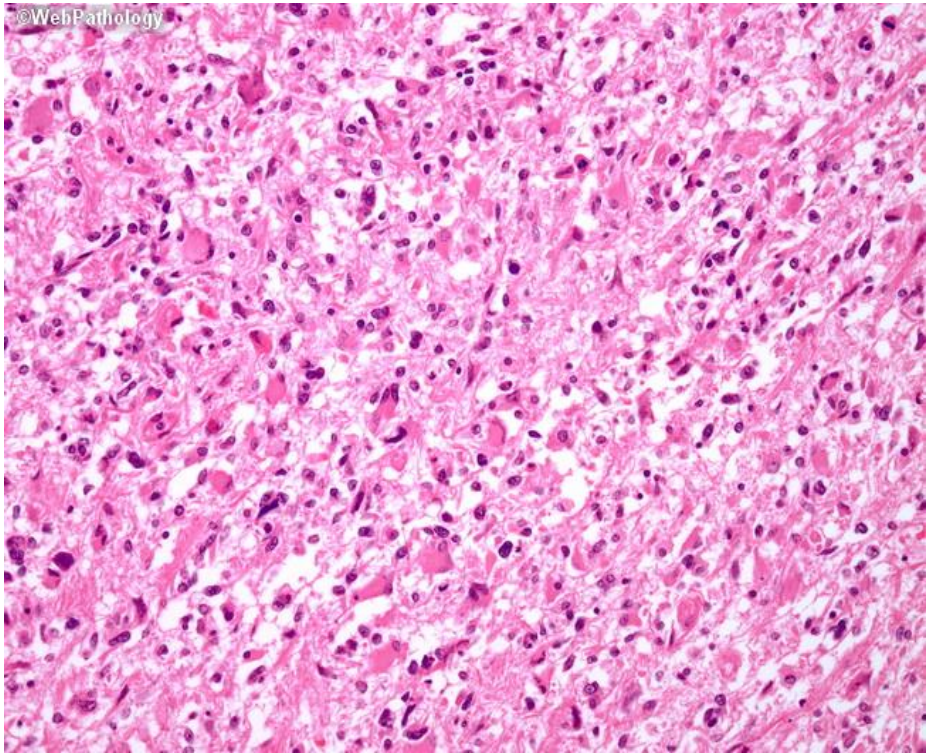
astrocytoma (WHO grade 2) - microscopic

- low-grade (WHO grade II) astrocytomas are characterized by a mild to moderate increase in the number of glial cell nuclei, some what variable nuclear pleomorphism.
- Notice how the margin is not distinct between the tumor & the normal adjacent brain at the right



astrocytoma WHO 2 vs WHO 3 – Microscopic: grade 3 shows more densely cellular & have greater nuclear pleomorphism; more mitotic figures.





IDH-mutant astrocytoma - Clinical

- can be static for several years.
- The mean survival is more than 5 years
- Clinical deterioration invariably occurs and is usually due to the emergence of a more rapidly growing tumor of higher histologic grade.
- Median overall survival
    - > 10 years, grade 2
    - - 5-10 years, grade 3
    - 3 years, grade 4

Glioblastoma *IDH*-wild-type (WHO grade 4)

- The most common malignant glioma, 50% of adult gliomas.
- They arise originally grade 4 (previously: **primary** glioblastoma).
- Previously called glioblastoma multiforme (GBM)
- Very poor prognosis.

Glioblastoma *IDH*-wild-type - Pathogenesis

- Harbor multiple genetic alterations →acquisition of cancer hallmarks

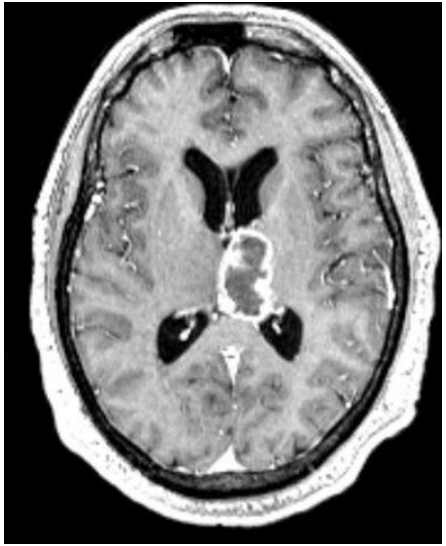
a) Evasion of senescence (telomerase mutations or mutations that lengthen of telomeres)
b) Escape normal growth controls (biallelic deletion of CDKN2A, which encodes the cyclin-dependent kinase inhibitor p16)
c) Activation of growth factor signaling pathways (EGFR or PDGFR gene amplification).
d) Resistance to apoptosis (TP53 mutation).

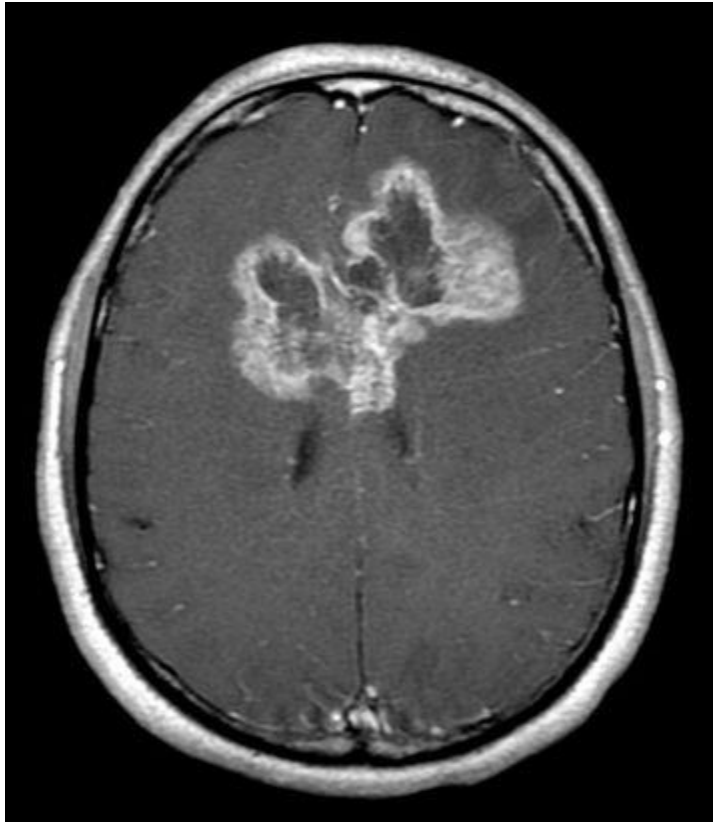
Glioblastoma *IDH*-wild-type - Clinical

- Affects older patients in their 6th to 8th decades of life.
- Sites: cerebral hemispheres (temporal, parietal, and frontal lobes; basal ganglia and thalamus).
- Develop rapidly, most patients presenting with seizures, neurocognitive impairments, nausea, vomiting, & occasionally severe pulsating headache.
- Butterfly glioma: Rapid infiltration of the corpus callosum with subsequent growth in the contralateral hemisphere → a bilateral symmetrical lesion
- Prognosis is very poor; even with treatment (resection, radiotherapy, and chemo-therapy), the median survival is only about 15 to 18 months

Glioblastoma (WHO grade IV) - MRI

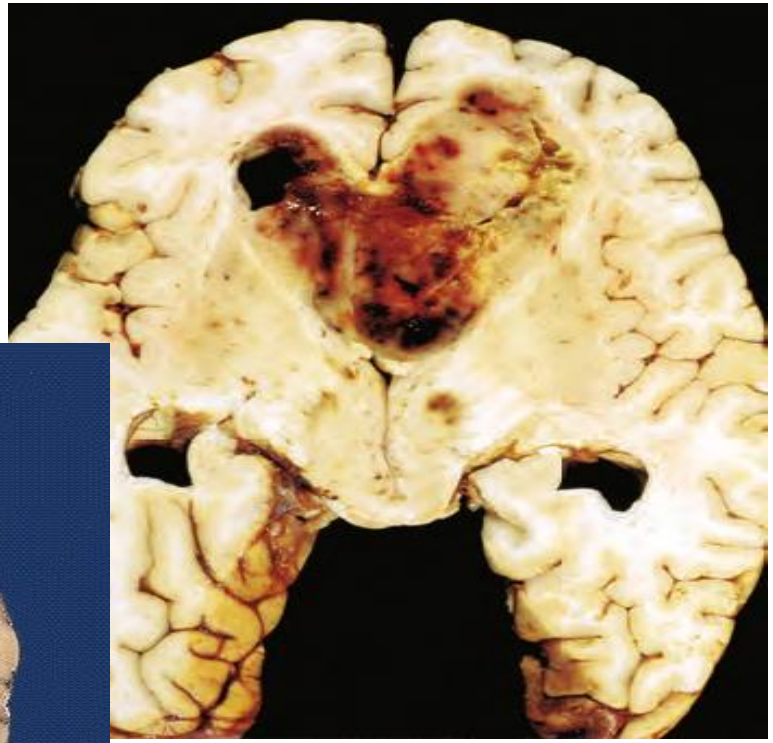
- Imaging studies most often reveal a ring-enhancing lesion, abnormal vessels that are “leaky,” + abnormally permeable blood-brain barrier (BBB) → contrast enhancement on imaging studies.

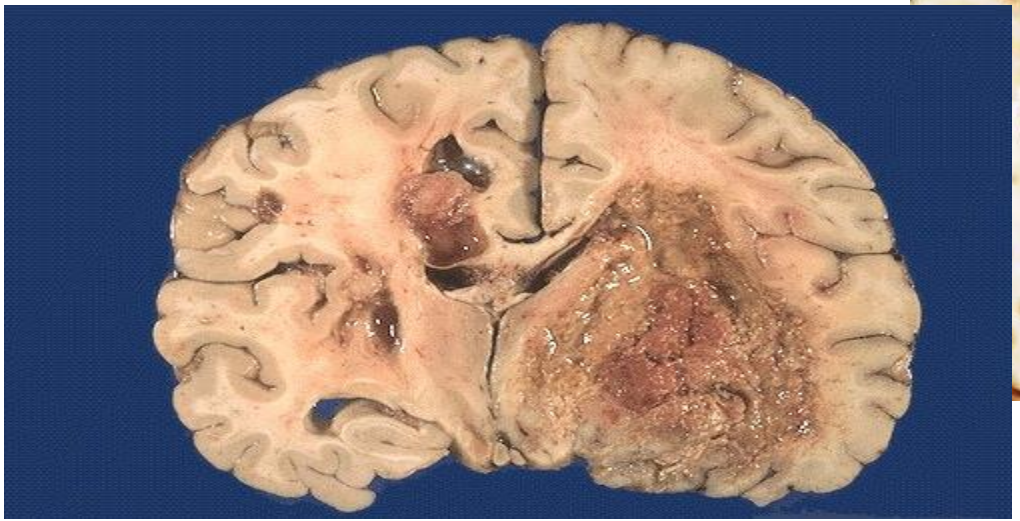




Glioblastoma (WHO grade 4) - Gross

- Characteristic variation from adjacent normal area.
- Soft & yellow (tissue necrosis), regions of cystic degeneration & hemorrhage.

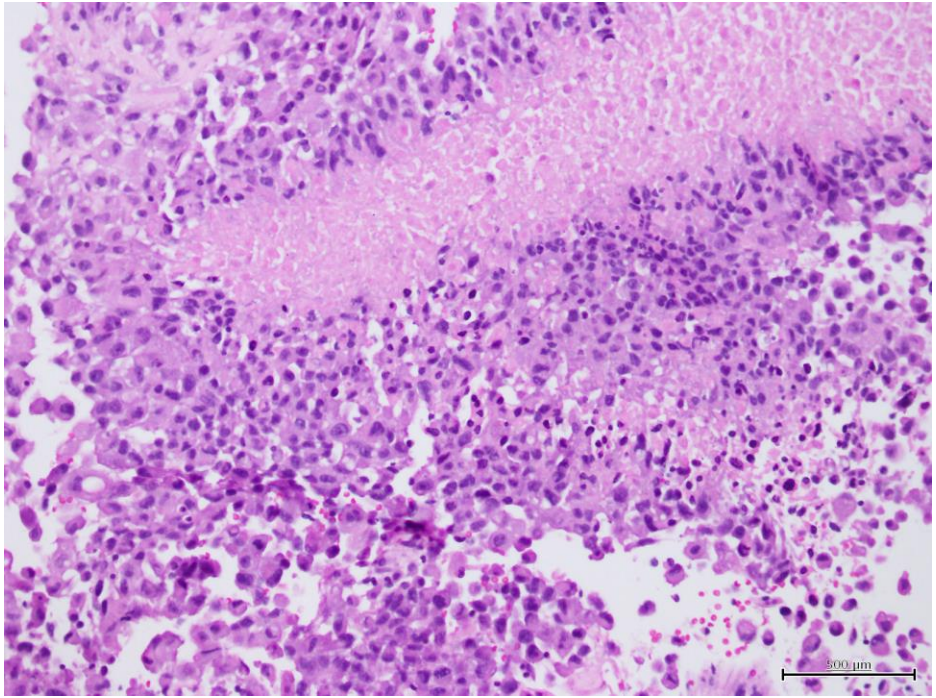




Glioblastoma (WHO grade 4) - Microscopic

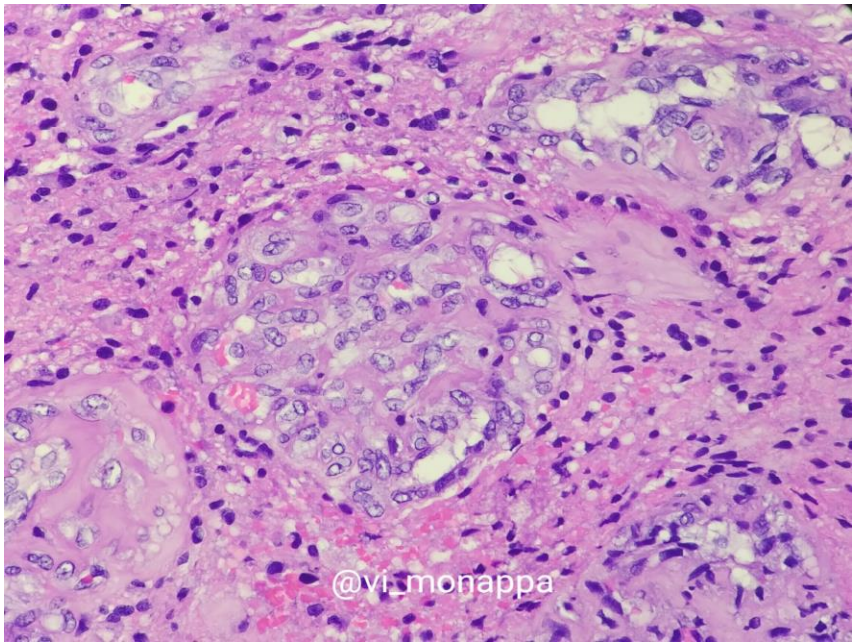
- Histologic appearance varies widely (hence: multiforme).
- Cellular features similar to that of astrocytoma – grade 4 , **as well as either**:

1. Necrosis (commonly present as wavy bands of necrosis with palisaded tumor cells along the border)
2. or Microvascular proliferation



Glioblastoma (WHO grade IV) - Microscopic

2. or Microvascular proliferation (forming tufts that bulge into the lumen → ball-like structures “glomeuloid” bodies)



Oligodendroglioma

Age

30s-40s
5% to 15% of gliomas

01

Location

In the cerebral hemispheres , mainly in **white matter** in frontal or temporal lobes.

02

Genetics

- IDH1/IDH2 mutations
- 1p and 19q co-deletions

03

Gross

Infiltrative tumors, form gelatinous, gray masses & may show **cysts, focal hemorrhage, & calcification.**

04

WHO garding (2 & 3)

grade 3 is a more aggressive, higher cellularity, nuclear anaplasia, more mitoses, & microvascular proliferation.

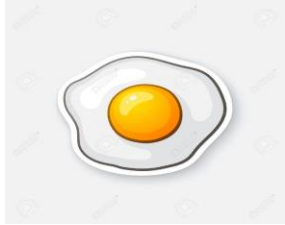
05

Prognosis

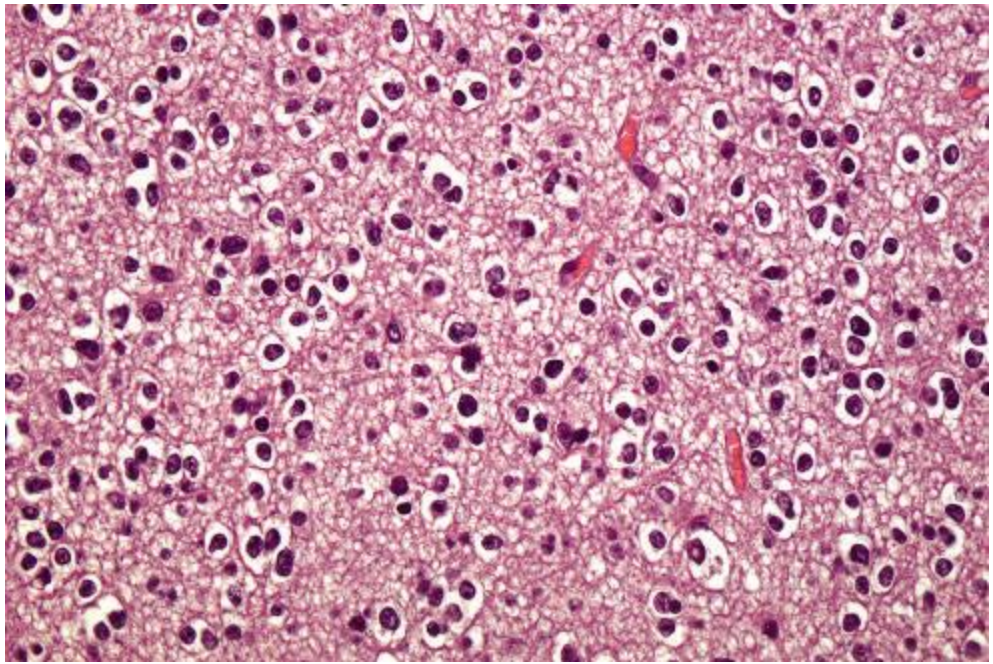
+ Best prognosis among diffuse gliomas.
+ surgery, chemo,& radio
average survival of 5 to 10 years

06

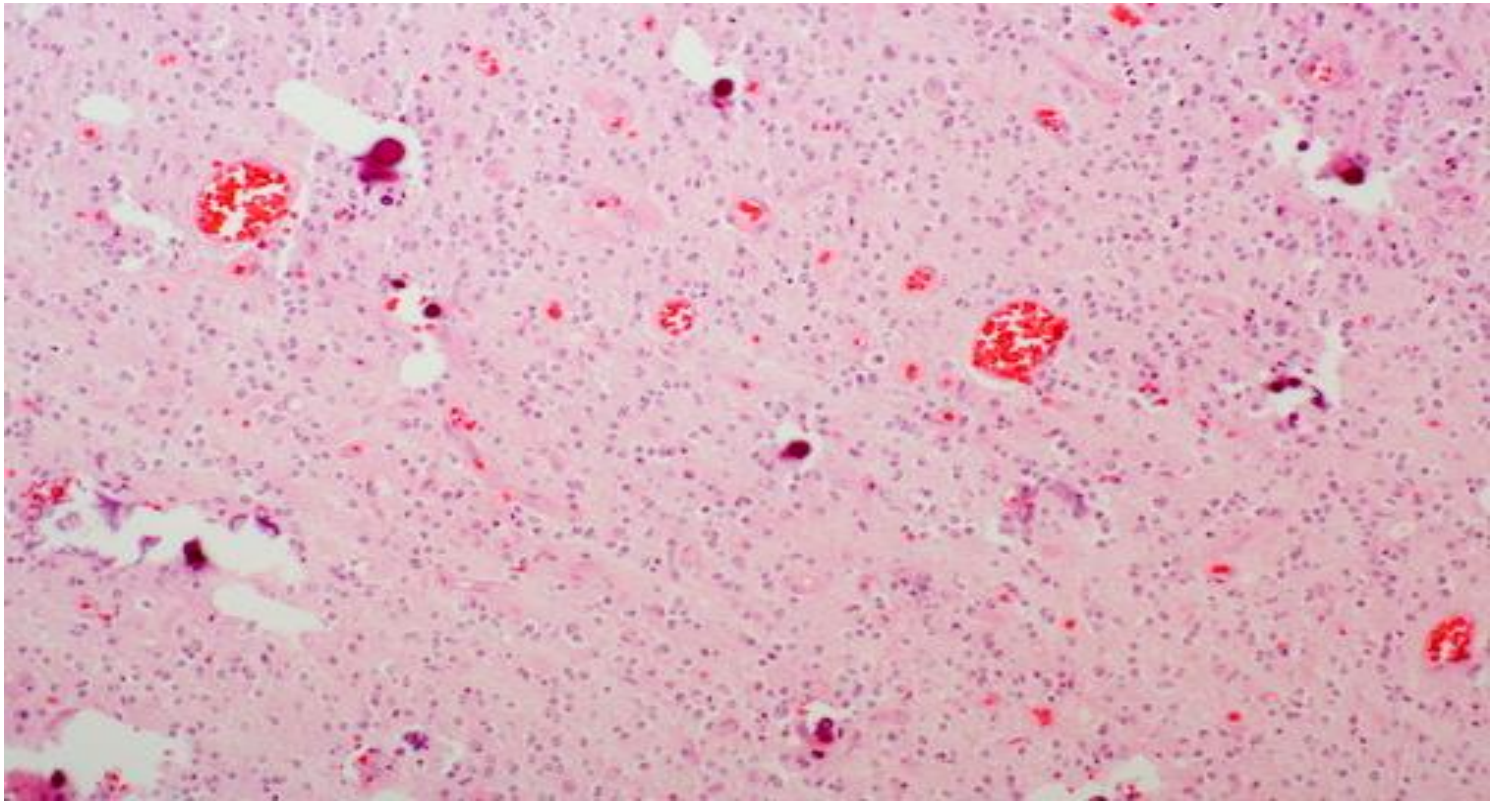
Oligodendroglioma - microscopic



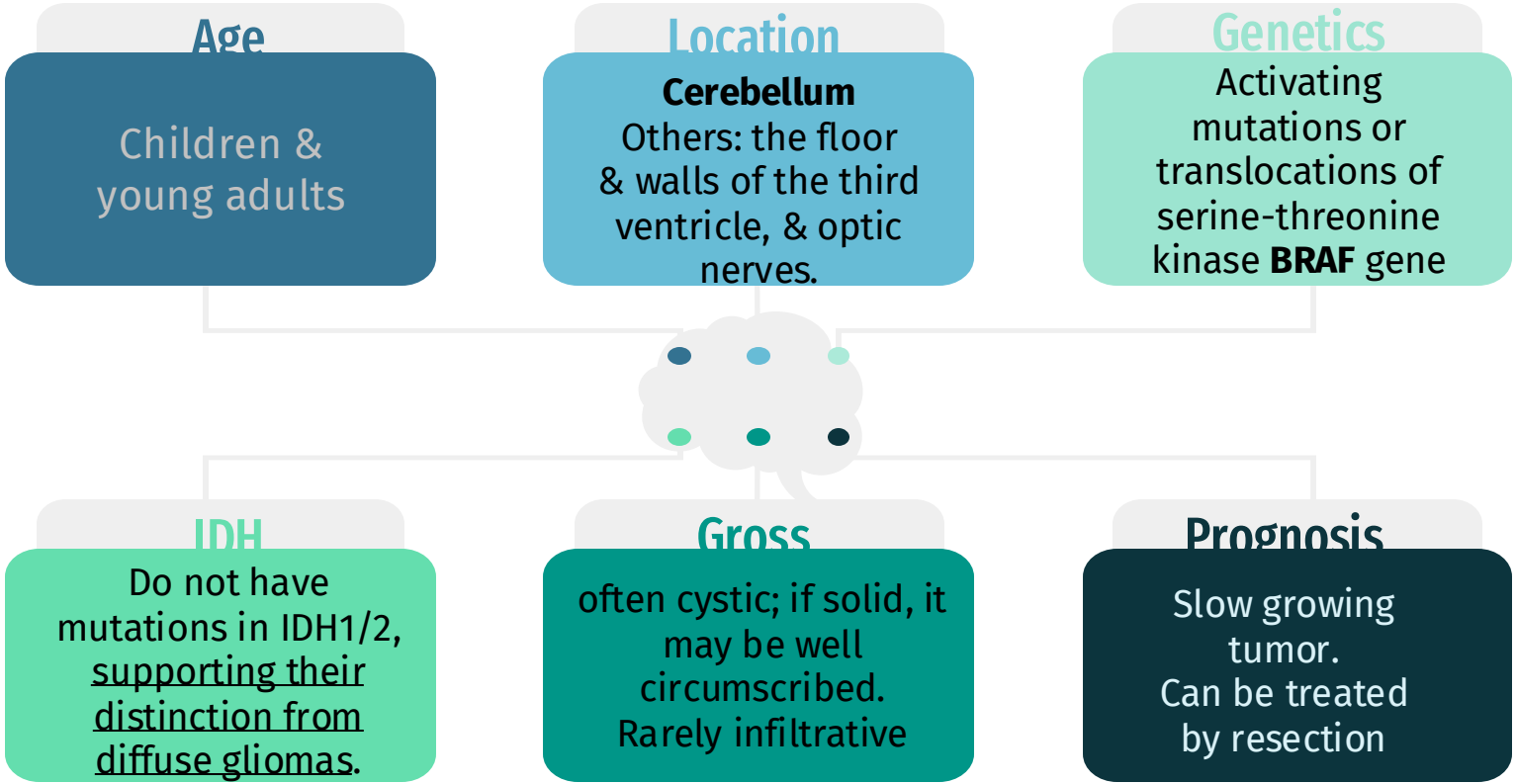
- Sheets of regular cells with spherical nuclei containing finely granular chromatin (similar to normal oligodendrocytes) surrounded by a clear halo of vacuolated cytoplasm “fried egg”
- Contains a delicate network of anastomosing capillaries.
- Calcification, in 90% of these tumors



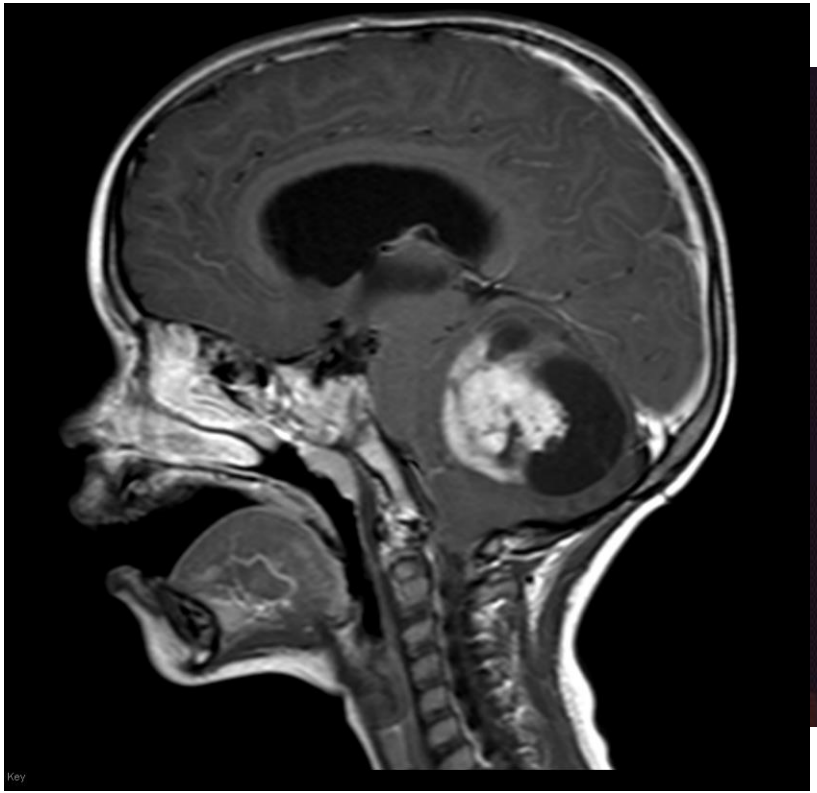
Oligodendroglioma - microscopic

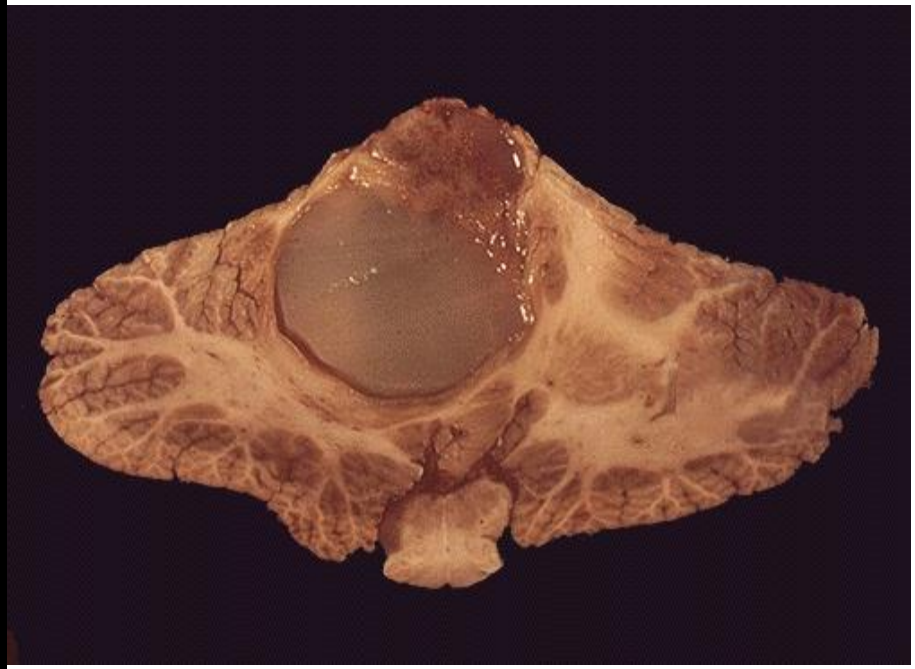


Localized astrocytoma- Pilocytic Astrocytoma (WHO grade I)



Pilocytic Astrocytoma (WHO grade I)

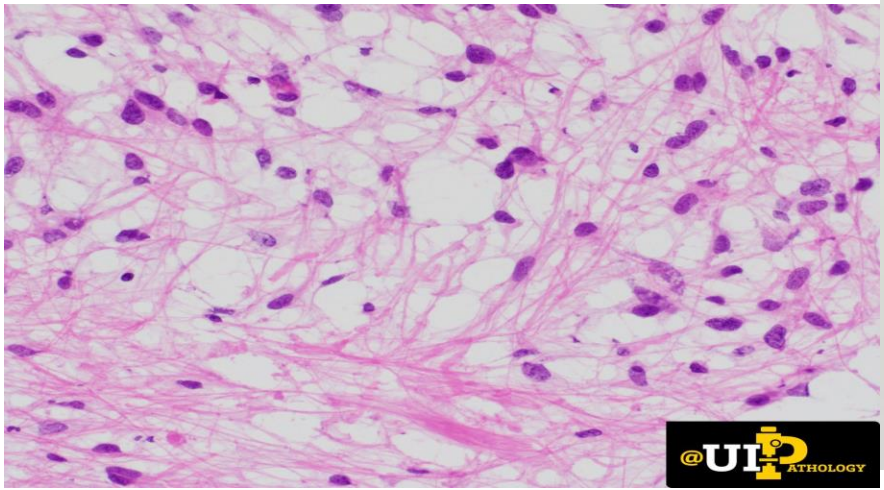


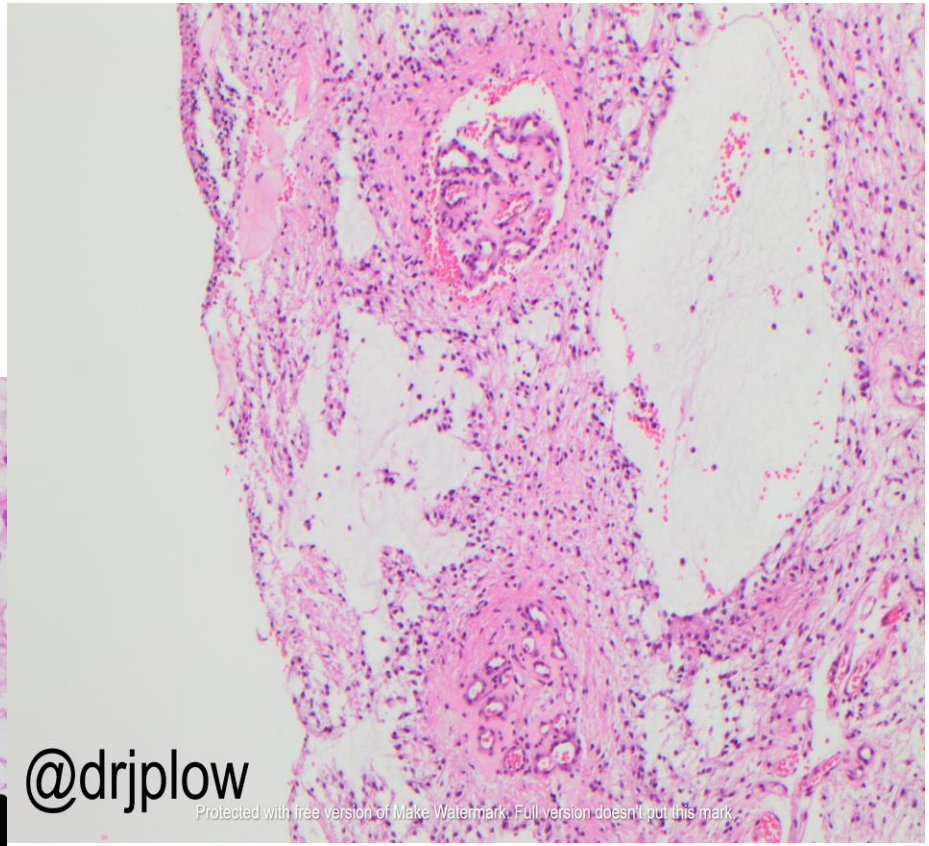


Pilocytic Astrocytoma (WHO grade 1) - microscopic

The tumor is composed of:

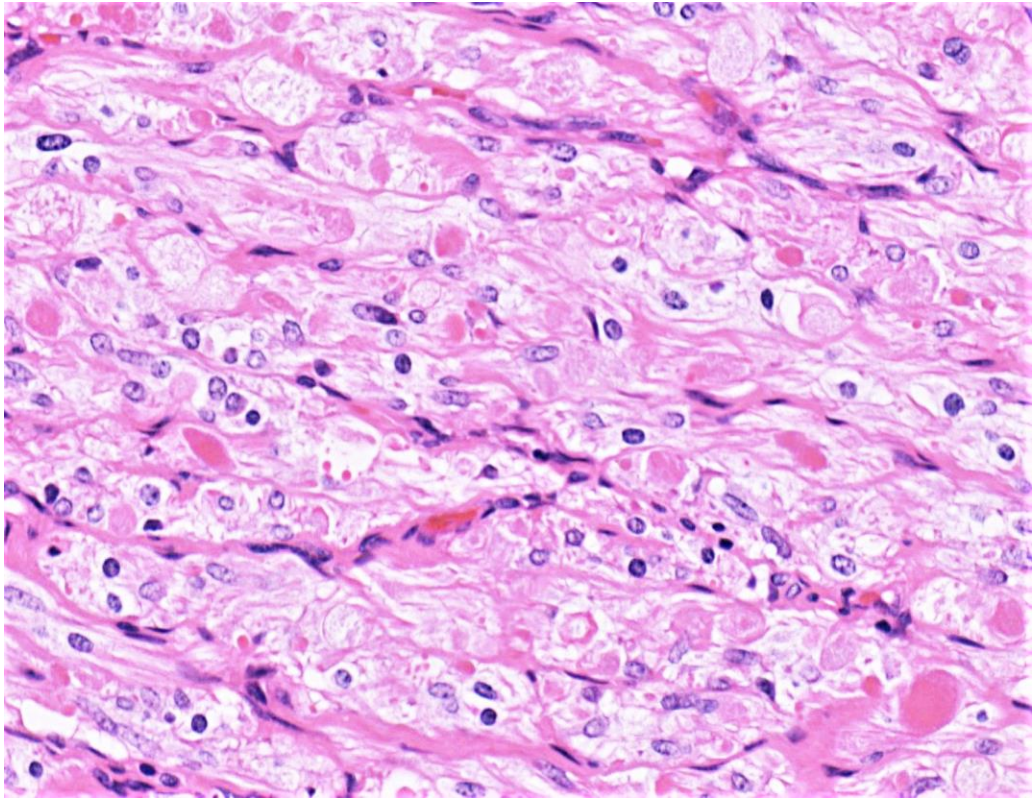
- Bipolar cells with long, thin “hair-like” (pilo) processes.
- Rosenthal fibers.
- Eosinophilic granular bodies.
- Microcysts often present.
- Necrosis & mitoses are rare.





Pilocytic Astrocytoma (WHO grade I) - microscopic

- Rosenthal fibers are thick, elongated, brightly eosinophilic, irregular structures that occur within astrocytic processes
- Rosenthal fibers are typically found in regions of longstanding gliosis and some brain tumors.



Ependymoma (WHO grade 2,3)

most often arise next to the ependymal lined→ ventricular system.

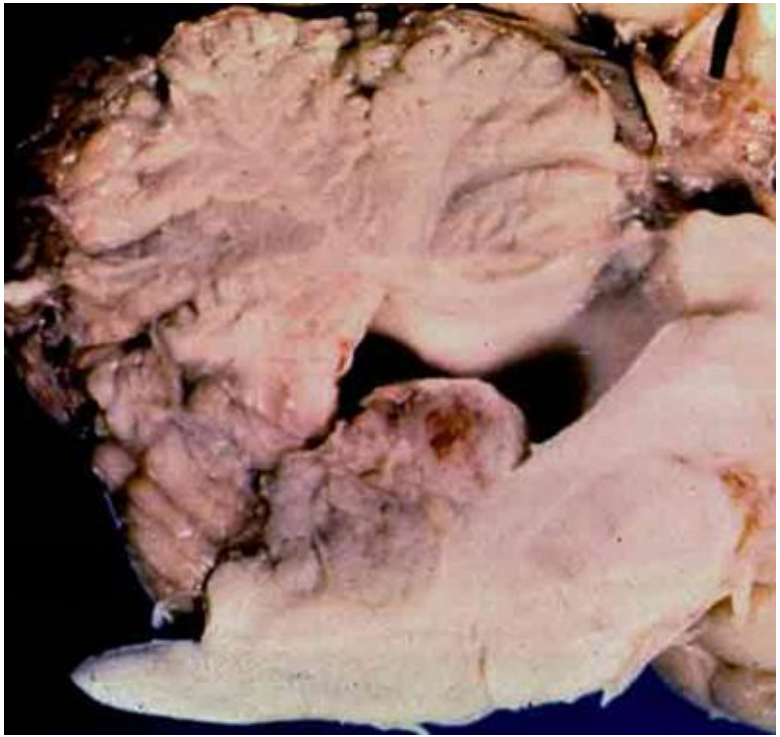
- first 2 decades of life, typically occur near the fourth ventricle.
- In adults, the spinal cord is their most common location

- 5% to 10% of the primary brain tumors in 1st two decades
- spinal cord site is particularly frequent in the setting of neurofibromatosis type 2

The clinical outcome for completely resected supratentorial and spinal ependymomas is better than for those in the posterior fossa.

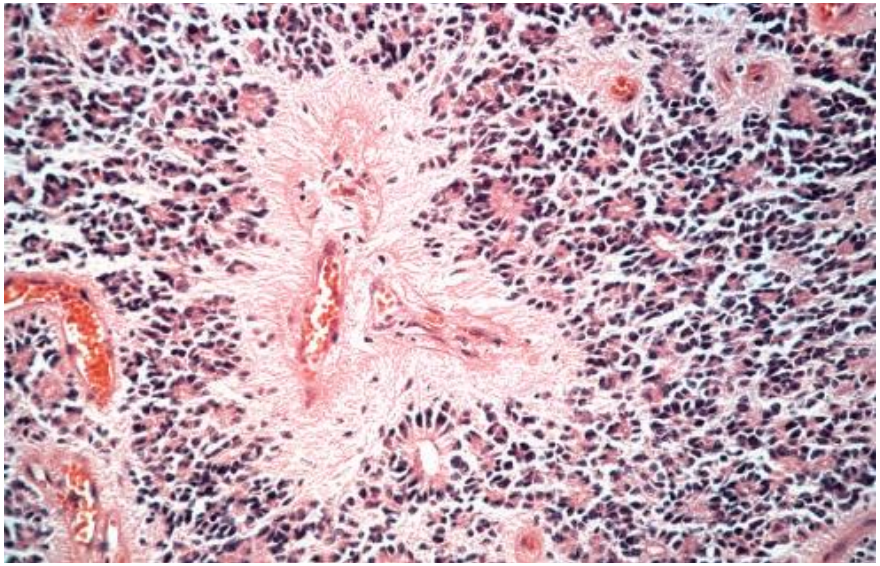
Ependymoma - Gross

- In the fourth ventricle, ependymomas typically are solid or papillary masses extending from the ventricular floor.



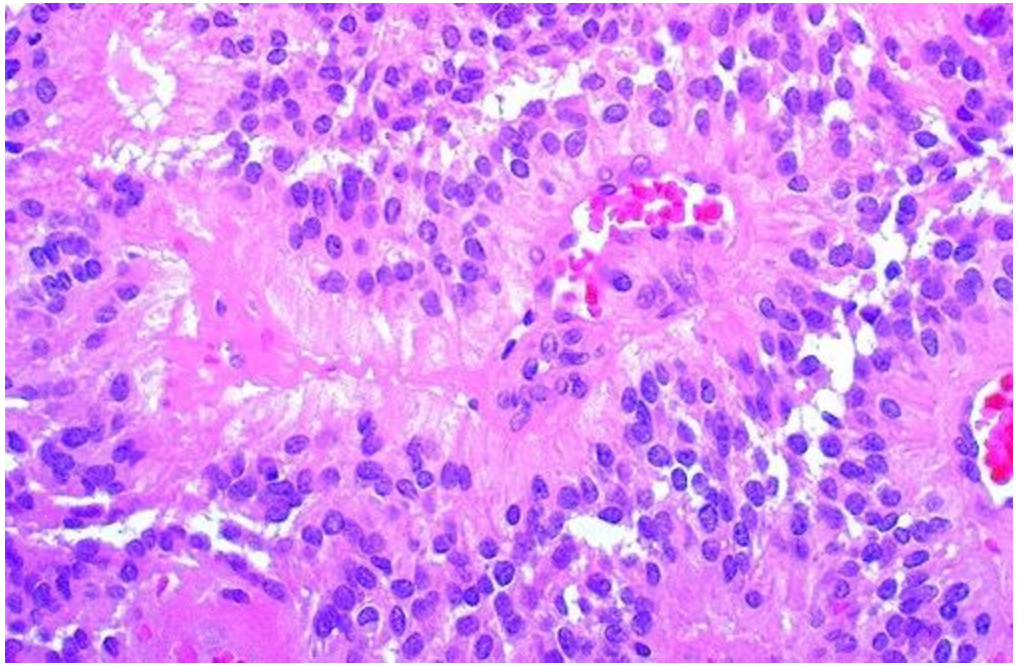
Ependymoma - microscopic

- Cells with round to oval nuclei & abundant granular chromatin.
- Dense fibrillary background.
- Cells may form round or elongated structures **(rosettes, canals) .**



Ependymoma - microscopic

- Or more frequently present are **perivascular pseudo-rosettes** in which tumor cells are arranged around vessels
- Anaplastic ependymomas (WHO grade 3) : cellularity, mitosis, & necrosis.



“Expect little from people.
Expect a lot from yourself.
That's the secret of happy
life.”

Q?..THANX!