CNS pathology
Third year medical students
lecture 9 CNS tumors/1

Dr Heyam Awad

FRCPath

2017

CNS TUMORS/ epidemiology

- Tumors in the CNS can arise in the brain or the spinal cord.
- Brain tumors : around 10- 17/ 100 000 population
- Spinal cord tumors : around 1-2 / 100 000

Key points:
Brain> Spinal cord
Primary (3/4)> Secondary (1/4)

- CNS tumors can be primary or secondary
- Secondary account for 1/4th to ½ of all CNS tumors
- CNS tumors account for 20% of childhood tumors.
- 70% of childhood tumors arise in the posterior fossa
- 70% of adulthood tumors arise within the cerebral hemispheres above the tentorium.

CNS tumors in Jordan according to 2013 cancer registry (latest published)

- CNS tumors are the 10th most common tumor among Jordanians
- Second most common among Jordanian children

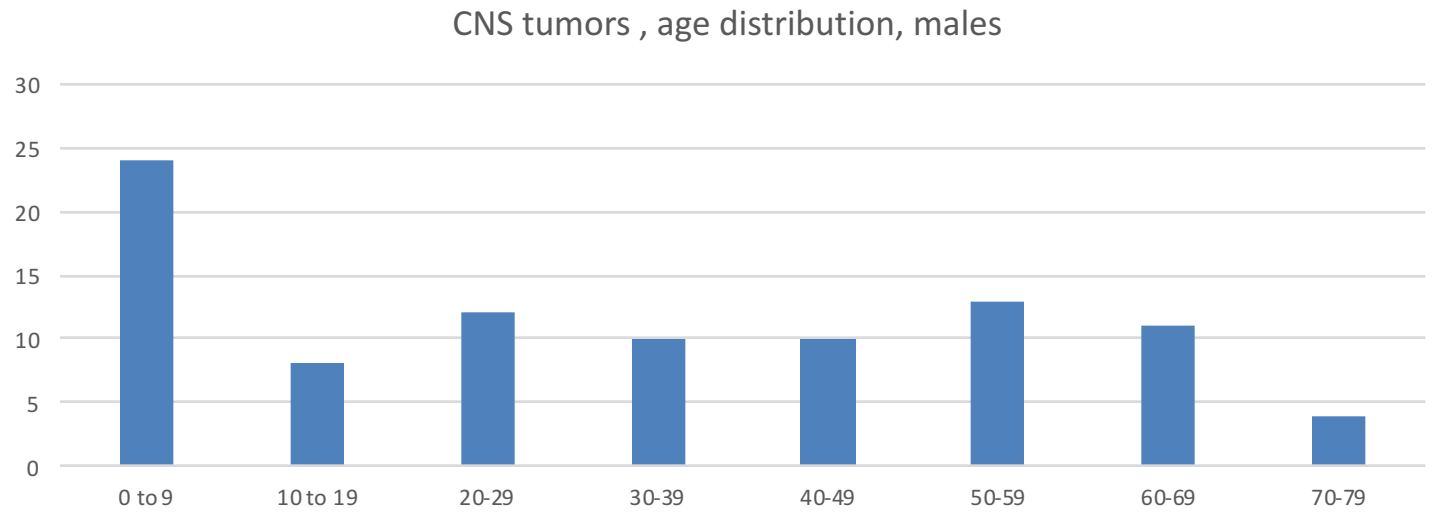
CNS tumors in Jordan/ 2013 stats according to Jordan Cancer registry

CNS tumors in 2013	Males Nubers in 2013	Males percentage of total cancers in 2013	Females No	Females %	Total No	Total %
	95	3.7%	58	2%	153	2.8%

Key points:
Children(Rank2) > Adults(rank10)
infratentorial supratentorial

Males>Females

Frequency of incidence of cases among Jordanians by site and age-group (Males) , 2013



What you need to know:
0-9 Most cases
Up to 39yrs: high incidence
Above 70: lowest incidence

CNS tumours/ characteristics

What makes these tumors different?

- *Tumors from stroma (glial cells)> Parenchyma (neuronal cells)*
- No premalignant or in situ stage
- *Benign (Low grade) lesions are also dangerous*: (1) can widely infiltrate with serious clinical deficit
- (2) Anatomical site important in outcome regardless of type, grade

LOCATION, LOCATION, LOCATION..

- Rarely metastasize outside CNS, *but is a common site for recieving metastasis*

Not for memorization

Examples of premalignant lesions:

- *Adenoma for colon cancer*
- *Dysplasia for stomach cancer*
- *Carcinoma in situ for breast cancer*
- *etc*

Classification of CNS tumors

- According to the cell of origin:

1. gliomas
2. Neuronal tumors
3. Embryonal (primitive) neoplasms: *Eg:Medulloblastoma*
4. Others:
   -lymphoma *(Extranodal, i.e. from lymphocytes not in lymph nodes →forms around blood vessels)*
   -germ cell tumors
5. Meningioma
6. Metastatic tumors

Grading vs staging:
-Grading: Morphology/ differentation
-Staging: Metastasis, more predictive for prognosis. (TNM system)
WARNING: This system doesn't apply to CNS tumors

WHO classification of CNS tumors

- The international classification of human tumors was published by the World Health Organization (WHO) to establish a classification and grading of human tumors that is accepted and used worldwide.
- The first edition on the histological typing of tumors of the nervous system was published in 1979
- 4th edition 2007
- **Newest edition 2016**

- Throughout the years, the classification was based on the consensus of an international Working Group.
- in 2007 the consensus group contained 25 pathologists and geneticists ,and the results of their deliberations and those of an additional 50 contributors were contained in the 2007 WHO classification of tumors of the central nervous system

2016 classification/ a shakeup of the traditional views on CNS tumors

- For the first time, the WHO classification of CNS tumors uses molecular parameters in addition to histology to define tumor entities, thus formulating a concept for how CNS tumor diagnoses should be structured in the molecular era.
- As such, the 2016 CNS WHO presents a major restructuring of several tumors including diffuse gliomas.
- The 2016 edition has added newly recognized neoplasms, and has deleted some entities, variants and patterns that no longer have diagnostic and/or biological relevance.

SO:

- The 20016 classification has changed our understanding of CNS tumors.
- It relies on genetic changes plus morphology (integrated layered diagnosis)
- The changes in classification are important because they have better prognostic and therapeutic implications.

NOTE

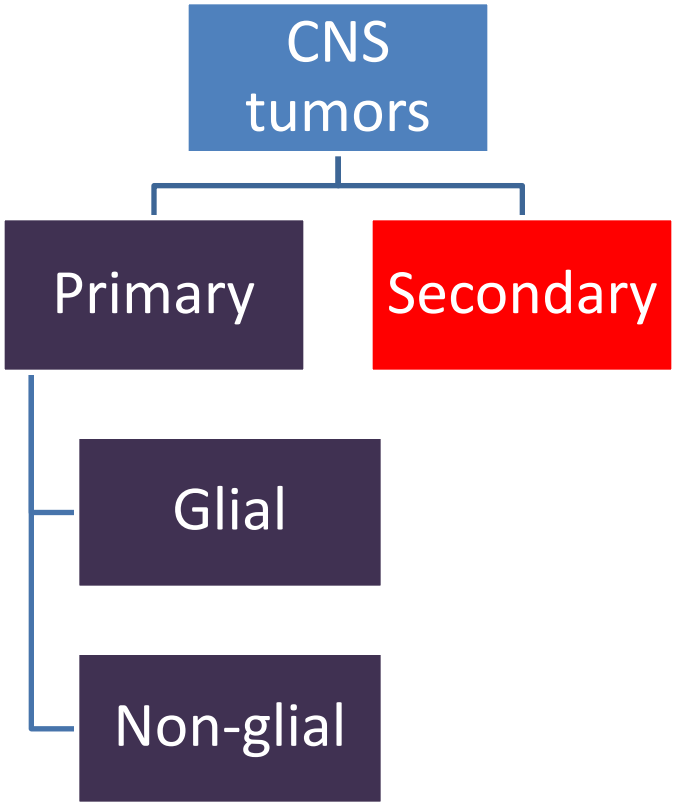
- In most centers in Jordan we are still using the 2007 WHO classification, because the new system needs expensive immunohistochemical and molecular tests to decide on genetic mutations.
- King Hussain medical center is better funded and they started working on the new system!
- **So, in these lectures we will mainly discuss the classical classification but will give some examples of the new changes.**

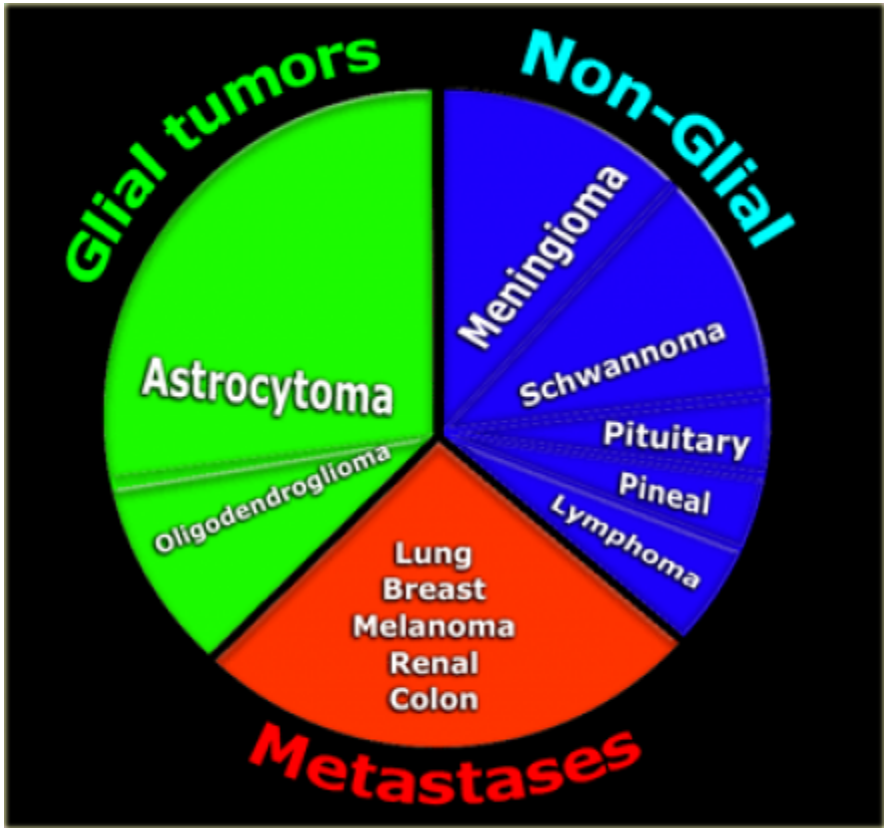
TOO MANY ENTITIES!!

WHO classification of tumours of the central nervous system

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*
Oligoastrocytoma, NOS	*9382/3*
Anaplastic oligoastrocytoma, NOS	*9382/3*
Other astrocytic tumours	
Pilocytic astrocytoma	9421/1
Pilomyxoid astrocytoma	9425/3
Subependymal giant cell astrocytoma	9384/1
Pleomorphic xanthoastrocytoma	9424/3
Anaplastic pleomorphic xanthoastrocytoma	9424/3
Ependymal tumours	
Subependymoma	9383/1
Myxopapillary ependymoma	9394/1
Ependymoma	9391/3
Papillary ependymoma	9393/3
Clear cell ependymoma	9391/3
Tanycytic ependymoma	9391/3
Ependymoma, *RELA* fusion–positive	9396/3*
Anaplastic ependymoma	9392/3
Other gliomas	
Chordoid glioma of the third ventricle	9444/1
Angiocentric glioma	9431/1
Astroblastoma	9430/3
Choroid plexus tumours	
Choroid plexus papilloma	9390/0
Atypical choroid plexus papilloma	9390/1
Choroid plexus carcinoma	9390/3
Neuronal and mixed neuronal-glial tumours	
Dysembryoplastic neuroepithelial tumour	9413/0
Gangliocytoma	9492/0
Ganglioglioma	9505/1
Anaplastic ganglioglioma	9505/3
Dysplastic cerebellar gangliocytoma (Lhermitte–Duclos disease)	9493/0
Desmoplastic infantile astrocytoma and ganglioglioma	9412/1
Papillary glioneuronal tumour	9509/1
Rosette-forming glioneuronal tumour	9509/1
Diffuse leptomeningeal glioneuronal tumour	
Central neurocytoma	9506/1
Extraventricular neurocytoma	9506/1
Cerebellar liponeurocytoma	9506/1
Paraganglioma	8693/1
Tumours of the pineal region	
Pineocytoma	9361/1
Pineal parenchymal tumour of intermediate differentiation	9362/3
Pineoblastoma	9362/3
Papillary tumour of the pineal region	9395/3
Embryonal tumours	
Medulloblastomas, genetically defined	
Medulloblastoma, WNT-activated	9475/3*
Medulloblastoma, SHH-activated and *TP53*-mutant	9476/3*
Medulloblastoma, SHH-activated and *TP53*-wildtype	9471/3
Medulloblastoma, non-WNT/non-SHH	9477/3*
Medulloblastoma, group 3	
Medulloblastoma, group 4	
Medulloblastomas, histologically defined	
Medulloblastoma, classic	9470/3
Medulloblastoma, desmoplastic/nodular	9471/3
Medulloblastoma with extensive nodularity	9471/3
Medulloblastoma, large cell / anaplastic	9474/3
Medulloblastoma, NOS	9470/3
Embryonal tumour with multilayered rosettes, C19MC-altered	9478/3*
Embryonal tumour with multilayered rosettes, NOS	*9478/3*
Medulloepithelioma	9501/3
CNS neuroblastoma	9500/3
CNS ganglioneuroblastoma	9490/3
CNS embryonal tumour, NOS	9473/3
Atypical teratoid/rhabdoid tumour	9508/3
CNS embryonal tumour with rhabdoid features	*9508/3*
Tumours of the cranial and paraspinal nerves	
Schwannoma	9560/0
Cellular schwannoma	9560/0
Plexiform schwannoma	9560/0

Classification in general





note

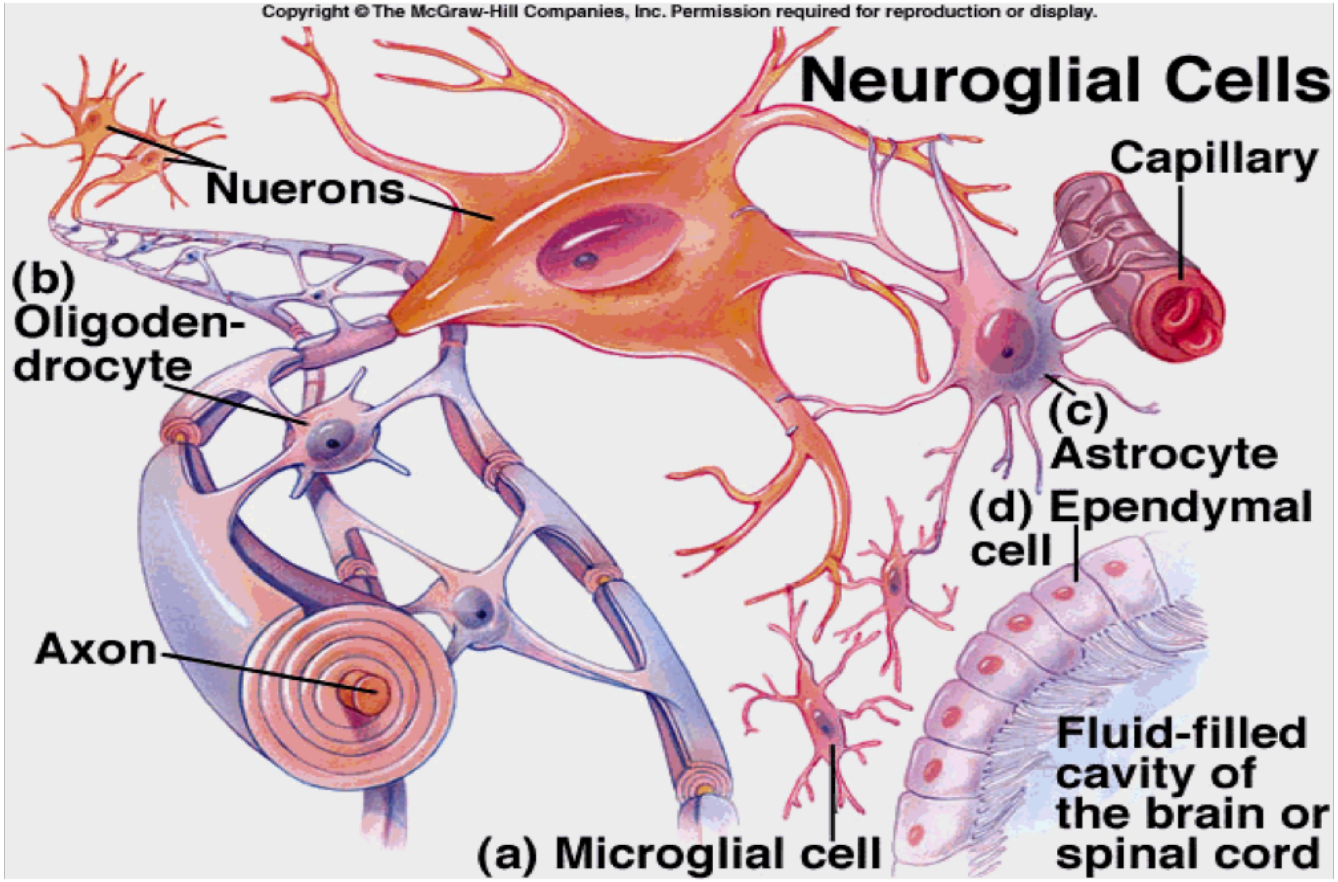
- Classification deals with types of tumors and entities
- We also need a grading system, That's why there is a WHO grading system for CNS tumors
- Regarding stage: note that CNS tumors rarely metastasize so we don't usually use the TNM staging for these tumors.
- **Grading in CNS tumors determines outcome, although site is also important.**

WHO grading

Grade	Example	Criteria
WHO I	Pilocytic astrocytoma Myxopapillary Ependymoma/Subendymoma	Low proliferating, discrete, non invasive tumor
WHO II	Diffuse astrocytoma Papillary, cellular and clear cell Ependymoma	Modest proliferating, partly invasive tumor
WHO III	Anaplastic astrocytoma Anaplastic ependymoma	Fast proliferating, invasive tumor
WHO IV	Glioblastoma multiforme Highly malignant glioma-like Pineoblastoma and Medulloblastoma	Rapidly proliferating, highly invasive tumor

Just know that:
Grade1: Benign whenever (by definition) eg: Pilocytic astrocytoma.
Grade2: and 3: icreased cellularity, mitosis and pleomorphism (3 more than 2)
Grade4: Necrosis and/or vascular (endothelial) proliferation.

Gliomas/ tumors of glial cells



gliomas

- Are the most common primary brain tumors.
- these three types originate from a progenitor cell that can differentiate to these three morphologic types.
- Gliomas are classified to:
  (1)astrocytomas,
  (2)oligodendrogliomas and
  (3)ependymomas.

Draw a flowchart while rading this and the next slides

Astrocytomas *(most common of gliomas)*

- Two major types
- 1, localized astrocytomas, GRADE1
  the most important one is the **PILOCYTIC ASTROCYTOMA** *(Benign tumor of astrocytes. Most common CNS tumor in children)*
- 2, diffuse (infiltrating) astrocytoma

WHO classification of astrocytomas

WHO designation	WHO grade
• pilocytic astrocytoma	I
• Astrocytoma, well diff	II
• anaplastic astrocytoma	III
• glioblastoma	IV

Diffuse astrocytoma *(WHO grade 2, 3 or 4)*

- Account for 80% of adult gliomas.
- Present at 40- 60 years of age
- Location: cerebral hemispheres
- Present with: seizures, headache ((خاصة إذا بصحي من النوم , focal neurologic deficit
- *M orphology: NO mass*

Diffuse astrocytoma

- Spectrum of histological differentiation:
- (1)Well differentiated.. WHO grade 2
- (2)Anaplastic astrocytoma… grade 3
- (3)Glioblastoma…. Grade 4

- Prognosis is affected by grade
- Note: there are no grade 1 diffuse astrocytomas

Well differentiated astrocytoma/ grade2

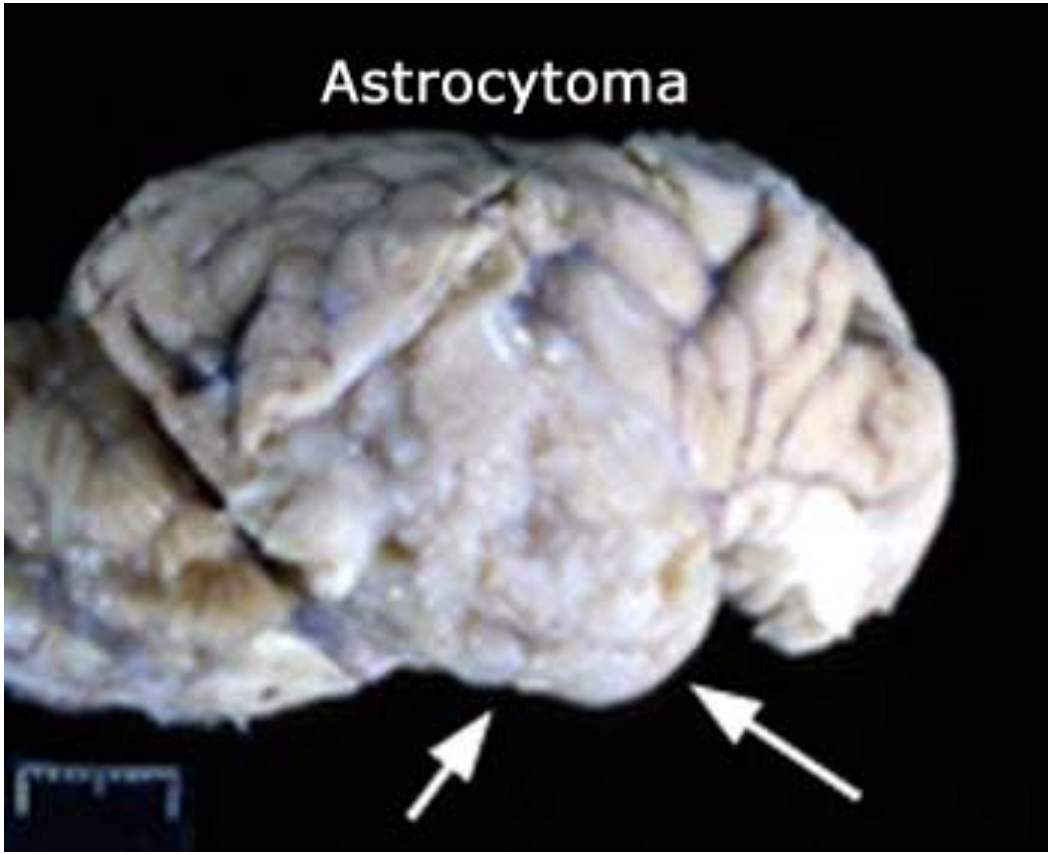
- Can be static for several years
- But progress
- Mean survival is more than five years
- When progress: rapid deterioration + anaplastic histological features develop.

Key facts:
Well-differentiated
high cellularity, no mitosis, pleomorphism, fibrillary background (astrocytic dendrites)
GFAP+
might look similar to gliosis.

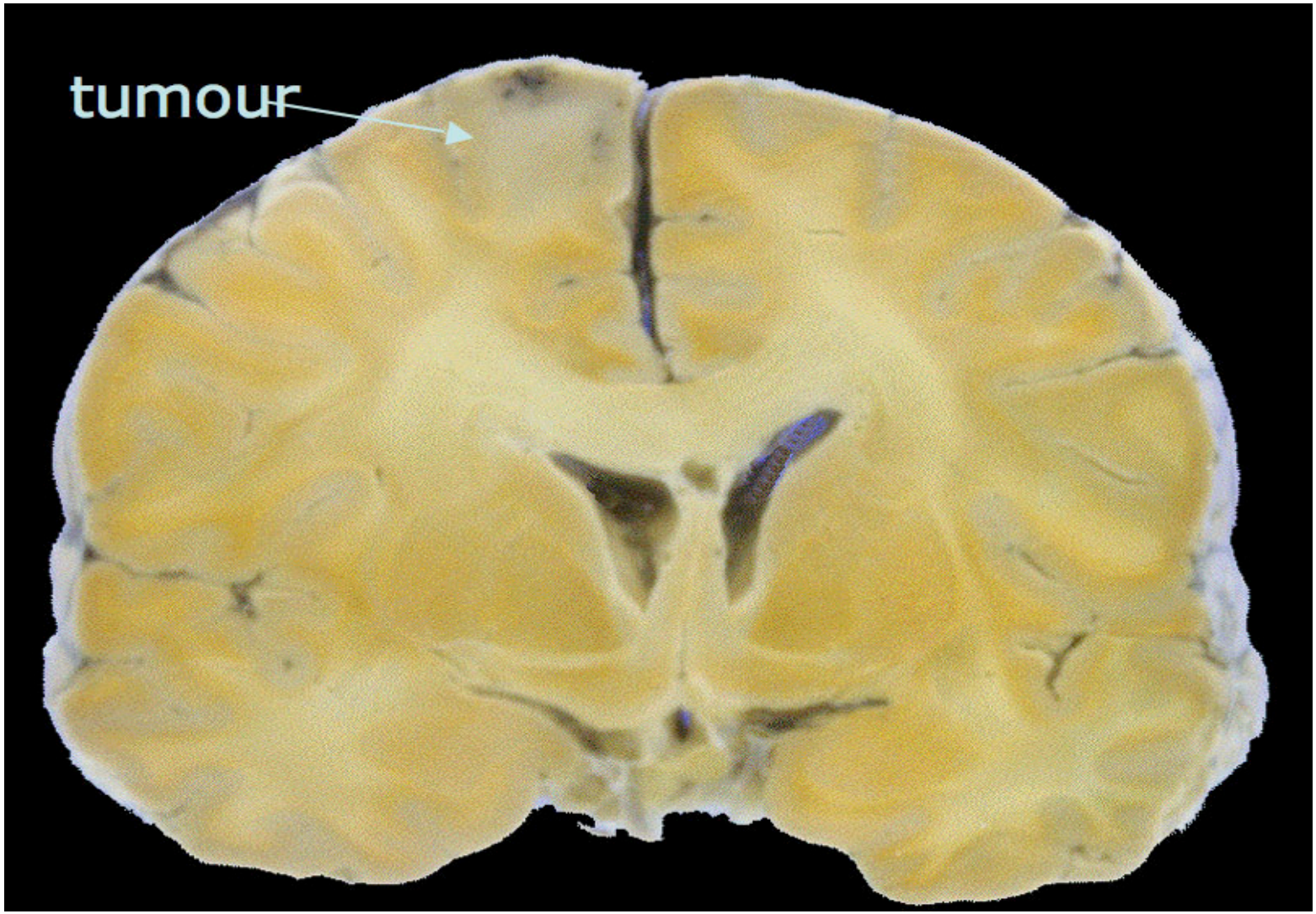
Well differentiated astrocytoma gross features

- Poorly defined grey, infiltrative tumors that invade the brain without forming a discrete mass:

Well diff astro



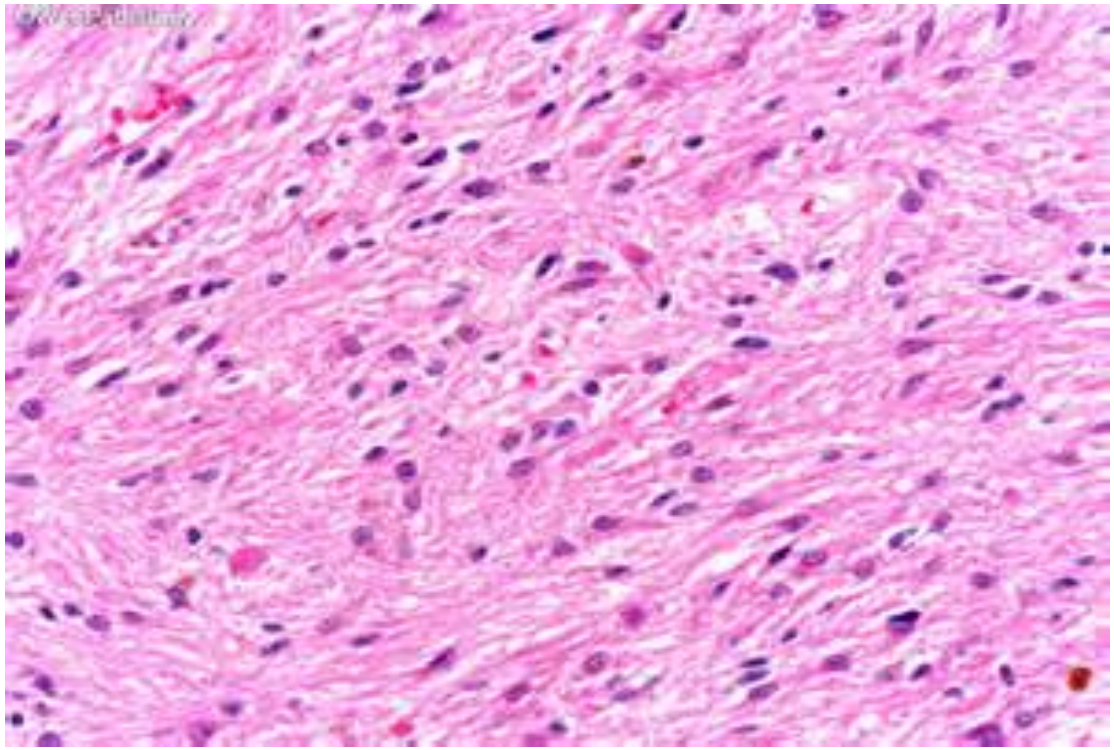
Mowell diff astrorphology



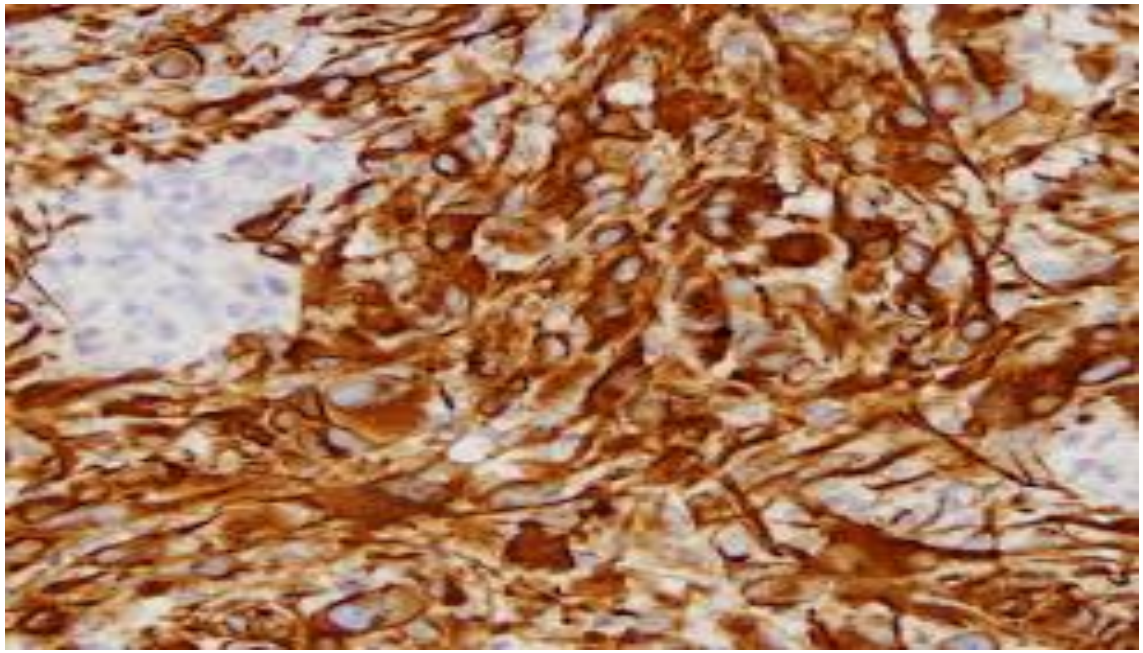
Microscopic features

- Well diff: mild to moderate increase in glial cells.
- Some nuclear pleomorphism
- Background: fibrillary due to fine astrocytic processes.. These are positive with glial fibrillary acidic protein (GFAP) *(this protein is present in all glial cells so when a cell stains positive we know it is derived form glial cells)*

Well diff astro



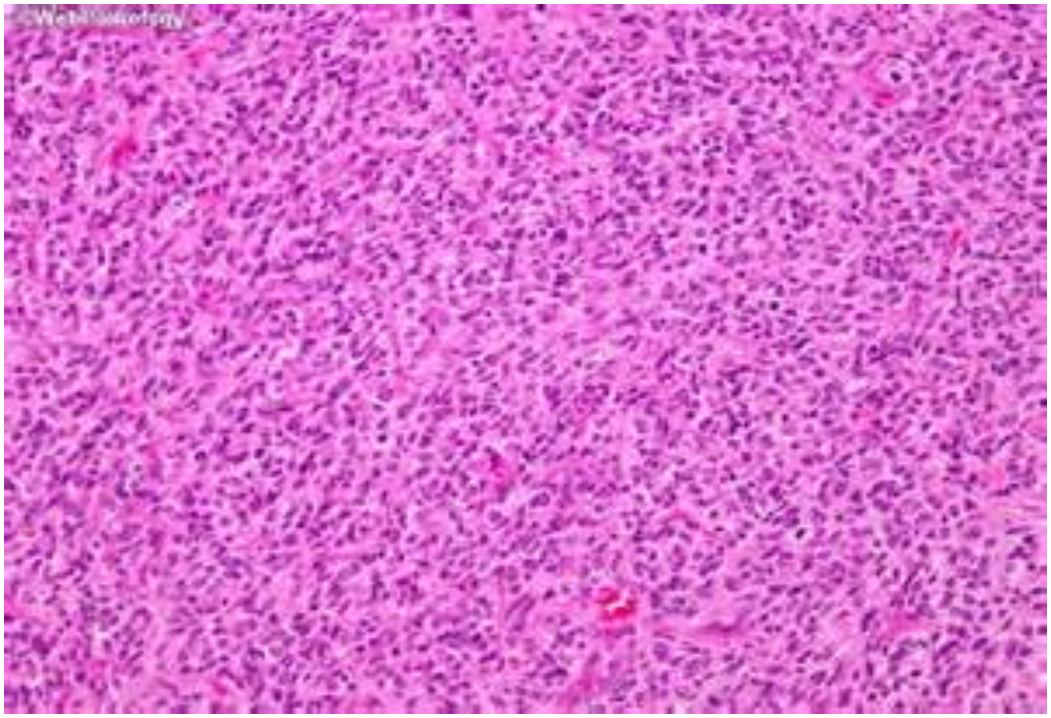
GFAP staining in astro



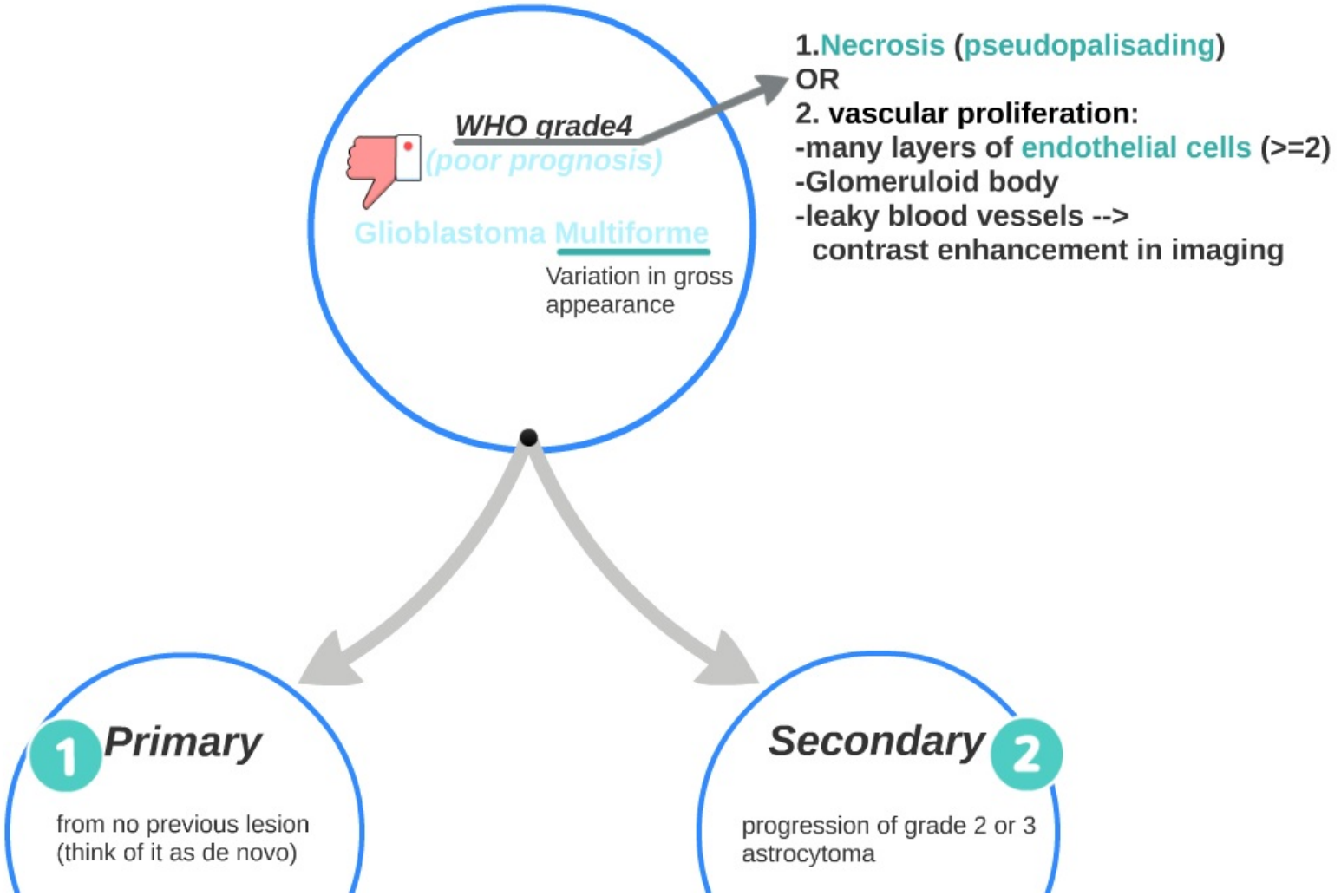
Anaplastic astro/ WHO grade 3

- More cellular than well diff astro.
- More pleomorphism
- Mitotic figures

Anaplastic astrocytoma.. note the high cellularity



Glioblastoma/ grade4


WHO grade4
(poor prognosis)
Glioblastoma Multiforme
Variation in gross appearance
1.Necrosis (pseudopalisading)
OR
2. vascular proliferation:
-many layers of endothelial cells (>=2)
-Glomeruloid body
-leaky blood vessels -->
contrast enhancement in imaging
1 Primary
from no previous lesion
(think of it as de novo)
Secondary 2
progression of grade 2 or 3
astrocytoma

-Poor prognosis

-15 months survival

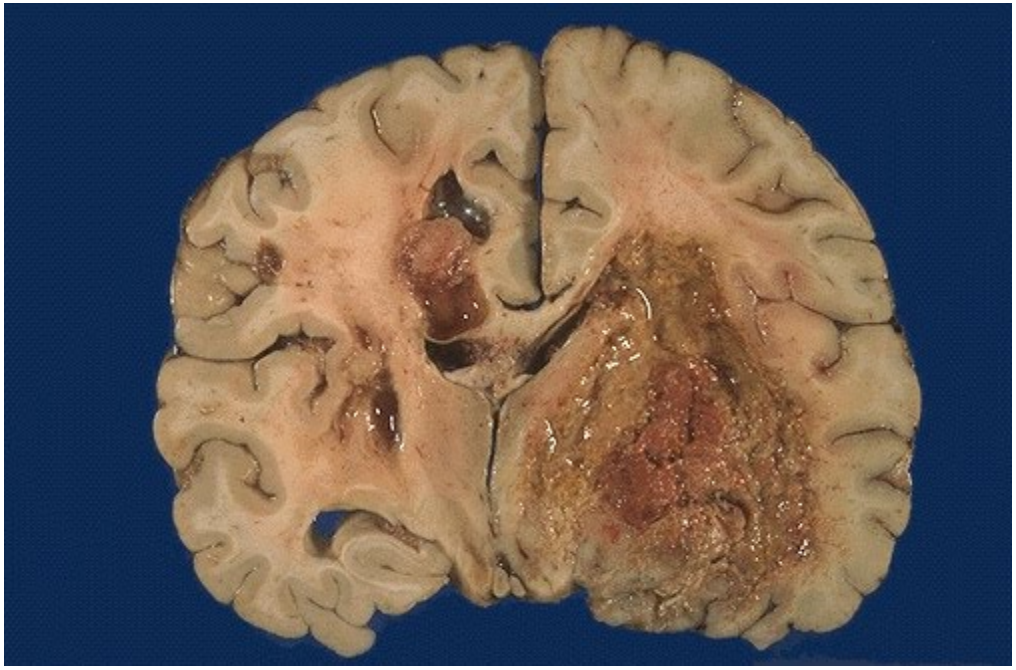
- Survival rate improved ; 25% live up 2 years or more with resection followed by chemo and radiotherapy

-Can result due to progression from a previous astrocytoma (**secondary** glioblastoma) or the tumor can start as glioblastoma from the beginning (**Primary** astrocytoma)

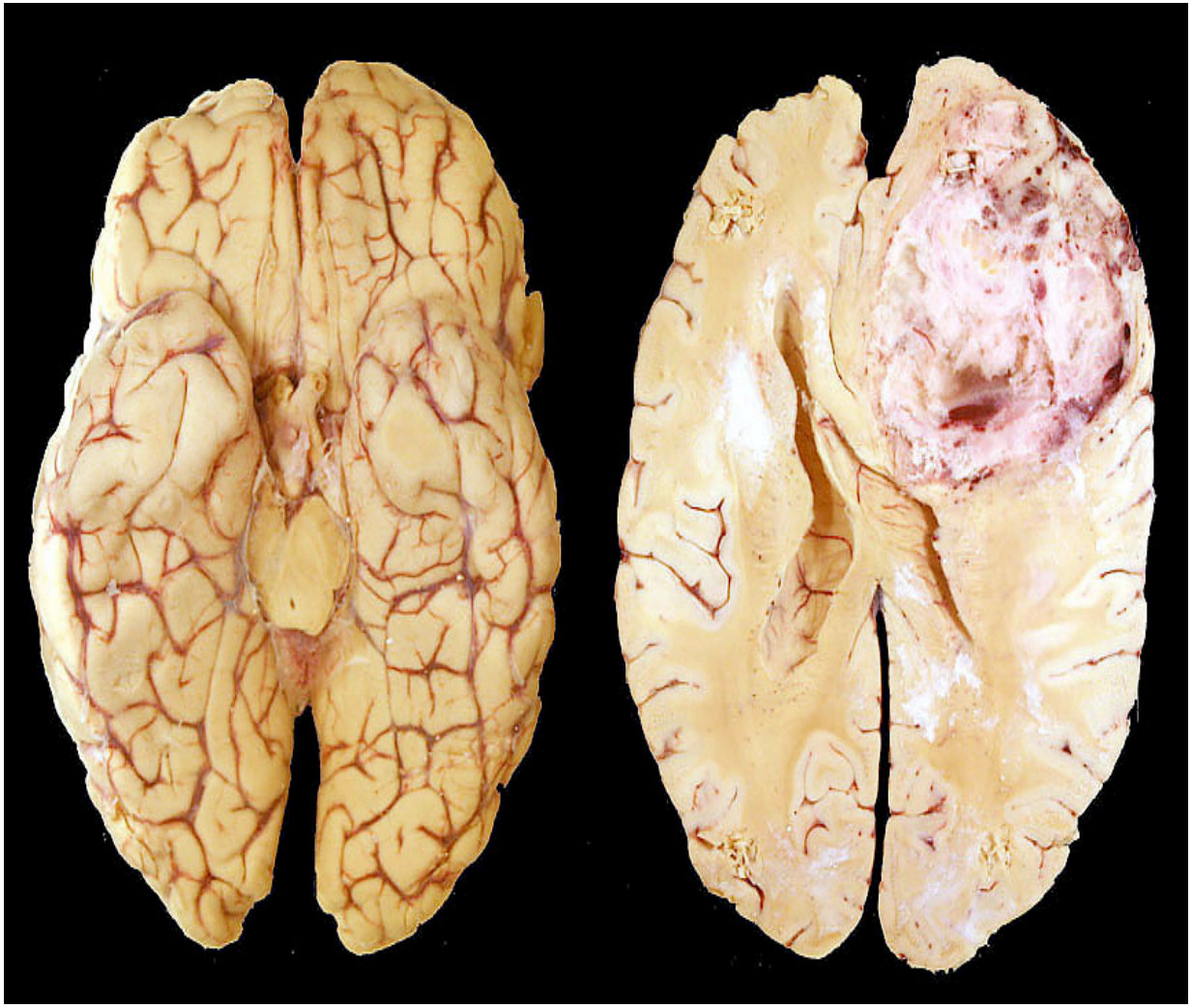
morphology

- Glioblastoma: charectarized histologically by variation of the tumor appearance (that's why it was called glioblastoma multiforme);
- So there will be soft , necrotic and hemorrhagic areas.

glioblastoma



glioblastoma



Glioblastoma multiforme

Looks like anaplastic plus

- Necrosis (usually pesudopalisading)

  viable cells make an edge to this area of necrosis
  Palisading= lining up.
  But cells aren't lining up, these are just the living cells at the edge of the necrosis=PSEUDOpalisading.

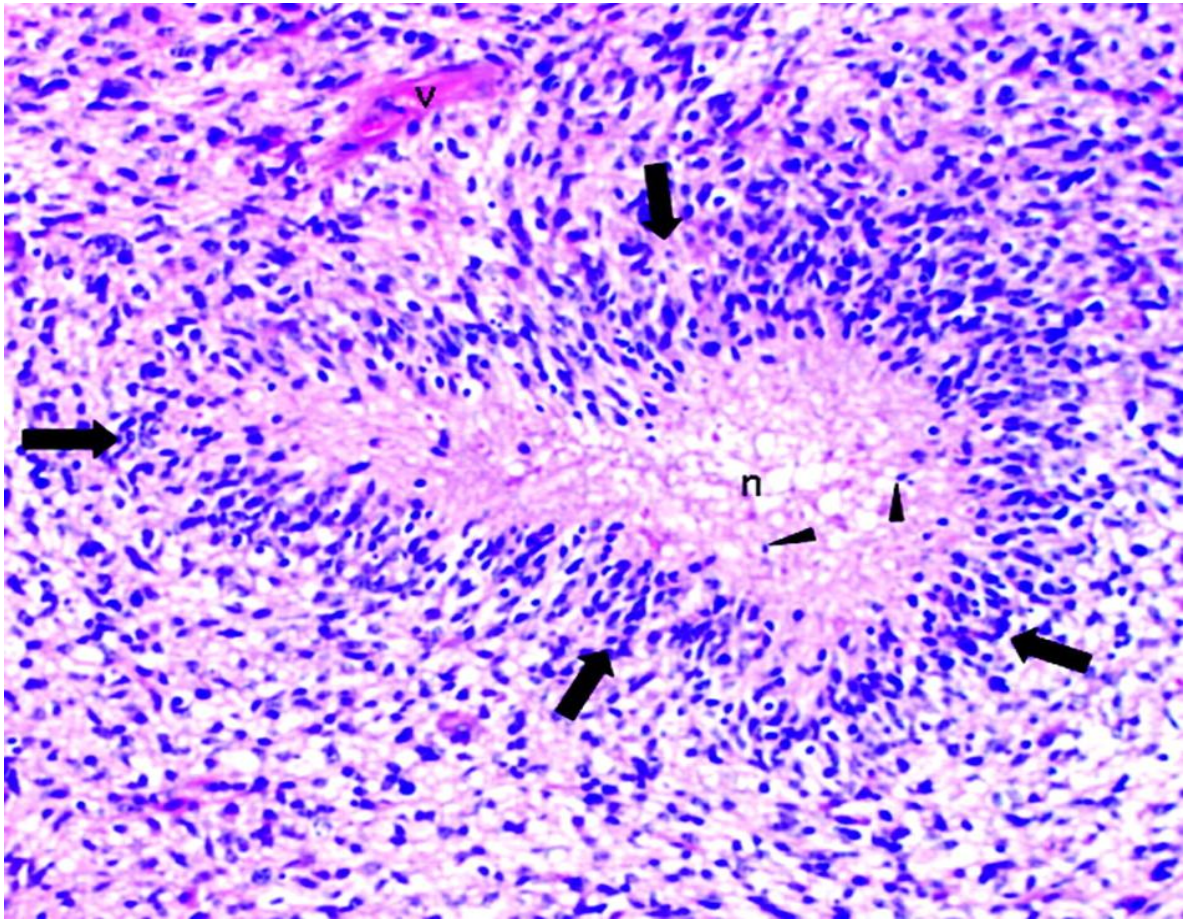
- or vascular proliferation (*endothelial cell prolifersation)*

palisade

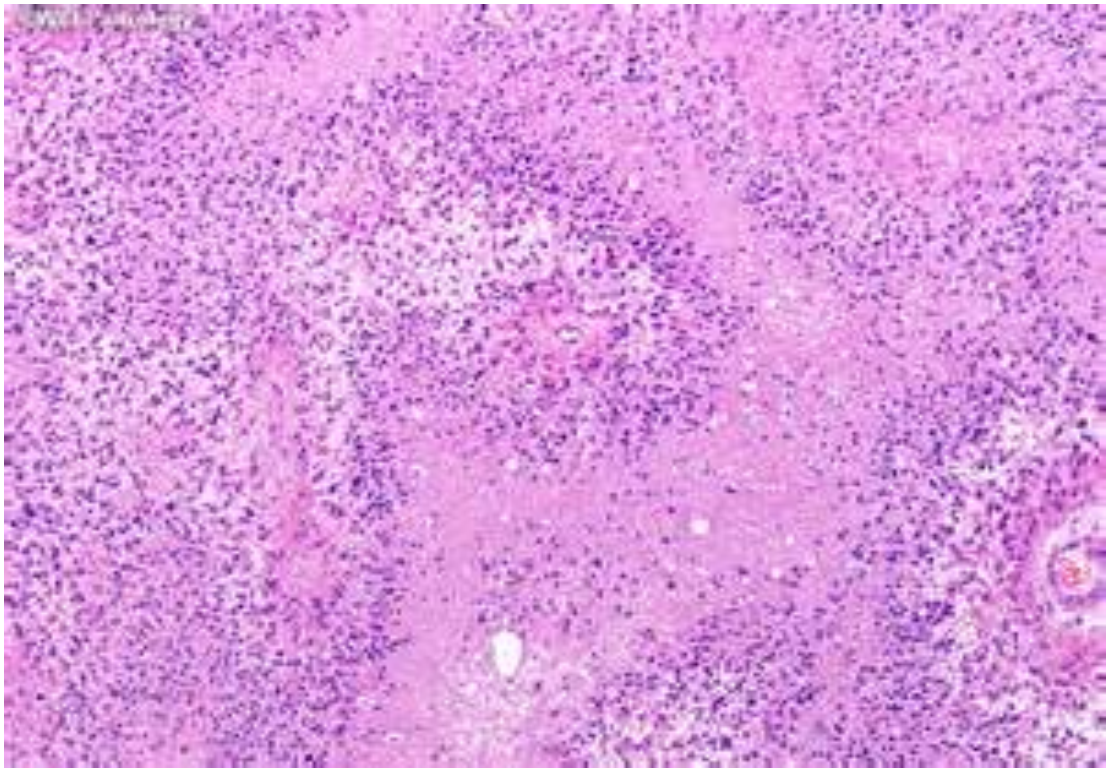
-high fence made of pointed stakes that was used in the past to protect a building or area

-palisades : a line of steep cliffs especially along a river or ocean

Glioblastoma/ palisaded nuclei around necrotic area



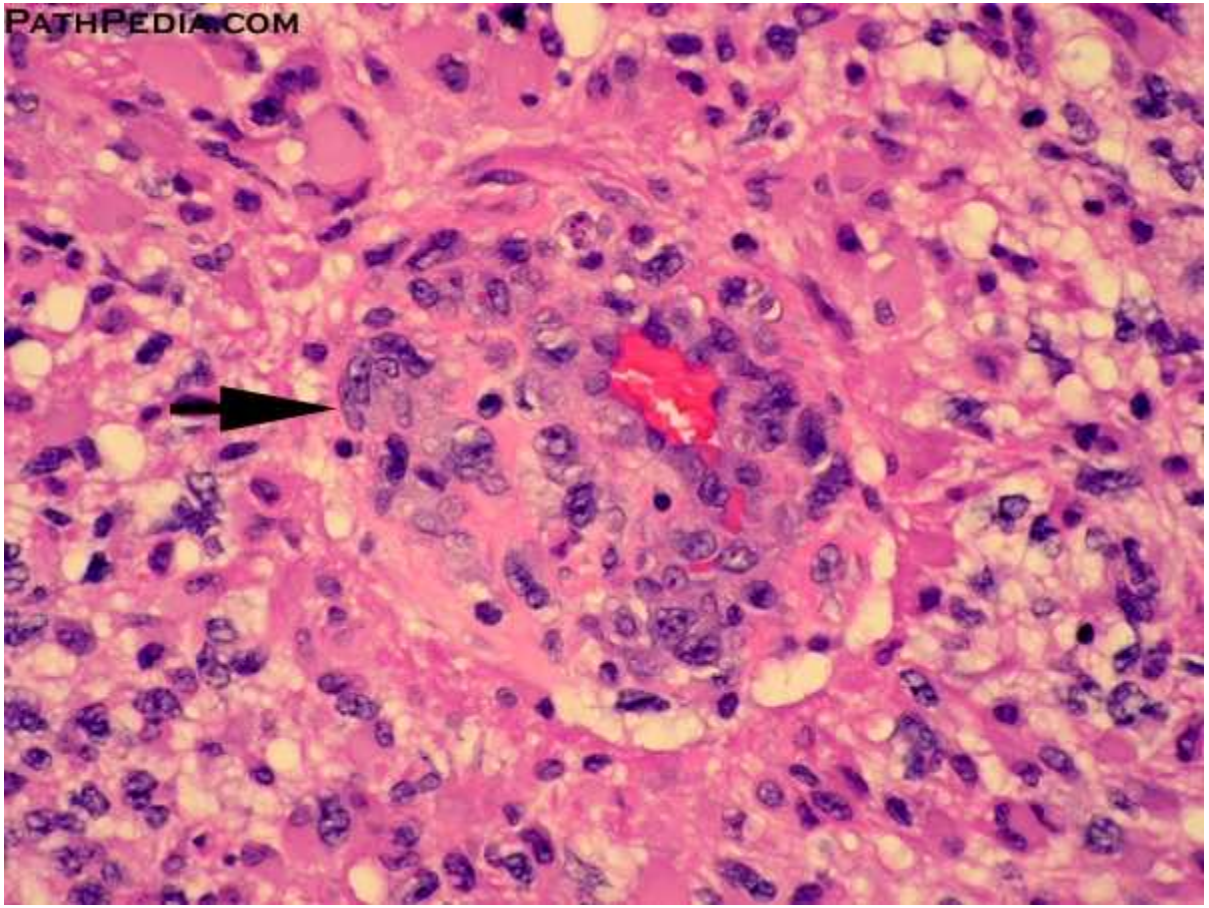
glioblastoma



Vascular proliferation in glioblastoma

- Manifests as tufts of cells that pile up and bulge into the lumen.
- Minimal criteria to diagnose vascular proliferation: is the presence of double endothelial layer.
- If it is marked and severe it forms: glumeruloid body.

Glomeruloid body

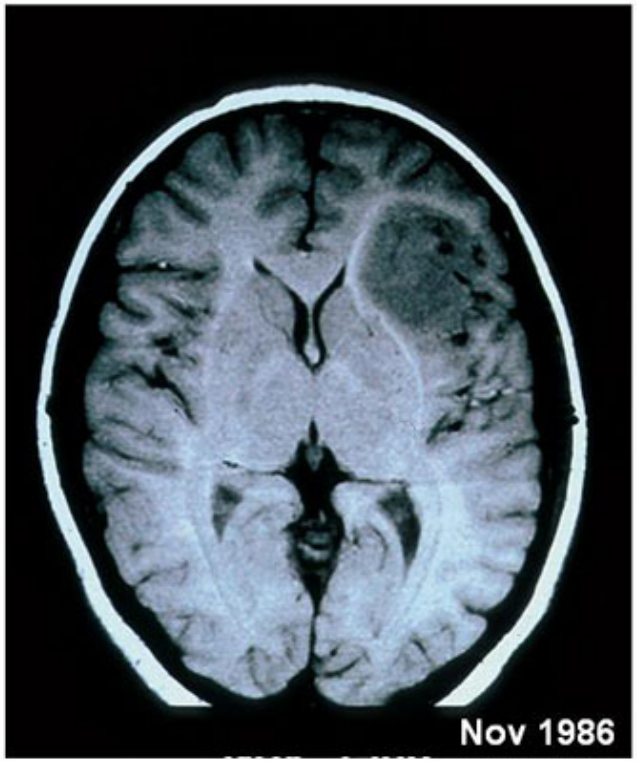


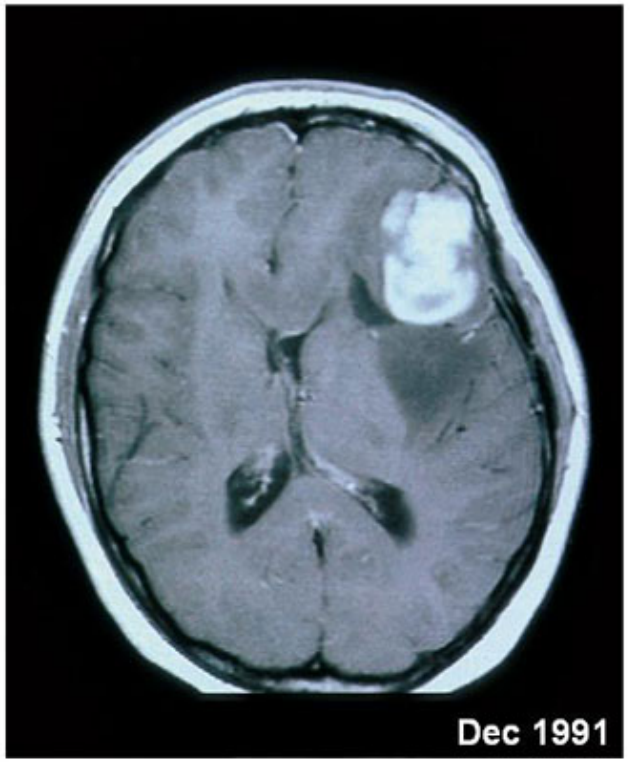
Radiological appearance

- High grade astro contains abnormal leaky vessels
- This gives contrast enhancement on imaging studies
- Contrast given before MRI scanning has limited capacity to reach the brain tissue due to blood brain barrier (BBB).
- If there is defect in BBB (like in the leaky vessels), the contrast material reaches the brain and forms obvious lesions.

Contrast enhancement / This slide is for your information. Not for the test!!

- In general, the terms 'enhancing' or 'non-enhancing' lesion refer to the uptake of Gadolinium-based contrast agent in the lesion.
- The difference between enhancing an non-enhancing is very pronounced in brain tissue, where the blood-brain barrier effectively hinders the contrast agent from accumulating in the tissue in normal circumstances. When the blood-brain barrier is leaking, e.g. due to an inflammatory process in a lesion or due to cancerous angiogenesis, the contrast can extravasate and accumulate in the tissue.
- Specifically in Multiple Sclerosis, 'active' and 'chronic' MS lesions are often differentiated based on their contrast enhancement, based on the fact that an active lesion exhibits acute inflammation and breakdown of the BBB, whereas chronic MS lesions usually don't enhance.



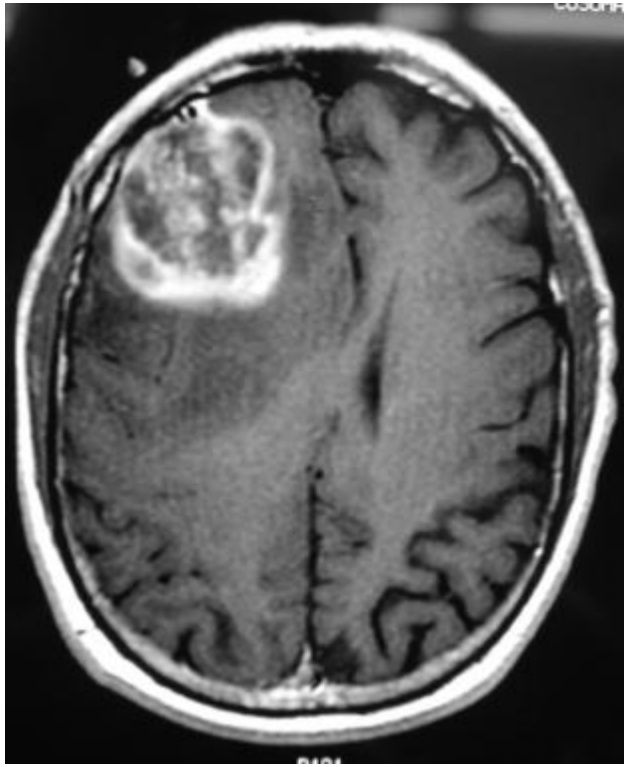


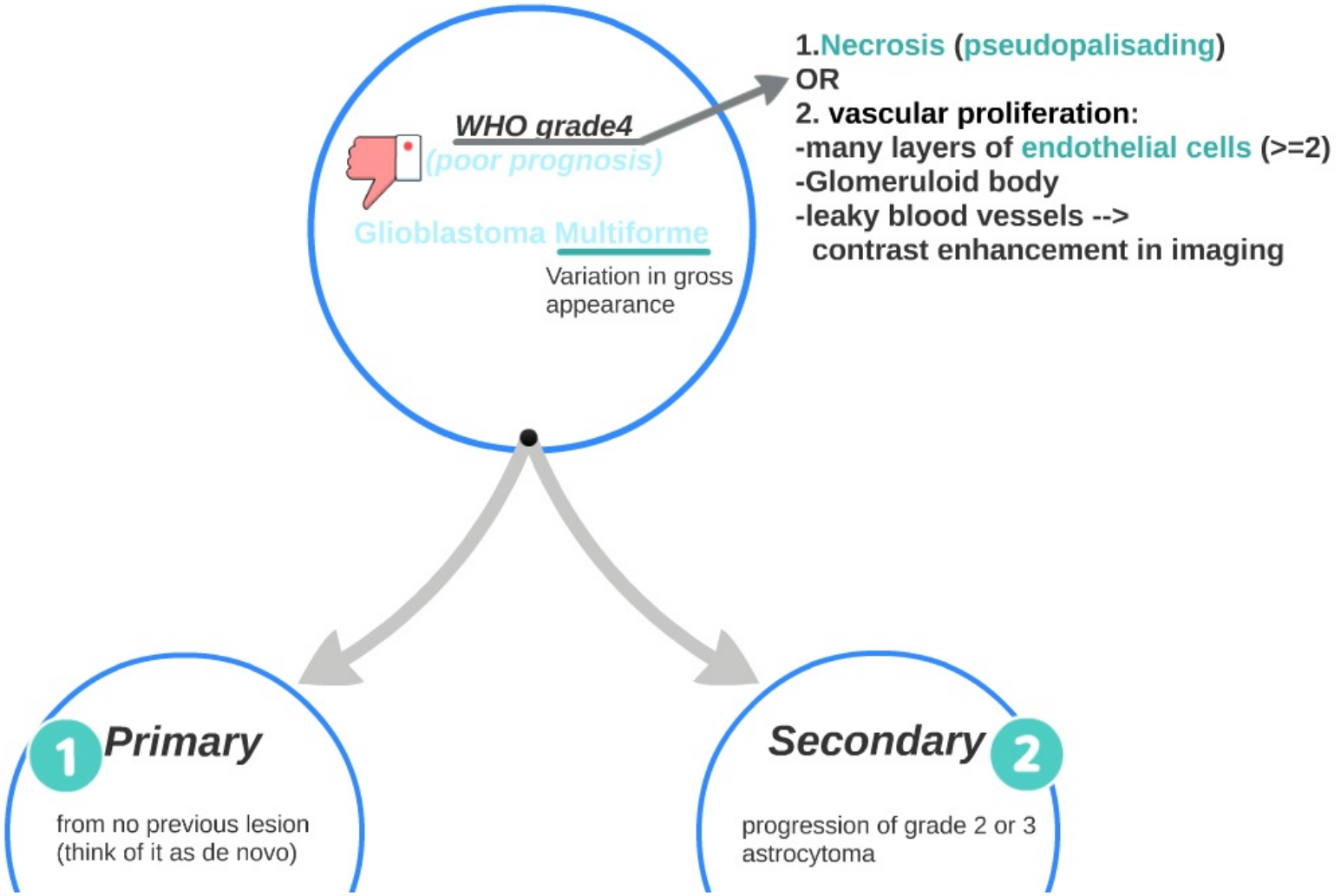
Low-grade astrocytoma
(WHO grade II)

5 years

Secondary glioblastoma
(WHO grade IV)

Enhancing lesion

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contrast enhancement in imaging
1 Primary
from no previous lesion
(think of it as de novo)
Secondary 2
progression of grade 2 or 3
astrocytoma

genetics

- 80% of astrocytomas have a mutation in IDH 1 and IDH2 (isocitrate dehydrogenase).
- This mutation is important in diagnosis and prognosis.
- This can be detected by immunohistochemistry and molecular studies.
- The mutations drive increased methylation in gliomas.so affect the epigenetics
- Gliomas with mutated IDH1 and IDH2 have better prognosis compared to gliomas with wild-type IDH.
- No drugs currently target mutated IDH, although this remains an area of active research.

2016 classification of glioblastoma

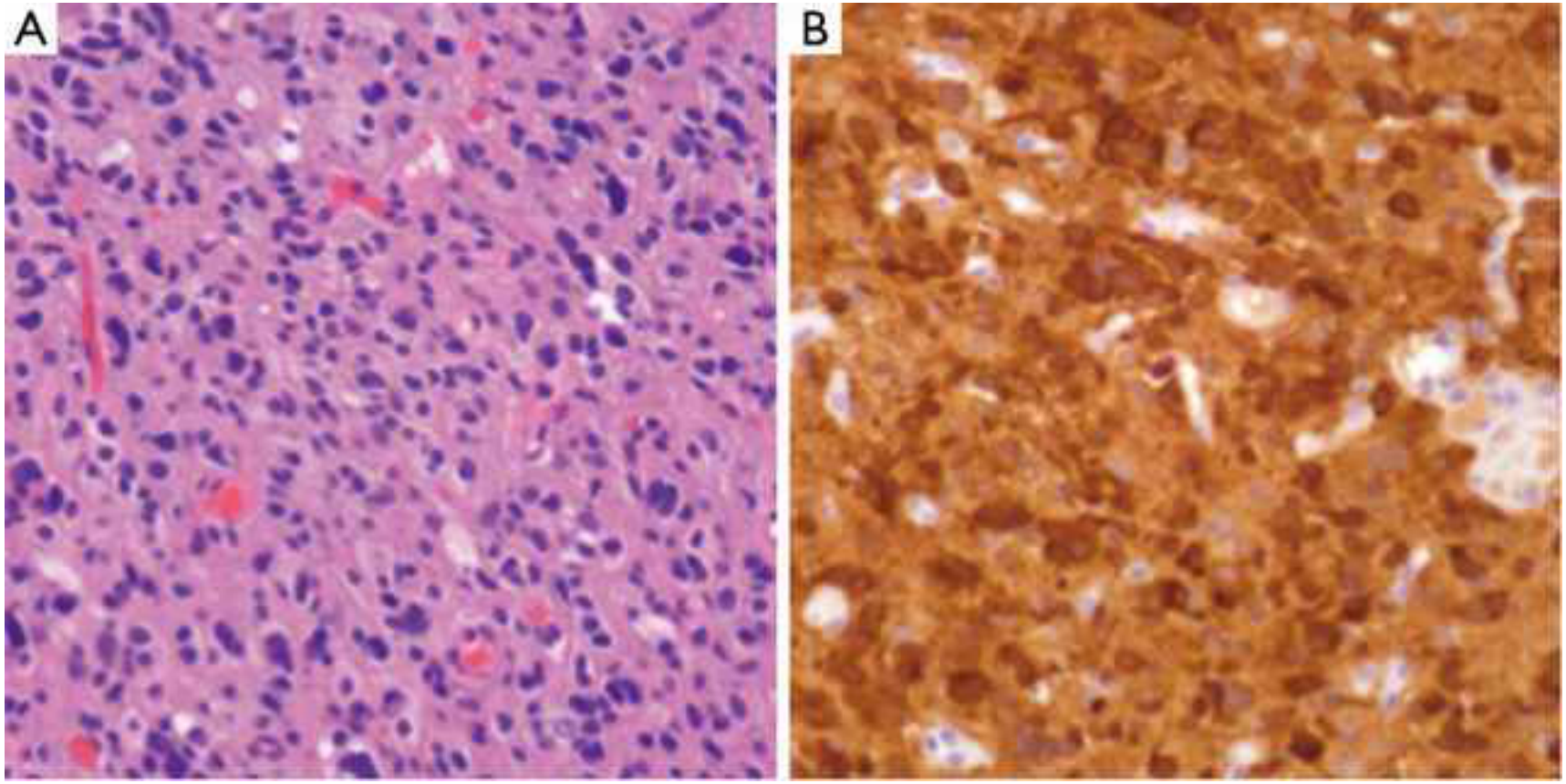
Glioblastomas are divided in the 2016 CNS WHO into

- (1) glioblastoma, IDH-wildtype (about 90 % of cases), which corresponds most frequently with the clinically defined primary or de novo glioblastoma and predominates in patients over 55 years of age
- (2) glioblastoma, IDH-mutant (about 10 % of cases), which corresponds closely to so-called secondary glioblastoma with a history of prior lower grade diffuse glioma and preferentially arises in younger patients
- (3) glioblastoma, NOS, a diagnosis that is reserved for those tumors for which full IDH evaluation cannot be performed.

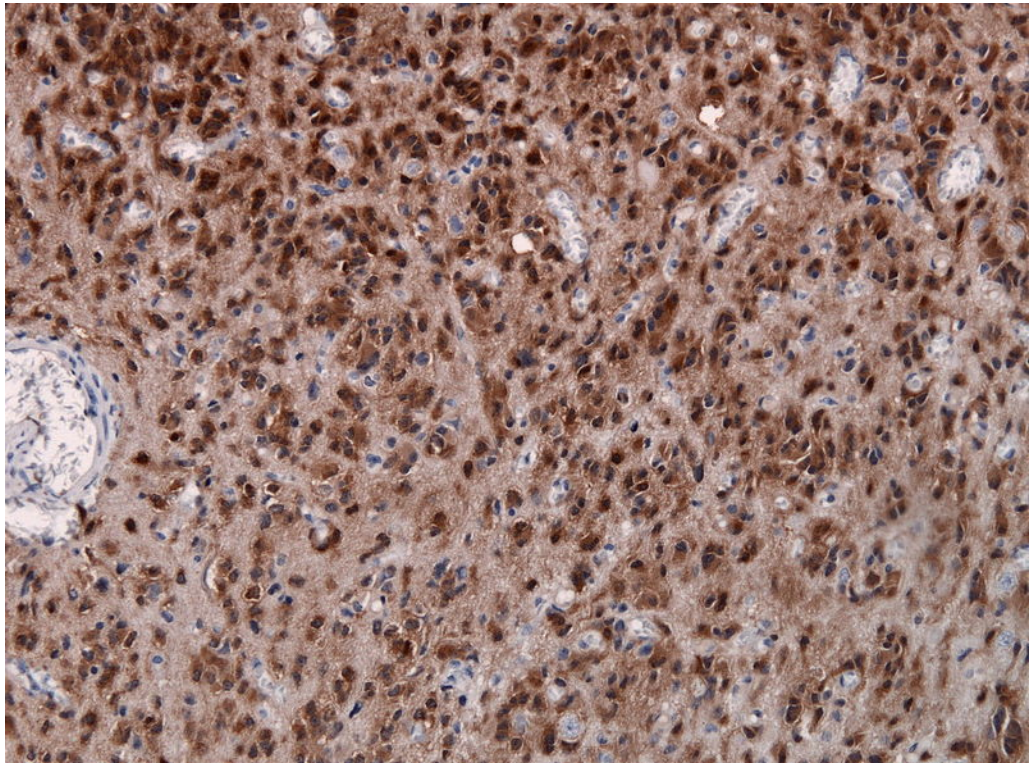
note

- Primary and secondary or IDH mutated or wild type glioblastomas are histopathologically similar

IDH 1 staining in anaplastic astrocytoma



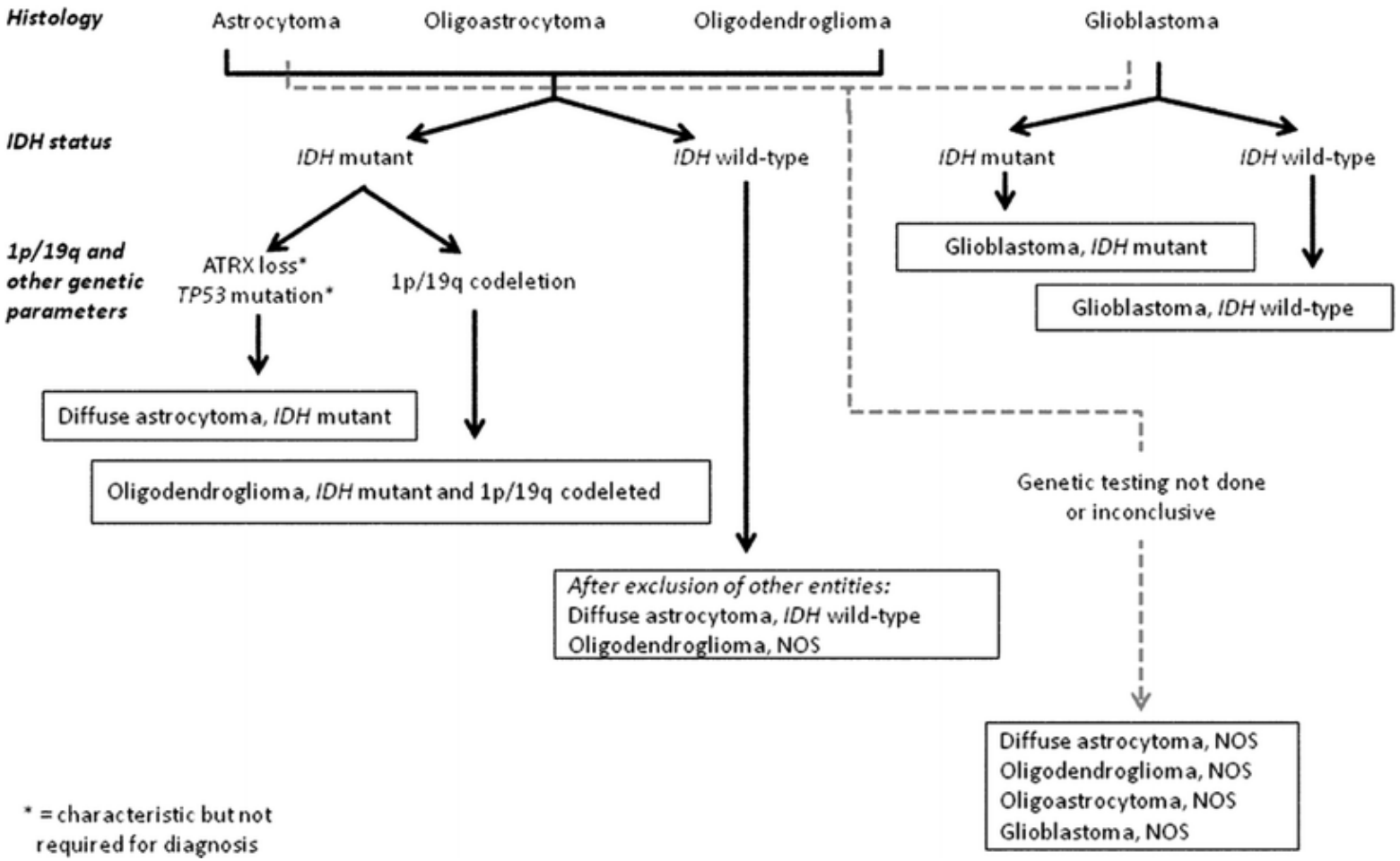
IDH staining



FYI

	IDH-wildtype glioblastoma	IDH-mutant glioblastoma	References
Synonym	Primary glioblastoma, IDH-wildtype	Secondary glioblastoma, IDH-mutant	{1830}
Precursor lesion	Not identifiable; develops de novo	Diffuse astrocytoma Anaplastic astrocytoma	{1827}
Proportion of glioblastomas	~90%	~10%	{1797}
Median age at diagnosis	~62 years	~44 years	{214,1078,1797, 2103}
Male-to-female ratio	1.42:1	1.05:1	{214,1417,1797}
Mean length of clinical history	4 months	15 months	{1797}
Median overall survival			
Surgery + radiotherapy	9.9 months	24 months	{1797}
Surgery + radiotherapy + chemotherapy	15 months	31 months	{2810}
Location	Supratentorial	Preferentially frontal	{1417}
Necrosis	Extensive	Limited	{1417}
TERT promoter mutations	72%	26%	{1801,1830}
TP53 mutations	27%	81%	{1797}
ATRX mutations	Exceptional	71%	{1519}
EGFR amplification	35%	Exceptional	{1797}
PTEN mutations	24%	Exceptional	{1797}

FYI


Histology
Astrocytoma
Oligoastrocytoma
Oligodendroglioma
Glioblastoma
IDH status
IDH mutant
IDH wild-type
IDH mutant
IDH wild-type
1p/19q and other genetic parameters
ATRX loss*
TP53 mutation*
1p/19q codeletion
Glioblastoma, IDH mutant
Glioblastoma, IDH wild-type
Diffuse astrocytoma, IDH mutant
Oligodendroglioma, IDH mutant and 1p/19q codeleted
Genetic testing not done or inconclusive
After exclusion of other entities:
Diffuse astrocytoma, IDH wild-type
Oligodendroglioma, NOS
Diffuse astrocytoma, NOS
Oligodendroglioma, NOS
Oligoastrocytoma, NOS
Glioblastoma, NOS
* = characteristic but not required for diagnosis


KEEP
CALM
YOU'RE
ALMOST
A DOCTOR