

# PATHOLOGY

☐ Sheet

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Number

9

Subject

CNS TUMORS

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Price:

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

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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

- CNS tumors can be primary or secondary
- Secondary account for  $1/4^{\text{th}}$  to  $1/2$  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.

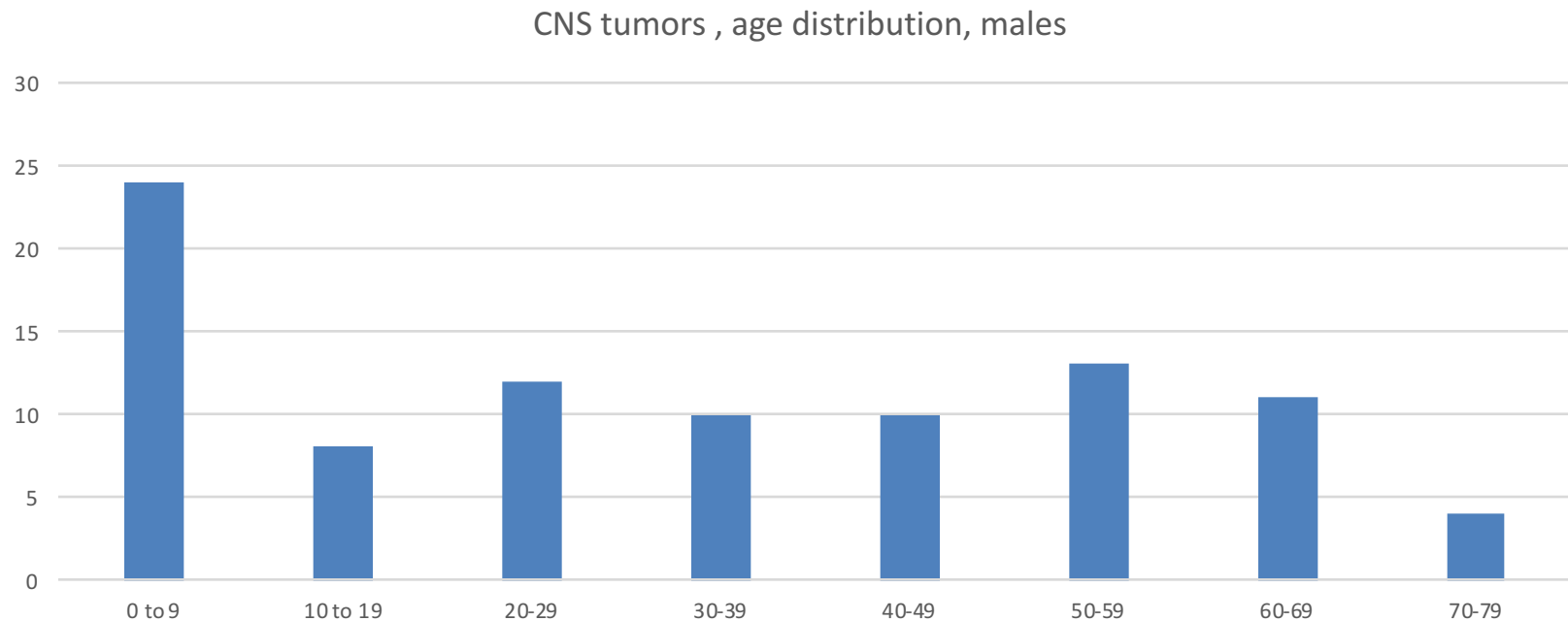
# CNS tumors in Jordan according to 2013 cancer registry ( latest published)

- CNS tumors are the 10<sup>th</sup> 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 percentag e of total cancers in 2013	Females No	Females %	Total No	Total %
	95	3.7%	58	2%	153	2.8%

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



# CNS tumours/ characteristics

- No premalignant or in situ stage
- Low grade lesions can widely infiltrate with serious clinical deficit
- Anatomical site important in outcome regardless of type, grade
- Rarely spread outside CNS



# Classification of CNS tumors

- According to the cell of origin:
  1. gliomas
  2. Neuronal tumors
  3. Embryonal (primitive) neoplasms:
  4. Others: lymphoma and germ cell tumors
  5. Meningioma
  6. Metastatic 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
- 4<sup>th</sup> 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 2016 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

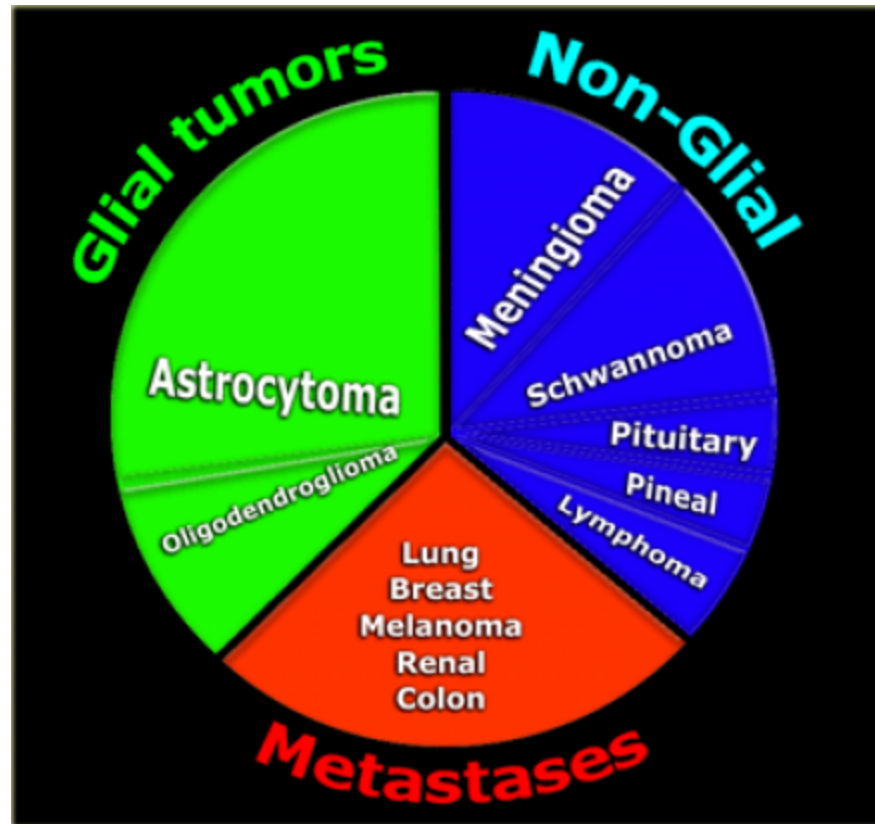
- In most centers in Jordan we are still using the 2007 WHO classification, because the new system needs **expensive** immunohistochemical and molecular tests to decide on genetic mutations.
- King Hussain medical center is better funded and they started working on the new system!
- **So, in these lectures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

<b>Diffuse astrocytic and oligodendroglial tumours</b>		<b>Neuronal and mixed neuronal-glial tumours</b>	
Diffuse astrocytoma, IDH-mutant	9400/3	Dysembryoplastic neuroepithelial tumour	9413/0
Gemistocytic astrocytoma, IDH-mutant	9411/3	Gangliocytoma	9492/0
<i>Diffuse astrocytoma, IDH-wildtype</i>	<i>9400/3</i>	Ganglioglioma	9505/1
Diffuse astrocytoma, NOS	9400/3	Anaplastic ganglioglioma	9505/3
Anaplastic astrocytoma, IDH-mutant	9401/3	Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)	9493/0
<i>Anaplastic astrocytoma, IDH-wildtype</i>	<i>9401/3</i>	Desmoplastic infantile astrocytoma and ganglioglioma	9412/1
Anaplastic astrocytoma, NOS	9401/3	Papillary glioneuronal tumour	9509/1
Glioblastoma, IDH-wildtype	9440/3	Rosette-forming glioneuronal tumour	9509/1
Giant cell glioblastoma	9441/3	<i>Diffuse leptomeningeal glioneuronal tumour</i>	
Gliosarcoma	9442/3	Central neurocytoma	9506/1
<i>Epithelioid glioblastoma</i>	<i>9440/3</i>	Extraventricular neurocytoma	9506/1
Glioblastoma, IDH-mutant	9445/3*	Cerebellar liponeurocytoma	9506/1
Glioblastoma, NOS	9440/3	Paraganglioma	8693/1
Diffuse midline glioma, H3 K27M-mutant	9385/3*	<b>Tumours of the pineal region</b>	
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9450/3	Pineocytoma	9361/1
Oligodendroglioma, NOS	9450/3	Pineal parenchymal tumour of intermediate differentiation	9362/3
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9451/3	Pineoblastoma	9362/3
<i>Anaplastic oligodendroglioma, NOS</i>	<i>9451/3</i>	Papillary tumour of the pineal region	9395/3
<i>Oligoastrocytoma, NOS</i>	<i>9382/3</i>	<b>Embryonal tumours</b>	
<i>Anaplastic oligoastrocytoma, NOS</i>	<i>9382/3</i>	Medulloblastomas, genetically defined	
<b>Other astrocytic tumours</b>		Medulloblastoma, WNT-activated	9475/3*
Pilocytic astrocytoma	9421/1	Medulloblastoma, SHH-activated and TP53-mutant	9476/3*
Piloxyoid astrocytoma	9425/3	Medulloblastoma, SHH-activated and TP53-wildtype	9471/3
Subependymal giant cell astrocytoma	9384/1	Medulloblastoma, non-WNT/non-SHH	9477/3*
Pleomorphic xanthoastrocytoma	9424/3	<i>Medulloblastoma, group 3</i>	
Anaplastic pleomorphic xanthoastrocytoma	9424/3	<i>Medulloblastoma, group 4</i>	
<b>Ependymal tumours</b>		Medulloblastomas, histologically defined	
Subependymoma	9383/1	Medulloblastoma, classic	9470/3
Myxopapillary ependymoma	9394/1	Medulloblastoma, desmoplastic/nodular	9471/3
Ependymoma	9391/3	Medulloblastoma with extensive nodularity	9471/3
Papillary ependymoma	9393/3	Medulloblastoma, large cell / anaplastic	9474/3
Clear cell ependymoma	9391/3	Medulloblastoma, NOS	9470/3
Tanycytic ependymoma	9391/3	<b>Embryonal tumour with multilayered rosettes, C19MC-altered</b>	
Ependymoma, <i>RELA</i> fusion-positive	9396/3*	<i>Embryonal tumour with multilayered rosettes, NOS</i>	9478/3
Anaplastic ependymoma	9392/3	Medulloepithelioma	9501/3
<b>Other gliomas</b>		CNS neuroblastoma	9500/3
Chordoid glioma of the third ventricle	9444/1	CNS ganglioneuroblastoma	9490/3
Angiocentric glioma	9431/1	CNS embryonal tumour, NOS	9473/3
Astroblastoma	9430/3	Atypical teratoid/rhabdoid tumour	9508/3
<b>Choroid plexus tumours</b>		<i>CNS embryonal tumour with rhabdoid features</i>	<i>9508/3</i>
Choroid plexus papilloma	9390/0	<b>Tumours of the cranial and paraspinal nerves</b>	
Atypical choroid plexus papilloma	9390/1	Schwannoma	9560/0
Choroid plexus carcinoma	9390/3	Cellular schwannoma	9560/0
		Plexiform schwannoma	9560/0

# Classification in general





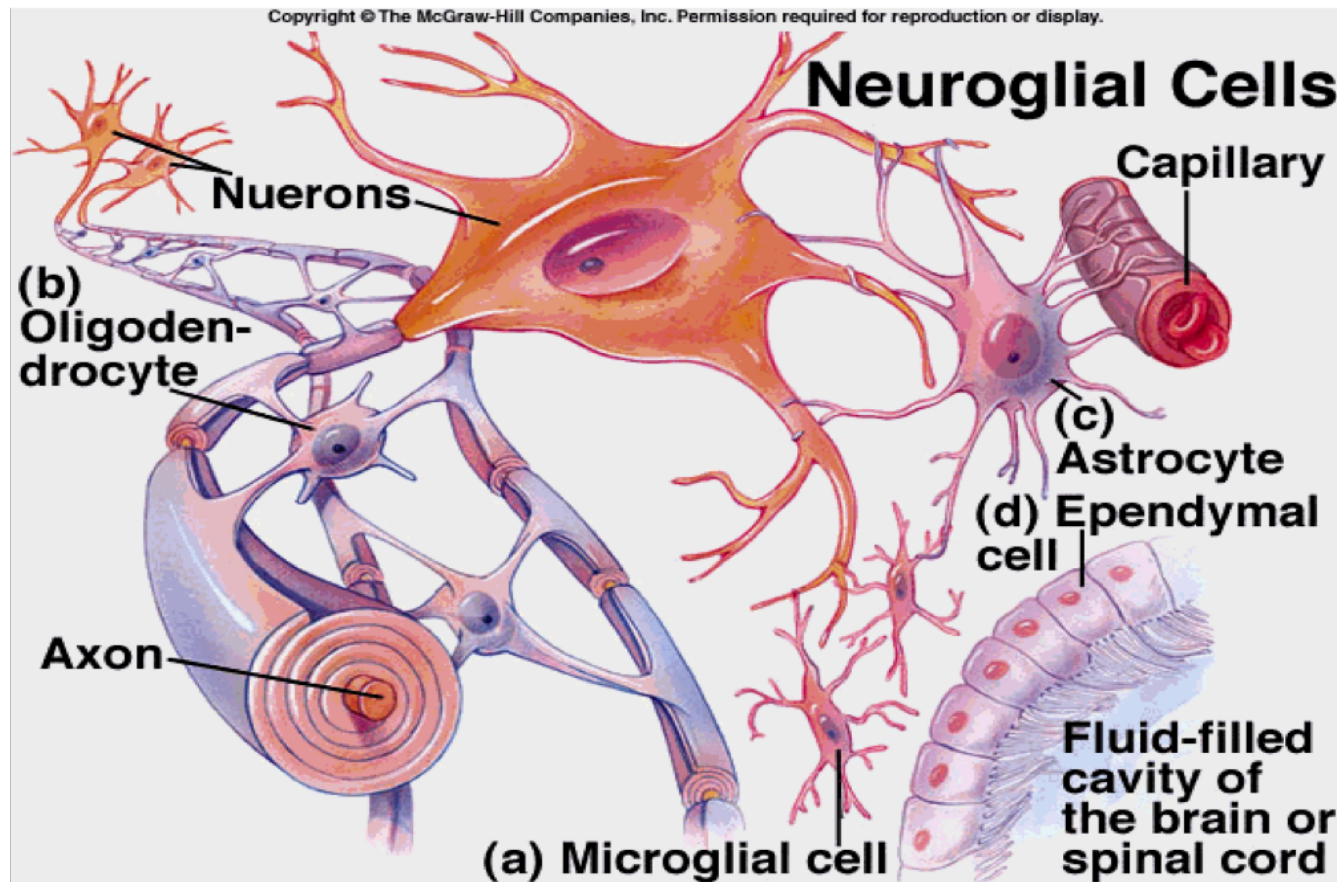
# note

- **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/Subependymoma	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

# Gliomas/ tumors of glial cells



# gliomas

- Are the most common primary brain tumors.
- Gliomas are classified to: astrocytomas, oligodendrogliomas and ependymomas.
- It is now thought that these three types originate from a **progenitor cell** that can differentiate to these three morphologic types.

# Astrocytomas

- Two major types
- 1. diffuse ( infiltrating ) astrocytoma
- 2. localized astrocytomas, the most important one is the PILOCYTIC ASTROCYTOMA

# WHO classification of astrocytomas

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

# Diffuse astrocytoma

- Account for 80% of adult gliomas.
- Present at 40- 60 years of age
- Location: cerebral hemispheres
- Present with: seizures, headache, focal neurologic deficit

# Diffuse astrocytoma

- Spectrum of histological differentiation:
- Well differentiated.. WHO grade 2
- Anaplastic astrocytoma... grade 3
- Glioblastoma.... Grade 4
  
- Prognosis is affected by grade
- Note: there are no grade 1 diffuse astrocytomas



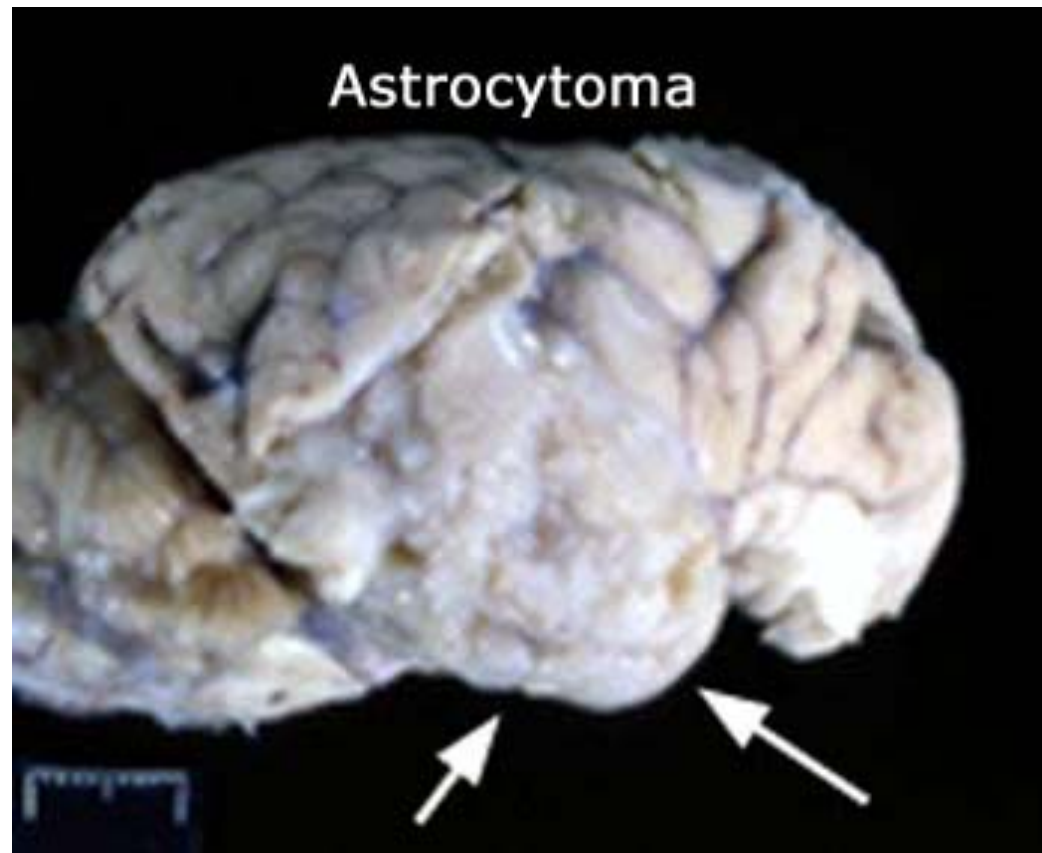
# Well differentiated astrocytoma

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

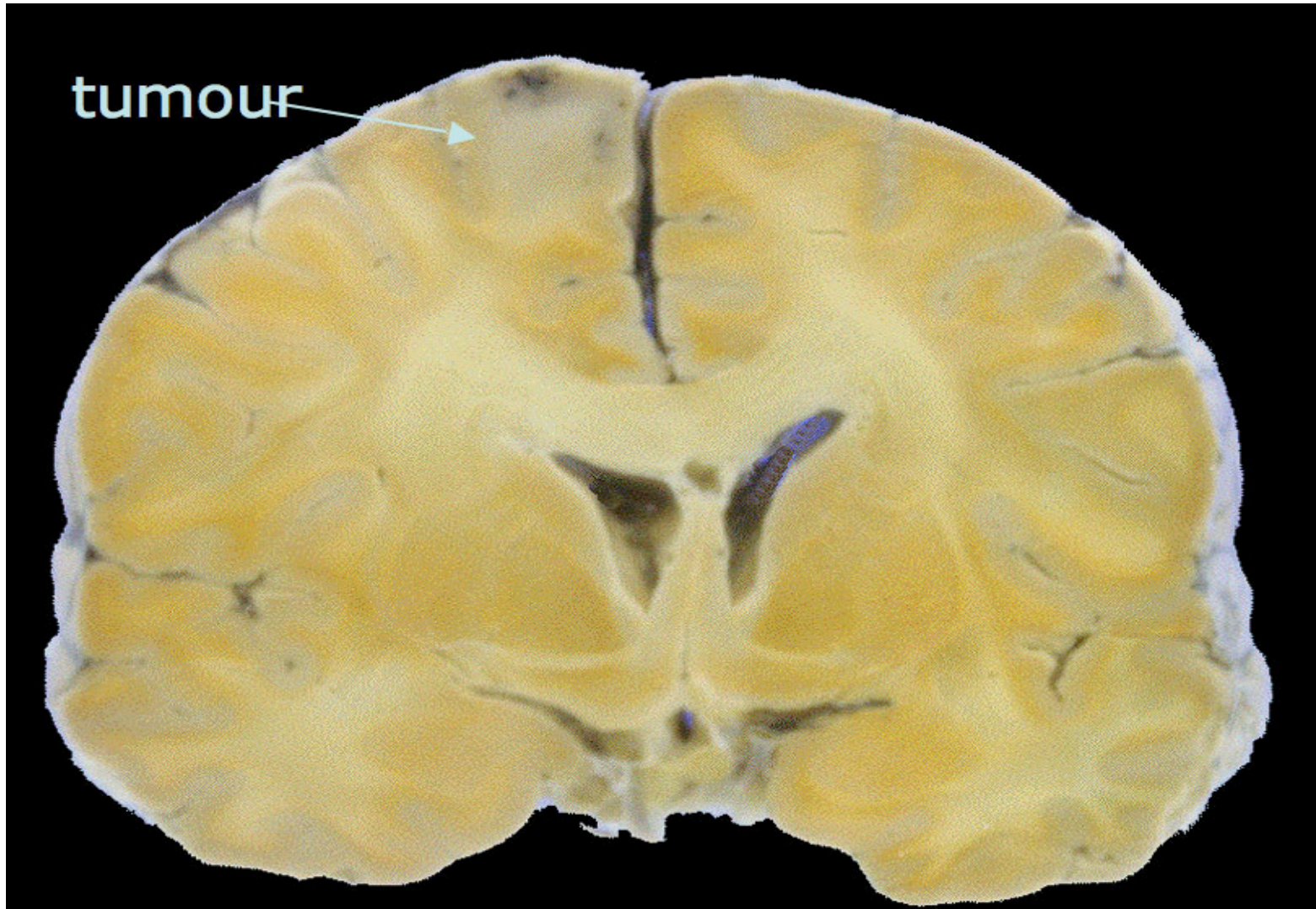
# Well differentiated astrocytoma gross features

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

# Well diff astro



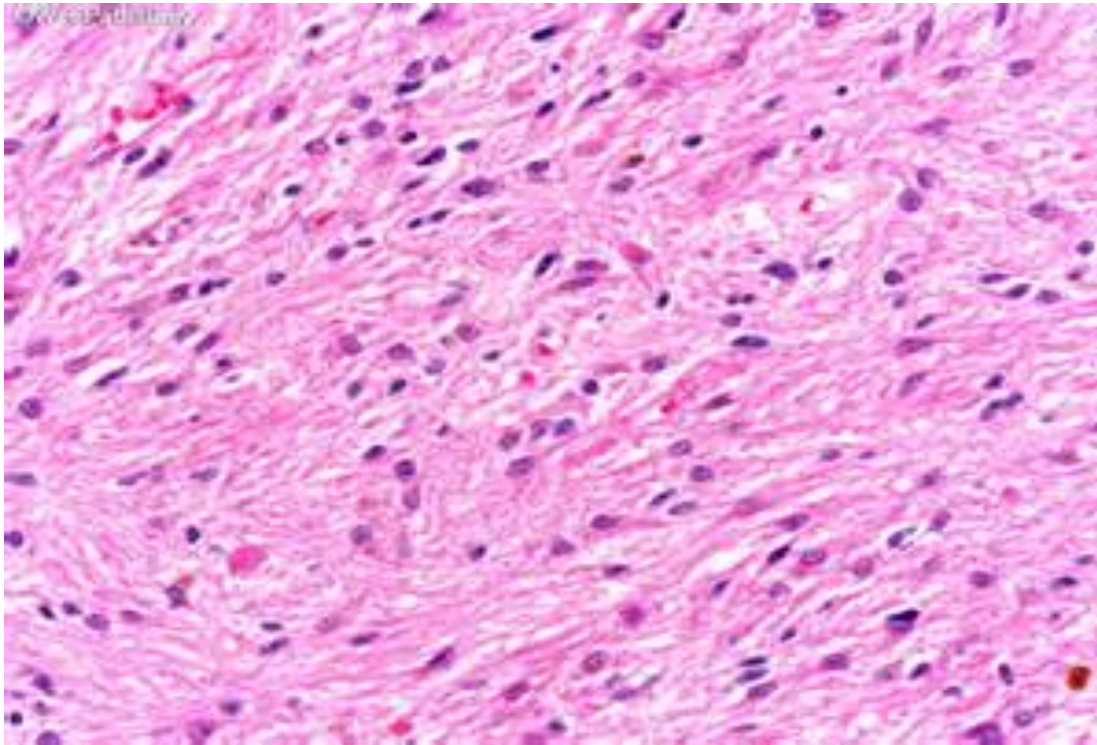
# Mowell diff astrophology



# Microscopic features

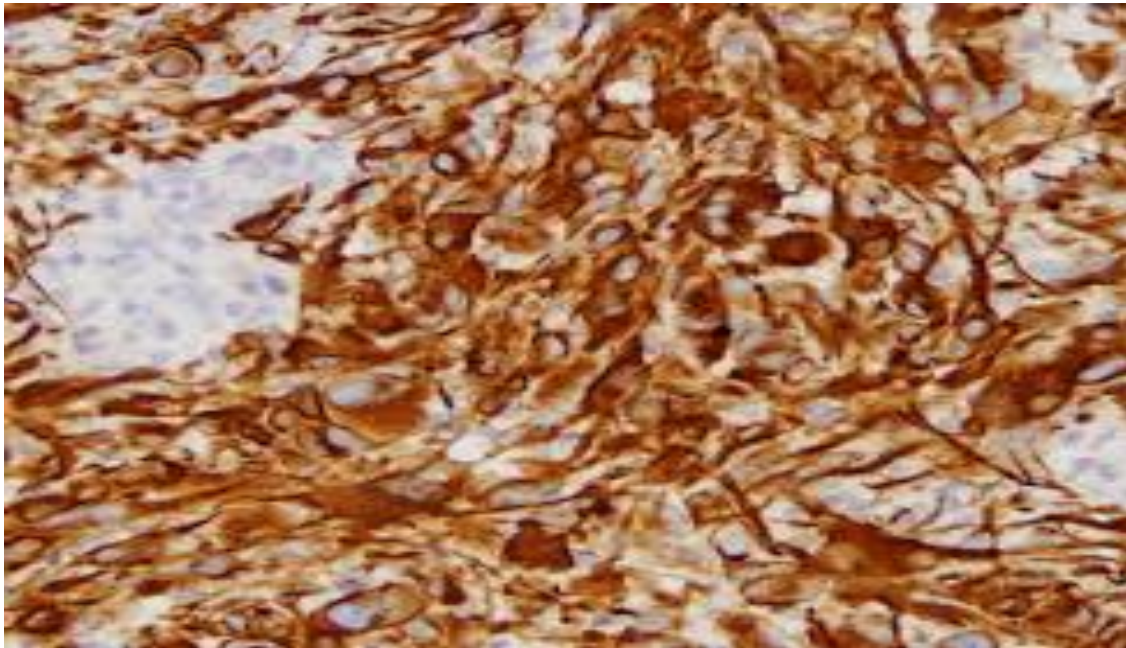
- Well diff: mild to moderate increase in glial cells.
- Some nuclear pleomorphism
- Background: fibrillary due to fine astrocytic processes.. These are positive with glial fibrillary acidic protein (GFAP)

# Well diff astro





# GFAP staining in astro

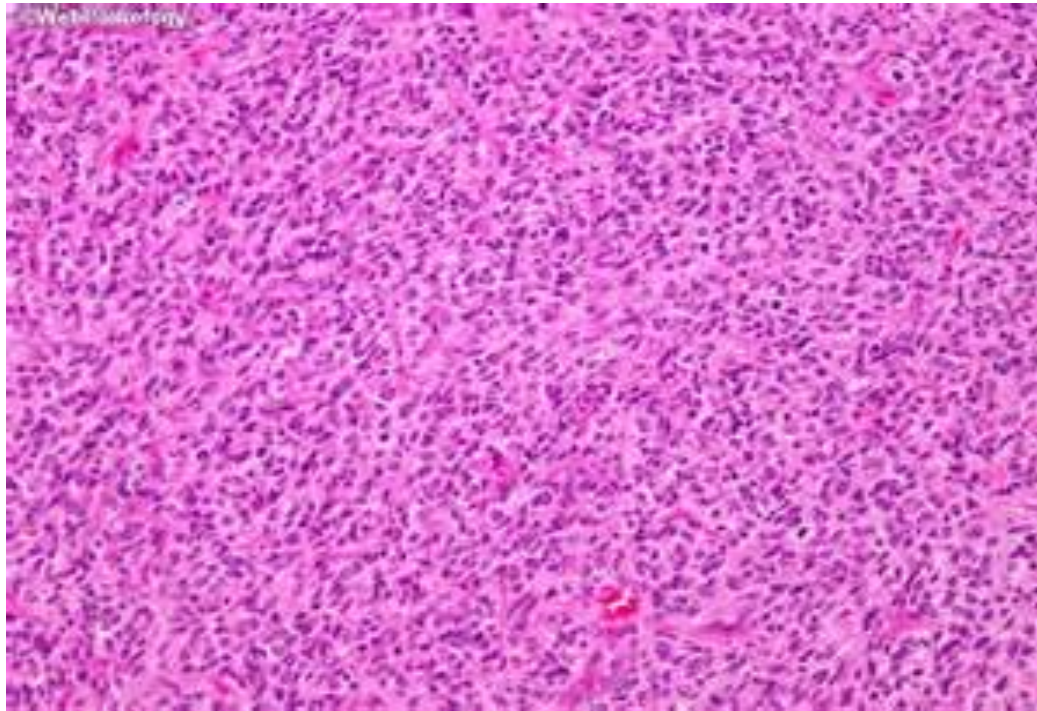


# Anaplastic astro

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



Anaplastic astrocytoma.. note the high cellularity



# glioblastoma

- 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)

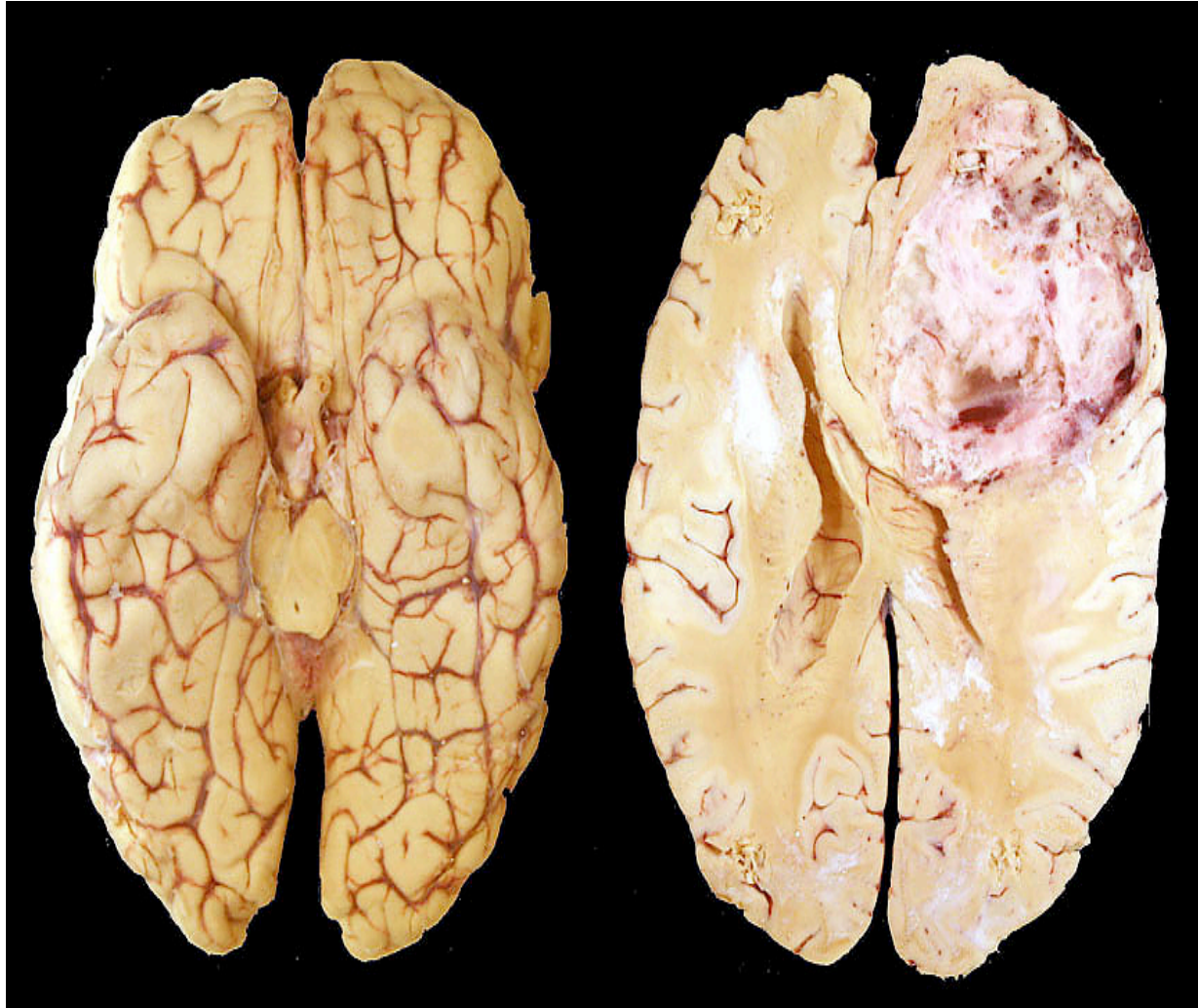
# morphology

- Glioblastoma: characterized 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 pseudopalisading)
- **or** vascular proliferation

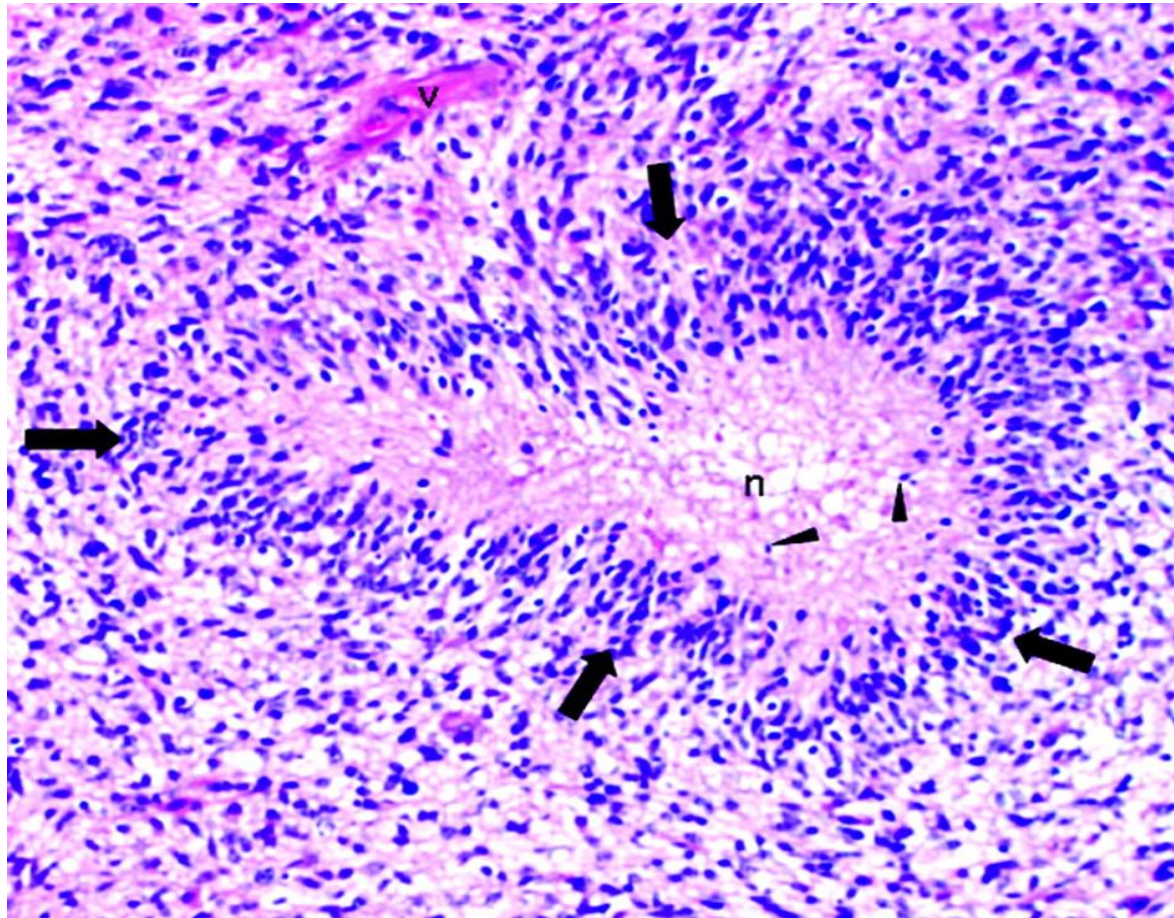


# palisade

- 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

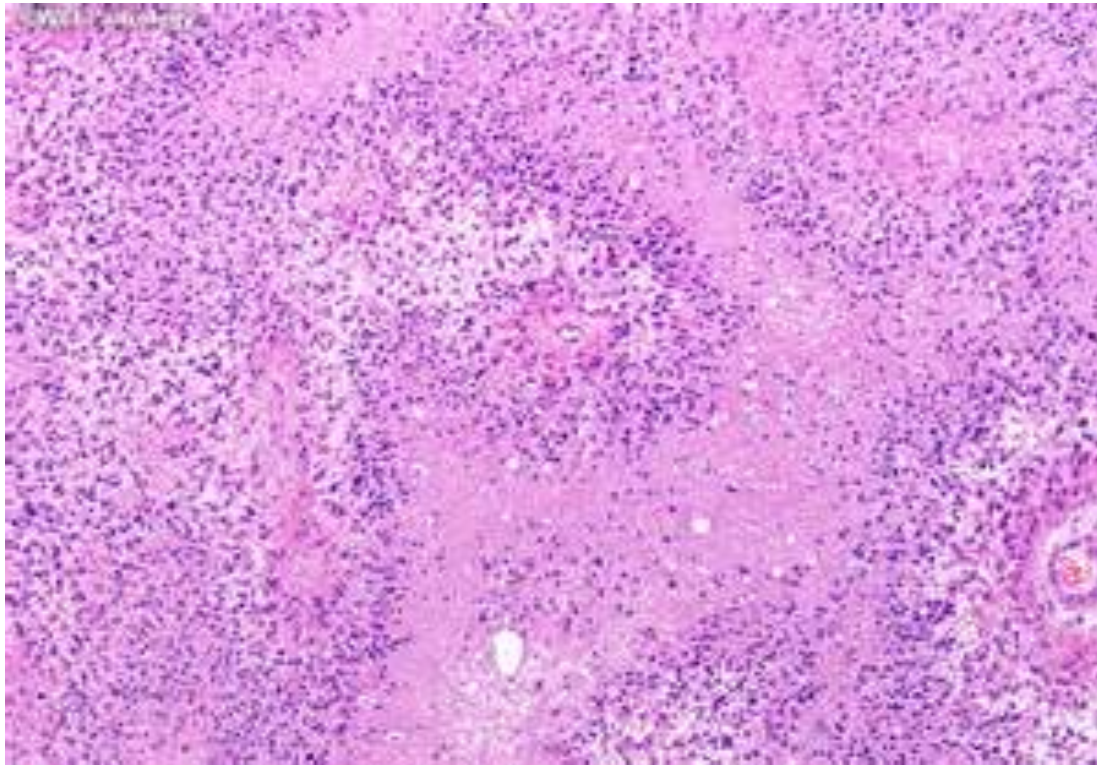


# Glioblastoma/ palisaded nuclei around necrotic area





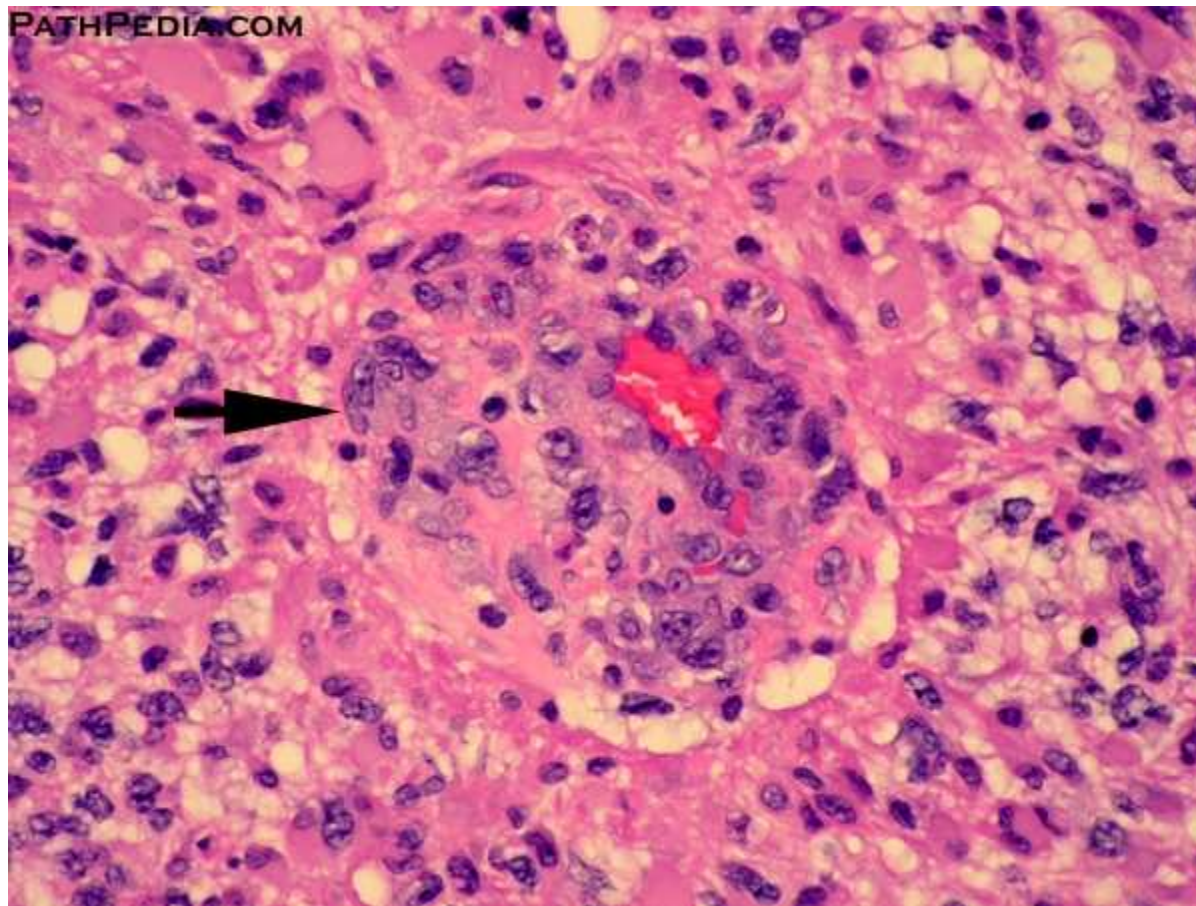
# glioblastoma



# 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: glomeruloid 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!!

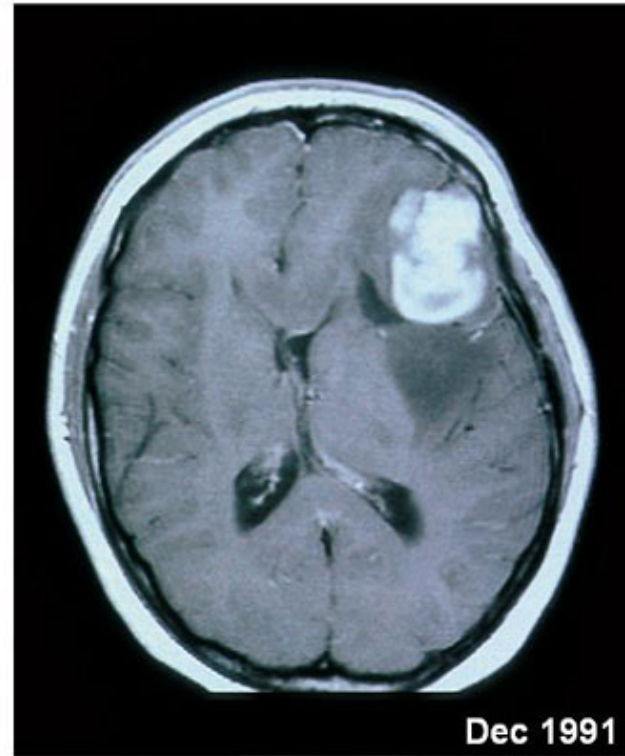
- In general, the terms 'enhancing' or 'non-enhancing' lesion refer to the uptake of Gadolinium-based contrast agent in the lesion.
- The difference between enhancing and non-enhancing is very pronounced in brain tissue, where the blood-brain barrier effectively hinders the contrast agent from accumulating 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.





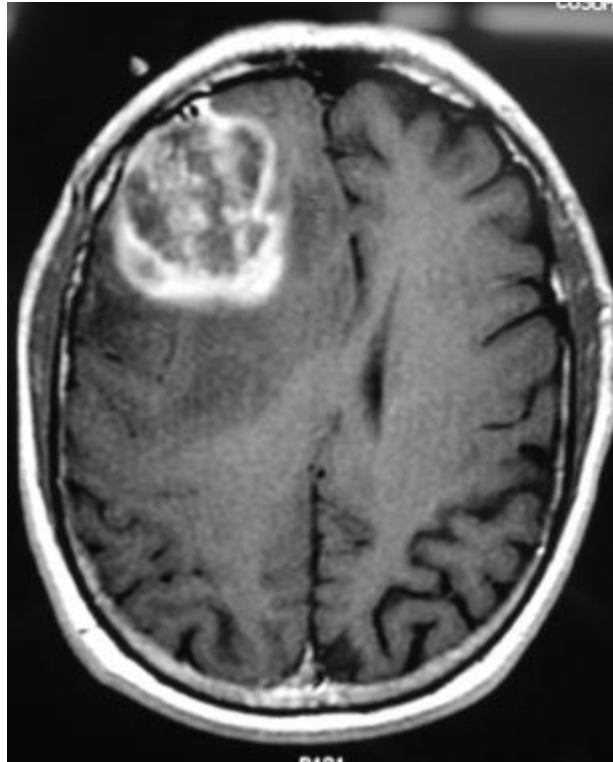
Low-grade astrocytoma  
(WHO grade II)

→  
5 years



Secondary glioblastoma  
(WHO grade IV)

# Enhancing lesion



# 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

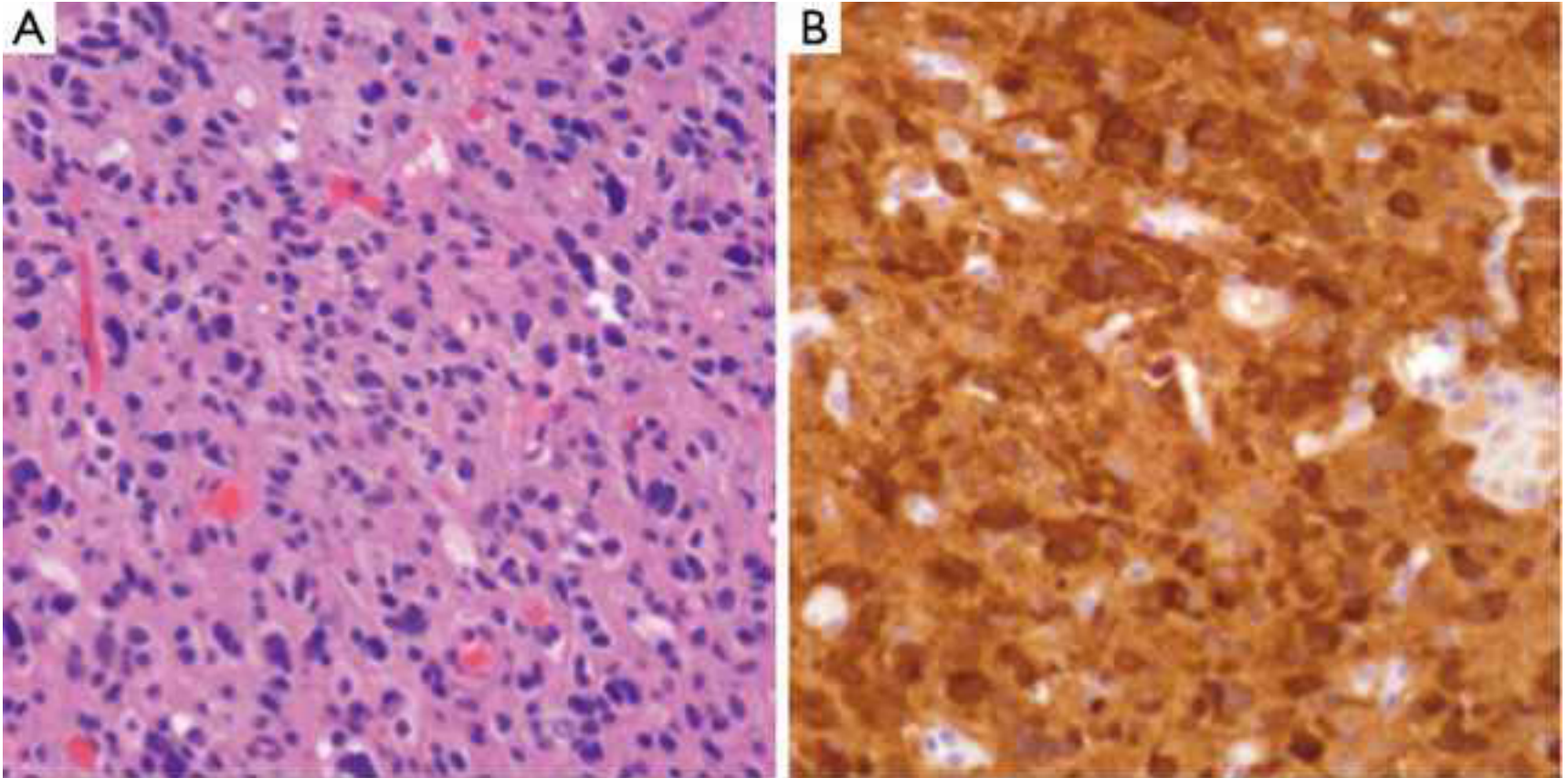
Glioblastomas are divided in the 2016 CNS WHO into

- (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.

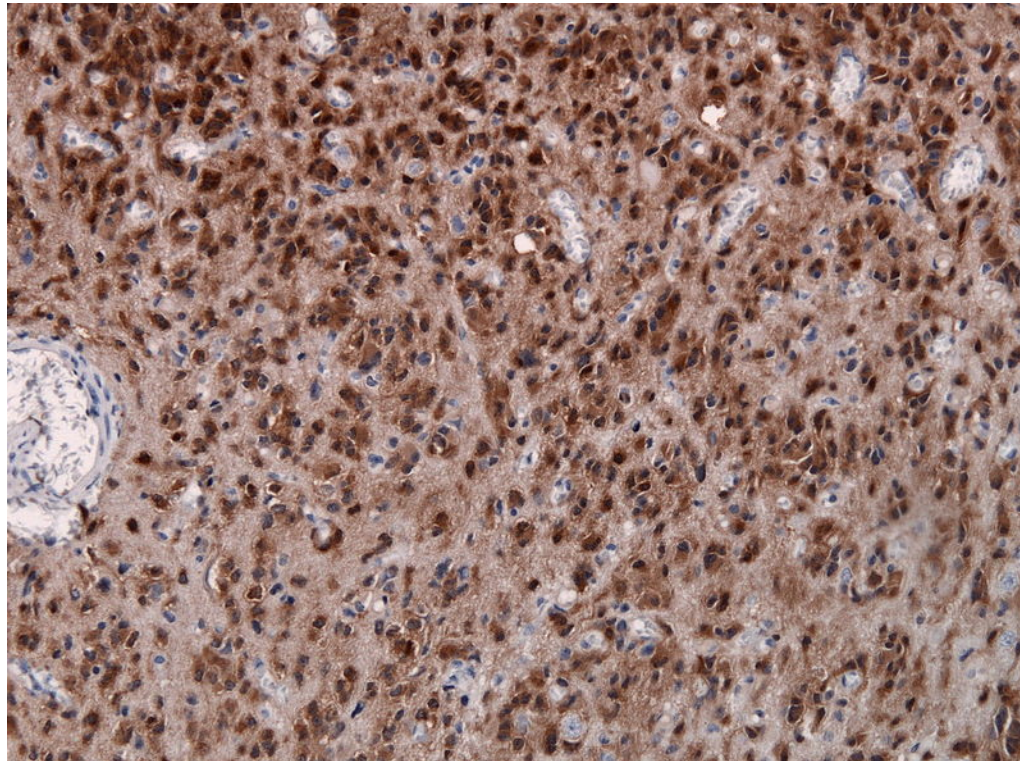
# note

- 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}
<i>TERT</i> promoter mutations	72%	26%	{1801,1830}
<i>TP53</i> mutations	27%	81%	{1797}
<i>ATRX</i> mutations	Exceptional	71%	{1519}
<i>EGFR</i> amplification	35%	Exceptional	{1797}
<i>PTEN</i> mutations	24%	Exceptional	{1797}

# FYI

