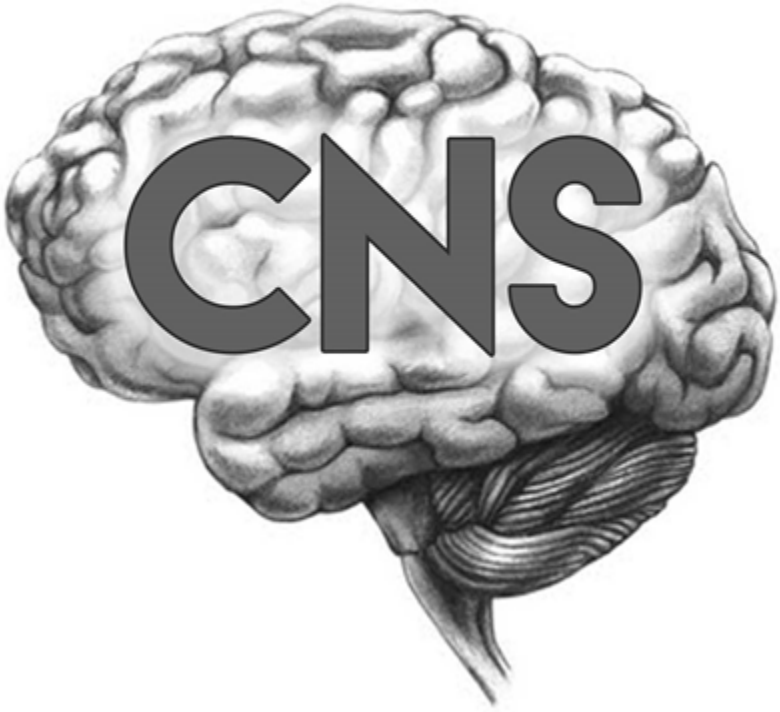

PATHOLOGY

☑ Sheet ○ Slide ○ Handout

Number

9

Subject

CNS tumors

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Date: **00/00/2016**

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In the name of Allah we start

CNS tumors

This sheet was written according to the records of all sections.

Topics of this lecture :

- Epidemiology of CNS tumors.
- Characteristics of CNS tumors.
- Classification of CNS tumors.
- Gliomas\ tumors of glial cells.

Epidemiology of CNS tumors

CNS might develops a tumor just like any other systems and organs in the body.

❖ The prevalence of CNS tumors depends on many factors :

- Tumors in the CNS can arise in the **brain** or in the **spinal cord**.
  - ⇨ It's more common in the brain.
  - ⇨ Brain tumors :around 10-17/100,000 population.
  - ⇨ While spinal cord tumors : around 1-2 /100,000 population.
  - ⇨ Which means that the prevalence of brain tumors is almost ten times the prevalence of spinal cord tumors.

- CNS tumors can be **primary** (tumors that originate from the cells of the brain itself for example) or **secondary** (tumors that metastasize to the brain from the rest of the body).
  - ⇨ Primary tumors are more common than secondary tumors in the CNS.

- ⇨ Secondary tumors account for 1/4th to ½ of all CNS tumors (25-50%).
- ⇨ The rest are primary tumors; so primary tumors account for 1/2th to 3/4th of all CNS tumors (50%-75%).
- ⇨ Note that : Although the brain is a common site to receive metastasis from the rest of the body, but still primary tumors are the most common.

- CNS tumors can be developed in **children** and **adults**.
  - ⇨ It's more common in children (20% of all childhood tumors); because a child's brain is undergoing several developmental changes which may affect the cellular mechanisms of neuronal & glial cells.
  - ⇨ 70% of childhood tumors arise in the posterior fossa.
  - ⇨ 70% of adulthood tumors arise within the cerebral hemispheres above the tentorium.

- So the prevalence of CNS tumors depends on the site (brain /spinal cord), age group, and also if it's a primary or secondary tumor.

❖ CNS tumors in Jordan :

According to national cancer registry in 2013 (latest published information):-

- CNS tumors are more common in males than females.
  - ⇨ It represents 3.7% of the overall tumors in males, and 2% of the overall tumors in females.
  - ⇨ In 2013, 95 cases have been diagnosed in males, and 58 cases in females.
- CNS tumors are the **10th** most common tumor among Jordanian **adults**.
- **Second** most common among Jordanian **children**.
- Frequency of incidence among Jordanians according to the age group, 2013:
  - ⇨ Most cases are in people between 0-9 age group.
  - ⇨ A large incidence in the age group less than 39.

So it's not that rare

- ⇨ The lowest percentage is in (over 70) age group.
- ⇨ Note that, there is no age immune; CNS tumors can be developed at any age group, however they are more common in young ages especially before 9 years old.

- These are the statistics in Jordan which are similar to the statistics in the rest of the world (there is no big difference between Jordan and other countries).

Characteristics of CNS tumors

❖ CNS tumors differ from the tumors in the rest of the body :

- They are mostly developed in the stroma, and rarely developed in the parenchymal cells, which means that the glial tumors are more common than the neuronal tumors.
- No premalignant or in situ stage.
  - ⇨ Normally, there is a pre-cancerous\pre-invasive stage for most of the tumors in the body which can be detected and recognized clinically (in other words, a tumor does not appear suddenly; there is a sequence of events that can be histologically detected). For example :

    -In the case of colon cancer or cervical cancer:

    Irritation\ genetic mutation → increased proliferation → adenoma → dysplasia → then the invasion occurs.

    -In the case of stomach cancer:

    gastritis → intestinal metaplasia → gastric atrophy → dysplasia → invasive malignancy.

    -In the case of breast cancer:

    Carcinoma in situ (CIS) → invasion.

CIS : An early stage **cancer** in which the cancerous growth or tumor is still confined to the site from which it started, and has not spread to surrounding tissue or other organs in the body.

Note: premalignant stage is usually associated with some clinical signs and symptoms but this is not always the case

In the case of CNS tumors this sequence of events is not recognized;

CNS tumors just come out of blue with no clinically recognizable premalignant stage.

- ⇨ How can we explain that the CNS tumors come suddenly with no clinically apparent pre-cancerous stage, although they have several mutations and it's a multi-step process like any other tumor in the body?
  → They might have a pre-cancerous stage, but we can't recognize it clinically due to the lack of signs and symptoms of that stage.
  → We can't examine the brain in a living individual, but we can examine other organs in the body; for example: we examine the GI tract by endoscopy.
  →They might actually don't have a pre-cancerous stage; because if it exists it will cause signs and symptoms.

*** These are just theories; the actual reasons are still unknown.

➔ So in general, clinically at least, there is no recognizable pre-cancerous stage for the CNS tumors.

- Low grade lesions can widely infiltrate with serious clinical deficit.

Note:

Infiltration: cancer or a lesion that has spread beyond the layer of tissue in which it developed and is growing into surrounding, healthy tissues. Also called invasive cancer.

Metastasis: the development of secondary malignant growth at a distance from a primary site of cancer

low grade lesion: a lesion in which the cells have undergone minimum cellular changes such as benign tumors.

So, even benign tumors in the CNS can be dangerous and cause problems to the patients because they tend to infiltrate widely.

Note: In the body (except in the CNS) benign tumors tend (not always) to be localized in the tissue they emerge from while in the CNS they tend to infiltrate. Please note that this doesn't apply all the times; for example: pleomorphic adenoma (benign tumor in salivary glands) tends to infiltrate but less aggressively than Gliomas.

In other words, criteria used to distinguish between benign and malignant tumors in the CNS isn't the same criteria used in the rest of the body

- Anatomical site is important in outcome or prognosis regardless of type, grade.
  - ⇨ If there is a tumor in the brain stem, even if it's small and benign, it can be dangerous and fatal. For example: a meningioma near the covering of the brain stem can compress it and can even be fatal although it's benign.
  - ⇨ So the location is very important to detect the outcomes of a lesion

- Rarely spread outside the CNS.
  - ⇨ CNS tumors don't metastasize (or very rarely metastasize), but they receive metastasis from the rest of the body.(يستقبل ولا يُرسل)
  - ⇨ Even the most malignant brain tumors don't metastasize (this is how they behave but they are not benign).
  - ⇨ Except if the tumors transmitted by the CSF, they can go metastasize to the spinal cord for example.
  - ⇨ The reason behind this characteristic may be: the presence of the BBB and lack of lymphatics in the brain.
  - ⇨ It's important to know that the CNS tumors can rarely metastasize; because if there is a patient with lung tumor and brain tumor, we can suspect that the tumor starts in the lung (primary) then spreads to the brain, and we take a biopsy from the lung to make sure.
  - ⇨ Note: although CNS tumor don't usually tend to metastasize but they are highly infiltrative

∞ So these are the characteristics of the CNS tumors that are not found in the rest of the body.

Classification of CNS tumors

- To understand the tumors of any organ in the body and detect how it will behave, we need a classification (2 types: grading system, and staging system).
  what is the difference between grading system and staging system in general (outside the CNS) ?

  Grading system has to do with the morphology of the tumor, its shape under the microscope, how much it's similar to the cell which it's originated from or the cell it's differentiated towards and accordingly the tumors will be classified into grade I, grade II, grade III; or into well differentiated, moderately differentiated, poorly differentiated.

  Staging system, on the other hand, deals with the extent of the Tumor, spread to the lymph Nodes, or forms a distant Metastasis. They are mostly 4 stages, but some organs might have 5 stages.

  Staging system is more important for prognosis than the grading system in most of body tumors (colon, breast, skin,...) , it can predict the prognosis is and if the patient will be able to live or not.
  For example: in the case of colon cancer; The five-year survival rate for the patient who is in the stage 1 of the tumor is 92-93% (the tumor is still localized and didn't spread to the lymph nodes or metastasized), while the five-year survival rate for the patient who is in stage 4 (spread to lymph nodes and metastasis) is only 6%.
  Note: There are different types of staging systems, but the most common and useful staging system for most types of cancers is the TNM (Tumor size, Node, Metastasis) system.

❖ In the CNS, the classification of tumors is quite different than the rest of the body due to the characteristics mentioned previously. so CNS tumors were classified according to :

a. The cell of origin
b. WHO classification
c. Classification in general

a. Classification according to the cell of origin:

- Gliomas (from glial cells).
- Neuronal tumors\ neural cell related tumors (from neural cells).
  - ⇨ Glial tumors are more common than the neural ones; because the glial cells are actively proliferating while the neural cells are permanent cells that don't proliferate.
- Embryonal (primitive) neoplasms: medulloblastoma from the primitive cells in the brain (blasts = primitive undifferentiated cells).
- Others: lymphoma and germ cell tumors.
  - ⇨ How can lymphoma develope in the brain (primary brain lymphoma) although it lacks large numbers of lymph nodes?
    - Blood vessels in the brain contain lymphocytes, if these lymphocytes have a problem or mutation they might cross the BBB and form a mass.
    We will notice when we talk about lymphomas that they grow around the blood vessels.
- Meningioma\ meningeal derived tumors.
- Metastatic tumors.

** Schwannomas (from Schwann cells) are tumors that develop in the PNS and around nerve roots in the spinal cord ➔ not a CNS tumor

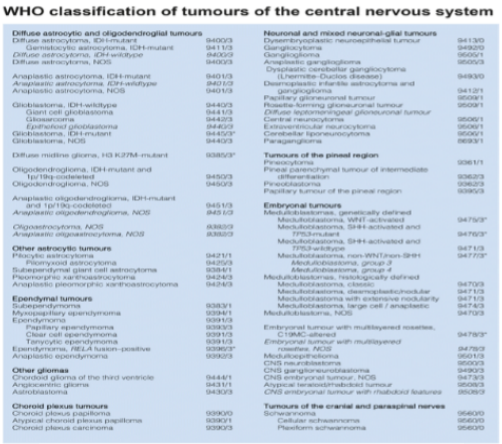
b. WHO classification of CNS tumors:

- Generally: 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. So each

organ has a book known as the blue book which contains all tumors associated with that organ.

The basis of WHO classification of tumors is dependent on a group of histological, immunohistochemical, and genetic factors.

- Regarding the CNS: The first edition was published in 1979, 4th edition was in 2007, and the newest edition in 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.
  - ⇨ The 2007 WHO classification depends on the histology of the tumor and its shape under the microscope; if it looks like the glial cells then it's a glioma, if it looks like the neural cells then it's a neuronal tumor, and so on...
  - ⇨ However in 2016, with the great progression of genetics, the tumors have been classified according to the genetic mutations in addition to the morphology (integrated layered diagnosis); thus formulating a concept for how CNS tumor diagnosis should be structured in the molecular era.
  - ⇨ The 2016 classification was also used in classifying tumors with similar morphological patterns. For example, we can't depend on the morphology only to diagnose lymphomas because they almost have the same shape under the microscope, so we depend largely on the genetic mutation to classify them.


WHO classification of tumours of the central nervous system

Not to be memorized

Follicular lymphoma has certain translocation, burkitt lymphoma has a big amplification, and so on...

- The 2016 WHO classification is very important because it has better prognostic and therapeutic implications; because if we know the genetic mutation and the protein product of this genetic mutation then we can target it. For example: in the case of Chronic Myeloid Leukemia (CML), we can target the kinase which is the product of Philadelphia translocation then we can cure the disease.
- That's why it's important to understand the new classification.
- In Jordan: most centers we are still using the 2007 WHO classification, because the new system needs expensive, specialized, and time consuming immunohistochemical and molecular tests such as PCR to diagnose according to genetic mutations.

- So the new classification is expensive and need more time to give the final result; while in the classification according to morphology, we use Hematoxylin and Eosin stain (2-3 JDs) and then get the primary result.
- Note: King Hussain medical center is better funded and they started working on the new system.
- In these lectures we will mainly discuss the classical classification (2007 WHO classification) but will give some examples of the new changes (2016 WHO classification).
- Note that CNS tumors rarely metastasize and the brain lacks to the lymph nodes so we don't usually use the TNM staging for these tumors. That's why there is a **WHO grading system** for CNS tumors, which is a hybrid of grading system and staging system (integration between the morphology and the behavior).
  WHO Grading of CNS tumors determines outcome, although site is also important; so the grade here means prognosis.

- WHO grading:

*(The table is not for memorization).

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

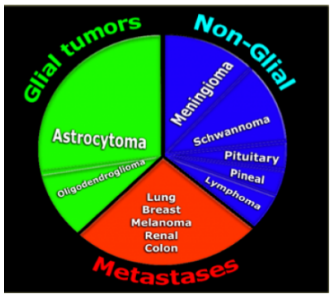
Grading system of WHO divides CNS tumors regardless of their cells of origin (i.e. glioma, neural tumors, meningioma,…) into 4 grades:

- WHO I : Specific tumors, we know by definition that they are benign; such as pilocytic astrocytoma (this tumor by definition is a WHO grade I).
- WHO II : A small increase in the cellularity, mitosis, and pleomorphism.

  *pleomorphism = variability in the size, shape and staining of cells and/or their nuclei.
- WHO III : large increase in the cellularity, mitosis, and pleomorphism.
- WHO IV : Has certain characteristics, and to say that the tumor is in the WHO IV we have to see either necrosis or vascular proliferation (or both) in the histological section.

c. Classification in general :

Simplest classification of the brain tumors : primary tumors and secondary tumors (metastases), Primary tumors can be glial tumors (which are the majority) or non-glial tumors.



Gliomas\ tumors of glial cells

a. The most common primary brain tumors.
b. Gliomas are classified to: astrocytomas, oligodendrogliomas, and ependymomas.
c. Previously, they thought that the ependymoma originates from ependymal cells, the astrocytoma originates from astrocytes, and the oligodendroma originates from oligodendrocytes.
d. It is now thought, according to the genetic studies, that these three types originate from one cell which is **glial progenitor cell** that can differentiate to these three morphological types.

e. ### Astrocytomas:

- ⇨ The most common among glial tumors; because astrocytes are the most abundant cells.
- ⇨ Two major types:
  - Localized astrocytomas: there is only one glioma that is considered as WHO I which is the **pilocytic astrocytoma** (will be discussed in the next lecture).
  - Diffuse (infiltrating) astrocytoma.
- ⇨ WHO classification of astrocytomas:

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

f. Diffuse astrocytoma : can be of WHO II, WHO III, or WHO IV; there are no WHO I diffuse astrocytomas.

- Spectrum of histological differentiation:
  i. Well differentiated → WHO II.
  ii. Anaplastic astrocytoma → WHO III.
  iii. Glioblastoma → WHO IV.

  These types will be discussed below

  *Prognosis is affected by the grade.

- Patients with diffuse astrocytoma present with :
  - Seizures (any mass or brain tumor affects the nerve impulses will cause Seizures).
  - Headache (صُداع بصحي من النّوم), one of the important symptoms.
  - Increased intracranial pressure with all its signs and symptoms.
  - Neurologic deficit (depending on the affected area).
  - Diffuse astrocytoma can affect the blood vessels and cause hemorrhage.

- Account for 80% of adult gliomas
- Present at 40-60 years of age

i. <u>Well differentiated astrocytoma (WHO II) :</u>
   - Can be static for several years, but can progress to a higher grade.
   - Mean survival is more than five years.
   - Gross features\ macroscopically [figure 1]:
     Poorly defined grey, infiltrative tumors that invade the brain without forming a discrete mass.

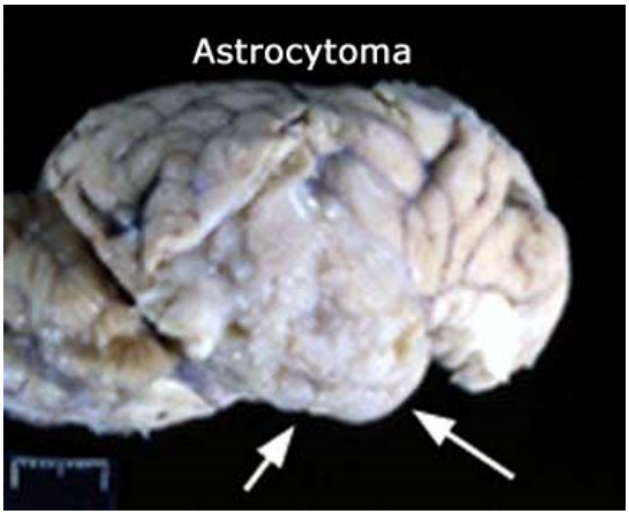


Figure 1: gross features of well differentiated astrocytoma.

Area which is not well defined; small bulging and expansion of the brain.

Asymmetric area with diffuse infiltrative and abnormal whitish color

we don't see a mass.

- Microscopic features[figure 2]:
  mild to moderate increase in astrocytes.
  Few or no mitosis.
  Some nuclear pleomorphism.
  Increase in fibrillary background.

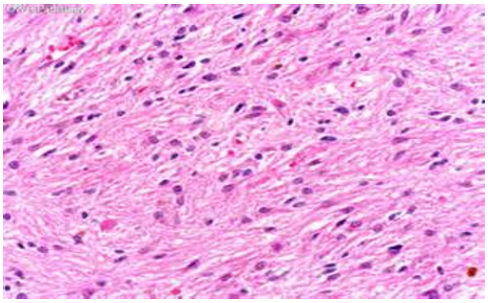


Figure 2 : microscopic features of well differentiated astrocytoma.

The background is fibrillary due to fine astrocytic processes which are positive with glial fibrillary acidic protein (GFAP)

Note: The glial fibrillary acidic protein (GFAP) stain is done to determine whether the lesion is glial or neural because glial fibrillary acidic protein is a protein found in glial cells. So when the specimen is stained in brown (positive) it indicates that the tumor is of glial origin.

By using this stain we can know if the tumor is of glial origin or not but we can't know its specific type (astrocytomas, oligodendrogliomas, or ependymomas).

notice that the microscopic features of well differentiated astrocytoma is similar to that of gliosis; so how we can differentiate between them? We examine more than one aspect (clinical / histopathological/ radiological/ genetics)

before we decide it is a well differentiated astrocytoma. For example:

-histopathological: increase in cellularity +positive GFAP stain ➔ strong evidence of well differentiated astrocytoma

- the diagnosis can be confirmed by using genetics to know if there is a mutation, then we can know if it's a tumor or gliosis.

❖ Anaplastic astrocytoma (WHO III) [figure 3]:

- ⇨ More cellular than well differentiated astrocytoma.
- ⇨ More pleomorphism.
- ⇨ Mitotic figures.

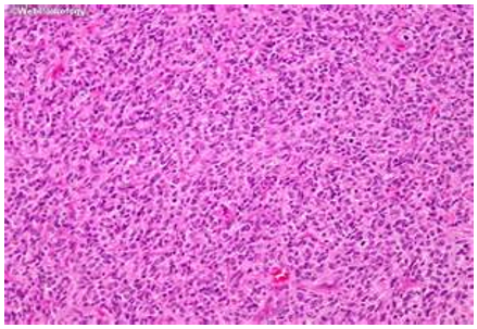


Figure 3 : microscopic features of Anaplastic astrocytoma.

Note the high cellularity.

❖ Glioblastoma (WHO IV) / also called Glioblastoma multiforme:

- ⇨ Advanced stage.
- ⇨ The most dangerous one among all types of glioma.
- ⇨ Survival rate 15 months without treatment
- ⇨ Survival rate with treatment has improved : 25% live up 2 years or more with resection followed by chemo and radiotherapy
- ⇨ Poor prognosis
- ⇨ Glioblastoma are two types (both have the same appearance):
  - Primary astrocytoma: the tumor started as glioblastoma from the beginning.
  - Secondary glioblastoma: the tumor results due to progression from a previous astrocytoma (from grade II or grade III).

→so if the patient was diagnosed with a well differentiated

astrocytoma for example, the tumor might progress to Glioblastoma which has a bad prognosis.

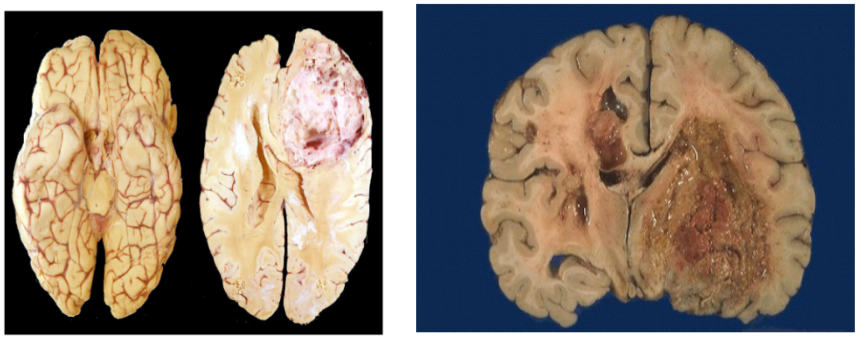
⇨ Macroscopic Morphology of glioblastoma [figure 4]:

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

Figure 4 : Morphology of glioblastoma.

Big mass.

There are several types of appearance (pale, soft, cystic, hemorrhagic, and necrotic areas); glioblastoma multiforme.



- Glioblastoma multiforme looks like Anaplastic astrocytoma plus: Either necrosis (usually pesudopalisading) [figure 5]: palisades here indicate that the cells arranged next to each other rather than being randomly distributed.

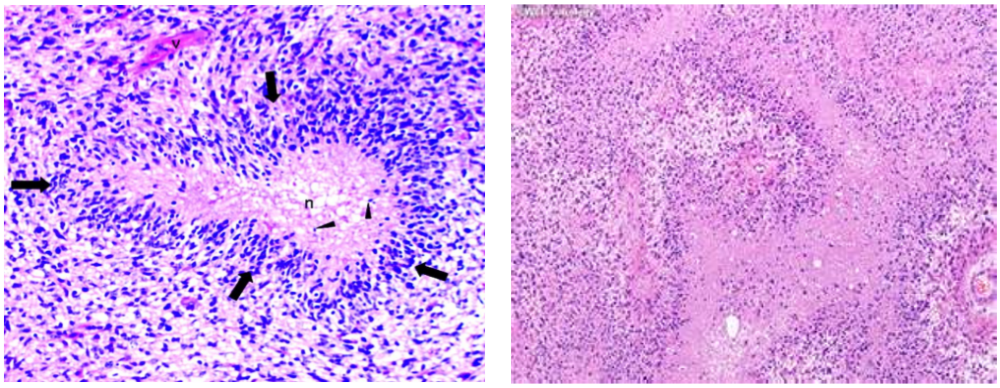


Figure 5: Glioblastoma/ arranged nuclei around necrotic area.

Or vascular proliferation:

- 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.
  Normally, the capillaries have one layer of endothelial lining.
- If it is marked and severe it forms: **glumeruloid body** because it's similar to the glomerulus in the kidney which is a tufts of capillaries. [Figure 6].

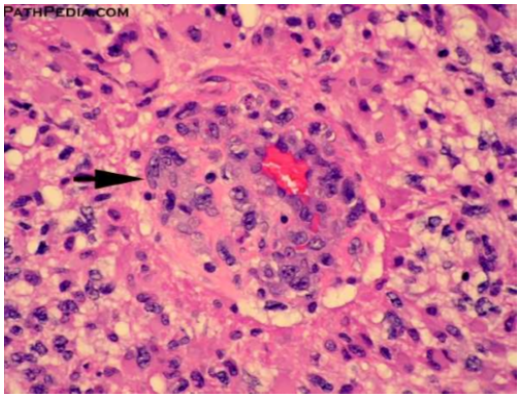


Figure 6 : Glomeruloid body.

Many layers of endothelium\ capillaries.

⇨ Radiological appearance [figure 7]:

- The formed blood vessels in high grade astrocytomas don't have the same structure as the BBB; they are leaky and the junctions between them are abnormal.
- This gives **contrast enhancement** on imaging techniques. Why??
  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.

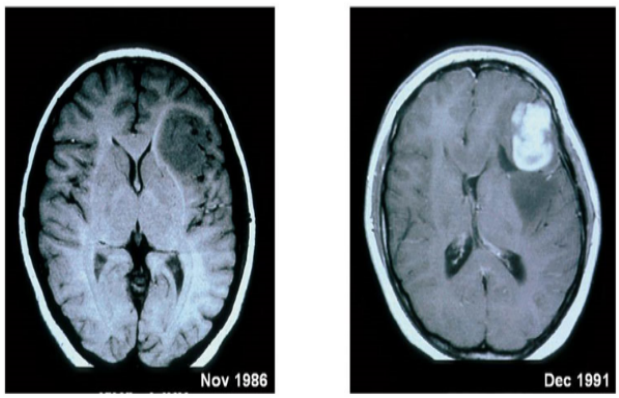


Figure 7: radiological appearance.

The more the leaky blood vessels, the more the contrast enhancement on imaging studies.

That's why we see more contrast in malignant tumors in comparison to the benign ones.

Left : most likely to be benign.

Right : most likely to be malignant.