Neoplasia
Lecture 2

CHARACTERISTICS OF BENIGN AND MALIGNANT NEOPLASMS

1. Differentiation and anaplasia

Differentiation refers to the extent to which neoplasms resemble their parenchymal cells of origin, both morphologically and functionall

- **Lack of differentiation is called Anaplasia**

Very important step in diagnosis is differentiating between benign and malignant tumors

→ Can undergo complete excision and the patient will continue his life normally

Diagnosis is dependent not only on examination but also on clinical data that may be collected
It's wrong to depend on one criteria

One of the important characteristic is the degree of differentiation of the tumor cell , normally tissues in side our body are in the most differentiated form that's what cells in different tissues are different from each other

Malignant tumor resemblance to normal tissue is variable

Degree of undifferentiation or loss of differentiation in tumor cells is called anaplasia

Malignant tissues loose normal cell characteristic and gain new abnormal characteristics

Look similar to normal tissues

Degree of resemblance of tumor tissues to the normal

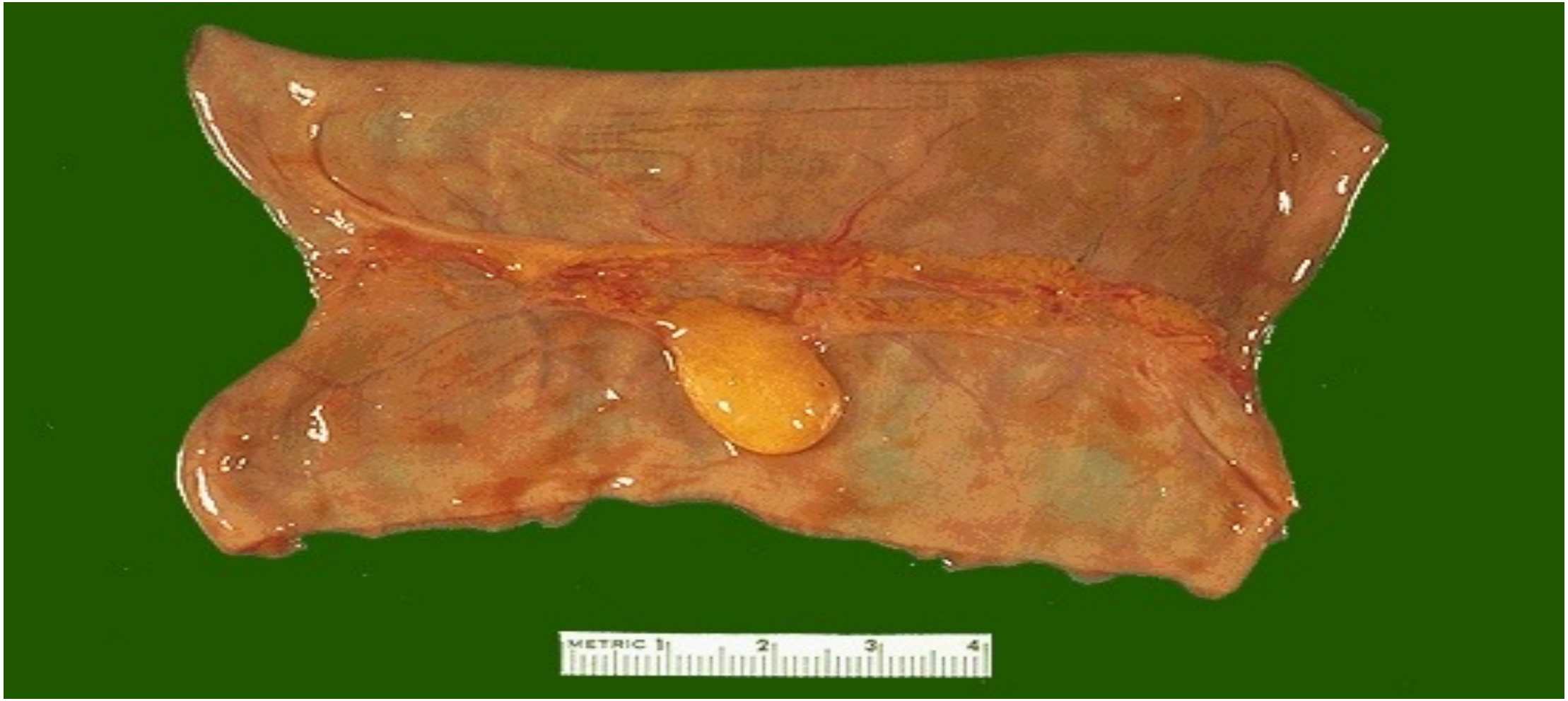
- **Benign neoplasms are composed of well-differentiated cells that closely resemble their normal counterparts.**
- **A lipoma is made up of mature fat cells laden with cytoplasmic lipid vacuoles, and a chondroma is made up of mature cartilage cells that synthesize their usual cartilaginous matrix—evidence of morphologic and functional differentiation.**

benign tumor made up of adipose tissue (fat cells).

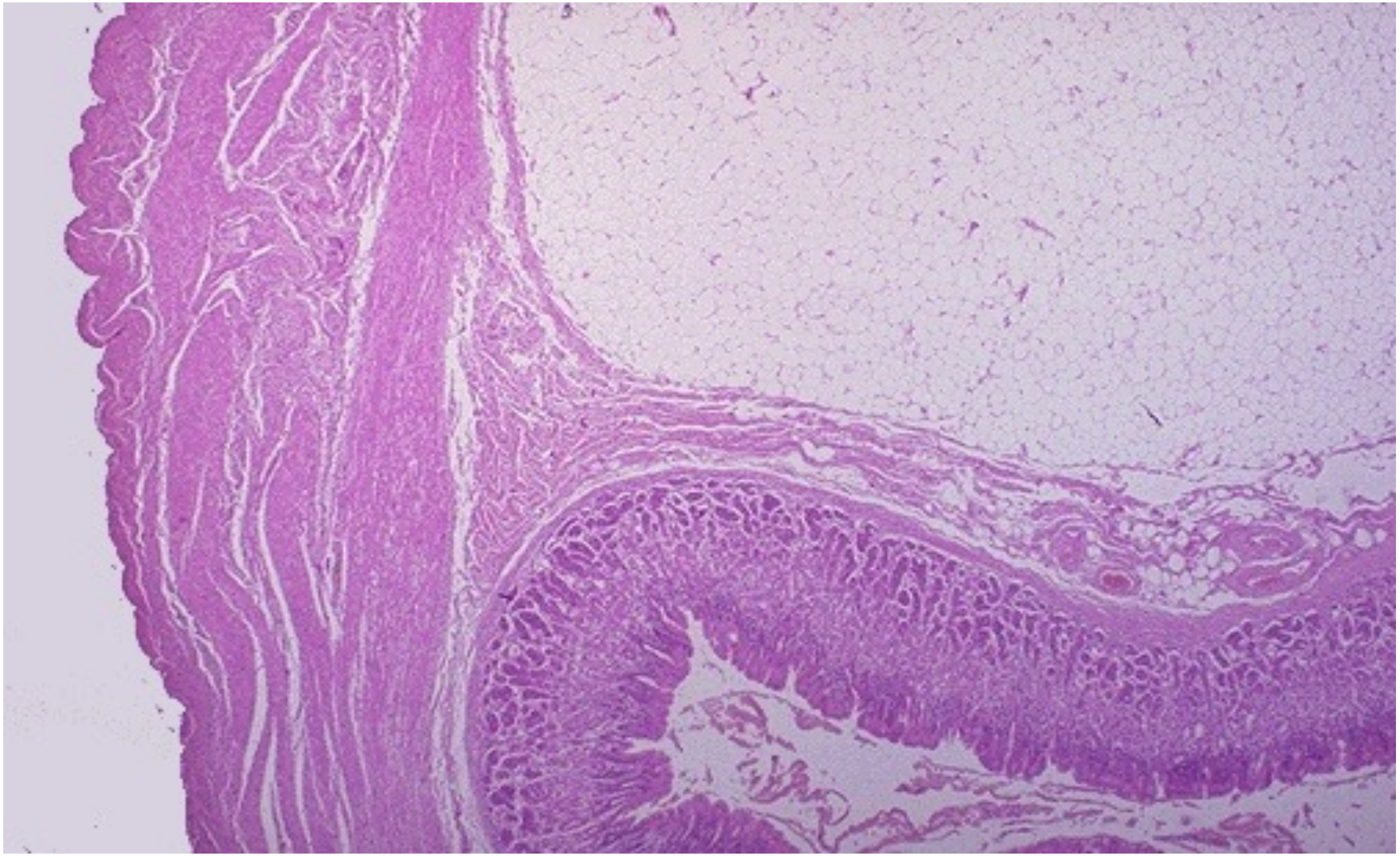
- **In well-differentiated benign tumors mitoses are usually rare and are of normal configuration.**

Benign tumor formed of fat tissue vs normal fat in the body, they will look like each other

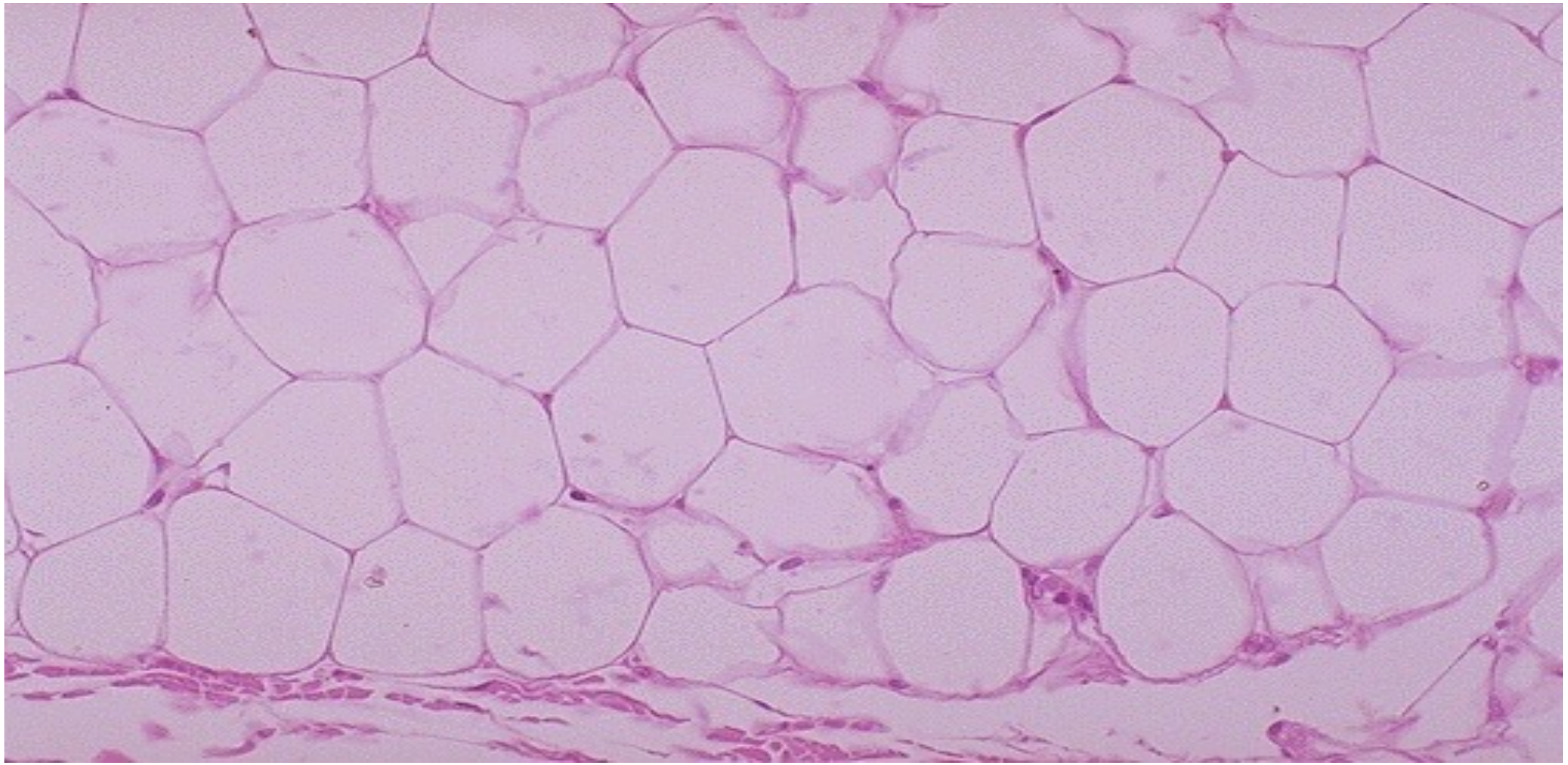
Lipoma



Lipoma



Mature adipose tissue (lipoma)



- **Malignant neoplasms exhibit a wide range of parenchymal cell differentiation most exhibit morphologic alterations**

- **Malignant tumors can exhibit:**
- **Well differentiation** Tumor site can be known
- **Intermediate differentiation**
- **Poor differentiation** When we look at the tumor tissue we can't be sure about the tumor origin (no resemblance) (they loose most of their similarity to the normal tissue)
- **Anaplasia (dedifferentiation, or loss of the structural and functional differentiation of normal cells)**

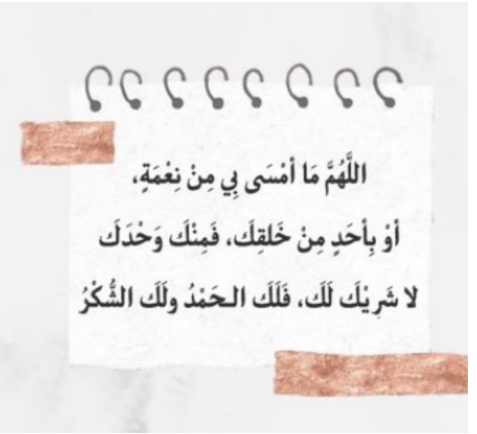
Why this is an important process ? because each will behave in a different way affecting the outcome of the tumor (well differentiated tumors behave better than poorly differentiated or anaplasia

Extreme hyperchromatism refers to cells having nuclei that appear unusually dark when viewed under a microscope. This happens because the nuclei contain an increased amount of DNA or are densely packed with chromatin, making them stain more intensely. It's often associated with malignancy or high cellular activity, indicating possible cancerous changes.

- **Malignant cells display the following:**
- **1. Nuclear Pleomorphism (variation in size and shape)**
- **2. Nuclear abnormalities (extreme hyperchromatism, variation in nuclear size & shape, or unusually prominent single or multiple nucleoli)**

Nuclear changes are more frequent in malignant cells than cytoplasmic

Normally cells in tissues sate the same size and nucleus but in malignant cells this is different, nuclei are in different sizes (enlarged in general) + hyper chromatic > black staining of nuclei because of increased amount of chromatin (large and dark nuclei may be an indicator for malignancy)



Reverse in nuclear cytoplasmic ration
It's normally (1:6 or 1:4) reaching (3:1) (reversed)

3. **Increased nuclear-to-cytoplasmic ratio that approaches 1 :**
4. **instead of the normal 1 : 4 or 1 : 6.**
5. **Enlargement of the Nucleoli**
6. **Increased mitotic activity** Dividing cells . Activated. In some types of tumors , differentiating between benign and malignant is due mitotic figures
7. **Atypical mitoses (tripolar or quadripolar)** Abnormal mitosis
8. **Tumor giant cells**
9. **Loss of polarity of tumor cells**

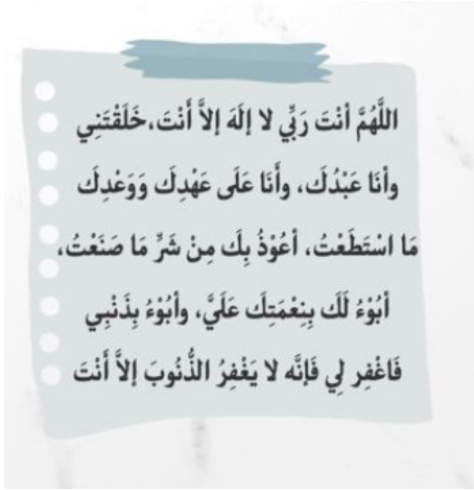
Important in tumors which are still localized. Cells are arranged in specific arrangement . Loss of arrangement is indicator of presence of malignancy

Increased or decreased or the may show new function

10. Alteration or loss of functional capacity (paraneoplastic syndrome)

When they start secreting proteins/ hormones or enzyme which are unusual to be secreted

Benign tumors don’t show these characteristics becausethey resemble normal cells



Well differentiated squamous cell carcinoma

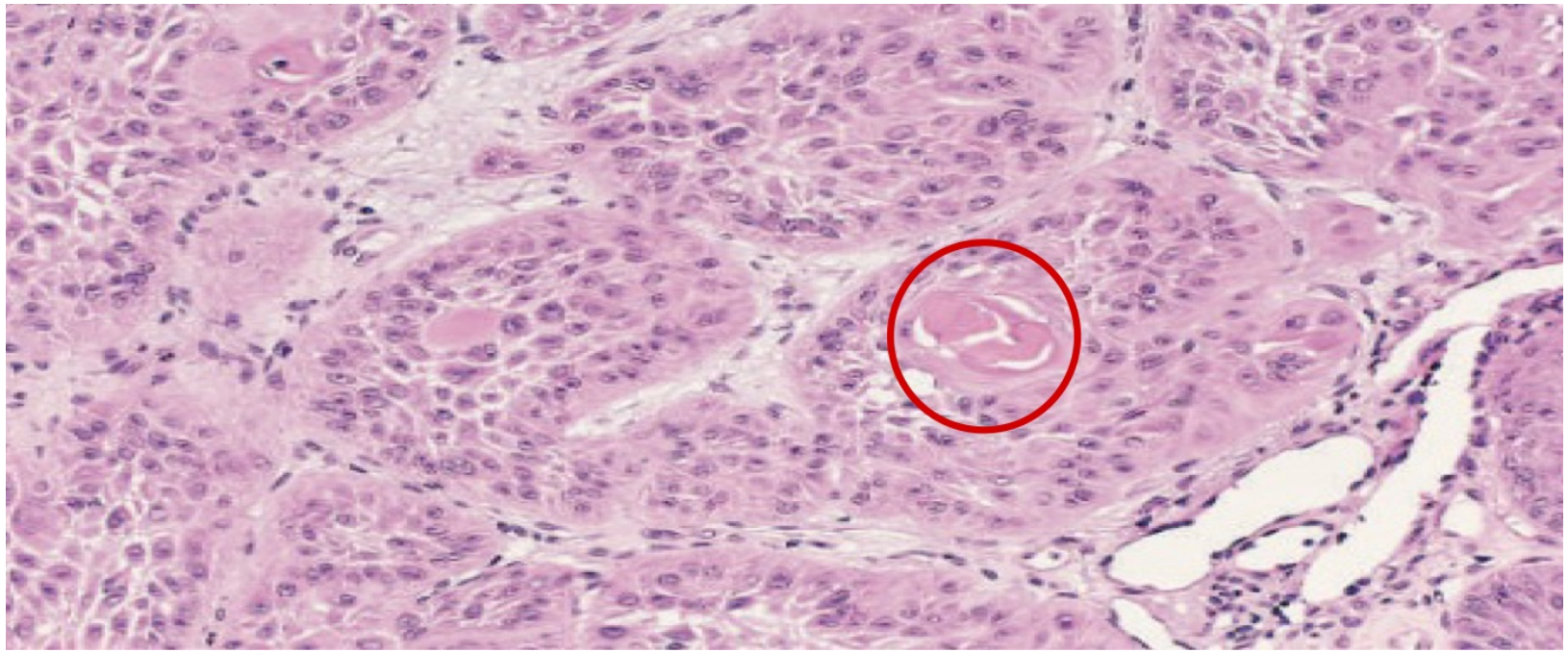
, arrangement isn't lost it's present normally as multilayer cells resting on basement membrane , they are large and have abundant cytoplasm + keratin is being formed (tumor is able to synthesize keratin) + well differentiated because tumor cells resemble normal cells

*benign tumors always resemble normal cells but malignant tumors reassembly varies but never complete (easily recognized + keratin = well differentiated) but this arrangement don't occur in normal tissues so it's totally abnormal (differentiated but not completely normal , not complete

There is some لخبطة in the structure which is not presented normally

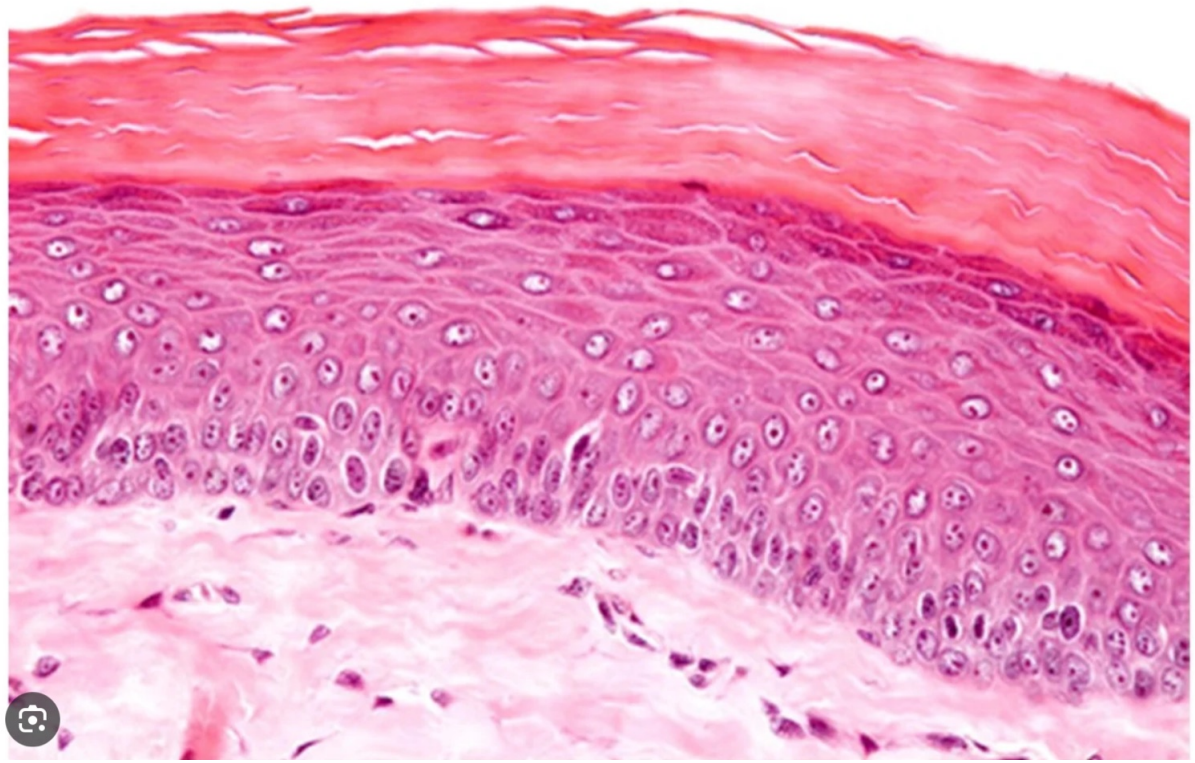
Well differentiated tissue is an evidence of some functions preservation

Remember, resemblance is neverrrrrrrr complicated in malignant tumors

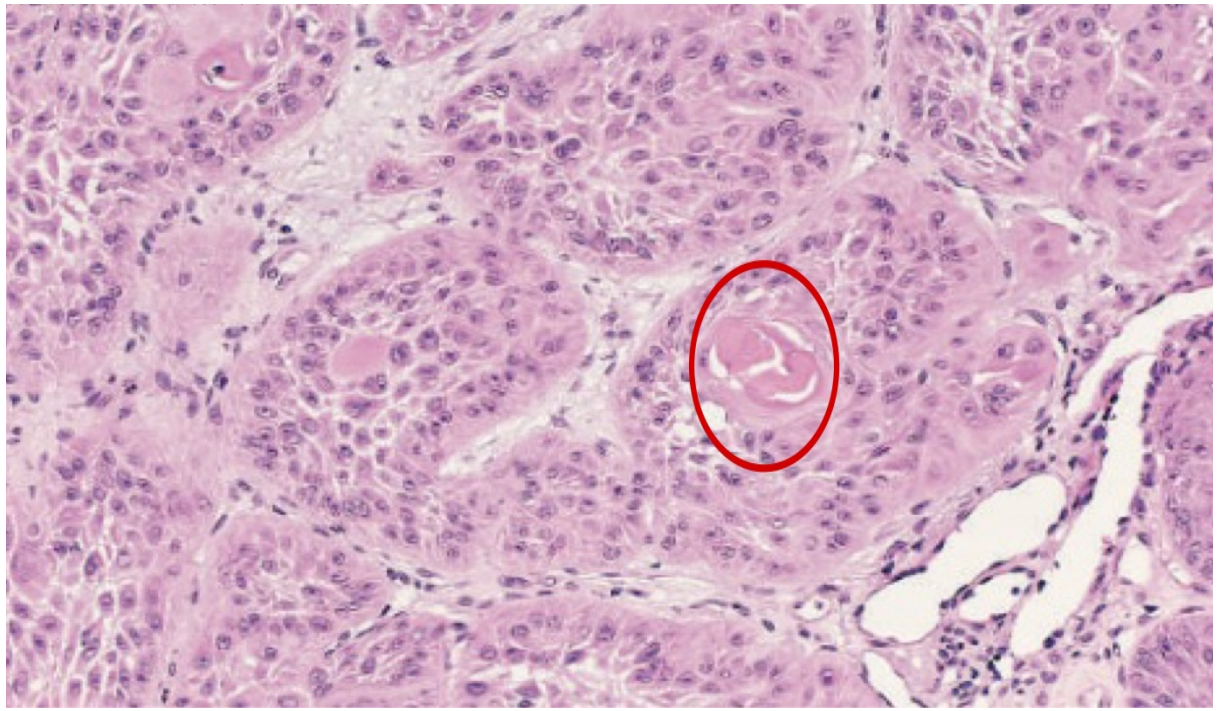


Eosinophilic cellular material = keratin

Normal keratinized squamous epithelium

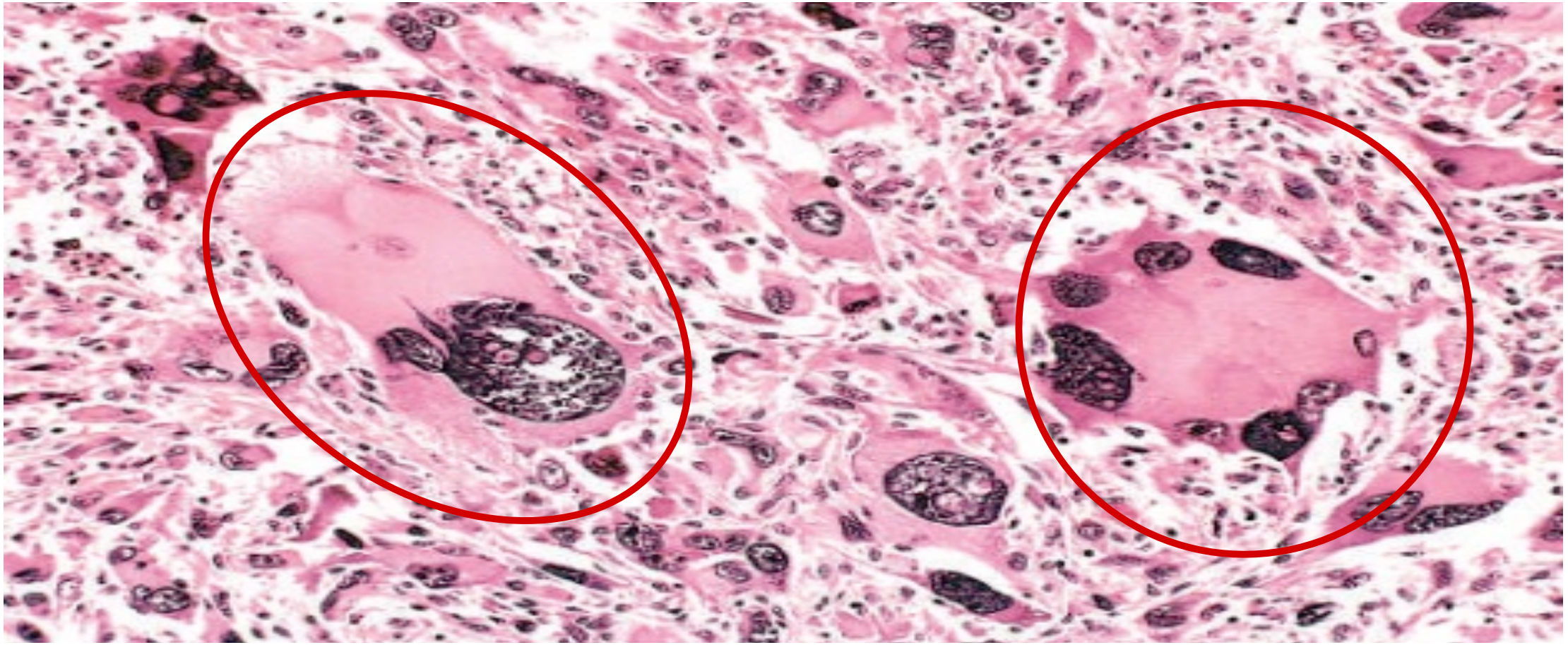


Well differentiated squamous cell carcinoma



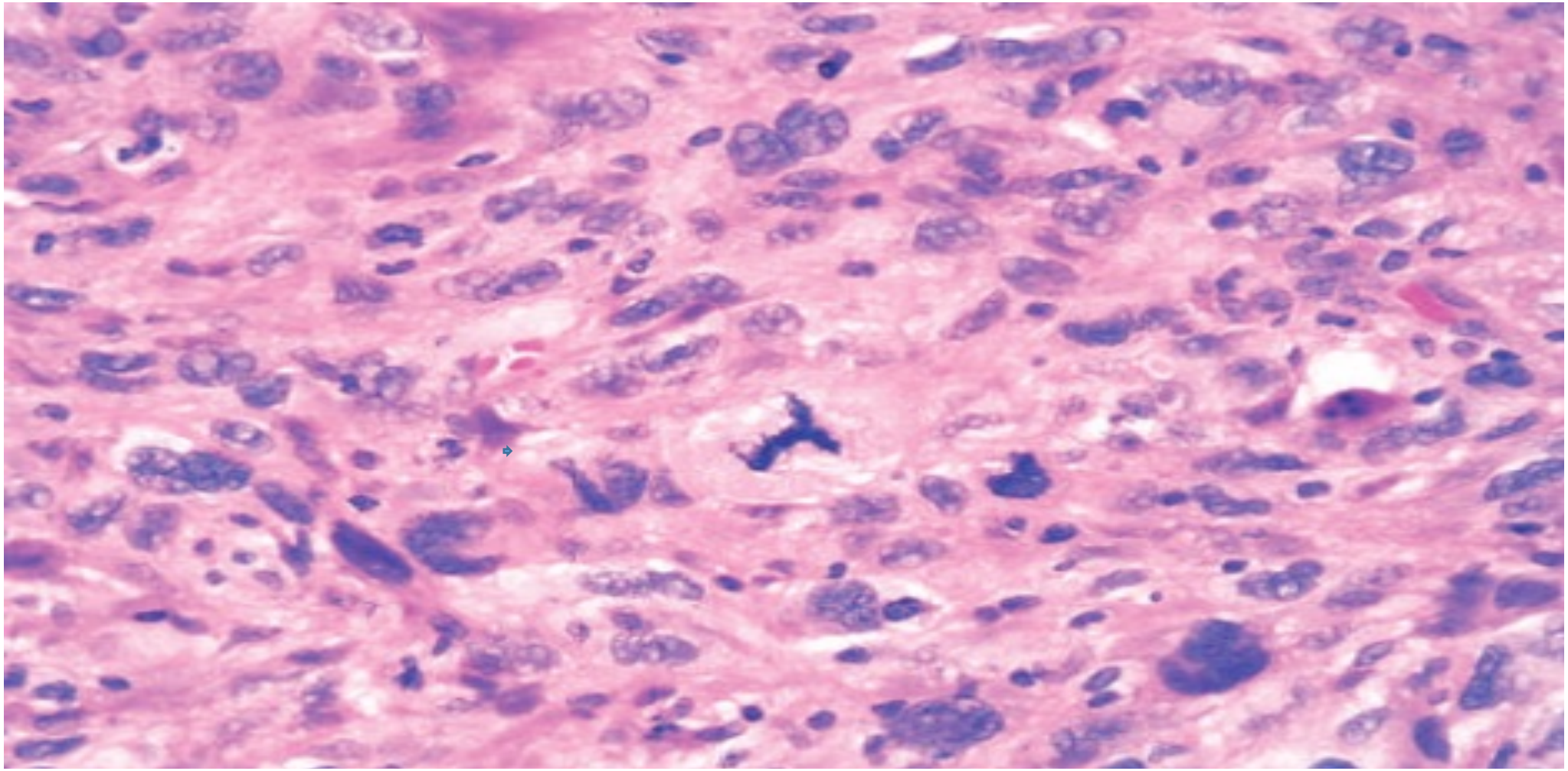
Anaplasia

We can't guess the origin of this tissue , no normal tissue present in our body like this
Loss of differentiation, many tumors can cause this tissue type
So what we do is immunohistochemical staining . Large and multinucleated cells
As a way to determine the tissue origin



Abnormal mitosis

Poorly differentiated tumor; No structures and no cells
Tripolar mitosis , they are usually seen in malignant tumors not benign



Dysplasia and carcinoma in-situ

- **Dysplastic epithelium is recognized by a loss in the uniformity of individual cells and in their architectural orientation**
- Dysplasia is not synonymous with cancer
- Mild to moderate dysplasias that do not involve the entire thickness of the epithelium sometimes regress completely, particularly if inciting causes are removed

Pre neoplastic > patients with risk of developing malignancy followed up by dysplasia and carcinoma in situ

Dysplasia and carcinoma in situ are characterised by presence of abnormal nuclear/ cellular features that are localized to the epithelium without reaching the basement membrane

Difference between dysplasia and carcinoma in situ which both affect epithelium (which rest in basement membrane and multilayered)
Dysplasia affects any layer of epithelium
When all changes occur it becomes carcinoma in situ(commonly for epithelium but can occur on other tissues)

It's important because it's pre cancerous process

If a smoker expressed dysplasia he is likely to develop carcinoma situ which may end up with invasive carcinoma (pre invasive conditions that can be followed up)

Female with Brest mass then developed carcinoma in situ so she is likely now to develop invasive carcinoma

- **When dysplastic changes are severe and involve the entire thickness of the epithelium, the lesion is referred to as *carcinoma in situ*, which is a preinvasive stage of cancer**

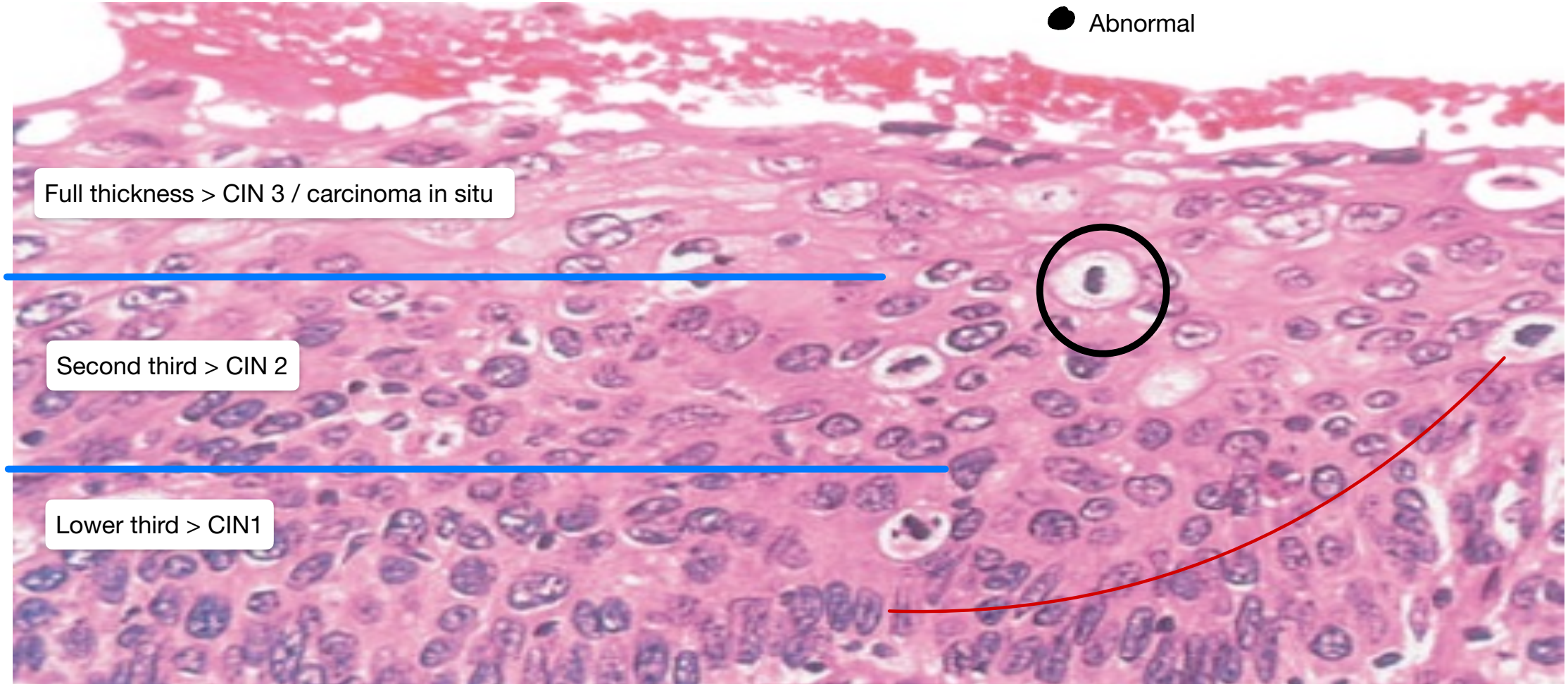
For betterunderstanding

- **Carcinoma in situ (CIS)**: This is a pre-cancerous condition where abnormal cells are present, but they have not spread beyond the tissue layer where they started. They are still localized and haven't invaded deeper tissues or spread to other parts of the body.
- **Malignant tumors**: These are cancerous tumors that can invade surrounding tissues and spread (metastasize) to other parts of the body. Malignant cells are more aggressive and can cause significant harm if untreated.

In short, carcinoma in situ is a localized, non-invasive condition, while malignant tumors are invasive and can spread throughout the body.

Squamous epithelium showing loss organisation , loss of layering

High-power view of another region shows failure of normal differentiation, marked nuclear and cellular pleomorphism, and numerous mitotic figures extending toward the surface



Basal layer , dividing cells

2. Local Invasion

Another feature used to differentiate between benign and malignant tumors

Indicates the infiltration of tumor cells to the surrounding tissue

- **The growth of cancers is accompanied by progressive infiltration, invasion, and destruction of surrounding tissues**
- **Most benign tumors grow as cohesive expansile masses that remain localized to their sites of origin**

Local invasion is Progressive process, initially the tumor may not show this .

Local invasion is Feature of malignancy , any doubts of invading carcinoma > malignancy

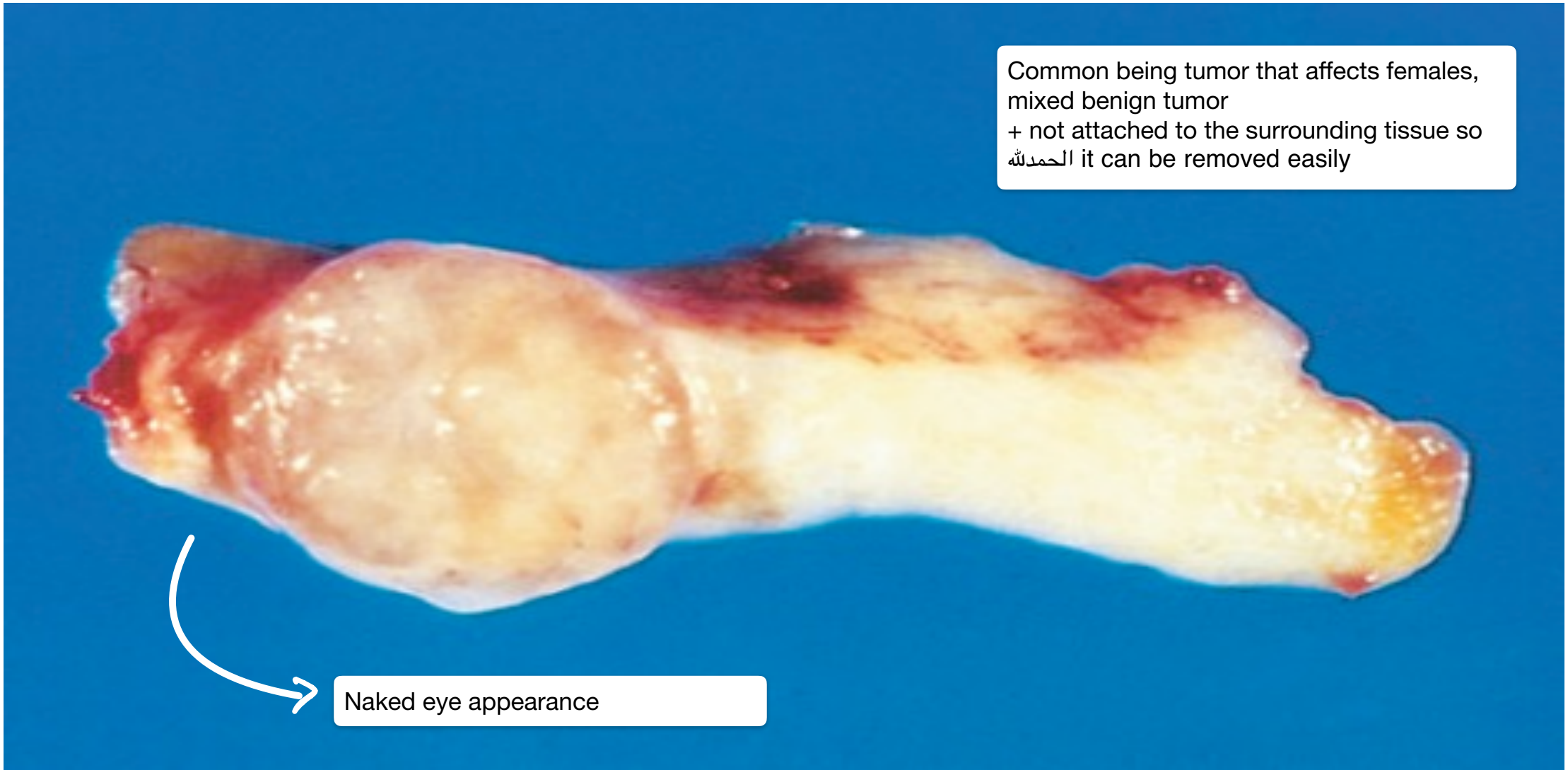
Benign tumors grow as cohesive expansile masses because their cells stick together tightly and don't invade nearby tissues. They are usually surrounded by a fibrous capsule that keeps them contained, making them easier to remove surgically. Since they don't spread (metastasize), they remain localized to their site of origin.

Benign tumors usually are encapsulated
Capsule is formed of fibrous tissue surrounding entire mass , tumor cells grow within the capsule , they shouldn't reach or infiltrate the surrounding
That's why we have to examine the entire capsule to ensure that there is no invasion

- **Benign tumors grow and expand slowly** This is advantage if the person was aware of the growth
- **Usually develop a rim of compressed fibrous tissue (capsule)**
- **This capsule consists largely of extracellular matrix that is deposited by stromal cells such as fibroblasts which are activated by hypoxic damage to parenchymal cells resulting from compression by the expanding tumor.**

Fibroadenoma of the breast.

The tan-colored, encapsulated small tumor is sharply demarcated from the whiter breast tissue



Exception > some being tumors lack capsules but still demarcated and separation between tumor and normal tissue is clear

- **Encapsulation creates a tissue plane that makes the tumor discrete, moveable (non-fixed), and readily excisable by surgical enucleation**
- **However, not all benign neoplasms are encapsulated**
- **For example,**

- leiomyoma of the uterus is discretely demarcated from the surrounding smooth muscle by a zone of compressed and attenuated normal myometrium but lacks a capsule.

Incapsulated benign tumer in uterus specifically in smooth muscles
+ well demarcated

- **A few benign tumors are neither encapsulated nor discretely defined**
- For example Lack capsules + appear infiltrated
  Commonly in skin and liver

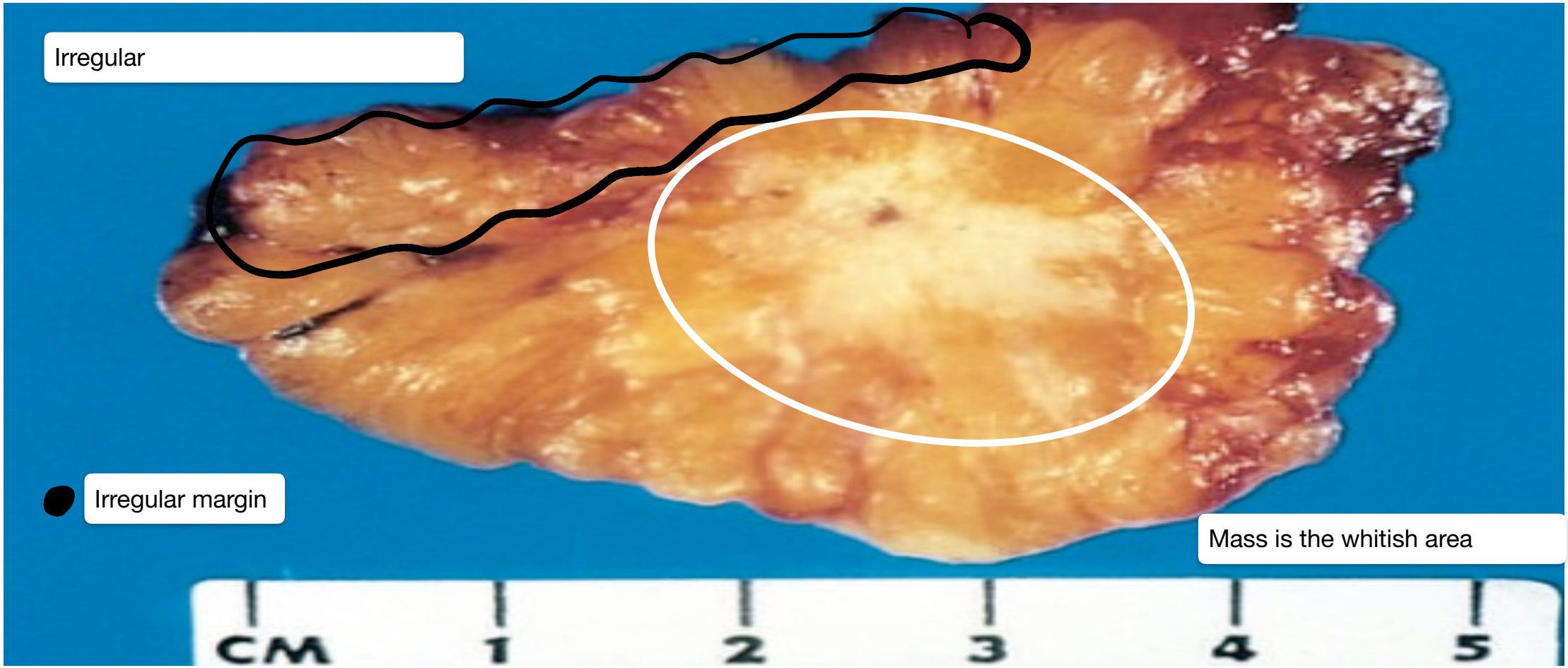
Benign vascular neoplasms (hemangiomas)

lack of demarcation makes them difficult to be excised

- **Malignant tumors lack well defined capsules** Infiltrated to the surrendering
- **Microscopic examination reveals tiny crablike feet penetrating the margin and infiltrating adjacent structures**
- **Malignant tumors are difficult to be removed totally**

Tumor cells infiltrate and are separated from Normal
Cells > very strong feature of malignancy
They are difficult to be removed

Cut section of invasive ductal carcinoma of the breast. The lesion is retracted infiltrating the surrounding breast substance



It's difficult to define the clear margin

3. Metastasis

The ability to spread away from the site of origin

- **The spread of a tumor to sites that are physically discontinuous with the primary tumor**
- **It unequivocally marks a tumor as malignant**
- **Benign neoplasms do not metastasize.**

Cells normally don't leave their original site

Spread of tumor will determine life expectancy of the patient

Once we have metastasis this mean this tumor is malignant

30% of patient at the first time of diagnosis have metastases which is detected by radiology

The phrase "excluding skin cancers other than melanomas" refers to the fact that the statistic does not include non-melanoma skin cancers, such as basal cell carcinoma and squamous cell carcinoma. These types of skin cancers are quite common but generally have a much lower tendency to metastasize (spread to other parts of the body) compared to other solid tumors.

- **30% of patients with newly diagnosed solid tumors (excluding skin cancers other than melanomas) present with clinically evident metastases**
- **20% have occult (hidden) metastases at the time of diagnosis** Can't be detected by radiology

There is no way to predict metastases , tumors of the same type in different types may behave differently

- **The more anaplastic and the larger the primary neoplasm, the more likely is metastatic spread**
- **Exceptions**

Extremely small cancers have been known to metastasize while some large and ominous-looking lesions may not

However there are some small tumors that may develop metastases on very early stages ex (carcinoma of gonads and chorionic carcinoma in placenta which develop metastases even the tumor is small

Some certain malignant tumors may not be metastasize
ex : basal cell carcinoma of the skin which is locally aggressive causing destruction to the surrounding tissues

- **Basal cell carcinomas of the skin and most primary tumors of the central nervous system are highly locally invasive but rarely metastasize**
- **Leukemias and lymphomas are taken to be disseminated diseases at diagnosis and are always considered to be malignant**

Leukemias and lymphomas are considered disseminated diseases at diagnosis because they involve the widespread presence of abnormal cells throughout the body, rather than being confined to a single location or organ.

Malignancy of blood cells

Pathways of metastasis

Pathway for spread of tumors

- **(1) Seeding within body cavities**
- **(2) Lymphatic spread**
- **(3) Hematogenous spread**

→ Brief quick explanation

Here's a brief explanation of the three pathways for the spread of tumors:

1. **Seeding within body cavities**: Tumor cells spread by direct extension into body cavities, such as the peritoneal (abdomen), pleural (lungs), or pericardial (heart) cavities. This allows the cancer to implant on nearby surfaces or organs within these spaces. For example, ovarian cancer often spreads by seeding in the peritoneal cavity.
2. **Lymphatic spread**: Tumor cells travel through the lymphatic system, which is a network of vessels that drain lymph fluid. As the lymph nodes filter the fluid, cancer cells can lodge in them and then spread to other lymph nodes or organs. This is common in cancers like breast cancer and lymphoma.
3. **Hematogenous spread**: Tumor cells enter the bloodstream (hematogenous route) and spread through the circulation to distant organs. This often leads to metastasis in the lungs, liver, or bones. It's typical of cancers like kidney, lung, and colon cancer.

Seeding

Spread of tumors through cavities , this happens because tumor cells get separated (they are loosely attached cells so they can easily spread (proteins which keep cells adjacent are lost)

- **Spread by seeding occurs when neoplasms invade a natural body cavity.**
- **For Example**

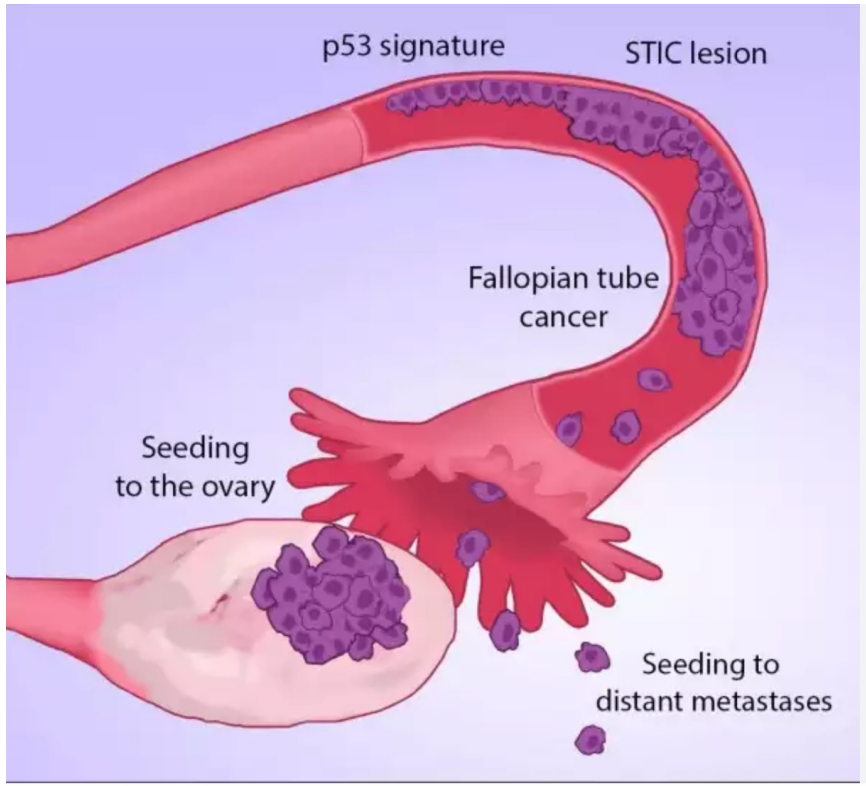
Commonly ovarian tumors , because ovarian tumors grow on the surface that's why they can detach

-Cancers of the ovary which often cover the peritoneal surfaces widely

Usually masses are small like seeds

-Neoplasms of the central CNS such as a medulloblastoma or ependymoma, may penetrate the cerebral ventricles and be carried by the cerebrospinal fluid to reimplant on the meningeal surfaces either within the brain or in the spinal cord.

Usually tumors of brain don't send metastases to the outside
Unless they reach spinal cord through CSF which able them to cause vertebral tumors and so on



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Brief quick explanation

Neoplasms like medulloblastomas or ependymomas are types of brain tumors that can grow in the central nervous system (CNS). When these tumors spread, they can penetrate the cerebral ventricles, which are spaces in the brain filled with cerebrospinal fluid (CSF). The CSF can carry tumor cells to other parts of the brain or spinal cord, where they can attach to the meninges (the protective layers around the brain and spinal cord). This process is known as "seeding," where tumor cells spread to new locations and grow in those areas.

The main channels for metastases is lymphatic and blood vessels

Lymphatic spread

The key difference between **sarcoma** and **carcinoma** lies in their tissue of origin:

- **Sarcoma**: Arises from **mesenchymal tissue**, such as bone, muscle, fat, cartilage, and connective tissues. Examples include osteosarcoma and liposarcoma.
- **Carcinoma**: Originates from **epithelial tissue**, which lines organs and surfaces. Examples include breast, lung, and colon cancer (e.g., adenocarcinoma, squamous cell carcinoma).

- **Lymphatic spread is more typical of carcinomas whereas hematogenous spread is favored by sarcomas.**
- **All forms of cancer may disseminate through either or both systems** All types of malignancy can spread by both
- **The pattern of lymph node involvement depends principally on the site of the primary neoplasm and the natural pathways of local lymphatic drainage.**

Lymphatic drainage will send metastases to lymph nodes
Brest > axillary lymph nodes
Part of evaluation patients with Brest mass is evaluating axillary lymph nodes

Usually lymph nodes with metastases become enlarged and harder so it can be detected

Patient with Brest mass on the lateral side > it will spread to axillary lymph nodes
Patient with Brest mass on medial side > internal mammary lymph node which can't be examined clinically

- **For example** Lung carcinoma sends metastases to hilar lymph nodes
- **Lung carcinomas arising in the respiratory passages metastasize first to the regional bronchial lymph nodes and then to the tracheobronchial and hilar nodes**
- **Upper outer quadrant breast lesions first spread to the axillary nodes.**
- **Medial breast lesions may drain through the chest wall to the nodes along the internal mammary artery.**

Next station is the supraclavicular lymph nodes
So patients with Brest mass should examine axillary and supraclavicular lymph nodes (second station)
Patient in supraclavicular stages means she is in an advanced stage

- **Then to supraclavicular and infraclavicular nodes**
- **Cancer cells can travel in lymphatic channels within the immediately proximate nodes to be trapped in subsequent lymph nodes producing so-called “skip metastases”**

Skip areas > chain of drainage reaches satiations ,
simecstations may show no evidence of metastases

- **The cells may traverse all of the lymph nodes ultimately to reach the vascular compartment by way of the thorasic duct.**

Axillary

- **A “sentinel lymph node” is the first regional lymph node that receives lymph flow from a primary tumor.**
- **It can be identified by injection of blue dyes or radiolabeled tracers near the primary tumor.**
- **Biopsy of sentinel lymph nodes allows determination of the extent of spread of tumor and can be used to plan treatment.**

Negative result means that Brest mass is still localised in the Brest
Positive result indicates that the tumor is outside the breast
By this we can evaluate the patient and the extent of surgery

Hematogenous spread

Site of involvement of hematogenous spread is related to Venous drainage

- **It is the favored pathway for sarcomas**
- **Carcinomas use it as well.**
- **Arteries are penetrated less readily than are veins.**
- **With venous invasion the bloodborne cells follow the venous flow draining the site of the neoplasm**
- **Liver and lungs are the most frequently involved secondary sites in hematogenous dissemination**

  Two common organs because of the two circulation (portal circulation , from abdominal organs to liver , and systemic circulation from other organs
- **Liver is the commonest secondary organ to be receive metastatic deposits from organs with portal venous drainage**

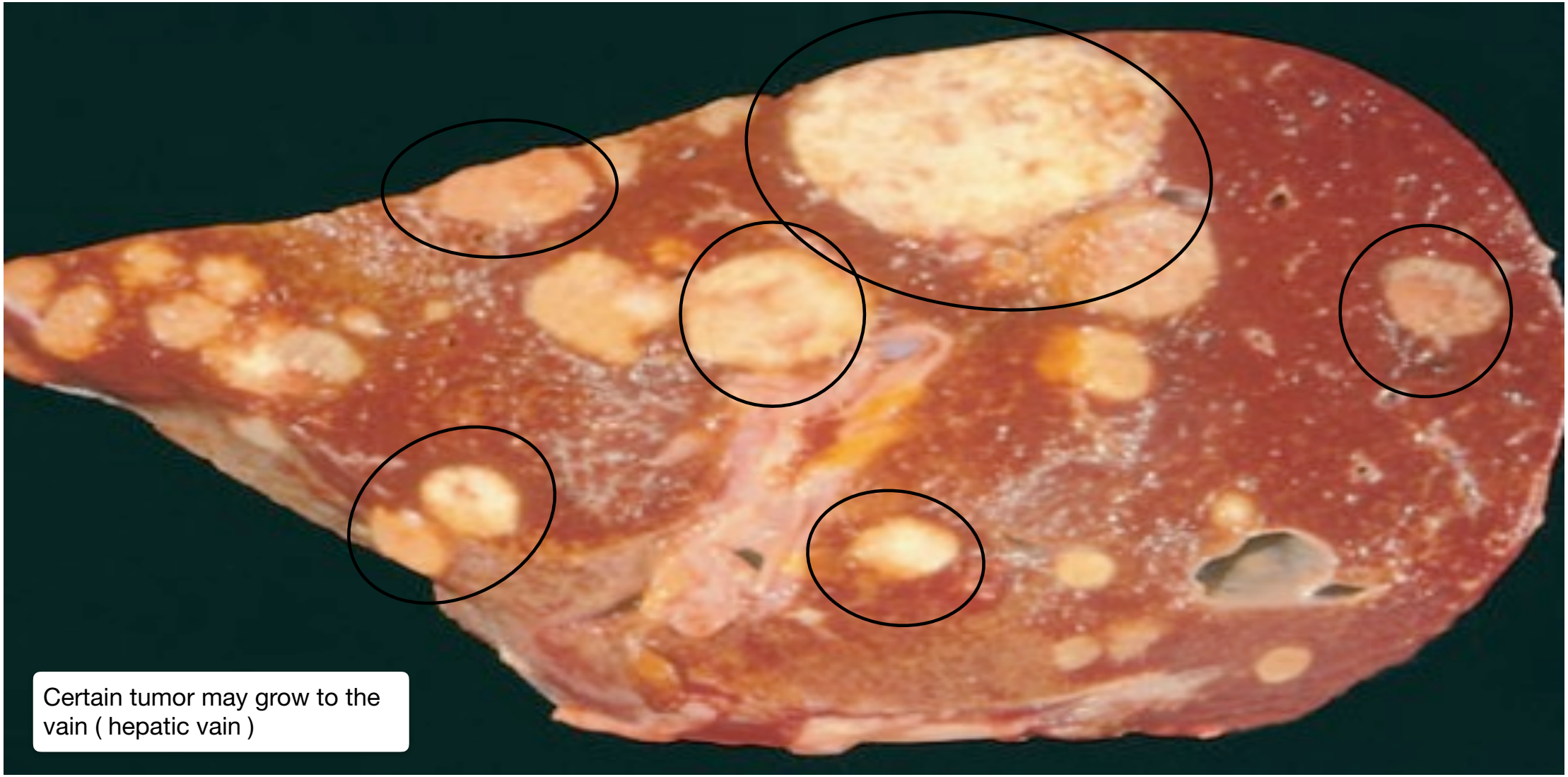
- **Lungs are the most common site to receive metastatic deposits from organs with caval venous drainage**
- **Cancers arising near the vertebral column often embolize through the paravertebral plexus as vertebral metastases of carcinomas of the thyroid and prostate glands.**

If we want to evaluate patient with colon cancer with mets (metastases)
we look for mets in lymph nodes
Osteosarcoma > we look at lung because venous drainage is systemic
and reaches lung (venous drainage determine involved organs

Prostrate > vertebra
Thyroid> cervical

A liver with metastatic cancer

Multiple tumor , whitish nodules
Metastases rather than primary , because primary is rare



- **Certain carcinomas have a propensity to grow within veins.**
- **Renal cell carcinoma often invades the renal vein to grow in a snakelike fashion up the inferior vena cava reaching the right side of the heart.**
- **Hepatocellular carcinomas often penetrate and grow within the radicles of portal and hepatic veins reaching reaching the main venous channels.**

Prostrate > vertebra
Lung carcinoma > adrenal (no connection)

- **The anatomic localization of a neoplasm and its venous drainage cannot explain the systemic distributions of metastases.**
- **<u>For example</u>**

Prostatic carcinoma preferentially spreads to bone

Bronchogenic carcinoma tends to involve the adrenal glands

Neuroblastoma spreads to the liver and bones

Skeletal muscles, although rich in capillaries, are rarely sites of tumor metastases Heart very rarely receives metastases

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