PATHOLOGY

◉ Sheets ○ Slides

Number: 14

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Subject: Neoplasia

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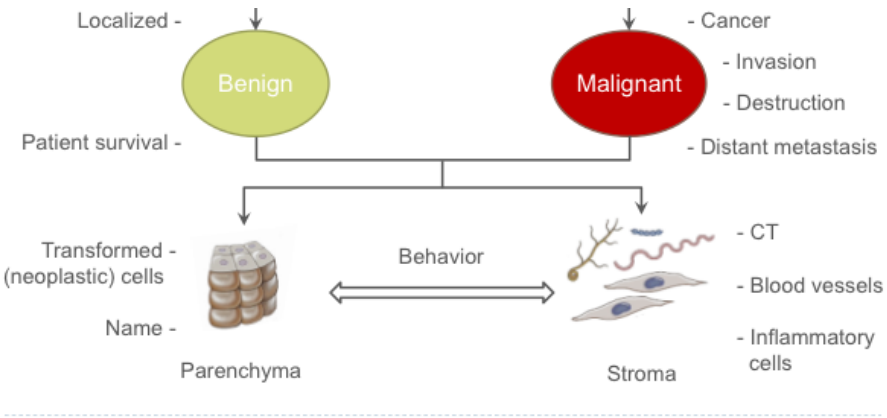
Neoplasia

In the next lectures we will be talking about neoplasia and its hallmarks, this is a very important subject so try to understand it well…and enjoy it :D

Neoplasia : means new growth
Nomenclature:
Oncology is the study of tumor
Now when we say tumor, this doesn't necessarily mean cancer
A neoplasm (tumor) is a bunch of transformed cells that could be

1- Benign: حميد
2- Malignant :خبيث



Now what's the deference between them??

• the benign tumor: is localized, well subscribed, and the patient usually survives it
Yet there are exceptions: depending on where the benign tumor lies it could be life threatening, eg: like tumor in the brain (there is no place for it to grow, even if it doesn't invade or metastasize, it increases the entercranial pressure, which leads to a brain herniat and that is fatal)

• malignant tumors (cancers): local invasion, destruction of local tissues, and metastasize.

Metastasis: means having a gap (space) between the primary tumor and the secondary growing one.

- Some cells of the primary tumor detach and reach the blood stream or the peritoneum, to reach another place where it colonizes and causes another tumor.

The tumor is made up of:
Parenchyma cells: cells of the tumor
Stroma cells: the connective tissue and vessels surrounding and supporting the neoplasm.

The behavior of the cancer is mostly based on the parenchymal cells ,ie: those cells that were transformed to abnormal (neoplastic cells) and the name of the tumor comes from the parenchyma.
There are theories that describes the mechanism behind the tumor,
One of them suggest that the cancer developed from only one cell that colonized and proliferated to become abnormal.
There is another theory called the somatic mutation theory , it suggests that the stromal cells also play a role In neoplasia

But how did they discovered that?
Some tumors if you take them out and put them in a whole different "environment" stroma they will completely die off.
So the tumors do originate from the parenchyma, but they also depend on the surrounding tissues to grow, this means that there is a conservation between the stroma and the parenchyma.

Naming:
This could be tricky, see there are some major rules but we as experts know that "RULES ARE THERE TO BE BROKEN" :P

Benign tumors:
We classify them according to the origin:

1- **Mesenchymal**
2- **Epithelial**

*mesenchymal origin:
Mesenchymal are all the tissues between our epithelial layers, it's typically from our mesodermal embryonic layer.

In naming mesenchymal tissue there is a suffix –oma
Eg: fibrous tissue: fibroma
Cartilage: chondroma
"On the other hand:
In malignant tumor: suffix –sarcoma ,eg: fibrosarcoma, chondrosarcoma."
A break to the rule :3
In malignant tumor the suffix-sarcoma only applies to solid tissues, this leaves blood and lymph ,what to do with them?!
Blood: leukemia (malignant)
Lymph: Lymphoma.

***Epithelial:**

Depends on the origin and the appearance of the tumor.

1- Adenomas : if it's a glandular tissue (makes glands) or originates from a gland, even if it doesn't look like a gland eventually. (So either it's because of its appearance or it arises from a gland)
2- Papilloma (surface tumors)they are commonly known as “polyps”

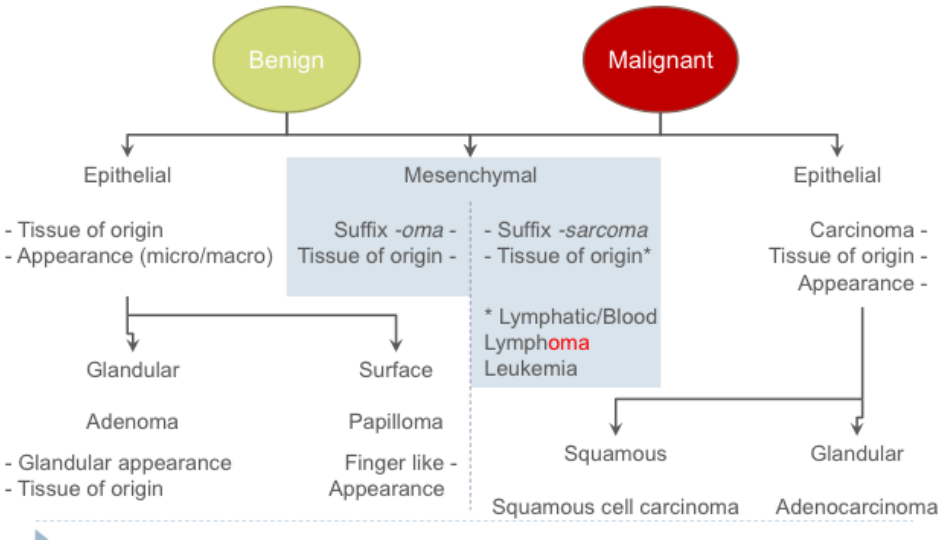
The term polyps could be misleading since it could indicate a benign or malignant tumors, or even non-neoplastic (like polyps that arise in our noses ,these are inflammatory polyps,) neoplastic polyps arise from increased proliferation.
Papilloma means “finger like appearance “

If it's a surface epithelium is called "papilloma"
They are locally known as "polyps"
Polyps is kind of misleading
Polyps can be benign
Polyps can be malignant
Polyps can be non-neoplastic "like polyps arising in your nose>> these are inflammatory polyps"
Hyperplastic polyps are those that arise from proliferation.
Papiloma is actually a "finger like appearance"

On the other hand malignant epithelial tumor these are collectively known as "carsinomas"
The naming is based on tissue of origin and their appearance
So they could be carsinoma of the thyroid gland or carsinoma of the skin
Squamous cell carcinoma "the appearance "of the skin so the appearance is squamous and it arose from the skin

In glandular tissue
Glandular carsinoma
Lipoma -liposarcoma
There are exceptions:
Mesothelioma: sounds benign but it's a malignant tumor of the plura of your lungs
"There's a table In the book " 90% follow the major rules

Unfortunately the names even though later on we tried to standardize, them some sub historical names stuck **so you have to know the exceptions.**



So..the question that your patient comes to know the answer for is what this whole lump is all about! Is it benign? Or is it malignant?

So how do we differentiate between them?
There are four major criteria:
1- differentiation anaplasia
2- rate of growth
3- local invasion
4- metastasis

*Differentiation anaplasia:

It's how close the morphology of the neoplastic tissue is compared to the original tissue.
If it's closer to the original tissue it's more likely to be "benign "-there are exceptions
If it's totally different this means it's more aggressive and more likely to be "malignant-again there are exceptions-
An anaplastic tumor is a very undifferentiated tumor "this is where grading comes along"
Remember when we talked about grading, and how abnormal it looks compared to normal state..this is exactly what we are talking about.
So a low grade tumor means a tumor that looks very much like the tissue it originated from
A high grade tumor "anaplastic tumor" a tissue that looks very different than the tissue it originated from

**rate of growth:

The faster the tumor grows ,the more it comes to counter, the more aggressive the tumor and more like to be malignant

**local invasion

This is the second hallmark of a malignant tumor
-benign tumors do not invade

**metastasis

It is this that really defines a malignant tumor
It's a loss of continuity between the primary site of the tumor and the other site, if you find a metastatic place it's most likely a malignant tumor.
**not all metastasis depend on invasion, lymphatic and blood metastasis depend on the tumor invading the blood vessel and the lymphatic vessels to get to a secondary place
But for example an ovarian tumor can metastasize inside the peritoneum through the peritoneal fluid without
invasion.

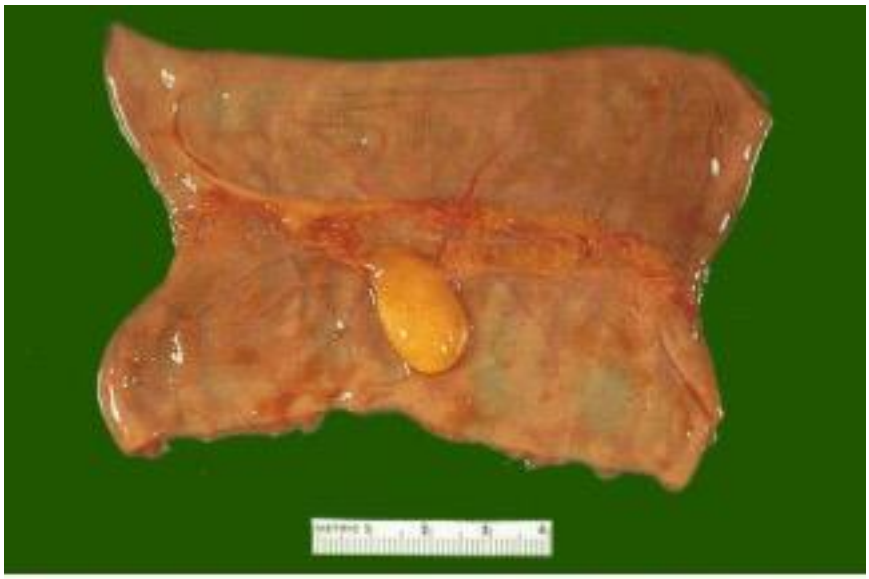
Now let's talk in more details

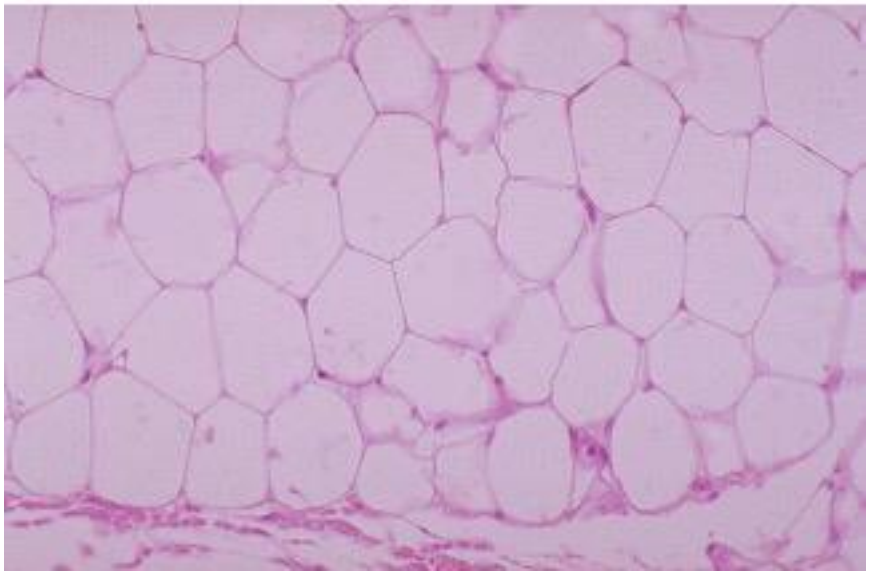
*Differentiation anaplasia:

A benign tumor is typically well differentiated. Now when we talk about differentiation we are not only talking about the morphology but also the function, so a benign tumor should serve the same function as the tissue it originated from but with overgrowth

(The figure to the right is lipoma)

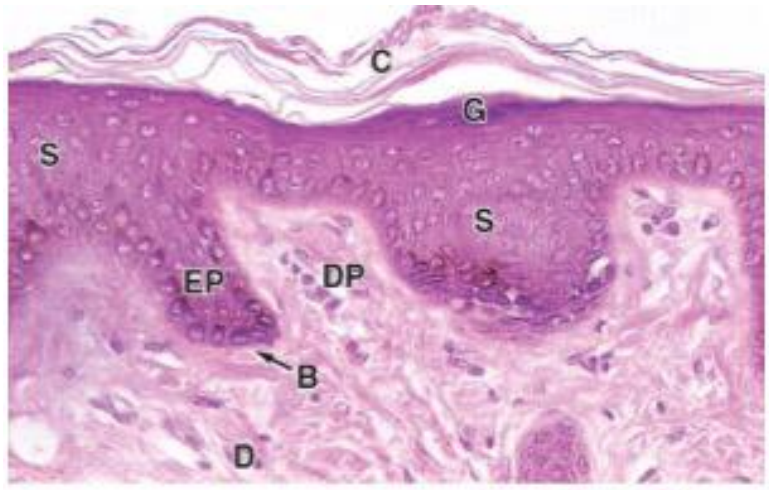
In lipoma if you look at it under the microscope you will not be able to differ between it and a normal adipose tissue, but because you were told that it's from a tumor you will know it's lipoma.

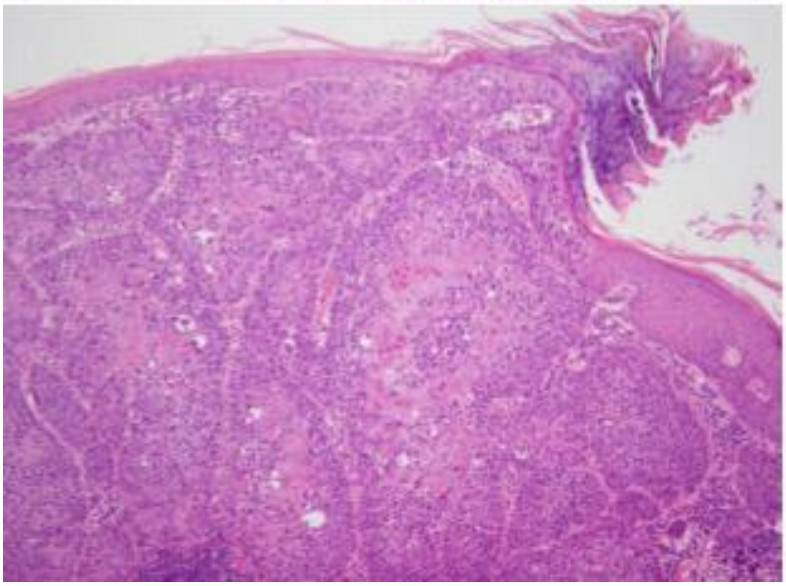




*Mitotic figures:

If you take a tissue and you fix it and look at it under the microscope, you might catch a cell in the middle of mitosis.
So mitotic figures are cells that were caught in the middle of mitosis.
Normally you shouldn't find many of them, but in case of benign tumor you might find one or two but they look normal "so if you compare the mitotic figures of a completely normal tissue with those of a benign tumor they will look the same"
Where as malignant Could be well or poorly differentiated.





If we don't tell the pathologist that the tissue he has "of a well differentiated squamous cell carcinoma " he will have a very hard time to tell that it's malignant.

Tissue could look moderately undifferentiated or completely different
"undifferentiated/anaplastic "here we are talking about **pleomorphism**
Pleomorphism = polymorphism "بسعاملينلهاجو"
Having multiple different shape of the cell.

Loss if polarity in epithelial cells:

Polarity: remember in histology we took that epithelial cells have a kind of polarity , meaning that their organelles and nucleus could be up "facing the lumen" or down facing the basement membrane
So here they lose their polarity

Giant cells :
Look very big compared to all cells around it
Hyper chromatic nuclei ,maybe the DNA has been doubling , this means that these are extra basophilic

Their neuclus could be:

- Hyperchromatic
- Very large
- Multiple
- Abnormally shaped

Abnormal mitotic figures:

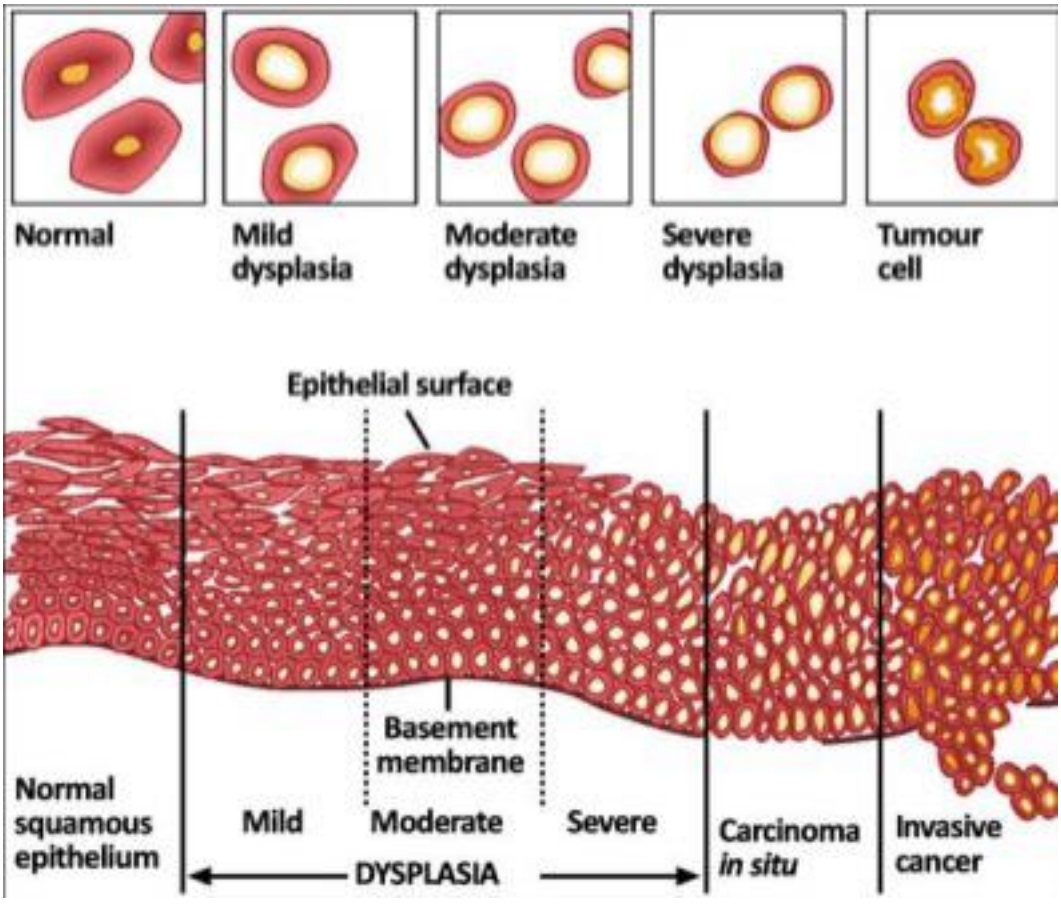
Tripolar mitotic figures
Normally the cells should have a bipolar mitotic figure.
When the cells are dividing their chromosomes should align in the middle in order to give two cells, in this case we have a tripolar mitotic figure,it's abnormal.
This is a characteristic of anaplastic tissue

Stem cells:
Undifferentiated cells.
They are immortal and can differentiate into any type of cells "depending if they are tissue stem cells or germ cells".
So the first theory of anaplastic tumors is that they arose from stem cells, where stem cells received the insult and because they are undifferentiated when they proliferate they will give a very undifferentiated abnormal tissue.

The other theory is there is dedifferentiation of the somatic cells because they receive the genetic mutation or abnormalities where they move backwards in differentiation matter and become stem cells like cells and that's how the cells become abnormal and they give anaplastic tissue.
There are examples of both theories, especially in blood cancers.

The functional significance:
This is a very well differentiated hepatoma and when you stain the liver it comes up looking as green ie producing bile same as the other stained tissue, the other thing that you can see is a very well circumscribed "meaning that there is a very well defined line separating the neogrowth from the other tissue ".
So well differentiated neoplasm will remain the tissue function, so if the tissue produces hormones it will continue producing hormones "in benign tumor".
Unfortunately some tissues that normally don't produce hormones, could in some cases where the tissue becomes undifferentiated produce hormones, these hormones are called "ectopic hormones" these are typical in lung cancer.
Sometimes lung cancer produces abnormal hormonal symptoms excess production of different hormones, this will disturb the hormonal balance in our bodies.
So a tumor may not be presented by a mass but with ectopic production of hormones.

Dysplasia:



Abnormal shape:

What's the difference between this and metaplasia, even though you lose the shape in both of them?
In dysplasia is changing the shape of your cells to another type that's not present at all in your body.
Whereas metaplasia "unless you tell the pathologist that a squamous tissue comes from the lung of a smoker" he won't know it's metaplastic.
Dysplasia, even though it's considered to be some how pre-cancer it doesn't necessarily turn into cancer.
It's also reversible,especially if it is a low grade dysplasia with no invasion.
Dysplasia is not a neogrowth otherwise it should be called neoplasia.

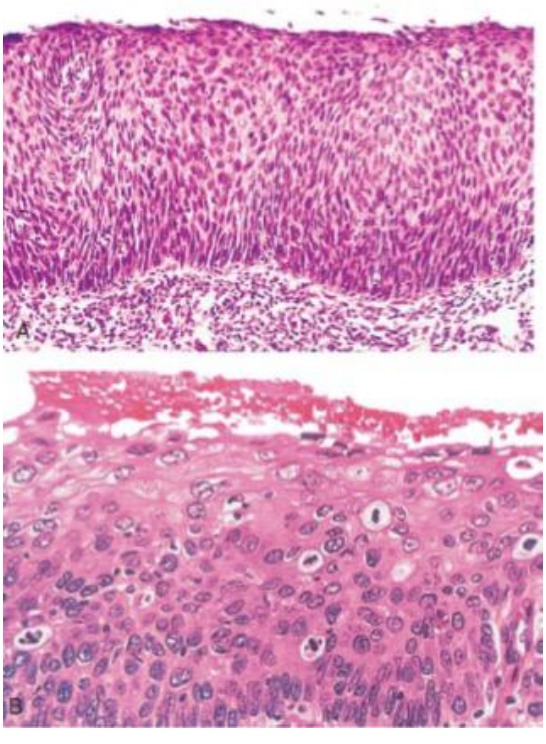
There are grades:

- Mild
- Moderate
- Severe

Once you have dysplasia involved in all layers of your epithelial tissue this is called carcinoma in-situ "when this preach the basement membrane it becomes basic cancer"
So there is dysplasia cancer pathway, but it's not always irreversible, we can still reverse dysplasia in this region.
We can notice that many of the characters we talked about for anaplastic tissue are applied here.
We have large cells, hyperchromatic cells, pleomorphism, mitotic figures and outside the basement membrane layer "that's where you generate your epithelial layers
But with dysplasia you can find mitotic figures further away from the basement membrane.

Carsinoma in-situ :

- Is preinvasive
- The whole thickness of the layers are involved
- But the basement membrane remain intact
- Once the membrane is preached this becomes basic cancer



** Rate of growth:

A benign well differentiated tumor is typically slow in growth rate.
There are exceptions: uterus >> smooth muscle >>benign tumor " lyomyoma " >>it's typically a slow growing benign tumor, however during pregnancy and stimulating these muscles leads to hyperplasia so the tumor is stimulated as well and grows fast,
Malignant poorly differentiated tumors are typically fast growers, but that's not always the case there are some malignant tumors where you end up not finding a primary tumor anymore because it already metastasized, the primary tumor is small and slow growing and it could be gone

The factors that determine the rate of growth are:

- Blood supply "the more we have the faster we go".
- Hormone-growth factors"like breast cancer, prostate cancer " these are hormonal dependent cancers which means that if you manipulate the hormones you can treat the patient.
- Anatomical limitations "like tumors in the brain, like a tumor behind your pituitary gland there is a bone that holds the gland ,so if the gland grows because of tumor this anatomical position will compromise the blood supply to the tumor and it won't grow , the patient will come with an (empty selladorsicla) syndrome. So the gland killed itself and killed the rest of the gland with it .
- Also the hypothesis of the stem cells.

This is an example of a fast growing cancer that out strict it's blood supply , the blood supply was able to supply the whole tumor except for its center where it became hypoxic and necrotic.
Usually when you take off a fast growing tumor you will find the center to be necrotic as the blood supply couldn't keep up with the rate of the growth.
The faster the tumor the worst it is for the patient if left untreated.
Some very fast tumors are very compatible to the therapy.
Depending on what the available therapy is fast growing tumors can be very treatable

We have already mentioned cancer stem cells hypothesis where if you insult the cells and cause genetic damage you can get a tumor this is one example of getting leukemia.

We already mentioned that some cells can dedifferentiate into what looks like a stem cell when the insult is received by a somatic cell acute myelogenous leukemia/ or chronic myelogenous leukemia.

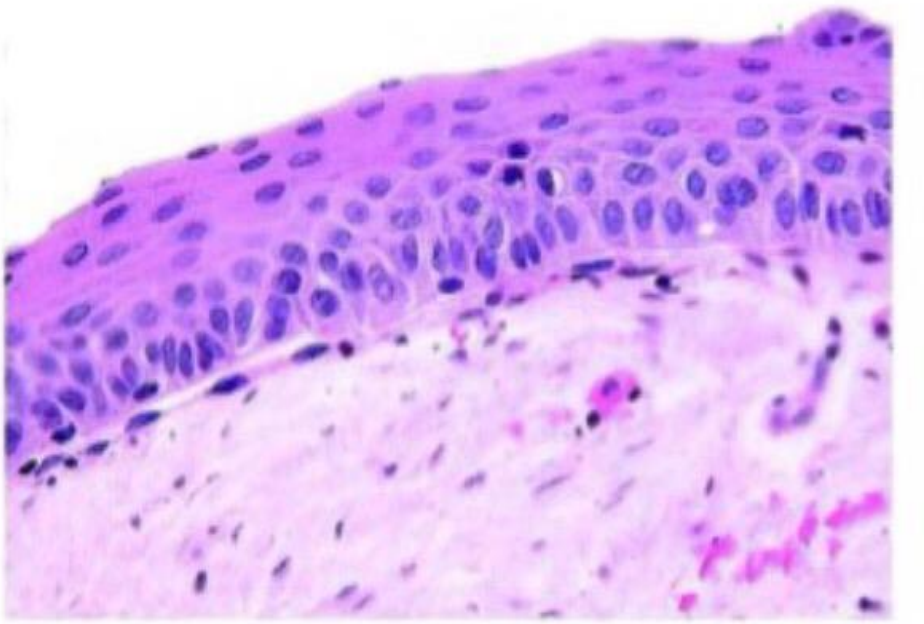
There's still a question mark on solid cancer stem cells.
The problem with cancer stem cells is that they have the same properties of the normal stem cells.
Stem cells are very resistant to treatment for examples they have multiple resistant genes that make them resistant to chemotherapy.

So if you treat a patient with chemotherapy, radiotherapy or anything you would kill the majority of the tumor cells except for the stem cells, so if the stem cells remain the tumor will come back.
So research right now is focused on finding new methods to kill the stem cells so that the tumor doesn't come back.

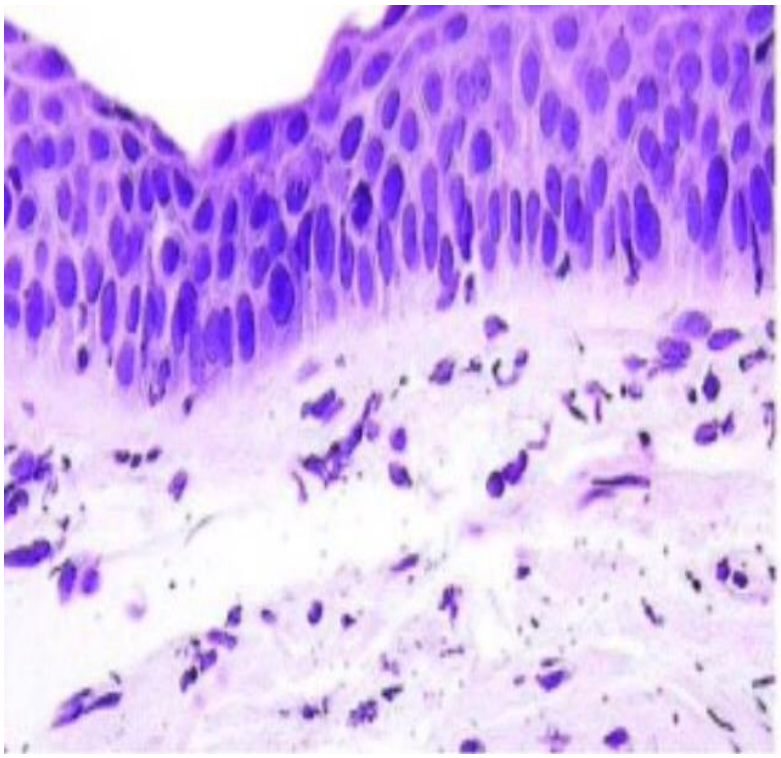
Invasion:

A benign neoplasm -most of them- have a fibrous capsule.
An example of a benign tumor that doesn't have a capsule : lyomyoma (but under the microscope you will find a thin line mainly of smooth muscle separating the tumor from the rest of the cells)
Some of the malignant slow growing tumors can have what looks like a fibrous capsule.
Benign tumors don't locally invade, they don't invade nor metastasize.
Malignant tumors don't have a fibrous capsule, although some of the slow growing tumors have what looks like a fibrous capsule due to stimulation of the fibrous tissue during its growth.

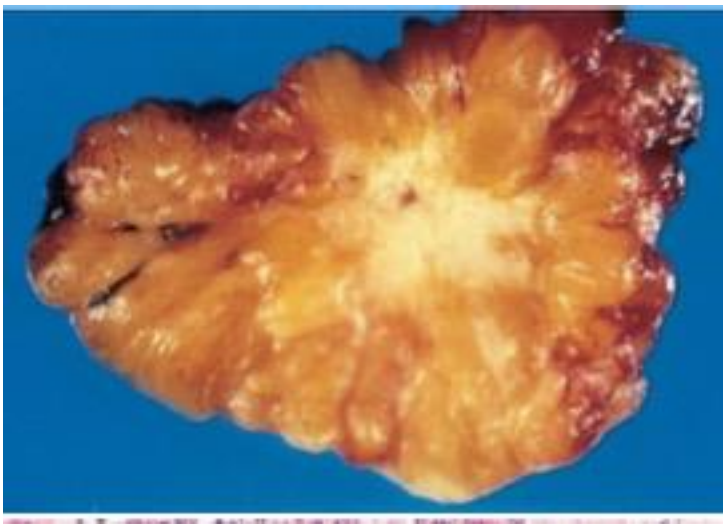
Metaplasia:



Dyplasia:



However if you look at the margin you will find a crab like edges toward the normal tissue "this is why a cancer is called cancer because cancer is a crab"



“In the figure notice the crap like edges”

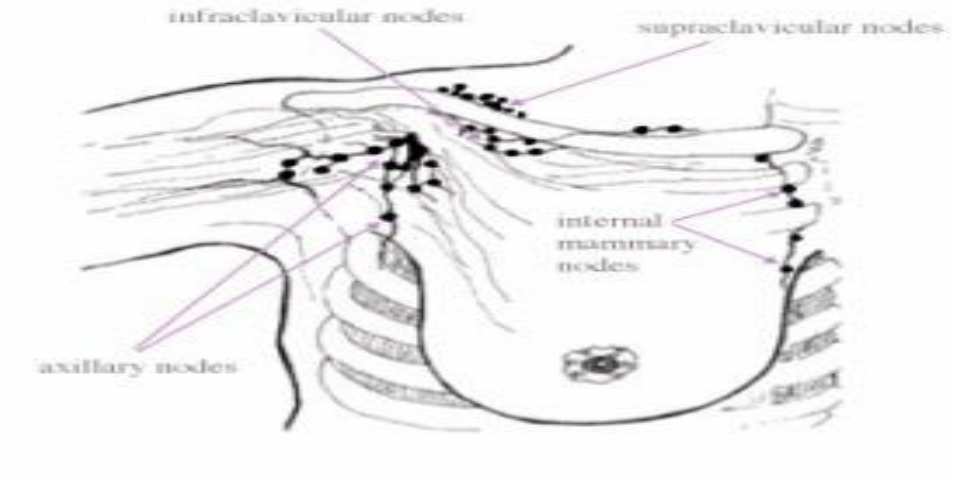
Malignant tumors do infiltrate, invade ,do metastasize, and what's called a clean margin is required for their section "so when you remove a tumor during surgery you frequently send the tumor in what's called frozen section "we will talk about it later "to the pathology lab.

please make sure that the margins you have has no tumor cells anymore. “the pathologist will look at the tissue under the microscope and find a clean edge".

Benign neoplasm don't metastasize .

Metastasis is a multi step process:
First you have to have cells to grow, then you need to have cells that lose their ability to stick together.
These cells need to have ability to invade "almost always (remember the ovarian tumors)"
These then have to enter the lymphatics or the blood stream, then evade your immune system and survive in a new environment, then find another new environment "remember that stroma is very important for the cells to grow".
So alot of things can go wrong that's why metastasis is rare if the tumor was discovered early.
If you leave the tumor to grow long enough eventually there will be metastasis.
Metastasis is a very very inefficient process because many things can go wrong.
This all depends on the tumor and how it is able to get the hallmarks of cancer ,and it's ability to survive a new place.
The more anaplastic and larger the tumor is the more likely to metastasize.
Not all malignant tumors will metastasize, depending on their biology, like cancer in the skin can cause damage locally but not metastasize whereas myoma can metastasize.
And also time, the earlier you discover the patient the more likely he is to survive.
Once the patient has metastasis the survival rate declines.
Spread can be through seeding in the cavities "remember the ovary and peritoneum"
Through the lymphatic channels "epithelial carcinoma "
Sarcoma solid mesenchymal malignant invade through the blood.
However there are many interconnections between the lymphatics and blood vessels.
So eventually they can invade through either.

Now some anatomy :P



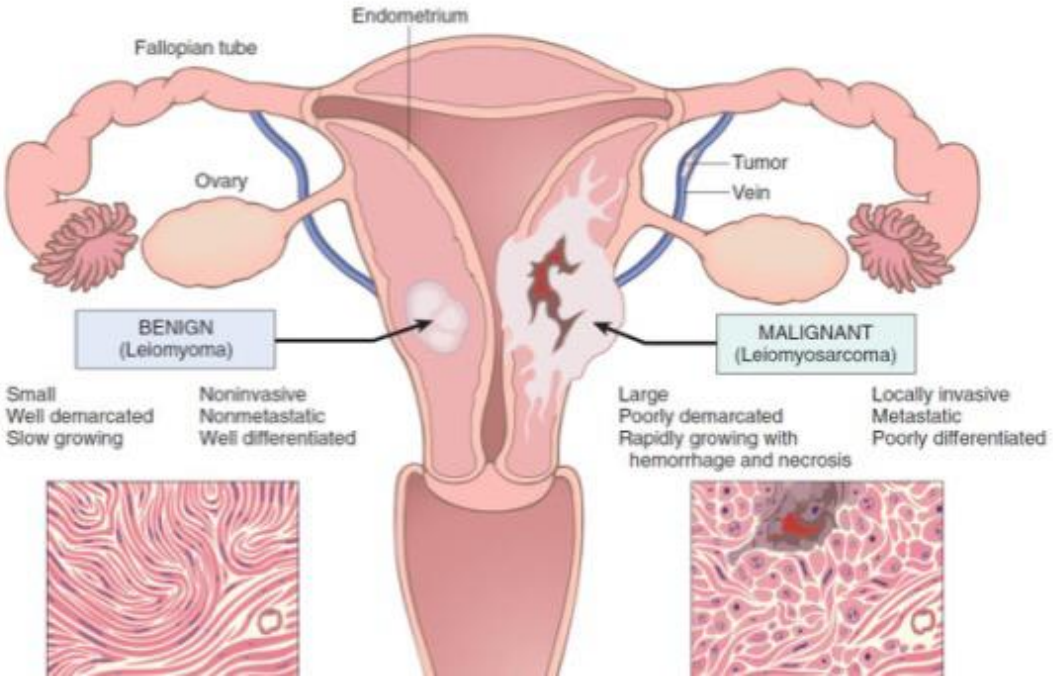
- A lung cancer will first go through the trachial lymph nodes to higher lymph nodes and then spread to the rest of the body.
- In breast cancers typically arise in the outer upper quarter the closest to them are the axillary lymph node and cancer goes there first
- Not all of the breast cancers arise in the upper quarter, some can arise in the medial part and the closest to those are internal mamary nodes
- All these breast cancers if left untreated can lead to supraclavicular or infraclavicular lymph nodes.
- The first lymph node that carcinoma goes to is called asentinellymph nodes.
- Sometimes the surgeon will inject a dye or reactive isotope to detect where the first node is and if there is involvement of the lymphatics to stage the patient.
- So the patient has a sentinel invaded lymph node and the surrounding cells are clean so most likely this tumor is localized.
- Now unfortunately some tumors skip these sentinel lymph nodes so when you diagnose you find it clean and think that there is no metastasis, this is skip metastasis.

For homogenous typically what's invaded is the vein,
Why the vein?
The vein is thinner so more easily invaded .
The first vein encountered the most likely where the metastasis occur "there are exceptions”

- If it goes in the portal circulation it will end up in the liver.
- In the caple circulation it will end up in the lung " this is why the lungs are the most commonly secondary place of tumor growth "metastasis

Anatomy doesn't explain all metastasis, skeletal muscle are very rare to have metastasis although we have a large capillary bed there, Because the stroma of the skeletal muscles is not preferable for cancer cells.

Summary of extremes



This topic is widely under research and we are in the era of molecular science, we all know at least one story “if not more” about cancer..
We are the doctors of the future..it's our responsibility to understand these topics to save lives..

Just remember that you are great and you can do it :)