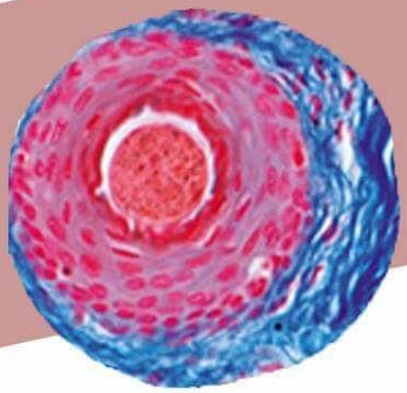
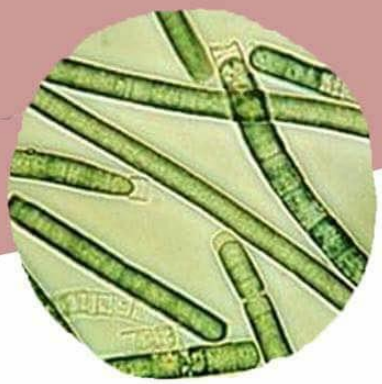
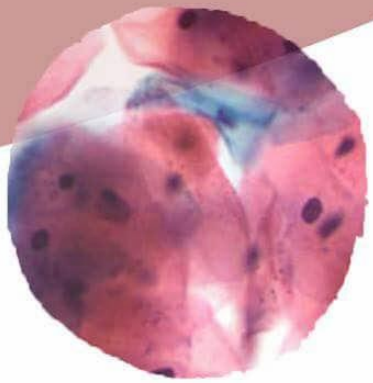
INTRODUCTION TO PATHOLOGY

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Sheet# 15

Neoplasia

p.s. The doctor clearly stated that this lecture is dense , so please please don't freak out , Good luck ☺

What is neoplasia?
Neo: is from the Latin word new
Plasia: growth
Neoplasia means a **new growth**

The difference between a tumor and hyperplasia is that tumors are independent of growth factor stimulation .

Are all neoplasia bad? Are they all malignant? Does neoplasia necessarily mean cancer?
No, neoplasia doesn't necessarily mean cancer.
Neoplasia is a synonym for the word tumor, so when you hear tumor , don't immediately think of cancer .

There are two types of Neoplasia:
1-Benign
2- Malignant

The main indicator between a benign and a malignant tumor is that a benign tumor doesn't spread .
Generally **benign tumors** are **localized**, which means that the patient typically survives (there are exceptions of course) , whereas malignant neoplasms are termed **cancers** and they **invade locally , destroy tissues and there is distant metastasis** .

Neoplasia = Tumor
Neoplasia ≠ Cancer (not necessarily)
Malignant neoplasm = Cancer

A clinical case where a tumor can be life threatening regardless of its type (a case where benign tumors can be lethal) :
If its in the brain , because of the mass effect , there is a limited space in the brain and if you add something new your intracranial pressure will increase ,

when this pressure becomes too high herniation will happen (the brain stem will herniate through the back of your skull and that's lethal).

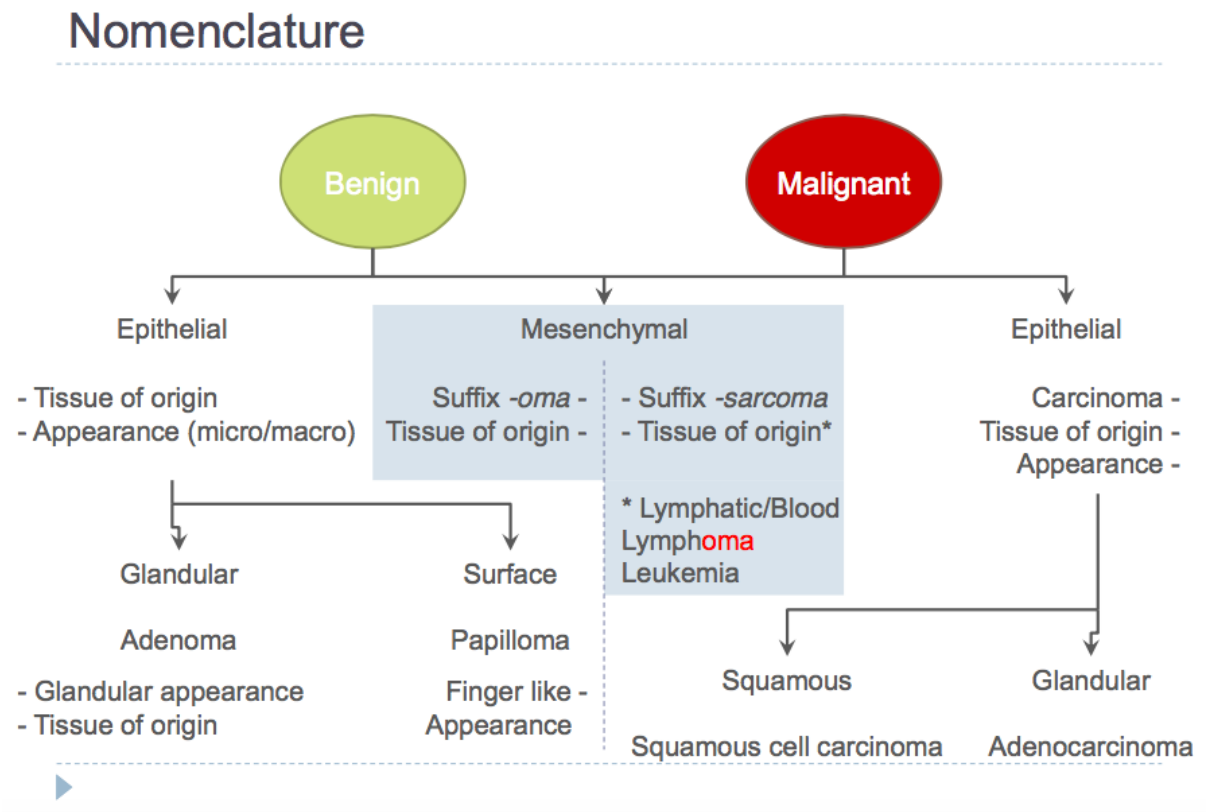
-Tumors are named according to the parenchymal cells , they are the cells that have transformed and gained a **replicative immortality **** , they have been genetically modified so they do things normal cells don't do . However , the behavior of a tumor isn't solely dependent on these parenchymal cells , these cells need nutrients and oxygen and need to stimulate angiogenesis in the same way you stimulate angiogenesis for healing and repair that's why Cancer is frequently termed ''the wound that won't heal '' because a lot of the cytokines , growth factors , angiogenic factors that wound healing involves are coopted by these cancer cells for their own nefarious needs .
From the introduction lectures : (remember how we talked about **Telomerase activity , in normal cells the telomere in the DNA gets shorter with each replication while in cancer cells the enzyme Telomerase has a high activity that prevents this from happening).

-There is a 2 way conversation between the transformed neoplastic cells(parenchymal cells) and the surrounding connective tissue , we are talking about blood vessels , inflammatory cells and connective tissue , because :
-Cancer uses these inflammatory cells for the same purposes you use for healing .
- The connective tissue itself is used by cancer to stimulate the production of metalloproteinase so that they destroy the extracellular proteins. By destroying the ECM components it lays a trail of cytokines and chemotactic factors that makes cells migrate and proliferate and protect it from apoptosis .

-Stromal tissue is extremely important for cancer , experiments have been done where you take some parenchymal cancer cells without their stromal cells and you put them inside the same organs somewhere else where the stromal cells haven't been coopted and here nothing happens , so you need to have a permissive stroma , everybody has a permissive stroma so maybe changes that occur in the stroma allow cancer parenchymal cells to grow .

-So rather than concentrating on the cancer cells only you need to look on the whole organ where the cancer is occurring.

Nomenclature :
The naming of benign and malignant tumors might be confusing but there is a unified theme :



Depend on the graph above for naming but below are additional notes :

-Adenoma : glandular like structure or it arose from a glandular organ
-Papilloma : If it's a surface projection (commonly known as polyp but polyp is not the correct term to use because not all polyps are neoplastic polyps , for example : polyps that arise in your nose because your allergic are inflammatory polyps , some polyps are hyperplastic polyps) .
-For example : benign tumors :
Lipid tissue / fat cells : lipoma
Fiber cells : fibroma
Cells in your cartilage : chondroma
-If they are malignant :
Liopsarcoma
Fibrosarcoma
Chondrosarcoma

10 minutes

There are exceptions to these rules :
Lymphoma : it sounds benign but its actually malignant

-For malignant mesenchymal tissues the suffix is sarcoma but it also depends on the tissue of origin , if we're talking about lymphaticas and blood then it's lymphoma and **leukemia** (leukemia doesn't follow any of the names here)
-Thyroid papillary carcinoma is a special case , here your not changing glandular cells but other cells .
-**Mesothelioma** : sounds benign but it's a malignant tumor that rises from the lining of your pleural tissue
-**Seminoma** : sounds benign but it's a malignant tumor rising from testicles in males
-**Wilm's tumor** : the most common type of kidney cancer in children (the doctor didn't mention any info about this one but asked us to look it up)

Table 5–1 Nomenclature of Tumors

Tissue of Origin	Benign	Malignant
Composed of One Parenchymal Cell Type		
Connective tissue and derivatives	Fibroma	Fibrosarcoma
	Lipoma	Liposarcoma
	Chondroma	Chondrosarcoma
	Osteoma	Osteogenic sarcoma
Endothelial and related tissues		
Blood vessels	Hemangioma	Angiosarcoma
Lymph vessels	Lymphangioma	Lymphangiosarcoma
Mesothelium		Mesothelioma
Brain coverings	Meningioma	Invasive meningioma
Blood cells and related cells		
Hematopoietic cells		Leukemias
Lymphoid tissue		Lymphomas
Muscle		
Smooth	Leiomyoma	Leiomyosarcoma
Striated	Rhabdomyoma	Rhabdomyosarcoma
Tumors of epithelial origin		
Stratified squamous	Squamous cell papilloma	Squamous cell or epidermoid carcinoma
Basal cells of skin or adnexa		Basal cell carcinoma
Epithelial lining of glands or ducts	Adenoma	Adenocarcinoma
	Papilloma	Papillary carcinomas
	Cystadenoma	Cystadenocarcinoma
Respiratory passages	Bronchial adenoma	Bronchogenic carcinoma
Renal epithelium	Renal tubular adenoma	Renal cell carcinoma
Liver cells	Liver cell adenoma	Hepatocellular carcinoma
Urinary tract epithelium (transitional)	Urothelial papilloma	Urothelial carcinoma
Placental epithelium	Hydatidiform mole	Choriocarcinoma
Testicular epithelium (germ cells)		Seminoma
		Embryonal carcinoma
Tumors of melanocytes	Nevus	Malignant melanoma
More Than One Neoplastic Cell Type—Mixed Tumors, Usually Derived from One Germ Cell Layer		
Salivary glands	Pleomorphic adenoma (mixed tumor of salivary gland)	Malignant mixed tumor of salivary gland
Renal anlage		Wilms tumor
More Than One Neoplastic Cell Type Derived from More Than One Germ Cell Layer—Teratogenous		
Totipotential cells in gonads or in embryonic rests	Mature teratoma, dermoid cyst	Immature teratoma, teratocarcinoma

ps. The doctor required checking the table above

The 4 major characteristics that differentiate between benign and malignant tumors :

1-**Rate of growth**: typically malignant tumors grow faster

Exceptions: an example of a benign tumor that grows faster than most malignant tumors : **leiomyoma** is a benign tumor of the smooth muscles of the uterus , these muscles are responsive for pregnancy hormones , so leiomyomas might be small and go undetected but they become a very big problem during pregnancy and they grow massively .

2-**Differentiaton and Anaplasia** :

well differentiated: If something looks very much like the original cells

poorly differentiated: If something looks really different from the original cells

typically benign tumors are well differentiated while malignant tumors could be anything from well to poorly differentiated .

Poorly differentiated = Anaplasia : Anaplastic means very poorly differentiated and looks nothing like the tissue of origin .

3-**Local invasion** : typically for metastasis to occur (not true in all tumors) local invasion must happen , benign tumors never ever locally invade .

4- **Metastasis**

Now we're going to go through examples on

1-Differentiation and Anaplasia :

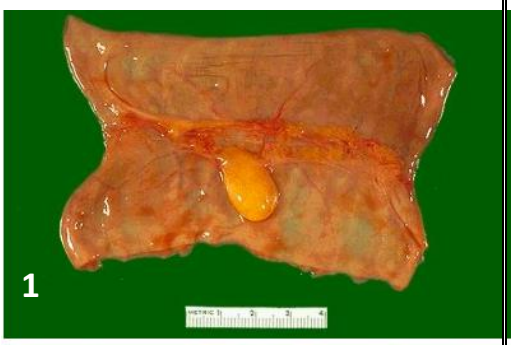
In benign neoplasia :

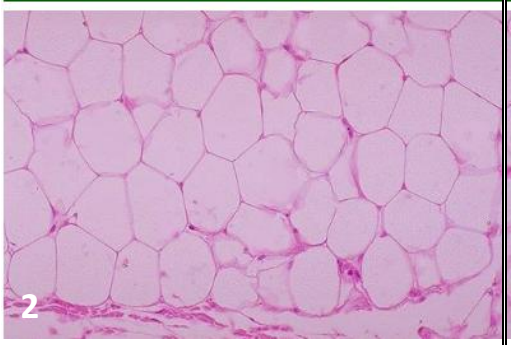
If the slide 2 was given to you without knowing from where it came, you would think its adipose tissue . But if you knew it came from a lump (1) then there will be a different diagnosis : lipoma (benign tumor from adipose tissue) .

So here we notice 2 points :

1-you must tell your pathologist that the sample is from a lump to get the right diagnosis because **functionally and morphologically it looks very much like the original tissue (well differentiated)**

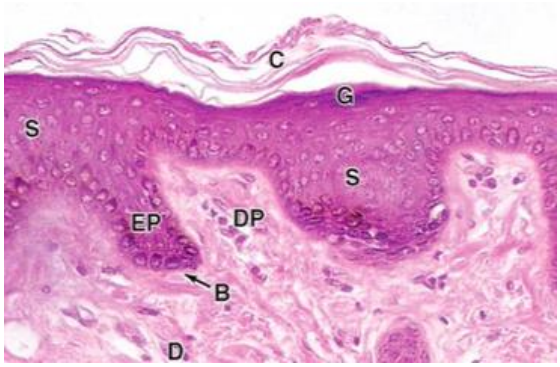
(keep in mind : Mitotic figures : catching the cell in the middle of mitosis)





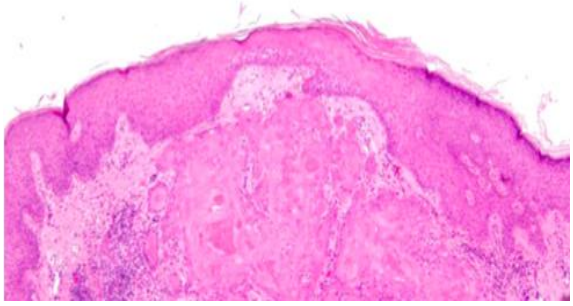
2-**Mitotic figures : rare , same as in normal tissues** , and if you found one it will look normal (normle spindles , normal genetic composition ..) .

In malignant neoplasia :
Could be well differentiated , moderately differentiated , poorly differentiated , anaplastic .

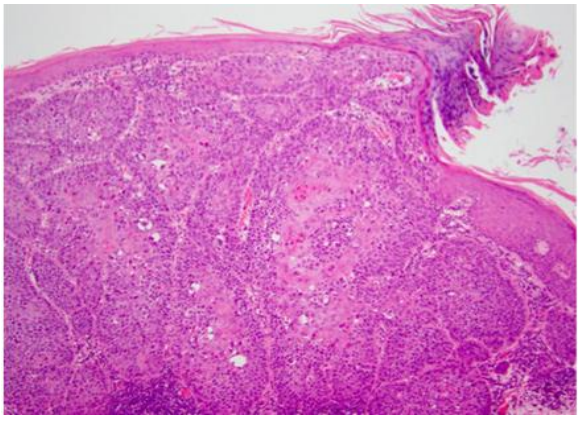


1 is normal skin

2 is well differentiated
not normal but still is skin-like , you have keratin , layers of skin although not that clear but you've got that change from cuboidal to spindle to flattened shape , the basement membrane is there and you can see a nice clear line between epithelium and sub epithelium, the dermis doesn't look right , it's a well differentiated squamous cell carcinoma of the skin that has grown into the sub epithelial layer



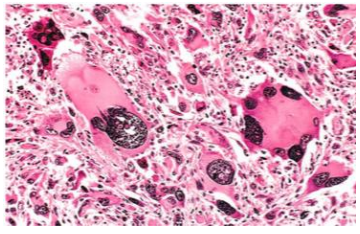
-well differentiated because the skin generally looks normal
-functionally well differentiated because even the neoplastic growth in the sub epithelia tissue is producing islets of keratin

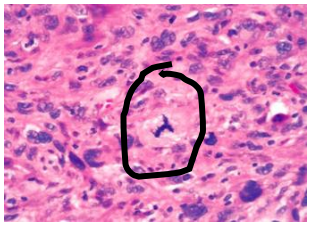


*keratin : Acellular tissue

3 is moderately differentiated
you still have keratinization and some layers but it doesn't look right , keratinization centers are gone so it functionally dedifferentiated to a point where they can become completely bizarre and abnormal which is **poorly differentiated/anaplastic (4)**

20 min





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Poorly differentiated = anaplastic
- Stem cells
- De-differentiation

- Pleomorphism
- Loss of polarity
- Giant cells
- Hyperchromatic Nuc.
- Large Nucleus
- Abnormal shape nuc.
- Multiple Nuclei
- Mitotic figures frequent/abnormal

Characteristics of anaplasia as mentioned in the slides

Focus on the circle in the right picture with number 4 , you will find an abnormal mitotic figure , it has 3 spindles , rather than dividing to 2 cells this cell is dividing to 3 cells .
So in malignant neoplasms especially the poorly differentiated you will find a lot of abnormalities (the ones listed above) .

Additional notes on these abnormalities :
Pleomorphic: multiple shapes, they don't look the same , there is no unifying form for the tissue .
Loss of polarity: you don't know which side is down and which side is up (in normal epithelial cells you know that) , this is part of a process called **epithelial to mesenchymal transition** , so cells in this case no longer look or behave like an epithelial cell and don't stop replicating just because it detached from the basement membrane **, it actually continues replicating just like fibroblasts on growth factors .
**normally when a cell loses polarity it stops replicating
Hyperchromatic nuclei: the nucleus is darker than the surrounding which means there is more DNA, frequently the malignant neoplasms has an abnormal composition of the DNA, sometimes multiple copies of the same chromosome.

Functionally:

Well differentiated tumors (especially glandular tissue) will continue to produce the same material that the normal cell produce.

-This is a hepatoma, it's a benign tumor of the liver parenchyma, it stained green here because it's producing bile.

-If we have a hormone producing tissue that has a neoplasm whether benign or malignant that is continuing to produce the same material, especially if the growth is large and is producing a lot more than what is normally produced, then that could be a symptom that makes patient visit a doctor.
-Some malignant tumors that arise in tissues that don't normally produce hormones dedifferentiate and become a different type of endocrine cell even though these cells are not present in that organ. For example, lung cancers can produce some hormone-like substances like ACTH / Parathyroid-like hormones / glucagon / insulin and patients present with symptoms of hormonal imbalances, this is called **Paraneoplastic syndrome**. (The cells in this case are producing these hormones for their own needs).

*mutations are random by definition.
***typically all cancers are clonal** because that particular cell is at such an advantage on the other cells that it survived and the other cells died **(Natural Selection)** , so if a certain mutation caused a cell to die off by apoptosis then it obviously died and the cell with the mutation that prevents apoptosis is the one that survived .

Metaplasia vs. Dysplasia vs. Carcinoma in situ

Metaplasia: a tissue changed from a normal tissue to another completely normal tissue just in the wrong place/organ.
Dysplasia: the cells in this tissue has become cells that look absolutely nothing like anything in the body.

-**Dysplasia can frequently precede neoplasia** but it's not inevitable.
-**Dysplastic lesions are considered preneoplastic lesions, it just means there is an increased risk of these lesions to become neoplastic but it doesn't necessarily mean they will always become neoplastic.**
-**Dysplasia** could include part of the surface, most of the surface or all of the surface but it **doesn't go beyond the basement membrane** (we're talking mainly about dysplasia in epithelium tissues).
-**If dysplasia has gone beyond the basement membrane** which means invasion has occurred, **we are no longer talking about dysplasia**, **this is invasive cancer**.

Carcinoma in situ:

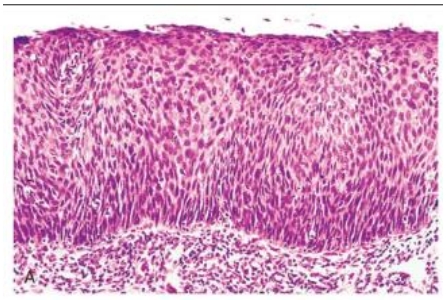
-In this case you can clearly see a line that separates the epithelial from the sub epithelial, the basement membrane is still intact.

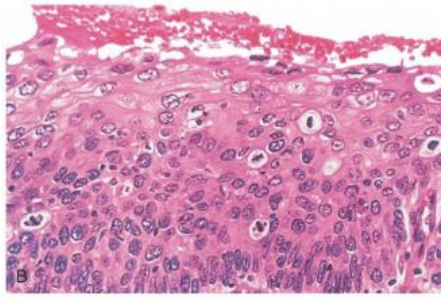
- Carcinoma in situ is **preinvasive, the whole epithelium is involved, and the basement membrane is intact.**

-Dysplastic tissue that is carcinoma in situ where the whole thickness of the epithelium is involved has **the same characteristics as anaplastic cancers: pleomorphism, hyperchromatic nuclei, mitotic figures are more frequent but normal and they are outside the basal layer.**

30 min

Neither of these tissues look normal, they are dysplastic tissues but the good thing is the basement membrane is still intact, this matters because it hasn't invaded yet so it's a lot easier to remove.





Clinical example:

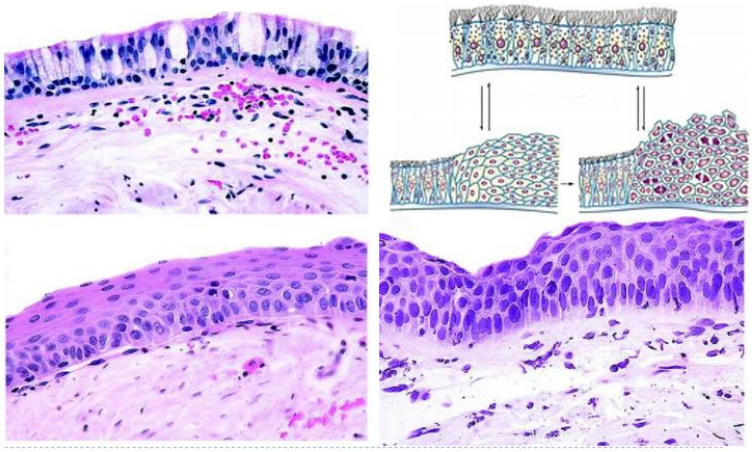
- married women (with the start of sexual activity) must go to the OB/Gyn about once every year or 2 and get a **pap smear**, it's an internal examination where the doctor takes **a sample from the cervix to detect dysplasia**, because it's easier to detect at this point before it becomes a cancer, this examination caused cervical cancer rates to go down worldwide.

-This test is important for women when they become sexually active because of **HPV** (human papilloma virus) which is a sexually transmitted virus that can **induce these cells to transform**, so when you detect dysplasia it's treatable which prevents having cervical cancer.

-Nowadays we have HPV vaccine, given to girls before they become sexually active so when they are exposed to the HPV they no longer are at risk for cervical cancer.

-The one in the first row is normal bronchial epithelium, you have columnar cells, you can see goblet cells and little bit of fuzziness that's cilia.

-Which one of the pictures in the second row is dysplasia and which one is metaplasia?



-The one on the right : dysplasia : elongated enlarged nuclei , very hyperchromatic nuclei ,the shapes are really different and there is no unifying shape that's going from cuboidal to flattened shape to the spindle shape that you see on the left picture .

-The on the left: metaplasia : stratified epithelium that you can find elsewhere normally .

2-Rate of growth : generally :

Malignant ---- fast growth

Benign ----slow growth (remember the example of leiomyoma)

-Malignant tumors can also grow slowly or fast , depending on the rate of growth of the tumor- which is mostly fast- they are either treatable or not treatable .

-which is more treatable , slow or fast growing malignant tumors ?

The answer is not clear, slow growing tumors might be so slow that they are not detected as a lump and if there is no screening program for this type of tumor then it could metastasize before its detected as a lump . On the other hand , fast growing tumors could be good especially if you have a molecular treatment that specifically targets their proliferation, so slow growing tumors could be more resistant to some treatments while fast are not .

Sometimes slow growing tumors could be lessened because we have a screening program for it so we detect it and it hasn't gone beyond a certain size so we remove it and the patient is fine .On the other hand , there might be no screening program , the tumor already metastasized which is bad for the patient .

-Survival figures are usually plummeting to the single digit range when you find a metastasis , there is not much you can do for a patient once the tumor has metastasized because we still don't have good treatments for it .

The size of the tumor : diffusion reaches a few millimeters, **so the bigger the tumor gets the more blood supply it requires**. As you remember from repair, immature blood vessels are leaky and easier to access, so the likelihood of a big tumor that is stimulating angiogenesis to metastasize is higher, that doesn't mean all big tumors will metastasize, some tumors will never ever metastasize like basal cell carcinoma of the skin, it can get very big but it's not in its genetic make up to metastasize.

-Sometimes the tumor can outstrip its blood supply, which means it gets too big for the blood supply that has stimulated it, so the center of the tumor becomes necrotic and dies off because there is no enough blood supply.

-Even small tumors can become necrotic as when we have space limitations, for example, when it's in the pituitary gland that is in a bony compartment - whether this tumor is benign or malignant- and it compresses on this bony space and the blood vessels that come through the stock, it will kill itself, and the patient will come to you with no pituitary hormones and all the hormonal imbalances that follow, this case is called **empty sella syndrome ESS**.

The factors that effect the rate of growth are :

1-Blood supply

2-Hormon/growth factor effect

3-Anatomical mutations

4-Somatic mutation theory SMT / subclone (this is the process of natural selection that we talked about)

It's not the only theory for cancer , there is also the **tissue field organization theory** which unifies not just the parenchymal cells and their mutations but also how they coopt stromal cells around it

so always keep the stroma in mind (is it permissive ? will it allow growth ?)

we don't frequently hear about metastasis in the cranial tissue , the stroma in it is not very permissive , it happens but very rare , but a lot of tumors metastasize to the lung and liver because the stroma there is permissive.

5-Cancer stem cell hypothesis

-Cancers arise from mutated stem cells, that's why they have unlimited proliferation potential, there are other examples where some somatic cells, when they gain mutations they dedifferentiate and become stem-like cells.

-The problem with this hypothesis is that stem cells are resistant to a lot of the treatments, so the treatment kills the cancer cells but cancer stem cells are still there and can potentially cause cancer reoccurrence.

Examples on these opinions on how cancer stem cells occur :

In Acute myelogenous leukemia , a differentiated cell becomes dedifferentiated and becomes a cancer stem cell .

40 min

In Chronic myelogenous leukemia , a stem cell can become mutated and become a cancer stem cells .

MDR-1 : a protein called multiple drug resistant -1 prevents drugs from affecting , they are actively pumped out of the cell .
*****There are also Solid tumor stem cells : some solid tumors has been defined , some solid tumors not , the basic idea is that we need to kill not only the parenchymal cells of the tumor but also the stem cells .

3-Local invasion

It means it's invading surrounding tissues .
Benign tumors ---- typically have a well-defined fibrous capsule, it doesn't locally invade
some benign tumors don't have a well-defined capsule but you can still identify the benign neoplasm from the surrounding tissue and you won't see any projections into the surrounding tissue .
Malignant tumors ---- they don't develop well defined capsules, you can see projections, columns of cells going into the tissue , they infiltrate and invade , clean margins are required for resection (which means that after a surgery in which you removed the tumor you must take a biopsy from the remaining surrounding tissue and send it to the histopathologist as a frozen section while the patient is still open to check if there is still tumor cells in this margin , if you have a clean margin you can close up the patient. This doesn't necessarily mean that malignant tumors don't develop capsules, for example, **slow growing tumors can be misdiagnosed as benign tumors because they can stimulate the stroma to produce a fibrous tissue so it looks like it has a capsule**, unless you take a biopsy and check it under the microscope you can never be able to tell grossly , generally you can't diagnose a tumor without a proper biopsy.
Cancer is called this name from the word crab because it has projections.

4-Metastisis

Malignant tumors ---- metastasize
Benign tumors ---- never metastasize
That NEVER changes , BUT some benign tumors can become malignant and metastasize , that depends on the tissue , like adenomas of GI tract , more than 50% of the colonic adenomas will turn into adenocarcinoma if left , while leiomyoma will never turn to leiomyosarcoma .
If a tumor is anaplastic and big, it's most likely to metastasize. (Exception: basal cell carcinoma of the skin never metastasize).

Also, some very small tumors have an incredible ability to metastasize (not big but very anaplastic).

Spread: could be either by :

1-Seeding :

invasion is not a prerequisite for metastasis.

Example : ovarian tumors , the ovary is draped by peritoneum , it can immediately seed into the peritoneal cavity with no invasion required.

2-Lymphatic

Example: carcinomas use this (think of TGF and angiogenesis and lymphomagenesis) , for a colon tumor to metastasis to your liver it will have to move through the layers to the lymphatics and then go to liver.

-You need to know the lymphatic drainage in order to know which is most likely to be the first lymphatic node to have the tumor , and then where ….., by this you can tell how long this tumor has gone .

-For example: breast cancer:

Typically arises in the outer upper quadrant --- the first lymphatics that are going to be affected are the axillary then the supraclavicular and infraclavicular lymph nodes.

It can also arise from the medial inner quadrant --- it will go to the internal mammary nodes but eventually end up at supraclavicular and infraclavicular nodes.

-When you know where the tumor is you can know which lymphatics to check and you'll take a biopsy from them, you do this by putting a radio labeled marker next to the lymphatics of the tumor and find which one was colored.

-Some tumors can skip a lymph node (Skip Metastasis), so you don't sample one lymph node , you sample multiple .

-If a lymph node is enlarged that doesn't necessarily means it contains a tumor, you have to send for biopsy, it could be just inflammatory cells because the tumor induced an inflammatory reaction so the lymph nodes got bigger.

3-Hematogenous

Typically sarcomas like to go through the blood .

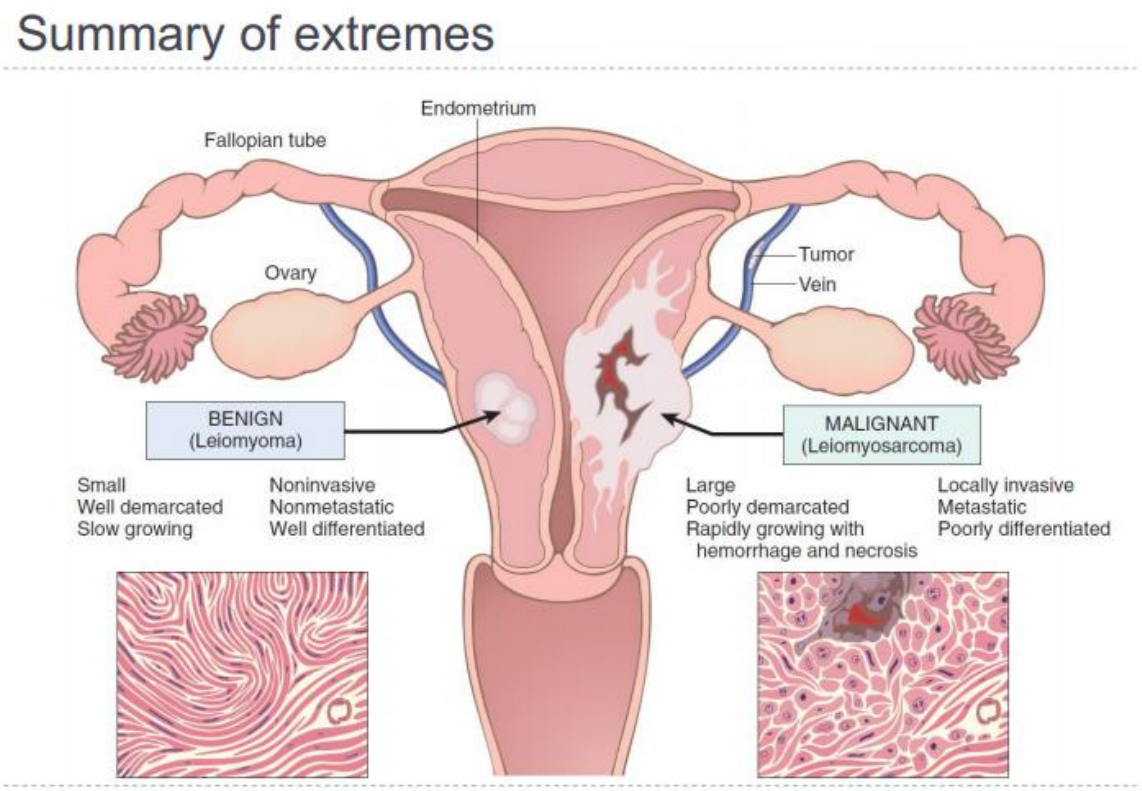
The 2 most common end points of metastasis :

-Liver : if you're in the portal circulation so you're talking about your GI.

-Lung : if it's in the systemic/caval circulation , it will go to the lung which is where the systemic circulation ends.

*Can you accurately predict where the tumor is going to go ?
No, this depends on the biology of the tumor and the stroma of the receiving tissue. So there are common places where a certain tumor would go but we can never have an accurate prediction (for example , you have large capillary beds in your skeletal muscles but you don't really see metastasis in them)

***Blood vessels and lymphatics are interconnected so both types of tumors can use both systems**



P.s. check the slides for more pictures / the doctor really recommended checking the slide above as a summary for everything.

''Temper us in fire and we grow stronger, when we suffer we survive ''