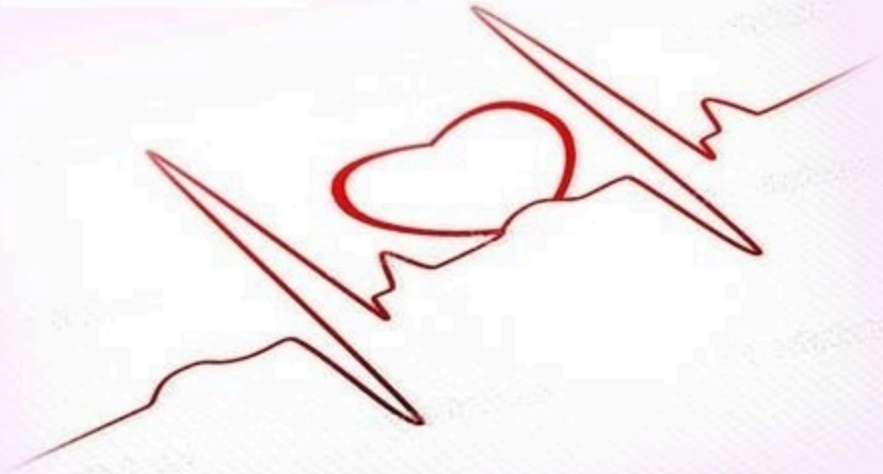
PATHOLOGY

Medical Committee
The University of Jordan

SHEET

SlIDE



Lecture Number: 16

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Neoplasia

This sheet has the underlying basis to understand the rest of the chapter.

Please read the pages in the book as it contains lots of examples and the doctor can't tell us every example in the lecture.

Not every rule we are going to take is exact, every rule has an exception.

Objectives : **المتوقع من الطالب بعد دراسته لهذه الشيت :**

-General characteristics of diff types of cancer

-Naming of different cancers

-Benign Neoplasia

-Neoplasia or Tumor means "New Growth".

-Neoplasia could be either **benign** or **malignant.**

-A benign tumor is typically localized and patients usually survive - no major consequences.

-Malignant tumors called **"cancers"** (cancer means crab → it's a description of the microscopic edge of the tumor where it has crab-like feet of cells infiltrating the neighboring tissue) they invade locally, destroy local tissue and metastasize (it's a discontinuity between the original tumor and tumors elsewhere) e.g.: the tumor that arises in the prostate could be found later in the bone even though there is no direct anatomical connection between them, it (the tumor) has moved either through lymphatic or blood spread of tumor cells .

But for every rule there is an exception:

*-*some benign tumors that could really be based on where they grow ,for example , a benign tumor in the cranium could raise the intracranial pressure , could cause

all these neurological problems (herniation..etc) and could kill you, so there is no real thing as benign tumor in the CNS, there are severe consequences even though they do not invade or metastasize .

- Not all malignant tumors metastasize "as an exception", for example **Basal cell carcinoma** they invade locally but rarely metastasize or never at all.

-Tumors are divided into two parts: 1- the parenchymal 2- the stromal

The parenchymal cells are the transformed cells or neoplastic cells, these are the cells that have a mutation that allows them to grow beyond the normal border, whether benign or malignant is the classification.

The stromal cells on the other hand include the connective tissue, blood vessels and some other cells, which provide nutrition and structure for the tumor. They also comprise inflammatory cells.

**Our book mentions a hypothesis about tumors → clonality and mutations, talking about "somatic mutation theory", or "Darwinian's theory of evolution (natural selection)."

Note → although it is called a theory, it is actually only a posed hypothesis

Natural selection: survival of the fittest , when a cell gains an advantage over its neighboring cells by being independent of growth factors so it grows faster than other cells and outpace the other cells taking away their nutrients .

This theory is based on the fact that tumors behave according to the parenchymal cells of the tumor, but there has been a growing realization that without the stroma the tumor couldn't survive (there is a two way conversation between stromal cells and parenchymal cells), so the theory has been modified to include the conversation that goes on between these two types.

Clonalitiy: that mutation that gave an advantage to that first cell is what gives rise to the rest of the tumor, so tumors are typically **monoclonal**, if u find tumors that have multiple clones of cells that's because of diversion of differentiation (which means that the original cell may have differentiated to other types of cells and

gained further mutation among the way so now the tumor looks more of a mixed origin but still the theory is that the tumor started with one cell).

Nomenclature (naming):

Tumors are divided into benign and malignant and these are further divided according to the tissue of origin to epithelial (could originate from any of the three germ cell layers: mesoderm, endoderm, ectoderm) and mesenchymal (mesodermal in origin).

In adult tissues we are talking about epithelial and mesenchymal.

Benign tumor → Epithelial in origin

The naming is based on the tissue of origin and its microscopic/macroscopic appearance:

1- Adenoma: forming glands, or if it's originally from a glandular tissue but does not look like a gland it's also called Adenoma, if you have a cyst (an empty space) accompanied with the adenoma it's called a "***cystadenoma***".
2- Papilloma(or Polyps): if it's a surface projection (finger like appearance), be careful: Papilloma is the right term because some malignant tumors grow as polyps , adding to that some polyps are not neoplastic (tumor) they are inflammatory in origin such as nasal polyps.

Benign tumor → Mesenchymal in origin

The naming is based on the tissue of origin.

They are defined by the suffix –oma–:

Fibroma (from a fibrous tissue), Chondroma (from chondrocytes), Lipoma (from fat cells).

Malignant tumor → Mesenchymal in origin

The naming is based on the tissue of origin.

They are defined by the suffix –sarcoma–:

Fibrosarcoma (from a fibrous tissue), Chondrosarcoma (from chondrocytes), Liposarcoma (from fat cells), Lieomyosarcoma (from smooth muscles).

**exception (non-solid tissues): Leukemia (from blood), Lymphoma (from lymphatic) even though it ends with the suffix –oma– it is malignant.

Malignant tumor → Epithelial in origin

The naming is based on the tissue of origin and its microscopic/macroscopic appearance:

1- Adenocarcinoma: glandular
2- Squamous cell carcinoma : of surface origin

Now based on the tissue of origin →just insert the tissue or organ of origin in the name of microscopic appearance either before Adenocarcinoma (Lung Adenocarcinoma), or in the middle of squamous cell carcinoma (Squamous cell Thyroid carcinoma) it is based on what the community has agreed on so far.

NOTE: learn the rule and know the exceptions, see table 5-1 in the book and be aware of the exceptions.

There are some tumors that are called mixed tumors (unknown tissue of origin and they contain multiple components):

- **Teratoma**: have multiple components from all three embryonic layers.
- **Tumor of the salivary gland**
- **Fibroadenoma of the breasts**: it's a mix of fibrous and edematous tissue; while not both of them are neoplastic it's a mixed tumor.

Written by **Saeed Ismail**

To be or not to be … neoplastic

Hamartoma: were originally thought to be disorders of development, where you have abnormally mixed tissues due to development of defects, although some recent studies are describing them as "neoplastic".

Choristoma: developing of embryonic rests (left-behind embryonic cells during embryogenesis) into an organ where they shouldn't be (like finding pancreatic tissue in the intestines or the underside of the stomach), but it's not neoplastic.

Now the big question when a patient comes with a lump → is it a tumor? (because not all lumps are tumors, as fat necrosis present as a lump but it's not a tumor) if it is a tumor→ is it benign or malignant??

Characteristics of Benign and Malignant tumors:

1- **Differentiation and Anaplasia:** how well they resemble the tissue they originated from, so well-differentiated tumor looks like the tissue it originated from, poorly-differentiated tumor (or anaplastic tumor) looks nothing like the original tissue so without knowing the tissue of origin pathologists can't know what this tumor is.

2- **Rate of growth:** faster tumors are worse tumors, but not all slow tumors are good and not all fast tumors are bad (a lieomyoma is very estrogen responsive when it is arising in the smooth muscle of the uterus, so during pregnancy this lieomyoma gets very big very quickly but it is BENIGN … lieomyoma after menopause regress very quickly and sometimes calcify and become fibrocalcific).
(Treating cancer targets abnormal cells like cells that proliferate rapidly so some of these malignant tumors are of the most treatable cancers)

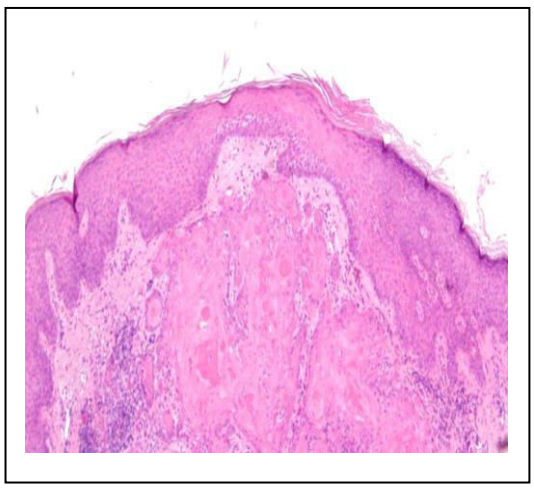
3- **Local Invasion:** compromising the capsule or the basement membrane.

4- **Metastasis: 'the 100% indication for malignant tumors'** going through the basement membrane to the lymphatic ducts or blood vessels, not all

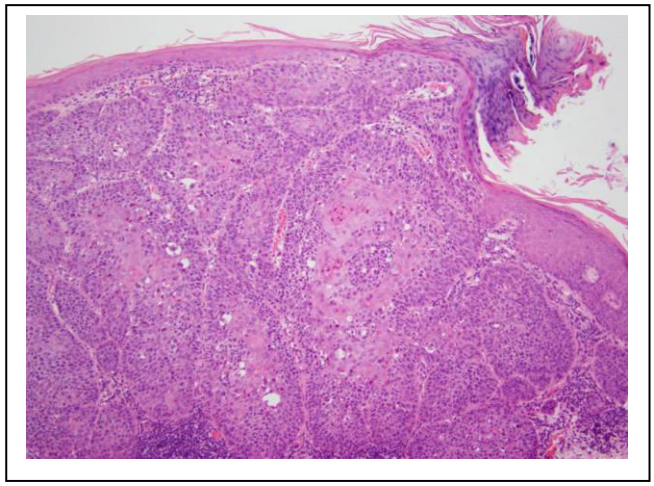
metastasis require invading (ovarian tube tumors can spread directly into the peritoneum)

*mitotic figure: is a cell that you caught (after fixing the tissue) in the middle of mitosis, in well differentiated it is normal but rarely seen .

Example (well vs. poorly) differentiated: squamous cell carcinoma of the skin→



A



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A: The epidermis invading into the dermis and we can see it is producing keratin as normal cells, B: Moderately differentiated cells and little keratin if not at all.

Benign

- well differentiated, functional, slow, don't invade locally (demarcated: by a fibrous capsule or a clear line between the new growth and the original tissue), no metastasis.

Malignant

- vary from well to poorly differentiated (worst patients), faster tumors are worse, they invade locally (crab feet edges), they metastasize.

Written by Saeed Ismail

I. Differentiation & Anaplasia:

Anaplastic tissue:

- Pleomorphism: multiple shapes (no unifying shape for this tissue anymore).
- Loss of polarity: the basement membrane guides the cells which way is up or down, where to put cilia or not…
- Giant cells
- Hyperchromatic nucleus
- Large nucleus
- Abnormal nucleus
- Multiple nuclei
- Mitotic figure: more frequent and abnormal (like seeing tripolar mitotic figures while the normal is bipolar).

There are two theories about how we reach Anaplasia:

1- The stem cells have received an insult and now they are replicating abnormally out of control and they already have no morphology of differentiated cells.
2- Differentiated cells gained the mutation, transformed then dedifferentiated (moved backwards along the differentiation pathway).
In lymphomas and leukemia they have found both theories (for example: acute myelogenous leukemia we have dedifferentiation, where as chronic myelogenous leukemia we have stem cell mutation).
This also pushed research to find stem cells in solid tissue tumors, but nothing yet.
A student asked that benign tumors in skin and normal skin histology looked the same?
::: the doctor said that there will be more layers and the skin will not be smooth and will have more thickness. (rises above the surface)
This is a well differentiated neoplasm of the liver, when this cell is fixed it turns green that means it produces bile so it is functional

**If you have a new growth in a glandular tissue (that produces a certain hormone) that new growth (if well-differentiated) will produce hormones like normal cells, but if poorly-differentiated it will stop producing that hormone. On the flipside some lung cancers will produce ectopic hormones, like: insulin and glucagon (they gain functions that they never had before) and it is a systemic effect that is not related to its growth invasion and metastasis.

Dysplasia

- Metaplasia: replacing one normal epithelium type with another normal epithelium type.
- Dysplasia: abnormal epithelium, variety in shape and Hyperchromatic.
- Dysplasia can involve part (mild), most (moderate to severe) or all of the thickness of the epithelium (carcinoma in-situ).
- Once that happens (carcinoma in-situ) this is the pre-invasive state of a potentially malignant tumor, and the basement membrane is intact.

II. Rate of growth:

Benign tumor → slow

Malignant tumor → fast

Don't forget the lieomyoma exception mentioned above.

Rate of growth - "factors":

- Blood supply
- Hormone: some tumors need hormone to grow, while some are independent of hormonal stimulation (prostate-some are testosterone dependent and some are independent- and breast cancers –some are estrogen dependent and some are independent-) the ones that are dependent are more controlled by manipulating the hormones levels.
- Anatomical limitations: a tumor needs space to grow, for example: a tumor in the pituitary grows till it hits the bone edge so it's going to constrict its own blood supply and we end up with a tumor that kills itself, no more pituitary

hormones – BIG problem) they grow so fast that they strip their blood supply; meaning that they switch to anaerobic glycolysis but the central area of the tumor that is growing so fast will not get enough blood supply you will find hemorrhage and necrosis in the center of the tumor.

Again think about the somatic mutation theory and the cancer stem cells hypothesis, if you gain an advantage that this is quickly replicating cells –fast growing tumor- that's the cell that is going to outplace all the other cells, so even though the initial mutation wasn't necessarily fast growing, a secondary mutation that made this tumor fast growing may overtake the rest of the tumor, and that doesn't mean that stem cells aren't there, they could replenish after killing the tumor cells.

*A stem cell that is transformed or mutated will become a cancerous stem cell

*A differentiated cell that gained a transformation mutation where the self renewal genes are turned on or the progenitor cells as well → can turn into a cancer stem cell.

Stem cells are hard to find and hard to keep and are resistant to most toxins, so to gain a mutation is not an easy thing otherwise most people would have cancer, also stem cells produce proteins (such as "multiple drug resistant 1" MDR1) that make them resistant to most of the cancer medication used, all tumors that are refractory express MDR1, so the hypothesis is that there is stem cells in tumors but hard to find and hard to purify.

If you miss the stem cells while chemotherapy or radiotherapy the tumor will recur and a lot of patients do recur.

Survival curves:

1. Overall survival curve: how long the patient has lived after the therapy has begun.
2. Cancer free survival curves: how long have they stayed cancer free after the therapy has ended.

III. Invasion:

**Benign tumors do not invade; they typically have a fibrous capsule.

Example: Fibroadenoma of the breast

Not all benign tumors have capsules (lieomyoma), but there is a demarcated line between new growth and original tissue.

**Malignant tumors don't have capsules, although some slow malignant tumors may look like they have but you will see the crab legs infiltrating what looks like a fibrous capsule

When surgeons are dissecting malignant tumors (biopsy) they send some fresh samples from the edges to a pathologist to make sure that there are no malignant cells (clean margins).

IV. Metastasis:

*If a tumor traveled to a distant location and implanted in a new organ. Blood and lymph vessels are very hostile environments, and these cells need a lot of survival factors to be able to go that journey and adapt to the new location.

*Benign tumors do not metastasize

*Malignant do, but not all of them, depending on the **time** and **biology**.

****Seeding**: the exception where you do not require invasion to metastasize (ovarian tumors seed to the peritoneum cavity).

*Lymphatic spread is typically for **carcinomas** (epithelial malignant tumors).

*Hematogenous spread for sarcomas (mesenchymal malignant tumors), and blood and lymphatic are interconnected so they spread in -either or- way.

Lymphatic drainage:

**A bronchial carcinoma will first go to the bronchio-arterial lymph nodes then to the tracheobronchial lymph nodes then to hilar lymph nodes.

**And depending how far it got, that is how we stage the tumor has progressed.

**Breast cancer typically arises in upper outer quadrant and it will go the axillary lymph nodes, if it arises in the inner quadrant it will go to the internal mammary lymph nodes, and from both it will end in the supra-infraclavicular lymph nodes

the first lymph node a tumor goes to is called the **sentinel lymph node.

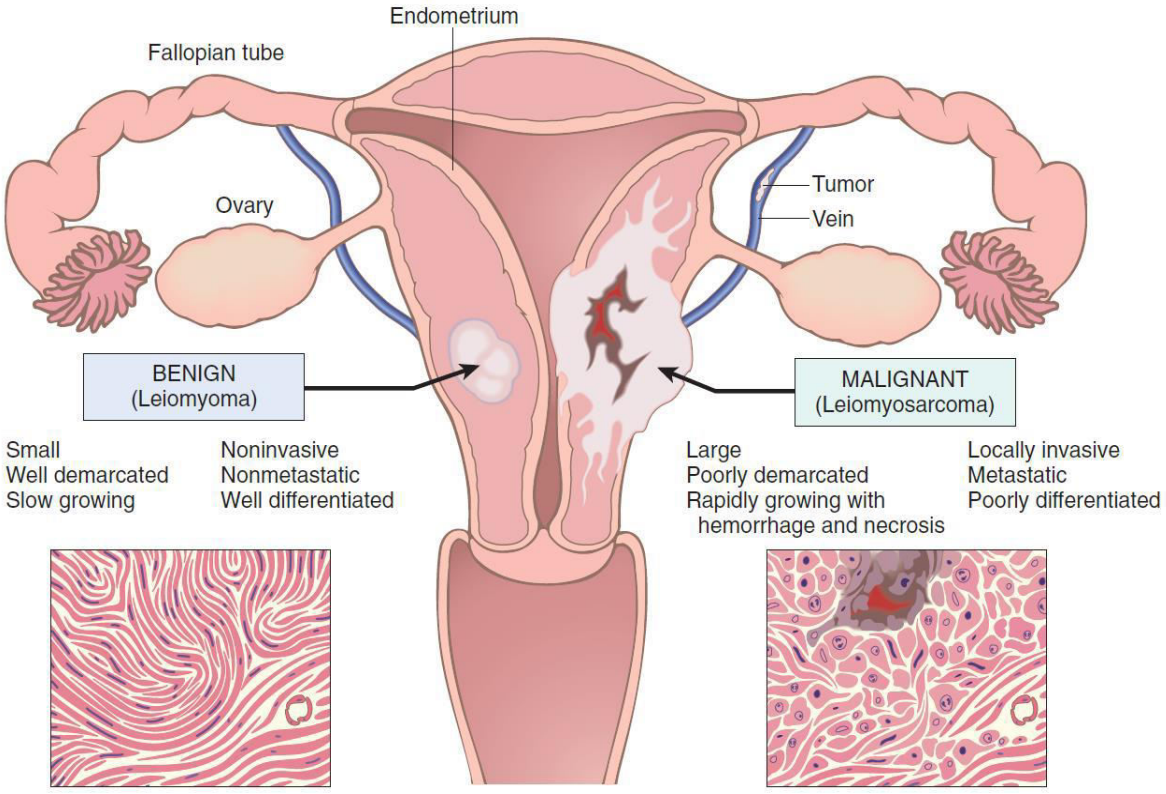
**before the surgeon takes out the tumor they will inject a radioactive substance or dye next to it, then allow it to go to the lymph node and look for that colored lymph node (or the one with radioactive tracer it it) and remove the node and the tumor together in order to prevent recurrence.

Hematogenous spread: ***portal*** circulation goes to the liver, and ***caval*** circulation goes to the lung (these are the two most common compartments involved in metastasis), however, thyroid likes to go to the vertebral column.

****veins are easier invaded than arteries because they are thinner (thinner wall).**

****the first capillary determines where the metastasis occurs.**

Summary of extremes



Leiomyoma vs. Leiomyosarcoma

Leiomyoma: nice and small, well demarcated, slow growing and you can tell the difference between new growth and the original cells.

Leiomyosarcoma: invasive, metastasize, poorly demarcated, rapidly growing, hemorrhage and necrosis in the middle and doesn't look like the original tissue.

Best Wishes ☺ Saeed Ismail