Introduction to NEOPLASIA

(Part 1)

APPROVED

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DUMC

Today: Vocab
Later: Epidemiology and Molecular Biology of Cancer followed by immunology and treatment of cancers

NEOPLASIA

Today's Goals and Objectives

1. Define neoplasm
2. Define benign and malignant
3. Differentiate benign from malignant neoplasms based on histologic appearance
4. Explain how neoplasms are named and infer properties of a neoplasm from its name
5. Explain what grade is, and how it impacts prognosis

1. What is a Neoplasm?

- **NEOPLASM = "New growth"**
- **Synonym: TUMOR = "swelling"**
  - **Originally used for inflammation, but now used as synonym for neoplasm**
- **Oncology = the study of tumors (Greek "oncos" = tumor)**

Tumor and neoplasm are used interchangeably nowadays.

NEOPLASM

Definition

mass lesion in tissue that outgrows what it normally should be

"A neoplasm is an abnormal mass of tissue **which exceeds and is uncoordinated** with that of the normal tissues, and **persists in the same excessive manner** after the cessation of the stimuli which evoked the change."

becomes autonomous

Sir Rupert Willis, 1952

Two Fundamental Features of Neoplasms

1. **Unregulated growth**
2. **Clonal genetic defects**

Derived from single cells, and all the cells within the neoplasm are clonally related

Subject of later lecture

Neoplasia III (Dr. Yan)

Mount Sacagawea,
Montana

2. What Do “Benign” and “Malignant” Mean?

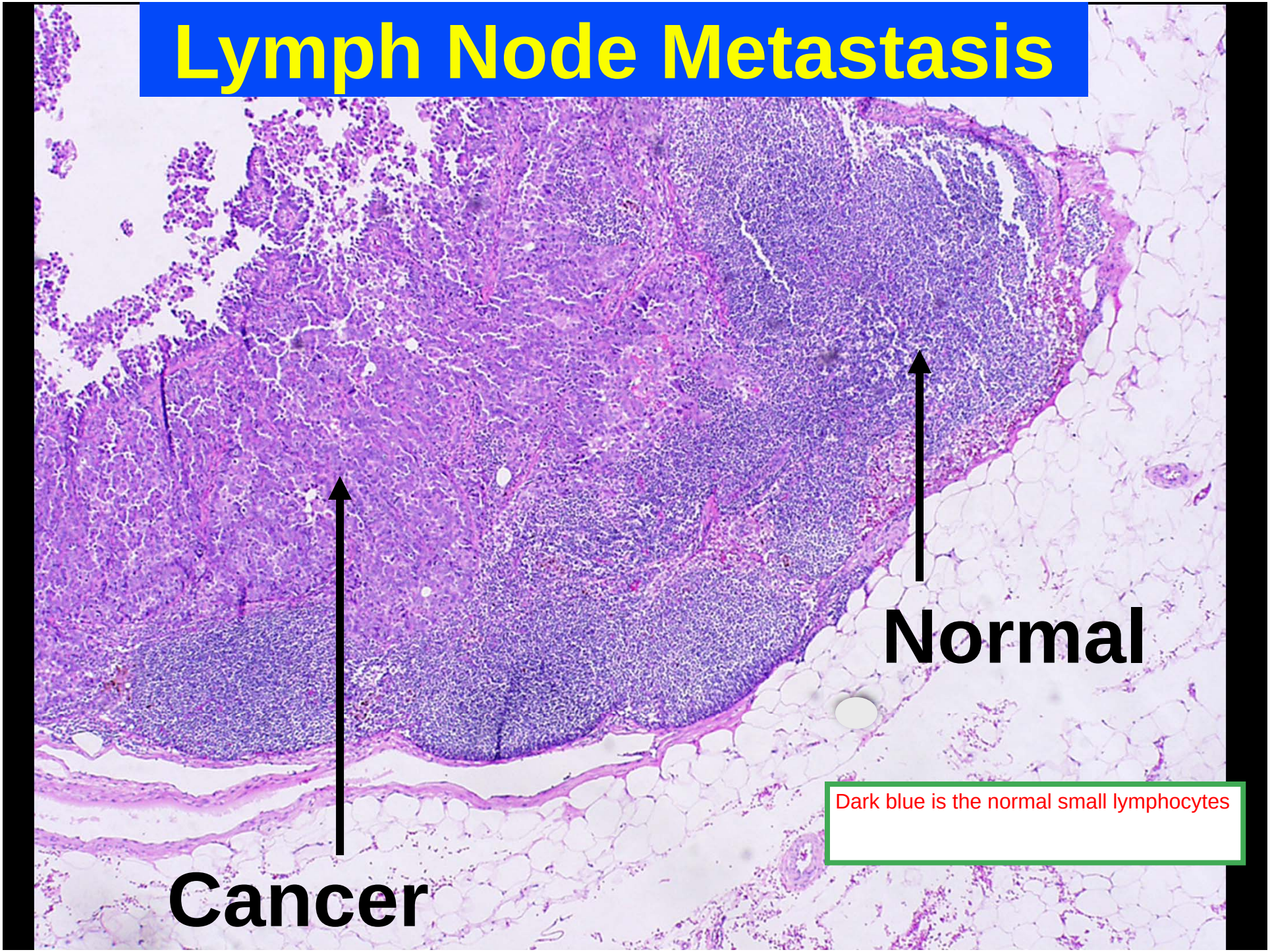
The fundamental difference for tumors arising from most tissues is the ability to metastasize - see next slide.
Brain tumors are the notable exception to this rule. Glioblastomas are malignant but they do not metastasize.

Malignant Neoplasm "CANCER"

- Metastasis = Malignant.
- Metastasis: spread to distant, non-contiguous site
  - Lymphatic metastases (nodes)
  - Hematogenous metastases (lung, liver, bone, brain)
  - Implantation in body cavities
- Fatal if untreated

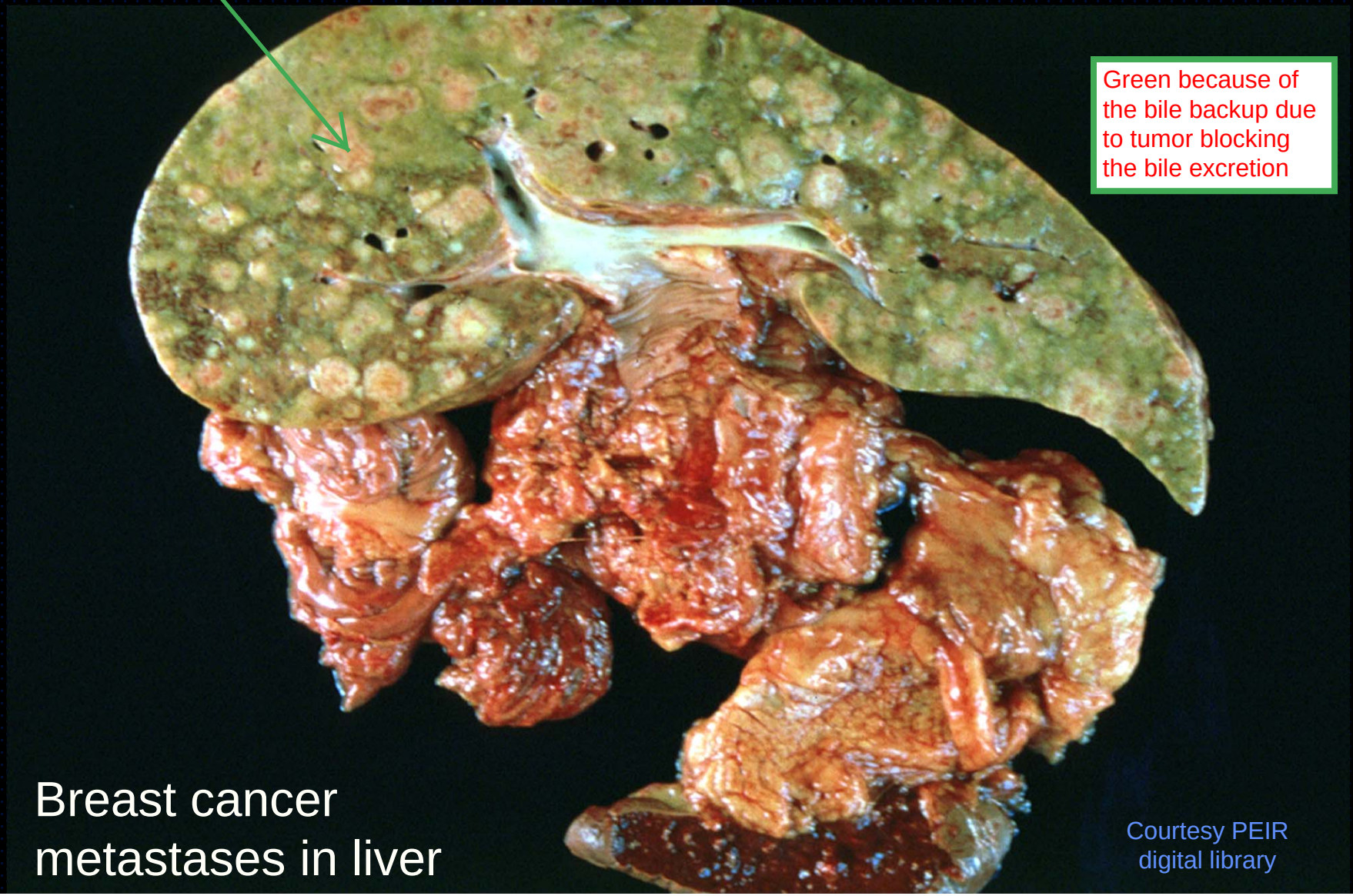
If the tumor gains access to body cavities (pleural space, etc) it can implant in these cavities

Lymph Node Metastasis



white nodules are foci of metastatic cancer

Hematogenous Metastases

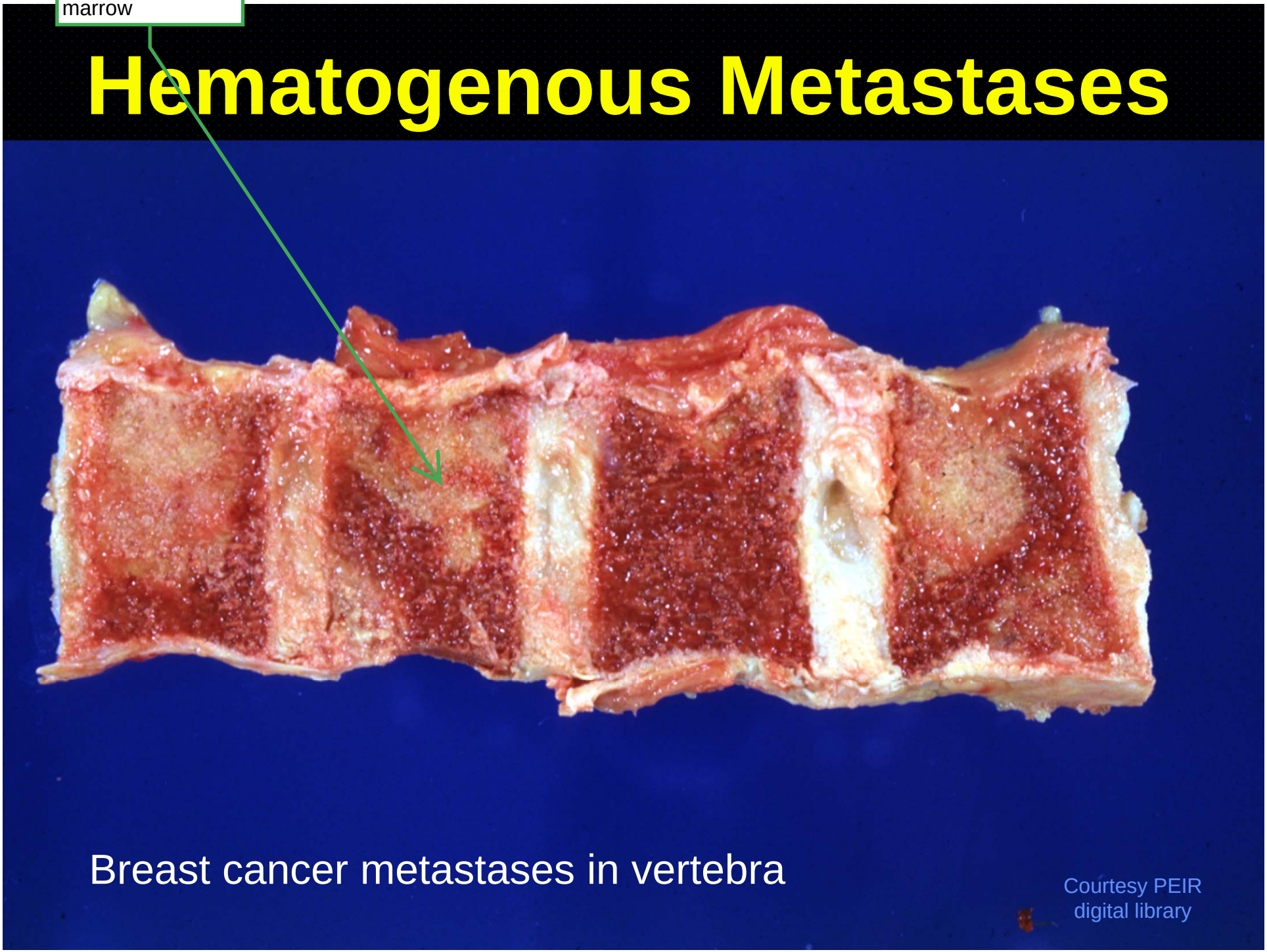


Green because of the bile backup due to tumor blocking the bile excretion

Breast cancer metastases in liver

Courtesy PEIR digital library

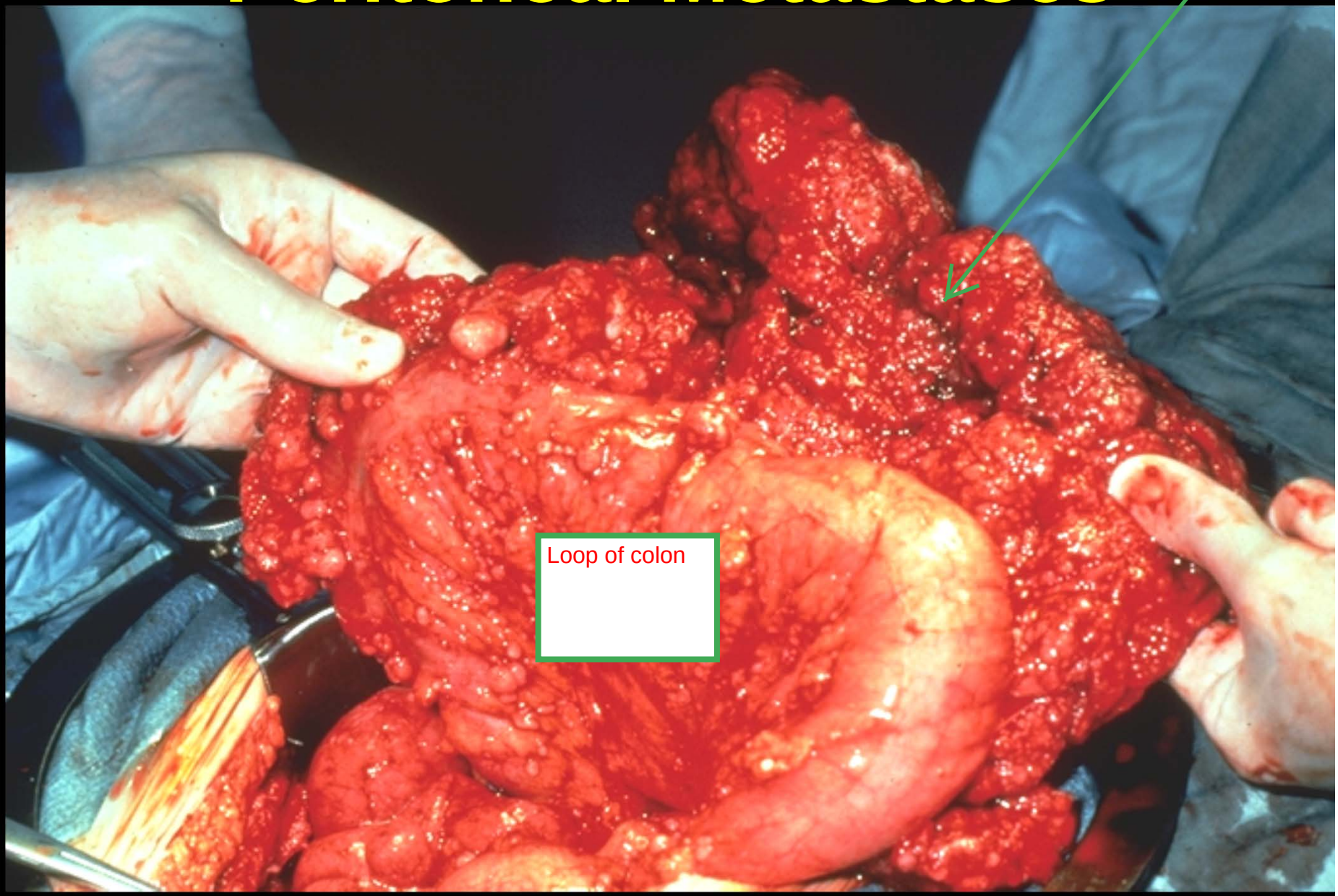
Hematogenous Metastases



Breast cancer metastases in vertebra

Courtesy PEIR digital library

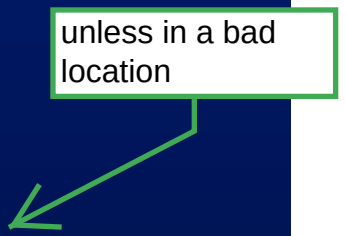
Peritoneal Metastases



Ovarian Cancer

Benign Neoplasms

- Do not metastasize
- In general, do not result in death of the patient
  - Location, location, location!
  - Secretory products can be lethal (e.g. endocrine tumors)



From a practical standpoint, benign neoplasms often can be cured by simple surgical excision while malignant neoplasms often cannot be cured by surgery alone

Benign vs. Malignant

Malignant neoplasms have the potential for metastasis

	Benign	Malignant
Distant Metastases?	No	Yes
Life-threatening	No (usually)	Yes

Benign vs. Malignant

	Benign	Malignant
Distant Metastases?	**No**	**Yes**

Definition correct but clinically not helpful…do you want to wait for your patient to develop metastatic disease before you start treatment for cancer?

The answer here is no

Cham
Museum,
Danang,
Viet Nam

3. How can we tell if a neoplasm is malignant BEFORE it metastasizes?

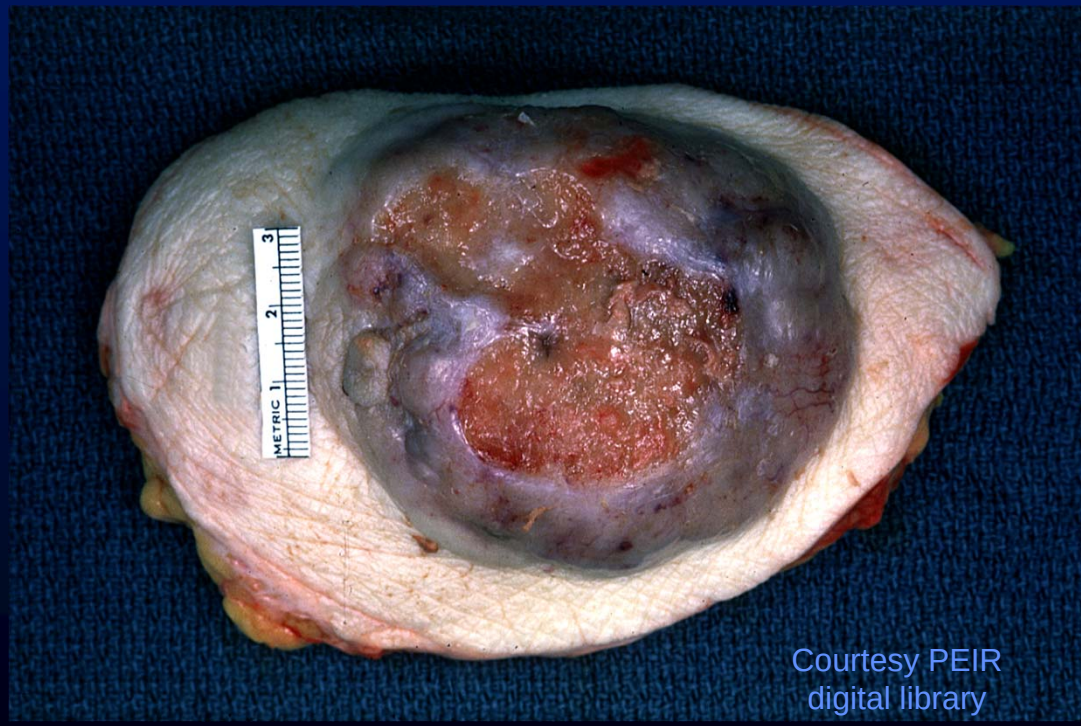
Histopathology!

Histologic Features Distinguishing Benign vs. Malignant

Three big things to look at

a) Borders
b) Growth rate
c) Anaplasia

Anaplasia - lack of differentiation



Courtesy PEIR digital library

Is this cancer or not?

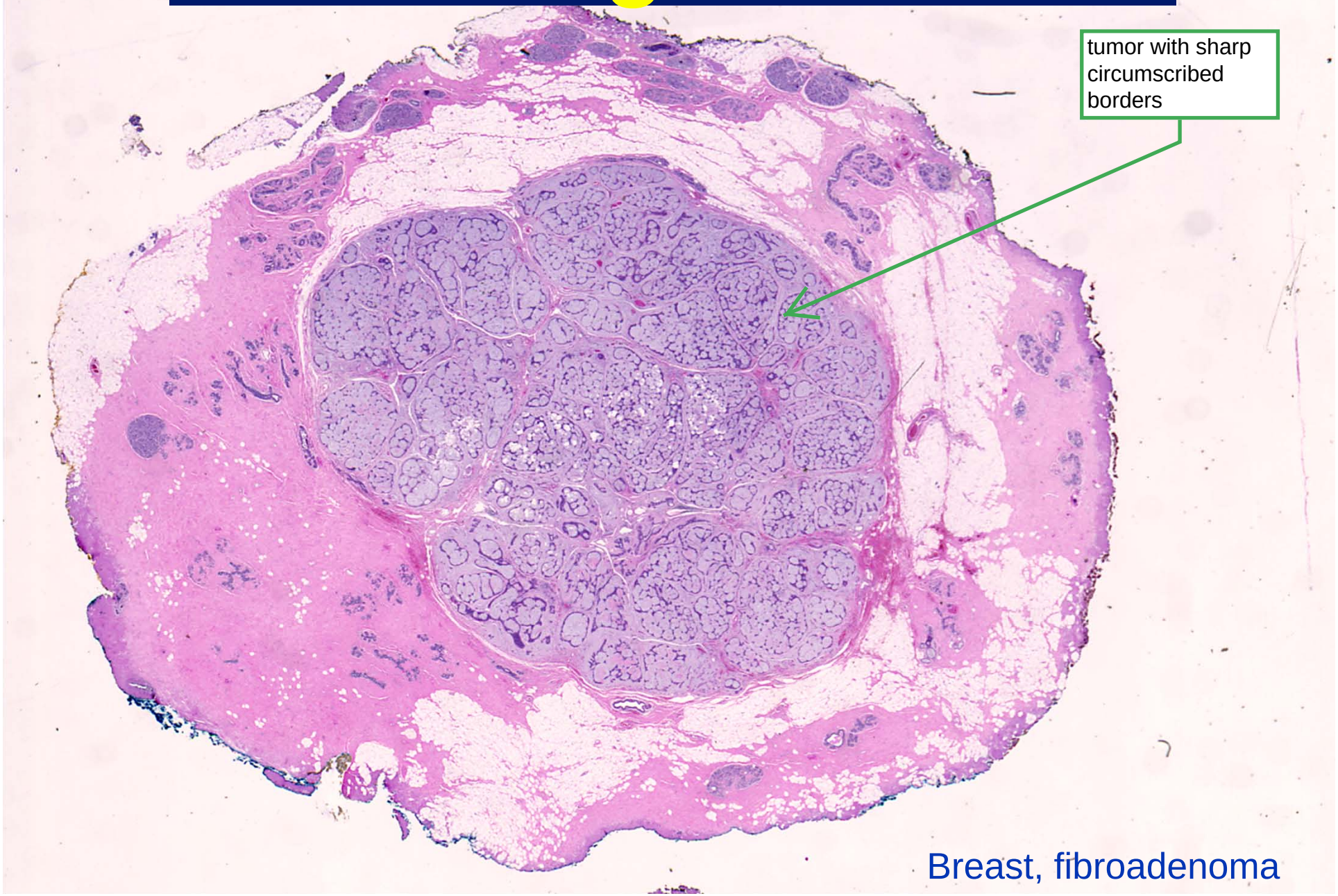
Benign Neoplasms

- **Encapsulated (pushing borders)**
  - **Do not invade locally**
- **Slow growth**
- **Mild anaplasia (well differentiated)**

Can push local structures aside / put pressure on them but don't invade

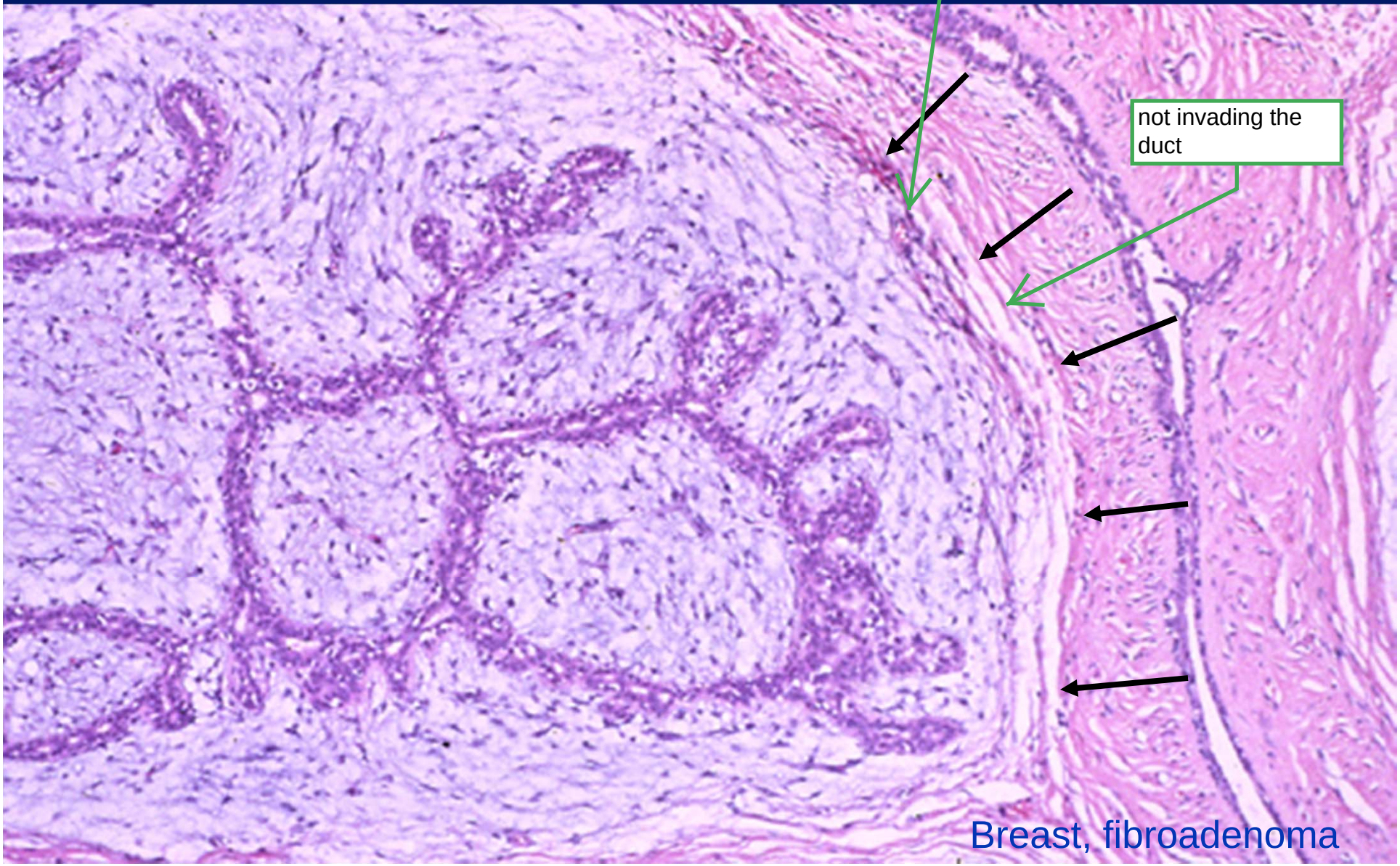
Can be evaluated both clinically and histopathologically - malignant tumors grow much faster

Pushing Borders



Breast, fibroadenoma

Pushing Borders

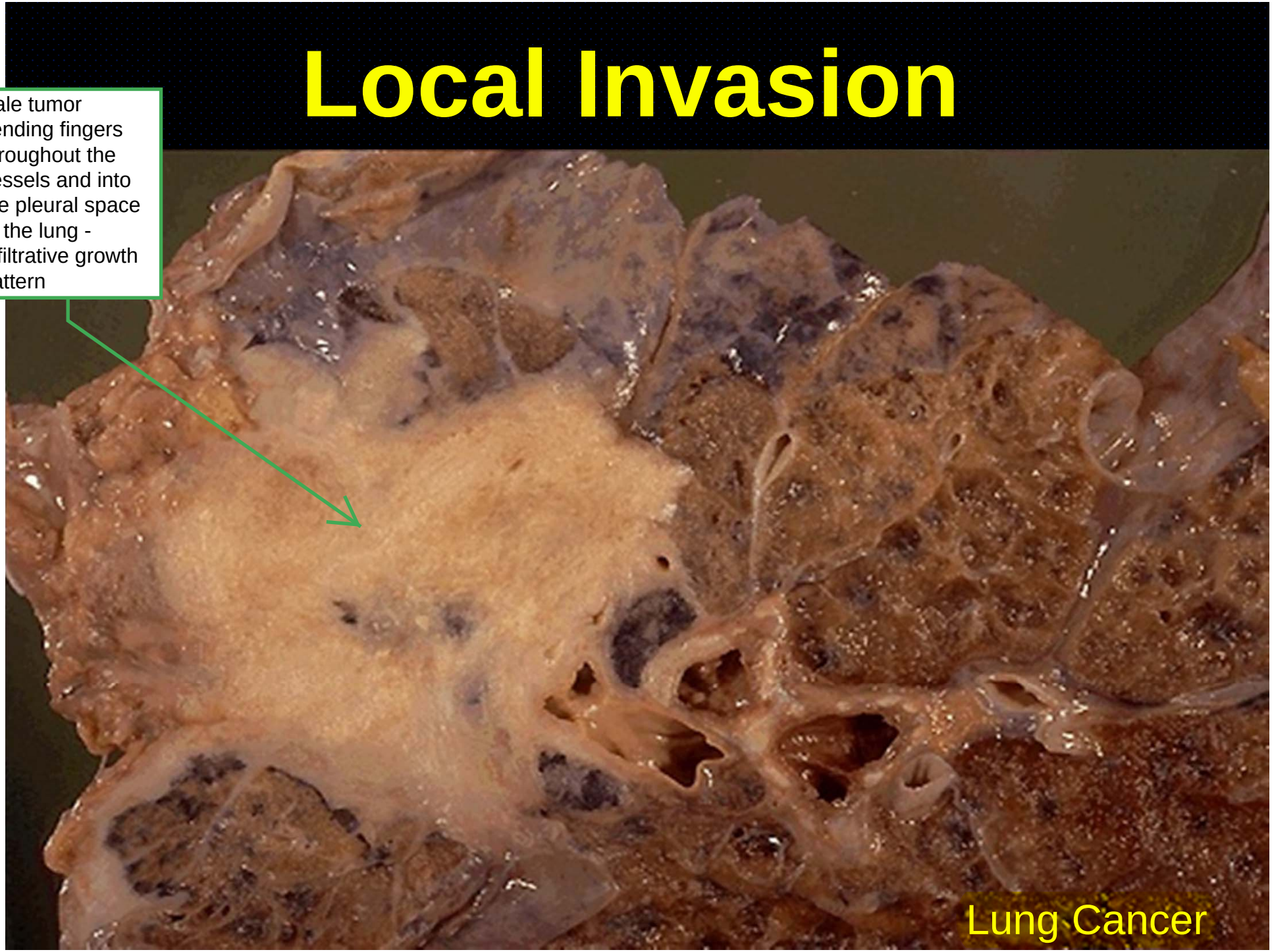


Malignant Neoplasms

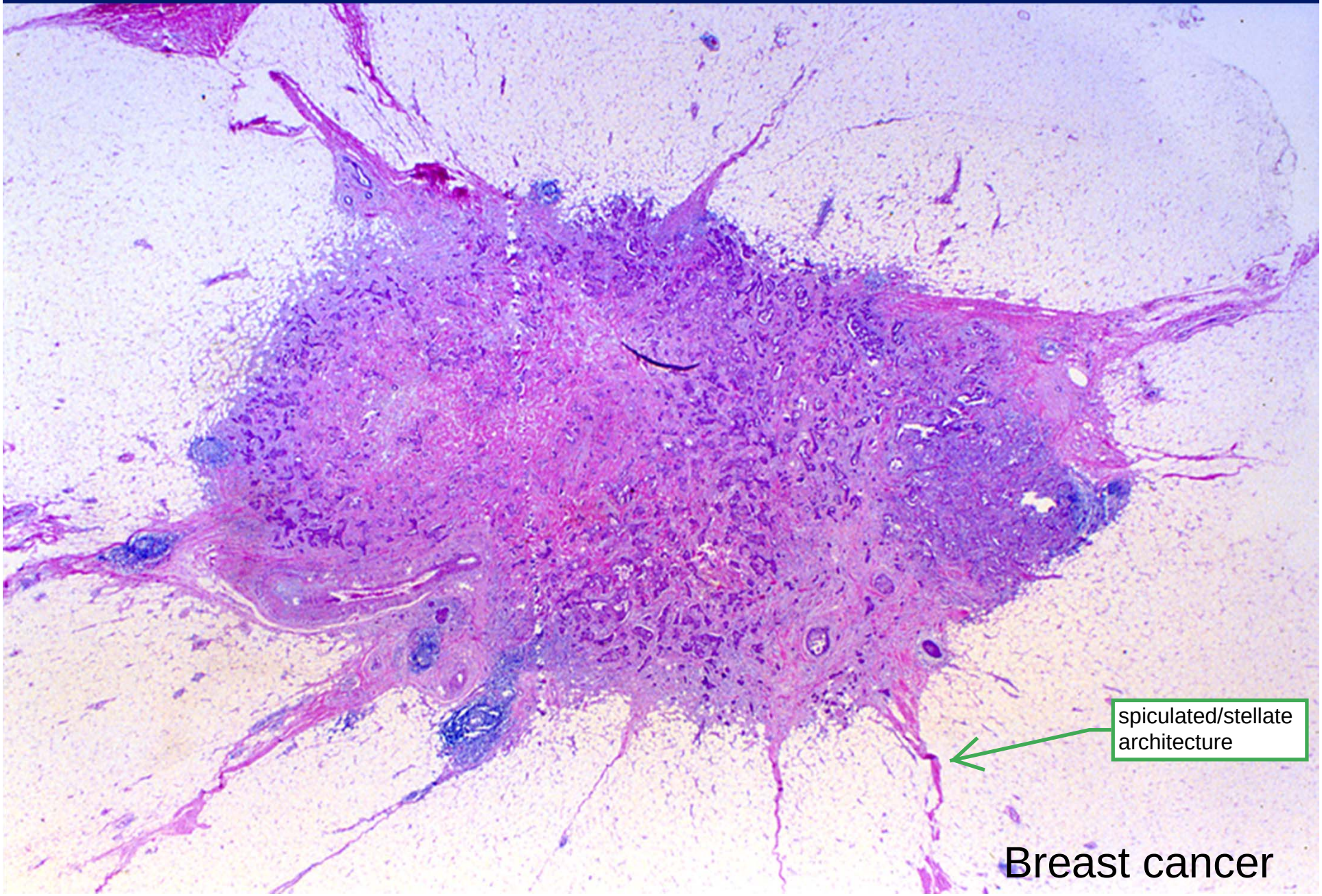
- **Local Invasion**
  - **–Infiltrative borde**
  - **–“Stellate” or “spiculated”**

Can be seen on x-rays and pathologically. Malignant tumors are fixed to adjacent structures, not mobile. This can be palpated on physical exam if the tumor is large.

Local Invasion



Local Invasion

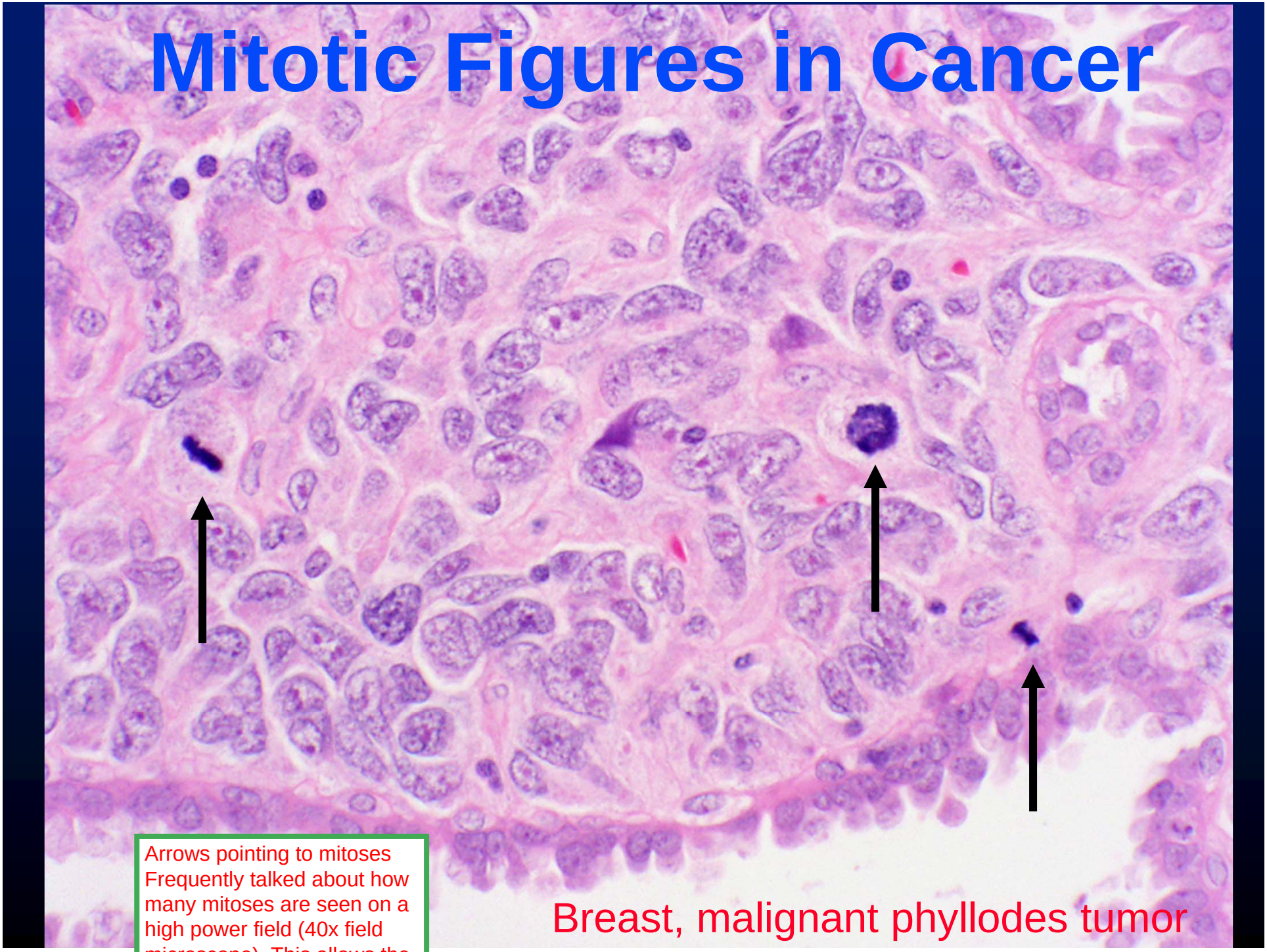


Malignant Neoplasms

- Local Invasion
- Rapid growth rate
  - Histology: Mitotic figures numerous
  - Not unique to malignancies, many normal tissues grow rapidly (GI mucosa, endometrium, bone marrow)

Can be seen clinically too - something that has grown over several weeks or months

Mitotic Figures in Cancer



Breast, malignant phyllodes tumor

Arrows pointing to mitoses
Frequently talked about how many mitoses are seen on a high power field (40x field microscope). This allows the pathologist to tell the clinician how badly the tumor is likely

Malignant Neoplasms

- Local Invasion
- Rapid growth rate
- Anaplasia Lack of differentiation

Earlier thinking was that tumor cells were reverting to an earlier embryologic state. However, we now realize they go to more of a stem cell state.

ANAPLASIA
"Lack of Differentiation"

- "Differentiation" is the extent to which neoplastic cells resemble normal tissues, both morphologically and functionally
  - Well-differentiated: closely resembles tissue of origin
  - Poorly-differentiated: unspecialized, little resemblance to tissue of origin

Anaplastic cells are poorly differentiated

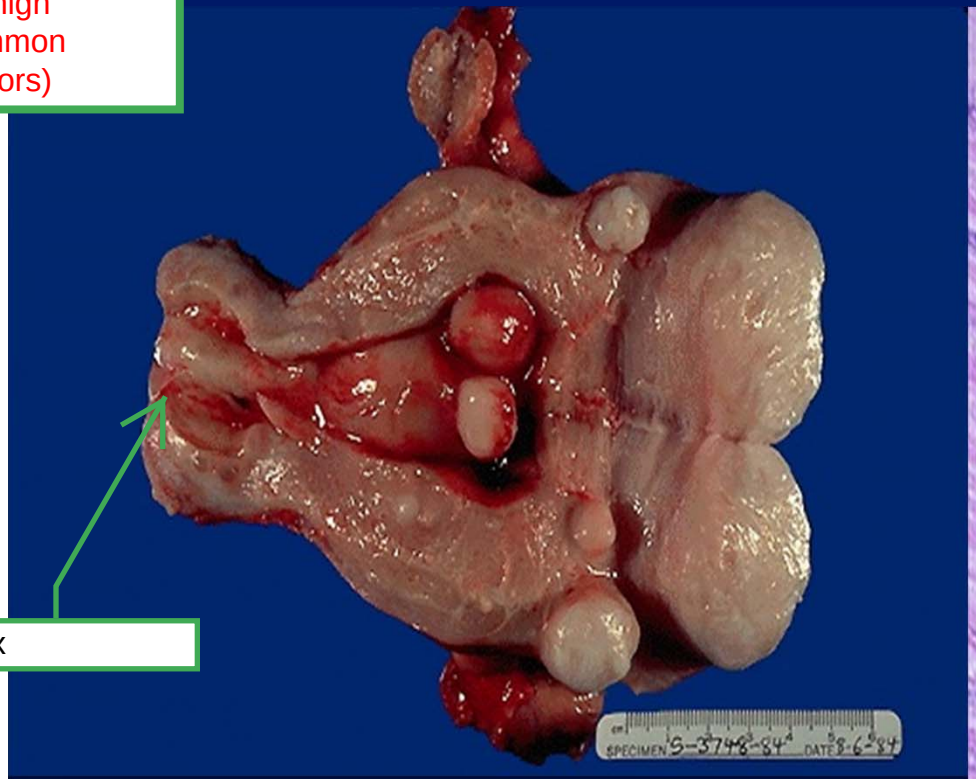
Some examples of Anaplasia:

ANAPLASIA
"Lack of Differentiation"

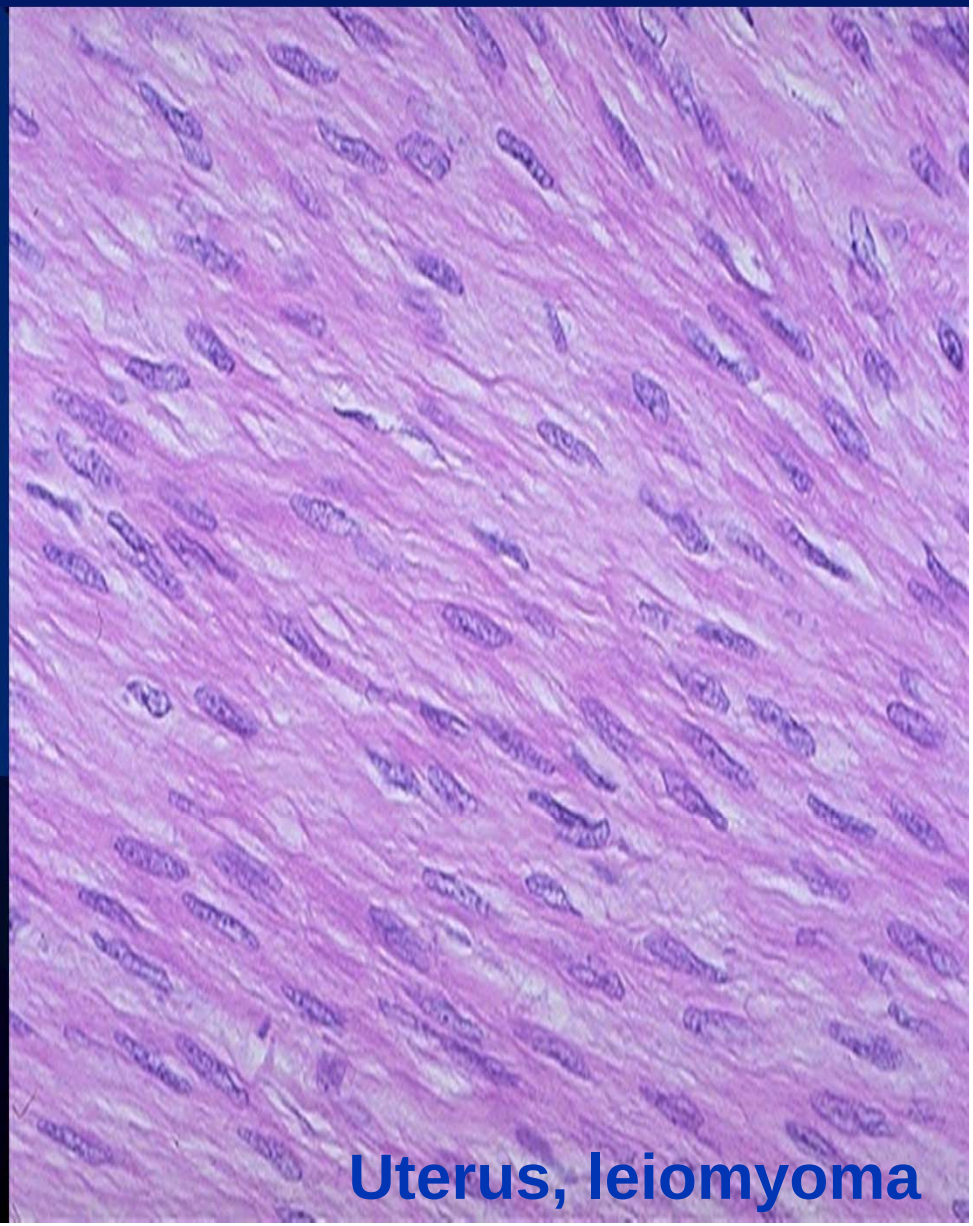
- Anaplastic skeletal muscle cells make little actin and myosin (lose cross striations)
- Anaplastic colonic epithelial cells make little or no mucin
- Anaplastic glandular cells make only few glands

Benign: No Anaplasia

uterus - the white nodules are fibroids (benign common tumors)



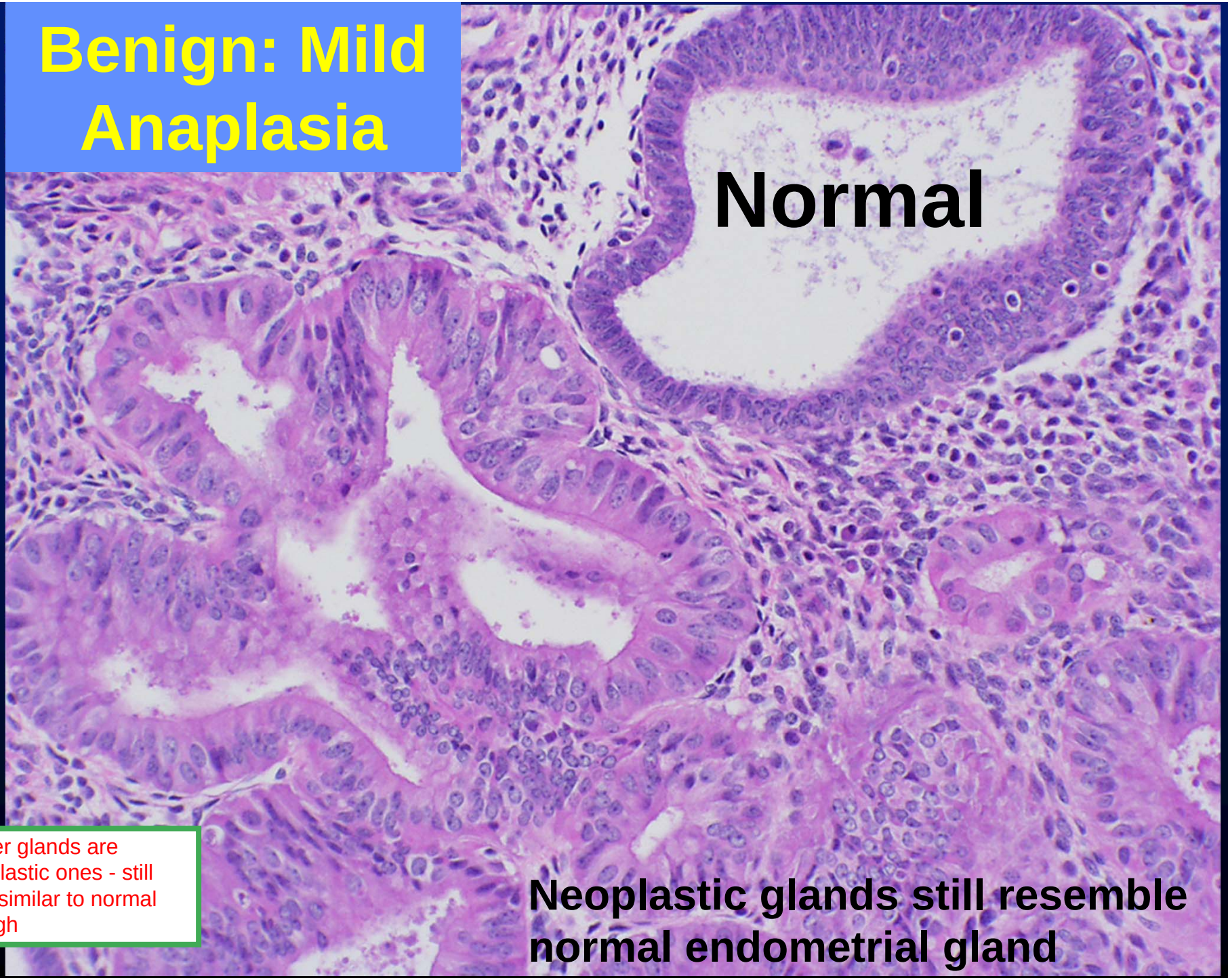
Note microscopic similarity to normal smooth muscle



Uterus, leiomyoma

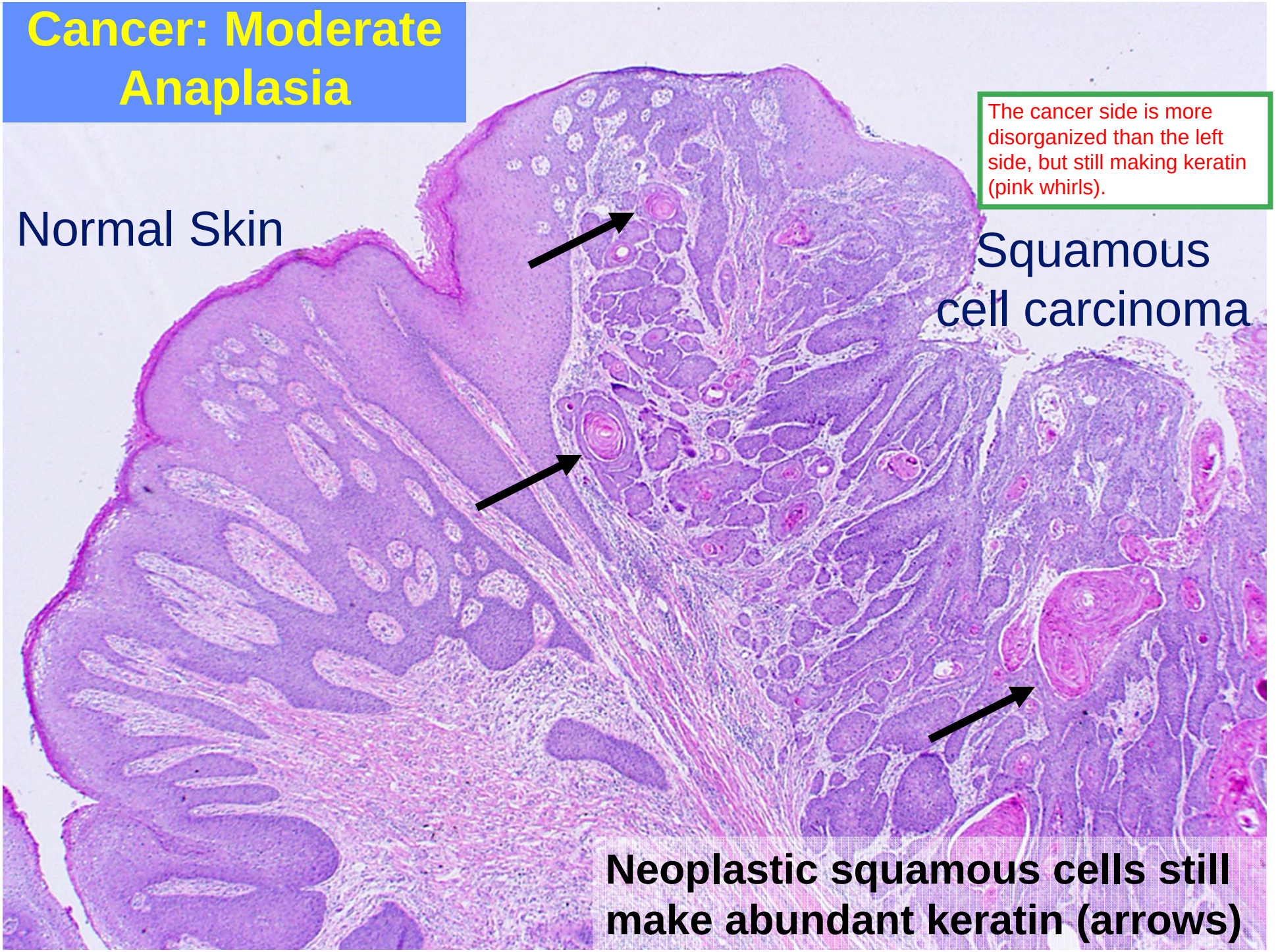
Tumor that has no anaplasia - histologically looks almost exactly the same as normal smooth

Benign: Mild Anaplasia



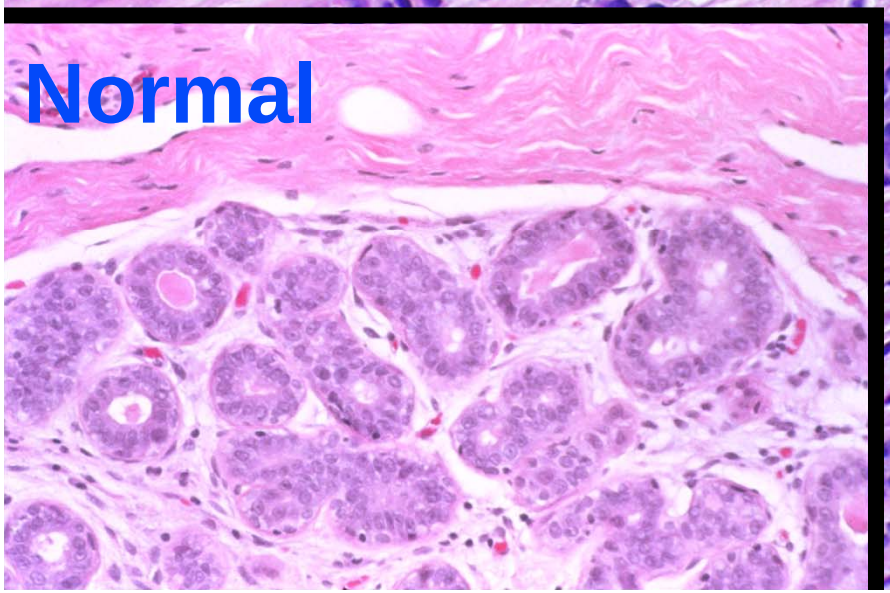
pinker glands are neoplastic ones - still look similar to normal though

Cancer: Moderate Anaplasia



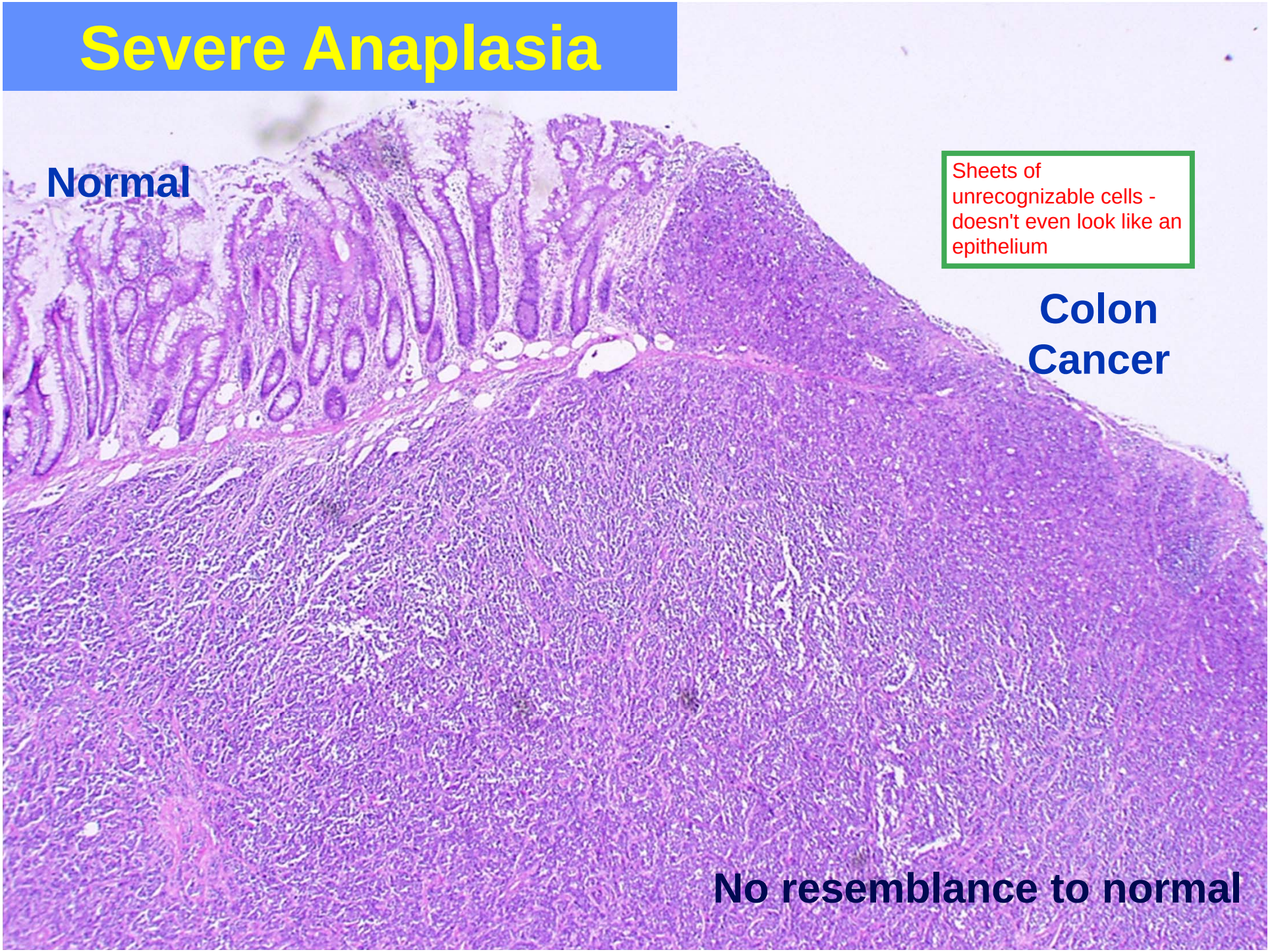
Severe Anaplasia

Can't even recognize the breast histologically - no glands, only solid cord of cells



Breast Cancer: No gland formation

Severe Anaplasia



ANAPLASIA: Abnormal Nuclei

Known as the N/C ratio

- High ratio of **nucleus to cytoplasm**
- Nuclear hyperchromasia.
- Clumped chromatin.
- Prominent nucleoli.

“Blue is BAD”

first impression of looking at a neoplasm under the microscope is blueness.

Does this correlate with the rate of growth?
A: Cells that are dividing rapidly have less cytoplasm, nuclear hyperchromasia is from replicating DNA so it's all related.
Anaplastic cells may have multiple copies of chromosomes and therefore more DNA

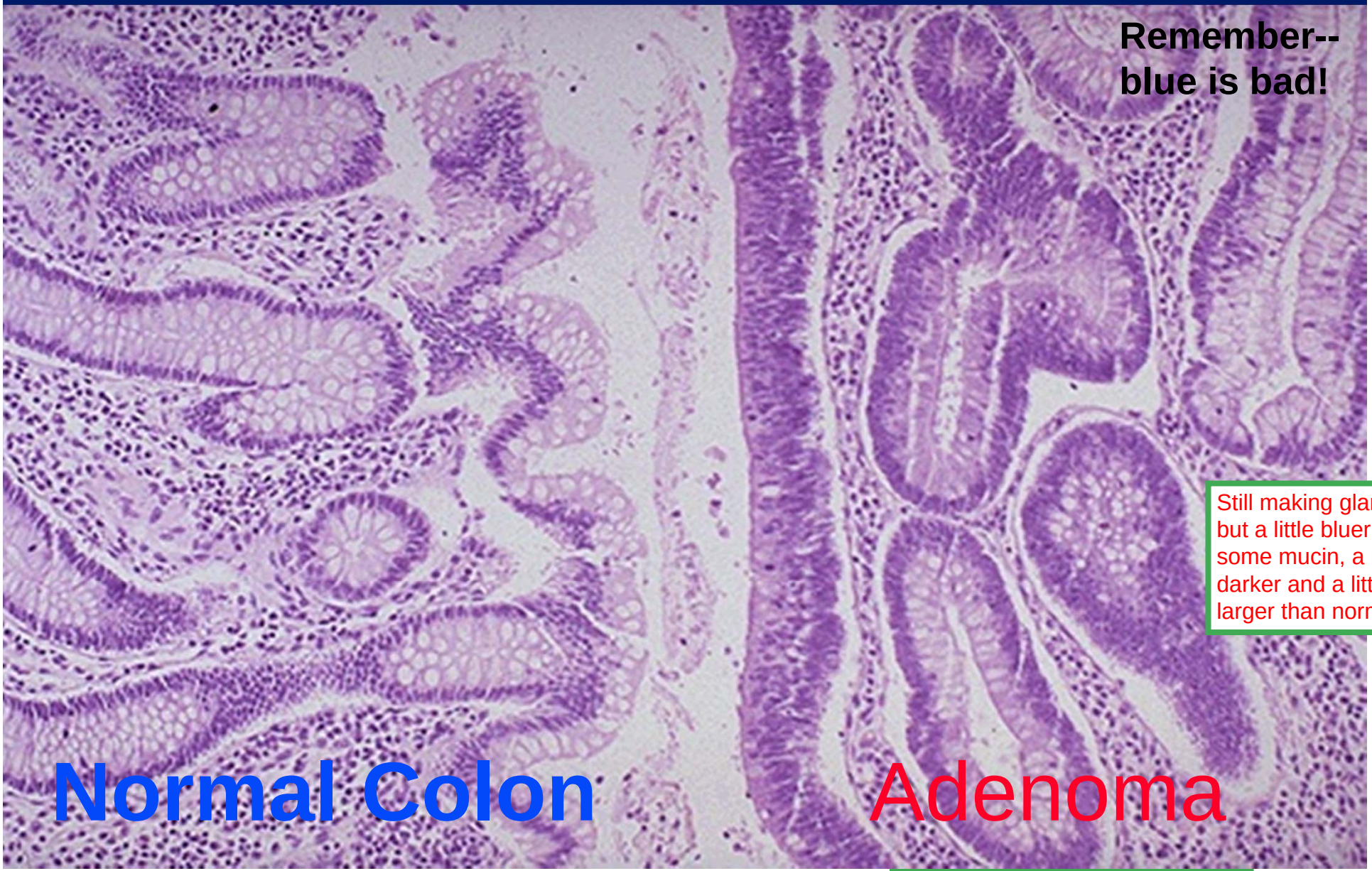
ANAPLASIA:

Other Nuclear Features

- **Pleomorphism**
  - **Variation in size and shape**
  - **Nuclear and cytoplasmic**
  - **Tumor giant cells**
- **Frequent and sometimes abnormal mitoses**

In normal tissues, the cells are relatively uniform

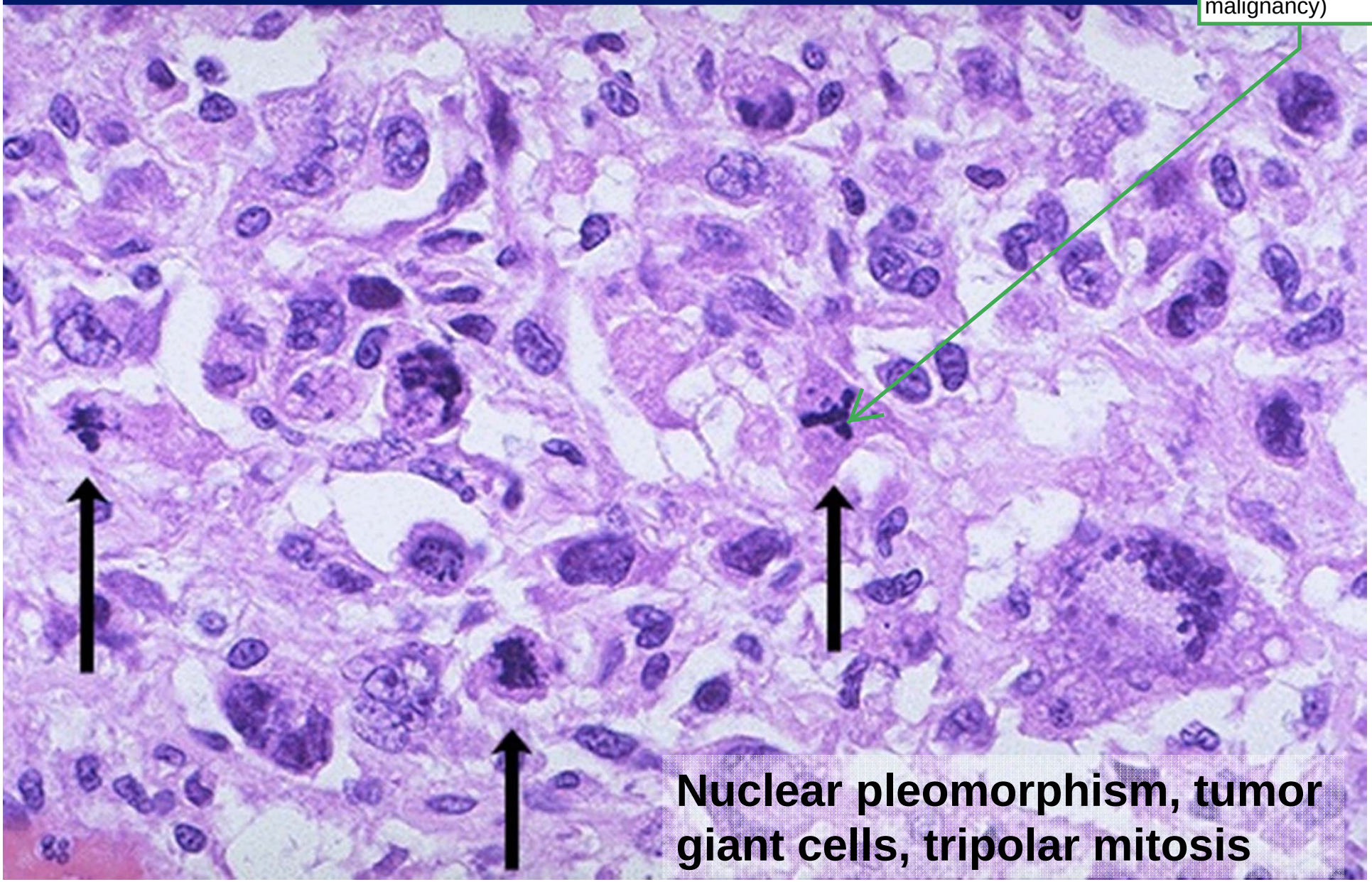
Mild Anaplasia: Nuclei



Still making glands, but a little bluer, lost some mucin, a little darker and a little larger than normal

Benign neoplasm of the colon

Severe Anaplasia: Nuclei



Histologic Diagnosis Of Malignancy

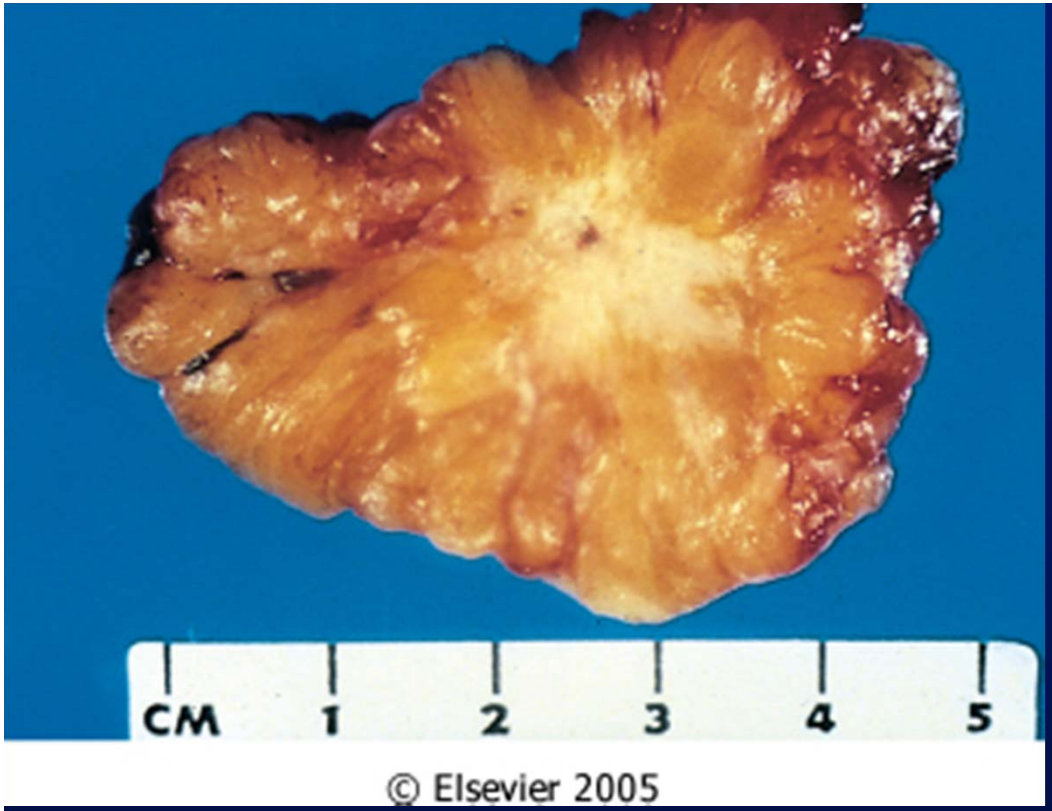
There is no single parameter (other than metastasis) which always allows recognition of a malignant neoplasm microscopically. However, the presence of **severe anaplasia** and a **pattern of invasiveness** are the criteria which are most generally useful.

NEOPLASMS

SPECTRUM

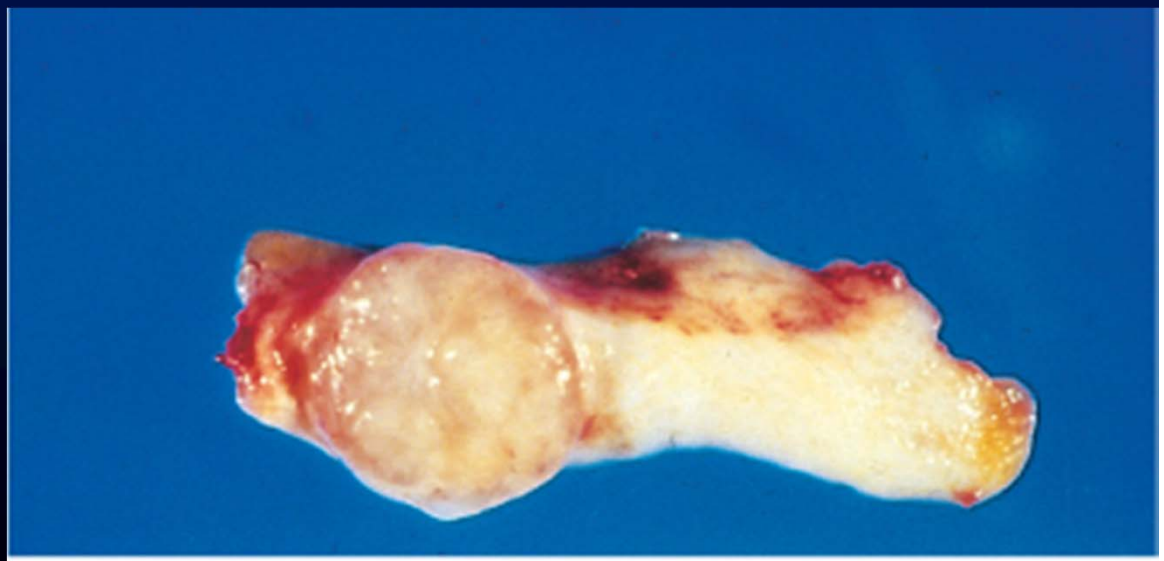
BENIGN **INTERMEDIATE** **MALIGNANT**

There is gray area with neoplasms. Can have tumors that metastasize 1/10 or 1/1000 times. You have to recognize lesions that are intermediate in their biology.

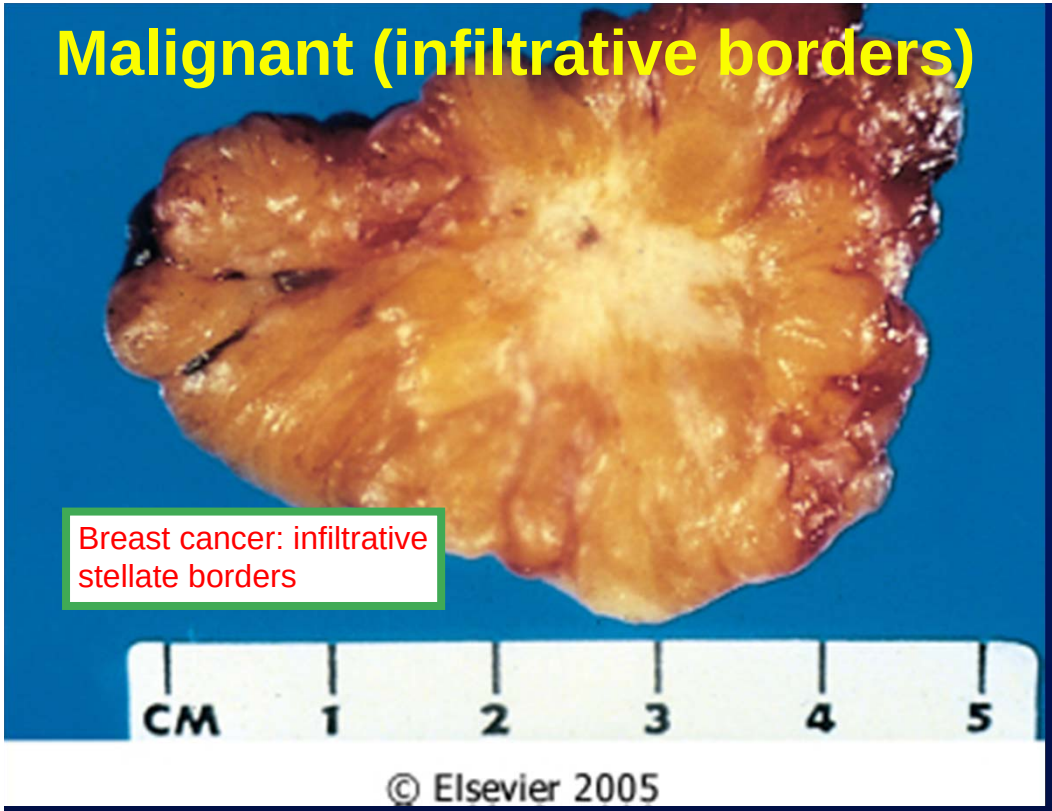


Quick Review: Which of these is malignant?

see next slide

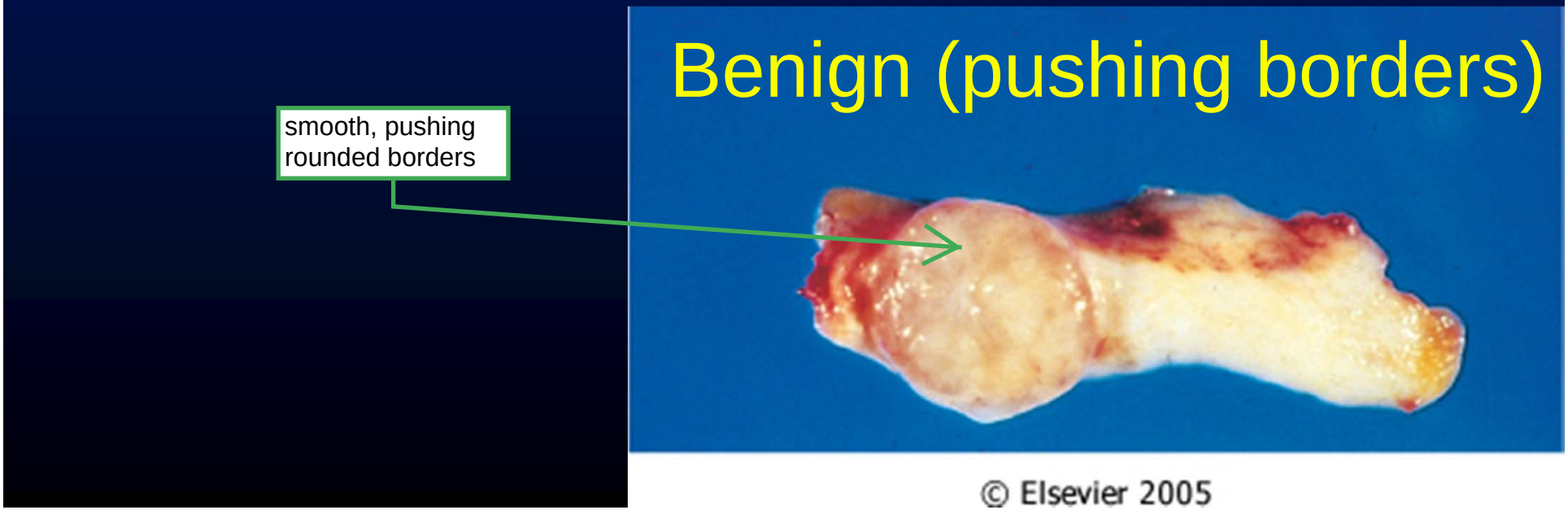


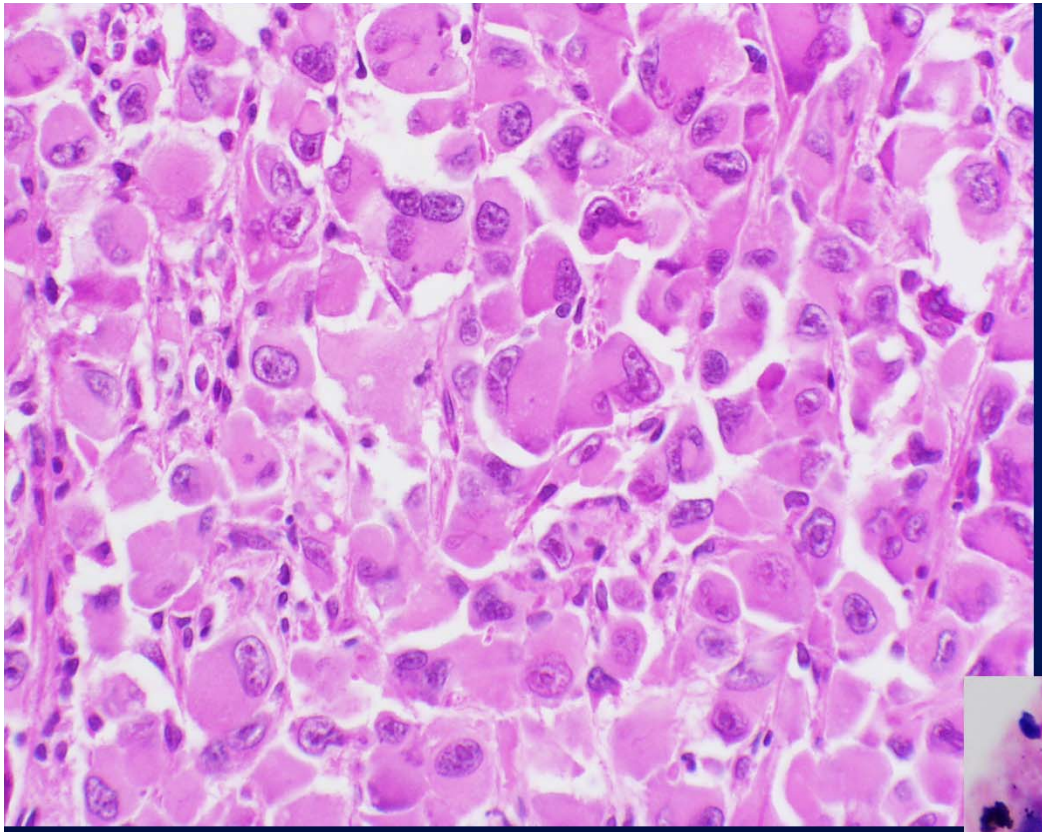
Malignant (infiltrative borders)



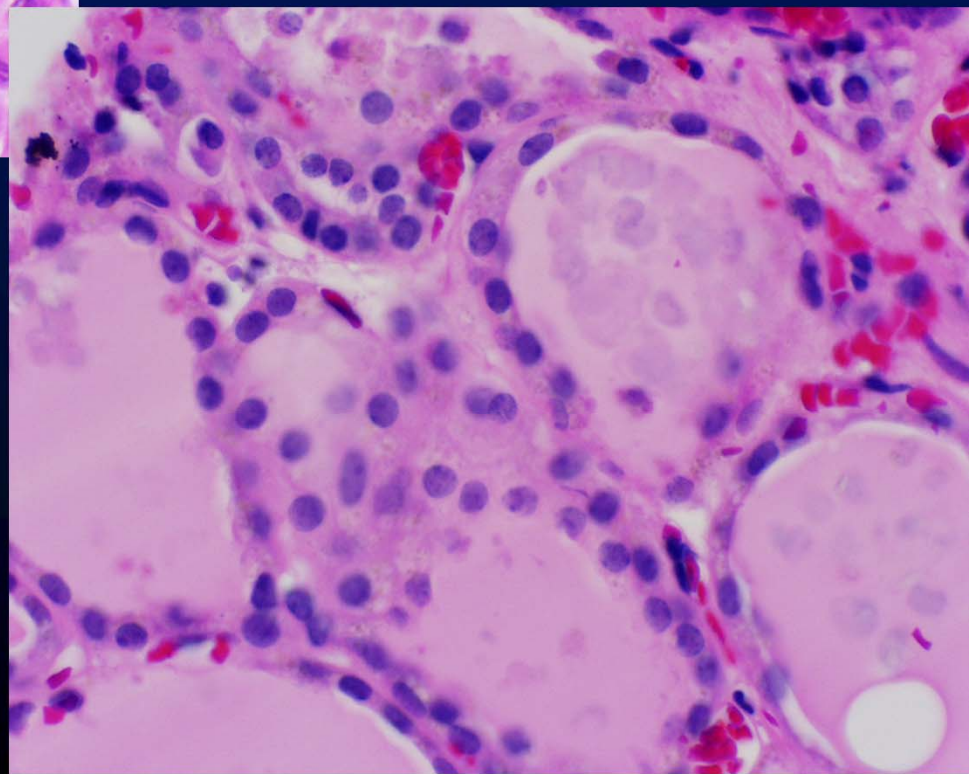
Quick Review: Which of these is malignant?

Benign (pushing borders)

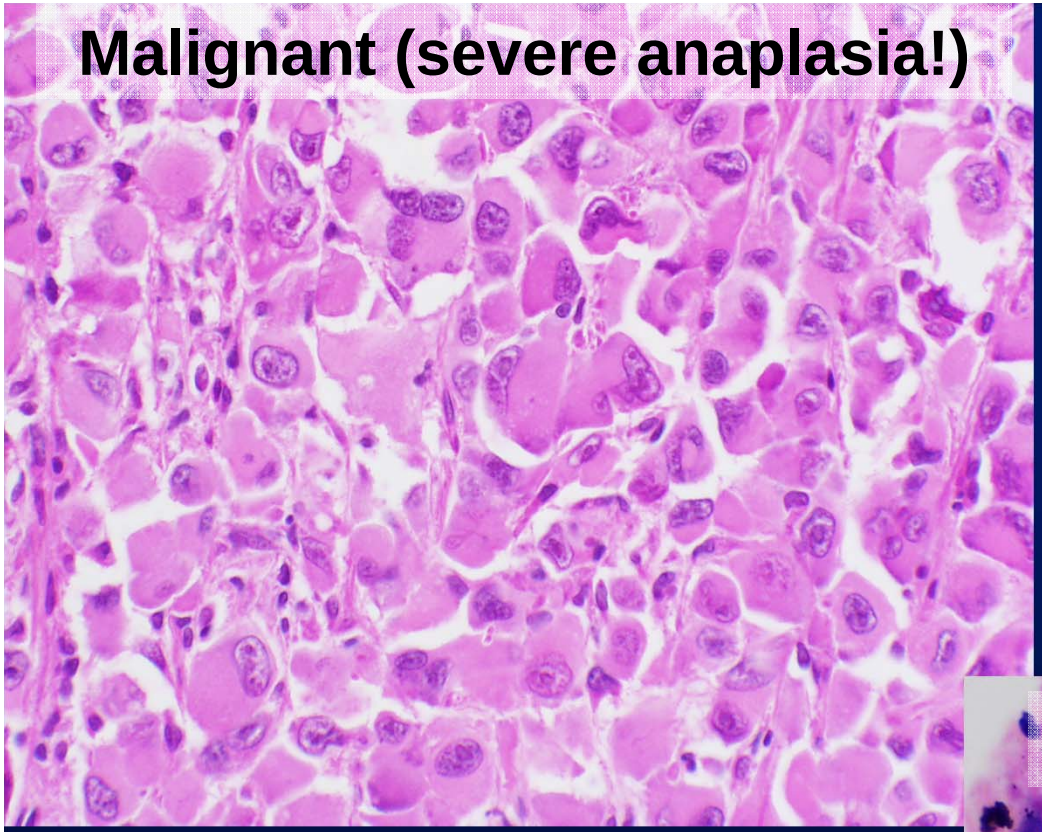




Quick Review: Which of these thyroid tumors is malignant?



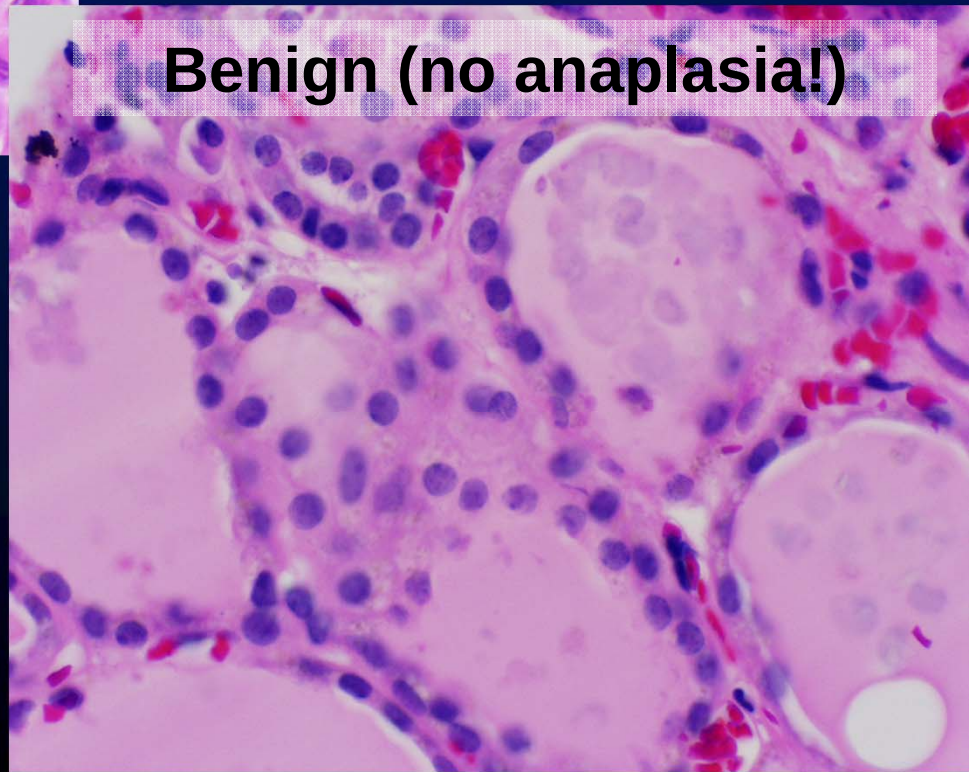
Malignant (severe anaplasia!)



Quick Review: Which of these thyroid tumors is malignant?

Upper left is super anaplastic. Big giant nuclei, very pleomorphic.

Benign (no anaplasia!)




Duke University, North Carolina
malignant

4. How do we name neoplasms?

Nomenclature

Neoplasms are composed of proliferating neoplastic cells but also contain non-neoplastic supportive stroma of connective tissue and blood vessels.

Ignore the supporting stroma - only look at the clonally neoplastic cells for nomenclature

Nomenclature

Tumors are named according to the neoplastic component

(Cell type) + (modifier to indicate benign/malignant) + (site of origin)

Benign Neoplasms: Nomenclature

- Benign tumors are often designated by the suffix - “oma”.
- Prefix designates the cell of origin

Benign Mesenchymal Neoplasms

CELL TYPE	BENIGN TUMOR
• Fat	☒Lipoma
• Smooth muscle	☒Leiomyoma
• Skeletal muscle	☒Rhabdomyoma
• Fibrous tissue	☒Fibroma
• Blood vessel	☒Hemangioma
• Cartilage	☒Chondroma

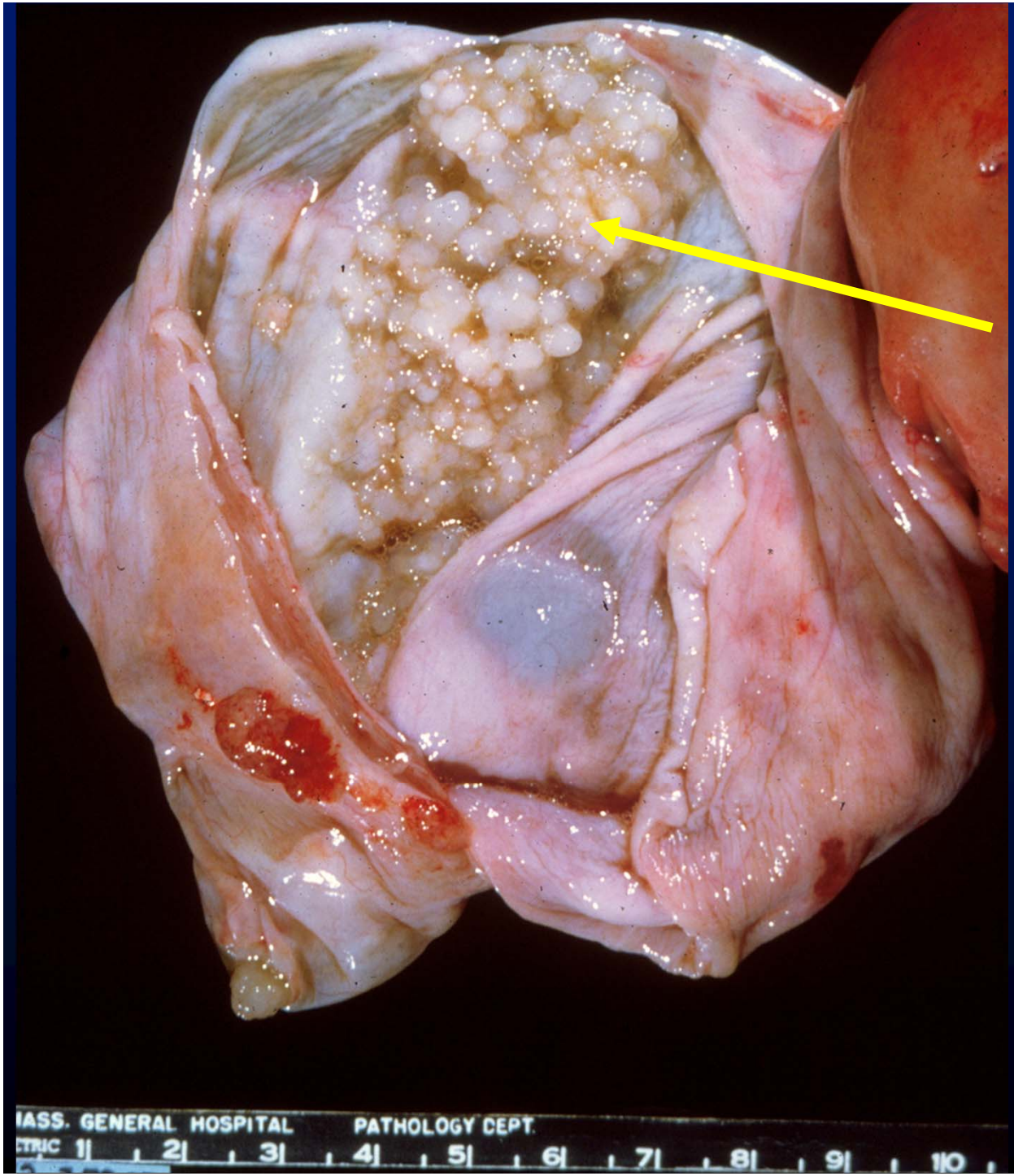
Benign Epithelial Neoplasms

epithelial cells are more complicated:

cystic + glandular

- **ADENOMA:** benign neoplasm derived from glandular epithelium
- **CYSTADENOMA:** benign epithelial neoplasm with cystic or fluid-filled cavity
- **PAPILLOMA:** benign epithelial neoplasm producing finger-like or papillary projections (think sea anemone)

Papillary growth pattern typically within a cyst but not always (bladder tumors are a common example)



Interior of tumor

Papillary growth inside cyst

papilloma - can see little fingers growing in the cyst

…Then add site of origin:

Examples of benign neoplasms

- **Leiomyoma of the uterus**
- **Chondroma of the femur**
- **Adenoma of the colon**
- **Cystadenoma of the ovary**
- **Papilloma of the larynx**

Malignant Neoplasms:
Nomenclature

CARCINOMA: arising from epithelial tissue

ADENOCARCINOMA: arising from glandular epithelium

SARCOMA: arising from mesenchymal tissue

Malignant Neoplasms
Nomenclature

hematopoietic tissue

LYMPHOMA = arising from lymphoid tissue

LEUKEMIA = arising from blood or bone marrow elements

…Then add site of origin:

Examples of malignant neoplasms

- **Leiomyosarcoma of the uterus**
- **Chondrosarcoma of the femur**
- **Adenocarcinoma of the colon**
- **Squamous cell carcinoma of the larynx**

Summary:
Neoplasm Nomenclature

Origin	Benign	Malignant
Fibroblasts	Fibroma	Fibrosarcoma
Glands	Adenoma	Adenocarcinoma
Smooth muscle	Leiomyoma	Leiomyosarcoma
Squamous	Squamous papilloma	Squamous cell carcinoma

Summary:
Neoplasm Nomenclature

Tissue	Benign	Malignant
Lymphocytes	(?) No real benign tumor because once lymphs proliferate in bloodstream, they go everywhere	Lymphoma
Granulocytes	(?)	Leukemia
3 germ cell layers	Teratoma	Teratocarcinoma
GI wall	GI stromal tumor	GI stromal tumor

Occurs in the wall of the GI tract and they have the same name with benign or malignant added in front (i.e. malignant GI stromal tumor)

Exceptions

- Many “-omas” are malignant
  - Lymphoma — lymphocytes
  - Hepatoma — liver cells
  - Seminoma — Seminifierous Tubules
  - Melanoma — Should be called "melanosarcoma" but it's not. Tumor of melanocytes

Exceptions

- Some “carcinomas” or “sarcomas” are benign
  - Basal cell carcinoma of skin
  - Cystosarcoma phyllodes of breast
  - Well differentiated liposarcoma of skin

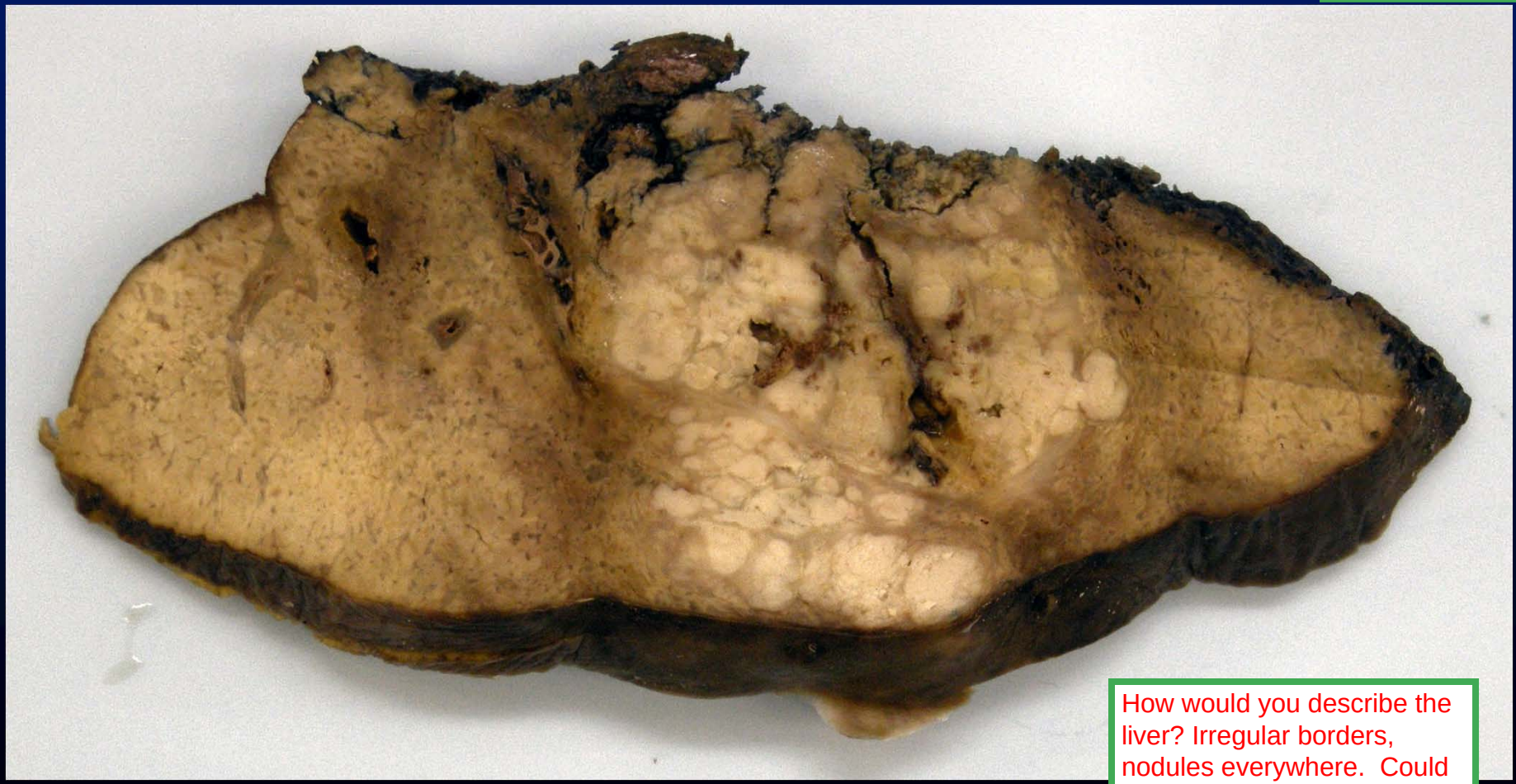
Most common cancer, but it almost never metastasizes

Point: If you're not sure about whether something is malignant or benign - look it up.

Name that tumor!

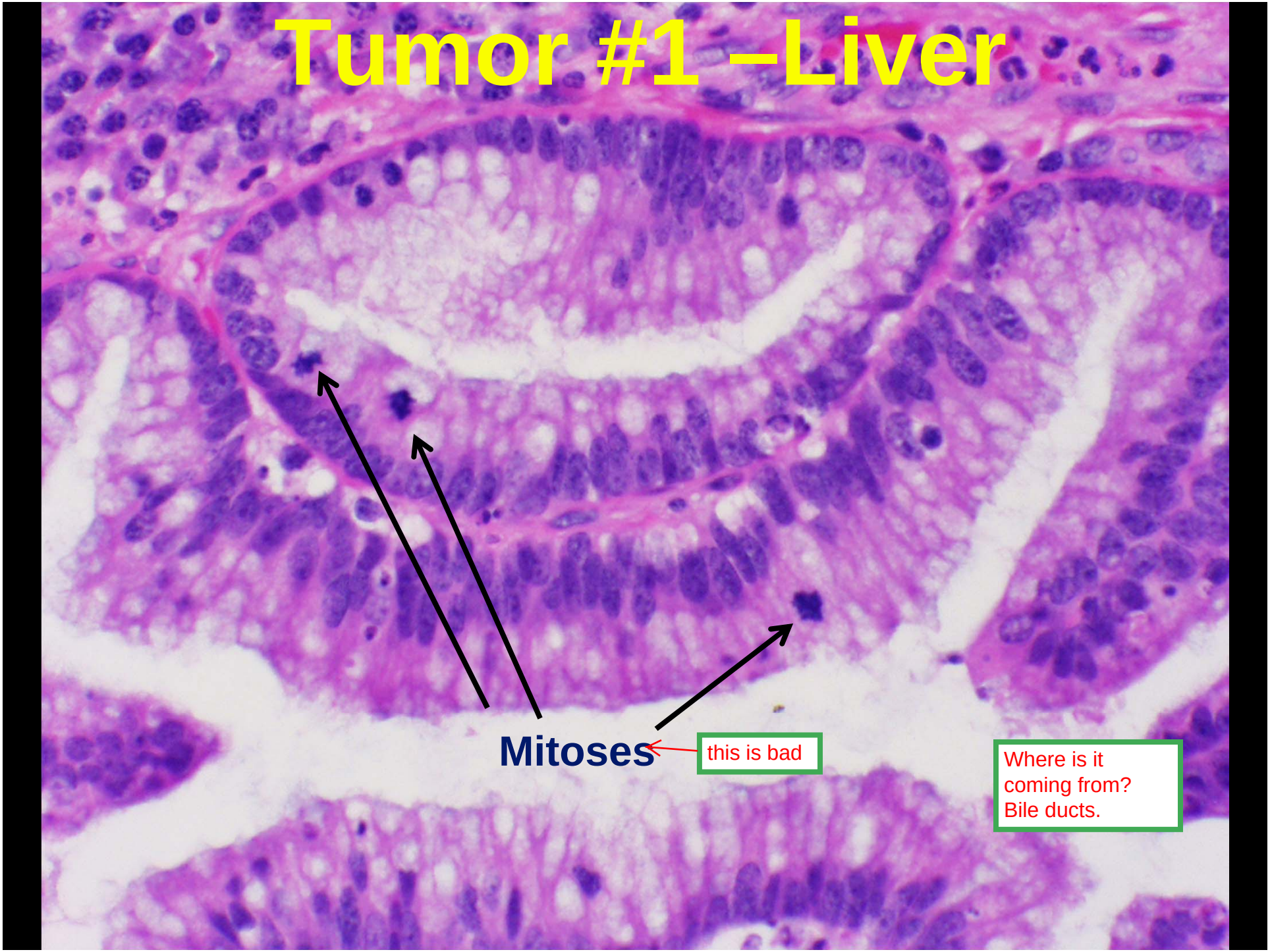
Tumor #1 –Liver

Answer in two slides



How would you describe the liver? Irregular borders, nodules everywhere. Could be necrotic in the center.

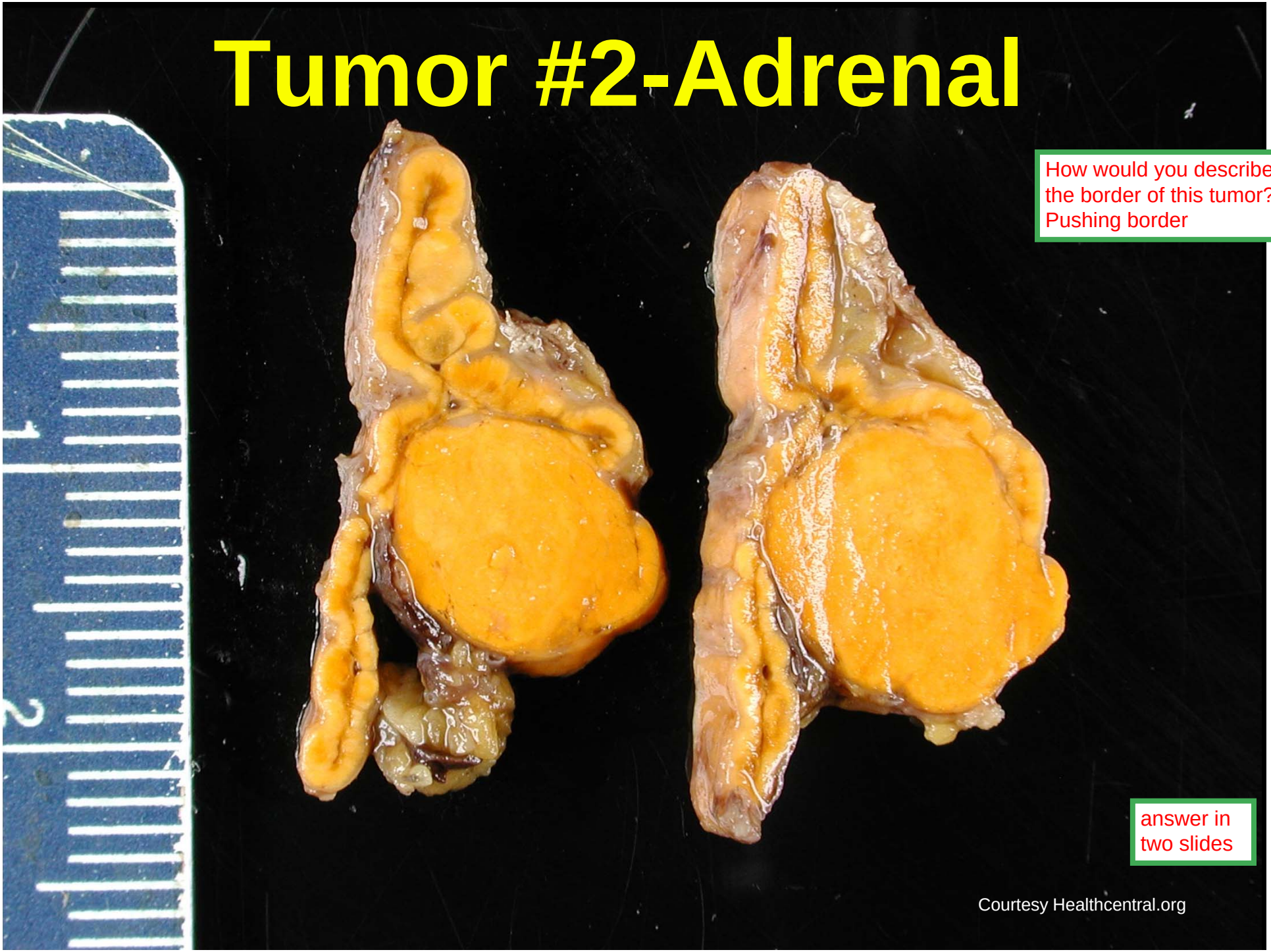
Tumor #1 –Liver



Tumor #1

- **Dx: Adenocarcinoma of the bile duct**
- **Malignant features**
  - **Infiltrative borders, many mitoses**
  - **Gland forming neoplasm**
- **aka “Cholangiocarcinoma”**

Tumor #2-Adrenal



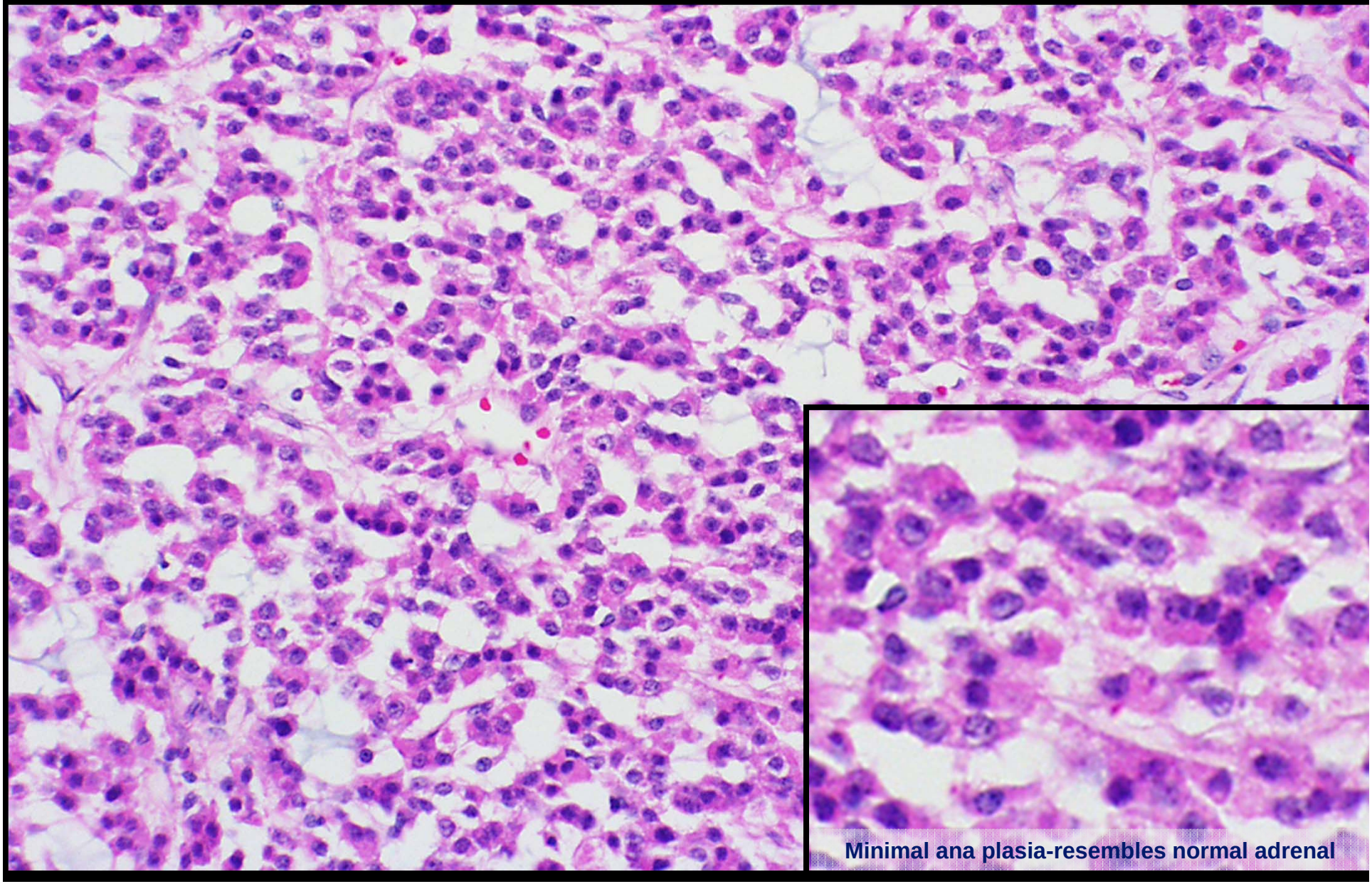
How would you describe the border of this tumor?
Pushing border

answer in two slides

Courtesy Healthcentral.org

Tumor #2-Adrenal

No mitoses or pleomorphisms



Minimal ana plasia-resembles normal adrenal

Tumor #2

- **Dx: Adenoma of the Adrenal Cortex**
- **Benign features**
  - **Pushing, circumscribed borders, no mitoses or anaplasia**

Is the adrenal gland an epithelial structure? No. Historically called this though

5. What is Grade?

Grading Of Cancer

Grade: A histologic parameter quantitating the degree of differentiation of the cancer cells.

capture the anaplasticity of the tumor.
Grade is a way to describe (quantify) how anaplastic the tumor cells are.

Differentiation

- **Well-differentiated (“low grade”) tumors resemble mature normal cells of the tissue of origin.**
- **Poorly differentiated (“high grade”) tumors show little resemblance to the tissue of origin.**

little anaplasia

highly anaplastic

Grading of Cancer

- Many tumors graded according to a three-tiered scheme: well, moderately, and poorly differentiated (grade 1, 2, 3).
- Grading systems vary by different tumor type.

1 are the well differentiated tumors (looks like normal)
3 is poorly differentiated tumors (look very little like normal)

Importance of Grade

Many tumors show a range of differentiation from low grade to high grade. For those that do…

Grade predicts behavior

(for many common malignancies)

Predicts response to chemotherapy, how they will metastasize, etc.

Grade and Prognosis

Breast Cancer

Grade	5 yr survival
1	95
2	75
3	50

Can base your treatment strategy based on the grade

Grading Of Cancer

- **Limitations:**
  - **Many tumors are of intermediate differentiation** Such as colon cancer
  - **There is sampling error with small biopsies**
  - **Grading is based on subjective light microscopic interpretation** observer variation and error based on the person looking at it

Quick Review

Factors that would influence whether a surgical resection would be curative include:

A. Whether it is benign or malignant
B. Location of the neoplasm
C. Cell type of the neoplasm
D. Degree of anaplasia of the neoplasm
E. All of the above

Quick Review

Factors that might influence whether surgery for a neoplasm will be curative include:

A. Whether the neoplasm is benign or malignant
B. Location of the neoplasm
C. Cell type of the neoplasm
D. Degree of anaplasia of the neoplasm

E. All of the above

The End
roduction to Neoplasia
(Part I)

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16A Duke South

Green Zone

Q: Some tumor types are class associated? i.e. GBM (glioblastoma multiforme - which is a common, aggressive brain tumor) have a grade and a class
GBM is always Grade 4. Staging is not applied to GBM because they do not metastasize (More detail after Spring Break)
A: Every tumor has its own grading scheme, but what we have learned is how most tumors are graded.

Q: Is there a range of differentiation in the same tumor?
A: Yes, within one tumor if there is a range, you use the worst looking area. It is assumed that this area will be the most aggressive area.

Can a benign tumor transfer into a malignant one? Sometimes - depends on the benign tumor. Fibroadenoma in breast never becomes. However, tubular adenomas of the colon, frequently lead to colon cancer. We think that the majority of colon cancers may come from colon adenomas (hence the colonoscopy screening after 50)

Very important Addendum: Staging a tumor - a different concept from grade. Grade is a histological parameter based on anaplasia in the tumor Stage is a clinical parameter that tells how far advanced a tumor is (How big it is, what critically local structures it has invaded, if it has any metastasis). Stage can put patients into prognostic categories. For example: Colon cancer invasiveness in the wall defines stage. Minimally invasive in the wall is a low stage and a good prognosis. If it goes deep into the wall, it will be a high stage. More details about staging will come in subsequent lectures.

Q: If you perform a surgery on a benign tumor, will it convert it to a malignant one?
A:Usually no. The only potential problem is that some benign neoplasms don't spread distantly but spread locally so if you do a bad job taking it out, you can spread benign neoplasms locally but you don't convert it to a malignancy.
Sometimes a pathologist (horrors) may make a mistake an call a malignant tumor benign. There are many reasons for this which include sampling error and communication difficulties.
Take home lesson - develop a good working relationship with your pathologist