CHS 2413
Pathology and Physiopathology

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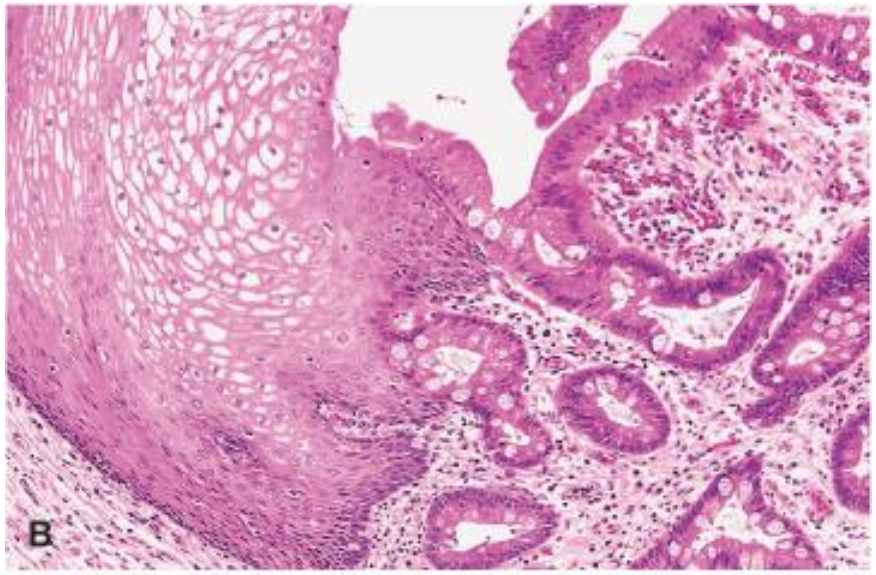
Neoplasia

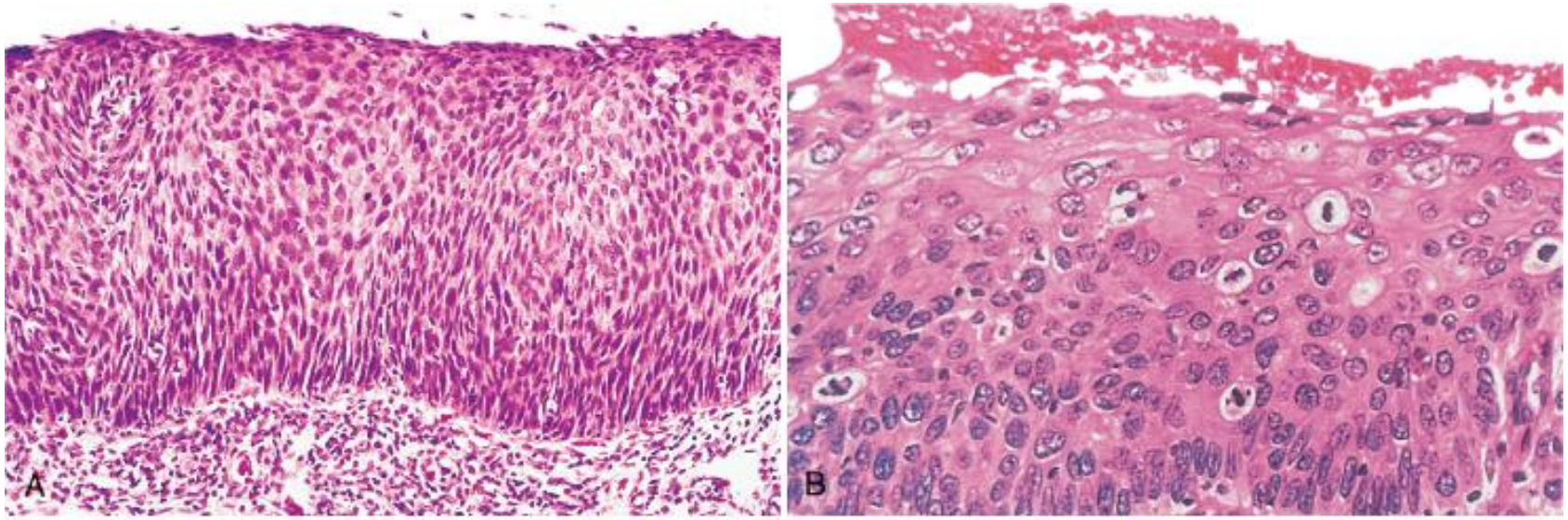
Metaplasia, dysplasia, neoplasia

- Metaplasia – an adaptive change in differentiation, reversible, no mutations necessary.
  - Eg- change of esophageal mucosa from squamous to gastric type in the setting of acid reflux ("heartburn"). Better able to withstand the corrosive effects of the acid.
  - Metaplasia is fertile ground for development of "dysplasia" (disordered growth)



Metaplasia, dysplasia, neoplasia

- Dysplasia refers to recognizable morphologic changes in cells that indicate the presence of genetic mutations beginning the development of a neoplasm
- Often graded, eg PAP smears for uterine cervical cancer are low and high grade



DYSPLASIA

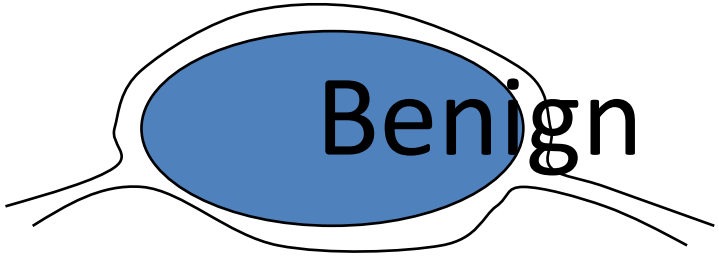
- Premalignant condition
- Increased cell growth
- Cellular atypia
- Altered differentiation
- Can range from mild to severe
- Sites -cervix
  -bladder
  -stomach

DIFFERENCES BETWEEN BENIGN AND MALIGNANT NEOPLASMS

- Size
- Growth characteristics
- Vascularity/necrosis
- Function
- Invasion/metastasis

DIFFERENCES BETWEEN BENIGN AND MALIGNANT NEOPLASMS

BENIGN	MALIGNANT
Nuclear variation in size and shape minimal	Nuclear variation in size and shape minimal to marked, often variable
Diploid	Range of ploidy
Low mitotic count, normal mitosis	Low to high mitotic count, abnormal mitosis
Retention of specialisation	Loss of specialisation
Structural differentiation retained	Structural differentiation shows wide range of changes
Organised	Not organised
Functional differentiation usually	Functional differentiation often lost



Benign

- Slow growing,
- capsulated,
- Non-invasive
- do not metastasize,
- well differentiated,
- Removable by surgery with recurrence
- No bleeding
- Good prognosis
- Name ended with -oma

Malignant:

- Fast growing,
- non capsulated, attached to deep structure
- Invasive & Infiltrate
- Metastasize.
- Poorly, well or moderate differentiated
- Recurrent after surgery
- Associated with bleeding
- Bad prognosis
- Named carcinoma or sarcoma

Type of tissues	Origin of tissues	Benign tumors	Malignant tumors
Mesenchymal tissues	fibrus	fibroma	Fibrosarcoma
	Fatty tissues	lipoma	Liposarcoma
	cartilage	chondroma	Chondrosarcoma
	bone	osteoma	Osteosarcoma
	Skeletal muscle	rhabdomayoma	Rhabdomyosarcoma
	Smooth muscles	leiomyoma	Liemyosarcoma
Parenchymal tissues	skin	Squamus cell papiloma	Squamus cell carcinoma
	skin	Basal cel papiloma	Basal cell carcinoma
	Glands	adenoma	Adenocarcinoma
	bladder	Transitional cell adenoma	Transitional cell carcinoma
	B blood vessels	haengioma	Haemangiosarcoma
	Lymphatic vessels	lymphangioma	lymphangiosarco

BIOLOGIC BEHAVIOR OF NEOPLASMS

- The biologic behavior of neoplasms constitutes a spectrum with two extremes: Benign and Malignant.
- **Benign:** benign neoplasms grow slowly and do not invade surrounding tissues or spread to distant sites (ie, no metastasis).
- Benign neoplasms are rarely life-threatening but may become so because of hormone secretion or critical location, eg, a benign neoplasm can cause death if it arises in a cranial nerve and compresses the medulla spinalis.

- Slow growth rate
- No infiltration
- No metastasis
- High patient survival rates after successful surgical removal

- Variable growth rate
- Locally infiltrative
- Low or no metastatic potential
- Intermediate patient survival rates; tendency for local recurrence after successful surgical removal

- Rapid growth rate
- Infiltrative
- Metastasizing
- Poor patient survival rates; tendency for local and distant recurrence (metastasis)

- **Malignant:** Malignant neoplasms grow rapidly, infiltrate and destroy surrounding tissues, and metastasize throughout the body, often with lethal results.
- Between Benign and Malignant; is a smaller third group of neoplasms that are locally invasive but have low metastatic potential.
- Such neoplasms are borderline neoplasms or locally aggressive neoplasms or low-grade malignant neoplasms. An example is basal cell carcinoma of the skin and serous borderline neoplasm of the ovaries.

- ***1. Rate of Growth:***

- Malignant neoplasms generally grow more rapidly than benign ones, but there is no critical rate that distinguishes malignant from benign.
- Assessment of the growth rate is based upon clinical information (eg, change in size of the mass in serial examinations).
- On microscopic examination, the number of mitotic figures and the metabolically active appearance of nuclei (enlarged, dispersed chromatin, large nucleoli) correlate positively with the growth rate of the neoplasm.

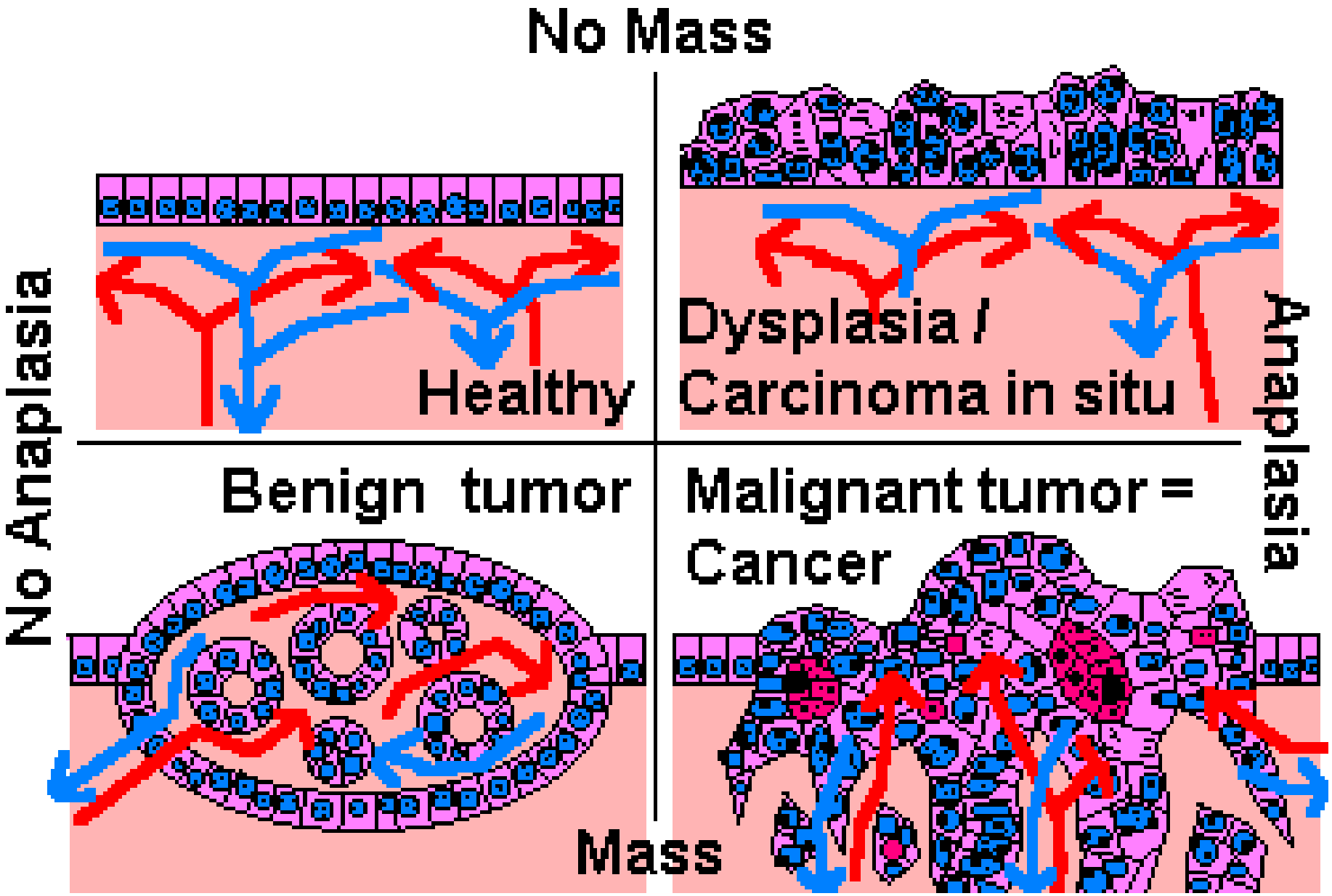
- ***2. Size:***

- The size of a neoplasm usually has no bearing on its biologic behavior.
- Many benign neoplasms become very large; conversely, highly malignant neoplasms may be lethal by virtue of extensive dissemination even though the original primary tumor is still small.
- In a few neoplasms (such as endocrine neoplasms), however, size is the deciding factor in distinguishing benign from malignant growths.

- ***3. Degree of Differentiation:***

- Denotes the degree to which a neoplastic cell resembles the normal mature cells of the tissue in question; this meaning is distinct from the more general use of the word to describe passage of a cell down a particular maturation pathway.
- Benign neoplasms are fully (well) differentiated, ie, they closely resemble normal tissue.
- Malignant neoplasms, show variable degrees of differentiation and frequently demonstrate little resemblance to normal tissue (ie, they are poorly differentiated).

- In anaplasia, the neoplastic cells have no morphologic resemblance whatsoever to normal tissue.
- The importance of these individual criteria varies with different neoplasms. For example, the mitotic rate is the major factor distinguishing benign from malignant smooth muscle neoplasms in the uterus; in many other neoplasms, the mitotic rate is of little relevance.


No Mass
No Anaplasia
Anaplasia
Healthy
Dysplasia /
Carcinoma in situ
Benign tumor
Malignant tumor =
Cancer
Mass

- ***4. Changes in Deoxyribonucleic Acid (DNA):***

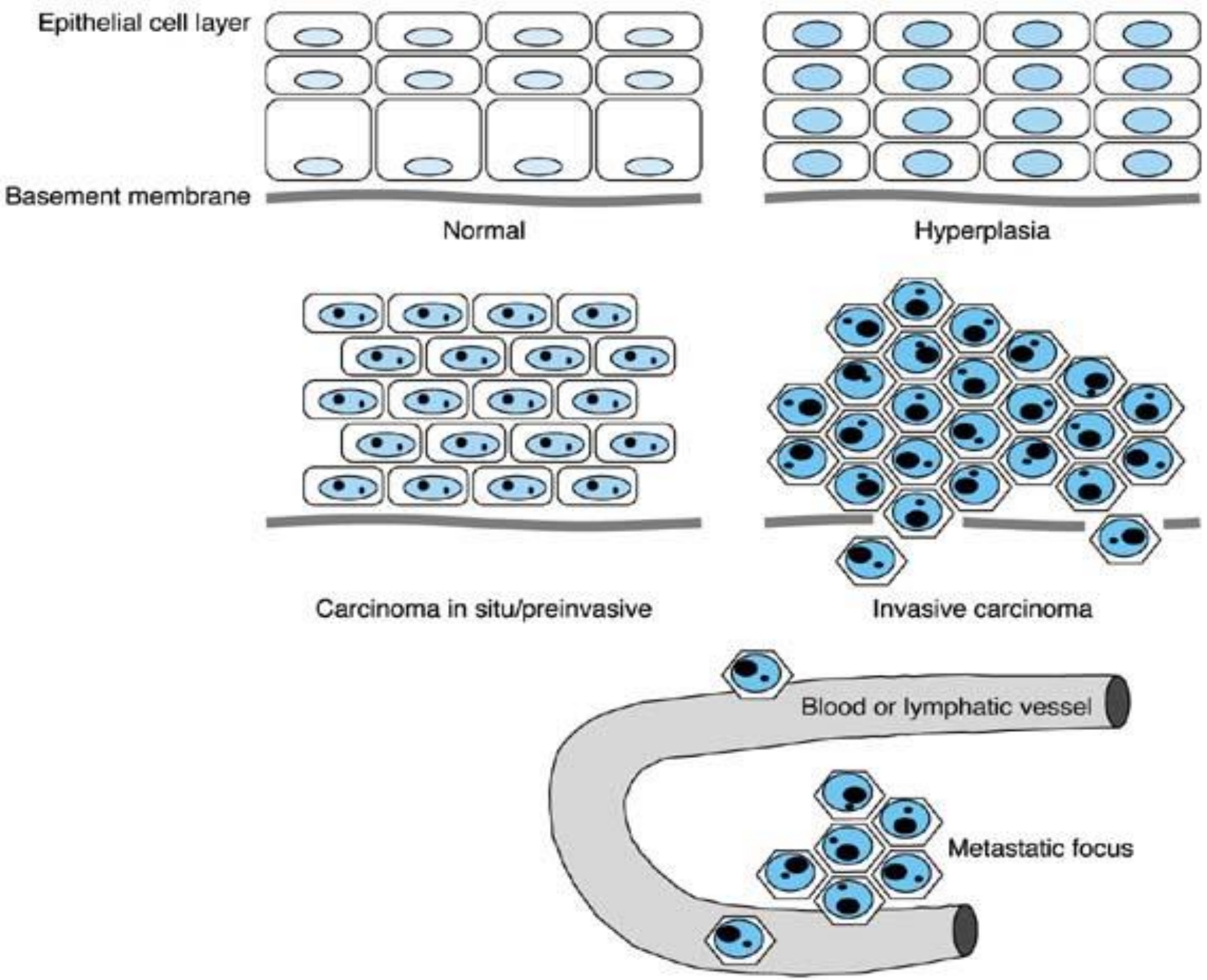
- Neoplasms are associated with abnormalities in their DNA content; this abnormality increases with the degree of malignancy.
- The degree of hyperchromatism (increased staining of the nucleus) provides a crude assessment of DNA content on microscopic examination; malignant cells are **hyperchromatic**.
- When measured precisely by flow cytometry, the DNA content of malignant cells correlates well with the degree of malignancy in malignant lymphoma, bladder neoplasms, and astrocytic neoplasms.
- Cytogenetic studies demonstrating aneuploidy and polyploidy also are indicative of malignancy.
- Molecular techniques that demonstrate clonal deletions, translocations, or abnormalities of oncogene expression are of increasing value.

The malignant looking tumor cell has;

- ✓ Increased nuclear DNA
- ✓ Increased nuclear/cytoplasmic ratio
- ✓ Hyperchromatic nucleus
- ✓ Coarsening of chromatin
- ✓ Wrinkled nuclear edges
- ✓ Multinucleation
- ✓ Macronucleoli
- ✓ Numerous and bizarre mitotic figures
- ✓ Failure to mature along normal functional lines
- ✓ Cells of widely varying sizes
- ✓ Loss of orientation of cells to one another

- ***5. Infiltration and Invasion:***

- Benign neoplasms are generally non-infiltrative and are surrounded by a capsule of compressed and fibrotic normal tissue.
- Malignant neoplasms, have infiltrating margins. Some exceptions to this rule exist, and some benign neoplasms (eg, granular cell tumor, dermatofibroma, and carcinoid tumors) lack a capsule and have an infiltrative margin.


Epithelial cell layer
Basement membrane
Normal
Hyperplasia
Carcinoma in situ/preinvasive
Invasive carcinoma
Blood or lymphatic vessel
Metastatic focus

- ***6. Metastasis:***

- The occurrence of metastasis (noncontiguous or distant growth of tumor) is absolute evidence of malignancy.
- The major reason for distinguishing benign from malignant neoplasms is to be able to predict their ability to metastasize before they do so.
- Gross and microscopic examination of a neoplasm usually enables a trained pathologist to classify most neoplasms as benign or malignant.
- In some instances, however, this identification is difficult, and the only reliable evidence of a neoplasm's biologic behavior is the occurrence of metastasis; about 90% of pheochromocytomas are benign, but there are no reliable criteria for identifying the 10% that will metastasize.

Grading and Staging

- Methods to quantify the probable clinical aggressiveness of a given neoplasm and its apparent extent and spread in the individual patient are necessary for making accurate prognosis and for comparing end results of various treatment protocols.
- For instance, the results of treating extremely small, highly differentiated thyroid adenocarcinomas that are localized to the thyroid gland are likely to be different from those obtained from treating highly anaplastic thyroid cancers that have invaded the neck organs.

Staging of cancer

The cancers are divided into stages 0 to IV, incorporating the size of primary lesions and the presence of nodal spread and of distant metastases.

- Stages of cancer spread:

  Stage 1 confined to site of origin

  Stage 2 cancer is locally invasive

  Stage 3 cancer has spread to regional structures

  Stage 4 cancer has spread to distant sites (metastasis)

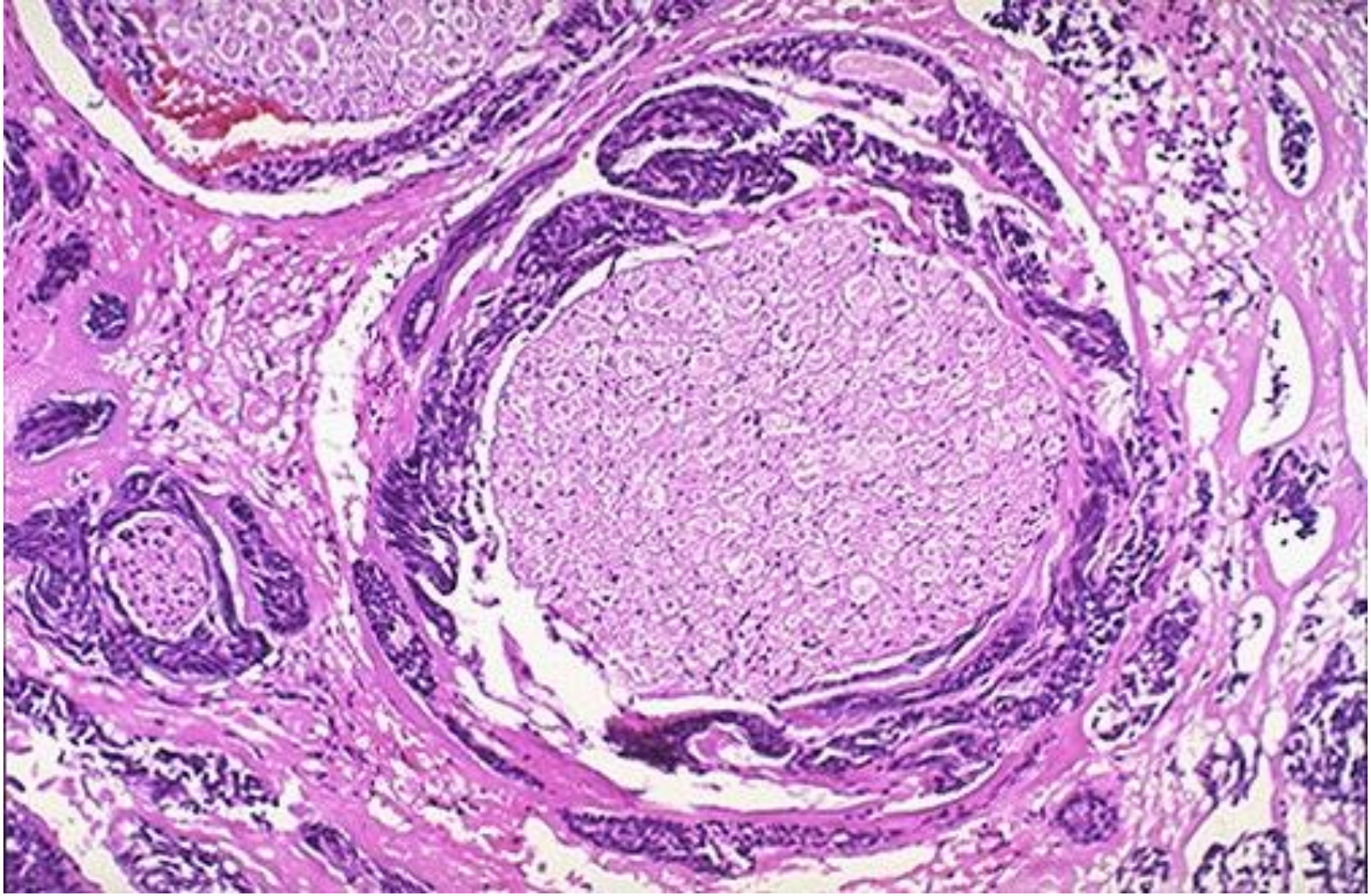
Clinical manifestations of Cancer

Pain

- Usually not in early stages
- 60 – 80 % of terminally ill
- Psychogenic, cultural and physiologic components
- Due to pressure, obstruction, stretching, tissue damage or inflammation

Fatigue

sleep disturbances
biochemical changes
loss of muscle function



Branches of peripheral nerve are invaded by nests of malignant cells. This is often why pain associated with cancers is intractable.

Clinical manifestations of Cancer

Cachexia – wasting

- anorexia
- early satiety
- weight loss
- anemia
- marked weakness
- taste alterations
- altered metabolism

Clinical manifestations of Cancer

Anemia

- chronic bleeding
- malnutrition
- medical therapies
- malignancy in blood forming organs

Leukopenia and thrombocytopenia

- tumor invasion of bone marrow
- chemotherapy or radiation

Infection

- most significant cause of complications and death

Clinical manifestations of Cancer

- Para-neoplastic Syndromes
  - Release of hormones by cancer cells
  - Hematological complications such as procoagulation factors
  - Causes weakness by attacking neuromuscular junction (similar to myasthenia gravis)

Cancer Treatment

- Chemotherapy
  - Cytotoxic drugs + body defenses
    - Single agent
    - Combination chemotherapy
      - Avoids single agent resistance
      - Can use lower dose
      - Better remission and cure rate

Cancer Treatment

Radiation
- targets DNA
- kill tumor without damage to surrounding tissues
- tumor must be accessible

Surgery
- method of choice
- can remove entire tumor
- debulking
- adjuvant chemotherapy or radiation
- palliation

Cancer Treatment

Immunotherapy

Nonspecific enhancement of the immune system – interferons or interleukins

protect against recurrence

eliminates cancer cells only

T- cell based or antibody responses

Conjugated antibodies

Targeted Therapies

Drugs that target the processes of cancer cells specifically: Thalidomide

Vaccines

Side effects of treatment

Gastrointestinal tract:

- Oral ulcers
- Malabsorption
- Diarrhea
- Vomiting – caused by effects on CNS

Bone marrow:

- chemo and radiation suppress bone marrow
- decrease in red blood cells, white blood cells and platelets

Hair and skin:

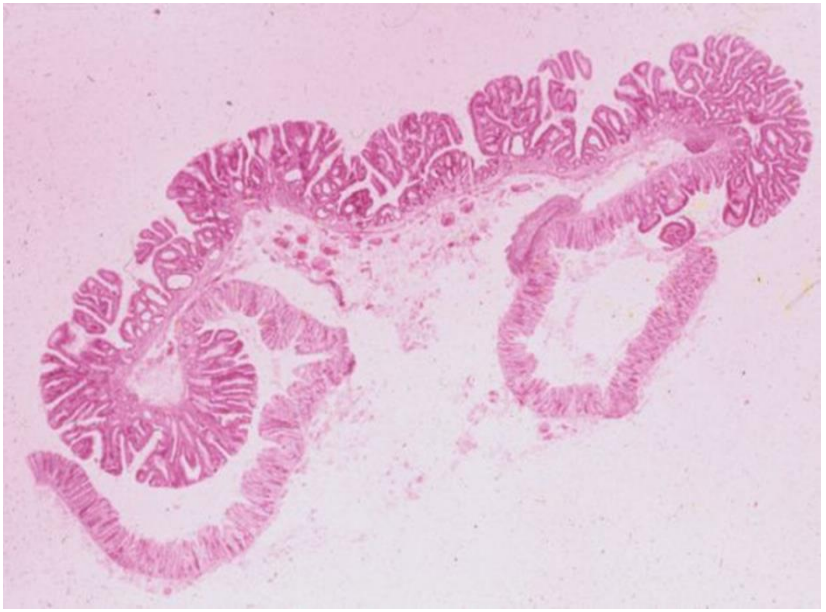
- alopecia
- skin breakdown and dryness

Reproductive tract:

- affects gametes
- premature menopause
- also due to damage of hypothalamus and/or pituitary
- sperm or embryo bank

BENIGN NEOPLASM

Cells grow as a compact mass and remain at their site of origin

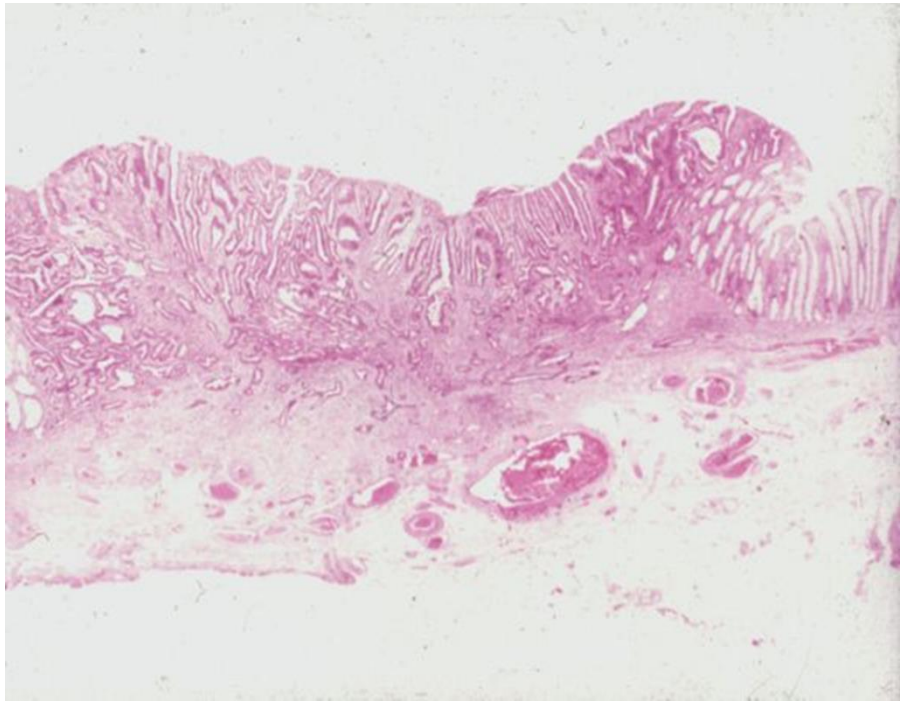


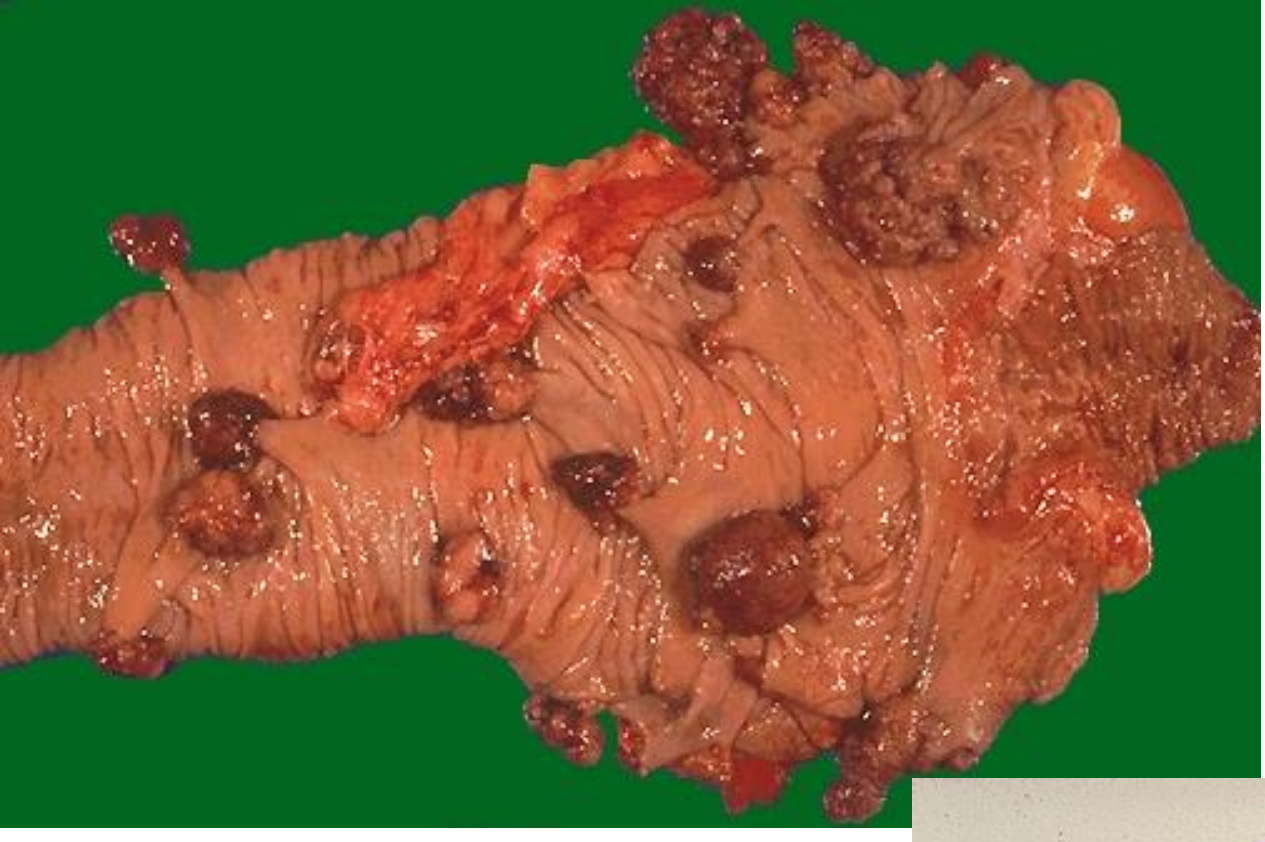
MALIGNANT NEOPLASM

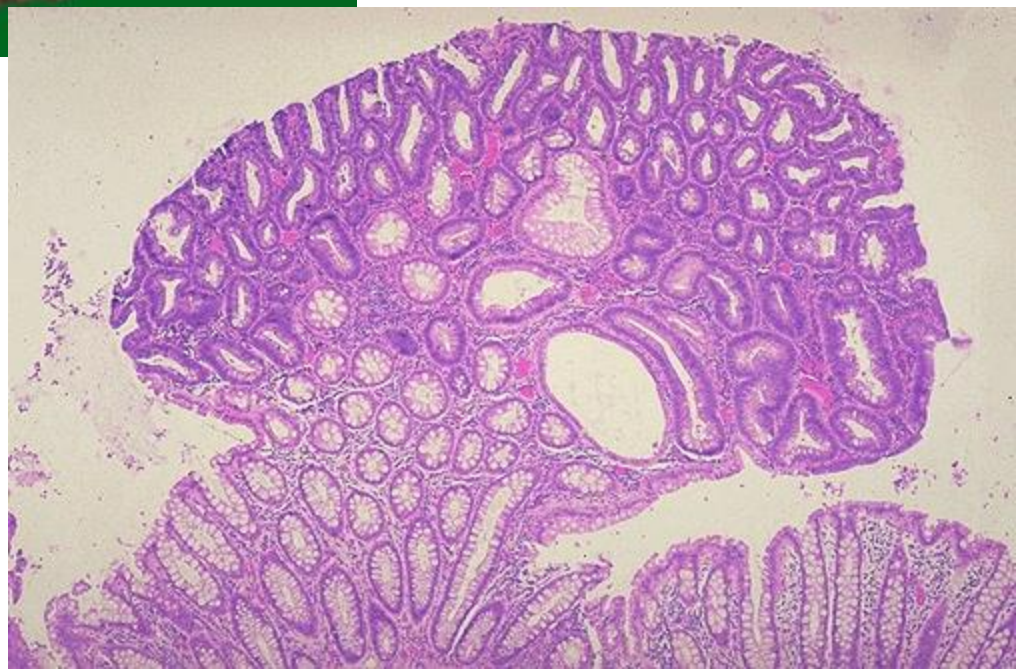
Growth of cells is uncontrolled

Cells can spread into surrounding tissue and spread to distant sites

Cancer = a malignant growth







มะเร็งลำไส้ใหญ่

HPV Pailloma หูด

- HPV 6,11 – low risk viruses
- HPV – 16, 18, 31, 33, 35, 39, 45 – High risk viruses
- 85% of cervical carcinomas that are HPV-positive contain a high risk HPV (70% have HPV 16 or 18)

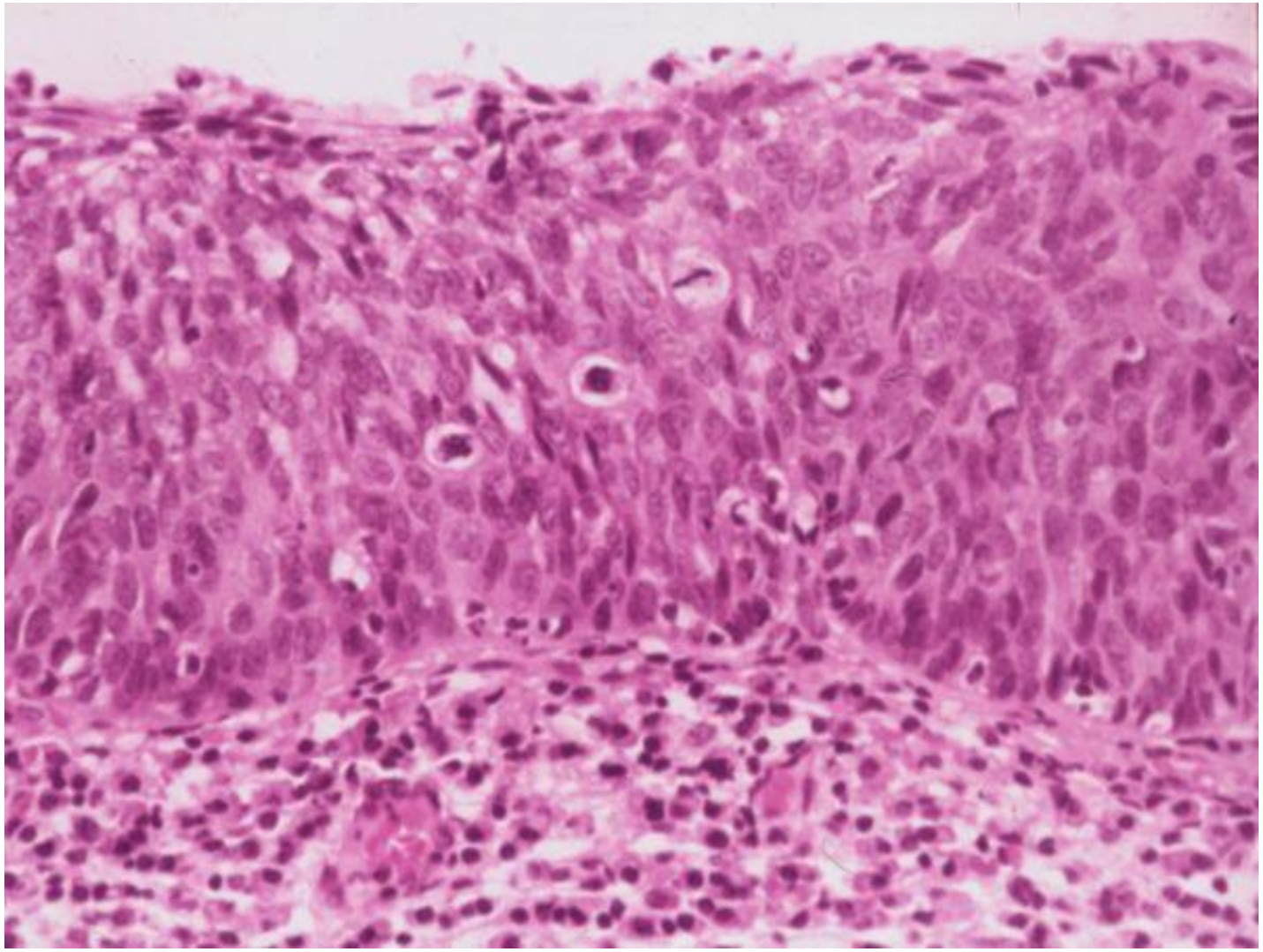

cm
1
2
3
KUMC S-96-5443

IN-SITU MALIGNANCY

Epithelial neoplasm with features of malignancy

- altered cell growth
- cytological atypia
- altered differentiation

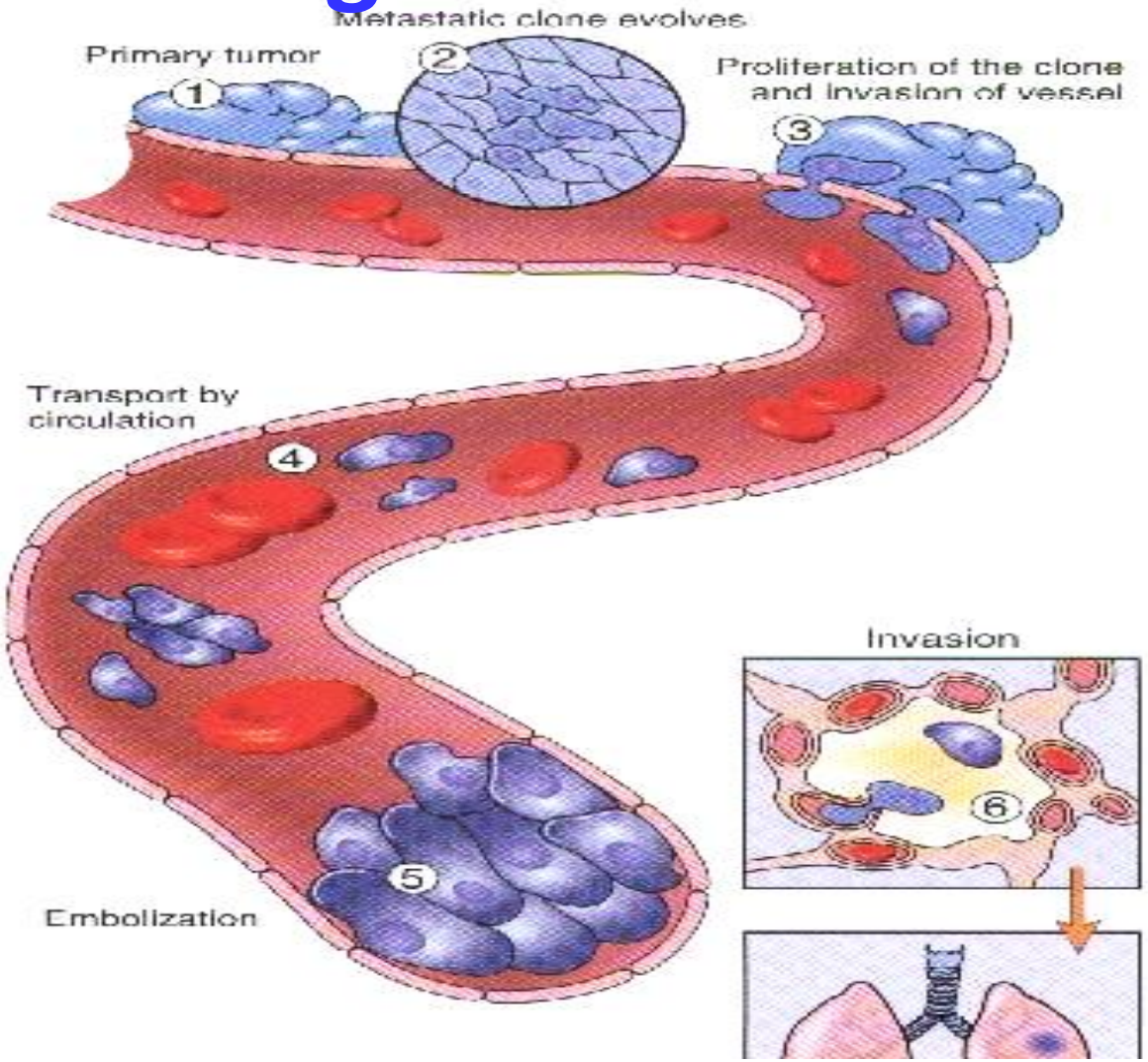
BUT-no invasion through basement membrane

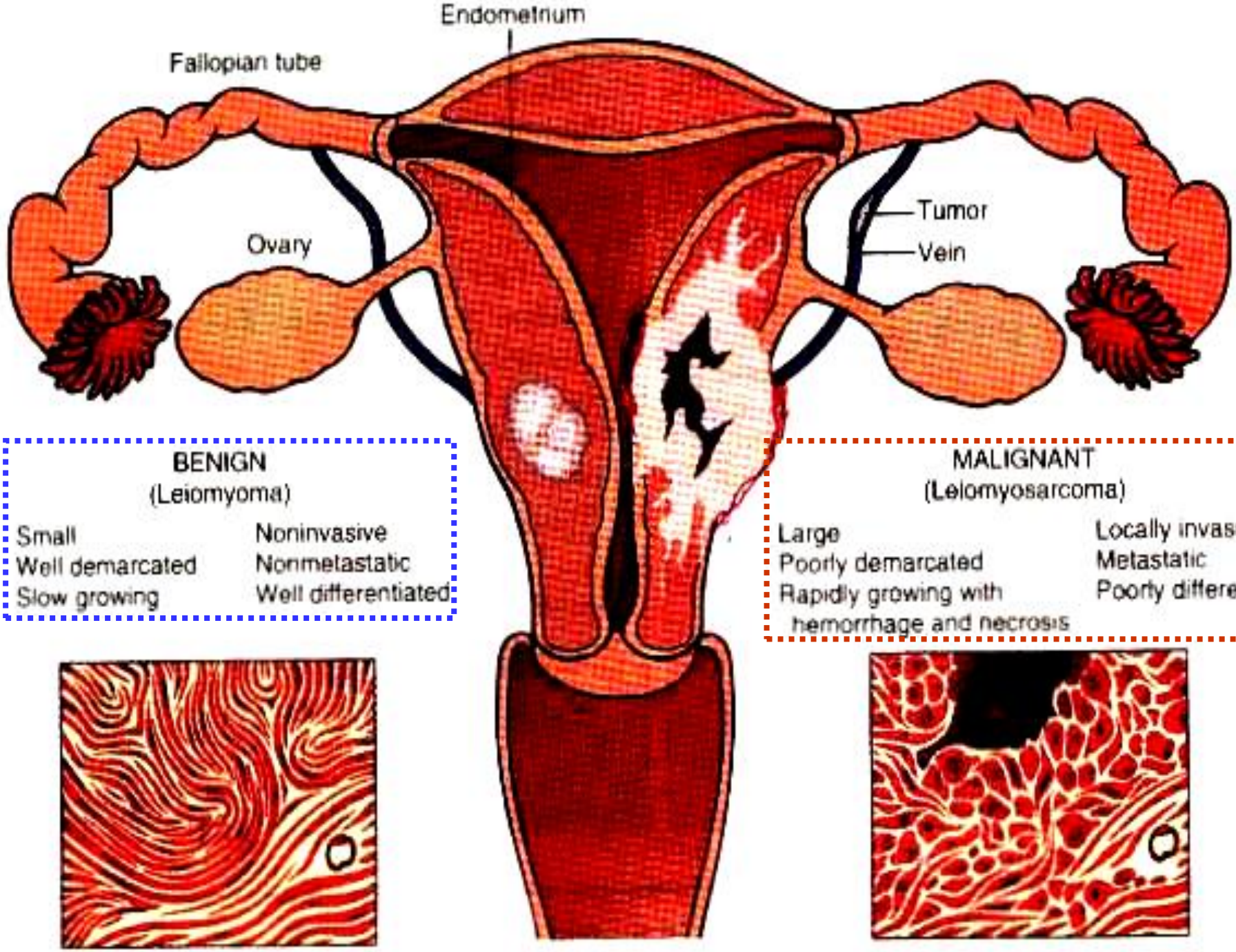


Cellular differentiation

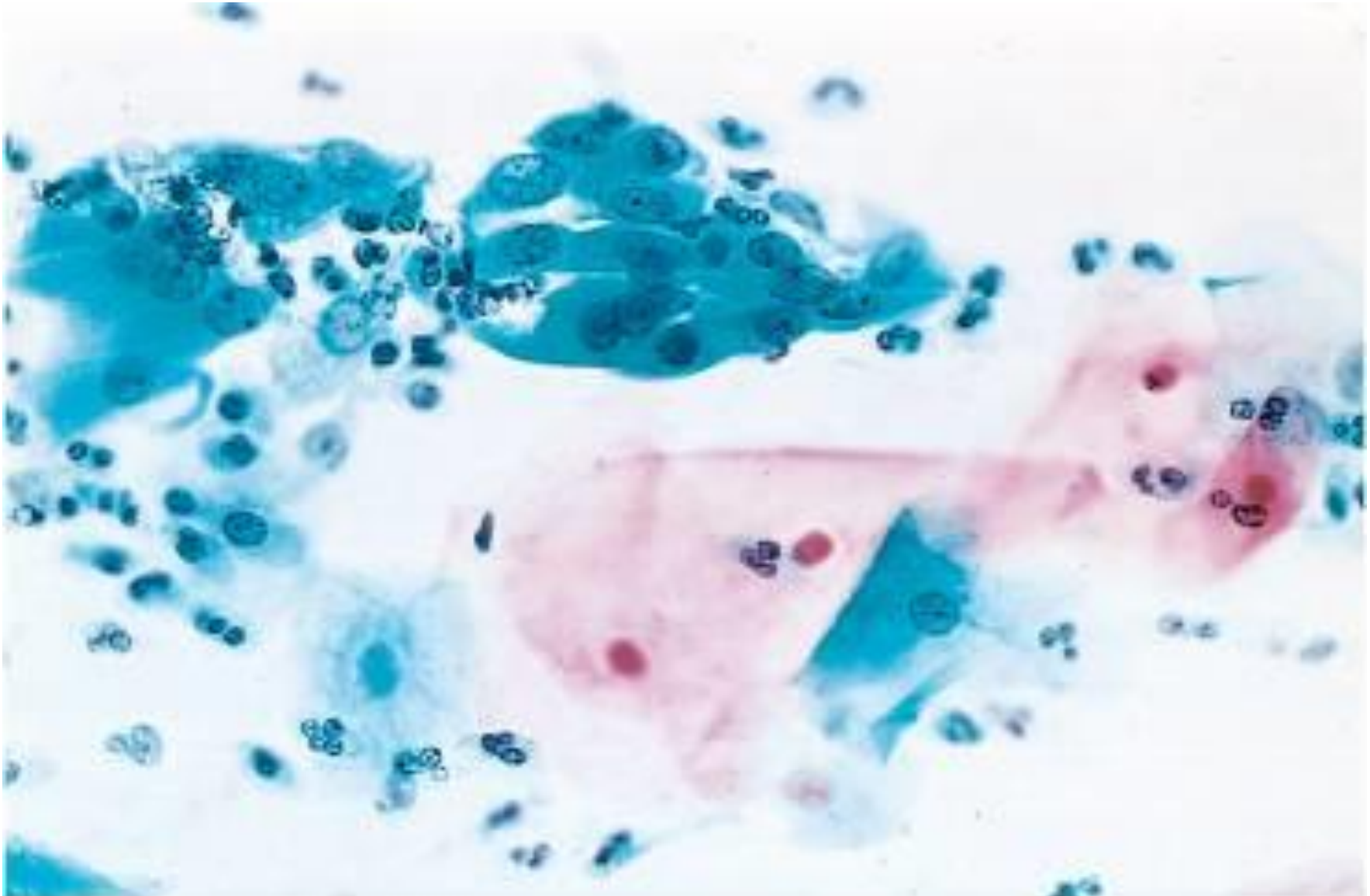
- Tumors are often “graded” as to how closely they resemble the normal parent tissue that they are derived from.
- Well-differentiated means the cells are very similar in appearance and architectural arrangement to normal tissue of that organ

Malignant Tumor

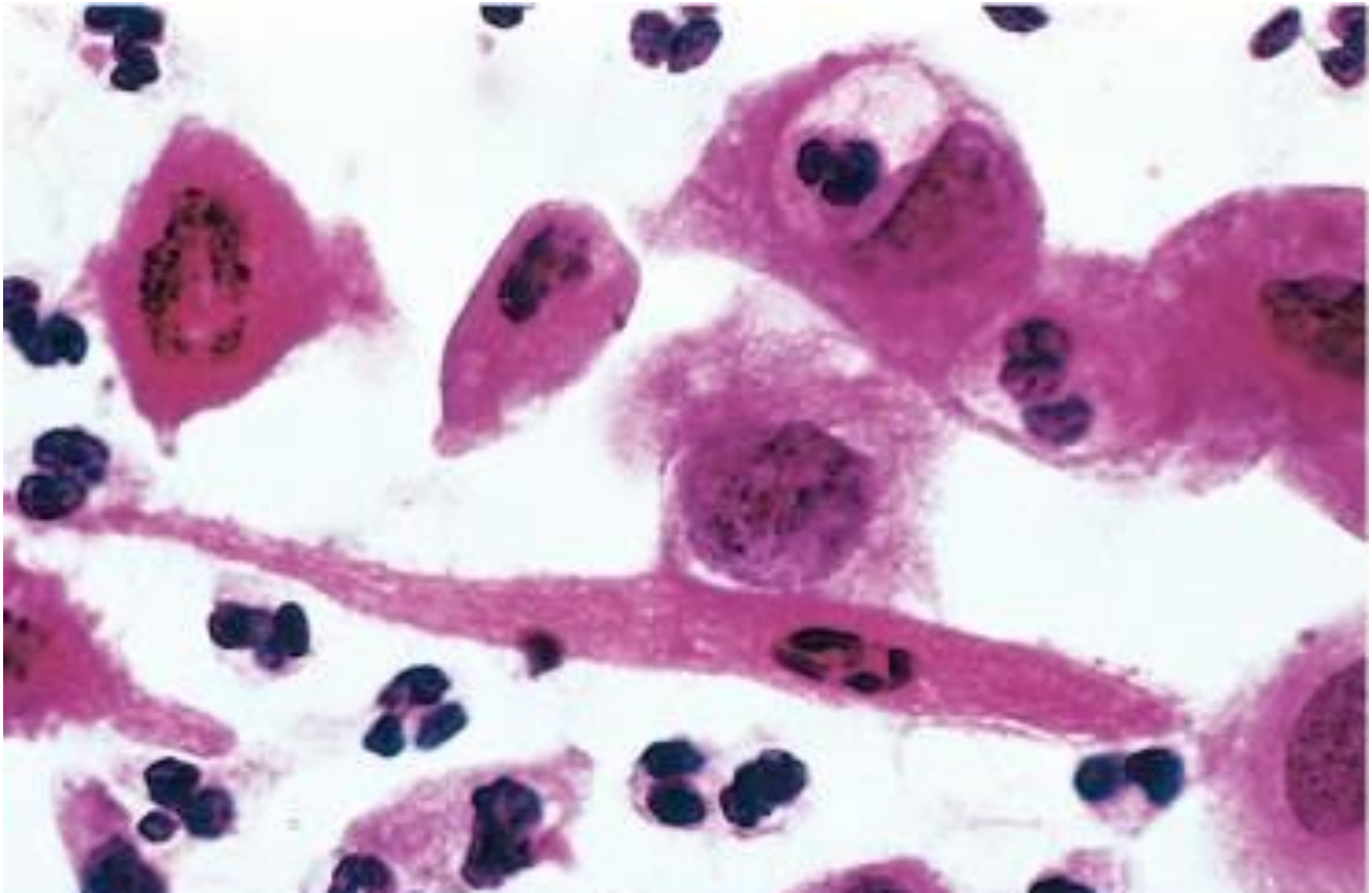


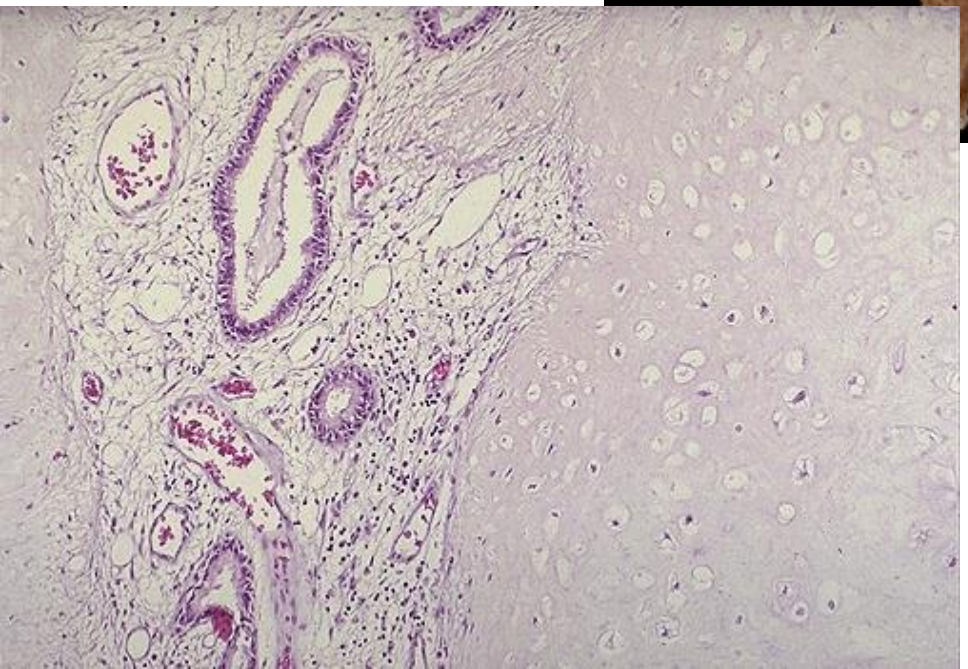

Endometrium
Fallopian tube
Ovary
Tumor
Vein
BENIGN
(Leiomyoma)
Small
Well demarcated
Slow growing
Noninvasive
Nonmetastatic
Well differentiated
MALIGNANT
(Leiomyosarcoma)
Large
Poorly demarcated
Rapidly growing with hemorrhage and necrosis
Locally invasive
Metastatic
Poorly differentiate

Normal cervical “Pap smear”

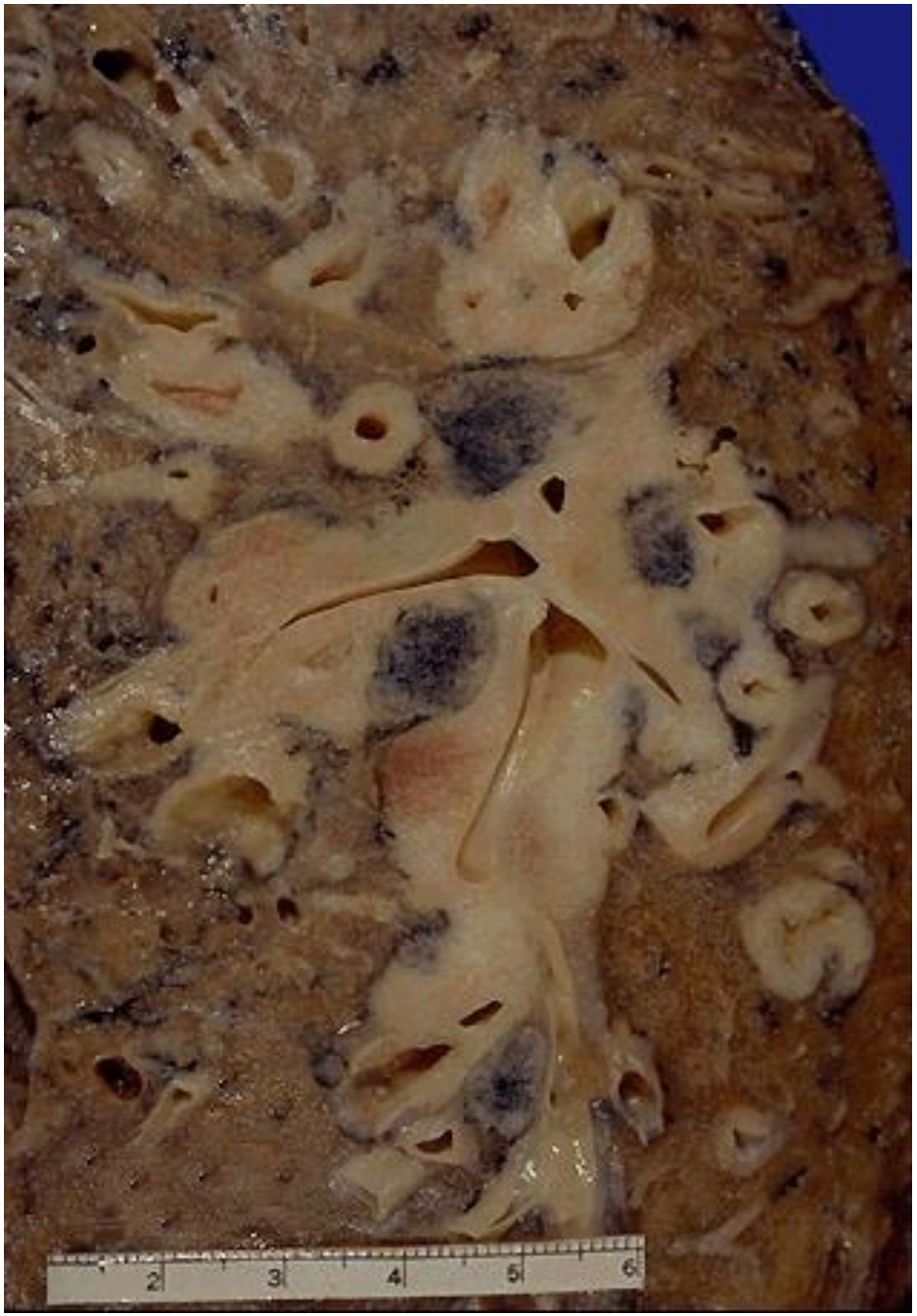


Malignant cervical “Pap smear”





Hamartoma (LUNG)

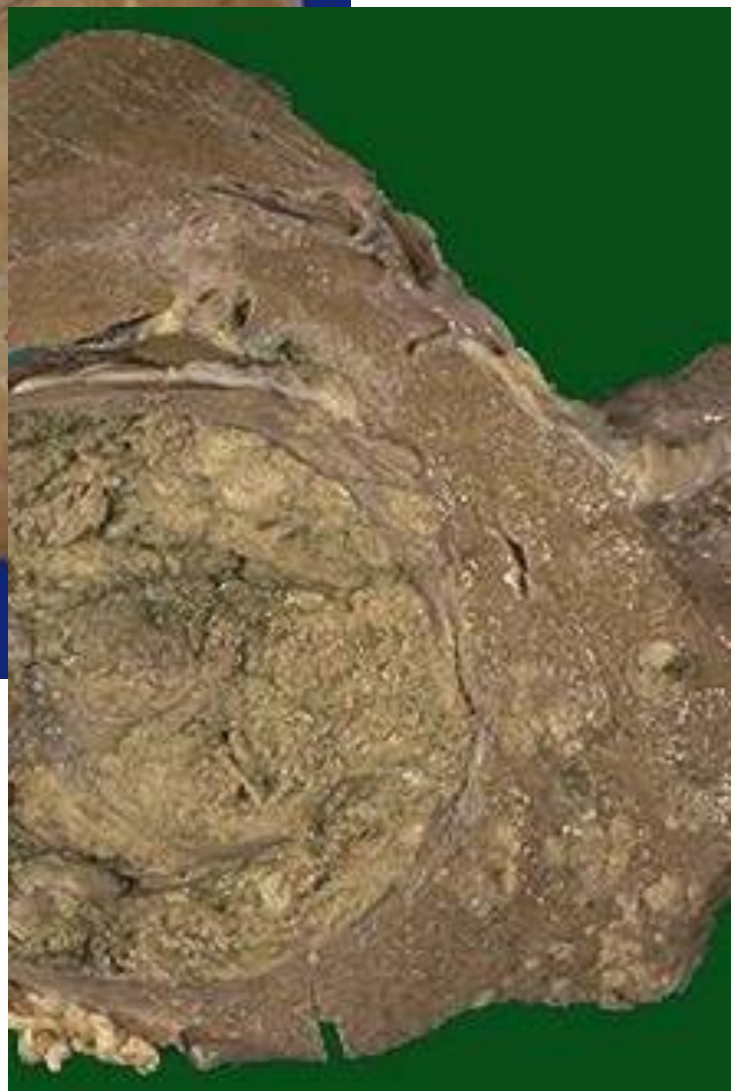


Malignant neoplasms are also characterized by the tendency to invade surrounding tissues. Here, a lung cancer is seen to be spreading along the bronchi into the surrounding lung.

Here is a small hepatic adenoma, an uncommon benign neoplasm, but one that shows how well-demarcated an benign neoplasm is. It also illustrates how function of the normal tissue is maintained, because the adenoma is making bile pigment, giving it a green color.

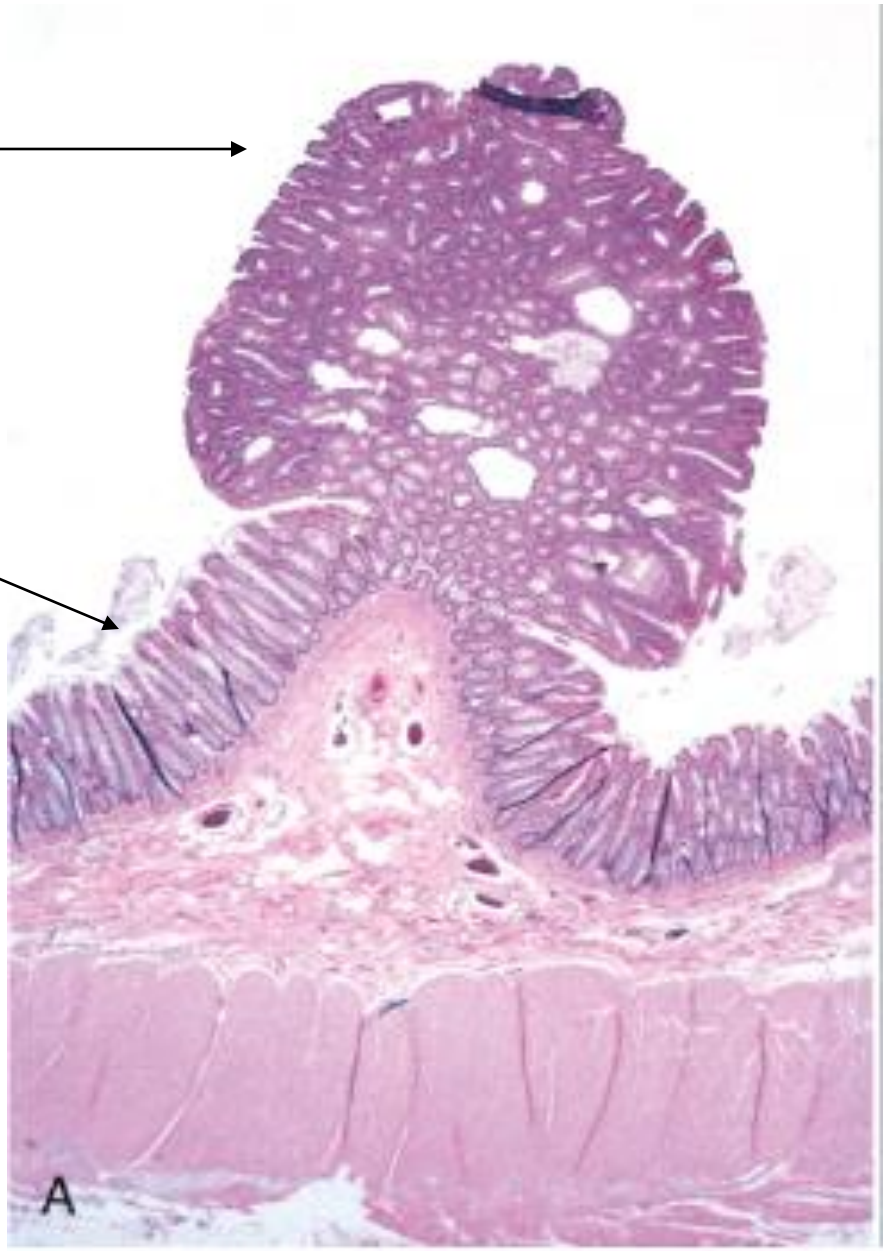
In contrast, this hepatocellular carcinoma is not as well circumscribed (note the infiltration of tumor off to the lower right) nor as uniform in consistency. It is

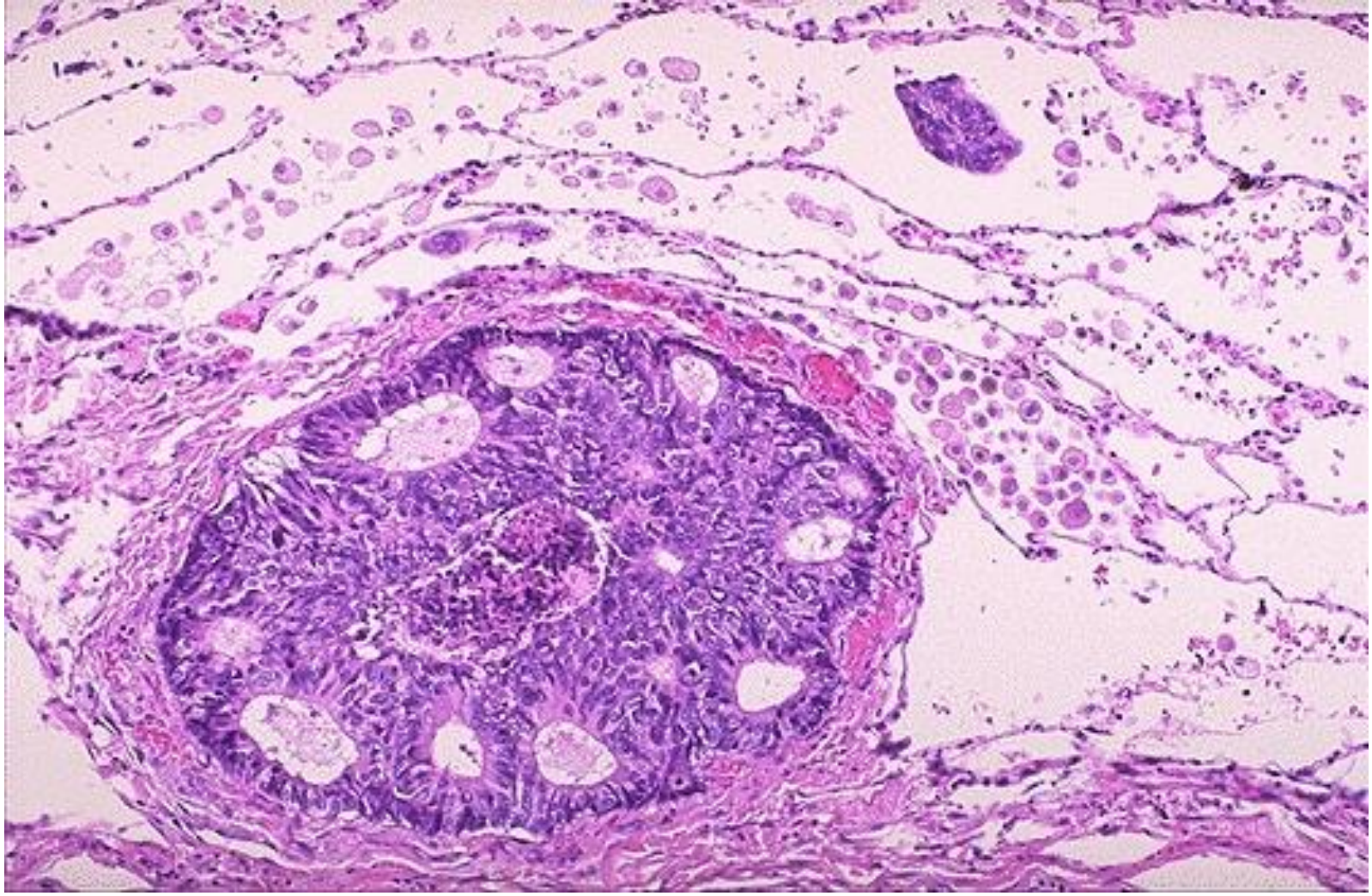
This is an example of metastases to the liver. Note that the tan-white masses are multiple and irregularly sized. A primary neoplasm is more likely



- Neoplasms can spread by seeding along body cavities, and this pattern is more typical for carcinomas than other neoplasms.
- Note the multitude of small tan tumor nodules seen over the peritoneal surface of the mesentery shown here.

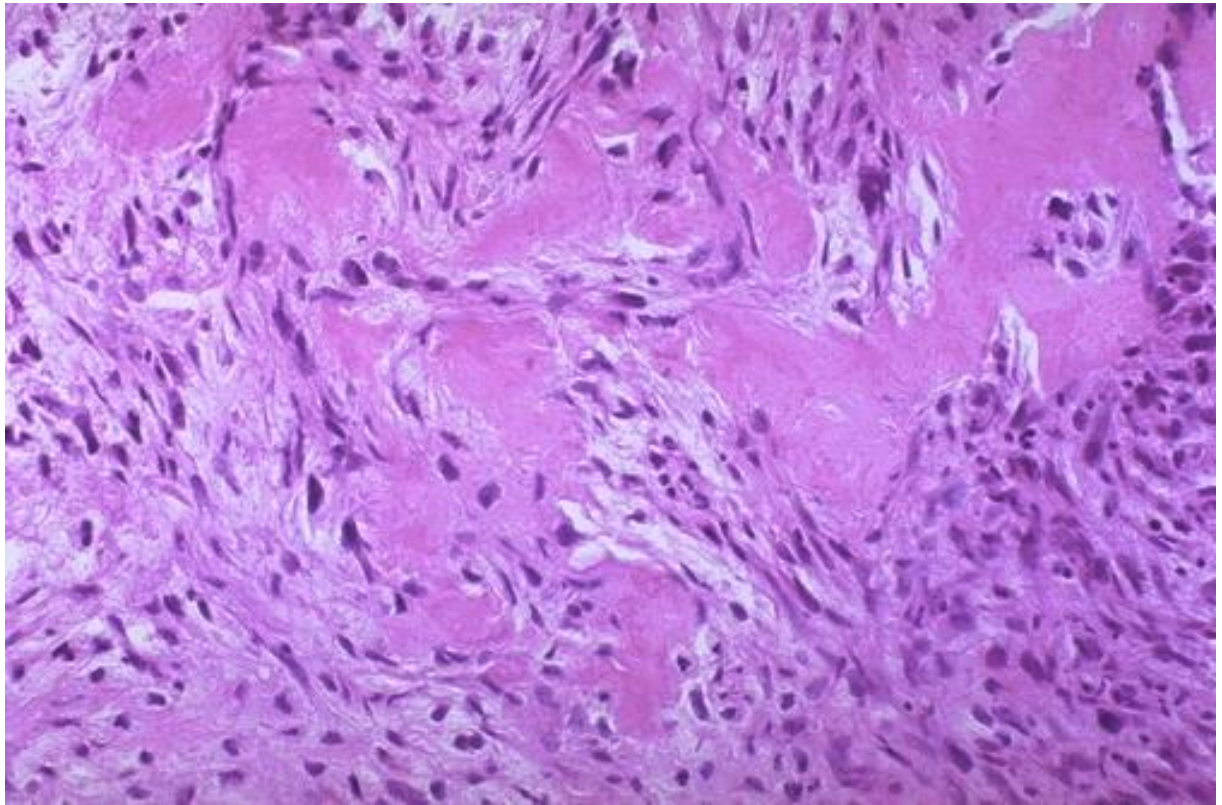
Colonic “adenoma” illustrating a “well-differentiated” neoplasm similar to normal colon mucosa



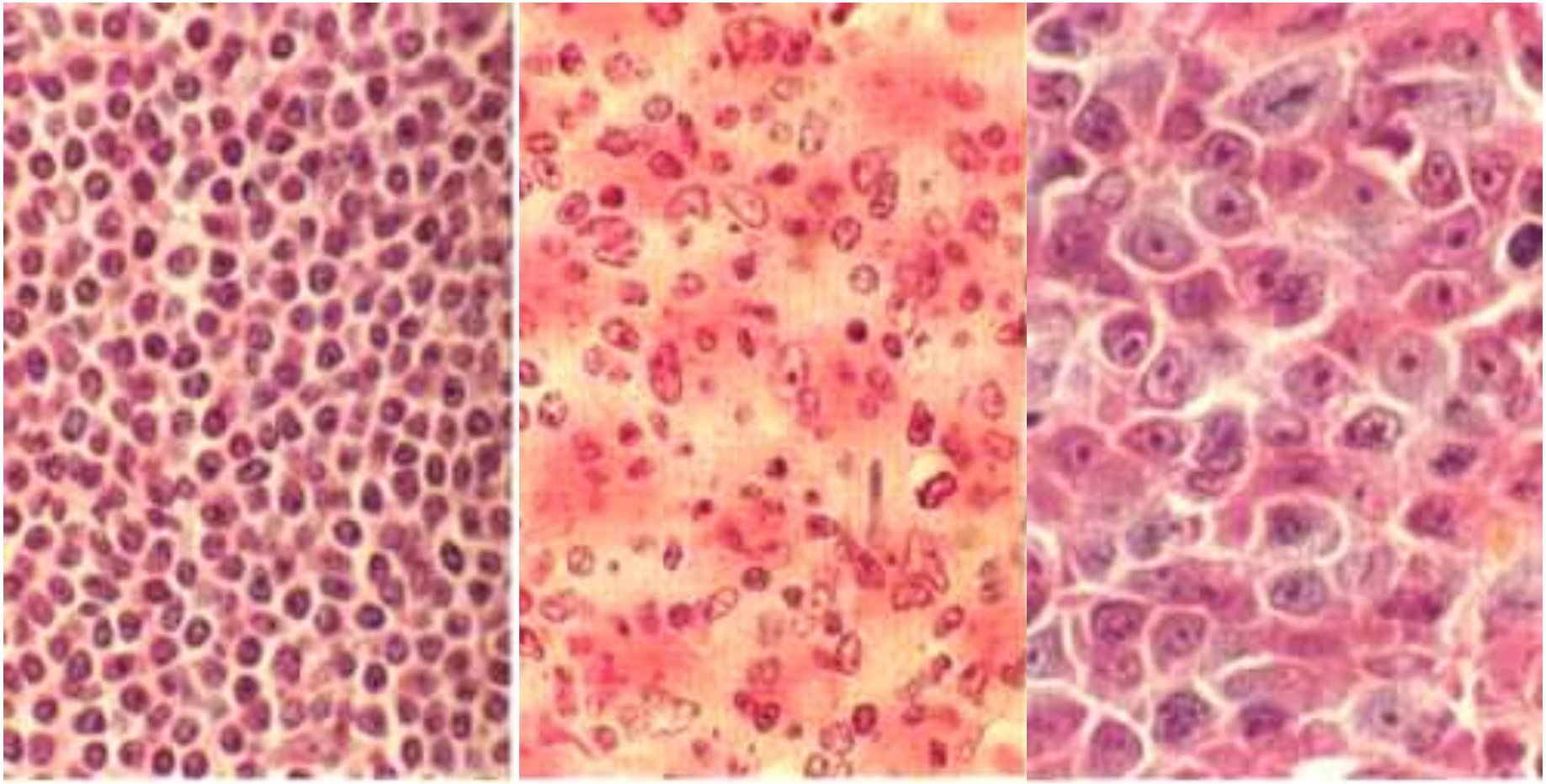


- Both lymphatic and hematogenous spread of malignant neoplasms is possible to distant sites.
- Here, a breast carcinoma has spread to a lymphatic in the lung.

Osteosarcoma

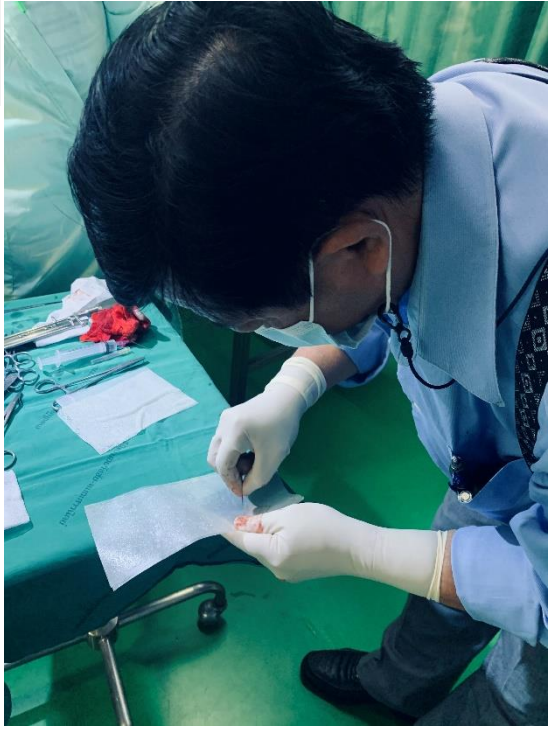


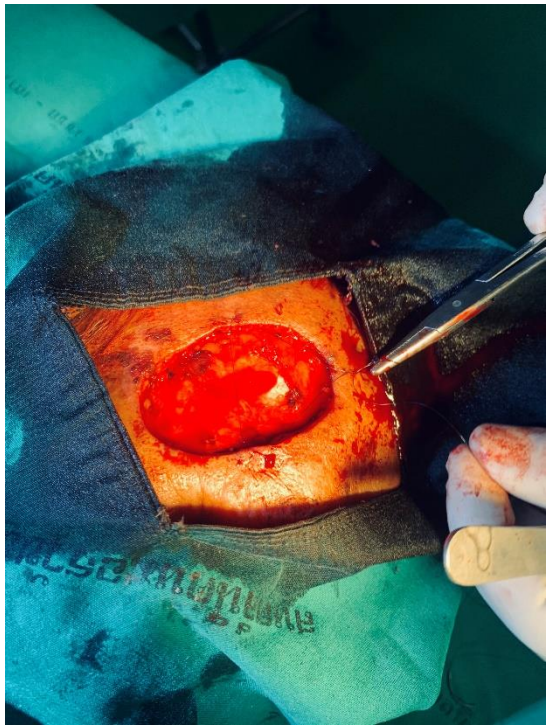
Lymphomas-Histologic types

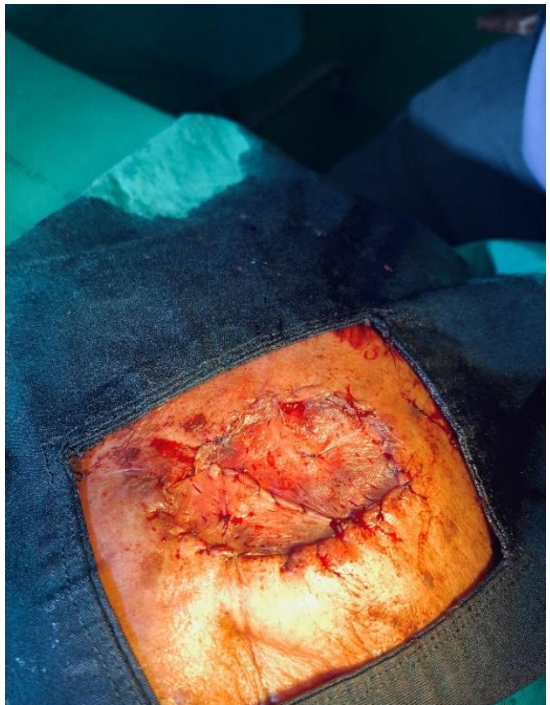


Small **Intermediate** **Large**

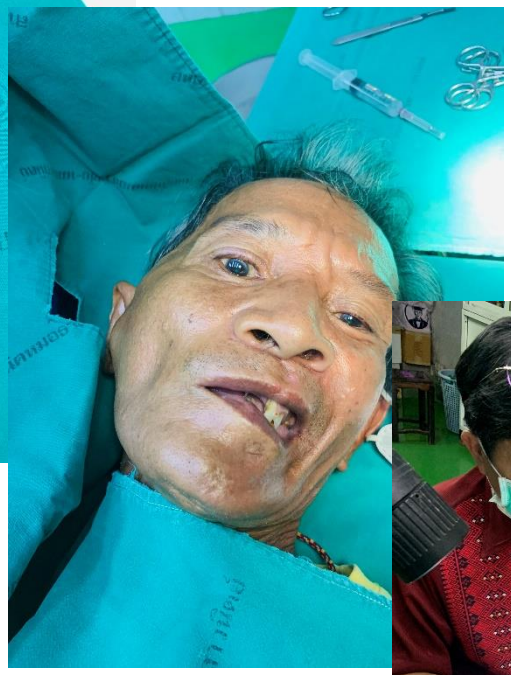
Basal cell Carcinoma

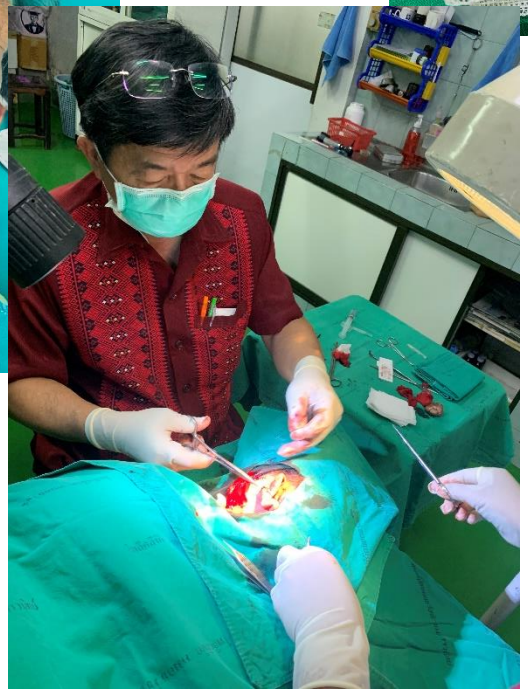


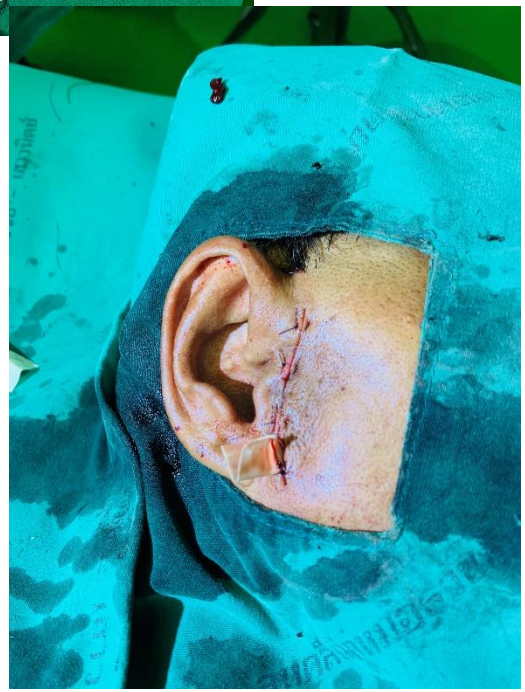




Mixed tumor-facial nerve palsy





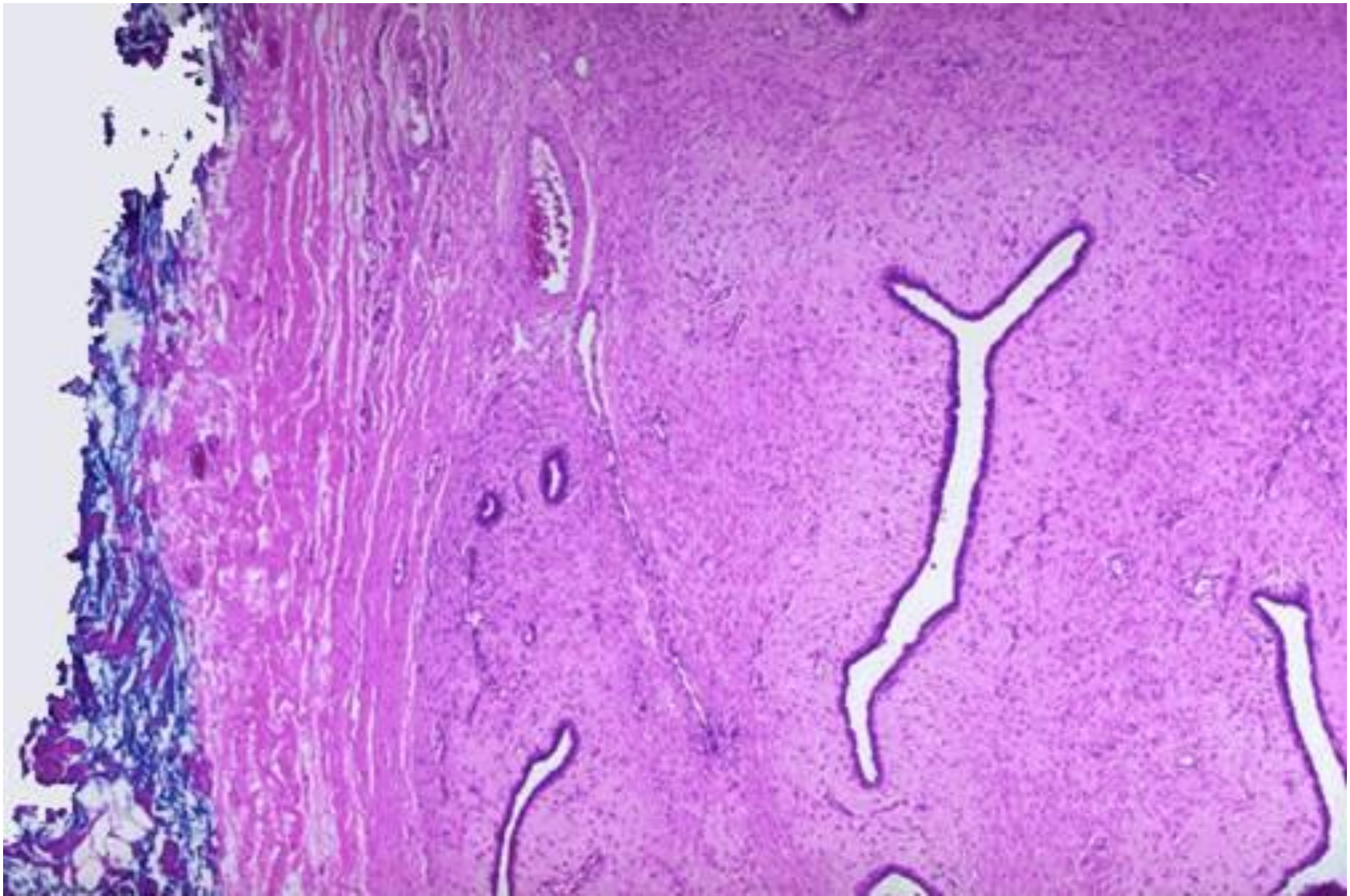


Carcinoma breast

Stage 2-3

Stage 4

Fibroadenoma



Gross (macroscopic) features of two breast neoplasms

Benign – circumscribed, often encapsulated, pushes normal tissue aside

Malignant – infiltrative growth, no capsule, destructive of normal tissues

Squamous cell carcinoma

Hemangioma

Lipoma