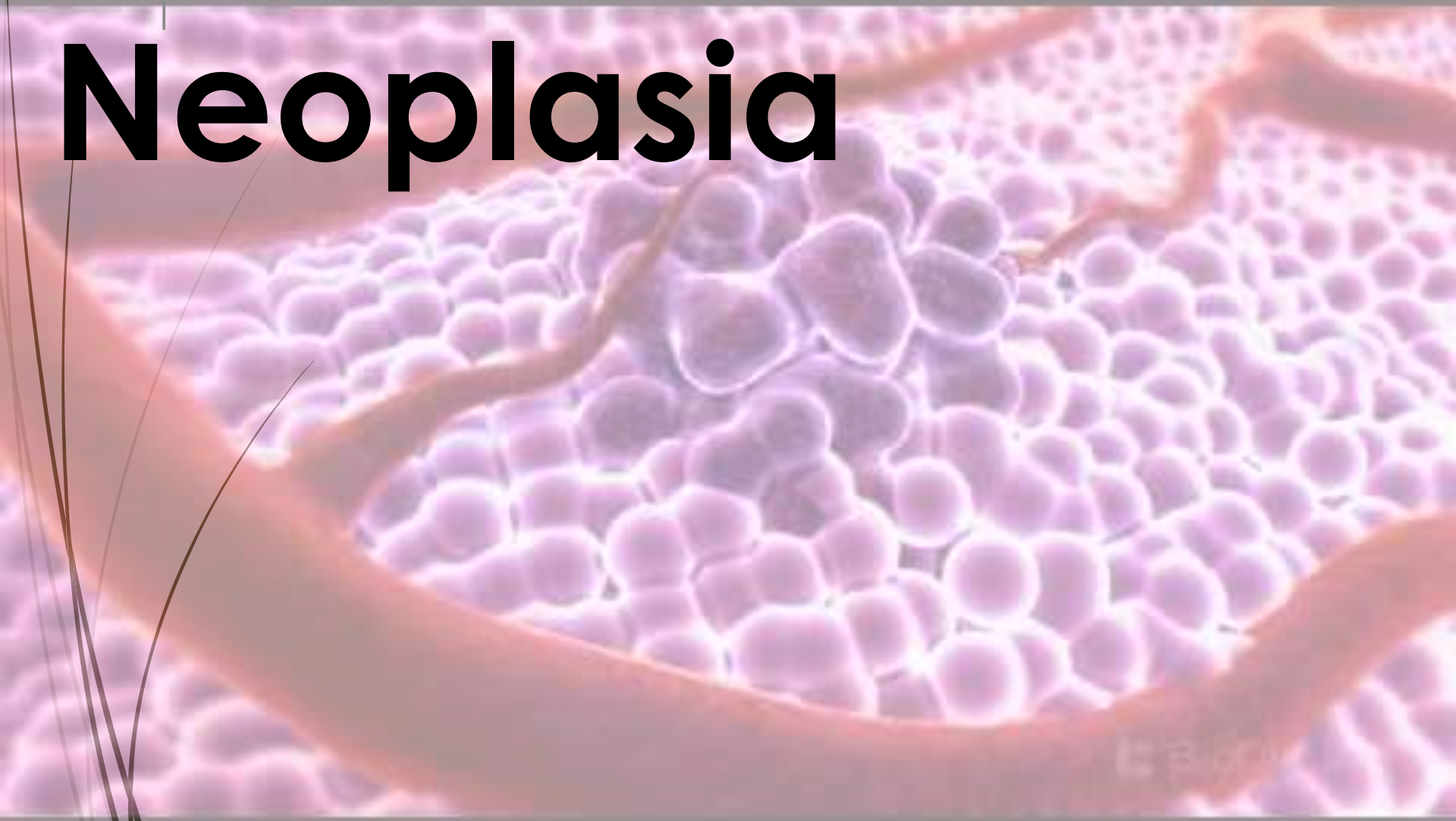
Neoplasia



Dr. Izzat Al Jaberi

contents

INTRODUCTION

- Different terms has been used in the past to describe abnormal growth

- Tumors, in the past has been used as a non-neoplastic term as used by Celsus in describing the cardinal signs of Inflammation meaning swelling but now is equated with Neoplasm

- Cancer(crab), is a term used mainly for Malignant tumors
- Cancer is the leading cause of death in the world, 2nd only to Cardiovascular disease

Definitions

Neoplasia derived from 2 Greek words Neos = New

Plasia = Thing Formed

Hence, Neoplasia in simple terms means the process of forming new things or simply, new growth.

A generally acceptable definition from a British Oncologist, Willis

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

Definitions

- Neoplasm or tumor is a result of **genetic alterations** that are passed down to the progeny of the tumor cells. These genetic changes allow **excessive** and **unregulated proliferation** that becomes **autonomous** (independent of physiologic growth stimuli)
- The entire population of neoplastic cells within an individual tumor arise from a single cell that has incurred genetic change, and hence tumors are said to be clonal.
- A neoplasm can be benign, potentially malignant(pre-cancer), or malignant (cancer)

NOMENCLATURE

All tumors (both benign and malignant) have two basic components:

- The Parenchyma: Which is made up of the proliferating Neoplastic cell that divide excessively
- The Stroma/Supporting tissue: Which consists of

mainly connective tissue, blood vessels and cells of the innate and adaptive immune response.

In cases where the parenchymal cells induce/stimulate the formation of abundant collagenous stroma, DESMOPLASIA results. e.g. stony hard breast cancer

NOMENCLATURE

- Nomenclature of tumors is based primarily on the parenchymal component

- The nomenclature is broadly divided into 2 groups depending on the origin of the tumor

Mesenchymal origin or
Epithelial origin

BENIGN TUMORS

- A benign tumor is a cohesive expansile mass of tissue with an innocent gross and microscopic appearance implying that it will remain localized to its site of origin and will be easily amenable to surgical removal

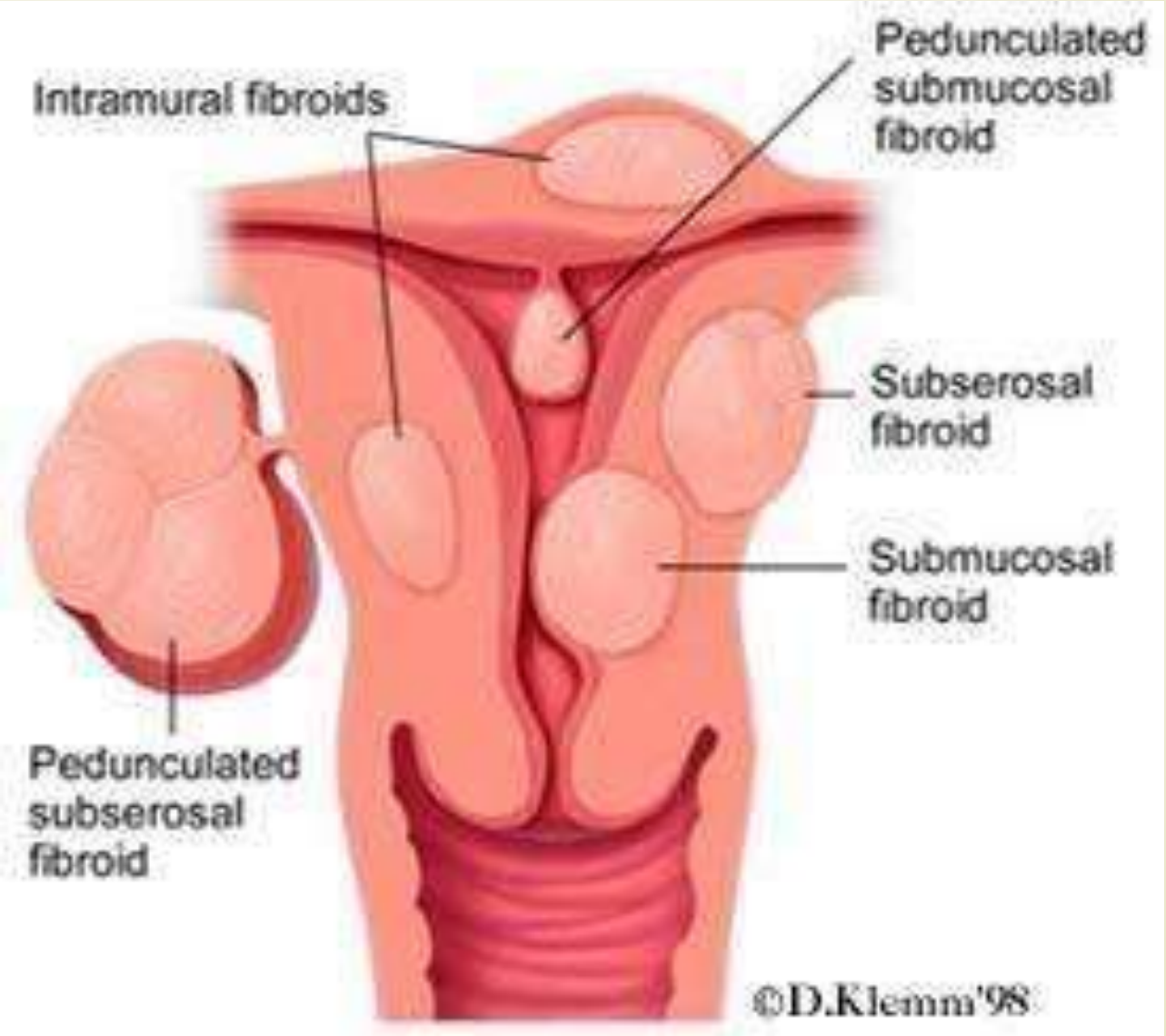
- The general principle of naming benign tumor is the addition of the suffix "-oma" to the cell of origin

- BENIGN TUMORS OF MESENCHYMAL ORIGIN

cells of mesenchymal origin follows this rule e.g.

- Fibroblastic cell: Fibroma
- Cartilaginous tissue: Chondroma
- Smooth muscle: Leiomyoma
- Skeletal muscle: Rhabdomyoma

Benign Tumours



NOMENCLATURE

BENIGN TUMOURS OF EPITHELIAL ORIGIN

- Their classification is more complex.
- They are classified based on:
  - Cells of origin
  - Microscopic architecture
  - Macroscopic patterns

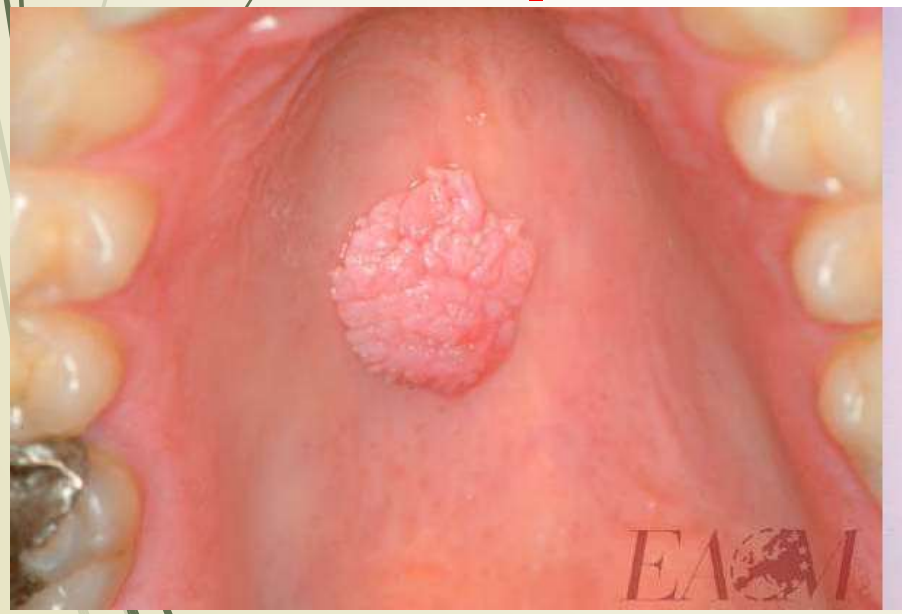
B.T OF EPITHELIAL ORIGIN

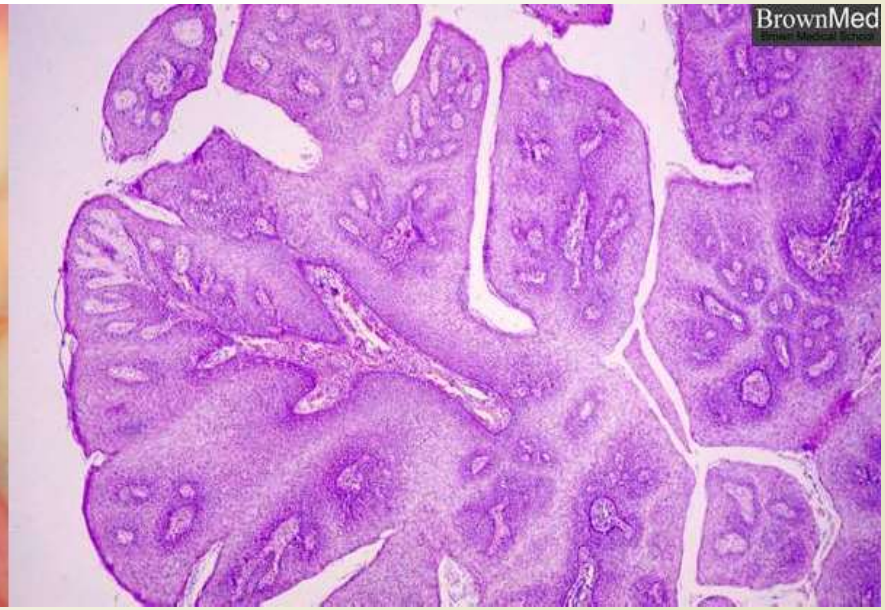
Papilloma

Microscopic or macroscopic visible finger-like or warty projections from epithelial surfaces. E.g. Oral papilloma

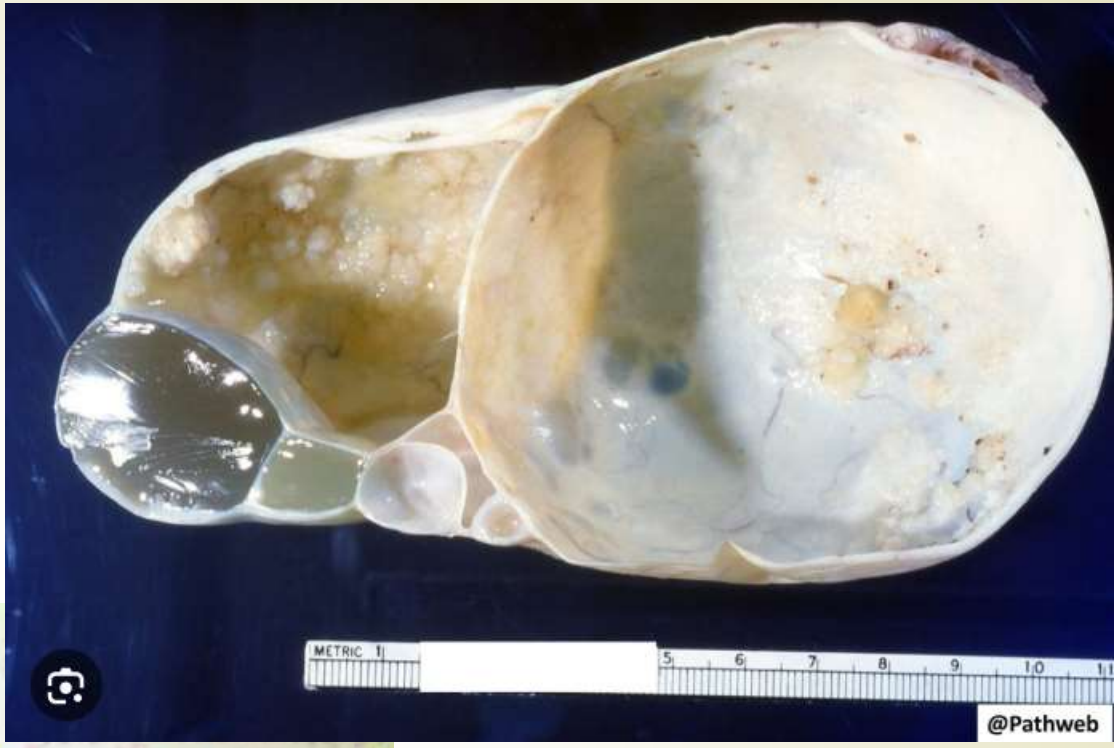
Cystadenoma

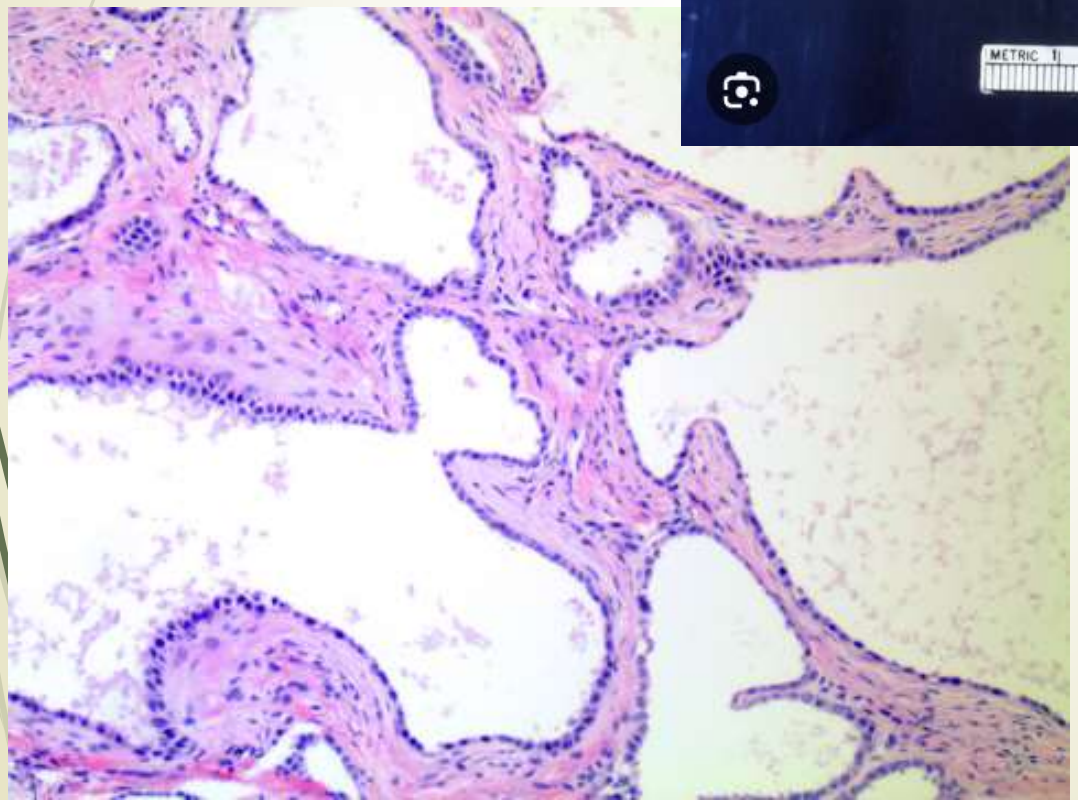
A form of adenoma that form cystic masses .E.g ovarian cystadenoma





Cystadenoma





MALIGNANT TUMORS

- They are collectively referred to as cancers
- Malignant tumors can invade and destroy adjacent structures and also spread to distant sites
- Malignant tumors arising of mesenchymal tissue: SARCOMA: e.g. Fibrosarcoma, chondrosarcoma, leiomyosarcoma, rhabdomyosarcoma etc.

Malignant tumour of epithelial origin

- M.T of epithelial origin, derived from any of the 3 germ layer (endoderm, ectoderm and mesoderm) are called CARCINOMA

Adenocarcinoma

M.T with glandular growth pattern microscopically

Squamous cell carcinoma

Arising from squamous cell epithelium, specificity of organ of origin is essential

Polyp / Polypoid

This is a macroscopically, visible projection that arise from the mucosal surface into the lumen, either benign or malignant

Mixed tumors

- They are tumors which appear to be composed of both epithelial and connective tissues because of divergent differentiation of a single neoplastic clone.

- It is made up of more than one cell type derived from a single germ layer.
- Eg Mixed tumor of salivary gland(Pleomorphic Adenoma)

Teratoma

- They are neoplasms with more than one cell type arising from more One germ layer.
- Teratomas originate from totipotent germ cells normally present in ovaries and testis.
- They differentiate along different germ layers producing fat, muscle, epithelium, any body tissue
- E.g Ovarian Cystic teratoma (dermoid cyst)

Special Nomenclature

- Malignant tumors that sound benign
  - Lymphoma
  - Mesothelioma
  - Melanoma
  - Seminoma
  - Astrocytoma/glioma

- **Blastoma:** tumors arising from immature tissue or nervous tissue. most of them are malignant e.g. medulloblastoma, retinoblastoma, nephroblastoma

Special Nomenclature

- Non-tumors that sound like tumors
  - **Hamartoma** –A focal growth that resembles a neoplasm but results from faulty development of the organ
  - E.g chondroma of the lung, adenoma of the liver
  - **choristoma** – heterotopic rest of cells.
  - A mass of histological normal tissue found in an abnormal location.
  - E.g mass of pancreatic tissue found in submucosal of the stomach,douodemum;

classification of tumors

Table 7.1 Nomenclature of Tumors

Tissue of Origin	Benign	Malignant
Composed of One Parenchymal Cell Type		
Tumors of Mesenchymal Origin		
Connective tissue and derivatives	Fibroma Lipoma Chondroma Osteoma	Fibrosarcoma Liposarcoma Chondrosarcoma Osteogenic sarcoma
Vessels and Surface Coverings		
Blood vessels	Hemangioma	Angiosarcoma
Lymph vessels	Lymphangioma	Lymphangiosarcoma
Mesothelium	Benign fibrous tumor	Mesothelioma
Brain coverings	Meningioma	Invasive meningioma
Blood Cells and Related Cell Types		
Hematopoietic cells		Leukemias
Lymphoid tissue		Lymphomas
Muscle		
Smooth	Leiomyoma	Leiomyosarcoma
Striated	Rhabdomyoma	Rhabdomyosarcoma

Tumors of Epithelial Origin		
Stratified squamous	Squamous cell papilloma	Squamous cell carcinoma
Basal cells of skin or adnexa		Basal cell carcinoma
Melanocytes	Nevus	Malignant melanoma
Epithelial lining of glands or ducts	Adenoma Papilloma Cystadenoma	Adenocarcinoma Papillary carcinomas Cystadenocarcinoma
Respiratory passages	Bronchial adenoma	Bronchogenic carcinoma
Renal epithelium	Renal tubular adenoma	Renal cell carcinoma
Liver cells	Hepatic adenoma	Hepatocellular carcinoma
Urinary tract epithelium (transitional epithelium)	Transitional cell papilloma	Transitional cell carcinoma
Placenta epithelium	Hydatidiform mole	Choriocarcinoma
Testicular epithelium (germ cells)		Seminoma Embryonal carcinoma

Characteristics of Benign & Malignant Tumor

- Differentiation and Anaplasia
- Rate of growth
- Local invasion
- Metastasis
- Clinical or gross features
- Microscopic features

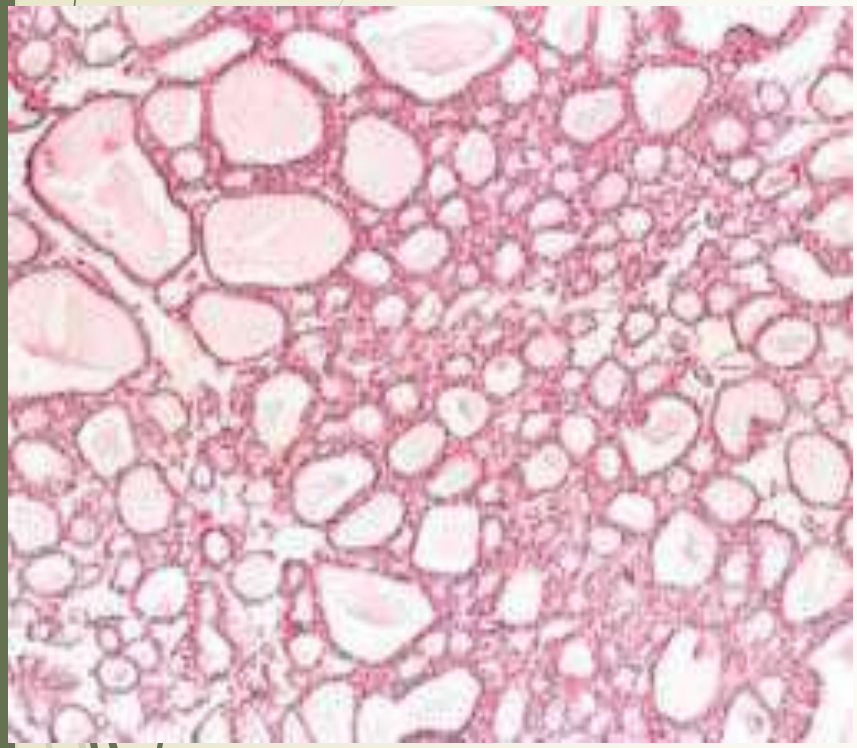
Differentiation And Anaplasia

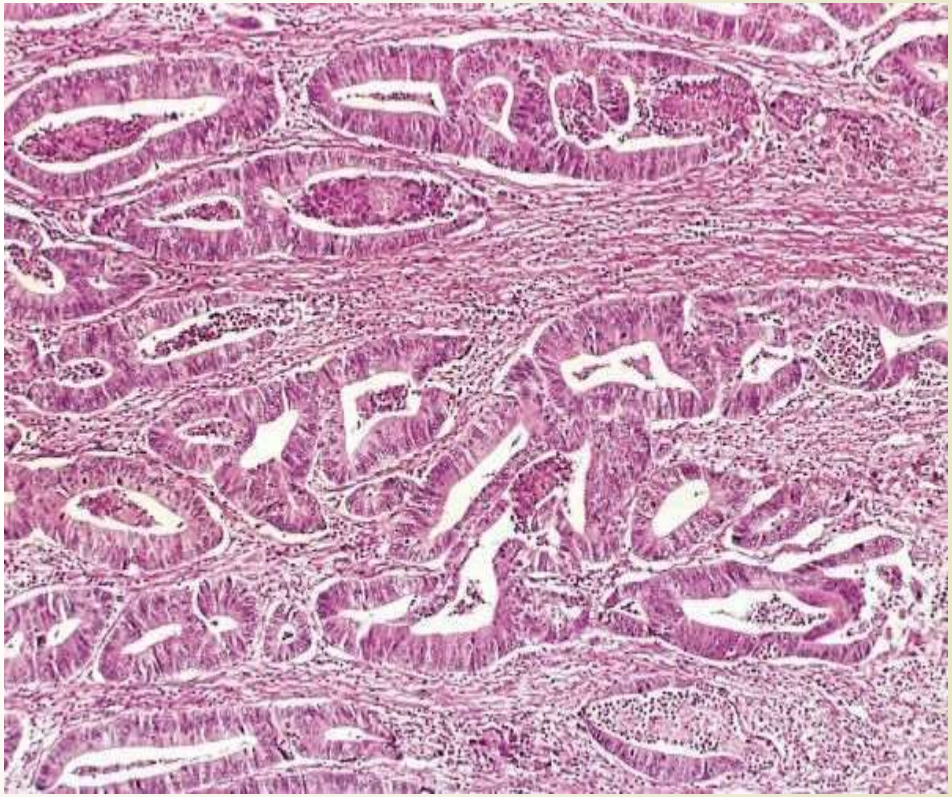
- Differentiation is the extent to which neoplastic parenchymal cells resemble the corresponding normal parenchymal cells, both morphologically and functionally

- Lack of differentiation is called **Anaplasia**
- This is the hallmark of malignancy

- Benign tumors are well-differentiated
- Malignant tumours are usually poorly differentiated and anaplastic

Tubular adenoma and adenocarcinoma



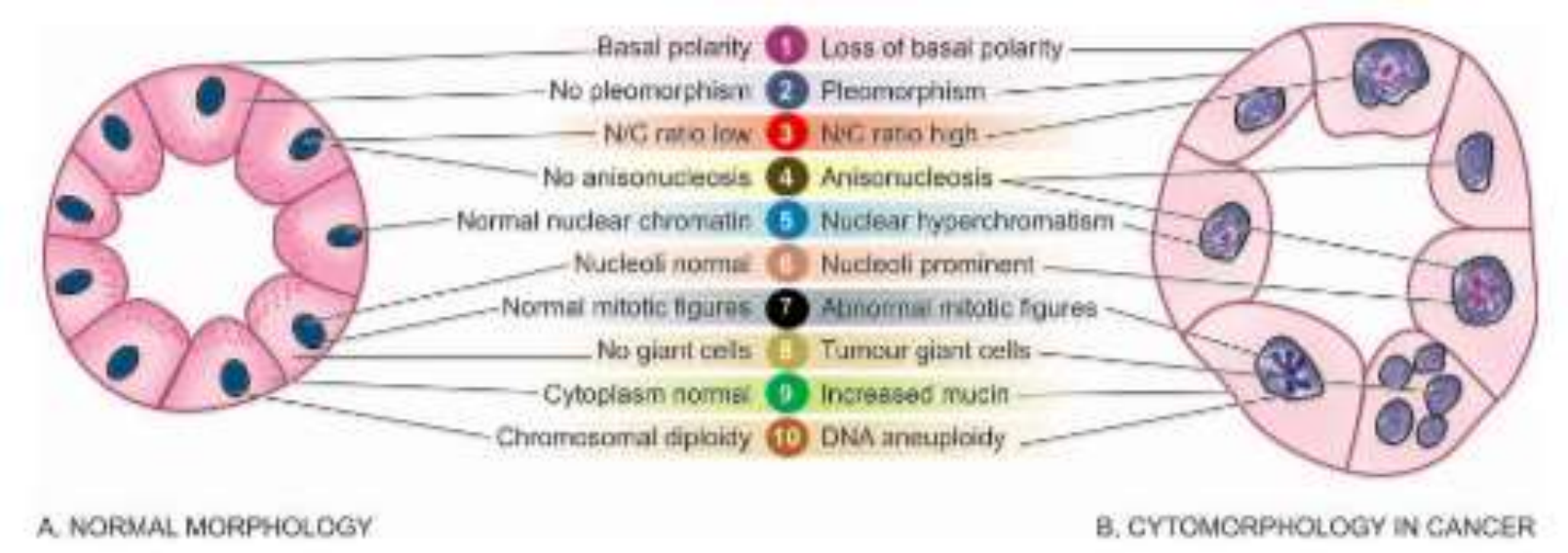


Differentiation And Anaplasia

- The Morphologic changes associated with Anaplasia are:-

  - Pleomorphism
  - Abnormal nuclear morphology
  - Mitosis-Many cells in malignant neoplasm are in mitosis (proliferative activity of the parenchymal cells)
  - Loss of polarity(Loss of orientation, organization and architecture of the cells)
  - Other changes: anisonucleosis

- The better the differentiation of a transformed cell, the more it retains the functional capability of its normal counterpart


Basal polarity
No pleomorphism
N/C ratio low
No anisonucleosis
Normal nuclear chromatin
Nucleoli normal
Normal mitotic figures
No giant cells
Cytoplasm normal
Chromosomal diploidy
1 Loss of basal polarity
2 Pleomorphism
3 N/C ratio high
4 Anisonucleosis
5 Nuclear hyperchromatism
6 Nucleoli prominent
7 Abnormal mitotic figures
8 Tumour giant cells
9 Increased mucin
10 DNA aneuploidy
A. NORMAL MORPHOLOGY
B. CYTOMORPHOLOGY IN CANCER

Rate of growth

The rate at which the tumour enlarges depends upon 2 main factors:

1. Rate of cell production, growth fraction and rate of cell loss
2. Degree of differentiation of the tumour.

- Most benign tumor grow slowly while malignant ones grow much faster eventually spreading locally and to distant sites and causing death.

Local invasion

- A benign tumor remains localized at its site of origin, it does not have the capacity to infiltrate, invade or metastasize to distant site like the malignant tumor does
- Benign tumor develop a rim of fibrous capsule that separates them from the host tissue(due to their slow growth and expansion) to make the tumor more discrete,easily palpable and excisable by local surgical removal.
- Some cancers seem to evolve from pre-invasive stage referred to as carcinoma in-situ e.g found in skin,breast,uterus etc which display the cytologic features of malignancy without invasion of the basement membrane

METASTASIS

- Metastasis is defined by the spread of a tumor to sites that are physically discontinuous with the primary tumour. This marks a tumor as malignant because benign tumors do not metastasize

The likelihood of a primary tumor to metastasize correlates with lack of differentiation, aggressive local invasion,rapid growth and large size

- **Exceptions:** *B*asal cell carcinomas of the skin which rarely metastasizes after invasion

- Metastatic spread strongly reduces the possibility of cure

Comparisons Between Benign and Malignant Tumors

Characteristics	Benign	Malignant
Rate of growth	Usually progressive and slow; may come to a standstill or regress; mitotic figures are rare and normal	Erratic and may be slow to rapid; mitotic figures may be numerous and abnormal
Metastasis	Absent	Frequently present; the larger and more undifferentiated the primary, the more likely are metastases

Compariso
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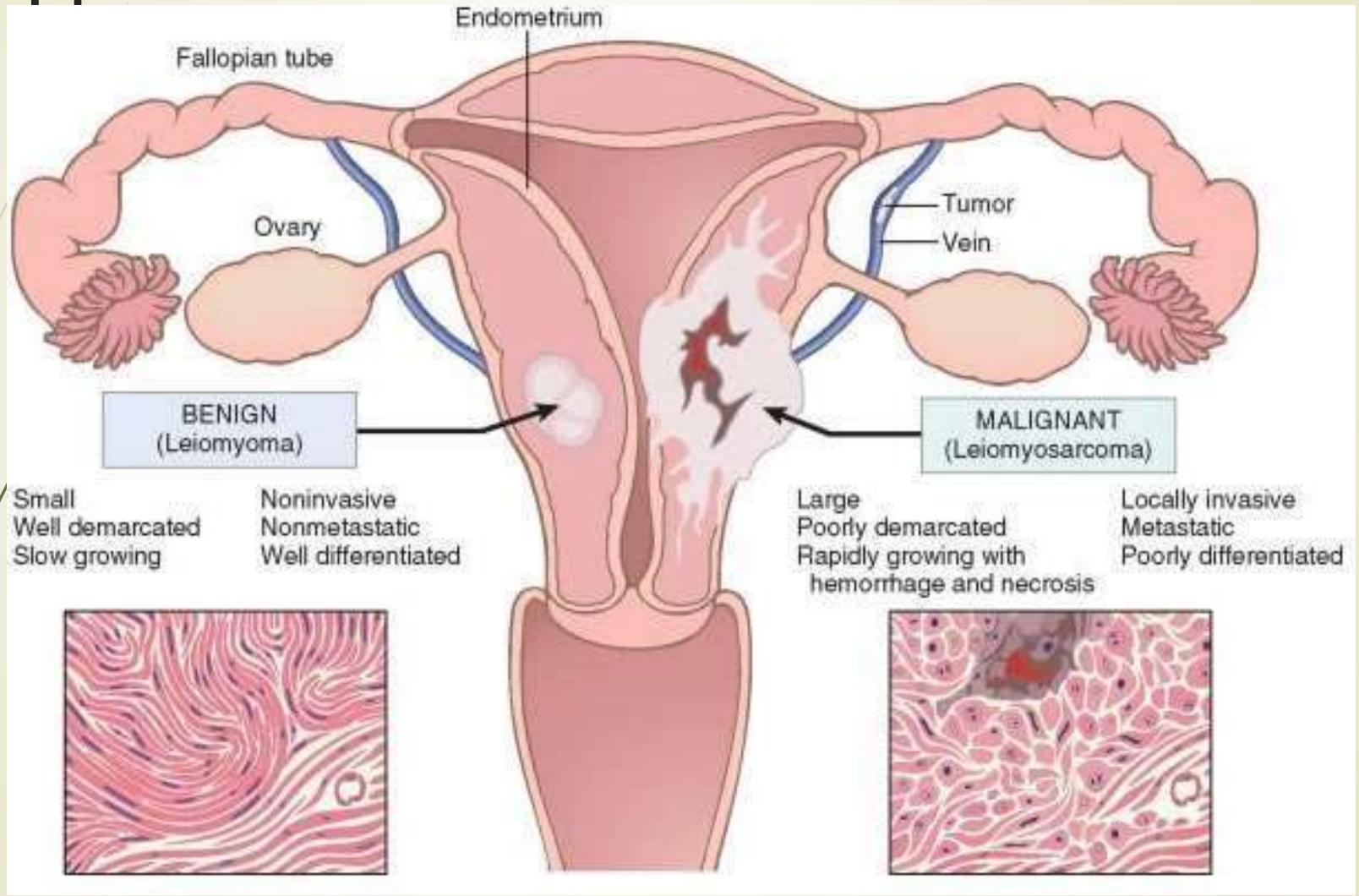

Endometrium
Fallopian tube
Ovary
Tumor
Vein
BENIGN
(Leiomyoma)
MALIGNANT
(Leiomyosarcoma)
Small
Well demarcated
Slow growing
Noninvasive
Nonmetastatic
Well differentiated
Large
Poorly demarcated
Rapidly growing with
hemorrhage and necrosis
Locally invasive
Metastatic
Poorly differentiated

Spread Of Tumors

Metastasis can occur by any of following methods:

- Direct seeding of body cavities or surfaces/Transcoelomic spread(via CSF, epithelium lined surfaces)
- Lymphatic spread
- Blood(haematogenous spread)

Seeding Of Body Cavities & natural passages

- The malignant neoplasm penetrates into a natural ‘’open field’’ lacking physical barriers.

- The most often involved is the peritoneal cavity
- Any other cavity: pericardial, subarachnoid, pleural and joint spaces may be affected

- This pathway is particularly characteristics of carcinomas arising from the ovaries

Transcoelomic spread: Certain cancers invade through the serosal wall of the coelomic cavity so that tumour fragments or clusters of tumour cells break off to be carried in the coelomic fluid and are implanted elsewhere in the body cavity.

Spread along epithelium-lined surfaces: unusual for a malignant tumour to spread along the epithelium-lined surfaces because intact epithelium and mucus coat are quite resistant to penetration by tumour cells.
Eg the fallopian tube from the endometrium to the ovaries or vice-versa;

Spread via cerebrospinal fluid: Malignant tumour of the ependyma and leptomeninges may spread by release of tumour fragments and tumour cells into the CSF

Implantation: a tumour may spread by implantation by surgeon's scalpel, needles, sutures, or may be implanted by direct contact such as transfer of cancer of the lower lip to the apposing upper lip.
It is rare

Lymphatic spread

- It is the principal mode by which carcinoma spread but sarcomas may also use this route.
- Wall of lymphatics is thin and can be readily penetrated by tumor cell tissue which is carried along to the sentinel node in the lymphatic node chain

⑩ Carcinomas may reach the thoracic duct and enter the superior vena cava from which further spread through the blood stream may occur

Pathways of spread: Lymphatic

- Tumors spread is by the nearby lymphatic vessels(regional lymph node)
- Follows natural routes of drainage e.g carcinomas of breast from outer upper quadrant will first drain into the axillary lymph nodes.
- **Sentinel lymph node**: first node to receive flow from the primary tumor

- LN enlargement may be caused by:-

  -growth of cancer cells

  -reactive hyperplasia; may limit the cancer growth

Haematogenous spread

- Haematogenous spread is typical of sarcomas but is also seen with carcinomas
- Thick walled arteries are resistant to invasion but the veins are readily penetrated
- With venous invasion, the blood borne tumour cells follow the venous flow draining the site of neoplasm, and the tumour cells often rest in the 1st capillary bed they encounter
- The **LIVER** and the **LUNGS** are most frequently involved in hematogenous dissemination because **all portal area drainage flows to the liver and all vena cava blood flows to the lungs**
- **Brain, bones, kidney and Adrenals** are also frequently involved

- Not all systemic distributions of metastases follows the natural pathway of venous drainage
  For example:-
- Breast and prostate carcinoma preferentially spreads to the bone
- Bronchogenic carcinomas tend to involve the adrenals and the brain
- Although well vascularized, the skeletal muscle and spleen are rarely sites of metastasis

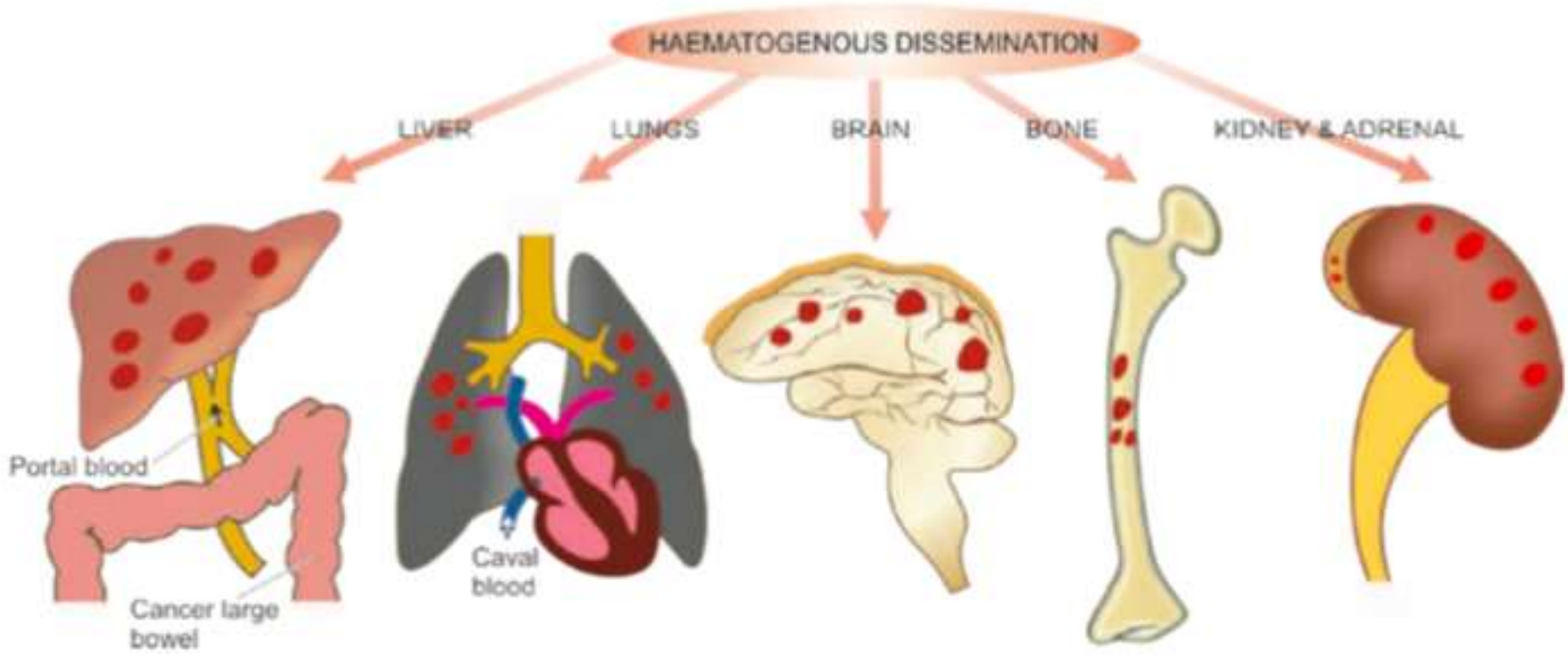
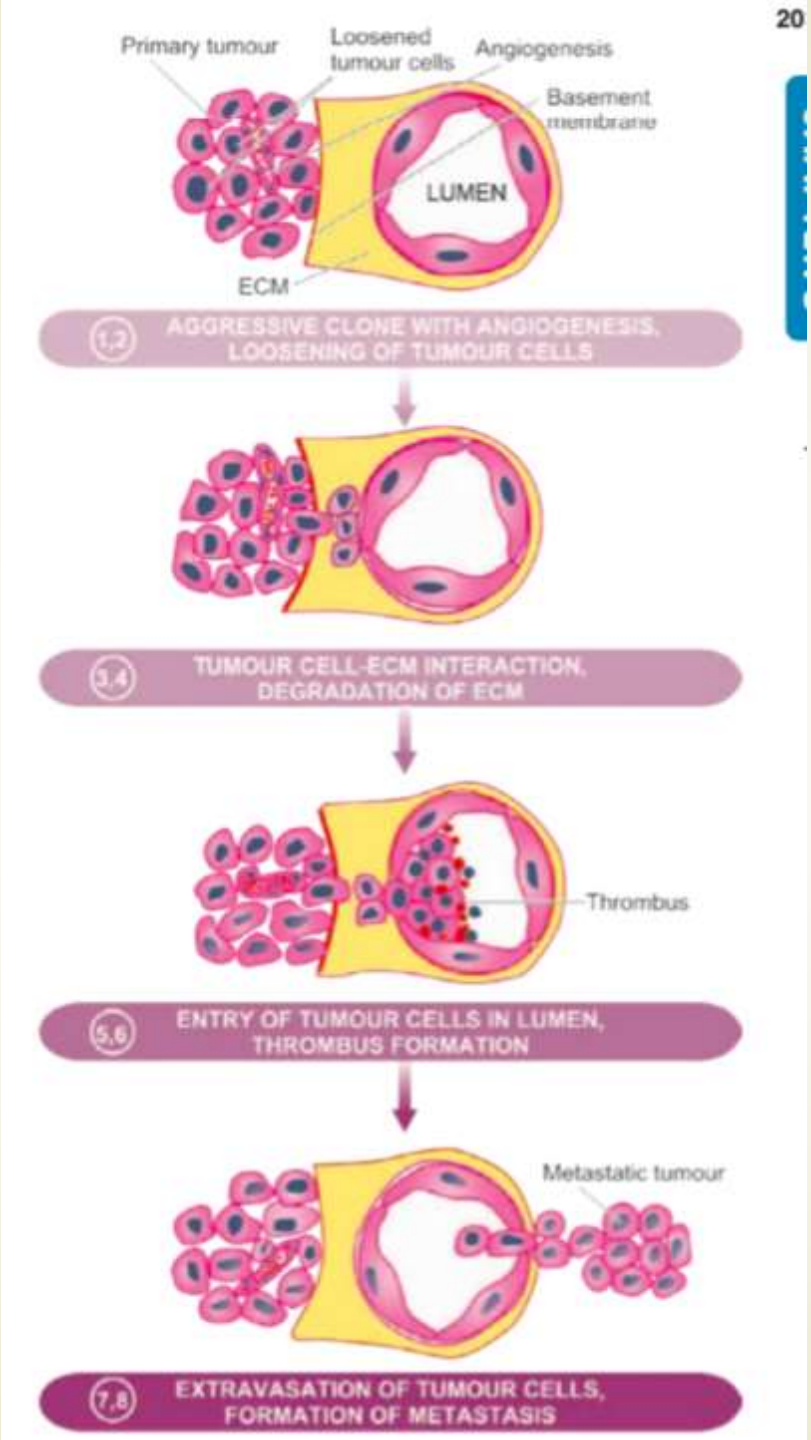


Figure 8.13 Gross appearance of haematogenous metastases at common sites.

Mechanism of metastasis

- The metastatic cascade is divided into 2 phases:
- (a) Invasion of the Extracellular matrix
- (b) Vascular dissemination, homing of tumor cells, and colonization

- This includes making the passage by the cancer cells by dissolution of extracellular matrix (ECM) at three levels— at the basement membrane of tumour itself, at the level of interstitial connective tissue, and at the basement membrane of microvasculature.


Primary tumour
Loosened tumour cells
Angiogenesis
Basement membrane
LUMEN
ECM
1,2
AGGRESSIVE CLONE WITH ANGIOGENESIS, LOOSENING OF TUMOUR CELLS
3,4
TUMOUR CELL-ECM INTERACTION, DEGRADATION OF ECM
Thrombus
5,6
ENTRY OF TUMOUR CELLS IN LUMEN, THROMBUS FORMATION
Metastatic tumour
7,8
EXTRAVASATION OF TUMOUR CELLS, FORMATION OF METASTASIS

Invasion of the ECM

- Invasion of the ECM initiates the metastatic cascade and it involves the following steps:
- Detachment of tumor cells from each other(loss of E cadherin).
- Degradation of ECM (Basement membrane and interstitial connective tissue)
- attachment of tumor cells to ECM proteins(nectin, fibronectin)
- Migration and invasion of tumor cells

- Within circulation, tumor cells tend to aggregate in clumps to enhance their survival & implantability.

- This is favoured by:

- Homotypic adhesion among tumor cells
- Heterotypic adhesion between tumor cells and blood cells, particularly platelets
- Tumor cells may also bind & activate coagulation factors, resulting in the formation of tumor-emboli

Vascular dissemination & homing of tumour cells

- Intravasation of tumor cells involves;
  - Adhesion molecules
  - Proteolysis of B.M of blood vessels

- Once in circulation, tumor cells are vulnerable to destruction by a variety of mechanisms:

(a)Mechanism of shear stress

b)Anoikis- Apoptosis of cells in circulation due to loss of adhesion

c)Innate and adaptive immune defences

- Arrest and Extravasation of tumor emboli at distant sites involves:

➢ Adhesion to vascular endothelium via **adhesion molecules** e.g Integrins, Laminin receptors and(**CD44 adhesion molecules** which is used by normally T- cells to migrate to selective sites in the lymphoid tissue).

➢ Migration through the B.M is by proteolytic enzymes

HOMING OF TUMOR CELLS

- The site at which circulatating tumor cells leave the capillaries to form secondary deposits is related to the :-

(a) Anatomic location and vascular drainage of the primary tumor:

Most metastases occurs in the 1st capillary bed available to the tumor

(b)The **tropism** of particular tumors for specific tissues.

ORGAN TROPISM

- Organ tropism may be related to the following mechanisms:-
- Affinity of organ for neoplastic cells by their endothelial cells expressing ligands for tumor cell receptors.
- Some target organs may liberate chemoattractants that invite tumor cells at that site
- E.g-some breast cancer express the chemokine receptors-CXCR4 and CCR7
- Some target tissues may be unpermissive i.e unfavourable soil, for the growth of tumor cells seedlings. E.g skeletal muscles and spleen

Tumor grading and staging

- ‘Grading’ and ‘staging’ are the two systems to predict tumour behaviour and guide therapy after a malignant tumour is detected.
- Grading is defined as the gross and microscopic degree of differentiation of the tumour
- Staging means extent of spread of the tumour within the patient.

GRADING OF TUMOR

- This is the description of the tumor based on the degree of differentiation of the tumor cells. i.e based on the extent to which tumor cells resemble their normal counterpart when a biopsy of tissue is viewed under a microscope
- It is an indication of how quickly a tumor is likely to grow and spread
- Well differentiated tumor tends to grow and spreads slowly than poorly & undifferentiated ones

CLASSIFICATION OF TUMOUR GRADE

- The grading is largely based on 2 important histologic features: the degree of anaplasia, and the rate of growth

- The generalized one used is:
- Gx :- Grade cannot be assessed(undetermined grade)
- G1:- Well differentiated(Low grade): less than 25% anaplastic cells
- G2:- Moderately differentiated(Intermediate grade): 25-50% anaplastic cells
- G3:- Moderately-differentiated (50-75% anaplastic cells): Grows rapidly
- G4:- Poorly differentiated(High grade): more than 75% anaplastic cells

Grading

- Some cancers are graded differently.
- Breast cancer: By the Nottingham grading system(score ranging from 3-9)
- Prostate cancer:By Donald Floyd Gleason scoring system (score ranging from 2 -10)
- Renal cell carcinoma:- By Fuhrman system

- More objective criteria for histologic grading include use of flow cytometry for mitotic cell counts, cell proliferation markers by immunohistochemistry.

STAGING OF TUMOR

- Staging is a way of describing the size of cancer and its extent of spread into surrounding tissues or to other parts of the body.
- The extent of spread of cancers can be assessed by 3 ways: by clinical examination, by investigations, and by pathologic examination of the tissue removed.
- Two important staging systems currently followed are: TNM staging and AJC staging.
- The major staging system currently in use is the American Joint Committee On Cancer Staging.

THE TNM STAGING SYSTEM

- TNM stands for:
- T= primary **T**umor,
- N= regional lymph **N**ode and
- M= **M**etastases

- This system uses number to describe the cancer.
- T0 to T4: In situ lesion to largest and most extensive primary tumour.
- N-refers to whether it has spread to the lymph nodes.
- N0 means no nodal involvement
- N1-N3 would denote involvement of an increasing number and range of nodes.
- M0 signifies no distant metastasis whereas M1 or M2 indicates the presence of metastases

AJC staging: American Joint Committee staging divides all cancers into stage 0 to IV, and takes into account all the 3 components (primary tumour, nodal involvement and distant metastases) in each stage.

Modern techniques(non-invasive).
computed tomography (CT) and magnetic resonance imaging (MRI) scan based on tissue density for locating the local extent of tumour and its spread to other organs.

Positron emission tomography (PET) scan: has overcome the limitation of CT and MRI scan because PET scan facilitates distinction of benign and malignant tumour on the basis of biochemical and molecular processes in tumours.

Radioactive tracer studies: in vivo such as use of iodine isotope 125 bound to specific tumour antibodies
small number of tumour cells in the body can be detected by imaging of tracer substance bound to specific tumour antigen.

Importance of staging

- Staging is important to help us know the type of treatment to give.
- If cancer is in just one place, a local treatment such as surgery or radiotherapy could get rid of it completely.
- But if it has spread, systemic treatment such as chemotherapy, hormone therapy & biological therapy that circulates throughout the body will be needed.
- Staging is of a greater clinical value.

Chronic Non-neoplastic(Pre-malignant) Conditions

Carcinoma in situ (intraepithelial neoplasia): When the cytological features of malignancy are present but the malignant cells are confined to epithelium without invasion across the basement membrane

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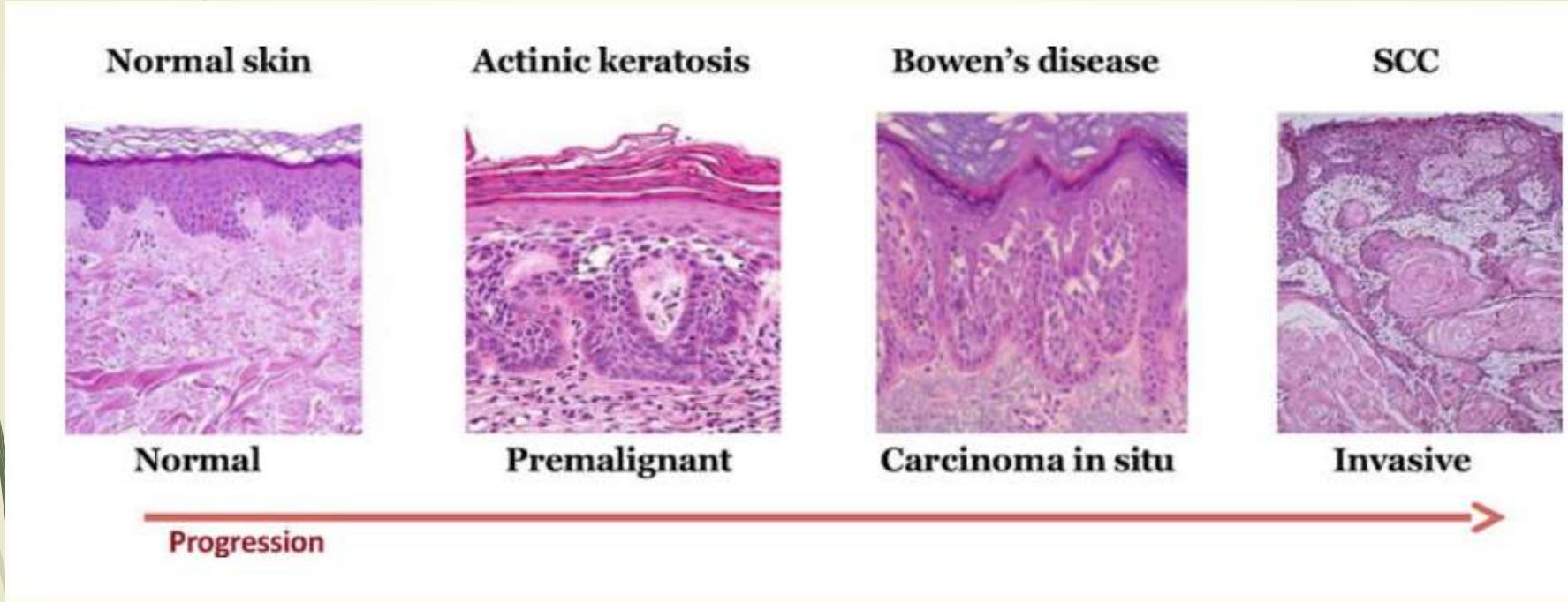

Normal skin
Actinic keratosis
Bowen's disease
SCC
Normal
Premalignant
Carcinoma in situ
Invasive
Progression

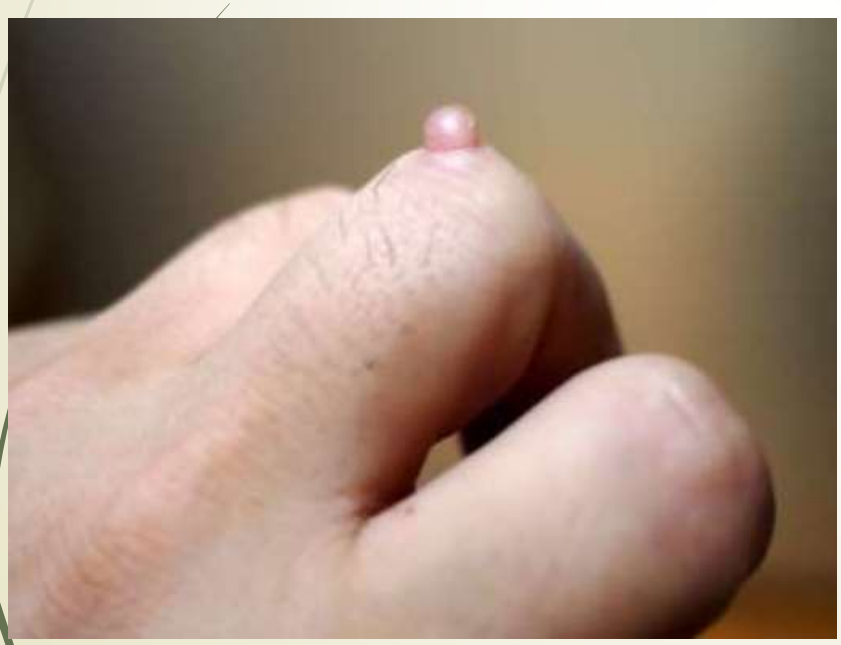
Certain inflammatory and hyperplastic conditions are prone to development of cancer

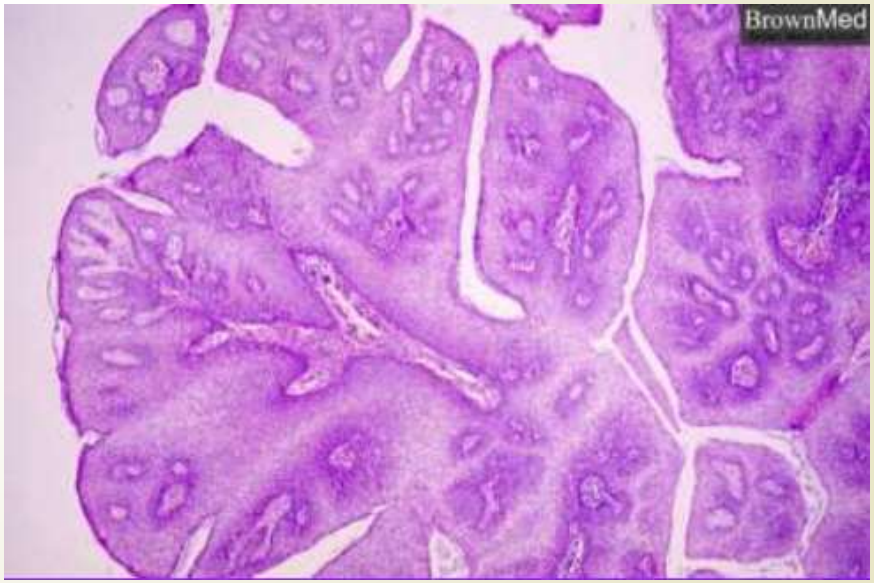
Cirrhosis of the liver has predisposition to develop hepatocellular carcinoma

Chronic bronchitis in heavy cigarette smokers may develop cancer of the bronchus.

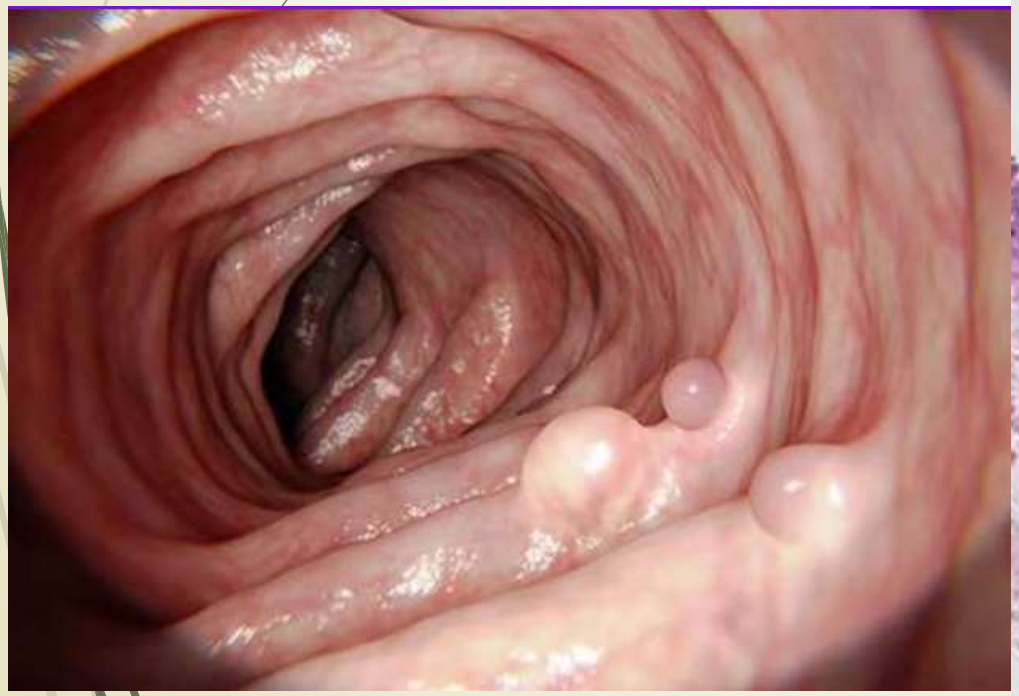
Squamous cell carcinoma developing in an old burn scar (Marjolin's ulcer)

Papillomas are benign epithelial neoplasms, growing on any surface with fingerlike fronds.

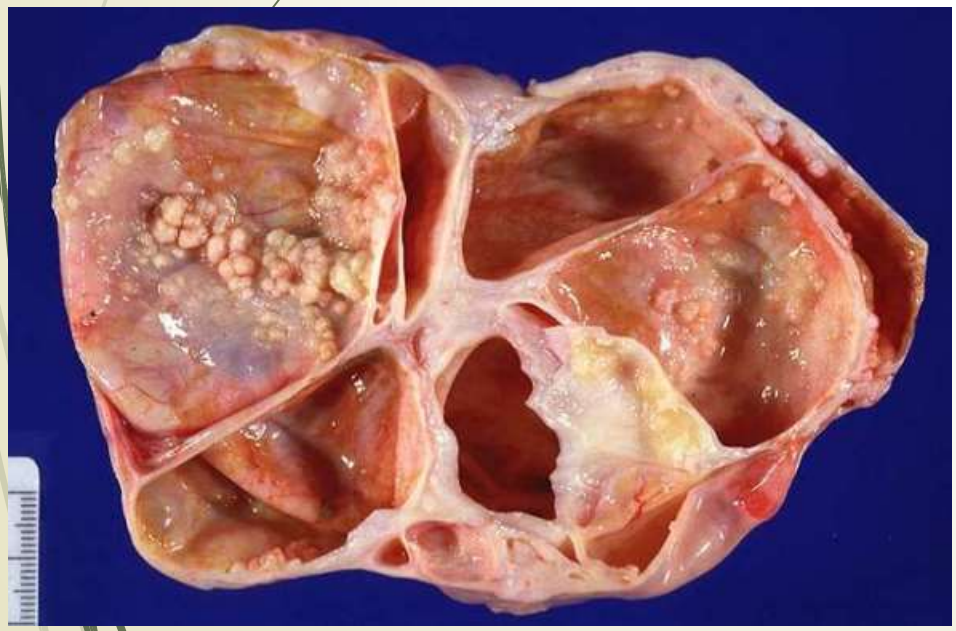


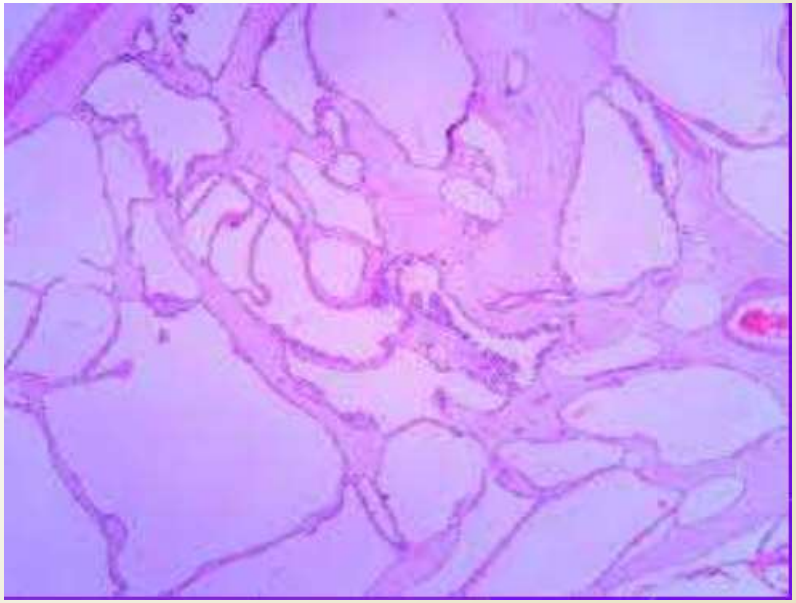


A polyp is a mass that ptojects above a mucosal surface, as in the gut

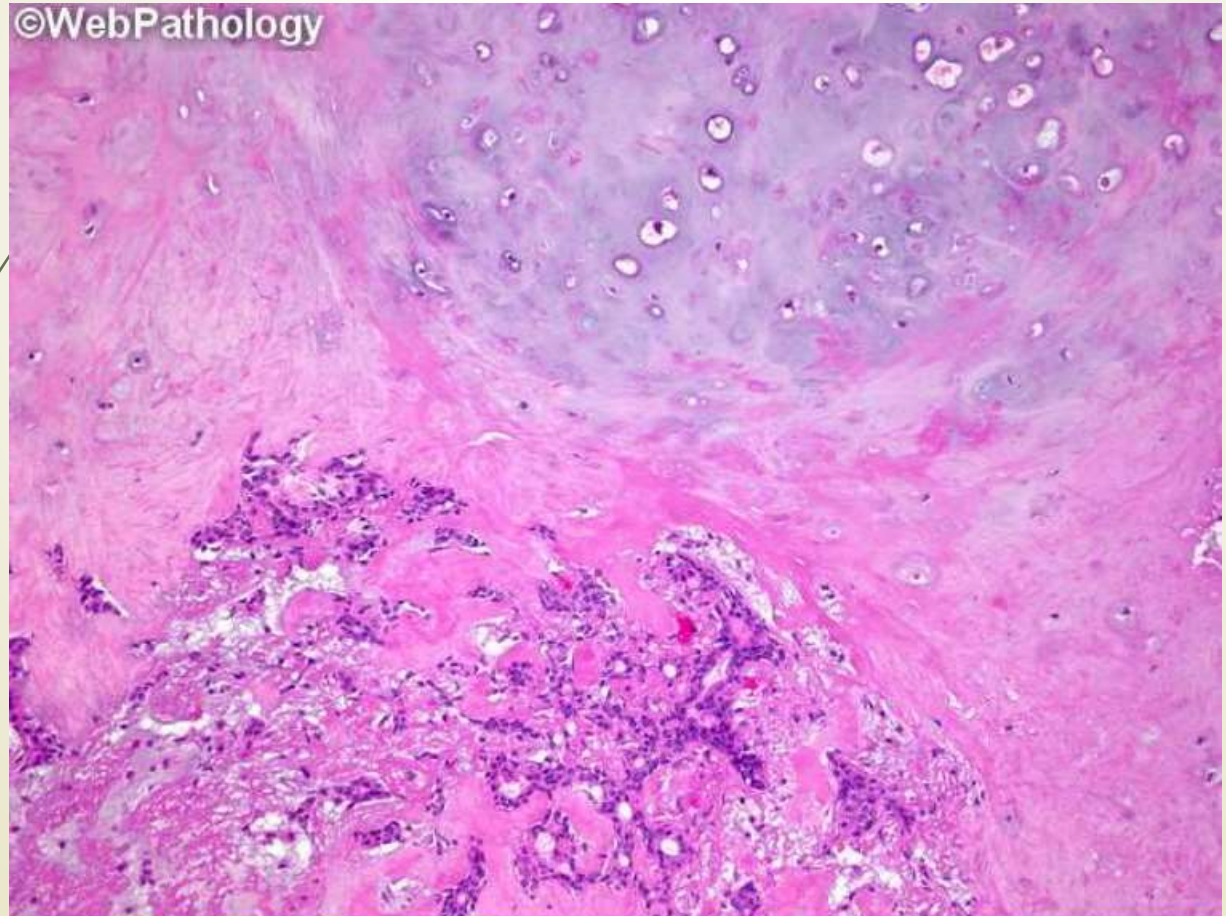


Cysadenomas are hollow cystic masses that typically arise in the ovary

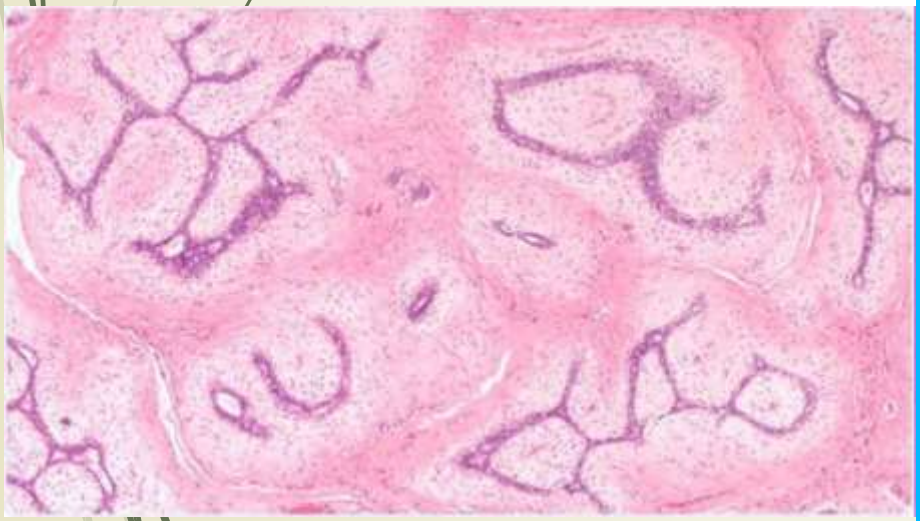


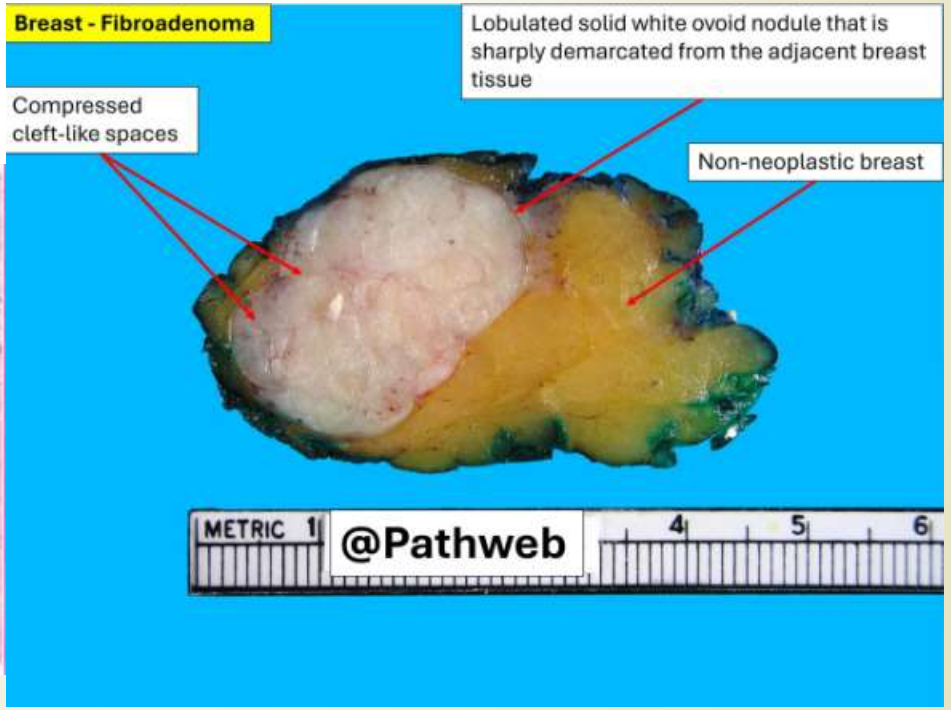


mixed tumor of salivary gland= pleomorphic adenoma It contain epithelial components with islands of cartilage or bone.

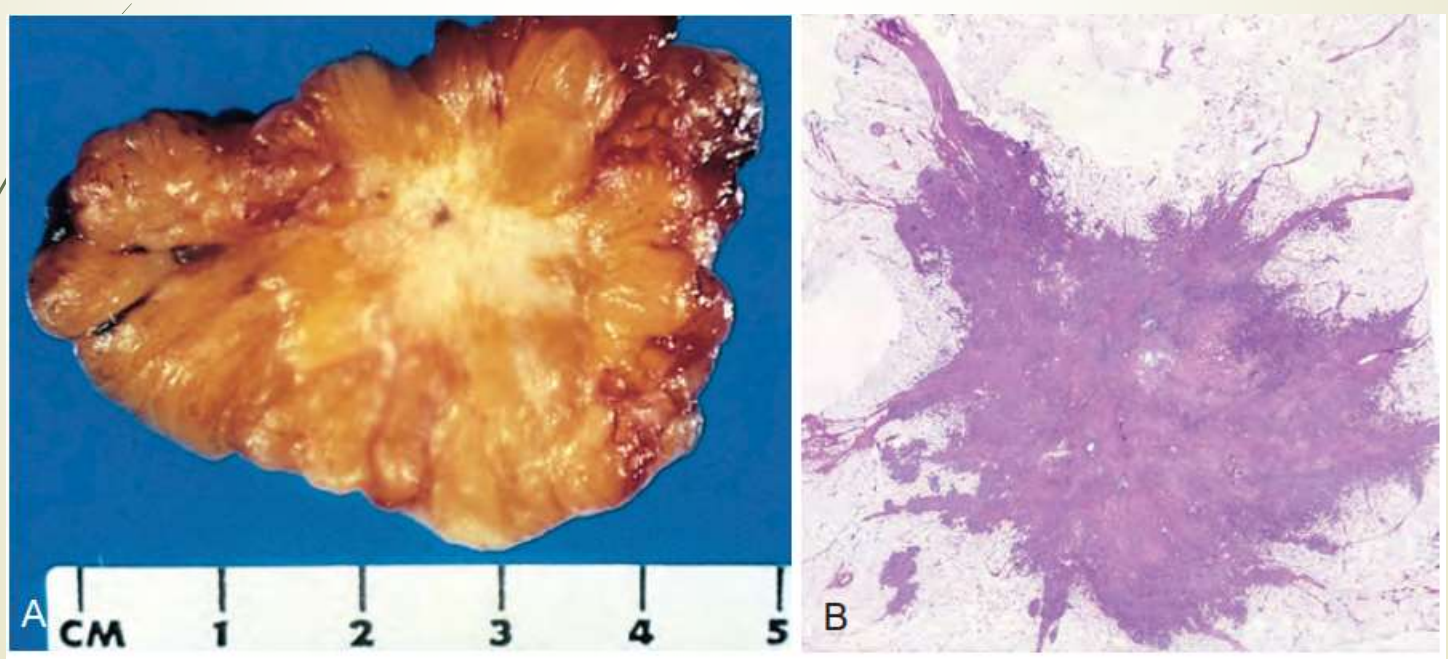


Fibroadenoma of the female breast contain: proliferating ductal elements (adenoma) embedded in loose fibrous tissue.

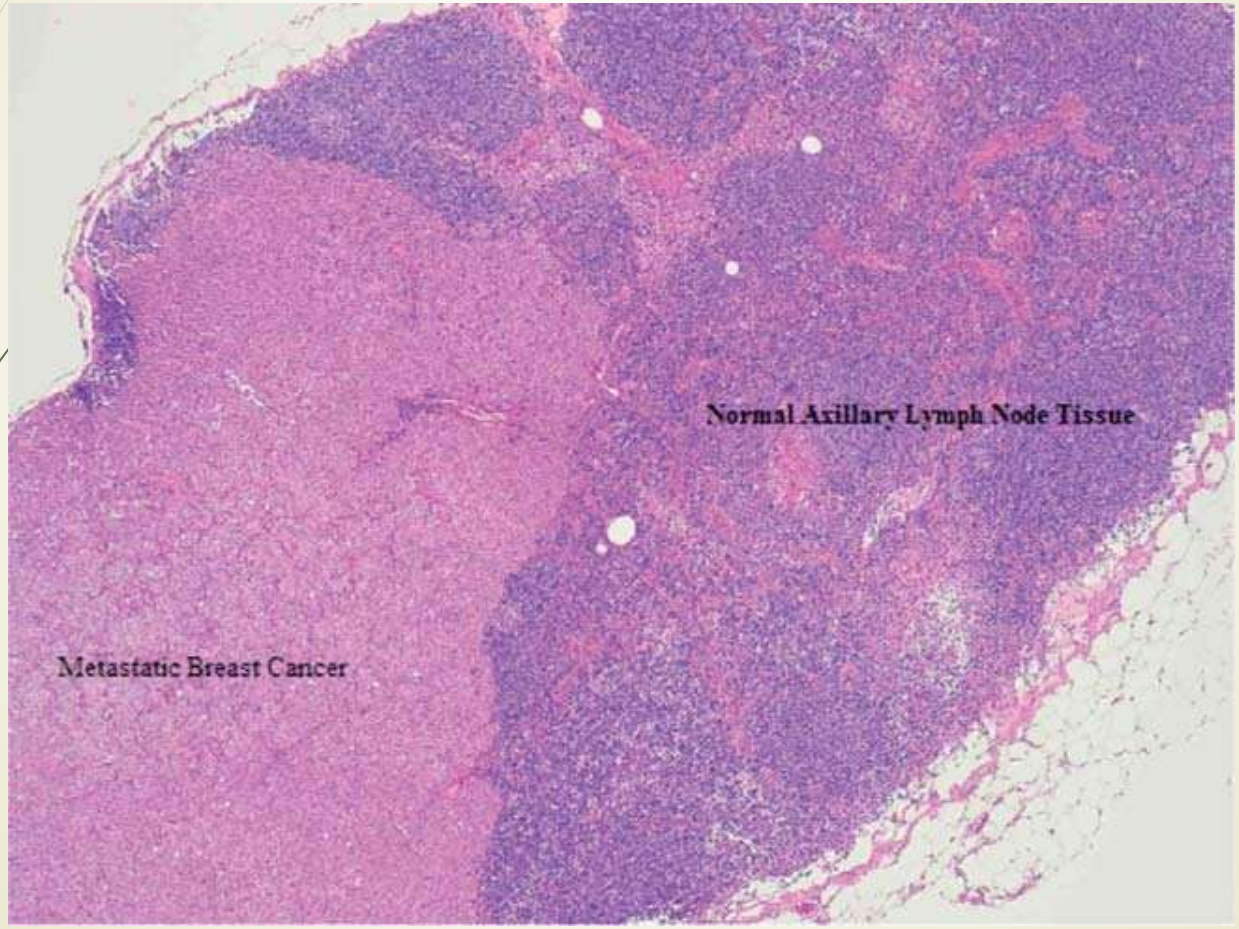




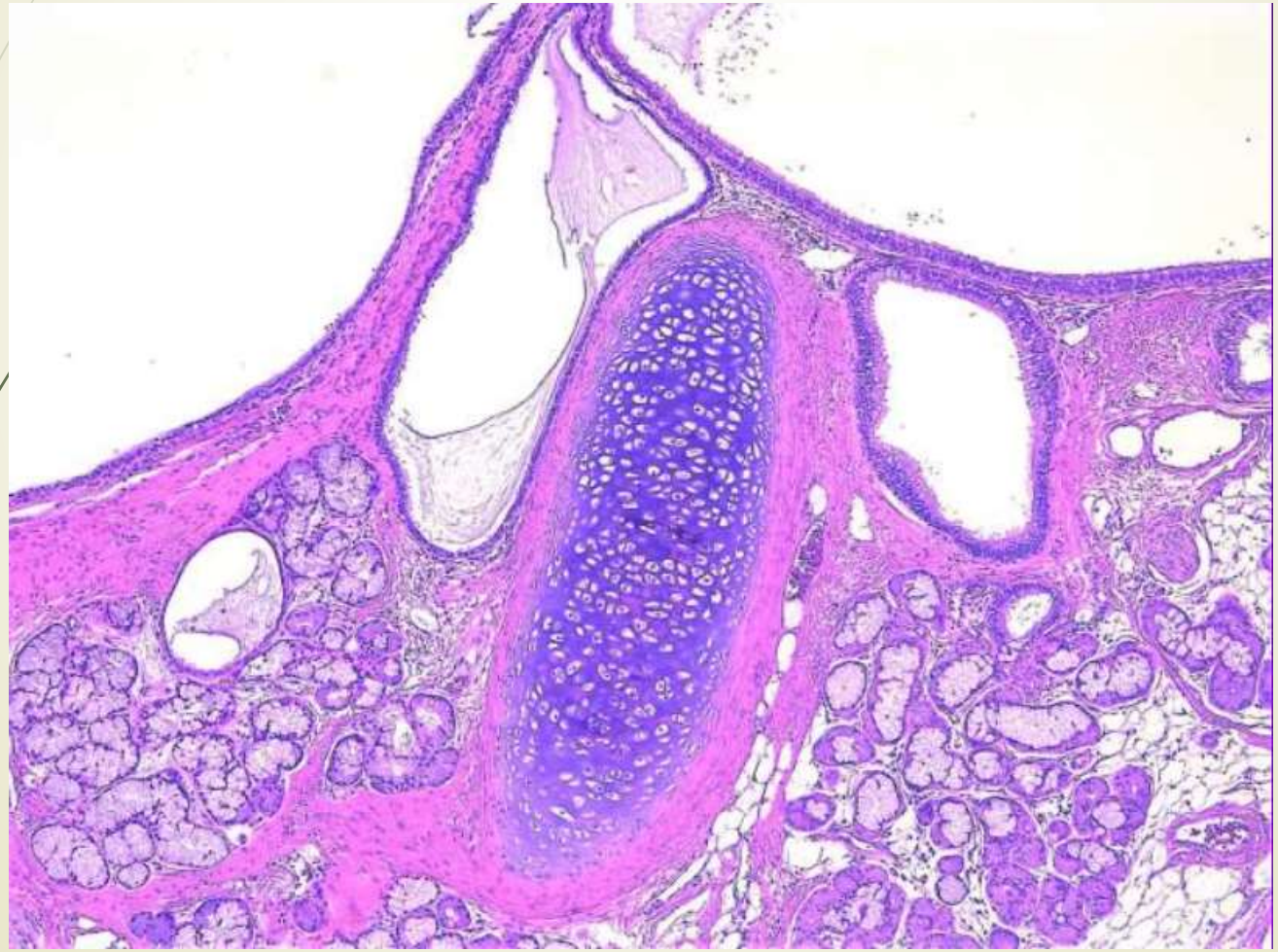
Breast, Invasive ductal carcinoma



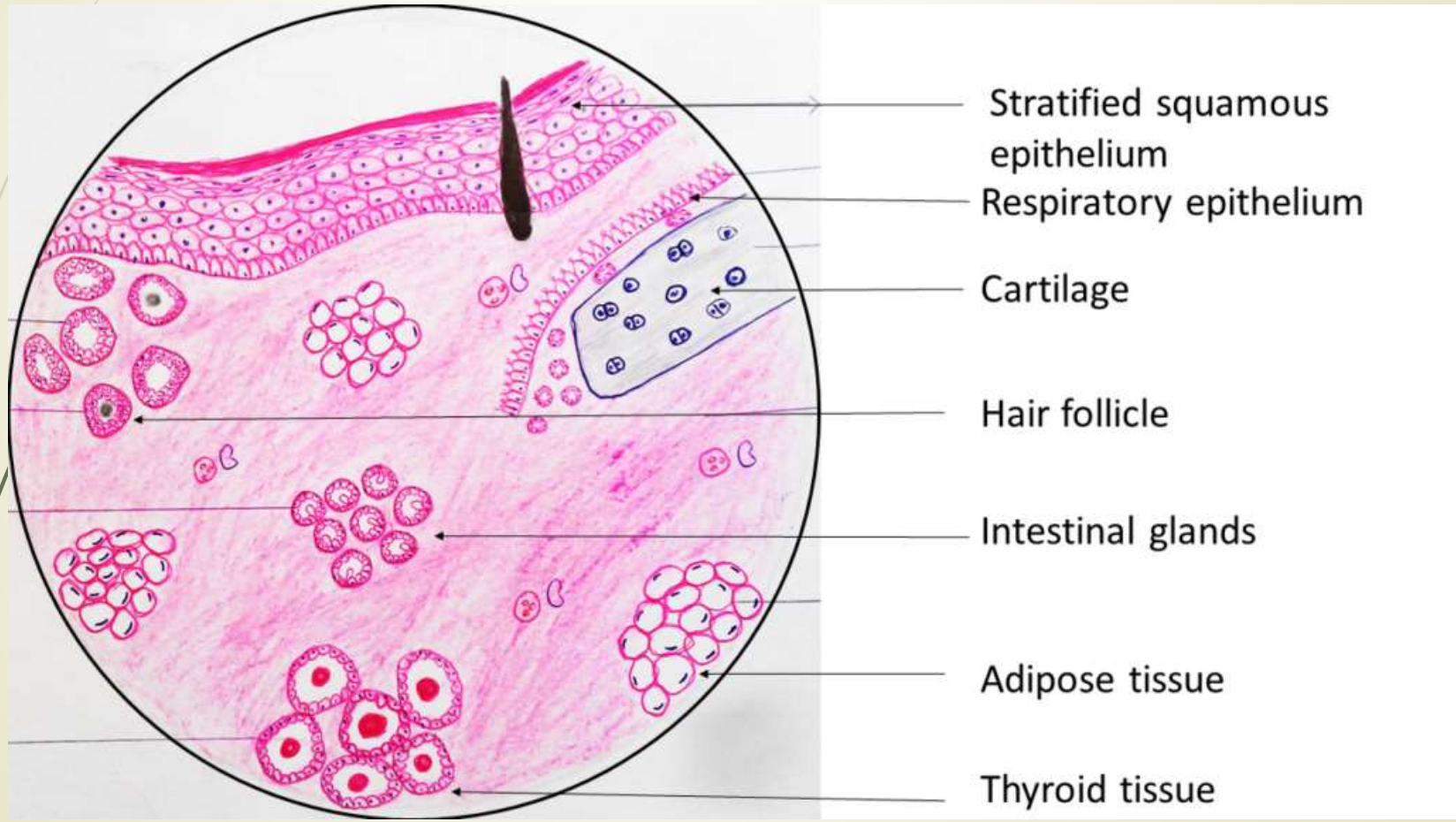
Axillary lymph node with metastatic breast carcinoma



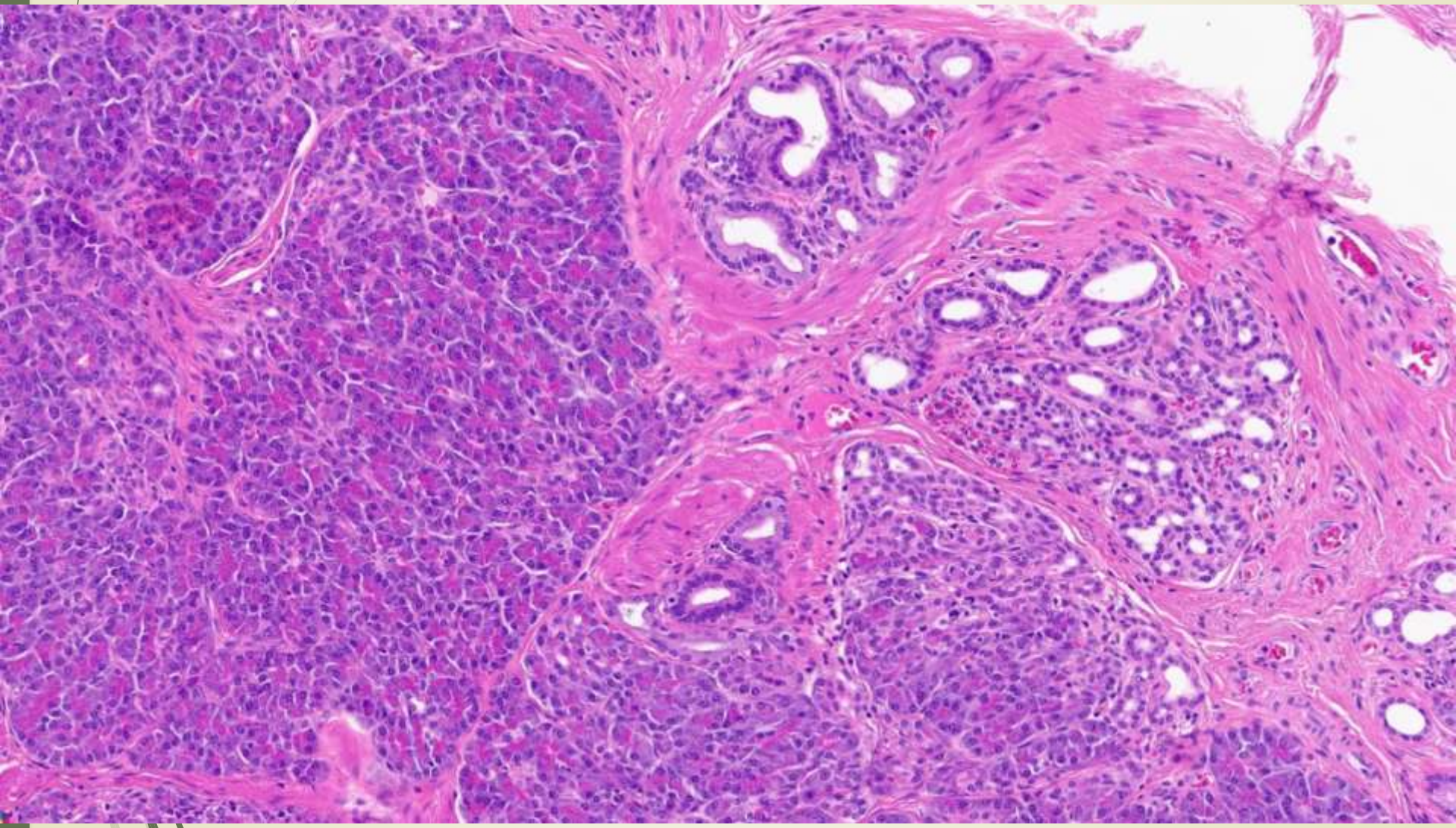
Teratoma: mixture of benign mature tissues



Mature teratoma



Choristoma



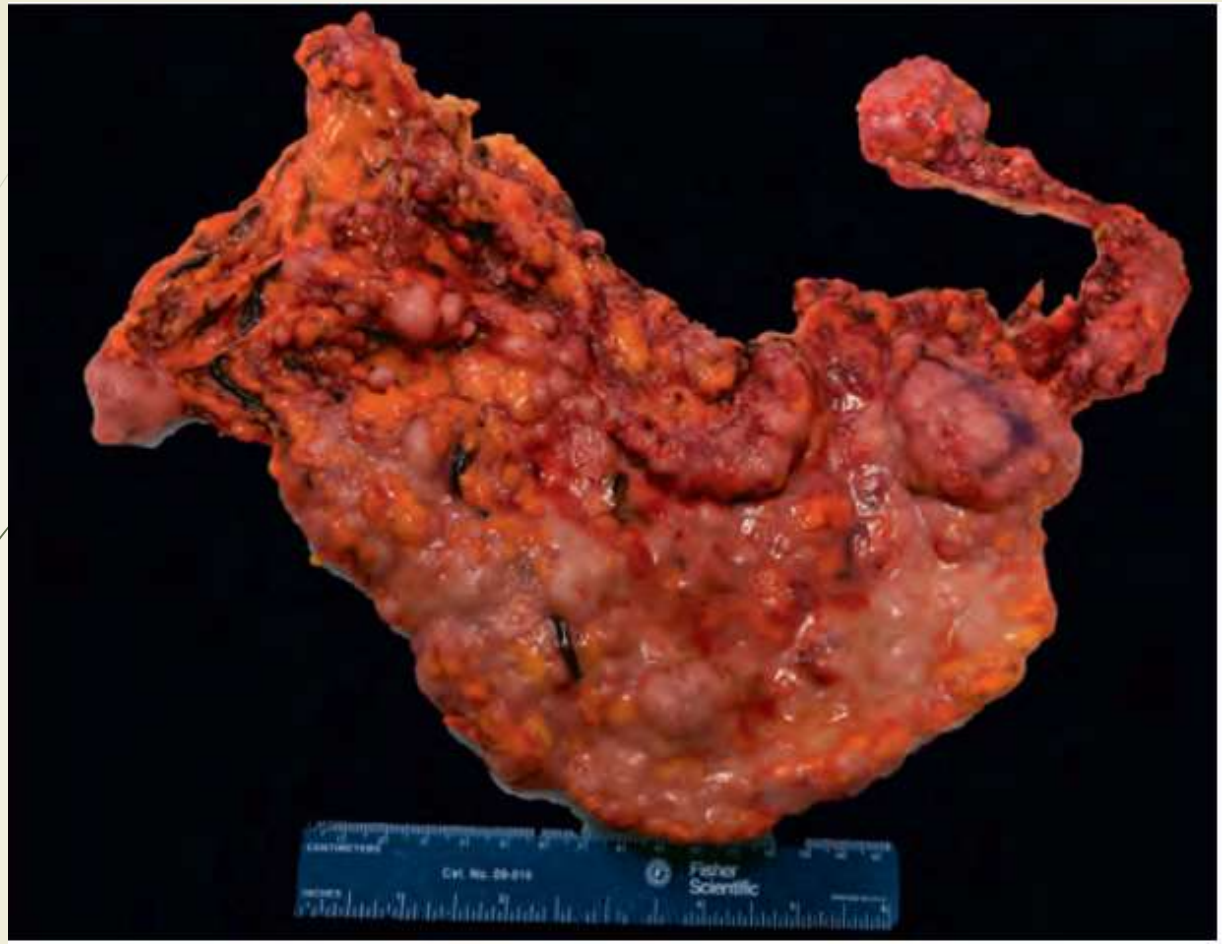
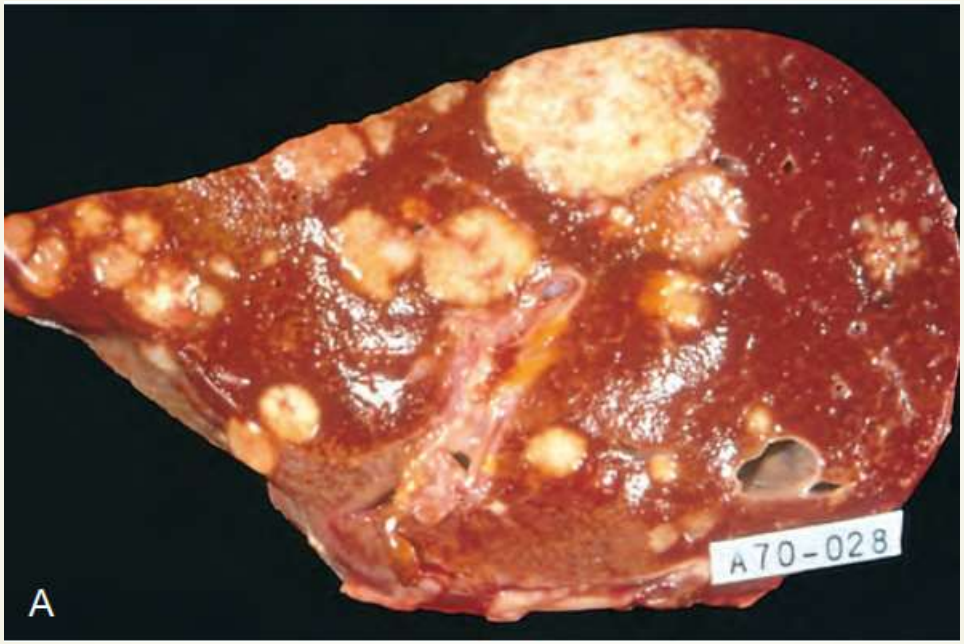
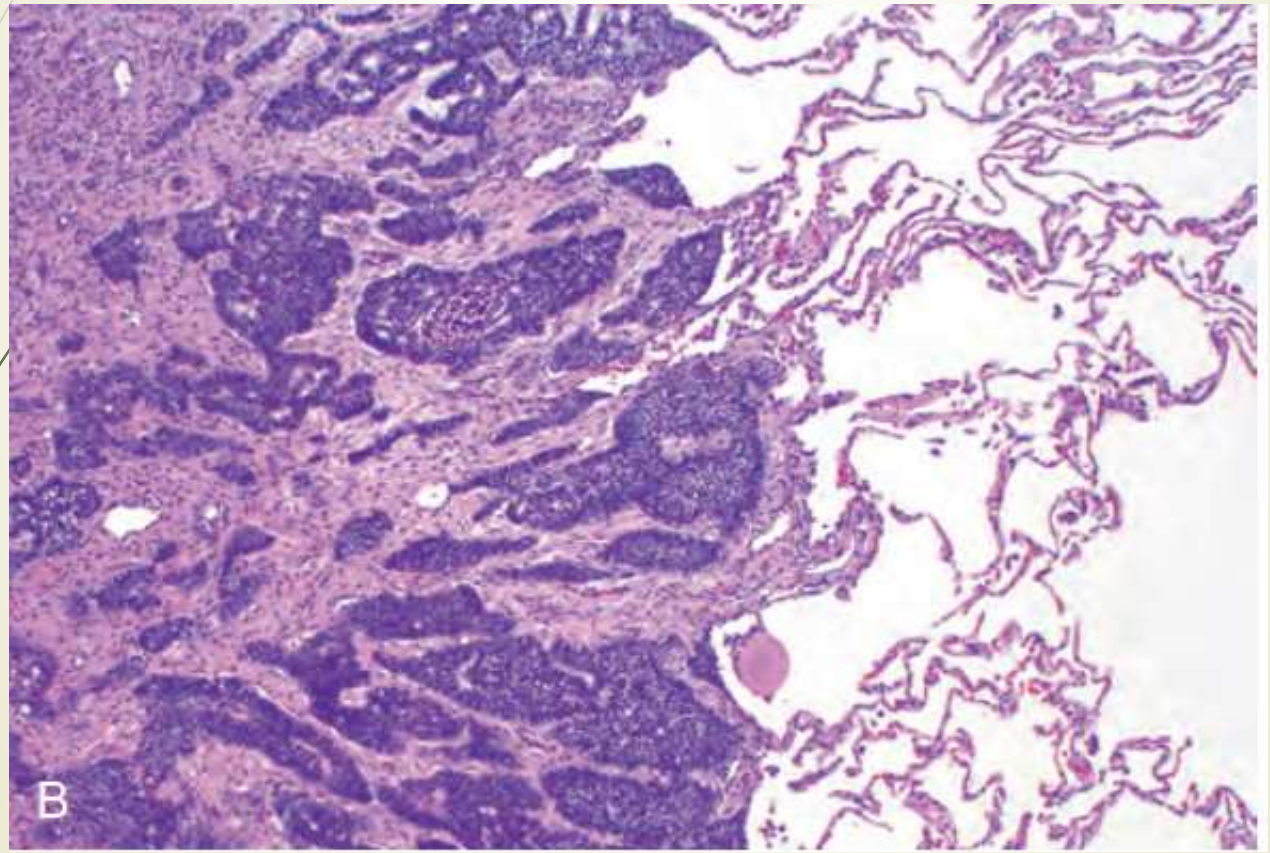


Figure 7.13 Involvement of omentum by metastatic ovarian carcinoma. Innumerable nodules and more subtle "glazing" are evident due to seeding by carcinoma cells via the peritoneal cavity. (Courtesy Dr. Sarah Hill, Brigham and Women's Hospital, Boston, Mass.)

Liver, metastatic cancer



Colonic adenocarcinoma metastasis to the lung



Normal vs Carcinoma in situ