ONCOLOGY I.

Csaba Bödör

Department of Pathology and Experimental Cancer Research

2020-11-09, MED-III.

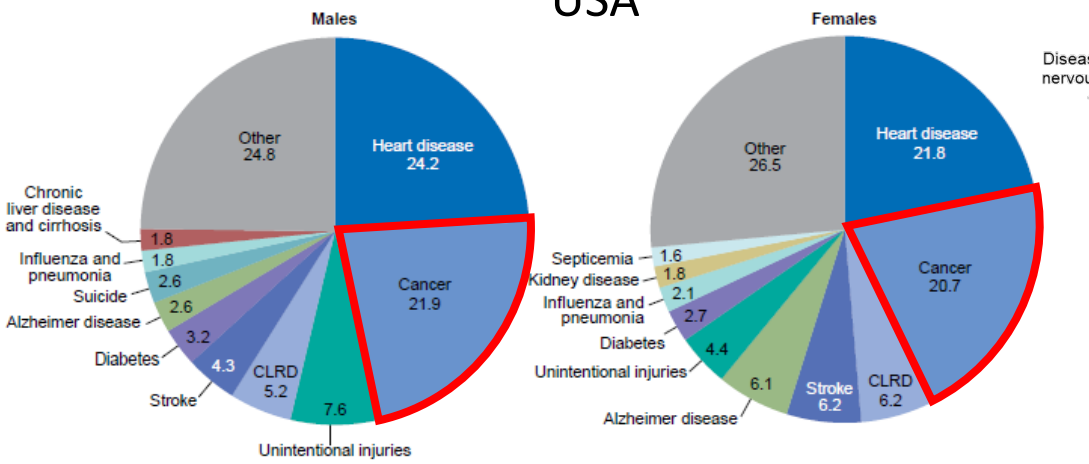
bodor.csaba1@med.semmelweis-univ.hu

ONCOLOGY

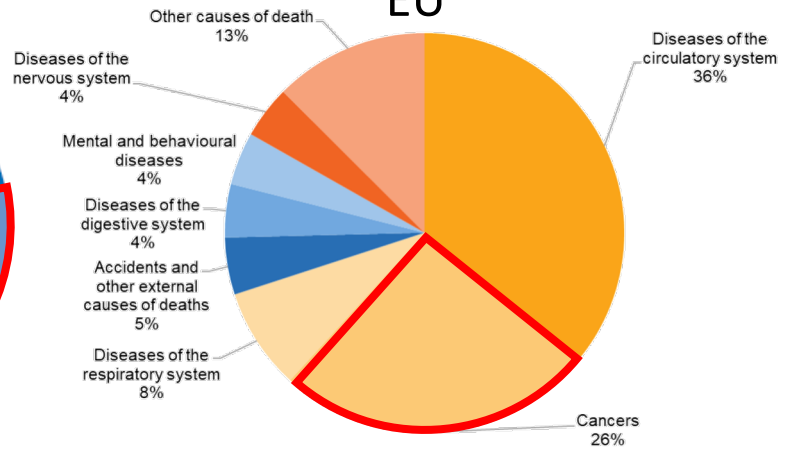
- **Characteristics of benign and malignant neoplasms**
- Molecular mechanism involved in cancer development
- Epidemiology of cancer, preneoplastic disorders
- Diagnosis and treatment of cancer
- Microbiology, chemical and radiation carcinogenesis, Tumor immunity

Cancer : Second leading cause of death in western world

USA



EU

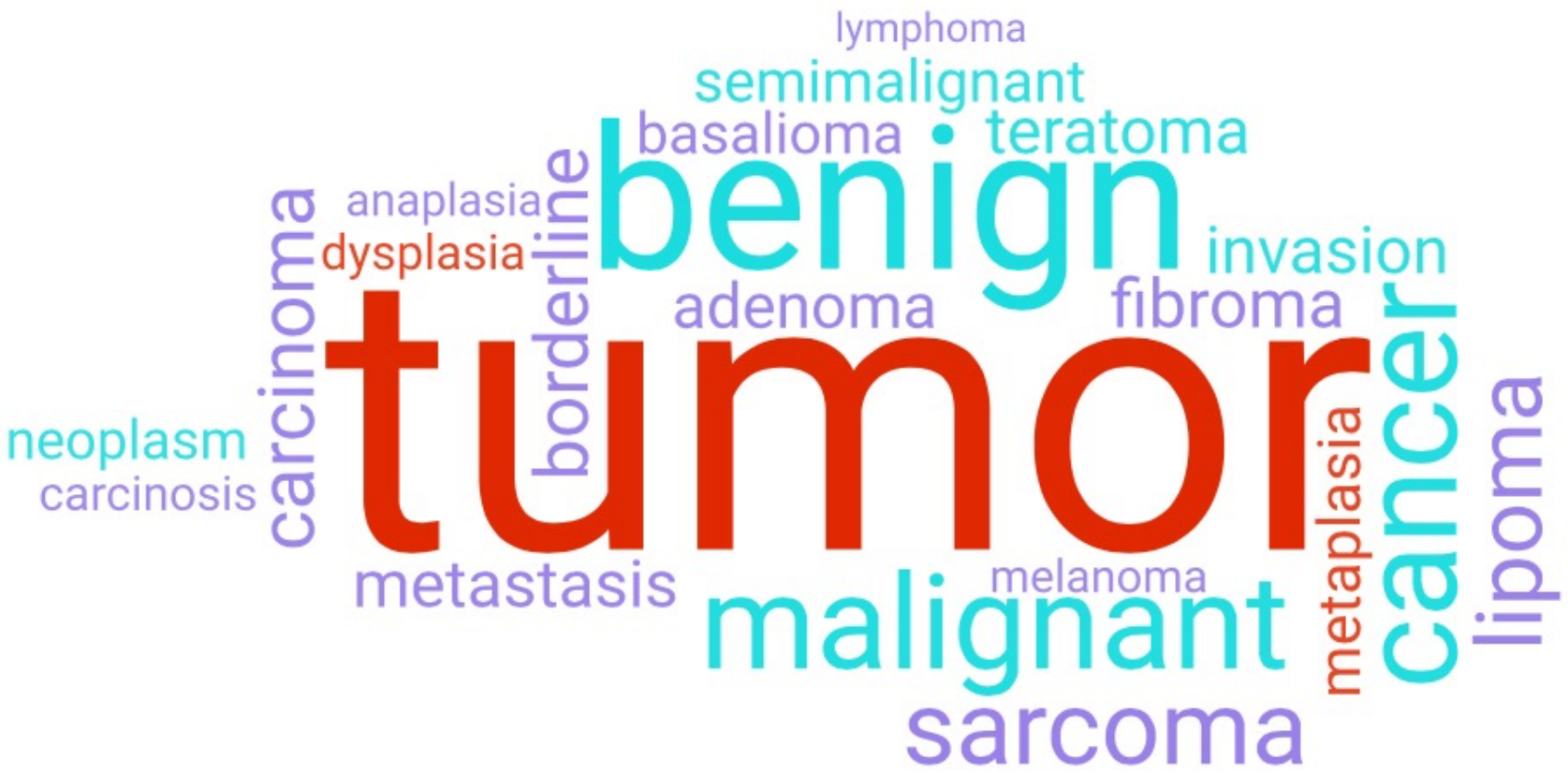


National Vital Statistics Reports, Vol. 68, No. 6, June 24, 2019

ec.europa.eu/eurostat

- Physical and emotional burden
- ‘When will there be a cure for cancer?’

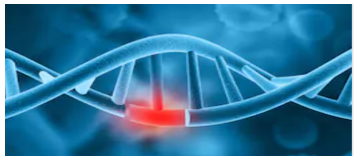
Learning objectives



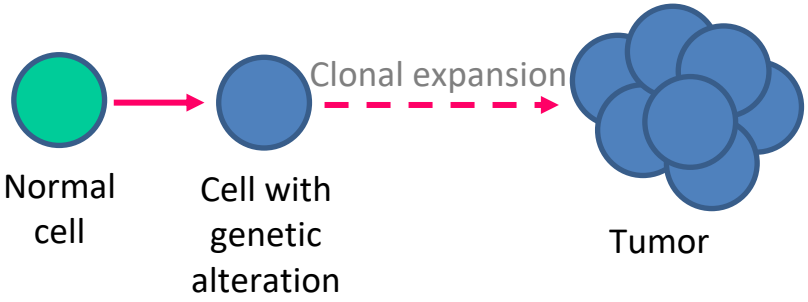
Basic characteristics of tumors

- Abnormal cell growth

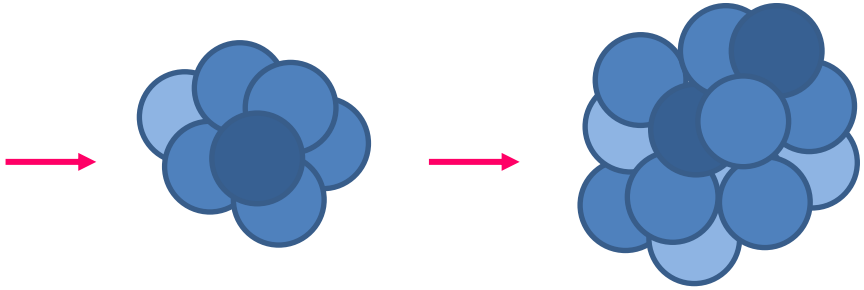
- Genetic disease caused by mutations



- Clonality, growth/survival advantage

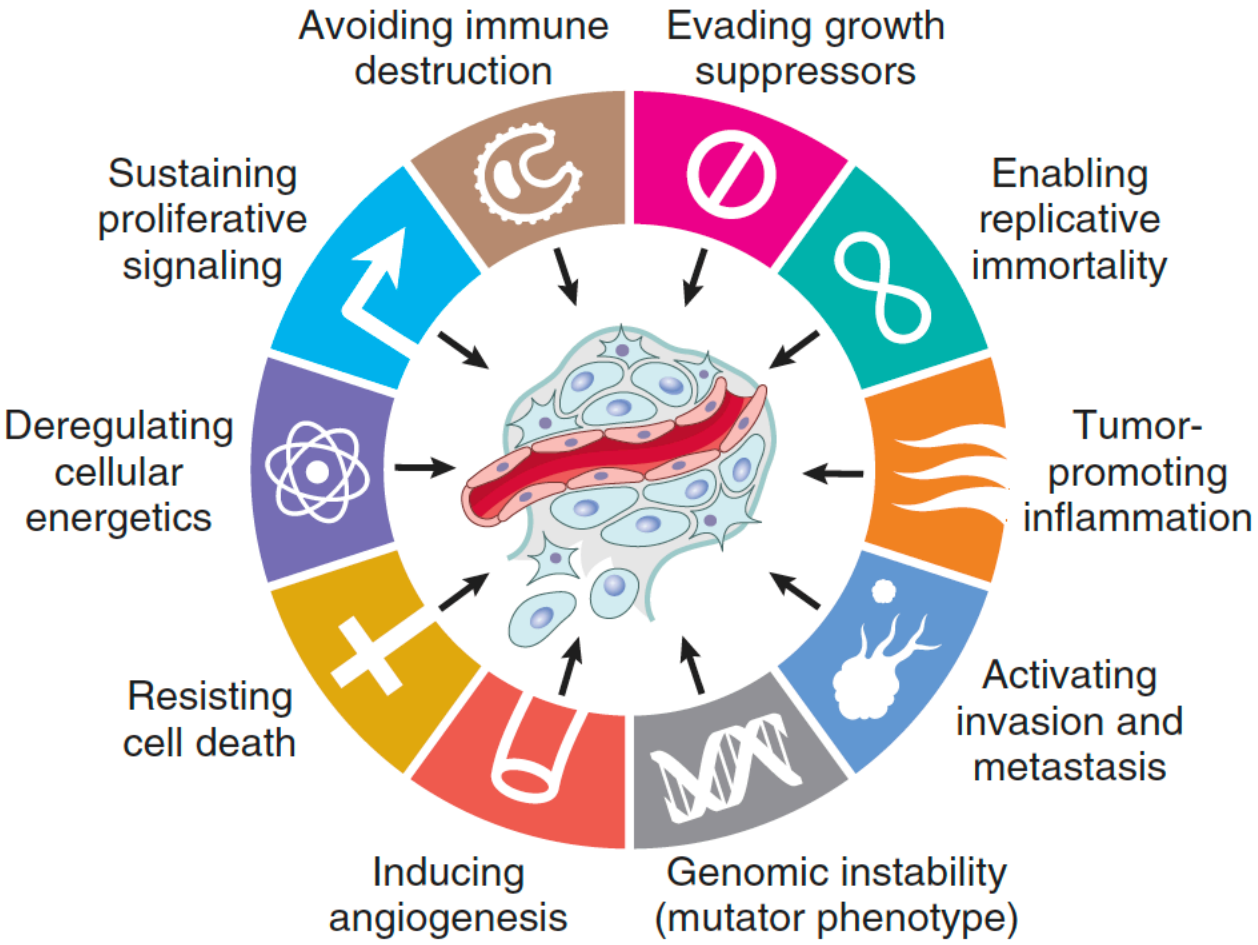


- Genetic alterations passed to daughter cells



- „Cancer hallmarks” (next slide)

Hallmarks of Cancer



(From Hanahan D, Weinberg RA: Hallmarks of cancer: the next generation. Cell 144:646, 2011.)

Oncology I. : Benign and Malignant neoplasms

Neoplasia = tumor ('new growth') resulting from autonomous cell proliferation

- Oncology (oncos=tumor, logos=study of)
- **Benign** and **malignant** tumors
  - based on the tumor's potential clinical behaviour

Benign

- will remain localized, can be removed surgically
- affected patients generally survive

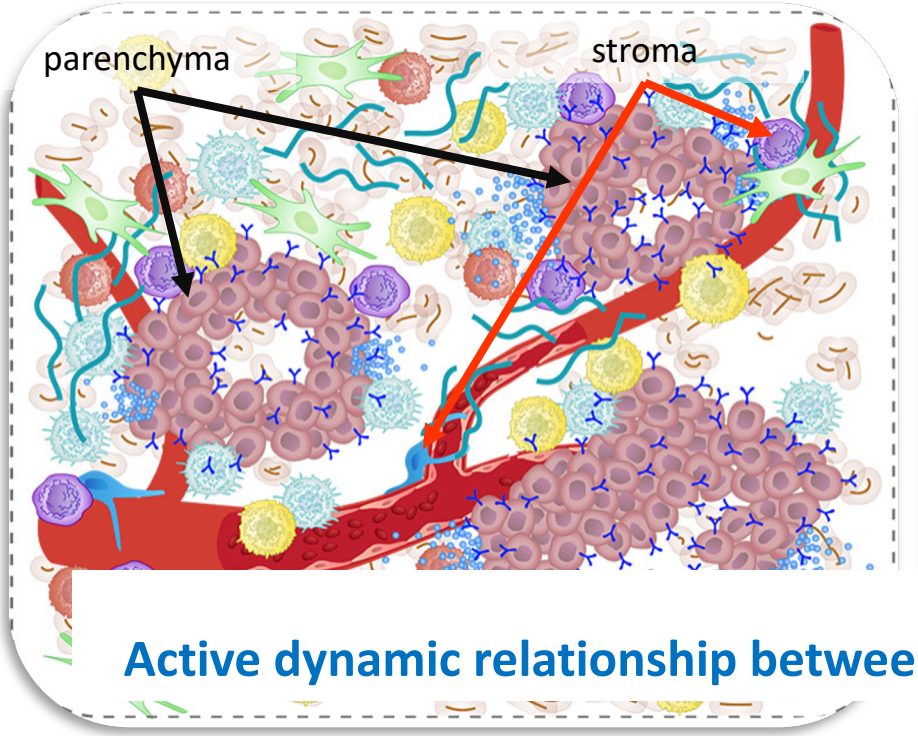
Malignant

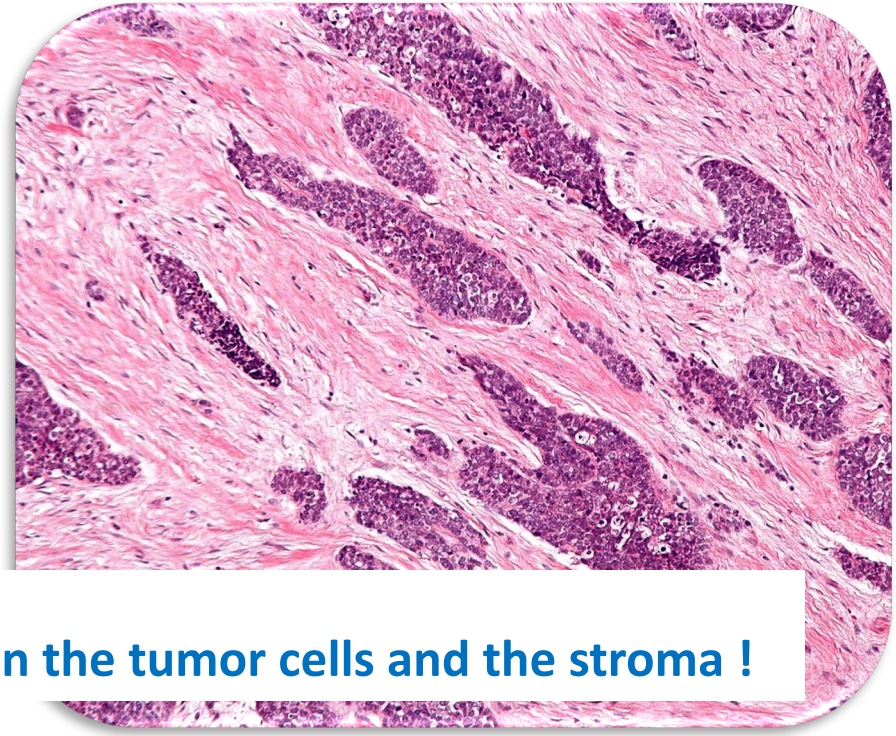
- Collectively termed as cancer (from latin word for crab)
- Can invade and destroy adjacent and distant structures (invasion and metastasis)
- Not all cancers pursue a deadly course

Oncology I. : Benign and Malignant neoplasms

Two main components

- **Parenchyma** (transformed neoplastic cells = tumor cells)
- **Stroma** (non-neoplastic cells, connective tissue and blood vessels)
  - dense fibrous stroma (desmoplasia) – scirrhous tumours





Active dynamic relationship between the tumor cells and the stroma !

https://www.halozyme.com/science/ By Nephron - Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=14829254

Nomenclature of Tumors

Table 6.1 Nomenclature of Tumors

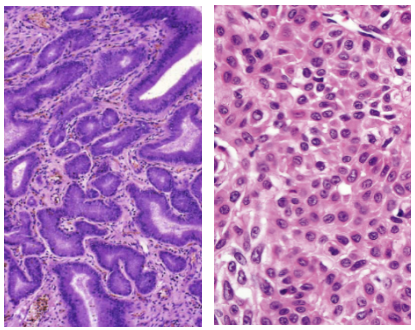
Tissue of Origin	Benign	Malignant
One Parenchymal Cell Type		
Connective tissue and derivatives	Fibroma Lipoma Chondroma Osteoma	Fibrosarcoma Liposarcoma Chondrosarcoma Osteogenic sarcoma
Endothelium and related cell types		
Blood vessels	Hemangioma	Angiosarcoma
Lymph vessels	Lymphangioma	Lymphangiosarcoma
Mesothelium		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
Skin		
Stratified squamous	Squamous cell papilloma	Squamous cell or epidermoid carcinoma
Basal cells of skin or adnexa		Basal cell carcinoma
Tumors of melanocytes	Nevus	Malignant melanoma
Epithelial lining of glands or ducts	Adenoma Papilloma Cystadenoma	Adenocarcinoma Papillary carcinomas Cystadenocarcinoma
Lung	Bronchial adenoma	Bronchogenic carcinoma
Kidney	Renal tubular adenoma	Renal cell carcinoma
Liver	Liver cell adenoma	Hepatocellular carcinoma
Bladder	Urothelial papilloma	Urothelial carcinoma
Placenta	Hydatidiform mole	Choriocarcinoma
Testicle		Seminoma Embryonal carcinoma
More Than One Neoplastic Cell Type—Mixed Tumors, Usually Derived From One Germ Cell Layer		
Salivary glands	Pleomorphic adenoma (mixed tumor of salivary gland)	Malignant mixed tumor of salivary gland
Renal anlage		Wilms tumor
More Than One Neoplastic Cell Type Derived From More Than One Germ Cell Layer—Teratogenous		
Totipotential cells in gonads or in embryonic rests	Mature teratoma, dermoid cyst	Immature teratoma, teratocarcinoma

Nomenclature of benign tumors

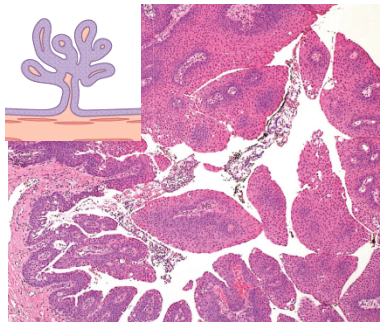
- **„oma”** suffix to the cell type from which they originate (t. of mesenchymal origin)
  - fibroma, chondroma, lipoma, osteoma, meningeoma
  - haemangioma, lymphangioma,
  - leiomyoma, rhabdomyoma

Based on macroscopic or microscopic features (tumors of epithelial origin):

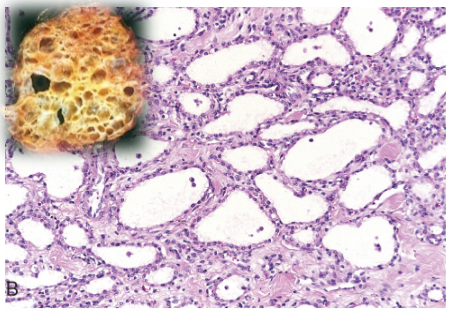
  - adenoma: derived from glands or showing glandular growth pattern
  - papilloma: benign epithelial tumor with finger-like fronds
  - cystadenoma: hollow cystic masses that typically arise in the ovary
  - polyp: mass that projects above a mucosal surface (e.g. in the gut)

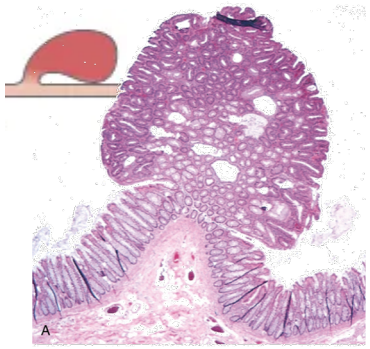


Elsevier; Diagnostic Histopathology of Tumors
& McKee's Pathology of the Skin: With Clinical Correlations



Elsevier; McKee's Pathology of the Skin: With Clinical Correlations





Nomenclature of malignant tumors

Mesenchymal origin

- **Solid:** **Sarcoma** (mesenchymal origin): e.g. fibrosc, chondrosc., osteosc., liposarcoma, angiosarcoma, etc …
- **Blood:** **Lymphoma, leukemia**

Epithelial origin

- **Carcinoma**
  - adenocarcinoma (growing in glandular pattern)
  - squamous carcinoma (produce squamous cells)
  - poorly differentiated, undifferentiated carcinoma

Important exceptions in the nomenclature of malignant tms

- lymphoma, melanoma, mesothelioma, seminoma, glioma !!
- e.g.: “malignant lymphoma” is incorrect !!

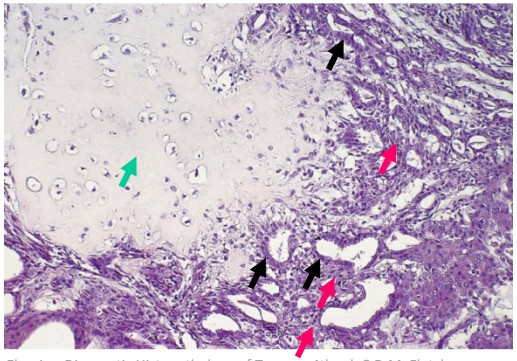
Unfortunately, these exceptions are firmly entrenched in medical terminology.

Mixed tumors and Teratoma

Mixed tumors (in terms of origin)

- divergent differentiation
  - **pleomorphic adenoma (mixed tumor of salivary gland)**
  - tumor cells of epithelial and myoepithelial origin,

    islands of cartilage or bone (stroma)



Elsevier, Diagnostic Histopathology of Tumors, 4th.ed. C.D.M. Fletcher

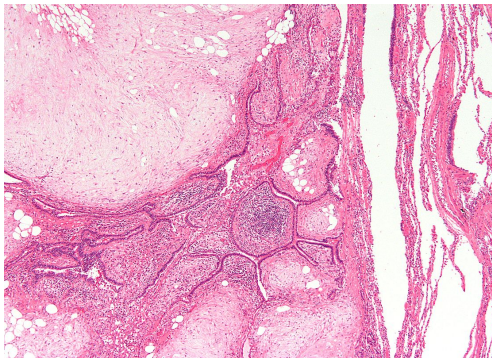
Teratoma

- tumor arising from totipotent germ cells (from ovary and testis)
  - **Capacity to differentiate into any cell type**
  - **Cells/tissues derived from 2-3 germ cell layers**

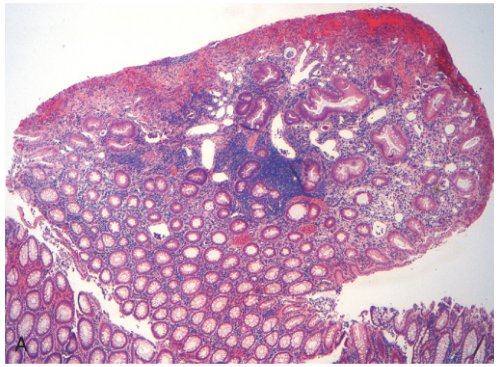
Hamartoma and choristoma

Hamartoma

- Traditionally considered developmental malformations, today considered to be neoplastic (with clonal chromosomal abnormalities)
- Mass of disorganized tissue indigenous to the particular site
  - **Lung hamartoma**
  - **Juvenile polyp**

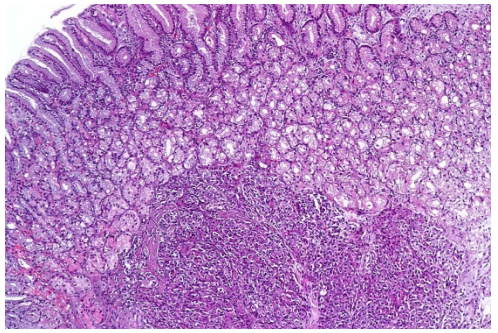


https://upload.wikimedia.org/wikipedia/commons/6/6d/Pulmonary_hamartoma_-_low_mag.jpg



Choristoma (heterotopy)

- congenital anomaly consisting of a heterotopic nest of cells
  - **Pancreatic heterotopia in the stomach**



https://commons.wikimedia.org/wiki/File:Stomach_with_pancreatic_heterotopia,_intermed._mag.jpg

Distinction between benign and malignant tumors

Distinction between benign and malignant tumors is not always straightforward

Three important criteria for malignant/benign

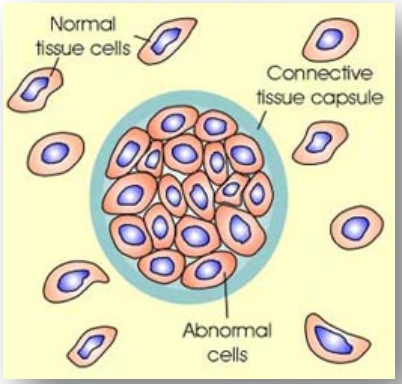
- **Differentiation and Anaplasia**
- **Local invasion**
- **Metastasis**
- ~~**Growth rate**~~

Differentiaton and anaplasia

- the extent to which the tumor cell resemble their cell of origin (morph./funct.)

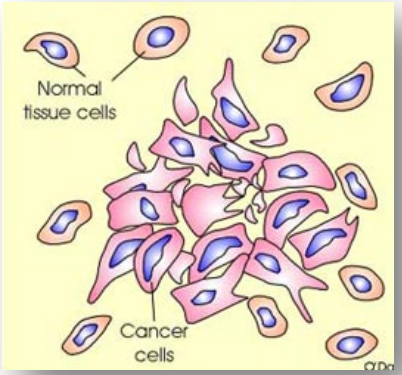
Benign

- well differentiated cells
- closely resembling their normal counterparts
- rare and normal mitoses



Malignant

- wide range of cell differentiation
- well differentiated tumors
- undifferentiated, so called. anaplastic tumors

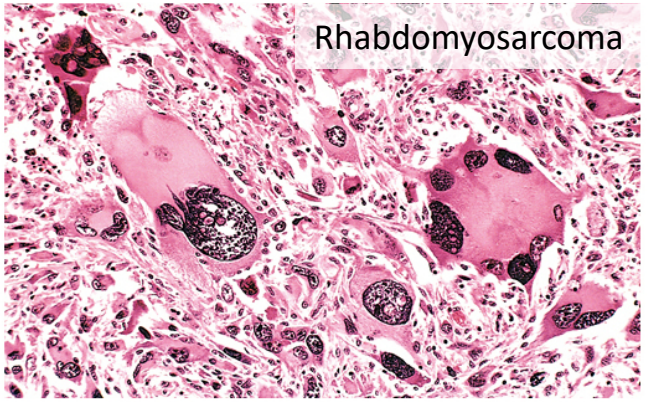


Well-differentiated tumor cells are likely to retain the functional capabilities of their normal counterparts
Anaplasia (dedifferentiation, “backward formation”) indicator of malignancy

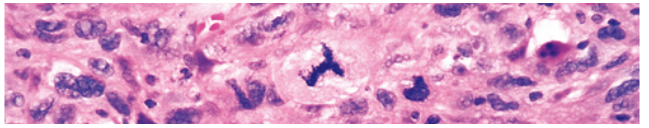
Features of the anaplastic cells

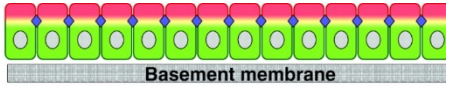
- **Pleomorphy:** variability in size and shape
- **Aberrant nuclear morphology**

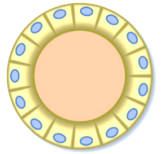
  (size, shape, chromatin)
- **Tumor giant cells**
- **Aberrant mitoses** (tri- quadripolar divisions)
- **Loss of polarity** (loss of patterns, communal strc.)

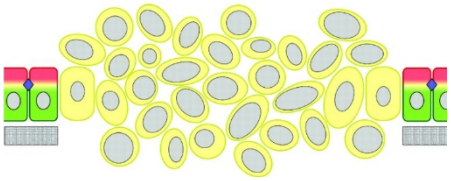


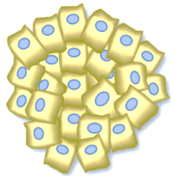
Courtesy Dr. Trace Worrell, University of Texas Southwestern Medical School, Dallas, Texas.











Minhui Lee, and Valeri Vasioukhin J Cell Sci 2008;121:1141-1150

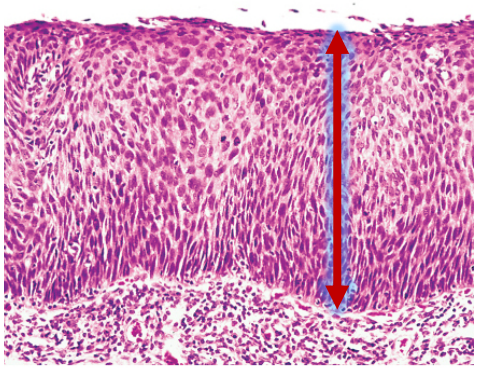
Chen N, et al. Cancer Res. 2014;74(20):5683-5689.

Dysplasia (precursor lesion)

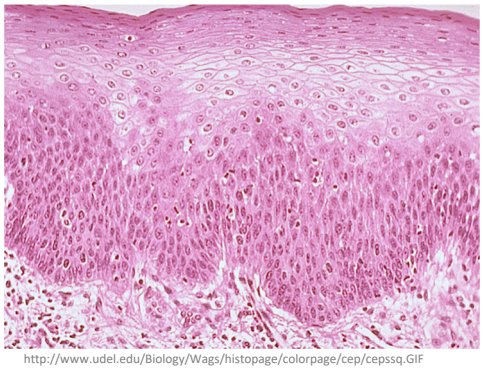
Aberrant, but not neopl. proliferation

- Loss of uniformity/orientation
  - Pleomorphic cells
  - large, hyperchrom nucl.
- Numerous mitoses
- Architectural anarchy

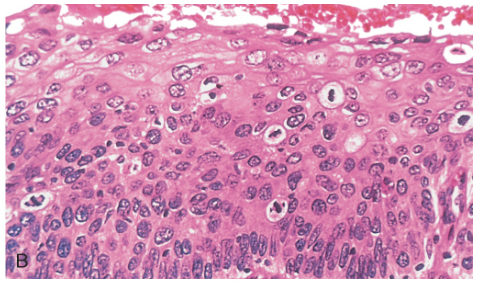
Dysplastic epithelium

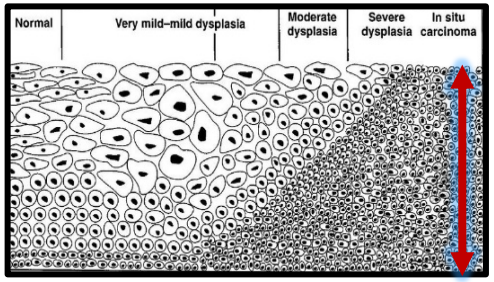


Regular epithelium



http://www.udel.edu/Biology/Wags/histopage/colorpage/cep/cepssq.GIF





Suthar et al RJLBPCS 2018, DOI: 10.26479/2018.0405.10

- ≠ Carcinoma, Mild to moderate dysplasias sometimes regress completely
- Marks tissues at cancer risk (not necessarily)
- if it affects the entire thickness of the epithelium **carcinoma *in situ***

  (preinvasive stage)

Distinction between benign and malignant tumors

Distinction between benign and malignant tumors is not always straightforward

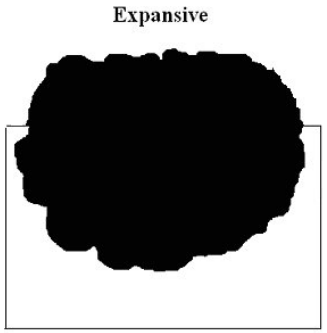
Three important criteria for malignant/benign

- **Differentiation and Anaplasia**
- **Local invasion**
- **Metastasis**

Local Invasion

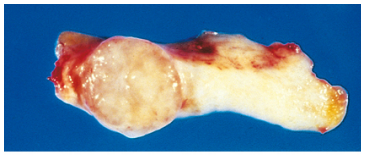
Benign tumors

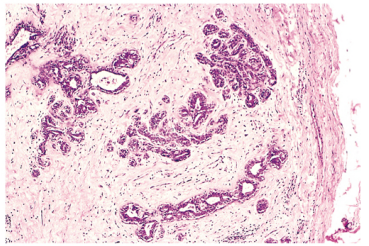
- grow as cohesive, expansile masses
- remain localised
- rim/capsule of compressed fibrous tissue
- discrete, excisable by surgical enucleation



Victoria Hahn-Strömberg, Cell adhesion proteins in different invasive patterns of colon carcinomas: a morphometric and molecular genetic study; : Örebro University 2008

Fibroadenoma mammae

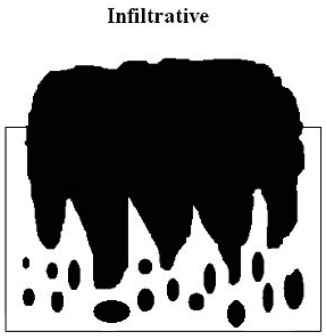




Courtesy Dr. Trace Worrell, University of Texas Southwestern Medical School, Dallas, Texas.

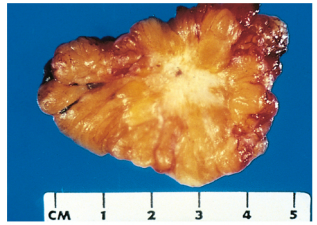
Malignant tumors

- Invasion and destruction of adjacent tissues
- lack of well defined capsules
- resection with clean margins



Victoria Hahn-Strömberg, Cell adhesion proteins in different invasive patterns of colon carcinomas: a morphometric and molecular genetic study; : Örebro University 2008

Invazív emlőcarcinoma



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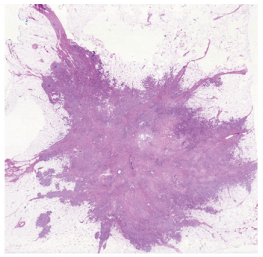

Courtesy Dr. Susan Lester, Brigham and Women's Hospital, Boston, Mass.

Distinction between benign and malignant tumors

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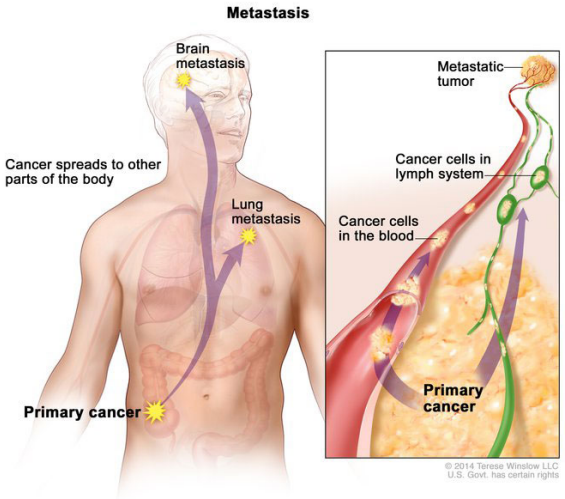
Three important criteria for malignant/benign

- **Differentiation and Anaplasia**
- **Local invasion**
- **Metastasis**

Development of metastases

Spread of a tumor to sites that are physically discontinuous with the primary tumor

- invasion into lymphatic/blood vessels, body cavities
- unequivocally marks a tumor as malignant
- metastatic capacity of the tumors is highly variable
- severe limitation of the successful therapy

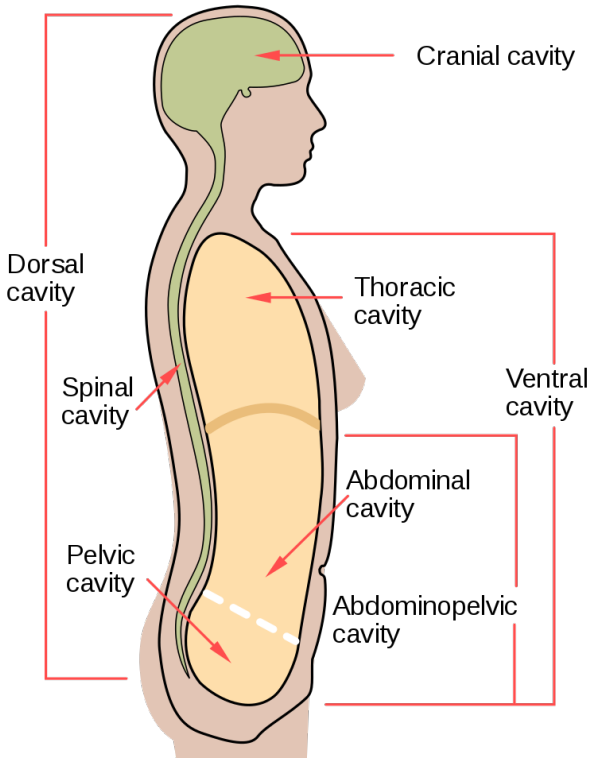


- Appr. 30% of patients with solid tumors present with clinically evident metastates,
- Occult (hidden) mets in additional 20 % of patients
- the more anaplastic and the larger the primary neoplasm, the more likely is metastatic spread

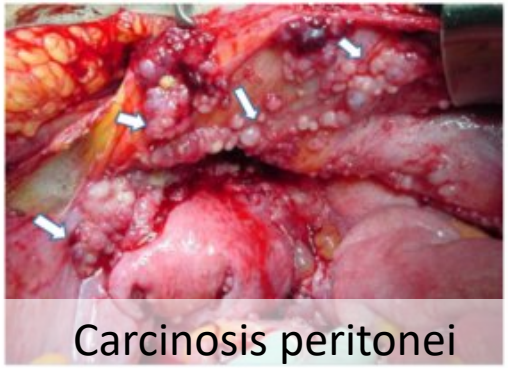
- Special consideration for leukemias and lymphomas (‘blood cancers’)

Pathways of metastasis formation I.

1. **seeding within body cavities**
   - Ovarian carcinoma – often cover the peritoneal surfaces widely
   - Medulloblastoma – cerebral ventricles – liquor – meningeal surfaces

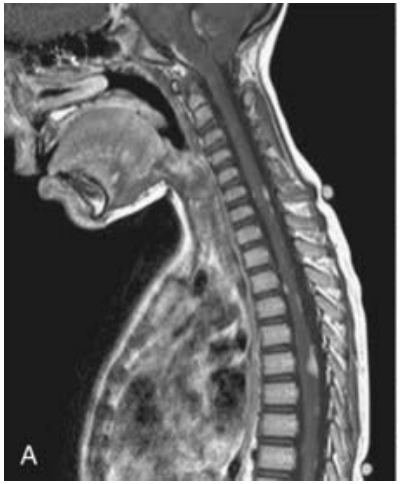


https://en.wikipedia.org/wiki/Body_cavity



Carcinosis peritonei

Thadi, A. et al. Early Investigations and Recent Advances in Intraperitoneal Immunotherapy for Peritoneal Metastasis. Vaccines 2018, 6, 54.

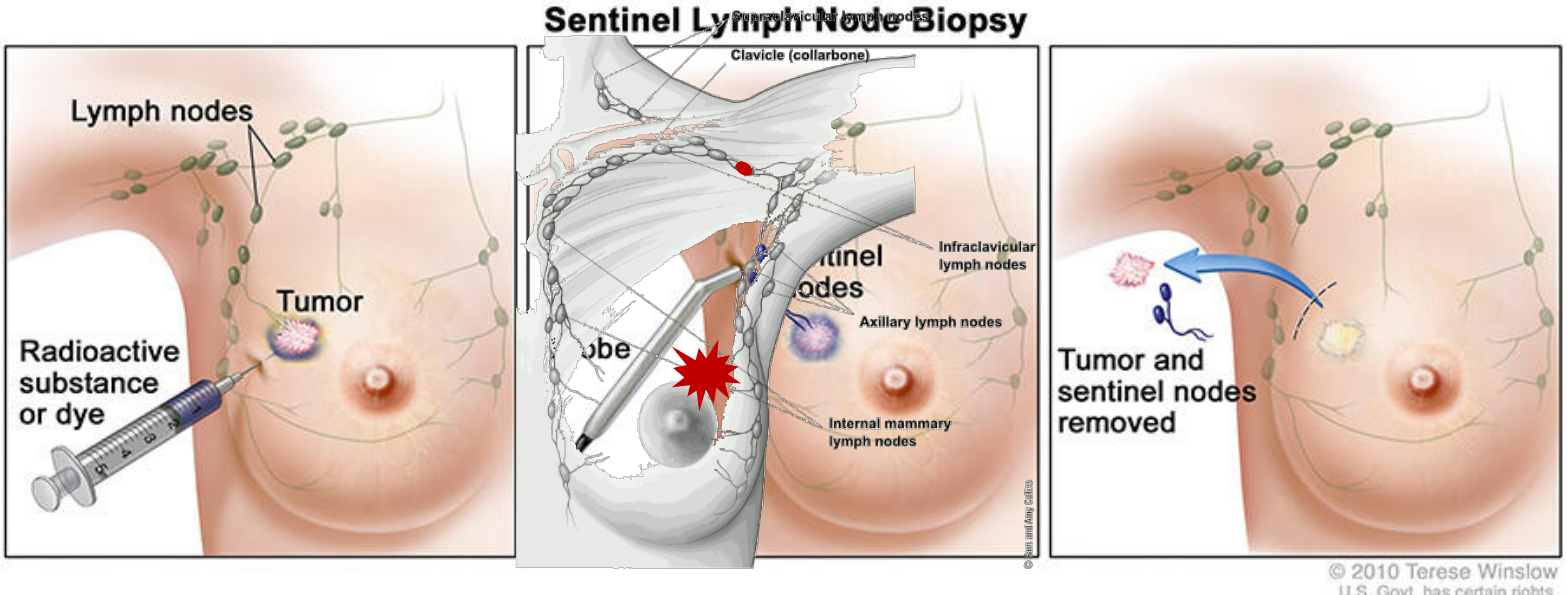


https://clinicalgate.com/primitive-neuroectodermal-tumors/

Pathways of metastasis formation II.

2. Lymphatic spread

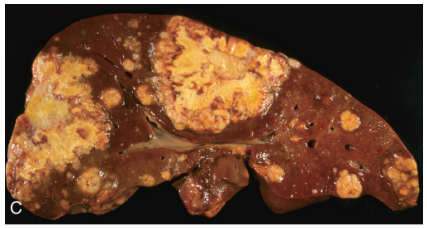
- More typical of carcinomas
- The pattern depends on the natural pathways of local lymphatic drainage
- “sentinel lymph node” is the first regional lymph node that receives lymph flow from a primary tumor
- „Skip” metastasis - sentinel lymph node not affected

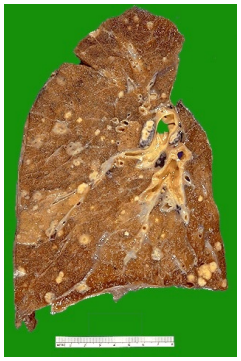


Pathways of metastasis formation III.

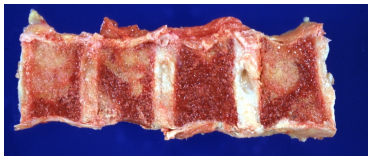
3. Hematogenous spread

- Favoured by sarcomas (carcinomas also use it)
- Mainly through veins
- Portal drainage: to the liver
  - e.g. colon-, pancreas-, gastric carcinoma
- Vena cava drainage: to the lung
  - e.g. kidney, bladder carcinoma
- Paravertebral plexus (tumors near the vertebral column):
  - e.g. prostate, thyroid carcinoma
- Some tumors may grow within veins
  - Renal cell carcinoma (v. cava inf. --- right side of the heart)
  - Hepatocellular carcinoma (portal and hepatic veins)

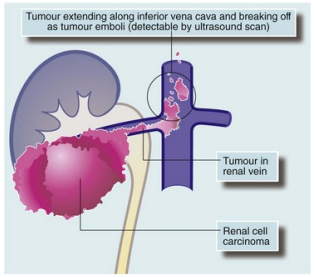




https://webpath.med.utah.edu/LUNGHTML/LUNG078.html



https://peir.path.uab.edu/library/picture.php?/3415

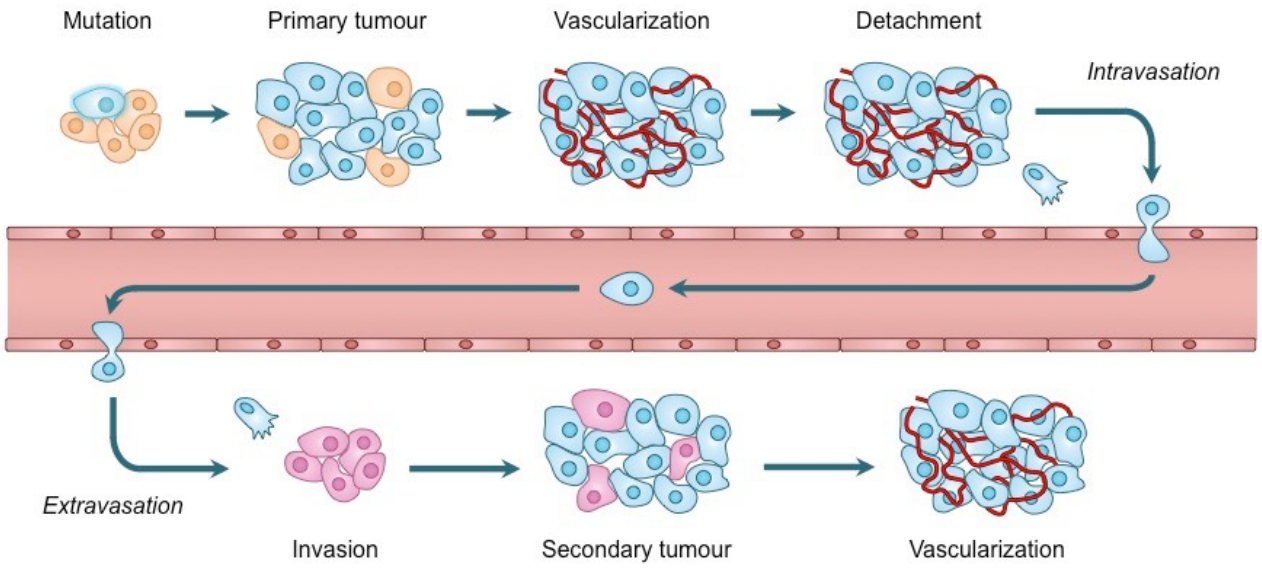


https://clinicalgate.com/tumours-of-the-kidney-and-urinary-tract/

The metastatic cascade

The metastatic cascade

- Detachment of tumor cells
- ECM and BM destruction
- Intravasation
- Migration of the tumor cells
- Vascular dissemination
- Extravasation
- Colonisation/sec. tu.



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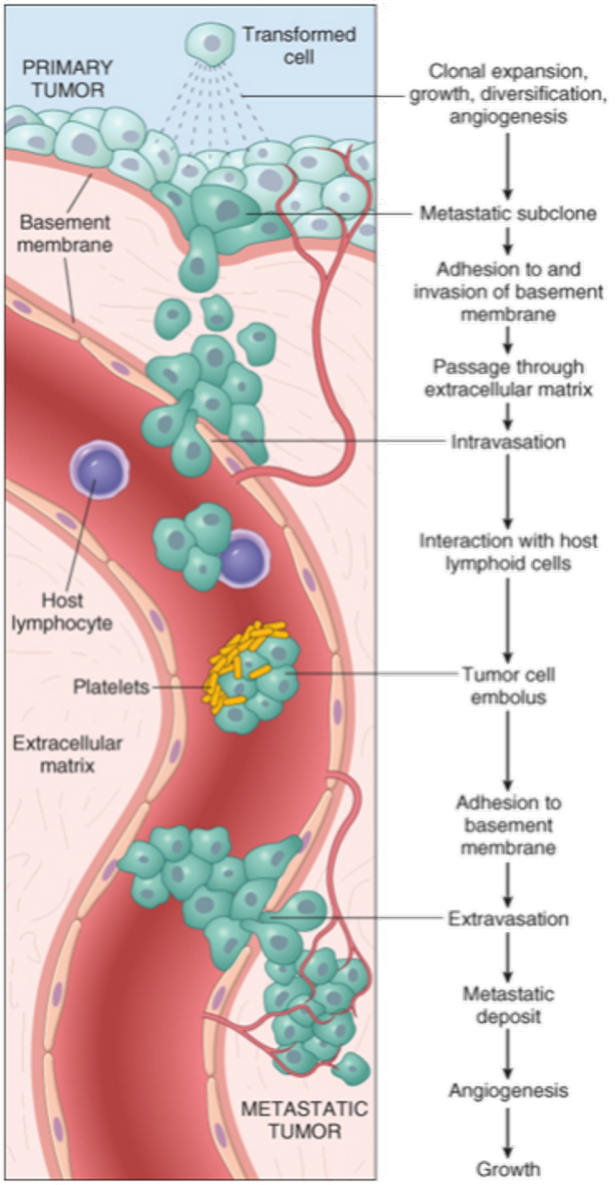
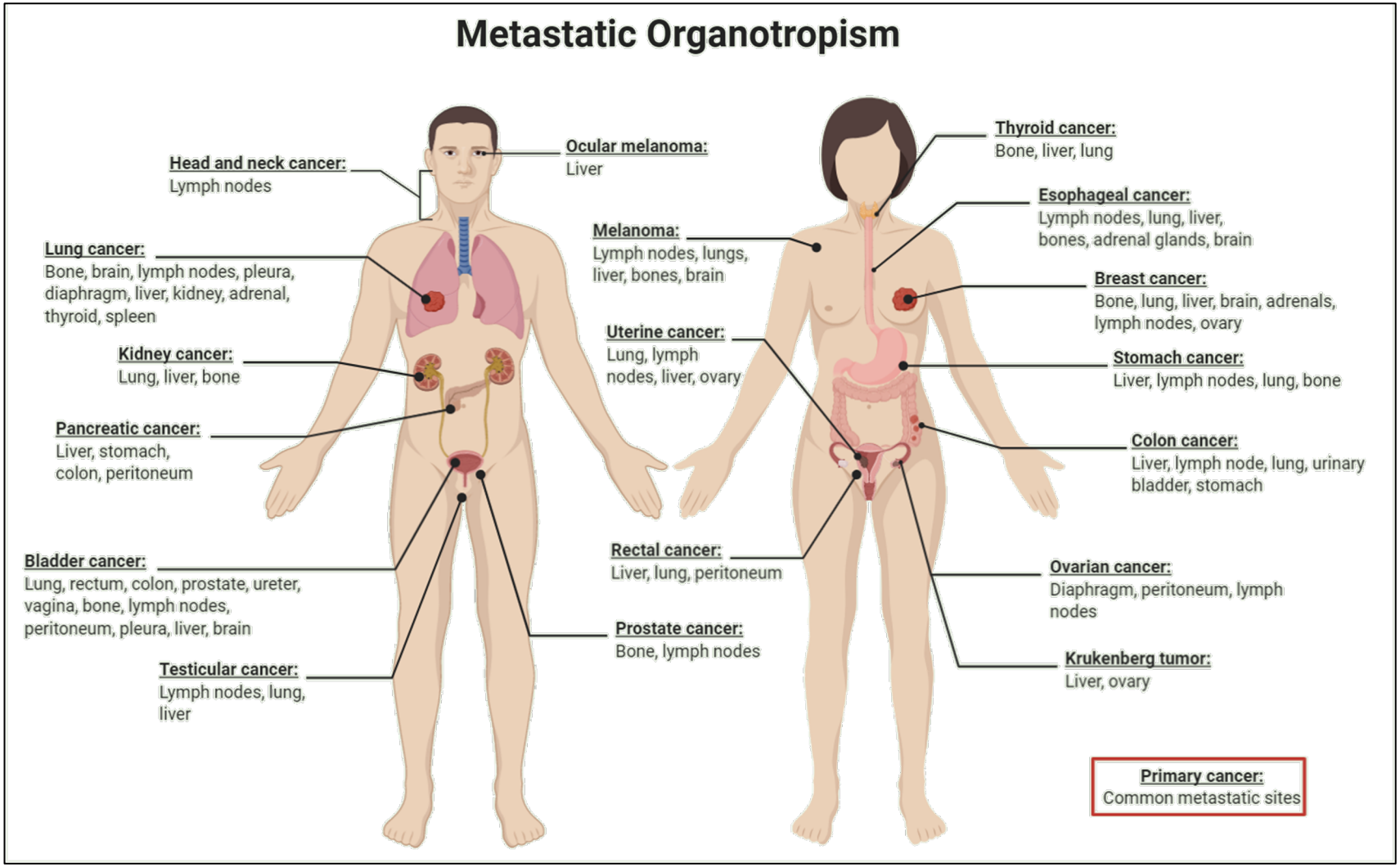


Typical metastatic sites

Anatomic localization of a neoplasm and its venous drainage cannot wholly explain the systemic distributions of metastases.



Fares, J., Fares, M.Y., Khachfe, H.H. *et al.* Molecular principles of metastasis: a hallmark of cancer revisited. *Sig Transduct Target Ther* **5**, 28 (2020). https://doi.org/10.1038/s41392-020-0134-x

Characteristics of Benign and Malignant tumors (Summary)

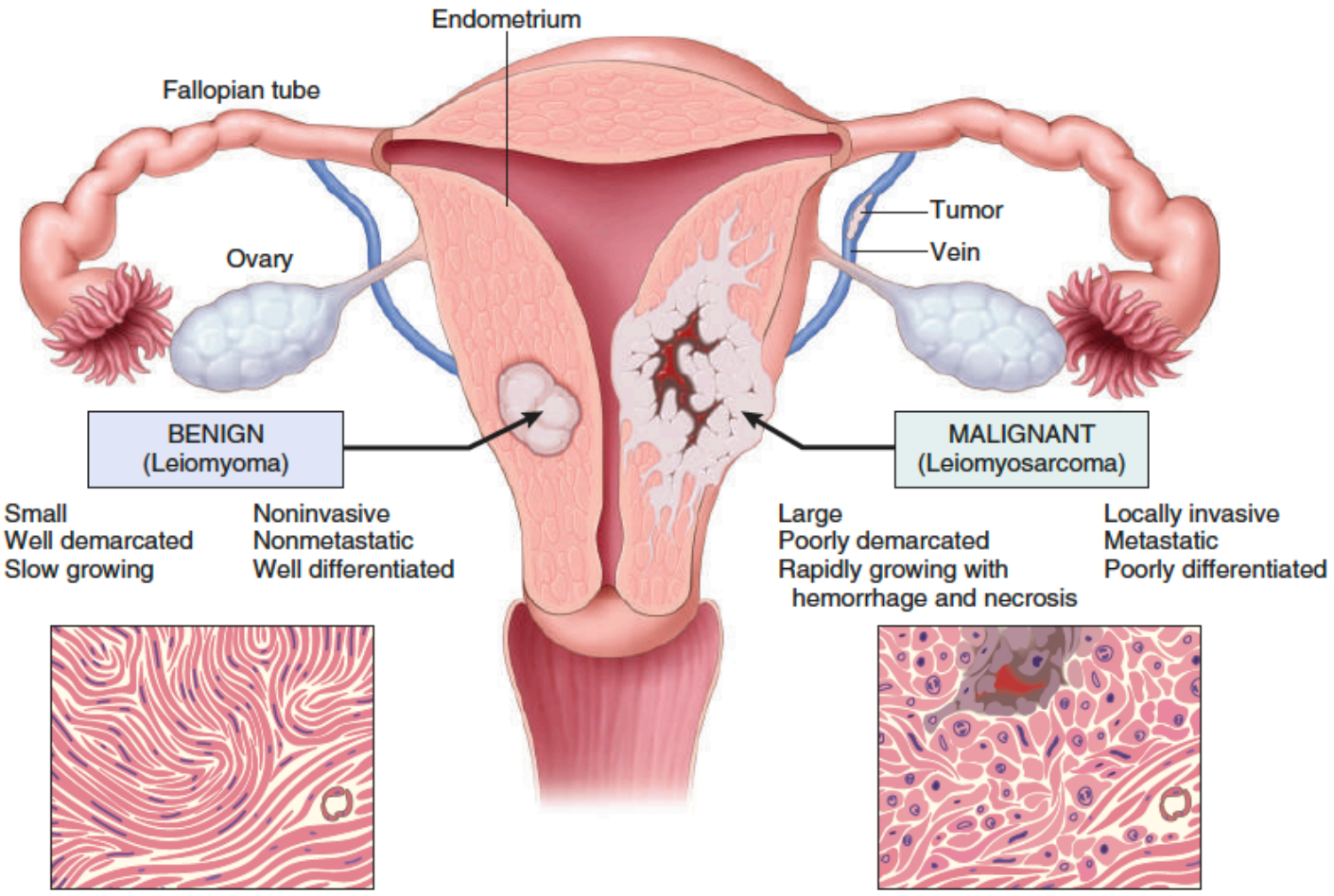


Fig. 6.12 Comparison between a benign tumor of the myometrium (leiomyoma) and a malignant tumor of similar origin (leiomyosarcoma).

Characteristics of Benign and Malignant tumors (Summary)

SUMMARY

CHARACTERISTICS OF BENIGN AND MALIGNANT TUMORS

- Benign and malignant tumors can be distinguished from one another based on the degree of differentiation, rate of growth, local invasiveness, and distant spread.
- Benign tumors resemble the tissue of origin and are well differentiated; malignant tumors are poorly or completely undifferentiated (anaplastic).
- Benign tumors tend to be slow growing, whereas malignant tumors generally grow faster.
- Benign tumors are well circumscribed and have a capsule; malignant tumors are poorly circumscribed and invade the surrounding normal tissues.
- Benign tumors remain localized to the site of origin, whereas malignant tumors are locally invasive and metastasize to distant sites.

	BENIGN	MALIGNANT	(SEMIMALIGN.) e.g.. basalioma, ameloblastoma	BORDERLINE Low mal. potential e.g. b. ovarial tumors, b. vascular tumors
Differentiation	Well diff.	variable	Well diff.	variable (more diff then malign.)
Anaplasia	no	yes/variable	no	yes/variable
Growths	slow	fast/variable	slow	slow
Local invasion	no/ expansive	infiltrative	infiltrative	no / yes
Metastasis	no	yes	no/rarely	possible
Local recurrence	possible	yes/possible	possible	possible