General oncology: benign and malignant tumors. Classification. Cancerogenesis.

Markéta Hermanová

Neoplasia, tumor - definition

- „abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues and persists after cessation of the stimuli which evoked the change“ (Willis)
- Genetic and regulatory changes →functional dysregulation of proliferation that becomes autonomous + failure of the process of natural cell death
- Clonal proliferation/expansion of the transformed cell (tumors are monoclonal)
- Sporadic mutations in somatic cell or germline mutations

Carcinogenesis

- Multistep process at both phenotypic and genetic levels

- Nonlethal genetic damage (or mutation)
  - exogenic factors (radiation, chemicals, viruses,…)
  - endogenic factors (toxic radicals, genome instability, failure of DNA damage repair, chromosomal rearrangements,…)
  - germline mutations

- Clonal expansion of a single precursor cell that has incurred the genetic damage (tumors are monoclonal)

Targets of genetic damage

- The growth-promoting protooncogenes

(dominant; support of cell proliferation)

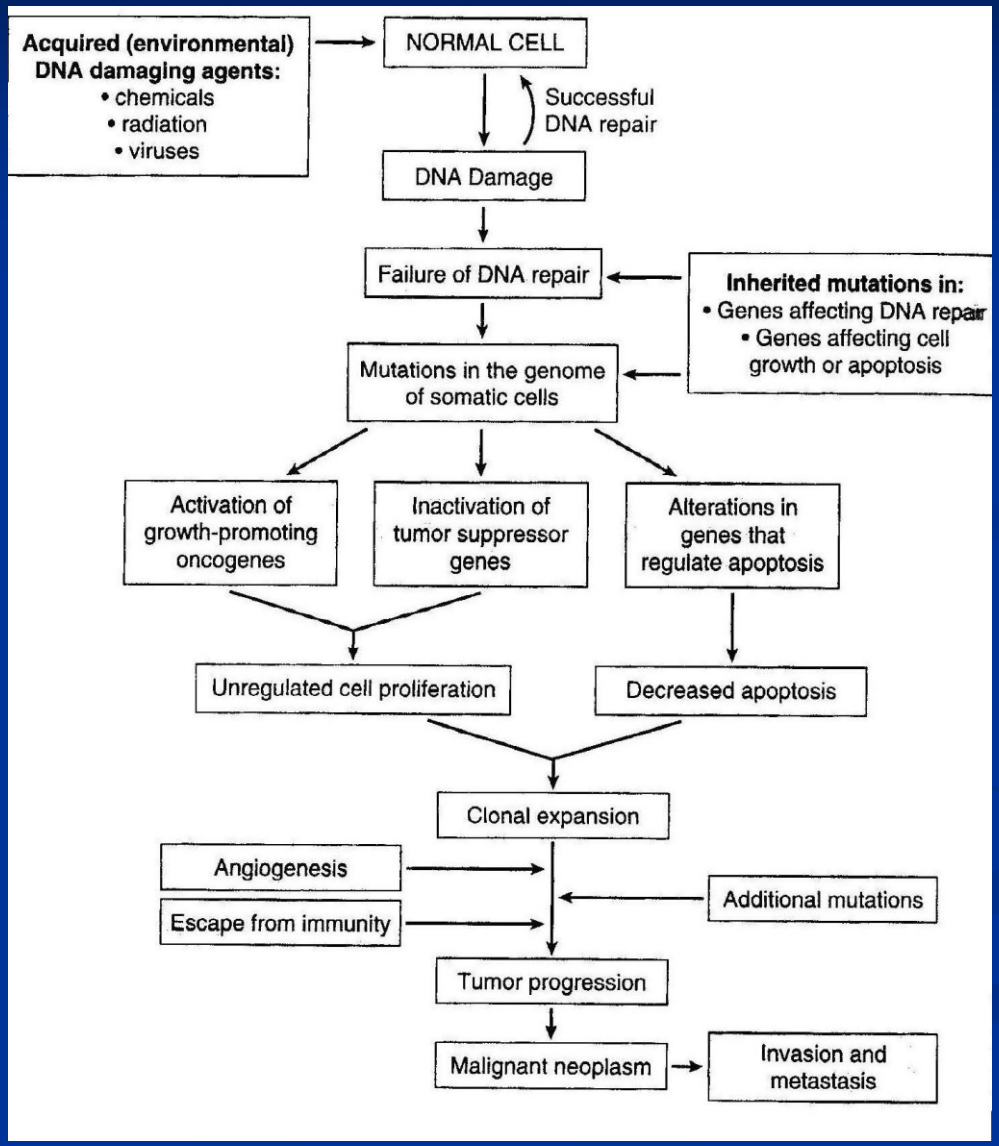
- The growth-inhibiting tumor suppressor genes

(recessive; inhibition of growth)

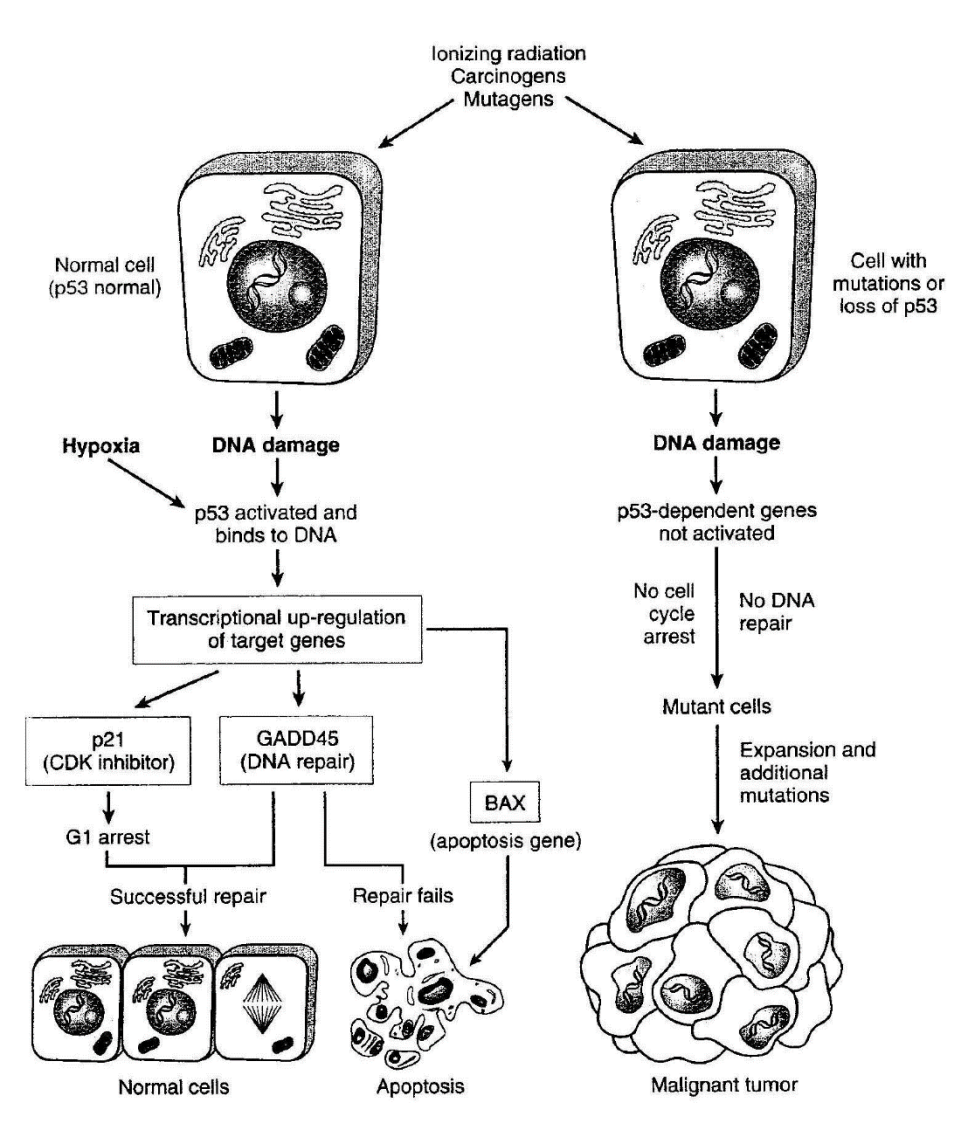
- Gatekeepers (p53, RB)
- Caretakers (genes involved in maintenance of genome integrity and DNA repair)

- Genes regulating he programmed cell death (apoptosis)
- Genes involved in DNA repair
- Oncogenic microRNA

Molecular basis of cancer



The role of tumor suppressor p53



Composition of tumors:

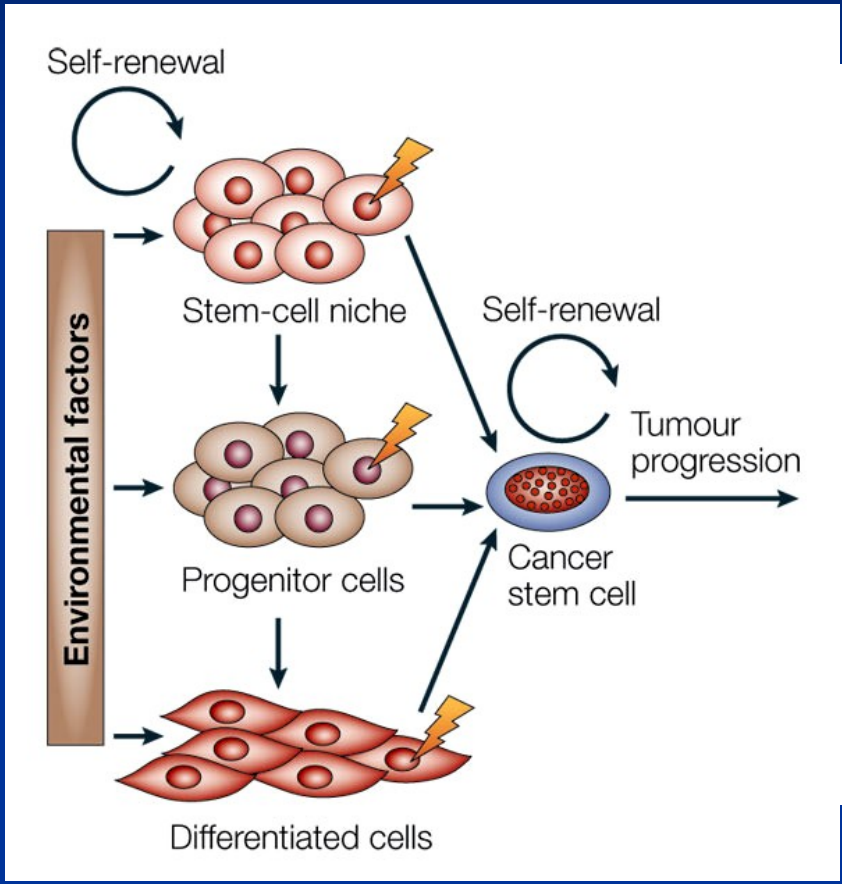
- Parenchyma (proliferating neoplastic cells)
- Stroma (connective tissue and blood vessels, source of mediators promoting the tumor growth and angiogenesis)
- (Cancer stem cells – tumor initiating cells)

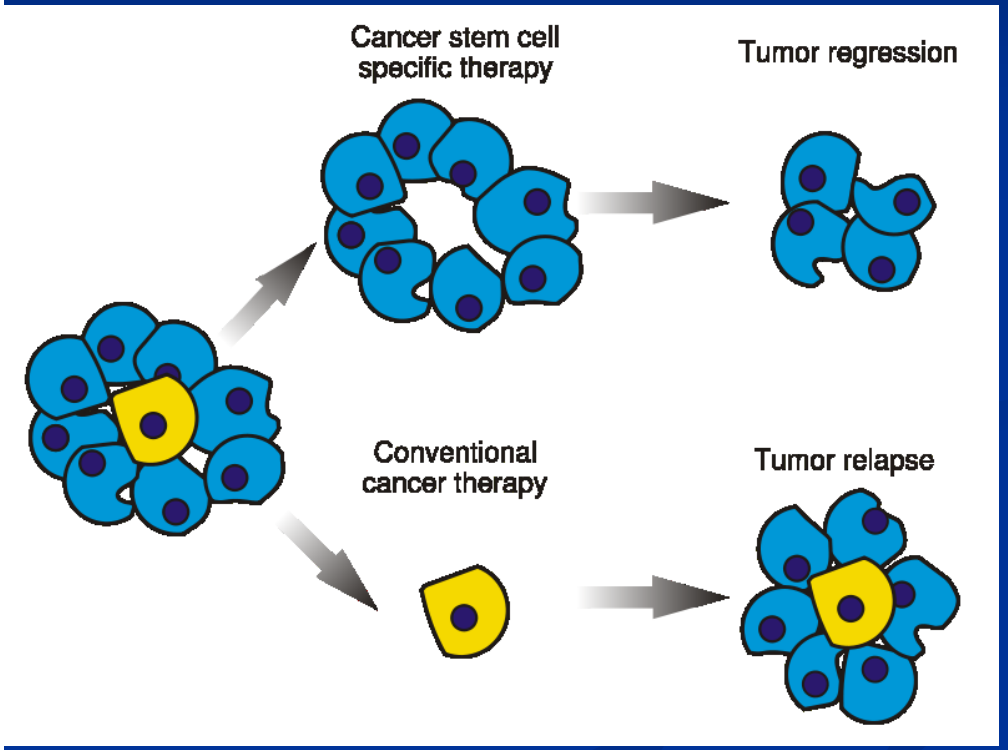
- Cross-talk between stroma and parenchyma
- Tumors with abundant parenchyma: soft and flashy
- Tumors with abundant collagenous stroma – with desmoplastic stroma: stony hard - scirrhous

Cancer stem cells – tumor initiating cells

- subpopulation of tumor cells that possess self-renewal properties and are able to differentiate into multiple cell types providing various cell lines, which enable the progression of an incipient tumor
- resistent to conventional therapies
- a source of the tumor relapse after eradication of the bulk of the tumor
- oncological research focused in further understanding of CSCs and in the development of terapeutic strategies targeted at CSCs.

Cancer stem cell therapy





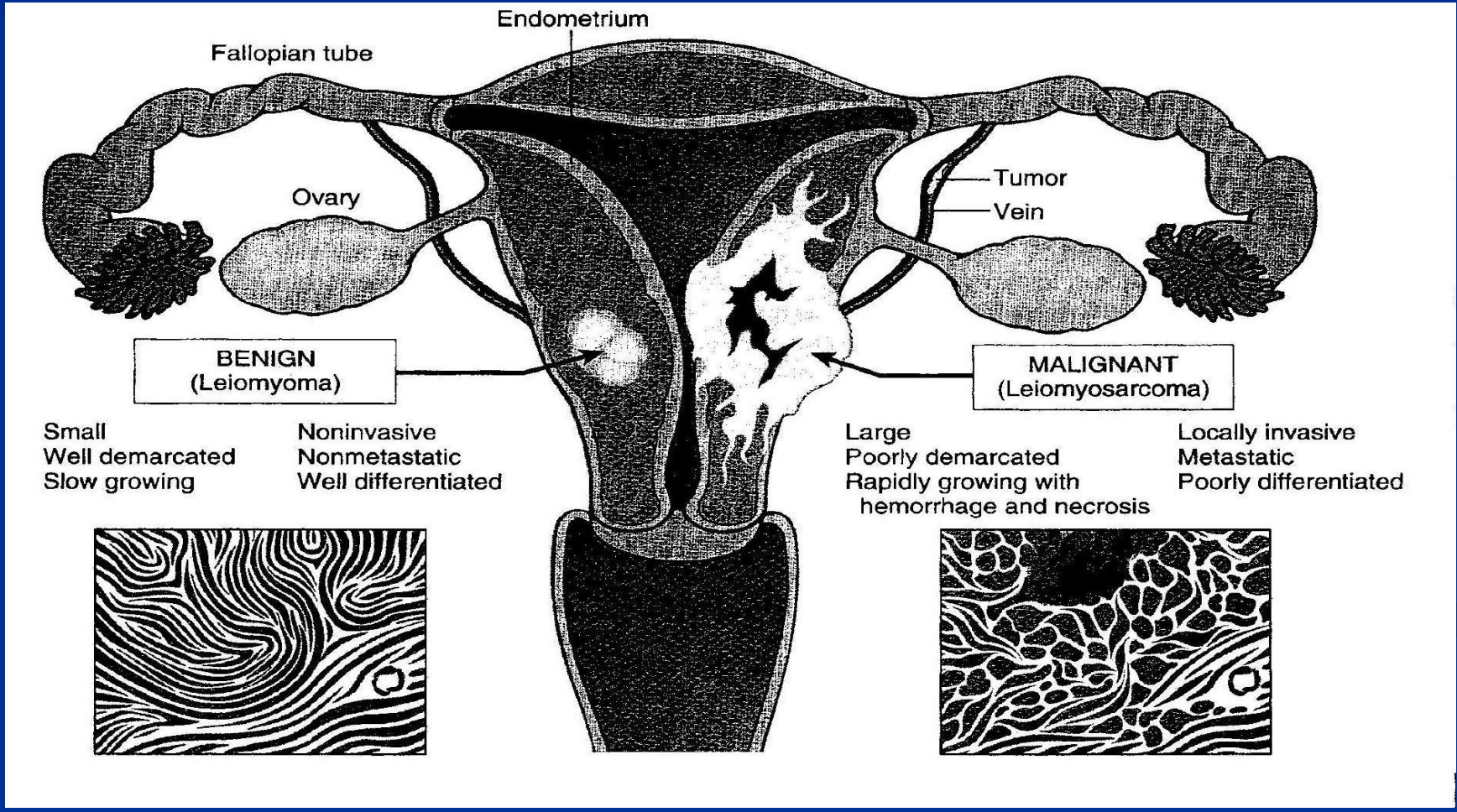
Feature	Benign tumors	Malignant tumors
Growth rate	slow	Relatively rapid
Mitoses	Infrequent	Frequent and often atypical
Differentiation	Good	Variable, often poor
Nuclear morphology	Often normal	Usually hyperchromatic, irregular outline, multiple nucleoli and pleomorphic
Invasion	No	Yes
Metastases	Never	Frequent
Border	Often circumscribed or encapsulated	Often poorly defined, irregular
Necrosis	Rare	Common
Ulceration	Rare	Common on skin and serous surfaces
Growth on skin or mucosal surfaces	Often exophytic	Often endophytic

Semimalignant and potentially malignant tumors

- Different levels of loss of differentiation
- Tissue and cellular atypia
- Usually increased proliferation, atypical mitoses
- Invasive, poorly demarcated; sometimes partially expansivelly growing
- No metastases
- *Basalioma of the skin*

- Differentiated
- No tissue and cellular atypia
- No atypical mitoses
- Expansivelly growing, often encapsulated
- Sometimes metastases
- *Pleomorphic adenoma of salivary glands*

Comparison between benign leiomyoma and malignant leiomyosarcoma



Differentiation

- The extent to which neoplastic cells resemble comparable normal cells, both morphologically and functionally
- Anaplasia: lack of differentiation (tumor parenchyma resembles the tissues of embryonal organs)

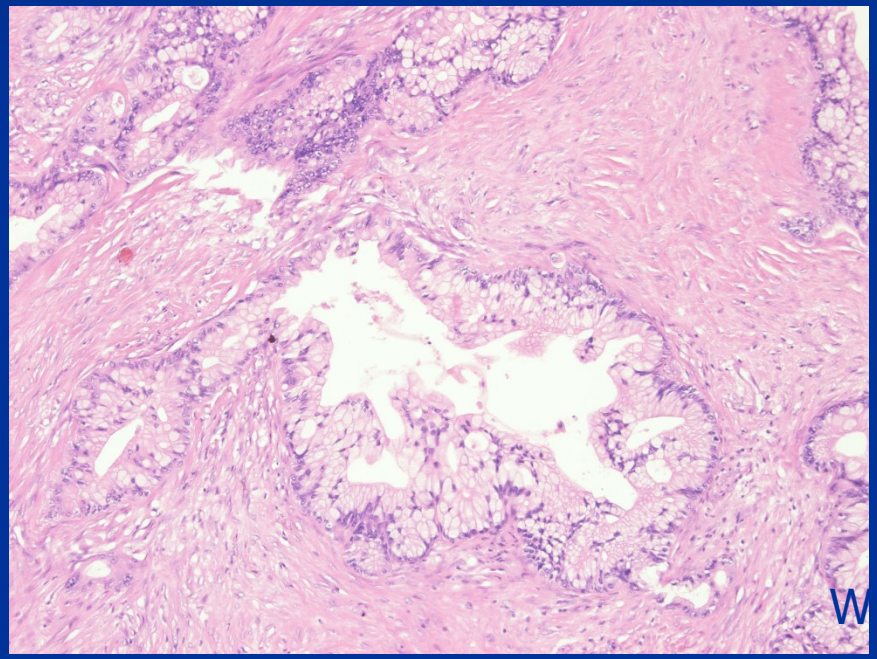
- Pleomorphism (variation of cells and nuclei in size and in shape)
- Increased size of nuclei
- Nuclear atypia (hyperchromasie due to the abundance of DNA, increased N/C ration (nucleus-to-cytoplasm ratio)
- Increased number and size of nucleoli
- Tumor giant cells
- Increased proliferation – mitoses (atypical, bizarre mitotic figures in malignant tumors)
- Loss of polarity
- Basophilic cytoplasm

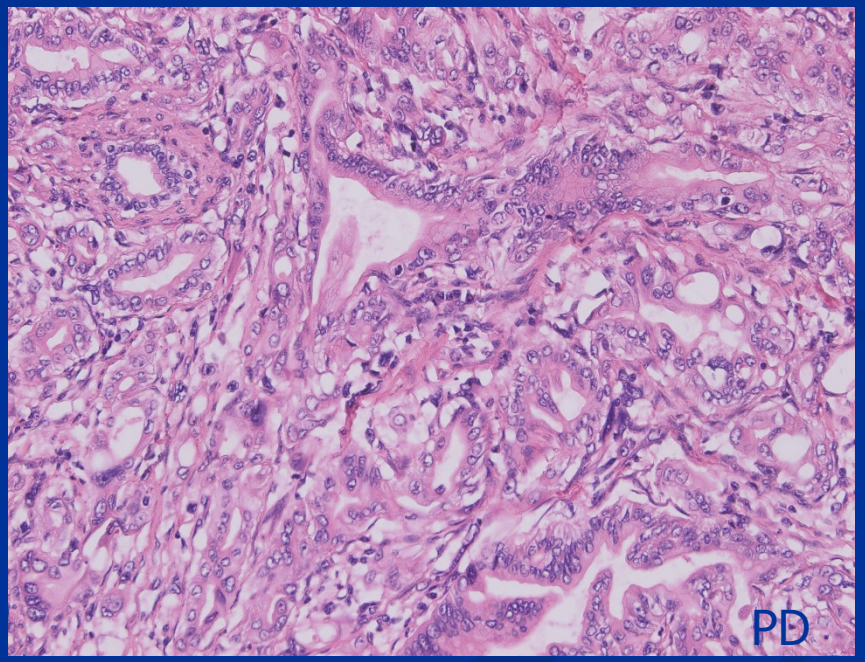
Grading of pancreatic ductal adenocarcinoma

Grade	Glandular structure	Mitoses (per 10 HPF)	Nuclear structure
Well differentiated (I)	- well differentiated tubular or duct-like structures; mucin secreting columnar cells in single layers or papillary projections - desmoplastic stromal reaction	<5	slight pleomorphism, small nucleolus
Moderately differentiated (II)	- moderately differentiated ductal, tubular, microglandular, cribriform structures - irregular mucin production	6-10	conspicious pleomorphism and nucleoli
Poorly differentiated (III)	- poorly differentiated glandular structures, mucoepidermoid and pleomorphic, undif. structures - abortive mucin production	>10	pronounced pleomorphism, enlarged nuclei and prominent nucleoli

+ **grade IV**: undifferentiated tumor

Well differentiated vs poorly differentiated pancreatic ductal adenocarcinoma





Metastases

- Benign tumors do not metastasize
- Invasiveness of malignant tumor enables metastatic spreading

- Three pathways of metastatic spreading:

1. Hematogenous spread
2. Lymphatic spread (especially in carcinomas; sentinel lymph node)
3. Direct seeding of body cavities or surfaces (implantation on serous surfaces (peritoneum, pleura, pericardium), on mucosal layers of tubular organs , withinjoint space, in subarachnoid space, ….)

Genetic predisposition to cancer

- AD inherited cancer syndromes (inherited mutation in a single allele of a tumor suppressor gene; the second hit in somatic cells):

1. *RB tumor suppressor gene* (childhood retinoblastoma)
2. *APC tumor suppressor gene* (familial adenomatous polyposis)
3. *p53 tumor suppressor gene* (Li-Fraumeni syndrome)

(MEN 1, 2; NF1,2; p16; BRCA1, 2; VHL; Peutz-Jeghers sy,….)

- Defective DNA repair syndromes (AD)
  (hereditary nonpolypoid colon cancer (Lynch sy); *MSH2, MSH6, MLH1*)

- Familial cancer (breast, pancreas, ovary)

- AR inherited cancer syndromes (defective DNA repair, genetic instability; Fanconi anemia, ataxia teleangiectasia, xeroderma pigmentosum,…)

- Interactions between genetic and epi-genetic factors

Nonhereditary predisposing conditions

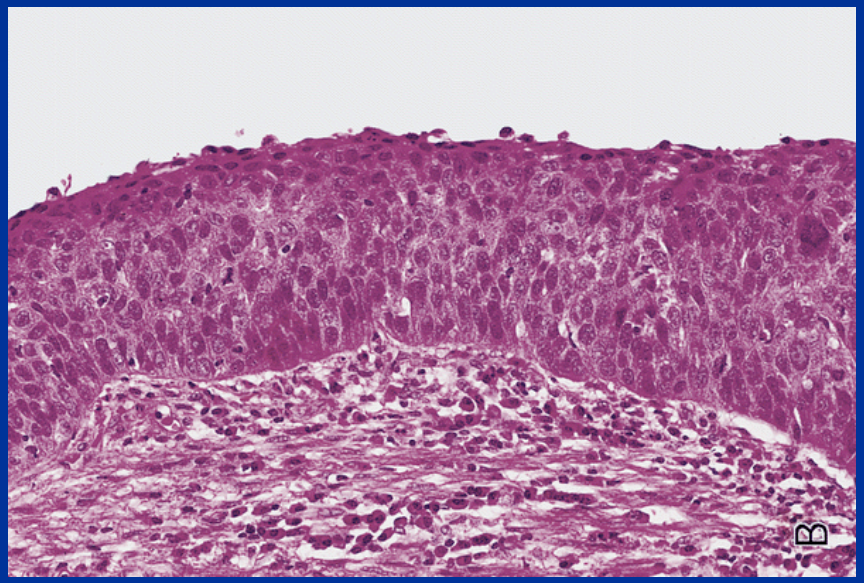
- Chronic inflammation and cancer

- Precancerous conditions/premalignant lesions (dysplasia/intraepithelial neoplasia)

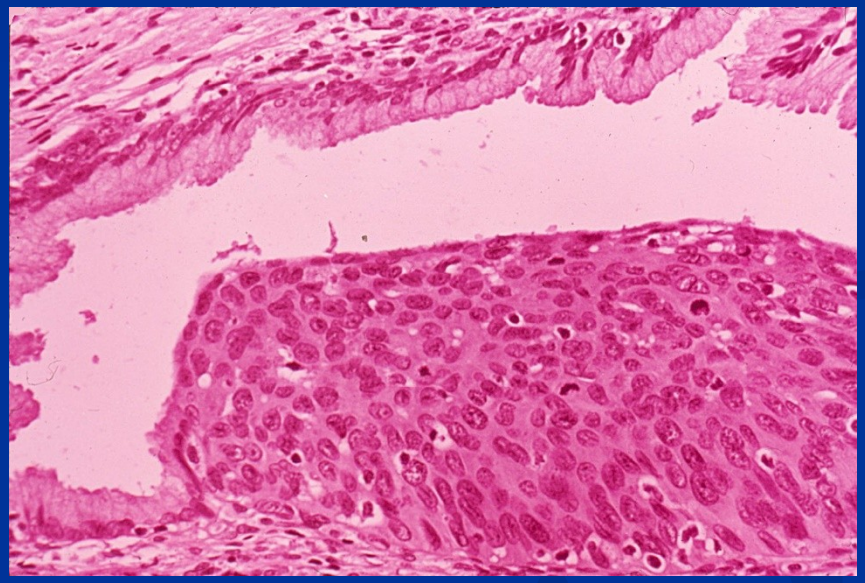
- Adenomatous polyps of colon
- CIN, VIN, EIN, PanIN, PIN,
- Atypical ductal or lobular hyperplasia

Dysplasia

- In epithelia
- A loss of uniformity of the individual cells as well as loss in their architectural orientation
- Low grade vs high grade dysplasia
  - most low grade dysplasias do not progress into invasive carcinoma
  - high risk of progression into invasive carcinoma in high grade dysplasia
- Intraepithelial neoplasia/dysplasia
- Dysplastic changes can involve the entire thickness of the epithelium – preinvasive neoplasm – *carcinoma in situ*



Carcinoma in situ



Cervical intraepithelial neoplasia grade III/ CIN III = high grade

The role of inflammation in carcinogenesis

- **production of reactive oxygen species (ROS), cytokine release, and upregulation of pro-inflammatory transcription factors**

- **Mediators of the inflammatory pathways (e.g., NF-κB, COX-2, 5-LOX, IL-8,…):**

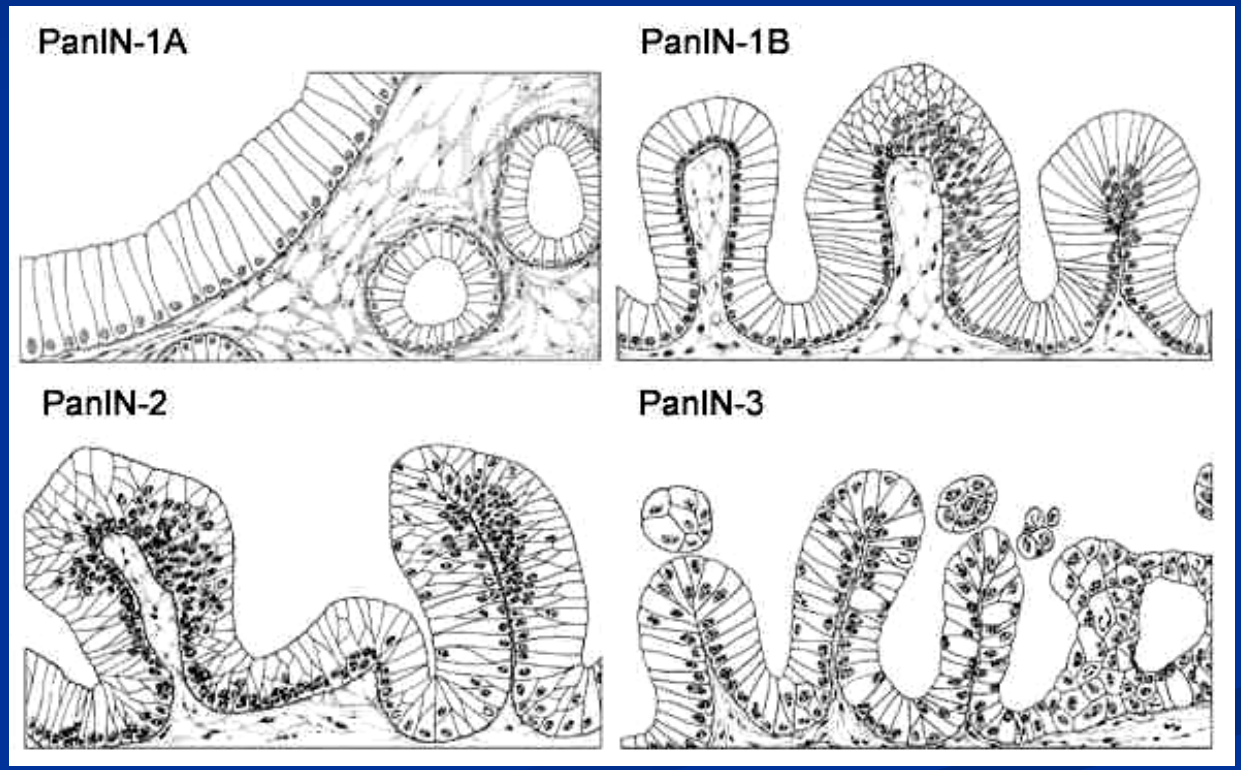
- induce genetic damage
- promote cell proliferation
- inhibit apoptosis
- regulate the tumor associated angiogenesis

Relationship between inflammation and cancer.

- IBD – colorectal cancer
- *Helicobacter pylori* chronic gastritis – gastric cancer
- chronic viral hepatitis – hepacellular carcinoma
- esophagitis (Barret´s esophagus) – esophageal carcinoma
- liver fluke infection – cholangiocellular carcinoma
- chronic pancreatitis – pancreatic cancer

Pancreatic intraepithelial neoplasms (PanIN): microscopic precursor of pancreatic ductal adenocarcinoma. PanIN 1A, 1B, 2 = low grade, PanIN3 = high grade

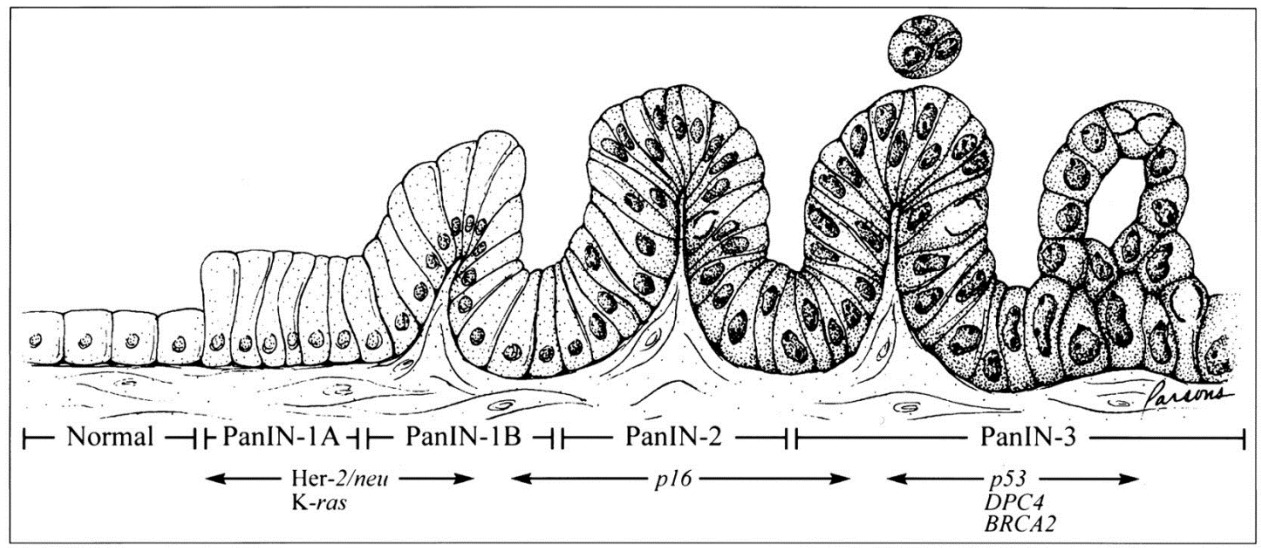
- PanIN-1A
- PanIN-1B
- PanIN-2
- PanIN-3



PanIN: non-invasive intraductal epithelial proliferation

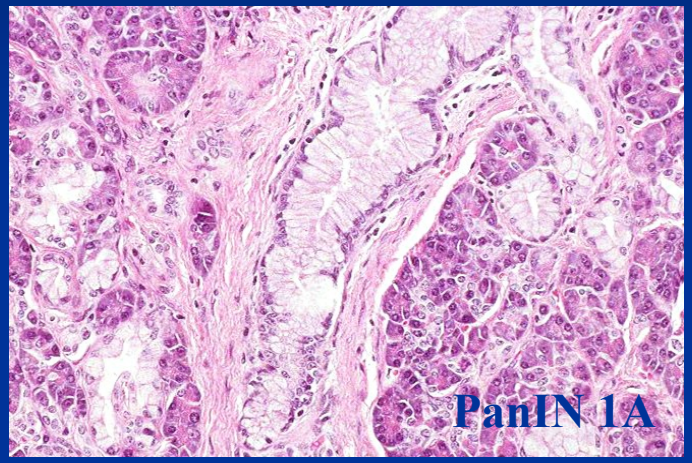
Oncogenesis of pancreatic ductal adenocarcinoma: current accepted linear model of progression.

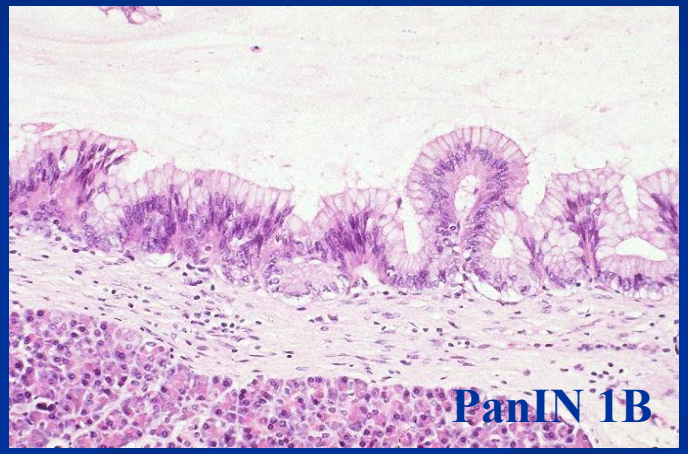
- **Activation of oncogenes**
  KRAS, MYB, AKT2, AIB1
- **Inactivation of tumor suppressor genes**
  p16, TP53, DPC4, BRCA2, LKB1/STK11
- **DNA Mismatch Repair**
  MSH2, MLH1,….
- **Epigenetic alterations, dysregulation of oncoproteins, activation of Hedgehog and Notch signalling pathways**

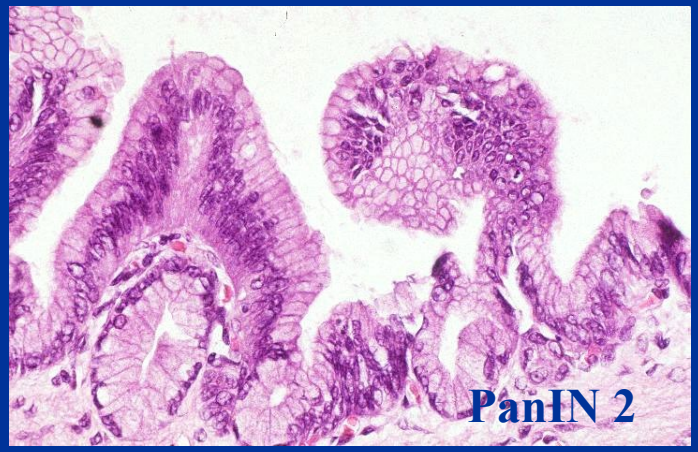


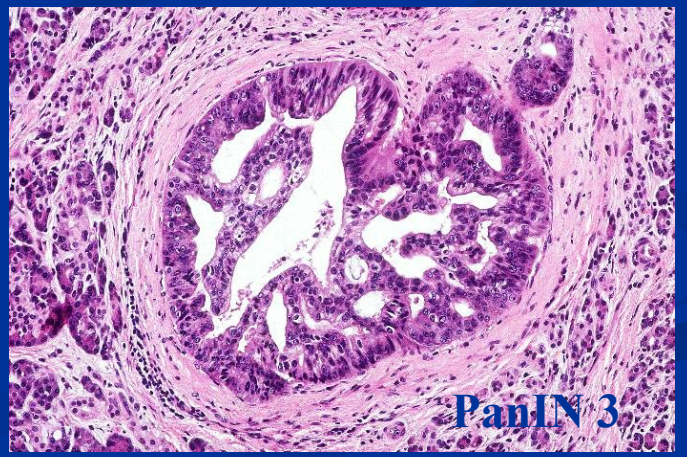
Hruban et al. Progression model of pancreatic cancer. Clin Cancer Res 2000; 6: 2969-2972.

PanIN lesions: low grade *vs* high grade









Histogenetic classification of tumors

- Epithelial tumors
- Mesenchymal tumors
- Neuroectodermal tumors
- Embryonal tumours
  (germ cell tumors + organ specific (hepatoblastoma, pancreatoblastoma, nephroblastoma,…)
- Mixed tumors

Principal characteristics of carcinomas and sarcomas

Feature	Carcinoma	Sarcoma
Origin	Epithelium	Connective/mesenchymal tissue
Behaviour	Malignant	Malignant
Frequency	Common	Relatively rare
Preferred route of metastasis	Lymph (into lymph nodes)	Blood (into liver, bones, brain,…..)
In situ phase	Yes	No
Age group	Usually over 50 years	Usually bellow 50 years

Epithelial tumours

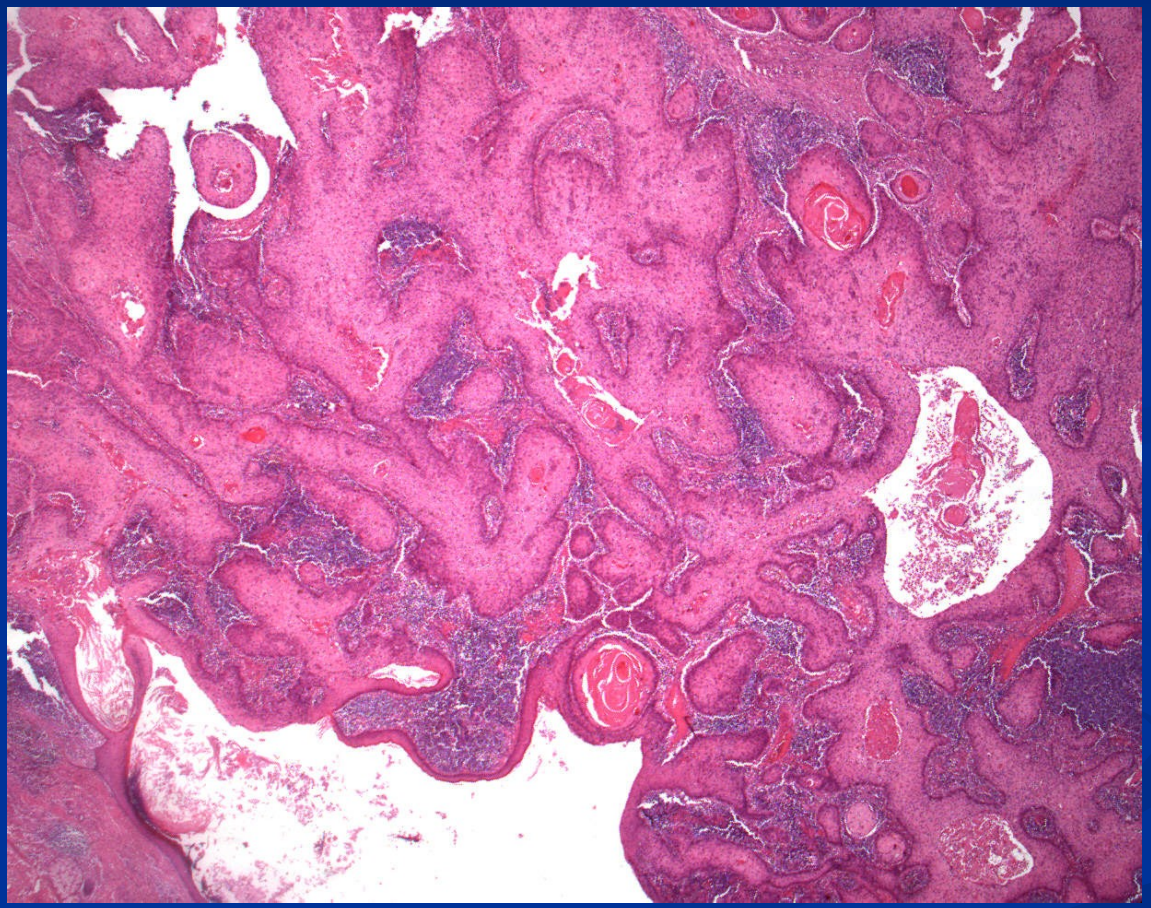
- From superficial epithelium (papilloma/carcinoma)
- From glandular epithelium (adenoma/adenocarcinoma)
- From specialized organs (adenoma/adenocarcinoma)…liver, kindey, adrenal gland

Epithelial tumors

Epithelium	Benign	Malignant
Squamous	Squamous cell papilloma	Squamous cell carcinoma
Transitional	Transitional cell papilloma	Transitional cell carcinoma
Basal cell	Basal cell papilloma	Basal cell carcinoma
Glandular	Adenoma	Adenocarcinoma

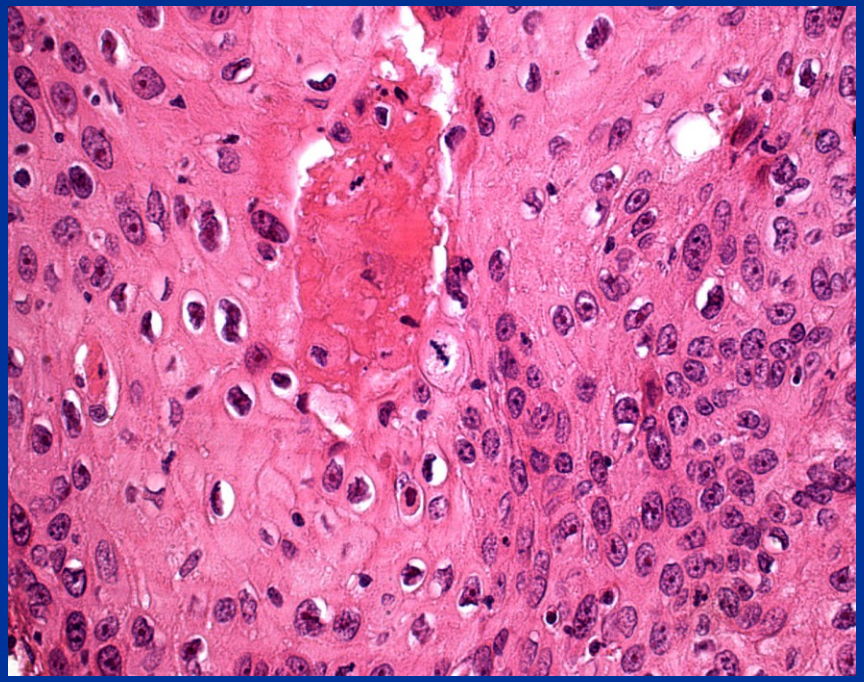
Squamous cell carcinoma

(skin, oral cavity, oesophagus,…lung (squamous metaplasia)

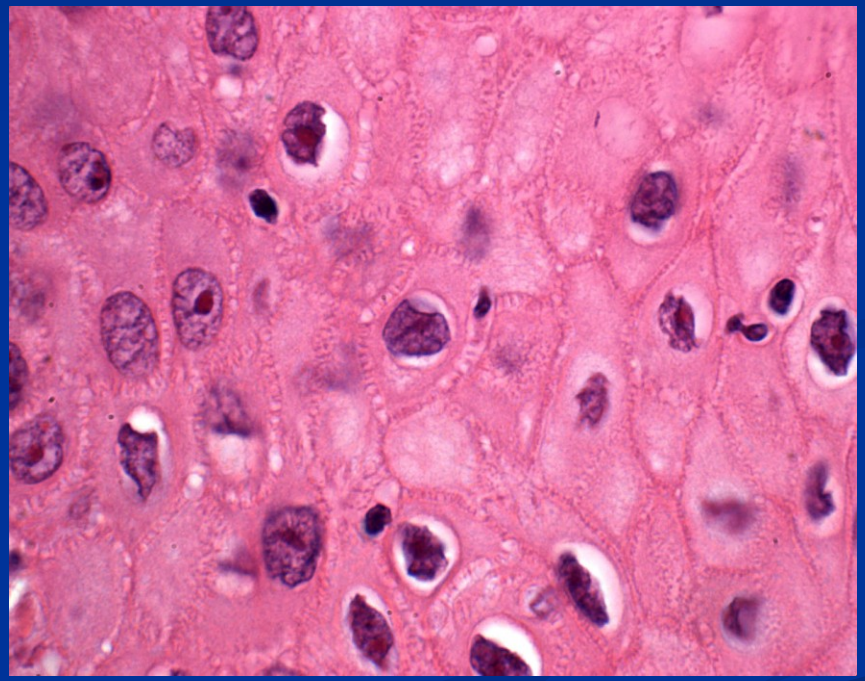


Squamous cell carcinoma

Squamous cell carcinoma

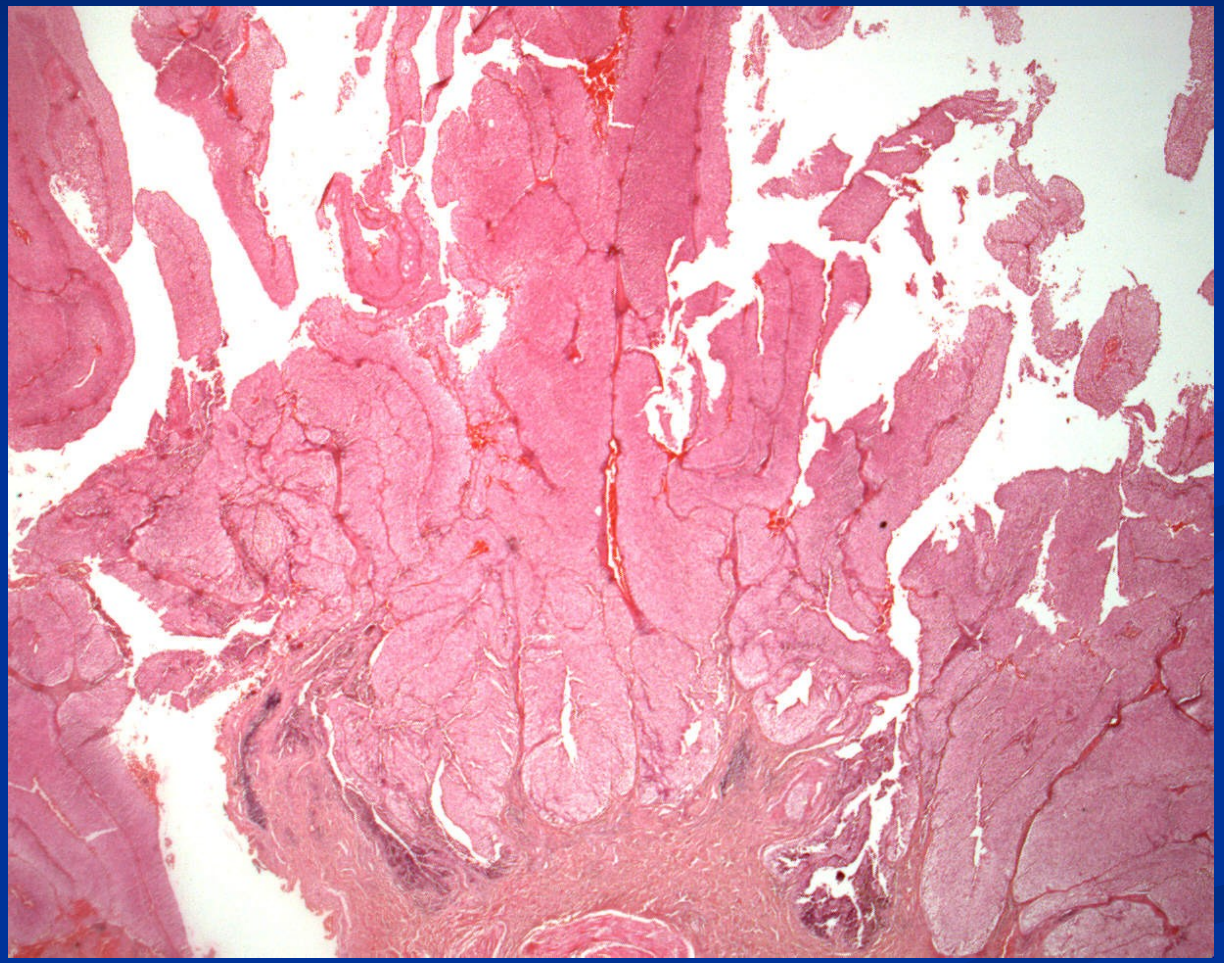


Keratinisation, mitoses in SCC

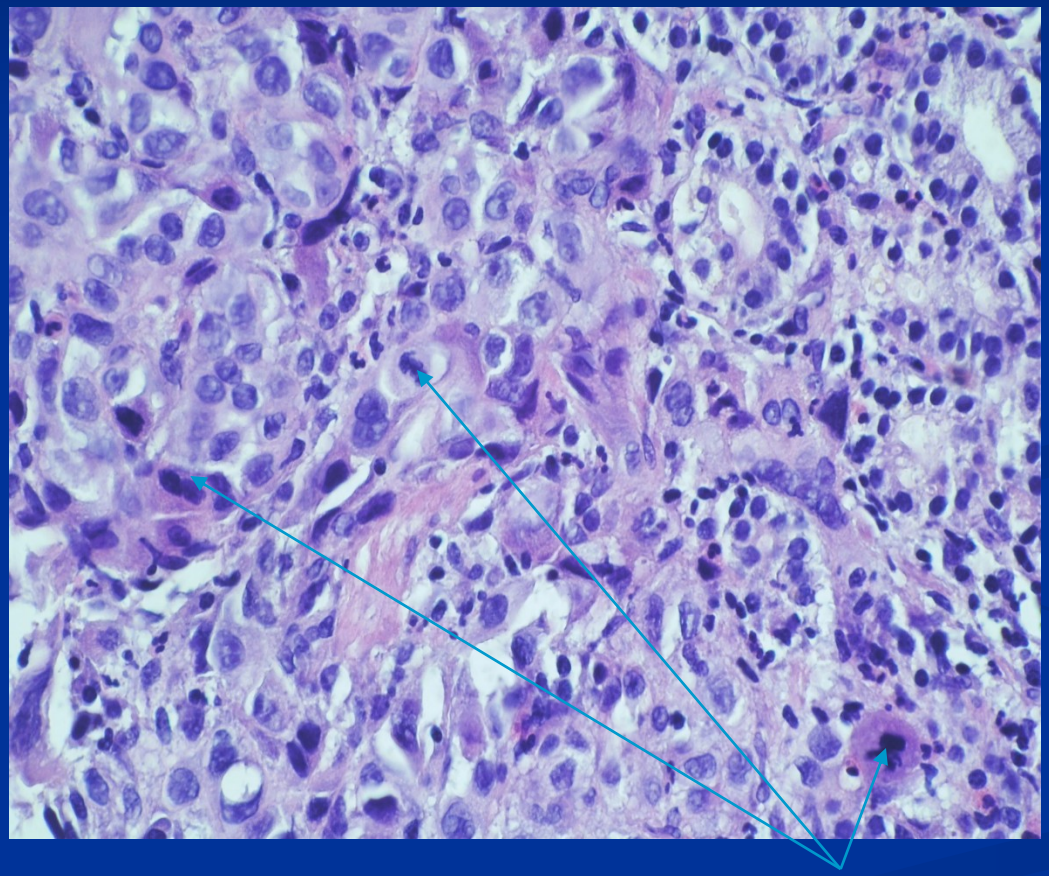


Intercellular bridges- tonofilaments

Papillocarcinoma – urinary bladder



Poorly differentiated carcinoma



High mitotic count

Pleomorfism, anizocytosis, anizonucleosis, hyperchromasia, prominent nucleoli, ….

Immunohistochemistry in dagnostics of poorly differentiated tumours, tumours of unknown origin,..

Markers of epithelial tissue: cytokeratins, EMA, CEA,….

Adenoma – benign tumour – glandular epithelium

Adenomatous polyps of colon and rectum - adenomas:

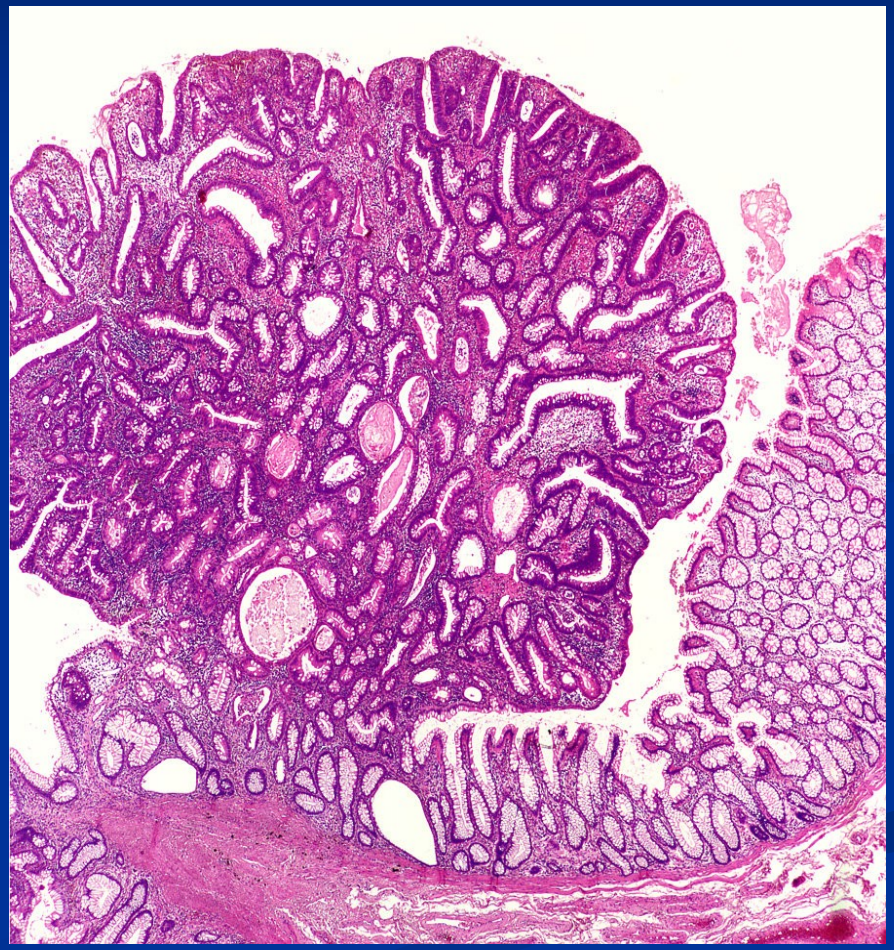
- tubullar
- vilous
- tubulovillous

- acinar (salivary glands)
- follicular (thyroid gland)
- solid (liver, adrenal gland)
- cystadenoma (ovarium): uniloculare, multiloculare; papilliferum, evertens)
- oncocytic - oncocytoma

Adenomatous polyp – tubullar adenoma

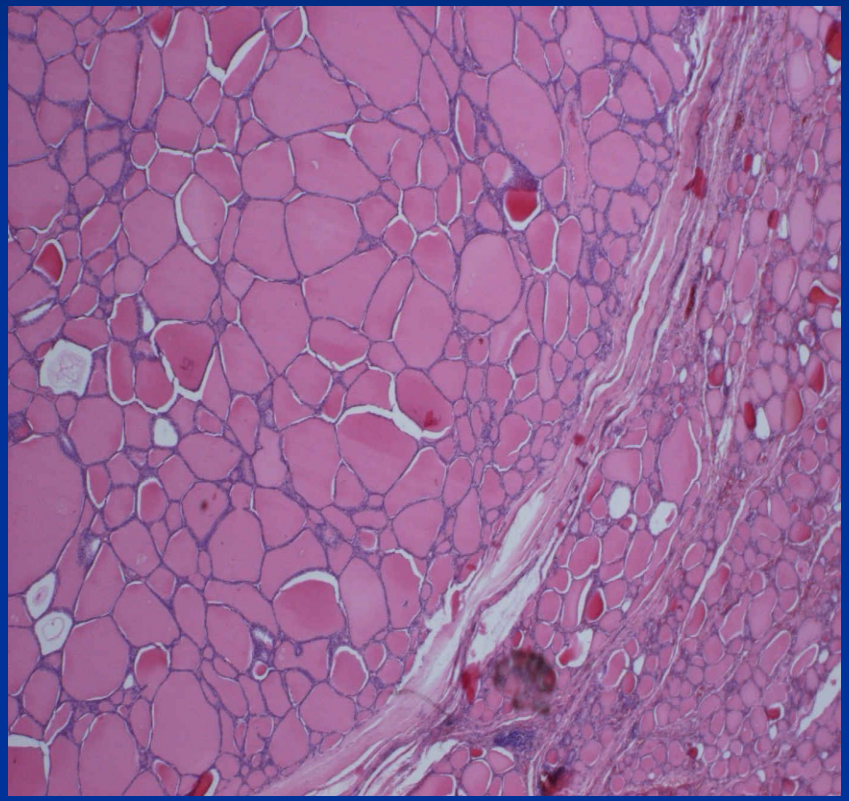
Multiple adenomatous polyps in familiar adenomatous polyposis (AD; *APC* gene)

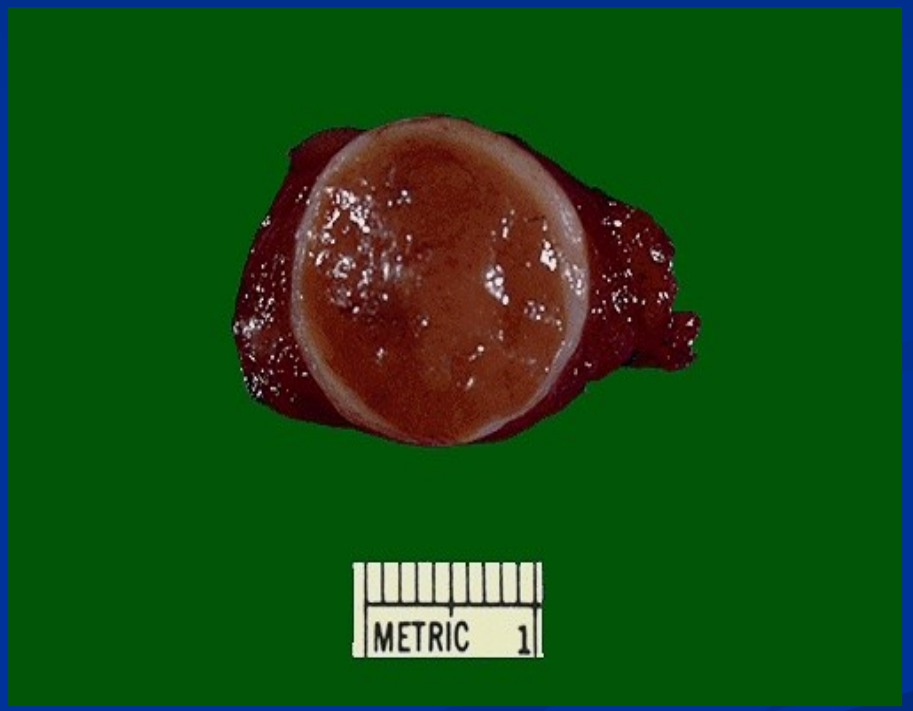
Adenomatous polyps of large intestine



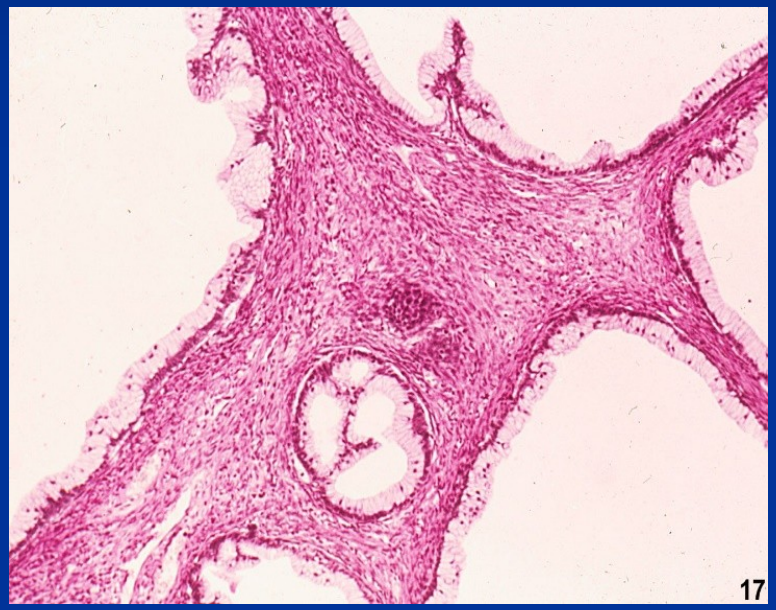
Tubular adenoma, low grade dysplasia

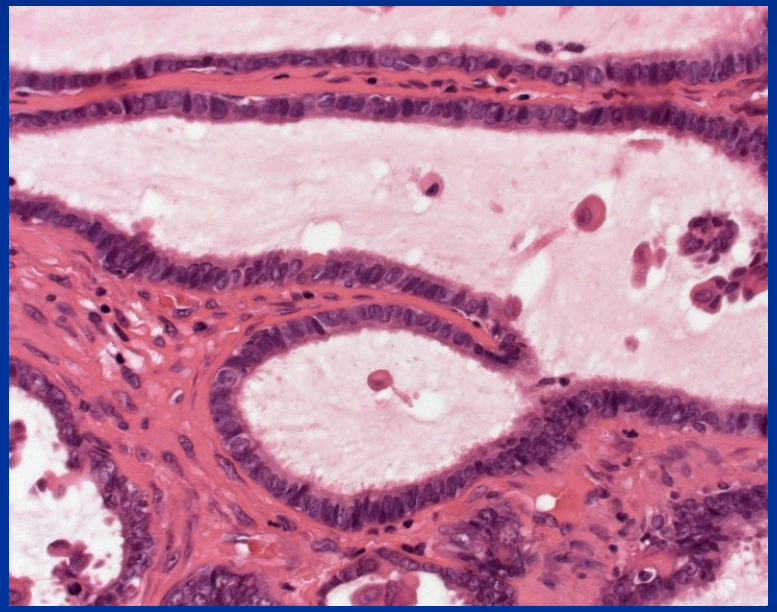
Follicular adenoma - thyroid



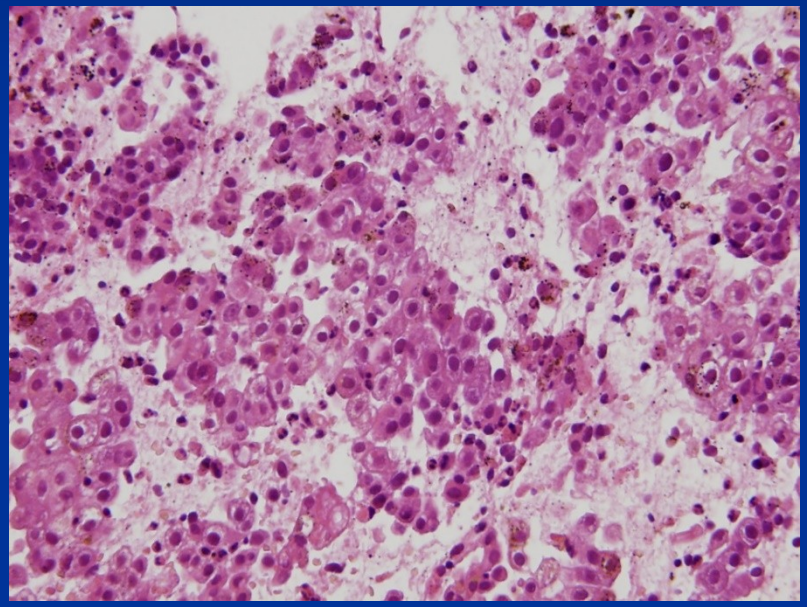


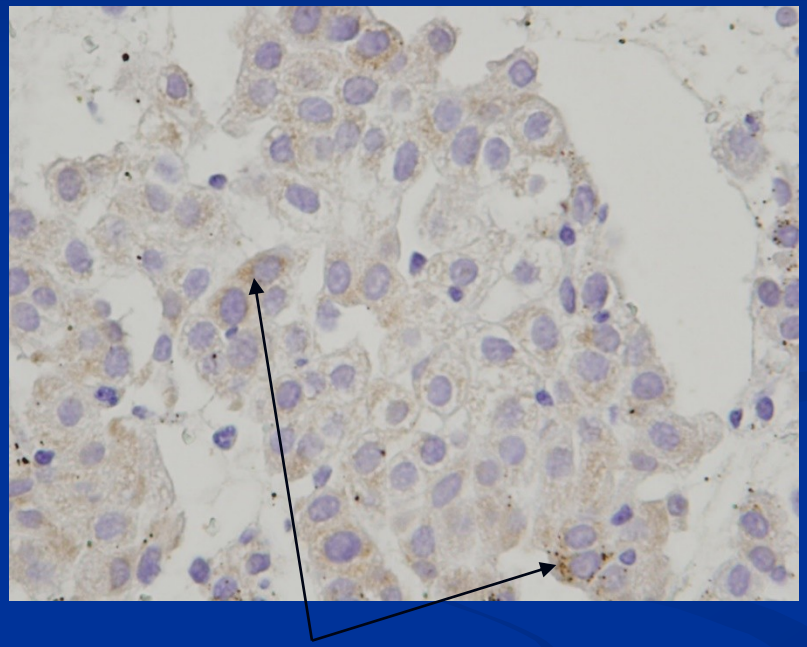
Cystadenoma – ovary
Mucinous versus serous





Oncocytoma





Expression of mitochondrial antigen - immunohistochemistry

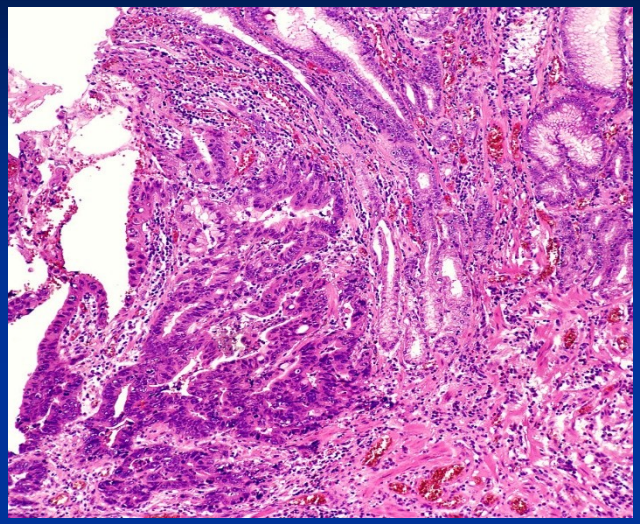
Adenocarcinoma
(malignant, from glandular epithelium)

- Medullary (parenchyma > stroma)
- Scirhotic (↑desmoplastic stroma)

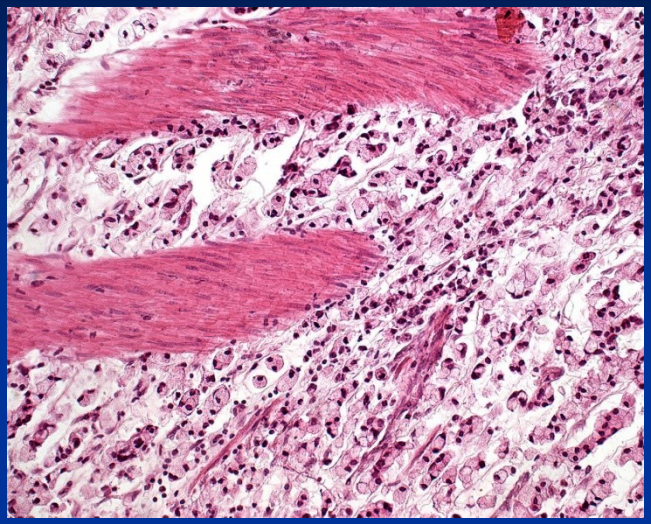
Adenocarcinoma - GIT (colorectal, stomach, …..):

- Intestinal type
- Diffuse (scirhotic)
- Mucinous, gelatinous

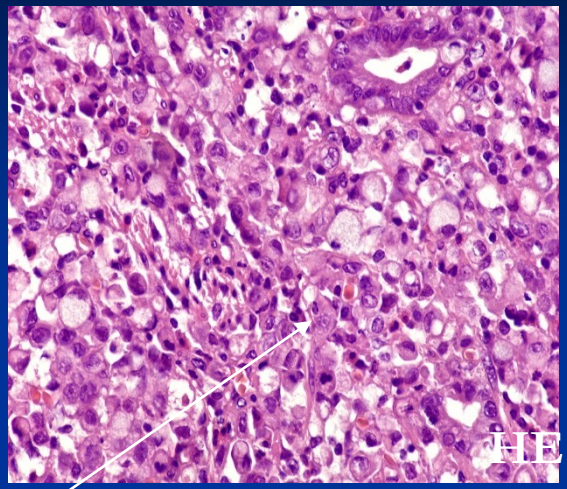
Hepatocelullar carcinoma (trabecular)
Adenoid cystic carcinoma (salivary gland, respiratory tract)
Carcinomas of glands of mesodermal origin (renal cel carcinoma)

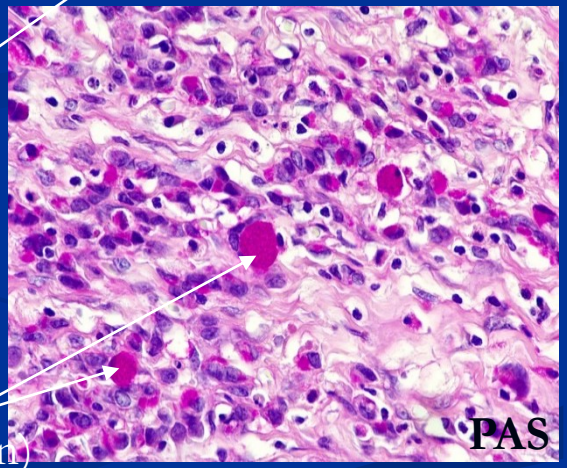


Adenocarcinoma, intestinal type

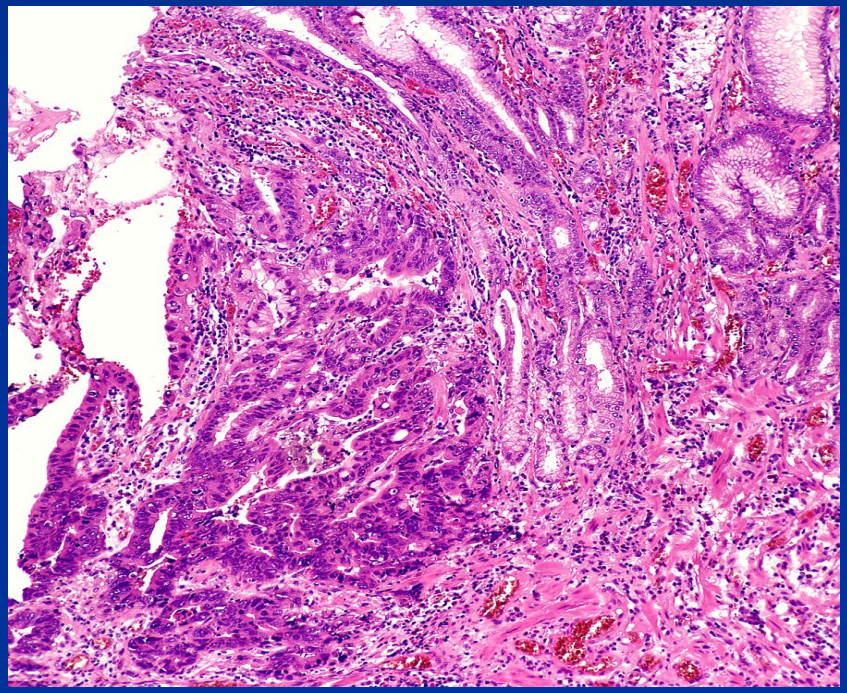


Adenocarcinoma – gelatinous, mucinous

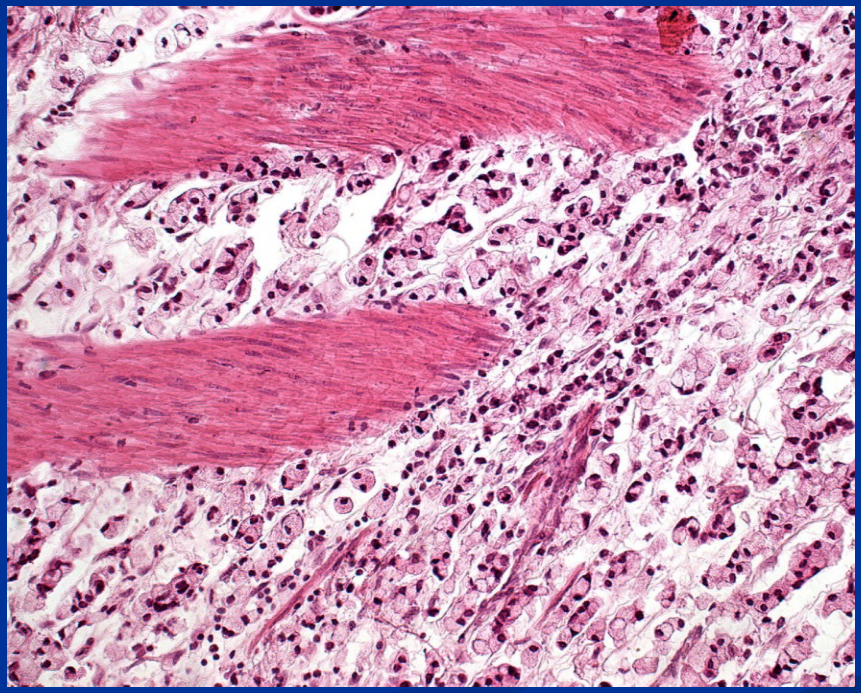




Diffuse adenocarcinoma; with signet ring cells (PAS+ mucin)



Adenocarcinoma, intestinal type



Adenocarcinoma – gelatinous, mucinous

Neuroendocrine neoplasia (NEN)

- **Definition**

NENs are epithelial or neuroectodermal neoplasias defined by the presence of small or large vesicular granules containing proteins with hormonal or neural effects, expressing markers of membrane proteines localized on small „synaptic“ vesicles (synaptophysin) or large „hormonal“ granules “ (chromogranin A)

Neuroendocrine neoplasia (NEN) (carcinoid tumours)

- Spectrum of tumours from well differentiated neuroendocrine tumours (previously called carcinoids) to poorly differentiated neoplasms with neuroendocrine features (small and large cell neuroendocrine carcinoma)

Localisation: GIT, respiratory tract,… (derived from neuroendocrine cells in this organs)

- **Neuroendocrine differentiation** (neurosecretory granules: chromogranin+, synaptofysin+ …detected by immunohistochemistry)

- **Associated paraneoplastic syndromas**

- **carcinoid syndroma- serotonin**

(skin flushing, abdominal pain, diarrhea, difficulty breathing, rapid heart rate, low blood pressure, skin lesions on the face (telangiectasias), and wheezing, fibrosis of tricuspidal and pulmonary valves)

- **Cushing syndroma – ACTH**

- **syndrome of inappropriate antidiuretic hormone (SIADH) secretion**

- **Eaton-Lambert syndroma**

(autoimmune myastenic disorder characterized by muscle weakness of the limbs, antibodies against presynaptic voltage-gated calcium channels)

Neuroendocrine tumour (NET)
Neuroendocrine carcinoma (NEC)

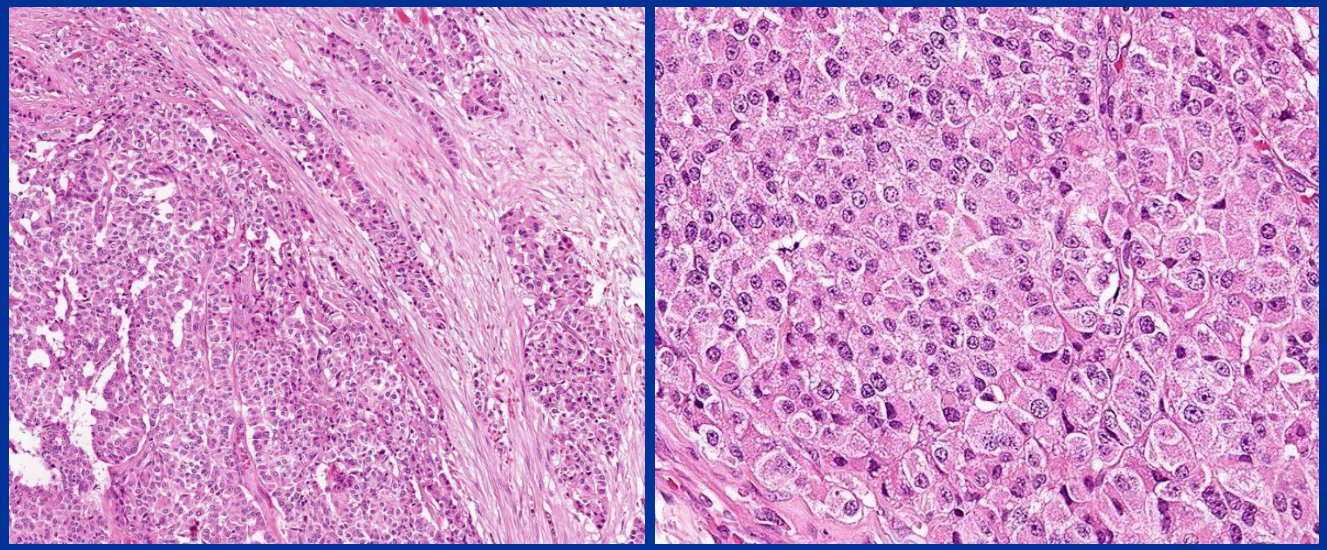
- **Neuroendocrine tumor - NET G1/G2/G3**
  well differentiated neuroendocrine tumor
  low grade (G1/G2) and high grade (G3)
  (previously called carcinoids and atypical, malignant carcinoids)

- **Neuroendocrine carcinoma - NEC (G3)**
  poorly differentiated neuroendocrine neoplasm
  neuroendocrine carcinomas, high grade malignant tumors
  - Small cell neuroendocrine carcinoma
  - Large cell neuroendocrine carcinoma

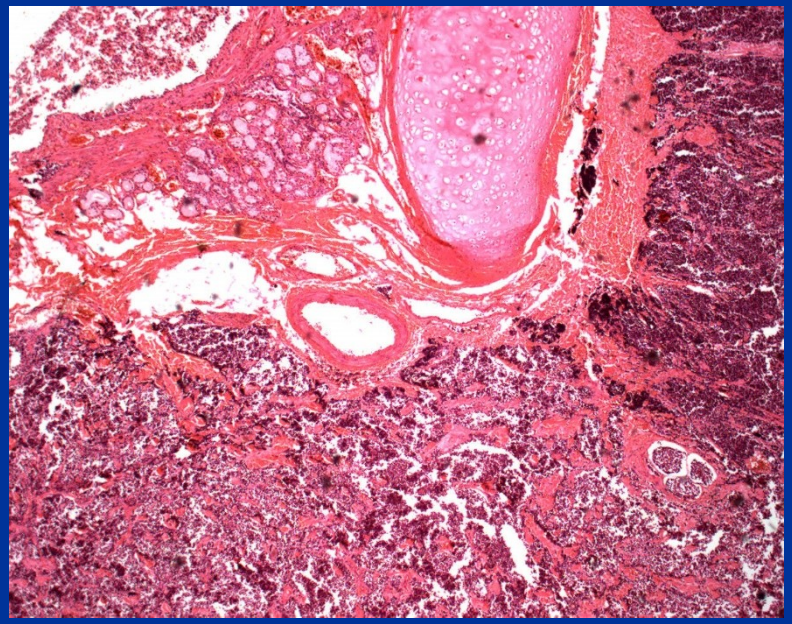
- **Mixed neuroendocrine noneuroendocrine neoplasm (MiNEN)**
- (previously called MANEC)

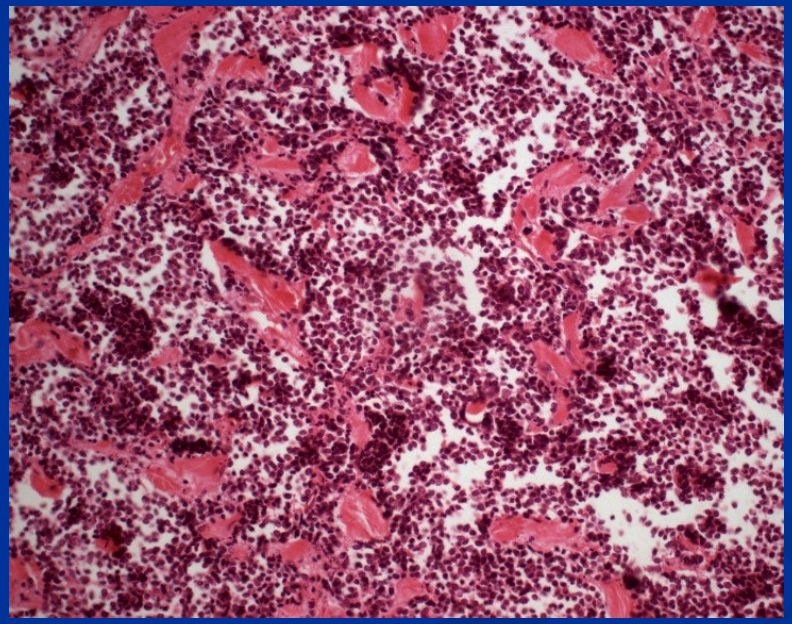
Well differentiated neuroendocrine neoplasia

Neuroendocrine tumour – NET (previously carcinoid)



Poorly differentiated neuroendocrine neoplasm
Neuroendocrine carcinoma (NEC)
Small cell neuroendocrine carcinoma





Mesenchymal tumors

Tissue of origin	Benign	Malignant
Smooth muscle	Leiomyoma	Leiomyosarcoma
Striated muscle	Rhabdomyoma	Rhabdomyosarco-ma
Adipose tissue	Lipoma	Liposarcoma
Blood vessels	Angioma	Angiosarcoma
Bone	Osteoma	Osteosarcoma
Cartilage	Chondroma	Chondrosarcoma

Germ cell tumors

- Derived from germ cells
- Somatic differentiation (teratomas – mature, immature)
- Extrasomatic differentiation (chorioncarcinoma, yolk sack tumor)
- testis, ovary + extragonadal germ cell tumors in mediastinum, retroperitoneum, epiphyseal region , sacrococcygeal localisation,…
- Precursor lesion of testicular germ cell tumours: germ cell neoplasia in situ (GCNIS)

Histogenesis of germ cell tumors

Differentiation of primitive cell along the gonadal line
(gonocyte, spermatogonia), without developed differentiation potencies
- **Seminoma**

Primitive germ cell of origin

Totipotent cell

Undifferentiated cell
- **Embryonal carcinoma**

Extraembryonally differentiated
- **Yolk sack tumor**
- **Chorioncarcinoma**

Intraembryonally differentiated
Teratoma (mature, immature, with malignant transformation of somatic elements)
- **(Polyembryoma)**

- **Germ cell tumor of a single histological type (pure forms)**

- Seminoma/dysgerminoma

Non-seminomatous germ cell tumour:

- Embryonal carcinoma
- Yolk sack tumor
- Polyembryoma
- Chorioncarcinoma
- Teratoma
  - differentiated mature
  - differentiated immature
  - with malignant transformation – with somatic type malignancy

- **Mixed germ cell tumor** (40 %)

- *Oncomarkers:* aFP, hCG, hPL, PLAP, CEA, LDH (detection in serum and/or tissues; diagnostics and monitoring of patients during/after a treatment)

Germ cell tumors characteristics

tumor	age	structure	oncomarker
Seminoma	40-50	Solid, polygonal clear cells, stromal lymfocytic infiltration.	10 % hCG
Embryonal carcinoma	20-30	Undifferentiated, pleiomorphic cells in sheets, solid, tubullary and papillary; necroses	90 % hCG and/or aFP
Yolk sack tumor	3	Poorly differentiated cells, broad spectrum arrangement of cuboidal and columnar cells, glomeruloid formation	90 % aFP
Chorioncarcinoma	20-30	Cytotrophoblast and syncytiotrophoblast withour villous formation, haemorhage, necroses	100 % hCG
Teratoma	*	Tissues of 3 germ layers in various stage of differentiation	50 % hCG and/or aFP
Mixed tumors	15-30	Variable presence of different components; e. g. teratoma+embryonal carcinoma	90 % hCG and/or aFP

* Prepubertal and postpubertal type (often within mixed germ cell tumorus)

Classification of testicular germ cell tumours

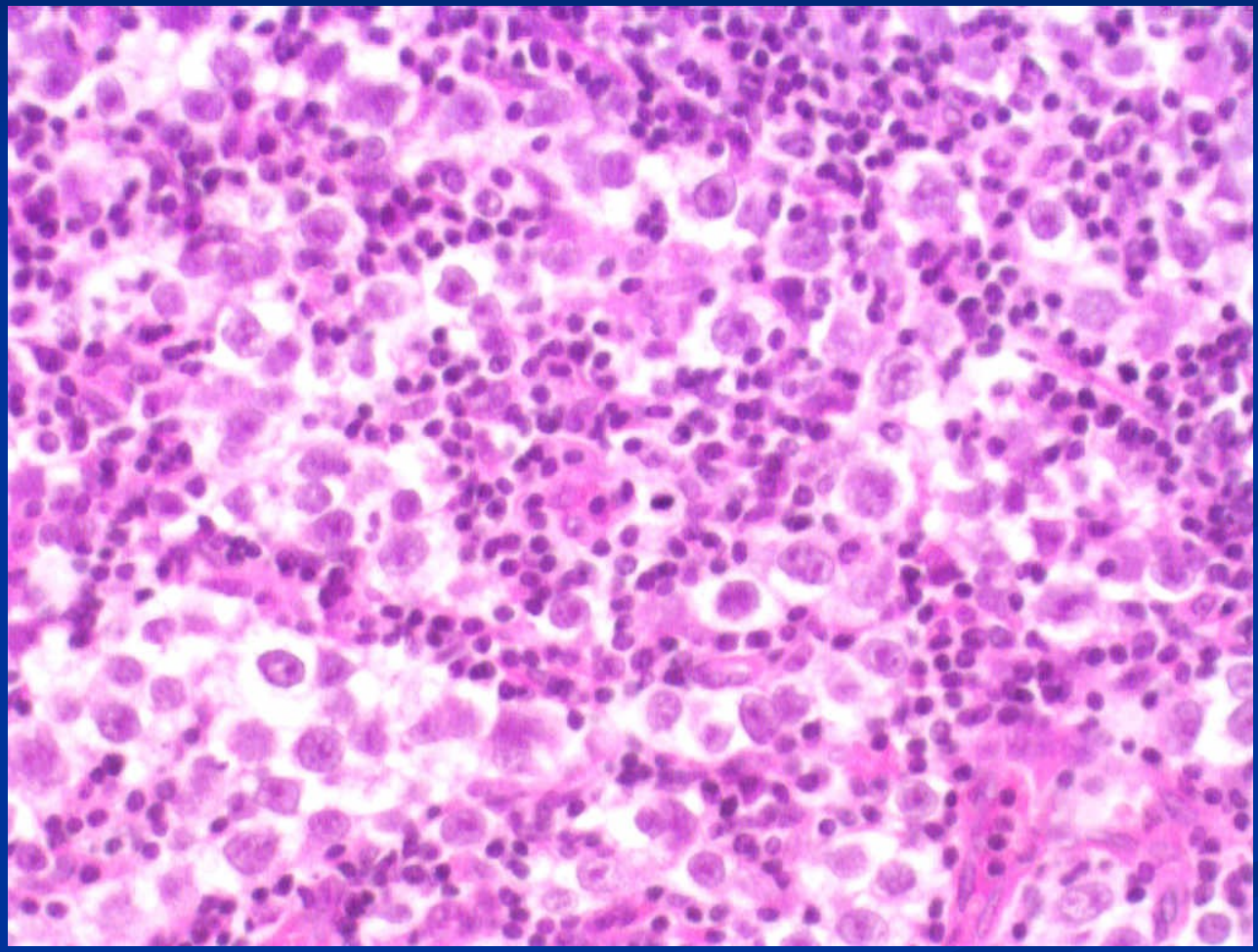
Germ cell tumours derived from GCNIS
(aggressive, oncological therapy)

Tumours of a single histological type (pure forms)
Seminoma
Non-seminomatous germ cell tumours
- Embryonal carcinoma
- Yolk sack tumours, postpubertal type
- Choriocarcinoma
- Teratoma, postpubertal type

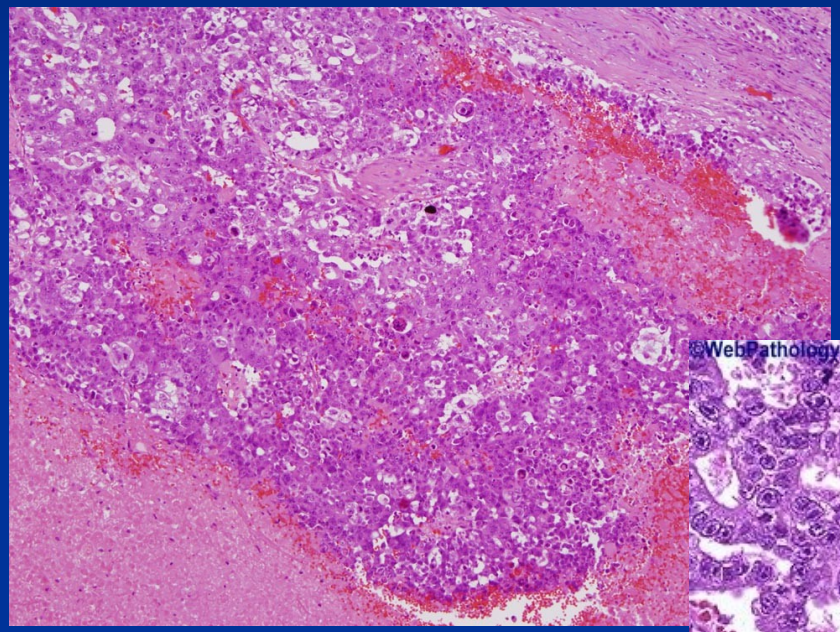
Mixed germ cell tumorus (of more than one histological type)

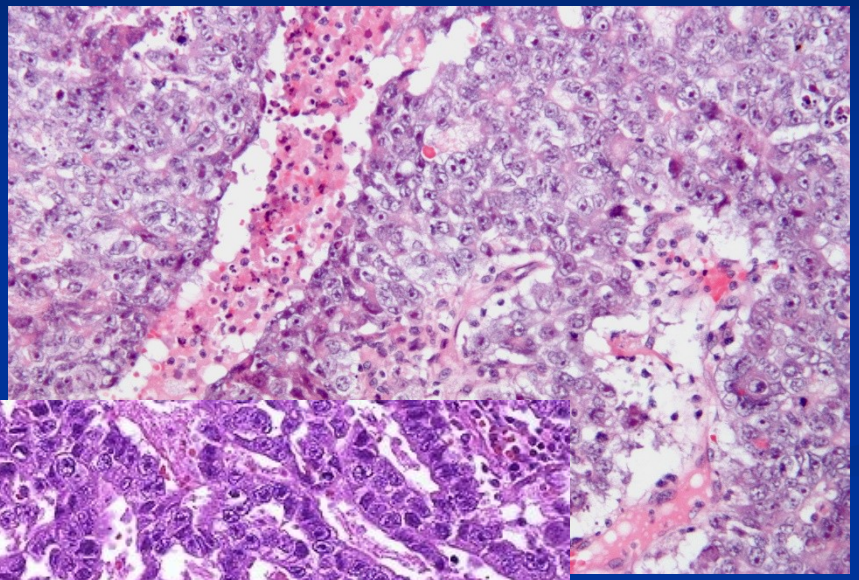
Germ cell tumours unrelated to GCNIS
(biologically favourable)
- Spermatocytic seminoma (older men, locally aggressive, nonmetastic)
- Teratoma – prebubertal type
- Yolk sack tumour – prepubertal type
- Mixed teratoma and yolk sack tumour – prepubertal type

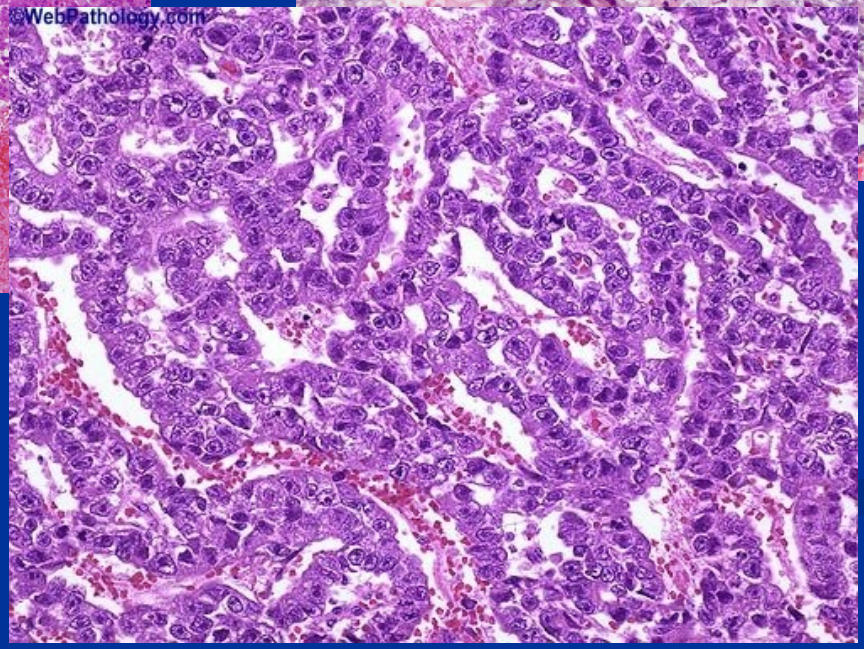
Seminoma



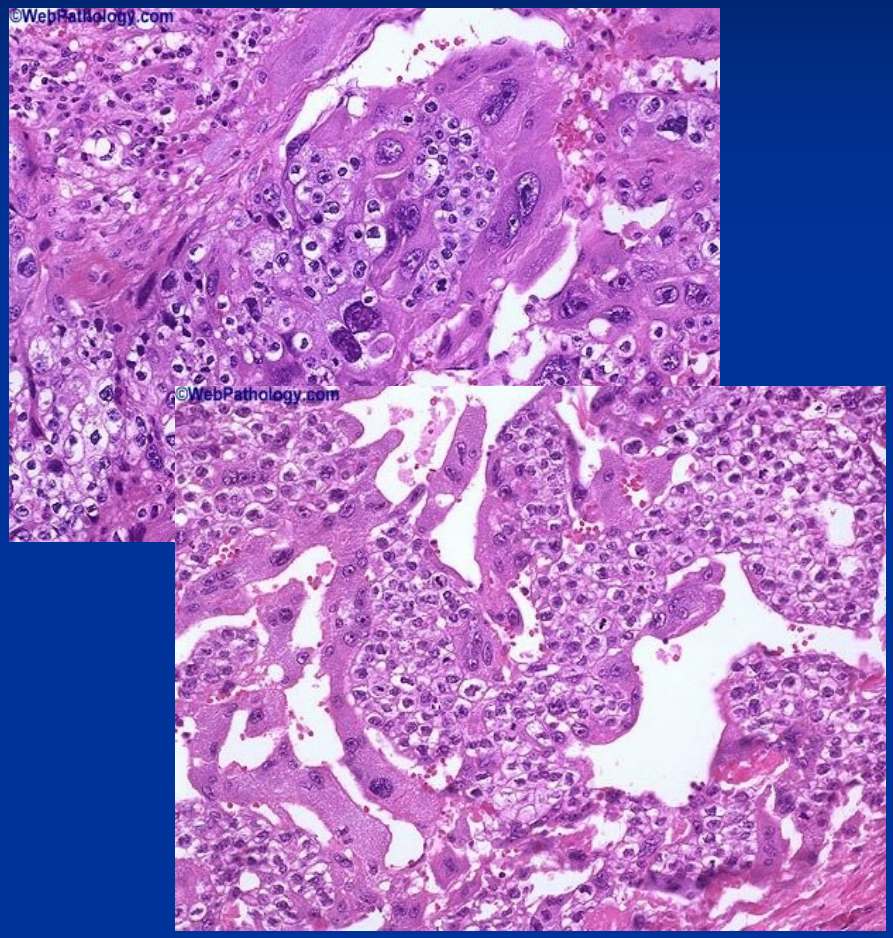
Germ cell tumors – undifferentiated: embryonal carcinoma



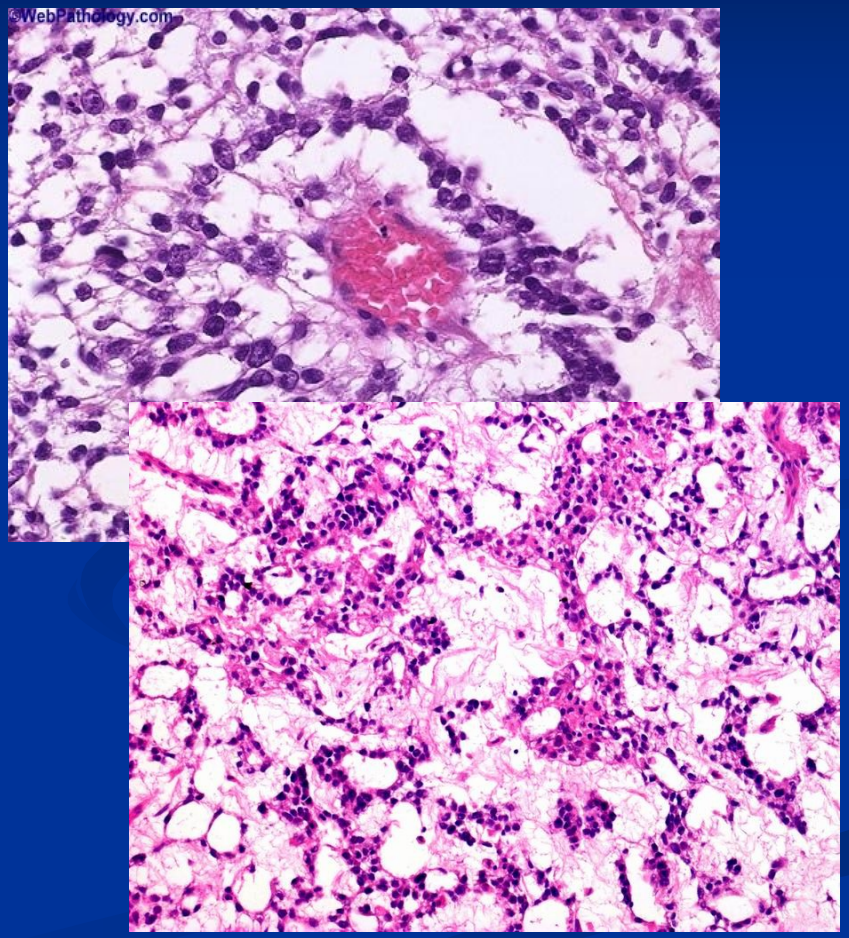




Germ cell tumors: extraembryonal differentiation

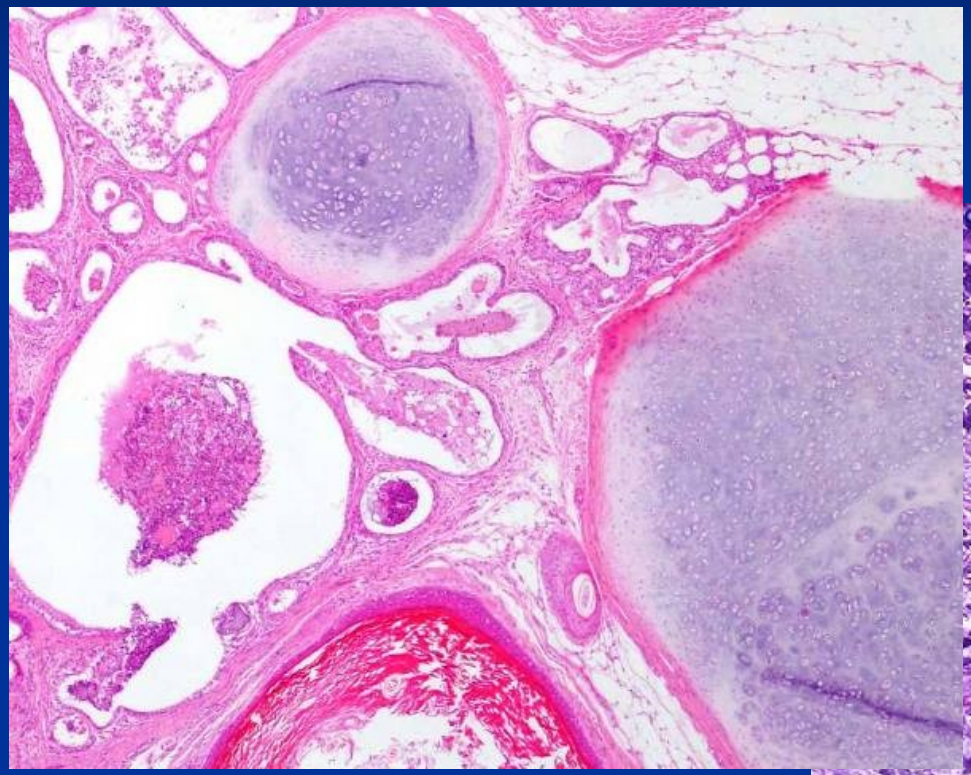


Choriocarcinoma

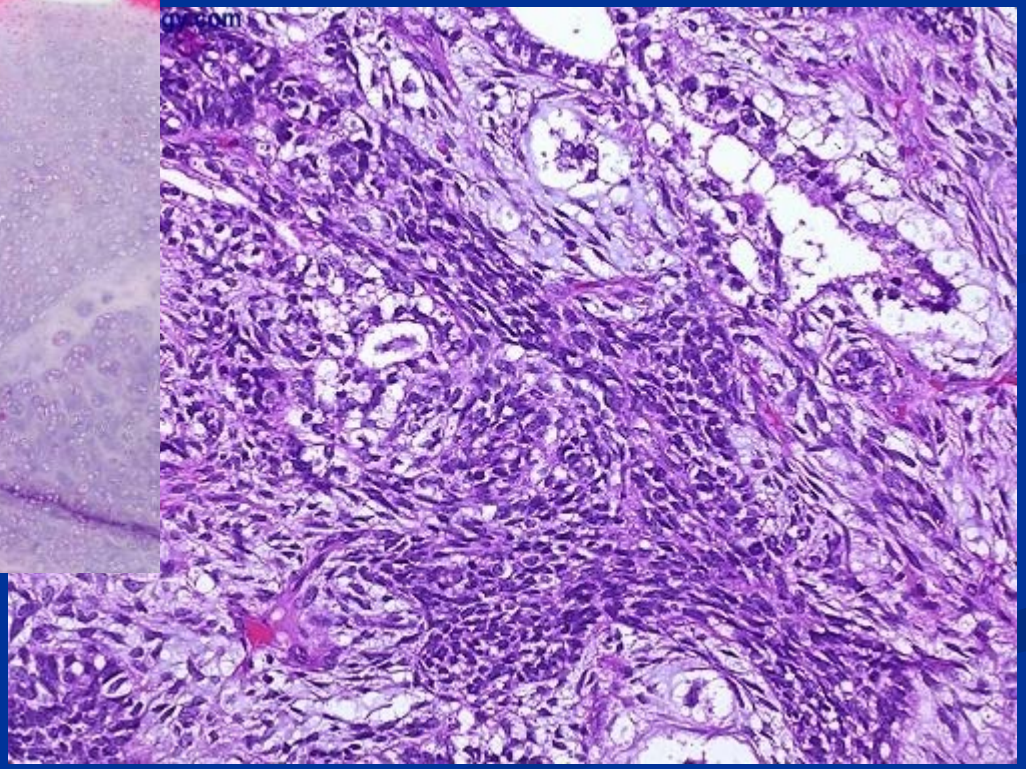


Yolk sack tumor

Germ cell tumors: intraembryonal differentiation



Mature teratoma



Immature teratoma

Extragonadal germ cell tumors (EGT)

- Germ cell tumor in primary extragonadal localisation, M>F
- From primordial germ cells? Migration failure? Localisation failure of totipotent cells? Ectopic germ cell in healthy individuals?
- In midline structures (descent tracts of germ cells into the gonadal blastema)
  - Diencephalopineal region, sacrococcygeal region, in anterior mediastinum, retroperitoneum,…, thymus, prostate, stomach,……
  - Seminomatous and nonseminomatous, both poor and mixed
  - A worse prognosis; exception: EG seminoma

Mesothelioma

- Pleura, peritoneum, pericardium, tunica vaginalis, genital tract (benign adenomatoid tumor)

- **Malignant mesothelioma**

1. Epitheloid type
2. Sarcomatoid type
3. Mixed type

- Asbestos exposure
- 50 % die within 12 months

Benign mesotheliomas rare:

- Well differentiated papillary mesothelioma
- Benign adenomatoid tumour (tunica vaginalis, genital tract)

- Solitary fibrous tumor – soft tissue tumour - previously called benign mesothelioma

Cell of origin	Tumor
Glial cells	Astrocytoma (both low grade and high grade) Oligodendroglioma (both low grade and high grade) Glioblastoma (Ependymoma)
Primitive neuroectodermal cells	Medulloblastoma (CNS; central nervous system, cerebellum) Neuroblastoma (PNS; peripheral nervous system, adrenals) Retinoblastoma …..*all mentioned are pediatric tumors*
Arachnoidal cells	Meningioma
Nerve sheath cells	Schwannoma, neurofibroma Malignant schwannoma, neurofibrosarcoma
ANS; autonomous nervous system	Paragangliomas, chemodectomas, pheochromocytoma

+ secondary, metastatic tumors

CNS tumors

- **Clinicopathological features:**
- **CNS tumors do not metastasise to othe organs**
  - (only infiltration of adjacent tissues and spreading through
  - CSF pathways)
- **Local effects**
  - Signs related to the site of the tumor
  - e.g. epilepsy with a temporal lobe tumor, paraplegis in spinal cord tumor
- **Mass effects**
  - Signs and symptoms of space occupying lesions
  - Vasogenic oedema around CNS tumor
  - Herniation
  - Hydrocephalus in posterior fossa tumor

Diagnosis of neoplasias

- Early detection and staging important for successful treatment
- The role of screening programs in early diagnostics

- Laboratory values (incl. tumor markers), radiography, endoscopy, isotope scan, CT scan, mammography, MRI and **tissue biopsy**
  (histopathological examination (incl. molecular pathology and genetics) → tumor typing))

diagnostic algorithm

clinical signs
clinical examination

cancer suspicion

yes

no

diagnostic imaging techniques
(x-ray, CT, MRI,...USG,...)

no

suspected cancer

yes

benign tumor, pseudotumor

Cancer staging → therapy

exploratory biopsy

malignant tumor

typing, grading, staging

Antineoplastic treatment modalities

- Curative (with intent to cure)
- Palliative (provides symptomatic relief but does not cure)

- Surgical treatment (in solid tumors with a goal of total resection)
- Adjuvant therapies:

- Irradiation therapy
- Chemotherapy (especially effective in hematooncological malignancies)
- Immunotherapy
- Hormonal therapy (breast, prostate)
- Targeted therapy (biologic therapy); individualized, personalized
- Hematopoietic cell transplantation

*neoadjuvant therapy

(aims to reduce the size or extent of the cancer before using radical treatment intervention)

Paraneoplastic syndromes

- **Local effects of tumor growth**

- **+paraneoplastic effects of tumors**

(=signs and symptoms undirect to either primary tumor or its metastases)

Causes of paraneoplastic syndromes

- Vasoactive tumor products, produced by tumor cells (e.g. serotonin, histamin, catecholamins, prostaglandins,…)
- Ectopic hormone production by tumor cells (ACTH in small cell lung carcinoma,..)
- Osteolytic skeletal metastases causing hypercalcaemia
- Unidentified tumor products or circulating immune complexes (vasculitis, nephritis,…)
- Production of autoantibodies by tumor cells (paraneoplastic polymyositis, myastenic syndrome, scleroderma,…)

* musculoskeletal, neurologic and cutaneous manifestations are often in paraneoplastic syndromes

Thank you for your attention…..