Cancerogenesis and neoplasia. Oncology.

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)

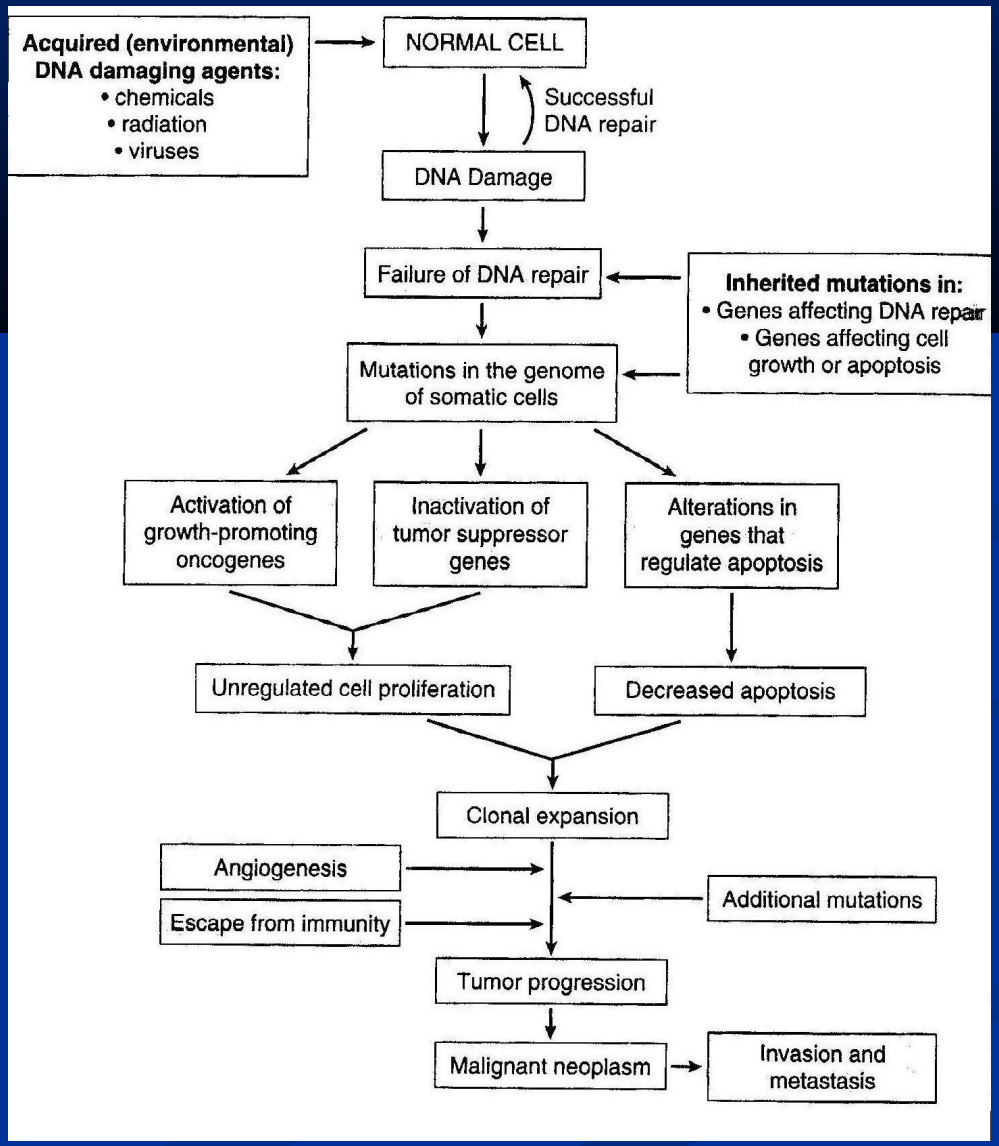
- The growth-inhibiting tumor suppressor genes

(recessive; inhibition of growth)

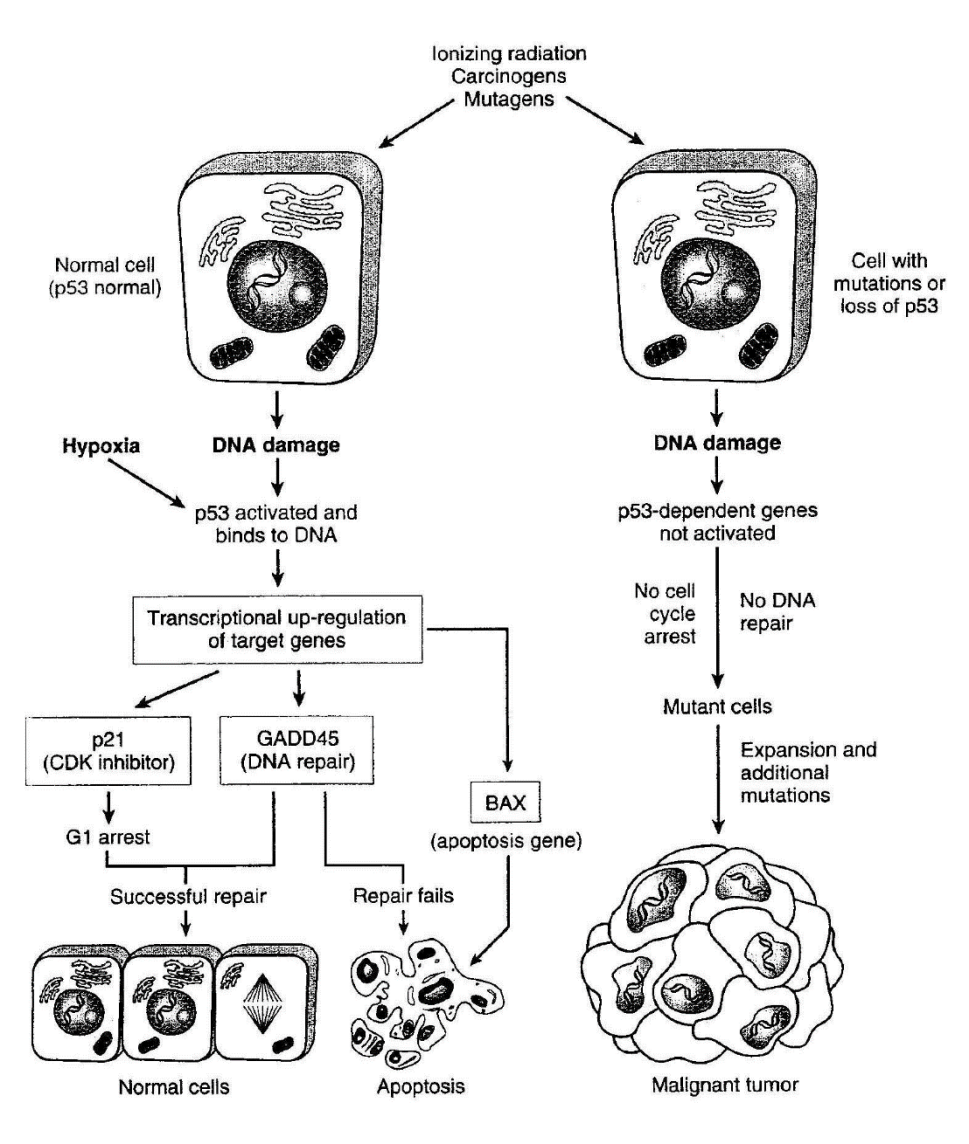
- Gatekeepers (p53, RB)
- Caretakers (genes involved in maintenance of genome integrity and DNA repair)

- 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:

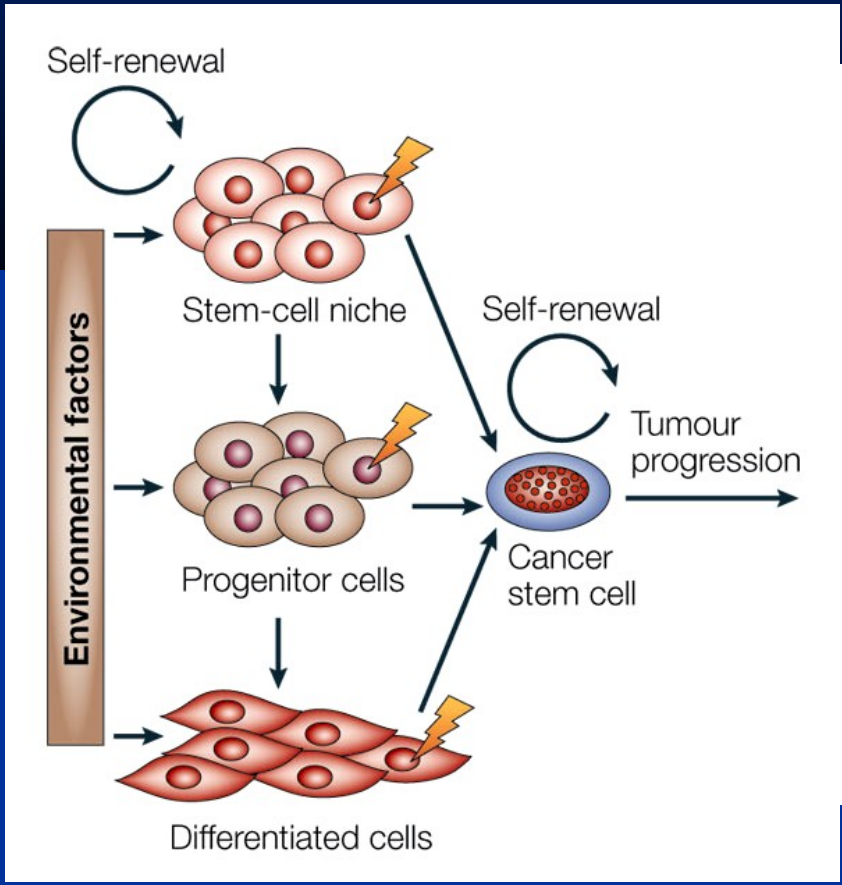
- Parenchyma (proliferating neoplastic cells)
- Stroma (connective tissue and blood vessels, source of mediators promoting the tumor growth and angiogenesis)
- (Cancer stem cells – tumor initiating cells)

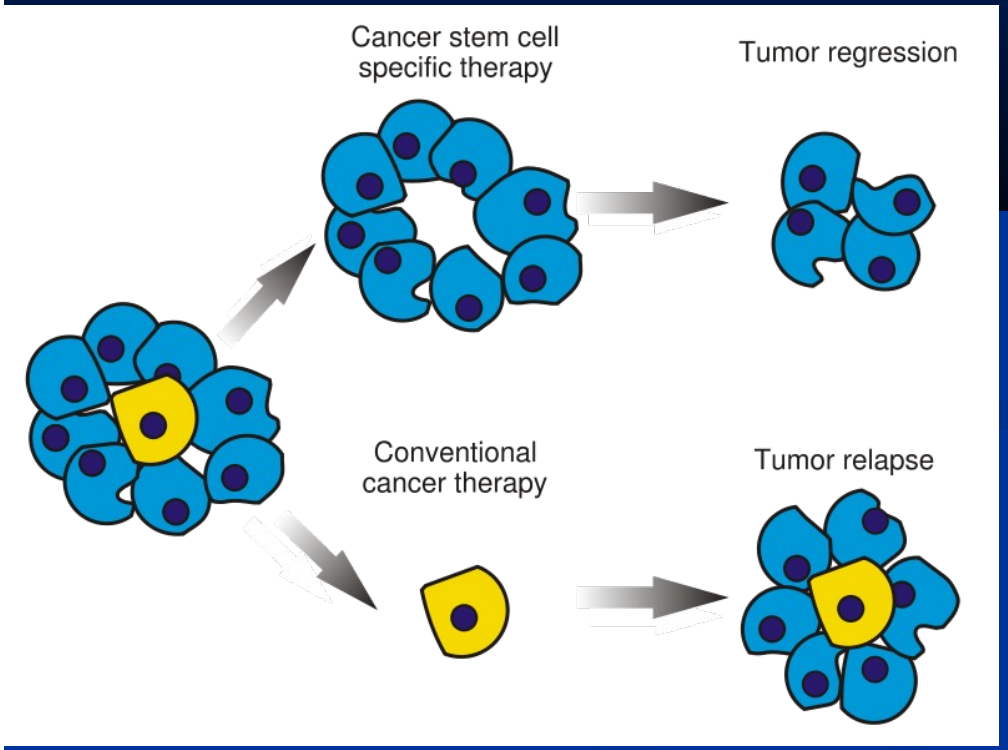
- Cross-talk between stroma and parenchyma
- Tumors with abundant parenchyma: soft and flashy
- Tumors with abundant collagenous stroma – with desmoplastic stroma: stony hard - scirrhous

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





Classification of tumors

- According to their biological behavior:
  - Benign
  - Semimalignant and potentionally malignant
  - Malignant

- Histogenetic classification of tumors (morphologic classification according to tissue of origin)
  - epithelial
  - mesenchymal
  - neuroectodermal
  - germ cell
  - mixed

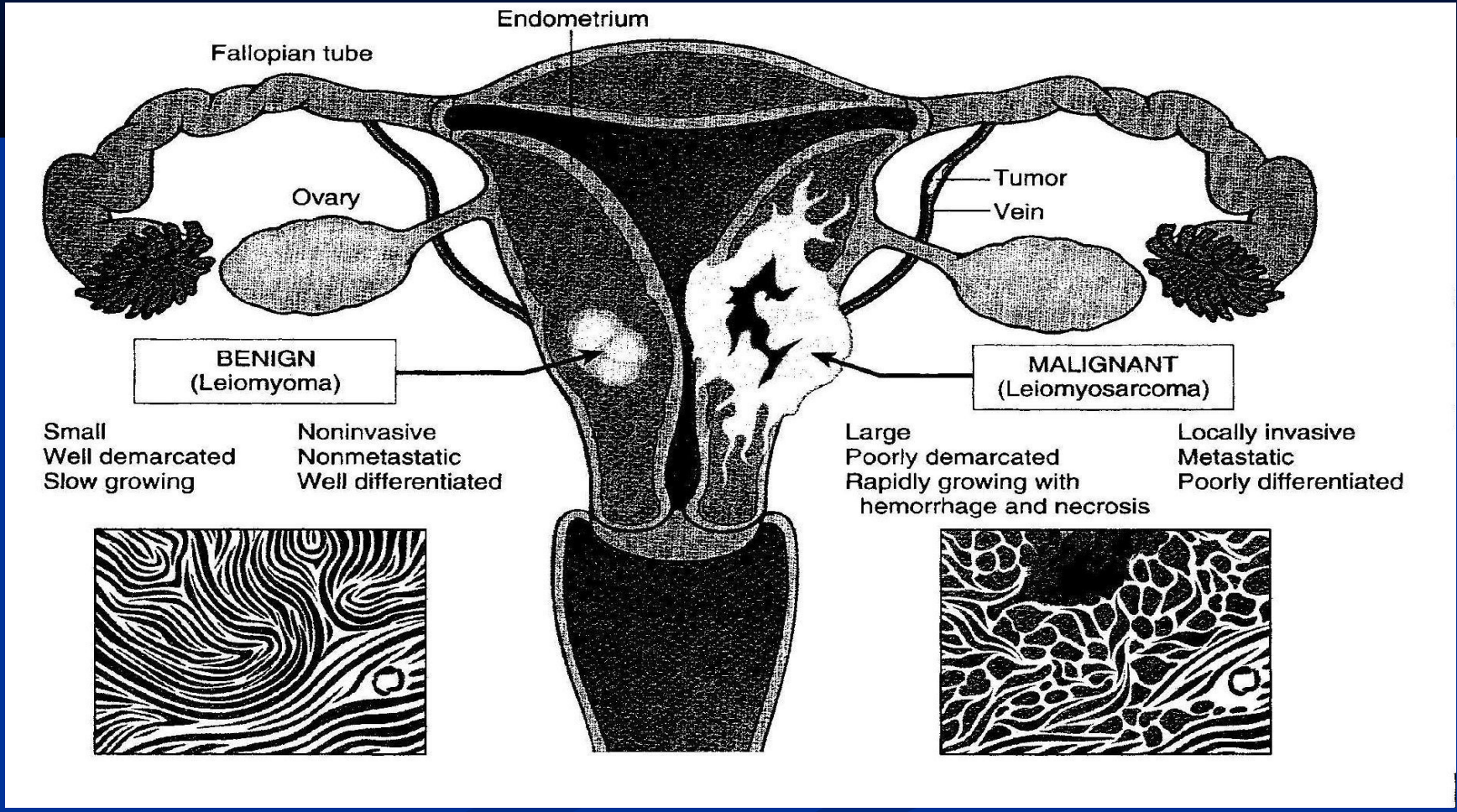
Feature	Benign tumors	Malignant tumors
Growth rate	slow	Relatively rapid
Mitoses	Infrequent	Frequent and often atypical
Differentiation	Good	Variable, often poor
Nuclear morphology	Often normal	Usually hyperchromatic, irregular outline, multiple nucleoli and pleomorphic
Invasion	No	Yes
Metastases	Never	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 of tumor

- 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)

Grading and differentiation of tumors

- Grade I: well differentiated tumor
- Grade II: moderately differentiated tumor
- Grade III: poorly differentiated tumor
- Grade IV: undifferentiated/anaplastic tumor

* **High grade tumors associated with poor prognosis.**

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, ….)

Risk factors of cancer

- Genetic predisposition to cancer
- Aging
- Lifestyle (tabacco, diet and nutrition, alcohol, sexual and reproductive behaviors, hormonal exposure)
- Occupational or environmental exposure to different carcinogens
- Stress, immune defficiency

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

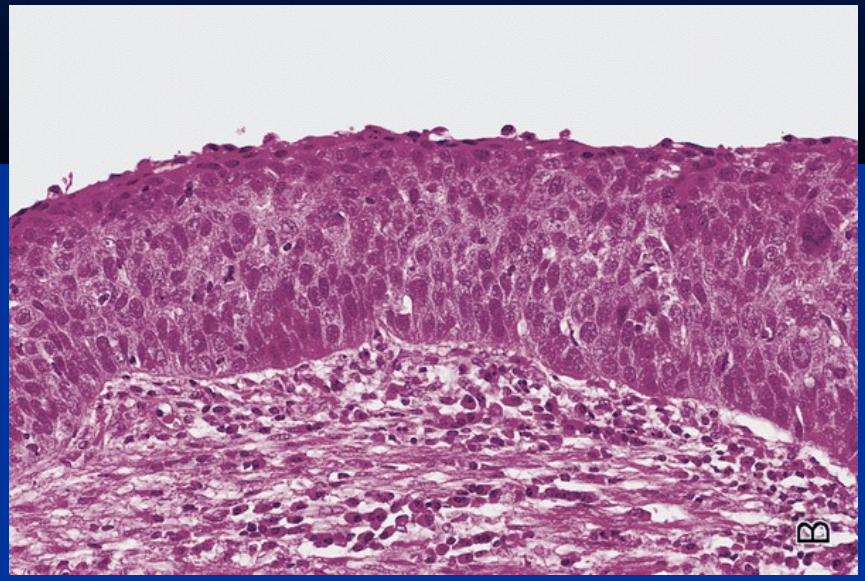
- Adenomatous polyps of colon
- Intraepithelial neoplasia (IN)/dysplasia

  (CIN (cervical), VIN (vulvar), PanIN (pancreatic), PIN (prostatic)
- Atypical ductal or lobular hyperplasia in breast

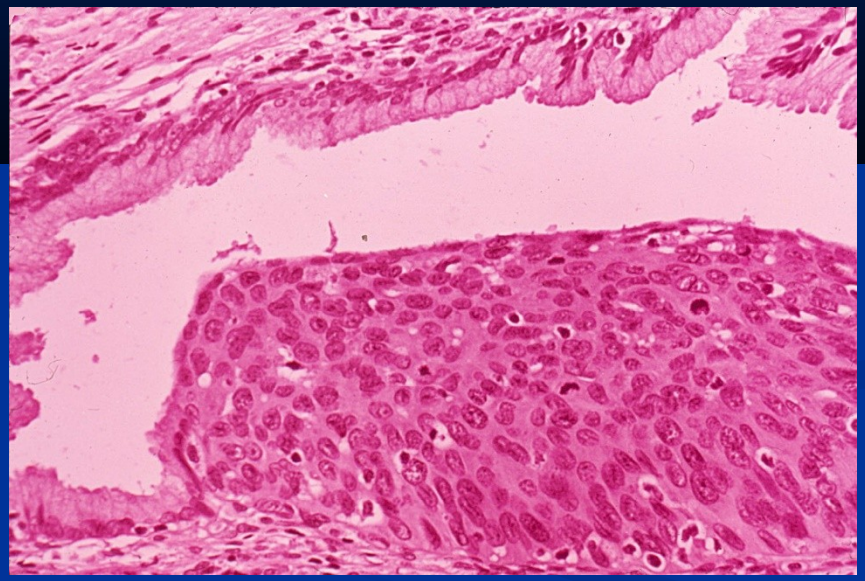
Dysplasia

- In epithelia
- A loss of uniformity of the individual cells as well as loss in their architectural orientation
- Low grade *vs* high grade dysplasia; low grade dysplasia often reversible, high grade dysplasia with a high risk of progression into invasive cancer
- Intraepithelial neoplasia/dysplasia = almost synonyms
- High grade dysplastic changes involving the entire thickness of the epithelium = preinvasive neoplasm = *carcinoma in situ*

High grade dysplasias/in situ carcinomas



HG dysplasia/carcinoma in situ in bronchi: dysplasia in metaplastic squamous epithelium in bronchi



CIN III : cervical intraepithelial neoplasia, high grade, in **metaplastic squamous epithelium in endocervical gland**

Relationship between inflammation and cancer: increased risk of cancer in chronic inflammation.

- IBD (idiopathic bowel disease) – colorectal cancer
- *Helicobacter pylori* chronic gastritis – gastric cancer
- chronic viral hepatitis – hepacellular carcinoma
- reflux esophagitis (Barret´s esophagus) – esophageal carcinoma
- liver fluke infection – cholangiocellular carcinoma
- chronic pancreatitis (both sporadic and hereditary)– pancreatic cancer

Histogenetic classification of tumors

- Epithelial tumors
- Mesenchymal tumors
- Neuroectodermal tumors
- Germ cell tumors
- Mixed tumors

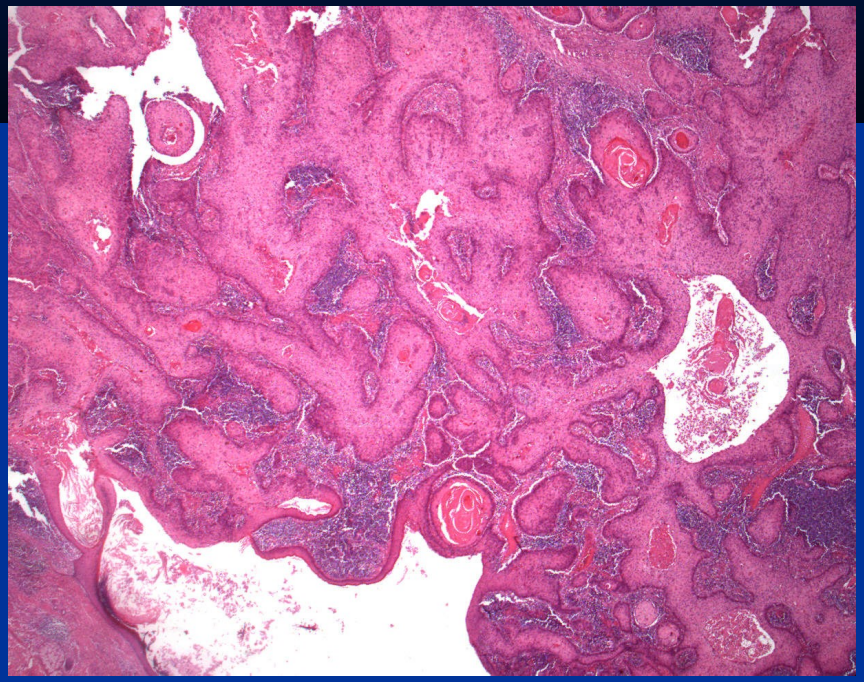
Principal characteristics of carcinomas and sarcomas

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

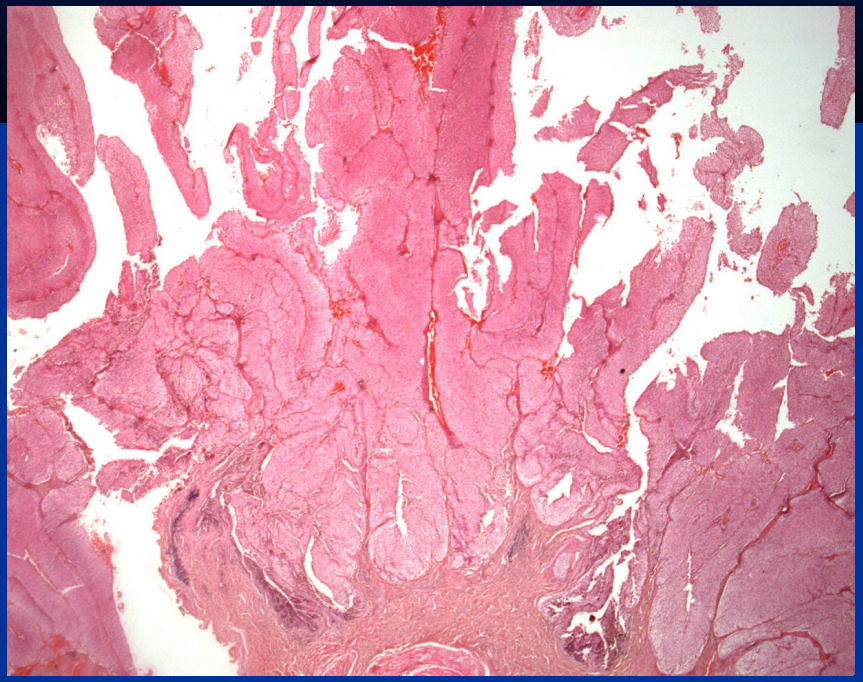
Epithelial tumors

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

Carcinomas



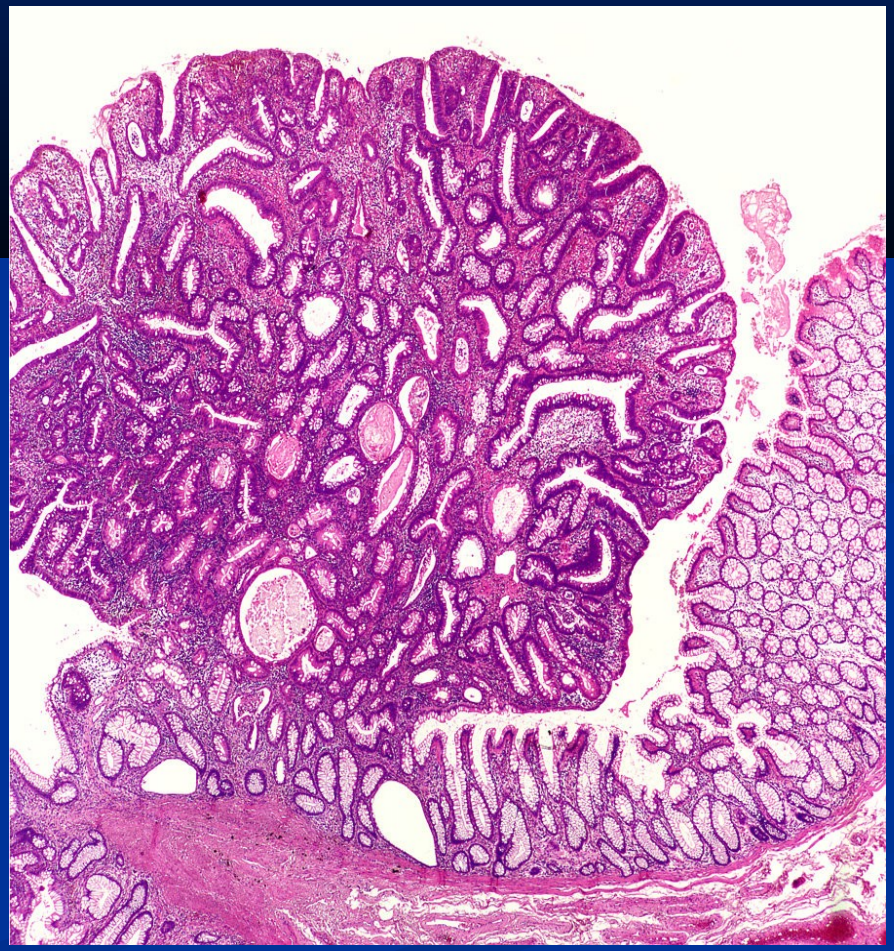
Squamous cell carcinoma



Papillocarcinoma

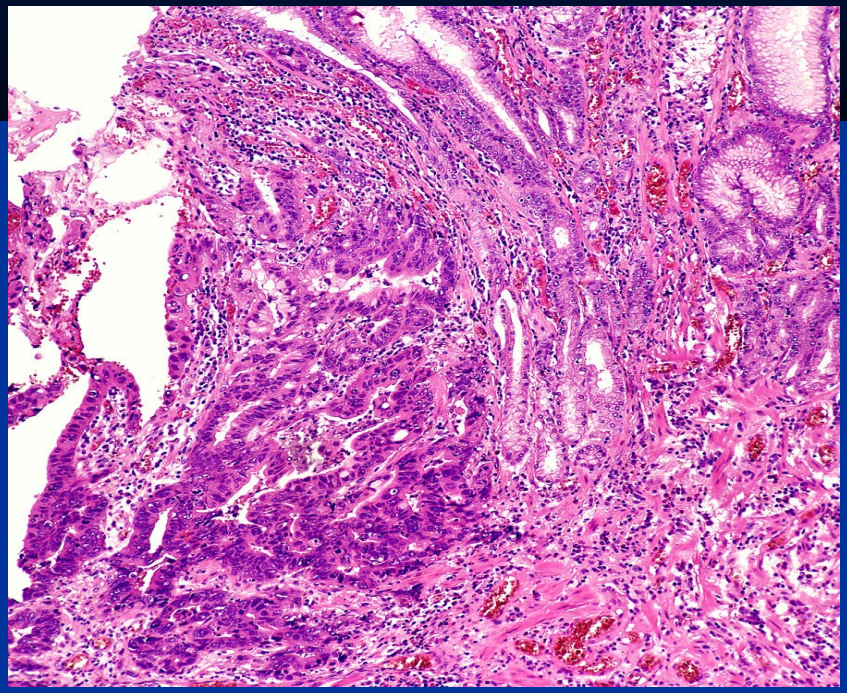
Polyps of large intestine

Adenomatous polyps of large intestine

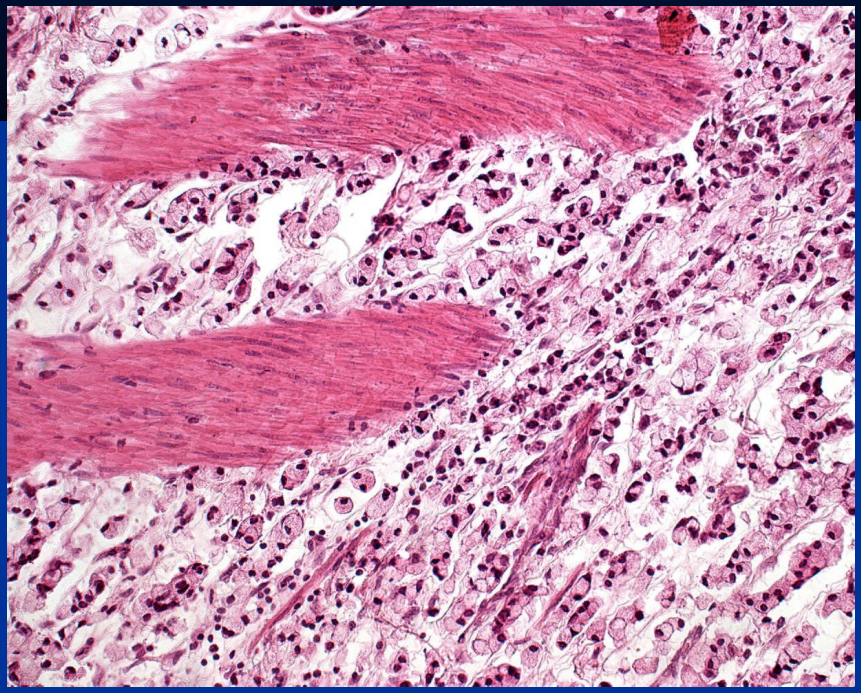


Tubular adenoma, low grade dysplasia

Adenocarcinomas



Adenocarcinoma, intestinal type



Adenocarcinoma – gelatinous, mucinous

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
Soft tissues		Synovial sarcoma
Mesothelium	Benign mesothelioma	Malignant mesothelioma

+ hematooncological malignancies: leukemias and lymphomas

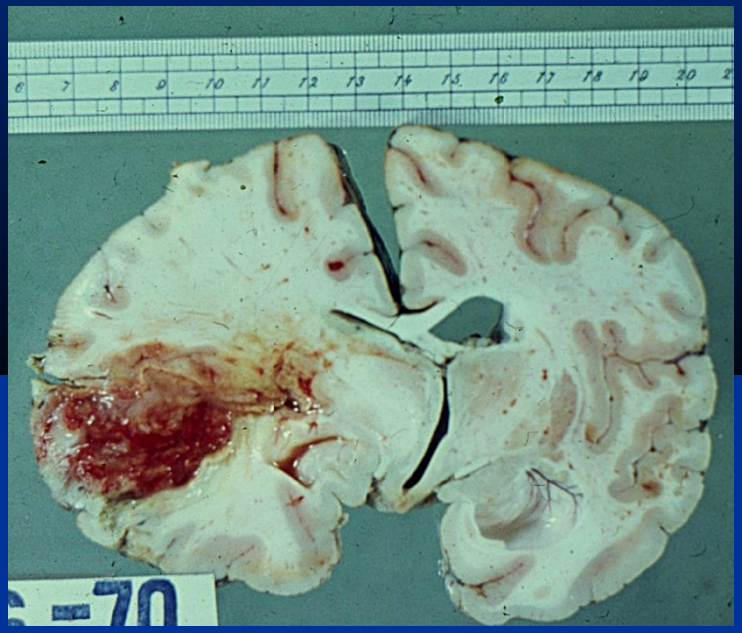
Neuroectodermal umors

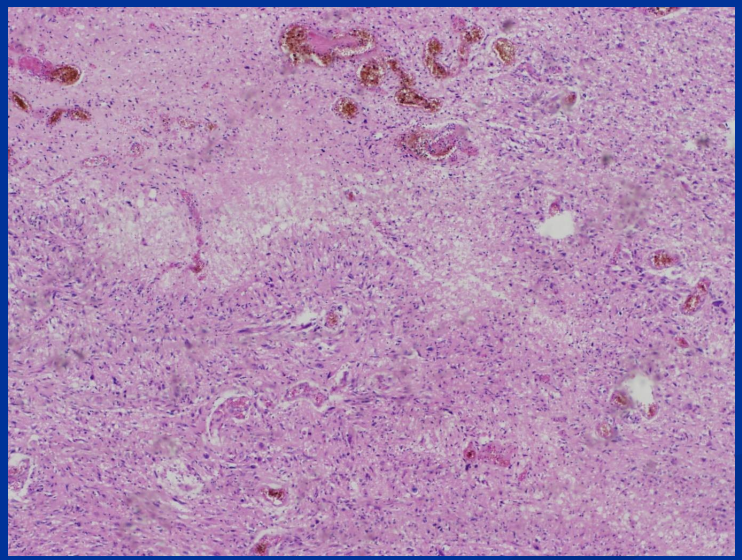
- Tumors of central nervous system (CNS)
- Tumors of peripheral nervous system (PNS)
- Tumors of autonomous nervous system (ANS)
  (parasympathetic and sympathetic)
- Melanocytic tumors

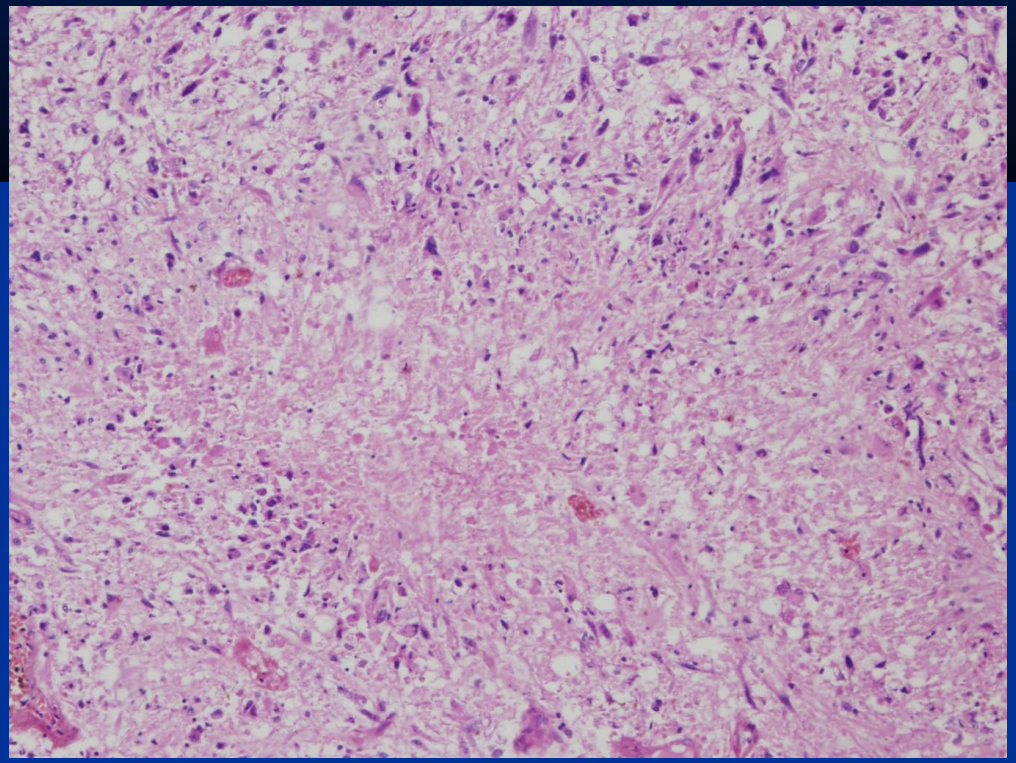
Classification of neuroectodermal tumors

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) Neuroblastoma (PNS) Retinoblastoma
Arachnoidal cells	Meningioma
Nerve sheath cells	Schwannoma, neurofibroma Malignant schwannoma, neurofibrosarcoma
ANS	Paragangliomas, chemodectomas, pheochromocytoma
Pigmented cells/melanocytes	Nevus Malignant melanoma

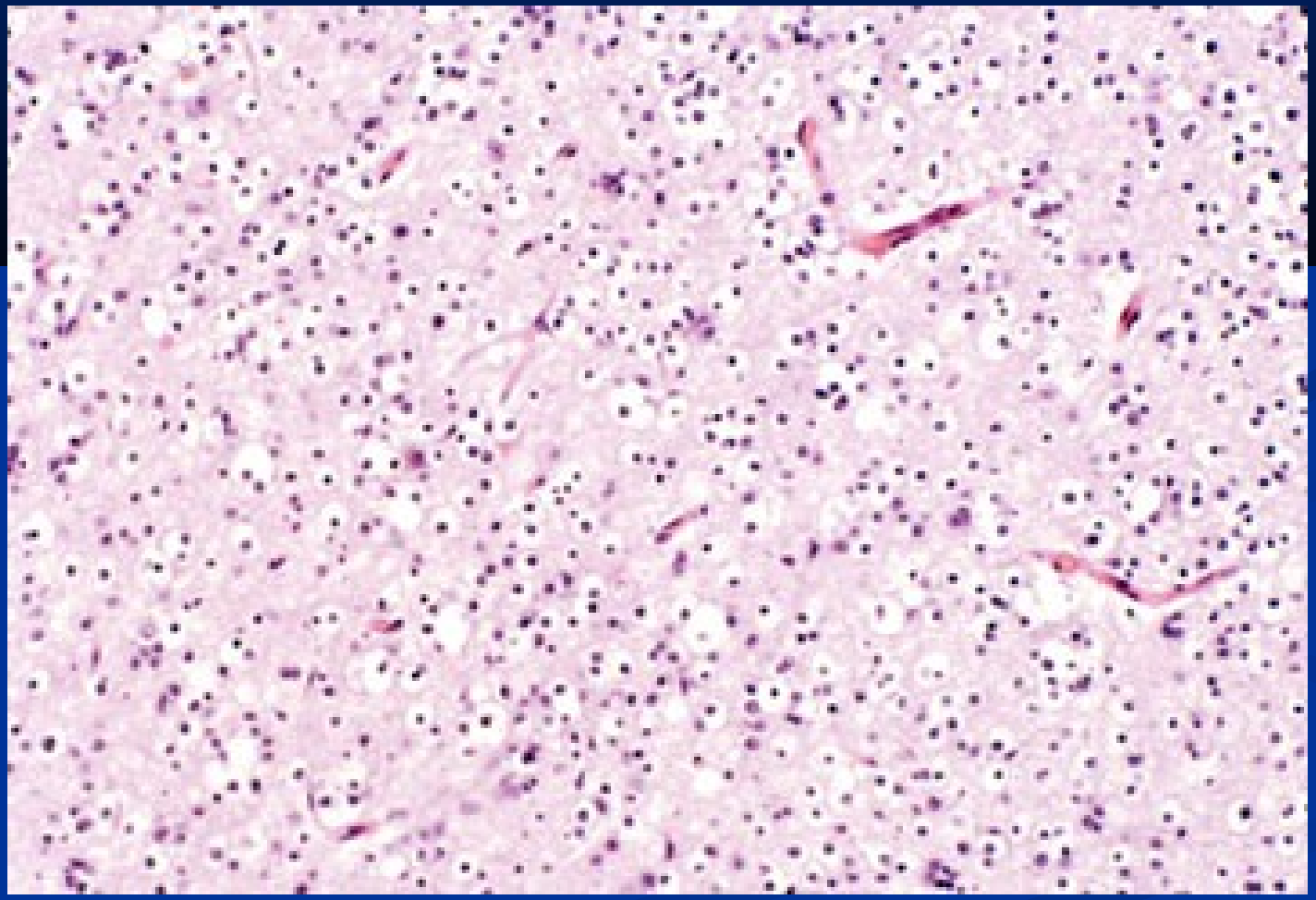
Glioblastoma multiforme



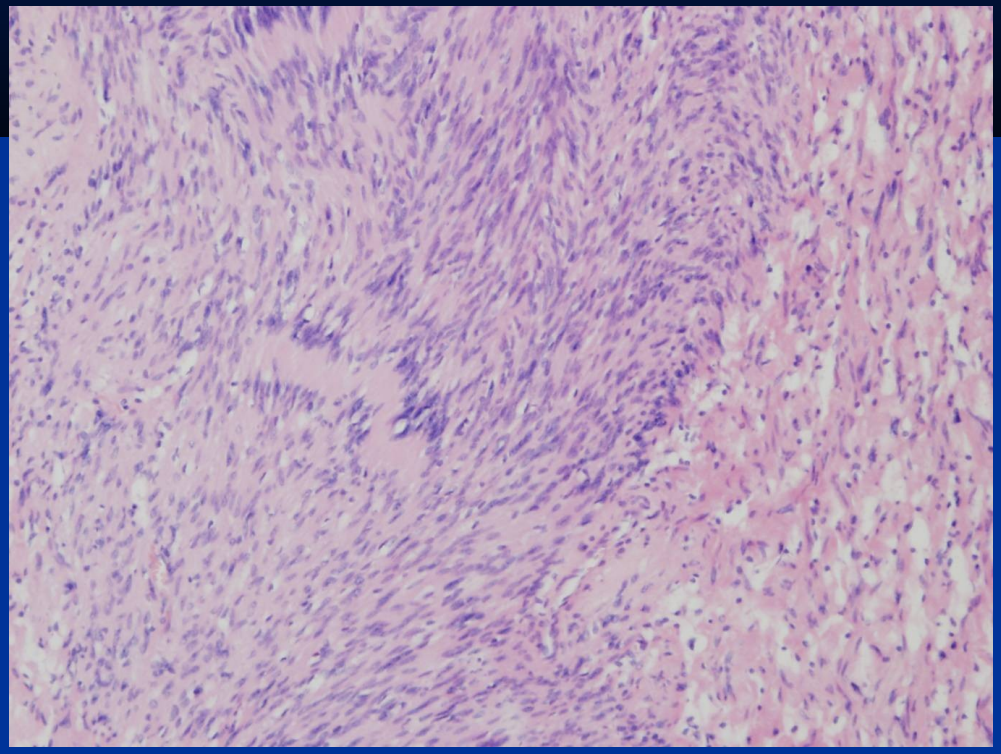


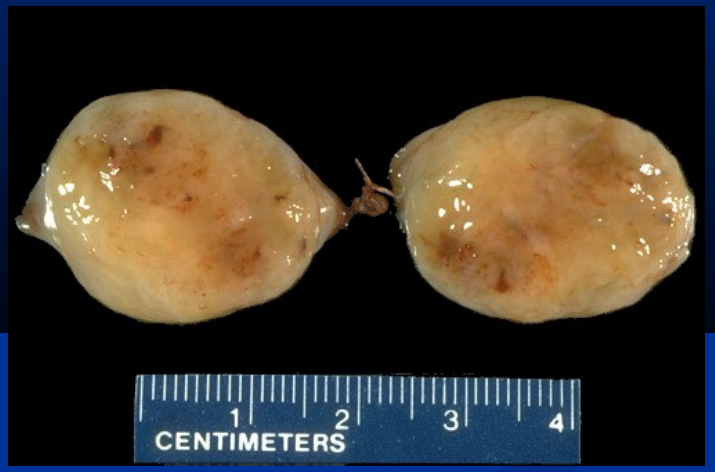


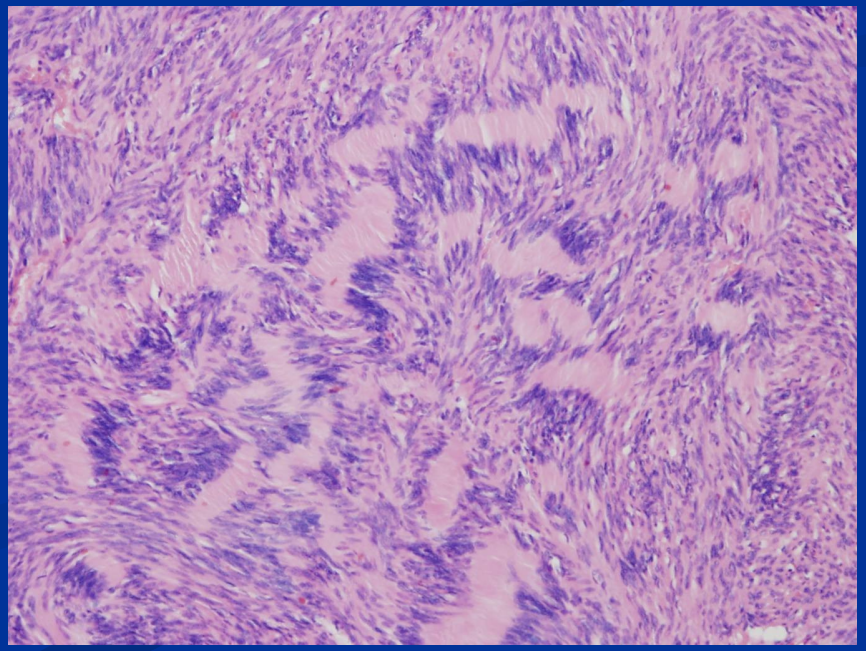
Oligodendrogliom



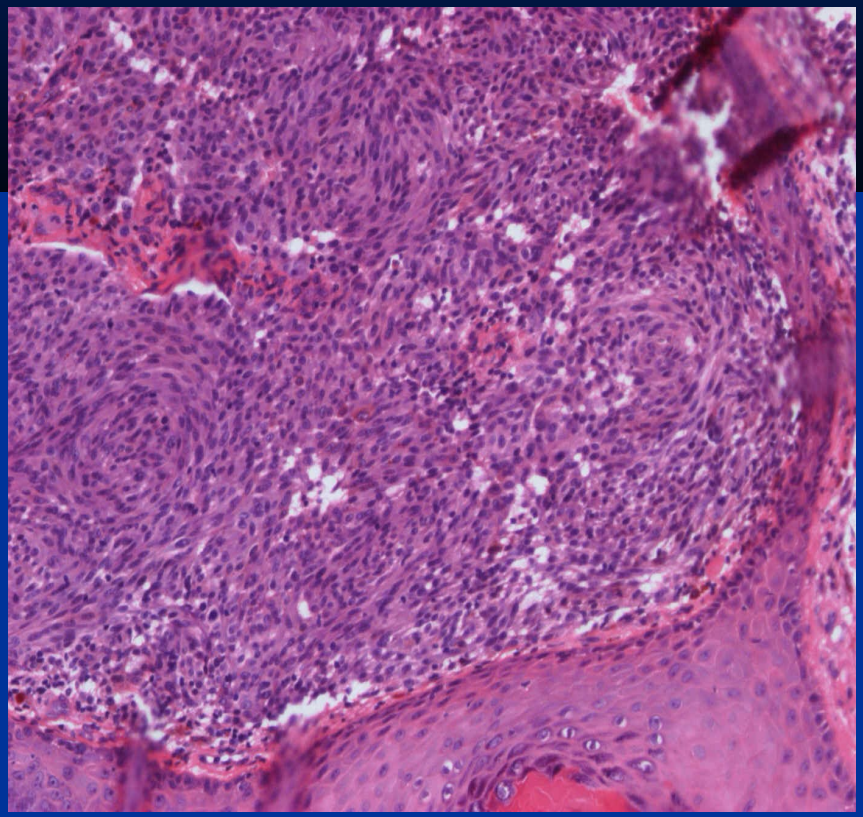
Neurinom (Schwannom, neurilemmom)

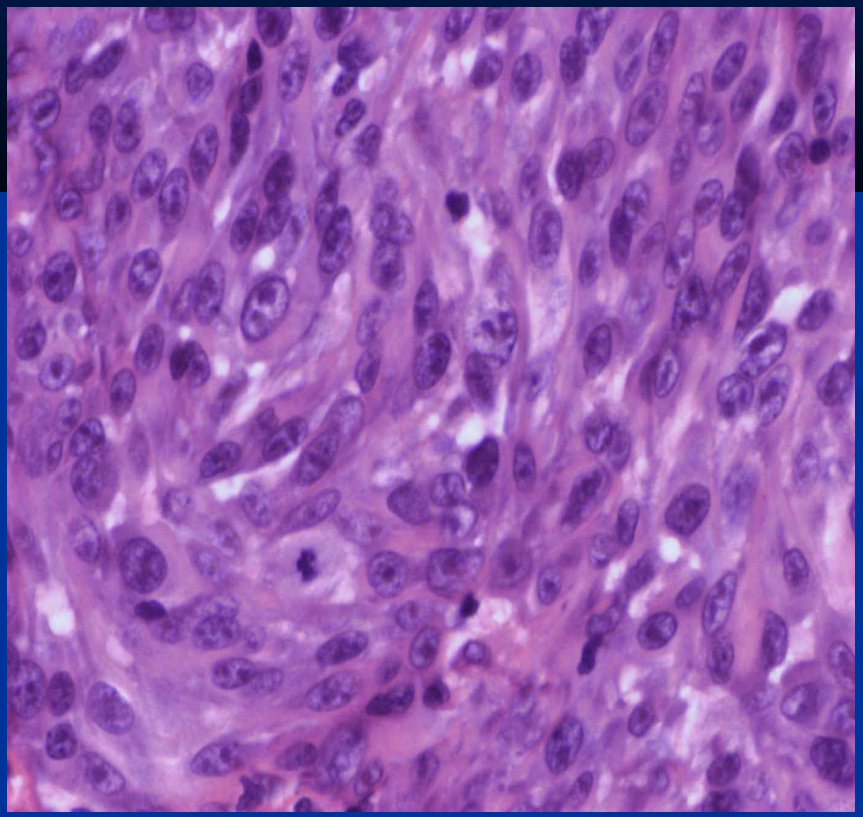






Malignant melanoma





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,…

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)

- Seminoma (dysgerminoma)
- Spermatocytic seminoma
- Embryonal carcinoma
- Yolk sack tumor
- Polyembryoma
- Chorioncarcinoma
- Teratoma (differentiated mature, differentiated immature, with malignant transformation)

- **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

* no age predilection

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

Tumor code

- WHO International Classification of Diseases for Oncology (ICD-O): numerical classification and coding system by topography and morphology

- TNM Classification of Malignant Tumors (UICC), AJCC Cancer Staging Manual: coding system of tumor stage

- WHO Classification of Tumours, Pathology and Genetics: histologic classification by organ system

Tumor code

- Topography (localization) C00.0 – C80.9 (lip – unknown primary localization)
- Subdivision: C34 lung

  C34.0 main bronchus

  C34.1 upper lobe

  …

Tumor code

Morphology (histology): digital

- 4 digits – basic histogenetic structure

  8070 – tumor of squamous cell

  8140 – tumor of glandular cell

Tumor code

Morphology (histology): digital

- 5. digit – biologic behaviour

  /0 benign (incl. low grade dysplasia)

  /1 uncertain, intermediate biologic behaviour, low malignant potential

  /2 high grade dysplasia, carcinoma/melanoma in situ

  /3 malignant, primary localization

  /6 malignant, metastasis

  /9 malignant, unknown if primary or metastatic

Tumor code

Morphology (histology): digital

- 6. digit : grading/differentiation of malignant tumors

1 – 4 well – moderate – low – undifferentiated

8140/0 adenoma

8140/31: well differentiated adenocarcinoma in primary localization

System of tumor staging

- **TNM (tumor, nodes, metastases)** system used for solid tumors

- Tumor (T): the size of primary tumor; 0-4
- Regional lymph nodes (N): regional lymph node involvement; 0-4
- Metastasis (M): 0 if no distant metastasis present; 1 if distant metastases are present

Tumor code

- T0 no evidence of primary tumor
- Tis tumor in situ
- T1,T2,T3,T4 increasing size/local extension
- TX primary tumor cannot be assessed
- similarly N0, N1-4, NX
- M0,M1

Tumor code

Example:

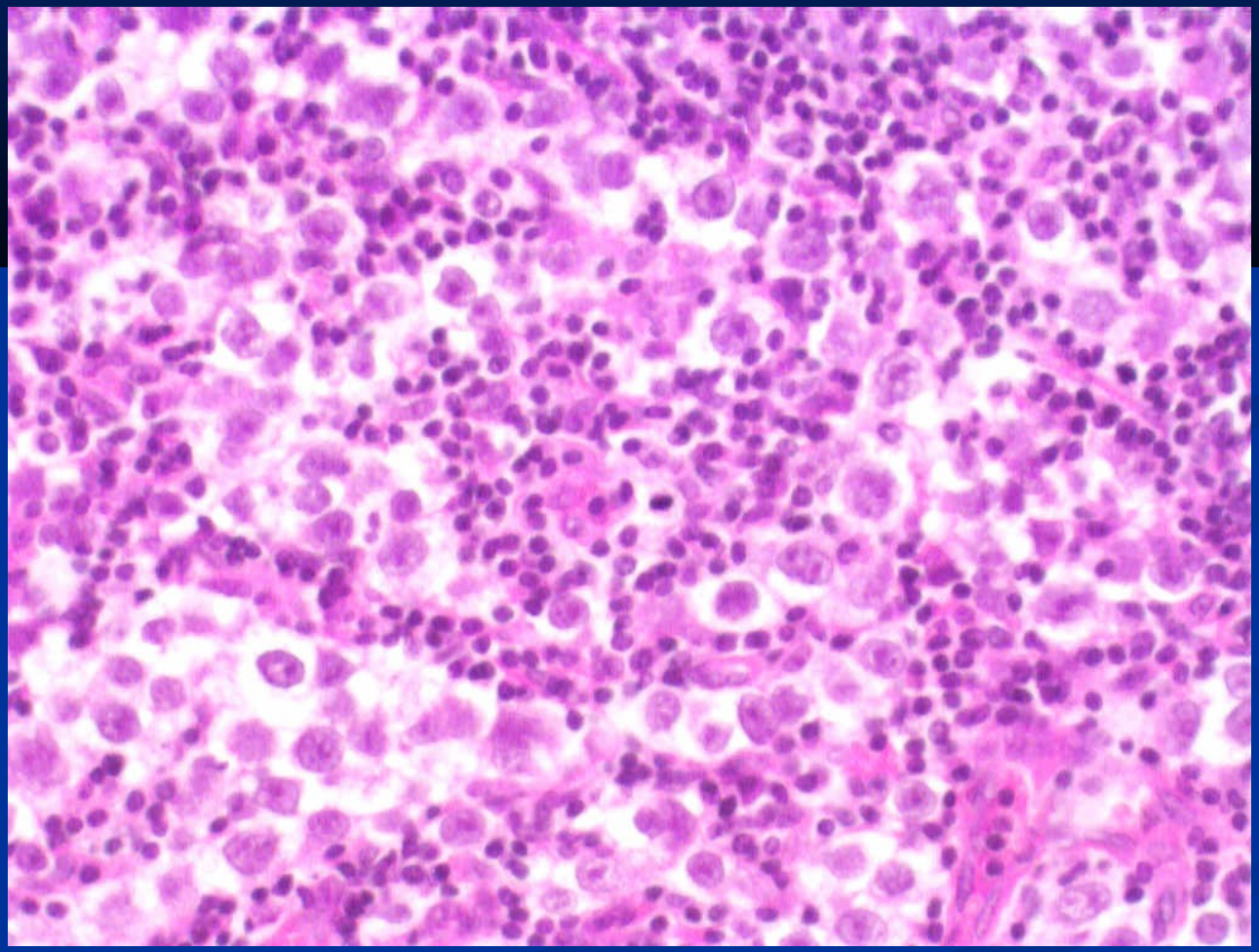
C16.1

M-8140/33

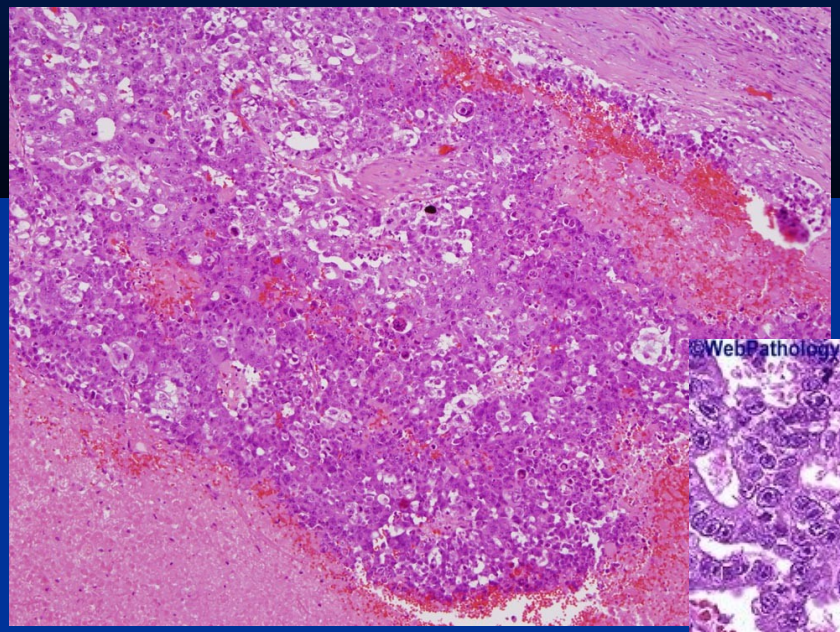
pT3,pN3,pM1

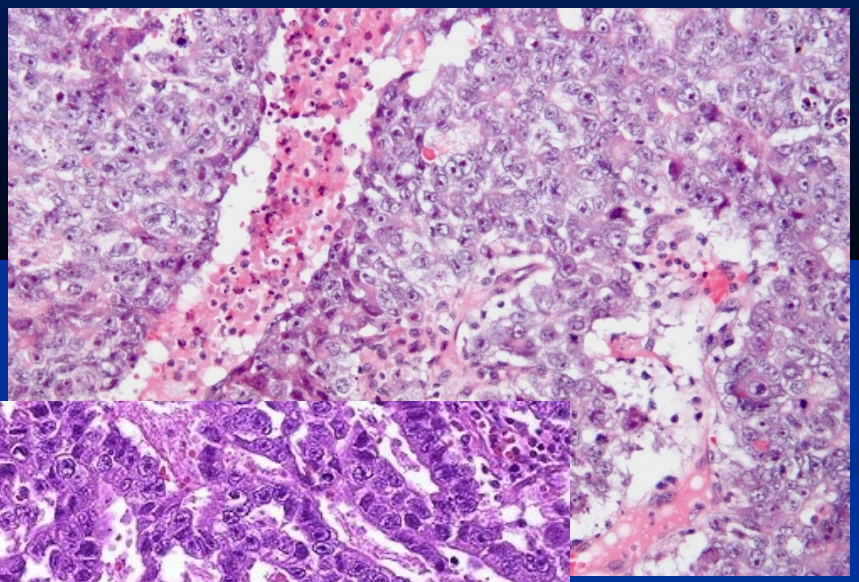
Poorly differentiated adenocarcinoma of stomach fundus with extension into subserosal connective tissue, metastases in 7 or more LN, with distant metastases

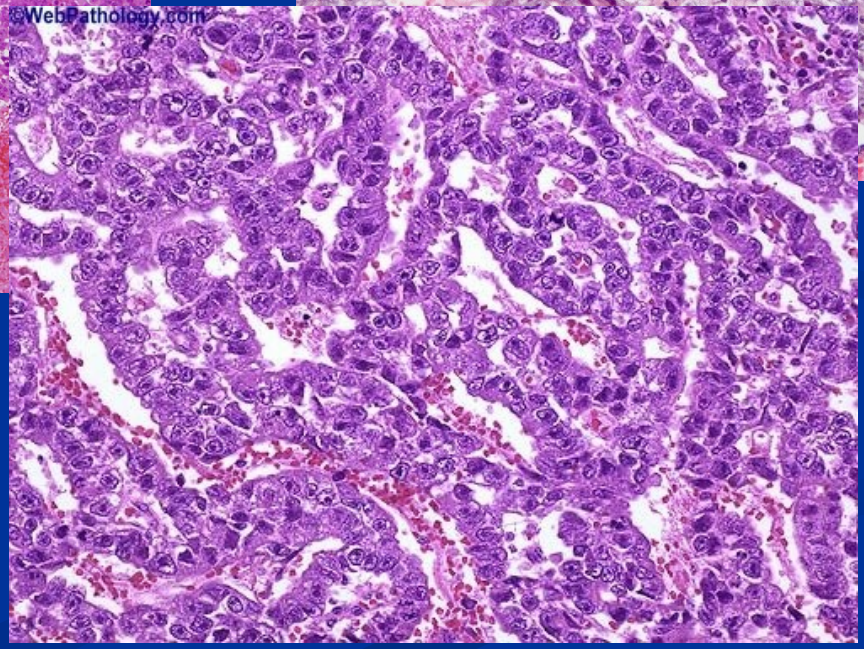
Seminoma



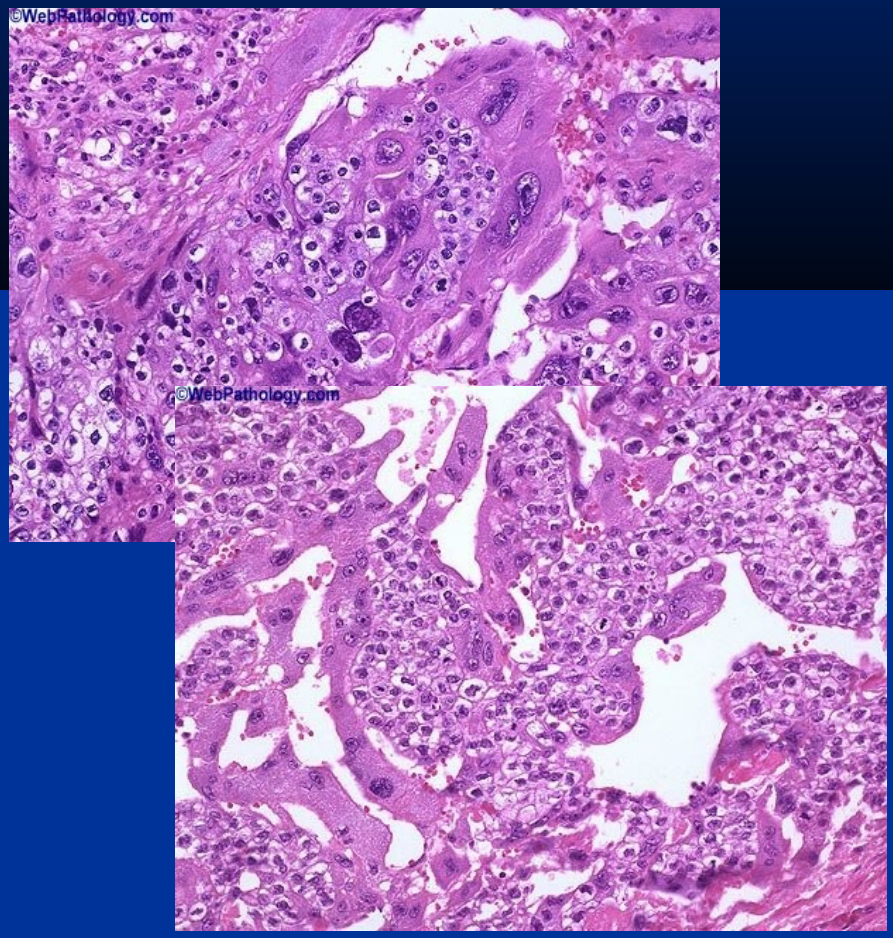
Germ cell tumors – undifferentiated: embryonal carcinoma



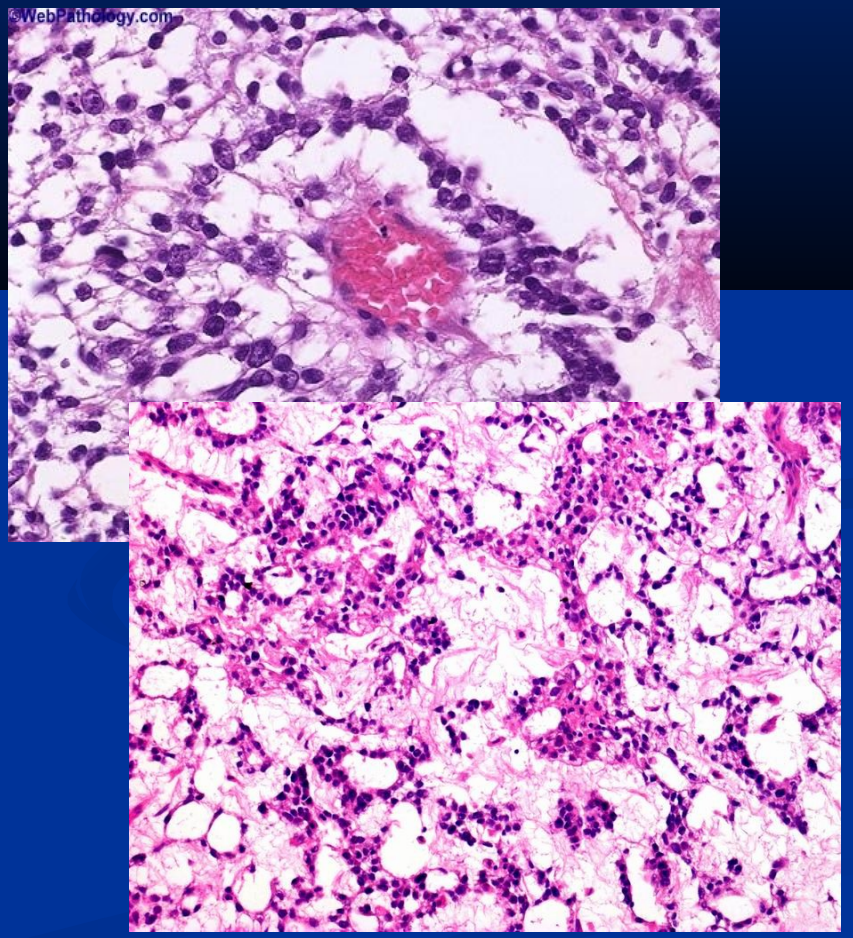




Germ cell tumors: extraembryonal differentiation

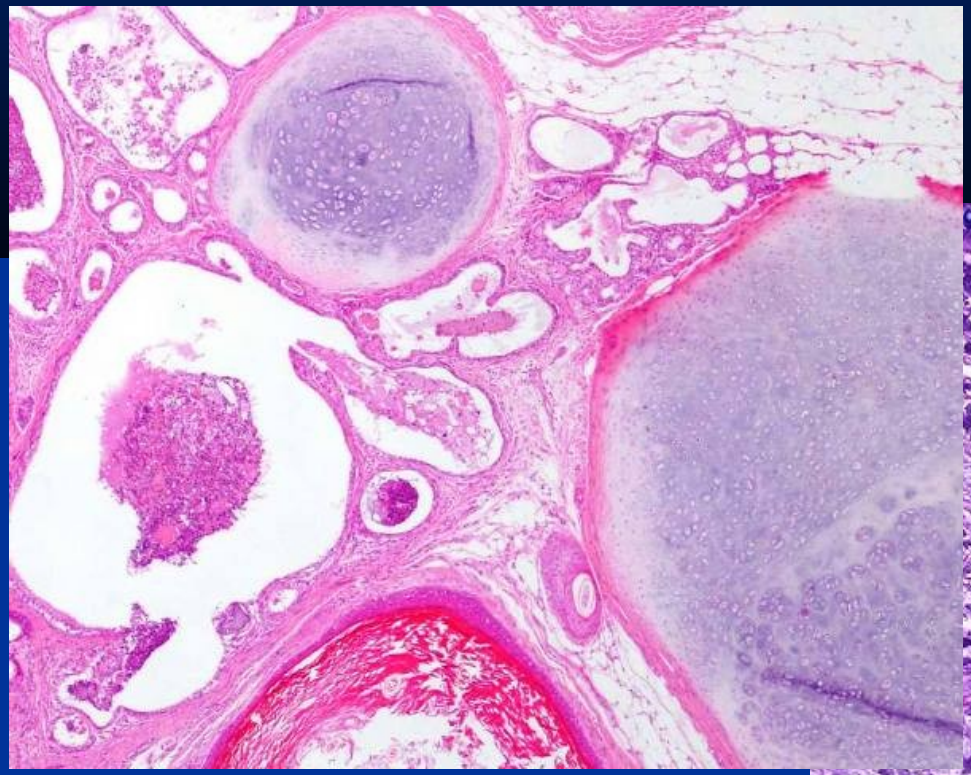


Choriocarcinoma

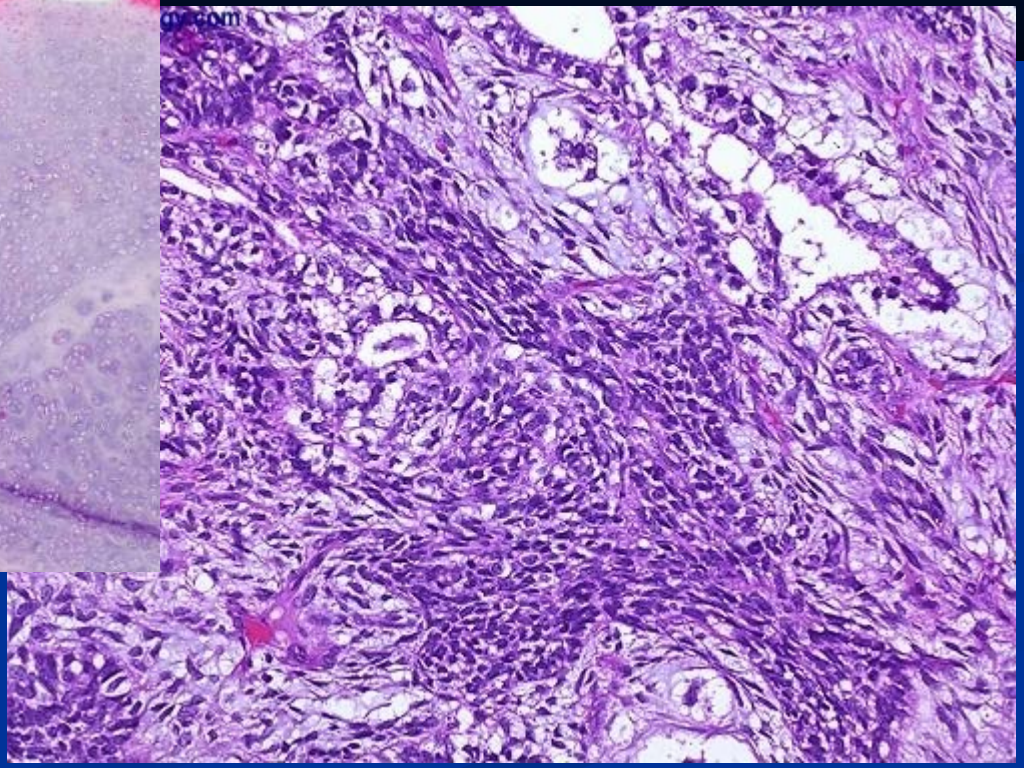


Yolk sack tumor

Germ cell tumors: intraembryonal differentiation



Mature teratoma



Immature teratoma

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…..