Neoplasia I
Definitions, Terminology, and Morphology

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Cancer - second leading cause of deaths in the US after CV disease

Nomenclature

- Neoplasia “new growth”
- Neoplasms arise from genetic changes that allow excessive, unregulated cell proliferation
- Cell type of parenchyma + OMA

Tissue Type	Cell Type	Benign	Malignant
Conn.Tissue	Fibroblast	Fibroma	Fibrosarcoma
	Adipocyte	Lipoma	Liposarcoma
	Cartilage	Chondroma	Chondrosarcoma
	Bone	Osteoma	Osteosarcoma
Vessels, etc	Endothelial cells	Hemangioma	Angiosarcoma
	Meninges	Meningioma	Invasive meningioma
Muscle	Smooth muscle	Leiomyoma	Leiomyosarcoma
	Skeletal muscle	Rhabdomyoma	Rhabdomyosarcoma
Epithelium	Stratified Squamous	Squamous papilloma	Squamous cell carcinoma
	Ducts or glands	Adenoma	Adenocarcinoma
Melanocytes	Melanocytes	Nevus	Melanoma

Characteristics of Benign & Malignant Neoplasms

- Tissue Architecture – histologic features
- Cytologic features
- Terminology
  - Differentiation/anaplasia
  - Dysplasia
  - Rate of growth
  - Local Invasion
  - Metastasis

Characteristics of Benign & Malignant Neoplasms

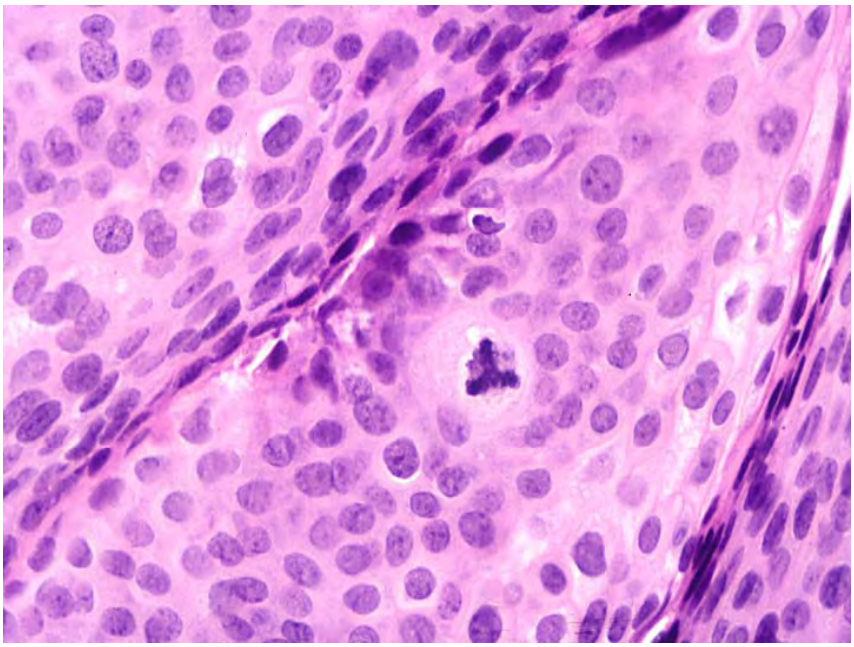
- **Tissue architecture**
  - **Benign** - well circumscribed, usually encapsulated
  - **Malignant** – poorly circumscribed, lack of cell polarity and epithelial cell connections

Characteristics, con't.

- **Cytologic features**
  - **Benign** – small, uniform cells, no visible nucleoli
  - **Malignant** – large, pleomorphic cells with large hyperchromatic nuclei, N:C ratio 1:1 (nl. 1:4), large nucleoli, irregular nuclear outlines

Differentiation

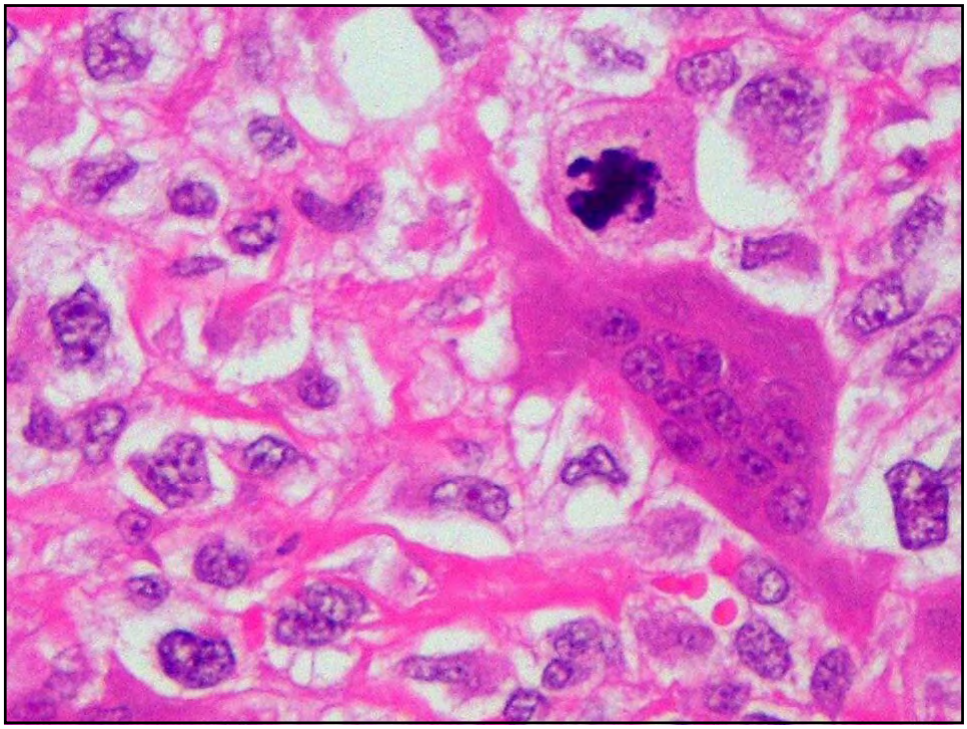
- Refers to original parenchymal cell, tissue appearance and function
  - **Benign** - well differentiated, resembles cell of origin with few mitoses, secretion of products, hormones, mucins, etc.
  - **Malignant** - well to poorly differentiated with numerous, bizarre mitoses

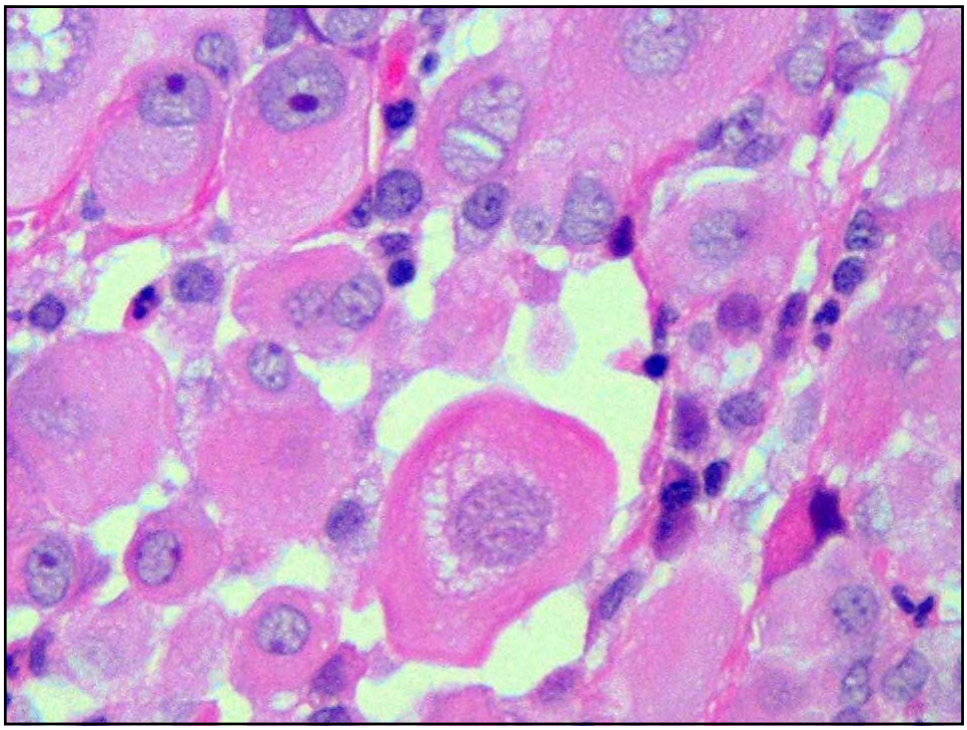


Abnormal mitosis

Anaplasia

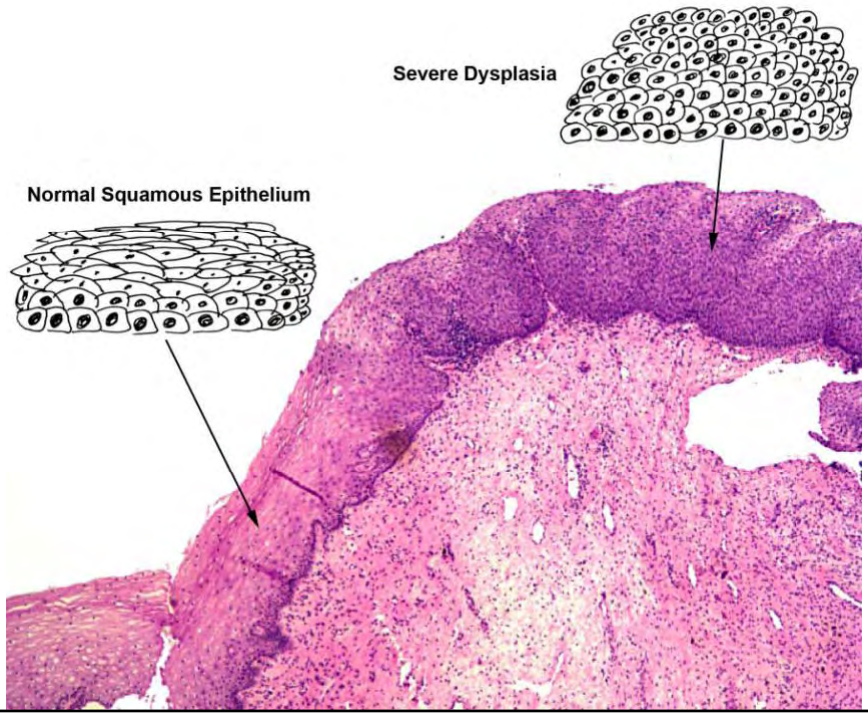
- Neoplasm without apparent differentiation, undifferentiated cells





Dysplasia

- Disorderly cellular maturation
- If, full epithelial involvement –carcinoma in situ, pre-invasive stage
- HPV – cervix
- Smoking- respiratory tract
- GERD – esophagus



Rate of Growth

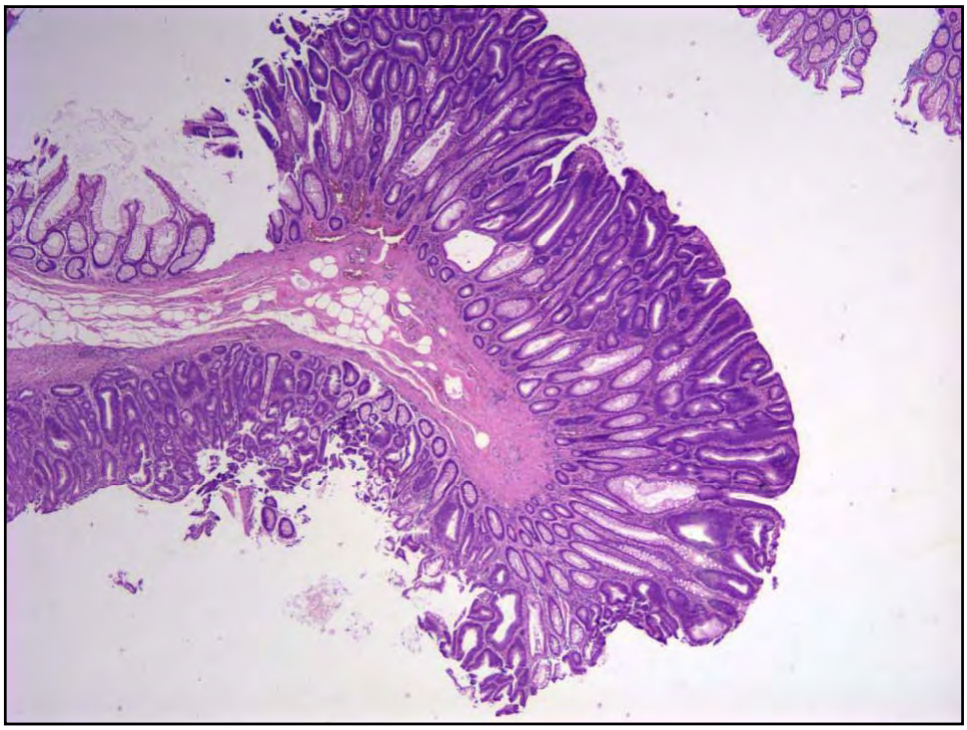
- Benign – slower growth, some dependent on hormones, leiomyoma
- Malignant – more rapid growth, areas of necrosis

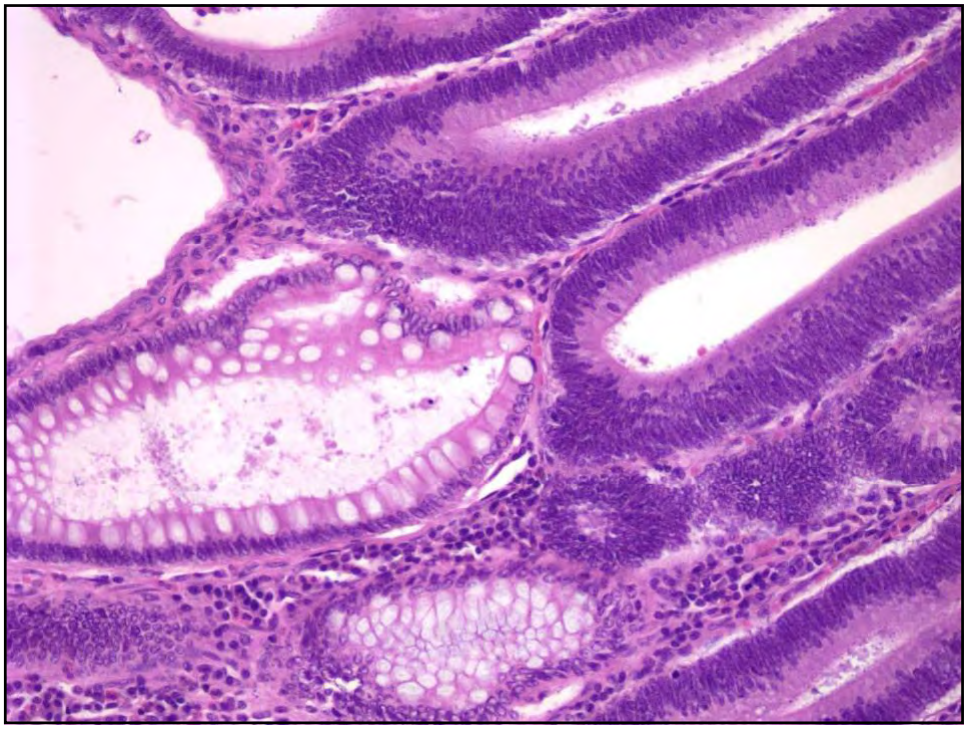
Local Invasion

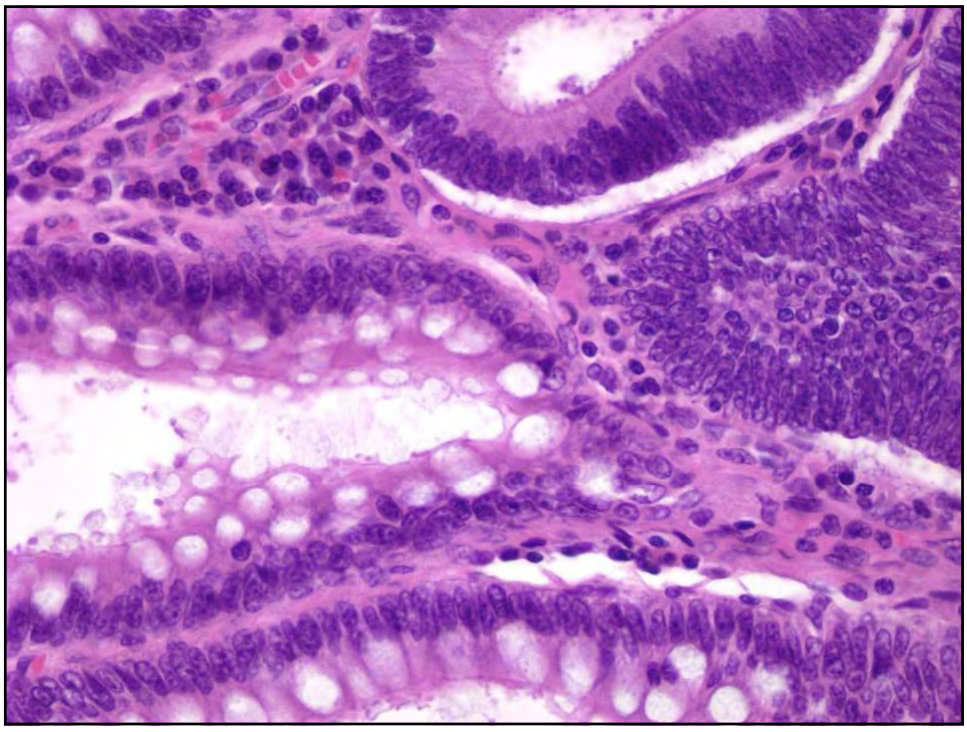
- Benign – most encapsulated and cannot invade or spread to other sites
- Malignant – not encapsulated and can invade

Benign Neoplasia

- Remains localized
- Cannot spread to other sites
- Most patients survive, but some tumor locations can cause serious problems (brain stem, spinal cord, pituitary)

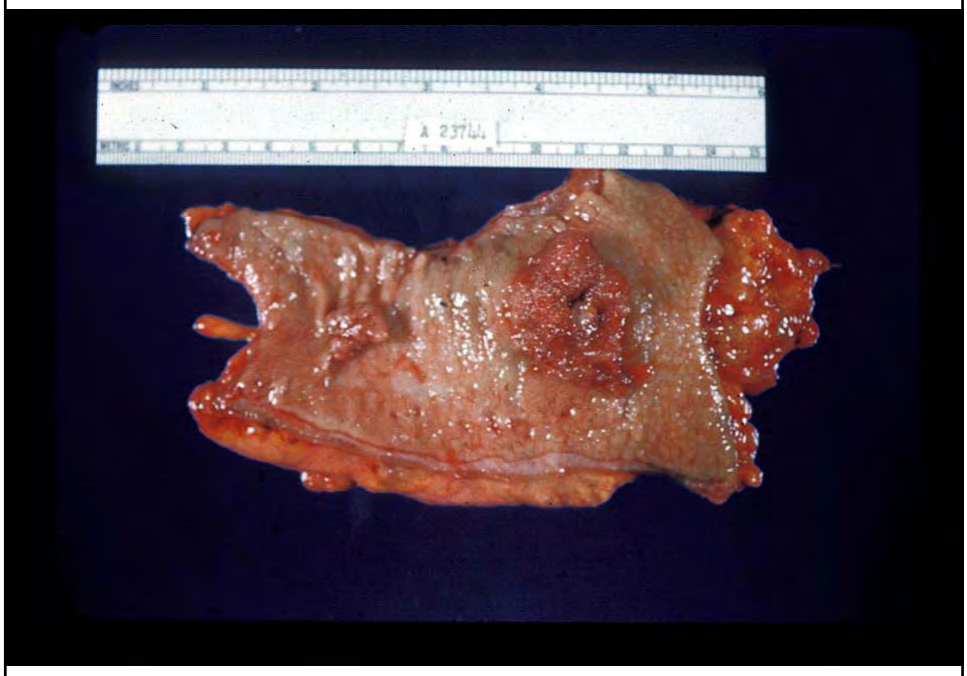


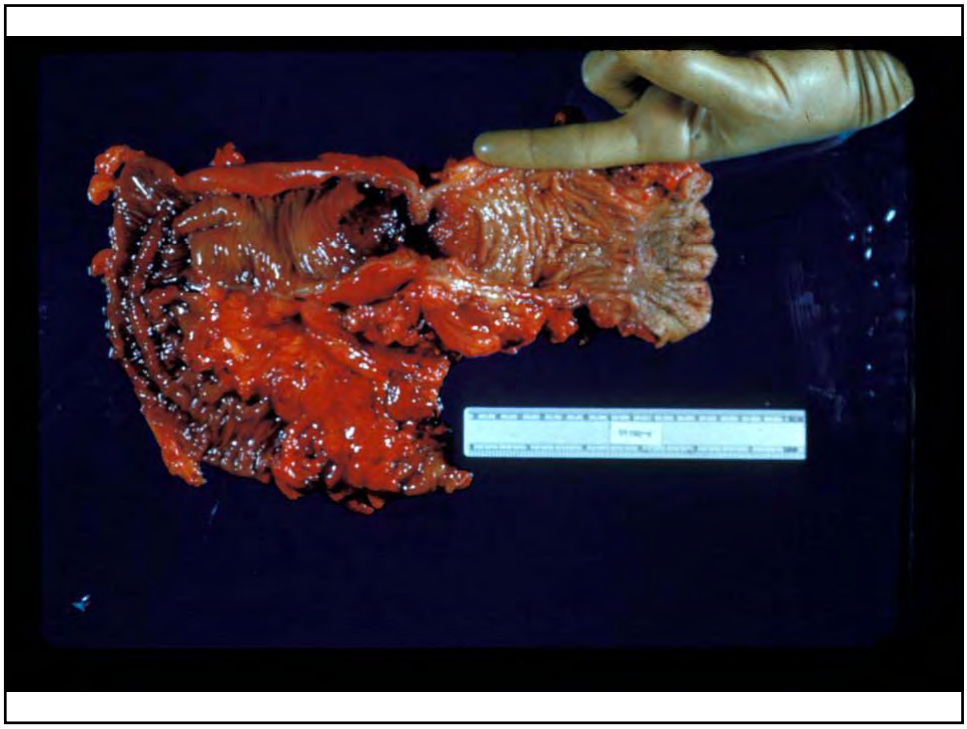


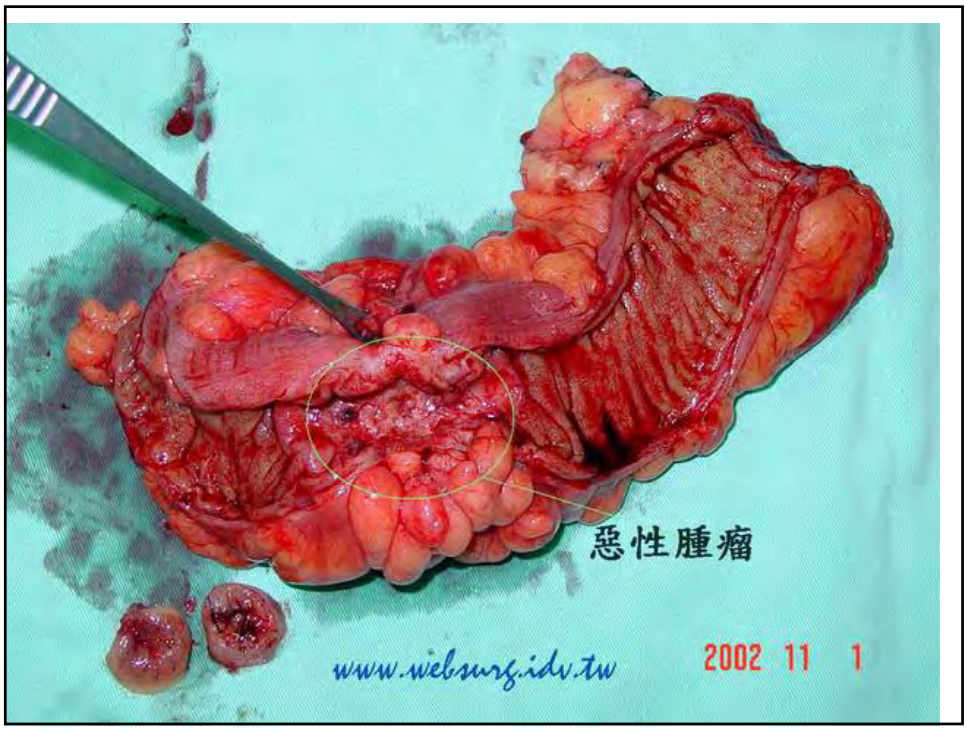


Malignant Neoplasia

- Can invade and destroy adjacent tissue
- Can spread to distant sites, metastasis



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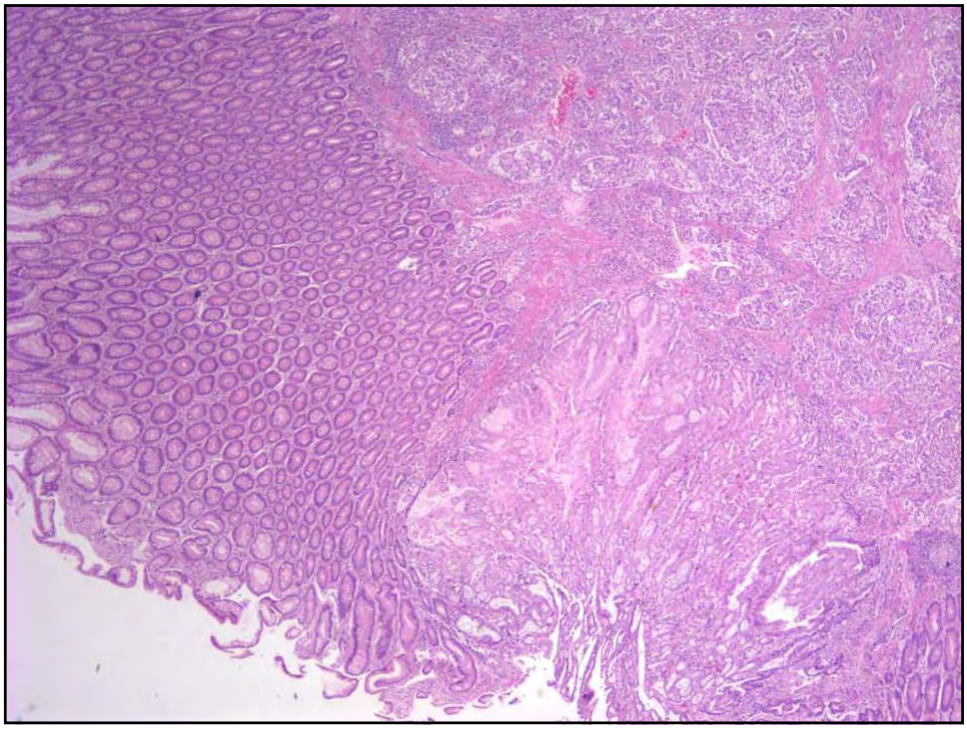
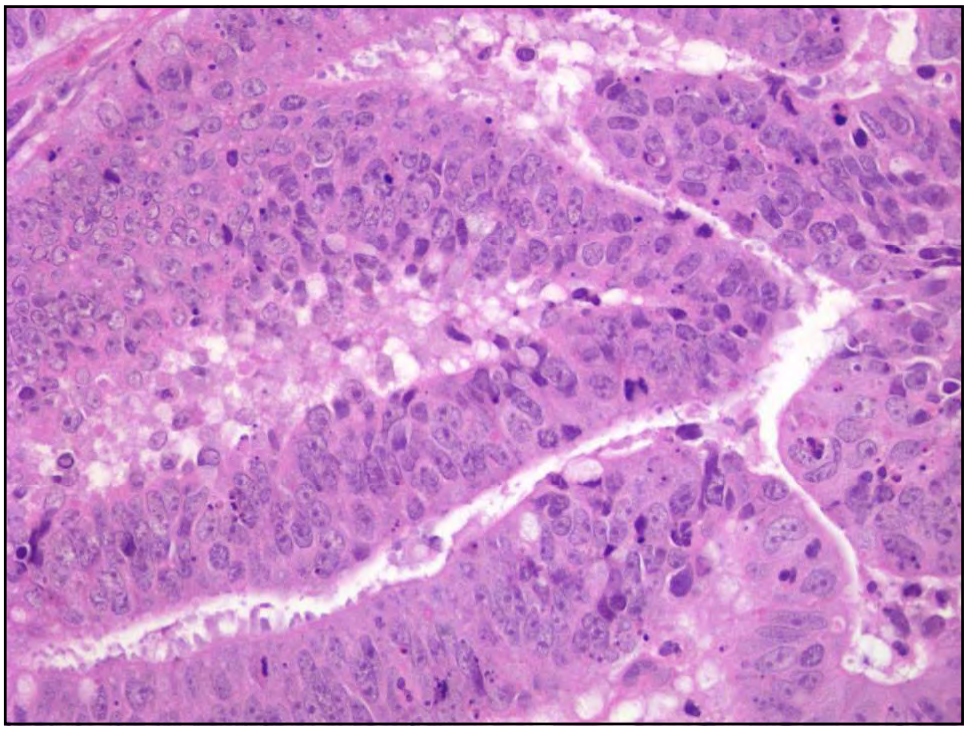
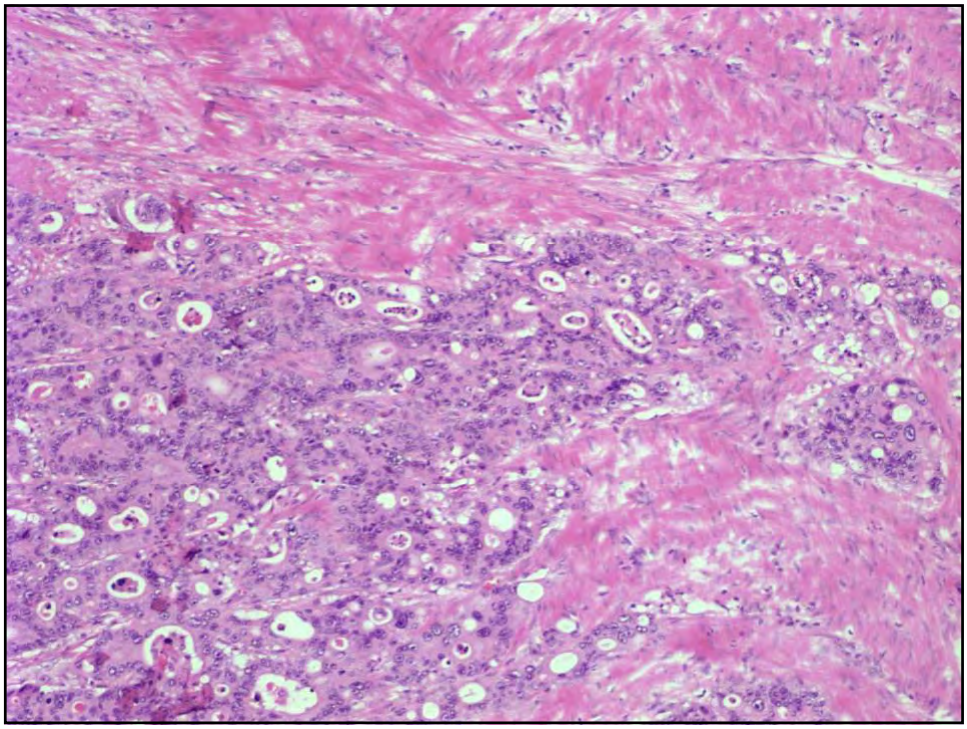
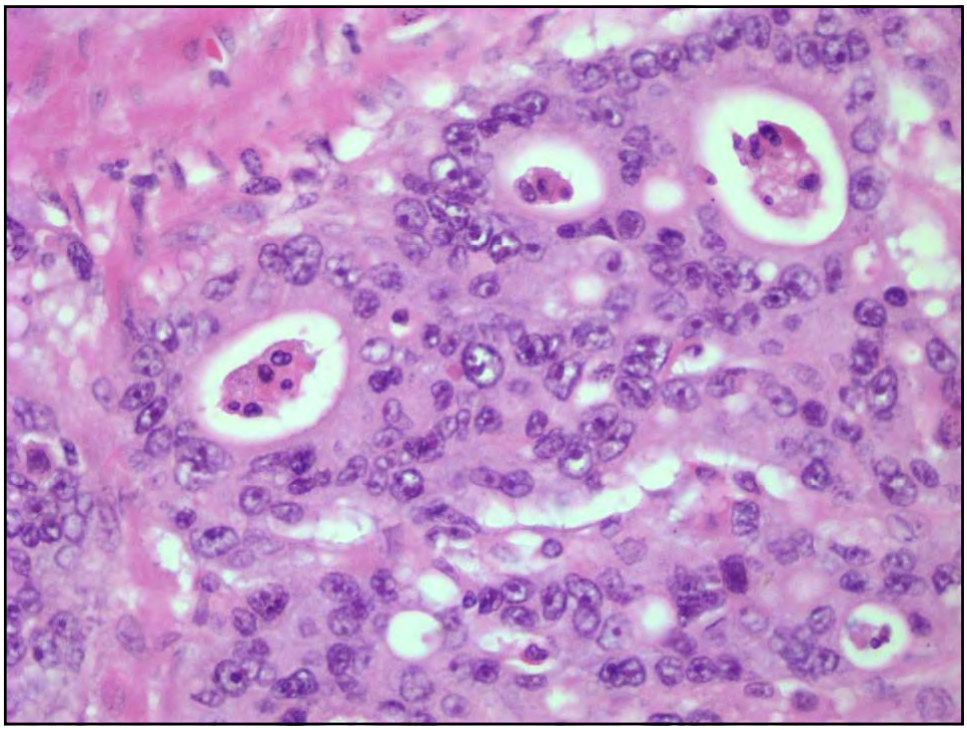






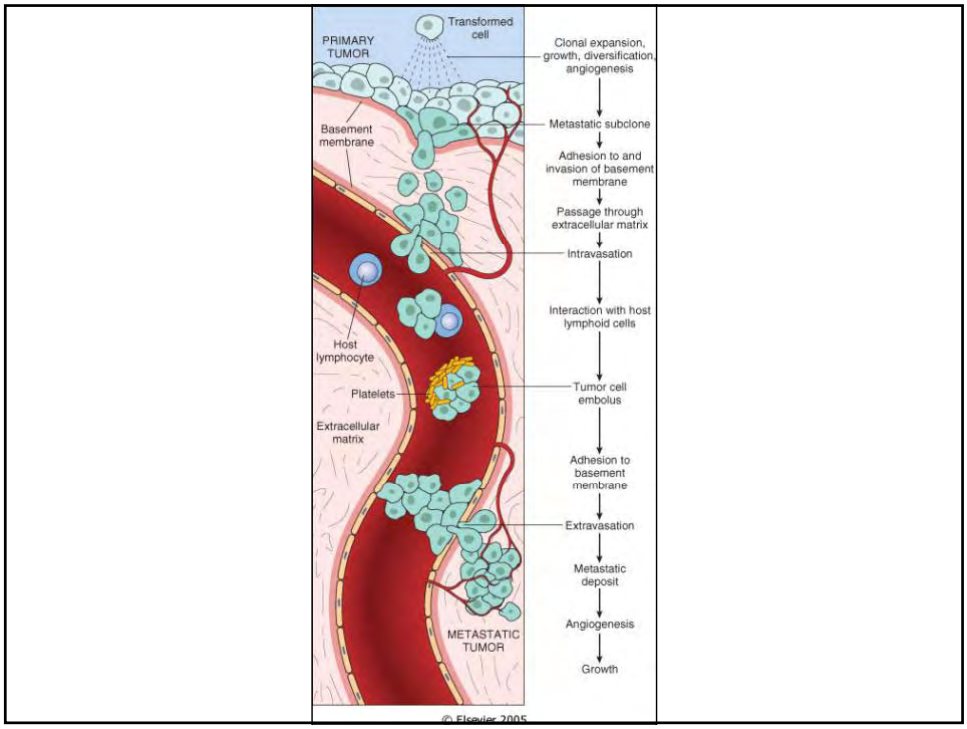


Metastasis

- Dissemination to other organs:
  - Seeding of body cavities (ovary)
  - Lymphatic spread (carcinoma)
  - Hematogenous dissemination (sarcoma)

Steps of Successful Metastasis

- **Detachment of tumor cells** (E-cadherin loss)
- **Degradation of ECM** (MMP's - overexpressed and TIMP's - reduced)
- **Attachment to new ECM proteins** (cleavage products of collagen and laminin bind to receptors on tumor cells - stimulate migration
- **Migration of tumor cells** (cytokines from tumor cells direct movement, autocrine, and stromal cells produce paracrine effectors, HGF/SCF, for motility that bind to tumor cells)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Transformed cell
Basement membrane
Host lymphocyte
Platelets
Extracellular matrix
METASTATIC TUMOR
Clonal expansion, growth, diversification, angiogenesis
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Passage through extracellular matrix
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Adhesion to basement membrane
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Angiogenesis
Growth
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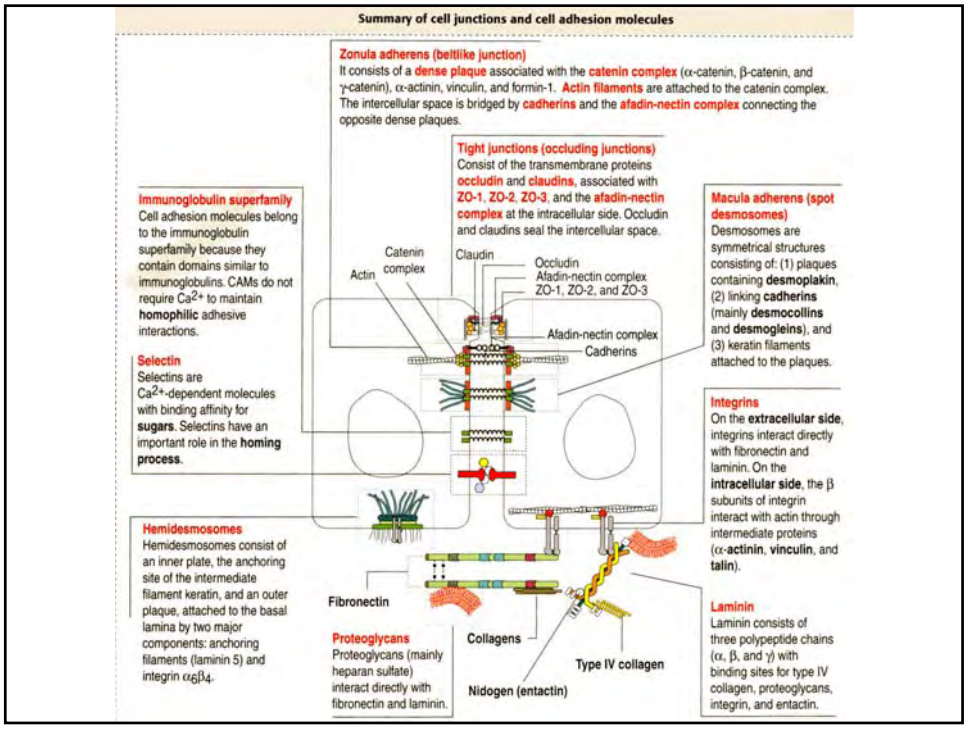
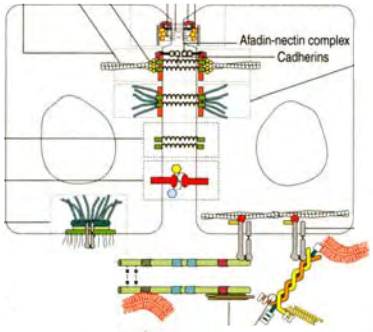
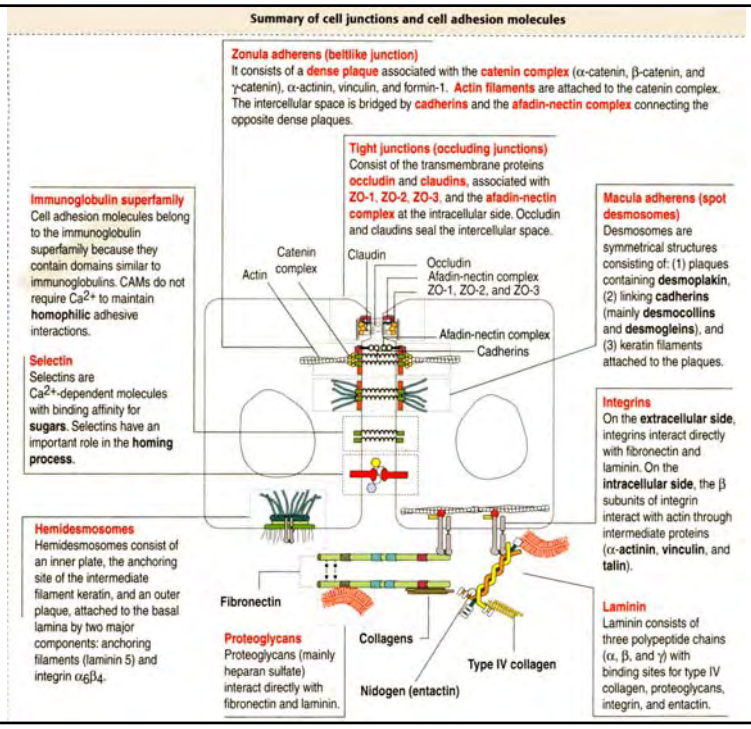

Summary of cell junctions and cell adhesion molecules
Zonula adherens (beltlike junction)
It consists of a dense plaque associated with the catenin complex (α-catenin, β-catenin, and γ-catenin), α-actinin, vinculin, and formin-1. Actin filaments are attached to the catenin complex. The intercellular space is bridged by cadherins and the afadin-nectin complex connecting the opposite dense plaques.
Tight junctions (occluding junctions)
Consist of the transmembrane proteins occludin and claudins, associated with ZO-1, ZO-2, ZO-3, and the afadin-nectin complex at the intracellular side. Occludin and claudins seal the intercellular space.
Immunoglobulin superfamily
Cell adhesion molecules belong to the immunoglobulin superfamily because they contain domains similar to immunoglobulins. CAMs do not require Ca^{2+} to maintain homophilic adhesive interactions.
Selectin
Selectins are Ca^{2+}-dependent molecules with binding affinity for sugars. Selectins have an important role in the homing process.
Hemidesmosomes
Hemidesmosomes consist of an inner plate, the anchoring site of the intermediate filament keratin, and an outer plaque, attached to the basal lamina by two major components: anchoring filaments (laminin 5) and integrin $\alpha_6\beta_4$.
Proteoglycans
Proteoglycans (mainly heparan sulfate) interact directly with fibronectin and laminin.
Macula adherens (spot desmosomes)
Desmosomes are symmetrical structures consisting of: (1) plaques containing desmoplakin, (2) linking cadherins (mainly desmocollins and desmogleins), and (3) keratin filaments attached to the plaques.
Integrins
On the extracellular side, integrins interact directly with fibronectin and laminin. On the intracellular side, the β subunits of integrin interact with actin through intermediate proteins (α-actinin, vinculin, and talin).
Laminin
Laminin consists of three polypeptide chains (α, β, and γ) with binding sites for type IV collagen, proteoglycans, integrin, and entactin.
Catenin complex
Actin
Claudin
Occludin
Afadin-nectin complex
ZO-1, ZO-2, and ZO-3
Afadin-nectin complex
Cadherins
Fibronectin
Collagens
Type IV collagen
Nidogen (entactin)


Afadin-nectin complex
Cadherins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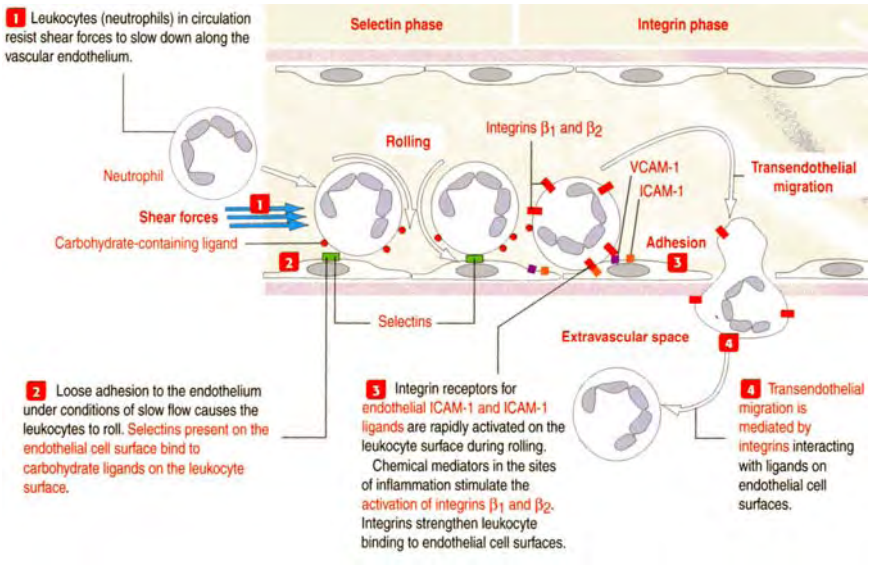
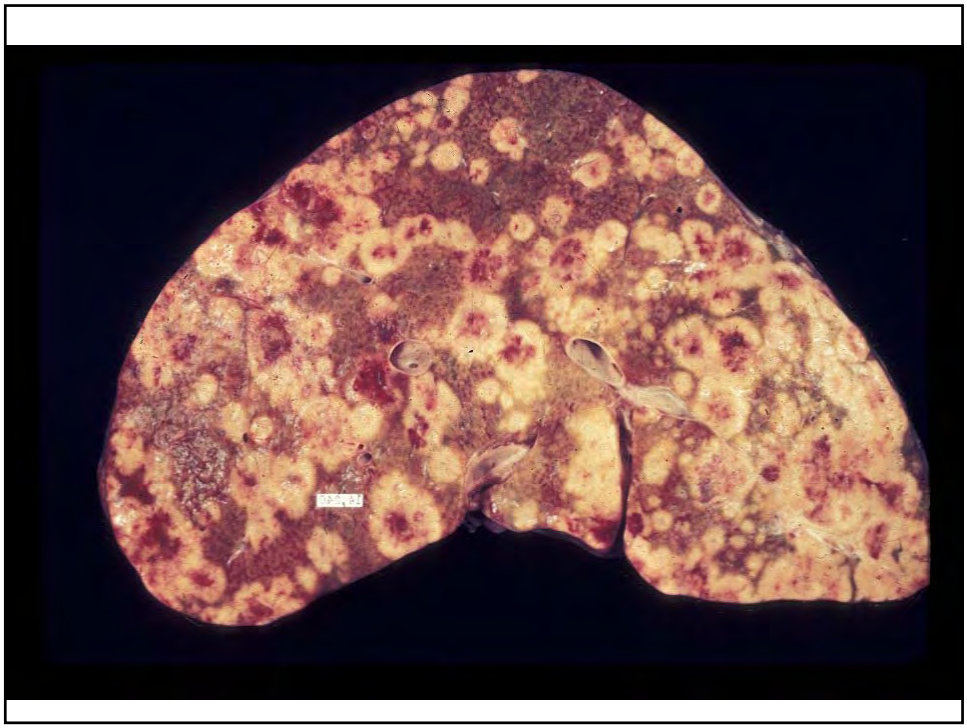
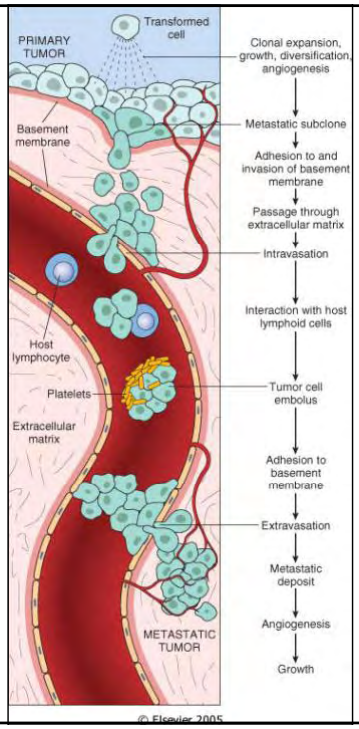
Homing of Tumor Cells



Homing of Tumor Cells

- Most metastases predicted by vascular and lymphatic drainage
- Some homing related to expression of endothelial adhesion molecules
- **Chemokines and chemokine receptors** are also involved in homing. (breast ca cells-chemokine receptors: CXCR-4 and -7 bind to the chemokines CXCL12 and CCL21 on distant organs)
- After extravasation, tumor cells survive only in receptive ECM and stroma

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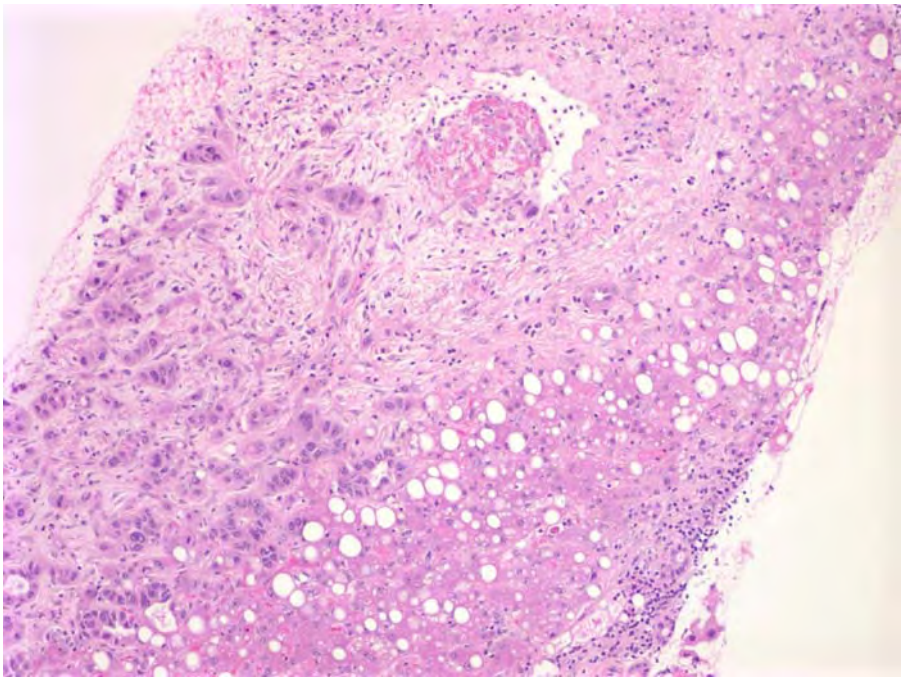
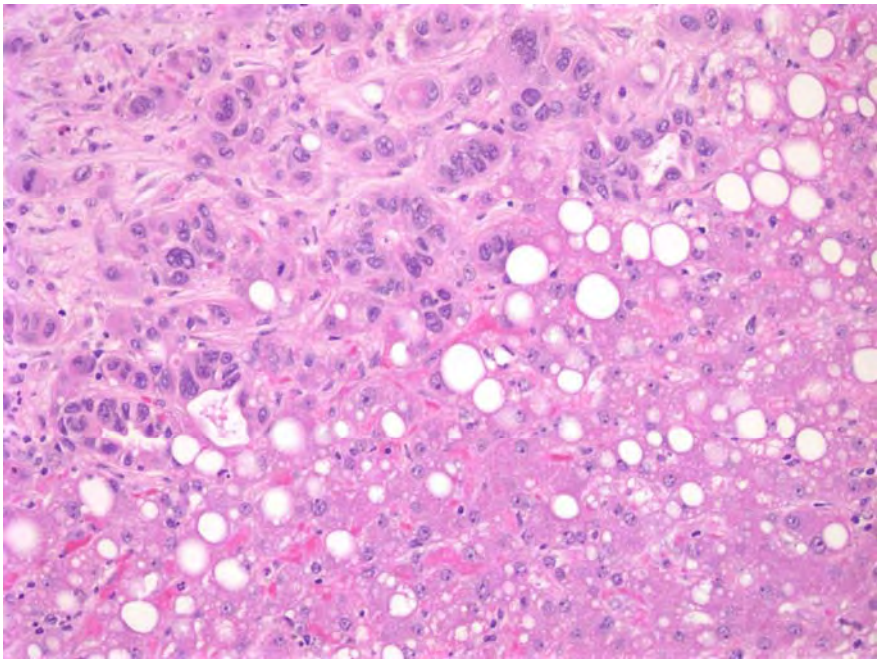
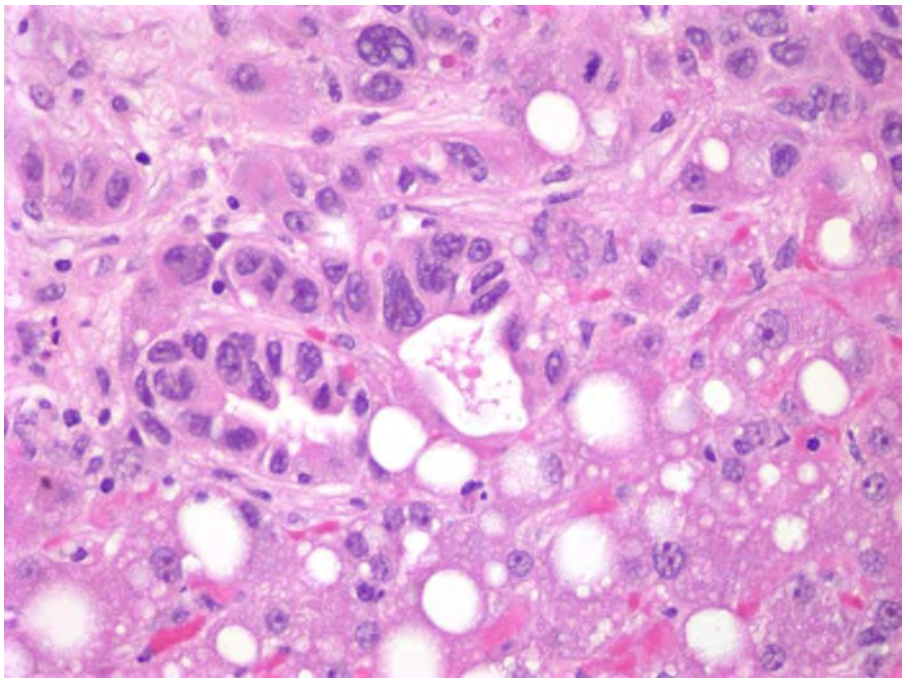
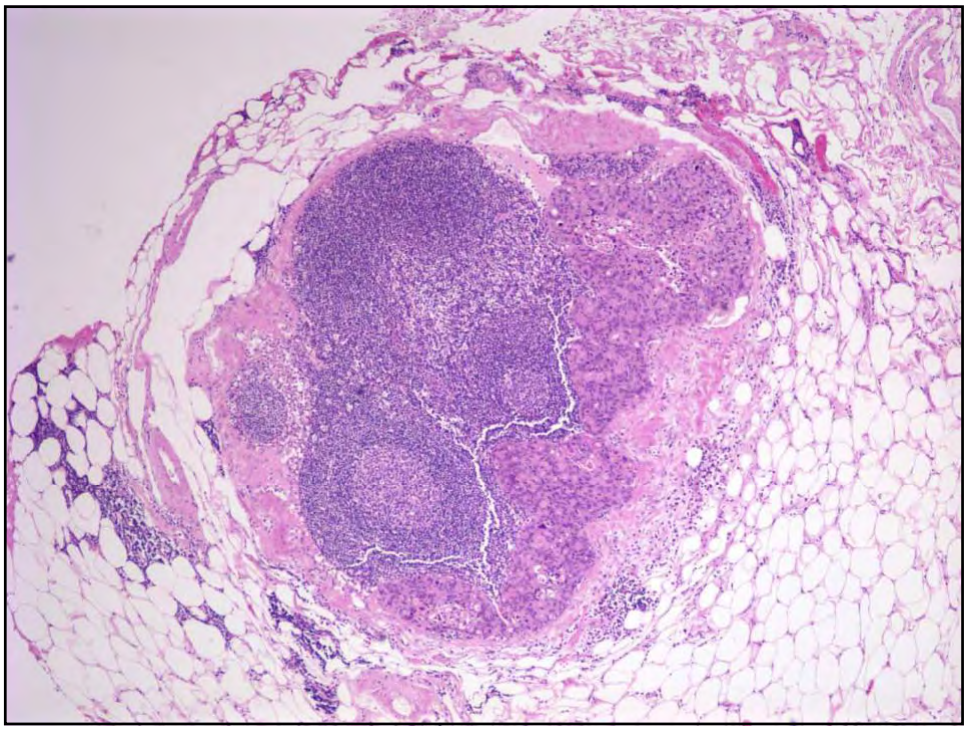








Cinical Aspects of Neoplasia

1. **Epidemiology:**

   Cancer incidence—Cancer deaths
2. **Pathogenetic factors: a balance of risks**
3. **Clinical effects of cancer**
4. **Death in cancer**
5. **Grading and Staging**
6. **Diagnosis**

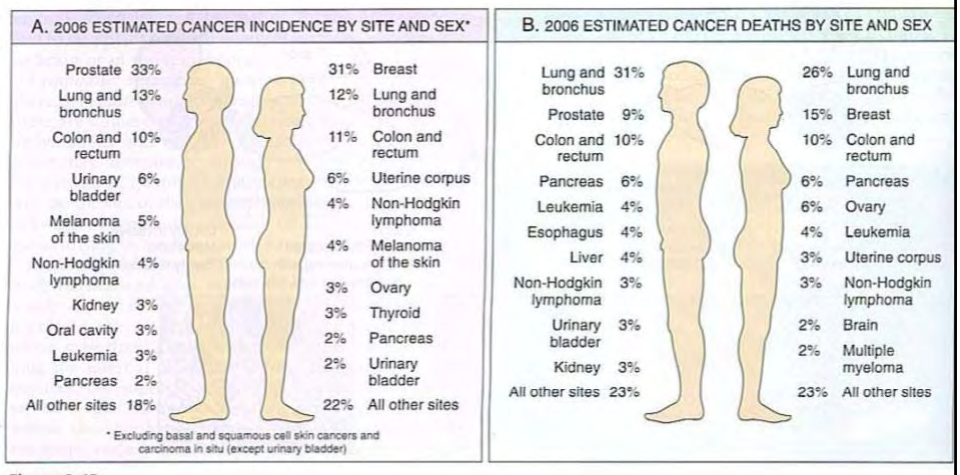
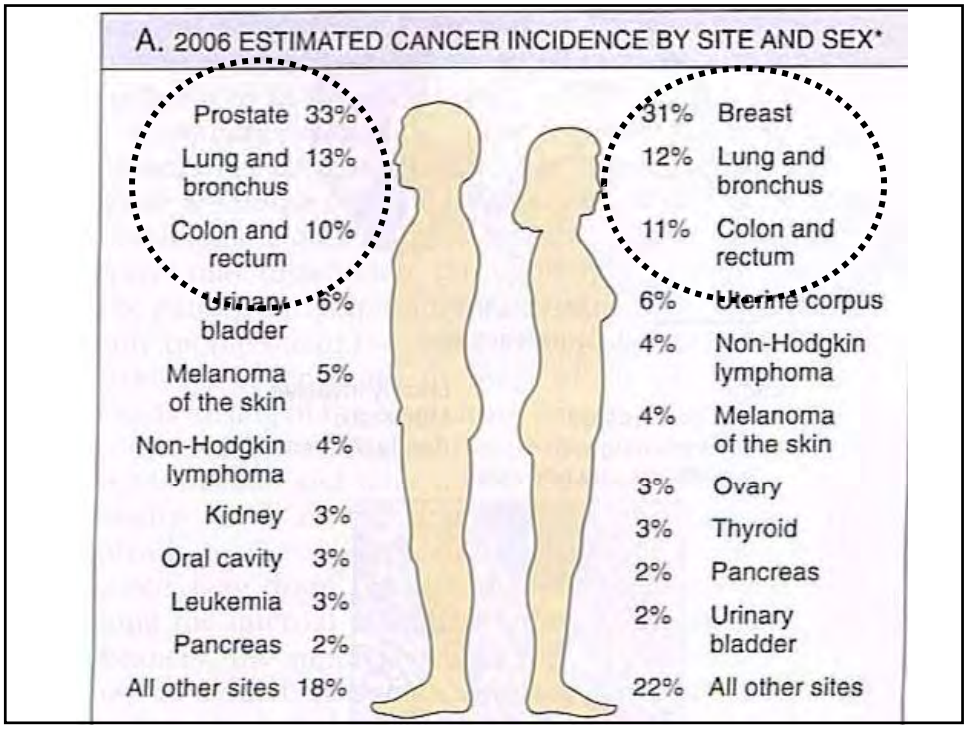
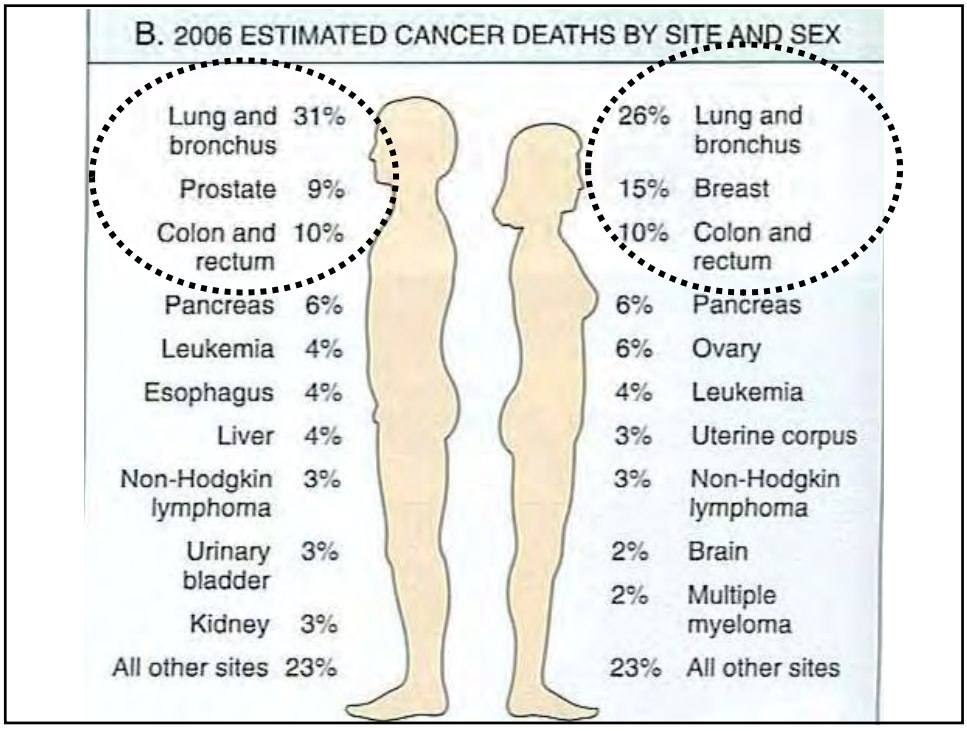
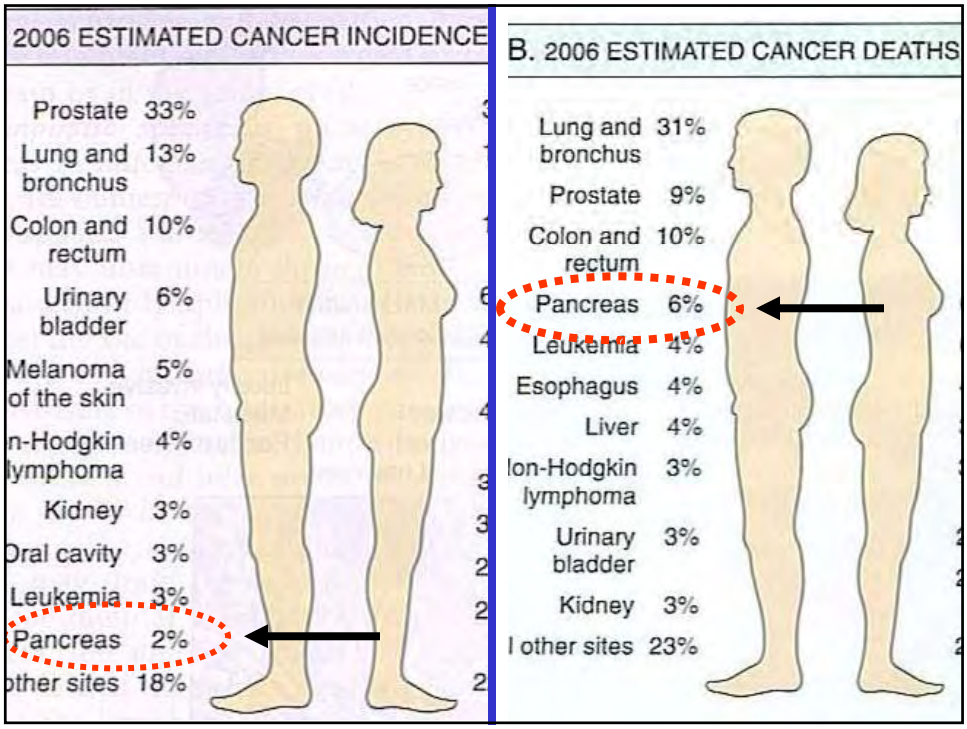


Figure 6–13

Cancer incidence and mortality by site and sex. (Adapted from Jemal A, et al.: Cancer statistics, 2006. CA Cancer J Clin 56:106, 2006.)


A. 2006 ESTIMATED CANCER INCIDENCE BY SITE AND SEX*
Prostate 33%
Lung and bronchus 13%
Colon and rectum 10%
Urinary bladder 6%
Melanoma of the skin 5%
Non-Hodgkin lymphoma 4%
Kidney 3%
Oral cavity 3%
Leukemia 3%
Pancreas 2%
All other sites 18%
31% Breast
12% Lung and bronchus
11% Colon and rectum
6% Uterine corpus
4% Non-Hodgkin lymphoma
4% Melanoma of the skin
3% Ovary
3% Thyroid
2% Pancreas
2% Urinary bladder
22% All other sites


B. 2006 ESTIMATED CANCER DEATHS BY SITE AND SEX
Lung and bronchus 31%
Prostate 9%
Colon and rectum 10%
Pancreas 6%
Leukemia 4%
Esophagus 4%
Liver 4%
Non-Hodgkin lymphoma 3%
Urinary bladder 3%
Kidney 3%
All other sites 23%
26% Lung and bronchus
15% Breast
10% Colon and rectum
6% Pancreas
6% Ovary
4% Leukemia
3% Uterine corpus
3% Non-Hodgkin lymphoma
2% Brain
2% Multiple myeloma
23% All other sites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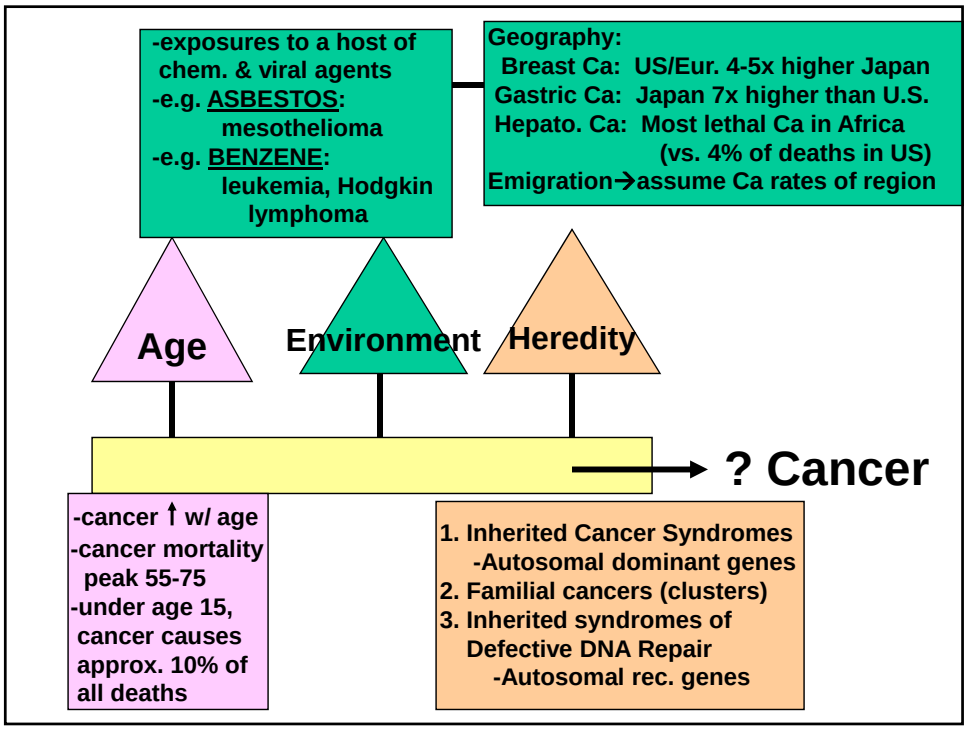

-exposures to a host of chem. & viral agents
-e.g. ASBESTOS: mesothelioma
-e.g. BENZENE: leukemia, Hodgkin lymphoma
Geography:
Breast Ca: US/Eur. 4-5x higher Japan
Gastric Ca: Japan 7x higher than U.S.
Hepato. Ca: Most lethal Ca in Africa (vs. 4% of deaths in US)
Emigration→assume Ca rates of region
Age
Environment
Heredity
? Cancer
-cancer ↑ w/ age
-cancer mortality peak 55-75
-under age 15, cancer causes approx. 10% of all deaths
1. Inherited Cancer Syndromes
-Autosomal dominant genes
2. Familial cancers (clusters)
3. Inherited syndromes of Defective DNA Repair
-Autosomal rec. genes

Table 6–3 Inherited Predisposition to Cancer

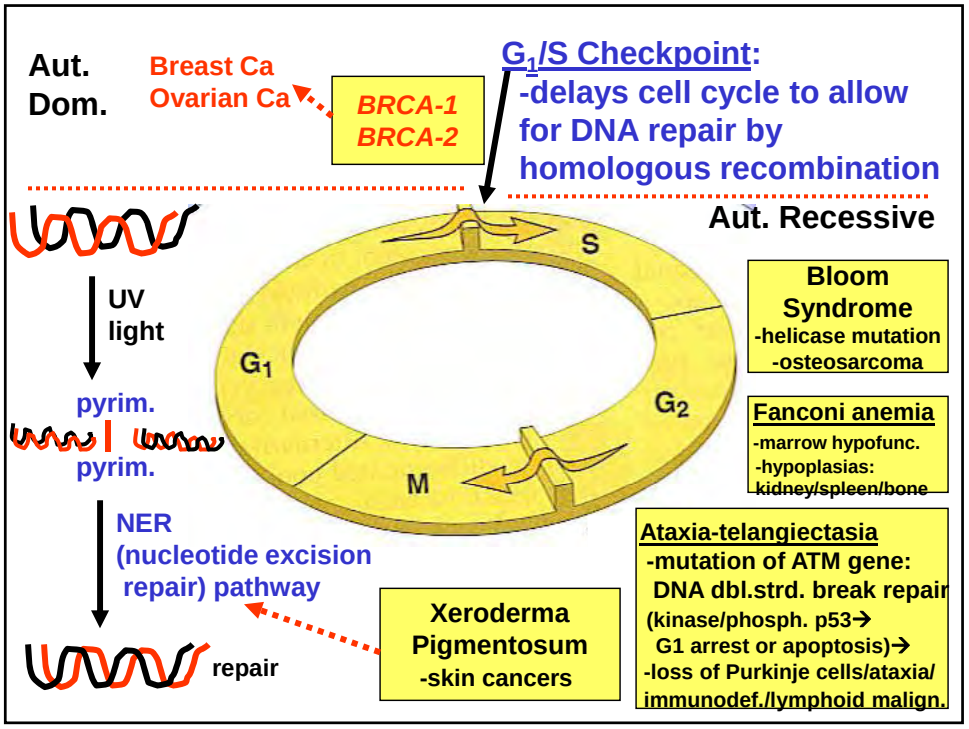
Inherited Cancer Syndromes (Autosomal Dominant) Gene	Inherited Predisposition
RB	Retinoblastoma
p53	Li-Fraumeni syndrome (various tumors)
p16INK4A	Melanoma
APC	Familial adenomatous polyposis/colon cancer
NF1, NF2	Neurofibromatosis 1 and 2
BRCA1, BRCA2	Breast and ovarian tumors
MEN1, RET	Multiple endocrine neoplasia 1 and 2
MSH2, MLH1, MSH6	Hereditary nonpolyposis colon cancer
PATCH	Nevoid basal cell carcinoma syndrome

Familial Cancers

Familial clustering of cases, but role of inherited predisposition not clear for each individual
- Breast cancer (not linked to BRCA1 or BRCA2)
- Ovarian cancer
- Pancreatic cancer

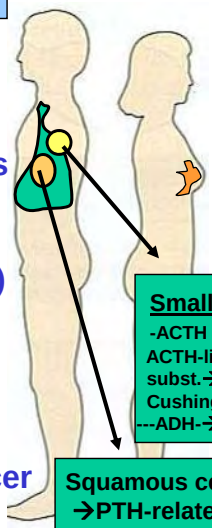
Inherited Autosomal Recessive Syndromes of Defective DNA Repair

Xeroderma pigmentosum
Ataxia-telangiectasia
Bloom syndrome
Fanconi anemia



Clinical Effects of Cancer

1. **Cachexia**
   - -cytokines→ anorexia
   - TNF: from macrophages/tumor cells
     - -suppresses appetite
     - -inhibits lipoprotein lipase
   - (inhibits FFA release from lipoprot's)
   - Proteolysis-inducing factor:
     - -breaks down skeletal muscle
2. **Paraneoplastic syndromes**
   - -hormone production by tumor cells
   - -present in 10% - 15% of pts. with cancer
3. **Venous thrombosis**
   - -mucins from Ca's activate clotting
   - e.g. Pancreas: Trousseau phenomenon



Small cell Ca
-ACTH or ACTH-like subst.→ Cushing syndrome
---ADH-→ SIADH

Squamous cell Ca
→PTH-related prot.
→hypercalcemia

Death in Cancer

1. Overwhelm organ function
   -liver: ↓coagulation, other protein synthesis
   -lung: ↓ diffusion/oxygenation
   -pancreas: biliary obstruction/liver mets → anorexia
2. Pulmonary embolus (pro-thrombotic Ca's)
3. Progressive somnolence: hypercalcemia, etc.
4. Systemic electrolyte imbalances:
   → cardiac arrhythmia
   → ↓mentation
5. Tumor-related products:
   -depression/other CNS effects

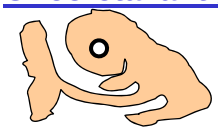
Diagnosis of Cancer

- History—physical—occupation—exposure
- Radiology
- Blood tests: tumor markers
- Morphologic Diagnosis
  - -light microscopy: biopsy
  - -cytology (Fine Needle Aspiration—FNA)
  - -immunohistochemistry
  - -fluorescence *in situ* hybridization (FISH)
  - -molecular probes, incl. gene microarray
  - -flow cytometry (lymphomas, leukemias)

Tumor Markers

*Molecules in plasma produced by tumor cells

Oncofetal antigens



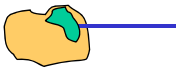
carcinoembryonic antigen (CEA)

colon Ca; pancreas, lung,breast Ca

alphafetoprotein (AFP)

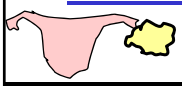
hepatocellular Ca, germ cell testis Ca

Specific proteins



PSA (prostatic specific antigen)

Mucins & other glycoproteins: CA's: carbohydrate antigens



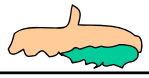
CA-125
ovary

CA-19-9
Bile ducts, panc.

CA-15-3
breast

Hormones

trophoblastic tumor (placenta)



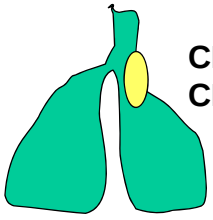
testis

HCG

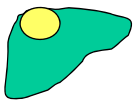
medullary Ca thyroid

calcitonin

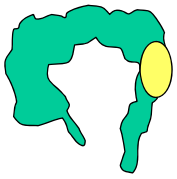
Immunohistochemistry:
--monoclonal Ab to specific cell Ag's



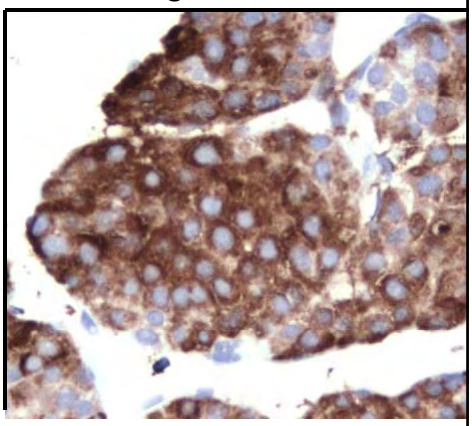
CK7+
CK20-

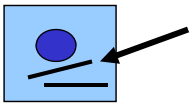


CK7-
CK20-



CK7-
CK20+





Cytokeratins in epith. cells:
CK7 and CK20

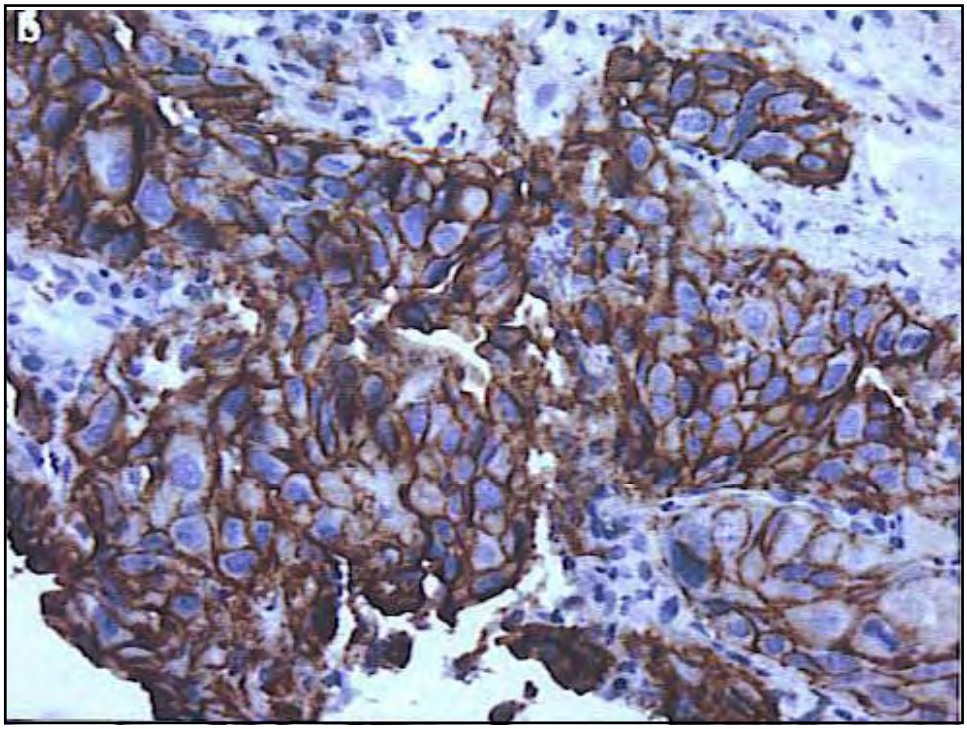
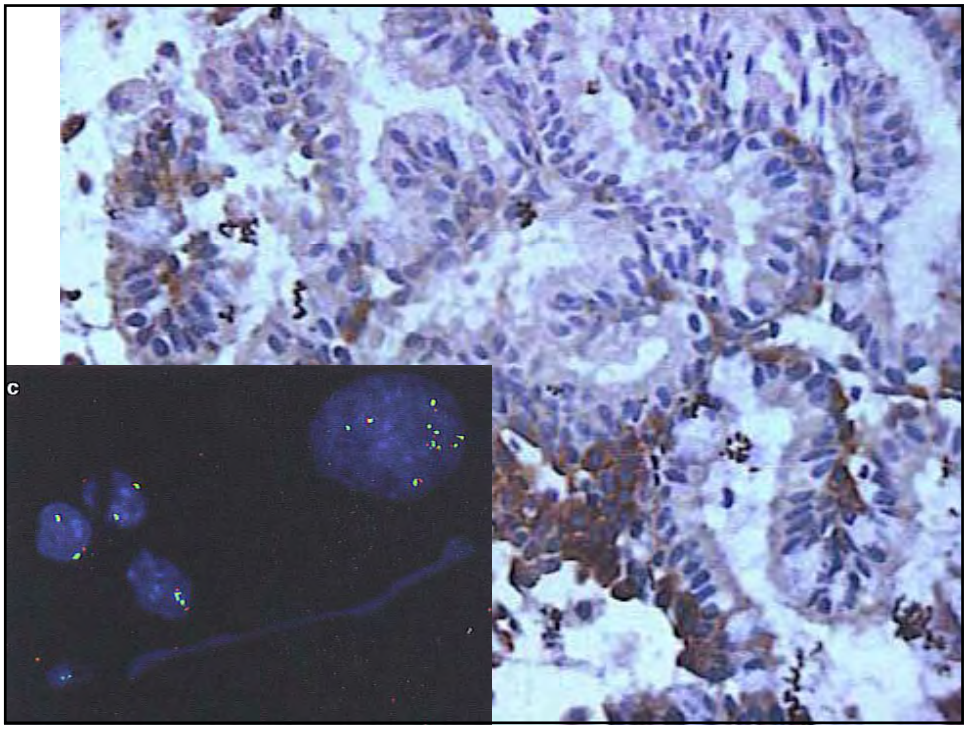
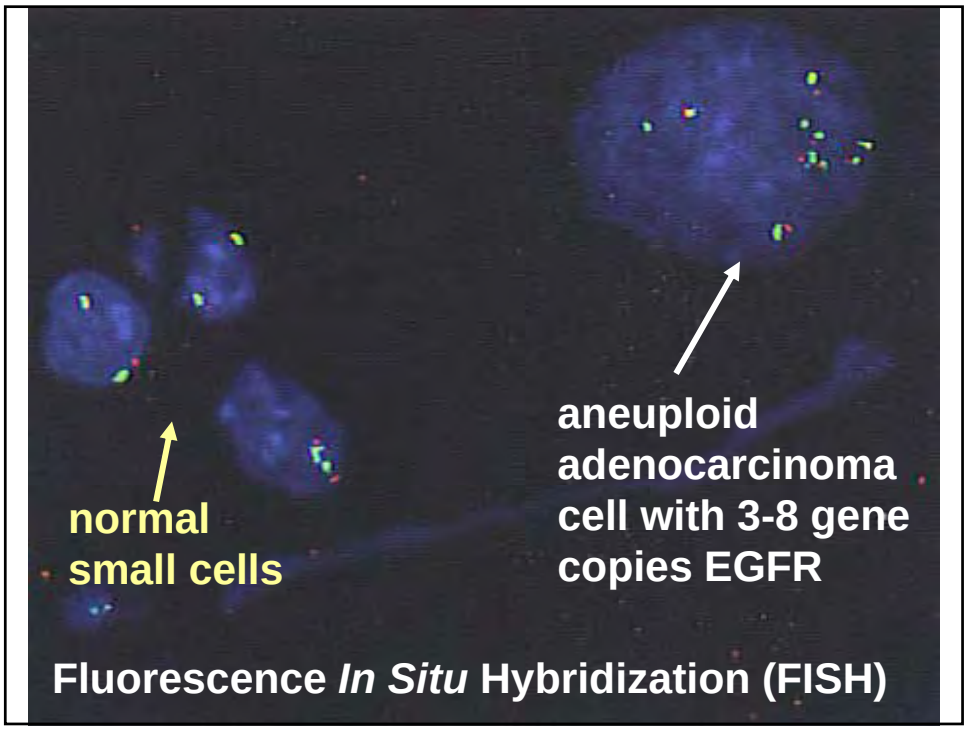


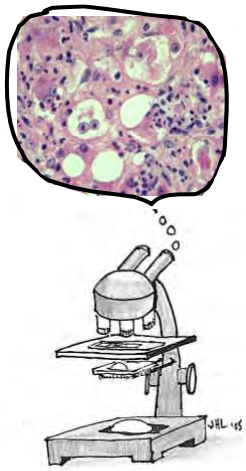
Table 2. Frequency of high epidermal growth factor receptor (EGFR) expression in lung cancer by histologic characterization

Histology	EGFR expression, % (*n*)
Small cell	0 (19)
Adenocarcinoma	65 (563)
Large cell	68 (72)
Squamous	84 (754)

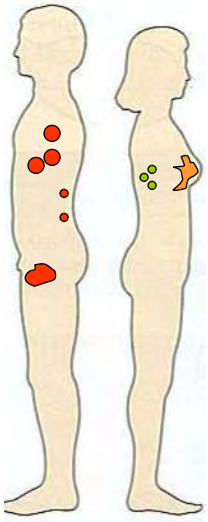
Reprinted from Bunn PA Jr, Franklin W. Epidermal growth factor receptor expression, signal pathway, and inhibitors in non-small cell lung cancer. Semin Oncol 2002;29(suppl 14):38–44, with permission from Elsevier.


c


normal
small cells
aneuploid
adenocarcinoma
cell with 3-8 gene
copies EGFR
Fluorescence *In Situ* Hybridization (FISH)

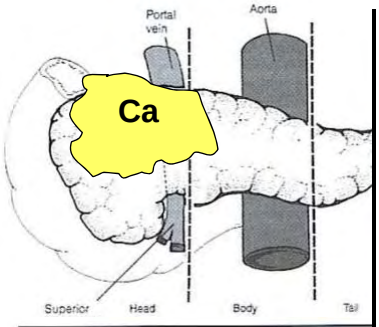


Grading



Staging

Staging: TNM
AJC (American Joint Committee)



STAGE GROUPING — **AJC**

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

DEFINITION OF TNM

Primary Tumor (T)

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Tis Carcinoma *in situ*
- T1 Tumor limited to the pancreas, 2 cm or less in greatest dimension
- T2 Tumor limited to the pancreas, more than 2 cm in greatest dimension
- T3 Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
- T4 Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

Regional Lymph Nodes (N)

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Regional lymph node metastasis

Distant Metastasis (M)

- MX Distant metastasis cannot be assessed
- M0 No distant metastasis
- M1 Distant metastasis