Neoplasia I
Definitions, Terminology, and Morphology

Patrice Spitalnik, MD
pfs2101@columbia.edu

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

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

Characteristics of Benign & Malignant Neoplasms

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

Nomenclature

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

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.

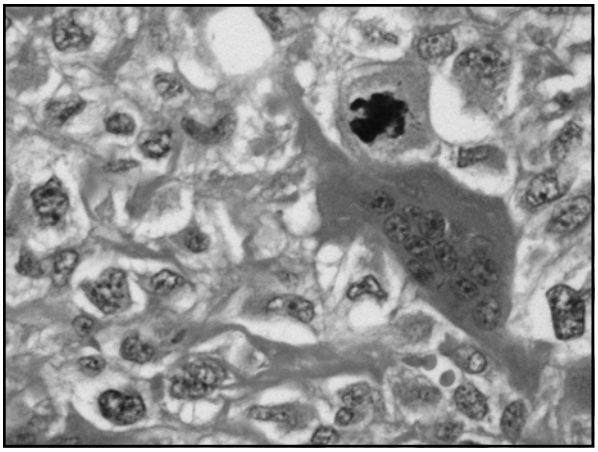
- **Cytologic features**
  - **Benign** – small, uniform cells, no visible nucleoli
  - **Malignant** – large, pleomorphic cells with large hyperchromatic nuclei, N:C ratio 1:1 (nl. 1:4), large nucleoli, irregular nuclear outlines

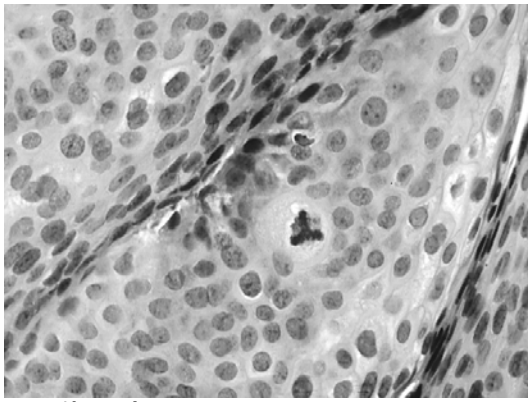
Anaplasia

- Neoplasm without apparent differentiation, undifferentiated cells

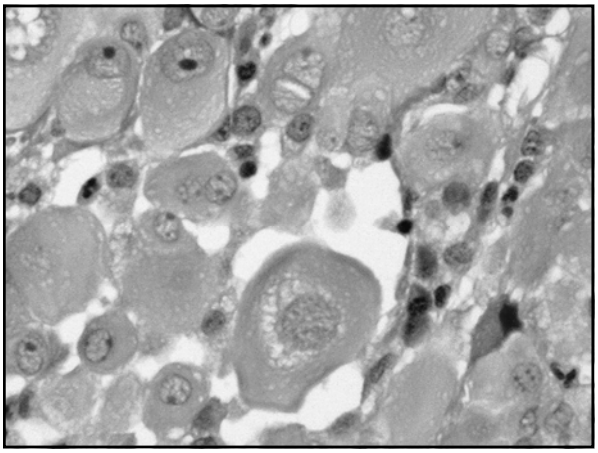
Differentiation

- 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

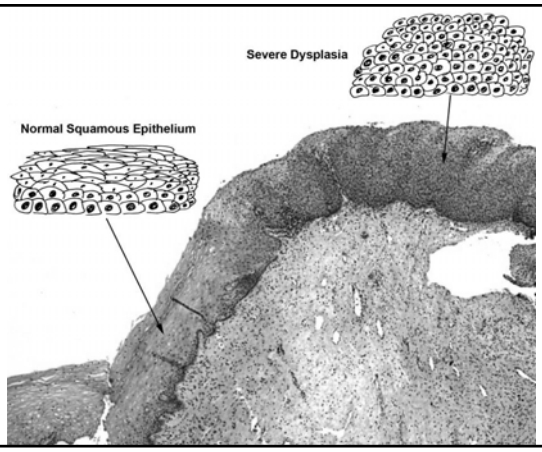


Dysplasia

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

Local Invasion

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

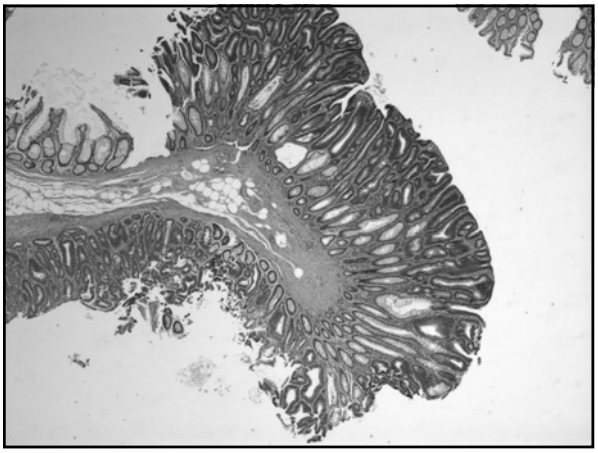


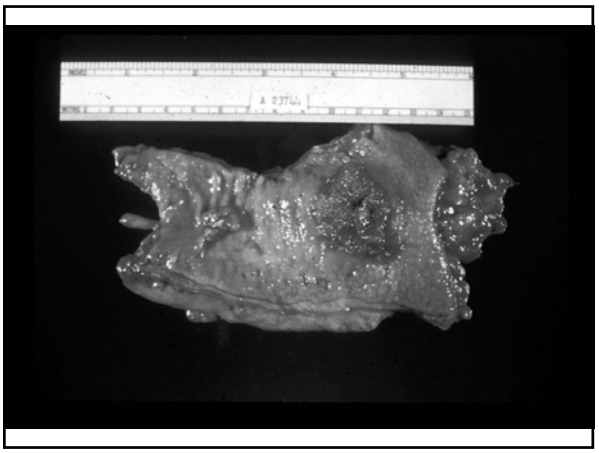
Benign Neoplasia

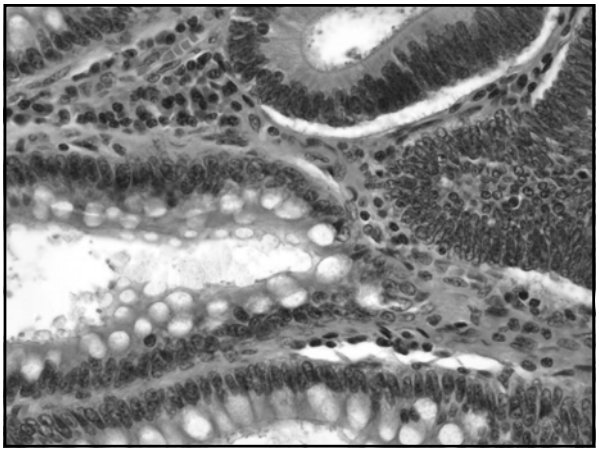
- Remains localized
- Cannot spread to other sites
- Most patients survive, but some tumor locations can cause serious problems (brain stem, spinal cord, pituitary)

Rate of Growth

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

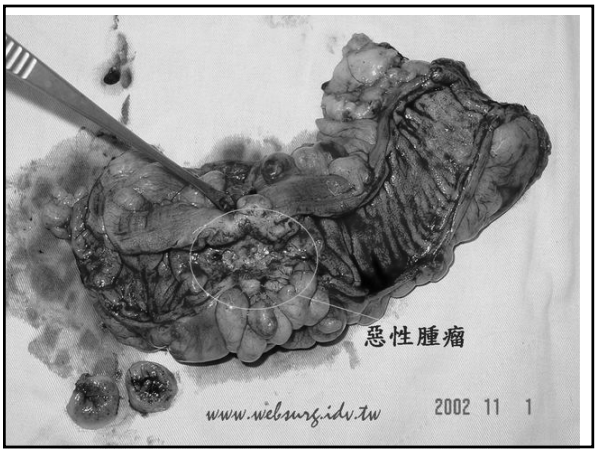


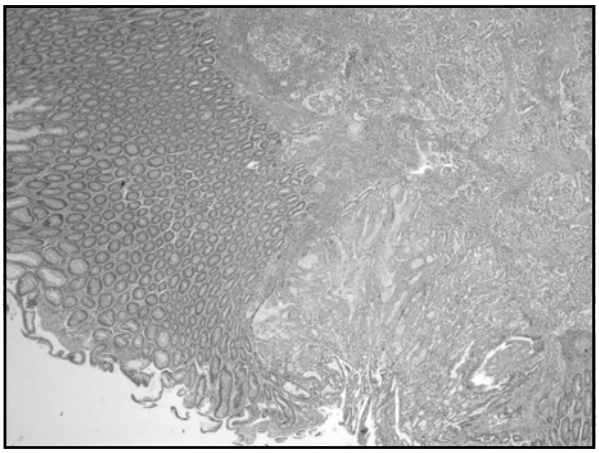


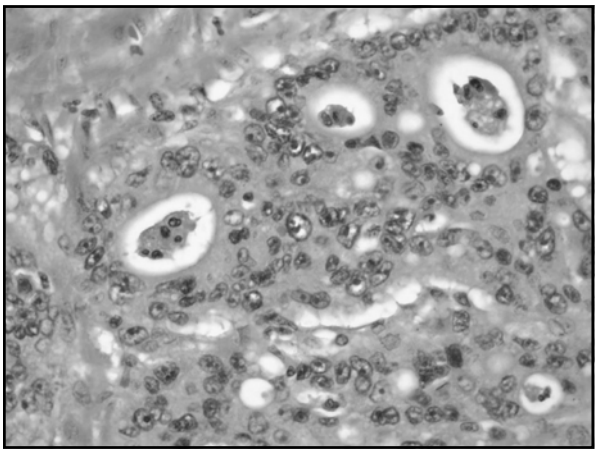


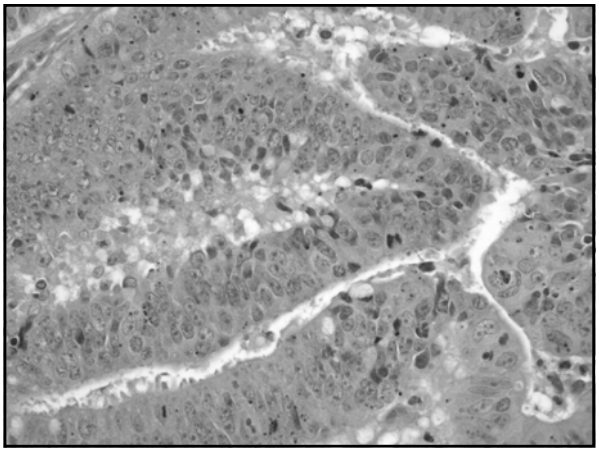
Malignant Neoplasia

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



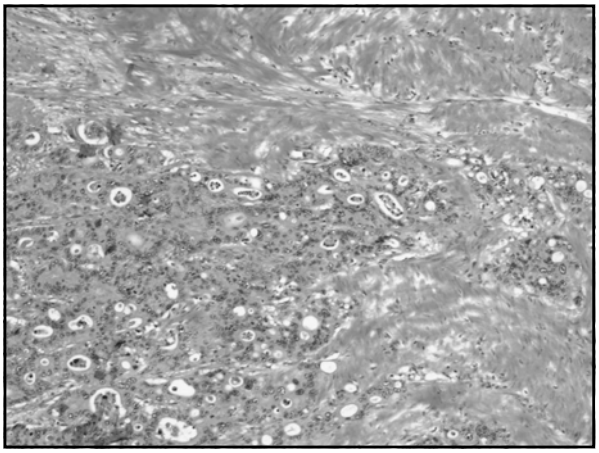






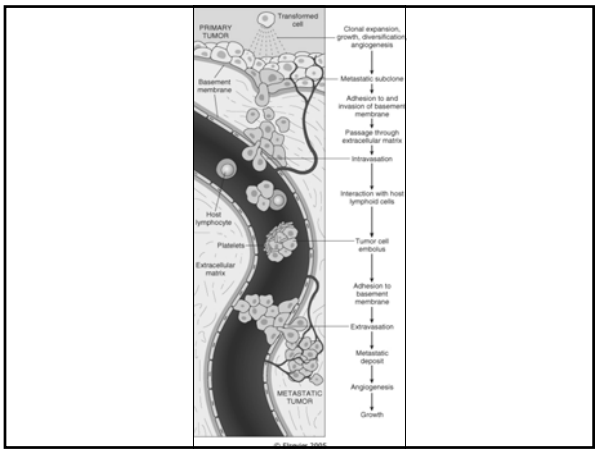
Metastasis

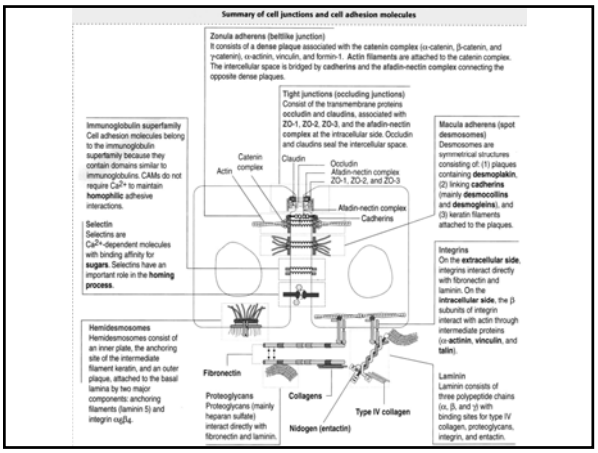
- Dissemination to other organs:
  - Seeding of body cavities (ovary)
  - Lymphatic spread (carcinoma)
  - Hematogenous dissemination (sarcoma)

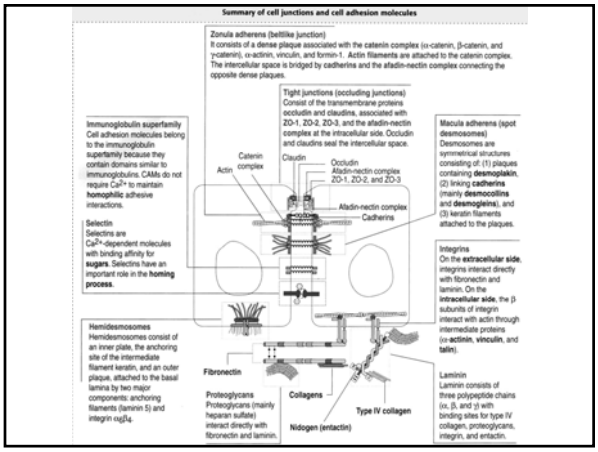


Steps of Successful Metastasis

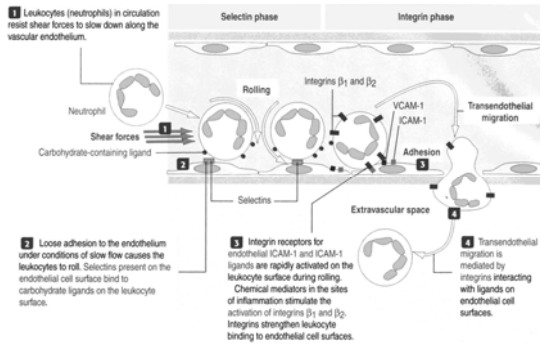
- **Detachment of tumor cells** (E-cadherin loss)
- **Degradation of ECM** (MMP's - overexpressed and TIMP's - reduced)
- **Attachment to new ECM proteins** (cleavage products of collagen and laminin bind to receptors on tumor cells - stimulate migration
- **Migration of tumor cells** (cytokines from tumor cells direct movement, autocrine, and stromal cells produce paracrine effectors, HGF/SCF, for motility that bind to tumor cells)

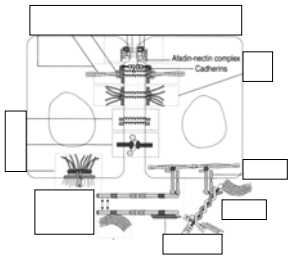






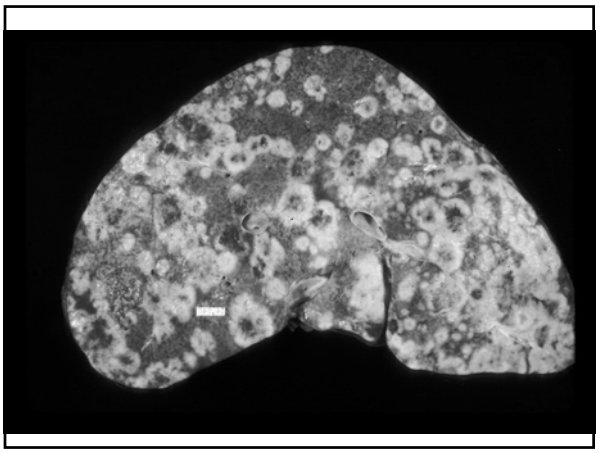
Homing of Tumor Cells

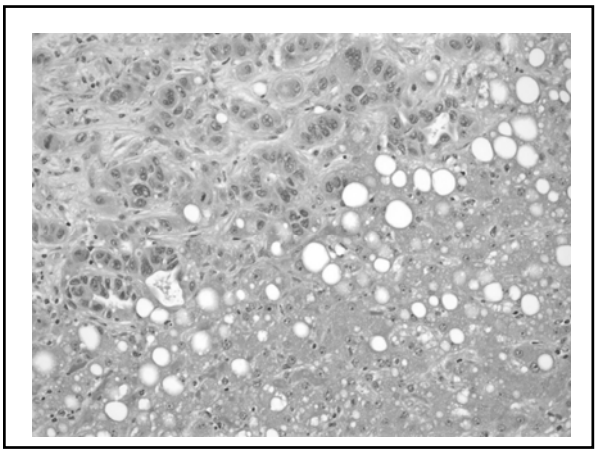


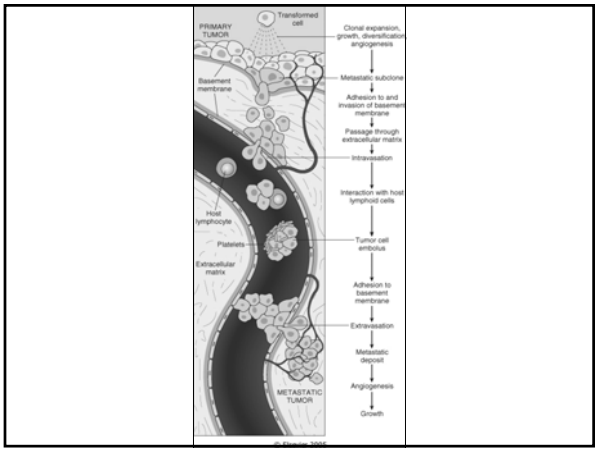


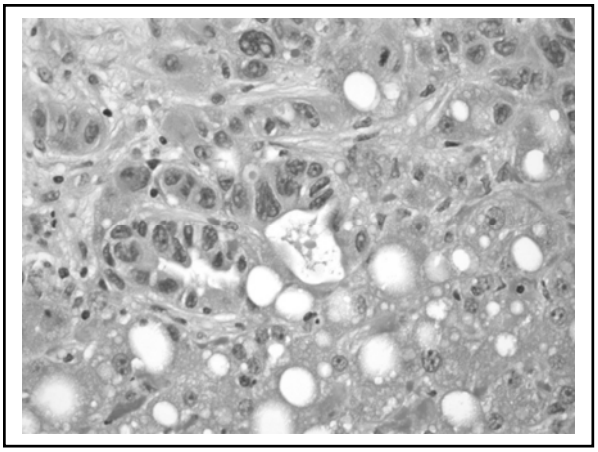
Homing of Tumor Cells

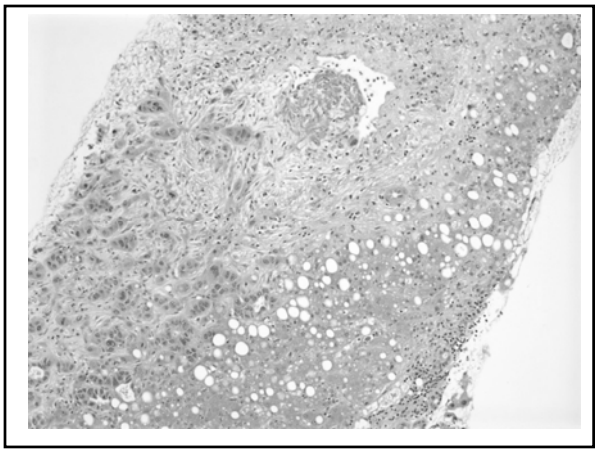
- Most metastases predicted by vascular and lymphatic drainage
- Some homing related to expression of endothelial adhesion molecules
- **Chemokines and chemokine receptors** are also involved in homing. (breast ca cells-chemokine receptors: CXCR-4 and -7 bind to the chemokines CXCL12 and CCL21 on distant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

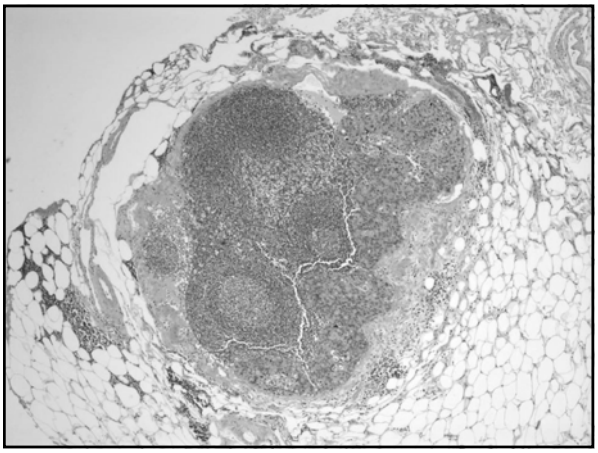





PRIMARY TUMOR
Transformed cell
Basement membrane
Host lymphocyte
Platelets
Extracellular matrix
METASTATIC TUMOR
Clonal expansion, growth, diversification, angiogenesis
Metastatic subclone
Adhesion to and invasion of basement membrane
Passage through extracellular matrix
Intravasation
Interaction with host lymphoid cells
Tumor cell embolus
Adhesion to basement membrane
Extravasation
Metastatic deposit
Angiogenesis
Growth

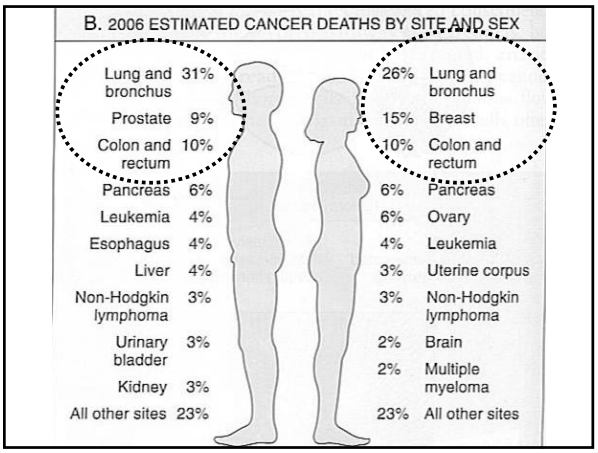


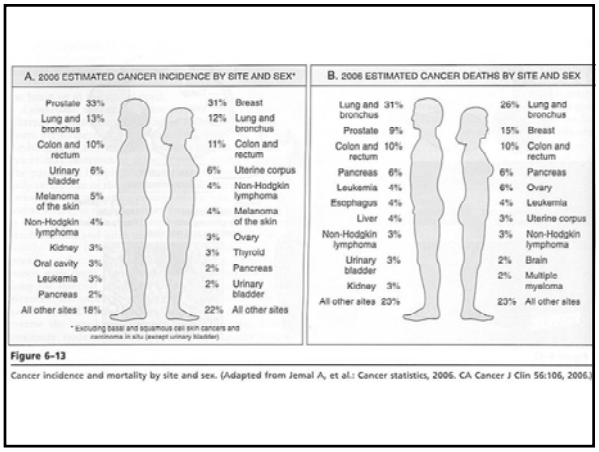


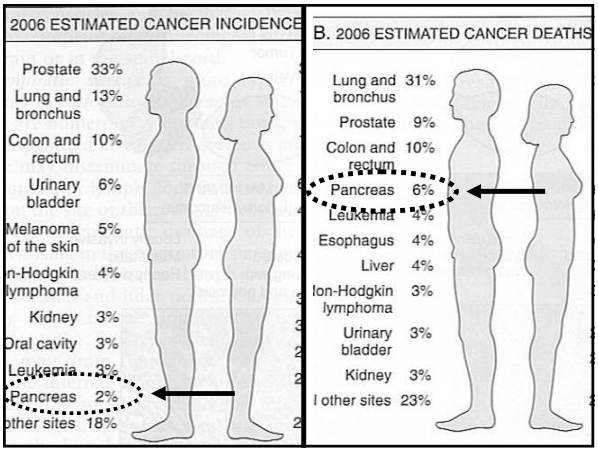


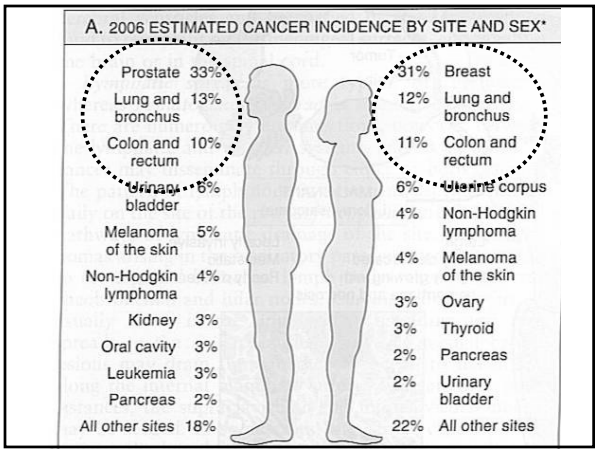
Cinical Aspects of Neoplasia

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**









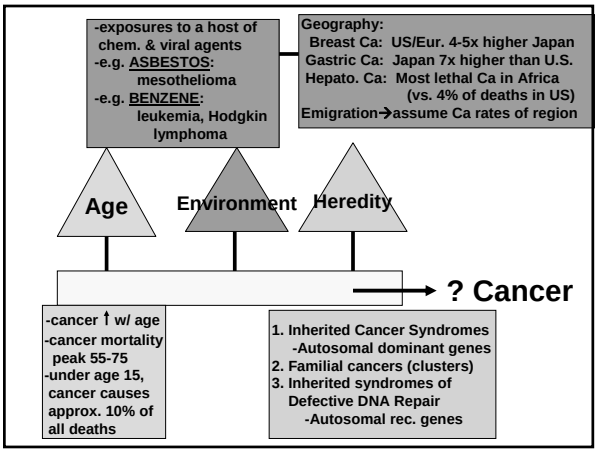
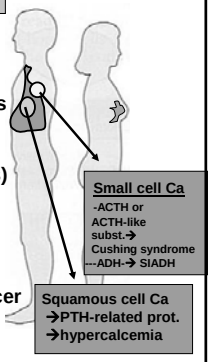


Table 6–3 Inherited Predisposition to Cancer

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

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

Familial Cancers

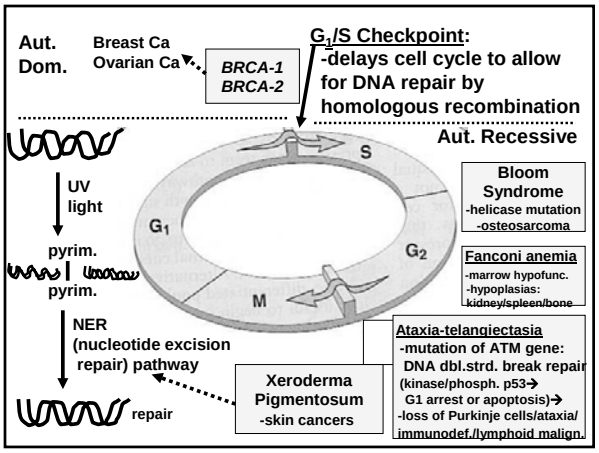
Familial clustering of cases, but role of inherited predisposition not clear for each individual
- Breast cancer (not linked to BRCA1 or BRCA2)
- Ovarian cancer
- Pancreatic cancer

Inherited Autosomal Recessive Syndromes of Defective DNA Repair

- Xeroderma pigmentosum
- Ataxia-telangiectasia
- Bloom syndrome
- Fanconi anemia

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

gut

carcinoembryonic antigen (CEA)

colon Ca; pancreas, lung,breast Ca

yolk sac,liver

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

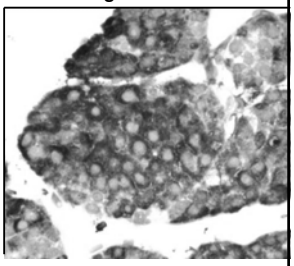
calcitonin

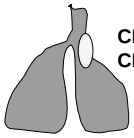
Table 2. Frequency of high epidermal growth factor receptor (EGFR) expression in lung cancer by histologic characterization

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.

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

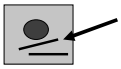




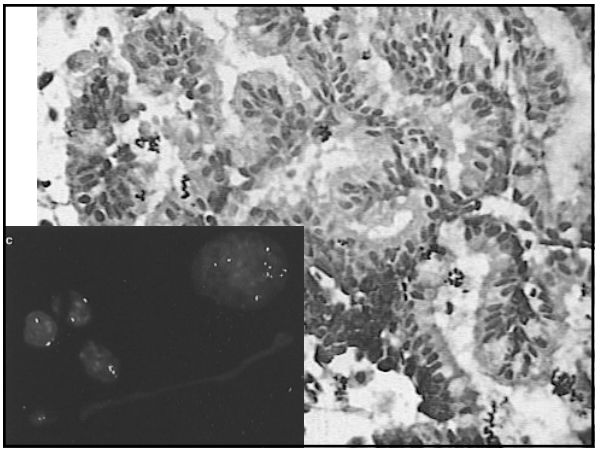
CK7+
CK20-

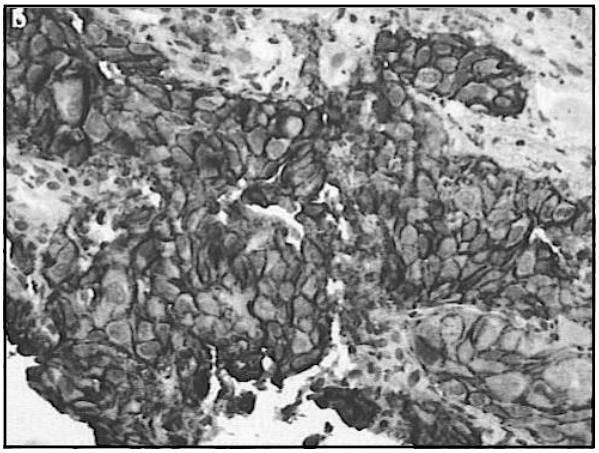
CK7-
CK20-

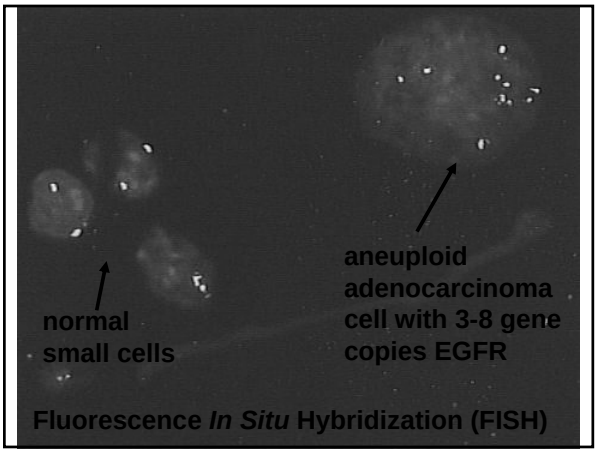
CK7-
CK20+



Cytokeratins in epith. cells:
CK7 and CK20



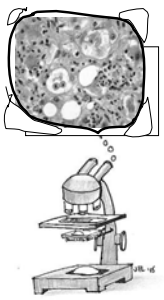




normal small cells

aneuploid adenocarcinoma cell with 3-8 gene copies EGFR

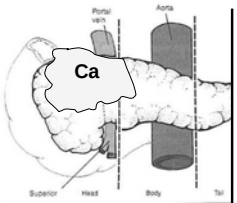
Fluorescence *In Situ* Hybridization (FISH)



Grading

Staging

Staging: TNM
AJC (American Joint Committee)



AJC

STAGE GROUPING			
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