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

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Cell Type</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conn. Tissue</td>
<td>Fibroblast</td>
<td>Fibroma</td>
<td>Fibrosarcoma</td>
</tr>
<tr>
<td></td>
<td>Adipocyte</td>
<td>Lipoma</td>
<td>Liposarcoma</td>
</tr>
<tr>
<td>Cartilage</td>
<td>Chondroma</td>
<td>Chondrosarcoma</td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>Osteoma</td>
<td>Osteosarcoma</td>
<td></td>
</tr>
<tr>
<td>Vessels, etc</td>
<td>Endothelial cells</td>
<td>Hemangioma</td>
<td>Angiosarcoma</td>
</tr>
<tr>
<td>Meninges</td>
<td>Meningioma</td>
<td>Invasive meningioma</td>
<td></td>
</tr>
<tr>
<td>Muscle</td>
<td>Smooth muscle</td>
<td>Leiomyoma</td>
<td>Leiomyosarcoma</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>Rhabdomyoma</td>
<td>Rhabdomyosarcoma</td>
<td></td>
</tr>
<tr>
<td>Epithelium</td>
<td>Stratified Squamous</td>
<td>Squamous papilloma</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Ducts or glands</td>
<td>Adenoma</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Melanocytes</td>
<td>Melanocytes</td>
<td>Nevus</td>
<td>Melanoma</td>
</tr>
</tbody>
</table>
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
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)
Summary of cell junctions and cell adhesion molecules

Zona occludens (tight junctions)
It consists of a dense plaque associated with the cadherin complex (α-catenin, β-catenin, and γ-catenin). Desmosomes also have a role.

Immunooglobin superfamily
Cell adhesion molecules belong to the immunoglobulin superfamily because they contain domains similar to immunoglobulins. CAMs do not require Ca²⁺ to maintain homophilic adhesive interactions.

Selectins
Selectins are Ca²⁺-dependent molecules with binding affinity to sugars. Selectins have an important role in the binding process.

Hemidesmosomes
Hemidesmosomes consist of an inner plaque, the anchoring site of the intermediate filament keratin, and an outer plaque, attached to the basal lamina by two major components: anchoring filaments (lamina n.n.) and integrin αβ3.

Integrins
On the extracellular side, integrins interact directly with fibronectin and laminin. On the intracellular side, the β subunits of integrins interact with actin through intermediate proteins (α-actinin, vinculin, and talin).

Laminin
Laminin consists of three polypeptide chains (α1, β1, and γ1) with binding sites for type IV collagen, proteoglycans, integrin, and entactin.
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
Clinical 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
A. 2006 ESTIMATED CANCER INCIDENCE BY SITE AND SEX

- Prostate: 33%
- Lung and bronchus: 13%
- Colon and rectum: 10%
- Urinary bladder: 5%
- Melanoma of the skin: 5%
- Non-Hodgkin lymphoma: 4%
- Kidney: 3%
- Oral cavity: 3%
- Leukemia: 3%
- Pancreas: 2%
- All other sites: 18%

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%

- Lung and bronchus: 26%
- Breast: 15%
- Colon and rectum: 10%
- Pancreas: 6%
- Ovary: 6%
- Leukemia: 4%
- Uterine corpus: 3%
- Non-Hodgkin lymphoma: 3%
- Brain: 2%
- Multiple myeloma: 2%
- All other sites: 23%
- cancer mortality peak 55-75
- under age 15, cancer causes approx. 10% of all deaths

- exposures to a host of chem. & viral agents
  - e.g. ASBESTOS: mesothelioma
  - e.g. BENZENE: leukemia, Hodgkin lymphoma

- Geology:
  - Breast Ca: US/Eur. 4-5x higher than Japan
  - Gastric Ca: Japan 7x higher than U.S.
  - Hepatic Ca: Most lethal Ca in Africa (vs. 4% of deaths in US)

- Emigration → assume Ca rates of region

- Inherited Cancer Syndromes
  - Autosomal dominant genes

- Familial cancers (clusters)

- Inherited syndromes of Defective DNA Repair
  - Autosomal rec. genes

? Cancer
### Table 6-3  Inherited Predisposition to Cancer

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

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## 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 $\rightarrow$ 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

**G$_1$/S Checkpoint**:
- delays cell cycle to allow for DNA repair by homologous recombination

- **BRCA-1**
- **BRCA-2**

**Bloom Syndrome**
- helicase mutation
  - osteosarcoma

**Fanconi anemia**
- marrow hypofunc.
- hypoplasias:
  - kidney/spleen/bone

**Ataxia-telangiectasia**
- mutation of ATM gene:
  - DNA dbl.strd. break repair
    (kinase/phosph. p53 $\rightarrow$
     G1 arrest or apoptosis)$\rightarrow$
  - loss of Purkinje cells/ataxia/
    immunodef./lymphoid malign.

**Xeroderma Pigmentosum**
- skin cancers

**Aut. Recessive**
- Breast Ca
  - Ovarian Ca
- UV light
- pyrim.
- pyrim.
- NER (nucleotide excision repair) pathway
- repair

**Aut. Dom.**
- BRCA-1
- BRCA-2
- G$_1$
- G$_2$
- S

**Clinical Effects of Cancer**

Small cell Ca
- ACTH or
  ACTH-like
  subst.$\rightarrow$
  Cushing syndrome
  -- ADH $\rightarrow$ SIADH

Squamous cell Ca
$\rightarrow$ PTH-related prot.
$\rightarrow$ 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, pancre.
  - CA-15-3
    - breast

**Hormones**
- trophoblastic tumor (placenta)
  - HCG
- testis
  - medullary Ca
- thyroid
  - calcitonin

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

Cytokeratins in epith. cells:
CK7 and CK20
Table 2. Frequency of high epidermal growth factor receptor (EGFR) expression in lung cancer by histologic characterization

<table>
<thead>
<tr>
<th>Histology</th>
<th>EGFR expression, % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small cell</td>
<td>0 (19)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>65 (563)</td>
</tr>
<tr>
<td>Large cell</td>
<td>68 (72)</td>
</tr>
<tr>
<td>Squamous</td>
<td>84 (754)</td>
</tr>
</tbody>
</table>

aneuploid adenocarcinoma cell with 3-8 gene copies EGFR

Fluorescence In Situ Hybridization (FISH)
Staging: TNM
AJC (American Joint Committee)

**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