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

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

<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>Ducts or glands</td>
<td>Adenoma</td>
<td>Adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Melanocytes</td>
<td>Melanocytes</td>
<td>Nevus</td>
<td>Melanoma</td>
</tr>
</tbody>
</table>
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

- 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
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>NFI, 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>

Clinical Effects of Cancer

1. **Cachexia**
   - cytokines → anorexia
   - TNF: from macrophages/tumor cells
   - 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

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)

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**
4. **Systemic electrolyte imbalances**:
   - cardiac arrhythmia
   - ↓ mentation
5. **Tumor-related products**: depression/other CNS effects
**Tumor Markers**

*Molecules in plasma produced by tumor cells*

**Oncofetal antigens**
- carcinoembryonic antigen (CEA)
- alphafetoprotein (AFP)

**Specific proteins**
- PSA (prostatic specific antigen)

**Mucins & other glycoproteins:**
- CA's: carbohydrate antigens
- Hepatocellular Ca, germ cell testis Ca

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

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

**Cytokeratins in epith. cells:**
- CK7 and CK20

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**Table 2. Frequency of high epidermal growth factor receptor (EGF-R) expression in lung cancer by histologic characterization**

<table>
<thead>
<tr>
<th>Histology</th>
<th>EGFR expression, % (n)</th>
</tr>
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<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>

Staging: TNM
AJC (American Joint Committee)

**Staging Groups: AJC**

<table>
<thead>
<tr>
<th>Stage Group</th>
<th>AJC</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIA</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IIB</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IIIA</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IIIB</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IIIC</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Definition of TNM**

- **T0**: Primary tumor cannot be assessed
- **T1**: No evidence of primary tumor
- **T2**: Carcinoma in situ
- **T3**: Tumor limited to the pancreas, more than 2 cm in greatest dimension
- **T4**: Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
- **T4a**: Tumor involves the celiac axis or the superior mesenteric artery
- **Regional Lymph Nodes (N)**
  - **N0**: Regional lymph nodes cannot be assessed
  - **N1**: Regional lymph nodes metastases
- **Distant Metastasis (M)**
  - **M0**: No distant metastasis
  - **M1**: Distant metastasis