1. Basic Human Pathology: Neoplasia

2007
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2. Neoplasia

- Overview - Lecture
  - Nature of neoplasia
  - Study of neoplasia (oncology)
  - Classification and diagnosis of tumors
  - Causes of neoplasia
  - Basic science of properties of neoplastic cells

- Definition
  - Neoplastic/Neoplasm
    - Certain stimuli causes changes in genetic material that result in permanent alterations of the normal cellular growth pattern
    - Fail to respond normally to signals controlling cell growth
    - Proliferate excessively in a poorly controlled manner forming a tissue mass called a neoplasm ("new growth")

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3. Neoplasia

Neoplasia

- **Tumor** = neoplastic mass of cells
- **Cancer** = layman use of any malignant neoplasm
  - Latin “crab” — seize upon adjacent tissues with pincher-like outgrowths
  - Does not describe the biological behavior
    - Slow growing and indolent vs. spread rapidly to many parts of the body and rapidly cause death

4. Neoplasia

Neoplasia

- A state of poorly regulated cell growth in which the neoplastic cells are transformed
  - A failure of the normal mechanisms that control cellular proliferation and maturation
  - **Carcinogenesis** — study molecular events of neoplasia
5. **Neoplasia**

   **Neoplasia**
   
   - Changes of the genome, the genetic material, which are transmitted to each new generation of cells within the neoplasm
   - Contrasts with **hyperplasia** in which abnormal proliferation of cells ceases with the removal of the causative stimulus
   - Alteration in key genes, **oncogenes**, controlling growth of cells underlies the majority of tumors

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6. **Neoplasia**

   **Neoplasia**
   
   - Two main types of neoplasms
     - Benign
       - Margins of tumor well defined
       - Neoplastic cells grow only locally
       - Generally have a **good prognosis** and lead only rarely to death
     - Malignant
       - Margins of tumor poorly defined
       - Neoplastic cells growing into and destroying surrounding tissues (morbidity)
       - Major cause of **death** (mortality)

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7. Neoplasia

Neoplasia

- Failure to achieve/retain cellular differentiation
  - Cell division from precursor/stem cell - - - > no cells acquiring specialized structures (i.e., differentiation) or retaining function and structures from prior mature well differentiated cells
  - Variable degree of differentiation may result
    - Well differentiated = closely resembles tissue of origin
    - Poorly differentiated = only a passing resemblance to tissue of origin
    - Anaplastic malignant neoplasm = not possible to identify the cell of origin on morphological observation; no resemblance
  - Degree of differentiation is generally related to its behavior
    - Poorly differentiated usually more aggressive

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8. Neoplasia

Neoplasia

- Atypical cell cytology accompanies failure of differentiation
  - Increased variation in shape and size of cells (cellular pleomorphism)
  - Increased variation in shape and size of nuclei (nuclear pleomorphism)
  - Increase in density of staining of nuclei (nuclear hyperchromatism)
  - Disproportionately large increase in the size of nuclei relative to the size of the cell cytoplasm (increased nuclear:cytoplasmic ratio)

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9. Histological loss of differentiation

Histological loss of differentiation

| Normal colon | Benign neoplasm of colon | Well differentiated malignant neoplasm of colon |

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10. Neoplasia

| Poorly differentiated malignant neoplasm of colon | Anaplastic malignant neoplasm of colon | Benign neoplasm of smooth muscle |

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Neoplasia

Benign tumors
- Closely resemble the tissue of origin
- Generally do not have highly abnormal dysregulation of growth
- Grow locally and generally have a slow pace of growth
- Two main factors influence the effects of such tumors
  - Compression of adjacent tissues may ----> blockage of a lumen
  - If endocrine function may ----> uncontrolled secretion of hormone

Benign neoplasm of thyroid gland – well circumscribed...

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13. Exophytic and Endophytic Tumor Growth

14. Neoplasia

- **Malignant tumors**
  - Most significant feature = growth not confined to site of origin of the tumor (i.e., primary tumor)
  - Significant abnormal control of cell growth so cells - --> adjacent local tissues (i.e., invasion) - --> damage/destruction
  - Most sinister property
    - Cells from primary tumor detach - --> grow as separate mass of tumor (i.e., metastasis; secondary tumor)
    - Metastases grow at expense of local tissues and usually - --> tissue destruction

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15. Malignant Tumor of Breast –

Malignant Tumor of Breast –

invasion and poor circumscription

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16. Neoplasia: Slide 16

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17. Neoplasia: Slide 17

<table>
<thead>
<tr>
<th></th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Behavior</strong></td>
<td>Expansile growth only, grows locally</td>
<td>Expansile and invasive growth; may metastasize</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>Resembles cell of origin (well differentiated)</td>
<td>Shows failure of cellular differentiation</td>
</tr>
<tr>
<td></td>
<td>Few mitoses</td>
<td>Many mitoses, some of which are abnormal forms</td>
</tr>
<tr>
<td></td>
<td>Normal or light increase of ration of nucleus:cytoplasm</td>
<td>High nuclear:cytoplasmic ratio</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cells vary in shape and size (cellular pleomorphism) and/or nuclei vary in shape and size (nuclear pleomorphism)</td>
</tr>
</tbody>
</table>

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18. Normal cartilage

**Normal cartilage**

with lacunae, chondrocytes, territorial matrix and interstitial matrix

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19. Neoplasia

Neoplasia

- Growth of neoplasms
  - Must obtain adequate nutrients via support tissues, particularly adequate vascular supply
    - Vascular endothelial growth factor
    - Basic fibroblastic growth factor
    - Growth also modulated by angiopoietins
  - Induce stroma formation (like normal cells) → genetically abnormal neoplastic cells w/ normal support tissues
    - Desmoplasia - tumor induces stromal response disproportionate to number of tumor cells
    - Well differentiated lesions
      - Stroma well developed; neoplastic cells grow without problems
    - Less well differentiated lesions
      - Stroma poorly developed; outstripped by proliferation of neoplastic cells → death of cells in the center of a tumor mass sometimes

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20. Neoplasia

Neoplasia

- Growth rate of neoplasms
  - Benign and well differentiated grow slower than poorly differentiated although many exceptions
  - If cell proliferation greatly exceeds cell death in the tumor, it grows in size rapidly

Factors of growth rate

- Proportion of cells in proliferating cell cycle as opposed to those in G0 (nonproliferating) cell cycle
- Death rate of cells in the tumor
  - If genetic change allows cells to escape from growth control by apoptosis then tend to grow rapidly
- Adequacy of supply of nutrients to the tumor derived from induction of a stroma

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21. Neoplasia

Neoplasia

- 4 main routes of malignant neoplasms spread (metastasis) from primary site
  - Local invasion
    - Most common route; direct growth into adjacent tissues; may also spread along tissue planes (e.g., along nerves)
  - Lymphatic spread
    - Frequently lymphatic vessels to local lymph nodes
  - Vascular (blood-borne) spread
    - Veins draining the lesion (e.g., GI to portal to liver; systemic to lung (most often), bone marrow, brain and adrenal glands)
  - Transcoelomic spread
    - Abdominal cavity or thorax tumors spread directly across coelomic spaces by seeding cells that migrate to the surface of other organs

22. Main Routes of Tumor Spread

Main Routes of Tumor Spread

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23. Symptoms from Metastasis

Symptoms from Metastasis

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24. Neoplasia

Neoplasia

• Some neoplastic cells acquire special attributes for invasion and metastasis
  – Expression of surface molecules for adhesion to grow through basement membrane - - > extracellular matrix - - --> vessel
    • Integrins that bind to laminin and fibronectin
  – Enzymes degrade extracellular matrix for metastasis; receptors to anchor to stroma
    • Metalloproteinases (degrades type IV collagen in basement membrane) vs. stromal inhibitors
  – During metastasis tumor cells and host organ tissues express complementary cell adhesion molecules
    • So certain tumors tend to spread to certain tissues

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25. Neoplasia: Slide 25

26. Steps to Metastasis of a Primary Neoplasm

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Neoplasia

Systemic symptoms
- Weight loss
- Loss of appetite
- Fever
- General malaise
- Anemia

- Most likely due to effects of secreted cytokines (e.g., tumor necrosis factor, IL-1) released by inflammatory cells
- Some retain function of organ of origin and if an endocrine function then harmful effects by secretion of excess hormone

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Paraneoplastic syndrome
- Not the result of direct effects of the tumor or metastases
  - Certain tumors derived from non-endocrine cells can secrete hormones (ectopic hormone secretion)
    - Ex. – lung tumor derived from squamous epithelium can secrete a parathormone-related product resulting in hypercalcemia
    - Ex. – other tumors related to weakness of muscles, malfunction of peripheral nerves, or cerebellar ataxia
- Thought to be due to antibodies generated by tumor cells which cross react with normal tissues and cause immune-mediated damage

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Neoplasia

- Most benign tumors will behave in a relatively innocuous manner and usually are not life-threatening
  - Location may cause death (e.g. brain stem tumor)
- Malignant tumors often result in death of patient due to:
  - Cachexia and development of poor nutrition from the effects of widespread tumor metastases
    - Progressive weakness and death from secondary infection such as pneumonia
    - Believed to be mediated by activation of cytokines from tumor and inflammatory cells
  - Obliteration of vital organ or system by either primary or metastatic tumor

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Neoplasia

- Histological assessment
  - Provides useful guide to likely behavior
  - Two main assessments
    - Grading = analysis of degree of differentiation and growth pattern of the tumor
    - Staging = evaluation of how far a tumor has spread
  - Also, special techniques may be employed

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31. Neoplasia

Neoplasia

❖ Grading
   – Determined by assessing cellular cytology
     • Degree of differentiation
     • Variation in size and shape of constituent cells (pleomorphism)
     • Number of cells containing mitotic figures (mitotic index)
       – Crude indication of rate of cell proliferation (X/10 HPF)
   – Ex. – carcinoma of the breast
     • Well differentiated
       – Exhibit structures that resemble small ducts or gland-like spaces; few mitoses
     • Poorly differentiated
       – No ducts or gland-like spaces; many mitoses

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32. Well differentiated squamous cell carcinoma

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33. Poorly differentiated spindle sq cell ca

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34. Poorly differentiated spindle sq cell ca

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Neoplasia

Staging

– The most important indicator of likely prognosis and of appropriate therapy
– Assessment of 3 factors of neoplasm
  • Size of primary tumor
  • Degree to which it has locally invaded
  • Extent to which it has spread distantly

Neoplasia - Staging

– TNM system - based upon extent of local tumor spread, regional lymph node involvement and presence of distant metastases (each site has own criteria)
  • T = size and extent of primary tumor (number varies according to site)
  • N = lymph node involvement; the higher the number the more extent of involvement
  • M = extent of distant metastasis
Neoplasia

- Example of Staging – Breast Cancer
  - T0 = breast free of tumor
  - T1 = lesion < 2cm
  - T2 = lesion 2-5 cm
  - T3 = skin and/or chest wall involved by invasion
  - M0 = no metastasis
  - M1 = demonstrable metastasis
  - MX = suspected metastasis
  - N0 = no axillary nodes involved
  - N1 = mobile nodes involved
  - N2 = fixed nodes involved

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Tumor – Nodes - Metastases

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39. Neoplasia

Neoplasia

**Carcinoma-in-situ**

- Epithelial (most often) neoplasm shows cytological features of malignancy but not invasive upon histological exam
- Represents a very early stage of neoplasia
- Molecularly, genetic abnormalities have not yet developed
- Important to diagnose at this stage since if left alone will become invasive whereas if treated now is often completely curative
- Examples
  - Breast – confined within ducts or lobules
  - Squamocolumnar junction of uterine cervix
  - Epidermis of sun-exposed skin
  - Colonic mucosa after long-standing chronic colitis
  - Gastric mucosa after long-standing chronic gastritis

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40. Breast Carcinoma in situ – Confined to the Ducts

Breast Carcinoma in situ – Confined to the Ducts

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Neoplasia

Dysplasia
- Cells that exhibit an increased rate of cell division and incomplete maturation
- Tend to exhibit increased n/c ratio and increased number of mitoses
- May also show loss of normal architectural relationships between cells
- Most frequently arises in epi tissues subject to chronic irritation
- May proceed to true neoplastic change over time
- May proceed from mild to moderate to severe to in-situ to invasive neoplasia (e.g., epi mucosa)
- May be reversible to a certain point with stimulus removed

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**Neoplasia**

- **Tumor nomenclature and classification**
  - Full of inconsistencies
    - Some named based on macroscopic, microscopic or behavior
    - Others given eponym or semi-descriptive names
    - Some have many synonyms
  - Nomenclature of tumors of epithelial origin
    - **Papilloma** - benign surface; frond-like growths; prefixed by cell of origin (e.g., squamous papilloma)
    - **Adenoma** – solid and surface; gland
    - **Carcinoma** – malignant tumor; surface; prefixed by cell type of origin
    - **Adenocarcinoma** – glandular; add tissue of origin

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**Neoplasia**

- **Tumor nomenclature and classification**
  - Tumors of mesenchymal origin (support cells or muscle)
  - More consistent schema than epithelium
  - Tissue of origin takes the suffix “-oma” if benign; “-sarcoma” if malignant
    - **Chondroma** – benign tumor of cartilage
    - **Chondrosarcoma** – malignant tumor of cartilage

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## Systematic Tumor Nomenclature

<table>
<thead>
<tr>
<th>Parent Tissue</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple tumors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epithelium (glandular)</td>
<td>Adenoma</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Epithelium (surface)</td>
<td>Papilloma</td>
<td>Carcinoma</td>
</tr>
<tr>
<td>Mesenchymal tissue</td>
<td>Tissue prefix + oma (fibroma)</td>
<td>Tissue prefix + sarcoma (fibrosarcoma)</td>
</tr>
<tr>
<td>Complex tumors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Totipotential cell</td>
<td>Tertoma</td>
<td>Teracarcinoma</td>
</tr>
<tr>
<td>Embryonic rest</td>
<td></td>
<td>Embryonal tumor</td>
</tr>
<tr>
<td>Mature tissue</td>
<td>Mixed tumor</td>
<td>Malignant mixed tumor</td>
</tr>
</tbody>
</table>

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## Classification of Neoplasms

<table>
<thead>
<tr>
<th>Cell or Tissue or Origin</th>
<th>Benign</th>
<th>Malignant (Cancer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous</td>
<td>Papilloma</td>
<td>Squamous Cell Carcinoma</td>
</tr>
</tbody>
</table>
| &nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&n...
### Classification of Neoplasms, cont’d

<table>
<thead>
<tr>
<th>Cell or Tissue or Origin</th>
<th>Benign</th>
<th>Malignant (Cancer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular Blood Vessels</td>
<td>Angioma</td>
<td>Angiosarcoma</td>
</tr>
<tr>
<td>Lymph Vessels</td>
<td>Hemangiendothelioma</td>
<td>Hemangiosarcoma</td>
</tr>
<tr>
<td>Pericytes</td>
<td>Cystic Hygroma</td>
<td>Lymphangiosarcoma</td>
</tr>
<tr>
<td>Granular Cells Blood</td>
<td>Hemangiopericytoma</td>
<td>Malignant Hemangiopericytoma</td>
</tr>
<tr>
<td>Forming Tooth</td>
<td>Granular Cell Tumor</td>
<td>Alveolar Soft Part Sarcoma</td>
</tr>
<tr>
<td></td>
<td>Odontogenic Fibroma</td>
<td>Lymphoma, Leukemia, Myeloma</td>
</tr>
<tr>
<td>Muscle</td>
<td>Leiomysarcoma</td>
<td></td>
</tr>
<tr>
<td>Smooth Skeletal Histocytes</td>
<td>Fibrous Histocytoma</td>
<td>Malignant Fibrous Histocytoma</td>
</tr>
<tr>
<td>Mixed – Epithelial and Connective Tissue Tooth</td>
<td>Odontoma</td>
<td>Ameloblastic Fibrosarcoma</td>
</tr>
<tr>
<td></td>
<td>Ameloblastic Fibroma</td>
<td></td>
</tr>
</tbody>
</table>

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### Neoplasia

- **Tumor nomenclature and classification**
  - **Nomenclature of other tumors**
    - Lymphomas – neoplastic lymphocytes
    - Malignant melanoma – derived from melanocytes; melanin
    - Leukemia – hematopoietic elements in bone marrow that circulate in the blood
    - Embryonal tumors – childhood; primitive embryonal blastic
    - Gliomas – non-neural support tissue of brain
    - Germ cell tumors – germ cells in gonads; also non-gonadal
    - Teratomas – form all 3 embryological germ cell layers
    - Neuroendocrine tumors – secrete polypeptide hormones or active amines
    - Hamartomas – non-neoplastic overgrowths of normal tissue at a normal expected site; developmental abnormalities
    - Choristomas - non-neoplastic overgrowths of normal tissue at an abnormal site; developmental abnormalities

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49. Non-systematic Terms for Prominent Human Neoplasms

Non-systematic Terms for Prominent Human Neoplasms

1. WART
2. FIBROID
3. MELANOMA
4. HEPATOMA
5. PHEOCHROMOCYTOMA
6. CHORIOCARCINOMA
7. WILM’S TUMOR
8. BOWEN’S TUMOR
9. LYMPHOMA

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50. Neoplasia

Neoplasia

- Tumor nomenclature and classification
  - Eponymous names
    - Ewing’s sarcoma
      - Young people; malignant tumor of bone
    - Hodgkin’s lymphoma
      - Sub-group of lymphoma
    - Kaposi’s sarcoma
      - Vascular malignancy often seen associated with AIDS
    - Burkitt’s lymphoma
      - B cell type non-Hodgkin’s lymphoma; EBV cause

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Neoplasia

❖ Biology of neoplasia
– Carcinogenesis is train of biological events that underlies the development of neoplasia
– Neoplasms at cellular level caused by genetic mutations resulting in abnormal control of growth
– Probably a multi-step development requiring the interaction of several processes, often over a period of many years

❖ 4 main genetic mechanisms
– Expression of genes resulting in inappropriate activity of products which normally stimulate growth
  • Oncogenes; act in dominant manner
– Loss of activity of genes that produce products that inhibit cell growth
  • Tumor suppressor genes or anti-oncogenes; act in dominant or recessive manner
– Over-expression of genes which usually produce products that prevent normal cell death
  • Failure to eliminate genetically damaged cells
– Loss of activity gene products which would repair DNA
  - - -> DNA instability - - -> somatic mutations in oncogenes or tumor suppressor genes
53. Neoplasia

Neoplasia

- Genetic reason for neoplastic transformation
- Tumors normally have several genetic aberrations the sum of which result in neoplastic transformation of cells
- Tumor may develop additional oncogene abnormalities with time resulting in more aggressive growth pattern
  - Point mutations in oncogenes -> production of abnormally functioning product or loss of a suppressor
  - Gene amplification causing excess production of oncogene
  - Chromosomal rearrangements in which an oncogene is activated inappropriately by another promoter region

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54. Neoplasia

Neoplasia

- Mechanisms by which oncogenes act
  - Increased production of secreted growth factor
  - Increased expression of growth factor receptors
  - Mutation in transducer protein gene
  - Mutant transcription factor production
  - Overproduction of factor that prevents cell death
  - Loss of activity in DNA repair systems

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55. Action of Oncogenes in Neoplastic Transformation of Cells

56. Action of Oncogenes in Neoplastic Transformation of Cells
57. Action of Oncogenes in Neoplastic Transformation of Cells

Action of Oncogenes in Neoplastic Transformation of Cells

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58. Neoplasia

Neoplasia

• Growth factors
  – Hormones, cytokines and classical growth factors
  – Bind to cell surface receptors (transmembrane proteins) having a cytosolic domain with tyrosine kinase activity
  – In response to a positive growth signal cells undergo:
    • Internal reorganization of actin-dependent adhesion mechanisms
    • Show an increase in intracellular calcium
    • Following activation and nuclear translocation of transcription factors the cell cycle is entered

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Neoplasia

Cell cycle – active state of proliferation

- Progression controlled by synthesis, degradation, and state of phosphorylation of cyclins
  - Form complexes with cyclin-dependent kinases (CDKs) and cyclin-dependent kinase inhibitors (CDKIs) modulate
- M (mitosis) phase followed by either non-dividing state, G0 phase, or continue through the cell cycle
- G1 interphase
- G1-S transition
  - Regulated by phosphorylation of Rb releasing E2F transcription factor
- S interphase – cells replicate DNA
- G2 interphase
- G2-M transition
  - Regulated by CDK1-cyclin B complex

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Cell Cycle

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Neoplasia

• Cell cycle (cont’d)
  – Important check points in cell cycle
    • Policed by surveillance systems in the cell nucleus
    • Prevent cells replicating if they become damaged (cell activates DNA repair mechanisms or apoptosis to eliminate itself)
  – Gene coding for p53 protein is activated in the presence of DNA damage and cause increase in the CDKI p21 protein (WAF1) - prevents phosphorylation and arrests cell in the cycle
    ● If abnormal type of p53 present then regulatory function impaired and so cells with damaged DNA may complete mitosis and thus propagate a mutation

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Neoplasia

● Oncogenes
  – Central to the development of tumors
  – Referred to by the abbreviated name of the tumor virus or system in which discovered
  – Originally isolated from tumor-forming RNA retroviruses
    • Viral oncogenes (v-oncs) – code for a protein involved in the development of neoplasia
    • Proto-oncogenes (p-oncs) – code for proteins involved in the control of cell growth; 3 mechanisms of tumor formation
      – Mutation – mutant protein product
      – Gene amplification – excess protein product
      – Abnormal gene promotion – host derived or virus derived
    • Cellular oncogenes (c-oncs) – code for proteins involved in the development of neoplasia

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<table>
<thead>
<tr>
<th>Protoncogene</th>
<th>Function</th>
<th>Oncogene type</th>
<th>Reason for activation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ras</td>
<td>GTP binding</td>
<td>Signal transduction</td>
<td>Point mutation</td>
</tr>
<tr>
<td>myc</td>
<td>Transcription activator</td>
<td>Nuclear regulator</td>
<td>Translocation</td>
</tr>
<tr>
<td>n-myc</td>
<td>Transcription activator</td>
<td>Nuclear regulator</td>
<td>Translocation</td>
</tr>
<tr>
<td>erb-B1</td>
<td>EGF receptor</td>
<td>Growth factor receptor</td>
<td>Amplification</td>
</tr>
<tr>
<td>erb-B2 (neu)</td>
<td>EGF-like receptor</td>
<td>Growth factor receptor</td>
<td>Amplification</td>
</tr>
</tbody>
</table>

EGF – epidermal growth factor  
PGDF – platelet derived growth factor  
FGF – fibroblast growth factor  
GTP = guanosine triphosphate

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Neoplasia

- Oncogenes (cont’d)
  - Abnormalities of oncogenes are found in tumors and thought to be primary events in malignant transformation
  - Usually multiple oncogene abnormalities are seen in a single tumor

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Neoplasia

Tumor suppressor genes
- Absence promotes neoplasia; “gatekeepers” that normally directly control
- First one, Rb, discovered in retinoblastoma
  - On chromosome #13; found in many other tumors
  - Affected children have one mutant gene (inactive) and one normal (active)
    - If familial form then second gene undergoes somatic mutation
    - If sporadic form both genes must undergo mutation

\*p53
- Most common genetic abnormality in neoplasia – many tumors
- On chromosome #17d
- Normally activate in response to DNA damage → DNA repair and arrest cell cycle
- If repair not achieved, p53 causes cell to enter apoptotic pathway of cell death; loss of p53 activity allows proliferation of cells with DNA damage

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Neoplasia: Slide 66

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Neoplasia

- Tumor suppressor genes
  - APC
    - Degrades alpha-catenin so if defective then alpha-catenin levels raise in the cell and drive cell proliferation
    - Absence responsible for development of familial adenomatous polyposis coli
    - Inherit a single inactive copy -> multiple benign adenomata of the large bowel
    - If cells develop a second mutation of the normal inherited gene on the other allele -> carcinoma of the colon

Colon Cancer Model of Multistep Carciogenesis

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Neoplasia

- DNA repair genes
  - Well developed system of detection and repair of DNA
    - Sometimes called ‘caretaker’ genes
  - Mutation in DNA repair genes allows proliferation of cells with DNA mutations, replication error positive phenotype (RER+)
    - Assessed by looking at tandem repeated DNA sequences in cells which normally remain constant
      - In DNA repair errors, cells develop changes in the repeat length of microsatellite DNA – microsatellite instability

Characterized Heritable Neoplasia Syndromes

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<tr>
<th>Syndrome</th>
<th>Tumor caused</th>
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</table>

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71. Diagram on the Progression of Cancer Growth

72. Neoplasia

- Progression
  - Tumors become less well differentiated and more aggressive with time
  - Due to emergence of subpopulations of cells with new genetic abnormalities that make growth control more abnormal and facilitate metastasis
  - Any large tumor is composed of a whole set of slightly different cells (tumor heterogeneity) as a result of further acquired somatic mutations
    - Any mutations that favor tumor survival or spread or chosen by a form of natural selection
      - Explains how a primary tumor may respond to therapy yet metastatic lesions do not (properties of invasion, motility, and growth in another site) AND resistance to chemotherapy arises

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Neoplasia

- Recurring chromosomal abnormalities
  - Seen in some specific tumors
  - Over-expression of an oncogene or deletion of a suppressor gene
  - Detection of these cytogenetic abnormalities is useful in diagnosis, prognosis, and abnormal gene expression
  - Techniques for detection
    - Traditional karyotype analysis on metaphase spreads with viable tumor in culture so only works for ~40% of solid tumors and only detect large changes
    - Fluorescent in situ hybridization (FISH) or reverse transcriptase polymerase chain reaction (RT-PCR) for structural changes when sequence data is known

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<table>
<thead>
<tr>
<th>Tumor</th>
<th>Cytogenetic abnormality</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic myeloid leukemia</td>
<td>Translocation between chromosome 9 and 22 (Philadelphia chromosome)</td>
<td>Forms a protein with tyrosine kinase activity (bcr-abl protein)</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>Translocation between chromosome 14 and 18</td>
<td>Production of protein that prevents cell death (bcl-2 product)</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>Homogeneous regions and double minute chromosomes</td>
<td>Amplification of n-myc in poor prognosis type</td>
</tr>
<tr>
<td>Ewing's tumor</td>
<td>Translocation between chromosome 11 and 22</td>
<td>Uncertain</td>
</tr>
</tbody>
</table>

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Neoplasia

Chemical carcinogens
- Polycyclic hydrocarbons
  - Tars; potent agents in cigarette smoke that cause lung cancer
- Aromatic amines
  - Industrial exposure (rubber, dye) and converted to active agents in the liver; concentrated in the urine and thus bladder cancers primarily
- Nitrosamines
  - Conversion of dietary nitrites and nitrates to nitrosamines by gut bacteria; thought to cause GI tract tumors
- Alkylation agents
  - Bind directly to DNA and directly mutagenic
  - Used in cancer chemotherapy (e.g., cyclophosphamide)

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3 main groups of chemical carcinogens
- Cause development of cancer directly or indirectly
- Genotoxic
  - Cause direct damage to DNA by forming chemical DNA adducts that are prone to damage in replication or resistant to DNA repair mechanisms
- Mitogenic
  - Bind to receptors on or in cells and stimulate cell division without causing direct DNA damage (e.g., protein kinase C)
- Cytotoxic
  - Tissue damage and lead to hyperplasia with cycles of tissue regeneration and damage
  - Can act as mitogenic factors

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77. Neoplasia

Neoplasia

- Chemical carcinogens (cont’d)
  - Can also be subdivided into 2 groups
    - Direct acting
      - Directly causes neoplasia
    - Procarcinogens
      - Requires conversion to an active carcinogen
      - Conversion takes place by normal metabolic pathways
      - Cytochrome P450 oxygenase system plays an impdoll role in conversion
      - Detoxification reactions with accumulation of carcinogen determined by balance between dose of procarcinogen, rate of detoxification and elimination, and rate of conversion to the active form

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78. Neoplasia

Neoplasia

- 2 types of chemical carcinogens
  - Initiating agents
    - Exposure does not directly cause neoplasia but renders cells susceptible to developing neoplasia if later exposed to certain other agents
    - Cause genetic abnormalities but not enough to result in abnormal cell growth
  - Promoting agents
    - Exposure to normal cell causes no abnormality
    - Prolonged exposure of initiated cells to promoting agent causes development of neoplasia
    - Transient exposure of initiated cells to a promoting agent will not result in developing neoplasia
    - Cause increased cell turnover; continued exposure to the promoting agent cells which have a genetic abnormality develops secondary genetic abnormalities in key genes regulating cell growth
    - Increased cell proliferation clones of cells develop which have lost of growth control

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Neoplasia: Slide 79

![Diagram showing stages of neoplasia]

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Neoplasia

"3 stages of chemical carcinogenesis"

- Initiation
  - Induction of genetic changes in cells (altered genome)

- Promotion
  - Induction of cell proliferation via mitogen or cytotoxic agent; initially reversible if promotion agent withdrawn

- Progression
  - If persistent cell proliferation then initiated cells acquire secondary genetic abnormalities in oncogenes → dysregulation → autonomous cell growth → invasive neoplasm with sub-clones

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Neoplasia

- Chemical carcinogenesis key factors
  - Most info gleaned from animal studies
  - Following exposure there is a long latent period before neoplasm develops
    - Altered cells are primed but require second change to bring about molecular genetic changes expressed as neoplasia
  - Carcinogenesis is a multi-stage process
    - Initiation
    - Promotion
    - Progression

Infections implicated in human neoplasia

- Epstein-Barr virus
  - Burkitt’s lymphoma, nasopharyngeal carcinoma, Hodgkin’s lymphoma
- Hepatitis B virus
  - Hepatocellular carcinoma
- Human papillomavirus
  - Cervical carcinoma, some skin carcinomas
- HTLV-1
  - T-cell leukemia/lymphoma
- Human herpes virus type 8
  - Kaposi’s sarcoma
- Helicobacter pylori
  - Gastric lymphoma
83. Neoplasia

Neoplasia

- 2 types of viral carcinogenesis to activate oncogenes
  - Slow-transforming viruses
    - Insert viral-derived DNA into the genome randomly
    - If by chance next to a proto-oncogene then it is promoted leading to neoplasia
  - Acute-transforming viruses
    - Contain a viral oncogene
    - When viral-derived DNA inserted into the host genome the transcribed viral oncogene is expressed leading to neoplasia

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84. Neoplasia

Neoplasia

- Irradiation-induced neoplasia
  - 2 main effects of DNA damage through irradiation
    - Formation of DNA breaks
    - Development of DNA instability
  - Direct exposure (e.g., x-rays) increases risk of tumors in bone marrow and skin of exposed areas
  - Environmental exposure more complex issue
    - Radon increases risk of carcinoma of the lung
    - Ingestion of radioactive iodine increases risk of carcinoma of the thyroid
    - Incorporation of radioactive metals into bone increases the risk of tumors of bone marrow and bone
  - Ultraviolet light
    - Major cause of neoplasia esp. many types of malignant skin tumor

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Neoplasia

- **Hormone-induced neoplasia**
  - Estrogens – carcinoma of the breast and endometrium in animals
    - Carcinomas of the breast that express estrogen receptors
      - Can be treated by anti-estrogen drugs
  - Carcinoma of the prostate
    - Can be treated by removal of testosterone stimulation
  - Children of woman treated with synthetic estrogen diethylstilboestrol develop carcinoma of the vagina (in utero effect)

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Neoplasia

- **Asbestos-induced neoplasia**
  - Physical agent, asbestos fibers, inhaled and a potent cause of neoplasia of lung and pleura
  - Often a long latent period after exposure
  - Association with mesothelioma of the pleura is particularly strong

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Neoplasia

- Proneoplastic conditions associated with increased risk of developing tumors
  - Hyperplasia
    - Endometrial HP of the epi of breast lobules and ducts
  - Dysplasia
    - Chronic gastritis predisposes carcinoma of stomach
    - Chronic colitis predisposes carcinoma of the colon
    - Hepatic cirrhosis predisposes liver cell carcinoma
  - Chronic immune diseases
    - Celiac disease predisposes gut lymphoma
    - Autoimmune thyroiditis predisposes thyroid lymphoma

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Neoplasia

- Epidemiology of neoplastic disease
  - Human association of between incidence and types of cancer encountered and age
    - Malignancies increase markedly after age 50
  - Small number of childhood tumors
    - Recapitulating embryonal tumors (blastomas) and leukemias
  - Uncommon in early adult life
    - Tumors of bone, lymphomas, germ cell tumors
  - Increasing incidence of a wide range of epi neoplasms in later adult life
    - Multi-step causation

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Cancer epidemiology key facts
- Cancer is 2nd most common cause of death (ischemic heart disease is #1) in most developed countries (~23% of all mortality)
- Occupational, social, and geographic factors cause incidence of different histological types of cancer to vary greatly between different populations
- Incidence of lung cancer is increasing rapidly in women as a result of cigarette smoking (> deaths than breast cancer)
- Incidence of malignant melanoma of the skin is increasing among Caucasians in many countries

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Cancer epidemiology key facts (cont’d)
- High incidence of stomach cancer in Japan compared to other countries (smoked raw fish)
- Survival rate for many tumors has greatly increased over past 25 years with advancement in treatment
- Cancer prevention strategies depend on elimination of causative factors
- Cancer detection strategies depend on screening population for early forms of neoplasia at an early stage of development

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91. Estimated 10 Leading Sites of New Cancer Cases

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92. 2006 Estimated US Cancer Cases*

See statistics link on American Cancer Society website:
http://www.cancer.org

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93. 2006 Estimated US Cancer Deaths

See statistics link on American Cancer Society website:
http://www.cancer.org

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94. Cancer Incidence by Age Groups

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Percent Distribution of Cancer Cases by Race and Stage at Diagnosis, US, 1989-1995

Neoplasia

- Length of survival varies greatly between different types of tumors and its bio nature, spread, and effective therapy available
- By convention, average 5-year survival rate is used
97. Neoplasia

Neoplasia

- Heritable neoplastic conditions
  - Some of the molecular genetic abnormalities underlying neoplasia have been discovered
  - Often in familial-tendency cancers, the tumors that occur tend to be atypical (e.g., present at an earlier age, unusual histological type)
  - Ex. – colorectal carcinoma
    - *Autosomal dominant familial polyposis coli* but now a larger group of families with colorectal carcinoma that occur a decade or two earlier than usual age for development.

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98. Characterized Heritable Neoplasia Syndromes

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</tbody>
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99. Neoplasia

Neoplasia

- Diagnosis of neoplasia
  - Based on clinical, imaging, and laboratory tests combined with histological examination of the tissue
- Techniques of obtaining tissue
  - Biopsy
    - Needle biopsy
      - Cutting needle obtains core of tissue 1-2 mm wide and 2 cm long; any tissue including brain
    - Endoscopic biopsy
      - Small forceps sample tissue during endoscopy; 2-3 mm fragments; e.g., GI, respiratory, genital, urinary
    - Incisional biopsy - scalpel
      - Portion of lesion is surgically removed when surgically accessible
    - Excisional biopsy - scalpel
      - Entire lesion is surgically removed when surgically accessible

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100. Needle Biopsy / Endoscopic Biopsy

Needle Biopsy / Endoscopic Biopsy

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101.

**Excisional Biopsy Scalpel / Excisional/Incisional Biopsy – Punch**

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102.

**Neoplasia**

- Techniques of obtaining tissue – cont’d
  - Cytology
    - Cells shed naturally into body fluids
      - Sputum, urine, CSF, fluid in pleural and peritoneal
    - Cells obtained by exfoliation
      - Scrapes smears of cervix; oral cavity
      - Brush lesions in GI tract by endoscopy; oral cavity
    - Cells aspirated by needle
      - Blood and bone marrow
      - Needle aspiration of solid tumors (breast, thyroid, pancreas) guided by imaging

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103. Brushing an Ulcer

Brushing an Ulcer

Source: TUSDM

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104. Pulmonary Fine Needle Aspiration (FNA)

Pulmonary Fine Needle Aspiration (FNA)

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105. Neoplasia

**Neoplasia**

**Tumor markers**
- Certain tumors liberate products that can be detected in blood samples
- May aid diagnosis
- Aid follow-up therapy
  - Blood levels become increased often before imaging can detect tumor recurrence

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106. Neoplasia: Slide 106

<table>
<thead>
<tr>
<th>Tumor Marker</th>
<th>Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha fetoprotein (AFP)</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td></td>
<td>Germ cell tumors</td>
</tr>
<tr>
<td>Human chorionic gonadotrophin (HCG)</td>
<td>Trophoblastic tumors</td>
</tr>
<tr>
<td>Acid phosphatase</td>
<td>Prostatic carcinoma</td>
</tr>
<tr>
<td>Carcinoembryonic antigen (CEA)</td>
<td>Gastrointestinal tract neoplasia</td>
</tr>
<tr>
<td>Hormone products</td>
<td>Endocrine tumors</td>
</tr>
</tbody>
</table>

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Neoplasia

- Special techniques for analysis of tumors once tissue removed
  - 10% neutral buffered formalin – routine
  - Glutaraldehyde – electron microscopy
  - Fresh-frozen – tumor marker or molecular genetic studies
  - Cell culture medium – cytogenetic analysis
  - Electron microscopy – ultrastructural evidence
  - Immunohistochemistry – determine undifferentiated tissue origin
    - Ex. – cytokeratin, leukocyte common antigen, desmin, smooth muscle actin

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