Chapter 8
Neoplastic Disease

Learning Objectives (1 of 2)
• Compare benign versus malignant tumors; discuss naming of tumors and exceptions to standard terminology
• Summarize principal types of lymphoma
• Differentiate infiltrating versus in situ carcinoma; role of Pap smear in early diagnoses of neoplasms
• Explain classification and clinical manifestation of leukemia
• Differentiate leukemia versus multiple myeloma
• Explain mechanism of body’s immunologic defenses against tumor

Learning Objectives (2 of 2)
• Summarize modalities and side effects of cancer treatment
• Describe applications and limitations of tumor-associated antigens
• Compare incidence and survival rates for various malignant tumors
• Explain role of late recurrence and role of adjuvant therapy
• Understand role of oncogenes and disturbance in suppressor gene function in the pathogenesis of tumors

Definition
• Neoplasm: NEO = new + PLASM = growth
• Cancer: any type of malignant growth
  – Unrestrained growth and spread
  – Cells do not respond to control mechanisms that normally regulate cell growth and differentiation
  – Serves no useful purpose
  – Terms neoplasm and tumor may be used interchangeably

Benign Versus Malignant
• BENIGN
  – Growth rate: slow
  – Growth character: expansion
  – Tumor spread: remains localized
  – Cell differentiation: well-differentiated cells
• MALIGNANT
  – Growth rate: rapid
  – Growth character: infiltration
  – Tumor spread: metastasis by bloodstream or lymphatic channels
  – Cell differentiation: poorly differentiated cells

Benign Tumors
• Named by adding suffix -oma to the name of the cells of origin
  – Adenoma: from glandular epithelium
  – Angioma: from blood vessels
  – Chondroma: from cartilage
  – Polyps or papilloma: benign tumor on stalk arising from an epithelial surface
Malignant Tumors (1 of 2)

- Start from a single cell that has sustained damage to its genome, causing it to proliferate abnormally
- Clone of identical cells is formed; if unchecked, eventually develops into a distinct tumor
- Exhibit behavior different from that of normal cells
- Do not respond to normal growth regulatory signals
- Proliferate unnecessarily

Malignant Tumors (2 of 2)

- May secrete growth factors to stimulate their own growth, allowing tumors to flourish at the expense of surrounding normal cells
- Secrete enzymes that break down normal cell and tissue barriers, allowing them to
  - Infiltrate into adjacent tissues
  - Invade lymphatic channels and blood vessels
  - Spread throughout the body
- Tumor cells do not normally "wear out" as normal cells, but become "immortal" and can proliferate indefinitely

Tumor Classification

- Sarcoma: arising from connective tissues such as fat, bone, cartilage, muscle
  - Less common, but spreads more rapidly
  - Little differentiation; anaplasia (lack of form)
  - Metastasis: bloodstream
- Leukemia: neoplasm of blood cells
  - Usually do not form solid tumors
  - Instead, proliferates diffusely within bone marrow, overgrows and crowds out normal blood-forming cells
  - Neoplastic cells "spill over" into the bloodstream and large number of abnormal cells circulate in the peripheral blood

Naming of Tumors

- Tumors are named and classified according to their cells and tissues of origin
- Tumor nomenclature: not completely uniform, but certain generalizations are possible
- Exceptions encountered in naming of
  - Lymphoid tumors
  - Skin tumors arising from pigment-producing cells within the epidermis
  - Certain tumors of mixed cellular components
  - Certain types of tumors composed of primitive cells seen in children

Principles of Naming Tumors

<table>
<thead>
<tr>
<th>General Term</th>
<th>Meaning</th>
</tr>
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<tbody>
<tr>
<td>Polyp, papilloma</td>
<td>Any benign tumor projecting from surface epithelium</td>
</tr>
<tr>
<td>+ oma [suffix]</td>
<td>A benign tumor. The prefix designates primary tissue of origin</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>Malignant tumor arising from surface, glandular, or parenchymal epithelium (but not endothelium or mesothelium)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>Malignant tumor of any primary tissue other than surface, glandular, and parenchymal epithelium</td>
</tr>
<tr>
<td>Leukemia</td>
<td>Neoplasm of blood cells</td>
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Common Prefixes in Tumor Names

<table>
<thead>
<tr>
<th>Prefix</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adeno-</td>
<td>Gland</td>
</tr>
<tr>
<td>Angio-</td>
<td>Vessels (type not specified)</td>
</tr>
<tr>
<td>Chondro-</td>
<td>Cartilage</td>
</tr>
<tr>
<td>Fibro</td>
<td>Fibrous Tissue</td>
</tr>
<tr>
<td>Hemangio-</td>
<td>Blood Vessels</td>
</tr>
<tr>
<td>Lymphangio-</td>
<td>Lymph Vessels</td>
</tr>
<tr>
<td>Lipo-</td>
<td>Fat</td>
</tr>
<tr>
<td>Myo-</td>
<td>Muscle</td>
</tr>
<tr>
<td>Neuro-</td>
<td>Nerve</td>
</tr>
<tr>
<td>Osteo-</td>
<td>Bone</td>
</tr>
</tbody>
</table>
Lymphoma (1 of 2)

- Neoplasm of lymphoid tissue
  - Usually malignant
  - Term “lymphoma” without classification refers to a malignant, not a benign tumor
  - To avoid confusion, the term “malignant lymphoma” may be used
- Two major classifications
  - Hodgkin’s lymphoma (Hodgkin’s disease)
  - Non-Hodgkin’s lymphoma
- Classification: often with poor correlation between histologic type and biologic behavior (growth rate and response to therapy)

Lymphoma (2 of 2)

- Basis of classification
  - Diffuse infiltration of lymph nodes
- Prognosis
  - Low-grade: patients have a favorable prognosis
  - Intermediate-grade: patients do not do nearly as well
  - High-grade: patients do poorly
- Type of cells giving rise to tumor (T cells, B cells, NK cells, histiocytes) and maturity of cells
  - 75% arise from B lymphocytes
  - Remainder mostly from T lymphocytes

Hodgkin and Non-Hodgkin Lymphoma (1 of 2)

- Hodgkin disease: variable histologic appearance consisting of large cells called Reed-Sternberg cells intermixed with lymphocytes, plasma cells, eosinophils, and fibrous tissues
  - Reed-Sternberg cell: large cell with abundant cytoplasm containing two nuclei appearing as mirror images
    - Some have a single nucleus
    - Each nucleus contains large nucleolus surrounded by clear halo
  - Four different histologic types of Hodgkin disease that differ in clinical behavior and prognosis

Hodgkin and Non-Hodgkin Lymphoma (2 of 2)

- Non-Hodgkin lymphoma: all other lymphomas are generally grouped together under this category
  - Variable in appearance and behavior
  - Classification system based on size, shape, growth pattern of malignant cells, and shape of nuclei and nuclear membranes

Skin Tumors

- Melanocytes
  - Benign: nevus (“birthmark” in Latin); common benign pigmented skin lesion derived from melanin-producing cells
  - Malignant: melanoma; malignant tumor of melanocytes
- Keratinocytes
  - Benign: keratoses
  - Malignant: basal cell carcinoma, squamous cell carcinoma

Malignant Skin Tumors

- Basal cell carcinoma
  - Composed of clusters of infiltrating cells that resemble the normal basal cells of the epidermis
  - Indolent, slowly growing tumor that can be locally destructive but rarely metastasizes
- Squamous cell carcinoma
  - Composed of abnormal infiltrating squamous cells
  - More aggressive tumor that sometimes metastasizes
- Both types can be cured by surgical excision with a very good prognosis
- Excessive sunlight exposure predisposes to all types of skin cancer, including melanoma and keratoses
Teratoma

- Tumor arising from cells that can differentiate into many different types of tissues: bone, muscle, glands, epithelium, brain tissue, hair
- Has mixed components, poorly organized
- Frequently occurs in reproductive tract, but may develop in other areas
- Must specify as benign or malignant based on maturity of cells

Primitive Cell Tumors

- Arise from persistent groups of primitive cells and may arise in children
  - Brain
  - Retina
  - Adrenal gland
  - Kidney
  - Liver
  - Genital tract
- Named after site of origin with suffix “-blastoma” added
  - Example: tissue of origin (retina) + blastoma = retinoblastoma

Cystic teratoma (dermoid cyst) of ovary.

Leukemia

- A neoplasm of hematopoietic tissue
- Leukemic cells **diffusely infiltrate the bone marrow and lymphoid tissues**, spill over into the bloodstream, and infiltrate throughout various organs of the body
- Cells may be mostly mature or extremely primitive
- Overproduction of white cells demonstrated in the peripheral blood by a very high white blood count
- **Aleukemic leukemia**: condition in which white cells are confined to the bone marrow such that their number in the peripheral blood is normal or decreased

Leukemia: Classification

- Any type of hematopoietic cells can give rise to a leukemia, but the most common types are:
  - Granulocytic
  - Lymphocytic
  - Monocytic

  - **Basis for Classification of Leukemia**
    - Cell type
      - Granulocytic, lymphocytic, monocytic
    - Maturity of leukemic cells
      - Acute if immature cells
      - Chronic if mature cells

A photomicrograph of a blood smear from a patient with acute leukemia
Leukemia: Clinical Features (1 of 2)

- Manifestations caused by impairment of bone marrow function
- Leukemic cells crowd out normal cells causing:
  - Anemia: inadequate red cell production
  - Thrombocytopenia: causes bleeding
  - Infections from inadequate number of normal white cells

Leukemia: Clinical Features (2 of 2)

- Caused by infiltration of organs by leukemic cells causing:
  - Splenomegaly: enlarged spleen
  - Hepatomegaly: enlarged liver
  - Lymphadenopathy: enlarged lymph nodes
- In chronic leukemia: evolution of disease proceeds at a relatively slow pace and often can be controlled
- In acute leukemia: a rapidly progressive disease, more difficult to control

Myelodysplasia (Preleukemia)

- A disturbed growth and maturation of marrow cells
  - Anemia: reduced number of erythrocytes
  - Leukopenia: reduced number white cells
  - Thrombocytopenia: reduced number of platelets
- Although called preleukemia, not all patients develop leukemia
- Recently grouped together under the general term myelodysplastic syndromes
- In general, the more severe the maturation disturbance in the bone marrow, the greater the likelihood that leukemia will occur

Multiple Myeloma

- Neoplasm from plasma cells within the bone marrow
- Resembles leukemia, but cell proliferation is confined to the bone marrow and organ infiltration is unusual
- Outpouring of large number of plasma cells into the peripheral blood is also uncommon
- Abnormal plasma cells either infiltrate the bone marrow diffusely or form discrete tumors that weaken the bone
- Leads to spontaneous fractures, pain, and disability
Photomicrograph illustrating aspirated bone marrow from a patient with multiple myeloma

Tumor Blood Supply and Necrosis (1 of 2)

• Tumors derive blood supply from tissues they invade
• Malignant tumors frequently induce new blood vessels to proliferate in adjacent normal tissues to supply the demands of the growing tumor (angiogenesis factor)
• Malignant tumor may outgrow its blood supply; the part of the tumor with the poorest blood supply undergoes necrosis
• Depending on the location of the tumor, the blood supply will be rich or poor

A skull x-ray from a patient with multiple myeloma

Tumor Blood Supply and Necrosis (2 of 2)

• In tumors in the lung, blood supply is best at the periphery of the tumor and poorest at the center
• If tumor is growing outward from an epithelial surface such as the colon, the best blood supply is at its base and poorest at the surface
• Often, small blood vessels are exposed in the ulcerated base of a tumor that blood may ooze continuously from vessels leading to anemia from chronic blood loss
• An ulcerated tumor may be the source of a severe hemorrhage

Noninfiltrating (in Situ) Carcinoma

• Arises from the surface epithelium
• Remains localized within the epithelium for many years
• Can occur in many locations of the body
  – Cervix
  – Breast
  – Urinary tract
  – Colon
  – Skin

Precancerous Conditions (1 of 2)

• Nonmalignant condition with a tendency to become malignant
  – Actinic keratoses: small, crusted, scaly patches that develop on sun-exposed skin; may develop into cancer if untreated
  – Lentigo maligna: freckle-like proliferation of melanin-producing cells that may develop on sun-exposed skin; may transform later into melanoma
  – Leukoplakia: thick white patches in the mucous membranes of the mouth from exposure to tobacco tars from pipe or cigar smoking or use of smokeless tobacco (snuff or chewing tobacco)
Precancerous Conditions (2 of 2)
- Leukoplakia may give rise to squamous cell cancers of the oral cavity
- Precancerous conditions should always be treated appropriately to prevent malignant change, which occurs in many but not in all cases

Etiologic Factors in Neoplastic Disease (1 of 2)
- Viruses
- Gene and chromosomal abnormalities
- Failure of immunologic defenses
- Heredity
- Viruses: cause some cancers in humans
  - Leukemia and lymphoma: T cell leukemia-lymphoma virus (HTLV-1) that is related to the AIDS virus
  - Kaposi’s sarcoma: human herpesvirus 8 (HHV-8)
  - Condylomas: papilloma virus; predisposes to cervical carcinoma
  - Chronic viral hepatitis: hepatitis B and C virus
  - Nasopharyngeal carcinoma: Epstein-Barr virus also causes infectious mononucleosis

Etiologic Factors in Neoplastic Disease (2 of 2)
- Gene and chromosomal abnormalities
- Three large groups of genes play an important role in regulating cell functions
- Mutations in these genes are associated with tumor formation
  - Proto-oncogenes
  - Tumor-suppressor genes
  - DNA repair genes

Proto-oncogenes
- Normal “growth genes” in the human chromosomes that promote some aspects of cell growth, differentiation, or mitotic activity
- Becomes an oncogene if mutation occurs or genes are translocated to another chromosome
- Oncogene: abnormally functioning gene that stimulates cell growth excessively, leading to unrestricted cell proliferation

Tumor Suppressor Genes
- Normally suppress cell proliferation
- Loss of function by mutation may lead to unrestrained cell growth
- Exist in pairs at corresponding gene loci on homologous chromosomes
- Both suppressor genes must cease to function before cell malfunctions

DNA Repair Genes
- Regulate processes that monitor and repair any errors in DNA duplication during cell division; DNA damage from radiation, chemicals, or other environmental agents
- Mutation: any change in the normal arrangement of DNA nucleotides on the DNA chain
- Failure in function of DNA repair genes increase the likelihood of DNA mutations within the cell
Failure of Immunologic Defenses

1. Cancers usually arise from multiple genetic "insults" to the genome rather than single gene mutations.
2. Characterized by activation of oncogenes and loss of function of ≥ 1 tumor suppressor genes.
3. Followed by additional random genetic changes in tumor cells that indicate instability of tumor cell genome.

Failure of Immunologic Defenses (2 of 2)

1. Mutant cell produces cell proteins not present in a normal cell; these proteins are recognized as abnormal by the immune system and are destroyed.
2. Immune system destroys abnormal cells via cell-mediated and humoral mechanisms.
3. Tumor: a reflection of the failure of the body’s immune defenses.

Heredity and Tumors

1. Predisposition apparently results from multifactorial inheritance pattern.
2. Individual at risk has inherited set of genes that influence hormonal or enzyme-regulated biochemical process in the body that can increase susceptibility to a specific cancer.
3. Example: breast cancer
   - 80% to 90%: no family history of the disease
   - 10% linked to gene mutations.

Diagnosis of Tumors

1. Recognize early warning signs and symptoms.
2. Complete medical history and physical examination.
3. Laboratory procedures:
   - Examination of rectum and colon
   - Vaginal examination and Pap smear in women
   - Examination of esophagus and stomach
   - X-ray studies
   - Abnormal smear: slides of abnormal cells shed from surface of tumors
   - Cytologic diagnosis: from smears, needle aspiration, biopsy
   - Frozen section: slides prepared and stained for rapid histologic diagnosis.

Photomicrograph of Pap smear, illustrating a cluster of abnormal cells from in situ carcinoma of cervix.
Normal cervical stratified squamous epithelium

In situ carcinoma of cervix

Diagnosis of Tumors (2 of 2)

- Tumor associated antigen tests: some cancers secrete substances that can be detected in the blood by lab tests
- CEA (carcinoembryonic antigen): present in amounts related to the size of tumor and its possible spread
  - Produced by most malignant tumors of the GI tract, pancreas, breast
- Alpha fetoprotein: normally produced by fetal tissues in the placenta but not adult cells; elevated in primary carcinoma of the liver
- Human chorionic gonadotropin: normally produced by placenta; elevated in testicular carcinoma
- Acid-phosphatase: normally produced by prostate epithelial cells, may be elevated in prostate cancer

Relation of carcinoembryonic antigen (CEA) to embryonic cells

The use of CEA to monitor response therapy

Treatment of Tumors

- Surgery
- Radiotherapy
- Hormones
- Anticancer drugs
- Adjuvant chemotherapy
- Immunotherapy
  - Nonspecific
    - Interferon
    - Interleukin-2
    - Cytokines
  - Specific
    - Tumor-infiltrating lymphocyte therapy
    - Tumor vaccines
    - Tumor antibody therapy
Chemotherapy

- Eliminates cells that divide frequently
- Cancer cells and rapidly dividing normal cells found in:
  - Mouth, skin, hair, bone marrow, digestive tract, kidneys, bladder
  - Lungs, nervous system, reproductive system
- Normal cells recover quickly, side effects disappear gradually
- How soon the patient will feel better depends on overall health, types of anticancer drugs used

Side Effects of Chemotherapy (1 of 2)

- Anemia: extreme fatigue, weakness, tiredness, paleness, dizziness experienced by more than half of patients; reduces bone marrow’s ability to make red blood cells
- Constipation: drugs, decrease in physical activity, unbalanced diet
- Depression: physical and emotional stress
- Diarrhea: drugs affect cells that line intestines
- Fatigue

Side Effects of Chemotherapy (2 of 2)

- Hair loss (alopecia)
- Infection due to reduced ability of bone marrow to produce white blood cells
- Loss of appetite (anorexia)
- Mouth, gum, and throat problems; sores
- Nausea and vomiting
- Sexual problems
  - Males: affect sperm cells; temporary/permanent infertility
  - Women: irregular menstrual periods; vaginal infections; menopause-like symptoms

Survival Rates in Cancer (1 of 2)

- Vary from 4% to more than 95%
- Survival rates:
  - Thyroid cancer, 95% 5-year survival rate
  - Pancreatic cancer, 4% 5-year survival rate
- Cancer second to heart disease as most common cause of death in the US
- 1 in every 4 people will eventually develop cancer
  - Lung cancer: most common cancer affecting males
  - Breast cancer: most common cancer affecting females
- Early diagnosis and treatment may enhance survival
- Chances for survival significantly reduced once tumor has metastasized to the regional lymph nodes or to distant sites

Survival Rates in Cancer (2 of 2)

- 5-year survival does not indicate cure; some types recur, prove fatal
- Tumor may have already spread by time of diagnosis and initial treatment, but metastatic deposits held in check by immune defense mechanisms
- Recurrence: failure of body’s defenses, reactivation of tumor; some malignant tumors recur and prove fatal many years after initial treatment
- Breast cancer and malignant melanoma prone to late recurrences
- Breast cancer: 65% 5-year survival rate and 50% 10-year survival rate

Survival Rates in Cancer (3 of 2)

- Malignant neoplasms: 5-year survival rates

<table>
<thead>
<tr>
<th>Type of Neoplasm</th>
<th>5-Year Survival (%)</th>
<th>White</th>
<th>Black</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid</td>
<td>96</td>
<td>93</td>
<td>52</td>
</tr>
<tr>
<td>Melanoma</td>
<td>99</td>
<td>66</td>
<td>Non-Hodgkin’s lymphoma 56</td>
</tr>
<tr>
<td>Uterus, cervix</td>
<td>72</td>
<td>60</td>
<td>53</td>
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<tr>
<td>Uterus, body</td>
<td>88</td>
<td>61</td>
<td>Multiple myeloma 30</td>
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<tr>
<td>Breast</td>
<td>88</td>
<td>73</td>
<td>Leukemia 47</td>
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<tr>
<td>Bladder</td>
<td>82</td>
<td>65</td>
<td>Stomach 21</td>
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<td>54</td>
<td>Lung 15</td>
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<td>93</td>
<td>Esophagus 15</td>
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<td>Hodgkin’s disease</td>
<td>85</td>
<td>77</td>
<td>Pancreas 4</td>
</tr>
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</table>

Continuing mortality from breast carcinoma after mastectomy, as a result of late occurrence of carcinoma

Discussion

- How does leukemia differ from multiple myeloma?
- How is a frozen section used in the diagnosis of tumors?
- What is the difference between a nevus and a melanoma?
- What are the clinical implications of late tumor recurrences and the 5-year survival rate?