Neoplasia
Cancer is the 2\textsuperscript{nd} leading cause of death in the US

Cancer is a genetic disorder caused by DNA mutations
Vocabulary (1)

- tumor (L.) = oncos (G.) = swelling = neoplasm
- neoplasm = new growth
- -oma = tumor; appended to tissue root = benign tumor of the tissue type
  - fibroma, adenoma, papilloma, lipoma
  - fibrous tissue, glandular tissue, warty, fatty
- cancer = crab = malignant neoplasm
- carcinoma = malignant tumor of epithelium
- sarcoma = fleshy swelling = malignant tumor of mesenchymal tissue
Vocabulary (2)

- **Benign-sounding malignancies**
  - lymphoma, melanoma, mesothelioma, seminoma

- **Malignant-sounding trivial lesions**
  - **Hamartoma** (*hamarto* = to sin, miss the mark, error)
    - disorganized mass of cells indigenous to the site
    - develops and grows at same rate as surrounding normally organized tissue without compression
      - pulmonary chondroid hamartoma—*island* of disorganized, but histologically normal, cartilage, bronchi, and vessels
    - clonal translocation involving chromatin protein genes
  - **Choristoma** (*chore* = to disperse)
    - mass of histologically normal tissue in an abnormal location
    - congenital anomaly—*heterotopic rest* of cells
      - duodenal pancreatoid choristoma—small nodule of well-developed and normally organized pancreatic substance in the submucosa of the duodenum
Pulmonary chondroid hamartoma

(A) Gross photograph of the lower lobe of left lung shows a large cystic and solid mass containing variable size of multilocular cysts and solid component with numerous interstitial cartilaginous small nodules. (B) Multilocular cystic spaces with intervening lobulated fragments of cartilaginous tissue and hyalinized stroma (H&E stain, original magnification ×1). (C) There are islands of mature cartilage, adipose tissues and immature mesenchymal tissue containing spindle cells within the intervening stroma (H&E stain, original magnification ×100).
Behavior of tumors

Benign tumors:
• are expansive, compressing adjacent tissue
• do not recur when completely excised
• do not metastasize
• usually grow slowly
• do not cause cachexia

Malignant tumors:
• are invasive, replacing adjacent tissue
• often recur even if completely excised
• may metastasize
• often grow quickly
• may cause cachexia
Gross features of tumors

**Benign:**
- Remain localized
- a solitary mass
- well-demarcated from adjacent normal tissues
- may be encapsulated
- cutaneous masses are usually easily moveable
- has a uniform consistency

**Malignant:**
- may be solitary or multiple
- indistinct demarcation from adjacent tissues
- usually not encapsulated
- cutaneous mass attached to underlying tissue
- may have a variable consistency due to soft or liquid center
- may have finger-like projections, indicative of growth into lymphatic vessels
- may have metastasized to lungs, liver, or any other organ, with masses observed at surgery necropsy, or by imaging analyses
# Histologic and cytologic features

<table>
<thead>
<tr>
<th>Benign:</th>
<th>Malignant:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Well-differentiated cells</td>
<td>• Poorly-differentiated (<em>anaplasia</em>)</td>
</tr>
<tr>
<td>• Uniform cell size and shape</td>
<td>• Variable size, shape (<em>pleomorphism</em>)</td>
</tr>
<tr>
<td>• Well-demarcated</td>
<td>• Poorly demarcated</td>
</tr>
<tr>
<td>• Encapsulated</td>
<td>• Unencapsulated</td>
</tr>
<tr>
<td>• Few mitotic figures</td>
<td>• Many mitotic figures</td>
</tr>
<tr>
<td>• Mitotic figures normal morphology</td>
<td>• Mitotic figures have bizarre shapes</td>
</tr>
<tr>
<td>• Uniform nuclei, euploid</td>
<td>• Variably sized nuclei, aneuploid</td>
</tr>
<tr>
<td>• One nucleus per cell</td>
<td>• Occasional multiple nuclei</td>
</tr>
<tr>
<td>• Nucleolus single or not visible</td>
<td>• Numerous or large nucleoli</td>
</tr>
<tr>
<td>• Tumor not within vessels</td>
<td>• Invasion of lymphatics and veins</td>
</tr>
<tr>
<td>• Uniform appearance</td>
<td>• Areas of necrosis and hemorrhage</td>
</tr>
<tr>
<td>• Epithelium arranged on basement membranes</td>
<td>• Epithelium invades past basement membranes</td>
</tr>
<tr>
<td>• Orderly supporting stroma</td>
<td>• Dense, abundant, fibrous supporting stroma (<em>desmoplasia</em>)</td>
</tr>
</tbody>
</table>

*Anaplasia* refers to poorly differentiated cells, while *pleomorphism* refers to variable size and shape.
Benign Vs Malignant

• Differentiation
• Rate of Growth
• Local Invasion
• Metastasis
Schwannoma
Benign v. Malignant liver tumors
Metaplasia, Dysplasia, Neoplasia

• Metaplasia is replacement of one type of cell for another normally present in tissue
  ▪ Stimulated by irritation or hormone
  ▪ Reversible upon removal of stimulus

• Dysplasia is loss of cellular uniformity and tissue architecture
  ▪ Stimulated and reversible to a point

• Neoplasia is new growth uncoordinated with normal tissue
  ▪ By definition is NOT reversible
Rhabdomyosarcoma (Anaplasia)
Metaplasia and dysplasia of esophagus
Progression of dysplasia to neoplasia

• Dysplasia is usually applied to epithelium
  ▪ abnormal variation in cell morphology (shape, size, nuclear and cytoplasmic staining)
  ▪ minor changes in architectural orientation
    • loss of cell polarity adjacent to a basement membrane
    • loss of orderly maturation from basal to superficial layers

• Cervical dysplasia in women
  ▪ usually associated HPV infection
  ▪ may progress to cervical carcinoma
    • detected by routine cytological exams (Pap test)
    • early detection has led to a dramatic decrease in the incidence of cervical cancer in US

• Dysplastic changes are often found adjacent to foci of invasive carcinoma
Rate of neoplastic growth

• How long does it take to produce a clinically overt tumor mass?
  ▪ original transformed cell ~1 ng mass
  ▪ 30 doublings (2^30) yields 10^9 cells, 1 g
  ▪ 10 more doublings yields 10^12 cells, 1 kg
  ▪ For more than ¾ total life span, tumor is not palpable

• How long does 30 to 40 doublings take?
  ▪ doubling time of tumor cells
  ▪ growth fraction of tumor cells
  ▪ rate at which tumor cells are shed or die
Tumor proliferation

• Proportion of cells in growth fraction declines as tumor grows
• High growth fraction tumors progress rapidly
  ▪ Leukemia, lymphoma, small-cell carcinoma
• Low growth fraction tumors progress slowly
  ▪ cell production 10% greater than loss
  ▪ Colon, breast adenocarcinoma
• Doubling time of clinically detectable colon or lung tumors averages about 2 to 3 months
• Causes infiltration, invasion, and destruction of the surrounding tissue
Cancer cell lineages

- **Tumor-initiating cells**
  - allow human tumor growth when transplanted into an immunodeficient mouse
  - 0.1% to 2% of the total cellularity, but could be as high as 25%

- **Cancer stem cells arise from**
  - normal tissue stem cells
  - transformed, differentiated cells

- **Cancer stem cells have a high intrinsic resistance to conventional therapies**
Metastasis

• Benign neoplasms do not metastasize
  ▪ Benign metastasizing leiomyoma?
• All malignant tumors “can” metastasize
• Metastatic spread strongly reduces the possibility of cure
• Overt metastases upon diagnosis in 30% cases, with occult metastases in 20% more
Pathways for metastases

• Direct seeding of body cavities or surfaces
  ▪ Most frequently peritoneal cavity by ovarian cancer

• Lymphatic spread
  ▪ common for dissemination of carcinomas
  ▪ sarcomas may also use this route
  ▪ pattern of lymph node involvement follows the natural routes of lymphatic drainage
  ▪ biopsy of sentinel nodes is often used to assess metastasis

• Hematogenous spread
  ▪ typical of sarcomas but is also seen with carcinomas
  ▪ blood-borne cells follow the venous flow draining the site of the neoplasm
  ▪ liver and lungs are most frequently involved
Location preference

• Despite pathway of venous or lymphatic flow, some metastatic sites are frequently associated with some primary tumors:
  ▪ breast carcinoma spreads to bone
  ▪ bronchogenic carcinomas tend to involve the adrenals and the brain
  ▪ neuroblastomas spread to the liver and bone

• Despite the large percentage of blood flow, skeletal muscles and spleen are rarely the site of secondary deposits
Cancer incidence, risk

- US risk of cancer death 1 in 5
- 1,437,180 new cancer cases and 565,650 deaths from cancer in 2008
  - Plus 1 million non-melanoma skin cancers and 122,000 cases of carcinoma in situ
- Cancers of the lung, female breast, prostate, and colon/rectum constitute more than 50% of cancer diagnoses and deaths
Epidemiology of cancer

- Incidence varies with age, race, geographic factors, and genetic backgrounds
- Cancers are most common at the two extremes of age
- Geographic variation results mostly from different environmental exposures
- Most cancers are sporadic, but some are familial
- Hereditary predisposition may be autosomal dominant or autosomal recessive
  - Dominant are usually linked to inheritance of a germ-line mutation of cancer suppressor genes
  - Recessive are typically associated with inherited defects in DNA repair
- Familial cancers tend to be bilateral and arise earlier in life than sporadic cancers
Chronic inflammation and cancer

• Virchow proposed that cancer develops at sites of chronic inflammation

• Unresolved chronic inflammation promotes tumorigenesis
  ▪ viral hepatitis or chronic gastritis
  ▪ immune response may become maladaptive
  ▪ compensatory proliferation
  ▪ growth factors, cytokines, chemokines, and other bioactive substances promote cell survival, tissue remodeling, and angiogenesis
Acquired (environmental) DNA damaging agents:
  - chemicals
  - radiation
  - viruses

NORMAL CELL
  - Successful DNA repair

DNA Damage

Failure of DNA repair

Mutations in the genome of somatic cells

Inherited mutations in:
  - Genes affecting DNA repair
  - Genes affecting cell growth or apoptosis

Activation of growth-promoting oncogenes

Inactivation of tumor suppressor genes

Alterations in genes that regulate apoptosis

Unregulated cell proliferation

Decreased apoptosis

Clonal expansion

Angiogenesis

Escape from immunity

Additional mutations

Tumor progression

Malignant neoplasm

Invasion and metastasis
Steps of normal proliferation

- Growth factor binds to its specific receptor
- Transient, limited activation of the growth factor receptor with signal transduction
- Transmission of signal across the cytosol to nucleus via second messengers or signal transduction cascade
- Initiation of DNA transcription
- Entry and progression into the cell cycle
Cancer growth self sufficiency

• Growth factors
  ▪ Autocrine loops

• Growth factor receptors
  ▪ Over-expression or always “on”

• Signal transduction proteins
  ▪ Intermediates in cascade, especially Gproteins, phosphorylases, kinases

• Transcription factors

• Cyclins and CDKs
  ▪ Uncontrolled cell cycle progression
• Cyclin D–CDK4, cyclin D–CDK6, and cyclin E–CDK2 regulate the G1-to-S transition by phosphorylation of the RB protein (pRB).
• Cyclin A–CDK2 and cyclin A–CDK1 are active in the S phase.
• Cyclin B–CDK1 is essential for the G2-to-M transition.
• Two families of CDKIs can block activity of CDKs and progression through the cell cycle. The INK4 inhibitors (p16, p15, p18, and p19) act on cyclin D–CDK4 and cyclin D–CDK6. The others (p21, p27, and p57) can inhibit all CDKs.
Molecular basis of cancer

• Nonlethal genetic damage
• Tumors are monoclonal
• Four classes of normal regulatory genes are principal targets of genetic damage
  ▪ growth-promoting proto-oncogenes
  ▪ growth-inhibiting tumor suppressor genes
  ▪ genes that regulate programmed cell death (apoptosis)
  ▪ genes involved in DNA repair
• Carcinogenesis is a multistep process
  ▪ accumulation of multiple mutations required
  ▪ monoclonally initiated tumors evolve
Determinants of malignant phenotype

- Self-sufficiency in growth signals
  - Oncogene activation
- Insensitivity to growth-inhibitory signals
  - Tumor suppressor gene mutation
- Evasion of apoptosis
  - Inactivation of p53 or activation of anti-apoptotic genes
- Limitless replicative potential
  - Telomerase
- Sustained angiogenesis
  - Required for nutrient/waste exchange
- Ability to invade and metastasize
- Defects in DNA repair
  - Leads to genomic instability, mutated proto-oncogenes and tumor suppressor genes
Oncogenes

- Oncogenes support the growth of tumors
- Proto-oncogenes have normal role in cellular growth and development
- Discovered as homologous to genes in transforming viruses
  - v-onc designation given to viral oncogenes
  - c-onc refers to cellular proto-oncogene
  - onc refers to mutant, activated oncogene
- Novel (nonviral) oncogenes discovered in human tumors
Oncogene products

• Growth factors
  ▪ PDGF-β encoded by SIS
  ▪ Fibroblast growth factor encoded by HST-1

• Growth factor receptors
  ▪ EGF receptors encoded by ERBB1, HER2/NEU

• Signal transduction proteins
  ▪ G-protein encoded by RAS
  ▪ Tyrosine kinase encoded by ABL

• Nuclear transcription factors
  ▪ MYC, MYB, JUN, FOS, REL

• Cyclins and cyclin-dependent kinases
  ▪ CDK4, RB, CDKN2A, cyclin D
Oncogene activation

- Mutations affect structure or regulation of gene product
- Resulting protein is either over-expressed or always “on”
Oncogene activation
Via Karyotypic Change

• Balanced Translocations
  ▪ Overexpression
  ▪ Fusion genes (chimeric proteins)

• Gene Amplifications

• miRNAs
Tumor suppressors

- Prototypical example: retinoblastoma gene
- Sporadic and familial occurrence of rare tumor explained by Knudson’s “two-hit hypothesis”
  - Retinoblastoma develops only when both alleles of RB are inactivated (Deletions!)
  - Autosomal dominant inheritance of one inactive allele accounts for familial cases
  - Homozygous loss of function leads to tumor development
    - Somatic mutation of retinoblasts causes retinoblastoma
    - Somatic mutation frequently found in breast, small cell lung and brain cancers
Tumor suppressor inactivation

- Deletions
- miRNAs
- Epigenetic Modifiers
  - DNA methylation
  - Histone modification
Tumor suppressor gene products

- Growth inhibition factors
  - TGF-β, p53
- Cell adhesion molecules
  - DCC, E-cadherin, APC-βCatenin
- Signal transduction proteins
  - NF-1 (a GTPase activating protein in the RAS pathway)
- Transcription factors, cell cycle regulators
  - RB, WT-1, p53
    - Homozygous loss of p53 in nearly all cancers
RB Gene and Cell Cycle

- RB controls G1-to-S transition of the cell cycle
  - active RB (hypophosphorylated) binds to E2F preventing transcription of genes like cyclin E that are needed for DNA replication, resulting in G1 arrest
  - Growth factor signaling leads to cyclin D expression, activation of the cyclin D-CDK4/6 complexes, inactivation of RB by phosphorylation, and thus release of E2F

- Loss of cell cycle control is fundamental to malignant transformation

- Almost all cancers will have disabled the G1 checkpoint, by mutation of either RB or genes that affect RB function, like cyclin D, CDK4, and CDKIs
  - Many oncogenic DNA viruses, like HPV, encode proteins (e.g., E7) that bind to RB and render it nonfunctional.
Apoptosis regulating genes

• Inactivation prevents death of cells that tend to be growing slowly
• Translocation of $BCL2$ from 18 to the Ig locus on 14q causes overexpression
• Others include $BCLX$, $BAK$, $BAX$, $BAD$, $BID$, $PUMA$ genes
  ▪ BAX opposes BCL, so mutation knocks it out
  ▪ p53 activity normally induces DNA repair and apoptosis if repair fails, so mutation knocks it out
Genomic instability and repair

• DNA repair genes and pathways

• Inherited defects in DNA repair proteins increase propensity for cancerous transformation
  ▪ HNPCC syndrom caused by defect in one of four mismatch repair proteins
  ▪ Xeroderma pigmentosum causes increased sensitivity to UV light, which causes pyrimidine crosslinks
  ▪ Bloom’s syndrome, ataxia telangiectasia, Fanconi’s anemia are also hypersensitive to UV radiation
  ▪ BRCA1 and-2 may be involved in ds break repair

• Replicating genome requires telomerase, which is reactivated in most tumors
Activation of normal p53 by DNA-damaging agents or by hypoxia leads to cell cycle arrest in G1 and induction of DNA repair, by transcriptional up-regulation of the cyclin-dependent kinase inhibitor CDKN1A (p21) and the GADD45 genes. Successful repair of DNA allows cells to proceed with the cell cycle; if DNA repair fails, p53 triggers either apoptosis or senescence. In cells with loss or mutations of p53, DNA damage does not induce cell cycle arrest or DNA repair, and genetically damaged cells proliferate, giving rise eventually to malignant neoplasms.
Tumor growth and angiogenesis

- Tumors cannot expand beyond 1-2 mm diameter without vascularization
- Neovascularization occurs when pro- / anti-angiogenesis balance is tilted
  - Inflammatory proteases activate growth factors
  - bFGF stored in ECM activated by proteases
  - plasminogen, collagen, transthyretin digested to angiostatin, endostatin, vasculostatin
- Hypoxia induced transcription
  - Lack of O2 dehydroxylates HIF1, fails to bind VHL
  - HIF1a transactivates VEGF
Tumor progression

Diagram showing the progression of tumor cells from normal to invasive and metastatic states.
Invasion and Metastasis

• ECM and vascular dissemination
  ▪ Loosening of intercellular junctions
  ▪ Degradation of ECM with collagenase, gelatinase
  ▪ Invasion of loosened ECM via laminin
  ▪ Migration, intravasation, extravasation

• Homing to tissues expressing attractive combination of chemokines
Etiology of cancer

• Genetic damage necessary for transformation or carcinogenesis
  ▪ Chemical carcinogens
    • Industrial/occupational
    • Dietary
    • Environmental
  ▪ Radiant energy
    • UV
    • Ionizing nuclear radiation
  ▪ Microbes
    • Viral
    • Bacterial—H. pylori
Chemical carcinogens

• Direct-acting agents
  - No metabolic conversion required
    • Generally weak damaging agents
    • Alkylating agents
      – Anticancer drugs
    • Acylating agents

• Indirect-acting agents
  - Activated by tissue or liver enzymes
    • Aromatic hydrocarbons and dyes
    • Natural products
    • Insecticides, food preservatives
Process of carcinogenesis

• Initiation
  ▪ DNA mutations that cause:
    • increased frequency of mitosis
    • inhibition of apoptosis
    • decreased ability to repair damaged DNA
    • increased lifespan of cell line

• Promotion
  ▪ stimulation of mitosis in initiated cells
    • mutation avoids repair with cell division
  ▪ inheritable change passed to daughter cells
    • terminally differentiated cells cannot become neoplastic
  ▪ factors include hormones, inflammation, epigenetic

• Progression
Tumor progression

**NORMAL COLON**

- Mucosa
- Submucosa
- Muscularis propria

**MUCOSA AT RISK**

- Germ-line (inherited) or somatic (acquired) mutations of cancer suppressor genes ("first hit")

- APC at 5q21

**ADENOMAS**

- Methylation abnormalities
- Inactivation of normal alleles ("second hit")

- APC
- β-catenin

- K-RAS at 12p12

**CARCINOMA**

- Proto-oncogene mutations

- Homozygous loss of additional cancer suppressor genes
- Overexpression of COX-2

- p53 at 17p13
- LOH at 18q21
- SMAD 2 and 4

- Additional mutations
- Gross chromosomal alterations
- Telomerase
- Many other genes

- Oncogene-induced senescence
# Tumor Antigens

<table>
<thead>
<tr>
<th>Normal Host Cell Displaying Multiple MHC-Associated Self Antigens</th>
<th>Tumor Cells Expressing Different Types of Tumor Antigens</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal self proteins</td>
<td>Oncogene Products: Mutated RAS, BCR/ABL Fusion Proteins</td>
<td>Tumor suppressor gene products: Mutated p53 protein</td>
</tr>
<tr>
<td>MHC Class I</td>
<td>CD8+ CTL</td>
<td>Various mutant proteins in carcinogen, or radiation, induced animal tumors; various mutated proteins in melanomas</td>
</tr>
<tr>
<td>No T cell response</td>
<td></td>
<td>Overexpressed: Tyrosinase, gp100, MART in melanomas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aberrantly expressed: Cancer-testis antigens (MAGE, BAGE)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Human papilloma virus E6, E7 proteins in cervical carcinoma; EBNA proteins in EBV-induced lymphoma</td>
</tr>
</tbody>
</table>

(Modified from Abbas AK, Lichtman AH: Cellular and Molecular Immunology, 5th ed. Philadelphia, WB Saunders, 2003.)
### Immune surveillance and escape

<table>
<thead>
<tr>
<th>Anti-tumor immunity</th>
<th>Immune evasion by tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor cell</td>
<td></td>
</tr>
<tr>
<td>T cell specific for tumor antigen</td>
<td></td>
</tr>
<tr>
<td>T cell recognition of tumor antigen leading to T cell activation</td>
<td></td>
</tr>
</tbody>
</table>

**Immune evasion by tumors**

- **Failure to produce tumor antigen**
  - Antigen-loss variant of tumor cell
  - Lack of T cell recognition of tumor

- **Mutations in MHC genes or genes needed for antigen processing**
  - Class I MHC-deficient tumor cell
  - Lack of T cell recognition of tumor

- **Production of immunosuppressive proteins**
  - Immunosuppressive cytokines (e.g., TGF-β)
  - Inhibition of T cell activation

Clinical aspects of neoplasia

• Local and hormonal effects
  ▪ Obstruction, compression, ectopic hormone secretion

• Cachexia
  ▪ Weakness, wasting of fat and lean muscle, anorexia, anemia
  ▪ TNF, IL-1 may be involved

• Paraneoplastic syndromes
  ▪ Hypercalcemia due to PTH/PTHR expression
  ▪ IL-1, TGFα, VitD may be involved
<table>
<thead>
<tr>
<th>Clinical Syndromes</th>
<th>Major Forms of Underlying Cancer</th>
<th>Causal Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ENDOCRINOPATHIES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cushing syndrome</td>
<td>Small-cell carcinoma of lung</td>
<td>ACTH or ACTH-like substance</td>
</tr>
<tr>
<td></td>
<td>Pancreatic carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neural tumors</td>
<td></td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>Squamous cell carcinoma of lung</td>
<td>Parathyroid hormone–related protein (PTHRP), TGF-α, TNF, IL-1</td>
</tr>
<tr>
<td></td>
<td>Breast carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Renal carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adult T-cell leukemia/lymphoma</td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Ovarian carcinoma</td>
<td>Insulin or insulin-like substance</td>
</tr>
<tr>
<td></td>
<td>Fibrosarcoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other mesenchymal sarcomas</td>
<td></td>
</tr>
<tr>
<td><strong>NERVE AND MUSCLE SYNDROMES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myasthenia</td>
<td>Bronchogenic carcinoma</td>
<td>Immunological</td>
</tr>
<tr>
<td>Disorders of the central and peripheral nervous system</td>
<td>Breast carcinoma</td>
<td></td>
</tr>
<tr>
<td><strong>VASCULAR AND HEMATOLOGIC CHANGES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venous thrombosis (Trousseau phenomenon)</td>
<td>Pancreatic carcinoma</td>
<td>Tumor products (mucins that activate clotting)</td>
</tr>
<tr>
<td></td>
<td>Bronchogenic carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other cancers</td>
<td></td>
</tr>
<tr>
<td>Nonbacterial thrombotic endocarditis</td>
<td>Advanced cancers</td>
<td>Hypercoagulability</td>
</tr>
</tbody>
</table>
Diagnosis—physical exam

• location and appearance of mass
  ▪ well demarcated or poorly demarcated
  ▪ expansile or invasive
    – invasion of lymphatics may show firm radiating cords
  ▪ single mass or multiple masses
  ▪ texture
    • uniform or with soft areas
    • hard (osteosarcoma), cystic (adenomas)
  ▪ color
    • black (melanoma, some basal cell tumors)
    • red (hemangioma or angiosarcoma)

• body condition

• clinical signs
  ▪ constipation, hematuria, coughing, icterus, paraparesis

• local and distant lymph nodes
  ▪ look for local metastasis or generalized lymphoid neoplasia
Laboratory methods

• Cytology excels in the diagnosis of
  • lymphoid tumors and hematopoietic tumors in blood, bone marrow, and lymph nodes
  • screening for cervical dysplasia

• Biopsy provides the most reliable method to diagnose most solid tumors
  • needle, punch, wedge, excisional

• Immunohistochemistry is increasingly relied upon to help determine or refine diagnosis
  • most cases will not distinguish between normal, benign, or malignant cell type
Liquid Biopsies
Molecular profiles and markers

ONCOFETAL ANTIGENS

- α-Fetoprotein: Liver cell cancer, nonseminomatous germ cell tumors of testis
- Carcinoembryonic antigen: Carcinomas of the colon, pancreas, lung, stomach, and heart

SPECIFIC PROTEINS

- Immunoglobulins: Multiple myeloma and other gammopathies
- Prostate-specific antigen and prostate-specific membrane antigen: Prostate cancer

MUCINS AND OTHER GLYCOPROTEINS

- CA-125: Ovarian cancer
- CA-19-9: Colon cancer, pancreatic cancer
- CA-15-3: Breast cancer

NEW MOLECULAR MARKERS

- p53, APC, RAS mutants in stool and serum: Colon cancer
- p53 and RAS mutants in stool and serum: Pancreatic cancer
- p53 and RAS mutants in sputum and serum: Lung cancer
- p53 mutants in urine: Bladder cancer
Grading and Staging

• Grading of a cancer (descriptive)
  ▪ two categories to four categories
  ▪ based on the degree of differentiation of the tumor cells
  ▪ correlation between histologic appearance and biologic behavior is less than perfect

• Staging cancers (somewhat quantitative)
  ▪ American Joint Committee on Cancer Staging TNM system
    • T1 to T4 denotes increasing size the primary lesion
    • N0 to N3 denotes involvement of increasing number and range of nodes
    • M0 to M1 or sometimes M2 indicates the presence, location, and number of metastases