Neoplasia

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Definition

- Cellular proliferation and growth
- Uncontrolled, autonomous
- Clonal
- Inherited or acquired genetic changes
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- Hamartoma: Proliferation of normal tissue
- Choriostoma: Normal tissue in abnormal site
- Metaplasia
  - Replacement by mature epithelium of different type
  - Induced by trauma, infection
  - Example: Cervix, lung
- Dysplasia
  - Loss of normal architecture and cell features
- Metaplasia-dysplasia-carcinoma sequence
- Carcinoma in situ vs invasive
- Desmoplasia: tumor induced fibrosis
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Types of neoplasms

Benign vs. Malignant

Benign tumors

– Well differentiated
– Minimal dysplasia, low mitosis, no necrosis
– Slow growing
– No constitutional symptom
– Well demarcated
– Encapsulated
– Do not infiltrate or metastasize
– May not recur
Malignant tumors

- Well to poorly differentiated
- Dysplasia, anaplasia
  - Pleomorphism
  - Nuclear changes: hyperchromasia, high N/C ratio, Nucleoli
  - Loss of polarity
- High mitosis
- Ill defined
- Grow rapidly, ulcerate, bleed
- Constitutional symptoms
- Infiltrate, metastasize, Recur

Metastasis: Definitive
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Malignant neoplasms

- self-sufficiency in growth signals
- insensitivity to growth inhibition
- evasion of apoptosis
- genomic instability
- Immortalization
- Angiogenesis
- Invasion and metastasis.
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Metastasis

– Detach from each other (E-cadherin)
– Bind to basement membrane; laminin and fibronectin receptors
– Degrade Extracellular matrix; Collagenease, plasminogen activator
– Migration and homing
– Angiogenesis

Fibroblastic growth factor (FGF)
Vascular endothelial growth factor (VEGF)
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Spread
- Direct extension
- Seeding of body cavities
- Hematogenous or lymphatic channels.

Hematogenous Spread:
- Sarcomas
- Route of venous drainage
- Frequent sites; Liver and lungs

Lymphatic Spread:
- Carcinomas
- Site: Regional lymph node
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- Common metastatic sites
- Liver
- Lung
- Bone
- Brain
- Adrenal; Lung and breast
- Virchow node: Supraclavicular lymph node- Gastric carcinoma
- Krukenberg tumor: Gastric met to ovary
Cancer associated chromosomal changes

Point mutations
- Tumor suppressor genes
- P53
- Retinoblastoma
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Cancer associated chromosomal changes

Translocation

- T(8;14), Burkitt lymphoma, c-myc oncogene, proliferation
- T(9;22), Chronic myelogenous leukemia, abl oncogene, tyrosine kinase, proliferation

Amplification

- DNA segment reduplicated and amplified
- Double minutes, homologous staining regions (HSR)
- N-myc, neuroblastoma; ERB B2, breast cancer
Cell Cycle Regulation

The Cell Cycle

- Cyclin B
- Cdc2
- G0
- M
- G2
- G1
- E2F
- RB
- Cyclin D
- Cdk4
- p16, p21, p53
- p27 etc

- Cyclin A
- Cdk2
- Cyclin E
- Cdk2
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Nomenclature

Benign neoplasms

- Named with suffix -oma,
- Example: Smooth muscle-leiomyoma (fibroid); Glandular epithelium-adenomas
- Papillomas- finger like projections raised from an epithelial surface.
- Polyps-benign projections from a mucosal surface.
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Nomenclature

Malignant neoplasms

– Named with suffix

– carcinoma for epithelial cell origin. Example adenocarcinoma, squamous cell carcinoma

– Sarcoma for those derived from mesenchymal tissue.

Exceptions

– Teratoma (benign or malignant),

– hepatoma, seminoma, melanoma, lymphoma; all malignant
<table>
<thead>
<tr>
<th>EPITHELIAL</th>
<th>BENIGN</th>
<th>MALIGNANT</th>
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<tbody>
<tr>
<td>Stratified squamous</td>
<td>Squamous cell papilloma</td>
<td>Squamous cell carcinoma</td>
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<td>Basal cells of skin</td>
<td></td>
<td>Basal cell carcinoma</td>
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<td>Epithelial lining from glands or ducts</td>
<td>Adenoma</td>
<td>Adenocarcinoma</td>
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<td>Hepatocytes</td>
<td>Hepatocellular adenoma</td>
<td>Hepatocellular carcinoma (hepatoma)</td>
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<td>Melanocytes</td>
<td>Nevus</td>
<td>Melanoma (malignant melanoma)</td>
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<td>Renal</td>
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<td>Renal cell carcinoma</td>
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<td>Urinary Epithelium (transitional)</td>
<td>Transitional cell papilloma</td>
<td>Transitional cell carcinoma</td>
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<td>MESENCHYMAL</td>
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<td>A. Connective Tissue</td>
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<td>Cartilage</td>
<td>Chondroma</td>
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<td>Adipose</td>
<td>Lipoma</td>
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<td>Lymphoid</td>
<td>Lymphocytic leukemia</td>
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<td>C. Muscle</td>
<td>Smooth muscle</td>
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<td>Skeletal muscle</td>
<td>Rhabdomyoma</td>
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<td>D. Vascular</td>
<td>Hemangioma</td>
<td>Angiosarcoma</td>
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<td><strong>Placental tissue</strong></td>
<td><strong>Hydatidiform mole</strong></td>
<td><strong>Choriocarcinoma</strong></td>
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<td><strong>Testes</strong></td>
<td><strong>Seminoma</strong></td>
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<td><strong>Salivary gland</strong></td>
<td><strong>Pleomorphic adenoma</strong></td>
<td><strong>Malignant mixed tumor</strong></td>
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<td><strong>GERM CELLS</strong></td>
<td><strong>Teratoma</strong> (dermoid cyst)</td>
<td><strong>Malignant Teratoma</strong></td>
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</table>
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**Etiologic Association**

**DNA oncogenic viruses**

- Epstein-Barr virus (EBV): Burkitt lymphoma, Hodgkin Lymphoma, lymphoma in immunocompromised, Nasopharyngeal carcinoma
  - Enter B cell via CD21
- Hepatitis B and C (HBV, HCV RNA): Hepatocellular carcinoma
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- Etiologic Association
- DNA oncogenic viruses
  - Human papilloma virus (HPV) 16, 18: Squamous cell carcinoma of cervix
    - Sexually transmitted
    - Integrate in host DNA
    - E6 binds to p53, E7 binds to RB
  - Human Herpes virus 8 (HHV8): Kaposi sarcoma
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Etiologic Association

RNA oncogenic viruses

- Human Immunodeficiency virus (HIV): Kaposi sarcoma, lymphoma
- Human T-cell lymphotrophic virus (HTLV-1): Adult T-cell leukemia/lymphoma

Japan, Caribbean, infects CD4, tropical spastic paraparesis
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Bacteria
- Helicobacter pylori: Gastric lymphoma, carcinoma

Parasites
- Schistosoma hematobium: Urinary Bladder cancer
- Clonorchis sinenesis: Gallbladder cancer
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Etiologic Association; Lifestyle

- Cigarette: Lung, oral, larynx, esophagus, urinary bladder carcinoma, pancreas
- Low fiber diet: Colon Carcinoma
- Food preservation: Gastric Carcinoma
- Alcohol: Hepatocellular carcinoma
- Obesity
Etiologic Association; Environmental/occupational

- Asbestos: Mesothelioma
- Ultraviolet radiation: Skin cancer
- Ionizing radiation: Thyroid carcinoma, leukemia
- Betanaphtylamine dye: Urinary bladder Ca
- Aflatoxin: Hepatocellular carcinoma
- Vinyl chloride, thorostat: Liver Angiosarcoma
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- Etiologic Association: Hereditary
- Tumor suppressor gene mutation
  - P53: Li-Fraumeni syndrome
  - RB: Retinoblastoma
  - NF-1: Neurofibromatosis
  - APC: Familial adenomatous polyposis
  - Multiple endocrine neoplasia
- DNA repair defects
  - Bloom’s syndrome
  - Ataxia Telangectasia
  - Xeroderma pigmentosum
- Familial cancers
  - Early age, 2 or more relatives, multiple/bilateral
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Etiologic Association

Chronic infection and tissue damage

– Cervix and lung; squamous metaplasia
– Acid reflux, esophagus
– Inflammatory bowel disease
– Chronic active gastritis

Sustained growth/hyperplasia

– Endometrial hyperplasia
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Etiologic Association

Precancerous conditions

- Chronic atrophic gastritis (pernicious anemia)
- Leukoplakia: oral, penis, vulva
- Solar keratosis
- Chronic ulcerative colitis
- Colon adenomas
“It begins to appear that almost everything one does to gain a livelihood or for pleasure is fattening, immoral, illegal or even worse oncogenic”
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- Anti-tumor defense
- Immune surveillance
- Cytotoxic T-cells
- Natural killer cells
- Macrophages
- Antibodies
  - Directly
  - Activating complement
  - Antibody dependent cell-mediated cytotoxicity
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- Escape of Immune surveillance
  - Outgrowth of antigen negative clones
  - Antigen masking
  - Reduced expression of MHC
  - Lack of costimulation
  - Immunosuppression
  - Apoptosis of cytotoxic T-cells
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Clinical

Non-specific
  – Anorexia, fatigue, weight loss (cachexia), pain, Anemia

Bleeding, secondary infection

Local symptoms: obstruction, compression, loss of function

Acute symptom

Hormone production
  – Pheochromocytoma: Catecholamines
Clinical Paraneoplastic syndrome

- Ectopic hormone: Small cell lung carcinoma, ACTH, Cushing
- Hypercalcemia
  - Multiple myeloma
  - Human T-cell leukemia/lymphoma
  - Bronchogenic carcinoma, parathyroid like hormone
- Neuromyopathic syndromes
  - Peripheral neuropathy, myasthenia gravis
- Acanthosis Nigricans
- Clubbing, hypertrophic arthopathy
- Migratory thrombophelbitis, Trousseau sign, disseminated intravascular coagulation (DIC)
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- Diagnosis
- History and physical exam
- Imaging studies (CT and PET scan)
- Morphology gold standard
  - Cytology
  - Fine needle aspiration biopsy
  - Excisional biopsy, frozen section
  - Resection
  - Lymph node sampling, sentinel node
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Diagnosis

- Immunohistochemistry/Flow cytometry: Antibody against a cellular antigen expressed by tumor
  - Classify tumor
  - Determine primary site
  - Prognostic

- Cytogenetics
- Flourscent in-situ hybridization
- Polymerase chain reaction (PCR)
- Gene expression: microarray
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Grading and Staging; Therapy & prognosis

Grading

- Histologic evaluation
- Degree of differentiation
- Number of mitosis

Staging

- Histologic and clinical
- Size of tumor
- Extent of invasion and metastasis
- TNM staging
  - \( T = \) tumor size; \( N = \) lymph node status, \( M = \) Metastasis
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Serum tumor markers

- Prostate specific antigen (PSA): Prostate carcinoma
- Carcinoembryonic antigen (CEA): Colorectal, pancreatic carcinoma
- CA-125: Ovarian carcinoma
- Alpha feto protein (AFP): Hepatocellular carcinoma, germ cell tumor of testes
- Beta human chorionic gonadotropin (BHCG): Choriocarcinoma
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Tumor progression
  - Multi step process
  - Step wise progression
  - Accumulation of non-lethal genetic changes
    - Proto-oncogenes - promote cell growth
    - Tumor suppressor genes - damaged cells progress
    - Anti-apoptotic genes - survival advantage
  - Initiating genetic change
  - Tumor progression
  - Cellular heterogeneity
MORPHOLOGY  GENETIC ALTERATION  PREDISPOSITION

Normal colonic epithelium

Dysplastic aberrant crypt foci

Early adenoma

Intermediate adenoma

Late adenoma

Carcinoma

Metastasis

APC tumor suppressor

KRAS protooncogene

DCC tumor suppressor

TP53 tumor suppressor

Variable e.g., proteases, adhesion molecules

GENETIC INSTABILITY

Mismatch repair deficiency

Aberrant chromosomal rearrangement

Aberrant chromosomal segregation
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Therapy

Prevention
  – Health Education

Screening
  – PAP smear
  – Mammogram
  – Colonoscopy
  – Prostate specific antigen (PSA)

Early diagnosis

Treatment

Palliative
Therapy

- Surgery
- Radiation

Chemotherapy
  - Cytotoxic
  - Signal Blocking
    - Anti-estrogen: Tamoxifen
    - Block Her2-neu receptor: Herceptin
    - Block EGFR receptor: Gefitinib
    - Block tyrosine kinase: Imatinib

Personalized
  - Genetic profiling
Colon Adenoma
Colon Adenocarcinoma
Pancreas Adenocarcinoma
Breast Fibroadenoma
Neurofibroma
Teratoma
Metastatic Carcinoma
Metastatic Carcinoma