NEOPLASIA I, II, III

Nomenclature/Definitions

- **Neoplasia** – New tissue growth. It is a process which is *unregulated* (neoplastic cells continue to replicate beyond the normal regulatory checks of cell growth triggered by a series of acquired mutations) and *monoclonal*.

- “**Tumors**” are abnormal growths of tissue; benign or malignant neoplasm can be implied.

- **Benign neoplasms** (tumors) remain localized and do not metastasize. They may, depending on factors such as size and location, nonetheless produce deleterious effects (i.e., a benign brain tumor may cause mass effect and neurologic compromise)

- **Malignant tumors** are referred to as “cancers”. They invade locally and have the potential to metastasize.

Two components of neoplasms:

- **Parenchyma** – the neoplastic cells; determines biologically behavior; name of tumor is derived from parenchyma

- **Stroma** – the supporting structures including connective tissue, blood vessels. The stroma plays an important role in the growth of the neoplasm (i.e., blood supply)

How are tumors named?

- Refer to Robbins Basic Pathology – Table 6.1
<table>
<thead>
<tr>
<th>Tissue of Origin</th>
<th>Benign</th>
<th>Malignant</th>
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<td><strong>Blood cells and related cell types</strong></td>
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<td>Lymphoid tissue</td>
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<td>Stratified squamous</td>
<td>Squamous cell papilloma</td>
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<td>Basal cells of skin or adnexa</td>
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<td>Tumors of melanocytes</td>
<td>Nevus</td>
<td>Malignant melanoma</td>
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<td><strong>Epithelial lining of glands or ducts</strong></td>
<td>Adenoma</td>
<td>Adenocarcinoma</td>
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<td>Papilloma</td>
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<td><strong>Lung</strong></td>
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<td><strong>More Than One Neoplastic Cell Type—Mixed Tumors, Usually Derived From One Germ Cell Layer</strong></td>
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<tr>
<td>Salivary glands</td>
<td>Pleomorphic adenoma (mixed tumor of salivary gland)</td>
<td>Malignant mixed tumor of salivary gland</td>
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<td>Renal anlage</td>
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<tr>
<td><strong>More Than One Neoplastic Cell Type Derived From More Than One Germ Cell Layer—Teratogens</strong></td>
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<tr>
<td>Totipotential cells in gonads or in embryonic rests</td>
<td>Mature teratoma, dermoid cyst</td>
<td>Immature teratoma, teratocarcinoma</td>
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</table>
Characteristics of Benign vs Malignant Neoplasms

Definitions:

- **Differentiation** - the extent to which parenchymal tumor cells resemble their normal tissue counterpart

- **Anaplasia** – “backward differentiation” – loss of the structural and functional differentiation of the cells from which a neoplasm is derived

- **Pleomorphism** – variation in the size and shape of cells. Anaplastic neoplasms generally display marked pleomorphism

- **Nuclear to cytoplasmic ratio (N:C ratio)** – normal cells generally have a N:C ratio of 1:4 or 1:6. This ratio may approach 1:1 in malignant cells

- **Dysplasia** – Disorderly architecture and altered cytology of cells, principally found in epithelium; Result of mutations. Cells may have pleomorphism, hyperchromatic nuclei, high N:C ratios, disorderly maturation, mitoses above basal layer. Cells do not penetrate basement membrane.

- **Dysplasia may be reversible** particularly if factors contributing to this change are removed (ie tobacco cessation may lead to reversal of mild to moderate dysplasia in bronchial epithelium).

  When dysplastic cells involve the entire thickness of an epithelial surface, it is referred to as **carcinoma in-situ** (“preinvasive cancer”). Refer to Robbins Basic Pathology Figure 5-6.

- **Metastasis** – secondary implants of a malignant tumor that are discontinuous with the primary tumor and may be in remote tissues. Metastases identifies a neoplasm to be malignant more than any other attribute.

  Three pathways of dissemination

  a) **Seeding within body cavities**

     Characteristic of ovarian carcinoma.

  b) **Via lymphatics (lymphatic spread)**

     More typical of carcinomas. Initial spread is to regional draining lymph nodes.

  c) **Via blood vessels (hematogenous spread)**

     More typical of sarcomas (but seen with carcinomas as well).

     Renal cell carcinoma has propensity to invade the renal vein;
     hepatocellular carcinoma often invades the hepatic vein.
### Cancer Epidemiology

Cancer is the second cause of death in the US (#1 cause is cardiovascular disease)

Incidence of cancer varies with factors including:

- **Patient age**
  - Most cancers develop in persons >50 years of age
    - Likely increased somatic mutations; decline of immune competence with age contribute
  - Cancer does account for greater than 10% of deaths in children <15 years old

- **Race**
- **Geography**
- **Environment**
  - Tobacco, alcohol and increasingly obesity have clear associations with cancers
- **Acquired predisposing conditions**
  - Chronic tissue injury
  - “Precursor lesions” are acquired disorders and are known to be associated with an increased risk of development of cancer
    - **Examples:**
      - Squamous metaplasia/dysplasia of bronchial mucosa in smokers is associated with lung cancer.
      - Endometrial hyperplasia/dysplasia in women with unopposed estrogen stimulation is associated with endometrial cancer
      - Barret esophagus – intestinal metaplasia of squamous epithelium of esophagus often a result of chronic reflux

- **Immunodeficiency states**
Hereditry. While most cancers are sporadic, those that are hereditary/familial can be divided into 3 categories:

- **Autosomal Dominant Cancer Syndromes**
  - Examples: Familial adenomatous polyposis of the colon: nearly 100% of patients develop colon cancer; Familial retinoblastoma: 100,000 times the risk of cancer than in the general population

- **Autosomal Recessive Syndromes of Defective DNA Repair**
  - Examples: Xeroderma pigmentosum

- **Familial Cancers of Uncertain Inheritance**
  - Evident familial clustering (colon, breast, ovary, brain), however pattern of inheritance is unclear

**Carcinogenesis: The Molecular Basis of Cancer**

Fundamental principles

- Cancer is a genetic disorder caused by DNA mutations
- Most mutations are spontaneous or are induced by environmental insults
- Some mutations are inherited in the germ line
- Cancer arises from clonal expansion of a single progenitor cell that has incurred damage (monoclonal)
- Four classes of normal regulatory genes are key targets of cell damage. They are
  - Growth promoting proto-oncogenes
  - Growth inhibiting tumor suppressor genes
  - Genes that regulate apoptosis
  - Genes involved in DNA repair

**Proto-oncogenes:**

- Proto-oncogenes are normal cellular genes whose products promote cell proliferation

**Oncogenes** are mutant or over-expressed versions of normal proto-oncogenes.

- Oncogenes function autonomously
- Oncogenes encode transcription factors, growth regulating proteins, cell survival proteins
- Oncogenes are potent carcinogenic factors. Of the more than 200 identified, some have a risk approaching 100% to develop cancer
- Oncogenes are considered dominant – a mutation of a single allele can lead to cellular transformation
- “Gain of function = cancer”

**Example of an Oncogene: RAS**

RAS is the most commonly mutated proto-oncogene in human tumors. (up to 30% of tumors contain mutated versions of RAS. The frequency is higher some cancers, such as colon and pancreatic adenocarcinomas.)

RAS is a signal transducer that relays receptor activation to the cell nucleus. It is a member of family of small G proteins that bind GTP and GDP.
In its inactive state RAS is bound to GDP. 
It its active state RAS is bound to GTP. 
  GTPase activity of RAS hydrolyzes GTP to GDP, releasing a phosphate 
group and returning the protein to its quiescent GDP-bound state. 
Mutations interfere with GTP hydrolysis trapping RAS in its activate GTP 
bound form. Active RAS stimulates downstream regulators of cell 
proliferation and the cell is forced into a continuously proliferating state.

Other important oncogenes you will encounter during MHD include (and will need to 
know for the USMLE step 1 exam): ABL, C-MYC, ERB-2, L-MYC, RET, C-KIT.

Tumor Suppressor Genes
Tumor Suppressor Genes normally prevent uncontrolled cell growth. 
Mutation (or loss) of a tumor suppressor gene leads to development of a transformed cell. 
Tumor suppressor genes are considered recessive: both alleles must be mutated/lost for cancer to develop 
“Loss of function = cancer”

Example of a Tumor Suppressor Gene: RB (Retinoblastoma gene)

RB is the first tumor suppressor gene discovered. It formed the Basis for Knudson’s 
two-hit hypothesis.

In 1971, Dr. Alfred Knudson proposed the two-hit hypothesis to explain the early onset of an 
inherited form of cancer - hereditary retinoblastoma. Inheriting one germline copy of a damaged 
gene present in every cell in the body was not sufficient to enable this cancer to develop. A 
second hit (or loss) to the good copy in the gene pair could occur somatically, though, producing 
cancer. This hypothesis predicted that the chances for a germline mutation carrier to get a 
second somatic mutation at any of multiple sites in his/her body cells was much greater than the 
chances for a noncarrier to get two hits in the same cell.

Role of Rb and consequences of mutation: 
Rb controls the G1 to S transition of the cell cycle. 
In its active form Rb is hypophosphorylated and binds to E2F transcription factor. This 
interaction prevents transcription of genes, like cyclin E (cyclins are proteins that 
regulate progression through the cell cycle), that are needed for DNA replication. The 
cells are therefore arrested in G1. 
E2F is released when RB is phosphorylated by the cyclinD/cyclin-dependent kinase 4 
(CDK4) complex. 
RB mutation results in constitutively free E2F allowing progression through the cell cycle 
and uncontrolled cell growth.

Sporadic RB mutations are characterized by unilateral retinoblastomas. Retinoblastoma 
is an intra-ocular neoplasm of children which is neuronal in origin.
Germline RB mutations are characterized by bilateral retinoblastomas as well as primary bone malignancies called osteosarcomas.

Another Example of a Tumor Suppressor Gene – p53
p53 is referred to as the “Guardian of the Genome”. It is one of the most commonly mutated genes in cancers
It regulates cell growth: progression from G1 to S phase of the cell cycle. In response to DNA damage, p53
- Activates temporary cell cycle arrest (quiescence)
- Induces permanent cell cycle arrest (senescence)
- upregulates DNA repair enzymes
If DNA repair is not possible, p53 triggers programmed cell death (apoptosis)

Germline p53 mutations with an additional “hit” results in Li-Fraumeni syndrome.
Patients with the syndrome have 25x greater risk of developing a malignancy by age 5.
Cancers include carcinomas, breast cancer, leukemia, brain tumors, adrenal cortex carcinomas, multiple primary tumors

Additional Tumor Suppressor Genes which you will learn during MHD and will need to know for USMLE include BRCA1, BRCA1, p16, APC,

Genes That Regulate Apoptosis
Apoptosis is mediated by caspases which activate proteases which break down the cell cytoskeleton and endonucleases that break down DNA
Caspases may be activated by:

Intrinsic mitochondrial pathway
- DNA damage leads to inactivation of BCL2. BCL2 normally stabilizes the mitochondrial membrane blocking release of cytochrome c. BCL2 is “Anti-apoptotic”.
- Disruption of BCL2 allows cytochrome c to leak from the inner mitochondrial matrix into the cytoplasm and activate caspases – activate apoptosis.
- BCL2 is overexpressed in follicular lymphomas.

Extrinsic receptor ligand pathway
- FAS ligand binds to the FAS death receptor (CD95) on the target cell, activating caspases
- Responsible mechanism for elimination of self-reactive lymphocytes
Other important characteristics of neoplasms

**Neoplasms Develop Limitless Replicative Potential via telomerase.**
Telomeres are short, repeat sequences of DNA. With each somatic cell duplication, a small section of each telomere is not duplicated….telomeres shorten. This eventually results in cell senescence - cell cycle arrest.
Telomerase stabilizes telomere length.
Cancers often have upregulated telomerase which leads to cellular “immortality”.

**Neoplasms Develop Sustained Angiogenesis**
Angiogenesis is the production of new blood vessels. Vascularization of neoplasms is necessary for growth:
- Nutrients, oxygen are provided
- New endothelial cells secrete growth factors such as PDGF, insulin-like growth factor

Inducers of angiogenesis such as VEGF are commonly produced by tumor cells.
- Hypoxia inducible factor (HIF-1a) is a transcription factor which increases VGEF production.
- Von Hippel-Lindau (VHL) is a tumor suppressor gene which inhibits HIF-1a. When VHL is lost it leads to the increased developed of VGEF. During the MHD renal block, we will see the important role of VGEF, HIF and VHL in the pathogenesis of renal cell carcinoma and development of new therapies.

**Malignant Neoplasms have the Capability to Metastasize**
Epithelial tumor cells are normally attached to one another by cellular adhesion molecules such as E-cadherin.
Downregulation of E-cadherin leads to dissociation of attached cells
Cells attach to laminin and destroy/degrade the basement membrane (key component is collage type IV) via collagenase.
Cells attach to fibronectin in the extracellular matrix and spread locally.
Cells invade the vascular and/or lymphatic spaces which allows for metastatic spread.

**Carcinogenic Agents**
Carcinogens are agents that inflict genetic damage -- damage DNA
Important groups of carcinogens are chemicals, oncogenic microbes (predominantly viruses) and radiation

**Chemical carcinogens**
- React with nucleic acids (RNA, DNA), and/or proteins
  - Chemical carcinogens may be
    - Direct Acting: They require no metabolic conversion.
Example: Cancer chemotherapeutics (alkylating agents)

Indirect Acting: They require metabolic conversion to become ultimate carcinogens.

Examples: Polycyclic hydrocarbons such as Benzo(a)pyrene formed in combustion of tobacco in cigarettes; Animal fats; Aromatic amines, azo dyes; B-naphthylamine in dye and rubber industries

*susceptibility of patients to the development of cancer by these agents may depend on the allelic form of converting enzyme inherited

Carcinogenicity may be augmented by agents called promoters

Promoters are compounds, which themselves are nontumorigenic, however they facilitate the induction of cell proliferation (clonal proliferation)

“initiation- promotion” sequence

Some chemical carcinogens may act in concert with viruses or radiation to induce neoplasias

Some specific chemical carcinogens and their cancer with which you should be familiar:

Vinyl chloride: angiosarcoma of the liver
Nitrosamine in smoked foods: stomach cancer
Asbestos: mesothelioma and bronchogenic carcinoma
Arsenic: Squamous cell carcinoma of the skin
Naphthylamine dyes: urothelial carcinoma of the bladder
Aflatoxin B: hepatocellular carcinoma (primary liver cancer)
Cigarette smoke: carcinoma of the oropharynx, lung, esophagus, kidney, bladder

**Radiation Carcinogens**

Sources:

- Sunlight - ultraviolet radiation
- X-rays
- Nuclear fusion/ Ionizing Radiation
- Fission by-products
- Radionucleotides

Mechanisms of action

Ionizing radiation results in chromosome breakage, translocations, point mutations which leads to genetic damage and carcinogenesis

Associated cancer – papillary carcinoma of the thyroid

UV light damages DNA by forming pyrimidine dimers; normally this process is repaired by the nucleotide excision repair pathway

Associated cancers – skin squamous cell carcinoma, basal cell carcinoma, melanoma

Radiation carcinogenesis has a long latent period

Radiation initiation is irreversible

Continued exposure is additive
Xeroderma Pigmentosum is an Autosomal Recessive Syndrome of Defective DNA Repair. There is a defect in nucleotide excision repair pathway and a resultant markedly increased predisposition to skin cancers.

Microbial Oncogenesis
RNA viruses:
Examples: Human T-cell lymphotropic virus (HTLV-1) which causes T cell leukemia/lymphoma

DNA viruses:
Examples: Human papillomavirus (HPV) causes Benign warts, cervical cancer; Epstein Barr Virus (EBV) causes Burkitt lymphoma, nasopharyngeal carcinoma; Hepatitis B and C virus causes Hepatocellular Carcinoma

Bacteria:
Example: Helicobacter pylori causes Gastric adenocarcinoma, MALT lymphoma

Host Defense against Tumors: Tumor Immunity
Cytotoxic T lymphocytes play a primary role in tumor immunity. Avoiding immune surveillance is important for the survival of neoplasms. Cancers can evade the immune system by
- Failing to express HLA class I and escaping CTL attack
- Eliminating strongly immunogenic subclones
- Suppressing the host immune response; examples: by secreting TGF-β (a potent immunosuppressant); Expressing FasL and inducing immune cell apoptosis; Activating regulatory T cells
- Producing a thicker coat of glycocalyx molecules blocking access to immune cells

It is well established that immunosuppression increased the risk for cancer development.

Clinical Aspects of Neoplasia
“Oncology” is the “the study of tumors”. Medical oncologists, surgical oncologists and radiation oncologists provide therapies for patients with neoplasms (cancer).

Effects of tumors on the host:
- Neoplasms, by virtue of their growth, can compress adjacent tissues and ulcerate through surfaces
- Neoplasms, particularly those arising from endocrine organs, can produce hormones. The production of hormones may be clinically significant or may be “silent”.
- Patients with cancer may develop “cancer cachexia”. This results on the loss of body fat, lean body mass, weakness, anorexia, anemia.
The development of cachexia is mediated by tumor produced cytokines, particularly TNF and proteolysis inducing factor. Today there is no treatment to reverse the cachexia (in no drugs or other therapies) except eradication of the cancer.

**Paraneoplastic Syndromes** are symptom complexes that cannot be readily explained by local or distant spread of the neoplasms. They may be mediated by hormone elaboration which is not indigenous to the tumor parenchyma.

Some examples:
- Cushing syndrome results from the production of ACTH or ACTH-like substances by small cell carcinoma of the lung.
- Hypercalcemia develops from the production of Parathyroid-hormone-related protein (PTHRP) by squamous cell carcinoma of the lung.
- Myasthenia gravis as an immunologic phenomena associated with thymomas.

**Grading and Staging of Cancer**
In order to quantify the clinical aggressiveness of any given neoplasms for selection of appropriate treatment the cytological grading, and staging (size and spread of tumor) is assessed.

- Grading of a cancer: Based on the cytologic differentiation (anaplasia, pleomorphism, loss of normal architecture, mitoses) of the tumor cells, an attempt is made to estimate the aggressiveness of the tumor.
  - Well-differentiated = low grade; poorly differentiated = high grade

- Staging of a cancer is based on the size of the primary tumor, extent of spread to regional lymph nodes, and the presence or absence of metastases. Staging has proved to be of greater clinical value than grading for most cancers.

**Diagnosis of Cancer**
- Clinical data invaluable for optimal pathologic diagnosis
  - HPI, social hx, family hx, ROS, PE
- Radiologic studies contribute significantly
- Tissue Sampling is necessary for precise classification
  - The tissue sampled should be adequate and representative of lesion
  - Means to obtain tissue is by excisional biopsy, core needle biopsy, fine-needle aspiration

Methods aiding diagnosis:
- Histologic and cytologic examination
- Immunohistochemistry
  - Monoclonal antibodies labeled with peroxidase
• Examples: epithelial neoplasms stain positive for keratin; mesenchyme stains positive for vimentin, prostatic epithelium stains positive for PSA, melanoma stains positive for S-100

• Flow cytometry
  • Used in the classification of lymphomas and leukemias

• Ultrastructural studies (electron microscopy)

• Molecular Biology Studies
  • Examples include PCR, FISH (fluorescent in-situ hybridization)

• Biochemistry – tumor markers are proteins released by tumors into the serum. The markers generally more valuable for detecting recurrence of disease rather than primary diagnosis

Examples: serum levels of alpha-fetoprotein (afp) may be elevated in hepatocellular carcinoma, some gonadal tumors; Carcinoembryonic antigen (CEA) may be elevated in Colon, Pancreas, Lung, Stomach, Breast cancers

Molecular analysis of tumors (an essential explosion of techniques and knowledge gained in the last decade) plays an important role in tumor

• **Diagnosis**
• Prognosis
• Detection of minimal residual disease
• Diagnosis of hereditary predisposition to cancer
• Therapeutics