Summer Academy 2009
Molecular Mechanisms of Human Disease
Solid Tumors: Transcripts, Tyrosine Kinases, and Therapeutics

Introduction to Cancer Pathobiology

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Lecture Goals

Introduce essential concepts in cancer pathobiology
Define neoplasia and cancer
Describe nomenclature for naming neoplasms
Describe characteristics of benign and malignant tumors
Describe some clinical features of neoplasms
Provide examples of benign and malignant neoplasms
Introduction to Cancer Pathobiology

Lecture Outline

What is cancer?
Classification of neoplasms
Characteristics of benign and malignant neoplasms
Tumor nomenclature
Clinical characteristics of malignant neoplasms

Examples of benign and malignant neoplasms
What is Cancer?

“Cancer is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells.”

Cancer Facts & Figures - 2008
American Cancer Society
www.cancer.org
Questions About Cancer

What are neoplasms?
What are tumors?
What is cancer?

Do all of these terms apply to the same pathologic lesions?
What are Neoplasms?

Neoplasm literally means “new growth”

A *neoplasm* (as defined by Willis) is “…an abnormal mass of tissue the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same manner after the cessation of the stimuli which evoked the change…”

*Robbins Basic Pathology, 8th Edition*
V. Kumar, A.K. Abbas, N. Fausto, and R.N. Mitchell (Eds.)
What are Neoplasms?

“…A tumour is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues, and persists in the same manner after cessation of the stimuli which evoked the change…”

From Chapter 1 – *Definition of Tumour Pathology of Tumours, Fourth Edition*
R.A. Willis
Butterworths, London, 1967
What are Tumors?

Tumor literally means “a swelling”

*Tumors* are the result of a disease process in which a single cell acquires the ability to proliferate abnormally, resulting in an accumulation of progeny cells.

*The Genetic Basis of Human Cancer, Second Edition*
B. Vogelstein and K.W. Kinzler (Editors)
What is Cancer?

Cancers are those tumors that have acquired the ability to invade the surrounding normal tissues.

The Genetic Basis of Human Cancer, Second Edition
B. Vogelstein and K.W. Kinzler (Editors)
Tumors and Cancers

Different Names for the Same Pathologic Lesion?

Neoplasm, Tumor, and Cancer

*Do all of these terms refer to the same pathological lesions?*

Not all neoplasms are cancerous...

However, all cancers are considered to be “tumors”

Classification of Neoplasms

Categorizes neoplasms according to histogenesis, morphologic features, and clinical behavior.
Introduction to Cancer Pathobiology

Lecture Outline

What is cancer?

Classification of neoplasms

Characteristics of benign and malignant neoplasms

Tumor nomenclature

Clinical characteristics of malignant neoplasms

Examples of benign and malignant neoplasms
Types of Neoplasms

Benign Tumors
Malignant Tumors

Tumors of Adults
Malignancies of Childhood

Solid Tumors
Hematopoietic Tumors

Sporadic Tumors
Hereditary Tumors
Classification of Human Neoplasms

Human Cancers

Hematopoietic

Leukemias and Lymphomas

Solid tumors

Sporadic or Hereditary

Malignancies of Childhood
Basic Classification of Neoplasms

Not all neoplasms are cancerous!

Neoplasms

Benign Tumors

Malignant Tumors
Classification of Neoplasms

In oncology, the division of neoplasms into **benign** and **malignant** categories is extremely important.

This classification is based on a judgement of a neoplasm’s **potential clinical behavior**.

*Malignant tumors are collectively known as cancers.*
Basic Classification of Neoplasms

Benign Neoplasms
Malignant Neoplasms

What characteristics of a neoplasm suggest that it is benign versus malignant?

Cellular Features
Tumor Growth Pattern
Clinical Findings
Basic Classification of Neoplasms

Benign Neoplasms

A tumor is said to be *benign* when its microscopic and gross characteristics are considered to be relatively innocent, implying that it will remain localized, it cannot spread to other sites, and is generally amenable to surgical removal.
Basic Classification of Neoplasms

Benign Neoplasms

A tumor is said to be *benign* when...

...it will remain localized...
...it cannot spread to other sites...
...is generally amenable to surgical removal...
Basic Classification of Neoplasms

Malignant Neoplasms

A tumor is said to be *malignant* when the lesion possesses the ability to invade and destroy adjacent structures, and spread to distant sites (metastasize) to cause death.
Basic Classification of Neoplasms

Malignant Neoplasms

A tumor is said to be *malignant* when...

...possesses the ability to invade...
...destroy adjacent structures...
...spread to distant sites (metastasize)...
...cause death...
Benign and Malignant Neoplasms

*The Good and the Bad?*

Most people think that benign neoplasms are good, and that malignant neoplasms are bad…

Benign neoplasm = good prognosis
Malignant neoplasm = bad prognosis
Benign and Malignant Neoplasms

*The Good and the Bad?*

Most people think that benign neoplasms are good, and that malignant neoplasms are bad…

…most people are wrong!

*All tumors are bad,*

*and some are worse than others.*
Morbidity and Mortality Associated with Benign Neoplasms

Problems associated with benign neoplasms depend upon several important factors:

Size of the Tumor
Location of the Tumor
Secondary Consequences

Consider several examples…
Tumors of the Brain

Images used with permission from *The Internet Pathology Laboratory for Medical Education*
http://library.med.utah.edu.edu/WebPath/webpath.html
Hemangioma of the Liver

Liver hemangioma represents a benign lesion derived from blood vessels. These can be dangerous due to their size and their tendency to rupture.
Introduction to Cancer Pathobiology

Lecture Outline

What is cancer?
Classification of neoplasms
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Examples of benign and malignant neoplasms
Benign and Malignant Neoplasms

*Distinguishing Characteristics*

Cellular Features, Tumor Growth Pattern, and Clinical Findings

Cellular Differentiation

- Anaplasia
- Rate of Growth
- Local Invasion
- Metastasis
## Comparison of the Characteristics of Benign and Malignant Neoplasms

<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Characteristics</strong></td>
<td><strong>General Characteristics</strong></td>
</tr>
<tr>
<td>• Slow growth rate</td>
<td>• Rapid growth rate</td>
</tr>
<tr>
<td>• No metastatic disease</td>
<td>• Metastases are common</td>
</tr>
<tr>
<td>• Produces local effects</td>
<td>• Can cause local and/or distant pathophysiological effects</td>
</tr>
</tbody>
</table>
Comparison of the Characteristics of Benign and Malignant Neoplasms

<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
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</thead>
<tbody>
<tr>
<td><strong>Gross appearance</strong></td>
<td><strong>Gross appearance</strong></td>
</tr>
<tr>
<td>• Smooth margins, encapsulated</td>
<td>• Rough margins, no capsule</td>
</tr>
<tr>
<td>• Center resilient, soft, viable</td>
<td>• Firm center, focal necrosis</td>
</tr>
<tr>
<td><strong>Microscopic pattern</strong></td>
<td><strong>Microscopic pattern</strong></td>
</tr>
<tr>
<td>• Resembles normal, well-differentiated</td>
<td>• Poorly differentiated</td>
</tr>
<tr>
<td>compressed adjacent tissue</td>
<td>• Invasive to adjacent tissues</td>
</tr>
<tr>
<td>• Intact basement membrane</td>
<td>• Disrupted basement membranes</td>
</tr>
<tr>
<td>• Cells and nuclei are normal size/shape</td>
<td>• Cells and nuclei are large/irregular</td>
</tr>
</tbody>
</table>
Benign and Malignant Neoplasms

Distinguishing Characteristics

Cellular Differentiation
Anaplasia
Rate of Growth
Local Invasion
Metastasis
Characteristics of Malignant Cells

Cell Differentiation and Anaplasia

The cellular differentiation of tumor cells refers to the extent to which they resemble their normal counterparts morphologically and functionally.

Malignant neoplasms that are composed of undifferentiated cells are said to be anaplastic.

Anaplasia - to form backward, implies dedifferentiation, or loss of the structural and functional differentiation of normal cells.
Characteristics of Malignant Cells

Cell Differentiation and Anaplasia

Examples of cellular pleomorphism in ductal carcinoma *in situ* (DCIS) of the breast (A) and in invasive adenocarcinoma of the breast (B).

*Pleomorphism* – variation in size and shape


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Characteristics of Malignant Cells

Cell Differentiation and Anaplasia

The dysplastic cells of this adenocarcinoma demonstrate marked pleomorphism with cells that vary widely in size and shape. The arrangement of the dysplastic cells is disordered, with only some residual glad formation.

Pleomorphism – variation in size and shape


Image used with permission of Academic Press - Elsevier
Characteristics of Malignant Cells

Cell Differentiation and Anaplasia

Poorly Differentiated Nasopharyngeal Carcinoma
Characteristics of Malignant Cells

*Nuclear Pleomorphism and Hyperchromism*

Hepatocellular Carcinoma
Characteristics of Malignant Cells

*Nuclear Pleomorphism and Hyperchromism*

Leiomyosarcoma

Several of the malignant stromal cells are very large and differ in shape from neighboring cells.


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Benign and Malignant Neoplasms

Distinguishing Characteristics

Cellular Differentiation
Anaplasia
Rate of Growth
Local Invasion
Metastasis
Characteristics of Malignant Cells

Excessive and Abnormal Mitosis

Abnormal Mitotic Figures
Malignant neoplasms often have increased numbers of mitotic figures (reflecting increased growth rates) and abnormal mitotic figures (reflecting mitotic catastrophe).


Image used with permission of Academic Press - Elsevier
Characteristics of Malignant Cells

Proliferation and Necrosis

Tumor Necrosis
Rapidly growing malignant neoplasms tend to contain a central area of necrosis that develops secondary to ischemia related n inadequate blood supply.


Image used with permission of Academic Press - Elsevier
Benign and Malignant Neoplasms

*Distinguishing Characteristics*

Cellular Differentiation
Anaplasia
Rate of Growth
Local Invasion
Metastasis
Tumor Invasion and Metastasis

The Major Cause of Cancer Morbidity and Mortality

Metastatic lesions tend to be multifocal and can come to occupy large portions of the tissue at the site of invasion and spread.
Cancer Metastasis
*Tumor Invasion and Spread*

Cancers grow by progressive infiltration, invasion, destruction, and penetration of the surrounding tissue.

*Next to the development of distant metastases, local invasiveness is the most reliable feature that distinguishes malignant from benign tumors.*

- **Local Invasion Spread**
- **Regional Invasion and Spread**
  - Invasion of Body Cavities
  - **Distant Metastasis**
  - Hematogenous Spread
  - Lymphatic Spread
Benign and Malignant Neoplasms

Local Invasiveness

Benign neoplasms are clearly delineated (circumscribed), indicating an absence of local invasion at the periphery of the lesion. In contrast, malignant neoplasms are poorly delineated and appear to have infiltrated local non-neoplastic tissue.

Benign
Adrenal adenoma

Malignant
Pancreatic adenocarcinoma


Images used with permission of Academic Press - Elsevier
Characteristics of Malignant Cells

Invasion and Spread

Invasion and Local Spread

For Example…Direct invasion of the normal lung tissue by squamous cell carcinoma (destruction of normal tissues adjacent to expanding neoplasm) OR spread of squamous cell carcinoma into the normal lung tissue through bronchioles (spread along a anatomical surface)

Metastatic Spread Through Body Cavities

For Example…Spread of breast carcinoma on the pleural surface of the lung After direct invasion into the body cavity through the chest wall
Tumor Metastasis

Hematogenous Versus Lymphatic Spread

Metastatic tumors can spread through either or both hematogenous (blood) or lymphatic routes.

*Lymphatic spread* and lymph node involvement by metastatic tumors will reflect the natural lymphatic drainage of the tissue site of the primary tumor.

*Hematogenous spread* occurs principally through the venous circulation. Consequently, the liver and lungs are the most frequently involved secondary sites.
Tumor Metastasis

Hematogenous Versus Lymphatic Spread

*Lymphatic spread* and lymph node involvement by metastatic tumors will reflect the natural lymphatic drainage of the tissue site of the primary tumor.

Metastatic colorectal carcinoma spreading through a lymph node.


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Tumor Metastasis

Hematogenous Versus Lymphatic Spread

Metastatic tumors can spread through either or both hematogenous (blood) or lymphatic routes.

_Hematogenous spread_ occurs principally through the venous circulation. Consequently, the liver and lungs are the most frequently involved secondary sites.

Lung adenocarcinoma metastatic to liver.
Tumor Invasion and Metastasis
The Major Cause of Cancer Morbidity and Mortality

Tumor metastasis can result in major clinical consequences and complications.

Loss of Tissue Function
Loss of Nervous Control
Pain and Discomfort
Tumor Invasion and Metastasis
The Major Cause of Cancer Morbidity and Mortality

Tumor metastasis can result in major clinical consequences and complications.

**Loss of Tissue Function**
Loss of tissue function due to extensive replacement by tumor nodules originating at another site.
*For Example*…Impaired respiration due to lung metastasis OR impaired liver function due to liver metastasis.

**Loss of Nervous Control**
Loss of voluntary motor function due to metastasis to major nerves and loss of cognitive function due to metastasis to the brain.
*For Example*…Impaired nervous control secondary to brain metastasis by breast or lung carcinoma.

**Pain and Discomfort**
Pain and discomfort related to specific sites of metastasis.
*For Example*…Pain associated with bone metastasis or ascites.
Introduction to Cancer Pathobiology

Lecture Outline

What is cancer?

Classification of neoplasms

Characteristics of benign and malignant neoplasms

Tumor nomenclature

Clinical characteristics of malignant neoplasms

Examples of benign and malignant neoplasms
Tumor Nomenclature

Benign Neoplasms

In general, benign tumors are named by attaching -"oma" to the cell type from which the tumor arises.

- **Fibroma** - a benign neoplasm of fibrous tissue
- **Chondroma** - a benign neoplasm of cartilagenous tissue
- **Osteoma** - a benign neoplasm of osteoid tissue
- **Lipoma** - a benign neoplasm arising from lipocytes
- **Hemangioma** - a benign neoplasm arising from blood vessels
- **Leiomyoma** - a benign neoplasm arising from smooth muscle cells
Benign Neoplasms

*Lipoma*

The gross appearance demonstrates a solitary nodular lesion, with coloration that is consistent with fatty tissue.

At low magnification the tumor is well demarcated and circumscribed.

At high power, cells within the lesion are indistinguishable from normal lipocytes.

Images used with permission from *The Internet Pathology Laboratory for Medical Education* [http://library.med.utah.edu.edu/WebPath/webpath.html](http://library.med.utah.edu.edu/WebPath/webpath.html)
Tumor Nomenclature

Benign Epithelial Neoplasms

Benign epithelial tumors are classified either on the basis of their microscopic or macroscopic pattern, or according to their cells of origin.

Adenoma - a benign epithelial neoplasm producing glandular patterns or a tumor arising from glandular cells

Papilloma - a benign epithelial neoplasm growing on any surface that produces microscopic or macroscopic finger-like fronds

Polyp - a benign epithelial neoplasm that projects above a mucosal surface to produce a macroscopically visible structure

Cystadenoma - consist of hollow cystic masses
Benign Epithelial Neoplasms

Adenoma

Adenoma - a benign epithelial neoplasm producing glandular patterns or a tumor arising from glandular cells

Benign Liver Adenoma

Images used with permission from The Internet Pathology Laboratory for Medical Education
http://library.med.utah.edu.edu/WebPath/webpath.html
Benign Epithelial Neoplasms

Polyp

Polyp - a benign epithelial neoplasm that projects above a mucosal surface to produce a macroscopically visible structure.

The gross appearance demonstrates a solitary nodular lesion, attached to the mucosa by a visible stalk.

The microscopic appearance of the polyp demonstrates hyperplastic epithelium connected to adjacent normal epithelium by a stalk.

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Tumor Nomenclature
Malignant Mesenchymal Neoplasms

Malignant neoplasms arising in mesenchymal tissues or its derivatives are called sarcomas.

*Sarcomas are designated by their histogenesis*

- **Fibrosarcoma** - a malignant neoplasm of fibrous tissue
- **Chondrosarcoma** - a neoplasm cartilagenous tumor
- **Liposarcoma** - a malignant neoplasm arising from lipocytes
- **Osteosarcoma** - a malignant neoplasm of osteoblasts
- **Angiosarcoma** - a malignant neoplasm arising in blood vessels
- **Leiomyosarcoma** - a malignant neoplasm arising from smooth muscle cells
Benign and Malignant Neoplasms

**Lipoma and Liposarcoma**

At low magnification the tumor is well demarcated and circumscribed.

At high power, cells within the lesion are indistinguishable from normal lipocytes.

The gross appearance demonstrates a solitary nodular lesion, with coloration that is consistent with fatty tissue.

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http://library.med.utah.edu.edu/WebPath/webpath.html
Tumor Nomenclature

*Malignant Epithelial Neoplasms*

Malignant epithelial neoplasms are called *carcinomas*.

**Adenocarcinoma** - a malignant neoplasm in which the neoplastic cells grow in a glandular pattern

**Squamous Cell Carcinoma** - a malignant neoplasm with a microscopic pattern that resembles stratified squamous epithelium

**Poorly Differentiated Carcinoma** - a malignant neoplasm that grows in an undifferentiated pattern
Malignant Epithelial Neoplasms

*Squamous Cell Carcinoma*

**Squamous Cell Carcinoma** - a malignant neoplasm with a microscopic pattern that resembles stratified squamous epithelium

Lung Squamous Cell Carcinoma
Malignant Epithelial Neoplasms

*Adenocarcinoma*

**Adenocarcinoma** - a malignant neoplasm in which the neoplastic cells grow in a glandular pattern.
Malignant Epithelial Neoplasms

Poorly Differentiated Carcinoma

Poorly Differentiated Carcinoma - a malignant neoplasm that grows in an undifferentiated pattern

Undifferentiated Nasopharyngeal Carcinoma
Benign and Malignant Neoplasms
Liver Adenoma and Hepatocellular Carcinoma

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http://library.med.utah.edu.edu/WebPath/webpath.html
Neoplasms of Mixed Cell Type

Some neoplastic cells undergo divergent differentiation during tumor formation, giving rise to tumors of mixed cell type. Examples of multifaceted mixed tumor include that of salivary gland origin and breast fibroadenoma.

Teratoma

*Teratomas* contain recognizable mature or immature cells or tissues representative of more than one germ-cell layer, and sometimes all three. These tumor originate from totipotent cells such as those found in ovary and testis.

Benign (mature) Teratoma
Malignant (immature) Teratoma
Comparison of the Characteristics of Mature Versus Immature Teratoma

Mature Teratoma
Demonstrates cartilage and skin.

Immature Teratoma
Demonstrates primitive blastema cells and focal rosette formation (arrow).

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Confusing Terminology

Some malignant neoplasms are conventionally referred to using terms that are suggestive of benign neoplasms based upon the usual nomenclature for naming tumors.

Examples

- **Lymphoma** – a malignant neoplasm of lymphoid tissue
- **Mesothelioma** – a malignant neoplasm of the mesothelium
- **Melanoma** – a malignant neoplasm arising from melanocytes
- **Seminoma** – a malignant neoplasm of the testicular epithelium

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http://library.med.utah.edu.edu/WebPath/webpath.html
Hamartoma refers to a developmental malformation that presents as a mass lesion of disorganized tissue that is indigenous to that particular tissue site.

Cartilagenous hamartoma of the lung

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Other Important Terms and Concepts

*Metaplasia, Hyperplasia, and Dysplasia*

**Metaplasia** is a reversible change in which one adult cell type (epithelial or mesenchymal) is replaced by another adult cell type. Metaplasia is a reactive condition.

**Hyperplasia** constitutes an increase in the number of cells in an organ or tissue. Hyperplasia can be physiologic or pathologic. Most forms of pathologic Hyperplasia result from excessive (abnormal) hormonal or growth factor stimulation.

**Dysplasia** is a loss in the uniformity of the individual cells and a loss in their architectural orientation. Dysplasia is a disorderly, but non-neoplastic cellular proliferation.
Preneoplastic Conditions

*Metaplasia, Hyperplasia, and Dysplasia*

Some metaplastic, hyperplastic, or dysplastic conditions are known to represent preneoplastic changes in specific tissues. *However, this is not always the case...*

Breast hyperplasia confers no increased risk of breast cancer.


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Neoplastic Progression

*Progression of Dysplasia in the Cervix*

(A) Normal squamous cervical epithelium; (B) Low-grade squamous dysplasia; (C) Moderate squamous dysplasia; (D) High-grade squamous dysplasia; (E) Invasive squamous cell carcinoma.


Images used with permission of Academic Press - Elsevier
Neoplastic Progression

Progression of Neoplastic Transformation in the Colon

(A) Low-grade glandular dysplasia
(B) High-grade glandular dysplasia
(C) Invasive adenocarcinoma.

Images used with permission of Academic Press - Elsevier
Preneoplastic Conditions

Metaplasia, Hyperplasia, and Dysplasia

*Metaplasia* is a reversible change in which one adult cell type (epithelial or mesenchymal) is replaced by another adult cell type. Metaplasia is a reactive condition.

Intestinal metaplasia in Barrett’s esophagus (left), and Barrett’s esophagus with early carcinoma development (right).
**Preneoplastic Conditions**

*Metaplasia, Hyperplasia, and Dysplasia*

Metaplastic changes in the stomach…

(A) Normal glandular stomach epithelium
(B) Intestinal metaplasia with goblet cells (arrows)


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Introduction to Cancer Pathobiology

Lecture Outline

What is cancer?

Classification of neoplasms

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Clinical characteristics of malignant neoplasms

Examples of benign and malignant neoplasms
Clinical Characteristics of Malignant Neoplasms

The Effects of Tumors on the Host
- Cancer Cachexia
- Paraneoplastic Syndromes

Grading and Staging of Cancer

Detection and Diagnosis of Cancer
- Morphologic/Imaging Methods
- Biochemical Assays
- Molecular Diagnosis/Molecular Profiling
The Effects of Tumors on the Host

Cancer Cachexia

*Cachexia* - a wasting syndrome characterized by progressive loss of body fat and lean body mass, accompanied by profound weakness, anorexia, and anemia.

Tumor size and extent of tumor spread generally correlates with severity of cachexia. Cachexia results from reduced caloric intake accompanied by increased caloric expenditure and increased basal metabolic rate.

There is no satisfactory treatment for cancer cachexia, except for removal of the underlying cause, *the tumor*. 
The Effects of Tumors on the Host

Paraneoplastic Syndromes

Paraneoplastic syndromes - symptom complexes (other than cachexia), that cannot be readily explained by local or distant spread of the tumor or by elaboration of hormones indigenous to the tissue of origin of the tumor.

Paraneoplastic syndromes may …

...represent the earliest manifestation of an occult neoplasm.

...present significant clinical problems and can be lethal.

…mimic metastatic disease, confounding treatment.
The Effects of Tumors on the Host

*Paraneoplastic Syndromes*

**Endocrinopathies**
Cushing Syndrome, Hypercalcemia, Hypoglycemia, Polycythemia, and others.

**Nerve and Muscle Syndromes**
Myasthenia, CNS and PNS disorders.

**Dermatologic Disorders**
Acanthosis Nigricans, Dermatomyositis

**Vascular and Hematologic Changes**
Trousseau Syndrome, Nonbacterial Thrombotic Endocarditis
The Effects of Tumors on the Host

Paraneoplastic Syndromes

**Cushing Syndrome**

*Caused by ectopic secretion of corticotropin (Hypercortisolism)*

Major effects: hyperglycemia, hyperkalemia, hypertension, and muscle weakness

- Small cell lung carcinoma
- Pancreatic carcinoma
- Neural tumors

**Trousseau Syndrome**

*Characterized by hypercoagulopathy*

Major effects: venous thrombosis of the deep veins

- Small cell lung carcinoma
- Pancreatic carcinoma
Grading and Staging of Cancer

Refers to methods for quantifying the probable clinical aggressiveness of a given neoplasm and to express its apparent extent and spread in the individual patient.

Useful for guiding therapeutic intervention

Grading
Staging

Of these two descriptions of malignant neoplasms, staging is the more valuable in the clinical setting.
Grading and Staging of Cancer

**Grading**

Estimates aggressiveness or level of malignancy based upon cytologic differentiation of tumor cells and the number of mitoses within a tumor.

Grade I, II, III, or IV

Reflects increasing anaplasia of tumor cells

Criteria for grading varies with tumor type
Grading and Staging of Cancer

Staging
Describes the size of the primary tumor, its extent of spread to regional lymph nodes, and the presence or absence of metastases.

The TNM System

*T* describes the **primary tumor** with T1, T2, T3, and T4 reflecting increasing size of the primary tumor

*N* describes **node involvement**, with N0, N1, N2, and N3 reflecting progressively advancing node involvement

*M* describes the absence or presence of distant **metastases**, with M0 and M1 reflecting absence and presence, respectively
Staging of Hepatocellular Carcinoma

Primary Tumor

**T0** - No evidence of primary tumor

**T1** - Solitary tumor, 2 cm or less in size, without vascular invasion

**T2** - Solitary tumor, 2 cm or less in size, with vascular invasion; or multiple tumors limited to one lobe (<2 cm) without vascular invasion; or a solitary tumor (>2 cm) without vascular invasion

**T3** - Solitary tumor more than 2 cm size with vascular invasion; or multiple tumors limited to one lobe (<2 cm), with vascular invasion; or multiple tumors limited to one lobe (>2 cm)

**T4** - Multiple tumors in more than one lobe of the liver, involving a major branch of the portal or hepatic vein(s) or invasion of adjacent organs
Staging of Hepatocellular Carcinoma

Node Involvement

N0 - No regional lymph node metastasis
N1 - Regional lymph node metastasis

Distant Metastasis

M0 - No distant metastasis
M1 - Distant metastasis
Staging of Hepatocellular Carcinoma

Treatment Based Upon TNM Status

Localized Resectable Disease
T1, T2, T3, selected T4; N0; M0
Confined to a solitary mass in a portion of the liver that allows the possibility of complete surgical removal with a margin of normal liver

Localized Unresectable Disease
Selected T2, T3, and T4; N0; M0
Appears to be confined to the liver, but surgical resection of the entire tumor is not possible despite the localized mass because of its location within the liver

Advanced Disease
Any T; N1 or M1
Cancer present in multiple liver lobes or has spread to distant sites
Staging of Hepatocellular Carcinoma

Treatment Based Upon TNM Status

Localized Resectable Disease
Surgery
Surgery + Chemotherapy

Localized Unresectable Disease
Chemotherapy or Radiation
Orthotopic Liver Transplant

Advanced Disease
No standard treatment
Chemotherapy or Radiation
Experimental Therapies
Lecture Summary

In this lecture, essential concepts related to cancer pathobiology were introduced, including (i) definitions of neoplasia, tumors, and cancer, (ii) description of the nomenclature for naming neoplasms, (iv) description of the features of benign and malignant tumors, (v) description of some clinical features of neoplasms. Throughout the lecture, examples of benign and malignant tumors were used to illustrate important terms, concepts, nomenclature, and other features of neoplasms.