General Tumor Pathology
General Definition of “Tumor”

Synonym: neoplasia

A tumor is an abnormal mass of tissue resulting from autonomous, progressive, excessive proliferation of body cells not integrated into normal tissue.

Fundamental to the origin of all neoplasms is loss of responsiveness to normal growth controls.
Note

“Tumor” in the original wider sense denotes any circumscribed increase in volume of a tissue (a swelling).
Tumors:

– **Benign**
  These are limited circumscribed tumors that do not metastasize into other regions of the body, do not recur after resection, and do not have a fatal outcome.

– **Malignant**
  These are ill-defined tumors that invade surrounding tissue and can metastasize into other regions of the body, recur after resection, and invariably lead to a fatal outcome if left untreated.
Benign tumors: Note!

Two exceptions:

1. A tumor occurring in an unfavorable anatomic location that causes compressive destruction of vital structures. For example, benign pituitary tumors cause compressive atrophy of glandular tissue.

2. A tumor with excessive hormone production that can cause fatal metabolic derangements. For example, an islet cell adenoma of the pancreas causes hyperinsulinism.
Malignant tumors: Note!

Several terms are used in referring to malignant tumors:

– **Cancer** is the common term for all malignant tumors.
– **Carcinoma** is the common term for malignant epithelial tumors.
– **Sarcoma** is the common term for malignant nonepithelial tumors.
– **Solid tumors** are circumscribed tumors such as carcinomas and sarcomas.
– **Non-solid tumors** are systemic autonomous proliferations of noncohesive individual cells, such as occur in leukemias.
Tumors of Limited Malignancy

Synonym: semimalignant

These include epithelial and nonepithelial tumors that invade and destroy surrounding tissue but rarely if ever metastasize.

Examples: basalioma, ameloblastoma
Tumorigenesis

• Causal tumorigenesis
  – tumors arise from division of a mother cell in which mutation causes inadequate activation of proto-oncogenes and often genes regulating development, together with the inactivation of tumor suppressor genes and differentiation genes that regulate developmental growth and tissue repair. (see. Robbins “Neoplasia”)

• Formal tumorigenesis
Formal tumorigenesis

• A neoplastic tissue proliferation develops into a malignant tumor in several stages:
  – Precursors and Early Stages
    • Precancerosis
    • Intraepithelial Neoplasia (= Dysplasia)
    • Carcinoma in Situ
    • Microinvasive Carcinoma
  – Cancer
Precancerosis

General definition: These are tissue changes with an increased statistical risk of malignancy.

General pathogenesis: Precancerous lesions may arise as a result of congenital cell characteristics or acquired tissue characteristics.

— A precancerous condition is one that predisposes the patient to a precancerous malady, i.e., xeroderma pigmentosum.

— A precancerous lesion is an acquired tissue change such as actinic keratosis.

These precancerous conditions may exhibit varying biologic behavior. Some become malignant tumors only occasionally and only after a prolonged period of time (“facultatively”). Others become malignant tumors often and within a short time (“obligatorily”).

Several histologic forms may be distinguished according to the specific tissue.
Leukoplakia

Definition: This is a white patch of altered superficial epithelium that cannot be wiped off.

The prognosis is favorable. Concurrent presence of dysplasia represents a precancerous condition.
Leukoplakia

**Histologic findings** include focal squamous tissue changes characterized by:

— **Hyperkeratosis**, increased cornification with formation of nonnucleated cornified scales;

— **Parakeratosis**, excessively rapid cornification with formation of nucleated cornified scales;

— **Basal cell hyperplasia**;

— **Inflammation**, lymphocytic infiltration of the stroma (not necessarily present)
Basal cell hyperplasia

Parakeratosis

Basal cell hyperplasia

Verrucous leukoplakia
Intraepithelial Neoplasia (= Dysplasia)

Definition: This refers to reversible histologic deviation of epithelial tissue from normal with deranged differentiation but controlled proliferation. It is a precancerous lesion. Histologic findings include cells that exhibit marked variability in the nuclear size (pleomorphism) and mitoses with loss of functional epithelial orientation. The prognosis is favorable.
Carcinoma in Situ

Definition and morphology: Severe epithelial atypia and loss of polarity are present with an intact basement membrane and histologic findings of noninvasive carcinoma.

The prognosis is favorable.
C Severe squamous dysplasia
(HE) x 100

E Carcinoma in situ: bronchus
(HE) x 100
Differentiation and Anaplasia

The *differentiation* of parenchymal cells refers to the extent to which they resemble their normal forebears morphologically and functionally.

- **Benign** neoplasms are composed of well-differentiated cells that closely resemble their normal counterparts, mitoses are extremely scant in number and are of normal configuration.

- **Malignant** neoplasms are characterized by a wide range of parenchymal cell differentiation, from surprisingly well differentiated to completely undifferentiated.
Well-differentiated squamous cell carcinoma of the skin. The tumor cells are strikingly similar to normal squamous epithelial cells, with intercellular bridges and nests of keratin pearls (arrow).
Differentiation and Anaplasia

Malignant neoplasms that are composed of **undifferentiated cells** are said to be **anaplastic**. Lack of differentiation, or anaplasia, is considered a hallmark of malignancy. The term anaplasia literally means "to form backward." It implies dedifferentiation, or loss of the structural and functional differentiation of normal cells. It is now known, however, that cancers arise from stem cells in tissues, so that failure of differentiation, rather than dedifferentiation of specialized cells, accounts for undifferentiated tumors.
High-power detail view of **anaplastic** tumor cells shows cellular and nuclear variation in size and shape. The prominent cell in the center field has an abnormal tripolar spindle.
Differentiation and Anaplasia

Anaplastic cells display marked pleomorphism (i.e., marked variation in size and shape).

Characteristically the nuclei are extremely hyperchromatic and large.

The nuclear-cytoplasmic ratio may approach 1:1 instead of the normal 1:4 or 1:6.

Giant cells that are considerably larger than their neighbors may be formed and possess either one enormous nucleus or several nuclei.

Mitoses are often numerous and distinctly atypical; anarchic multiple spindles may be seen and sometimes can be resolved as tripolar or quadripolar forms
Anaplastic tumor of the skeletal muscle (rhabdomyosarcoma). Note the marked cellular and nuclear pleomorphism, hyperchromatic nuclei, and tumor giant cells.
Tumor Angiogenesis

Every tumor makes use of the existing vascular network at least to a certain extent. This leads to qualitative and quantitative changes in the affected portion of the vascular network.
Tumor Dissemination

A benign tumor remains within its tissue of origin and cannot extend across long distances into other organs. In contrast, the spread of malignant tumors exhibits the following four characteristics:

— **Infiltration**: The tumor cells penetrate the surrounding tissue.

— **Invasion**: The tumor cells penetrate lymph and blood vessels.

— **Tissue destruction** occurs in the vicinity of the tumor as a result.

— **Metastasis**: Tumor cells colonize other tissues far from the original tumor site.
A. Muscle infiltration: prostate carcinoma (HE) x 200

B. Penetration of the vena cava: renal carcinoma

C. Tissue destruction: carcinoma of the maxillary sinus

D. Invasion of a nerve sheath: carcinoma (HE) x 100
Metastasis

Definition: Dissemination of tumor cells from one part of the body to another remote location, where they establish themselves and grow into secondary tumors.

- **Lymphatic metastasis** (dissemination of tumor cells via the lymphatic system)
- **Hematogenous metastasis** (dissemination of tumor cells via bloodstream)
- **Cavitary metastasis** (tumor cells invade a body cavity such as the pleura, peritoneum etc)
Lymphatic metastasis:  
Formal pathogenesis

Three stages:

— **Tumorous lymphangiosis**: Tumor cells that separate from the margin of a tumor usually initially invade lymph vessels. Then the tumor cells usually migrate through the vascular wall. Where the flow in the respective lymph vessel is conducive to it, tumor cells may even proliferate within the lymph vessels and grow along them.

— **Lymph-node metastasis**: Tumor cells usually spread to the next lymph node.

— **Remote metastases**: From the initial infestation of a lymph node, tumor cells spread into the immediate downstream nodes and later to more remote nodes. They can then enter the venous bloodstream via the thoracic duct.
Hematogenous metastasis: Formal pathogenesis

Three stages

— **Invasion phase**: Most tumor cells pass from the lymph system into the bloodstream. There most of them are destroyed within 24 hours.

— **Embolus phase**: In circulation, tumor cells aggregate in clumps and surround themselves with a coat of fibrin, forming a tumor embolus that lodges in precapillary arterioles.

— **Implantation phase**: As time passes, individual tumor cells break out of the embolus and pass through the postcapillary venules. They then extravasate and invade the organ tissue. The invading tumor cells establish their own vascular system and develop into secondary tumors.
Hematogenous metastasis: patterns

There are four basic patterns of hematogenous metastasis:

**Lung Pattern**
- A primary tumor located in the lung initially spreads via the pulmonary veins. From there, tumor cells spread to the left heart, and the tumor can colonize any of the organs supplied by the extrapulmonary vessels.

**Liver Pattern**
- A primary tumor located in the liver initially spreads via the hepatic veins. From there, tumor cells spread to the right heart, lungs, and left heart. From there, the tumor can colonize any of the organs supplied by the extrapulmonary vessels.

**Vena Cava Pattern**
- Here, the primary tumor is located in the area drained by the superior or inferior vena cava (such as a kidney, bone, or thyroid tumor). The tumor cells initially spread to the right heart and can colonize the lung.

**Portal Vein Pattern**
- A primary tumor located in the intestine initially spreads via the portal vein to the liver, where it metastasizes. From there, tumor cells spread via the hepatic veins and vena cava to the lung in the same manner as the liver pattern.
Cavitary Metastasis

Tumor cells invade a body cavity such as the pleura, peritoneum, pericardium, subarachnoid space, or tendon sheath. From there, they spread within the respective cavity and colonize it with one or more metastases. Manifestations of such metastatic disease include:

— Pleural carcinosis/sarcomatosis;
— Peritoneal carcinosis/sarcomatosis;
— Pericardial carcinosis/sarcomatosis;
B Tumor embolism
(HE) x 100

C Peritoneal carcinosis: metastatic rectal carcinoma

D Pleural sarcomatosis:
metastatic sarcoma of the uterus

E Pericardial sarcomatosis:
metastatic sarcoma of the uterus
Secondary changes in tumors

Secondary changes in a malignant tumor, and occasionally in a benign one, are attributable to the following mechanisms:

— Rapid tumor growth;
— An insufficient vascular network;
— Immune system intervention.

Characteristic morphologic findings:

— Necroses may be spontaneous or iatrogenic.
— Spontaneous hemorrhages may occur due to tumor necrosis or therapy.
— Scarring may occur, producing crater-like retraction of the surrounding tissue.
— Dystrophic calcification occurs in patients with certain tumors, where tumor clusters calcify into concrements resembling grains of sand ("psammomatous" calcification).

Note!: Psammomatous calcification is typical of papillary ovarian carcinomas, papillary thyroid carcinomas, and meningiomas.
Recurrence

This refers to the *reappearance* of a tumor following resection or complete remission.

Depending on the type and differentiation of the tumor, the patient’s immune status, and the success of therapy, recurrence may be early or late.

— Early recurrence involves compromised immune defenses; the tumor reappears after a few months usually in the same place (*local recurrence*).

— Late recurrence involves good immune defenses; the tumor reappears only after a period of years usually in a different place (*remote recurrence*).
Tumor Complications

• Local Complications
  – Stenosis
  – Circulatory disruption (obstruction of venous drainage, vascular thrombosis, bleeding)
  – Tumor necrosis
    • Complications of tumor necrosis:
      – Ulceration of the inner or outer body surface may occur, primarily in gastrointestinal, skin, and breast cancer.
      – Perforation of the tumor necrosis may occur into hollow organs or through the surface of the skin.
      – Fistulas may form that communicate with adjacent organs.

• Systemic Complications
  – Tumor metastases
  – Cancer cachexia: involves weight loss in cancer patients.
  – Tumor anemia
Tumor Classification

**Staging:** The stage of neoplastic disease is defined according to three criteria. Together, they comprise what is known internationally as the TNM system.

— T refers to local tumor growth.
— N refers to spread to regional lymph nodes.
— M refers to distant metastasis.
Tumor Classification

**Grading:** This involves histologic evaluation of the extent to which a tumor corresponds to its tissue of origin.

- G1 indicates a high degree of differentiation (low malignancy).
- G2 indicates a moderate degree of differentiation (moderate malignancy).
- G3 indicates a low degree of differentiation (high malignancy).
- G4 indicates no differentiation (very high malignancy, indicating an anaplastic tumor).
Rule of thumb

The less differentiated a tumor is, the greater its malignancy, the more rapid its growth (mitosis count). Its sensitivity to radiation and spontaneous rate of necrosis will also be correspondingly high.
Tumor Classification

**Typing:** Tumors are classified as follows according to their tissue of origin:

- Epithelial tumors;
- Nonepithelial tumors:
  - Tumors of connective tissue
  - Leukemias and lymphomas
  - Melanocytic tumors
  - Brain and nerve sheath tumors
  - Dysontogenetic tumors
## Benign vs. malignant tumors

<table>
<thead>
<tr>
<th></th>
<th>Benign tumors</th>
<th>Malignant tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Growth</strong></td>
<td>Slow with</td>
<td>Rapid with</td>
</tr>
<tr>
<td></td>
<td>- Expansion, displacement</td>
<td>- Destruction</td>
</tr>
<tr>
<td></td>
<td>- Compression</td>
<td>- Infiltration (➡️ D)</td>
</tr>
<tr>
<td></td>
<td>- Compressive atrophy of surrounding tissue</td>
<td>- Thigmotaxis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Vascular invasion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Metastases</td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td>Increases slowly; tumor may become very large (“knapsack tumor”; ➡️ B)</td>
<td>Increases rapidly</td>
</tr>
<tr>
<td><strong>Capsule</strong></td>
<td>Present; tumor can be surgically “enucleated” from capsule due to compression of local stroma</td>
<td>Partially or entirely absent; tumor frequently recurs after resection</td>
</tr>
<tr>
<td><strong>Maneuverability</strong></td>
<td>maneuverable</td>
<td>non-maneuverable</td>
</tr>
<tr>
<td><strong>Histologic findings</strong></td>
<td>Usually a perfect image of the histologic mother tissue with a low mitosis count and absence of necrosis</td>
<td>Primitive image of the histologic mother tissue with a high mitosis count and necrosis</td>
</tr>
<tr>
<td><strong>Variability of cell size</strong></td>
<td>Cellular and nuclear isomorphism (cells and nuclei of largely the same size)</td>
<td>Cellular and nuclear polymorphism (cells and nuclei of varying size)</td>
</tr>
<tr>
<td><strong>DNA content</strong></td>
<td>Nuclear euploidy (uniform coloration of nuclei) with the exception of endocrine tumors, which exhibit nuclear polyploidy</td>
<td>Nuclear aneuploidy, polyploidy, and polychromasia (varying coloration of nuclei)</td>
</tr>
<tr>
<td><strong>Ratio of nucleus to cytoplasm</strong></td>
<td>Normal</td>
<td>Nuclei predominate</td>
</tr>
<tr>
<td><strong>Nucleoli</strong></td>
<td>Invisible or small and round</td>
<td>Enlarged and irregular</td>
</tr>
<tr>
<td><strong>Clinical course</strong></td>
<td>Usually clinically asymptomatic except for compression symptoms; do not recur or metastasize</td>
<td>Produce a wide range of late symptoms; frequently recur and metastasize</td>
</tr>
</tbody>
</table>
Epithelial Tumors
Epithelial Tumors

• Benign epithelial tumors
  – Papillomas
  – Adenomas

• Malignant epithelial tumors
  – Squamous cell carcinomas
  – Adenocarcinomas
  – Scirrhous carcinomas
  – Medullary carcinomas

• Semimalignant epithelial tumors
  – Basalioma
Papillomas

**Definition**: Broad-based superficial tumor of branching villous vascular stroma covered by neoplastic epithelium.
Papillomas

Types:

- Squamous cell papilloma (skin)
- Mucosal papilloma (oral cavity, nose, nasopharynx, and larynx).
- Papilloma of glandular excretory ducts (exocrine glands and breast)
- Urothelial papilloma (urinary tract)
A Papilloma of a lactiferous duct (HE) x 25

E Squamous cell papilloma (HE) x 25
NOTE!!!

All glandular, mucosal, urothelial papillomas and papillomas of excretory ducts should be regarded as potentially precancerous lesions.
Adenomas

**Definition**: Tumor arising from glandular, parenchymal, or mucosal epithelium and consisting of proliferative epithelial folds or tubules in or on a stroma.
Adenomas

**Solid Adenoma** (glandular organs)
The lesion is a nodular tumor with proliferation of glandular epithelium in a stroma. It is sharply demarcated from its surrounding tissue of origin and exhibits a smooth surface with a fibrous tumor capsule.

**Tubular Adenoma** (primarily in the intestinal tract).
The lesion is generally a pediculate, superficially smooth tumor nodule of proliferating epithelial tubules (a mucosal polyp) in the lumen of a hollow organ.

**Villous Adenoma** (primarily in the intestinal tract.)
The lesion is generally a broadbased tumor of epithelial villi on a highly vascularized stroma that projects into the lumen of a hollow organ. Its villous surface is easily injured, resulting in bleeding.

**Cystadenoma** (primarily in the ovaries and salivary glands.)
This ballooning tumor consists of epithelium that forms a hollow cavity due to stasis of a secretion. It has a smooth surface.

**Fibroadenoma** (primarily in the breast).
The lesion is a smooth nodular tumor of epithelial tubules that become compressed and folded as the stroma proliferates.
Solid

Tubular

Villous

Fibroadenoma
Epithelial Tumors

• Benign epithelial tumors
  – Papillomas
  – Adenomas

• Malignant epithelial tumors
  – Squamous cell carcinomas
  – Adenocarcinomas
  – Scirrhous carcinomas
  – Medullary carcinomas

• Semimalignant epithelial tumors
  – Basalioma
Squamous Cell Carcinoma

**Definition**: A collective term for carcinomas that mimic squamous epithelium, exhibiting filamentous eosinophilic cytoplasm, sharply demarcated cell borders, and often keratinization.

Tissue patterns in a squamous cell carcinoma range between two extremes according to the **degree of differentiation** of the tumor:

- **Highly Differentiated Forms**: exhibit layers of cells that tend to keratinize and form cornified clumps that are layered like an onion.
- **Undifferentiated Forms**: are polymorphic carcinomas with a high mitosis count that usually do not keratinize.
B Squamous cell carcinoma
(HE) x 150
Epithelial Tumors

- Benign epithelial tumors
  - Papillomas
  - Adenomas
- Malignant epithelial tumors
  - Squamous cell carcinomas
  - Adenocarcinomas
  - Scirrhous carcinomas
  - Medullary carcinomas
- Semimalignant epithelial tumors
  - Basalioma
Adenocarcinoma

**Definition:** Collective term for carcinomas of the mucosa or exocrine or endocrine glandular epithelium with formation of lumina within the tumor cell complex or lumina within the tumor cells themselves in the form of inner surfaces.
Adenocarcinoma

Highly Differentiated Forms

- **Acinic carcinoma**: The epithelium of the carcinoma exhibits a histologic tissue pattern resembling a glandular acinus.

- **Tubular carcinoma**: The carcinoma mimics glandular tubules. These tubules lie “back-to-back” due to slight stromal reaction.
Adenocarcinoma

Moderately Differentiated Forms

- **Cribriform Carcinoma**: The epithelium of the carcinoma exhibits a “gland in a gland” pattern resembling a sieve.
  - Examples: prostate carcinomas, and adenoid cystic carcinoma of salivary gland.

- **Papillary Carcinoma**: The epithelium of the carcinoma folds to form a tumor papilla.
  - Examples: bronchial, thyroid, and ovarian carcinoma
Adenocarcinoma

Mucigenous Carcinomas (mucin-producing carcinomas)

- **Mucinous carcinomas** produce massive amounts of mucin in the glandular acini of the tumor. This causes the acini to burst, creating extracellular deposits of a mucin and giving the cut section of the tumor a glassy, transparent appearance.

- **Signet-ring cell carcinomas** are undifferentiated carcinomas characterized by loss of intercellular cohesion with massive vacuolar accumulations of mucin in all the cells of the tumor. This produces a typical “signet ring” cellular deformation with peripheral displacement of the nucleus.
C Tubular adenocarcinoma
(HE) x 75

D Adenoid cystic carcinoma of the salivary gland
(HE) x 75

E Papillary ovarian carcinoma
(HE) x 75

F Papillary carcinoma of the bladder
Carcinomas of Specific Organs
Breast Carcinoma: Histologic Tumor Types

• Ductal Carcinoma
  – Ductal carcinoma in situ
  – Invasive ductal carcinoma

• Lobular Carcinoma
  – Lobular carcinoma in situ
  – Invasive lobular carcinoma
Breast Carcinoma: Ductal Carcinoma

70% of all cases

Histogenesis: Carcinoma arises from the epithelium of the lactiferous ducts, often as a multifocal lesion.

- **Ductal carcinoma in situ** is a tumor that initially spreads only within the lactiferous ducts. Within the ducts, the tumor issue disintegrates and develops central calcifying necroses that appear as radiographic “microcalcifications” in mammograms. The tumor detritus can be expressed from the duct like the contents of a blackhead. This is known as a comedocarcinoma.

- **Invasive ductal carcinoma** is a tumor that penetrates the basement membrane with duct-like epithelial strands several cells in width, stromal proliferation (scirrhous carcinoma), and microcalcification.
Breast Carcinoma: Lobular Carcinoma

Histogenesis: Carcinoma arises from the lobular terminal ducts (acini), usually as multifocal lesions.

- Lobular carcinoma in situ often arises as bilateral multicentric lesions. The tumor often initially spreads only within the lobules, and may do so for years. This leads successively to stasis of secretions and calcification.

- Invasive lobular carcinoma penetrates the basement membrane, producing strands of tumor tissue one cell in width along collagen fibers with tumor-induced stromal proliferation (scirrhous carcinoma).
E  Breast carcinoma

F  Paget’s disease of the nipple
Semimalignant Tumors

Definition: These are destructive, locally invasive tumors that rarely if ever metastasize

Examples: basalioma, ameloblastoma
Basal Cell Carcinoma

Definition: A semimalignant, locally invasive skin tumor of basaloid epidermal cells.

Morphology: The tumor arises from the basal layer of the epidermis as a roughly conical nodular arrangement of minimally polymorphic cells. The peripheral epithelial layer exhibits radial palisades interspersed with tumor-induced stroma.
Ameloblastoma

Definition: This semimalignant, locally invasive tumor of the jaw arises from vestiges of the odontogenic epithelium.

Morphology: The tumor lacks a capsule of connective tissue. It grows in a polycystic pattern and invades the medulla space of the mandible.

Histologic findings include a tumor consisting of complexes of columnar epithelium that form a peripheral palisade bordering the stroma and merge in the center with a reticulum resembling odontogenic pulpa.
Ameloblastoma
(HE) x 75