

**Introduction to Neoplastic Diseases (Part 1)**  
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## **LEARNING OBJECTIVES**

**At the end of this section you should be able to:**

1. Know the definitions and basic terminology of Tumor, Dysplasia, Neoplasia, Differentiation, Anaplasia
2. Describe the characteristics of/and differences between benign and malignant neoplasia based on biological behavior.
3. Understand the histogenetic classification of neoplasia
4. Understand the basic growth characteristics of neoplasms
5. Understand the basic role of angiogenesis in neoplasia

## **I. BACKGROUND AND SIGNIFICANCE OF CANCER**

### **A. What is Cancer?**

Cancer is a “lay” term describing malignant diseases. Cancer should not be thought of as a single disease but rather a group of diseases which may have many characteristics in common but not necessarily the same causative agents, etiology or molecular profiles. In general, cancer defines diseases that have the capacity to invade surrounding normal tissue, metastasize (spread to distant sites) and kill the host in which it originates.

### **B. Historical Perspective**

1. All multicellular organisms have the potential to develop cancer.
2. Probable bone tumors have been identified in fossils
3. A number of ancient civilizations recognized cancerous lesions and/or disease.
4. The incidence of total neoplasia (not necessarily every type of neoplasia) increases with age, therefore as the life-span of humans has increased the incidence of neoplastic diseases has also increased.

## **II. BASIC TERMINOLOGY**

**A. Tumor** - A swelling; could be due to any number of causes

**B. Dysplasia** - Alterations in size, shape and staining characteristics of cells in non-neoplastic tissue.

**C. Neoplasia** - A relatively autonomous growth of tissue; the growth of which exceeds and is uncoordinated with that of normal tissue and persists in some manner after cessation of the inducing stimulus.

1. Differentiation (of a neoplasm). Refers to the extent to which the cells comprising the neoplasm resemble comparable normal cells both morphologically and functionally.
2. Anaplasia. Denotes a lack of differentiation in a malignant neoplasm, making it difficult to determine the tissue or cell of origin.
  - a. anaplasia is evidenced by wide variety in size, shape, staining and organization of malignant cells within a neoplasm
  - b. anaplasia **is not** a characteristic of benign neoplasms

Neoplasms are derived from cells that have proliferative capability. In general, cells that are terminally differentiated can not divide and do not give rise to neoplasms.

### III. CLASSIFICATION OF NEOPLASMS

#### A. Based on Biological Behavior : Benign vs Malignant

Criteria	Benign	Malignant
1. Differentiation	Well-differentiated	Well to undifferentiated (anaplastic)
2. Growth limits	Limited, encapsulated	Unrestricted
3. Growth rate	Usually slow	Often rapid, but can be slow to moderate
4. Invasiveness	Non-invasive	Invasive, destructive
5. Metastasis	Non-metastatic	Metastatic
6. Mitotic figures	Rare	Sometimes numerous, atypical
7. Cell size&shape	Uniform	Pleomorphic (varied)
8. Nuclear to cytoplasmic ratio	Normal 1:4 to 1:6	Increased, disproportionately large 1:1
9. Stroma	Usually abundant	Often scanty
10. Cell orientation	Resembles normal	Disorganized, haphazard
11. Nuclear chromatin	Nearly normal amount	Hyperchromatic (abundant DNA staining darkly)
12. Blood supply	Adequate	Often inadequate thus areas of necrosis

The most critical criteria are invasion and metastasis. Metastasis is a secondary growth of a malignant neoplasm at a site distant from and non-contiguous with the primary neoplasm. By definition only a malignant neoplasm can metastasize. In general, neoplastic cells must first develop the capacity to invade before they can metastasize.

All tumors, benign and malignant have 2 basic components (1) proliferating neoplastic cells that constitutes their parenchyma and (2) supportive stroma of connective tissue and blood vessels. Although the parenchymal cells represent the proliferating edge and so determine the neoplasm's nature, the growth and evolution of a neoplasm are critically dependent on their stroma. An adequate stromal blood supply is necessary for parenchymal cell growth.

In general, there are criteria by which benign and malignant neoplasms can be differentiated and they behave accordingly. These differences can be discussed under the following headings: (1) pattern of differentiation and presence of anaplasia (2) rate of growth (3) local invasion and (4) metastases. It should be kept in mind, however, that all morphological diagnoses are subjective and predictive of the future course of the neoplasm. Occasionally, this prediction is confounded by a discrepancy between the morphological appearance and biological behavior of the neoplasm. The biological behavior is the ultimate criteria for diagnosis with the presence of invasion and/or metastasis unequivocally demonstrating malignancy.

## B. Histogenetic Classification (based upon cell/tissue of origin)

### NOMENCLATURE BASED ON HISTOGENETIC CLASSIFICATION

Tissue of Origin	Benign	Malignant
<b>Mesenchymal origin</b>	suffix-oma	Sarcoma
1. Connective Tissue a. Fibroblast b. Adipocyte	Fibroma Lipoma	Fibrosarcoma Liposarcoma
2. Endothelial Cells	Hemangioma	Hemangiosarcoma
3. Muscle a. Smooth b. Striated	Leiomyoma Rhabdomyoma	Leiomyosarcoma Rhabdomyosarcoma
<b>Epithelial Origin</b>	suffix-oma	Carcinoma
1. Stratified squamous	Squamous cell papilloma	Squamous or Epidermoid carcinoma
2. Other Epithelia ( some examples) a. Glandular b. Liver c. Transitional (urinary tract)	Adenoma Hepatocellular adenoma Transitional cell papilloma	Adenocarcinoma Hepatocellular carcinoma Transitional cell carcinoma
<b>More than 1 Cell Type</b> (derived from 1 germ layer)		
1. Salivary glands	Pleomorphic adenoma	Malignant mixed tumor, salivary gland origin
<b>More than 1 Cell Type</b> (derived from more than 1 germ layer- <b>Teratogenous</b> )	teratoma, dermoid cyst	Immature teratoma

## 1. Basic guidelines for histogenetic classification and terminology

a. If a neoplasm is malignant and was derived from epithelial cells then it is called a carcinoma.

b. Descriptors are added based on the tissue of origin and morphological pattern of the neoplasm. For example: a malignant neoplasm of the colon with a typical glandular morphological pattern is called a colon adenocarcinoma (adeno = glandular, carcinoma designating epithelial)

c. If a neoplasm is malignant and derived from stroma, supporting or nonepithelial (mesenchymal) cells it is called a sarcoma. For example, a malignant neoplasm of fibroblast origin is a fibrosarcoma.

d. The suffix –oma is usually applied for benign neoplasms. It is used for both epithelial and mesenchymal cells of origin. For example, A benign neoplasm of fibroblast origin is a fibroma. A benign neoplasm of epithelial cell origin in the colon is an adenoma.

## IV. Neoplastic Growth

How long does it take to produce a clinically detectable neoplasm ?

1. It can be readily calculated that it takes at least 30 population doublings to produce  $10^9$  cells (about 1 gram in weight) from a single, initial transformed cell. It then takes only about 10 population doublings to produce a neoplasm of  $10^{12}$  cells (weight about 1 Kg, which is the maximal size compatible with life).
2. By the time a solid neoplasm is clinically detected, it has already completed a major portion of its life cycle.
3. Total cell cycle time for neoplastic cells is equal to or longer than that for the corresponding normal cells.
4. The rate of growth of a neoplasm is determined by the proportion of cells in the growth fraction and the degree of imbalance between cell proliferation and cell loss. In the submicroscopic phases of neoplastic growth most cells are in the proliferative pool (growth fraction). By the time a neoplasm is clinically detectable most cells in a neoplasm are not in the growth fraction.
5. The growth fraction of neoplastic cells has a profound effect on their susceptibility to cancer chemotherapy.
6. The latent period before which a neoplasm becomes clinically detectable is quite unpredictably long, usually years.

## V. Angiogenesis and Neoplasia

An important mediator of neoplastic growth is blood supply. To grow beyond 1 to 2 mm in diameter a neoplasm must become vascularized.

1. Neovascularization has a dual effect on neoplastic cells. It supplies nutrients and oxygen and newly formed endothelial cells stimulate neoplastic cell growth by secreting polypeptide growth factors, such as IL-1, PDGF and insulin-like growth factor.

2. Angiogenesis is a necessary biological correlate of malignancy. Some research has demonstrated a correlation between the extent of angiogenesis and the probability of metastasis.

3. Neoplasms contain factors capable of affecting the entire series of events needed to form new capillaries. Two of the most important are vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF). These 2 factors are commonly elevated in a wide variety of different types of neoplasms. Elevated levels can be detected in the serum and urine of a significant number of cancer patients.

4. These factors are produced by neoplastic cells or be derived from inflammatory cells that infiltrate the neoplasms.

5. Neoplastic cells can also induce antiangiogenic molecules. Neoplastic growth is thus controlled by the balance between angiogenic and antiangiogenic stimuli.

6. Most human neoplasms are not angiogenic early in their life history. It has been hypothesized that mutations/decreased expression of critical tumor suppressor genes may act as a molecular switch since some tumor suppressor gene protein products are inhibitors of angiogenesis.

Sources . Robbins- Pathologic Basis of Disease, 6<sup>th</sup> edition. Cotran RS, Kumar V and Collins TC, eds. W.B.Saunders Company, Philadelphia, PA, 1999.