

# Pathobiology of Human Neoplasia: Introduction and Overview

Edward Gabrielson, M.D.

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The word “cancer” is perhaps the most feared word in our language. This is largely due to the aggressive nature of this disease, but also because so much is yet unknown about this disease.

This lecture will provide an overview of our current understanding of cancer, or more generally, neoplasia.

**Neoplasia** can be defined as a **clonal** proliferation of cells with **somatic** genetic alterations and aberrant regulation of growth. Some neoplasms do not seriously threaten the life of the individual, and these are commonly called “**benign**” neoplasms. On the other hand, **malignant** neoplasms (i.e., **cancers**) are characterized by the ability to **invade** into adjacent normal tissues and **metastasize** to distant tissues. Many neoplasms form masses (i.e., “**tumors**”), but some neoplasms, particularly pre-invasive (or *in situ*) neoplasms do not.

As an introduction to neoplasia, this first session will focus on 1) the morphological pathology of cancer, 2) the biologic properties of human neoplasia (particularly cancers), and 3) general aspects of cancer genetics..

## Pathology of Neoplasia

This section will focus on neoplasia from the perspective of the diagnostic pathologist. When pathologists evaluate tissues, a first level of decision obviously involves that of recognizing and diagnosing neoplasia. In addition, the pathologist is expected to classify the neoplasia with regard to tissue of origin, benign vs. malignant, and extent of malignancy. The lecture will use a number of cases to illustrate how anatomic features (including histology) remain the cornerstone in diagnosis of neoplasia. However, molecular methods are increasingly being used to complement pattern recognition in diagnostic pathology.

### *Pathology of Neoplasia*

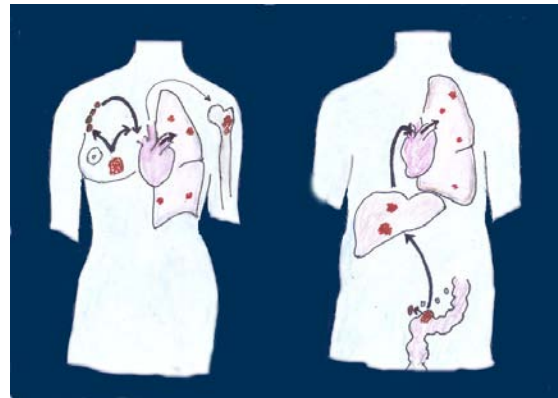
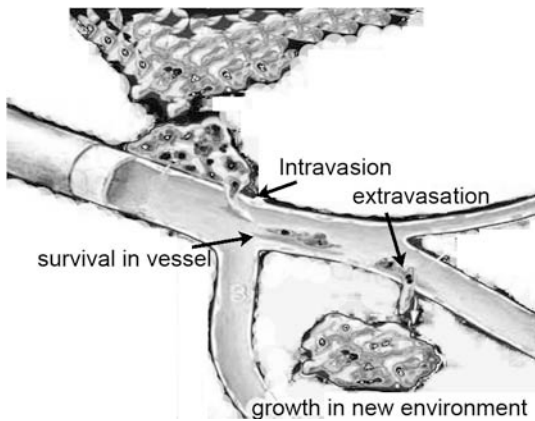
Remember, our contemporary definition of neoplasia is a clonal proliferation of cells with genetic alterations that confer dysregulation of growth characteristics. Yet, pathologists are routinely able to diagnose neoplasia – and classify neoplasms as benign or malignant - without molecular analysis of tissues. This diagnosis of cancer in the examination of tissues depends on recognizing architectural changes as well as cytological changes.

### ***Invasion and metastasis:***

“Normal” tissues are typically confined to grow within a specific compartment; for example, skin epithelial cells grow only in the epidermal layer of the skin, and colonic epithelial cells grow only in the mucosa of the colon. Furthermore, these normal tissues show organization within these compartments, with distinct patterns of maturation within the epidermis or within colonic crypts. By contrast, neoplasms virtually always show some disorder in these growth patterns, and in the case of malignant neoplasms, show growth of cells in a compartment that is not normally allowed for the particular cell type (i.e., invasion). Thus, squamous cell cancers of the skin show loss of the stratification that is seen in normal squamous epithelium and nests of these disorganized squamous cells infiltrating below the basement membrane that normally defines the epidermal layer. Similarly, colon cancers show disorganized growth of cells within the mucosa and infiltrating nests of these atypical cells into deeper layers of the colon.

While normal epithelial tissues generally reside in distinct layers, such compartmentalization is not so readily apparent for stromal tissues. Cancers that arise in stromal tissues (sarcomas) do have infiltrative appearances, though, which is important for determining the diagnosis.

In addition to invading into adjacent normal tissues, cancers frequently have the ability to spread to distant sites throughout the body. This property is known as *metastasis*. The morphologic appearance of metastatic growth of a cancer is that of the tissue of origin, rather than that of the metastatic site. Metastases do not develop randomly throughout the body – rather, the distribution appears to reflect the anatomy of lymphatic drainage for the tissue of origin. This cannot entirely explain the distribution of metastases, however, and the “seed and soil” concept for determining where metastases can grow has also developed. According to this concept, certain tissues have an environment that is receptive (soil) for the growth of particular tumor cells (seeds). Substantial clinical data supports the “seed and soil” concept; for example, large numbers of cancer cells can circulate without ever forming metastases, suggesting that tumor cells must acquire the ability to grow in a new environment before forming a metastasis. An additional barrier to forming metastases is the requirement of tumor cells to survive in the vasculature, where they are unattached to surfaces and must withstand shear stress. General issues related to formation of metastases are summarized below in figure 1.



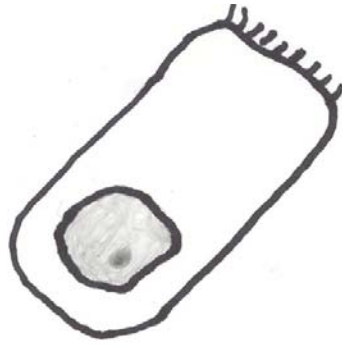
Obviously, any theory regarding mechanisms of metastases must fit clinical data. It is important, therefore, to recognize clinical patterns of metastases for various types of human cancers. Figure 2 summarizes patterns of metastases that are common for breast cancer and colon cancer. Our understanding of mechanisms of metastases will be discussed further in the Pathology of Cancer course.

### **“Benign” neoplasia**

Clinical experience has led the field to recognize that many neoplasms have minimal potential for invasion or metastases. Fortunately, these neoplasms can usually be distinguished based on their morphology, and are called “benign” neoplasms based on the expectation of this clinical course. The differentiation of benign from malignant tumors involves consideration of architectural features as well as cytological features. Benign tumors are generally well circumscribed and sometimes encapsulated. The architectural features used to diagnose malignancy, include local invasion and metastatic spread are not present in benign tumors. Furthermore, the cells of benign tumors often more closely resemble the normal cells of the tissue of origin.

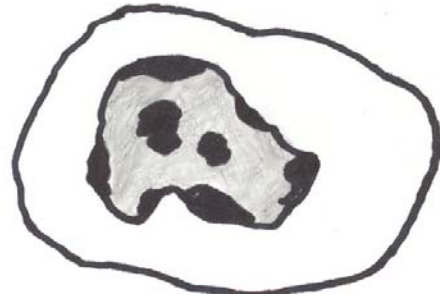
### **Cytological Characteristics of Cancer Cells**

In many situations, pathologists can rely on cytological characteristics of tumor cells to differentiate benign from malignant. It is important to recognize that the characteristics of benign and malignant cells diagrammed below are very general in nature, and rarely are all of the characteristics observed in any particular situation.



#### **Characteristics of benign cells**

Relatively low nuclear:cytoplasmic ratio  
 Round nucleus, even distribution of chromatin,  
 small or inconspicuous nucleoli  
 Maintenance of cellular polarity and  
 differentiation  
 Mitoses are uncommon, are located in usual  
 location (e.g., basal layer), and have typical  
 appearance



#### **Characteristics of malignant cells**

Increased nuclear size (high N:C ratio)  
 Irregular nuclear shape, irregular distribution of  
 chromatin, prominent nucleoli  
 Loss of cellular polarity and variable loss of  
 differentiation  
 Mitoses are common, located above basal cell  
 layer, and have atypical appearance.

It is important to recognize these are descriptive characteristics, not rules! Not all malignant cells have each of the characteristics listed above, and conversely, some of these characteristics typical of malignancy can be seen in benign conditions. For example, reactive epithelial cells in areas of inflammation can have many features that make them difficult to differentiate from malignancy. The accurate diagnosis of malignancy depends on the consideration of all features in the appropriate context.

The cytological characteristics of malignancy have become so well defined that cytopathology has emerged as an important subspecialty of pathology. This field first made an impact in the evaluation of exfoliated cells of the uterine cervix (the Pap smear). In contemporary practice of medicine, cytopathologists routinely diagnose cancer in small aspirated tissue samples.

#### ***Growth of Cancers and Clinical Staging***

The term “stage” is used to designate the extent of spread of a cancer. For almost all cancers, the stage is more influential than grade in predicting clinical behavior. (Often, though, grade and stage are correlated.) The most commonly used staging system is the American Joint Committee on Cancer (AJCC) system, also known as the TNM system. T stands for tumor (its size and the extent of spread into nearby organs), N stands for spread to lymph nodes, and M is for metastasis (spread to distant organs). In TNM staging, information about the tumor, lymph nodes, and metastasis is combined and a stage is assigned to specific TNM groupings.

The criteria used for particular TNM stages differ among various types of cancer, based on clinical experience. For example, the cut-off between T<sub>1</sub> and T<sub>2</sub> may be 2 cm for one organ and 7 cm for another.

Some examples of TNM staging are shown in the table below.

	<b>Breast cancer</b>	<b>Renal cell cancer</b>	<b>Lung cancer</b>
T <sub>0</sub>		No evidence of primary tumor	
T <sub>1</sub>	Primary tumor < 2 cm	Primary tumor < 7 cm	Primary tumor < 3 cm, does not affect pleura or main bronchus
T <sub>2</sub>	Tumor >2 cm, <5 cm	Primary tumor > 7 cm	Tumor > 3 cm or involves pleura or involves main bronchus
T <sub>3</sub>	Tumor > 5 cm	Tumor extends into renal veins or adrenal	Tumor involves chest wall or bronchus within 2 cm of trachea
T <sub>4</sub>	Tumor extends to chest wall or inflammatory ca.	Tumor invades beyond Gerota's fascia	Tumor involves mediastinum, trachea, or esophagus, or has pleural effusion
N <sub>0</sub>		No LN metastases	
N <sub>1</sub>	Metastases to same-side movable nodes	Metastases in single regional node	Involves ipsilateral hilar or peribronchial nodes
N <sub>2</sub>	Metastases to same-side fixed nodes	Metastases in > one regional node	Involves ipsilateral mediastinal nodes
N <sub>3</sub>	Metastases to internal mammary nodes		Contralateral spread
M <sub>0</sub>		No distant metastases	
M <sub>1</sub>		Distant metastases	

For clinical management, another level of staging (grouped staging) uses the number 0 and Roman numerals from I to IV (1 to 4). An example of grouped staging for lung cancer is outlined in the table below.

### Stage-specific survival for lung cancer

<b>Overall Stage</b>	<b>T Stage</b>	<b>N Stage</b>	<b>M Stage</b>	<b>5-year survival</b>
Stage 0	Tis (In situ)	N0	M0	
Stage IA	T1	N0	M0	47%
Stage IB	T2	N0	M0	
Stage IIA	T1	N1	M0	
Stage IIB	T2	N1	M0	26%
	T3	N0	M0	
Stage IIIA	T1	N2	M0	
	T2	N2	M0	8%
	T3	N1	M0	
	T3	N2	M0	
Stage IIIB	Any T	N3	M0	
	T4	Any N	M0	2%
Stage IV	Any T	Any N	M1	

### Pre-invasive (in situ) neoplasia and cancer progression

*In situ* neoplasia refers to an epithelial neoplasm that grows entirely within the normal tissue compartment for the cell of origin. This disease state is important, because we now recognize that some *in situ* neoplasms have the potential to develop into invasive cancers. For this situation we use the term “in situ carcinoma”, which is actually an oxymoron, since a neoplasm has to be invasive to determine that it is a cancer. Lesions recognized as *in situ* neoplasms characteristically have highly atypical cells and a disordered growth pattern within the epithelial layer. (This raises the interesting question of whether there are in situ cancers without such atypical features that cannot be recognized.)

The significance of *in situ* neoplasia is the well-established risk of progressing on to invasive cancer. Clinical experience has shown, for example, that *in situ* neoplasia of the uterine cervix can unequivocally progress on to invasive cancer, and the likelihood of this occurring is roughly proportional to the degree of atypia in the *in situ* neoplasia. (Note that historically, *in situ* neoplasia of the cervix was called “dysplasia” before molecular studies confirmed that these lesions are indeed neoplastic.) It is generally accepted that most (if not all) epithelial cancers arise through a series of steps that include *in situ* neoplasia, though many *in situ* neoplasms have low potential for invasion. One of the major clinical challenges that we face is that of accurately stratifying these *in situ* neoplasms according to their malignant potential.

### Classification and Nomenclature of Neoplasia

The general nomenclature used for neoplasia recognizes the pattern of differentiation (which typically reflects the tissue of origin) and whether the tumor is benign or malignant. (Note that some *in situ* neoplasms, such as adenomas of the colon, are classified as benign, although they do have a potential for progressing on to malignancy.) Thus, it is important to understand terms used to describe patterns of differentiation and to describe level of malignancy.

In most cases, benign tumours are named by attaching the suffix *-oma* to the name of the tissue or cell from which the cancer arose. For example, a benign tumour that is composed of cells related to cartilage (chondrocytes) is classified as a chondroma. Benign tumors derived from glandular epithelial cells are classified as adenoma. There are some important exceptions to this generalization; hepatoma, melanoma, and astrocytoma are all types of malignant tumors.

The suffix *-carcinoma* always refers to a malignant tumor of epithelial origin, and the suffix *-sarcoma* always refers to a malignant tumor of mesenchymal (stromal) origin. Hematopoietic neoplasms are classified as leukemia or lymphoma, depending upon whether the neoplasm manifests primarily in the circulation or in lymph nodes.

The five major **patterns of differentiation** are epithelial, mesenchymal, hematopoietic, melanocytic, and glial. Each of these major patterns of differentiation has multiple different sub-types of differentiation. For example, epithelial neoplasms can be classified as squamous, glandular (adeno), basal (or basaloid), transitional (i.e., urothelial), or undifferentiated. In addition, terms such as “papillary”, “cystic”, “polypoid”, or “mucinous” are often applied to describe the morphology of neoplasms.

Neoplasms are not classified based on embryological derivation; for example, although most mesenchymal tumors are from the mesoderm, some epithelial tumors (renal cell carcinoma, adrenal carcinoma, mesothelioma) are also derived from mesoderm.

We usually try to classify tumors as benign or malignant, and we know that most tumors classified as benign have minimal potential to progress to malignancy. However, for many organ systems, there are categories of neoplasms that have intermediate levels of malignant potential, and terms such as “low malignant potential” or “borderline tumors” are used to describe these neoplasms. One particularly important type of neoplasm that falls into this intermediate zone is carcinoid tumor. Carcinoid tumors are distinctive neoplasms with neuroendocrine differentiation, and they occur most commonly in the respiratory and digestive systems. Carcinoid tumors range from completely benign to moderately aggressive in terms of malignant behavior.

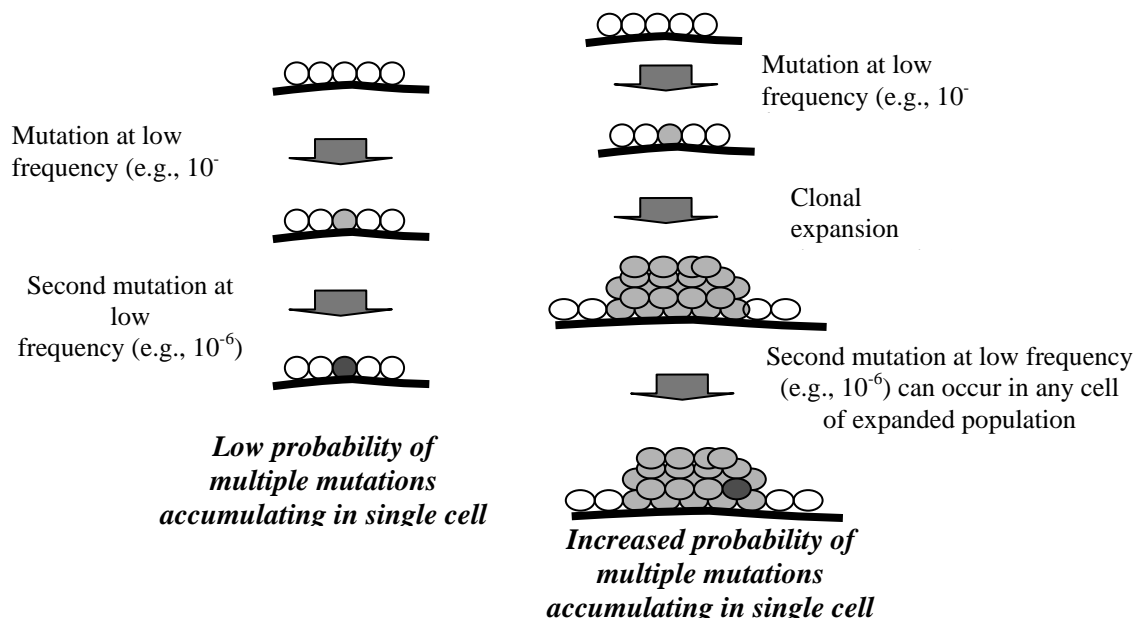
Unfortunately, the only way to learn the nomenclature of neoplasia is to memorize the names. The chart below lists nomenclature of some common human tumors.

Pattern of differentiation	Benign	Malignant
<b>Epithelial</b>		
Glandular/ ductal epithelium	Adenoma	Adenocarcinoma
Squamous epithelium	Squamous papilloma	Squamous cell carcinoma or epidermoid carcinoma
Liver	Hepatic adenoma	Hepatoma (a.k.a., hepatocellular carcinoma)
<b>Mesenchymal</b>		
Smooth muscle	Leiomyoma	Leiomyosarcoma
Adipocytes	Lipoma	Liposarcoma
Cartilage	Chondroma	Chondrosarcoma
Bone	Osteoma	Osteosarcoma
Endothelial	hemangioma	Hemangiosarcoma
<b>Melanocytic</b>	Melanocytic nevus	Melanoma
<b>Glial</b>		Astrocytoma, ependymoma, oligodendroglioma
<b>Hematopoietic</b>		Leukemia, lymphoma

Some tumors have multiple patterns of differentiation. Tumors with mixed epithelial and mesenchymal differentiation are known as fibroadenoma (benign) or carcinosarcoma (malignant). Teratoma is a tumor that involves more than one germ cell layer from pluripotential cells.

### Carcinogenesis, Cancer Development, and Growth of Cancers

1. *Clonal evolution and carcinogenesis.* Based on both histologic observations of early neoplasia and molecular studies of these lesions, we now understand that cancers arise as a result of clonal evolution. This means that a single cancer cell does not acquire all of its genetic alterations all at one time, but rather that sequential genetic changes are accompanied by clonal expansion of cells with selective advantages for growth or survival. For example, an initial mutation could result in a cell that has a proliferative advantage over neighboring cells, leading to clonal proliferation of cells with this same mutation. When a subsequent mutation to one of the progeny results in additional growth advantage, clonal expansion cells with this new complement of mutations could occur.

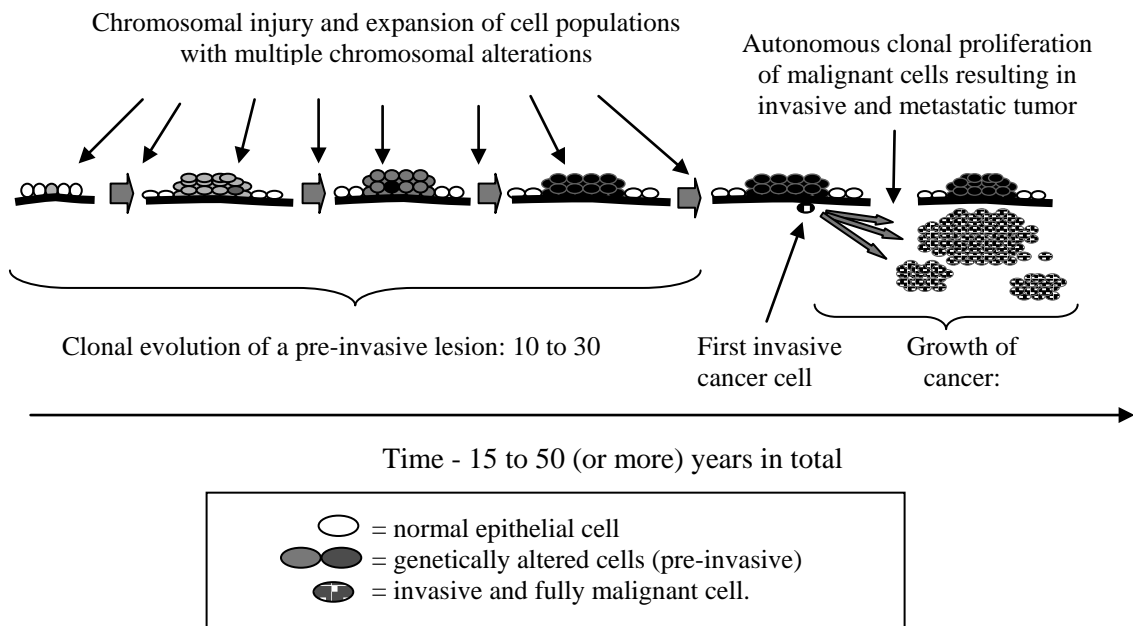


Clonal expansion of genetically altered cells (tumor promotion) increases probability of multiple mutations accumulating in an individual cell

Thus, the carcinogenesis process has **non-genetic** as well as **genetic** components. The process whereby genetically altered cells are stimulated to divide is known as tumor promotion. Tumor promotion may be intrinsic (i.e., the early genetic alteration changes the cell to a more rapidly growing phenotype) or extrinsic (an external stimulus may result in greater rate of cell division). Note that injury to tissue probably has tumor promoting effects because injury stimulates cell division for tissue repair. The importance of the **tumor promotion** process in contributing to the carcinogenesis process is summarized in the figure above.

The concept of tumor promotion is discussed in the Robbins text in the context of the mouse skin model of multistep carcinogenesis. In this model, recognized steps of carcinogenesis are initiation, promotion, and conversion. Initiation refers to an irreversible alteration of DNA (i.e., mutation). Initiators are genotoxins. Promotion refers to stimulation of the initiated cell to clonally proliferate (i.e., neoplasm). In most cases, mouse skin tumors that form after the sequence of initiation/ promotion are benign tumors (note that Figure 8-41 of the Robbins text designates the outcome as “tumors”, not as “cancers”). The frequency of conversion of benign to malignant tumors is greatly increased in this experimental model by applying a genotoxin (initiator) to the benign tumors. The mouse skin model would imply that only two mutations are required to produce the malignant phenotype, but human cancers clearly require more than two mutations. Mouse chromosomes appear to be less stable than human chromosomes and perhaps a number of genetic changes occur spontaneously in mouse skin carcinogenesis.

2. *Growth of human cancers.* As emphasized above, human cancer cells have multiple genetic alterations, and arise as a result of a complex process that includes clonal expansions of cells as well as multiple mutations. Pathologists have long observed non-invasive lesions with cells that have the atypical features of neoplastic cells. Through a combination of morphologic and molecular studies, we now understand these lesions to be early forms of neoplasia, with a potential to evolve into malignant (e.g., invasive) neoplasms. The general paradigm that links the clonal selection concept of carcinogenesis with histologic observations of *in situ* neoplasia is summarized in the figure below.



It is not surprising that the pathogenesis of cancer is a prolonged process. Furthermore, a cancerous tumor arises from a single malignant cell, and a long period of time is usually required for a tumor to grow to a size where it is clinically relevant. These factors contribute to a long “latency period” from the time that injury

occurs at the cellular and molecular level until a cancer grows to a clinically relevant size (as noted in the figure above).

Examples of *in situ* neoplasia have been well characterized in studies of the uterine cervix, endometrium, breast, prostate, respiratory epithelium, colon, liver, and pancreas. In general, lesions with the greatest extent of nuclear atypia are called “carcinoma *in situ*”, and lesions with less nuclear atypia have been called “hyperplasias”. (Note that the term hyperplasia is probably misused in situations such as this: these early forms of neoplasia are clonal, whereas true hyperplasia is polyclonal.) Early neoplasms with intermediate degrees of nuclear atypia are classified as “dysplasia”.

Recognizing the early lesions clinically is of great importance. For example, cytologic examination of cervical cells - and treatment of early lesions - has resulted in a dramatic decrease in mortality due to cervical cancer. Not all early neoplasias will develop into invasive cancers. In general, the probability of an early neoplastic lesion developing into an invasive cancer increases with the pathologic grade of the lesion. For example, an untreated severe dysplasia of the cervix is more likely to develop into invasive cervical cancer than an untreated mild dysplasia. Similarly, an untreated adenomatous polyp of the colon that has atypical features (and has more genetic alterations) is more likely to develop into invasive cancer than an adenomatous polyp without atypical features. The significance of early lesions in specific tissues will be covered more extensively in lectures devoted to organ systems.