Cancer: Foundations and Frameworks

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Learning Objectives (3)

After completing this brick, you will be able to:

1. Define metaplasia and dysplasia, and explain the clinical significance of both.
2. Explain the concept of tumor cell differentiation, and define anaplasia.
3. Describe the main difference between benign and malignant tumors.

we use the word to describe only neoplastic masses of tissue. In this brief, we'll use the terms tumor and neoplasm interchangeably.

What does the term neoplasm describe?

What's the Difference Between Benign and Malignant Tumors?

There are two kinds of tumors:

- Benign tumors do not have the ability to metastasize (spread) to other tissues. In general, benign tumors tend to be smaller and grow more slowly than malignant tumors. Benign tumors are usually surrounded by a capsule, making them more surgically removable and leading to a better prognosis.
- Malignant tumors (cancerous tumors) are those that can invade tissues or spread to other parts of the body. The potential for metastasis is a characteristic feature of a malignant tumor. Malignant tumors usually do not have a capsule and often have a worse prognosis.

These are generalizations, but the core defining feature of a malignant tumor is that it can metastasize, while benign tumors do not metastasize. However, just because benign tumors do not metastasize, that does not mean that they cannot be life-threatening. For example, a meningioma is a benign tumor of the meninges that can compress brain tissue and cause neurological problems such as seizures, paralysis, and changes in vision. Benign brain tumors in particular are dangerous because of the limited space in the skull.

Table 1 summarizes tumor terminology.

Table 1

Term	Definition
Neoplasm/tumor	A new and abnormal growth of tissue in the body
Invasion	Local growth of a tumor into surrounding tissue
Metastasis	Spread of a tumor to distant sites in the body
Benign	Describes a localized tumor that does not metastasize
Malignant	Describes a tumor that may metastasize; may be resistant to treatment and recur after removal

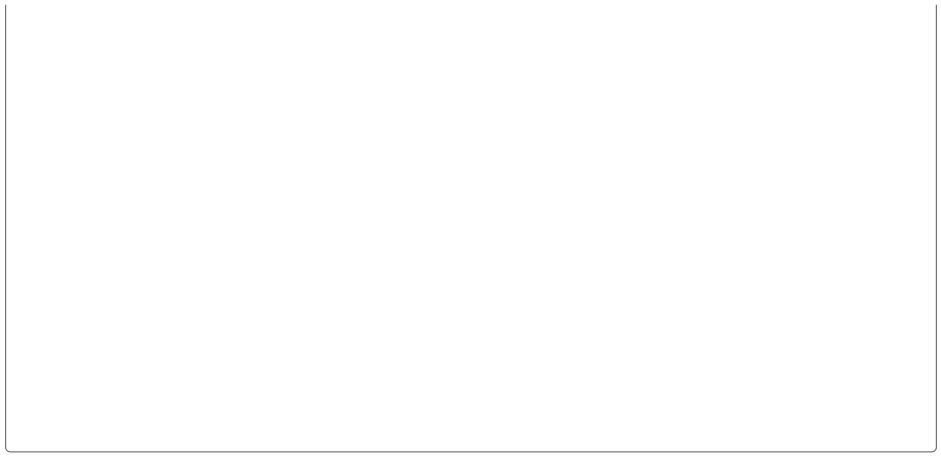
How can a benign tumor be harmful?

What Is Tumor Differentiation?

The term “tumor differentiation” has a very specific meaning that might seem a little counterintuitive at first. Let’s start with some definitions, and then we’ll clear up some common misconceptions.

The differentiation of a tumor refers to the degree to which the tumor cells resemble their normal cell counterparts (the cells from which they originated). Well-differentiated tumors are composed of cells that look very much like their cell of origin. Poorly differentiated tumors are composed of cells that bear very little resemblance to their cell of origin.

Figure 1 shows a well-differentiated squamous cell carcinoma. The tumor cells are polygonal and have a lot of eosinophilic cytoplasm, like normal squamous cells. There’s a little piece of normal stratified squamous epithelium in this biopsy specimen that you can use for comparison.

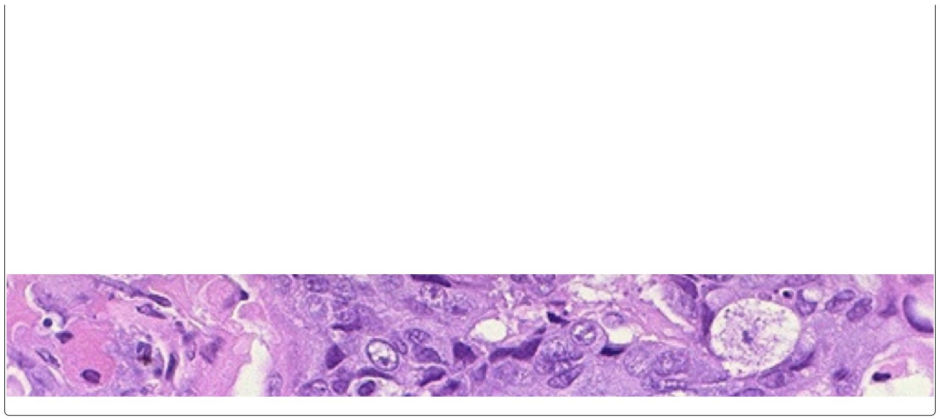


QUIZ

Tap image for quiz

Figure 1

Figure 2 shows a poorly differentiated squamous cell carcinoma composed of cells that show very little resemblance to normal squamous cells. Like most poorly differentiated tumors, the cells in this image are pleomorphic (vary in size and shape), with hyperchromatic (dark-staining) nuclei and an increased nuclear-to-cytoplasmic ratio.



QUIZ

Tap image for quiz

Figure 2

Our use of “differentiation” here might seem a little backwards at first. After all, wouldn’t well-differentiated tumor cells look significantly different from their cell of origin?

This is such a common point of confusion that it’s worth spending a little time on it. Using “differentiation” this way when we’re talking about tumors has to do with the way we use that word to describe normal (non-neoplastic) cells. When we’re talking about normal cells, differentiation refers to the presence of unique, characteristic features in a particular type of cell.

Take red blood cells (RBCs), for example. At their youngest, RBCs are virtually indistinguishable from other very early hematopoietic cell precursors. But as they mature, these cells learn how to make hemoglobin, and they develop an unusual cytoskeletal structure that gives the cell its characteristic biconcave disc shape. This process of acquiring the characteristics of a mature cell is called differentiation. Very young RBCs are said to appear undifferentiated, and mature RBCs are differentiated.

With that in mind, it makes a little more sense to use well-differentiated to describe a tumor that looks very much like its tissue of origin and poorly differentiated to describe tumor cells that seem to have none of the characteristic features of their normal counterpart cells.

Clinical Implications

Why do we care whether a tumor is well-differentiated or poorly differentiated? In general, poorly differentiated tumors are more aggressive and have a worse prognosis compared with well-differentiated tumors. This is an important characteristic that can be identified by pathologists and is critical in the grading of tumors.

An **anaplastic tumor** does not resemble its tissue of origin at all. The cells have none of the characteristics of their normal counterparts, and it’s impossible to tell what types of cells they are just by looking at them. Anaplastic tumors are composed of undifferentiated cells (cells that don’t show any characteristics pointing toward a particular cell type). On the differentiation spectrum, anaplastic tumors are at the extreme far end, past poorly differentiated tumors.

Anaplastic tumors tend to be composed of cells that are very strange looking (they may be gigantic, contain multiple nuclei, or have huge nucleoli). These odd-looking cells are often called anaplastic. If you never learned the true definition of the term, you might think that anaplastic just means bizarre-looking, and this of course is not the case.

In general, benign tumors tend to be well-differentiated, and malignant tumors can be anywhere on the spectrum of differentiation (from well-differentiated to anaplastic). It is important to know where a malignant tumor falls on the spectrum because well-differentiated malignant tumors tend to have a better prognosis than poorly differentiated or anaplastic malignant tumors.

CLINICAL CORRELATION

Tumor grading is a useful histological tool that incorporates the degree of differentiation of a cancer, among other things. There are specific grading systems for specific cancers, such as the Gleason grading for prostate cancer. Note that tumor grading is not the same as cancer staging. The grade of a tumor refers to the way a tumor looks under the microscope, and the stage of a tumor refers to its size and the degree to which it has spread (metastasized).

INSTRUCTOR NOTE

Very important concept

MARIA PLUMMER

What are three histological characteristics of poorly differentiated tumor cells?

What Is Metaplasia?

TRUCTOR NOTE

This is a review from the Cellular Adaptation session

MARIA PLUMMER

The term metaplasia is based on the Greek word metaplassein, which means to mold into a new form. Metaplasia refers to the replacement of one cell type by another, for example, the replacement of squamous epithelium with columnar epithelium (Figure 3). It's important to note that the cells don't actually change from one type to another. Instead, the change occurs at the stem cell level; instead of producing the normal cell type, the stem cells start producing cells of a different type. Metaplasia

often occurs as an adaptive change in response to repeated or chronic cell stress. Typically, it is reversible, meaning that if the stressor is removed, the cells can revert back to their original type.

Figure 3

Two classic examples of metaplasia are airway epithelial metaplasia and Barrett esophagus. In airway epithelial metaplasia, the pseudostratified columnar epithelium of the airways undergoes squamous metaplasia in response to irritants such as cigarette smoke.

In Barrett esophagus, the squamous epithelium of the esophagus is damaged by chronic gastric exposure from acid reflux. Over time, the esophageal squamous epithelium is replaced by columnar epithelium, which secretes protective mucus as a compensatory measure. Figure 4 shows both normal esophageal squamous epithelium and the metaplasia with goblet cells in the glandular epithelium. While initially reversible, a small number of cases of Barrett esophagus can develop into esophageal adenocarcinoma if untreated.

QUIZ

Tap image for quiz

Figure 4

What Is Dysplasia?

The word dysplasia literally means disordered (dys) growth or formation (plasis). Dysplastic cells look abnormal. They can show various types of morphologic changes, including:

- Pleomorphism
- Hyperchromatic nuclei
- Irregularly shaped nuclei
- High nuclear-to-cytoplasmic ratio
- Loss of polarity (lack of distinction between the top and bottom of the cell)
- Disorderly architecture (for example, cells piling on top of each other instead of sitting in a neat row)

Why do we pay attention to dysplastic changes in non-neoplastic cells? Because dysplasia often precedes cancer. In cancers of epithelial tissue (squamous cell carcinoma and adenocarcinoma), cells often show dysplastic changes long before they turn into cancer cells.

There is a spectrum of dysplasia: mild, moderate, and severe. Let's take a look at an example. Figure 5 shows a section of stratified squamous epithelium from a cervical biopsy. The epithelium on the far left is normal in appearance, but the remaining epithelium shows varying degrees of dysplasia. The mildly dysplastic region contains a few large cells with hyperchromatic nuclei but otherwise looks quite similar to normal epithelium. The severely dysplastic region, however, has lost all architectural structure; the cells are pleomorphic and show no polarity.

QUIZ

Tap image for quiz

Figure 5

Why does it matter how "bad" the dysplasia is? Because the degree of dysplasia is directly correlated with the likelihood of developing cancer. Sometimes, dysplasia disappears and the cell reverts to normal, never progressing to become cancerous. This is especially true for cells that are mildly dysplastic. However, once dysplastic changes become severe, chances are very high that cancer will follow.

The Papanicolaou (Pap) smear is based on the fact that dysplasia precedes cancer. Cells from the cervix are removed with a swab and examined under the microscope for dysplastic changes. If severe dysplasia is present, the patient can undergo a separate procedure to remove the dysplastic epithelium, preventing cancer from developing.

There is a stage after severe dysplasia called carcinoma in situ (CIS). In situ is Latin, meaning in its original place. In CIS, the cells are cancerous, but

they are pre-invasive: they have not broken through their basement membrane and penetrated the underlying tissue. CIS is the very earliest stage of cancer, also referred to as stage 0. Removal of a cancer at this stage is curative because the tumor has not metastasized.

TRUCTOR NOTE

This is an important concept

MARIA PLUMMER

How does metaplasia differ from dysplasia?

CASE CONNECTION

BACK TO INTRODUCTION

Thinking back to TF, how do you explain these results to her?

Your intent is to reassure TF quickly so you say, "It's benign." She responds, "I have no idea what that means. Is it cancer?" You explain that a uterine fibroid is the growth of uterine muscle but that it is not cancer. "Benign means that the growth is localized, in your case the growth of uterine smooth muscle cells, and that it will not spread or metastasize to other parts of the body." You explain that the fibroid can be removed for symptoms. Because of persistent pain and bleeding, TF opts for surgery, which she tolerates well without postoperative complications.

Summary

- The defining feature of a malignant tumor is its ability to metastasize, or spread to the rest of the body.
- Tumors range from well-differentiated to poorly differentiated to anaplastic.
- Well-differentiated tumors tend to grow slowly and have a better prognosis than poorly differentiated tumors.
- Histologic features of poorly differentiated tumors include pleomorphism, hyperchromatic nuclei, and a high nuclear-to-cytoplasmic ratio.
- Metaplasia is the replacement of one cell type by another.
- Metaplasia is often an adaption to some type of chronic damage to tissue, such as in Barrett esophagus.
- Dysplasia is the disordered growth of non-neoplastic epithelial cells characterized by morphologic changes such as pleomorphism and hyperchromatic nuclei.
- Both metaplasia and dysplasia are reversible but in some cases precede cancer.