Unit 4: Where are we heading?

Unit 1: What is cancer and why should we care?
Unit 2: What does it mean to be a 'normal' cell?
Unit 3: How do normal cells become cancerous?
Unit 4: How does cancer make us sick?
Unit 5: How is cancer diagnosed and treated?

In Unit 4 we’ll take a step back and a broader approach to looking at cancer as a disease.

Lesson 4.1 will explore the difference between benign and malignant tumors and give you the opportunity to learn how to differentiate between them. Lesson 4.2 grapples with the concept of metastasis - that is that tumors often don’t stay in one place but migrate in the bloodstream to find new homes. Lesson 4.3 investigates what factors a migrating, metastatic cell needs in order to settle into a site and form a secondary tumor. Lesson 4.4 explores the role of the immune system in tackling and neutralizing more than 95% of cancers before we are even aware of them!
LESSON 4.1 WORKBOOK

What is cancer?

In the previous two units we have examined the mutations that cause cell behavior to become abnormal so that cells hyper-proliferate, become immortal and form tumors. But tumor formation is only the first stage in developing cancer, and not all tumors will become malignant. For a benign tumor to cause disease it needs to acquire the ability to migrate beyond the site where it initially developed. In this lesson we will begin to explore how a benign tumor becomes malignant, and the rest of this unit will focus on cancer as a disease.

From benign to malignant: what is cancer?

We have seen how cells in normal tissue interact as a community. But if a cell acquires mutations that affect critical proteins such as proto-oncogenes and tumor suppressors it turns its back on its community and becomes unresponsive to regulatory signals. Instead it starts to hyper-proliferate and becomes immortal. The primary tumor that forms as a result is called a focal tumor because it is confined to a specific place, usually within the epithelium. Focal tumors may be large but while they are confined to the epithelium and don’t cause disseminated symptoms of disease they are considered benign.

For instance, the salivary gland tumor depicted in Figure 1 is very large and unattractive and probably quite uncomfortable to live with, but because it is confined within the salivary gland epithelium it is considered benign. If cells in a benign focal tumor acquire additional mutations that enable them to spread beyond the epithelium into the stroma they are considered malignant and are able to cause disseminated symptoms. The ability of tumors to spread beyond the stroma into the bloodstream and lymph and to secondary organs is known as metastasis.

Because of this definition even a tiny tumor, like that depicted in Figure 2, is considered malignant because it has spread into the stroma and will be able to cause metastasis.
LESSON READINGS

Melanoma – A malignant tumor of the skin that is often asymmetrical and multicolored.

Mole – A focal tumor of the skin

Cancer grade – a classification system that characterizes cancer cells based upon how similar they look to their normal counterparts.

Cancer stage – a classification system that describes the extent to which a tumor has spread.

Disseminated symptoms. We know that the transformation from benign, focal skin tumor (called a mole) into a malignant, metastasized tumor (called a melanoma) has occurred because of changes in the tumor’s appearance: Benign moles are most often symmetrical and evenly colored, while malignant tumors, like the one in Figure 2 are asymmetrical and multicolored even if they are small. The purpose of Figures 1 and 2 are to emphasize the point that the size of the primary tumor does not correlate with the severity of the disease it may cause. The important characteristic is whether or not the tumor has acquired the ability to spread.

**As tumors transform into cancer: grade and stage**

Clearly not all tumors are visible on the surface of the body, so we need another way to identify whether a primary tumor is benign or malignant. Two main criteria are used clinically: tumor grade and stage.

A tumor’s grade depends on the appearance of the tumor cells themselves. As we have learned, tumors occur when cells abandon their normal functions and proliferate uncontrollably. As they do this they also abandon their normal appearance. For instance different kinds of epithelial cells have different appearances that reflect their different functions in the body. Once epithelial cells start to form tumors they lose these distinctive shapes and become much more like cells that have not fully differentiated. The grade of a tumor therefore reflects how different the cells in the tumor are from normal cells. Hence cells in a high-grade tumor will have changed so much in size and/or shape that they don’t look normal at all. Grading scales vary depending on the tumor in question. For example breast tumors are graded on a 1-3 scale with a grade 1 indicating a focal tumor and a grade 3 indicating that the cells look so abnormal they probably have acquired the potential to spread to other tissues and cause disease. A diagnosis of grade 4 is made when evidence that the tumor has spread has been found. In contrast prostate tumors are graded on a 2-10 scale, but using the same principle – low looks more normal, high looks most abnormal.

**Figure 2:** This is a skin cancer. Its characteristics indicate that it has acquired the capacity to metastasize to surrounding tissue.

**Figure 3:** A tumor’s grade defines how different the cells have become from normal cells. Grade 1 are most normal, while higher-grades look more abnormal.

**MC Questions:**

2. True or False: It is impossible to tell whether a tumor is benign or malignant.
   a. True.
   b. False.

3. Which of the following is characteristic of a cancerous tumor?
   a. High stage.
   b. Symmetrical tumor.
   c. Low grade.
   d. All of the above.
LESSON READINGS

A tumor’s stage depends on how much the tumor has spread to surrounding tissues. Again the scale reflects the extent to which spread has occurred, generally within a 5-point system. Stage 0 and Stage I are therefore focal, benign tumors that have not spread into surrounding tissues. Stage II tumors have begun to spread into the stroma. Stage III are more metastatic, and have spread through the blood/lymph to nearby lymph nodes, while Stage IV tumors have also spread beyond the lymph nodes to other organs.

Both stage II and stage IV are considered malignant. We will explore the importance of spreading to lymph nodes in the next few lessons.

It is worth noting that while bigger tumors are more likely to have acquired enough mutations to spread, very small tumors can also metastasize, as you may remember from the Steve Jobs lesson. It is when the spreading starts, and where tumor spreads to that determines the extent that a cancer will cause disease, not the size of the primary tumor.

Cancers that have a high grade and that are at Stage III or Stage IV are the most difficult to treat, as we shall see in Unit 5.

But low grade and stage tumors present their own problems, since the appearance of the tumor itself is not enough for us to predict when or even whether that tumor will become metastatic in the future. Hence leaving a low-grade/stage tumor in place in the hope it will never metastasize can be a successful strategy when a tumor is known to grow slowly, as prostate tumors do, but may cause problems when a tumors mutates rapidly.

**Tumors, cancer and disease: local and systemic symptoms**

Even a benign tumor can cause local symptoms if it is large enough, but as it becomes malignant and begins to metastasize it can cause symptoms well beyond the area in which the tumor first arose.
**LESSON READINGS**

Purely localized symptoms will initially entail:

- Formation of a ‘lump’ (like the salivary gland tumor in Figure 1) as the tumor starts to grow.

Then as the tumor becomes malignant and invades the stroma the symptoms might include:

- Pain where the ‘lump’ presses on nerves in the stroma.
- Bleeding (If the pressure of the ‘lump’ causes blood vessels in the stroma to break).

If the tumor metastasizes, bleeding can become more generalized and cause:

- Impaired blood flow to vital organs.
- Loss of energy when the bleeding is really excessive.

The symptoms a tumor causes will depend on where the tumor first formed and where it has metastasized. Tumors from epithelial cells, which line tubes that run through the body will block the activity of that area of the tube and if they grow large enough sometimes disrupt the function of the entire organ. For example, tumors of the epithelia of the gastrointestinal tract such as the stomach and colon are often associated with weight loss and a loss of energy. This maybe because food processing itself has been blocked, or because the presence of the tumor leads to a feeling of fullness that causes decreased appetite. Together these symptoms lead to Cachexia.

In the case of pancreatic cancer, weight loss observed is caused by blockage of bile ducts, which are responsible for secreting bile, a fluid important for digestion (you may remember bile as “yellow bile” from Galen’s work). Blocking bile secretion prevents digestion and also leads to anorexia.

Damage to the liver or gall bladder prevents them disposing of old blood cells and leads to jaundice, a yellowing of the skin and mucous membranes.

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**MC Questions:**

6. When is cachexia likely to be seen? (Circle all correct.)
   a. In a large focal tumor.
   b. In a small focal tumor.
   c. In an extensive metastasis.
LESSON READINGS

Tumors of the lungs impair breathing, often leading to coughing. Unfortunately, coughing can be due to many causes (such as inhaling toxic environmental chemicals such as cigarette smoke). Because of this lung cancer is often difficult to diagnose.

Because the brain controls so many bodily functions tumors in the brain can have many different effects on function and behavior. Symptoms are usually caused by the pressure the growing tumor exerts in the closed environment of the skull and may range from general headaches to very specific symptoms that relate to where the tumor is located, such as:

- Double vision
- Trouble speaking
- Trouble moving

Symptoms are not even necessarily physical. Again depending on where the tumor is located typical symptoms are emotional problems and memory loss.

One interesting case of a brain tumor's unusual symptoms involved a man imprisoned on charges of child molestation. Before his arrest he had been hospitalized with frequent severe headaches. Eventually, his doctors discovered an egg-sized tumor in the part of his brain responsible for impulse control and social behavior. After the doctors removed the tumor, his behavior returned to normal until the tumor began to regrow, at which time he began to exhibit the antisocial behavior he had displayed before. While behavioral disorders are not always related to brain tumors, tumors often cause unexpected symptoms.

MC Questions:

7. Why is it often hard to diagnose lung cancer at early stages?
   a. There are no good diagnostic tools.
   b. Coughing symptoms are present in cancer and in 'healthy' people.
   c. Lung cancer doctors are not paid well.
   d. All are reasons.

8. Which of the following are NOT disrupted by brain tumors?
   a. Memory.
   b. Behavior.
   c. Speech.
   d. All are disrupted.
Describe the relationship between cancer grade/stage and disease. What distinguishes the type of symptoms caused by benign tumors from those caused by malignant tumors?
### TERMS

<table>
<thead>
<tr>
<th>TERM</th>
<th>DEFINITION</th>
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<tbody>
<tr>
<td>Bile</td>
<td>A fluid produced by the liver that aids in the digestion of lipids.</td>
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<tr>
<td>Bile ducts</td>
<td>Tubes that move bile from the liver to the intestine.</td>
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<tr>
<td>Cachexia</td>
<td>Loss of weight, muscle atrophy, fatigue, significant weakness or significant loss of appetite in someone who is not actively trying to lose weight.</td>
</tr>
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<td>Cancer grade</td>
<td>A classification system that characterizes cancer cells based upon how similar they look to their normal counterparts.</td>
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<td>Cancer stage</td>
<td>A classification system that describes the extent to which a tumor has spread.</td>
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<tr>
<td>Focal Tumor</td>
<td>A tumor that is localized to a specific part of an organ.</td>
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<tr>
<td>Hyperproliferation</td>
<td>The rapid growth of cells.</td>
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<td>Jaundice</td>
<td>Yellow color of the skin, mucus membranes or eyes caused by bilirubin a byproduct of old red blood cells that cannot be broken down properly by the liver.</td>
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<tr>
<td>Lymph nodes</td>
<td>Organs of the lymphatic system that collect and process lymph fluid from nearby organs.</td>
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<td>Melanoma</td>
<td>A malignant tumor of the skin that is often asymmetrical and multicolored.</td>
</tr>
<tr>
<td>Metastasis</td>
<td>The spread of malignant tumor cells to other parts of the body through blood/lymph vessels.</td>
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<td>Mole</td>
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For a complete list of defined terms, see the [Glossary](#).