Unit 5: 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 do we treat cancer?

In Unit 5 we’ll look at how we diagnose and treat cancer and the challenges and opportunities for designing better screens and treatments in the future.

Lesson 5.1 will explore the difference ways in which tumors can be detected. Lesson 5.2 grapples with the limitations of these screens and what they can and can’t tell us. Lesson 5.3 investigates the different methods of treating cancer that are commonly available and allows you to discuss their strengths and weaknesses. Lesson 5.4 follows the patients you studied in the previous lesson to investigate how effective cancer treatments really are, and what other options for care exist. Lesson 5.5 brings us into the 21st century - what would an effective treatment for cancer look like and how close are we to having one? Lesson 5.6 takes a big step back to review the whole module. The war on cancer has cost us nearly $100 billion dollars over 50 years. What were the challenges, could they have been foreseen? Did we get our money’s worth? You decide!
LESSON 5.1 WORKBOOK

How do I know if I have cancer?

In the previous 4 units we have learned about how cancer occurs, its pathology of cancer. But no investigation of cancer will be complete without an understanding of how it is diagnosed and treated. It will not be surprising that cancer is best treated when it is detected early, but every detection method has strengths and weaknesses.

In this lesson we will begin to explore the methods used to diagnose cancer, and their strengths and weaknesses.

Detecting and diagnosing cancer: Self examination

In the last several units we have learned that 90% of deaths from cancer are due to metastasis. Clearly we need to identify a cancer before metastasis occurs. But we have also learned that metastasis can occur very early after a primary tumor becomes malignant. Clearly we also need to be able to identify which primary tumors are likely to become malignant. These two critical problems in tumor detection — ‘Which tumors will become malignant?’ and ‘When will a malignant cancer metastasize?’ — must be solved if we are to treat cancer effectively. Unfortunately each tumor behaves very individualistically: A tumor acquires mutations randomly, so while we can define the route a tumor must take to become malignant, we cannot predict the order in which the mutations will occur. This means that a tumor might have mutations that allow it to enter the bloodstream even before it acquires mutations that allow it to break through the basement membrane and become malignant. In this case it will be primed and ready to metastasize as soon as it becomes malignant — maybe this happened to Steve Jobs’ pancreatic tumor. Another benign tumor may never experience the selective pressure that favors metastasis, so may remain benign or even if it turns malignant it may stay localized. Because we can’t design a ‘recipe book’ for how tumors will behave, our best option is to detect all tumors as early as possible.

Detecting the tumor in the first place needs to be individualized too: Each person is a unique combination of appearance and behavior, and only they know what is normal for themselves, and therefore which changes are just part of the normal ups and downs of day to day life and which might need to be

MC Questions:

1. Why is it important to identify cancer at an early stage?
   a. The tumor is small.
   b. To prevent the tumor turning malignant.
   c. To prevent the tumor metastasizing.
   d. To reduce symptoms.
DEFINITIONS OF TERMS

Self-examination – the practice of checking one’s to establish normal conditions and then identify any abnormal changes.

Mole checks – Self-examination of moles on the skin to identify changes in appearance that might indicate malignant changes.

Screening program – any recommended test that is performed on a regular basis with the purpose of identifying cancers at an early stage.

Baseline – The normal status of an organ or body without any detectable changes.

For a complete list of defined terms, see the Glossary.

LESSON READINGS

investigated further. Does that mole look different than it did before? How long has that cough been lingering? Are any changes persistent?

Physicians recommend that individuals of both sexes should perform regular self-examination of observable organs such as skin, breast and testicles after the changes due to puberty have settled down. The purpose of these examinations is to get a sense of how one’s normal body looks and feels, so any changes are more obvious.

For instance, skin self-examination includes “mole checks” to look for any changes in the size and shape of moles that might indicate they have become invasive (remember the “ABCDE” system from Unit 4). Clearly, vast areas of the skin (like the back!) are obscured, so people with large numbers of moles should also schedule regular dermatological check ups. Breast and testicular self-examinations involve feeling the tissue for hardened “lumpy” tissue. This is where a good idea of one’s own ‘normal’ is crucial. Lumpy tissue, especially in the breast, is very usual in some people. Only lumps that change noticeably over time, and then persist, are of concern.

One obvious problem with self-examination is that many symptoms that are associated with cancer may also occur in other diseases. In fact if you Google headache, fatigue, fever, weight-loss, nausea, anemia and jaundice, cancer comes up as an option for all of them, even though there are many other much more likely causes, particularly infectious disease. However, in contrast to most infectious diseases which usually clear up in a couple of weeks with or without treatment, cancer symptoms persist for much longer. Again this is where your knowledge of your ‘own normal’ is critically important. Only you can know when the symptoms started and whether they have lasted longer than might be expected.

Detecting cancer: Screening methods

Self-examination is critical but limited to direct observation. Other types of physician-directed screening programs that can access more areas and provide tissue samples for analysis are more informative but more invasive. Just like self-exams, routine screens compare a person’s current status with a past normal – the baseline. The goal is to identify a tumor just after it has turned malignant but before it

MC Questions:

2. What is the purpose of self-examinations? (Circle all correct.)
   a. Familiarize self with the body to know what is normal.
   b. Feeling a tumor reduces its size.
   c. Identify abnormalities.
   d. Reduce symptoms of cancer.

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3. True or False: Only doctors are responsible for detecting cancer at an early stage.
   a. True.
   b. False.
LESSON READINGS

has metastasized so it can be removed and eradicated, or to identify a benign tumor that is likely to turn malignant. Less acceptable, but unfortunately very common, is identifying a benign tumor but having no idea whether it will turn malignant, or identifying a malignant tumor that has already metastasized. These are two common limitations of screening. The question of who should receive routine screens, and what should be done with the information is another difficult one in cancer prevention and treatment. It seems obvious that people with large numbers of moles should undergo routine screening simply because it is impossible to self-examine all areas of one's own body and because melanoma is such a devastating cancer. Similarly post-puberty girls are recommended to have annual screens for abnormalities that might lead to cervical cancer. But whether invasive screens for slow growing cancers in elderly people are appropriate if they are more likely to die from non-cancer related causes is a matter of great debate, as we will see. Common routine cancer screening programs include:

The Pap screen identifies abnormalities in the cervix that can lead to cervical cancer. The pap screen is minimally invasive – a swab of the cervix is taken and a smear of the mucus that contains cells spread out thinly on a glass microscope slide. The cells are stained with dye that reveals any abnormalities including pre-malignant cells. Pap smears are important because cervical cancer can be caused by human papilloma virus (HPV), an extremely common sexually transmitted infection. For this reason screening is recommended for sexually active females, or women with a family history of cervical cancer. A vaccine for HPV is now available and women who have had a course of vaccine are protected from HPV-induced cervical cancer.

Mammograms use X-rays to take pictures of breast tissues. They can be used routinely in the absence of symptoms, or as a follow-up if self-examination has detected a suspicious lump. The low-intensity radiation in X-rays can reveal dense, fibrous tissue as a light area within the breast in contrast with the less dense fatty tissue the breast is mostly composed of. However the mammogram cannot tell what that tissue is, and it may be (a) normal – many women, particularly young women, have dense breasts normally (b) a benign tumor that may or may not turn malignant or (c) a malignant tumor that may or may not metastasize. So after a dense area is detected a tissue sample is commonly taken to determine whether the cells in the tissue are abnormal.

MC Questions:

4. Which of the following is NOT a screening program?
   b. Endoscopy for colon cancer.
   c. Pap smear for ovarian cancer.
   d. Rectal exam for prostate cancer.

5. Which of the following people should have a Pap smear?
   a. Sexually active females.
   b. Women with family history of cervical cancer.
   c. Women who haven't had one in the last 5 years.
   d. All of the above.

6. True or False: Mammograms should be done on all women who are sexually active.
   a. True.
   b. False.
**Prostate screening.** The prostate gland is located behind the male reproductive organs and a physician can examine it manually by inserting their fingers through the rectum and feeling for any abnormalities in size, shape or texture. The prostate gland provides a good example of best intentions in screening gone awry. Prostate cancer is quite common in elderly men, but is usually slow growing and patients often die from other age-related causes rather than the cancer itself. This is fortunate because prostate surgery is extremely invasive and has serious side effects such as *incontinence*. For a time the decision to operate was based on a blood-based screen that detected a protein damaged prostate glands secrete. If levels of the protein were high, surgery or invasive radiation treatment was recommended. However the prostate secretes this protein (prostate specific antigen or PSA) whenever it is damaged or inflamed, not just when a tumor is present, leading to many unnecessary and debilitating surgeries. Now, a ‘watchful waiting’ approach is recommended: men after age 40 who have a family history of prostate cancer and after age 50 who don’t receive annual digital rectal exams to detect changes in the prostate gland.

**Endoscopy** and **colonoscopy** are the most invasive routine screens, that require anesthesia in order to insert a small tube with an attached camera into either the esophagus or the colon, (“colon endoscopy” is shortened to “colonoscopy”). Esophageal endoscopy is used to detect **ulcers** or tears in the lining of the lower esophagus, commonly found in people with gastro-esophageal reflux disease, in which acid in the stomach enters into the esophagus. Ulcers are often pre-cancerous and can lead to esophageal or stomach cancers.

Colonoscopy is used to detect **polyps**, which are small tumors that form in the lining of the colon. If they are detected during a colonoscopy screen the surgeon can remove them on the spot, using the same device that holds the camera. Polyps are often pre-cancerous and can lead to colon cancers.

**Genetic mutations.** Years of research have identified gene mutations that are commonly observed in certain types of cancer. We have investigated some of these genes throughout the module, including: p53, Rb, and BRCA1/BRCA2. Now reliable, cheap and quick gene sequencing means it is possible to test for inherited mutations that may predispose to developing cancer even before tumors have formed! Sometimes mutations in a specific gene are so well correlated with a high possibility of developing a particular kind of cancer (such as the association between mutations in the BRCA genes and breast and ovarian cancer) that detecting this kind of mutation in a genetic screen will lead to the recommendation.

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**MC Questions:**

7. Which of the following can be detected by an endoscopy? (Circle all correct.)
   a. Tumors of the prostate.
   b. Polyps in the colon.
   c. Ulcers in the stomach.
   d. Tumors of the cervix.

8. What is the difference between a screen and a diagnostic test? (Circle all correct.)
   a. Diagnostic tests use invasive measures.
   b. Screens are done before cancer is observed.
   c. Diagnostic tests can identify benign and malignant tumors.
that the organ should be preemptively removed, even before a tumor appears. This is particularly true if the mutation is in the context of a family history of the cancer.

**Tumor or cancer: diagnostic tests?**

Screens detect abnormalities by comparing current conditions to a normal baseline, but often are unable to conclusively determine whether abnormal tissue is benign or malignant, so further follow-up **diagnostic tests** are needed to complete the diagnosis of whether the abnormality is benign or malignant. There are three major types of diagnostic tests to confirm the presence of a cancer: taking an image of the affected organ, extracting tissue, or sampling blood.

**Organ Imaging**

Both X-rays and endoscopy are used both to screen for abnormalities, as we saw above, and also to diagnose whether those abnormalities are benign or malignant tumors of the breast and lungs (using X-rays) and esophageal, stomach, or colon/rectum (using endoscopy). Organ imaging is popular because it is cheap and non-invasive but has a number of drawbacks, including undue exposure to radiation (in the case of X-rays). Other than X-rays and endoscopy, other major types of organ imaging include:

- **Ultrasound** – uses sound waves to detect tissue density. While it is cheap and doesn't require radiation, it is limited to visualizing tumors of the breast, thyroid, and genital tissues.
- **MRI** – magnetic resonance imaging (MRI) pulses radio waves into an organ that is positioned within a strong magnetic field. The combination of the radio waves, magnetic field and water in the body provides an accurate image of tissues. MRIs are expensive ($1000-$3000) and time consuming (~30 min) and limited to bone, brain, and muscle tissues.
- **PET** – positron emission tomography (PET) used injected radioactive glucose to detect cancer cells because they are more metabolically active than normal cells. PET produces high quality images and is useful because it can detect metastases, but it uses radiation and is very expensive ($3000-$6000) and time consuming (2-4 hrs).

**DEFINITIONS OF TERMS**

**Diagnostic test** – a test performed to identify the nature of a tumor especially grade and stage.

**Ultrasound** – a type of imaging that uses sound waves to detect tissue density.

**MRI** – magnetic resonance imaging, a type of imaging that uses the properties of water in a magnetic field to visualize tissues.

**PET** – positron emission tomography, a type of imaging that uses uptake of radioactive glucose to identify metabolically active tumor cells.

**MC Questions:**

9. Which of the following allows visualization of an organ without using radiation? (Circle all correct.)
   a. **MRI**.
   b. **PET**.
   c. **Ultrasound**.
   d. **X-ray**.

10. Which of the following imaging techniques can detect primary AND secondary tumors at the same time?
    a. **MRI**.
    b. **PET**.
    c. **Ultrasound**.
    d. **X-ray**.

**Figure 4:** A PET scan measures glucose uptake into cells. Cancer cells require more glucose to grow, so they appear more red than surrounding tissue. Images show glucose uptake from two angles.
**Biopsies and Blood Samples**

Any imaging technique can only provide limited information about a tumor. Tissue biopsies, which extract small pieces of tissue from a tumor provide better information about the organization of the cells in the tumor and the surrounding tissue – critical to define whether a tumor is malignant.

There are two major types of biopsies: A needle biopsy uses a needle to remove cells from a tumor (that was originally identified by imaging). The cells are then visualized under the microscope. This type of biopsy provides information on how some of the cells in the tumor look (i.e. what stage it is) not whether the tumor has spread or not (i.e. what stage it is). A surgical biopsy removes a portion of the tumor including the surrounding tissue, providing information on both tumor grade and possibly stage.

Biopsies can provide a lot of information about the tumor and how far has progressed but are sometimes painful or difficult, particularly if the affected organ is located in the body cavity, such as the pancreas, liver, kidneys or difficult to access, such as the brain. In these cases, it would be preferable to sample the blood for markers that provide indirect evidence of the tumor characteristics. Fortunately these types of marker exists and include:

- **Red cell count** – many cancers cause anemia, or loss of red blood cells
- **White cell count** – leukemias or cancers of white blood cells, elevate white cell counts in the blood.
- **Tumor-specific antigens** – as mentioned in Unit 4 and above some tumors express specific proteins that are not normally found in normal tissues and sometimes secrete them, so they circulate in the blood. Examples of tumor antigens include: prostate specific antigen (PSA), alpha-feto-protein (AFP) for liver and germ cells, and carcino-embryonic antigen (CEA) for the large bowel.

We have talked about the drawbacks of PSA above. Indeed many tumor ‘specific’ antigens, while secreted by tumors are not ‘specific’ at all. It can also be challenging to establish a ‘normal’ baseline. As a result it is not unusual for a blood test to inaccurately indicate presence of a tumor. This is called a “false positive” result. False positives are a problem, particularly with cancer treatment, which is often painful and inconvenient, and we will explore this concept in more detail in Lesson 5.2.

**MC Questions:**

11. What is the main difference between a surgical and needle biopsy? (Circle all correct.)
   a. Size of incision.
   b. Ability to identify tumor stage.
   c. Ability to identify tumor grade.
   d. Amount of tissue collected.

12. Which is a marker for cancer that can be detected from a blood test?
   a. Anemia.
   b. Tumor antigens.
   c. High immune cell count.
   d. All of the above.

13. What is the main difference between a surgical and needle biopsy? (Circle all correct.)
   a. Size of incision.
   b. Ability to identify tumor stage.
   c. Ability to identify tumor grade.
   d. Amount of tissue collected.

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**DEFINITIONS OF TERMS**

**Biopsy** – a sample of tissue used for diagnostic purposes.

**Needle biopsy** – a sample of tissue extracted from the body using a needle inserted directly into the tumor. Only a small amount of cells is gathered.

**Surgical biopsy** – a sample of tissue extracted from the body using surgery. The sample includes both tumor and surrounding cells for diagnostic purposes.

**Tumor-specific antigens** – proteins expressed by tumor cells that are not expressed by normal cells. They can sometimes be secreted into the blood.

**False positive** – a positive result from a diagnostic test, even though disease is not present.

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**Workbook**

**Lesson 5.1**
What would the most useful routine screen for liver cancer look like? What are the strengths and weaknesses of the three most common diagnostic tools? How could they be improved?
### TERMS

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<td>Biopsy</td>
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<td>Colonoscopy</td>
<td>The visualization of the colon or rectum using a flexible camera.</td>
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<td>Diagnostic test</td>
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<td>Endoscopy</td>
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<td>False positive</td>
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<td>Incontinence</td>
<td>The inability to regulate bladder function</td>
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<td>Mammogram</td>
<td>An X-ray examination of breast tissue intended to serve as a diagnostic test for cancers of the breast.</td>
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<td>Mastectomy</td>
<td>Surgery that removes the entirety of the breast as a treatment or preventative measure for cancer.</td>
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