CANCER & NEOPLASIA

(CHAPTER 12)

QUESTION 1

Are all neoplasms malignant?

No. The word **neoplasia**—meaning "new growth"—refers to **any tumor**, whether benign, "in situ," or malignant.

Think of the forms of abnormal growth we talked aobut during week 1: metaplasia, dysplasia, anaplasia, etc.

Anaplasia, which we already defined as cancerous, falls under the category of neoplasia; however, many growths such as dysplasias, uterine fibroids, or some colon polyps are **also** considered neoplastic.

In **some cases**, non-malignant neoplasia can progress to cancer, in other forms it does not.

The key to pick up here is that neoplasia has to be **different** from the surrounding tissue. Not all forms of excessive tissue growth are neoplastic.

In benign prostatic hyperplasia (BPH,) for example, the new tissue **isn't** tumorous; you simply have **more** prostate tissue than before.

QUESTION 2

What are the characteristics of a benign neoplasm?

Remember that benign tumors mostly "**keep to themselves**."

They are **slow-growing**, **well-contained**, and **well-differentiated** (e.g. **not** anaplastic—look like "normal" cells.)

They also generally have a **low mitotic index**, meaning that they take longer "breaks" before undergoing mitosis, so fewer cells are splitting at any given moment.

In general, just think of benign tumors as being non-invasive. They might cause problems locally, but for the most part, they're going to stay where they are.

QUESTION 3

What are the characteristics of a malignant neoplasm?

In contrast, malignant tumors are **invasive** and like to grow into **everything**.

They are **fast-growing**, **poorly-contained**, and **poorly-differentiated** (e.g. they **are** anaplastic—look like stem cells.)

As you might expect, they have a **high mitotic index**, meaning that new cells split shortly after reaching maturity, and a large percentage will be undergoing mitosis at a time.

In general, think of malignant tumors as being the "warmongers" of the cellular world; they want to spread everywhere!

QUESTION 4

Describe the grading and staging systems.

Grading and **staging** are two similar but **different** systems for describing the extent, and by extension often the prognosis, of a cancerous growth.

Grading looks at cancer on the **cellular level**.

As a mnemonic, think about how you might get a "grade" on a single assignment. Likewise, cancer can be graded from just a **single tissue sample**.

Cancer **grades** run from **1 to 4**.

Grade 1 is typically the **least** aggressive, and has the **most normal-looking** cells. It tends to be slower-growing, and is unlikely to metastasize.

Grade 4 is typically the **most** aggressive, and has the **most anaplastic** cells. It tends to be faster-growing, and is likely to be quite aggressive.

Staging, on the other hand, looks at cancer on the **whole-body level**.

As a mnemonic, think about the stage of a theater; it encompasses the bigger picture, and contains the action of the entire scene.

It follows what is known as the **TNM system**, where the stage is represented by three numbers, e.g. T2 N1 M0.

The first number, **T**, represents the **size** and **extent** of the primary tumor.

The "**best**" stage for a **known** tumor is **T1**. Technically you **can** have T0, but this just means there's a suspected tumor that's still too small to find.

The "**worst**" stage is **T4**. These tumors have spread well beyond the primary organ and into the surrounding tissue.

The second number, **N**, represents the infiltration of the tumor into nearby **lymph nodes**. Lymph vessels are like "superhighways" for metastasis, so this number is very important!

N0 means that the lymph nodes are **unaffected**. N3 represents **extensive** lymph node involvement.

The third number, **M**, represents the **metastasis** of the cancer to distant organs.

Unlike the other numbers, M can **only** be 1 or 0: the cancer has either metastasized, or it hasn't.

Note that there is actually a second, simpler staging system that is commonly used in patient education and common speech, due to it being easier to understand.

In this system, non-metastatic cancer is classified as "stage 0" (in situ) through "stage 3" (extensive local infiltration,) and metastatic cancer is referred to as "stage 4."

(You shouldn't need to know this system for the exam; focus on understanding TNM staging first.)

QUESTION 5

Which tumor grade would most likely have the worst prognosis?

As we mentioned before, **higher grades** of cancer tend to behave **more aggressively**.

As such, **grade 4**, the highest grade, would likely spread the fastest and have the least promising prognosis.

QUESTION 6

Give an example of the "best" possible tumor stage.

Assuming that there **is** a tumor present, but its infiltration is **limited** and there is **no lymph node involvement** and **no metastasis**, the **least severe** stage possible would be:

T1 N0 M0

QUESTION 7

How does the spread of a tumor contribute to damage to healthy tissue?

Bear in mind that tumors don't "convert" healthy tissue into tumor tissue. Rather, tumor tissue comes from the **hyperproliferation** of the **existing** unhealthy tissue.

Healthy tissue becomes damaged due to the **infiltration** of the tumor into healthy areas, displacing it and potentially starving it of nutrients.

QUESTION 8

When a tumor metastasizes, what name would we use to describe the secondary tumor?

Cancers are **always** named by the originating location (the location of the **primary** tumor.)

When cancer spreads from this location to other parts of the body, we call these secondary tumors **metastases**.

Remember that the metastases retain the name of the originating disease: if pancreatic cancer spreads to the lungs, it is **not** lung cancer.

Rather, it is considered **pancreatic cancer** with **lung metastases**.

QUESTION 9

What general factors predispose a tissue to the development of a tumor?

The vast majority of cancers arise from **epithelial tissues**. There two main reasons for this:

- Epithelial cells **multiply quickly**, resulting in more chances for **initiation** through **random mutation**
- Epithelium separates the bulk of organs from the body's internal or external environment, increasing exposure to **carcinogens**

QUESTION 10

What is an oncogene?

An **oncogene** is essentially the genetic "on switch" that triggers a cell to be predisposed to cancerous activity.

These are usually **normal** DNA sequences (called **proto-oncogenes**) which contribute to signaling cell division, that have become **overexpressed** leading to rapid multiplication.

QUESTION 11

What is a tumor suppressor gene? How might one be involved in the development of cancer?

Tumor suppressor genes or **anti-oncogenes** are DNA sequences that act against cancer formation by either regulating **DNA repair**, slowing the **growth cycle**, or inducing **apoptosis** in cells that "step out of line."

Typically, the behavior of these genes **inhibits the promotion** of mutations by either repairing the mutation, preventing the initiated cell from proliferating, or apoptosing the cell itself.

Cancer can occur when the behavior of suppressor genes is **suppressed** or **modified**, leaving an opening for the cell to multiply excessively.

QUESTION 12

What are tumor markers? How can they be used in the diagnosis and treatment of cancer?

Tumor **markers** are essentially any substance in the body which we can test for, that **suggest** or **correlate with** the presence of cancer if found in elevated levels.

It is important to understand that tumor markers are **not** 100% sensitive, nor 100% specific, for cancer, so aren't "foolproof."

(Ca19-9 elevated → Pancreatic cancer? Liver cancer? 😱 Or could just be pancreatitis...)

However, tumor markers are a fast and easy way to **screen** for cancer, and an elevated level can be a red flag that warrants **further investigation**, like imaging or a biopsy.

Tumor marker **trends** are also useful in cases of **known** cancer, to determine whether treatment is having a positive effect.

QUESTION 13

Why would cancer drugs (chemotherapy) affect the gastrointestinal system?

Many chemotherapy drugs are specifically designed to target **fast-growing** tissues, particularly **during cell division**.

However, these drugs are distributed systemically and **not specific** to cancer cells, so they end up also affecting **healthy cells** that happen to multiply quickly.

Many of the **side effects** of chemotherapy can be explained by this damage to normal, fast growing tissues, such as the hair follicles and the **gastrointestinal epithelium**.

The collateral damage to the GI tract can cause unpleasant side effects such as **nausea**/**vomiting**, **diarrhea**, and **abdominal pain**.

QUESTION 14

What immune approaches can be used in cancer treatment?

Immunotherapy is a newly emerging field of cancer treatment that relies on teaching the body's **immune system** to **selectively** fight cancer cells without the systemic damage that can be caused by traditional chemotherapy.

Currently, immunotherapy is typically used as an **adjuvant therapy**, meaning it is used **alongside** other treatment modalities such as surgical resection, chemo, or radiation therapy.

However, there is interest in continuing research to refine immunotherapy to the point where it can be used as a primary treatment.

One of the commonly used types of immunotherapy involves the administration of **interferons**, a type of cytokine naturally produced in the body as a signal for the immune system.

It is given IV or IM, 3-5 times per week for up to a year, often in combination with another form of cancer therapy.

QUESTION 15

What is a carcinogen? Give some examples.

A **carcinogen** is simply a substance that can induce the development of cancer.

Some examples would be **asbestos**, **tobacco smoke**, and many chemicals and pollutants.

QUESTION 16

Distinguish between carcinogens and agents that induce cancer.

Carcinogens, by definition, are **substances** that induce cancer. Many cancer-causing agents are carcinogens, but not all fit into this category.

For example, human papillomavirus (HPV) can induce cervical cancer, but it is not a **substance**, so we would not refer to it as a carcinogen.

QUESTION 17

Describe some risk factors for cancer.

Inflammation, especially chronic inflammation, is a **very important** risk factor for cancer, due to its potentially damaging effects on cellular DNA.

Think about chronic smokers: inflammation of the airways, combined with carcinogens in the tobacco smoke, leads to a huge risk of oral/lung cancer.

Other general risk factors include:

- Age
- Sun or radiation exposure
- Family history
- Obesity/sedentary lifestyle

QUESTION 18

How does estrogen act as a cancer promoter?

Hormones can actually play a role in cancer **promotion**, which we'll talk about in a second. Basically, this means that they can take a mutated cell and help it to grow into a tumor.

In particular, estrogen is connected with the development of **breast cancer** due to its **proliferative effect** on breast tissue (both healthy **and** cancerous.)

QUESTION 19

Describe the multi-step model of carcinogenesis.

The **multi-step model** describes the **complex sequence of events** that **must occur** in order for a malignancy to develop.

These events are divided into three stages: **initiation**, **promotion**, and **progression**.

In **initiation**, a potentially cancer-causing **mutation** occurs in a **single cell**.

This transformation is **permanent** and only needs to occur once! The initiated cell will be vulnerable to promotion **until it dies**!

The body has **natural defenses** (such as **tumor suppressors**) that work to prevent initiated cells from multiplying.

If these defenses **fail**, the mutation can be **promoted**, allowing the mutated cell to multiply faster and proliferate into a **benign tumor**.

Finally, if the tumor is untreated, it can **progress** to a **carcinoma in situ** ("contained" cancerous lesion) and then a **malignant tumor**

If these defenses **fail**, the mutation can be **promoted**, allowing the mutated cell to proliferate into a **benign tumor**.

QUESTION 20

What are proto-oncogenes?

A **proto-oncogene**, as we mentioned earlier, is a **normal** segment of DNA that plays an important role in managing cellular division, but has the **capacity** to become overexpressed through mutation.

When this happens during **initiation**, it becomes an **oncogene**, predisposing the cell to hyperproliferation in the future.

QUESTION 21

Give examples of initiation, promotion, and progression.

Let's use the example of **cervical cancer** to examine each of the steps in tumor progression.

Usually, we start with an infection by human papillomavirus (HPV.) The viral DNA **mutates** a cell somewhere in the cervical epithelium; this is the **initiation**.

Many of these initiated cells may be dealt with by the body's natural defenses; however, a cell that breaks through may begin to multiply and form a **cervical dysplasia**.

The mutation has now been **promoted**, resulting in a benign growth, but it is **not yet cancerous**.

If untreated, usually for many years, a **further mutation** may occur which kicks the tumor's growth into overdrive. At this point, the tumor has **progressed** to a **carcinoma in situ**.

This now-cancerous tumor will eventually infiltrate through the basal membrane, at which point it becomes **malignant** and has the capacity to spread to other tissues.

QUESTION 22

Why is the multi-step model relevant?

Understanding the sequential steps of cancer development gives us **insight** into **treatment and prevention modalities**.

For example, we can control risk factors to decrease the risk of **induction**, or screen for benign growths and deal with them before **progression** occurs.

QUESTION 23

Why is it useful to look at colorectal cancer as an example of multi-step carcinogenesis?

Colorectal cancer is a great example of how understanding multi-step cancinogenesis can be useful in **preventing cancer development**.

Cancerous lesions on the epithelium of the colon typically begin as benign **polyps**, which then risk **progression** to cancer.

By undergoing routine **colonoscopy**, we can remove these polyps **before** progression occurs, thus negating the risk of malignancy developing.

QUESTION 24

Describe some early signs and symptoms of colorectal cancer.

- **Hematochezia** or, more often, **occult blood** in the stool
- **Altered bowel habits** due to blockage of the intestinal lumen
- Persistent **abdominal pain**, **diarrhea**, or **constipation**

QUESTION 25

Describe the pathogenesis of colorectal cancer.

Adenomatous polyps, which are **benign tumors** of the epithelium of the colon, are actually quite common.

We often find them during colonoscopies, and they are usually surgically removed to prevent their progression to cancer.

Progression is enabled by the mutation of a tumor suppressor gene called **APC**, which allows the previously-benign growth to begin to exhibit malignant behavior.

At this point, the growth is no longer classified as an **adenoma** (non-cancerous) but as an **adenocarcinoma** (cancerous.)

QUESTION 26

How does an epigenetic event affect the cells?

An **epigenetic event** is a random mutation that alters the **structure and function** of the DNA **without** altering the actual allele sequence.

Although the DNA sequence itself is unaffected, structural changes can affect the way DNA is **used** and **interpreted**.

For example, an epigenetic event might **activate an oncogene**, causing hyperproliferation, or **damage** or **deactivate** a tumor-suppressor gene.

Although the DNA sequence itself is unaffected, structural changes can affect the way DNA is **used** and **interpreted**.

QUESTION 27

List some ways that metastasis can cause serious problems in the body.

Metastasis, or the spread of a primary cancer to **distant secondary locations** throughout the body, is generally regarded as a **serious complication** of cancer.

This often occurs when a malignancy spreads into the **lymphatic system** or the **blood stream**, enabling cancer cells to quickly jump to distant areas.

The problem with metastasis is twofold:

First, it **makes treatment more difficult**, as surgical resection and radiation therapy can no longer address the bulk of the cancer cells.

Second, it can cause **more varied** and **more severe symptoms** as further organs and body systems become involved.

Secondary metastases most often occur in organs and tissues that receive lots of blood flow, such as the **lungs**, **liver**, and **bone marrow**.

These metastases can then cause all sorts of serious problems, such as respiratory distress, liver failure, and chronic anemia.

QUESTION 28

Why can it be hard to detect a primary cancer?

Primary cancers can be hard to detect because, while the malignancy is still localized, there are often **few symptoms**, and the symptoms that do occur tend to be mild and non-specific.

For example, mild intermittent abdominal pain may not provoke a patient to seek out medical care due to the non-specific nature of abdominal pain.