**The Biology of Cancer – Week 4 Notes**

* Metastasis Overview

As you listen to Dr. Valkenburg remember that metastasis is the lethal event In the pathogenesis of cancer. And we need to develop new ways to prevent metastasis and treat cancer.

* Introduction to Metastasis

“Metastasis: The Real Killer”

Meta “alter, beyond”

Stasis “state of inactivity, stagnation”

Metastasis, the process by which tumor cells move from the primary tumor to a different organ via lymph and/or blood. Example: prostate cancer cells metastasize to bone.

-Metastasize- verb- act of moving from primary to secondary site

-Metastatic – adjective – the state of being able to metastasize

Metastases – noun – multiple metastatic tumors.

Benign – tumors are masses of cells that are unable to invade neighboring tissue or metastasize

Malignant – tumors are cancerous masses of tumor cells that are able to invade neighboring tissue and metastasize.

Hallmarks of cancer – 10 – all of them promote metastasis.

The term metastasis was first used in various writing in the 18th and 19th centuries to describe breast cancer “metastasis of milk,” which was metastatic tumors growing in lactating women.

“Metastasis” or “metastases” in the context of diagnosis and treating cancer was used first in 1829 by French Surgeon J.C. Recamier.

Tumor dissemination was described in 1858 by German doctor and biologist Rudolf Virchow.

Liquid cancers like leukemia do not metastasize because there is no primary tumor.

Most people who die of cancer, will die because they have a metastatic tumor.

The rate at which cancers are metastatic at the time of diagnosis are different by cancer.

Five-year survival rate is a measure of cancer lethality following diagnosing.

Why do metastases kill people?

-Loss of tissue function in the metastatic site.

Bleeding: up to 10% of advanced cancer patients experience bleeding.

Pulmonary embolism: blocked artery in the lung due to tumors

Infection: due to the cancer damaging immune arsenal, or the cancer treatment.

Cancer treatments can cause irreparable damage to various organs. This includes treatments for pain, which metastatic cancer patients experience a lot of.

Cachexia – weakness and wasting of the body due to severe chronic illness.

Systemic disruption of ion homeostasis (e.g. hypercalcemia in the case of bone metastasis)

* (Tumor Node Metastasis) TNM Staging

TNM – **T**umor, Lymph **N**ode, **M**etastasis.

Most cancers use this system except for blood cancers and some nervous system cancers.

Tumor staging describes the size of a person’s tumor. Determined via physical exam, imaging, surgery.

The Lymphatic System – vessels that carry lymph fluid to lymph nodes and then to bloodstream. It drains excess fluid to maintain volume and composition of tissue; to act as a defense against infection.

Lymph is interstitial fluid (fluid from between cells) composed of water, white blood cells, proteins, fats, sugars, salts. Move cellular waste.

Cells from primary tumors move to nearby lymph nodes.

N-Lymph Node: N0, cancer has not been found in the lymph nodes. N1, cancer has been found in regional or nearby lymph nodes. When cancer has been found in lymph nodes beyond the local region, it represents the worst diagnosis and prognosis.

Millions of immune cells comprise most of the lymph node.   
A tumor will fill/occupy the lymph node, crowding out the normal cells.

Metastasis: Has cancer spread to other organs?   
Bone metastasis, Lung metastasis, Liver metastasis, Brain metastasis.

T1, T2, T3 (increasing size, and if it has become invasive)

N0, N1: has it spread to the nearby LN

M0-M1: has metastasis occurred.   
M1a – far away lymph node  
M1b – to bone tissue  
M1c – to other tissues

* The Metastatic Process

How does metastasis occur? 8 major steps

1-Primary tumor growth

2-Angiogenesis

3- Epithelial-to-Mesenchymal transition (EMT)

4-Invasion

5-Intravasion

6-Survival in circulation

7-Extravasation

8-Dormancy and or secondary tumor growth

Step 1: There must be a primary tumor that grows large enough to metastasize. Some tumors never become metastatic.

Hyperplasia – just an increase of proliferation and division in these cells. This is not cancer.

Cancer in situ, is cancer that has not become invasive. “cancer in place” This is considered benign cancer.

Step 2: Angiogenesis (Formation of New Blood Vessels)

Tumor cells grow more quickly than normal cells and outgrow their source of nutrients—blood.

Tumors make new blood vessels to provide necessary nutrients and oxygen. This process is not natural, these new blood vessels are poorly made and leaky. This provides an avenue for the cancer cells to enter the bloodstream and become metastatic.

Step 3: Epithelial-to-Mesenchymal Transition (EMT) – Cells Become Mobile

Loss of contact with the ECM is one of the major ways for cells to undergo the EMT.   
Once cells start moving around they can invade surrounding tissue and enter the bloodstream.

Step 4: Invasion (Breaking through the ECM).   
Invasion requires the cells to be able to secrete enzymes to chew through the molecules of the ECM to create a hole for mobile cells to go through. Invasion is the last straw to make a diagnosis of cancer. If invasion is seen in histology, cancer becomes the diagnosis because the cancer cell has the ability to possibly metastasize. INVASION pushes the severity of the cancer to a higher level.

Step 5: Intravasation. (Cells get into the blood vessel).   
Actively: usually do this by pushing through the endothelial cells of the blood vessel.   
Passively: tumor cells are shed from a tumor and enter presumably leaky blood vessels.

Cancer cells can get into the bloodstream via the lymphatic system as well. Lymph system interfaces with the veins which carry de-oxygenated blood to the heart. In this way, cancer can metastasize without ever having intravasating a blood vessel.

Step 6: Survival during systemic circulation

-Cancer cell must traverse venous system, lungs, and arterial system

-Tumors that are circulating in the bloodstream are called circulating tumor cells, or CTCs.

-During this transit, CTCs must avoid various sources of cellular death.

The bloodstream is a place where most detached cells die. In normal cells, if cells become detached from the ECM, they are programmed to die. Immune surveillance occurs in the blood looking for abnormal cells. Also, must handle the shearing force of blood pressure. Cells that survive these forces become CTCs and can become metastases.

Consequently, more CTCs in the blood is associated with a worse prognosis. In about 7ml of blood there are about 50 million wBC on average. Detecting 5 cancer cells in that volume is very challenging.

Step 7. Extravasation. Cells get to their destination and leave the blood. They can do this by getting stuck in capillaries. They can become attracted to a secondary site via secreted molecular factors. Once they get to a secondary site, they become known as disseminated tumor cells (DTCs).

Cancers go to different organ sites. The distribution is not random. The phenomenon behind this is not entirely understood at this point. “Cancer cells (seed) home to certain secondary sites because they thrive better in that environment (soil).” This is the seed and soil hypothesis.

Step 8: Dormancy and or secondary tumor growth.

Many DTCs begin growing in the secondary site into metastatic tumors.

DTCs may not begin to divide immediately when they get to their destination; they may go dormant and grow into a tumor later. It is known that a DTC can reside in a patient’s bone marrow for decades before undergoing reactivation.

Summary:

*So this slide is just a summary of the metastatic process, and we've gone over all of these steps. And I'll just summarize it for you here. Cancer cells can grow into a tumor, cause new blood vessels to grow, which is angiogenesis, undergo physical changes, that's just EMT, and invade through the ECM. And get into the bloodstream, which is intravasation. CTCs must survive circulation until they extravasate into a secondary site. Once there as a DTC, they can either grow into a metastatic tumor or go dormant. I hope I have conveyed the metastatic process to you. And in the next section of the module we'll talk about cancer ecology as an analogy for the cancer metastatic process.*

* An Ecological Paradigm: Why do cancer cells metastasize from the primary tumor?

Trying to understand metastatic disease through the lens of ecological mechanisms.

Cancer and associated processes can be compared to parallel ecological phenomena.

Cancer cells must move to metastasize

-Long-distance dispersal is a high-risk endeavor.   
-Decreased short-term fitness of the emigrant   
-Loss of the ability to replicate  
-Change in metabolism  
-Energy spent to transition to a migratory phenotype  
-Unfamiliar and hostile environment   
-Future risk of a hostile secondary site, or no secondary site at all

Individuals do not leave their native ecosystems unless the risks of remaining in the ecosystem are higher than the risks associated with dispersal.

Unregulated proliferation of cancer cells leads to tumor formation  
Increased proliferation (despite angiogenesis) causes hypoxic, acidic, and nutrient-poor conditions.   
Cancer cells with migratory ability that able to thrive in the harsh conditions are selected.   
Metastatic cells migrate to a secondary site.

Applying these and other ecological paradigms to cancer biology problems allows researchers to gain insight into cancer biology phenomena common to ecosystems, communities, and habitats in ecological science.

Cancer ecology has applied ecological principles to investigate:  
-Engineering of the tumor microenvironment.  
-Movement ecology of metastatic cells  
-Ability of circulating tumor cells to survive in transit  
-Causes of the cytokine-mediated syndromes, a major cause of death in cancer patients.  
-Designs of novel “ecotherapy” drugs to dismantle cancer ecosystems.