Hello. My name is Bonnie Brice. I am a nurse practitioner at The University of Texas MD Anderson Cancer Center. Today we will be talking about Breast Cancer Survivorship: Common Sites of Metastasis.

Learning Objectives: Define metastatic breast cancer. We'll talk about the overview of the metastatic cascade; identify common sites of distant breast cancer metastases; and describe the symptomatology of metastatic breast cancer by site.

“What is metastatic breast cancer?” Metastatic Stage IV breast cancer is an advanced stage of breast cancer. The disease process poses life-threatening complications. Cancer cells from the primary tumor travel to distant locations of the body hematogenously or through the lymphatic system. The tumor formed by metastatic cancer cells is called a metastatic tumor or a metastasis.

Metastatic breast cancer has the same name and similar type of molecular features common to the primary tumor. For example, breast cancer that spreads to the liver is metastatic breast cancer, not liver cancer.

Microscopically the metastatic lesion expresses proteins having certain chromosomal changes specific to the primary breast cancer.

Pathology Overview and Specific Points: There are many processes influencing the metastatic process. Two important factors influencing metastatic lesions are the ability of the primary tumor to form variations of cellular copies. Patterns of genetic changes in a tumor may predispose for metastasis, called the “metastatic signature.”

On a cellular level, solid tumors such as breast cancer have a specific structure with two distinct interconnected levels: the parenchyma, neoplastic cells, and stroma that the abnormal cellular growth induces and disseminates.

Tumor stroma allows for larger growth and is in an area that functions between malignant cells and normal host cells. Stroma mostly develops from the host and facilitated through tumor cell-host interactions. The stroma includes nonmalignant supporting tissue, connective tissue, blood vessels, and inflammatory cells. A layer called the basal lamina generally separates clumps of tumor cells from the stroma.

Tumor stroma impacts the metastatic process by supporting angiogenesis, which is new blood vessel formation, the vascular supply that tumor cells require for nutrients, gas exchange, waste disposal, local infiltration, and resistance to immune elimination.

The series of events leading to metastases is termed the metastatic cascade. Distant spread of the primary tumor involves invasion of extracellular matrix --- matrix which is the basic membrane correction --- basement membrane and interstitial connective tissue, vascular dispersion, and homing of tumor cells. Invasion of extracellular matrix is that the tumor cells must interact with extracellular matrix at several stages in the metastatic
Cancer cells must breakthrough the underlying basement membrane, interstitial connective tissue, and access circulation, which is the blood supply by penetrating the vascular basement membrane. The cycle is repeated when tumor cell emboli exudes at a distant site, creating a metastatic deposit allowing for angiogenesis and growth. With vascular dissemination, once in circulation, tumor cells can be destroyed by immune defenses. In circulation, tumor cells form clumps. The tumor emboli will halt growth, adhere to the endothelium, and invade the basement membrane. The process involves adhesion molecules and proteolytic enzymes. That is, the enzyme that breaks down proteins into simpler compounds. At the new site, tumor cells proliferate, develop a vascular supply, and invade host defenses. “What is homing of tumor cells?” Certain proteins, such as chemokines, are significant in determining the target tissues for metastases. Some breast cancer cells express chemokine receptors. CXCR4 and CCR7 are examples. The chemokines that bind to these receptors are highly expressed in tissues that breast cancer commonly metastasize.

Within the microenvironment, chemical and molecular functions include continued protein signaling and receptor regulations.

So, “What are the main steps of the metastatic cascade?” The primary tumor clone, expansion, growth, and angiogenesis forms. Metastatic cells adhesion into basement membrane of local tissue. Passage through the extracellular matrix. Number 4, entrance of tumor cells into blood supply. Host and lymphoid cell interaction occur. The formation of tumor cell embolus.

Adhesion to basement membrane of vessel. Extravasation of tumor emboli cells into a distant site to form a metastatic deposit. To form a metastasis, tumor cells must proliferate, develop a vascular supply through angiogenesis, and evade host defenses.

This is a simple graph of the approximate incidence of metastatic breast cancer by site. As you can see, bone cancer is the most common, followed by lung, liver, and brain the least common. Metastatic breast cancer to the bone, as stated, is the most common site of breast cancer metastases and is related to the exchange pattern of the unique bone marrow environment and tumor cells creating a hospitable environment for tumor growth and bone destruction. The tumor secretes factors, such as parathyroid, hormone-related peptide that stimulates osteoplast development, leading to breakdown of the bone. Bone stroma produces growth factors, such as transforming growth factor-beta, promoting tumor growth in the bone. Most breast cancer to the lung creates a symptomatic clinical finding. And the likelihood of finding an asymptomatic metastasis with routine surveillance, such as a chest x-ray has been reported to be quite low. Metastatic breast cancer to the liver is less common. Hepatic failure from metastatic disease is a major cause of death in about 20% of patients. At the time of diagnosis, 5-10% of patients have metastatic hepatic metastases. Thirty-five to 45% will develop metastatic liver tumors after resection of primary tumors. Metastatic breast cancer to the brain diagnosis ranges from 5-15% of patients. Breast tumor cells must pass through the less permeable blood-brain barrier to form micrometastases in the
Dysfunction of the blood-brain barrier with specific molecular mediators is thought to occur with breast cancer patients who develop metastatic lesions to the brain, more likely to occur in premenopausal women with aggressive disseminated disease.

Symptomatology by Site: The bone pain of metastatic breast cancer is generally dull, gradually progressive pain, occasionally intermittent, and not relieved by rest. Swelling may be present at associated sites. Liver metastasis creates nausea, vomiting, loss of appetite, with late signs including ascites and jaundice. Right upper quadrant pain and generalized abdominal pain with large --- with the larger hepatic tumors.

The lung cancer metastasis often creates a chronic cough, shortness of breath, and can create chest pain. Brain metastases have variable neurologic symptoms. Often there is a progressive headache, dull, non-throbbing, early morning headache that can be associated with vomiting in the absence of nausea, acute seizures, stroke, hemiparesis, visual changes, and cognitive dysfunction.

According to the American Cancer Society, the 5-year survival rate on the number of people diagnosed with metastatic breast cancer in 2001 and 2002 was 15%. The number was derived from the National Cancer Database.

In summary, breast cancer metastases develop when disseminated cancer cells from the primary breast tumor travel to distant locations and colonization proceeds to form life-threatening lesions. Thank you for your attention. We welcome your feedback.