Lay Abstract

Breast cancer is one of the most common cancers in the United States, and the number of new cases continues to rise. Many patients with breast cancer now live longer because of better treatments and earlier detection, but people with stage IV breast cancer still have low survival. This is especially true when the cancer spreads to the fluid layer around the brain and spinal cord (called cerebrospinal fluid [CSF]) in a condition named leptomeningeal disease (LMD). Treatments for LMD have changed very little over the past couple decades, in part because 1) the disease is hard to detect with current tests and 2) these tests cannot reliably show how well the treatments work. Without accurate tools, doctors cannot change treatments in time to meaningfully help patients.

Our **long-term goal** is to establish effective treatments for BC LMD by finding better ways to detect and track breast cancer LMD and brain metastasis so doctors can adjust treatment sooner while reducing treatment side effects. One of the most effective treatments for LMD is providing radiation to the entire brain and spine to slow disease spread and help patients live longer. We are conducting a clinical trial combining this treatment with a modern radiation technique. During the trial, we will collect circulating tumor DNA (ctDNA), which are tiny DNA fragments from cancer, from both the bloodstream and directly from CSF. We believe that ctDNA is a promising tool to monitor disease and understand how well the treatment works. We will also study inflammatory markers in the blood because these often change just before symptoms appear and may offer possible early warning signs for treatment side effects.

There are several **short-term outcomes** for this study. First, we will complete our clinical trial and determine how effective and well-tolerated radiation therapy is to the brain and spine using a modern radiation technique (Aim 1). Next, we will determine if ctDNA levels in the CSF are better than standard detection methods for LMD treatment success and how different ctDNA is from the other cancer cells in the body by sequencing the genes using computer modeling over several time points along a patient's treatment journey (Aim 2). Lastly, we will determine whether inflammatory markers from the blood are related to LMD radiation side effects so we can manage symptoms better and earlier (Aim 3).

If successful, this research will result in important **clinical benefits** for breast cancer LMD. This work will support wider use of an effective radiation treatment and give doctors and patients better tools to track whether treatment is working sooner which can help tailor care to each patient's disease. Finally, identifying specific inflammation markers may allow doctors to prevent or lessen side effects better which will improve patients' quality of life.

In conclusion, breast cancer LMD treatment has not changed significantly for several decades. Successful completion of this research is a **significant** step towards establishing more effective and better tolerated treatments against LMD by determining better tools that (1) provide earlier signs of treatment response and (2) predict treatment side effects and provide a unique opportunity to proactively minimize their occurrence.