PUBLIC ABSTRACT

The outcome for women who have metastatic breast cancer that has spread to brain remains significantly poor. Little of the current therapies (surgery, chemotherapy and radiotherapy) have failed to extend survival and or improve neurocognitive decline to a significant degree. After decades of work, this is unacceptable. In this application, we set out to understand what happens to the blood vessels in the tumor and in brain after radiation therapy. We know clinically that it most likely causes the vessels to be more porous or leaky, as women will with time, develop symptoms of edema in the brain. However, while this is qualitatively known, it is not been studied rigorously as to how long after, and what strength of radiation doses and where in the brain does this occur.

We have demonstrated using state of the art preclinical mouse brain metastases models (NIH; Steeg) that radiation at doses as low as 6 Gy and as high as 26 Gy result in leakiness of the vessels in the tumor but not in the normal brain. To administer the radiation to our mice our hospital radiation physicist developed protocols to mimic both whole brain clinical dosing protocols. To our knowledge, no other lab has the ability to combine this technology.

This application sets out to understand the radiation dependent response of leakiness of the blood vessels in tumor and the normal brain. Critically, we then propose to take advantage of vessel leakiness by giving chemotherapy during the period that the vessels in the tumor (not in the brain) are leaky. We will determine and map out the concentrations of the various chemotherapeutics in the tumor and normal brain as control. We will do this at two of radiation doses and timeframes. This data will help us determine if increased drug concentrations in the tumor after radiotherapy will improve tumor kill.

How does this help women with Stage IV metastatic disease?

It is important to note that the proposed work is simply coordinating timing of the current standard of care in both radiotherapy and systemic chemotherapy. It is well established that the two therapies are given to the vast majority of patients already. However, often they are distinct. While this work will answer a major question and controversy in the literature, additional work demonstrating that there is no additional neurotoxicity than current therapies given alone and must be done in future applications. It is our hope we will find a lower dose of radiotherapy that can induce tumor kill and combined with chemotherapy will have better effectiveness than either separately. We acknowledge there is an element of risk to the application, but if we are successful, it may provide a reason for different physician teams to come together and provide interdisciplinary care. This would be a revolution in treatment.

Importantly, while we do not believe this will cure metastatic brain cancer, if it can prolong survival or reduce the number of visits associated with progression we will have made strides in improving quality and duration of life in women with Stage IV metastatic brain disease. Further, while it is difficult to project, I believe clinical trials could be implemented within five years, and if successful protocols could be changed within ten.