Quantitative Tomographic In Vivo Imaging of Syngeneic Breast Cancer Metastasis to the Lung and Therapeutic Response

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1 Abstract

Breast cancer is a clinical challenge today, with almost 200,000 new breast cancer cases reported annually in the United States alone. In 20% breast cancer metastasis occurs in the body such as bone, liver, and lung, decreasing the 5-year relative survival rate to 20%. It is therefore critical to develop robust in vivo imaging approaches that can help dissect the metastatic process and assist in the development of effective targeted therapeutic agents. Using imaging and agent approaches that are transferrable from preclinical to clinical application further strengthens the utility of such efforts.

To best establish robust imaging measures of the metastatic disease process in a model resembling clinical disease, we used 4T1 murine breast adenocarcinoma cells injected intravenously into normal, immunologically-competent BALB/c mouse recipients. Three near infrared imaging agents, ProSense® 750 (PerkinElmer), a cathepsin-activatable agent; AngioSense® 860 (PerkinElmer), an integrin-targeted agent and IntegriSense® 680 (PerkinElmer), a vascular agent, were injected IV to detect the protease activity and vascular leak associated with aggressive breast cancer growth. Disease-specific fluorescence was imaged and quantified in vivo using the optical fluorescence Molecular Tomography (FMT) 2500®-quantitative imaging system, PerkinElmer, showing a consistent and significant increase in ProSense signal with time as early as 7-10 days, with accompanying increases in lung weight, a current standard measure in lung metastasis models. A standard clinical metric using 5-Fluorouracil (5-FU) to detect vascular leak was also measured, indicating that AngioSense provides a new, more sensitive measure of metastatic disease. Finally, 4T1 cells were injected into the tail vein of BALB/c mice, and mice were imaged by FMT 24 hours later. Three dimensional regions of interest (ROIs) were drawn to encompass the lung areas of 4T1 recipients and analyzed using careful quantitative imaging of reflectance (FRI), H&E, and fluorescence microscopy of lung tissue.

2 Results

Figure 1: Experimental protocol

4T1 Breast Cancer Lung Metastasis Model

BALB/c mice were injected intravenously with 5 x 10⁴ 4T1 cells. At six different time points after inoculation, mice were imaged by FMT 2500®-quantitative imaging system, PerkinElmer, showing a consistent and significant increase in ProSense signal with time as early as 7-10 days, with accompanying increases in lung weight, a current standard measure in lung metastasis models.

3 Summary

Mouse models of breast cancer metastasis rely predominantly on ex vivo tissue weight, nodule counts, and/or histologic analysis to assess disease burden. These measures are noninvasive, but quantitative imaging of deep tissue metastasis is needed. To achieve this, PerkinElmer developed a syngeneic breast tumor model in BALB/c mice, the 4T1 breast cancer cell line. Following tail vein injection of 4T1 cells, lung metastases were imaged by FMT 2500®-quantitative imaging system, PerkinElmer, to track disease progression and measure therapeutic benefit.

4 References