Multimodality Imaging: Development of Nude Rat Model of Metastatic Breast Cancer to the Brain

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Introduction

Brain metastasis occurs in ~20% of breast cancer patients with only 20% of those patients surviving 1 year after diagnosis. The purpose of this study was to develop a metastasis brain breast cancer rat model to monitor the natural history of disease using 3T MRI and bioluminescence imaging (BLI) to determine the extent of metastasis following intracardiac injection of luciferase and iron oxide nanoparticle labeled human MDA-MB-231BR cell line.

Methods

MDA-MB-231BR-Luc cell line was labeled with ferumoxides-protamine sulfate (FePro). Eighteen nude rats underwent intracardiac infusion of 1-3 × 10^6 labeled breast cancer cells under ultrasound guidance. MRI and BLI were done on day 1 - 3, and week 1 - 4 respectively. BLI was performed following IP dose of luciferin at 150mg/kg at 15 minutes post injection using IVIS™ camera and analyzed with Xenogen software to determine photoflux from animals. MRI was performed on 3-Tesla Philips in a solenoid 4 cm coil using T2w and T2* weighted imaging with 0.5mm slice thickness and 100-200 µm in-plane resolution. Immunohistochemistry and Prussian blue staining was performed.

Results

BLI demonstrated high photon flux from MDA-MB-231BR-luc in the brain on day 1 through 3 and decreased below threshold level at week 1. By 2 weeks, all animals in brain and skeletal metastasis on BLI that increased in photoflux to week 4. MR T2* weighted image of day 1-3 showed numerous hypointense regions corresponding to FePro labeled MDA-MB-231BR-luc cells in the brain (Figure). Hypointensities were no longer appreciated from weeks 1-4 following injection of FePro labeled cells. T2 w images showed hyperintense lesions. Cytokeratin (CK) staining of the brain show brown colored tumor cells attached and clogged in the microvasculature of the brain at the early period of metastatic event (day 1 - 3). Tumor grew over to over 200µm in size by week 2. Prussian blue positive cells were observed at early time points and corresponded to CK positive cells however Prussian blue positive cells could not be identified on histology at the late time points. All rats that had brain metastatic lesions were found to have spinal cord along with skeletal metastasis (vertebral body, shoulder, knees, pelvis and femurs). Diffuse tumor cell infiltrations were detected to the lung, lymph nodes, and spleen by CK staining. MRI of spinal cord demonstrated enhancing lesions along with vertebral body metastasis.

Discussion

MDA-MB-231BR breast cancer cell line was originally developed as a brain metastasis model in the mouse (3) and skeletal and systemic metastases were not reported. We developed the nude rat model using MDA-MB-231BR human breast cancer cell line in order to be able to monitor the development of cerebral metastasis using a clinical 3T scanner. Diffuse metastasis in the brain, spinal cord, skeletal, and other organs that were not always apparent on BLI. This difference in the distribution in metastasis between mouse (4) and rat may be due to species used or gene transfection with luciferase of the original cell line. By using multimodality imaging we were able to characterize the pattern and distribution of metastatic breast cancer in the nude rat allowing for the evaluation and monitoring of novel treatment strategies.

References

1. Melisko ME, et al Expert review of anticancer therapy 2005;5: 253-68. 2. Arbab AS, *et al.* Blood 2004;104: 1217-23. 3. Yoneda T, et al. J Bone Miner Res 2001;16: 1486-95., 4 . Heyn C et al MRM 2006;56:1001-10.

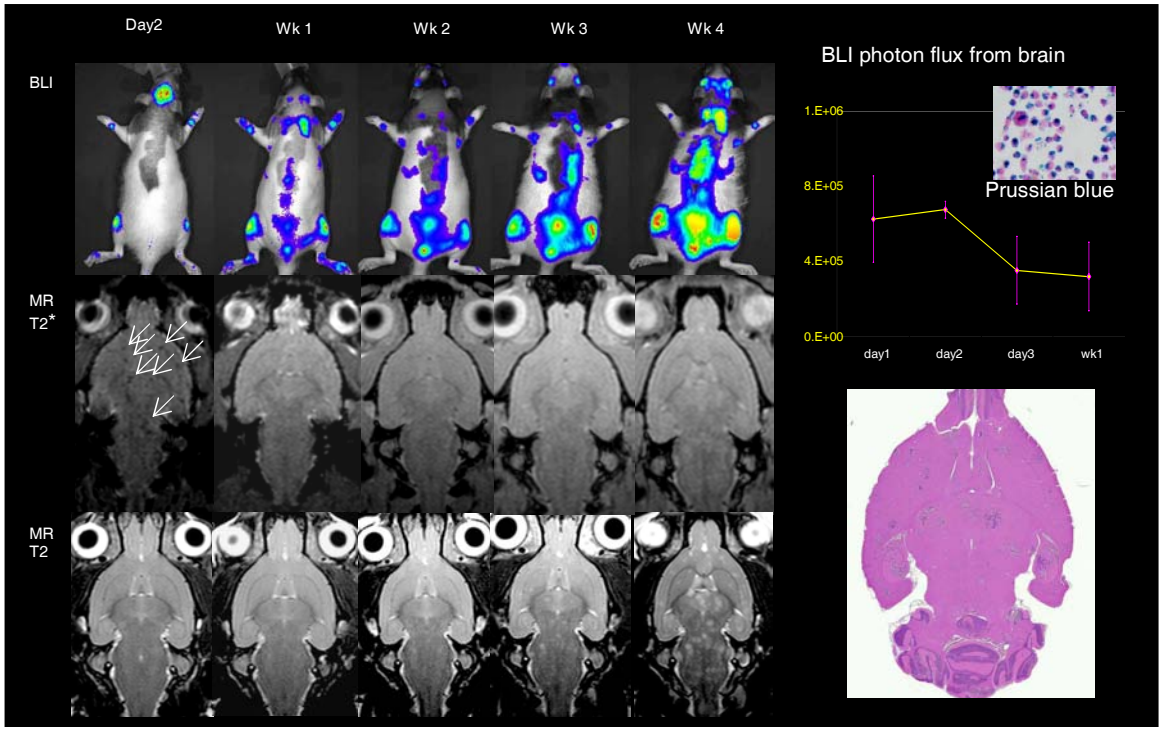

Figure. Serial BLI and MRI of rat following IC injection of 1×10^6 FePro labeled MDA-MB-231BR-Luc cells. Hypointense lesions on T2* weighted MR image on day 2 correlates well with high photon flux of the brain (arrows). Brain lesions are seen by week 2 and BLI photon flux activity is seen in skeleton and brain by week 3-4. H&E shows numbers metastatic lesions in brain.