Microscopic Morphology of Brain and Bone Metastases in a Rat Breast Cancer Model by Diffusion MRI

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Introduction

Diffusion MRI is a widely used technique to probe the tissue microstructure of the central nervous system and has shown promise as an early marker of therapeutic response in malignant gliomas[1]. However, metastatic tumors are the primary cause of intracranial tumors[2], and it is unknown whether brain metastases exhibit similar diffusion characteristics as the more commonly studied orthotopic brain tumor model.

Methods

1×10^6 MDA-MB-231-BR-eGFP[3] cells were delivered to 8 week old NIH-*rnu* rats by intracardiac injection. Rats underwent weekly MRI in a 7T Bruker Biospec with a 40 mm ID birdcage coil (Doty Scientific, Inc.). Diffusion tensor imaging (DTI) was performed with a pulsed gradient multiple-echo spin-echo sequence (TR/TE=2500/30 ms, echoes=4) with a 0.5 mm slice thickness and a 3×3 cm^2 FOV, resulting in an in-plane resolution of 234×234 μm^2. Diffusion weighted images were acquired along 15 directions using a b-value of 800 s/mm^2, a diffusion gradient separation (Δ) of 12 ms, and a diffusion gradient duration (δ) of 4 ms. Animals were perfusion fixed with 4 % paraformaldehyde, and brains were excised, cryoprotected overnight, and frozen in liquid nitrogen. Sections were cut at a thickness of 8 μm and imaged under a fluorescent microscope at 20x.

Results and Discussion

Brain metastases had higher apparent diffusion coefficient (ADC) values than the surrounding brain and had diffuse borders, characteristic of edematous and infiltrative tumors (**Fig. 1**). Consistent with these changes, the microscopic morphology of brain metastases was highly infiltrative and early tumor growth progressed as perivascular tumor clusters co-opting the existing vasculature (**Fig. 2, top**). In contrast, bone metastases had well-demarcated borders and grew as solid masses with little infiltration (**Fig. 2, bottom**). Consistent with these observations, brain metastases had significantly higher ADC values compared to both the surrounding normal brain and bone metastases.

Conclusions

Diffusion MRI is sensitive to the microscopic morphology of brain and bone metastases that develop organ-specific growth patterns as a consequence of their differing microenvironments.

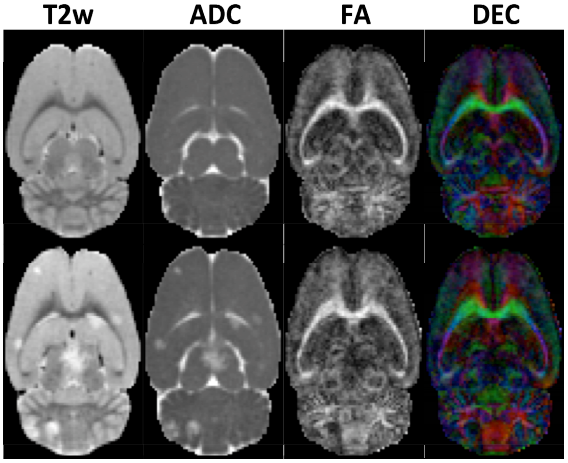
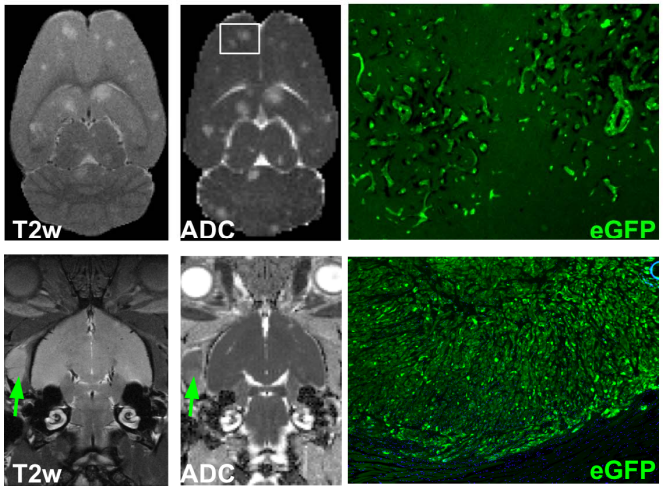


Figure 1. In vivo DTI before (top) and 4 weeks after (bottom) intracardiac injection of MDA-MB-231-eGFP cells demonstrates multiple breast cancer metastases in the rat brain.



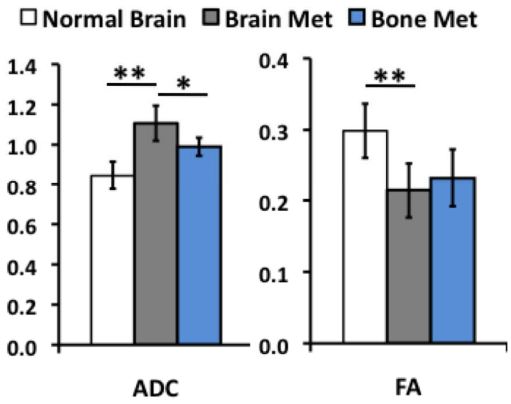


Figure 2. MDA-MB-231 brain metastases (top) had poorly demarcated borders and were highly infiltrative with significant vasogenic edema. In contrast, bone metastases (bottom) had well-demarcated borders and developed as solid masses with minimal infiltration. Brain metastases (n=10) had significantly higher ADC and lower FA values than the normal brain tissue whereas bone metastases (n=5) had a significantly lower ADC than brain metastases. **- $p < 0.001$, *- $p < 0.05$.

References [1]Padhani AR, et al. *Neoplasia* 2009; [2]Krumina G. *Eur Radiol* 2005; [3]Palmieri D, et al. *Clin Cancer Res.* 2007