High Resolution MR Angiography of Tumors using Iron-Oxide Contrast Agent

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Motivation: Tumor vessels play a pivotal role in tumor growth, and thus many new anticancer agents target tumor vasculature. Therefore, noninvasive monitoring of changes in the tumor vasculature is one of the most fascinating interests in cancer therapy and imaging. Although MR angiography (MRA) allows direct visualization of the tumor vasculature, its spatial resolution is limited by the method and only relatively large mature blood vessels can be imaged using current techniques. We propose to use SPIO-based blood pool contrast agents for susceptibility contrast enhanced MRA. These agents remain intravascular in the leaky tumor vasculature, and provide improved visualization of small blood vessels due to the 'blooming effect' in T_2*-weighted MR images.

Methods: Orthotopic xenograft models were grown in female SCID mice by injecting 10^6 of human breast carcinoma MDA-MB-231 cells into the mammary fat pad of the animal. In this study, we used high molecular weight contrast agent, GdDTPA conjugated with BSA (GdDTPA-BSA), and superparamagnetic iron oxide (SPIO) nanoparticles as a positive and a negative contrast agent, respectively. Anesthetized mouse with catheterized tail vein was placed in a cradle with the tumor positioned in a home-built solenoid coil. To obtain tumor angiograms, pre- and post-contrast images were acquired on a horizontal bore Bruker Biospec 4.7T spectrometer using 3D gradient echo imaging sequence with a spatial resolution of 140×250×250µm zerofilled to the uniform 140µm. MRA with GdDTPA-BSA contrast agent were acquired using T1 weighted sequence with parameters TE/TR=3/10ms, NEX=8, and flip angle of ~30^0. The agent was injected in the tail vein of the animal at a dose of 600 mg/kg. MRA with Feridex® (2.5 ml/kg) were acquired with T2* weighted GE sequence using TR=10ms, NEX=8, flip angle of ~10^0, and three echo times of 1.5, 3.0, and 5.0ms. All images were reconstructed using IDL (ITT Visual Information Solutions) software and 3D images and 2D slices where visualized and analyzed using Amira (Visage Imaging, Inc, USA) and ImageJ (National Institutes of Health, USA) visualization software, respectively.

Results: As illustrated in Fig. 1, GdDTPA-BSA displayed only a few vessels at the peripheral area of the tumor, while SPIO provided tumor angiography with higher resolution due to the 'blooming effect' in T_2*-weighted MR images. As echo time increased from 1.5 to 5ms, progressively more blood vessels in the tumor center were visualized by the method (white arrow in Fig. 1). However, the 'blooming effect' also resulted in significant signal decay from the large blood vessels next to the tumor periphery that masks morphological details. Therefore, to reconstruct high-resolution angiograms a combined analysis of MRA acquired with different echo times is required. In this approach short echo time images will provide information regarding large blood vessels whereas long echo time images can be used to reconstruct geometry of smaller blood vessels.

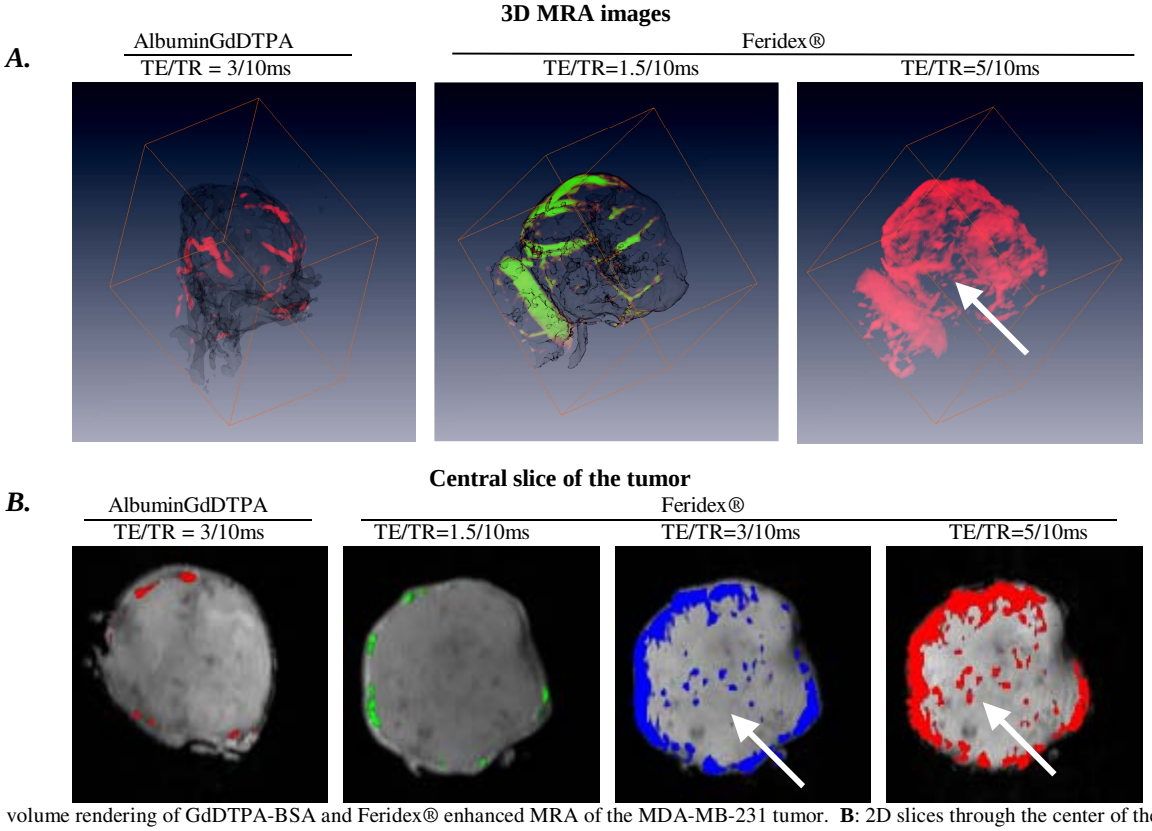

Figure 1. A: 3D volume rendering of GdDTPA-BSA and Feridex® enhanced MRA of the MDA-MB-231 tumor. **B**: 2D slices through the center of these tumors demonstrate significant enhancement of small tumor blood vessels at long echo times (white arrows) combined with extensive 'blooming' from large blood vessels.

Conclusion: MRA with SPIO-based T2* contrast agent provides more detailed information on tumor angiography compared to GdDTPA-BSA enhanced MRA. Combination of short and long echo times enables reconstruction of tumor angiography with high spatial resolution for blood vessels with the diameter smaller than the spatial resolution of MR imaging.