Simultaneous MR and Optical Imaging of Tumor Microenvironment

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Introduction: Physiologic parameters obtained from MR imaging, like other modalities, could be corroborated if compared with a gold standard, or as there is usually no such standard, to a different independent measurement. Various studies have compared MR results with other imaging modalities such as PET, optics and ultrasound [1]. If preclinical animal experiments, it is usually advantageous to do the measurements simultaneously since it can reduce the time of the experiment and possible confounding side effects such as anesthesia and contrast agent injection. In certain studies, due to the dynamic nature of the study, measurements can only be compared if they are done in one single experiment simultaneously. One specific application of this kind is the measurement of vascular permeability.

Measuring vascular permeability is critical both in the study of tumor microenvironment and cancer therapy. Altered biochemical communication between the vascular system and tumor tissue is responsible for many abnormalities in the tumor microenvironment such as hypoxia, low tumor pH and high interstitial fluid pressure. In cancer treatment, the goal of chemotherapy is to maximize specificity of intravascularly administered therapeutic agents to malignant cells. Blood perfusion in the tumor can vary in as short an interval as one hour [1]. In the case of measuring the permeability effect on the delivery of therapeutic agents, the condition of tumor might be considerably different after each experiment. In addition, many studies of vascular permeability are done on subjects under anesthesia. Anesthesia has many side effects including changes in blood flow and metabolism and subsequently in vascular permeability.

In addition to cross-validation of results, simultaneous multi-modality imaging allows to measure various physiological quantities in one single study [2].

We report on a new methodology that allows high resolution focused MR imaging to be compared to optical microscopy in one simultaneous study. The methodology is based on a system the can perform optical and MR imaging in a dorsal skin-fold animal model. We have tested this methodology to study vascular permeability within a tumor model microenvionment. By using this methodology, we were able to measure mircovascular permeability with MR and optical modalities and cross-validate the results.

Methods: Green fluorescent protein (GFP)-transfected PC-3 human prostate cancer cells were injected in the mouse dorsal skin-fold window chamber. The window chambers have 11mm diameter and are made from plastic to eliminate interference with the magnetic field. The mouse was located in a platform that relayed the image of the window chamber at the center of the MR bore to a camera outside of it. White light and two laser line illuminations were provided through illumination fibers from under and above the window chamber, respectively. Laser line illuminations, accompanied by corresponding notch filters in the imaging path, allowed fluorescence imaging of both the GFP transfected tumor cells and the injected contrast agent. MR signal excitation and reception was accomplished with an open surface coil located on top of the window chamber. Figure 1 illustrates the imaging system.

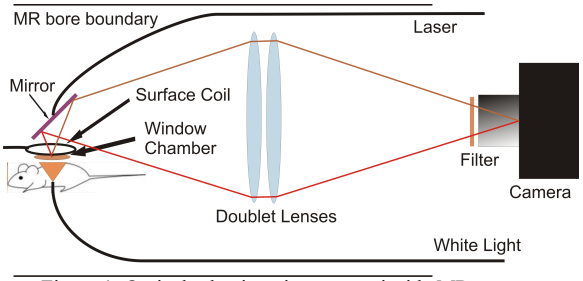

Figure 1: Optical relay imaging system inside MR scanner

MR images consisted of a sequence of images with varying TR to measure T1 and a sequence of images at fixed TR to measure dynamic signal intensity after contrast agent injection. Both imaging sets were 2D spin-echo with 2.56 cm square field of view and 5mm slice encompassing the entire window chamber volume. The contrast agent was bovine serum albumin (BSA) dual labeled by GdDTPA and Alexa Fluor 647. The contrast agent was injected thorough a tail vein catheter.

Image analysis in both modalities was performed using a program written in Matlab. Arterial input function in the MR was obtained by our new methodology from the vessels inside the window chamber. This eliminated the issue of flow effects in large arteries as well as phase delay between the artery and the measurement site in conventional DCE measurements [3]. Our method allowed for separation of interstitial and vascular signal in each voxel. This was done by comparing the signal prior to and immediately after injection of contrast agent and the sequence of images obtained at various TRs. Optical measurement of vascular permeability was done by the method described by Dewhirst et al [4].

Results: Sample images from both modalities before and after contrast agent injection are shown in figure 2. In figure 2.a, the MR image was obtained with TR = 500 ms, TE = 10.7 ms, image matrix = 256x256. The optical image is a combined fluorescence imaging of GFP in tumor cells and white light imaging to illustrate the tissue structure. Figure 2.b illustrates contrast agent distribution in both modalities after injection of the dual-labeled contrast agent. The MR imaging parameters were TR = 250 ms, TE = 10.7 ms, image matrix = 128x128. The source of illumination for Alexa Fluor excitation in the optical image is a HeNe laser at 632 nm. All four images in figures 1 and 2 were taken from one mouse during one imaging session.

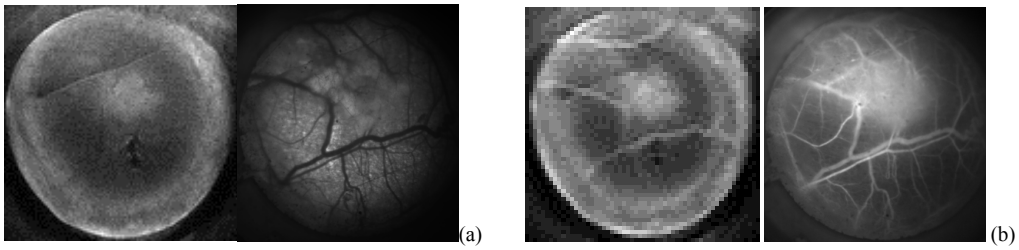

Figure 2: MR and Optical image before (a) and after contrast agent injection (b)

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