Comparison of Diffusion and DCE-MRI as Markers for Response to Therapy in HCC Patients

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Introduction: Both diffusion tensor and diffusion weighted MRI have been used extensively in the evaluation of neurological disorders including stroke, Alzheimer's disease, and multiple sclerosis [1 – 3]. More recently, interest has grown in the use of diffusion MRI to evaluate and predict response to therapy in various cancers [4 – 6]. Diffusion tensor imaging, which is most useful in the brain for mapping the layout of white matter bundles, is not particularly applicable to the analysis of cancers, where an orderly arrangement of barriers to diffusion is not expected. Apparent diffusion coefficient (ADC), however, can be a useful proxy for cellular density within a tumor. In this study, we have evaluated the practicality and utility of using changes in ADC as an indicator of response to therapy in hepatocellular cancer (HCC). In the first phase of the study, 12 normal volunteers were imaged twice with a temporal separation of roughly 40 minutes between scans. ADC values were then calculated for regions of normal liver tissue and these results were used to estimate the scan-rescan coefficient of variability (CoV) for this measurement. In the second phase of the study, seven HCC patients were imaged at baseline and again after (1) administration of an anti-angiogenic agent, and (2) chemoembolization. Patients were also imaged at each time point using DCE-MRI [7], and changes in ADC were correlated with changes seen in blood flow and vascular permeability.

Methods: Imaging of normal volunteers was carried out at the University of Rochester Medical Center. IRB approval was obtained for this experiment, and all experimental subjects provided informed consent. Images were obtained in the axial plane. 24 slices were obtained with 5mm slice thickness. The slab was positioned to cover as much of the liver as possible. Each acquisition included a B0 image and three directional images. Four separate diffusion acquisitions were obtained at each imaging session (B0 = 700/1000, ASSET on/off) in order to determine the effects of these parameters on ADC reproducibility. Total acquisition time for each ADC map was ~24s, and each was obtained during a single breath hold.

Imaging of HCC patients was carried out at Roswell Park Cancer Institute. IRB approval was obtained for this study, and all patients provided informed consent. ADC maps were acquired in a similar manner to that used in normal volunteers, with B0=1000 and ASSET off. The primary difference between normal volunteer and patient imaging was that the HCC patients also were imaged using DCE-MRI. DCE-MRI data were obtained in the coronal plane. A 12 slice slab (8 retained) was obtained with 8mm slice thickness, with the slab positioned to include both the target lesion and the descending aorta. T1 weighted images were acquired using the inherent body coil. 44 phases were acquired with ~8s temporal resolution. A .1mM/kg injection of Gd-DTPA was administered after the fourth phase using a power injector at 3cc/s followed by a 20cc saline flush. Patients were imaged at baseline and on Day 8 after the initiation of anti-angiogenic therapy. Patients were then treated with chemoembolization and imaged again one day later. A fourth imaging session was conducted after approximately four more weeks of anti-angiogenic therapy.

Results: In Phase 1 of this study CoV for ADC measurements in liver tissue for normal volunteers were estimated for each of the four parameter combinations mentioned above. CoV for the four parameter sets ranged from a low of 7.8% to a high of 9.5%. The differences among the four parameter sets were not significant. Based on these results, we can conservatively estimate that the change in ADC necessary to demonstrate statistical significance in a single patient is approximately 20%.

In Phase 2 of this study we calculated change from baseline in the target lesions for both median ADC and median K^{Trans}. A total of 14 (of a possible 21) post-baseline imaging sessions were obtained in which both diffusion and DCE-MRI imaging were successful. Reasons for the loss of the remaining 7 session included early patient withdrawal from the study, excessive patient motion, and failed contrast injection. A plot showing correlation of change from baseline in median ADC with change from baseline in median K^{Trans} is given in Figure 1 below.

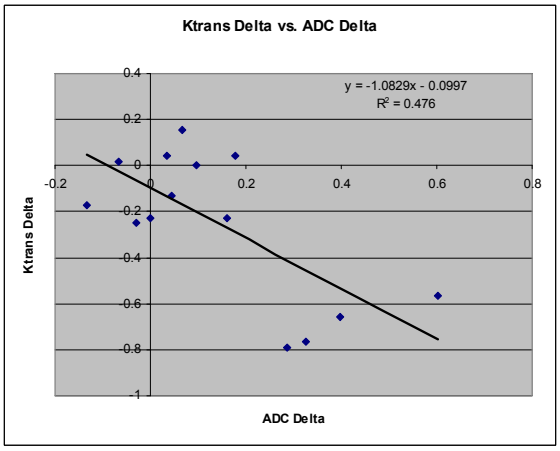

Figure 1: Plot comparing change in ADC to change in K^{Trans} for the 14 successful post-baseline imaging sessions in Phase 2 of this study. Note that the correlation seen here is statistically significant (p = 0.006).

Discussion: These results show a clear relationship between reductions in K^{Trans} measured using DCE-MRI and reductions in ADC. DCE-MRI has been shown to be a reliable marker for response to anti-angiogenic or anti-vascular therapy [8 – 10]. It is reasonable to conclude from these results that, at least for this disease and treatment regimen, ADC measurements provide substantially similar information. From an acquisition standpoint, diffusion imaging has significant advantages over DCE-MRI. The acquisition is much faster, and it does not require a contrast injection, making patient compliance more likely. Moreover, diffusion measurements can be made over much or all of the body in a single session if necessary, while DCE-MRI is limited to a single slab acquisition due to the necessity to wait at least 24 hours prior to a second contrast injection. Finally, it is possible (as in this study) to include both DCE-MRI and diffusion measurements in a single acquisition protocol, providing some insurance against failure in one modality or the other.

References: [1]Kidwell C, Alger J, *et al.,* Stroke 30:1174-1180, 1999. [2] Bozzali M, Franceschi M, *et al.,* Neurology 57:1135 - 1137, 2001. [3] Werring D, Brassat D, *et al.,*Brain 123:1667 – 1676, 2000. [4] Chenevert T, Meyer C, *et al.,* Mol Imaging 1:336 – 343, 2002. [5] Ross B, Moffat B, *et al.,* Mol Cancer Ther 2:581 – 587, 2003. [6] Theilmann R, Borders R, *et al.,* Neoplasia 6:831 – 837, 2004. [7] Tofts P, J Magn Reson Imag 7:91 – 101, 1997. [8] Rugo H, Herbst R, *et al.,* JCO 23:5474 – 5483, 2005. [9] Hahn O, Yang C, *et al.,* JCO 26:4572 – 4578, 2008. [10] Checkley D, Tessier J, *et al.,* Br J Cancer 89:1889 – 1895, 2003.