Dynamic Glucose Enhanced (DGE) MRI for Imaging Brain Cancer

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Target audience: Clinicians/researchers interested in using MRI for noninvasive monitoring of tumor perfusion and glucose uptake.

Purpose: Recently, simple D-glucose was suggested as a potential biodegradable contrast agent for MRI based on the exchangeable hydroxyl protons which can either be detected using chemical exchange saturation transfer (CEST or glucoCEST)[1-3] T1ρ[4,5] or T2 relaxation[6] . Here the feasibility of using D-glucose for dynamic perfusion and permeability imaging is explored as applied to the detection of brain cancer.

Methods: Animal preparation: SCID mice (n = 4) were innoculated orthotopically with human U87EGFRVIII glioma cells. As these cells grow very fast the protocol was optimized for post-implantation imaging time on a group of mice. Four mice were then imaged at the optimal time of 7 days post inoculation. The tail vein was catheterized for glucose and Gd contrast infusion. Dynamic glucose enhanced (DGE) imaging was used to measure the tissue response to an intravenous bolus of 50% D-glucose in water. CEST MRI: Time-resolved D-glucose signal changes were detected using chemical exchange saturation transfer (glucoCEST) MRI at the hydroxyl proton frequency. The DGE images were acquired over 20 minutes using a short-echo Rapid Acquisition with Relaxation Enhancement (RARE) sequence using a temporal resolution of 10s, TR/TE = 5.0 s/3.8 ms, RARE factor of 23,a matrix of 128x64 and a FOV of 1.6 cm^2 (All images were normalized to an image without saturation acquired prior to infusion). A single slice with 0.12 x 0.25 mm^3 in plane resolution and thickness of 1 mm was imaged with fat suppression. Saturation was achieved by a single continuous wave magnetization transfer (MT) pre-pulse of 3 s at B_1 = 1.6 μT[1]. A bolus of 0.15mL 50% D-glucose was infused through the tail vein over 1 minute starting at 3 minutes (defined as time 0) after the dynamic imaging acquisition started. DCE MRI: Gd dynamic contrast enhanced (DCE) images were acquired one hour post glucose infusion, without repositioning the mouse,. Multi-slice T_1 weighted images were obtained using a saturation recovery gradient echo sequence[7] with TE/TR/FA= 1.5 ms/26 ms/ 90˚ over a slice package centered at the slice for CEST imaging. The image resolution was the same as the CEST images and the temporal resolution was 10 s. After a series of 8 pre-contrast images, a bolus injection of 0.1 mL of 0.1 M Gd-DTPA was given and 32 post-contrast images were collected over ~5 min. Data analysis: Glucose dynamic difference images were generated by taking the difference between the average pre-infusion images and each dynamic image. Area under curve (AUC) images were calculated by integrating the images acquired over the first 5 minutes after the beginning of the glucose/Gd infusion.

Results and Discussion: Glucose dynamic difference images (Fig. 1a) showed negligible contrast change during the pre-infusion period, whereas during and after infusion of glucose, the vessels became visible and contrast between tumor and brain emerged. When plotting the dynamic profile from the tumor and contralateral brain regions, it can be seen in Fig 1b that the tumor takes up more glucose than the contralateral side of the brain and the glucose level remains at an elevated level during the course of the dynamic study. These results indicate a difference in perfusion and uptake between the tumor and normal brain tissue. AUC images over 5 min of DGE (middle), Gd-DCE (right) were overlaid on the anatomical image (left) in Fig 2a. The DGE AUC images show similar hyper-intensity over the tumor region as the DCE AUC images. This result indicates that DGE reflects comparable tumor perfusion as DCE.The statistics plotted in Fig 2b shows the difference in perfusion is consistently observed in 4 mice.

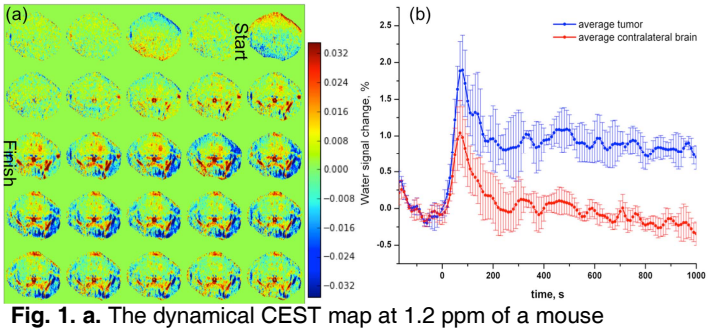

Fig. 1. a. The dynamical CEST map at 1.2 ppm of a mouse glioblastoma model. **b.** The average change in signal intensity (n=4) for the tumor and the contralateral brain.

Conclusions: DGE MRI is a highly feasible technique for the study of brain tumor enhancement and related perfusion and permeability parameters. We expect DGE will provide a low-risk and low-cost alternative for cancer studies in which DCE CT and MRI are used for diagnosis and prognosis. Further studies are underway to study the features of the DGE and DCE models.

References: 1. Chan KW, et al. *Magn Reson Med* 2012, 68:1764-1773. 2. Walker-Samuel S, et al. *Nat Med* 2013, 19:1067-1072. 3. Nasrallah FA, et al. *J Cereb Blood Flow Metab* 2013. 4. Jin T, et al. *J Cereb Blood Flow Metab* 2014, 34:1402-1410. 5. Zu Z, et al. *Magn Reson Imaging* 2014, 32:1078-1084. 6. Nirbhay Yadav, et al, Magn Reson Med 2014, 72:823-828. 7. Zhu W, et al. *Magma* 2014, 27:161-170. **This study was supported by NIH P50CA103175 (NCI), R01EB015032 (NIBIB), S10RR028955 (NCRR) and R21EB018934 (NIBIB)**

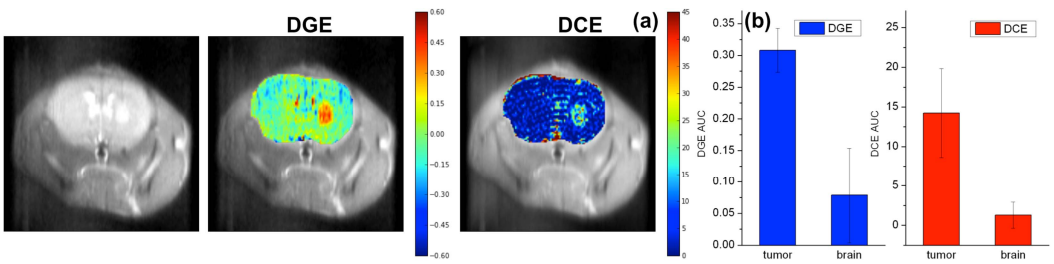

Fig. 2. a. Anatomical reference image and the AUC images for the DGE and DCE. **b.** The mean AUC for the tumor and the contralateral brain obtained from DGE and DCE. Both methods show significant difference between the tumor and brain at $p<0.05$.