In vivo Detection of a PARACEST Agent in Mouse Brain Tumors

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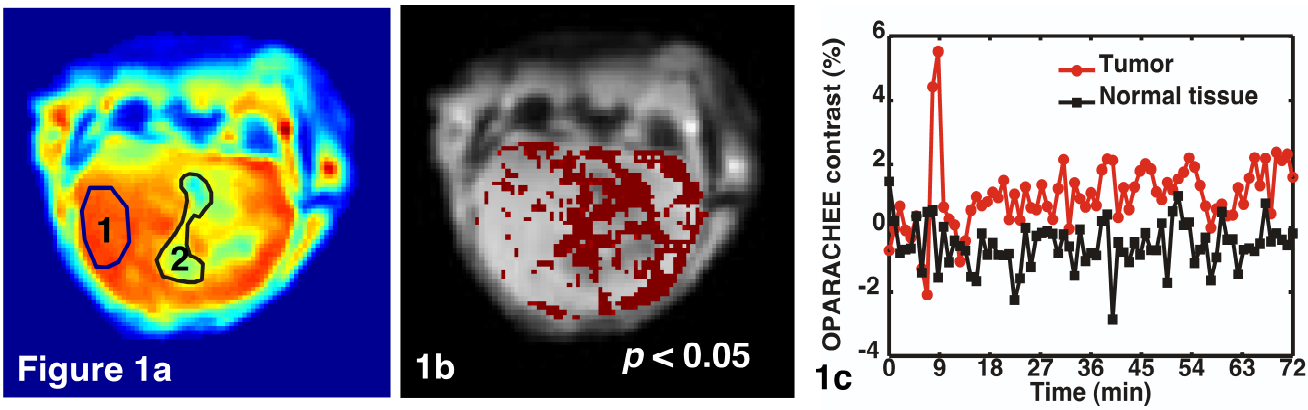
Introduction: Paramagnetic chemical exchange saturation transfer (PARACEST) contrast agents (1-3) are being developed for biological target identification by magnetic resonance imaging (MRI). Image contrast associated with PARACEST agents can be generated by radiofrequency (RF) irradiation of agent bound protons, or on-resonance irradiation of the bulk water protons (4). The observed image signal changes induced by PARACEST contrast agents include the effects of altered relaxation time constants and the CEST effect. The purpose of this study was to demonstrate the in vivo detection of PARACEST contrast agents in a mouse Glioblastoma Multiforme (GBM) tumor model and to isolate the relaxation effects induced by the PARACEST agent from the on-resonance paramagnetic chemical exchange effects (OPARACHEE) (5).

Methods: GBM tumors were induced in NU/NU mice (N = 4) by stereotactically injecting 10^5 U87MG cancer cells in the left frontal lobe at coordinates 0.5 mm anterior to bregma, 1.5 mm lateral from midline, and 3.3 mm deep. Two to three weeks after cancer cell injection, images were acquired on a 9.4 Tesla Varian MRI scanner following tail vein injection of 150 µL 50 mM Tm^{3+}-DOTAM-Glycine (Gly)-Lysine (Lys). A fast low angle shot (FLASH) pulse sequence preceded by a WALTZ-16 pulse train (6) was used to produce the OPARACHEE contrast. Images were continuously acquired using the FLASH pulse sequence (Field of view = 25.6 × 25.6 mm^2, data matrix = 256 × 256, repetition time = 25 ms, echo time = 4.04 ms, flip angle = 11°, 3 averages, and thickness = 2 mm), preceded by a 5 second delay. A WALTZ-16 pulse train (pulse power = 10.0 µT and pulse duration = 0.24 s) was applied prior to every second acquisition to generate OPARACHEE contrast. The alternating image without WALTZ-16 preparation was used as a control. For the dynamic studies of PARACEST agent uptake, 5 to 25 image pairs (one OPARACHEE image and one control image) were acquired before the injection of PARACEST agent and 40 to 80 image pairs were acquired continually during and after the agent administration. The signal intensity difference between the control image and the OPARACHEE image was estimated using $100\times(I_{control}-I_{OPARACHEE})/I_{control}$, and the OPARACHEE contrast was calculated by comparing the signal intensity difference of the image pairs acquired before and after the agent administration. The averaged contrast following agent administration was used to create the OPARACHEE contrast map. Pixels that showed significant OPARACHEE contrast before and after the agent administration were determined using a *t*-test ($p < 0.05$ considered significant).

Results and Discussion: Isolated OPARACHEE contrast was observed within tumor in all animals (~ 1-3 %). Data for one animal is shown in Figure 1 (Figure 1a: colorized FLASH image showing regions of healthy tissue (1) and tumor (2)). Immediately after contrast agent injection OPARACHEE contrast was observed (~5%) and then maintained at 1~2% in the hour following injection (Figure 1c). This result is the first in vivo observation of OPARACHEE contrast in brain tumors and demonstrates the isolation of OPARACHEE contrast from T_1 and T_2 relaxation effects. Pixels showing a significant increase in OPARACHEE contrast are shown in the *p*-value map (Figure 1b, $p < 0.05$ indicated in red). Significant OPARACHEE contrast was observed mostly in the tumor region (Figure 1b).



Conclusion: The results demonstrate that the OPARACHEE method can detect PARACEST agent uptake in brain tumors and the OPARACHEE contrast can be isolated from the T_1 and T_2 relaxation effects induced by this class of contrast agent.

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