DETERMINATION OF HYPOXIC TUMOR FRACTION USING MRI AND PET IN C6 RAT BRAIN TUMORS

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Target Audience: This research is targeted toward researchers and clinicians interested in advanced methods for imaging hypoxia.

Purpose: Tumor hypoxia is associated with both poor treatment response and poor long-term prognosis. With the advent of new hypoxia-activated cytotoxic prodrugs, there is significant interest in developing non-invasive hypoxia imaging methods, which may ultimately guide patient selection for clinical treatment. In this preliminary study, we aimed to optimize MR and PET acquisition techniques in order to compare the ability of ^{18}FMISO PET, ^{64}Cu-ATSM PET, and quantitative BOLD (qBOLD) MRI to measure hypoxic tumor fraction in a known hypoxic tumor model (3). ^{18}FMISO and ^{64}Cu-ATSM PET tracers are known to target tumor hypoxia (1), while the qBOLD method was recently developed to map local oxygen saturation (LSO_2) (2).

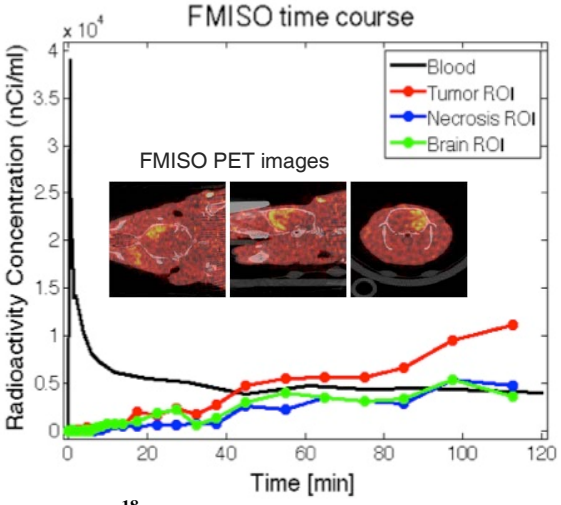

Figure 1: ^{18}FMISO time courses for blood and tumor, necrotic, and normal tissue. Inset: Sum of all dynamic ^{18}FMISO PET images.

Methods: C6 glioblastoma cells were implanted in Wistar rats, and imaging was started after 12 days using ^{18}FMISO PET, ^{64}Cu-ATSM PET and qBOLD MRI. Intravenous and arterial catheters were inserted for contrast administration and PET blood sampling, respectively. Dynamic ^{18}FMISO PET (42 timeframes/2 hrs) was performed following bolus injection of ~1mCi ^{18}FMISO. Static (2-hr) ^{64}Cu-ATSM PET was performed 18 hours after bolus injection of ~1mCi ^{64}Cu-ATSM. MRI was performed at 4.7T (Agilent). The qBOLD protocol included T_2 mapping (multiple spin-echo sequence: TR=3s, TE=9ms, ΔTE=9ms, NE=18) and T_2* mapping (pre- and post-contrast 3D multi-gradient-echo sequence: TR=100ms, TE=2.82ms, ΔTE=3.4ms, NE=20, 0.2 mmol/kg MION dose), where the steady-state BV maps are produced from the pre- and post-contrast T_2* maps. The LSO_2 maps were computed from the qBOLD data as previously described (2).

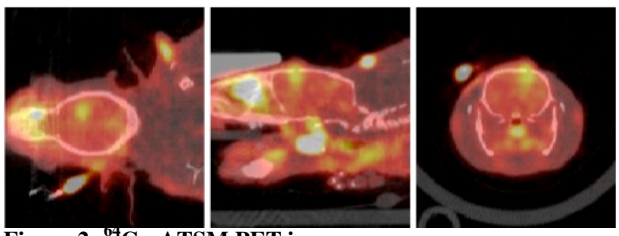

Figure 2: ^{64}Cu-ATSM PET images

Results: Preliminary data acquired in three separate rats show promising results for determining the hypoxic tumor fraction. Figure 1 demonstrates ^{18}FMISO time courses for ROIs selected from tumor, normal brain, and necrotic tissue, along with the blood activity obtained from arterial sampling. Consistent with previous results, the tumor activity increases while the normal and necrotic tissue regions plateau at the later times. The tumor is readily visible on the PET images (inset). Kinetic modeling will be used to quantify the hypoxic tumor regions, for comparison to the total tumor volume obtained with MRI. Figure 2 shows ^{64}Cu-ATSM images, where the tumor region is clearly visible, and can be compared to MRI tumor volume. Figure 3 shows the parametric LSO_2 map obtained with the qBOLD protocol. Tumor LSO_2 values are much lower than those found in the surrounding normal tissue.

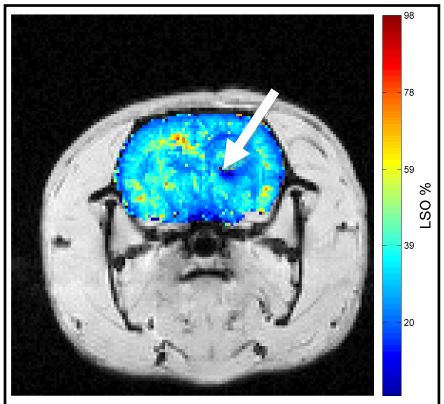

Figure 3: qBOLD LSO_2 map

Discussion/Conclusions: The direct comparison of these imaging modalities in the same tumors is of great clinical interest as their ability to detect hypoxia differs due to the underlying targeting mechanisms in the PET and MRI methods: where the PET agents are selectively sensitive to hypoxia via irreversible binding following reduction in the hypoxic tumor environment, while qBOLD is sensitive to the local blood oxygen saturation. Though qBOLD does not provide a direct measure of hypoxia, it may prove advantageous because of improved spatial resolution and more readily available contrast material. We are currently acquiring these datasets in a larger cohort of rats and tumor models that do and do not exhibit hypoxia. We aim to compare and contrast their ability to determine the hypoxic tumor fraction and predict response to a hypoxia-activated cytotoxic agent.

References: 1. O'Donoghue JA, et al. International Journal of Radiation Oncology Biology Physics 2005;61(5):1493-1502. 2. Christen T, et al. Nmr in Biomedicine 2011;24(4):393-403. 3. Khan N, et al. International Journal of Radiation Oncology*Biology*Physics 2009;73(3):878-885.