Imaging pH in Glioblastoma Multiforme with CEST MRI (IMAGO Trial): Preliminary Findings

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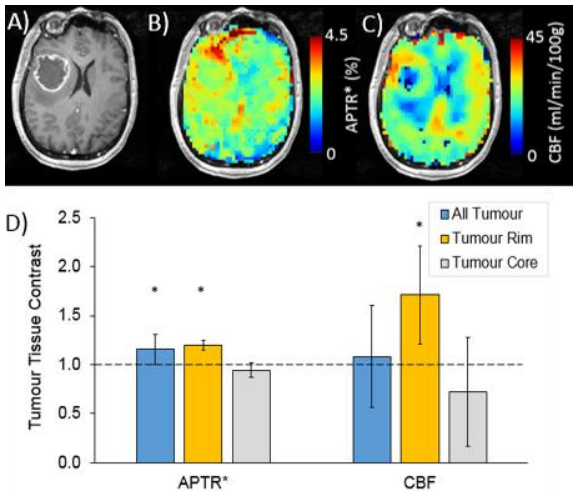
Introduction: Amide Proton Transfer (APT) CEST MRI has potential value as a cancer imaging tool, however, the pathophysiology underlying APT contrast in tumours is not well understood, likely reflecting both intracellular alkalosis, and disruptions in protein content[1-4]. Here, we present preliminary results from an ongoing clinical study integrating APT CEST MRI, with arterial spin labeling (ASL), and image-guided tissue based assays in patients with Glioblastoma Multiforme (GBM).

Methods: 8 patients with primary occurrence of GBM scheduled for surgical resection/debulking were imaged at 3T (Siemens TimTrio), with research and presurgical standard of care imaging performed in one session. Acquired images included MPRAGE (with/without Gadolinium, TR/TE=1900/3.17ms, 0.7×0.7×1mm), APT CEST (40ms duration, 184°, 50% duty cycle, CW: 0.55μT, 53 saturation frequencies -100:100ppm, TR/TE=5s/27.2ms), ASL MRI (5 PLD, 3.4×3.4×5mm, TR/TE =5484/14ms)[5], and a T_1 map acquired with the VFA technique (FA's=5-25°, TR/TE=20/3.67ms, 1.7×1.7×5 mm). APTR* was fitted using Bayesian model-based analysis, assuming 3 pools (water, amide, NOE/MT), and voxelwise T_1 priors[6,7]. CBF was quantified in FSL[8], assuming the general kinetic model[9]. Tumour and normal tissue (NT) ROI's were manually defined on the Gd-enhanced MPRAGE, and APTR* and CBF compared between ROIs using a paired *t*-test (α=0.05).



1A) Contrast-enhanced MPRAGE, B) APTR* map and C) CBF map in representative subject with GBM and rim-core structure. D) APTR* and CBF contrast (Tumour/contralateral tissue) across all subjects (blue, N=8) and rim-core subcohort (orange, grey, N= 5). Data shown as mean ± SD, * denotes a significant difference (p < 0.05).

Results: Mean tumour APTR* was significantly elevated in comparison to normal tissue, but CBF was not. 5/8 patients presented with a rim-core structure, with both APTR* and CBF significantly increased in the tumour-rim (Fig.1D).

Discussion: Here we show that APTR* is globally elevated in GBM, consistent with intracellular alkalosis and/or increase in protein concentration[2], with further regional changes in tumours with cystic/necrotic cores. In the rim-core subcohort, we observe an additional disruption in CBF, consistent with an angiogenic infiltrating tumour rim. However, CBF contrast was more variable than APTR*, which could reflect either suboptimal CBF quantification in tumours, or their sensitivity to different pathophysiological mechanisms. The ability to map pH-sensitive metrics, suggests that APT CEST could be valuable in surgical resection, to overcome challenges faced by conventional MRI. Future work will use CEST-guided biopsies which have been acquired as part of presurgical planning and snap-frozen, to better understand the pathophysiological basis of APT contrast in tumours; to include tissue based assays of hypoxia, pH and proteomic analysis.

References: [1] Zhou et al., 2003, *Nat. Med.* [2] Ray et al., 2018, *Proc. ISMRM.* [3] Xu et al., 2014, *NMR Biomed.* [4] Yan et al., 2015, *Mol. Imaging Biol.* [5] Harston et al., 2015, *Brain* [6] Chappell et al., 2009, *IEEE Trans Signal Process.* [7] Chappell et al., 2013, *MRM.* [8] http://www.fmrib.ox.ac.uk/fsl/basil [9] Buxton et al., 1998, *MRM*.