Tumour progression with parametric maps of endogenous CEST at 7T

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Introduction: Endogenous chemical exchange saturation transfer (CEST) shows promise for detection and measurement of protons in several metabolites in vivo, including amide groups in the protein backbone [1], and hydroxyl groups in glycogen[2]. One area where this concept has been applied is in the imaging of cancer where higher cell density leads to an enhanced amide effect [1,3,4]. Although much of the focus has been on the changes in the amide peak, we were interested in examining the lipid and hydroxyl peaks as well to determine whether they could further characterize the evolution of the tumour. The purpose of this study was to measure the evolution of CEST spectra over time in a rapidly growing murine model of lung cancer (LLC).

Method: 5 mice with LLC tumours implanted in the left hind leg were imaged on a 7T preclinical MRI (Bruker Biospin) a week post-implantation. The CEST imaging sequence consisted of a single rectangular off-resonance RF pulse which was 490 ms in duration followed by a spoiled gradient-echo (FLASH) readout with TR/TE = 500/3.1 ms at a resolution of 0.5x0.5x2mm. This sequence was performed for a saturation pulse amplitude of 0.57 μT and the off-resonance frequency ranged between -2000 and 2000 Hz (6.71 ppm) in increments of 50 Hz and with 5 reference images at 20000 Hz interspersed throughout the acquisition to allow retrospective correction for signal drift. The water peak was shifted to 0 Hz offset on a voxel-wise basis to correct for B_0 inhomogeneities across the image as well as shifts due to susceptibility differences between tissues. Fast spin-echo images with 8 echoes per TR were acquired at a resolution of 0.1x0.1x1mm with 5 slices as a reference to aid in definition of ROIs. The time to acquire each CEST spectrum and the high-resolution slices was approximately 50 minutes per animal. Parametric maps were constructed reflecting the properties of the z-spectrum peaks by using a peak-fitting algorithm in MATLAB [5] which removed the baseline signal and decomposed each CEST spectrum into four Lorentzian lineshapes and yielded the amplitude, width, area and offset frequency of each peak (Figure 1).

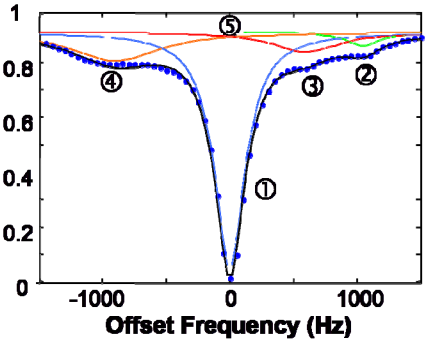

Figure 1. Example output of peak-fitting algorithm. 1. Direct effect (light blue), 2. Amide peak (green), 3. OH^- peak (red), 4. Lipid peak (orange), 5. baseline offset /magnetization transfer.

Results and Discussion: Based upon this preliminary data in five animals, several trends were observed (see Table 1). As expected [1,3,4], the amide peak is several percent larger in the tumours compared to the adjacent muscle. There appear to be hotspots in the amide maps which may be regions of increased proliferation and/or increased amide proton exchange rate (Figure 2). We also noted an increase in OH^- and mobile lipid peaks (Figure 2) in the tumour which becomes more prevalent with time as the tumour increases in size. The increase in the OH^- peak could either be due to an increase in the rate of glycolysis [6] within the tumour or an increase in lactic acid produced as the result of hypoxia [7]. The latter argument could also explain why the muscle adjacent to the tumour also undergoes an increase in the OH- peak over time, if it is also becoming hypoxic. Lipids have also been known to increase during tumour development[8], which could be as a result of the increased requirement of fatty acids for membrane synthesis [9].

Conclusion: The peak fitting method is useful for isolating the influence of individual metabolites within the CEST spectrum, which should reduce correlation between CEST metrics. It is clear from this analysis that with multiple overlapping peaks of variable amplitude, asymmetry based techniques for quantifying the CEST effect may be oversimplified and changes that occur with tumour growth could be underestimated. In this study, the tumour could be readily distinguished from adjacent normal tissue, whether assessing the amide, OH^- or lipid CEST peaks. Furthermore, it is apparent that as the tumour continues to grow, there is a corresponding increase in the amplitude of the CEST peaks. This method has potential for monitoring of tumour invasiveness and response to therapy, and may provide metrics which are more specific than conventional T1 and T2 measurements.

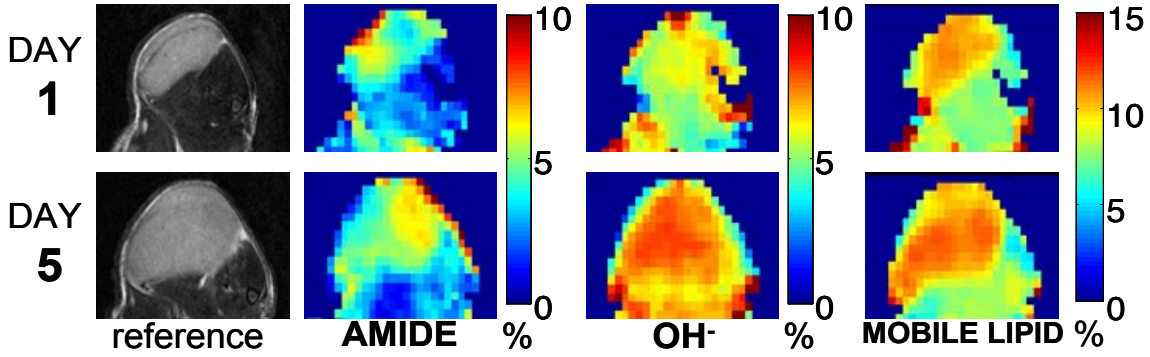

Figure 2.

Table 1. Mean values of peak heights and change between day 1 and 5 in tumour ROIs.

animal	amide (%)		OH^- (%)		mobile lipid (%)	
	day 1	change	day 1	change	day 1	change
1	3.4 ± 1.5	1.4 ± 1.9	5.3 ± 1.0	0.7 ± 1.1	8.6 ± 1.4	1.6 ± 1.6
2	4.6 ± 1.6	0.5 ± 1.8	5.9 ± 0.5	1.7 ± 0.9	10.0 ± 1.0	0.8 ± 1.4
3	3.1 ± 1.4	2.1 ± 1.7	5.3 ± 0.6	0.8 ± 0.9	8.9 ± 2.6	1.2 ± 2.8
4	2.5 ± 0.6	0.8 ± 1.5	3.9 ± 0.9	1.4 ± 1.4	7.0 ± 0.6	3.4 ± 1.3
5	4.6 ± 0.9	-0.8 ± 1.6	5.9 ± 1.5	-0.9 ± 1.7	10.3 ± 1.4	-0.1 ± 1.8
mean	**3.6 ± 0.6**	**0.8 ± 0.8**	**5.3 ± 0.4**	**0.7 ± 0.6**	**9.0 ± 0.7**	**1.4 ± 0.8**

References: **1.**Jones *et al. MRM* **2006**, *56*, 585-92. **2.**van Zijl *et al. PNAS* **2007**, *104*, 4359. **3.**Salhotra *et al. NMR Biomed* **2008**, *21*. **4.**Wen *et al. NeuroImage* **2010**, *51*, 616-622. **5.**O'Haver; Peakfit for Matlab v. 2.2 ed. October, 2011. **6.**Young *et al. Breast Cancer Res* **2008**, *10*, 202. **7.**Brahimi-Horn *et al. Jour. Molec. Med.* **2007**, *85*, 1301-1307. **8.**Swinnen *et al. Curr. Op.in Clin. Nut. & Metab. Care* **2006**, *9*, 358. **9.** Medes *et al. Cancer Res* **1953**, *13*, 27.