Early Tumor Response to Radiochemotherapy using 1D PRESS and 2D Correlated Spectroscopy

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TARGET AUDIENCE: Spectroscopists, radiologists, physicists, and radiation oncologists interested in brain cancer and treatment monitoring.

BACKGROUND: One of the great strengths of magnetic resonance spectroscopy (MRS) is its non-invasive and quantitative nature, making it ideally suited for therapeutic monitoring in brain cancer. Studies have shown that reductions in typically high levels of choline (Cho) after therapy may indicate remission whereas a change or increase would suggest progression. Other metabolite changes could also provide prognostic value. Recently, Ramadan et al have demonstrated that two-dimensional correlated spectroscopy (2D-COSY) in gliomas[3]. Unlike conventional MRS studies, the second dimension is spectral and not spatial allowing for up to 35 different metabolites in the brain. This method could have great potential for therapeutic monitoring however to our knowledge there have not been any studies that have used 2D-COSY for treatment monitoring. The goal of this study was to compare the efficacy of conventional one-dimensional (1D) MRS and 2D-COSY in monitoring the effects of chemoradiotherapy.

METHODS: 10 subjects with pathologically confirmed gliomas were recruited and examined on a 3T Siemens Skyra using a 32 channel head coil before and after one month of radiochemotherapy. In addition, three healthy subjects underwent repeated scans in order to determine the reproducibility of this method for longitudinal studies. In this study we utilize two methods of characterizing MRS: 1) 1D MRS was required using conventional PRESS (TE=30ms, TR=2 sec, 128 averages) 2) 2D-COSY was acquired using 64 increments of 0.8 ms with a starting TE=30 ms and 8 averages as previously described[1]. Baseline scan images and voxel locations were used for reference when placing the voxel position in the follow-up study. Manual shimming was also matched between exams. 1D MRS was post-processed using LCmodel (Provencher) and both metabolite values and ratios were obtained for N-acetyl aspartate (NAA), creatine (Cr), Cho, glutamate/glutamine (Glx), myo-inosoitol (mI), and Lac. 2D-COSY was processed using commercially available software (FelixNMR). For NAA and Cho, the primary diagonal peak volume was used at 2.02 and 3.02 ppm respectively. Glx crosspeaks were obtained at 2.10-3.75 and 3.75-2.16 ppm. Crosspeaks at 1.33-4.08 and 4.08-1.33 were measured for lactate. All data was then normalized to Cr. Paired t-tests were conducted of the MRS values obtained before and after therapy.

RESULTS/DISCUSSION: 2D-COSY was highly reproducible with less than 5% variation (95% reproducibility) in crosspeak volumes of NAA, Cho, Cr, Glx, and mI. Much greater changes were observed in metabolite levels before and after radiochemotherapy. These changes include significantly reduced ($p<0.05$) Cho/Cr and Lac/Cr ratios as shown in Figure 1. Interestingly, the choice of crosspeaks below or beneath the diagonal altered the significance with the 4.08-1.33 ppm crosspeak providing a greater difference. This is likely due to the F1 and F2 having different resolution given that there are 1024 data points for each acquisition but only 64 total increments. As a result the shape of the volume can affect those metabolites that may be observed. It is likely that the ROI used for lactate above the diagonal (Figure 1 bottom) contains other chemicals such as threonine and fucosylated protiens which would alter based on tumor differentiation[4]. NAA/Cr and Glx/Cr ratios were not significantly different after therapy using either 1D or 2D MRS.

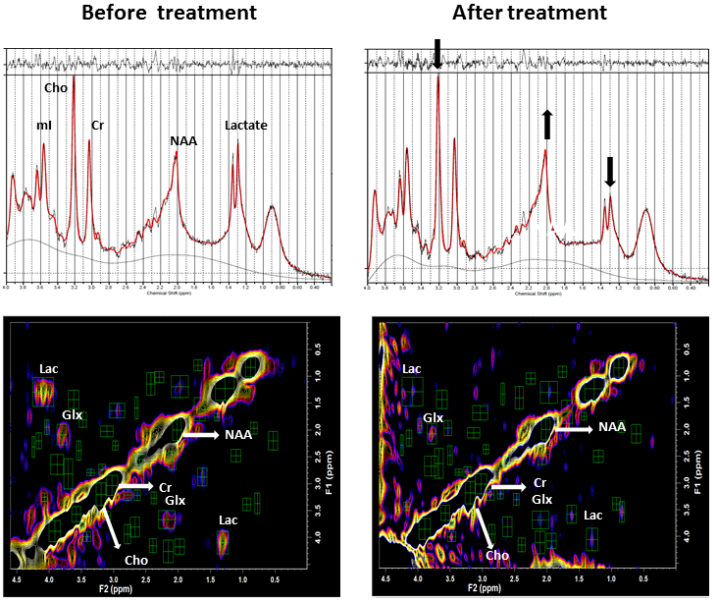

Figure 1. Representative 1D (top) and 2D (bottom) MRS of a glioma patient before (left) and after (right) radiochemotherapy.

CONCLUSION: Our results demonstrate that 2D-COSY methods are comparable to 1D-MRS results but may provide additional information that can be of diagnostic or prognostic value. Future studies include greater exploration of potential differences in other crosspeaks, such as 2-hydroxyglutarate[4], specific to IDH-mutated gliomas, that may provide additional pathophysiological information.

REFERENCES: [1]Horska and Barker. Neuroimaging Clin N Am. 2010; 20(3): 293–310. [2]Graves EE, et al.. AJNR Am J Neuroradiol. 2001;22(4):613–624. [3]Ramadan S et al. Radiology. 2011;259(2):540-9. [4]Mountford C et al. NMR Biomed 2014; in press. [5]Andronesi OC. Sci Transl Med. 2012 11;4(116):116

Table 1. Metabolite values before and after radiotherapy using 1D and 2D MRS **p<0.05, NAA = N-acetylaspartate ; Cho =choline; Glx = glutamate and glutamine; Lac= Lactate*

	NAA/Cr		Cho/Cr		Glx/Cr		Lac/Cr	
	before	after	before	after	before	after	before	after
1D	0.90±0.35	1.00±0.31	0.49±0.14	0.41±0.10 *	1.27±0.34	1.13±0.22	0.55±0.49	0.30±0.23 *
2D(Top)					0.07±0.01	0.08±0.02	0.12±0.07	0.16±0.08
2D(Bottom)	0.91±0.21	0.86±0.13	1.25±0.18	1.13±0.21 *	0.07±0.01	0.09±0.04	0.04±0.02	0.08±0.06 *