Serial Assessment of Lactate in GBM Patients Undergoing Treatment Using Lactate-Edited 3D 1H MR Spectroscopic Imaging at 3T

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Introduction: Lactate is an indicator of anaerobic glycolysis and reduced cellular oxygenation. Previous studies have shown that combined high lactate/lipid values measured by 1H MR Spectroscopic Imaging (MRSI) at 1.5T were related to poor survival in glioblastoma multiforme (GBM) patients when evaluated prior to radiation/chemo treatment [1]. Assessment of lactate prior to the initiation of radiation/chemo treatment and over the course of treatment is also of interest to test lactate as a predictive marker for treatment outcome. The purpose of this study is to evaluate and compare lactate values prior to radiation (preRT) and during treatment in GBM patients. The emphasis was on both quantitative and qualitative assessment of the patterns of lactate.

Materials and Methods: Eleven GBM patients (9 male, 2 female; median age 55, range 41-67) were examined for this study. All patients underwent surgical resection and were treated with fractionated external beam radiation therapy in combination with Temozolomide and Enzastaurin. A previously developed lactate edited 3D MRSI (TR/TE=1104/144 ms with 1 cc nominal resolution, 16x16x16 for readout coverage, total acquisition time=9:34 min) incorporating a flyback echo planar readout gradient [2] was acquired with point resolved spectroscopic (PRESS) volume localization and very selective saturation (VSS) bands [3] using a 3T MR scanner (GE Healthcare, Milwaukee, WI) with an 8-channel phased array head coil. Spectral quantification was performed as published previously [4]. Lactate SNR was normalized (nLac) by median SNR of NAA in normal appearing white matter (NAWM) for each exam. Lactate appearing in necrotic region, resection cavity or cerebrospinal fluid were excluded. Patients were classified into 3 groups based on radiologist's report: those who *progressed* at any time point, those who were *non-progressors*, and *undefined* who only had exams less than 2 months from preRT.

Results: Three patients showed tumor progression, four were non-progressors, and four were undefined (Figure 1). Patients 1 and 2 showed a consistent increase in the level of nLac. nLac was significantly different across all exams between progressing and non-progressing patients (P=0.00004). Two patients (patient 1 and 7) lacked the preRT scan and were excluded from preRT. The 75th percentile of nLac was significantly different between progressing and non-progressing patients at the preRT exam (Table 1).

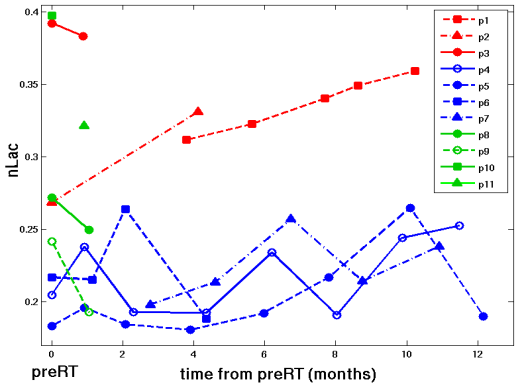

Figure 1. Normalized lactate (nLac) change over time from preRT (months). Each marker represents median value. Red, blue, and green lines/markers indicate progressed, non-progressed, and undefined patients respectively.

parameter	progressed (N=2)	non-progressed (N=3)	P value
median nLac	0.33±0.088	0.20±0.017	0.075
75th% nLac	0.39±0.084	0.22±0.022	0.037
90th% nLac	0.43±0.12	0.24±0.029	0.058

Table 1: Comparison between progressed and non-progressed patients at their preRT examination

Discussion: In two of the three progressing patients (patient 1 and 2), the location of tumor recurrence at the time of progression coincided with the regions of lactate appearance at earlier exams. More interestingly, the recurrent region possessed no indication of progression by other radiological parameters in T1, T2 weighted images and MRSI, but constantly showed lactate at exams prior to progression. Figure 2 shows T1-weighted post-Gd, T2 weighted images and the corresponding spectra at preRT and 4-month FU for patient 2. T1 enhancement (e) and T2 hyperintensity (f) as well as high Cho-to-NAA ratio (Cho/NAA) in summed spectra (blue voxels in g) indicate tumor progression in the temporal lobe posterior to resection cavity at 4-month FU. This recurrent location overlaps with the region of lactate at preRT shown in the subtracted spectra (yellow voxels in d). Lactate is still present at 4-month (h). Figure 3 also shows similar findings between 6-month and 10-month FU in patient 1. This patient showed lactate in regions that later-progressed. The fact that both of these patients showed no radiographic signs of progression, but consistently had lactate at the site of subsequent progression suggests that monitoring of lactate during treatment with radiation/chemo may assist in characterizing tumor tissue and predicting outcome.

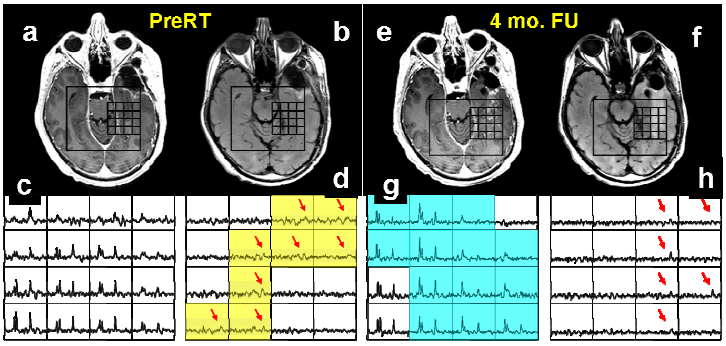

Figure 2. Patterns of lactate between preRT and 4-month FU in patient 2. T1-weighted post Gd (a,e) and T2-weighted (b,f) images and corresponding summed (c,g) and subtracted (d,h) spectra at each time point. Cho, Cre, NAA, and lipids are observed in summed spectra and lactate in subtracted spectra (red arrow). Notice that tissues with lactate (yellow in d) at preRT became abnormal in T1 (e), T2 (f) images with high Cho/NAA (blue in g), indicative of recurrent tumor after 4 months.

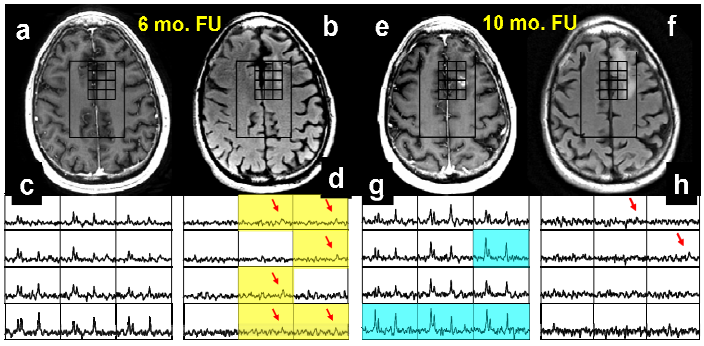

Figure 3. Patterns of lactate between 6- and 10-month FU in patient 1. At 6 month, no sign of progression is observed in T1-weighted post Gd (a), T2-weighted (b) images, or spectra (c,d). Decreased metabolites in summed spectra are typical of radiation effect (c). At 10 month, tumor progression is indicated by T1 (e), T2 (f) images and high Cho/NAA ratio in summed spectra (blue in g), and coincides with regions of lactate at 6 month (yellow in d).

Conclusion: This study showed that lactate may give important information in predicting the outcome of radiation/chemo treatment. Future studies that include image guided surgical sampling of tissue containing lactate, as well as monitoring lactate levels after surgery and during radiation/chemo treatment in a larger patient population are underway, and will help to characterize the patterns of changes in lactate for patients with GBM.

References: [1] Saraswathy S, et al., *Proc. ISMRM, 15th Annual Meeting, Berlin*, 2007. p.2834. [2] Park I, et al., *Proc. ISMRM, 15th Annual Meeting, Berlin*, 2007. p 775. [3] Tran TKC, et al,. *Magn Reson Med.* 2000;43(1):23-33. [4] Nelson SJ, et al., *Magn Reson Med.*2001;46: 228-239.

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