Relationship between lactate, choline, creatine and perfusion parameters in newly-diagnosed high-grade gliomas

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INTRODUCTION

It has been shown that respiratory capacity decreases and the reliance on glycolysis for energy production increases in tumors. Evaluation of metabolic activities in human tumor tissue has the potential to improve diagnosis and help to guide treatment planning and monitoring. As the end product of the anaerobic glycolysis, abnormally increased lactate may be a sensitive indicator of reduced cellular oxygenation and hypoxia in these lesions. The concentration of lactate may involve complicated interplay between the tumor proliferation, energetic activities, hemodynamics and substrate supply [1]. The goal of this study was to explore this relationship in newly diagnosed human glioma using *in vivo* magnetic resonance spectroscopic imaging and perfusion MR imaging techniques.

MATERIALS AND METHODS

Fourteen newly-diagnosed patients with histologically classified glioma were studied prior to surgery (five grade-III and nine glioblastoma multiforme, GBM). MR data were acquired on a 1.5T GE Signa Echospeed MR scanner. The MRI protocol included axial FLAIR images (10000/147/2200), pre and post contrast agent T1-weighted volume SPGR images (27/6) and perfusion MR obtained with T2*-weighted gradient-echo echo-planar images (1250/54/1) during the first pass of a bolus of contrast agent. J-difference lactate-edited 3D-MRSI was performed using PRESS localization in conjunction with dual BASING (band selective inversion with gradient dephasing) pulses [2] (1000/144). Ellipsoidal k-space sampling was applied to reduce the acquisition time to approximately 17 minutes [3]. Levels of choline (Cho), creatine (Cr), N-acetyl aspartate (NAA) lactate (Lac) and mobile lipids (Lip) were estimated with in-house developed quantification algorithms [4] and a non-linear fitting algorithm using the Voigt model [5]. Metabolic indices, particularly Cho-to-NAA (CNI), Cho-to-Cr (ChCrI) and Cr-to-NAA (CrNI) indices, were generated for each voxel using an auto-regression method [6], showing the number of standard deviations of difference between the ratio of two metabolites within one voxel and the mean ratio in the control voxels. The contours with CNI, ChCrI and CrNI higher than 2.0, and with Lac and Lip four times higher than the noise standard deviation were generated respectively to define the metabolic abnormalities. Volumes and levels of these metabolic abnormalities were measured using software developed in our laboratory. The T2* signal time curve of the perfusion data was converted to relative concentration. Peak height and percent recovery of the post bolus signal were calculated for each voxel within the T2 and contrast enhancing (CE) lesions. Peak height values were normalized to the peak of a model curve function derived from normal appearing brain tissue. Two-way stepwise multiple linear regression models were applied to correlate level of elevated lactate with other metabolic abnormalities and perfusion parameters. Q-Q plots were used to determine outliers and normality. The dependent parameters were volume of elevated lactate (vLac), and median (medLac) and maximum (maxLac) level of lactate within CNI abnormalities. The covariates included volume (vCNI, vChCrI, vCrNI), median (medCNI, medChCrI, medCrNI) and maximum (maxCNI, maxChCrI, medCrNI) values within CNI contours of other metabolic abnormalities as well as the maximum (maxPeakH) and median (medPeakH) peak height of the perfusion curves within T2 lesions. Variables with P-value less than 0.1 were considered as significant.

RESULTS

Three out of 5 grade-III and 8 out of 9 GBM patients showed significantly elevated lactate. Table 1 shows the median and range of selected parameters. No significant models were found for the median and maximum values of lactate within CNI contours. The vLac was significantly related with vCNI, vCrNI, and maxPeakH as shown in table 2(a). The regression coefficients reveal the positive relationship between vLac and vCNI, vLac and maxPeakH, and the negative relationship between vLac and vCrNI. Figure 1 shows example spectral and perfusion data for a grade-III (a) and a GBM (b) patient respectively. The Q-Q plot showed that the data in figure 1(a) might be an outlier due to the atypically very high lactate. We then excluded this outlier and re-ran the regression. The same relationship held between the vLac and the covariates, with a better significance as shown in table 2(b).

Table 1 Median and range for spectral and perfusion parameters (volume in cc)

	vLac	vCNI	vCrNI	eedLac	medCNI	medCrNI	maxPeakH	medPeakH
Median	3.2	26.4	7.1	2.1	3.3	1.5	5.4	1.6
Range	0-29.9	1.5-54.9	0-25.2	0-8.3	2.2-7.0	0.1-2.8	3.0-15.0	0.7-2.3

Table 2(a) Linear regression model for vLac

	Intercept	vCNI	vCrNI	maxPeakH
Coeff	-6.42	0.48	-0.61	1.30
P	0.182	0.020	0.084	0.043

** 14 patients*

Table 2(b) Linear regression model for vLac

	Intercept	vCNI	vCrNI	maxPeakH
Coeff	-4.78	0.47	-0.56	0.79
P	0.063	0.0004	0.007	0.026

** 13 patients with one outlier excluded*

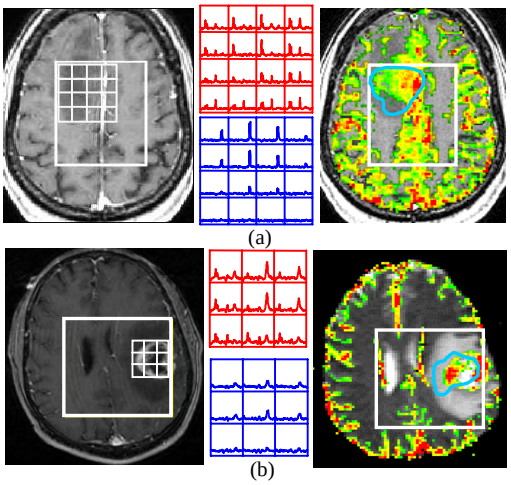

Figure 1. Spectral and perfusion data for a grade-III (a) and a GBM(b) patient. Left: post-contrast SPGR images; middle: summed (red) and difference (blue) spectra; right: rCBV map overlaid on anatomic images with Lac contours

DISCUSSIONS

Hypoxia in tumors has been shown to be predictive of poor response to radiotherapy and chemotherapy, and metastatic spread of a tumor [7]. Increased lactate may be an indicator of hypoxia in brain tumors and the proposed model may help to understand the possible factors that affect the generation of lactate. High choline is indicative of a high proliferation rate or high cell density in tumor regions, while decreased creatine may be related with attenuation of respiratory metabolism. The positive correlation between vLac and vCNI, and negative correlation between vLac and vCrNI supported the hypothesis that lactate is produced in viable neoplastic regions with high glycolytic activities. The measured peak heights of perfusion data were related to regional blood volumes. The positive correlation between maxPeakH and vLac suggested a close relationship between angiogenesis and hypoxia. The prognostic implication of the presence of lactate either in terms of response to therapy or clinical outcome is being evaluated.

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