MR Perfusion and 1H Spectroscopic imaging in the longitudinal evaluation of brain tumor angiogenesis

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PURPOSE

To track and correlate the changes in relative cerebral blood flow with metabolite concentrations in the prognosis and longitudinal assessment of angiogenesis *in vivo* in patients with primary brain cancer.

INTRODUCTION

Angiogenesis, or the sprouting of new blood vessels, is believed to be one of the chief mechanisms by which primary malignant brain cancer invades and proliferates. This work attempts to assess angiogenesis *in vivo*, via measurements of metabolite distributions and perfusion parameters such as relative cerebral blood flow (CBF). ^{1}H Magnetic Resonance Spectroscopic Imaging (MRSI) is able to assess tumor metabolism needed for new blood vessels to form and spread indirectly by evaluating the molecular composition of tissue and the levels of cerebral metabolites that are altered by abnormal pathology. The combination of perfusion MRI and multivoxel localized MRSI data has been attempted by others earlier[1] although we focus our efforts on utilizing the data to investigate angiogenesis.

MATERIALS AND METHODS

This study was approved by the University of Alabama at Birmingham institutional review board. Twelve patients (40 total studies) with new clinical diagnoses of primary brain cancer were studied. All imaging/spectroscopy was performed on a 3T clinical scanner (Intera, Philips Medical Systems, Cleveland OH) at diagnosis (baseline), and follow-up scans were performed at 8, 16, and 24 weeks. The MRI protocol consisted of T1-weighted (TR/TE=400/12 ms) scout images, followed by the 2D chemical shift imaging (2D-CSI, TR/TE=1500/80 ms, CHESS water suppression pulse, 24x24 matrix, FOV 24cm^2) sequence, run on a 15 mm thick axial slice positioned on the basis of the survey images to include both tumor and uninvolved brain tissue, to provide a reference for analyses. After automated shim optimization, the outer volume fat suppression slabs were positioned so as to cover fat tissue from the skull and subcutaneous fat. Total acquisition time for the CSI sequence was around 12 minutes, with an additional 3 minutes for shim-optimizing before spectroscopic acquisition. The hybrid gradient spin echo GRASE sequence with (TR/TE of 14/20 ms, 128x128, FOV=25 cm^2, 30 slices of 3.5 mm thickness) was used for dynamic susceptibility contrast enhanced MRI (DSC-MRI) studies. All slices were parallel to the CSI acquisition slice, to allow correlation of perfusion and MRSI data. Magnevist (Gd-DTPA, 0.2 mmol/kg) was the contrast agent used for DSC-MRI studies. All studies were visually aligned with respect to the baseline study for intra-patient data registration.

Parametric CBF and CBV maps were generated using Medx (Medical Numerics Inc, Sterling, VA). A two-stage automatic algorithm[2] was used for identifying arterial voxels in the DSC-MRI data and constructing the arterial input function (AIF). The relative CBF maps were generated from the amplitude of the residue curve that results from deconvolution of the tissue curve via singular value decomposition.

2D-CSI data were processed off-line using the Xunspec1 package (Philips) and included Fourier transforms in the *kx* and *ky* directions, zero-filling to 2048 points, Lorentz-Gauss apodization, and direct current (DC) offset correction. Time domain filtering was applied to eliminate the residual water peak using the Lanczos HSVD filter[3]. The data were then Fourier transformed to yield a stack of spectra, one per voxel. Levels of Choline (Cho), Creatine (Cre), and N-Acetyl aspartate (NAA) were estimated as the peaks at 3.2, 3.0, and 2.0 parts per million (ppm), respectively, and used to generate metabolite maps.

RESULTS

Patients consistently demonstrated increased Cho, reduced NAA and Cre at the tumor margins besides the absence of discernable metabolite peaks in the tumor core. Areas with high Cho also had elevated blood flows, usually at least twice the flow in healthy brain tissue. In patient 4, whose data are presented in Figure 1 and Table 1, longitudinal monitoring yielded consistently elevated Cho and reduced Cre peaks at the tumor margin. This patient also showed a longitudinal increase in the Cho and Cre in the tumor margins over the 4 studies.

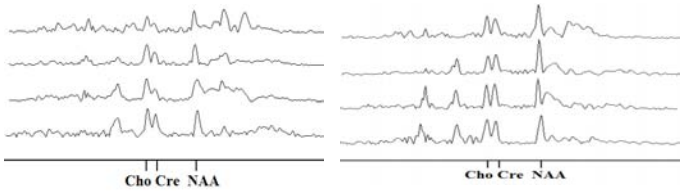

Figure 1 CSI spectra from (left) tumor margin and (right) healthy tissue at baseline (top), and 8, 16 and 25 weeks (bottom) follow up studies on patient 4

Study	Normalized relative CBF in tumor core	Normalized relative CBF in tumor margin
Baseline	0.09	2.44
+ 8 weeks	0.39	3.03
+16 weeks	0.23	1.97
+24 weeks	0.04	2.39

Table 1 Relative CBF values from patient 4

CONCLUSION AND DISCUSSION

Areas in the tumor margin demonstrated high relative CBF. Patients also showed a decrease in Cho and a sharp decrease in NAA at the center of the tumor, presumably from necrosis. In the margins of the tumors, the levels of Cho were elevated compared to uninvolved tissue, and the NAA peak was reduced. Metabolite measurements in this study are not influenced by contrast administration because 2D-CSI was performed before the DSC-MRI. The spectra from the tumor margins as well as CBF data agree with the "stable" clinical status of patient 4. Our data suggest that spatial variations of the CBF and concentration of metabolites like Cho and NAA correlate strongly with each other. Quantitating these variations will improve the understanding of angiogenesis and its role in brain cancer progression.

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