

Longitudinal MRSI study in newly diagnosed Glioblastoma Multiforme

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Introduction

Glioblastoma Multiforme (GBM) is the most common and the most malignant type of glioma. Despite the advances in multimodality treatments that combine surgery, radiation and chemotherapy, patients with GBM have a limited prognosis, with a median survival of one year. The standard criteria for assessing tumor progression and response to therapy are based upon changes in cross sectional diameters of the contrast enhancing lesion in combination with the clinical worsening that results from accumulated changes at the molecular and cellular levels. This makes it difficult to make an early determination of response using convention MR imaging. Proton magnetic resonance spectroscopic imaging (MRSI) is a powerful noninvasive tool for the assessment of metabolic changes in the tumor and surrounding brain tissue. The purpose of this study was to assess serial metabolic changes in patients with newly diagnosed GBM, to examine the predictive value of MRS parameters in relation to progression, and to evaluate the importance of such parameters in scans obtained prior to progression.

Methods

A total of eighteen patients (8 females and 10 males, median age = 56 years) with newly diagnosed GBM were studied after surgical resection but prior to RT and chemotherapy, immediately after RT (post-RT) and every 2 months thereafter until tumor progression. Progression (PG) was defined as clinical deterioration and/or radiological progression, and confirmed by subsequent surgery. Chemotherapy was given concurrently as temozolomide alone (3 patients), temozolomide with Tarceva (10 patients), Poly ICLC (4 patients) or R115777 (1 patient). The MR data were acquired from either 1.5 T or 3 T GE scanners (GE Healthcare Technologies, Waukesha, WI). Anatomic MR images included a T1-weighted sagittal scout, axial fluid attenuated inversion recovery (FLAIR), pre- and post- Gadolinium T1-weighted spoiled gradient echo (SPGR). The 3D H-1 MRSI data (TE/TR = 144/1000 -1100 ms), were obtained using PRESS volume selection, VSS outer volume suppression and CHESS water suppression. Spectral array sizes were 12x12x8 or 16x16x8, acquired with k-space sampling and fields of view corresponding to a nominal spatial resolution of 1 cc. The MRSI data were processed as described previously [1]. The choline to NAA index (CNI) was calculated using an automated regression technique [2]. The 3D MRSI data were referenced to the 3D SPGR image. To evaluate the predictive role of MRSI in progression, the images at the time of progression were aligned to those at the time of pre-progression (Pre-PG) to define the region of new contrast enhancement (CEL) lesion. Figure 1 is an example of New CEL shown in the red box. Volumes of CEL within PRESS box and CNI in CEL were evaluated from the baseline to PG. Wilcoxon rank tests were applied to evaluate the difference between a single time point and progression time point, with a P-value of <0.05 being regarded as significant.

Results

The median time to progression was 115 days (range, 52-301 days). Figure 2 showed mean CEL volumes (cc) and CNI values in CEL during the treatment. There were n=2, 5, 6, 7 and 13 subjects at 10, 8, 6, 4, 2 months prior to progression, and n=18 total subjects at the time of progression. The CEL volume significantly increased with time prior to PG. The difference in CEL volume between 2 months prior to progression and progression in 13 patients was statistically significant using a signed-rank test (P = 0.021). The CNI values increased with time up until 2 months prior to PG, but no significance was found from the Pre-PG vs. PG values. The median time to PG from Pre-PG was 60-day. ROIs representing New CEL were generated for the Pre-PG scan based on the difference in CELs between Pre-PG and PG. No significance was found in the CNI within the CEL at Pre-PG and PG and the new CEL at Pre-PG (Figure 3). An example of high CNI values at the time of pre-progression that showed new CEL two months at the time of PG is illustrated in Figure 1.

Discussion

Conventional MRI is a powerful tool for delineating structural abnormalities in gliomas and areas where the brain-blood barrier (BBB) has been compromised, but is not a direct reflection of changes in tumor biology. MRSI provides parameters for estimating tissue function and may therefore contribute to the prediction of progression. In this study, we assessed changes in metabolism based upon the choline to NAA index (CNI) and demonstrated characteristics of these changes following response to treatment in patients with GBM using MRSI. We found that the CNI values in CEL are elevated at 2 months prior to progression while having less changes in CEL volume at that time. Patients who have a CEL volume with high CNI values are more likely to progress compared with those who have with smaller CEL volume and lower CNI values. We also noticed that the regions with high CNI values outside the CEL region could subsequently become enhancing. This suggests that metabolic abnormalities more accurately reflect the underlying tumor burden and may provide useful information for following response to therapy in patients with GBM. The values obtained using MRSI may be valuable in predicting early progression and for the clinical management of the disease.

References

1. Nelson, S.J. et al. Magn Reson Med 2001;46(2):228-39.
2. McKnight, T.R. et al. J Magn Reson Imaging 2001;13(2):167-77.

Acknowledgements

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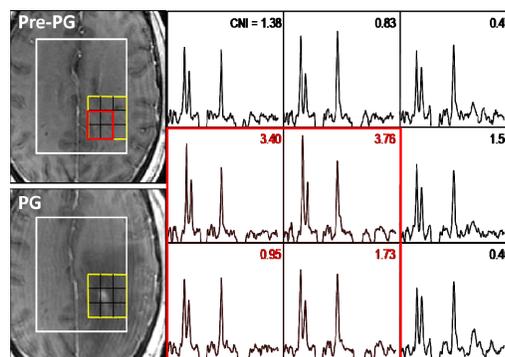
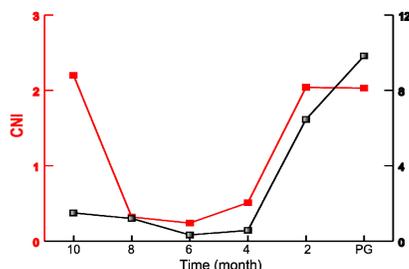


Figure 1. MRSI data from a patient with newly diagnosed GBM at the time of pre-progression that corresponded to new CEL two months later.



P-value	8-mo	6-mo	4-mo	2-mo
VCEL	0.009	0.001	0.001	0.096
CNI	0.006	0.003	0.009	0.534

Figure 2. Mean CNI values in CEL and CEL volumes along with the P-values between each time point and PG using a ranksum test.

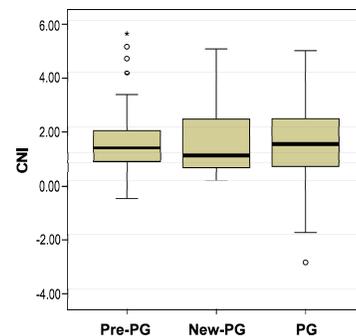


Figure 3. Box plot showing similar CNI values in the region of CEL at the pre-progression, progression, and the new CEL at pre-progression.