

MR Spectroscopy as a Biomarker to Predict the Responses of Glioblastoma to an Anti-angiogenic Treatment

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INTRODUCTION

Proton magnetic resonance spectroscopy (¹H-MRS) is increasingly used in clinical studies of brain tumor to provide information about tissue metabolic profiles. It shows clear differences between the spectral profiles of brain tumor and normal tissues. This study investigated early changes in predominant metabolites for predicting tumor responses to an anti-angiogenic treatment in recurrent malignant glioblastoma (rGBM).

PATIENTS and METHODS

Thirty-one patients with rGBM treated with daily cycles of cediranib (45mg oral dose) were studied [1]. The patients were scanned using a 3T Siemens MRI scanner at different time points throughout the course of their treatment. In this study, we focused on the metabolic changes at the early post-treatment time points (i.e days 1, 28, 56) because early indications of therapeutic outcome provide a better opportunity to optimize therapeutic intervention and improve survival.

Chemical Shift Imaging, multi-voxel MRS, using a PRESS sequence with TR/TE/NS=1700ms/144ms/3 was used to acquire data from 16×16 voxels (1×1×1.4 cm³). First and second order shimming was performed automatically, followed by a manual adjustment for an optimization. 23 slices of T1-weighted images were also acquired before and after a contrast (Gd.DTPA) injection with TR/TE=600ms/12ms, 5mm slice thickness, and 1mm inter-slice gap for anatomical details [1].

Spectroscopic raw data were processed using LC Model 6.1 software (Provencher, Ontario, CA). Using software written in Matlab, outputs were analyzed in two ROIs defined on the corresponding MRIs: enhancing tumor (ET) and normal tissue on the contralateral side (cNT). The changes in NAA and choline (Cho) after the treatment were analyzed with respect to the values of pre-treatment (Day -1). The concentrations of the metabolites were normalized to creatine on the normal side (norCre).

RESULTS and DISCUSSION

The spectra obtained from 19 out of 31 subjects were available for quantitative analysis based on data quality. The subjects were classified as either good or poor overall survival responders based on six-month survival threshold. **Figure 1** demonstrates serial T1 post-contrast MR images and raw spectra in one representative voxel (Blue-lined box) of enhancing tumor in the time-course of treatment for a representative good responder.

The spectra display dynamic changes of each metabolite's peak in the range of 0.5 – 4 ppm.

There was no significant difference in the ratios of the metabolites in MRS including NAA/norCre, Cho/norCre, NAA in tumor/NAA in normal tissue, and Cho in tumor/Cho in normal tissue between high and low overall survival populations. However, NAA/Cho, the most commonly used clinical criterion in MRS for discriminating normal and abnormal tissues [2], notably showed an increase in high overall survival population (15%, 9%, 40% with p<0.05 on day 1, 28, 56, respectively), while showing a decrease in low overall survival population (-12%, -10%, -20% on day 1, 28, 56, respectively) in **Figure 2**. Based on this finding, the ROC analysis was performed to determine the probability of the prediction of NAA/Cho to 6-month survival. In **Table 1**, the values of an area under the ROC curve (AUC) on early time points, particularly on day 28 and 56, demonstrated the highly acceptable possibilities of prediction (74% and 95%). It suggests that NAA/Cho is a likely biomarker for predicting tumor responses to an anti-angiogenic treatment as reflecting a combined picture for the opposite changes of two primary metabolites.

CONCLUSION

This prospective study provides preliminary evidence that NAA/Cho in ¹H-MRS could serve as a biomarker for predicting treatment responses in rGBM patients. These observations have important implications for treatment management.

REFERENCES

[1] Batchelor TT et al., Cancer Cell 11:83-95 (2007)
[2] Nelson SJ et al., jMRM 21:701-708 (2005)

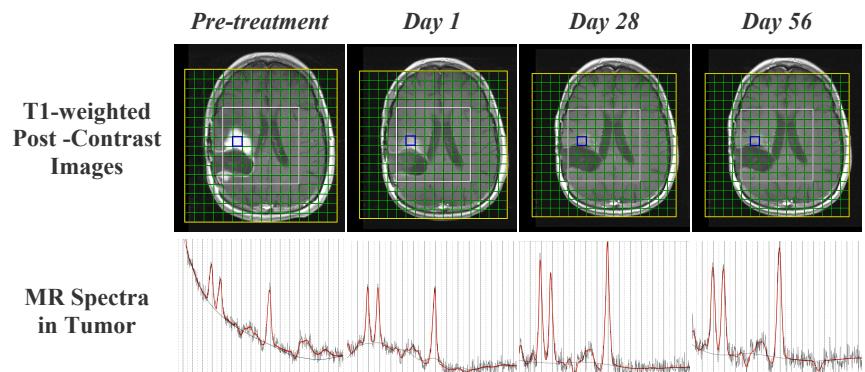


Figure 1. Serial T1 post-contrast MR images and raw spectra in one representative voxel (blue-lined box) of enhancing tumor region in the time course of treatment. The spectra exhibit the dynamic changes of each metabolite's peak in the range of 0.5–4 ppm at every time point of treatment.

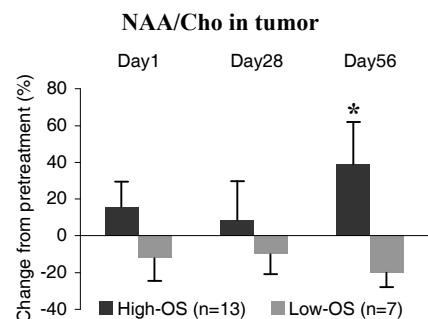


Figure 2: Relative changes in NAA/Cho separately grouped by the patients' overall survival (OS) periods based on six-month survival threshold at the early time points post-treatment in tumor. (* p<0.05)

Table 1. Area Under the ROC curve on early time points (i.e. 1 day, 28 day, 56 day) to determine the prediction of NAA/Cho to 6-month survival

	1 day (95% CI)	28 day (95% CI)	56 day (95% CI)
NAA/Cho	0.68 (0.65-0.72)	0.74 (0.71-0.78)	0.95 (0.91-1.00)