Can Susceptibility-Weighted Imaging determine response to combined anti-angiogenic, cytotoxic, and radiation therapy in GBM patients?

J. M. Lupo1, S. Cha1, E. Essock-Burns1,2, N. Butowski3, and S. J. Nelson1,2

1Department of Radiology and Biomedical Imaging, University of California, San Francisco, San Francisco, CA, United States, 2Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco, San Francisco, CA, United States, 3Department of Neurosurgery, University of California, San Francisco, San Francisco, CA, United States

Introduction: Susceptibility-weighted imaging (SWI) is a powerful tool for high resolution imaging of the vasculature that has been shown to improve the diagnosis of brain neoplasms [1]. SWI provides unique and potentially valuable contrast that is not always present on conventional anatomical or perfusion scans, highlighting heterogeneity within the contrast enhancing lesion and regions of elevated blood volume or blood-brain-barrier compromise [2,3]. The biological basis behind the hypointensity observed on SWI images within the contrast-enhancing lesion (CEL) that is not the result of hemorrhage, residual blood products, or calcification is still unclear. However, this contrast mechanism is expected to be advantageous both as a predictive biomarker in identifying likely responders to therapy, as well as in assessing treatment effect and response for anti-angiogenic and radiotherapy. The goal of this study is to investigate whether the amount of SWI hypointensity within the post-gadolinium contrast enhancing lesion on the post-surgery, pre-treatment scan can predict response in patients with glioblastoma multiforme (GBM) brain tumors receiving concomitant anti-angiogenic, cytotoxic, and radiation therapy.

Methods: Nineteen patients with newly diagnosed GBM were examined in this study. All patients underwent surgical resection and were treated with radio-, chemo- and anti-angiogenic therapy. Patients were imaged prior to beginning therapy (post surgical resection) and scanned serially every 2 months while on therapy until progression. High resolution T2*-weighted SWI was acquired on a 3T GE EXCITE scanner with an 8-channel phased array receive coil using a 3D flow compensated SPGR sequence with TE/TR 28/56ms, flip 20°, 24cm FOV, 512x144 image matrix with GRAPPA R=2 plus 16 autocalibrating lines [4], and an in-plane resolution of .5x.5mm. The coverage in z was varied to image the extent of the entire tumor at 2mm resolution. Standard clinical pre- and post-contrast T1-weighted SPGR images were also acquired for defining anatomic regions of interest. The SWI processing employed a 72x72 Hanning filter and the resulting phase mask was multiplied with the magnitude image four times. A low pass filter with edge completion was applied to the combined images and minimum intensity projections (mIPs) through 8 mm thick slabs were generated to obtain the final SWI images used for analysis. The pre-contrast T1-weighted SPGR images were registered to the SWI images through rigid body transformations that maximized the normalized mutual information [5], and the resulting transformation was applied to the post-contrast T1 SPGR images. The CEL region was manually defined from the registered post-contrast T1 SPGR images. Any enhancement that was also present on the pre-contrast T1 images, indicative of acute blood products and therefore always hypointense on SWI, was excluded. The SWI images were thresholded within the CEL mask to calculate the volume of SWI hypointensity (SWI-h) within the CEL, expressed as a fraction of CEL volume, for each patient’s pre-treatment scan. Time-to-progression (TTP) was defined as the time from this baseline pre-therapy scan to radiologic progression. Patients were subsequently characterized into 3 response groups based on their TTP: (1) non-responders (TTP ≤ 6 months), (2) partial responders (TTP between 6-12 months), and (3) full responders (TTP ≥ 12 months).

Results & Discussion: As shown in the top panel of Figure 1, the volume fraction of SWI-h within the CEL was significantly higher in full responders than non-responders (.58 vs .25 with p=0.01, Wilcoxon ranksum test). Although a trend was observed in the amount of SWI-h within the CEL with improved response, the difference in SWI-h volume fraction between full responders and partial responders, and partial-responders and non-responders, did not reach significance. However, the spearman rank correlation coefficient showed a good association between the SWI-h volume fraction with TTP, (r = 0.6, p = 0.006), with a greater amount of SWI-h indicating a more favorable prognosis (Figure 1, bottom). The spatial differences in the pattern of SWI-h among response groups can be visualized in the images in Figure 2. These results suggest that tumors with a larger extent of damaged vasculature initially are more likely to benefit from a treatment regimen containing an anti-angiogenic agent that aims to normalize the existing vasculature.

Conclusions: While ongoing investigation is needed to understand whether these susceptibility-weighted signal changes on can be predictive of overall patient survival, these early differences do suggest that SWI could be especially advantageous for determining which patients would be the best candidates for diverse therapeutic strategies. Future studies will investigate the patterns of SWI-h immediately prior to progression and incorporate functional imaging changes such as parameters derived from perfusion and diffusion weighted imaging to determine which patients would benefit the most from a given therapy.

![Figure 1: Boxplot of % SWI-h in each response group (top), and correlation with time-to-progression (bottom)](image)

![Figure 2: SWI images with CEL contour overlay (top) and corresponding post-gad T1 images (bottom) for each response group](image)


The research was supported by grants ITL-BIO04-10148 and R01 CA127612-01A1, and a Joelle Syverson American Brain Tumor Association Fellowship.