Post-bevacizumab ΔT1 maps detect residual contrast enhancement and predict survival in recurrent glioblastoma

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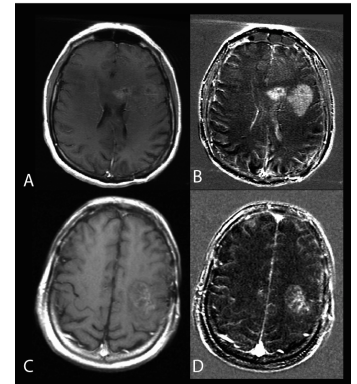
Target Audience – Neuroradiologists and neuro-oncologists interested in accurate assessment of recurrent glioblastoma response to anti-angiogenic therapy

Introduction

Glioblastoma multiforme (GBM) is the most common and most aggressive form of malignant glioma for which there is no cure. Median survival for patients with GBM is approximately 14 months[1] when treated with gross-total surgical resection, radiotherapy, and temozolomide. Bevacizumab, a VEGF inhibitor, is now a common option for second line treatment for GBM patients at recurrence; however, administration of bevacizumab often results in dramatic reduction in the volume of contrast enhancement due to decreased vascular permeability. This reduction in contrast enhancement is independent of any anti-tumor affects of bevacizumab. Thus, there is a great clinical need for new, robust, and easy to implement imaging biomarkers and technologies to predict response to bevacizumab and other anti-angiogenic therapies.

One method for circumventing the issues associated with lack of contrast enhancement is through the use of "Delta T1 Maps", or ΔT1 [2,3]. Specifically, ΔT1 maps involve subtracting intensity normalized pre-contrast T1-weighted images from intensity normalized post-contrast T1-weighted images. This technique has shown some initial value in separating T1 shortening from blood products on pre-contrast T1-weighted images from contrast enhancement on post-contrast T1-weighted images, although only a few patients have been examined to date. In the current study, we examined the use of ΔT1 maps to isolate the volume of contrast enhancement after treatment with bevacizumab in *n* = 101 recurrent GBM patients. We hypothesized that volume of residual contrast enhancement identified with ΔT1 maps at the first follow-up post-treatment could be used as a predictive biomarker for progression free (PFS) and overall survival (OS).


Figure 1: *A,C) Post-bevacizumab, post-contrast T1-weighted image in recurrent GBM patients showing reduction in discernable contrast enhancement. B,D) ΔT1 maps showing regions of contrast enhancement otherwise undetected by conventional post-contrast T1w images.*

Methods

All patients participating in this study signed institutional review board-approved informed consent to have their information in our neuro-oncology database. A total of *n* = 101 patients with histology confirmed GBM were enrolled in this retrospective study who met the following criteria: 1) pathology confirmed GBM with recurrence based on MRI and clinical data, 2) regular treatment every 2 weeks per cycle with bevacizumab (Avastin; Genentech; 10 mg/kg body weight), alone or in combination with chemotherapy (ie, carboplatin, irinotecan, etoposide, and lomustine), and 3) pre- and post-contrast T1 weighted MRI scans at both baseline (before bevacizumab treatment) and after bevacizumab treatment. Pre and post-contrast T1-weighted images were normalized by dividing the image intensity of each voxel by the standard deviation of the image intensity throughout the entire brain, similar to a previous study involving normalization of relative cerebral blood volume maps [4]. Next, voxel-wise subtraction was performed between pre- and post-contrast normalized T1-weighted images, resulting in hyperintensity within regions of contrast enhancement. The regions of ΔT1 hyperintensity were then isolated, tumor volumes were calculated, and the results were compared to manual contours on the post-contrast T1-weighted images (the "standard" approach to tumor volume calculation). A paired *t*-test was used to determine whether there was a significant difference in calculated enhancing volumes between the standard approach and the ΔT1 method. Survival analysis was performed using log-rank statistical analysis on Kaplan-Meier data. All statistical tests were performed using GraphPad Prism, version 4.0.

Results

After administration of bevacizumb, the degree and volume of contrast enhancement decreased appreciably, as illustrated in *Figure 1A* and *Figure 1C*. However, ΔT1 maps clearly demarcate the region of residual contrast enhancement, suggesting ΔT1 maps may more accurately quantify residual tumor burden after bevacizumab therapy. Specifically, ΔT1 maps evaluated after the first bevacizumab treatment had a significantly larger volume compared to manually contoured T1+C lesions (*Figure 2A; paired t-test, P < 0.0001; Mean difference Pre-Treatment = 2.1cc; Mean difference Post-Treatment = 3.0cc*). Tumors with a ΔT1 map-defined hyperintense volume greater than 15cc (75th percentile) had a significantly shorter PFS compared with patients having a smaller volume on ΔT1 (*Figure 2B; Log-rank, P < 0.0001; High volume median PFS = 77.5 days; Low volume median PFS = 190 days; Hazard Ratio = 2.4*). Tumors with a post-bevacizumab ΔT1 map hyperintense volume greater than 15cc (75th percentile) also had a significantly shorter OS compared with patients having a smaller volume on ΔT1 maps (*Figure 2C; Log-rank, P < 0.0001; High volume median OS = 199 days; Low volume median OS = 376 days; Hazard Ratio = 2.5*).
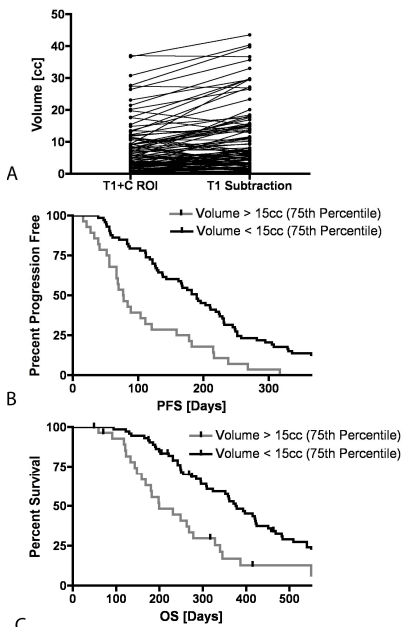
Figure 2: *A) Standard T1+C ROI volume (left) and ΔT1 volume (right). B) Post-tx volume of ΔT1 hyperintensity stratifies short and long-term progression-free survival (PFS). C) Post-tx volume of ΔT1 hyperintensity stratifies short and long-term overall survival (OS).*

Discussion

The ΔT1 mapping technique improves visualization and quantification of tumor burden, particularly in the context of anti-aniogenic therapy where contrast regions of appreciable enhancement are difficult to discern. Further, the residual volume of ΔT1 map-defined hyperintensity after bevacizumab therapy is a sensitive biomarker for survival in recurrent GBM.

References

1) Stupp, *N Eng J Med*, 2005. 2) Bedekar, *J Clin Oncol* (*ASCO Abstract*), 2011. 3) Bedekar, *Proc ISMRM,* 2010. 4) Ellingson, *JMRI,* 2012.