

Quantification of edema reduction using differential quantitative T2 (DQT2) mapping in recurrent glioblastoma treated with bevacizumab

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Introduction

Although the T2-weighted signal abnormality is now used to assess changes in non-enhancing tumor burden and the extent of vasogenic edema according to the RANO criteria¹ and many studies have illustrated the dramatic reduction in vasogenic edema after administration of anti-VEGF therapy as measured on T2-weighted images²⁻⁴, no studies have quantified the change in T2 associated with administration of anti-VEGF therapies. In the current study, we quantify the distribution of T2 before and after treatment with anti-VEGF therapy within regions of containing both suspected non-enhancing tumor and vasogenic edema, explore the voxel-wise change in T2 due to anti-VEGF therapy using a novel technique termed differential quantitative T2 (DQT2) mapping, and determine if these parameters are predictive of progression-free (PFS) and overall survival (OS) in recurrent GBM treated with bevacizumab.

Methods

All patients participating in this study signed institutional review board-approved informed consent. Patients were retrospectively selected from our institution's neuro-oncology database. A total of $n = 26$ patients who met the following criteria were selected: 1) pathology confirmed GBM with recurrence based on MRI and clinical data, 2) regularly treated every 2 weeks per cycle with bevacizumab (Avastin, Genentech; 5 or 10 mg/kg bw), alone or in combination with chemotherapy and 3) pre-bevacizumab treatment and minimum of one follow-up MRI scans that include multiple echo T2 images (proton density+T2-weighted images) before and after treatment. Baseline scans were obtained approximately 1 week pre-treatment (mean = 6.9 days \pm 2.5 days SEM). Follow-up scans were obtained at approximately 4-6 week intervals. All patients were treated with radiation therapy and maximal tumor resection at time of initial tumor presentation. Data was collected on a 1.5T MR system (GEMS; Waukesha, WI) using pulse sequences supplied by the scanner manufacturer. Quantitative T2 maps were generated using two echoes acquired during a fast-spin echo preparation (i.e. proton density weighted images (TE/TR=9.6-16ms/4000ms) and T2 weighted fast spin-echo (TE/TR=126-130ms/4000ms)). All images for each patient were registered to a high-resolution (1.0 mm isotropic), T1-weighted brain atlas (MN1152) using a mutual information algorithm and a 12-degree of freedom transformation using FSL (FMRIB, Oxford, UK). After proper registration was visually verified, voxel-wise subtraction was performed between T2 maps acquired post-treatment and baseline, pre-treatment T2 maps to create the resulting DQT2 maps.

Results

For the majority of patients, standard post-contrast T1-weighted and T2-weighted images demonstrated significant changes following the first dose of bevacizumab (Fig. 1). This change in T2-weighted image features was also evident on quantitative T2 maps and easily visualized and quantified using the DQT2 mapping technique. Specifically, qualitative examination of DQT2 maps suggested patients having a larger decrease in T2 following the first treatment of bevacizumab were more likely to have a longer PFS and OS. These results suggest DQT2 maps may provide added value to standard anatomical MR evaluation of response to bevacizumab.

As expected, the distribution of T2 within regions of abnormal T2 signal intensity prior to treatment were significantly elevated with respect to normal white matter⁵ for all patients (*F-test*, $P < 0.0001$ for all patients). Similarly, the distributions of T2 within pre-treatment regions of abnormal T2 signal intensity evaluated after treatment were also elevated with respect to normal white matter⁵ (*F-test*, $P < 0.0001$ for all patients). DQT2 maps generated after administration of bevacizumab suggest a significant reduction in T2 (Fig. 2A; *F-test*, $P < 0.0001$ for all patients). Median T2 within pre-treatment T2/FLAIR signal abnormality was significantly reduced after treatment compared to the median T2 estimate prior to treatment (Fig. 2B; *Wilcoxon signed rank test*, $P < 0.0001$). The median DQT2 value was significantly different than median change in T2 (*Wilcoxon signed rank test*, $P = 0.002$). These results support the hypothesis that anti-VEGF therapy reduces vasogenic edema, which is manifested as a decrease in tissue T2 on MRI, and the DQT2 mapping technique provides a unique perspective on the change in T2 accompanying anti-VEGF therapy. Results suggest patients having a post-treatment median T2 higher than 160ms were more likely to progress earlier than patients having a post-treatment median T2 lower than 160ms (Fig. 2C; PFS: *Log-rank*, $P = 0.0236$); however, these patients did not differ significantly in overall survival (Fig. 2D: OS: *Log-rank*, $P = 0.0824$). The median PFS for patients having a post-treatment median T2 higher than 160ms was 68 days, compared with a median PFS of 169 days for patients having a post-treatment median T2 lower than 160ms. Median OS for patients having a post-treatment median T2 higher than 160ms was 166.5 days, compared with a median OS of 315.5 days for patients having a post-treatment median T2 lower than 160ms. These results suggest post-treatment median T2 may be a predictive imaging biomarker for early disease progression, but not overall survival, recurrent GBM treated with bevacizumab.

Discussion

Although most studies examining the effects of anti-VEGF therapy have noted a reduction in vascular permeability resulting in decreased vasogenic edema as manifested on T2-weighted images^{6,7}, this is the first study to find that treatment with anti-VEGF therapy results in a significant reduction in tissue T2 within regions of T2/FLAIR signal abnormality thought to contain both non-enhancing tumor and vasogenic edema. Specifically, we found a decrease in tissue T2 around 50ms (at a field strength of 1.5T) with respect to pre-treatment T2/FLAIR abnormal regions, which is likely due to the reduction in water concentration within these brain regions. The lack of prediction of OS using the DQT2 technique suggests that changes in water concentration due to clearing of vasogenic edema ultimately does not reflect the inherent aggressiveness of the tumor, nor does it reflect growth characteristics, which are both thought to influence overall patient survival in GBM.

References ¹Wen, JCO, 2010. ²Iwamoto, *Neurology*, 2009. ³Nghiemphu, *Neurology*, 2009. ⁴Norden, *Neurology*, 2009. ⁵Whittall, *MRM*, 1997. ⁶Ananthnarayan, *J Neurooncol*, 2008. ⁷Bokstein, *Cancer*, 2008.

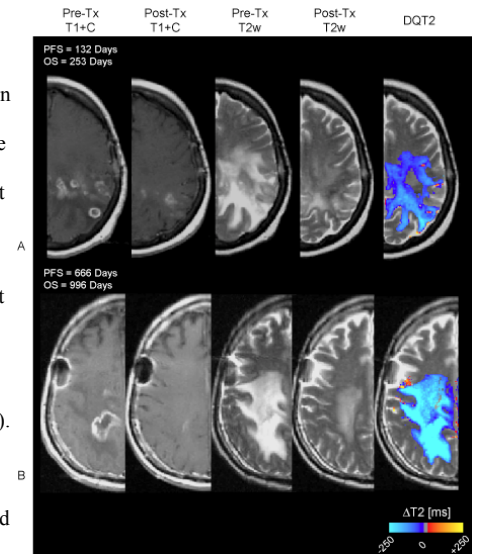


Fig.1: A) Standard MR images before and after treatment in a patient with a modest PFS and OS. Note that the DQT2 images showed a subtle decrease in T2 within areas of signal abnormality on pre-treatment T2-weighted images. B) A patient with a similar radiographic response on standard MR images; however, DQT2 images showed a substantial reduction in tissue T2 after bevacizumab treatment.

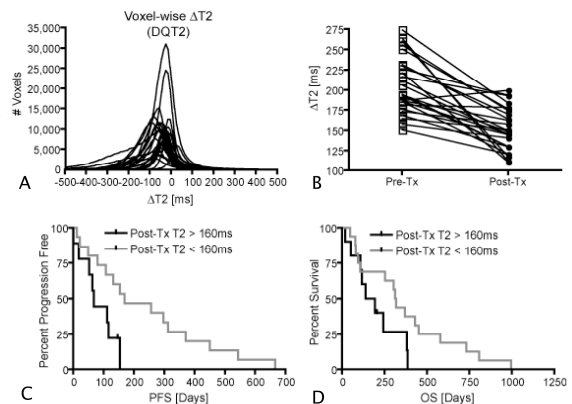


Fig.2: A) Voxel-wise $\Delta T2$ for all patients. B) Median T2 before and after treatment. C) PFS for patients with $T2 > 160$ ms and $T2 < 160$ ms. D) OS for patients with $T2 > 160$ ms and $T2 < 160$ ms.