Tracking the "DSC-based perfusion abnormality" and contrast enhancing lesion in patients newly diagnosed with GBM treated with upfront anti-VEGF therapy

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Introduction: Common contrast-enhancement (CE) based measures have limited effectiveness in assessing response to antiangiogenic therapy for patients with glioblastoma multiforme (GBM) and alternate imaging assessment methods are needed [1]. Antiangiogenic therapies are believed to induce vascular remodeling, which subsequently alters the appearance of contrast enhancement, especially during the early months of therapy [2]. Dynamic susceptibility contrast (DSC) MR imaging allows for noninvasive assessment of underlying vasculature, which has been related to response in newly diagnosed GBM patients [3]. The aim of this study is to compare the "DSC-based perfusion abnormality" to the standard CE lesion in patients with newly diagnosed glioblastoma multiforme (GBM) during the initial two months of treatment with upfront anti-VEGF therapy. The ultimate goal is to define the characteristic perfusion abnormality that identifies a likely responder at the pre-therapy MRI scan to aid clinicians in individually tailoring antiangiogenic treatment strategies.

Methods: 27 patients with newly diagnosed with GBM received anatomic and physiologic imaging prior to therapy, at 1 month and at 2 months into treatment using a 3T GE scanner. In addition to standard temozolomide and radiotherapy, patients received concurrent and adjuvant anti-VEGF therapy. Exams included gradient-echo echo-planar DSC imaging (Flip=35°, TE/TR=54ms/1.5s, 24x24 cm FOV, 128x128 matrix, 0.01mmol/kg Gd-DTPA at 3 ml/s) and anatomic imaging (pre- and post- gadolinium SPGR, T2 FLAIR). Parametric maps of peak height (PH) and percent signal recovery (%REC) were calculated to non-parametrically describe the deltaR2* curve. PH was normalized to mean normal white matter. The T1-weighted contrast-enhancing lesion (CEL) and T2 FLAIR non-enhancing lesion (NEL) were defined using the anatomic imaging data. The putative tumor region was defined as the union of the CEL and NEL. The "perfusion abnormality" was defined as the region within the putative tumor that exceeded twice the standard deviation above (for PH) or below (for %REC) the mean within the normal white matter on the respective parametric perfusion map. Both the volume and median value of the perfusion abnormality were recorded. Within patient changes in the perfusion abnormality volume were assessed using a Wilcoxon sign-rank test.

Results: Patients showed the anticipated significant decrease in volume of the CE lesion between baseline and month 1 of therapy (p<.007; Fig. 1, green). Interestingly, patients had an exaggerated reduction in volume of the %REC abnormality (p=.005; Fig. 1, red), even while the median value within the %REC abnormality remained stable (range of population median = [68.5%, 69.7%], p>.1). Patients had a significant reduction in both volume (Δvol,0.2 p=.007, Fig. 1 blue) and median value (Δvalue,0.2 p=.03, data not shown) of the PH abnormality between the baseline and 2-month scan. Figure 2 shows the T1w-CE images of an example patient with the %REC abnormality overlaid in red. Please note that along with the clinically expected reduction in CEL volume between the baseline and 1-month scan, there is a greater reduction in volume of %REC abnormality. Furthermore, even after the initial reduction and stabilization of the CEL volume by 1 month of therapy, volume changes in the %REC and PH abnormality are still observable.

Conclusions: This study suggests that the pattern of perfusion abnormality differs from that of the standard CEL for newly diagnosed GBM patients treated upfront with anti-VEGF therapy. Patients showed an exaggerated reduction of the volume, but not value, of the %REC abnormality, which may reflect underlying biological changes behind the "steroid-like" effect that has been clinically observed with this therapy. On the other hand, by 2-months into therapy patients had a reduction in both volume and value of the PH abnormality, which may be reflective of the vascular remodeling effect that has been reported for this type of therapy. Further studies are planned to (1) characterize the type of pre-therapy perfusion abnormality that may identify a responder patient and (2) determine whether these volume changes in perfusion abnormality, which may persist after CEL volume has been greatly reduced from upfront anti-VEGF therapy, relate to patient outcome.


Figure 1. Median volume of perfusion abnormality and CEL during upfront anti-VEGF therapy (error bars depict inner-quartile range). Note large decrease in volume of %REC abnormality by 1 month and decrease of PH abnormality by 2 months of therapy.

Figure 2. Example of a treatment naïve GBM patient displaying the %REC (red ROI) and PH (Blue ROI) abnormality in comparison to CEL during upfront anti-VEGF therapy. Note the large volume decrease in %REC after 1 month of therapy and moderate volume decrease of PH after 2 months. Additionally, even after the initial reduction and stabilization of CEL volume by 1 month of therapy, volume changes in the perfusion abnormalities between 1 and 2 months are still observable.