Comparison of DSC-derived Perfusion Parameters in Response to Conventional Therapy or Adjuvant Anti-angiogenic Therapy in Patients Newly-Diagnosed with GBM

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Introduction: The current clinical standard of care for patients with glioblastoma multiforme (GBM) includes combined radio- and cytotoxic therapy [1]. Anti-angiogenic therapy, thought to normalize the vasculature of these tumors [2], has shown improved disease management in recurrent patients [3] and is hoped to increase survival in newly diagnosed patients. Dynamic susceptibility contrast (DSC) MR imaging can be used to assess aspects of the tumor vasculature that may be altered in response to angiogenic inhibitors. The purpose of this study was to (1) compare early perfusion parameters between patients receiving conventional therapy and patients receiving adjuvant anti-angiogenic therapy and (2) assess whether these parameters relate to 6-month progression-free survival (PFS) status.

Methods: Sixty-two patients newly diagnosed with GBM (27 that received radio- and cytotoxic therapy and 35 that received radio-, cytotoxic, and adjuvant anti-angiogenic therapy) were examined in this study. Patients were imaged serially at pre-therapy (post-surgery) and at every subsequent 2-month follow-up exam on a 3T GE scanner. Exams included DSC perfusion imaging (gradient-echo, echo-planar sequence, TE/TR = 54/1500ms, flip angle = 35°, 26x26cm^2 FOV, 128x128matrix, 0.1mmol/kg Gd-DTPA injection at 3 ml/s), 3D lactate-edited spectroscopic imaging (TE/TR = 144/1100ms, 16x16x6 cm FOV, nominal voxel size =1x1x1 cm), and anatomic imaging (pre- and post-gadolinium SPGR, T2 FLAIR). Parametric maps of peak signal height (∝ blood volume) and percent of signal recovery (∝ leakage), derived from the DSC relaxivity over time curves were generated. At each exam, the putative tumor region was defined to include all anatomically and metabolically abnormal regions (union of contrast enhancing lesion, FLAIR hyperintensity, and elevated Choline-to-NAA index [CNI>2] lesion) (Figure 2: pink overlay). Within this putative tumor region, the value corresponding to highly abnormal perfusion was extracted for both parametric maps (90th percentile for peak signal height, 25th percentile for percent signal recovery).

Results:

Comparison of Perfusion Changes: Patients receiving adjuvant anti-angiogneic therapy had a significant within patient reduction in normalized peak height between baseline and 2-months into therapy (mean change = -0.33, Wilcoxon signrank p=.002), while patients receiving only conventional therapy did not (mean change = -0.09, Wilcoxon signrank p=.3) (Figure 1).

Predicting PFS based on Perfusion: Both conventional therapy and adjuvant anti-angiogneic therapy patients had similar patterns of percent recovery across the entire population, however there were differences in percent recovery related to 6-month PFS status between therapy groups (Figure 2). For the adjuvant anti-angiogenic therapy group, those patients with PFS greater than 6 months showed a significant increase in percent recovery within the first two months of treatment (Wilcoxon signrank , p=.008), while for the conventional therapy group there was no significant change in percent recovery for either 6-month PFS status group. The greater dispersion of percent recovery at 2-months for the adjuvant anti-angiogenic therapy patients was not only related to 6-month landmark PFS status, but was also predictive of the full course of PFS (Cox Regression, adjusted for control factors, p=.008). For the conventional therapy patients, neither value nor change in percent recovery was predictive of PFS by this time point (Cox Regression, all p>.7).

Conclusions: In response to anti-angiogenic therapy, patients showed a marked decrease in vascularity, which was not observed in response to conventional therapy. Further studies are underway to identify whether patients with an initially highly vascularized tumor derive a greater survival benefit from adjuvant anti-angiogenic therapy over conventional therapy. An immediate improvement in percent recovery may dominate 6-month PFS status for patients that receive adjuvant anti-angiogenic therapy, while early percent recovery markers are not reflective of PFS for patients that receive conventional therapy. These results emphasize that conventional contrast enhancement based outcome measures (e.g. PFS) may not be appropriate to assess response to anti-angiogenic therapy, as they are strongly influenced by early leakage changes, therefore highlighting the need for alternate functional imaging methods.

References: [1] Stupp, et al. (2007) J Clin Oncol 25(26):4 4127-36 [2]Jain (2001) Nat Med 7(9):987-9 [3] Vredenburgh, et al.(2007) J Clin Onc 25(30):4722-9

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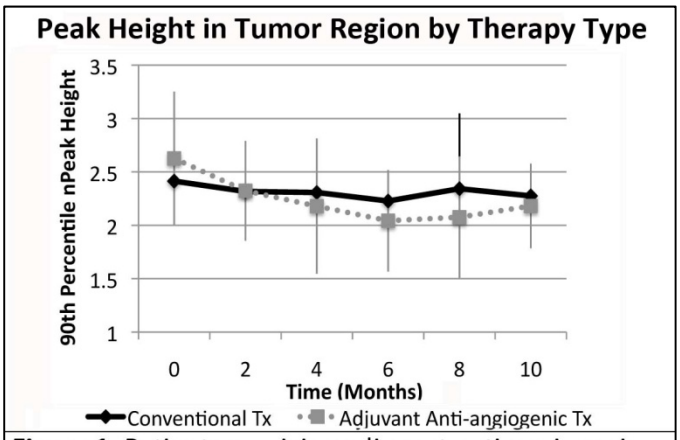
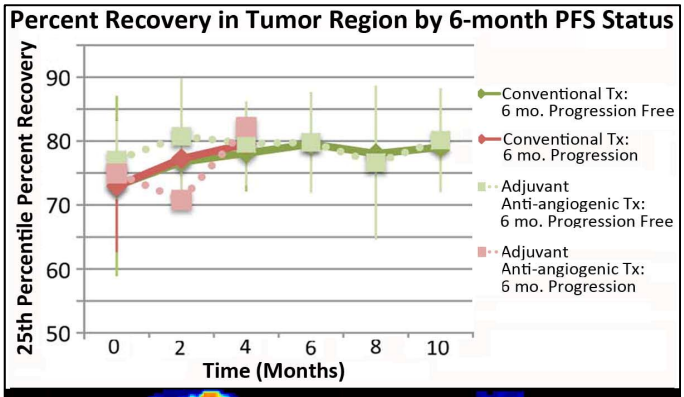


Figure 1. Patients receiving adjuvant anti-angiogenic thearpy show decrease in vascularization by 2-months, while patients receiving conventional therapy do not.



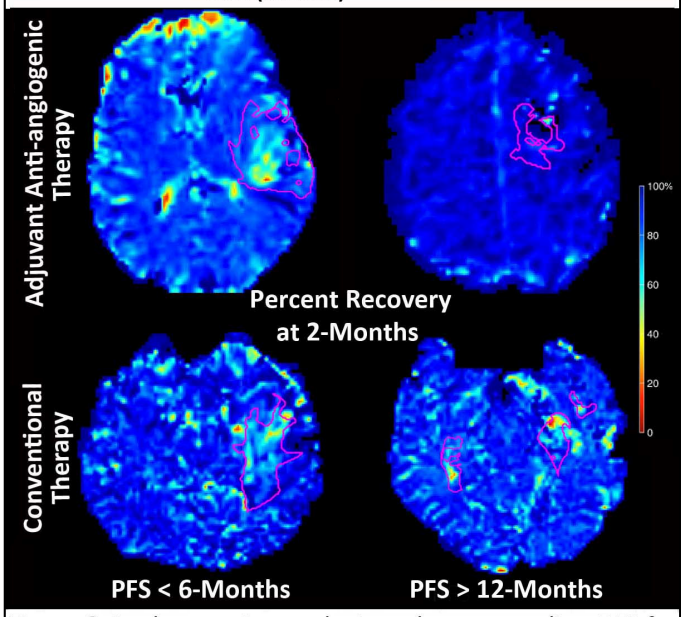


Figure 2. Leakage at 2-months into therapy predicts PFS for patients with adjuvant anti-angiogenic therapy and does not for patients with conventional therapy.