The Functional Perfusion Map: A Novel Imaging Biomarker for Early Prediction of Tumor Patient Response

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Introduction: Perfusion MRI has been actively pursued as a promising imaging biomarker for treatment response assessment in cancer patients with equivocal prognostic accuracy. Moreover, there has been a lack of consensus as to the specific analytical approach needed for optimization of prognostic value using current volumetric averaging of MR quantifiable hemodynamic parameters. In this study, we propose a fundamentally different approach for analysis of MR perfusion data which relies on voxel-wise comparison of perfusion changes following therapeutic intervention of patients with Grade III/IV gliomas.

Methods and Materials:

Dynamic Contrast Enhancing- Magnetic Resonance Imaging

Forty-five patients with Grades III/IV glioma were recruited for this study. Patients underwent MRI 1-2 weeks before RT and at weeks 3-4 during RT. When MRI was performed at Weeks 1-2 during RT, the patients had received a median dose of 12 Gy (range, 5-6). At Weeks 3-4, the median dose was 32 Gy (range, 26-40). MRI scans were acquired on a 1.5T GE clinical scanner (General Electric Medical Systems, Milwaukee, WI) or a 3T Philips clinical scanner (Philips Medical Systems, Andover, MA). Dynamic contrast-enhanced (DCE) T2*-weighted imaging with intravenous administration of a standard dose (0.1 mL/kg) bolus of gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA), and post contrast T1-weighted images were acquired by a gradient-echo echo-planar imaging pulse sequence (TR=2s, T2=60ms, field of view 220x220 mm^2, matrix 128x128, flip angle 60°, and 14 interleaved slices with 6mm thickness and 0mm gap). The relative CBV in the brain and tumor were computed as described by Ostergaard [1].

Functional Perfusion Mapping (fPM) and Percent Difference of rCBV

All images were co-registered to Gd-enhanced T1-weighted images acquired before RT using an automated mutual information and simplex optimization module [2]. Following co-registration, brain tumors were manually contoured on the Gd-enhanced T1-weighted images by radiologists. The rCBV values of each voxel within the tumor at week 3 were compared with the pre-RT values. fPM_{rCBV} was performed by thresholding the absolute difference of rCBV in a voxel into three categories: $\Delta rCBV>1.56$ (V_I: red); $\Delta rCBV<-1.56$ (V_D: blue); and $\geq 1.56 \Delta rCBV \leq -1.56$ (V_0: green). The thresholds were empirically determined to be the 95% confidence intervals calculated from normal contralateral brain tissue. Percent difference of the mean rCBV (pdCBV) pre and post therapy were also acquired and compared with fPM_{rCBV} results.

Statistics

Patient population was stratified based on the median V_I, V_D, V_0 and pdCBV. Kaplan-Meier survival curves and the log-rank test were used to characterize and compare the groups in terms of overall survival. Statistical significance was assessed at $P<0.05$.

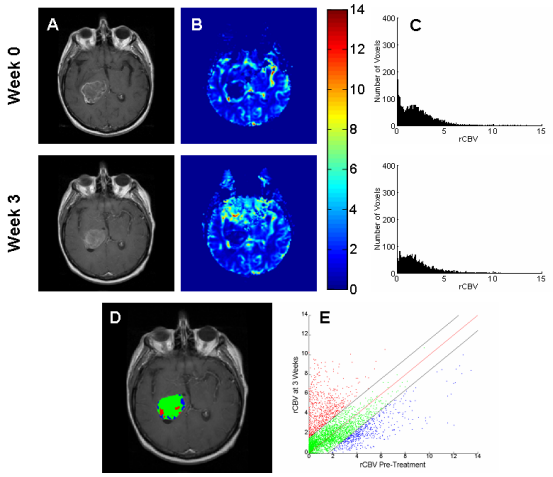

Figure 1: Patient with a glioblastoma multiforme designated by fPM_{rCBV} stratification as a non-responder (survival time=2.9 months). (A) Gd-enhanced T1-weighted MR image, (B) rCBV map and (C) rCBV histogram of tumor at 0 and 3 weeks post-radiotherapy., with color scale for rCBV. (D) fPM_{rCBV} color-encoded ROI superimposed onto a Gd-enhanced T1-weighted MR image 3 weeks post-radiotherapy. (E) Scatter plot showing the distribution of rCBV pre and post-radiotherapy for the entire 3D tumor volume.

Results: In general, patients with low survival times (Figure 1; survival time of 2.9 months) exhibited larger volumes of increasing and decreasing rCBV when compared to patients with high survival times. Voxels with statistically different rCBV were primarily found along the periphery of the tumor mass.

Percent difference of mean rCBV was found to not correlate with patient outcome (Fig. 2A). Patients with pdCBV below the cutoff had a median survival slightly less than patients whose pdCBV were above the cutoff (12.8 months and 16.0 months, respectively; P=0.933). In contrast, fPM_{rCBV} exhibited a significant correlation with overall survival. From the three partial volumes acquired from fPM_{rCBV}, V_D produced the most significant result. Patients whose V_D was below the cutoff (median V_D for population: 6.31) had a significantly longer median survival than patients whose V_D was above the cutoff (18.2 months and 8.3 months, respectively; P=0.009). V_I also produced significant results, with patients below the cutoff (median V_I for population: 10.60) having a significantly longer median survival than those above the cutoff (18.8 months and 10.2 months, respectively; P=0.044). Finally, patients with V_0 below the cutoff (median V_0 for population: 76.32) had a median survival less than those above the cutoff (10.9 months and 16.8 months, respectively; P=0.099).

Discussion: We have developed a novel, voxel-wise method for monitoring treatment response in glioma patients using perfusion maps, which we refer to as functional perfusion mapping (fPM_{rCBV}). This approach is made possible by measuring functional changes in blood perfusion, as assessed by relative cerebral blood volume (rCBV), within the tumor pre-therapy and at three week follow-up. fPM_{rCBV} was found to have predictive value for survival in patients with high-grade gliomas. Most notable was the volume fraction associated with decreasing rCBV, V_D, which best correlated with overall survival (P=0.009).

References:

1. Ostergaard, L., et al., Magn Reson Med, 1996. 36, 715-25.
2. Meyer, C.R., et al., Med Image Anal 1997. 1, 195-206.

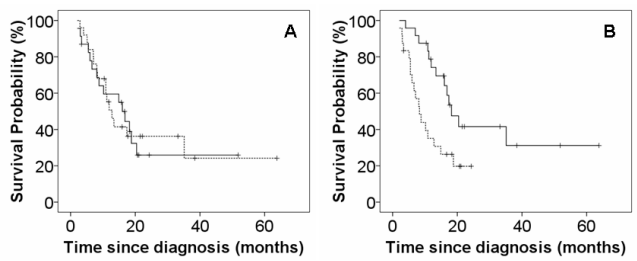

Figure 2: OS as a function of percent difference of rCBV and fPM stratification at week 3 post-treatment. (A) The Kaplan-Meier survival plot of OS for patients stratified by percent difference of rCBV at week 3 post-treatment (n=23; solid line; <median) with a median survival of 16.0 months vs. those stratified (n=25; dashed line; ≥median) with a median survival of 12.8 months [P=0.933; log-rank test]. (B) The Kaplan-Meier survival plot of OS for patients stratified by fPM_{rCBV} (V_D) at week 3 post-treatment (n=24; solid line; <median) with a median survival of 18.2 months vs. those stratified (n=24; dashed line; ≥median) with a median survival of 8.3 months [P=0.009; log-rank test].