"Hot spot" Analysis for Glioblastoma multiforme

P. Yeo[1], P. J. Chen[1,2], W. T. Zhang[1], E. di Tomaso[1], D. G. Duda[1], R. K. Jain[1], T. T. Batchelor[1], and A. G. Sorensen[1]

[1]Massachusetts General Hospital, Charlestown, MA, United States, [2]Nuclear Science and Engineering, Massachusetts Institute of Technology, Cambridge, MA, United States

Introduction: Tumors typically consist of heterogeneous groups of cells differing in morphology, vascularity and microenviromental characteristics, and their extent of variability can be difficult to determine precisely. There are currently few clear prognostic indicators of patient survival, especially as related to angiogenic activity of tumors and response to new classes of targeted anti-angiogenic agents. Imaging has been used to routinely monitor therapeutic end points for patients with glioblastoma multiforme (GBM), specifically, dynamic contrast-enhanced magnetic resonance imaging (MRI). Although tumor vascularity can be readily studied, the approach of averaging overall volumes in the region of interest (ROIs) of the lesions, though widely used, has not been a uniform success in determining clinical outcomes [1]. Past studies indicate that there is value in using tumor areas with extremes in density of distinctly visible microvessels ("hot-spots") as a prognostic indicator for various cancers. Here, we suggest using a spatial method of locating hot-spots in glioblastoma to improve prediction of survival outcome in GBM patients.

Patients/Methods: Thirty consecutive patients (mean age 51.1, range 20-77 years) with recurrent GBM underwent repetitive MRI with Auto-Align technique [2] in a 3T MRI scanner (TimTrio, Siemens Medical Solutions, Malvern, PA) 3-7 days before, 1 day before (day -1), 1 day (day +1), 26-28 days (day +28), 54-56 days, 110-112 days after cediranib treatment (45 mg daily by mouth). Blood volume, blood flow and relative vessel size maps were synthesized using a standard deconvolution technique [3]. Apparent diffusion coefficient (ADC) maps were calculated from low and high b-value images using custom-written software implementing the standard Steskjal-Tanner diffusion approximation. T2-TSE, FLAIR, pre- and post-contrast T1 images were also acquired at each visit. We investigated ADC, vessel size, K-trans, Gradient-echo and Spin-echo Cerebral blood flow (GE and SE CBF), GE and SE Cerebral blood volume (CBF), and GE and SE Mean transit time (MTT). The ROIs based on T1 post Gd enhancement of all visits were outlined by a blinded neuroradiologist. Hot spot values were created by searching for the highest values in each slice within the ROIs using voxel sizes of 2x2mm, 3x3mm and 4x4mm. Average overall volumes of lesions were calculated using a volumetric approach that includes outlining each enhancing voxel on postcontrast scans and then summing the voxels [4]. The variables for hot spot volumes and average volumes were correlated against overall survival (OS, survival period since trial) and progression free survival (PFS, survival period that is progression free since trial). Pearson product-moment correlation coefficient (r-values) and corresponding p-values were obtained by correlating the variables against OS and PFS for change over baseline (day -1) between day -1 and day +1 (Δday +1), and day-1 and day +28 (Δday +28).

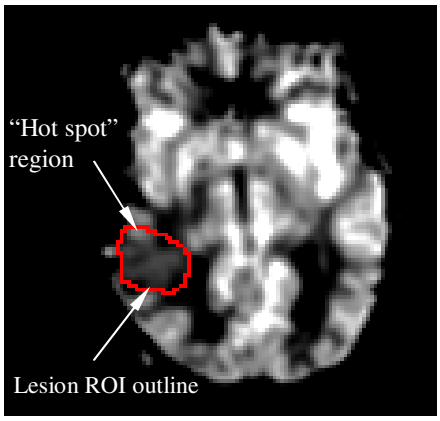

Fig.1 An example of a GE CBF image showing the ROI (outlined in red) based on T1 post Gd enhancement. Average volume is calculated by summing all voxels within the outline. "Hot spot" region, defined as distinctly visible microvessels, is shown at the edge of the lesion.

Results: Results for average volume were significant only for ADC Δday +1 on OS ($r=0.500$, $p<0.05$) and PFS ($r=0.388$, $p<0.05$). Hot spot analysis for voxel size 2x2mm (**Fig.1**) demonstrated statistically significant correlations for GE MTT Δday +28 ($r=-0.4336$, $p<0.05$) and SE MTT Δday +1 ($r=0.474$, $p<0.05$) as compared to PFS. Using a voxel size of 3x3mm showed that PFS was correlated with vessel size Δday +1($r=0.435$, $p<0.05$) and GE CBF Δday +28. Voxel size 4x4mm showed that OS was correlated with vessel size Δday +1 ($r=0.444$, $p<0.05$), GE CBF Δday +28 ($r=0.435$, $p<0.05$), SE CBF Δday +1 ($r=-0.470$, $p<0.05$), and SE CBF Δday +28 (-0.450, $p<0.05$). PFS was also correlated with ADC Δday +1 (-0.376, $p<0.05$).

Conclusions: This work suggests that several hot spot volume maps are correlated with OS and PFS, when average volume analysis of maps showed only correlation on one map. Future work will investigate multivariable analysis of hot spot maps for prediction of OS and PFS and expand the analysis for larger voxel sizes and other time point changes.

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