How Blood Perfusion maps are analyzed can greatly improve the predictive potential for assessing survival in patients treated for gliomas.

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Introduction: Gliomas continue to be the most common form of brain malignancy in adult patients. Even with advancements in the clinical management for these patients, assessment of therapeutic induced response continues to be based on late or serial changes in tumor volume as measured by CT or MRI [1,2]. We have developed a method to quantify regional changes in tumor perfusion for early assessment of therapeutic response in glioma patients, referred to as the parametric response map (PRM). The PRM approach when applied to rCBV (PRM_{rCBV}) has been shown to be, as early as 1 week into therapy, highly predictive of survival and is capable of differentiating pseudoprogression from true progression [3; 4]. In this study we tested the hypothesis that the type of method used to analyze the physiological parameter can greatly improve the parameter's predictive value. As such we compared the voxel-based technique (PRM) to several common methods for assessing response (i.e. whole-tumor histogram-based and segmentation-based approaches). In addition, we evaluated for each metric the impact of the volume of interest (VOI) and the time the mid-treatment perfusion map was acquired on the metrics predictive value of one-year and overall survival in a cohort of glioma patients.

Materials/Methods:

Patient: Patients (n=44) with Grade III/IV glioma were recruited in a retrospective imaging trial. Patients underwent MRI before RT, 1 and 3 weeks after RT. The median dose were 12 Gy (range, 5-6) and 32 Gy (range, 26-40) at week 1and 3, respectively. MRI scans were acquired on a 1.5T GE clinical scanner (GE Medical Systems, Milwaukee, WI) or a 3T Philips clinical scanner (Philips Medical Systems, Andover, MA). **MRI**: The MRI protocol included contrast-enhanced T1-weighted imaging, fluid-attenuated inversion recovery imaging (FLAIR) and dynamic contrast-susceptibility (DSC) T2*-weighted imaging. DCS-MRI was performed following an intravenous administration of a standard dose (0.1 $mL.kg^{-1}$) bolus of gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA) using 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 6 mm thickness). The relative cerebral blood volume (rCBV) in the brain and tumor were computed as described previously [2]. **Data analysis**: All images were co-registered to Gd-enhanced T1-weighted images acquired before RT using a fully automated, affine, mutual information-based, simplex optimization algorithm [1]. Following co-registration, the tumor VOIs were manually contoured either on the Gd-enhanced T1-weighted or on the FLAIR images by a neuroradiologist and applied to the rCBV maps. For each patient, mid-treatment time point and VOI the following parameters were analyzed: ***histogram based approach*** for monitoring percent change of the rCBV mean, median and percentiles in increments of 10% [5] (plus 25th and 95th [6]), a ***histogram segmentation approach*** for monitoring the percent change of the tumor volume fraction with low-rCBV, medium-rCBV or high-rCBV values [3] and ***voxel-based approach*** which is PRM. Briefly, PRM was performed by calculating the difference in the rCBV values of each voxel within the tumor at mid-treatment values with respective pre-treatment values. A threshold was then applied to the absolute difference of the rCBV in a voxel and all like voxels were summed to obtain tumor volume fractions that showed significantly increasing (PRM_{rCBV+}: red), significantly decreasing (PRM_{rCBV-}: blue), and unchanged (PRM_{rCBV0}: green) rCBV values following therapy [4]. **Statistics**: Receiver operator characteristic analysis (ROC), assessed for 12 month survival, was used to determine the optimal cutoff for each parameter. Only those parameters that generated significantly large area under the curves where further analyzed for predicting overall survival. The patient population was then stratified based on the optimal cutoffs obtained from the ROC analysis. Overall survival for each parameter was then determined using Kaplan-Meier curves and the log-rank test. Statistical significance was assessed at $p<0.05$.

Results: Among all the parameters tested (20 parameters multiplied by 2 VOIs and 2 time points), only 4 were statistically significant using the ROC analysis (Fig. 1e). Indeed only the PRM_{rCBV-} parameters at week 1 and 3 and using the Gd or the FLAIR VOIs appeared significant using the ROC analysis (Fig. 1a-d blue voxels). Considering the various time points and VOIs, the optimal cutoffs had a small range of 4.6-6.8 which deviated by only 32% from the 6.8% previously reported by our group [4]. The Kaplan-Meier survival curves, the cutoff used and the log-rank tests are presented for the 4 PRM_{rCBV-} in Fig. 1f-i. The 4 PRM_{rCBV-} were able to predict significantly different patient outcomes irrespective of the time the mid-treatment rCBV map was acquired or VOI.

Conclusions: Among all the parameters tested, only PRM was found to be predictive of response. In addition, this voxel-based approach is shown to be very robust with negligible sensitivity to the choice of VOI (volumes delineated by Gd or FLAIR) or the time the mid-treatment rCBV map was acquired. The application of PRM to blood perfusion maps show promise as an early and robust surrogate imaging biomarker of treatment response in patients diagnosed with high grade gliomas. Further evaluation of this technique in a multi-center trial is warranted.

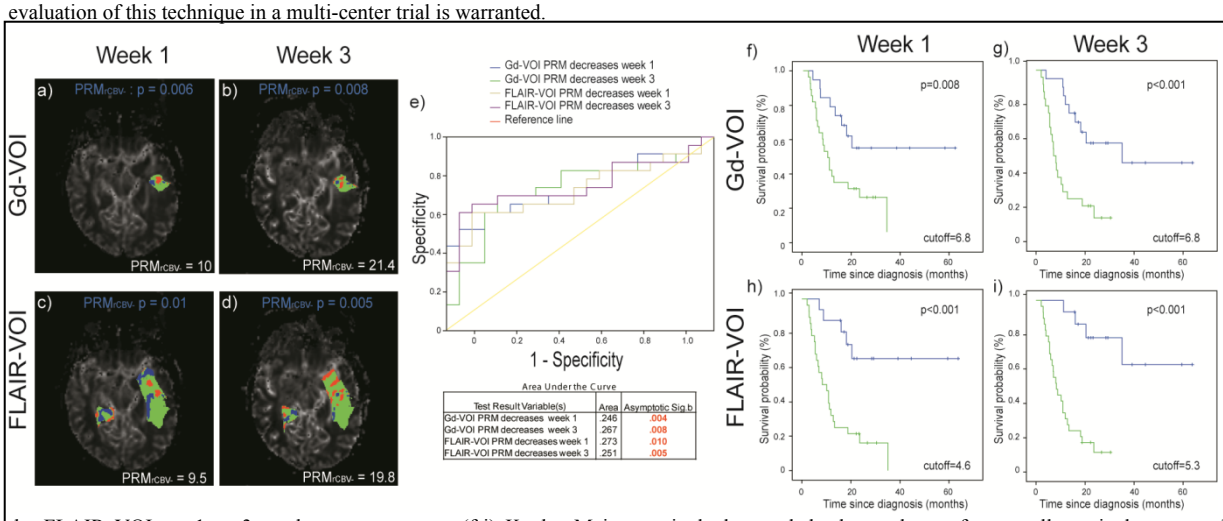

Figure 1: (a-d) Patient with a glioblastoma multiforme designated by PRM_{rCBV-} stratification as a non-responder (survival time=8.1 months). PRM_{rCBV} color-encoded Gd-VOI (a-b) or FLAIR-VOI (c-d) superimposed onto rCBV map at 1 (a-c) and 3 (b-d) weeks post treatment (blue voxels: PRM_{rCBV-} and red pixels: PRM_{rCBV+}). e) ROC curves (the area under the curve and the p-values) for PRM_{rCBV-} using either the Gd or the FLAIR VOIs at 1 or 3 weeks post-treatment. (f-i) Kaplan-Meier survival plots and the log-rank test for overall survival, presented as function of PRM_{rCBV-} stratification using either the Gd-VOI or the FLAIR-VOI at 1 or 3 weeks after treatment initiation. Blue line indicates PRM_{rCBV-}- lower than or equal to the cutoff and green line indicated PRM_{rCBV-} more than the cutoff.

References:

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