Comparison of diffusion and perfusion parameters in distinguishing radiation effect and necrosis from GBM

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Target Audience: Neuro-oncologists, neuroradiologists, neurosurgeons, brain tumor imaging scientists.

Purpose: In glioblastoma (GBM), pseudoprogression (PsP), an inflammatory response associated with radiation and necrotic induced changes reflective of effective treatment, appears as increased enhancement on T1-weighted imaging following concurrent chemoradiotherapy (CRT), making it difficult to distinguish from true progression.[1,2,3] The goal of this study was to determine the ability of the apparent diffusion coefficient (ADC) to distinguish treatment-related radiation effect and necrosis (RE/Necrosis) from GBM compared to perfusion measures derived from dynamic susceptibility contrast (DSC) MRI.

Methods: ***Acquisition:*** All participants gave informed written consent according to IRB policy. Thirty tissue samples from eight previously treated subjects were spatially correlated with pre-surgical MRI. Biopsy locations were determined via a StealthStation® S7™ surgical navigation unit (Medtronic, Minneapolis, MN), and all tissue samples were reviewed by a neuro-pathologist. Imaging data was acquired on a 1.5T or 3T system and included SPGR, DWI, DSC GRE-EPI (TE=31ms, TR=1.48sec, 0.05-0.1 mmol/kg preload, 0.05-0.1mmol/kg dose during DSC data collection), and a T1w reference scan. ***Processing:*** ADC maps were calculated from DWI with b-values of 0 and 1000. Perfusion metrics were calculated from DSC data in IB Neuro (Imaging Biometrics, Elm Grove, WI), which also incorporates a leakage correction algorithm, and includes standardized (sRCBV) and normalized (nRCBV) relative cerebral blood volume, and normalized relative cerebral blood flow (nRCBF).[4,5] Perfusion metrics were standardized using built-in standardization files or normalized with manually drawn normal appearing white matter reference regions, respectively.[4] All processed maps were rigidly co-registered to the pre-surgical Stealth exam using a normalized mutual information cost function. Positive, non-zero median values for the parameter maps were obtained within 3-mm spherical regions that were visually matched to the surgically recorded biopsy locations. ***Statistical Analysis:*** Generalized Estimating Equations (GEE) analysis using a robust estimator for the variance was performed to account for multiple samples from the same subject. Receiver operator curves were then created from the binary logistic output derived from the GEE analysis to determine thresholds and corresponding sensitivity and specificity for distinguishing RN from GBM for all diffusion and perfusion parameters.

Table 1: *Statistical results for diffusion and perfusion measures in distinguishing RE/Necrosis and GBM. Units for ADC are in mm2/sec and are arbitrary for perfusion metrics.*

Metric	Threshold	AUC	Sensitivity	Specificity	Significance
ADC	1600	0.73	70.0%	80.0%	$p < 0.01$
nRCBV	1.23	0.91	81.8 %	90.9 %	$p < 0.0001$
sRCBV	4002	0.91	81.8 %	90.9 %	$p < 0.0001$
nRCBF	1.08	0.81	72.7 %	81.8 %	$p < 0.001$

Results: Pathologic diagnosis confirmed 11 samples with pure RE/Necrosis and 22 samples with pure GBM. All metrics showed significant differences between RE/Necrosis and GBM ($p < 0.01$). All perfusion metrics distinguished RE/Necrosis from GBM with greater statistical power and better sensitivity and specificity than did ADC as is displayed in Table 1. Additionally, both sRCBV and nRCBV showed equally higher sensitivity and specificity than nRCBF for differentiating RE/Necrosis and GBM. Using the thresholds obtained for rCBV, which provide the best discernment, fractional tumor burden (FTB) maps can be created to spatially visualize the portion of enhancing tumor that is RE/Necrosis or GBM, as seen in Figure 1.[2,3]

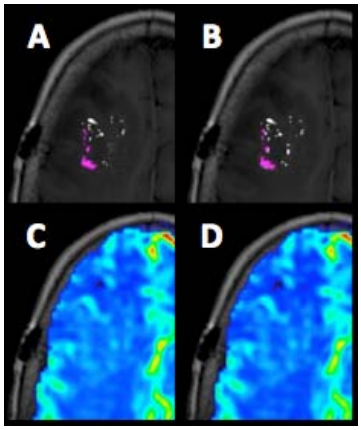

Figure 1: *FTB maps (a,b) above corresponding nRCBV (c) and sRCBV (d) maps. FTB maps (within enhancing ROI) are thresholded based on the ROC value distinguishing RN (white) from GBM (pink). Biopsy samples obtained for this subject were reported as mixed RE/Necrosis and GBM.*

Discussion: These results demonstrate that nRCBV and sRCBV offer an equally clear advantage over ADC and nRCBF in distinguishing RE/Necrosis from GBM. The nRCBV threshold of 1.23 is somewhat greater than a previously published value of 1.00 for distinguishing RE/Necrosis from GBM.[2,3] However, in this study, only subjects with pure RE/Necrosis or pure GBM were included in the analysis, where in prior studies GBM samples that contained an admixture of both GBM and RE/Necrosis were included.

Conclusion: Accurate assessment of treatment response using nRCBV or sRCBV is promising, as these measures show high statistical power and increased sensitivity and specificity for differentiating RE/Necrosis and GBM. Both nRCBV and sRCBV provide equally greater accuracy than ADC and nRCBF. An additional advantage for sRCBV is that it precludes the need for the manual step of drawing a normal reference ROI as does nRCBV. Visualizing differentiated regions of rCBV on imaging could help clinicians better assess treatment response following CRT, with potential to impact treatment management decisions.

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