Minimum sample size requirements for rCBV measures in patient glioblastoma trials

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Target Audience: Neuro-oncologists, neuro-radiologists, neuro-surgeons, brain tumor imaging scientists.

Purpose: Brain tumor vascularity has been increasingly evaluated using relative cerebral blood volume (rCBV), derived from dynamic susceptibility contrast (DSC) MRI. Measures of rCBV have been shown to assist with the identification of tumor grade, type, progression, aggressiveness, and treatment response. This has led to growing interest in the use of rCBV as a biomarker of clinical outcome or in research, with the potential to provide non-invasive monitoring at earlier disease stages. The purpose of this study was to provide an estimate of the minimum sample size requirements for powering a clinical imaging trial involving glioblastoma (GBM) patients in order to detect an rCBV parameter change of 10% or 20% for six of the most commonly used rCBV estimation methods.[1,2]

Methods: ***Acquisition:*** MRI was performed twice, within eight days, for 38 subjects with newly diagnosed GBM. Five subjects were excluded from analysis due to extreme motion artifact (1), poor contrast injection (2), and initiation of treatment (2). Data acquired included DSC-MRI and pre- and post-contrast T1-weighted images (T1+C). All data was acquired on a 3T system, using the same imaging protocol (DSC GRE-EPI: TE=31ms, TR=1.45sec, 0.1 mmol/kg preload, 0.1-0.2mmol/kg dose during DSC data collection). ***Processing:*** Normalized (nRCBV) and standardized (sRCBV) rCBV derived from six common estimation methods were calculated using software developed at the Medical College of Wisconsin (MCW)[2]. Table 1 provides a summary of these methods.[3] Data was then normalized or standardized for each visit separately, with standardization files created at MCW[2] or manually drawn NAWM ROIs, respectively. ***Analysis:*** All images were rigidly co-registered with T1+C using a normalized mutual information cost function. For each visit, enhancing tumor volume ROIs were determined using a semi-automated, threshold-detection algorithm which incorporates standardized T1+C and T1w images.[4] Within the tumor ROI, positive, median values of rCBV were obtained. The minimum sample size required to detect a parameter change of 10% or 20% was calculated for each nRCBV or sRCBV estimation method with statistical significance set at $\alpha = 0.05$ and power = 0.90, where the percent changes were based on the population means for each estimation method in this study.[1,5]

Table 1: *rCBV Estimation Methods*

rCBV Estimation Methods	
Method 1	120-point Numeric Integration of ΔR2*(t) with the Trapezoid Rule
Method 2	120-point Numeric Integration of ΔR2*(t) with the Trapezoid Rule and Correction for T1 Extravasation Effects
Method 3	Area under Gamma-Variate Fit to ΔR2*(t)
Method 4	Area under ΔR2*(t) after Post-bolus Baseline Correction
Method 5	Maximum Signal Drop of S(t)
Method 6	Negative Enhancement Integral of S(t)

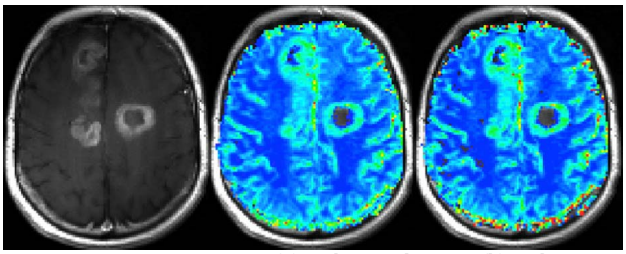

Figure 1: *Post-contrast T1 (a) with typical nRCBV (b) and sRCBV (c) maps.*

Results: Typical nRCBV and sRCBV maps for one patient are shown in Figure 1. Minimum sample-size requirements are displayed in Table 2. For all methods, standardized estimates of rCBV were found to require fewer participants than normalized estimates of rCBV to detect a 10% or 20% change in rCBV. Also, the range in minimum number of participants appeared to be more consistent for sRCBV across all methods than did nRCBV to detect a 10% (109-215 vs. 118-643, respectively) or 20% (28-54 vs. 30-161, respectively) change in rCBV parameter value.

Table 2: *Sample Size Requirements*

Minimum Sample Size for rCBV Estimation Methods				
Method	To detect a 10% Change		To detect a 20% Change	
	nRCBV	sRCBV	nRCBV	sRCBV
1	234	115	59	29
2	176	145	44	37
3	118	109	30	28
4	643	147	161	37
5	275	215	69	54
6	215	194	54	49

Discussion/Conclusion: This study provides an estimate of the minimum sample size required to power a clinical trial or research study involving GBM patients where rCBV is evaluated as a biomarker of outcome. Utilizing sRCBV in clinical trials has the potential to improve efficiency by requiring considerably fewer participants to address a given hypothesis. Additionally, unlike nRCBV, sRCBV does not require an extra step of drawing a reference ROI.

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