

# Exploring Two Methods of CBV Estimation in Two Groups of Grade III Gliomas with Different Appearance on Post-Contrast T1 Images

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## ABSTRACT

**Background:** Many studies have used Cerebral Blood Volume (CBV) for gliomas grading and there has been in good agreement between CBV and tumor grade. Almost all of those studies have emphasized the importance of leakage correction due to the underestimation/overestimation of CBV caused by T1/T2\* leakage effect in enhanced cases of tumors, especially high grade ones.

**Objectives:** The aim of this study is to investigate two methods of CBV estimation in two groups of gliomas with the same grade and different appearance on post contrast T1 images (Enhanced vs. Non-enhanced ones).

**Material and Methods:** In this retrospective study, eight glioma patients with histopathologically confirmed grade III were equally divided into two groups (with enhancement (group 1) and without enhancement (group 2)), and retrospectively studied. Imaging was performed on a 3 tesla MR Scanner and included gradient-echo DSC, 3D T1-weighted dataset and FLAIR images. The conventional method of CBV measurement (Integration over the whole curve of CTC- method 1) and the GVF fitting (method 2) was done using Matlab.

**Results:** The observed mean rCBV in the tumor ROI was 2.85 and 2.12 for group 1 with method 1 and 2, respectively. Mean rCBV in the tumor ROI for group 2 was 1.24 and 1.11 with method 1 and 2, respectively.

**Conclusion:** In conclusion, this pilot study demonstrated that with combined use of pre-bolus and accounting for T2\* effect, CBV could be considered as a criterion for the categorization of glioma tumors.

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## Keywords

Neoplasm Grading; Magnetic Resonance Imaging; Cerebral Blood Volume

## Introduction

Owing to differences in process and type of treatment for low- and high-grade tumors, the type, and grade of the tumors must be determined before the correct treatment. For this purpose, the golden standard is the stereotactic biopsy. Owing to the invasive nature of biopsy, MRI imaging techniques have been being important. Since a high percentage of non-enhanced tumors have been malignant, conventional MRI imaging based on post-contrast T1 images cannot be a good

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criterion for tumor grading [1].

Advance MRI techniques like Dynamic Susceptibility Contrast (DSC) perfusion provide supplementary information regarding grading of glioma tumors [2,3]. This technique is based on signal drop during bolus passage of Contrast Agent (CA) through capillary bed [4]. Cerebral Blood Volume (CBV) is the most widely used parameter, which is obtained from DSC.

Many studies have used CBV for gliomas grading and there has been in good agreement between CBV and tumor grade [5-8]. Almost all of these studies have emphasized the importance of leakage correction due to the underestimation/overestimation of CBV caused by T1/T2\* leakage effect in enhanced cases of tumors, especially high grade ones [9].

The effect of leakage-correction in higher grades is particular importance due to higher permeability in these types of tumors [6]. The leakage of CA has two effects on the concentration-time curve (CTC) and eventually the CBV. These effects include T1 and T2\* leading to the negative and positive tail of the CTC, respectively.

The conventional method for CBV estimation is the integration over the whole CTC [10]. Thus, when the conventional method of CBV was used, the effect of T1 underestimates the CBV and the effect of T2\* would overestimate it [11,12]. The T1 leakage effect can be reduced by contrast agent injection as a pre-bolus prior to perfusion imaging, but the effect of T2\* remains due to the accumulation of contrast media in the extravascular space and can lead to a higher estimate of CBV [13]. The previous study suggested that gamma fitting can be used to eliminate T2\*-base leakage effect from the tail of CTC [14]. The conventional method of measuring CBV (Integration over the whole curve of CTC-hereafter will be called method 1) and the GVF fitting (herein called method 2).

The aim of this study is to investigate these two methods of CBV estimation in two groups

of gliomas with the same grade and different appearance on post contrast T1 images (Enhanced vs. Non-enhanced ones).

## Material and Methods

### Participants

In this retrospective study, eight glioma patients with histopathologically confirmed grade III, were selected out of 37 subjects with a brain tumor and retrospectively studied. The difference in signal between T1 images before and after contrast agent injection was considered as the criterion to categorize patients into two groups. Accordingly, four patients showed enhancement in post-contrast T1 images and categorized as group1 and the rest of them who did not have any enhancement classified into group2.

### Imaging protocols

All images were acquired on a 3 Tesla clinical MRI scanner (Discovery MR750, GE Healthcare). GE-DSC examination was performed with 60 repetitions and TE for GE: 25 ms, TR: 1500 ms, FOV: 240 mm, matrix size: 128\*128, slice thickness: 5 mm. Structural images include 3D T1-weighted dataset with TR: 8.4 ms, TE: 3.2 ms, FA: 12°, TI: 450 ms, FOV: 256 mm, slice thickness: 1 mm.

In addition, FLAIR images were obtained with the following parameters: TR: 7000 ms, TE: 140 ms, FA: 160°, TI: 2200 ms, FOV: 220 mm, matrix size: 320\*224, and slice thickness: 5 mm.

### Administration of Contrast Agent

Due to high molarity and decent concentration after intravenous injection, new generation of CA (Gadobutrol; Gadovist®; Bayer Schering Pharma AG, Berlin, Germany) was used [15]. CA was administered automatically with a 5  $\text{ml}/\text{sec}$  rate followed by a 20 ml saline

flush in the same rate using an MR-compatible injector (Ulrich medical, tennessee™).

**Data analysis**

Data Preprocessing and analysis were performed using FSL software (University of Oxford) and MatLab (The Math Works, Inc., Natick, MA). Correction of GE images motion was made with respect to their first time point using MCFLIRT FSL tool. Skull stripping was implemented using BET FSL tool and brain-extracted images were used for further analyses.

$\Delta R2^*$  maps were calculated based on the motion-corrected time series of GE images using the following equation:

$$\Delta R2^*_{(t)} = \frac{\bar{\Delta R2^*}_{(t)}}{TE} = \frac{-1}{TE} \ln \frac{S(t)}{S(0)} \tag{1}$$

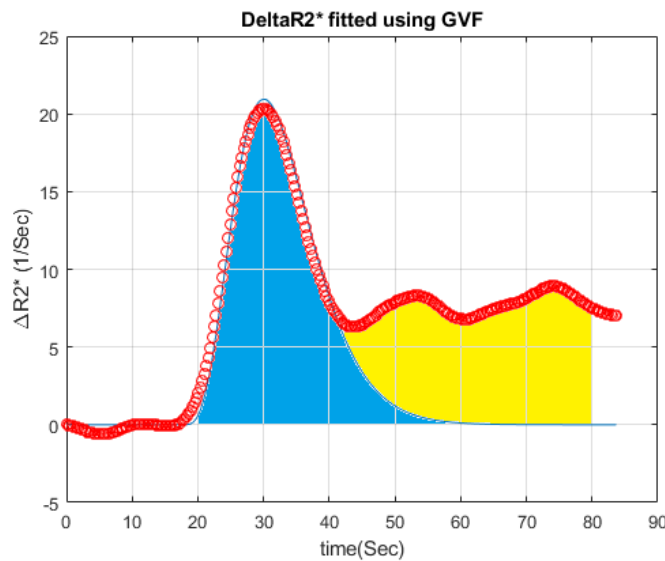
Where TE is the echo time, S(0) is the base-

line (pre-bolus) signal, and S(t) is the recorded signal at the time.

Baseline signal was determined as the mean of signals from the 5<sup>th</sup> to the 15<sup>th</sup> dynamic volumes. First, four time points were discarded due to the unsaturated signal.

Gamma variate function (GVF) fitted to CTC to eliminate T2\* leakage effect from the tissue CTC (Figure 1). CBV was calculated as a fraction of GVF integral into the integral of the Arterial Input Function (AIF), and normalized to the average normal contra-lateral WM (equation 2). AIFs were selected manually in the M3 segment at the top of the ventricle.

$$CBV = k \int C(t)dt / \int C(a)dt \tag{2}$$



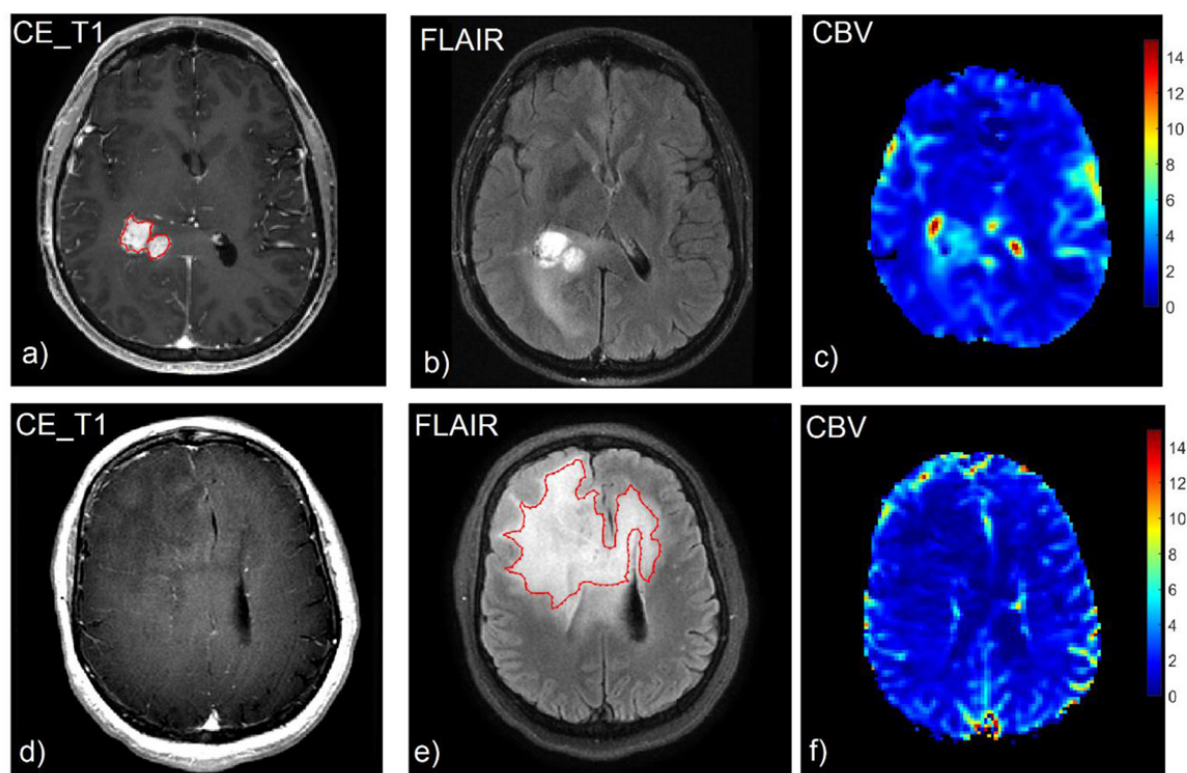
**Figure 1:** Blue and yellow areas show T2\* leakage corrected CTC and T2\* leakage contamination effect, respectively.

Where C (t) is tissue CTC, C (a) is AIF and k is the proportionality constant accounting for brain tissue density and hematocrit difference between the selected artery and microvasculatures, which was considered 0.733.

**Regions of interest selection**

The Flair and post contrast T1 images were

co-registered to the baseline perfusion images using Flirt tool and used for tumor ROI delineation. For each patient, the tumor masks were drawn manually based on contrast enhanced rim in post-injection T1-weighted images and in the area of high signal intensity on FLAIR images in the cases of non-enhancing tumors (Figure 2).



**Figure 2:** The upper row is related to images of a patient with anaplastic astrocytoma grade III WHO and the lower row is related to images of a patient with anaplastic oligoastrocytomas grade III WHO. a), b), c), d), e) and f) are related to Contrast enhanced T1 weighted, Fat saturated fluid attenuation inversion recovery and relative Cerebral blood volume in each row.

## Results

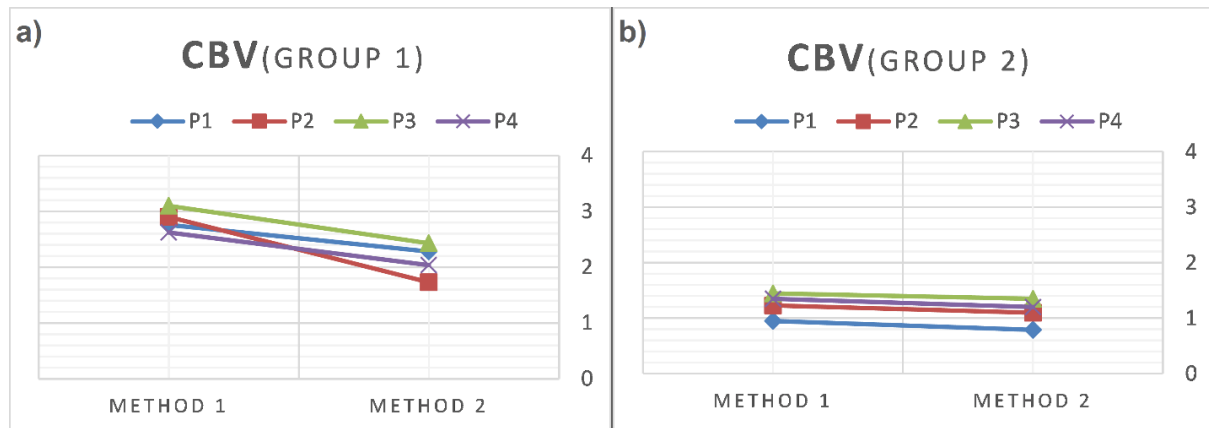
Our results are shown in Table 1. The mean ages of first-group and second-group of patients were 40 years (range from 31 to 51 years) and 45 years (range from 37 to 53 years), respectively. Representative images from two patients within group 1 and 2 are shown in Figure 2.

All anaplastic gliomas had high rCBV ratios compared with those of normal contralateral white matter ( $rCBV > 1.0$ ) (Figure 3). The observed mean rCBV in the tumor ROI in group 1 was 2.85 and 2.12 for method 1 and 2, respectively. Mean rCBV in the tumor ROI for group 2 was 1.24 and 1.11 with method 1 and 2, respectively.

**Table 1:** Patient’s characteristics and corresponding rCBV results obtained using method 1 and 2. Data presented as mean  $\pm$ SD.

Patient/ age/ sex	Group	Pathologic diagnosis	rCBV	
			Method 1	Method 2
1/36/F	1	AA	2.76 $\pm$ 0.91	2.28 $\pm$ 0.79
2/42/M	1	AOA	2.9 $\pm$ 1.02	1.73 $\pm$ 0.8
3/51/M	1	AA	3.1 $\pm$ 0.49	2.43 $\pm$ 0.35
4/31/M	1	AA	2.62 $\pm$ 0.96	2.04 $\pm$ 0.93
5/46/F	2	AO	0.95 $\pm$ 0.49	0.79 $\pm$ 0.35
6/53/M	2	AOA	1.23 $\pm$ 0.53	1.1 $\pm$ 0.41
7/44/M	2	AO	1.45 $\pm$ 0.38	1.35 $\pm$ 0.3
8/37/F	2	AOA	1.35 $\pm$ 0.31	1.2 $\pm$ 0.27

AA: Anaplastic Astrocytomas, AO: Anaplastic Oligodendrogloma, AOA: Anaplastic Oligo-Astrocytomas



**Figure 3:** Relative CBV values in all cases of group 1 (a) and 2 (b) before and after leakage correction.

## Discussion

In this study, the remaining T2\* effect during bolus passage was ignored and could be considered in future investigations.

This results confirm that the T2\* leakage effect leads to overestimation of rCBV (Figure 3). This overestimation depends on the amount of the area, which has been in CTC tail (yellow in Figure 2) used in CBV estimation.

Moreover, no T1 leakage effect was observed in each subject of group 1 due to the administration of the complete dose (0.1 mmol/kg) of CA as a pre-bolus. On the other hand, Hu et al. showed that the dose of 0.1 mmol/kg of CA as a pre-bolus combined with the correction of T2\* effect could increase the differentiation between tumors and radiotherapy necrosis in patients with glioma [16].

It could be noted that this amount of contrast injection may not be enough to significantly reduce the T1 leakage effect when examining high-permeability tumors such as GBM or using a field strength lower than 3 Tesla.

Our results for non-enhanced gliomas are in good agreement with the study of Morita et al. [5] and Sahin et al. [17] who have investigated the grading of non-enhanced gliomas

(Table 2).

Maia et al. [18] reported relatively a high values for rCBV of non-enhanced gliomas with grade III; in addition, it may be due to the use of SE-DSC for CBV estimation, which has the sensitivity to microvascular vessels size [18]. Whereas study of Donahue et al. [19] indicated that spin-echo Perfusion Weighted Imaging (PWI) is less accurate in predicting glioma grade than gradient echo PWI.

Moreover, Fan et al. [20] reported higher values for rCBV of non-enhanced gliomas with grade III that may originate from the method of tumor delineation. They used maximum regions of perfusion for measuring rCBV of the tumor, but we used ROI-base delineation for this purpose (using co-registered T1 and Flair images).

Our results for enhanced cases of gliomas with grade III were in line with the previous studies of Falk et al. [21] and Boxerman et al. [6], who have evaluated the grading of enhanced gliomas using PWI. However Falk et al. used Boxerman's proposed method for leakage correction; they did not observe any significant difference between grade II and III gliomas unlike Boxerman et al.

The number of subjects was one of the limi-

**Table 2:** Patient demographics and corresponding imaging findings reported in different studies.

Study	Contrast enhancement	Number of patient with grade III gliomas	rCBV grade III	Correlation of rCBV with pathological grade
Maia et.al 2005	None	7	3.2	Yes
Morita et.al 2010	None	11	1.74	Yes
Sahin et.al 2013	None	6	1.39	No
Fan et.al 2006	None	8	3.27	Yes
Boxerman et.al 2006	Yes	9	2.8	Yes
Falk et.al 2014	Yes	7	2.42	No

tations on this study due to the rarity of the non-enhanced gliomas with grade III. Besides, there may be a sampling error because the grading of all patients in this study was done using biopsy.

## Conclusion

In conclusion, this pilot study demonstrated that with combined use of pre-bolus and accounting for T2\* effect, CBV could be considered as a criterion for the categorization of glioma tumors.

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## Conflict of Interest

None

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