

A COMPARISON OF WHITE MATTER NORMALIZATION APPROACHES FOR PERFUSION AND DIFFUSION MRI IN BRAIN TUMOURS

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Abstract

Background: There is currently no generally accepted method for normalising the appearance of normal-appearing white matter in brain tumours that may be used to compute normalised relative cerebral blood volume and apparent diffusion coefficient. This reader study investigated the differences in nrCBV and nADC by utilising a variety of NAWM normalisation approaches. **Materials and Methods:** The study included 25 patients with newly diagnosed gliomas. A single plane in the centrum semiovale (CSOp), three spheres in the centrum semiovale (CSOs), a single plane in the slice of the tumour centre (TUMp), and four spheres in the slice of the tumour centre were all created by two readers for each patient. One month later, readers repeated NAWM segmentations. Time to segment NAWM and differences in nrCBV and nADC of the FLAIR hyperintense tumour inter-/intra-reader variability were evaluated. The diagnostic effectiveness of each approach for predicting IDH-status was assessed as a validation step. **Result:** Between the four normalising techniques, both readers achieved significantly different nrCBV and NAWM segmentation times. In the same NAWM region, nrCBV and nADC were significantly different between CSO and TUM approaches but not between planar and spherical methods. In general, spherical methods were faster than planar methods, while CSO approaches were faster than TUM methods. The IDH-status prediction performance was consistent across all normalisation methods, and inter-reader reproducibility and intra-reader repeatability were both excellent. **Conclusion:** The particular NAWM region that was chosen has a significant bearing on the nrCBV and nADC values. When compared to TUM methods, CSO methods, particularly CSOs, may be preferred due to the reduction in the amount of time required, similar reader variability, and similar diagnostic performance.

INTRODUCTION

In both research and clinical settings, the relative cerebral blood volume (rCBV) values of brain tumours obtained from dynamic susceptibility contrast (DSC) perfusion MRI are routinely normalised (nrCBV) in order to reduce the amount of variability that can occur between different MR protocols, scanners, and timepoints within the same patient. However, despite the fact that the nrCBV values are influenced by the normalising approach that is selected itself, there is still no normalisation method that has achieved unanimity.^[1-3] Common normalisation methods involve positioning a reference region of interest (ROI) on the contralateral normal-appearing white matter (NAWM). However, numerous other regions, including the white matter directly opposite to the tumour, the posterior limb of the internal capsule, the temporal lobe, and the

centrum semiovale, have also been reported.^[4] Additionally, there are variations in the placement of a single ROI or multiple ROIs anteriorly to posteriorly. Automated normalising approaches have also been published. Some examples of these methods include Gaussian-normalized nrCBV and "standardised" nrCBV utilising training-set data. However, these methods require specialised software, which limits their practical feasibility.^[5] Additionally, there has been an increase in interest in standardising the apparent diffusion coefficient (ADC) values of brain tumours obtained using diffusion MRI. It is interesting to note that the ADC values of the contralateral NAWM have also been shown to be significantly different across lobes in glioma patients.^[6] Despite this, numerous NAWM normalisation methods for normalised ADC have been reported. These methods include ROIs directly opposite to the tumour, the posterior limb of the

internal capsule, and the centrum semiovale.^[7] However, to the best of our knowledge, there is no study that contrasts the different methods of nADC normalisation in glioma patients. This reader study aimed to evaluate single-planar and multiple-spherical ROI NAWM normalisation methods for measuring nrCBV and nADC in the centrum semiovale and slice of the tumour centre respectively.^[8,9] These normalisation methods were validated by assessing their diagnostic performance when discriminating between IDH-wild-type gliomas and IDHmutant 1p/19q-intact gliomas. This was done because previous literature extensively showed the predictive value of ADC and nrCBV for this molecular profiling. In addition to assessing the impact of normalisation methods on nrCBV and nADC values and reader variability, these normalisation methods were evaluated for their ability to distinguish between I We hypothesised that the normalisation method would have a significant impact on the values of nrCBV and nADC, and that the centrum semiovale ROI method and the multiple-spherical ROI method would provide a significant benefit in significantly less time compared to the tumour slice ROI method and the single-planar ROI method, respectively.^[10,12]

MATERIALS AND METHODS

The Health Insurance Portability and Accountability Act was followed carefully during the course of this research project. The scans of the patients were performed between the months of August 2020 and August 2022. IDH-mutant 1p/19q co-deleted tumours were not included in the study because previous research has shown that the usefulness of ADC and rCBV to detect this type of tumour is limited due to the intermediate characteristics that they share with IDH-wild type gliomas and IDH-

mutant 1p/19q intact gliomas. This is because the IDH-mutational status assessment was not the primary focus of the study but rather performed as a benchmark for the validation of the IDH mutation was evaluated using immunohistochemistry, genomic sequencing analysis, and/or polymerase chain reaction. The status of 1p/19q codeletion was determined utilising fluorescence in situ hybridization.

Statistical analysis

MATLAB and GraphPad Prism were used as the primary tools for carrying out all of the computations and analysis. The D'Agostino and Pearson test was carried out in order to determine whether or not the data followed a normal distribution and to determine whether or not appropriate parametric or nonparametric statistical methods should be applied. The repeated-measures ANOVA test and the Friedman test with post hoc Dunn's multiple comparisons tests were performed for normally distributed data and non-normally distributed data, respectively, to assess intra-reader differences in nrCBV, nADC, and the time it took to create NAWM ROIs based on the normalisation method. This was done in order to evaluate differences in nrCBV, nADC, and the amount of time it took to create NAWM ROIs. The intraclass correlation coefficient (ICC) model was utilised in order to evaluate the inter-reader reproducibility of nrCBV and nADC from each normalisation method during each trial. Additionally, the ICC model was utilised in order to evaluate the intra-reader repeatability of nrCBV and nADC of each normalisation method between trials.

RESULTS

The clinical data of the selected patients are shown in [Table 1], along with the data related to those clinical data.

Table 1: Clinical Data of the selected patients

Sr. No.	Characteristic	Patients (n = 25)
1.	Average age (years) ± SD	45 ± 12
2.	Sex (male/female)	15/11
3.	Tumor location	
4.	Hemisphere (left/right)	16/19
5.	Frontal lobe	8
6.	Frontotemporal lobes	3
7.	Temporal lobe	10
8.	Temporoparietal lobes	3
9.	Parietal lobe	6
10.	Parieto-occipital lobes	2
11.	Occipital lobe	1
12.	Thalamus	2
13.	Tumor grade (2/3/4)	8/12/11

Image Acquisition and Processing

On either a 1.5T or a 3T MRI scanner, anatomical, diffusion, and DSC perfusion MRI images were produced. In accordance with the internationally accepted brain tumour imaging methodology, anatomical magnetic resonance imaging (MRI) and diffusion-weighted imaging (DWI) were obtained

(BTIP). ADC maps were computed using either diffusion tensor imaging (DTI) or diffusion spectroscopy imaging (DWI) data with b-values ranging from 0 to 1000 s/mm². Images were obtained using single-echo and multi-echo imaging procedures in order to perform DSC perfusion MRI. These imaging techniques have been detailed in

earlier research. The motion in the DSC data was first corrected with FSL, and then the rCBV maps were calculated using a method that accounts for bidirectional contrast agent leakage. All of the parameter maps were registered to the post-contrast T1-weighted images with the assistance of the FSL programme, which utilised a stiff transformation with six degrees of freedom and a mutual information cost function.

A radiology resident with ten years of expertise in neuroimaging analysis and a board-certified radiologist were the two readers for this study. The board-certified radiologist has ten years of experience in neuroimaging analysis. Both readers were blinded to patient information, and each reader segmented four contralateral NAWM ROIs using ITK-SNAP software. These ROIs avoided the cortex, large vessels, and ventricles and were given the following names and instructions: a planar ROI of 400–450 mm² drawn on a single slice in the contralateral centrum semiovale approximately 3 mm superior to the lateral ventricles similar to Conte et al.; CSOs: three intra-slice.

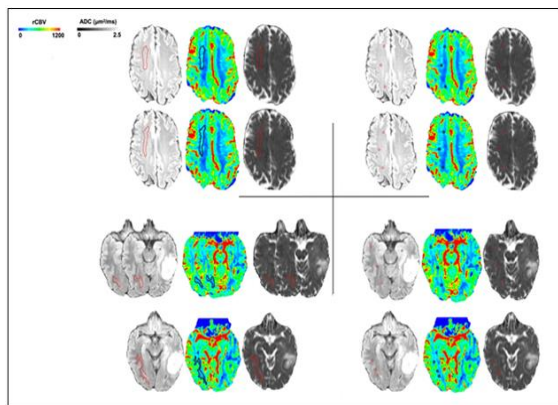


Figure 1: NAWM segmentations using the planar approach in the centrum semiovale (CSOp), the spherical method in the centrum semiovale (CSOs), and the planar approach in the slice contralateral to the tumour centre.

In the additional information, we give a comprehensive summary of the study's findings, which includes figures for the outcomes of trial 2. Normality tests revealed that the data for nADC were distributed in a normal fashion, whereas the data for nrCBV and the amount of time it took to create NAWM ROIs were found to be non-normally distributed; consequently, appropriate parametric and nonparametric statistical methods were selected for each metric. Each reader produced overall nrCBV values that were significantly different between the four different normalisation procedures for each individual trial. The CSO and TUM normalisation procedures produced significantly different results in post-hoc comparisons of nrCBV and nADC. These differences were significant. For instance, when comparing the CSO technique with the TUM approach in trial 1, the median difference in nrCBV

and the mean difference in nADC ranged in size between 0.10 and 0.27 and between 0.07 and 0.09, respectively. This was the case when comparing the two methods. Within the same normalising zone, however, there were no discernible variations in nrCBV or nADC between the planar and spherical techniques. The median difference in nrCBV and the mean difference in nADC in trial 1 were considerably reduced to magnitudes ranging between 0.02 and 0.05 and 0.002 and 0.001, respectively, for these comparisons. According to Koo et al., ICC studies showed that each normalisation approach had outstanding repeatability both between readers and among readers when they repeated NAWM segmentations after one month. This was the case when the segmentations were performed again. In the process of validating the IDH-mutation status prediction, ROC curve analyses showed that the nrCBV and nADC values produced comparable area under the curve values independent of the normalisation approach. This was discovered during the validation step. There were notable disparities in the amounts of time required to generate each ROI. In general, CSO methods were faster than TUM methods, notably for the planar method, and the spherical method was quicker than the planar approach, particularly for the TUM region. In addition, the CSO methods produced more accurate results.

DISCUSSION

The key finding of the current research was that the values of nrCBV and nADC varied significantly depending on the NAWM region, but they did not vary much depending on whether the approaches were planar or spherical within the same NAWM region.^[12,13] As a consequence of this, the current findings provide support for the contention that it is essential to maintain consistency in the approaches of normalisation that are based on ROI for both nrCBV and nADC. This study contributes to the existing body of research by demonstrating that the nrCBV can be significantly altered depending on the NAWM normalisation method used. In addition, to the best of our knowledge, this study is the first to demonstrate differences in nADC in glioma patients based on the NAWM normalisation method. These findings are consistent with earlier findings that ADC can be significantly altered depending on the contralateral NAWM region in glioma patients. It is essential for research studies to describe the anatomical location and size of the NAWM ROI for rCBV and ADC normalisation, as was done in some studies. This will help increase reproducibility and provide a better guide for threshold-based interpretations of nrCBV and nADC across institutions.^[14] In addition, this will improve the quality of interpretations of nrCBV and nADC. For instance, the excellent interreader reproducibility for nADC that was observed in the current study is consistent with the high ICC values

for nADC that were measured by two readers in a study by Thust et al. The authors of that study explicitly stated that each rater segmented NAWM ROIs in the CSO with similar volume to the tumour. The results of the present study are in line with those findings. Furthermore, providing additional detail on the selection of a specific slice of the target NAWM region (e.g., CSO 3 mm above the lateral ventricles in the present study) may reduce variability and subjectivity in the normalisation process.^[15] This was done by Smits et al. and Cho et al. for nrCBV and Hagiwara et al. for nADC. In the current study, all four normalisation methods had comparable intra-reader repeatability and inter-reader reproducibility as well as IDH-mutation status predictive performance. On the other hand, there were significant time savings when performing the CSO methods in comparison to the TUM methods. In cases where the tumour was located in regions with minimal contralateral white matter, such as near subcortical structures or in the temporal lobes,^[16,17] it was particularly difficult to delineate a NAWM ROI that avoids grey matter, normal vessels, and ventricles. This is one likely explanation for the increased time it took to create NAWM ROIs in TUM regions. In addition, if there was bilateral tumour infiltration, finding a NAWM ROI in the tumour slice of those regions would be an even greater challenge. As a consequence of this, the current findings may lend credence to the utilisation of the centrum semiovale as a target NAWM region rather than the white matter directly opposite the tumour.^[18,19] This is due to the fact that the centrum semiovale is reliably identifiable to neuroradiologists and members of research labs alike, as was also similarly stated by Thust et al. Noteworthy is the fact that the most recent guidelines for nrCBV, which were issued by QIBA's Stage 2 Consensus Profile, propose a > 2 x 2 cm TUMp NAWM ROI. The current results of a similar 400–450 mm² TUMp ROI—which the study authors proposed given the difficulty of creating a 2 cm ROI in certain tumour regions described above—suggest that although tumor-slice ROIs provide similar diagnostic performance, intra-reader repeatability, and inter-reader reproducibility compared to CSO ROIs, CSO NAWM methods may be better options in terms of time efficiency and ease. This is because tumor-slice ROIs are difficult to create in certain tumour.^[19,20]

In addition, both readers experienced a significant decrease in the amount of time required to create TUMs ROIs in comparison to the time required to create TUMp ROIs, and one reader experienced a significant decrease in the amount of time required to create CSOs ROIs in comparison to the time required to create CSOp ROIs. The simplicity of use may possibly be another factor that contributes to the shorter amount of time required by the spherical procedures as compared to the planar approaches.^[20,21] A significant benefit of the separable, spherical method is that, in comparison to

the continuous, planar method, it may be simpler to avoid grey matter, vessels, and ventricles when using the separable, spherical method. This is particularly useful in research settings where members of the lab who are not radiologists may be involved. In addition, if the tumour is bilateral, it is possible that spherical procedures, as opposed to planar methods, will make it simpler to avoid the lesion.^[21] The CSOp approach may be favoured in clinical contexts for reviewing quantitative maps generated from the scanner or from clinical software products since it does not need the creation of 3D ROIs, which may not be possible in clinical software. To make the method applicable in clinical settings, Smits et al. suggested that rather than using 3D CSOs, the researchers may instead place 2D circular ROIs within the CSO. This would be an alternative to the strategy used in the current study. In the previous study, the researchers placed their 2D planar ROIs on the original rCBV maps with a large slice thickness of 5 mm. In the current study, however, all ROIs were placed on rCBV and ADC maps registered to the post-contrast T1-weighted image with a slice thickness of 1 mm. This is one of the most significant differences between the two studies.^[22] In subsequent research, it may be desirable to study variations in nrCBV and nADC normalization-based 2D and 3D ROIs, as well as to take slice thickness into mind.^[23,24]

It is also essential to keep in mind that the application of nADC is still the subject of debate. Since the absolute values of the ADC are measured in units, it is possible that normalisation is not warranted. In addition, there have been conflicting findings on the possible benefits of nADC in comparison to ADC in the treatment of glioma patients. In spite of this, the ADC values of NAWM and CSF fluid have been observed to vary across patients in a multicenter trial. This finding may promote the increased application of nADC in the future. As a consequence of this, the characterization of various NAWM approaches for nADC that was conducted in the current work is still valuable despite the fact that more research into the potential clinical utility of nADC is still being conducted.

CONCLUSION

It is possible for there to be significant differences in the values of nrCBV and nADC depending on the NAWM region that is chosen. Normalization of CSOs might be helpful in research settings, while normalisation of CSOp might be helpful in therapeutic contexts. Studies that involve normalised MRI metrics and are based on ROI methods should clearly state the anatomical region, size, and approximate slice location of the normalisation ROI. This will improve the reproducibility of the findings as well as the interpretation of the data by institutions that are not involved in the study.

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