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Comparison of Perfusion- and Diffusion-weighted Imaging Parameters in Brain Tumor Studies Processed Using Different Software Platforms

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Abstract

Rationale and Objectives—To compare quantitative imaging parameter measures from diffusion- and perfusion-weighted imaging magnetic resonance imaging (MRI) sequences in subjects with brain tumors that have been processed with different software platforms.

Materials and Methods—Scans from 20 subjects with primary brain tumors were selected from the Comprehensive Neuro-oncology Data Repository at Washington University School of Medicine (WUSM) and the Swedish Neuroscience Institute. MR images were coregistered, and each subject's data set was processed by three software packages: 1) vendor-specific scanner software, 2) research software developed at WUSM, and 3) a commercially available, Food and Drug Administration–approved, processing platform (Nordic Ice). Regions of interest (ROIs) were chosen within the brain tumor and normal nontumor tissue. The results obtained using these methods were compared.

Results—For diffusion parameters, including mean diffusivity and fractional anisotropy, concordance was high when comparing different processing methods. For perfusion-imaging parameters, a significant variance in cerebral blood volume, cerebral blood flow, and mean transit time (MTT) values was seen when comparing the same raw data processed using different software platforms. Correlation was better with larger ROIs (radii ≥ 5 mm). Greatest variance was observed in MTT.

Conclusions—Diffusion parameter values were consistent across different software processing platforms. Perfusion parameter values were more variable and were influenced by the software used. Variation in the MTT was especially large suggesting that MTT estimation may be unreliable in tumor tissues using current MRI perfusion methods.

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SUPPLEMENTARY DATA

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Keywords

Tumor imaging; cerebral perfusion; cerebral diffusion; MRI

Diffusion tensor imaging (DTI) measures the microscopic diffusion properties of water and is often altered in pathologic conditions. Mean diffusivity (MD) represents the average mobility of free water molecules within tissue. Fractional anisotropy (FA) measures the asymmetry of water diffusion due to the microstructure of the underlying tissue and is a predictor of the architecture and integrity of the brain white matter (WM) (1). MD has been shown to be decreased in dense cellular tumors such as primitive neuroectodermal tumors and lymphomas (2,3).

Dynamic susceptibility contrast (DSC) magnetic resonance imaging (MRI) is an imaging method that measures the passage of a bolus of contrast through the brain tissue and estimates cerebral perfusion parameters, such as cerebral blood volume (CBV), cerebral blood flow (CBF), and mean transit time (MTT).

DSC MRI has been applied to the study of brain tumors. Specifically, CBV has been shown to be helpful in characterization of brain tumors (4–8). In particular, the CBV of glial tumors, typically normalized to contralateral WM, has been established as a predictor of glioma grade (9–11). Many studies have investigated the use of diffusion and perfusion parameters to monitor the response to therapy and differentiate radiation necrosis from tumor recurrence (4,8,12–16). Perfusion imaging appears to have a significant impact on clinical decision making and physicians' confidence in management plans for patients with brain tumor (17). Thus, an incorrect estimation of tumor grade, response, or recurrence resulting from a misestimation of the CBV value could lead to incorrect treatment and patient morbidity.

With increasing use of quantitative and semiquantitative measurements for diagnosis and treatment decisions, it is important for measurements to be accurate and precise across different software platforms. The effect of scanner type and acquisition methods has been discussed with respect to MD in a phantom study (18), and the effect of software platform has been investigated with respect to DSC computed tomography (CT) in stroke (19). With regard to brain tumors, Paulson and Schmainda (20) investigated the effect of acquisition and postprocessing methods on the value of the relative CBV. However, in subjects with brain tumors, the impact of variations in image processing methodology has not been considered in multiple DTI and DSC parameters.

MATERIALS AND METHODS

MRI Acquisition and Preprocessing

Preoperative MRI scans from 20 subjects with malignant primary brain tumors were selected for comparison from the Comprehensive Neuro-oncology Data Repository (CONDR) at Washington University School of Medicine (WUSM) and Swedish Neuroscience Institute (SNI). For each subject, the following structural images were obtained: T₁-weighted (T₁W), fluid attenuation inversion recovery, susceptibility-weighted

imaging, and magnetization prepared rapidly acquired gradient echo. Physiological imaging data included DTI and DSC imaging. The image acquisition was relatively standardized across both institutions, although some differences exist between the two sites. Specifically, diffusion-weighted imaging scans at WUSM were acquired using 12-direction gradient scheme and $b = 1000 \text{ s/mm}^2$, and SNI diffusion sequences were obtained using 25-direction gradient encoding with $b = 1000 \text{ s/mm}^2$. In the DSC sequence, the only difference was the repetition time of 2000 milliseconds at WUSM and of 1500 milliseconds at SNI. Raw data from each individual subject's MRI sequences were coregistered to a target postcontrast T_1W image. Spatial registration was performed using affine registration using WU developed software. Each subjects T_1W image was registered to a T_1W atlas template image, and other T_1W and T_2W sequences were coregistered with the subject's T_1W target image. $T_1W \rightarrow T_1W$ registration used maximization of spatial correlation (21), whereas cross-modality registration (eg, $T_2W \rightarrow T_1W$) used alignment of intensity gradients (22). Perfusion and diffusion parameter maps were transformed to the T_1W target space using a transformation matrix obtained from coregistering respective anatomy sequences.

Diffusion and Perfusion Processing Packages

Following these acquisition and registration steps, each subject's raw diffusion and perfusion data were processed. Multiple parameter maps were created for each subject. The parameter maps included measures of CBV, CBF, MTT, FA, and MD. The processing was performed for each subject using three different software platforms:

1. Anx in-house software developed at WUSM, Saint Louis, MO (based on Lee et al. (23) for perfusion processing and Basser et al. (24) for diffusion processing).
2. An Food and Drug Administration (FDA)-approved commercial stand-alone package NordicNeuroLab (NNL; Bergen, Norway)
3. The FDA-approved Siemens (Erlangen, Germany) Leonardo workstation v. 8 (SL).

In all cases, the perfusion processing was done using a selection for the arterial input function (AIF) and a convolution/deconvolution method. In the case of method 1, the local AIF was computed automatically, and in the case of methods 2 and 3, the AIF was selected by an experienced operator. For subjects whose data were acquired at WUSM, where Siemens MR scanners are used, raw data were processed using all three software platforms. For subjects whose data were acquired at SNI, where GE scanners are used, data were processed and compared using the NNL and WUSM software platforms. All parametric maps were obtained in native space and transformed to the target space using the transform for echo planar imaging scans computed at the registration step.

Region of Interest (ROI) Analysis

ROIs were chosen by a neuroradiology fellow (the same individual chose all of the ROIs) within three types of tissue, using T_1 post-Gd contrast image as a reference. The regions of the first type were selected from abnormal tissue regions (labeled as "tumor") and were drawn within areas of tumor enhancement rim on T_1 post-Gd and in the center of surrounding edema. A half of ROIs labeled as tumor contained a single tissue, and another half had several tissue types mixed (this was validated by comparing respective histograms

from T₁ post-Gd ROIs). The second tissue type was selected in ipsilateral normal tissue regions. The third tissue type was chosen within each patient's contralateral normal WM for normalization of perfusion metrics. The ROI selection was validated by an experienced member of the neuroradiology faculty. CBV, MTT, and CBF maps were converted to dimensionless units by dividing each voxel's value by the average signal of a spherical region within contralateral WM of the same radius as the original region. Of note, we designate these normalized values as “relative”, which is different than the convention used by other authors (20) which refer to relative CBV as a common name for parameters derived from the concentration curve in the given voxel. The same ROIs were used to compare quantitative parameter data from each processing method. Each ROI was spherically shaped with variable radii (2.5, 5.0, 7.0, and 10.0 mm). The results obtained performing analysis using each of the processing methods were compared using linear regression plots and Bland–Altman (BA) plots (25,26). From the linear regression plots, we extracted the slope, intercept, and the linear regression coefficient (Pearson's R²). For two measurements to be considered equal, the null hypothesis is that the slope is equal to 1, the intercept equal to 0, and the regression coefficient must be statistically significant with a $P < .05$. Normalized BA plots were performed to evaluate for spread and systemic bias in the results (26).

The BA plots were constructed as follows: if m_1 represents a measurement using method 1 and m_2 representing the measurement using method 2, the points in the BA plots were plotted as the average of the two methods [$m_{avg} = (m_1 + m_2)/2$] along the horizontal axis (our best estimate of the true value) and the relative difference between the two methods [$r_{diff} = (m_1 - m_2)/m_{avg}$] along the vertical axis. The results were tabulated as the mean of the relative difference between the two methods and the confidence interval (CI) was expressed as mean $\mu \pm 2$ standard deviations σ of the relative differences. The slope of the linear trend line is plotted in the BA plot to identify systemic deviations in the results across the range of values.

Institutional Review Board (IRB) Approval Statement

The anonymized imaging data for this study was obtained from the CONDR, online neuro-oncology research registry (human subject data collection for research purposes within CONDR was approved by the IRB of the institution's Human Research Protection Office on January 29, 2010).

RESULTS

Imaging sessions from 20 different subjects were included in the study, 14 from WUSM and 6 from SNI. All subjects had grade IV or III malignant primary brain tumors, and all imaging sequences considered were obtained before any surgical intervention or adjunctive therapies. Eleven subjects had perfusion data processed using all three software packages. Sixteen subjects had diffusion data processed using all three packages.

A total of 42 ROIs for the tumor set and 20 ROIs for the normal WM set were chosen. Figures 1 and 2 demonstrate calculated parametric maps for a representative patient with a heterogeneously enhancing mass lesion with areas of enhancement and necrosis in the right posterior parietal region. Note that diffusion maps appear to be virtually identical (Fig 1),

whereas perfusion maps demonstrate high variability between the different software packages, especially in the lesion region (Fig 2). For this patient, this variability also appeared in intensity distributions of tumor ROIs (Fig 3) but was milder for contralateral WM ROIs (Fig 4). This tendency for all subjects was confirmed by BA analysis, as detailed in the following.

Tables 1 and 2 summarize the quantitative comparison results across all tumor ROI comparisons and all ROI sizes. A notable trend seen in both the DTI (Table 1) and DSC (Table 2) is that as the ROIs increase in size, the BA CI decrease in size. This is expected because the larger ROIs are expected to give a more robust estimate of the measured parameter value. From the results in the tables, it is clear that the ROIs with radius 2.5 mm give unacceptably large CI, even in the case of the more robust DTI comparisons. For the DTI data (Table 1), the R^2 values are high and improve with the larger ROI size. This is not the case in the DSC data (Table 2) in which the R^2 values are lower and more variable. Figure 5 presents a visual example of the data in Table 1 comparing MD across the three processing methodologies in ROIs with a radius of 5 mm. The BA plots (Figs 5a and c) are centered near the zero mark (the value at which the methods give the exact same answer), and most of the comparison ROIs fall within 10% of the central value. The linear trend line in the BA plots show a mild linear bias between low and high MD values. The linear regression plots (Figs 5b and d) show a robust correlation with high R^2 values. Figure 6 presents similar but less robust results for FA. The CI in the BA plots (Figs 6a and c) is larger, with most points falling within 20% of the central value. The linear regression plots (Figs 6b and d) demonstrate persistence of strong correlations across the three methods.

Figure 7 demonstrates the weaker concordance seen with comparison of the CBV parameter which demonstrates higher CI values compared to the DTI comparisons in Figures 5 and 6. The BA plots (Figs 7a and c) indicate weaker correspondence for low CBV values. Higher CBV values show improved correspondence between the WUSM and SL methods (also manifesting as higher $R^2 = 0.88$ in Fig 7d). Weaker correspondence is noted for high CBV values when comparing the WUSM and NNL methods (see scatter in BA plot, and lower $R^2 = 0.52$ in Fig 7b). The ROI chosen for this comparison remains 5 mm in radius. Relatively similar results were seen for comparisons between methods for the CBF parameter; however, comparisons between the MTT values were poor, with R^2 values near zero in many cases (Table 2).

When the same comparisons were performed for ROIs in ipsilateral nontumor WM from the same subjects, perfusion-weighted imaging parameters fell within smaller confidence intervals compared to all ROIs combined (Table 3). Also, because ipsilateral WM perfusion parameters were normalized by contralateral WM, nonzero means in the “ipsilateral WM” columns 4 and 5 of Table 3 reveal systematic biases between contra- and ipsi-lateral WM perfusion parameters. These biases cannot be attributed to MR inhomogeneity or anatomy difference, because they were not consistent across the three methods, especially for CBV and CBF (Table 3, columns 4 and 5).

DISCUSSION

Increasingly, physiologic imaging sequences are used in clinical imaging studies for a variety of reasons including the evaluation of brain tumors (11), stroke (27,28), and dementia (28). As both qualitative and quantitative analyses of these sequences have become routine, questions arise as to the accuracy and precision of quantitative data acquired using different methodologies.

When considering perfusion-weighted imaging in neurooncology, CBV parameter estimates have been shown to be of use in predicting glioma grade and patients' prognosis (4,6–9,14,29). Perfusion metrics have been shown to reliably estimate tumor grade and correlate with overall survival in patients with glial tumors (11,14). CBV has also been used to differentiate between recurrent neoplasm and radiation necrosis (30). Some authors have argued that perfusion imaging can provide a diagnostic alternative to the histopathologic examination (11). For these reasons, CBV and other perfusion-weighted imaging parameters have been suggested as a potentially useful marker for consideration in future prospective clinical neuro-oncology trials (14).

DTI parameters can serve as surrogate markers for tumor cellularity (11,27). MD has been shown to be inversely proportional to cellular density, presumably because of the resultant limitation in water movement from cellular membranes (31,32). Increases in water diffusion after treatment of tumors have been shown to correlate with a positive response to therapy (6). Some studies propose a role for diffusion metrics in differentiating radiation effects from tumor recurrence or progression by assessment of MD and FA of enhancing regions in the follow-up of treated high-grade gliomas (16,33,34).

Because many of these imaging parameter measures are used as surrogate markers for clinical outcomes in neurooncology, it is critical to understand the details of the image acquisition as well as the image processing and their impact on the values of these parameter estimates. Typically, in the present literature, details of the image acquisition are provided; however, the details of the image processing and data analysis, particularly the software packages used to process imaging data, are rarely discussed in detail. Specifics of analysis methodology, such as placement of the ROIs within heterogeneous tissue regions, variation of ROI size, and how these factors impact the reproducibility of these quantitative imaging measures are usually not investigated or mentioned. Based on our results from this study, we recommend attention to these details in future studies and publications.

The impact of software platform choice on variations in quantitative parameter measures is particularly relevant in the clinical setting, where patients with brain tumors undergo serial imaging studies, often on different scanners and occasionally at different institutions. These patients' studies are compared over time to make determinations about tumor growth, progression, or response to therapy. As quantitative physiologic imaging parameters are increasingly used as surrogate markers for these clinical outcomes, variations in quantitative measures related to the methodology of data collection or processing, and in this specific study, differing software platforms, could impact clinical decision making if these methodology differences are not established and not well understood.

The impact of variability in processing methods on quantitative image parameter estimates has been considered in nontumor diseases, especially cerebrovascular diseases (35–37). As an example, CT perfusion-imaging maps were significantly different when the parameter outputs from different commercial software platforms were compared, even when using identical source data in patients with acute stroke (19). Paulson et al. (20) have looked at variations in DSC image processing methodology in subjects with brain tumors; however, their analysis was limited to parameters derived directly from voxelwise concentration curve, without performing a deconvolution. This study, on the other hand, evaluated commercially available software packages that use perfusion signal deconvolution and are more commonly used in general clinical practice.

In this study, we compare the contribution of different software processing methods to variability for two specific physiologic imaging sequences, DSC and DTI. Our results are consistent with these previous studies and confirm the variability seen in perfusion measurements when using different software platforms. These results can be mitigated somewhat by selecting larger ROIs; however with larger ROIs, there is a risk of inaccurate results because of volume averaging effects, particularly in relatively heterogeneous tissue types such as primary brain tumors, similar to the heterogeneity noted in our ROI selection. When considering quantitative perfusion parameter measures for a patient with a brain tumor, it is important to consider the processing method used, and ideally, all data should be processed using the same method for the purposes of removing methodological variance.

Our results for processing of DTI parameters show much more consistency across software platforms and suggest that DTI data can be compared across platforms, although this may not be true when doing research studies that require a higher level of reproducibility (38). In addition, when comparing imaging processing methods in nonpathologic tissue types, less variability was seen for both diffusion-weighted and perfusion-weighted imaging processing methods, again suggesting that although these methodologic variables should be considered in all imaging situations, they should be most seriously considered when brain tissue's structural characteristics may not fit the imaging models' assumptions (particularly when blood vessels and cellular densities are a factor as they are for physiological methods such as diffusion- and perfusion-weighted imaging).

The mathematical methods that underlie the methods used for software processing may also help to explain the variability seen in these studies. For DTI maps, all three software packages considered in this study compute FA and MD based on a logarithmic linear computation of the standard diffusion tensor model (39). Perfusion processing in NNL and Leonardo is based on (5) using a manual AIF selection; the WUSM software implements a modification of this method with an automatic local AIF calculation (23).

It is clear that variations in image processing methods can impact quantitative measures of imaging parameters in neuro-oncology studies, particularly when considering perfusion-weighted imaging parameters. To avoid the confounding effects of such variability, in clinical practice and in clinical research studies, consistency in imaging processing methods ought to be a significant goal, and this potential variable should be taken into account when considering quantitative physiologic imaging data obtained from patients with brain tumors.

CONCLUSIONS

In this work, we investigated the concordance between cerebral perfusion and diffusion MRI measures computed by three different software packages in patients with cerebral tumor. Derived perfusion measures showed significant variation, whereas diffusion parameters were similar among the three packages. It is therefore important to use a single perfusion analysis package for evaluation of brain tumors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Svolos P, Tsolaki E, Kapsalaki E, et al. Investigating brain tumor differentiation with diffusion and perfusion metrics at 3T MRI using pattern recognition techniques. *Magn Reson Imaging*. 2013; 31(9):1567–1577. Available at: <http://www.sciencedirect.com/science/article/pii/S0730725X13002270>. [PubMed: 23906533]
2. Erdem E, Zimmerman RA, Haselgrove JC, et al. Diffusion-weighted imaging and fluid attenuated inversion recovery imaging in the evaluation of primitive neuroectodermal tumors. *Neuroradiology*. 2001; 43(11):927–933. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11760795>. [PubMed: 11760795]
3. Guo AC, Cummings TJ, Dash RC, et al. Lymphomas and high-grade astrocytomas: comparison of water diffusibility and histologic characteristics. *Radiology*. 2002; 224(1):177–183. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12091680>. [PubMed: 12091680]
4. Law M. Advanced imaging techniques in brain tumors. *Cancer Imaging*. 2009; 9 Spec No:S4–S9. Available at: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2797460&tool=pmcentrez&rendertype=abstract>.
5. Ostergaard L, Sorensen AG, Kwong KK, et al. High resolution measurement of cerebral blood flow using intravascular tracer bolus passages. Part II: Experimental comparison and preliminary results. *Magn Reson Med*. 1996; 36(5):726–736. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8916023>. [PubMed: 8916023]
6. Provenzale JM, Mukundan S, Barboriak DP. Diffusion-weighted and perfusion MR imaging for brain tumor characterization and assessment of treatment response. *Radiology*. 2006; 239(3):632–649. Available at: <http://radiology.rsna.org/content/239/3/632>. [PubMed: 16714455]
7. Rollin N, Guyotat J, Streichenberger N, et al. Clinical relevance of diffusion and perfusion magnetic resonance imaging in assessing intra-axial brain tumors. *Neuroradiology*. 2006; 48(3):150–159. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16470375>. [PubMed: 16470375]
8. Tout DA, Rogers A, Van Aswegen A, et al. Left ventricular function parameters obtained from gated myocardial perfusion SPECT imaging: a comparison of two data processing systems. *Nucl Med Commun*. 2005; 26(2):103–107. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15657501>. [PubMed: 15657501]
9. Thomsen H, Steffensen E, Larsson E-M. Perfusion MRI (Dynamic susceptibility contrast imaging) with different measurement approaches for the evaluation of blood flow and blood volume in human gliomas. *Acta Radiol*. 2012; 53(1):95–101. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22114021>. [PubMed: 22114021]
10. Law M, Yang S, Wang H, Babb JS, Johnson G, Cha S, et al. Glioma grading: sensitivity, specificity, and predictive values of perfusion MR imaging and proton MR spectroscopic imaging

compared with conventional MR imaging. *AJNR Am J Neuroradiol.* 24(10):1989–1998. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/14625221>. [PubMed: 14625221]

11. Law M, Young RJ, Babb JS, et al. Gliomas: predicting time to progression or survival with cerebral blood volume measurements at dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging. *Radiology.* 2008; 247(2):490–498. Available at: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3774106&tool=pmcentrez&rendertype=abstract>. [PubMed: 18349315]
12. Fink JR, Carr RB, Matsusue E, et al. Comparison of 3 Tesla proton MR spectroscopy, MR perfusion and MR diffusion for distinguishing glioma recurrence from posttreatment effects. *J Magn Reson Imaging.* 2012; 35(1):56–63. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22002882>. [PubMed: 22002882]
13. Goh V, Halligan S, Bartram CI. Quantitative tumor perfusion assessment with multidetector CT: are measurements from two commercial software packages interchangeable? *Radiology.* 2007; 242(3):777–782. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17325066>. [PubMed: 17325066]
14. Hu LS, Eschbacher JM, Heiserman JE, et al. Reevaluating the imaging definition of tumor progression: perfusion MRI quantifies recurrent glioblastoma tumor fraction, pseudoprogression, and radiation necrosis to predict survival. *Neuro Oncol.* 2012; 14(7):919–930. Available at: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3379799&tool=pmcentrez&rendertype=abstract>. [PubMed: 22561797]
15. Kosior JC, Frayne R. PerfTool: a software platform for investigating bolus-tracking perfusion imaging quantification strategies. *J Magn Reson Imaging.* 2007; 25(3):653–659. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17326077>. [PubMed: 17326077]
16. Hein PA, Eskey CJ, Dunn JF, et al. Diffusion-weighted imaging in the follow-up of treated high-grade gliomas: tumor recurrence versus radiation injury. *AJNR. Am J Neuroradiol.* 2004; 25(2):201–209. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14970018>. [PubMed: 14970018]
17. Geer CP, Simonds J, Anvery A, et al. Does MR perfusion imaging impact management decisions for patients with brain tumors? A prospective study. *AJNR. Am J Neuroradiol.* 2012; 33(3):556–562. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22116105>. [PubMed: 22116105]
18. Kivrak AS, Paksoy Y, Erol C, et al. Comparison of apparent diffusion coefficient values among different MRI platforms: a multicenter phantom study. *Diagn Interv Radiol.* Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24004973>.
19. Kudo K, Sasaki M, Yamada K, et al. Differences in CT perfusion maps generated by different commercial software: quantitative analysis by using identical source data of acute stroke patients. *Radiology.* 2010; 254(1):200–209. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20032153>. [PubMed: 20032153]
20. Paulson ES, Schmainda KM. Comparison of dynamic susceptibility-weighted contrast-enhanced MR methods: recommendations for measuring relative cerebral blood volume in brain tumors. *Radiology.* 2008; 249(2):601–613. Available at: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2657863&tool=pmcentrez&rendertype=abstract>. [PubMed: 18780827]
21. Hajnal J V, Saeed N, Soar EJ, Oatridge A, Young IR, Bydder GM. A registration and interpolation procedure for subvoxel matching of serially acquired MR images. *J Comput Assist Tomogr.* 19(2):289–96. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7890857>. [PubMed: 7890857]
22. Rowland DJ, Garbow JR, Laforest R, et al. Registration of [18F]FDG microPET and small-animal MRI. *Nucl Med Biol.* 2005; 32(6):567–596. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16026703>. [PubMed: 16026703]
23. Lee JJ, Bretthorst GL, Derdeyn CP, et al. Dynamic susceptibility contrast MRI with localized arterial input functions. *Magn Reson Med.* 2010; 63(5):1305–1314. Available at: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3014609&tool=pmcentrez&rendertype=abstract>. [PubMed: 20432301]
24. Bassar PJ, Mattiello J, LeBihan D. Estimation of the effective self-diffusion tensor from the NMR spin echo. *J Magn Reson B.* 1994; 103(3):247–254. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8019776>. [PubMed: 8019776]

25. Dewitte K, Fierens C, Stockl D, et al. Application of the Bland-Altman Plot for interpretation of method-comparison studies: a critical investigation of its practice. *Clin Chem.* 2002; 48(5):799–801. Available at: <http://www.clinchem.org/content/48/5/799.full>. [PubMed: 11978620]
26. Stöckl D, Rodríguez Cabaleiro D, Van Uytvanghe K, et al. Interpreting method comparison studies by use of the Bland-Altman plot: reflecting the importance of sample size by incorporating confidence limits and predefined error limits in the graphic. *Clin Chem.* 2004; 50(11):2216–2218. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15502104>. [PubMed: 15502104]
27. Parsons MW, Yang Q, Barber PA, et al. Perfusion magnetic resonance imaging maps in hyperacute stroke: relative cerebral blood flow most accurately identifies tissue destined to infarct. *Stroke.* 2001; 32(7):1581–1587. Available at: <http://stroke.ahajournals.org/content/32/7/1581.long>. [PubMed: 11441205]
28. Petrella JR, Provenzale JM. MR perfusion imaging of the brain: techniques and applications. *AJR. Am. J. Roentgenol.* 2000; 175(1):207–219. Available at: <http://www.ajronline.org/doi/full/10.2214/ajr.175.1.1750207>. [PubMed: 10882275]
29. Ostergaard L, Weisskoff RM, Chesler DA, et al. High resolution measurement of cerebral blood flow using intravascular tracer bolus passages. Part I: Mathematical approach and statistical analysis. *Magn Reson Med.* 1996; 36(5):715–725. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8916022>. [PubMed: 8916022]
30. Sugahara T, Korogi Y, Tomiguchi S, et al. Posttherapeutic intraaxial brain tumor: the value of perfusion-sensitive contrast-enhanced MR imaging for differentiating tumor recurrence from nonneoplastic contrast-enhancing tissue. *AJNR. Am J Neuroradiol.* 2000; 21(5):901–909. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10815666>. [PubMed: 10815666]
31. Al-Okaili RN, Krejza J, Wang S, et al. Advanced MR imaging techniques in the diagnosis of intraaxial brain tumors in adults. *Radiographics.* 2006; 26(Suppl 1):S173–S189. Available at: http://radiographics.rsna.org/content/26/suppl_1/S173.abstract. [PubMed: 17050514]
32. Bulakbasi N, Kocaoglu M, Ors F, et al. Combination of single-voxel proton MR spectroscopy and apparent diffusion coefficient calculation in the evaluation of common brain tumors. *AJNR Am J Neuroradiol.* 2003; 24(2):225–233. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12591638>. [PubMed: 12591638]
33. Schmainda KM. Diffusion-weighted MRI as a biomarker for treatment response in glioma. *CNS Oncol.* 2012; 1(2):169–180. Available at: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3734866&tool=pmcentrez&rendertype=abstract>. [PubMed: 23936625]
34. Ellingson BM, Malkin MG, Rand SD, et al. Volumetric analysis of functional diffusion maps is a predictive imaging biomarker for cytotoxic and anti-angiogenic treatments in malignant gliomas. *J Neurooncol.* 2011; 102(1):95–103. Available at: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3033973&tool=pmcentrez&rendertype=abstract>. [PubMed: 20798977]
35. Christensen S, Mouridsen K, Wu O, et al. Comparison of 10 perfusion MRI parameters in 97 sub-6-hour stroke patients using voxel-based receiver operating characteristics analysis. *Stroke.* 2009; 40(6):2055–2061. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19359626>. [PubMed: 19359626]
36. Galinovic I, Brunecker P, Ostwaldt A-C, et al. Fully automated postprocessing carries a risk of substantial overestimation of perfusion deficits in acute stroke magnetic resonance imaging. *Cerebrovasc Dis.* 2011; 31(4):408–413. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21346342>. [PubMed: 21346342]
37. Kane I, Carpenter T, Chappell F, et al. Comparison of 10 different magnetic resonance perfusion imaging processing methods in acute ischemic stroke: effect on lesion size, proportion of patients with diffusion/perfusion mismatch, clinical scores, and radiologic outcomes. *Stroke.* 2007; 38(12):3158–3164. Available at: <http://stroke.ahajournals.org/content/38/12/3158>. [PubMed: 17975106]
38. Jones DK, Cercignani M. Twenty-five pitfalls in the analysis of diffusion MRI data. *NMR Biomed.* 2010; 23(7):803–820. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20886566>. [PubMed: 20886566]
39. Bassar PJ, Mattiello J, LeBihan D. MR diffusion tensor spectroscopy and imaging. *Biophys J.* 1994; 66(1):259–267. Available at: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1275686&tool=pmcentrez&rendertype=abstract>. [PubMed: 8130344]

Figure 1.

Sample output fractional anisotropy (FA; *top row*) and mean diffusivity (MD; *bottom row*) of the three diffusion-weighted imaging processing packages. FA and MD maps created by Siemens Leonardo (**a, d**), Washington University School of Medicine (**b, e**), and NordicNeuroLab (**c, f**) look virtually identical.

Figure 2.

Normalized perfusion processing output of three packages for a single two-dimensional slice with tumor (*left*) and magnified tumor area (*right*). CBV_{SL} (a), CBV_{WUSM} (b), CBV_{NNL} (c), CBF_{SL} (d), CBF_{WUSM} (e), CBF_{NNL} (f), MTT_{SL} (g), MTT_{WUSM} (h), MTT_{NNL} (i) are shown. T_1 image (I) and CBV image (II) in the center show the location of magnified tumor area shown on the right, in relation to the whole brain. In tumor region, note the absence of elevated signal in area 1 in (c) compared to (a) and (b). Also note elevated signal in area 2 (e) compared to (d) and (f). Finally, note signal variability in the enhancement area 3 between (g), (h), and (i). CBF, cerebral blood flow; CBV, cerebral blood volume; MTT, mean transit time; NNL, NordicNeuroLab; SL, Siemens Leonardo; WUSM, Washington University School of Medicine.

Figure 3.

Histograms for diffusion and perfusion maps in a tumor T_1 post-Gd enhancement region of interest with $r = 5$ mm (shown in the *top left*) for the same patient. The diffusion parameter distributions are more homogenous (*top row*) as compared to the perfusion parameter histograms (*bottom row*) which reveal larger differences between the three methods. CBF, cerebral blood flow; CBV, cerebral blood volume; FA, fractional anisotropy; MD, mean diffusivity; MTT, mean transit time; NNL, NordicNeuroLab; SL, Siemens Leonardo; WUSM, Washington University School of Medicine.

Figure 4.

Histograms for diffusion and perfusion maps in a contralateral white matter region of interest with $r = 5$ mm (shown in the *top left*), for the same patient. Both diffusion (*top row*) and perfusion (*bottom row*) histograms reveal similar intensity distribution for all packages, with the exception of MTT_{WUSM} which shows slower variance compared to SL and NNL. CBF, cerebral bloodflow; CBV, cerebral blood volume; FA, fractional anisotropy; MD, mean diffusivity; MTT, mean transit time; NNL, NordicNeuroLab; SL, Siemens Leonardo; WUSM, Washington University School of Medicine.

Figure 5.

Bland–Altman (BA) and linear regression comparisons of MD computed by NNL, WUSM, and SL for all regions of interest with $r = 5$ mm. BA plot (a) and linear regression (b) of MD_{WUSM} versus MD_{NNL} demonstrate excellent concordance and minimal bias. BA plot (c) and linear regression (d) of MD_{WUSM} versus MD_{SL} also demonstrate excellent concordance, although the MD values calculated by SL slightly underestimate those calculated by WUSM for values less than $1.5 \times 10^{-3} \text{ mm}^2/\text{s}$. MD, mean diffusivity; NNL, NordicNeuro-Lab; SL, Siemens Leonardo; WUSM, Washington University School of Medicine.

Figure 6.

Comparison of fractional anisotropy computed by NNL, WUSM, and SL for regions of interest with $r = 5$ mm. Bland–Altman (BA) plot (a) and linear regression (b) of FA_{WUSM} versus FA_{NNL} , demonstrate excellent concordance and minimal bias. BA plot (c) and linear regression (d) of FA_{WUSM} versus FA_{SL} demonstrate excellent concordance, although the FA values calculated by the SL method appear to underestimate those calculated from the WUSM method for all values. FA, fractional anisotropy; NNL, NordicNeuroLab; SL, Siemens Leonardo; WUSM, Washington University School of Medicine.

Figure 7.

Comparison of CBV computed by NNL, WUSM, and SL for regions of interest with $r = 5$ mm. Bland–Altman (BA) plot (a) and linear fit (b) of CBV_{WUSM} versus CBV_{NNL} , demonstrate poor concordance and large biases between the two methods. BA plot (c) and linear fit (d) of CBV_{WUSM} versus CBV_{SL} demonstrate equally poor results. CBV, cerebral blood volume; NNL, NordicNeuroLab; SL, Siemens Leonardo; WUSM, Washington University School of Medicine.

TABLE 1Linear Regression R^2 and Bland–Altman Confidence Intervals $\mu \pm 2\sigma$ for FA and MD Comparisons

Comparison	Radius, mm	Pearson's R^2	Bland–Altman $\mu \pm 2\sigma$
FA _{SL} –FA _{NNL}	2.5	0.80	0.19 $\pm$ 0.70
	5	0.89	0.26 $\pm$ 0.48
	7	0.89	0.26 $\pm$ 0.41
	10	0.91	0.27 $\pm$ 0.34
FA _{WUSM} –FA _{SL}	2.5	0.90	–0.24 $\pm$ 0.46
	5	0.89	–0.24 $\pm$ 0.33
	7	0.90	–0.24 $\pm$ 0.27
	10	0.93	–0.24 $\pm$ 0.22
FA _{WUSM} –FA _{NNL}	2.5	0.87	0.02 $\pm$ 0.63
	5	0.89	0.05 $\pm$ 0.47
	7	0.90	0.05 $\pm$ 0.41
	10	0.92	0.06 $\pm$ 0.35
MD _{SL} –MD _{NNL}	2.5	0.90	0.07 $\pm$ 0.26
	5	0.93	0.07 $\pm$ 0.18
	7	0.95	0.06 $\pm$ 0.14
	10	0.95	0.06 $\pm$ 0.13
MD _{WUSM} –MD _{SL}	2.5	0.99	–0.06 $\pm$ 0.14
	5	1.00	–0.05 $\pm$ 0.10
	7	0.99	–0.06 $\pm$ 0.11
	10	0.99	–0.06 $\pm$ 0.11
MD _{WUSM} –MD _{NNL}	2.5	0.91	0.02 $\pm$ 0.22
	5	0.94	0.01 $\pm$ 0.16
	7	0.95	0.01 $\pm$ 0.14
	10	0.95	0.00 $\pm$ 0.13

FA, fractional anisotropy; MD, mean diffusivity; NNL, NordicNeuroLab; SL, Siemens Leonardo; WUSM, Washington University School of Medicine.

TABLE 2

Linear Regression R^2 and Bland–Altman Confidence Interval $\mu \pm 2\sigma$ for CBV, CBF, and MTT Comparisons

Comparison	Radius, mm	Pearson's R^2	Bland–Altman $\mu \pm 2\sigma$
CBV _{SL} –CBV _{NNL}	2.5	0.78	0.14 $\pm$ 1.53
	5	0.59	0.30 $\pm$ 1.08
	7	0.52	0.34 $\pm$ 0.85
	10	0.38	0.33 $\pm$ 0.78
CBV _{WUSM} –CBV _{SL}	2.5	0.82	0.14 $\pm$ 1.40
	5	0.88	0.11 $\pm$ 0.98
	7	0.78	0.05 $\pm$ 0.78
	10	0.66	0.05 $\pm$ 0.62
CBV _{WUSM} –CBV _{NNL}	2.5	0.58	0.25 $\pm$ 1.34
	5	0.52	0.30 $\pm$ 1.03
	7	0.54	0.29 $\pm$ 0.93
	10	0.45	0.29 $\pm$ 0.86
CBF _{SL} –CBF _{NNL}	2.5	0.40	0.25 $\pm$ 1.12
	5	0.44	0.29 $\pm$ 0.92
	7	0.50	0.29 $\pm$ 0.79
	10	0.56	0.28 $\pm$ 0.67
CBF _{WUSM} –CBF _{SL}	2.5	0.78	–0.01 $\pm$ 1.34
	5	0.65	–0.02 $\pm$ 1.14
	7	0.70	–0.08 $\pm$ 0.93
	10	0.74	–0.08 $\pm$ 0.61
CBF _{WUSM} –CBF _{NNL}	2.5	0.44	0.22 $\pm$ 1.07
	5	0.41	0.25 $\pm$ 0.92
	7	0.51	0.22 $\pm$ 0.71
	10	0.47	0.21 $\pm$ 0.62
MTT _{SL} –MTT _{NNL}	2.5	0.28	0.24 $\pm$ 1.35
	5	0.29	0.23 $\pm$ 0.88
	7	0.38	0.22 $\pm$ 0.66
	10	0.42	0.20 $\pm$ 0.52
MTT _{WUSM} –MTT _{SL}	2.5	0.00	0.31 $\pm$ 1.16
	5	0.00	0.27 $\pm$ 0.86
	7	0.00	0.29 $\pm$ 0.67
	10	0.01	0.24 $\pm$ 0.57
MTT _{WUSM} –MTT _{NNL}	2.5	0.01	0.42 $\pm$ 1.38
	5	0.03	0.42 $\pm$ 1.03
	7	0.02	0.44 $\pm$ 0.86
	10	0.00	0.39 $\pm$ 0.74

CBF, cerebral blood flow; CBV, cerebral blood volume; MTT, mean transit time; NNL, NordicNeuroLab; SL, Siemens Leonardo; WUSM, Washington University School of Medicine.

TABLE 3

Bland–Altman Confidence Intervals (CI) $\mu \pm 2\sigma$ for Plots Comparing the Following Region of Interest (ROI) Groups with $r = 5$ mm (*Left to Right*): Tumor, Ipsilateral Healthy White Matter (WM), and All ROIs Combined (Tumor + WM)

Comparison	Tumor CI	Ipsilateral WM	All ROIs Combined
CBV _{SL} –CBV _{NNL}	0.37 ± 1.20	0.11 ± 0.55	0.30 ± 1.08
CBV _{WUSM} –CBV _{SL}	0.17 ± 1.08	–0.07 ± 0.50	0.11 ± 0.98
CBV _{WUSM} –CBV _{NNL}	0.44 ± 1.09	–0.01 ± 0.55	0.30 ± 1.03
CBF _{SL} –CBF _{NNL}	0.37 ± 1.01	0.08 ± 0.42	0.29 ± 0.92
CBF _{WUSM} –CBF _{SL}	0.03 ± 1.25	–0.14 ± 0.74	–0.02 ± 1.14
CBF _{WUSM} –CBF _{NNL}	0.37 ± 0.97	0.00 ± 0.55	0.25 ± 0.92
MTT _{SL} –MTT _{NNL}	0.31 ± 0.98	0.03 ± 0.30	0.23 ± 0.88
MTT _{WUSM} –MTT _{SL}	0.38 ± 0.90	–0.04 ± 0.31	0.27 ± 0.86
MTT _{WUSM} –MTT _{NNL}	0.63 ± 0.94	–0.04 ± 0.51	0.42 ± 1.03
FA _{SL} –FA _{NNL}	0.25 ± 0.51	0.27 ± 0.39	0.26 ± 0.48
FA _{WUSM} –FA _{SL}	–0.21 ± 0.26	–0.30 ± 0.44	–0.24 ± 0.33
FA _{WUSM} –FA _{NNL}	0.07 ± 0.50	0.00 ± 0.39	0.05 ± 0.47
MD _{SL} –MD _{NNL}	0.07 ± 0.19	0.04 ± 0.10	0.07 ± 0.18
MD _{WUSM} –MD _{SL}	–0.04 ± 0.09	–0.09 ± 0.13	–0.05 ± 0.10
MD _{WUSM} –MD _{NNL}	0.03 ± 0.18	–0.02 ± 0.09	0.01 ± 0.16

CBF, cerebral blood flow; CBV, cerebral blood volume; FA, fractional anisotropy; MD, mean diffusivity; MTT, mean transit time; NNL, NordicNeuroLab; SL, Siemens Leonardo; WUSM, Washington University School of Medicine.