Received:
29 November 2017

Revised:
23 January 2018

Accepted:
01 February 2018

<https://doi.org/10.1259/bjr.20170912>

Cite this article as:

Togao O, Hiwatashi A, Yamashita K, Kikuchi K, Momosaka D, Yoshimoto K, et al. Measurement of the perfusion fraction in brain tumors with intravoxel incoherent motion MR imaging: validation with histopathological vascular density in meningiomas. *Br J Radiol* 2018; **91**: 20170912.

FULL PAPER

Measurement of the perfusion fraction in brain tumors with intravoxel incoherent motion MR imaging: validation with histopathological vascular density in meningiomas

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Objective: To evaluate the quantification performance of the perfusion fraction (f) measured with intravoxel incoherent motion (IVIM) MR imaging in a comparison with the histological vascular density in meningiomas.

Methods: 29 consecutive patients with meningioma (59.0 ± 16.8 years old, 8 males and 21 females) who underwent a subsequent surgical resection were examined with both IVIM imaging and a histopathological analysis. IVIM imaging was conducted using a single-shot SE-EPI sequence with 13 b-factors (0, 10, 20, 30, 50, 80, 100, 200, 300, 400, 600, 800, 1000 s mm⁻²) at 3T. The perfusion fraction (f) was calculated by fitting the IVIM bi-exponential model. The 90-percentile f-value in the tumor region-of-interest (ROI) was defined as the maximum f-value (f-max). Histopathological vascular density (%Vessel) was measured on CD31-immunostained histopathological specimens. The correlation and agreement between the f-values and %Vessel was assessed.

Results: The f-max (15.5 ± 5.5%) showed excellent agreement [intraclass correlation coefficient (ICC) = 0.754] and a significant correlation (r = 0.69, p < 0.0001) with the %Vessel (12.9 ± 9.4%) of the tumors. The Bland-Altman plot analysis showed excellent agreement between the f-max and %Vessel (bias, -2.6%; 95% limits of agreement, from -16.0 to 10.8%). The f-max was not significantly different among the histological subtypes of meningioma.

Conclusion: An excellent agreement and a significant correlation were observed between the f-values and %Vessel. The f-value can be used as a noninvasive quantitative imaging measure to directly assess the vascular volume fraction in brain tumors.

Advances in knowledge: The f-value measured by IVIM imaging showed a significant correlation and an excellent agreement with the histological vascular density in the meningiomas. The f-value can be used as a noninvasive and quantitative imaging measure to directly assess the volume fraction of capillaries in brain tumors.

INTRODUCTION

The assessment of vascularity and the perfusion status of brain lesions has become an indispensable role of MR imaging in the characterization of the etiologies of various diseases. For instance, the cerebral blood volume measured with dynamic susceptibility contrast perfusion-weighted (DSC PW) imaging has proved to be of great utility for differentiating different cerebral mass lesions,¹⁻³ and for estimating the malignancy and prognosis of gliomas.⁴⁻⁶ More recently,

arterial spin labelling (ASL) has become available in the clinical setting as a noninvasive PW imaging technique using the blood as an endogenous tracer.⁷ However, in these methods, the quantification of perfusion parameters largely depends on the arterial input function and arterial transit time, which are difficult to accurately measure due to the dispersion and delay effects of the bolus.⁸ In addition, the quantification can be affected by many variables or parameters that produce errors in these perfusion measurements.⁹

Intravoxel incoherent motion (IVIM) is the concept and method proposed by Le Bihan et al¹⁰ in the 1980s to quantitatively assess all of the microscopic motion that can contribute to the signal intensities measured on diffusion-weighted (DW) MR imaging.¹⁰ This theory aimed to separate diffusion and perfusion parameters based on an IVIM model using a single DW acquisition scheme. The apparent diffusion coefficient (ADC), which is frequently calculated with a pair of b-values (e.g. 0 and 1000 s mm⁻²), includes contributions from the microcirculation of blood in capillaries (perfusion) in *in vivo* tissues.¹⁰ The IVIM model applies bi-exponential fitting to the signal decay obtained with multiple b-values and then separates the true diffusion and the capillary perfusion. In other words, IVIM MR imaging allows us to simultaneously obtain both diffusion and perfusion imaging with complete geometrical matching.

IVIM imaging has some clear theoretical advantages over DSC PW imaging and conventional DW imaging. First, it is not necessary to use contrast agents and a rapid i.v. injection with IVIM imaging, as it is in DSC PW imaging. Second, IVIM exploits a relatively simple mathematical analysis,¹⁰ and there is no need to obtain the arterial input function^{11,12} or perform deconvolution¹¹ and leakage correction¹³ as in DSC PW imaging. Third, the geometry for diffusion and perfusion imaging is identical in IVIM, since these parameters are obtained from the same data set. Fourth, the true diffusion coefficient (D) measured with IVIM imaging can reflect the diffusion status more accurately compared to the ADC, since the influence of perfusion is excluded in the calculation of the D.¹⁴ Finally, IVIM is inherently quantitative and does not need any corrections.¹⁰

Among the IVIM-derived parameters, the perfusion fraction (f) was reported to be a simple and robust measure to assess the tissue perfusion status, and the f-value was shown to be useful in differentiating high-grade from low-grade gliomas^{15–17} and in differentiating recurrent gliomas from therapy-related effects.¹⁸ However, to date, there have been no studies that validated the f-value with a histological analysis in brain tumors. The purpose of the present study was to evaluate the quantification performance of the perfusion fraction (f) by comparing it with the histologically determined vascular density in meningiomas, which have a relatively homogenous histological solid composition and are suited for such a comparison.

METHODS AND MATERIALS

Patients

This study was approved by the Institutional Review Board of our hospital. Informed consent for study participation was waived due to the retrospective nature of the study. The patient series was 29 consecutive patients with meningioma (59.0 ± 16.8 years old, 8 males and 21 females) who underwent a subsequent surgical resection between January 2013 and October 2014. The patients' histological subtypes of meningioma were as follows: 6 fibrous, 5 meningothelial, 2 angiomatous, 6 transitional and 10 atypical. All MR images were obtained as pre-operative routine examinations, and the interval between the MR imaging and the surgery was <2 weeks in all patients.

IVIM MR imaging

IVIM MR imaging was performed on a 3T clinical scanner (Achieva 3.0TX, Philips Healthcare, Best, Netherlands) with an 8-channel head coil. IVIM imaging was performed in axial planes by using a single-shot echo-planar imaging diffusion sequence, with 13 b-values (0, 10, 20, 30, 50, 80, 100, 200, 300, 400, 600, 800, 1000 s mm⁻²) in three orthogonal directions.^{3,14} The other imaging parameters were: repetition time = 2,500 ms; echo time = 70 ms; matrix = 128 × 126 (reconstructed to 256 × 256); slice thickness = 5 mm; field of view = 230 × 230 mm; number of slices = 11; sensitivity encoding factor = 1.5; scan time = 2 min 7 s. For reference, several standard MR images, including T₁ weighted, T₂ weighted, fluid attenuation inversion recovery and contrast-enhanced T₁ weighted images were acquired.

IVIM data analysis

The standard IVIM two-compartment diffusion model was used, with a capillary perfusion component and a non-vascular compartment.¹⁰ Signal decay was estimated by using the following bi-exponential equation:

$$SI/SI_0 = (1 - f) \times \exp(-bD) + f \times \exp(-bD^*)$$

where D and D* are the true diffusion coefficient and the pseudodiffusion coefficient, respectively; SI and SI₀ are the signal intensity at a given b-value and b = 0 s mm⁻², respectively; and f is the volume fraction within a voxel of water flowing in perfused capillaries. The signal decay was fitted in a single step on a voxel-by-voxel basis to create each parameter map of D, D* and f-values by using the interactive data language-based software program (DWI TOOL R1.5, Philips Medical Systems, Best, Netherlands).

Measurement of f-value

A two-dimensional region-of-interest (ROI) was manually drawn to include the entire enhancing lesion on a single section with the maximum area of the tumor by a trained neuroradiologist (15 years of experience in neuroradiology), using an ImageJ plugin (v. 1.43u; U.S. National Institutes of Health, Bethesda, MD). It was confirmed on conventional MR images that no tumors include large necrosis or hemorrhage. The ROI was copied and transferred to the f-map, and the 90-percentile value within the tumor ROI was recorded as the maximum f-value (f-max) of the tumor.^{18,19} The mean f-value was also recorded as the average f-value (f-ave). The aim of the use of 90-percentile value was to avoid observer bias.

Histopathological evaluation

The histopathological diagnosis was determined with resected specimens according to the World Health Organization criteria by two established neuropathologists with 22 and 31 years of experience.²⁰ To evaluate the vascular density of the meningiomas, we immunostained the tissue sections for CD31 (Novocastra Laboratories, Newcastle, UK), which identified vascular endothelial cells. Five microscopic fields (× 200) of the most intense vascularization on each specimen were photographed as a TIFF file with a microscopic digital camera. For each tumor, the relative vascular density (%Vessel) was defined as the total area of vessel lumina surrounded by the endothelial cell layer as

a percentage of the entire tumor tissue area as described.²¹ The vessel lumina were recognized as an area surrounded by the CD31-positive endothelial cell layer. On the image, we used the imageJ program to distinguish the vessel area by its color. The image was analyzed to measure the %Vessel value by counting the pixel number of the total vessel lumina and that of the entire tissue. The measurements on the five microscopic fields were averaged to represent the tumor.

Statistical analysis

All values are expressed as mean $\pm$ standard deviation. The comparison between the f-max and %Vessel values was performed with the paired t-test. The agreement between the f-values and %Vessel was analyzed by calculating the intra-class correlation coefficient (ICC), Pearson correlation and a Bland-Altman plot analysis. ICCs were considered to be excellent when > 0.74 .²² The f-values were compared among the histological subtypes of meningioma by one-way analysis of variance followed by Tukey's multiple comparison test. Statistical analyses were performed with commercially available software packages (SPSS, IBM 19, Armonk, NY; Prism 5.0, GraphPad Software, San Diego, CA). p -values < 0.05 were considered significant.

RESULTS

Comparisons and agreement between the f-values and %Vessel

The f-max ($15.5 \pm 5.5\%$, $p = 0.0523$) was tended to be larger than the %Vessel ($12.9 \pm 9.4\%$) but not statistically significant. The f-ave ($9.7 \pm 3.7\%$, $p = 0.0145$) was significantly smaller than the %Vessel ($12.9 \pm 9.4\%$). A significant positive correlation was observed between f-max and %Vessel ($r = 0.69$, $p < 0.0001$, Figure 1a). The f-max showed excellent agreement with the

%Vessel, with the ICC of 0.754. The Bland-Altman plot analysis showed an excellent agreement between the f-max and %Vessel (bias, -2.6% ; 95% limits of agreement, from -16.0 to 10.8% , Figure 1b). No proportional bias was found between the average and the difference in this analysis.

A significant positive correlation was observed between f-ave and %Vessel ($r = 0.82$, $p < 0.0001$, Figure 1c). The f-ave showed moderate agreement with %Vessel with the ICC of 0.715. The Bland-Altman plot analysis showed good agreement between the f-ave and %Vessel (bias, 3.2% ; 95% limits of agreement, from -9.9 to 16.4% , Figure 1d), but strong proportional bias was observed between the average and the difference ($r = 0.88$, $p < 0.0001$) in this analysis.

Comparisons of the f-values and %Vessel among the histological subtypes of meningioma

Table 1 summarizes the average f-max, f-ave and %Vessel values in each histological subtype of meningioma. The f-max and f-ave were not significantly different among the histological subtypes of meningioma. The %Vessel was significantly higher in the angiomatous meningiomas than the other subtypes of meningioma (vs meningothelial, $p < 0.05$; vs fibrous, $p < 0.0001$; vs transitional, $p < 0.05$; vs atypical, $p < 0.05$).

Figures 2–4 show representative cases of fibrous, atypical and angiomatous meningioma, respectively. Although both lesions demonstrated strong and homogenous contrast enhancement after the administration of a gadolinium-based contrast agent, the slope of the signal reduction against the b-value was steeper at lower b-values in the atypical and angiomatous meningioma than in the fibrous meningioma, which resulted in larger f-values

Figure 1. (a) A significant positive correlation was observed between f-max and %Vessel ($r = 0.69$, $p < 0.0001$). (b) The Bland-Altman plot analysis showed excellent agreement between the f-max and %Vessel (bias, -2.6% ; 95% limits of agreement, from -16.0 to 10.8%). No proportional bias was found between the average and the difference in this analysis. (c) A significant positive correlation was observed between f-ave and %Vessel ($r = 0.82$, $p < 0.0001$). (d) The Bland-Altman plot analysis showed good agreement between the f-ave and %Vessel (bias, 3.2% ; 95% limits of agreement, from -9.9 to 16.4%), but strong proportional bias was observed between the average and the difference ($r = 0.88$, $p < 0.0001$).

Table 1. The f-values and %Vessel in Each Histological Subtype of Meningioma

	Meningothelial <i>n</i> = 5	Fibrous <i>n</i> = 6	Transitional <i>n</i> = 6	Angiomatous <i>n</i> = 2	Atypical <i>n</i> = 10	Average
f-max (%)	14.4 ± 4.1	10.8 ± 3.7	18.1 ± 6.2	17.4 ± 3.5	16.9 ± 5.9	15.5 ± 5.5
f-ave (%)	12.5 ± 1.8	10.8 ± 3.4	6.7 ± 2.0	8.7 ± 3.4	10.6 ± 4.8	9.7 ± 3.7
%Vessel (%)	11.3 ± 5.1	4.4 ± 2.0	13.0 ± 12.7	31.8 ± 2.2	15.1 ± 5.9	12.9 ± 9.4

f-max, maximum f-value; f-ave, average f-value; %Vessel, Histopathologic vascular density

in the atypical meningioma than in the fibrous meningioma (f-max: 7.9% in the fibrous meningioma vs 25.0% in the atypical and 19.9% in the angiomatous meningioma). Histological evaluations revealed larger vascular volumes in the atypical meningioma than in the fibrous meningioma (%Vessel: 3.9% in the fibrous meningioma vs 22.5% in the atypical and 33.3% in the angiomatous meningioma).

DISCUSSION

The perfusion fraction (*f*) measured by the IVIM approach is the parameter used to evaluate tissue blood volumes. Wirestam *et al* reported that the cerebral blood volume calculated by the *f*-value was correlated with that derived from DSC PW imaging in both grey and white matter in healthy subjects.²³ To date, there have been two studies that investigated the correlation between the *f*-value by IVIM and cerebral blood volume (CBV) by DSC PW imaging in brain tumors.^{17,24} In both studies, the *f*-value by IVIM was well correlated with the relative CBV of tumors by DSC PW imaging. On the other hand, it was also reported that the CBV of tumor by DSC PW imaging was significantly correlated with %Vessel in astrocytic tumors,²⁵ and the signal intensity on ASL

was significantly correlated with %Vessel in various types of brain tumors including gliomas²¹ as well as in meningiomas.²⁶ These facts indicate that the *f*-value could be an alternative marker to assess the vascularity of brain tumors. The *f*-value may be suited for the clinical use since it has been reported to be more accurate and reproducible compared to the other perfusion parameter *D*^{*}, which showed wide variability in measurements,^{15,17,27} and could be strongly influenced by the cardiac cycle.²⁸

The present study elucidated the significant correlation (*r* = 0.69, *p* < 0.0001) between the *f*-max and %Vessel. There have been three studies that compared the *f*-value and histological vascular density, although no studies have been conducted on brain tumors. Lee *et al*²⁹ demonstrated, using a mouse model with subcutaneously implanted colorectal cancer cells, that the *f*-value was well correlated with histological vascular density (*r* = 0.749, *p* < 0.001). Klau *et al*³⁰ reported an excellent correlation between the *f*-value and microvessel density in pancreas tumors (*r* = 0.85). Bauerle *et al* showed that the *f*-value is correlated with the vascular area fraction (*r* = 0.60, *p* < 0.05) in rectal carcinomas.³¹ The results of our present analyses are in agreement with these studies.

Figure 2. A 41-year-old female with a fibrous meningioma. (a) A post-contrast *T*₁ weighted image showing the strongly enhancing mass in the left parietal region. (b) IVIM diffusion decay in the ROI showing a rather linear slope of signal decay for *b*-values near 0 s/mm² as well as in *b*-values > 200 s/mm². (c) The *f*-map showing almost the same *f*-value in the tumor (*f*-max = 7.9%) as in the normal white matter. (d) The CD31-immunostained histopathological specimen showing scattered vascular proliferation (%Vessel = 3.9%). IVIM, intravoxel incoherent motion; ROI, region-of-interest.

Figure 3. A 64-year-old female with an atypical meningioma. (a) A post-contrast T_1 weighted image showing the strongly enhancing mass along the falx. (b) IVIM diffusion decay in the ROI showing a steeper slope of signal decay for b-values near 0 s/mm² than in b-values > 200 s/mm². (c) The f-map showing the high f-value in the tumor (f-max = 25.0%). (d) The CD31-immunostained histopathological specimen showing dense vascular proliferation (%Vessel = 22.5%). IVIM, intravoxel incoherent motion; ROI, region-of-interest.

In addition, our study showed excellent agreement between the f-value and %Vessel with the ICC of 0.754, indicating that the f-value could be an accurate and direct measure of the volume fraction of capillaries within brain tumors. The high agreement between the f-value and %Vessel in our study might be due to the following reasons. (1) The brain is less sensitive to motion artifacts compared to the trunk of the body. (2) Typically, meningiomas are histologically homogenous without large necrosis or hemorrhage in tumors, unlike high-grade gliomas or other malignant tumors. (3) The degree of vascularity in meningiomas ranges from low to high. Better agreement was observed between %Vessel and the f-max rather than the f-ave, and proportional bias was observed in the Bland-Altman plot analysis for the f-ave. This was reasonable since %Vessel was measured in the most intense area within each tumor and was related to the f-max rather than the f-ave.

In the present study, the f-values were not statistically different among subtypes of meningioma while the %Vessel was significantly higher in the angiomatous meningiomas than the other subtypes of meningioma. Our findings are not in line with a study that showed higher signal on ASL PW imaging in angiomatous meningiomas than other subtypes.²⁶ This could be partially explained by the locational differences between the area for f-values and %vessels. There was a tendency of overestimation of the f-value compared with %Vessel except for the angiomatous meningiomas. In IVIM imaging, it is assumed that blood protons stay in the capillary network during the measurement time.¹⁰ An exchange between extra- and intra-capillary water may be a source of incorrect estimation of f-values. This

could have also affected the measurements of f-values and resulted in the discrepancy between the f-value and %Vessels in the present study to some extent. In addition, the IVIM model is based on the assumption that the flowing component (f) and the static component (1 - f) have identical T_2 relaxation times. If this is not true, the f-value can be influenced by the difference in T_2 between the two components.¹⁰ We did not take T_2 relaxation times into account in the IVIM analysis in the present study. In particular, the T_2 of an angiomatous meningioma should be prolonged as seen in Figure 4, reflecting its rich vascular component. This could be the reason for the underestimation of the f-value compared with %Vessel only in the angiomatous subtype. The IVIM model which incorporated diffusional kurtosis to take non-Gaussian diffusion into consideration may be able to provide more accurate values compared to the conventional bi-exponential model.^{32,33}

There were study limitations. First, the cohort was relatively small, as was the number of some of the subtypes of meningioma. This could be the reason why we did not observe significant differences in the comparisons of the subtypes. Second, there was difficulty reaching agreement regarding the location for the ROIs for IVIM measurements with the areas for histological vascular density. Direct matching between MR imaging and histology was not possible because the tumors were surgically removed piece by piece in most of the cases, and the resected specimens provided scant locational information. In addition, the 90-percentile f-values might not exactly match the selected microscopic fields of the most intense vascularization on histology.

Figure 4. A 43-year-old female with an angiomatous meningioma. (a) A post-contrast T_1 weighted image showing the strongly enhancing mass along the falx. (b) A T_2 weighted image showing the high signal intensity in the tumor. (c) IVIM diffusion decay in the ROI showing a steeper slope of signal decay for b-values near 0 s mm⁻² than in b-values > 200 s mm⁻². (d) The f-map showing the high f-value in the tumor (f-max = 19.9%). (e) The CD31-immunostained histopathological specimen showing dense vascular proliferation (%Vessel = 33.3%). IVIM, intravoxel incoherent motion; ROI, region-of-interest.

CONCLUSION

The f-value measured by IVIM imaging showed a significant correlation and an excellent agreement with the histological

vascular density in the meningiomas. The f-value can be used as a noninvasive and quantitative imaging measure to directly assess the volume fraction of capillaries in brain tumors.

REFERENCES

1. Hakyemez B, Erdogan C, Bolca N, Yildirim N, Gokalp G, Parlak M. Evaluation of different cerebral mass lesions by perfusion-weighted MR imaging. *J Magn Reson Imaging* 2006; **24**: 817–24. doi: <https://doi.org/10.1002/jmri.20707>
2. Yamashita K, Yoshiura T, Hiwatashi A, Togao O, Yoshimoto K, Suzuki SO, et al. Arterial spin labeling of hemangioblastoma: differentiation from metastatic brain tumors based on quantitative blood flow measurement. *Neuroradiology* 2012; **54**: 809–13. doi: <https://doi.org/10.1007/s00234-011-0977-5>
3. Yamashita K, Yoshiura T, Hiwatashi A, Togao O, Yoshimoto K, Suzuki SO, et al. Differentiating primary CNS lymphoma from glioblastoma multiforme: assessment using arterial spin labeling, diffusion-weighted imaging, and ¹⁸F-fluorodeoxyglucose positron emission tomography. *Neuroradiology* 2013; **55**: 135–43. doi: <https://doi.org/10.1007/s00234-012-1089-6>
4. 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* 2003; **24**: 1989–98.
5. Law M, Young R, Babb J, Pollack E, Johnson G. Histogram analysis versus region of interest analysis of dynamic susceptibility contrast perfusion MR imaging data in the grading of cerebral gliomas. *AJNR Am J Neuroradiol* 2007; **28**: 761–6.
6. Law M, Young RJ, Babb JS, Peccerelli N, Chheang S, Gruber ML, 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**: 490–8. doi: <https://doi.org/10.1148/radiol.2472070898>
7. Cebeci H, Aydin O, Ozturk-Isik E, Gumus C, Inecikli F, Bekar A, et al. Assessment of perfusion in glial tumors with arterial spin labeling: comparison with dynamic susceptibility contrast method. *Eur J Radiol* 2014; **83**:

- 1914–9. doi: <https://doi.org/10.1016/j.ejrad.2014.07.002>
8. Zaharchuk G, El Mogy IS, Fischbein NJ, Albers GW. Comparison of arterial spin labeling and bolus perfusion-weighted imaging for detecting mismatch in acute stroke. *Stroke* 2012; **43**: 1843–8. doi: <https://doi.org/10.1161/STROKEAHA.111.639773>
9. Willats L, Calamante F. The 39 steps: evading error and deciphering the secrets for accurate dynamic susceptibility contrast MRI. *NMR Biomed* 2013; **26**: 913–31. doi: <https://doi.org/10.1002/nbm.2833>
10. Le Bihan D, Breton E, Lallemand D, Aubin ML, Vignaud J, Laval-Jeantet M. Separation of diffusion and perfusion in intravoxel incoherent motion MR imaging. *Radiology* 1988; **168**: 497–505. doi: <https://doi.org/10.1148/radiology.168.2.3393671>
11. Ostergaard L, Weisskoff RM, Chesler DA, Gyldensted C, Rosen BR. High resolution measurement of cerebral blood flow using intravascular tracer bolus passages. Part I: Mathematical approach and statistical analysis. *Magn Reson Med* 1996; **36**: 715–25. doi: <https://doi.org/10.1002/mrm.1910360510>
12. Knutsson L, Ståhlberg F, Wirestam R. Absolute quantification of perfusion using dynamic susceptibility contrast MRI: pitfalls and possibilities. *MAGMA* 2010; **23**: 1–21. doi: <https://doi.org/10.1007/s10334-009-0190-2>
13. Uematsu H, Maeda M, Sadato N, Matsuda T, Ishimori Y, Koshimoto Y, et al. Blood volume of gliomas determined by double-echo dynamic perfusion-weighted MR imaging: a preliminary study. *AJNR Am J Neuroradiol* 2001; **22**: 1915–9.
14. Togao O, Hiwatashi A, Yamashita K, Kikuchi K, Mizoguchi M, Yoshimoto K, et al. Differentiation of high-grade and low-grade diffuse gliomas by intravoxel incoherent motion MR imaging. *Neuro Oncol* 2016; **18**: 132–41. doi: <https://doi.org/10.1093/neuonc/nov147>
15. Federau C, Meuli R, O'Brien K, Maeder P, Hagmann P. Perfusion measurement in brain gliomas with intravoxel incoherent motion MRI. *AJNR Am J Neuroradiol* 2014; **35**: 256–62. doi: <https://doi.org/10.3174/ajnr.A3686>
16. Bisdas S, Koh TS, Roder C, Braun C, Schittenhelm J, Ernemann U, et al. Intravoxel incoherent motion diffusion-weighted MR imaging of gliomas: feasibility of the method and initial results. *Neuroradiology* 2013; **55**: 1189–96. doi: <https://doi.org/10.1007/s00234-013-1229-7>
17. Togao O, Hiwatashi A, Yamashita K, Kikuchi K, Mizoguchi M, Yoshimoto K, et al. Differentiation of high-grade and low-grade diffuse gliomas by intravoxel incoherent motion MR imaging. *Neuro Oncol* 2016; **18**: 132–41. doi: <https://doi.org/10.1093/neuonc/nov147>
18. Kim HS, Suh CH, Kim N, Choi CG, Kim SJ. Histogram analysis of intravoxel incoherent motion for differentiating recurrent tumor from treatment effect in patients with glioblastoma: initial clinical experience. *AJNR Am J Neuroradiol* 2014; **35**: 490–7. doi: <https://doi.org/10.3174/ajnr.A3719>
19. Kim DY, Kim HS, Goh MJ, Choi CG, Kim SJ. Utility of intravoxel incoherent motion MR imaging for distinguishing recurrent metastatic tumor from treatment effect following gamma knife radiosurgery: initial experience. *AJNR Am J Neuroradiol* 2014; **35**: 2082–90. doi: <https://doi.org/10.3174/ajnr.A3995>
20. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, et al. The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol* 2007; **114**: 97–109. doi: <https://doi.org/10.1007/s00401-007-0243-4>
21. Noguchi T, Yoshiura T, Hiwatashi A, Togao O, Yamashita K, Nagao E, et al. Perfusion imaging of brain tumors using arterial spin-labeling: correlation with histopathologic vascular density. *AJNR Am J Neuroradiol* 2008; **29**: 688–93. doi: <https://doi.org/10.3174/ajnr.A0903>
22. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. *Psychol Bull* 1979; **86**: 420–8. doi: <https://doi.org/10.1037/0033-2909.86.2.420>
23. Wirestam R, Borg M, Brockstedt S, Lindgren A, Holtås S, Ståhlberg F. Perfusion-related parameters in intravoxel incoherent motion MR imaging compared with CBV and CBF measured by dynamic susceptibility-contrast MR technique. *Acta Radiol* 2001; **42**: 123–8. doi: <https://doi.org/10.1080/028418501127346459>
24. Federau C, O'Brien K, Meuli R, Hagmann P, Maeder P. Measuring brain perfusion with intravoxel incoherent motion (IVIM): initial clinical experience. *J Magn Reson Imaging* 2014; **39**: 624–32. doi: <https://doi.org/10.1002/jmri.24195>
25. Haris M, Husain N, Singh A, Husain M, Srivastava S, Srivastava C, et al. Dynamic contrast-enhanced derived cerebral blood volume correlates better with leak correction than with no correction for vascular endothelial growth factor, microvascular density, and grading of astrocytoma. *J Comput Assist Tomogr* 2008; **32**: 955–65. doi: <https://doi.org/10.1097/RCT.0b013e31816200d1>
26. Kimura H, Takeuchi H, Koshimoto Y, Arishima H, Uematsu H, Kawamura Y, et al. Perfusion imaging of meningioma by using continuous arterial spin-labeling: comparison with dynamic susceptibility-weighted contrast-enhanced MR images and histopathologic features. *AJNR Am J Neuroradiol* 2006; **27**: 85–93.
27. Lee Y, Lee SS, Kim N, Kim E, Kim YJ, Yun SC, et al. Intravoxel incoherent motion diffusion-weighted MR imaging of the liver: effect of triggering methods on regional variability and measurement repeatability of quantitative parameters. *Radiology* 2015; **274**: 405–15. doi: <https://doi.org/10.1148/radiol.14140759>
28. Federau C, Hagmann P, Maeder P, Müller M, Meuli R, Stuber M, et al. Dependence of brain intravoxel incoherent motion perfusion parameters on the cardiac cycle. *PLoS One* 2013; **8**: e72856. doi: <https://doi.org/10.1371/journal.pone.0072856>
29. Lee HJ, Rha SY, Chung YE, Shim HS, Kim YJ, Hur J, et al. Tumor perfusion-related parameter of diffusion-weighted magnetic resonance imaging: correlation with histological microvessel density. *Magn Reson Med* 2014; **71**: 1554–8. doi: <https://doi.org/10.1002/mrm.24810>
30. Klau M, Mayer P, Bergmann F, Maier-Hein K, Hase J, Hackert T, et al. Correlation of histological vessel characteristics and diffusion-weighted imaging intravoxel incoherent motion-derived parameters in pancreatic ductal adenocarcinomas and pancreatic neuroendocrine tumors. *Invest Radiol* 2015; **50**: 792–7. doi: <https://doi.org/10.1097/RLI.0000000000000187>
31. Bäuerle T, Seyler L, Münter M, Jensen A, Brand K, Fritzsche KH, et al. Diffusion-weighted imaging in rectal carcinoma patients without and after chemoradiotherapy: a comparative study with histology. *Eur J Radiol* 2013; **82**: 444–52. doi: <https://doi.org/10.1016/j.ejrad.2012.10.012>
32. Pavilla A, Gambarota G, Arrigo A, Mejdoubi M, Duvauferrier R, Saint-Jalmes H. Diffusional kurtosis imaging (DKI) incorporation into an intravoxel incoherent motion (IVIM) MR model to measure cerebral hypoperfusion induced by hyperventilation challenge in healthy subjects. *MAGMA* 2017; **30**: 545–54. doi: <https://doi.org/10.1007/s10334-017-0629-9>
33. Wu WC, Yang SC, Chen YE, Tseng HM, My PC. Simultaneous assessment of cerebral blood volume and diffusion heterogeneity using hybrid IVIM and DK MR imaging: initial experience with brain tumors. *Eur Radiol* 2017; **27**: 306–14. doi: <https://doi.org/10.1007/s00330-016-4272-z>