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ORIGINAL ARTICLE

IVIM perfusion fraction is prognostic for survival in brain glioma

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Abstract
Introduction The interest in measuring brain perfusion with intravoxel incoherent motion (IVIM) MRI has significantly increased in the last 3 years. Our aim was to evaluate the prognostic value for survival of intravoxel incoherent motion perfusion fraction in patients with gliomas, and compare it to dynamic susceptibility contrast relative cerebral blood volume and apparent diffusion coefficient.
Methods Images were acquired in 27 patients with brain gliomas (16 high grades, 11 low grades), before any relevant treatment. Region of maximal perfusion fraction, maximal relative cerebral blood volume, and minimal apparent diffusion coefficient were obtained. The accuracy of all three methods for 2-year survival prognosis was compared using the area under the receiver operating characteristic curve and Kaplan–Meier survival curves.
Results Death or survival for at least 2 years after imaging could be documented in 22/27 patients. The cutoff values of 0.112 for the perfusion fraction, of 3.01 for the relative cerebral blood volume, and 1033×10^{-6} mm²/s for apparent diffusion coefficient led to an identical sensitivity of 0.889, and a specificity of 0.833, 0.517, and 0.750, respectively for 2 year survival prognosis. The corresponding areas under the receiver operating characteristic curves were 0.84, 076, and 0.86, respectively. All three methods had a significant log rank test considering overall survival ($p = 0.001$, $p = 0.028$, and $p = 0.002$).
Conclusion In this relatively small cohort, maximal IVIM perfusion fraction, similarly to maximal relative cerebral blood volume and minimal apparent diffusion coefficient, was prognostic for survival in patients with gliomas. Maximal IVIM perfusion fraction and minimal apparent diffusion coefficient performed similarly in predicting survival, and both slightly outperformed maximal relative cerebral blood volume.

Keywords Glioma · Prognosis · Survival · Perfusion · Intravoxel incoherent motion MRI

Abbreviations

IVIM	intravoxel incoherent motion
rCBV	relative cerebral blood volume
D	diffusion coefficient
f	perfusion fraction

Introduction

Gliomas represent approximately 28 % of all central nervous system tumors in the United States, and 80 % of the malignant ones [1]. They arise from glial or precursors cells, and include astrocytoma, oligodendroglioma, ependymoma, glioblastoma, mixed glioma, and a few rare histologies. They can be classified into four grades based on the World Health Organization's (WHO) histologic criteria. For example, for astrocytoma: tumors with cytological atypia alone are considered grade II, those also showing anaplasia and mitotic activity are considered grade III, and tumors additionally showing microvascular prolifera-

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Tab. 1 Demographic characteristics, measured IVIM f, DSC rCBV, and ADC of the patients at imaging, grouped as function of pathologic grading or diagnosed based on radiologic criteria. Data are means ± standard deviation. *IVIM*: Intravoxel Incoherent Motion MRI; *DSC rCBV*: Dynamic Susceptibility Contrast relative Cerebral Blood Volume; *ADC* Apparent Diffusion Coefficient

	Number of patients	Male/female	Age at imaging (years)	IVIM f (unitless)	DSC rCBV (unitless)	ADC (10^{-6} mm^2/s)
High grades	16	12/4	59.5 ± 15.5	0.127 ± 0.031	6.37 ± 2.45	949 ± 312
Grade 4	12	8/4	62.6 ± 11.4	0.130 ± 0.030	6.38 ± 2.64	872 ± 221
Grade 3	4	4/0	50.0 ± 24.0	0.118 ± 0.037	6.34 ± 2.28	1181 ± 460
Low grades	11	9/2	40.8 ± 16.5	0.076 ± 0.016	3.42 ± 3.04	1227 ± 376
Grade 2	5	5/0	38.0 ± 22.0	0.084 ± 0.016	3.28 ± 1.30	1193 ± 545
Radiology	6	4/2	43.1 ± 11.8	0.070 ± 0.014	3.51 ± 3.95	1256 ± 207
Total	27	21/6	51.9 ± 18.2	0.106 ± 0.036	5.14 ± 3.04	1062 ± 360

Tab. 2 Patients' treatment after imaging pooled by IVIM f, DSC rCBV, and ADC thresholds. *IVIM* Intravoxel Incoherent Motion MRI; *DSC rCBV* Dynamic Susceptibility Contrast relative Cerebral Blood Volume; *ADC* Apparent Diffusion Coefficient

	Surgery	Chemotherapy	Radiotherapy	Antiangiogenic	Total
Low grade	3 (27 %)	4 (36 %)	2 (18 %)	1 (9 %)	11
High grade	11 (69 %)	12 (75 %)	13 (81 %)	9 (56 %)	16
IVIM f > 0.112	9 (82 %)	8 (73 %)	8 (73 %)	5 (45 %)	11
IVIM f ≤ 0.112	5 (31 %)	8 (50 %)	7 (44 %)	5 (31 %)	16
DSC rCBV > 3.01	10 (59 %)	12 (71 %)	10 (59 %)	7 (41 %)	17
DSC rCBV ≤ 3.01	4 (57 %)	4 (57 %)	5 (71 %)	3 (43 %)	7
ADC ≤ 1033×10^{-6} mm^2/s	8 (57 %)	10 (71 %)	9 (64 %)	8 (57 %)	14
ADC > 1033×10^{-6} mm^2/s	6 (46 %)	6 (46 %)	6 (46 %)	2 (15 %)	13
Total	14 (52 %)	16 (59 %)	15 (56 %)	10 (37 %)	27

tion and/or necrosis are considered glioblastoma grade IV [2]. Survival rate following diagnosis of malignant glioma is poor, and the majority of glioblastoma patients succumb to the disease within 2 years [3].

MR Imaging plays an important role in both the initial evaluation and follow-up of brain tumors, and it is important to remember that some low-grade tumors tend to progress to higher grades of malignancy. In this context, perfusion- and diffusion-weighted imaging have both demonstrated their added value to conventional imaging. Dynamic Susceptibility Contrast (DSC) MRI correlates with neovascularization [4], tumor grading [5], and prognosis [6]. Apparent Diffusion Coefficient (ADC) has been found to have a better correlation with overall survival than relative Cerebral Blood Volume (rCBV) values [7].

Intravoxel incoherent motion (IVIM) imaging is a method that extracts quantitative microvascular perfusion information out of diffusion-weighted images acquired at multiple b-values. It was proposed over 25 years ago [8], but has been found difficult to apply, for various technical reasons. During the last 3 years, the method could be validated in the brain [9, 10] and successfully applied in various brain pathologies [11]. Further, it has been found helpful for differentiating high- from low-grade brain gliomas [12, 13], for differentiating central nervous system lymphoma [14], as well as for differentiating recurrent tumor from treatment effect in both glioblastoma [15] and cerebral metastatic tumor [16]. Recently, functional imaging with IVIM could be demonstrated in visual cortex [17].

In this context, the purpose of this study was to evaluate, in patients with gliomas reported in a previous study [12], the prognostic value for survival of IVIM perfusion fraction f, and compare it with DSC rCBV and with ADC.

Materials and methods

Patient demographics

The present study was approved by the local ethics committee at University of Lausanne, in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Patient consent was waived. Images were acquired from May 2011 to December 2012 in

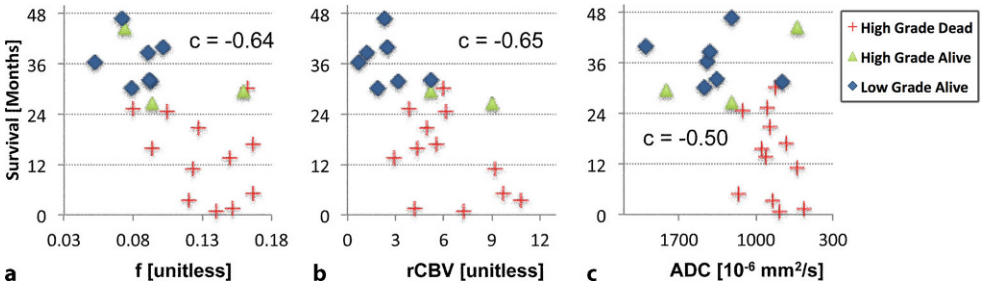

Fig. 1 Scatterplots and correlations: survival (months) against **a** IVIM f, **b** DSC rCBV, and **c** ADC, in the patients (n = 22) with a documented 2 year minimum survival or death. Correlation coefficient c was –0.64 for f, –0.65 for rCBV, and –0.50 for ADC. *IVIM* Intravoxel Incoherent Motion MRI; *DSC rCBV* Dynamic Susceptibility Contrast relative Cerebral Blood Volume; *ADC* Apparent Diffusion Coefficient

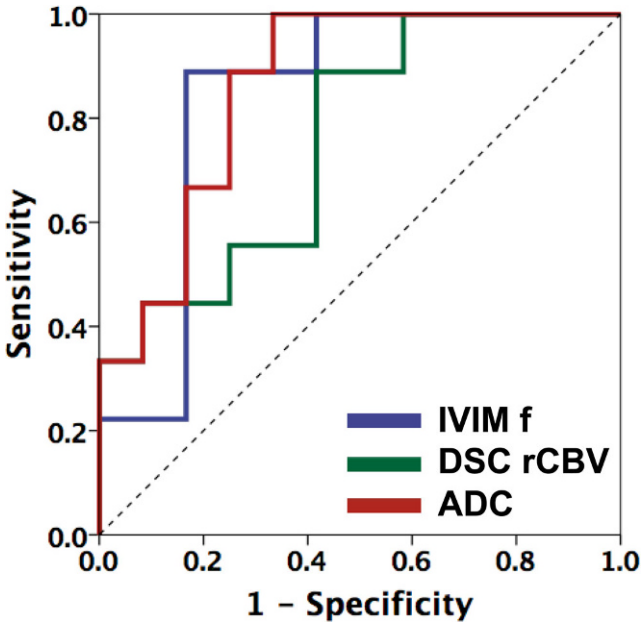

Fig. 2 Receiver operating characteristic curve for 2-year survival prognosis for IVIM f, DSC rCBV, and ADC. *IVIM* Intravoxel Incoherent Motion MRI; *DSC rCBV* Dynamic Susceptibility Contrast relative Cerebral Blood Volume; *ADC* Apparent Diffusion Coefficient

27 patients with glioma – 21 males, 6 females, mean age 51.9 ± 18.2 years, 16 high grades (12 histologic grade IV, 4 histologic grade III), 11 low grades (5 histologic grade II, 6 based on radiology criteria) – before any relevant treatment (Tab. 1 and 2). This study is an extension of a previously reported work [12].

MR Imaging

The images were acquired on 3T MR scanners (Trio, Verio, or Skyra; Siemens, Erlangen, Germany) equipped with 32 multichannel receiver head coils. Before the examination, an 18- or 20-gauge needle was inserted in either the right or the left antecubital vein. Conventional T1-weighted sagittal, T2-weighted axial images were acquired, followed by diffusion-weighted imaging, IVIM, and DSC. Finally, T1-weighted images post-contrast injection were acquired in the sagittal and axial planes.

IVIM imaging parameters

16 b-values (0, 10, 20, 40, 80, 110, 140, 170, 200, 300, 400, 500, 600, 700, 800, 900 s/mm^2) diffusion-weighted images were acquired, using as standard Stejskal-Tanner diffusion-weighted spin-echo EPI pulse sequence [18], in three orthogonal directions, from which the corresponding trace was calculated. A single acquisition was obtained (no average). Fat was suppressed with a spectrally selective saturation pre-pulse. The images were acquired in the axial plane with a section thickness of 4 mm, and an in-plane resolution of 1.2 × 1.2 mm^2 (Field of view [FOV] = 297 × 297 mm^2; matrix 256 × 256). Other parameters were: Repetition time [TR] = 4000 ms, Echo time [TE] = 99 ms, parallel imaging acceleration factor = 2, partial Fourier encoding = 75 %, number of slices = 20, receiver bandwidth = 1086 Hz/pixel. Acquisition time was 3 min 7 s.

Diffusion-weighted imaging parameters

A standard monopolar, spin-echo diffusion sequence was acquired with the following parameters: TR = 5900 ms; TE = 95 ms; matrix = 128 × 128; FOV = 179 × 179 mm^2; slice thickness 3 mm; b-value = 0, 500, and 1000 s/mm^2 in six orthogonal directions; bandwidth = 1510 Hz/pixel.

DSC imaging parameters

Echo-planar images (TR = 1950 ms, TE = 43 ms, section thickness = 6 mm, FOV = 230 × 230 mm^2, acquisition matrix = 128 × 128) were acquired after a gadolinium-based agent (gadoterate meglumine, Dotarem; Guerbet, Paris, France) was intravenously injected at a dose of 0.2 mL per kilogram of body weight at a rate of 3 mL/s, followed by a 20-mL saline flush.

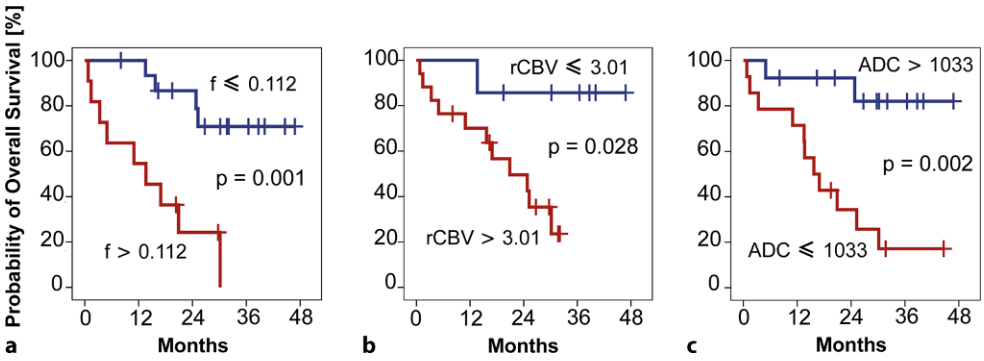

Fig. 3 Kaplan–Meier estimates of overall survival according to **a** IVIM f threshold of 0.112 ($p < 0.001$), **b** DSC rCBV threshold of 3.01 ($p = 0.028$), and **c** ADC threshold of 1033 × 10^{-6} mm^2/s ($p = 0.002$). Crosses represent censored data. *IVIM* Intravoxel Incoherent Motion MRI; *DSC rCBV* Dynamic Susceptibility Contrast relative Cerebral Blood Volume; *ADC* Apparent Diffusion Coefficient

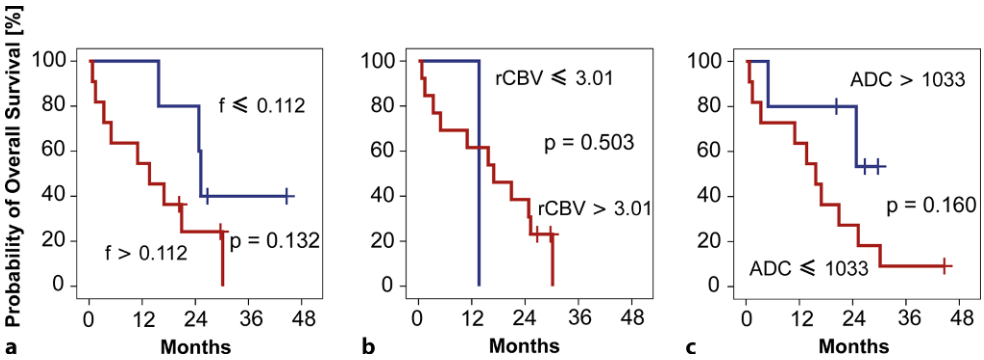

Fig. 4 Kaplan–Meier estimates of overall survival in the subset of patients with high-grades gliomas, according to **a** IVIM f threshold of 0.112 ($p = 0.132$), **b** DSC rCBV threshold of 3.01 ($p = 0.503$), and **c** ADC threshold of 1033 × 10^{-6} mm^2/s ($p = 0.160$). Crosses represent censored data. *IVIM* Intravoxel Incoherent Motion MRI; *DSC rCBV* Dynamic Susceptibility Contrast relative Cerebral Blood Volume; *ADC* Apparent Diffusion Coefficient

Perfusion images reconstruction

IVIM reconstruction

IVIM perfusion fraction maps were obtained voxel by voxel, in two steps, as previously described [10]: first, a mono-exponential decay model for values of b > 200 s/mm^2 was fitted, obtaining the diffusion coefficient D, which was then kept fix for the second step to obtain the perfusion fraction f and the pseudo-diffusion coefficient D*, by fitting the full IVIM biexponential signal equation model, using the nonlinear least squares Levenberg–Marquardt fitting algorithm [19, 20], implemented within Matlab version 2009b (MathWorks, Natick, MA, USA).

DSC rCBV calculation

Leakage corrected CBV maps were computed using the Boxerman-Weiskoff correction [21] as implemented in the DSCoMan plugin [22] for ImageJ version 1.48 [23], using a region of interest which was placed in the vicinity of an identified artery on the selected axial slice and which defined the arterial input function. Due to artifacts, rCBV calculation was not possible in three cases.

Regions of interest

Multiple regions of interests (ROI; at least four) were placed in the region of the tumor with maximal perfusion on the IVIM f maps, as well as on the DSC CBV. The largest result was then kept. For DSC, a region in the contralateral white matter was selected to permit normalization and obtain rCBV. Similarly, multiple ROIs were drawn in the region of the tumor with minimal ADC, and the lowest result was kept. Cystic, hemorrhagic, necrotic areas, as well as larger vessels were carefully avoided as much as possible. Mean ROI size was 322 ± 187 mm^2 for IVIM f, 184 ± 105 mm^2 for DSC CBV, and 256 ± 145 mm^2 for ADC. For simplicity, in the results section, f will refer to maximal f, rCBV will refer to maximal rCBV, and ADC will refer to minimal ADC.

Statistical analysis

Statistical analysis was performed using SPSS version 22.0 (IBM, Armonk, NY, USA) and Excel for Mac, version 14.1.0 (Microsoft, Redmond, Washington; USA). The endpoint of the study was minimal survival, which was defined as the time in days from the date of initial imaging to death or, for living patients, from imaging to

Tab. 3 2-Year survival (n = 22) characteristics. Data are means ± standard deviation. *IVIM* Intravoxel Incoherent Motion MRI; *DSC rCBV* Dynamic Susceptibility Contrast relative Cerebral Blood Volume; *ADC* Apparent Diffusion Coefficient

Variable	Dead	*Alive*	*P-value*
Total	9	13	–
High grade	9	6	–
Low grade	0	7	–
Age (years)	64.2 ± 10.6	42.6 ± 18.0	0.002
IVIM f (unitless)	0.137 ± 0.024	0.096 ± 0.032	0.011
DSC rCBV (unitless)	6.5 ± 2.8	3.9 ± 2.4	0.017
ADC (10^{-6} mm^2/s)	825 ± 177	1244 ± 403	0.002

Tab. 4 Area under the receiver operating characteristic curve, with optimal threshold, sensitivity and specificity for IVIM f, DSC rCBV, and ADC. *IVIM* Intravoxel Incoherent Motion MRI; *DSC rCBV* Dynamic Susceptibility Contrast relative Cerebral Blood Volume; *ADC* Apparent Diffusion Coefficient

	AUC	Threshold	Sensitivity	Specificity
IVIM f (unitless)	0.843	0.112	0.889	0.833
DSC rCBV (unitless)	0.759	3.01	0.889	0.517
ADC (10^{-6} mm^2/s)	0.861	1033	0.889	0.750

Tab. 5 2-Year survival characteristics, for the high-grades (n = 15) gliomas. Data are means ± standard deviation. *IVIM* Intravoxel Incoherent Motion MRI; *DSC rCBV* Dynamic Susceptibility Contrast relative Cerebral Blood Volume; *ADC* Apparent Diffusion Coefficient

Variable	Dead	Alive	*P*-value
Total	9	7	
Grade IV	8	4	–
Grade III	1	3	–
Age	64.2 ± 10.6	49.6 ± 18.0	0.058
IVIM f (unitless)	0.137 ± 0.024	0.112 ± 0.039	0.102
DSC rCBV (unitless)	6.56 ± 2.80	6.03 ± 1.90	0.342
ADC (10^{-6} mm^2/s)	825 ± 177	1083 ± 417	0.099

the last documented day alive. Means ± standard deviation of IVIM f, rCBV, and ADC were assessed in the subgroup of patients where either death or a minimum of 2 years survival was documented. Student t tests assuming unequal variances were used to reject the null hypothesis of equal means of f, rCBV, and ADC in the dead and alive population at 2 years. Correlation coefficient between f, rCBV, and ADC and documented minimal survival was calculated. The area under the receiver operating characteristic curve was used to compare the 2-year prognostic accuracy of f, rCBV, and ADC. A threshold with maximal specificity and sensitivity for f, rCBV, and ADC was obtained by choosing the upper left corner of the receiver operating characteristic curve. Overall survival and progression-free survival were analyzed by the Kaplan–Meier method, using two-sided log-rank statistics. Finally, means ± standard deviation at 2 years survival, as well as Kaplan–Meier survival curves were obtained in the subset of patients with high-grades gliomas. Statistical significance was set at $p < 0.05$.

Results

Death or survival for at least 2 years after imaging could be documented in 22/27 patients. f was 0.137 ± 0.024 in the group of patients who died, and 0.096 ± 0.032 ($p < 0.05$) in the group of patients who survived at least 2 years. In those same two groups, rCBV was 6.5 ± 2.8 and 3.9 ± 2.4 ($p < 0.05$), and ADC was 825 ± 177 × 10^{-6} mm^2/s and 1244 ± 403 × 10^{-6} mm^2/s ($p < 0.05$; Tab. 3). The correlation c was slightly better between survival and f (c = –0.64), and between survival and (inverted) ADC (c = –0.65), compared to between survival and rCBV (c = –0.50; Fig. 1). The area under the receiver operating characteristic (ROC) curve for the f, rCBV, and ADC was 0.84, 076, and 0.86, respectively (Fig. 2 and Tab. 4). The cutoff values of 0.112 for f, 3.01 for rCBV, and 1033 × 10^{-6} mm^2/s for ADC led to identical sensitivity of 0.889 for the 2 year survival prognosis, but better specificity for f (0.833) and ADC (0.750) compared to rCBV (0.517; Tab. 4). The Kaplan–Meier survival curves using those three thresholds were statistically significant (Fig. 3), with a log-rank test of $p = 0.001$, $p = 0.028$, and $p = 0.002$, respectively. In the subgroup of high-grades gliomas, the differences in means and the log-rank test for

overall survival did not reach statistical significance for all three variables (Tab. 5 and Fig. 4), but were smaller for f (p = 0.102 and, respectively, p = 0.132) and ADC (0.099 and p = 0.160) than for rCBV (0.342 and p = 0.503).

Discussion

This report demonstrates that maximal IVIM perfusion fraction f, similarly to maximal DSC relative blood volume and minimal ADC, is prognostic for survival in patients with gliomas. Diagnostic accuracy, as measured as the area under the receiver operating characteristic curve, was better for IVIM f and ADC compared to DSC rCBV. Interestingly, although not reaching statistical significance, a trend toward a similar prognostic value in high-grades gliomas was also observed.

There is to our knowledge no published study correlating IVIM perfusion fraction f with survival in gliomas. Concerning ADC and rCBV, our results are in accordance with several previously published studies. Several studies have shown that low ADC was associated with a decrease in survival in gliomas [24–28]. Hilario et al. [29] found that ADC values had a better correlation with overall survival than relative CBV values [29]. Law et al. demonstrated that DSC rCBV could be used to predict median time to progression in patients with gliomas, independent of pathology, but found that rCBV was not significantly associated with overall survival [6]. Zacharaki et al. [30] reported that ROI-based characteristics in rCBV were not among the top-ranked variables for predicting survival in high-grade gliomas. Mills et al. [31] found that CBV relates directly to histologic grade but provides no independent prognostic information over and above that provided by grade. On the other hand, Hilario et al. [7] found in a multivariate analysis that patient age, rCBV, and ADC were associated with survival, independent of pathology.

IVIM perfusion imaging has many theoretical advantages over currently widely used DSC. It does not require contrast media, which is very valuable in patients with contraindication to gadolinium-chelate contrast injection, such as renal insufficiency [32], but also considering growing concerns of gadolinium deposition in brains of patients with normal renal function [33–35]. Also, it can be repeated in case of technical problems such as patient motion. Furthermore, it is intrinsically quantitative, and because both excitation and readout happen in the same slice, it provides essentially local perfusion information (i. e., does not require knowledge of the arterial input function to be quantitative). Finally, it permits the acquisition of perfusion and diffusion information in a time-efficient manner and in a single sequence.

The quality of brain perfusion imaging with IVIM is challenged by a variety of factors, such as low cerebral perfusion fraction in the brain; requirement of high signal to noise ratio for appropriate biexponential fitting [36]; cerebrospinal fluid pulsations [37]; dependence on the cardiac cycle [9]; and susceptibility artifacts, in particular at the base of the brain. In addition, the exact relationship between IVIM perfusion parameters and standard perfusion parameters [38] might deserve further detailed investigation [39].

This study suffers several limitations. It is monocentric. The cohort studied is relatively small. Various variables known to correlate with prognosis, such as age, treatment, and histo-biomolecular markers, were not taken into consideration. Heterogeneity in provided treatment might have been a source of bias in this study. Only 5/11 of the low-grade tumors were histopathologically proven, while the diagnosis of the other 6/11 was based on radiological criteria and evolution.

Conclusion

In a relatively small cohort of patients, this report demonstrates that an increase in maximal IVIM f, similar to an increase in maximal rCBV and a decrease in minimal ADC, is associated with a decrease in survival in patients with brain gliomas. Maximal IVIM f and minimal ADC performed relatively similarly in predicting survival, and both slightly outperformed maximal rCBV.

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Compliance with ethical guidelines

Conflict of interest C. Federau, M. Cerny, M. Roux, P.J. Mosimann, P. Maeder, Reto Meuli, and M. Wintermark state that there are no conflicts of interest.

All studies on humans described in the present manuscript were carried out with the approval of the responsible ethics committee and in accordance with national law and the Helsinki Declaration of 1975 (in its current, revised form) Informed consent was waived

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