

ORIGINAL

Correlation of 3D Arterial Spin Labeling and Multi-Parametric Dynamic Susceptibility Contrast Perfusion MRI in Brain Tumors

Delgerdalai Khashbat¹, MD ; Takashi Abe¹, MD ; Mungunbagana Ganbold¹, MD ; Seiji Iwamoto¹, MD ; Naoto Uyama¹, MD ; Saho Irahara¹, MD ; Youichi Otomi¹, MD, PhD ; Masafumi Harada¹, MD, PhD ; Teruyoshi Kageji², MD, PhD ; and Shinji Nagahiro², MD, PhD

¹Department of Radiology and Radiation Oncology, ²Department of Neurosurgery, Institute of Biomedical Sciences, Tokushima University Graduate School

Abstract : Purpose : Arterial spin labeling (ASL) is an alternative method to Dynamic susceptibility contrast (DSC) perfusion MRI for brain tumors. However, ASL cerebral blood flow (CBF) can be easily affected by transit time. DSC MRI derived time to maximum of the residue function (Tmax) is possible to assess the transit time on ASL. **Methods :** Thirty patients with brain tumors were studied using ASL and DSC MRI. The relative cerebral blood flow (rCBF), relative cerebral blood volume (rCBV), Tmax, and mean transit time (MTT) were obtained from DSC MRI. The ratios of the parameters were analyzed. **Results :** ASL CBF ratio correlated with the DSC rCBF ratio ($r=0.78, p<0.001$) and rCBV ratio ($r=0.74, p<0.001$). There was a moderate correlation between ASL CBF ratio and Tmax ratio ($r=-0.43, p<0.05$) in brain tumors. **Conclusions :** ASL CBF strongly correlated with DSC rCBF and rCBV. In addition, a negative correlation was found between ASL CBF and Tmax in brain tumors, indicating that these parameters would be affected by transit time. This may explain why ASL CBF is different from DSC rCBF and rCBV. The decreased DSC Tmax value may suggest high vascularity in a tumor. **J. Med. Invest. 63 : 175-181, August, 2016**

Keywords : magnetic resonance imaging, arterial spin labeling, dynamic susceptibility contrast perfusion, time to maximum, brain tumor

INTRODUCTION

Dynamic susceptibility contrast (DSC) perfusion magnetic resonance imaging (MRI) is a frequently used standard technique to assess cerebral perfusion. It relies on the first passage of contrast agent through the brain tissue (1) and allows estimation of multiple perfusion parameters, such as relative cerebral blood volume (rCBV), relative cerebral blood flow (rCBF), mean transit time (MTT), and time to maximum (Tmax) of the residue function with deconvolution. Of these DSC parameters, rCBV and rCBF are commonly used for brain tumor perfusion, including grading (2, 3), diagnosing (3-5), monitoring treatment (6), differentiating tumor recurrence from radiation necrosis (1, 7) etc.

Meanwhile, several studies have shown that the Tmax parameter, which is the time to maximum of the residue function after deconvolution, was reliable in evaluating cerebral hemodynamics (8, 9). It represents the delay in contrast agent arrival between the arterial input function (AIF) and the brain tissue (9, 10).

As an alternative to DSC MRI, arterial spin labeling (ASL) has been considered as a comparable perfusion technique for evaluating brain tumor angiogenesis (11-13). ASL is non-invasive and uses magnetically labeled proton in the arterial blood water as an endogenous tracer to quantify CBF (14). ASL perfusion imaging has been continuously improving with three-dimensional (3D) imaging and background suppression, higher signal-to-noise ratio (SNR), and low artifacts (15, 16). It would be a desirable perfusion method without the use of exogenous contrast agent ; however,

the utility of ASL has been challenging in clinical practice due to transit time effect (17, 18).

In stroke assessment in which the hypoperfused area is identified, good correlations have been shown between ASL and DSC MRI parameters, including Tmax and MTT (8, 19). It has also shown that DSC Tmax could assess the effect transit time on ASL perfusion (19). The purpose of this study was to compare ASL CBF with DSC MRI parameters including new parameter Tmax, and to assess the influence of transit time in ASL for brain tumors.

MATERIALS AND METHODS

Patients

Patients with brain tumor (n=30 ; 11 women, 19 men ; mean age \pm SD, 58.26 \pm 14.02 years) prospectively underwent MRI examinations, including both ASL and DSC at the Tokushima University Hospital between December 2009 and February 2012. The inclusion criteria were as follows ; (1) the patient was histopathologically confirmed, (2) the patient was examined both 3D ASL and DSC MRI at the same machine, (3) the patient has undergone MRI examinations prior to the treatment.

The patients who were diagnosed with high-grade gliomas (HGG) (n=21), primary central nervous system lymphomas (PCNSL) (n=4), brain metastasis (n=4), and hemangioblastoma (n=1) were included in this study.

Gliomas were graded according to the 2007 World Health Organization (WHO) classification. A total of 14 patients had glioblastoma (GBM) (WHO IV), 4 had anaplastic astrocytoma (WHO III), 2 had anaplastic oligoastrocytoma (WHO III), and 1 had anaplastic oligodendroglioma (WHO III). Among four patients with brain metastasis, the primary sites were the lungs, bladder, ovaries, and colon.

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Address correspondence and reprint requests to Delgerdalai Khashbat, MD, Department of Radiology and Radiation Oncology, Institute of Biomedical Sciences, Tokushima University Graduate School 3-18-15 Kuramoto-cho, Tokushima City, Tokushima 770-8509, Japan and Fax : +81-88-6337174.

In our study, we excluded non enhancing tumors or low-grade gliomas for the following reasons ; (1) The regions of the interest (ROI)'s were only placed on the contrast enhancement lesions of the tumors, (2) There were a few number of low-grade gliomas which met the inclusion criteria during the study period.

This study was approved by the local institutional ethics committee and written informed consent was obtained from all patients.

MRI

MRI was performed on a 3-T scanner (Discovery 750, GE Healthcare, WI) using a standard 8-channel head coil. All MRI examinations were performed with DSC MRI, ASL, and conventional sequences, including post contrast enhanced T₁-weighted images (CE-T1WI), T2WI, FLAIR, T1WI, and DWI.

ASL was performed by pseudo-continuous labeling, background suppression, and a stack of spiral 3D fast-spin echo imaging sequences. ASL was acquired based on the following parameters : 512 sampling points on eight spirals, field of view (FOV) 24 cm, repetition time (TR) 4632 ms, echo time (TE) 10.5 ms, receiver band with 62.50 kHz, reconstructed matrix size 64×64, number of excitation (NEX) 2, labeling duration 1525 ms, post-labeling delay 1525 ms, slice thickness 4 mm, number of slices 36, and acquisition time of 3 : 15 min. Inplane resolution was 3.6×3.6 mm.

The rCBV, rCBF, Tmax, and MTT were obtained by DSC MRI, which was performed using gradient-echo echo-planar imaging (GE-EPI), FOV 24 cm, TR 1990 ms, TE 30 ms, reconstructed matrix size 128×128, flip angle 90 degrees, ASSET factor 2, NEX 1, slice thickness 4 mm, number of slices 20, and acquisition time 100 s (50 phases).

A standard single dose of 0.1 mmol/kg body weight of a Gd-based contrast agent (Magnevist, Bayer HealthCare, Berlin, Germany) with saline (20 ml) was injected intravenously at a rate of 2.5 ml/s by using a power injector.

Data analysis

The DSC MRI and ASL images were transferred to a workstation with commercially available software (Advantage workstation AW 4.6, GE Healthcare Milwaukee, WI). The rCBF, rCBV, Tmax, and MTT that were derived from DSC MRI were processed using Brainstat AIF post-processing software (GE Healthcare, Milwaukee, WI). AIF pixels were generated by using automatic vessel detection and motion correction was enabled prior to post-processing. The residue function was determined by using deconvolution with singular value decomposition (SVD) with a block circulant matrix (20).

The ROI placement of the present study is shown in Fig. 1. ROIs were defined by two neuroradiologists, based on maximal signal enhancement of the tumor lesions on CE-T1WI and by avoiding necrotic and non-tumoral areas. If a tumor had rim enhancement on CE-T1WI, ROIs were placed only on the contrast-enhancing rim for measurement of the parameters. All ROIs were copied to maps of ASL CBF, DSC rCBV, rCBF, Tmax, and MTT parameters. In addition, another circular ROI, measuring approximately 1 cm in diameter, was placed on the unaffected contralateral white matter (WM) to obtain normalized ratios of the perfusion parameters. The ratio of all parameters was estimated by dividing the mean perfusion value of the tumor by the mean perfusion value of WM ($mean\ perfusion\ value_{tumor}/mean\ perfusion\ value_{wm}$).

Statistical analysis

All statistical analyses were performed using SPSS Ver. 20 (IBM, Armonk, NY, USA). Pearson's correlation and Linear regression were used to assess the relationships of ASL with each of the DSC MRI parameters. Pearson's correlation test was two-tailed and a p value of less than 0.05 was considered to be significant. Data were presented as mean±standard deviations (SD).

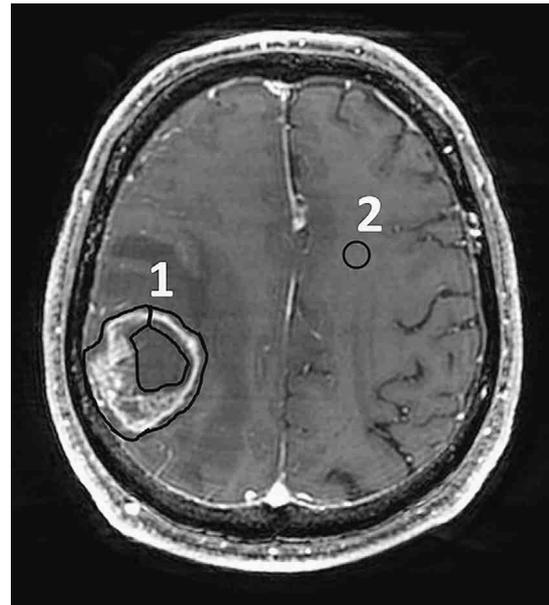


Fig. 1. Contrast enhanced T₁-weighted image (CE-T1WI) of a glioblastoma. (1) Tumor region of interest (ROI)s were placed on the CE-T1WI and then copied to all corresponding perfusion maps. (2) Normal contralateral white matter (WM) was used as reference to obtain ratios of the perfusion parameters.

RESULTS

Fig. 2 shows the relationships of ASL with all DSC MRI parameters in brain tumors. ASL CBF ratio had the highest significant correlation with DSC rCBF ratio ($r=0.78, p<0.001$). There was a strong correlation between ASL CBF ratio and DSC rCBV ratio in brain tumors ($r=0.74, p<0.001$). Interestingly, ASL CBF ratio was negatively correlated with DSC Tmax ratio ($r=-0.43, p<0.05$), but it was not correlated with DSC MTT ratio ($r=-0.30, p=0.126$). The correlations between ASL CBF and the DSC MRI parameters in brain tumors are shown in the Table 1. There were strong correlations between DSC rCBF ratio and rCBV ratio ($r=0.86, p<0.001$) and between Tmax ratio and MTT ratio ($r=0.76, p<0.001$). Tmax ratio did not show significant correlation with rCBF ratio or rCBV ratio in the present study.

The mean ratios of all tumors were 2.71 ± 1.63 for ASL CBF, 2.27 ± 1.06 for DSC rCBF, 2.91 ± 1.46 for rCBV, 1.31 ± 0.74 for Tmax, and 1.54 ± 0.96 for MTT. The mean values of the parameters for the tumor groups are shown in Table 2. Compared with PCNSL and metastatic brain tumors, HGG showed higher values of ASL CBF, DSC rCBF, and rCBV. The ratio of the metastasis was higher than that of PCNSL for ASL CBF, DSC rCBF and rCBV. Tmax demonstrated a higher value for HGG than for PCNSL and metastasis.

The only one hemangioblastoma demonstrated the highest perfusion values in ASL CBF, DSC rCBF, and rCBV (Table 2). For Tmax, hemangioblastoma demonstrated the lowest value compared with other tumors. Among the perfusion parameters, MTT was similar in all tumor types.

DISCUSSION

In the past, there have been several brain tumor studies that compared ASL CBF with DSC rCBF (11, 21, 22) or with both DSC rCBF and rCBV parameters (12, 13, 23, 24). The present study included comparisons of ASL CBF with additional DSC MRI parameters, including Tmax and MTT.

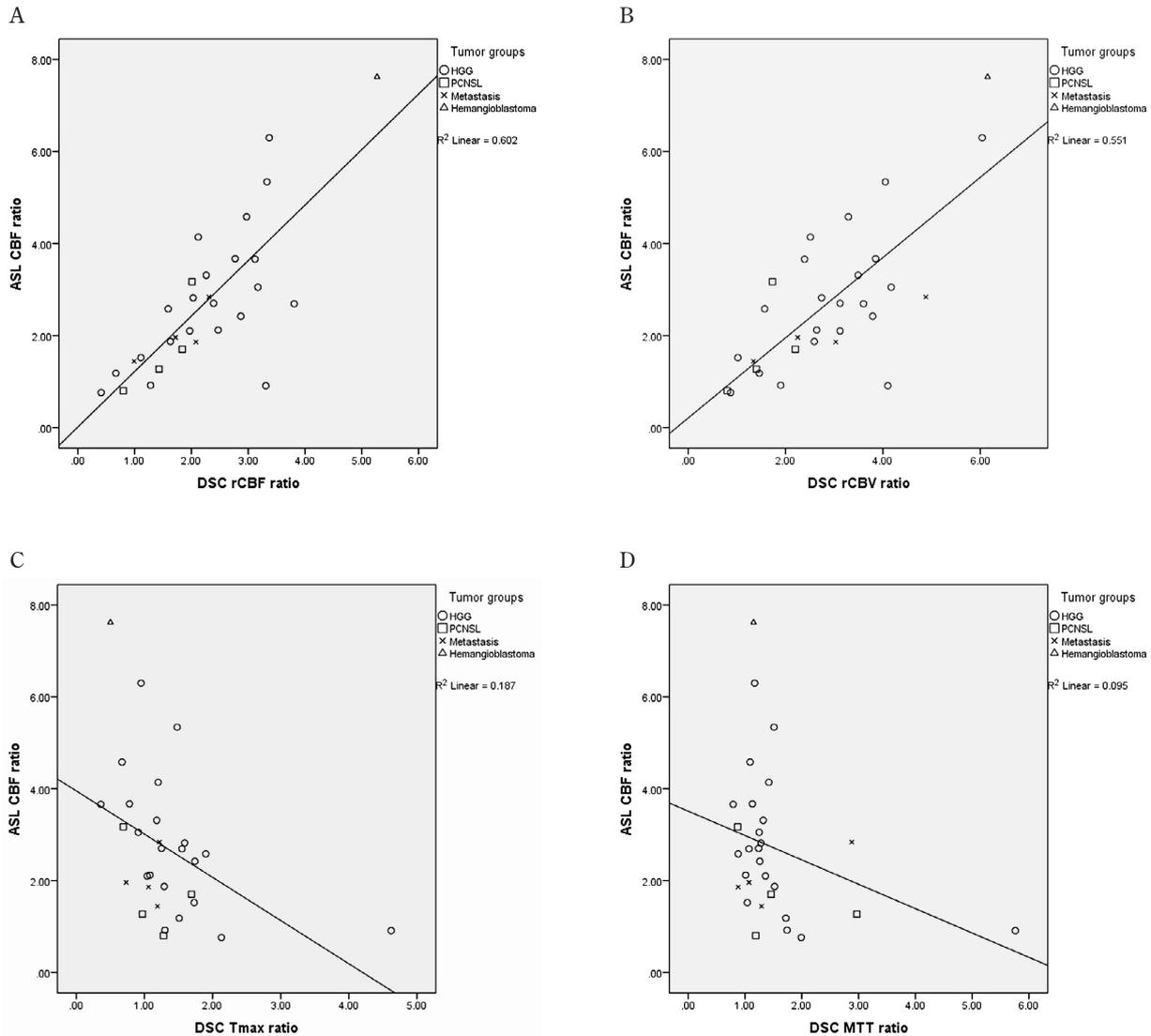


Fig. 2. The graphs show the correlations between ASL CBF and each of the DSC MRI parameters in brain tumors (n=30). (A) ASL CBF ratio and DSC rCBF ratio, (B) ASL CBF ratio and DSC rCBV ratio, (C) ASL CBF ratio and DSC Tmax ratio, and (D) ASL CBF ratio and DSC MTT ratio. ASL, arterial spin labeling ; CBF, cerebral blood flow ; DSC, dynamic susceptibility contrast ; rCBF, relative cerebral blood flow ; rCBV, relative cerebral blood volume ; Tmax, time to maximum ; MTT, mean transit time.

Table 1. Correlation analysis between ASL and DSC MRI parameters for brain tumors (n=30)

	ASL CBF ratio	DSC rCBF ratio	DSC rCBV ratio	DSC Tmax ratio	DSC MTT ratio
ASL CBF ratio	-				
DSC rCBF ratio	0.78**	-			
DSC rCBV ratio	0.74**	0.86**	-		
DSC Tmax ratio	-0.43*	-0.10	-0.07	-	
DSC MTT ratio	-0.30	0.01	0.12	0.76**	-

Pearson’s correlation (two-tailed). *Correlation significant, $p < 0.05$; **correlation significant, $p < 0.01$. ASL, arterial spin labeling ; CBF, cerebral blood flow ; DSC, dynamic susceptibility contrast ; MRI, magnetic resonance imaging ; rCBF, relative cerebral blood flow ; rCBV, relative cerebral blood volume ; Tmax, time to maximum ; MTT, mean transit time.

Based on our results, ASL CBF could be an equally efficient parameter to DSC MRI for the evaluation of brain tumor perfusion. Particularly, DSC rCBF had the highest correlation with ASL CBF in brain tumors, probably because both depend on blood flow rate. The higher ASL CBF ratio compared with the DSC rCBF ratio in the study could be explained by ASL underestimation of WM with

a long transit time (11, 25).

In addition, the present study showed a moderate negative correlation between ASL CBF and DSC Tmax in brain tumors (Fig. 2C). This finding suggests that ASL CBF and DSC Tmax could be influenced by some similar factors. ASL perfusion is sensitive to the effects of transit time, leading to inaccurate ASL CBF estimation

Table 2. Comparison of perfusion imaging parameters among the different types of brain tumors

Ratio	All tumors (n=30)	HGG (n=21)	PCNSL (n=4)	Metastasis (n=4)	Hemangioblastoma (n=1)
ASL CBF	2.71 (1.63)	2.79 (1.46)	1.73 (1.02)	2.10 (0.59)	7.62
DSC rCBF	2.27 (1.06)	2.31 (0.94)	1.51 (0.54)	2.02 (0.96)	5.27
DSC rCBV	2.91 (1.46)	2.96 (1.22)	1.53 (0.59)	2.87 (1.58)	6.14
DSC Tmax	1.31 (0.74)	1.44 (0.84)	1.15 (0.42)	1.04 (0.22)	0.50
DSC MTT	1.54 (0.96)	1.54 (1.03)	1.62 (0.93)	1.53 (0.91)	1.54

The values shown are mean (standard deviation). ASL, arterial spin labeling ; CBF, cerebral blood flow ; DSC, dynamic susceptibility contrast ; rCBF, relative cerebral blood flow ; rCBV, relative cerebral blood volume ; Tmax, time to maximum ; MTT, mean transit time ; HGG, high grade glioma ; PCNSL, primary central nervous lymphoma.

(15, 16). Similarly, Tmax parameter derived from DSC could be strongly affected by tracer arrival delay, unlike in deconvolution methods (9, 10). Therefore, DSC Tmax has been considered a normalized bolus arrival time by deconvolution (26).

As known that DSC rCBF, rCBV and MTT are related parameters to creating each other as the theory of central volume ($MTT = CBV/CBF$ ratio) (20). DSC rCBF, rCBV and MTT mostly depend on tracer dispersion, while Tmax particularly remains on tracer arrival delay (27, 28). Besides, we used a delay-insensitive deconvolution analysis (20) to compensate the tracer arrival differences. This method is applied to perform the delay-insensitive estimation of DSC CBF and MTT. From these findings, ASL CBF and DSC Tmax are both sensitive to tracer arrival differences, unlike other DSC perfusion parameters.

In the present analysis, we did not find a significant correlation between ASL CBF and DSC MTT (Fig. 2D). According to the previous works, DSC MTT is different from transit time in ASL imaging. ASL transit time is defined as the duration time for the labeled blood between labeling region and brain tissue, whereas DSC MTT represents the mean time for contrast agent to traverse from the arterial to the venous end (19, 29). It noted that transit time in ASL is conceptually similar with DSC Tmax. To the best of

our knowledge, this report is the first study to demonstrate relationship between ASL CBF and DSC Tmax in brain tumors, indicating the sensitivity of transit time on ASL in brain tumors.

The vascularity of malignant tumors are usually expanded, tortuous and leaky, containing the variable blood transit times (30). The labeled blood reaches the tumor regions within different times due to heterogeneous blood supply. ASL CBF could be underestimated by transit delay of labeled blood in the core of the tumors, where arterial supply is delayed compared with the outer regions (30, 31). Alternatively, the peripheral or hypervascularized regions of the tumor probably present short arrival time for the labeled blood (5).

Moreover, the relationship of ASL CBF with DSC Tmax in brain tumors may be accounted for by tumor vascularization. It has been said that ASL was very sensitive in detecting hypervascularity by reflecting microvascular density (12, 32, 33). The highly vascular malignant tumors, such as HGG, metastasis, hemangioblastoma, and PCNSL that were included in this study demonstrated high perfusion values. In the present study, the hyperperfused tumors often showed higher perfusion values and lower Tmax values (Fig. 3-6). Further, the most hypervascular tumor, hemangioblastoma, demonstrated the highest ASL CBF value and the lowest DSC Tmax

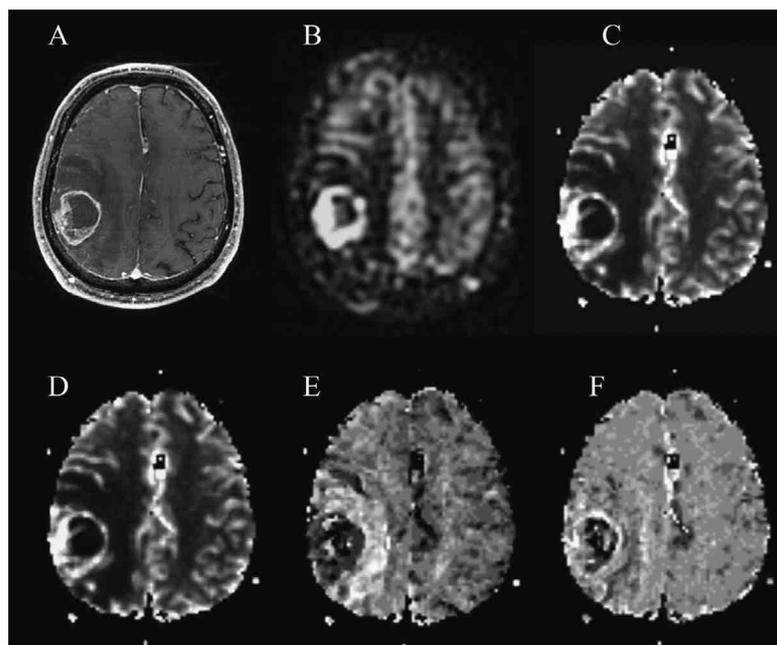


Fig. 3. MRI images of a patient with glioblastoma in the right temporal lobe with peritumoral edema. The tumor shows contrast rim-enhancement on (A) CE-T1WI and hyperperfusion on the (B) ASL CBF map, (C) DSC rCBF map, and (D) DSC rCBV map. (E) Tmax map demonstrates a corresponding perfusion defect in the tumor lesion that disappears on the (F) DSC MTT map. MRI, magnetic resonance imaging ; CE-T1WI, contrast enhanced T₁ weighted image ; ASL, arterial spin labeling ; CBF, cerebral blood flow ; DSC, dynamic susceptibility contrast ; rCBF, relative cerebral blood flow ; rCBV, relative cerebral blood volume ; Tmax, time to maximum ; MTT, mean transit time.

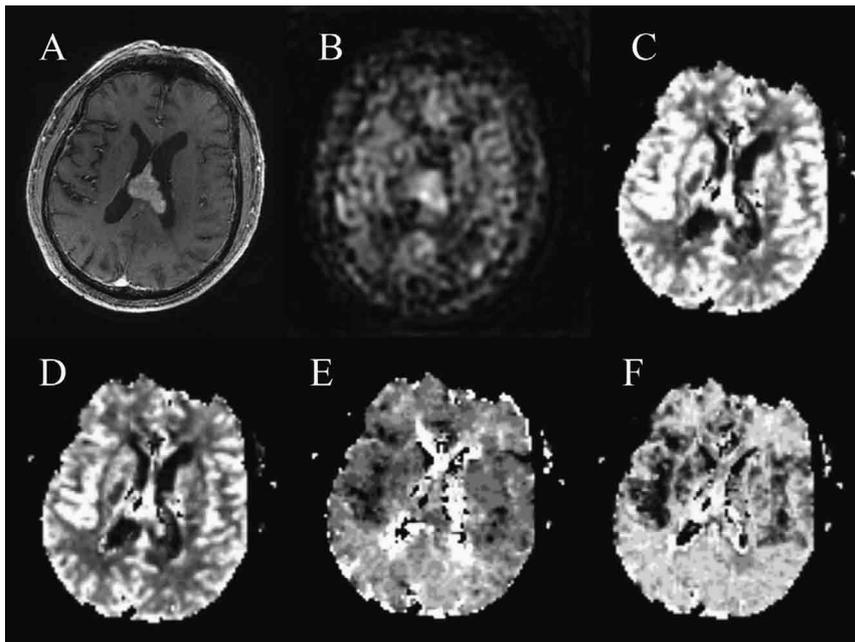


Fig. 4. MRI images of a patient with primary CNS lymphoma. The tumor demonstrate contrast-enhancement on (A) CE-T1WI and hyperperfusion on the (B) ASL CBF map, (C) DSC rCBF map, and (D) DSC rCBV map. The tumor shows a slightly decreased perfusion signal on the (E) DSC Tmax map and but not on the (F) DSC MTT map. MRI, magnetic resonance imaging ; CE-T1WI, contrast enhanced T₁ weighted image ; ASL, arterial spin labeling ; CBF, cerebral blood flow ; DSC, dynamic susceptibility contrast ; rCBF, relative cerebral blood flow ; rCBV, relative cerebral blood volume ; Tmax, time to maximum ; MTT, mean transit time.

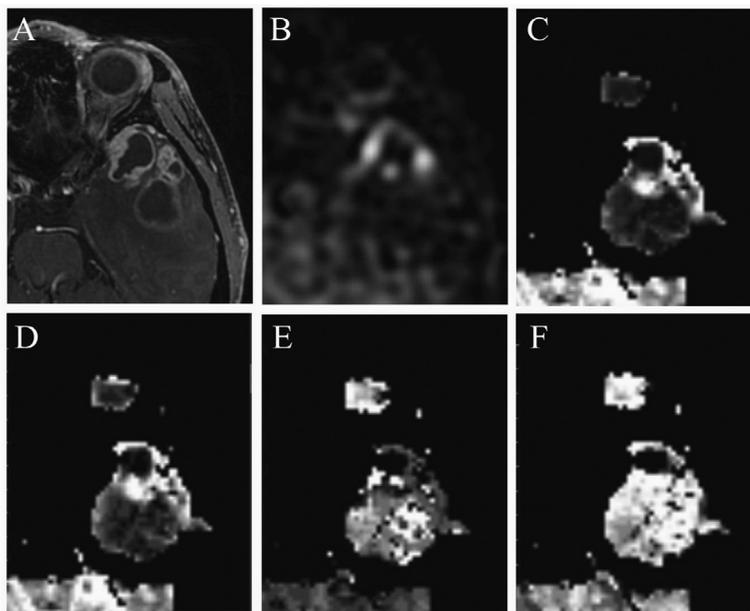


Fig. 5. MRI images of a patient with brain metastasis. The tumor shows contrast-enhancement on (A) CE-T1WI and hyperperfusion on the (B) ASL CBF map, (C) DSC rCBF map, and (D) DSC rCBV map. The tumor lesion shows a decreased perfusion signal on the (E) DSC Tmax map and, an increased perfusion signal on the (F) MTT map. MRI, magnetic resonance imaging ; CE-T1WI, contrast enhanced T₁ weighted image ; ASL, arterial spin labeling ; CBF, cerebral blood flow ; DSC, dynamic susceptibility contrast ; rCBF, relative cerebral blood flow ; rCBV, relative cerebral blood volume ; Tmax, time to maximum ; MTT, mean transit time.

value compared with those of other tumor groups (Table 2).

In this study, we did not focus on comparing perfusion parameters by tumor histology because of the small number of tumor types. Nevertheless, the results of highest perfusion values in HGG and lowest perfusion values in PCNSL are concordant with previous studies (3-5, 33). The DSC Tmax value decreased in trend from

HGG to PCNSL to metastasis. However, some grade III glioma, such as anaplastic oligodendroglioma, anaplastic oligoastrocytoma showed very high Tmax values compared with other HGG. Furthermore, the number of PCNSL was very small and relatively consistent in Tmax. The DSC MTT perfusion parameter was constant in all tumor groups.

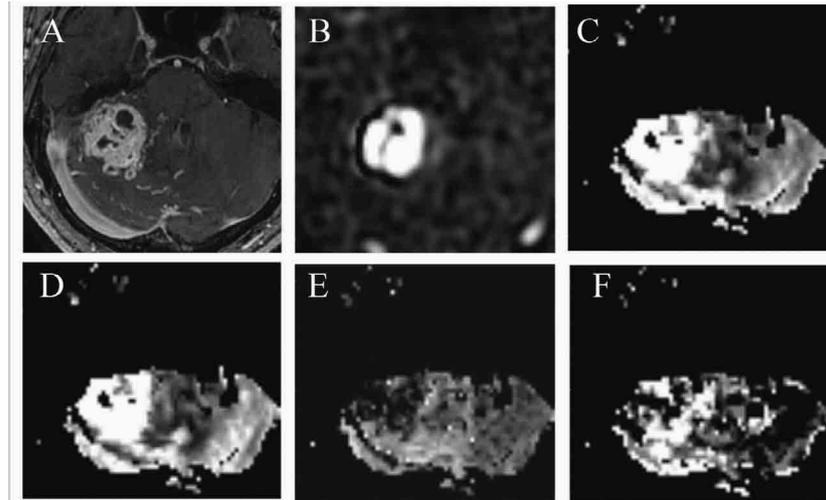


Fig. 6. MRI images of a patient with cerebellar hemangioblastoma. The tumor shows contrast-enhancement on (A) CE-T1WI. (B) ASL CBF, (C) DSC rCBF and (D) DSC rCBV maps demonstrate markedly a hypervascularity in the tumor. The tumor can be detected as a lesion with low perfusion signal on the corresponding (E) DSC Tmax map. (F) However, the tumor was unclearly demonstrated on the MTT maps compared with other perfusion maps. MRI, magnetic resonance imaging; CE-T1WI, contrast enhanced T₁ weighted image; ASL, arterial spin labeling; CBF, cerebral blood flow; DSC, dynamic susceptibility contrast; rCBF, relative cerebral blood flow; rCBV, relative cerebral blood volume; Tmax, time to maximum; MTT, mean transit time.

ASL may be an alternative method to DSC MRI for cerebral perfusion. ASL is completely non-contrast and is repeatable, making it a suitable option to evaluate brain tumor progression and treatment response, especially for patients with renal insufficiency. The disadvantages of ASL, compared with DSC MRI, are transit time sensitivity, lower SNR and longer acquisition time. However, ASL perfusion imaging was recently improved with higher SNR, lower artifacts, and 3D imaging with background suppression (15, 16).

It would be interesting to study DSC Tmax in brain tumors. DSC Tmax is a novel and complex parameter discussed in the literature (9, 10). As from our data, shorter value of DSC Tmax is often related with hyperperfused tumors on ASL imaging. DSC Tmax is practically available for free and heterogeneously different from other DSC MRI parameters; therefore, it may contain microvascular information on brain tumors.

There were some limitations in the present study, such as the few tumor types that were included. The only one hemangioblastoma included in the current study that is insufficient to represent the tumor group. In the future, larger studies would be needed to validate the results of our study, especially the correlation of ASL CBF with DSC Tmax and the significance of DSC Tmax in brain tumors. Because DSC Tmax is a complex parameter, it could be affected by many factors (9). The physiologic and experimental mechanisms of the parameter should be defined well in future studies. In this work, we did not use a pre-dose of contrast agent or leakage correction to compensate T₁ leakage effect of Gd when obtains DSC MRI parameters, which is possible to affect the estimation accuracy (1).

CONCLUSIONS

The strong correlations were between ASL CBF and DSC rCBF, ASL CBF and DSC rCBV in brain tumors, which are consistent with previous studies. In addition, a negative correlation was found between ASL CBF and DSC Tmax in brain tumors, suggesting that ASL CBF and DSC Tmax parameters would be affected by transit time, which is one of the reasons why ASL CBF is different from DSC rCBF and DSC rCBV. The decreased DSC Tmax value may

suggest high vascularity in a tumor.

CONFLICT OF INTEREST

none

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