

MAJOR PAPER

Benefit of 3T Diffusion-weighted Imaging in Comparison to Contrast-enhanced MR Imaging for the Evaluation of Disseminated Lesions in Primary Malignant Brain Tumors

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Purpose: We aimed to determine whether 3T diffusion-weighted imaging (DWI) has an additive value relative to contrast-enhanced MR imaging for the detection of disseminated lesions in patients with primary malignant brain tumors.

Methods: We included consecutive 12 patients with nodular disseminated lesions of primary malignant brain tumors that were confirmed by surgery or follow-up MR imaging. All underwent conventional MR imaging, DWI at $b = 1000$ and 3000 s/mm², post-contrast T₁-weighted and 3D gradient-echo imaging at 3T. For the largest lesion per person, two radiologists independently evaluated the presence of additional information on DWI compared with postcontrast MR images using a 4-point scoring system. On DW images, one radiologist measured the lesion-to-brain contrast ratio (LBCR).

Results: Compared with postcontrast studies, radiologists 1 and 2, respectively, assigned more apparent lesion conspicuity in 2 (17%) and 1 (8%) DWI at $b = 1000$ s/mm² and 4 (33%) and 5 (42%) DWI at $b = 3000$ s/mm² studies. For one of them, the mean score was significantly higher for $b = 3000$ s/mm² than $b = 1000$ s/mm² ($P < 0.05$). Interobserver agreement for DWI at $b = 1000$ s/mm² and $b = 3000$ s/mm² was very good ($\kappa = 0.85$; 95% CI, 0.63–1.00) and excellent ($\kappa = 0.93$; 95% CI, 0.78–1.00), respectively. The mean LBCR was significantly higher for DWI at $b = 3000$ s/mm² than DWI at $b = 1000$ s/mm² ($P < 0.01$).

Conclusion: In the detection of disseminated lesions in patients with primary malignant brain tumors, 3T DWI has an additive value relative to contrast-enhanced MR imaging. DWI at $b = 3000$ s/mm² may be more useful than DWI at $b = 1000$ s/mm².

Keywords: *diffusion-weighted imaging, 3T MRI, dissemination, high-b value*

Introduction

Primary malignant brain tumors represented by glioblastoma often develop local recurrence and disseminates throughout the central nervous system. Saito et al.¹ reported that 25% of patients with anaplastic astrocytoma or glioblastoma developed cerebrospinal fluid (CSF) dissemination.

The patients with dissemination at first relapse had significantly shorter survival times than a control group with local recurrence.² The MR imaging and CSF cytology techniques play a role of detecting CSF dissemination. Prompt and accurate diagnosis may have a significant impact on clinical treatment decision making because of poor prognosis of the patients with CSF dissemination. However, CSF cytology has a false negative rate of 40 to 50% in patients with clinically suspected neoplastic meningitis proven at the time of autopsy.³ On the other hand, contrast-enhanced MRI has a $\geq 30\%$ incidence of false-negative results.⁴

Diffusion-weighted MR imaging (DWI) is very useful for the diagnosis of various brain diseases (e.g., acute brain infarction, Creutzfeldt-Jakob disease, encephalitis).^{5–7} High b-value DWI for these diseases has been also reported to be useful.^{8–10} To our knowledge, however, the usefulness of

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Received: July 6, 2016 | Accepted: September 9, 2016

DWI for the detection of disseminated lesions in patients with primary malignant brain tumors has not been investigated.

The purpose of this study was to determine whether 3T DWI including high b-value DWI has an additive value relative to contrast-enhanced MR imaging for the detection of nodular disseminated lesions in patients with primary malignant brain tumors.

Materials and Methods

Subjects

All human studies have been approved by the review board of the Medical Ethical Committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Patient consent was waived due to the retrospective nature of this study. We reviewed and collected the record of having disseminated lesions of primary malignant brain tumors during post-treatment follow up in our MR database between March 2010 and March 2013. We found a total of 34 patients who met the record. The inclusion criteria were 1) patients with nodular disseminated lesions (type Ia, the presence of a mass lesion along the subarachnoid space) based on the classification scheme of Bordignon¹¹ and 2) patients with lesions confirmed by pathology or follow-up MRI. The exclusion criteria were 1) patients with diffuse leptomeningeal (type Ib) and subependymal (type II) disseminated lesions, and very small nodular disseminated lesions that were not able to put a region-of-interest in a lesion and 2) patients with molecular treatment (e.g., bevacizumab) or administration of steroids. Thus, we finally included 12 patients (eight men, four women; age range, 11–80 years old; mean age, 47 years) with disseminated lesions of primary malignant brain tumors in this study. According to the 2007 WHO classification, the malignant tumors included glioblastoma multiforme in five patients, anaplastic oligodendroglioma in two patients, and anaplastic ependymoma, anaplastic astrocytoma, giant cell glioblastoma, gliomatosis cerebri and primitive neuroectodermal tumor in one each.

MR image acquisition

We used 3T MR scanners (Magnetom Trio, Siemens; Achieva 3T, Philips Medical Systems, Best, the Netherlands) and an 8-channel head coil. The imaging sequences in this study included 3-plane scout localizers and axial spin-echo T₁-weighted [TR/TE/number of signals averaged (NSA), 450 ms/10 ms/1; matrix, 320 × 320; section thickness, 5 mm; intersection gap, 1 mm], turbo spin-echo T₂-weighted (TR/TE/NSA, 4060 ms/80 ms/1; turbo factor, 9; matrix, 512 × 512; section thickness, 5 mm; intersection gap, 1 mm), and FLAIR images (TR/TE/NSA/TI, 9000 ms/120 ms/1/2500 ms; turbo factor 15; matrix, 352 × 352; section thickness, 5 mm; intersection gap, 1 mm), DWI at b = 1000 and 3000 s/mm², and postcontrast T₁-weighted and 3D gradient-echo images. The 3D gradient-echo MR imaging studies included 3D turbo field echo (TR/TE/NSA 450 ms/10 ms/1, matrix 320 × 320) and

magnetization-prepared rapid acquisition of gradient echo (TR/TE/TI 1900 ms/4.7 ms/900 ms, matrix 256 × 256) sequences. DWI were acquired with a spin-echo echo-planar imaging sequence (TR/TE/NSA, 3500 ms/63–74 ms/1; matrix, 256 × 256; section thickness, 5 mm; intersection gap, 1 mm; sensitivity encoding factor, 2). The field of view was 23 cm on all MR images. The postcontrast 3D gradient-echo MR images had a section thickness of 1 mm and no intersection gap.

Image Evaluation

Qualitative assessment

The largest disseminated lesion per person was qualitatively and quantitatively assessed. Two radiologists (8 and 25 years of experience in neuroradiology, respectively) independently evaluated the presence of additional information on DWI at b = 1000 or 3000 s/mm² compared with postcontrast T₁-weighted and 3D gradient-echo images. All DW images were analyzed in conjunction with the corresponding postcontrast MR images. All images were assessed on a PACS workstation. The presence of additional information on DW images compared with postcontrast MR images was evaluated with a 4-point scoring system, where 4 = The information about the presence of the lesions was provided only by using DW images, but not by using postcontrast studies, 3 = The conspicuity of the lesions was more apparent for DWI than postcontrast studies, 2 = DW images provided similar conspicuity of the lesions to postcontrast studies, 1 = The information about the presence of the lesions was provided only by using postcontrast studies, but not by using DW images.

Quantitative assessment

On DW images, one radiologist performed region-of-interest measurements of the signal intensity (SI) of nodular disseminated lesions and the adjacent cerebral cortex. The lesion-to-brain contrast ratio (LBCR) was calculated using the following formula: $LBCR = SI_{\text{lesion}}/SI_{\text{brain}}$, where SI_{lesion} and SI_{brain} are the SI of the lesion and adjacent cerebral cortex, respectively.

Statistical Analysis

The statistical significance of differences for the qualitative assessment was determined with the Wilcoxon-signed rank test. Measurement differences for the quantitative assessment were assessed with the paired *t*-test. Differences of *P* < 0.05 were considered significant. The levels of interobserver agreement between radiologist 1 and radiologist 2 were determined by calculating the κ coefficient (κ < 0.20 indicated poor agreement; κ = 0.21–0.40, fair agreement; κ = 0.41–0.60, moderate agreement; κ = 0.61–0.80, good agreement; κ = 0.81–0.90, very good agreement; and κ > 0.90, excellent agreement) and 95% confidence intervals (CIs). A statistical package (MedCalc; MediSoftware, Mariakerke, Belgium) was used to perform the calculations.

Results

The summary of the qualitative assessment for 12 disseminated lesions of 12 patients is shown in Table 1. Readers 1 and 2, respectively, assigned grade 3 in 2 (17%) and 1 (8%) DWI at $b = 1000 \text{ s/mm}^2$ studies and 4 (33%) and 5 (42%)

DWI at $b = 3000 \text{ s/mm}^2$ studies (Figs. 1 and 2). For the reader 2, the mean score was significantly higher for $b = 3000 \text{ s/mm}^2$ than $b = 1000 \text{ s/mm}^2$ ($P < 0.05$). For the reader 1, there was no significant statistical difference between the two types of DWI. Interobserver agreement for DWI at $b = 1000 \text{ s/mm}^2$ and $b = 3000 \text{ s/mm}^2$ was very good ($\kappa = 0.85$; 95% CI,

Table 1. Summary of the qualitative assessment in 12 patients with tumor dissemination

Case	DWI at $b = 1000 \text{ s/mm}^2$		Interobserver agreement*	DWI at $b = 3000 \text{ s/mm}^2$		Intermodality agreement*
	Reader 1	Reader 2		Reader 1	Reader 2	
1	1	2		3	3	
2	2	2		2	2	
3	1	1		1	1	
4	2	2		2	3	
5	1	1		1	1	
6	1	1	$\kappa = 0.85$ (0.63–1.00)	2	2	$\kappa = 0.93$ (0.78–1.00)
7	3	3		3	3	
8	3	2		3	3	
9	1	1		1	1	
10	2	2		2	2	
11	2	2		2	2	
12	2	2		3	3	
Mean	1.75 ± 0.75	$1.75 \pm 0.62^*$		2.08 ± 0.79	$2.17 \pm 0.83^*$	

The number of readers indicates grading score, where 4 = The information about the presence of the lesions was provided only by using DW images, but not by using postcontrast studies, 3 = The conspicuity of the lesions was more apparent for DWI than postcontrast studies, 2 = DW images provided similar conspicuity of the lesions to postcontrast studies, 1 = The information about the presence of the lesions was provided only by using postcontrast studies, but not by using DW images. For the reader 2, the mean score was significantly higher for $b = 3000 \text{ s/mm}^2$ than $b = 1000 \text{ s/mm}^2$ ($P < 0.05$). For the reader 1, there was no significant statistical difference between the two types of DWI.

*: interobserver agreement between reader 1 and reader 2, Data are κ statistics, with 95% CIs in parentheses.

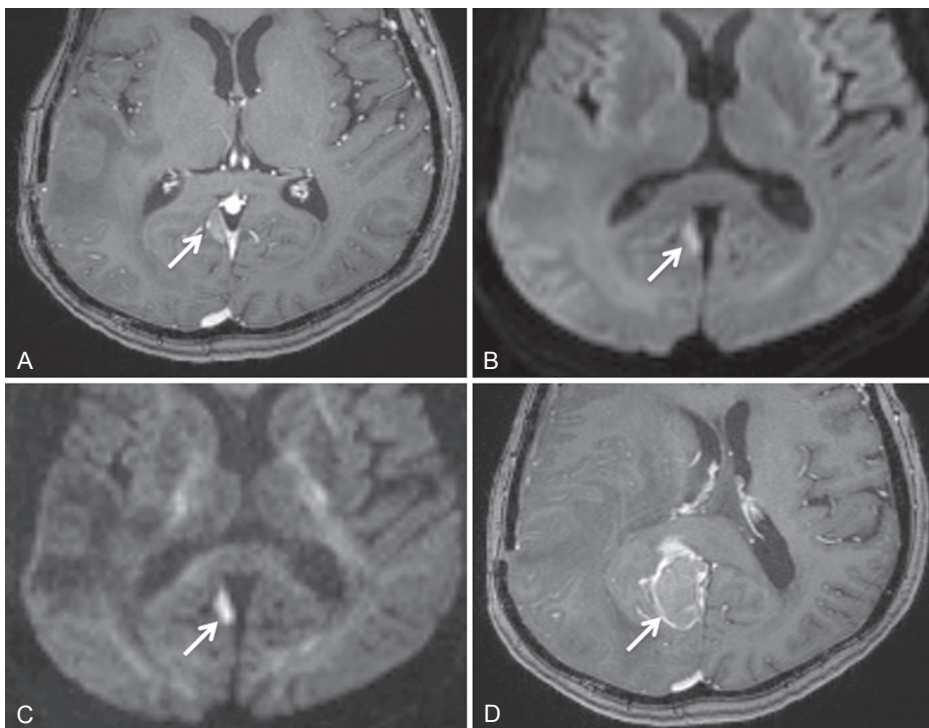


Fig 1. MR images at the level of the splenium of the corpus callosum in a 49-year-old woman with giant cell glioblastoma (case 8). Postcontrast 3D gradient-echo image (A) shows a small enhanced lesion (arrow) adjacent to the inferomedial part of the right parietal lobe. Diffusion-weighted image at $b = 1000 \text{ s/mm}^2$ (B) demonstrates a slight hyperintense area (arrow) corresponding to the contrast-enhanced lesion. One reviewer ranked the image as grade 3 and the other as grade 2. Diffusion-weighted image at $b = 3000 \text{ s/mm}^2$ (C) shows a definite hyperintense lesion (arrow) corresponding to the contrast-enhanced lesion. Both reviewers ranked the image as grade 3. Postcontrast 3D gradient-echo image (D) after 3 months reveals enlargement of the lesion (arrow).

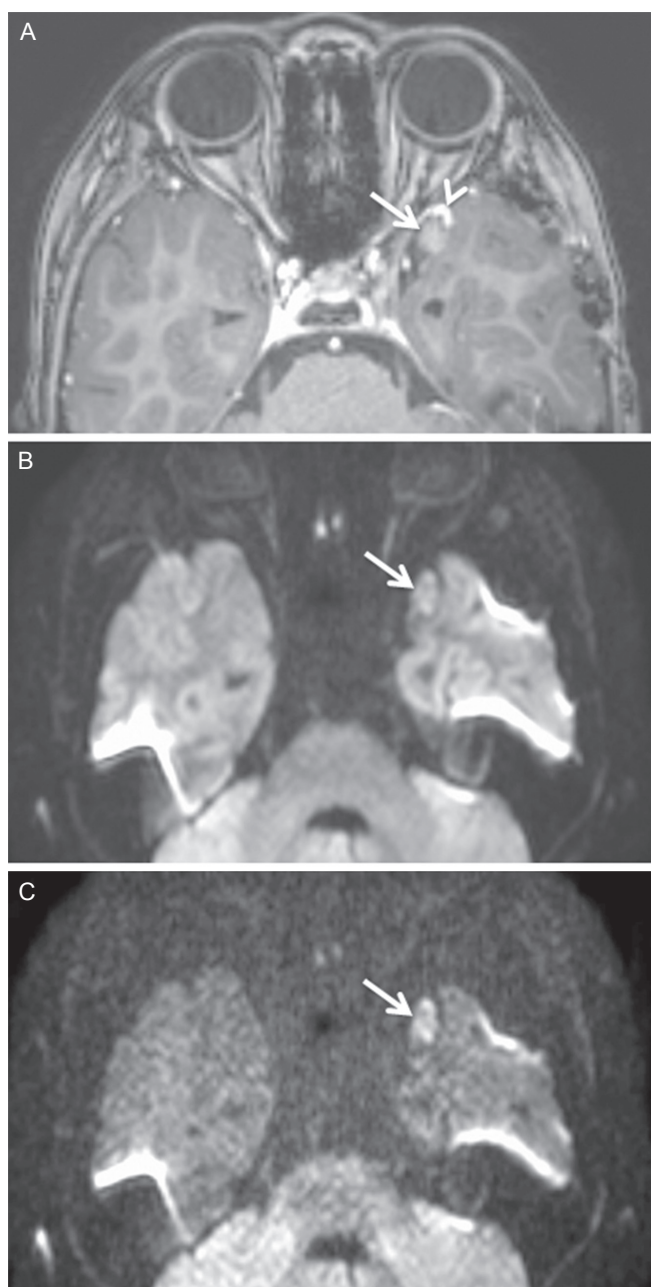


Fig 2. MR images at the level of the pons in an 11-year-old boy with primitive neuroectodermal tumor (case 12). Postcontrast 3D gradient-echo image (A) shows a lesion (arrow) adjacent to the anteromedial part of the left temporal lobe. The lesion adjacent to a vessel (arrow head) shows very subtle enhancement. Diffusion-weighted image at $b = 1000 \text{ s/mm}^2$ (B) demonstrates a slight hyperintense lesion (arrow) corresponding to the slightly-enhanced lesion. The vessel adjacent to the lesion is completely suppressed. Both reviewers ranked the image as grade 2. Diffusion-weighted image at $b = 3000 \text{ s/mm}^2$ (C) shows a remarkable hyperintense lesion (arrow) corresponding to the slightly-enhanced lesion. Both reviewers ranked the DWI as grade 3. This lesion was surgically resected and confirmed by pathological examination.

Table 2. Summary of lesion-to-brain contrast ratio (LBCR) for 12 disseminated lesions

Case	DWI	
	$b = 1000 \text{ s/mm}^2$	$b = 3000 \text{ s/mm}^2$
1	1.26	1.60
2	1.51	1.40
3	1.26	1.31
4	1.21	1.46
5	1.05	1.10
6	1.30	1.33
7	1.34	1.97
8	1.67	2.25
9	1.25	1.31
10	1.62	1.82
11	1.31	1.53
12	1.10	1.43
Mean	1.33 ± 0.19	1.55 ± 0.32

The lesion-to-brain contrast ratio (LBCR) was calculated using the following formula: $LBCR = SI_{\text{lesion}}/SI_{\text{brain}}$, where SI_{lesion} and SI_{brain} are the SI of the lesion and adjacent cerebral cortex, respectively. The mean LBCR score was significantly higher for DWI at $b = 3000 \text{ s/mm}^2$ than DWI at $b = 1000 \text{ s/mm}^2$ ($P < 0.01$).

0.63–1.00) and excellent ($\kappa = 0.93$; 95% CI, 0.78–1.00), respectively.

The quantitative assessment for 12 disseminated lesions is shown in Table 2. The mean LBCR score was significantly higher for DWI at $b = 3000 \text{ s/mm}^2$ than DWI at $b = 1000 \text{ s/mm}^2$ ($P < 0.01$).

Discussion

For detecting nodular disseminated lesions of primary malignant brain tumors in our study, 3T DWI was able to provide additional information relative to postcontrast MR studies. This may be due to the following reasons. On postcontrast MR studies including postcontrast 3D gradient-echo images, insufficiently-enhanced disseminated lesions like our cases may be difficult to detect. In such situations, DWI may be especially useful for detecting the lesions. On the other hand, some well-enhanced disseminated lesions may be missed on postcontrast MR images because of their overlap with enhanced superficial vessels. As DWI suppresses the signal of intracranial vasculatures and provides a more uniform background, it may make disseminated lesions easier to detect.

When evaluating disseminated lesions from primary malignant brain tumors, 3T DWI at $b = 3000 \text{ s/mm}^2$ provided more additional information than at $b = 1000 \text{ s/mm}^2$. In addition, interobserver agreement was higher at $b = 3000 \text{ s/mm}^2$ than $b = 1000 \text{ s/mm}^2$. This advantage of DWI at 3000 s/mm^2 is

considered to be attributed to the following reasons. A higher b-value DWI provides better contrast with its reflection of more tissue diffusivity and less T_2 shine-through effect.^{12,13} Then, DWI at $b = 3000$ s/mm² provide less signal of the cerebral cortices compared with DWI at $b = 1000$ s/mm² which would make more contrast between the disseminated lesion and the cortices.¹⁰

Among various high-b-values on DWI, we selected $b = 3000$ s/mm². On DWI, the signal-to-noise ratio of the brain decreases as the b-value increases.^{12–15} At $b = 3000$ s/mm², the signal of the gray matter is suppressed and the signal-to-noise ratio of the brain is appropriate at 3T.¹⁰ Therefore, $b = 3000$ s/mm² was chosen as the most appropriate high-b-value in our study.

Antiangiogenic therapies (e.g., bevacizumab) and steroid administration reduce the degree of contrast enhancement of gliomas.^{16,17} In patients with such situations, DWI might be useful for evaluating disseminated lesions of primary malignant brain tumors. Further studies are required to clarify the clinical role of DWI in patients with antiangiogenic therapies and/or steroid administration.

There are some limitations in our study. First, our patient population was relatively small and only the largest lesion was assessed. However, our study warrants further studies on large numbers of patients to clarify the clinical role of 3T DWI. Second, we did not assess the ADC value for the disseminated lesions. ADC maps have poorer tissue contrast than diffusion-weighted images. In patients with disseminated lesions, prompt and easy identification and localization of brain lesions are primarily important for making the accurate diagnosis. Therefore, we did not use ADC maps for this reader observation study. Third, we only evaluated nodular disseminated lesions (type Ia, the presence of a mass lesion along the subarachnoid space) based on the classification scheme of Bordignon.¹¹ We did not include very small disseminated lesions and diffuse leptomeningeal (type Ib) and subependymal (type II) disseminated lesions in this study. DWI might have additional values for detecting these disseminated lesions. Further investigations with very small lesions and various types of disseminated lesion are needed to clarify the role of DWI in a clinical setting. Fourth, we did not evaluate the effect of tumor type on diffusion restriction. Some types of disseminated lesions (e.g., tumor with small round cell) may show high-signal intensity on DWI. Further studies are needed to clarify the effect of tumor type on the detection of disseminated lesions. Fifth, we did not evaluate postcontrast 3D fast spin-echo T_1 -weighted- and 3D FLAIR images. When evaluating leptomeningeal lesions, these 3D MR images may be more useful than 3D gradient-echo MR images.^{18,19} Further investigations with the 3D MR images are needed to clarify the usefulness of DWI for detecting disseminated lesions.

In conclusion, 3T DWI can provide additive information relative to contrast-enhanced MR imaging for the detection of nodular disseminated lesions from primary malignant brain tumors. In certain cases, 3T DWI at $b = 3000$ s/mm² may provide more additional information than $b = 1000$ s/mm². Although contrast-enhanced MR studies are the gold standard method for evaluating disseminated lesions, DWI may have a complementary role to the contrast-enhanced MR studies.

Conflicts of Interest

We declare that we have no conflict of interest.

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