



## Original Article

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# Comparison of Contrast-Enhanced T2 FLAIR and 3D T1 Black-Blood Fast Spin-Echo for Detection of Leptomeningeal Metastases

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**Purpose:** Imaging plays a significant role in diagnosing leptomeningeal metastases. However, the most appropriate sequence for the detection of leptomeningeal metastases has yet to be determined. This study compares the efficacies of contrast-enhanced T2 fluid attenuated inversion recovery (FLAIR) and contrast-enhanced 3D T1 black-blood fast spin echo (FSE) imaging for the detection of leptomeningeal metastases.

**Materials and Methods:** Tube phantoms containing varying concentrations of gadobutrol solution were scanned using T2 FLAIR and 3D T1 black-blood FSE. Additionally, 30 patients with leptomeningeal metastases were retrospectively evaluated to compare conspicuous lesions and the extent of leptomeningeal metastases detected by T2 FLAIR and 3D T1 black-blood FSE.

**Results:** The signal intensities of low-concentration gadobutrol solutions (< 0.5 mmol/L) on T2 FLAIR images were higher than in 3D T1 black-blood FSE. The T2 FLAIR sequences exhibited significantly greater visual conspicuity scores than the 3D T1 black-blood sequence in leptomeningeal metastases of the pial membrane of cistern ( $P = 0.014$ ). T2 FLAIR images exhibited a greater or equal extent (96.7%) of leptomeningeal metastases than 3D T1 black-blood FSE images.

**Conclusion:** Because of its high sensitivity even at low gadolinium concentrations, contrast-enhanced T2 FLAIR images delineated leptomeningeal metastases in a wider territory than 3D T1 black-blood FSE.

**Keywords:** Leptomeningeal metastases; Black-blood; Contrast-enhanced T2 FLAIR

## INTRODUCTION

Early detection of leptomeningeal metastases is important to ensure appropriate therapy for preservation of neurologic function (1). Imaging plays a key role in the diagnosis and management of leptomeningeal metastases because CSF examination results are often false-negative and leptomeningeal metastases may be asymptomatic (2).

Previous studies established the value of contrast-enhanced fluid attenuated inversion recovery (FLAIR) sequence in imaging leptomeningeal metastases (3, 4), which may be attributed to three main factors. First, the FLAIR sequence does not allow

contrast enhancement of vessels (5–8). Second, it reveals an observable T1 contrast with dark CSF signal (5). Third, T2 FLAIR with contrast is more sensitive than T1 weighted image (T1WI) in detecting low concentrations of gadolinium (5, 9).

Recently, three-dimensional T1 black-blood (3D T1 BB) fast spin-echo (FSE) imaging has been found effective for selective suppression of blood vessels and better detection of brain metastases (10–12). Two different techniques are used in black-blood imaging. The first technique is a velocity-selective preparation pulse (or motion-sensitized driven-equilibrium, MSDE), using a spin-echo-based preparative pulse with a velocity-encoding gradient that suppresses blood flow signal (13, 14). This technique utilizes a preparative sequence composed of three nonselective radiofrequency pulses with flip angles of 90°–180°–90°, with symmetric gradients around the 180° pulse. The flow signal is suppressed due to the phase rotation of the magnetized blood flow caused by the motion-probing gradient pulses. The MSDE implemented with 3D FSE imaging increases the contrast-to-noise ratio for brain metastases compared with the conventional gradient echo (GRE) sequence (15). The other technique entails variable flip angle modulation (16) of FSE. In case of small and variable refocusing flip angles, flow signal is suppressed. Similar sequences using this technique are commercially available (CUBE, VISTA, and SPACE from GE Healthcare, Milwaukee, WI, USA; Philips Healthcare, Best, the Netherlands; and Siemens, Erlangen, Germany, respectively) (16–18). In variable flip angles, blood suppression varies from blood inflow, since blood suppression results from phase dispersion (10).

Although contrast-enhanced 3D T1 BB-FSE imaging presumably improves the diagnostic yield of leptomeningeal metastases, it is not established. In addition, comparison with contrast-enhanced T2 FLAIR in the detection of leptomeningeal metastases has yet to be performed. Thus, the purpose of this study was to compare contrast-enhanced T2 FLAIR and contrast-enhanced 3D T1 BB-FSE imaging for the detection of leptomeningeal metastases.

## MATERIALS AND METHODS

### Phantom Study

In order to determine the underlying mechanisms of contrast in contrast-enhanced FLAIR, and 3D T1 BB-FSE images, tube phantoms containing gadobutrol solutions

(Gadovist; Bayer Schering Pharma, Berlin, Germany) of varying concentrations (range, 0.0125 to 0.9 mmol/L) were scanned with a 3.0-MRI unit (Discovery MR750; GE Healthcare, Milwaukee, WI, USA). A reference tube phantom containing 0.9% normal saline was also scanned simultaneously. The MSDE The pulse was applied before the 3D T1 CUBE sequence for 3D T1 BB FSE imaging. Detailed MR parameters for T2 FLAIR and 3D T1 BB-FSE are summarized in Table 1.

### Clinical Study

#### Patients

We retrospectively screened consecutive patients diagnosed with clinically suspected brain metastasis at our hospital. Between May and December 2016, 372 patients were evaluated without the MRI protocol for brain metastasis, and identified 30 patients (6 males and 24 females; mean age, 60.6 years; age range 35–74 years) with leptomeningeal metastases. The MRI protocol was similar to the phantom study, and 3D T1 BB-FSE and T2 FLAIR images were acquired sequentially after injection of a gadolinium contrast agent (0.2 mmol/kg gadobutrol; Gadovist; Bayer HealthCare, Germany). The order of sequences was 3D T1 BB-FSE followed by T2 FLAIR in 20 patients, and the order of T2 FLAIR and 3D T1 BB-FSE was reversed for 10 patients. Leptomeningeal metastases were diagnosed by the presence of one of the following positive findings on T2 FLAIR or 3D T1 BB-FSE images: 1) enhancement in the sulci of the

**Table 1. Imaging Parameters for the T2 FLAIR and 3D T1 BB FSE Sequences**

	T2 FLAIR	3D BB T1 FSE
FOV (mm)	210	220
TR (ms)	12000	500
TE (ms)	144.46	24.511
Inversion time (ms)	2517	
Matrix (RO/PE)	352 × 224	256 × 224
Slice thickness (mm)	4	1
ETL	30	24
Flip angle	111	Variable
Scan FOV (cm)	21	22
Scan time (min)	3 min 12 sec	4 min 54 sec

3D = three dimensional; BB = black blood; ETL = echo train length; FLAIR = fluid attenuated inversion recovery; FOV = field of view; FSE = fast spin echo; FSPGR = fast spoiled gradient-echo; PE = phase encoding; RO = readout; TE = echo time; TR = repetition time

cerebral hemisphere or folia of the cerebellum, 2) cranial nerve enhancement, 3) subependymal enhancement, or 4) pial enhancement in the cistern (19–21). Focal enhancement restricted to a single gyrus suggested a sluggish flow. We also excluded patients exposed to supplemental oxygen, or carried a trauma history, or infarct symptoms, which may produce false positive interpretations (22–25). Our MRI protocol for leptomeningeal metastasis also includes routine T2WI and DWI. Primary malignancies among the 30 patients included lung cancer ( $n = 21$ ), diffuse large B-cell lymphoma ( $n = 4$ ), and breast ( $n = 2$ ), liver ( $n = 1$ ), cervical ( $n = 1$ ), and rectal ( $n = 1$ ) cancer. Our Institutional Review Board waived patient consent for this retrospective study.

### Image Assessment

Image assessment was based on T2 FLAIR and 3D T1 BB FSE sequences. Sixty sequences (30 patients  $\times$  2 sequences) were saved as DICOM files and randomly sorted by the study coordinator (Y.W.P.). Two neuroradiologists with 6 and 11 years of experience in brain MRI, blinded to patients' clinical history and diagnosis, independently reviewed these 60 sequences for evaluation of lesion conspicuity and the extent of leptomeningeal metastases. Cases presenting with prominent cerebrospinal fluid (CSF) flow artifacts on T2 FLAIR were excluded from the leptomeningeal metastases on pial membrane of cistern. Coronal and sagittal multiplanar reconstruction (MPR) images as well as axial images were included in the review of the 3D T1 BB FSE sequence.

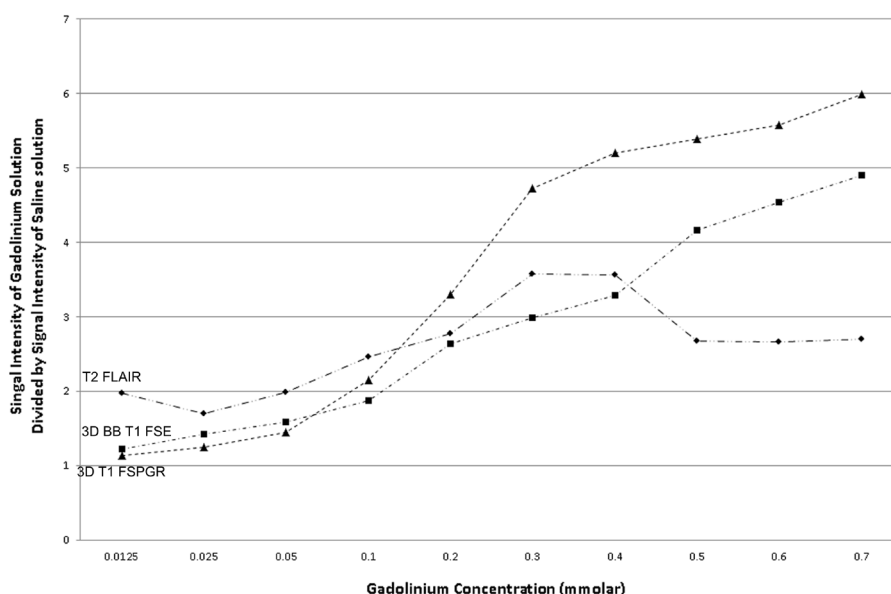
Lesion conspicuity was assessed according to findings

of enhancement in the sulci of the cerebral hemisphere or folia of the cerebellum, cranial nerve enhancement, subependymal enhancement, and pial enhancement in the cistern. Each positive finding was scored 0–2 according to the degree of conspicuity: 0, negative; 1, suspicious of leptomeningeal metastases, but not clearly distinguished from adjacent structures; and 2, certain leptomeningeal metastases, clearly distinguished from adjacent structures.

In a second session, a week later, the reviewers compared T2FLAIR and 3D T1 BB FSE images to determine whether the extent of leptomeningeal seeding on T2 FLAIR images was larger, equal, or smaller compared to those on 3D T1 BB FSE images.

### Statistical Analysis

Subjective assessments of the two reviewers were tabulated and summarized for each sequence. The visual conspicuity scores among the T2 FLAIR and 3D T1 BB FSE sequences were compared using Wilcoxon signed rank test. The interobserver agreement for visual conspicuity was analyzed using weighted Cohen kappa coefficient. The  $\kappa$  values  $> 0.81$ , in the range of 0.61–0.80, and  $< 0.60$  were considered to reflect excellent, good, and poor agreement, respectively. All  $P$ -values  $< 0.05$  were statistically significant in the statistical analysis performed using SPSS Statistics 23.0 (IBM, Armonk, NY, USA) and MedCalc Statistical Software version 14.8.1 (MedCalc Software, Ostend, Belgium).



**Fig. 1.** Relative signal intensities of gadolinium solution based on gadolinium concentration at various pulse sequences: The signal intensities of low-concentration gadobutrol solutions ( $< 0.5$  mmol/L) relative to normal saline on T2 FLAIR images are higher than in 3D T1 BB FSE images. 3D = three dimensional; BB = black blood; FLAIR = fluid attenuated inversion recovery; FSE = fast spin echo; FSPGR = fast spoiled gradient echo

## RESULTS

### Phantom Study

The results of the phantom study are shown in Figures 1 and 2. The signal intensity ratios of various concentrations of gadobutrol solution to normal saline on T2 FLAIR and 3D T1 BB-FSE images were plotted according to gadobutrol concentration. The results indicate that the signal intensities of low-concentration gadobutrol solutions (< 0.5 mmol/L) relative to normal saline on T2 FLAIR images were higher compared with the values in 3D T1 BB-FSE.

### Clinical Study

The visual conspicuity scores of the T2 FLAIR sequence for leptomeningeal metastases of the pial membrane in cistern were significantly greater than those of the 3D T1 BB-FSE sequence ( $P = 0.014$  for reviewer 1 and  $P = 0.023$  for reviewer 2). However, no significant differences were observed in visual conspicuity scores for leptomeningeal metastases of the cranial nerve, subependymal line, and pial membrane in the cistern among the three sequences (Table 2). The interobserver agreement for visual conspicuity scores was excellent ( $\kappa = 0.87$ ). A representative case is illustrated in Figure 3.

In a majority of patients, T2 FLAIR images exhibited

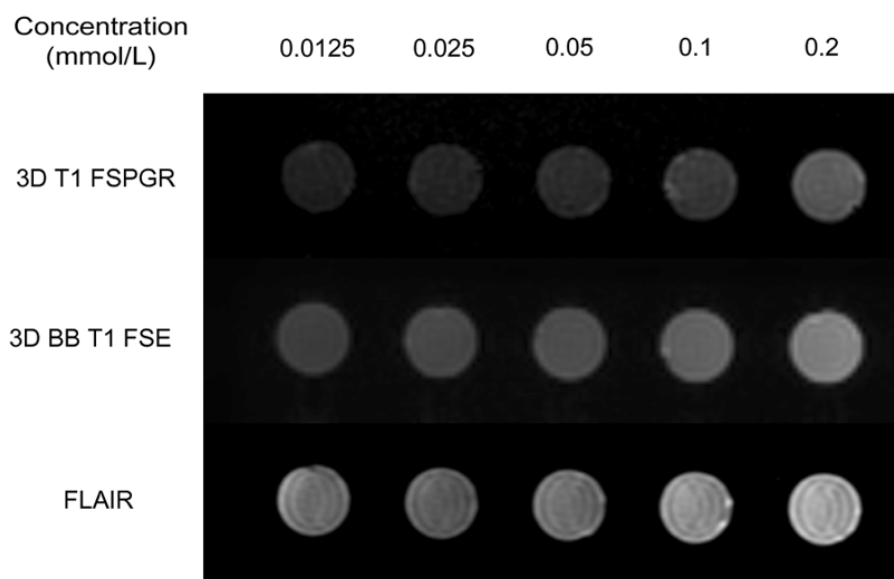
**Table 2.** Visual Conspicuity Scores of Each Sequence for Detection of Leptomeningeal Metastases

		T2 FLAIR	T1 BB FSE	P value
Sulci of cerebral hemisphere or folia of cerebellum (n = 29)	R 1	1.90 ± 0.41	1.69 ± 0.60	0.124
	R 2	1.86 ± 0.52	1.72 ± 0.59	0.056
Cranial nerve (n = 16)	R 1	1.56 ± 0.63	1.13 ± 0.89	0.068
	R 2	1.63 ± 0.62	1.19 ± 0.91	0.053
Subependymal line (n = 1)	R 1	2	2	NA
	R 2	1	2	NA
Pial membrane in cistern (n = 10)	R 1	1.60 ± 0.70	0.70 ± 0.82	0.014*
	R 2	1.50 ± 0.85	0.70 ± 0.82	0.023*

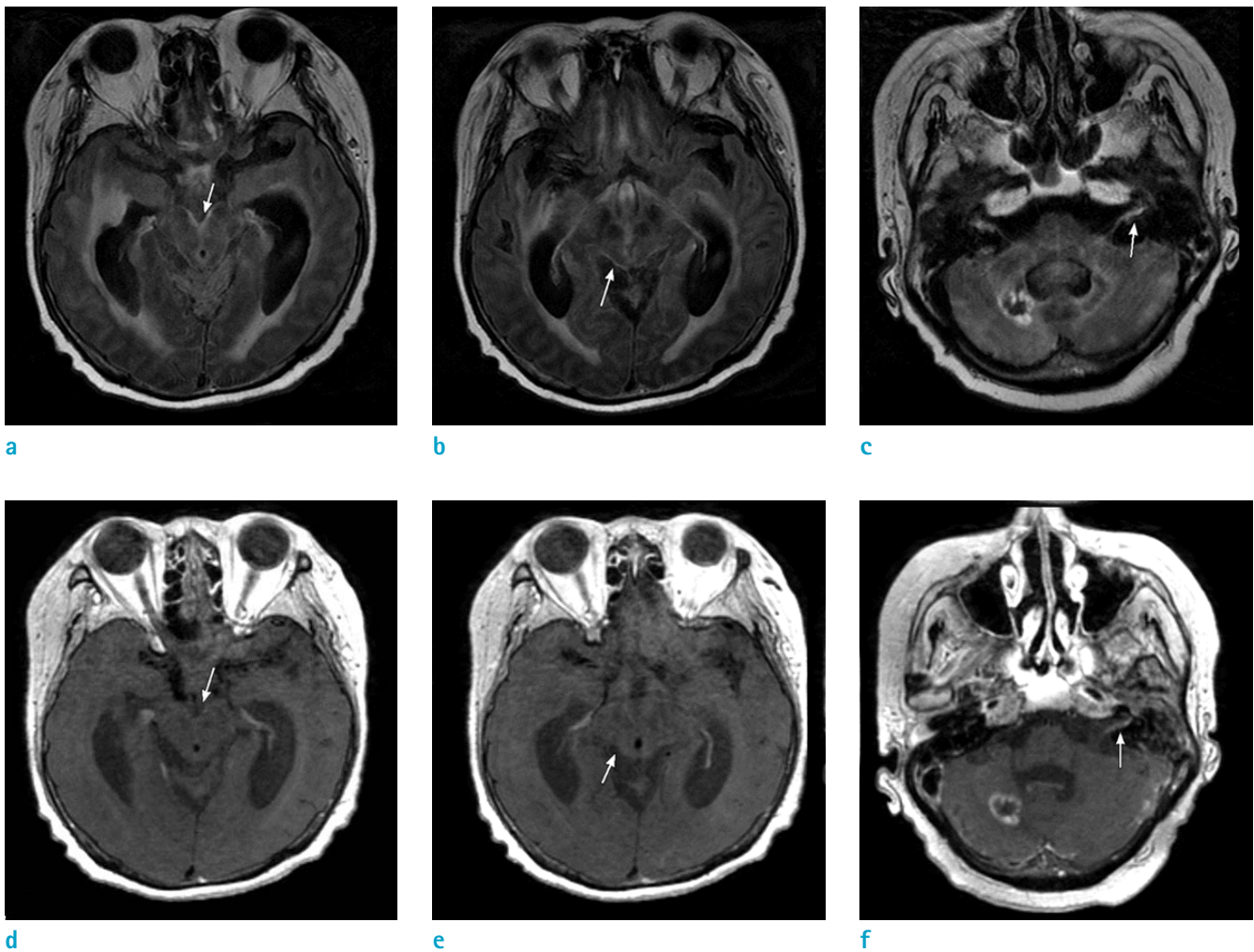
Visual conspicuity scores for leptomeningeal metastases: 0, negative; 1, suspicious of leptomeningeal metastases, but not clearly distinguished from adjacent structures; and 2, certain leptomeningeal metastases, clearly distinguished from adjacent structures.

\* $P < 0.05$

BB = black blood; FLAIR = fluid attenuated inversion recovery; FSE = fast spin echo; NA = not applicable; R1 = Reviewer 1; R2 = Reviewer 2



**Fig. 2.** Images of phantom tubes containing low concentrations of gadobutrol solution (0.0125–0.9 mmol/L) acquired by T2 FLAIR and 3D T1 BB FSE MRI. 3D = three-dimensional; BB = black blood; FLAIR = fluid attenuated inversion recovery; FSE = fast spin echo; FSPGR = fast spoiled gradient echo



**Fig. 3.** Images of a 73-year-old female patient with primary lung cancer acquired using the contrast-enhanced T2 FLAIR (a–c) and T1 BB-FSE (d–f) sequences. In T2 FLAIR images, leptomeningeal enhancement is clearly visualized in the pial membrane of the cistern and the cranial nerve (arrows; visual conspicuity score: 2). In 3D T1 BB-FSE images, leptomeningeal enhancement is not clearly demarcated in the pial membrane of the cistern (arrow; visual conspicuity score: 0) but suspected in the cranial nerve (conspicuity score: 1). 3D = three-dimensional; BB = black blood; FLAIR = fluid attenuated inversion recovery; FSE = fast spin echo

**Table 3.** Extent of Leptomeningeal Seeding

	Reviewer 1	Reviewer 2
T2 FLAIR > 3D T1 BB FSE	13/30 (43.3)	10/30 (33.3)
T2 FLAIR = 3D T1 BB FSE	16/30 (53.3)	19/30 (63.4)
T2 FLAIR < 3D T1 BB FSE	1/30 (3.3)	1/30 (3.3)

Data are presented as numbers of patients/total patients (%).  
BB = black blood; FLAIR = fluid attenuated inversion recovery; FSE = fast spin echo

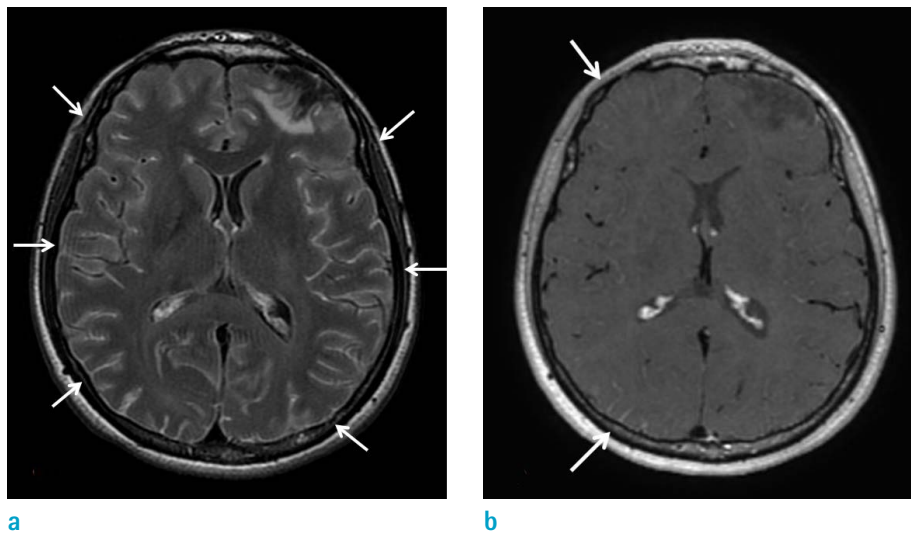
greater (43.3% and 33.3% for reviewers 1 and 2, respectively) or equal (53.4% and 63.4% for reviewers 1

and 2, respectively) extent for leptomeningeal metastases compared with 3D T1 BB FSE images (Table 3; Fig. 4).

DISCUSSION

In this study, leptomeningeal metastases of the pial membrane in cistern were more conspicuous in contrast-enhanced T2 FLAIR images than in contrast-enhanced 3D T1-weighted BB-FSE. In addition, the T2 FLAIR sequence demonstrated leptomeningeal metastases across wider or equal regions than the 3D T1 BB-FSE sequence.





**Fig. 4.** Images of a 50-year-old female patient acquired using the T2 FLAIR (a) and 3D T1 BB-FSE (b) sequences. The extent of leptomeningeal seeding in the T2 FLAIR image is greater than in the 3D T1 BB-FSE image (white arrows). 3D = three-dimensional; BB = black blood; FLAIR = fluid attenuated inversion recovery; FSE = fast spin echo

These results are clinically significant. Imaging with the T2 FLAIR sequence after gadolinium injection during MRI for brain metastases might be disputed given that the 3D T1 BB-FSE sequence might serve as an alternative to MRI for detection of leptomeningeal metastases. However, considering our results, T2 FLAIR imaging after gadolinium injection may still be of value.

Previous studies reported a higher signal intensity of T2 FLAIR compared with variants of T1-weighted images at lower concentrations of gadolinium (5, 7). In the previous studies, the signal intensity of gadolinium on T2 FLAIR was higher than that of 2D T1-weighted images (repetition time [TR]/echo time [TE] = 650 ms/25 ms) at lower gadolinium concentrations with magnetization transfer pulse (< 1 mmol/L) and without magnetization transfer pulse (< 0.5 mmol/L). Further, in a study comparing 3D T2 FLAIR with 3D magnetization prepared rapid acquisition gradient echo (MPRAGE) (TR/TE/inversion time [TI] = 1900 ms/4.7 ms/900 ms), the signal intensity of 3D T2 FLAIR was higher than that of 3D MPRAGE at lower gadolinium concentrations (< 0.5 mmol/L) (7). Our study suggested that the addition of preparation pulse to 3D T1 FSE may not affect the superiority of T2 FLAIR over T1-weighted image in demonstrating low gadolinium concentration (< 0.5 mmol/L). This phenomenon is explained by the unique T1 weighting of the T2 FLAIR sequence. Because of the mild T1 weighting induced by the long inversion time and T1 shortening caused by gadolinium, the T2 FLAIR sequence is more sensitive than conventional contrast-enhanced T1 sequence as well as black-blood T1 sequence in demonstrating lower concentrations of gadolinium (5, 9,

24).

In our *in vivo* study, the contrast-enhanced T2 FLAIR sequence revealed leptomeningeal metastases more clearly than the 3D T1 BB-FSE sequence in pial membrane of cistern. Moreover, although statistically not significant, both reviewers graded the T2 FLAIR highly even in the leptomeningeal metastases of cerebral hemisphere or folia of the cerebellum and cranial nerves. In addition, visualization of leptomeningeal metastases was wider on contrast-enhanced T2 FLAIR than on 3D T1 BB. In leptomeningeal metastases, gadolinium leaks into the adjacent CSF through damaged vessels and is diluted, which corresponds to the low-concentration setting used in the phantom study (26). Therefore, the T2 FLAIR sequence might be superior to 3D T1 BB-FSE in terms of visualization of leptomeningeal metastases (5, 9).

Different acquisition time, different MR parameters, and different types of gadolinium-based contrast agents may affect the conspicuity of leptomeningeal seeding. A delay in imaging time may be effective in increasing the contrast intensity, because it prolongs the perfusion of contrast agent by the aberrant and leaky neovasculature within the metastases (27). However, an optimal MR acquisition time has yet to be determined for evaluation of leptomeningeal metastases. We presume that the optimal acquisition time may vary from that of brain parenchymal metastases, because extravasated gadolinium diluted by CSF affected the leptomeningeal metastasis. In our protocol, 2D FLAIR yielded a thicker slice (4 mm) than 3D sequences (1 mm), and the partial volume effects may have affected the assessment of the images. However, even at a lower

spatial resolution along the z-axis, T2 FLAIR identified leptomeningeal metastases wider than the 3D T1 BB FSE. Further, the use of a different contrast agent may have affected the conspicuity of different types of sequences due to varying R1 and R2 relaxation times (28). However, a previous study did not reveal a significant difference in efficacy of evaluation based on differences in contrast agents used in central nervous system applications (29).

The present study has several limitations. First, our hospital does not perform CSF analysis routinely for the diagnosis of leptomeningeal metastases. We did not perform CSF analysis due to the invasive procedure involved (30) and the low sensitivity (20, 31, 32). We assumed that appropriate neuroimaging abnormalities, along with clinical features, are adequate for the diagnosis of leptomeningeal metastases. Second, we did not assess the diagnostic accuracies of both sequences for detection of leptomeningeal seeding, in the absence of a gold standard sequence for diagnosis. However, all of our cases showed leptomeningeal enhancement in both sequences, without significant variation in diagnostic accuracy. Third, the extent of leptomeningeal metastases may be exaggerated due to the contrast leakage. Fourth, we could not directly measure the gadolinium concentration *in vivo*. Fifth, we used a double-dose contrast media solution, which may have improved the lesion detection. However, we speculate that a similar trend may occur in a single-dose study.

In conclusion, the contrast-enhanced T2 FLAIR sequence delineates leptomeningeal metastases of the pial membrane in cistern more clearly than the contrast-enhanced 3D T1 BB-FSE sequence. In addition, because of its higher sensitivity even at low gadolinium concentrations, the contrast-enhanced T2 FLAIR sequence demonstrates leptomeningeal metastases in a wider region than the contrast-enhanced 3D T1 BB-FSE sequence.

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