

## MAJOR PAPER

# Comparison between Two Separate Injections and a Single Injection of Double-dose Contrast Medium for Contrast-enhanced MR Imaging of Metastatic Brain Tumors

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**Purpose:** As stereotactic radiotherapy (SRT) becomes widespread, precise information including number, location, and margin of lesions is required when magnetic resonance (MR) imaging of brain metastasis is performed. We compare methods using 2 separate injections and a single injection for the administration of a double dose of contrast medium for contrastenhanced MR imaging.

**Materials and Methods:** We divided 40 patients with brain metastasis into 2 groups of 20 patients. Group A received 2 separate injections ( $0.2 + 0.2$  mL/kg) of contrast medium (gadoteridol); Group B received a single injection of the same total dose (0.4 mL/kg). Group A underwent spin echo (SE)  $T_1$ -weighted imaging ( $T_1$ WI) and magnetization prepared rapid acquisition with gradient echo sequence (MPRAGE) after each injection, and Group B underwent the same MR studies at the same timing as Group A. We evaluated the number, signal-to-noise ratio (SNR), diameter, margin delineation, and volume of lesions and compared them between early and delayed studies by the 2 methods.

**Results:** The number of detected lesions was largest in delayed studies of MPRAGE in both groups. The SNR of the lesions was statistically lower in early studies of Group A than other studies. Delayed studies of Group B showed statistically better margin delineation than other studies on both SE- $T_1$ WI and MPRAGE studies. Diameter and enhanced volume were statistically significantly larger on delayed phase than early phase in both groups.

**Conclusion:** Use of a single injection of double-dose contrast medium and longer delay time may improve margin delineation of lesions for the study of brain metastasis. Enhanced volume was larger on delayed phase, and it may influence selection of therapeutic strategy.

**Keywords:** *contrast-enhanced MRI, double-dose contrast study, metastatic brain tumor, number of injections*

## Introduction

High dose, concentration, and relaxitivity of con-

trast material are known to improve visualization of brain metastasis on magnetic resonance (MR) imaging.<sup>1,2</sup> For patients with suspected brain metastasis, gadoteridol is approved for use in a triple dose (0.3 mmol/kg body weight [BW] cumulative dose) in the United States and England and in a double

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dose (0.2 mmol/kg BW cumulative dose) in Japan. When no lesion is detected or when enhancement is insufficient after initial administration of a single dose (0.1 mmol/kg BW), Japanese regulations allow additional administration of 0.1 mmol/kg BW within 30 min.<sup>3</sup> Although current regulations allow only the separate injection, contrast MR study with a single double dose injection of contrast material (0.2 mmol/kg BW) is expected to improve enhancement and shorten imaging time. However, the effect of the number of injections and timing of image acquisition has not been fully explored. We evaluated the number of injections and image acquisition using 2 methods for administering a double dose of contrast material (gadoteridol), comparing methods using 2 separate injections and a single injection with respect to lesion enhancement, detection, and delineation for contrast-enhanced study for brain metastasis.

## Materials and Methods

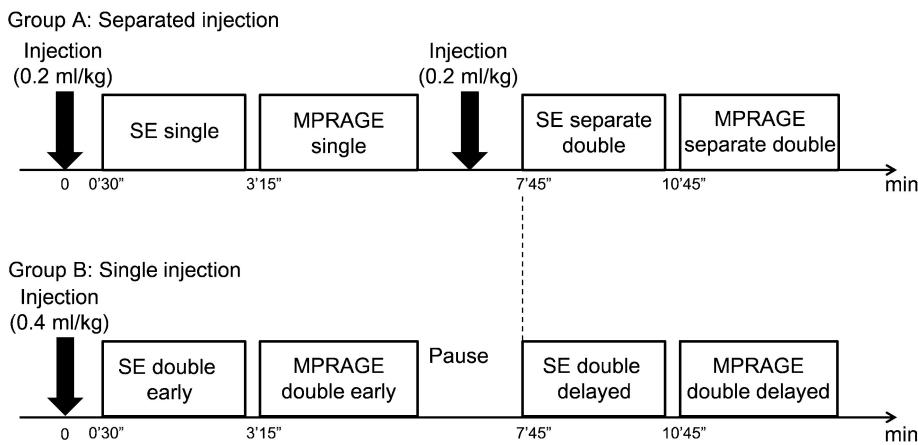
Japanese regulations do not permit the administration of double-dose gadoteridol in a single injection, so we obtained approval of our institutional review board to alter the injection pattern of the contrast medium. We obtained written informed consent from all patients after explaining that possible side effects might include nausea, vomiting, obstructed liver function, hives, anaphylactic shock, and convulsion as well as usual contrast enhanced MRI. We also explained to patients that the single injection of a double dose of gadoteridol is approved in the United States. The corresponding author (T.O.) had complete access to the results of the study, and all authors had control of the data and statistical results included in this article.

This prospective study was performed from January 2011 to February 2012. Subjects were 40 patients with a known primary malignancy and brain metastases detected by previous imaging including plain or contrast-enhanced computed tomography (CT) or MR imaging. Primary neoplasms included lung cancer, 34 cases; breast cancer, 4 cases; anal fistula cancer, one case; and colon cancer, one case. Subjects were randomly divided into 2 groups of 20 each—Group A (10 men, 10 women; mean age, 69 years, range, 48 to 84 years) and Group B (13 men, 7 women; mean age, 63 years; range, 48 to 86 years). Patients in Group A received 2 separate injections of contrast material (0.2 + 0.2 mL/kg), and patients in Group B received a single injection (0.4 mL/kg).

Imaging was performed on a 1.5-tesla clinical MR system (Magnetom Avanto, Siemens, Munich,

Germany). The protocol included acquisition of non-contrast T<sub>1</sub>- and T<sub>2</sub>-weighted images followed by contrast-enhanced study. We administered gadoteridol as the contrast medium (Gd-10-[2-hydroxypropyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid; ProHance®, Eisai, Tokyo, Japan) at 0.1 mmol/kg BW for a single dose and 0.2 mmol/kg BW for a double dose. The contrast medium was administered intravenously through a peripheral vein as a bolus at a rate of 0.5 to 1.0 mL/s followed by a flush with 20 mL of saline using a power injector. For the contrast-enhanced images, we applied 2 imaging sequences—spin-echo T<sub>1</sub>-weighted sequence (SE-T<sub>1</sub>WI) (repetition time [TR], 480 ms; echo time [TE], 8.1 ms; flip angle [FA], 80°; field of view [FOV], 23; matrix, 256 × 256; 5-mm thickness; image acquisition time, 2'45'') and magnetization prepared rapid acquisition with gradient echo sequence (MPRAGE) (TR, 10 ms; TE, 3.5 ms; FA, 10°; FOV, 23; matrix, 256 × 256; 2-mm thickness; image acquisition time, 3'47''). We applied MPRAGE to obtain thin-slice images to prevent overlooking small lesions and to adapt the planning software for stereotactic radiotherapy (SRT), and we applied SE-T<sub>1</sub>WI, which has a higher signal-to-noise ratio (SNR) than the gradient echo method, to reduce such oversight.

The imaging protocol for Group A was: non-contrast T<sub>1</sub>/T<sub>2</sub>, injection of a single dose of contrast medium (30''), SE-T<sub>1</sub>WI (acquisition time 2'45'', scan initiation time after injection (SIT) 0'30''), MPRAGE (acquisition time 3'47'', SIT 3'15''), additional injection of a single dose of contrast medium, SE-T<sub>1</sub>WI (acquisition time 2'45'', SIT 7'45''), and MPRAGE (acquisition time 3'47'', SIT 10'45''). The imaging protocol for Group B was: non-contrast T<sub>1</sub>/T<sub>2</sub>, injection of a double dose of contrast medium, SE-T<sub>1</sub>WI (acquisition time 2'45'', SIT 0'30''), MPRAGE (acquisition time 3'47'', SIT 3'15''), pause (30''), SE-T<sub>1</sub>WI (acquisition time 2'45'', SIT 7'45''), and MPRAGE (acquisition time 3'47'', SIT 10'45''). Thus, the timing for corresponding postcontrast imaging was identical between the 2 groups (Fig. 1). Regarding the dose and timing of contrast medium administration, early phase images in Group A were acquired as single-dose contrast images including SE-T<sub>1</sub>WI (SE single) and MPRAGE (MPRAGE single), and delayed phase images in Group A were acquired as double-dose contrast images including SE-T<sub>1</sub>WI (SE separate double) and MPRAGE (MPRAGE separate double). In contrast, early phase images in Group B were acquired as double-dose contrast images including SE-T<sub>1</sub>WI (SE double early) and MPRAGE (MPRAGE double early), and delayed



**Fig. 1.** Protocol for contrast study. The patients in Group A received 2 separate injections. Each injection was a single dose. Patients underwent spin echo (SE) T<sub>1</sub>-weighted imaging (T<sub>1</sub>WI) and magnetization prepared rapid acquisition with gradient echo sequence (MPRAGE) after each injection. The patients in Group B received a single injection of a double dose of the contrast medium and underwent the same magnetic resonance (MR) studies with the same timing as Group A.

phase images in Group B were acquired as double-dose contrast images including SE-T<sub>1</sub>WI (SE double delayed) and MPRAGE (MPRAGE double delayed).

Two readers blinded to the injection parameters (T.O., T.T.) evaluated images by consensus. MPRAGE images were evaluated in their source images. The readers assessed 5 variables—number of lesions, SNR of lesions, diameters of enhanced lesions, delineation of margins of enhanced lesions, and volume of enhanced lesions.

We evaluated the number of detected lesions in the early and delayed phases from Groups A and B, including SE single, MPRAGE single, SE separate double, MPRAGE separate double, SE double early, MPRAGE double early, SE double delayed, and MPRAGE double delayed.

We measured signal intensities of lesions to give the SNR for the images listed above and compared them between early and delayed phase in Groups A and B. The SNR was calculated for each post-contrast image based on the measured signal intensity (SI) values.

We placed a region of interest (ROI) in a lesion and its background to cover the lesion as completely as possible. We measured diameters of lesions on MPRAGE and compared them between the early and delayed phases. We scored the delineation of lesion margins from 0 to 5 (0, no enhancement; 1, ill-defined lesion margin; 3, half circumference; 5, definition of the whole circumference [Fig. 2]; scores of 2 and 4 were intermediate between 1 and 3 and 3 and 5.) and compared the distribution of scores between the early and delayed phases of

Groups A and B.

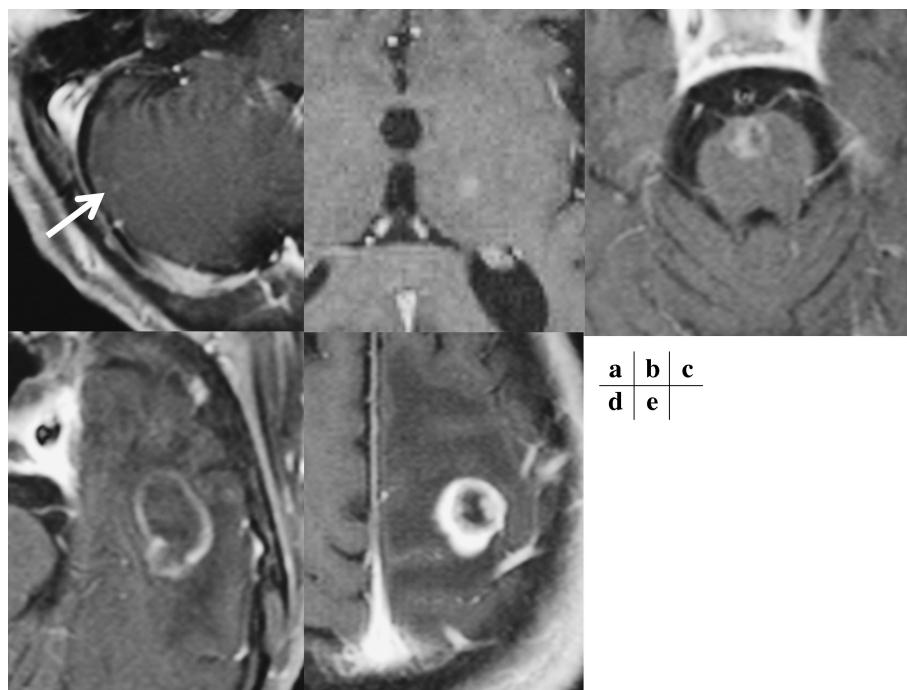
We calculated enhanced lesion volume with iPLAN® image radiation therapy planning system software (BRAINLAB AG, Feldkirchen, Germany) based on MPRAGE images and compared volumes between the early and delayed phases. We classified lesions by enhanced lesion volume based on the delayed phase as follows: small lesions, <0.5 mL; intermediate lesions, 0.5 mL > 10 mL; and large lesions, >10 mL.

We used a t-test to evaluate quantitative results for the mean number of enhanced lesions per case, and their SNR, mean diameter, and volume and used Mann-Whitney U test to evaluate quantitative results of delineation of enhanced lesions.  $P < 0.01$  was considered statistically significant.

## Results

**Number of lesions:** The number of detected lesions was largest in the delayed phase of MPRAGE in both groups (Table 1). The number of lesions detected on early and delayed phases did not differ significantly. The mean numbers of detected lesions per case on the delayed phase of MPRAGE were 4.5 in Group A and 3.9 in Group B. The numbers of lesions detected in the 2 groups did not differ significantly.

**Signal-to-noise ratios of lesions:** In SE-T<sub>1</sub>WI, the SNR of lesions was statistically lower in the early phase of Group A (SE single) than in other studies. The SNRs did not differ significantly among the delayed phase of Group A (SE separate double), early phase of Group B (SE double early), and de-



**Fig. 2.** Scoring of margin delineation. Delineation was graded 1 for ill-defined margin (**a**), 2 when it fell between 3 and 1 (**b**), 3 for half circumference (**c**), 4 when it fell between 5 and 3 (**d**), and 5 for delineation of the whole circumference (**e**).

**Table 1.** Number of lesions

		Number of lesions	
		Early phase	Delayed phase
Separated injection (Group A)	SE T <sub>1</sub> WI	80 (89.9%)	88 (98.9%)
	MPRAGE	84 (94.4%)	89 (100%)
Single injection (Group B)	SE T <sub>1</sub> WI	67 (87.0%)	72 (93.5%)
	MPRAGE	75 (97.4%)	77 (100%)

MPRAGE, magnetization prepared rapid acquisition with gradient echo sequence; SE, spin echo; T<sub>1</sub>WI, T<sub>1</sub>-weighted imaging

The number of detected lesions was largest on delayed studies of MPRAGE in both groups.

layed phase of Group B (SE double delayed). We obtained the same results using MPRAGE (Fig. 3).

Diameter of enhanced lesions: The diameter of lesions was larger during the delayed phase than the early phase for both Groups A and B (Table 2).

Delineation of margins of enhanced lesions: The score of margin delineation was the lowest of all on SE-T<sub>1</sub>WI of SE single (early phase of Group A) and the second lowest score on SE double early (early phase of Group B). The score was larger for SE separate double (delayed phase of Group A) than SE double early and highest for SE double delayed (delayed phase of Group B). Differences were sig-

**Table 2.** Mean diameter of lesions

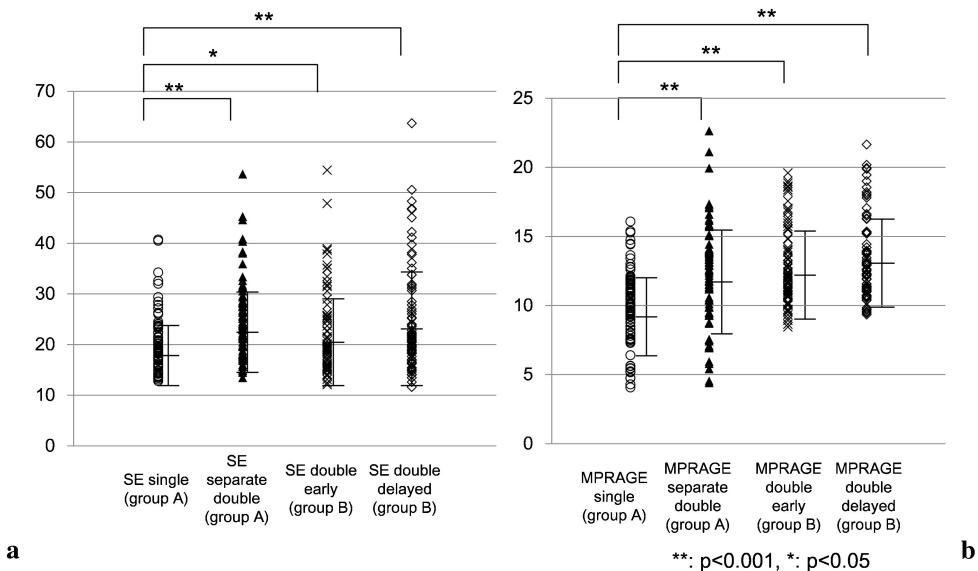
	Mean diameter of lesions (mm)		
	Early phase	Delayed phase	P value
Separated injection (Group A)	7.09 (±SD)	7.81 (±SD)	<0.001
Single injection (Group B)	8.01 (±SD)	8.44 (±SD)	<0.001

The mean diameter of lesions during the delayed phase is statistically larger than the diameter of early study in both Groups A and B.

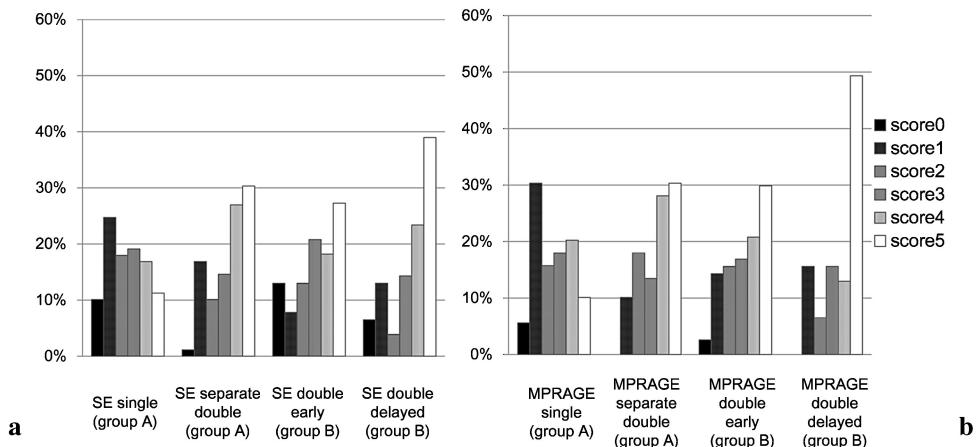
SD, standard deviation

nificant between SE single and SE double early ( $P < 0.001$ ), between SE double early and separate double ( $P < 0.001$ ), and between SE separate double and SE double delayed ( $P < 0.001$ ). A similar result was obtained on MPRAGE (Fig. 4, Table 3).

Volume of enhanced lesions: In Group A, the volume of lesions based on delayed phase (MPRAGE separate double) was statistically larger than that on early phase (MPRAGE single) ( $P < 0.001$ ). Likewise, in Group B, the volume of lesions based on delayed phase (MPRAGE double delayed) was significantly larger than that on early phase (MPRAGE double early) ( $P < 0.001$ ). In the analysis by sub-groups determined by small, intermediate or large size of lesions, there were also statistically significant differences between early and delayed phase in



**Fig. 3.** Signal-to-noise ratios (SNR) of lesions. Lesions of early spin echo (SE) study of Group A (SE single) showed statistically lower SNR than lesions of other studies (**a**). Magnetization prepared rapid acquisition with gradient echo sequence (MPRAGE) studies demonstrated similar results (**b**).



**Fig. 4.** Distribution of margin delineation score. Percentage of higher score region is largest on delayed spin echo (SE) study of Group B (SE double delayed) (**a**). Magnetization prepared rapid acquisition with gradient echo sequence (MPRAGE) studies showed similar results (**b**).

both Groups A and B. Differences between the delayed and early phases tended to be larger in larger lesions (Figs. 5–7).

## Discussion

We compared single and separate injection methods to administer a double dose of contrast medium with respect to detection ratio, SNR, margin delineation, and volume of lesions. We used SNR in comparing the degree of enhancement in the current study. We did not use CNR for this comparison in order not to be influenced by the 2 different imaging methods (SE and MPRAGE). We also evalu-

ated the effect of delayed imaging time.

Lesion detection improved with a double dose of contrast medium and delayed imaging time. We could detect more lesions on MPRAGE than SE study. SNR improved with a double dose of contrast medium possibly because there was a higher concentration of contrast medium in the lesions. However, SNR was better on SE than MPRAGE study. In addition, a double dose of contrast medium and delayed imaging time can improve delineation of lesions, especially in the margin. Lesion delineation is improved using a single injection of a double dose of contrast medium compared with separate injection in the same timing for image acquisition

**Table 3.** Mean score per lesion

		Mean score per lesion	
		Separated injection (Group A)	Single injection (Group B)
SE-T <sub>1</sub> WI	Early phase	2.4	3.1
	Delayed phase	3.4	3.5
MPRAGE	Early phase	2.5	3.3
	Delayed phase	3.5	3.7

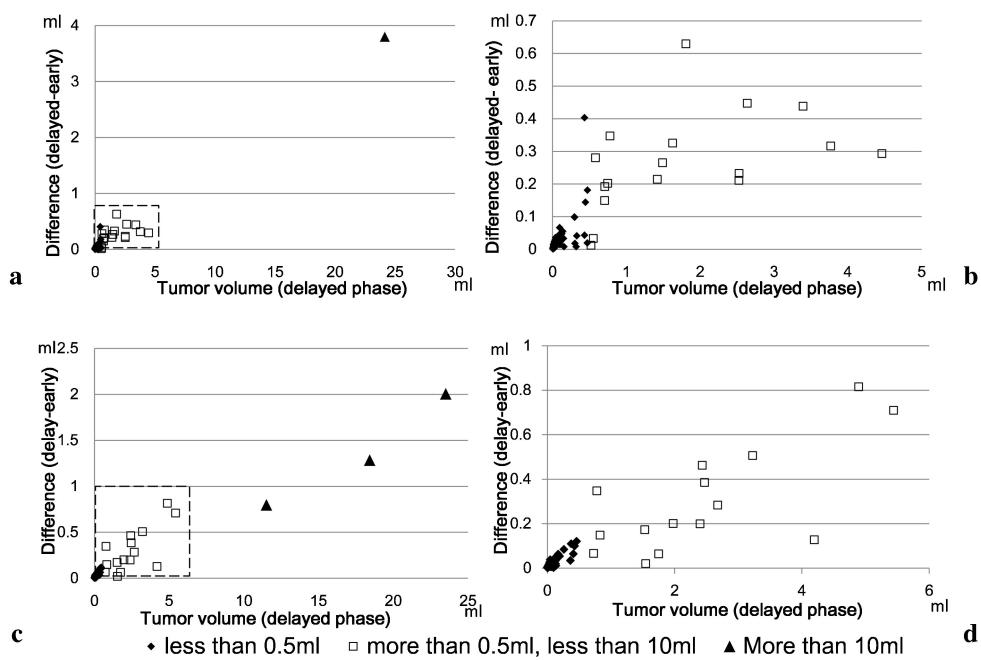
\* $P < 0.001$

MPRAGE, magnetization prepared rapid acquisition with gradient echo sequence; SE, spin echo; T<sub>1</sub>WI, T<sub>1</sub>-weighted imaging

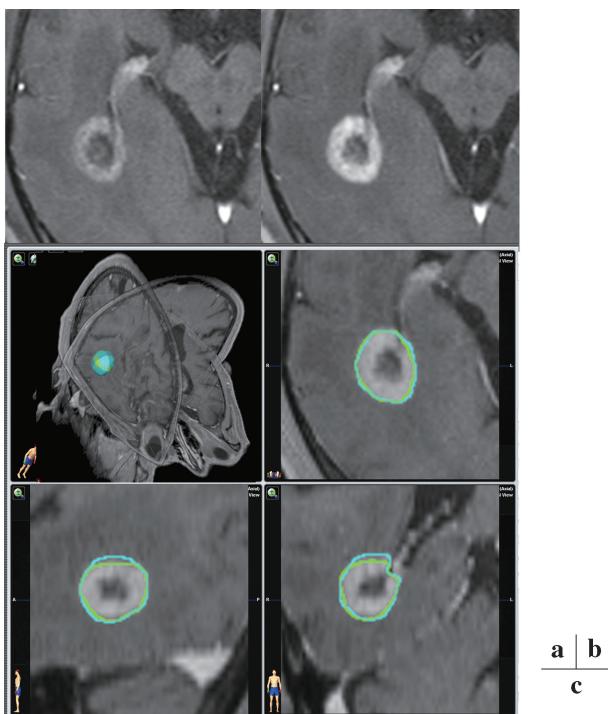
The margin delineation of SE single (early phase of Group A) was scored lowest of all SE-T<sub>1</sub>WI studies. The SE double early (early phase of Group B) showed the second lowest score. The score was larger of SE separated double (delayed phase of Group A) than that of SE double early and largest for SE double delayed (delayed phase of Group B). There was a statistically significant difference between single and double early, double early and separate double, separate double and double delayed ( $P < 0.001$ ). A similar result was obtained on MPRAGE and SE-T<sub>1</sub>WI.

after initial injection. However, margin delineation was worse in the early phase of the single injection study than the delayed phase with separate injection. Therefore, timing of image acquisition after the initial injection of contrast material should not be shortened even if a double dose is administered in a single injection. Larger lesion volume was depicted with a high dose of contrast medium and delayed imaging time. This trend was seen more strongly in larger lesions. We attribute this to the shape of the difference between the early and delayed phases, which resembles a belt of one- to 2-mm width in most lesions.

In the 1990s, it was reported that a higher dosage of contrast medium and delayed imaging time after its injection could improve the detection rate of metastasis, especially in the evaluation of small lesions (<10 mm).<sup>1,2</sup> Based on these findings, Japan, where we conducted this study, approved the double-dose administration of contrast medium to assess metastatic brain tumor.<sup>3</sup> The approved sequence allows for an additional injection of 0.1 mmol/kg of gadoteridol within 30 min after the initial administration of 0.1 mmol/kg when a tumor is not detected or contrast enhancement is not sufficient. When this approved injection sequence is used, the contrast medium injected first is already partially excreted by the time of the second single dose, so the concentration of the contrast material



**Fig. 5.** Enhanced lesion volume difference between the early and delayed phases. In Group A (separated injection) and B (single injection), enhanced lesions were depicted larger on delayed than early phase (a, c). Intermediate and small lesions were also depicted larger on delayed phase (b, d). (Graph b and d represents the area of the dotted line in graph a and c.)



**Fig. 6.** A 62-year-old man with lung cancer underwent contrast-enhanced magnetic resonance (MR) imaging with separate injections of a double dose of contrast medium (Group A). Early phase of spin echo (SE) T<sub>1</sub>-weighted imaging (T<sub>1</sub>WI) shows a tumor with ring-like enhancement in the right temporal lobe (**a**); delayed phase shows more thick and intense enhancement (**b**). We outlined the enhanced lesion on the early phase of magnetization prepared rapid acquisition with gradient echo sequence (MPRAGE) in green and on the delayed phase in blue and used these outlines to calculate the volume of the enhanced lesion with radiation planning software (**c**). The volume of the enhanced lesion is 2.95 mL in the early phase and 3.39 mL in the delayed phase.

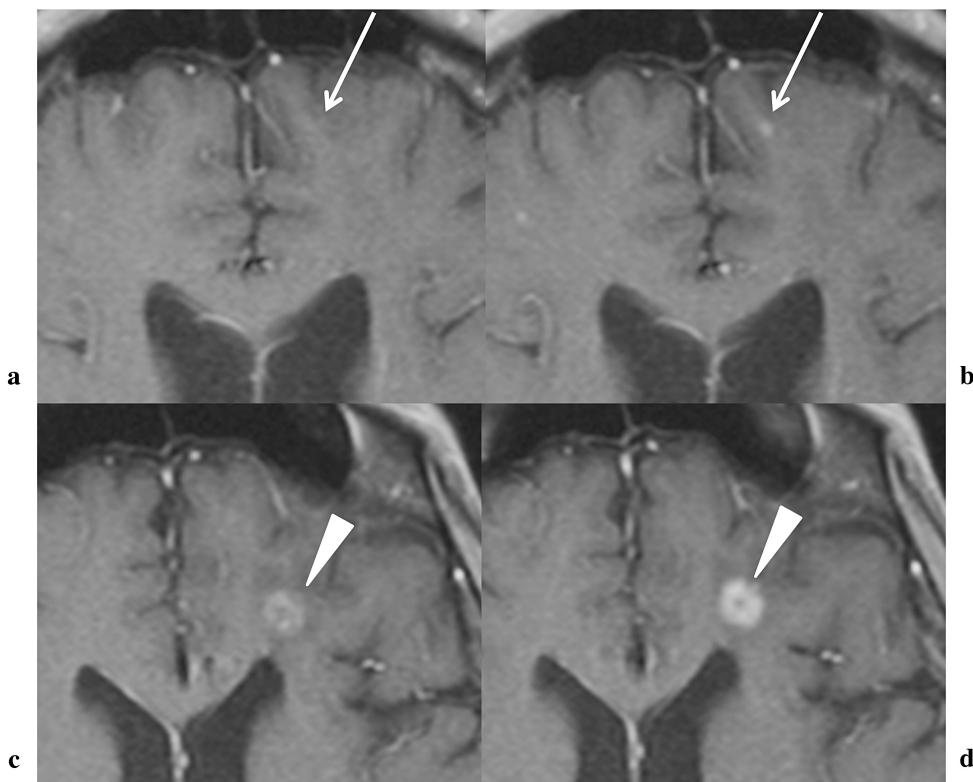
is less than that following a single injection of a double dose of the contrast medium. Thus, a single injection of a double dose of contrast material would yield a higher concentration and offer better delineation of the tumor.

The application of a double or higher dose of contrast medium appears to have fallen out of favor. One reason may be related to the risk for the development of nephrogenic systemic fibrosis (NSF). NSF in patients with renal insufficiency who underwent gadolinium-enhanced MR imaging was first recognized in several patients in 1997 and first described in the literature in 2000. Administration of a high dose of gadolinium-based contrast medium is a known risk factor for the development of NSF.<sup>4,5</sup> The United States Food and Drug Administration (FDA) requested that a “black box” warning (a more extreme mechanism invoked by the

FDA to call attention to observed serious adverse reactions) regarding the potential risk of NSF for patients with renal failure be added to the product descriptions of all 5 FDA-approved gadolinium-based MR contrast agents marketed in the United States, including gadoteridol.<sup>6</sup> However, gadoteridol contains a cyclic nonionic chelate and has a high thermodynamic stability constant and long dissociation half-time, so its use carries a relatively low risk for the development of NSF. Moreover, it is reported that the appropriate additional contrast injection can facilitate differential diagnosis of suspected brain metastasis and improve the number and conspicuity of detected lesions.<sup>7</sup> Thus, the benefits of the double-dose injection of contrast medium for the detection of metastatic brain tumor shown in the current study should be emphasized and reconfirmed in the context of today’s clinical practice. We noted no adverse clinical effects that could be attributed to the injection of contrast medium.

Clinical practice concerning metastatic brain tumors has changed from previous days, when surgical resection was the first choice for a case with a single metastasis and total brain radiation was chosen for cases with multiple metastases. As the survival of patients with cancer improves, total brain irradiation has become less popular because of the quality of life issues related to the side effects of treatment, such as cognitive decline, which becomes more apparent with longer survival. Instead, stereotactic radiotherapy (SRT) including Gamma Knife (Elekta Instruments AB, Stockholm, Sweden), Cyber Knife (Accuray, Inc., Sunnyvale, CA, USA), or Novalis<sup>®</sup> (Brainlab AG, Feldkirchen, Germany) is more commonly used because it can deliver radiation more precisely to the tumor to minimize damage to surrounding healthy tissue. In these SRT systems, the margin of the radiation plan is small and the dose gradient is steep, so a precise treatment plan is necessary.<sup>8,9</sup> MR imaging is required for sufficient detectability of small lesions and precise delineation of targets to be treated. The current study showed that the single injection of a double dose of contrast medium improved delineation of the tumor margin, which is necessary to devise an appropriate radiation plan.

In the practice of stereotactic radiation, the significance of better delineation of the tumor by double-dose contrast MR imaging differs by the size of the tumor. For lesions smaller than 0.5 mL, better detectability is important because the number of lesions affects the treatment plan. For intermediate lesions larger than 0.5 mL and smaller than 10 mL, precise delineation of the lesion margin is impor-



**Fig. 7.** A 61-year-old man with lung cancer received a single injection of a double dose (group B) of contrast medium to enhance contrast on magnetic resonance (MR) imaging. A retrospective review of spin echo (SE) T<sub>1</sub>-weighted imaging (T<sub>1</sub>WI) during the early phase suggests a small nodule in the left frontal lobe (arrow), although it does not show definite enhancement (a). SE-T<sub>1</sub>WI during the delayed phase shows a more clearly enhanced lesion (b). SE-T<sub>1</sub>WI during the early phase shows a rim of enhancement in the left frontal lobe (arrowhead) (c). A thicker and more intense enhancing rim is seen on the delayed phase image (d).

tant to ensure coverage of the dose even at the edge of the tumor. For lesions larger than 10 mL, precise delineation of the margin is also important because it may be necessary to reduce the dose to control damage to the surrounding tissue.<sup>10,11</sup>

One limitation of the current study is the histological nature of the area in which the double-dose study can't be depicted. Histologically, a typical metastatic brain tumor shows clear margins surrounded by gliosis of one-mm thickness,<sup>12,13</sup> so the approximately one-mm difference between the diameters we measured during the early and late phases of enhancement may correspond with gliosis surrounding the tumor margin. We did not evaluate histology, so we could not correlate it with enhancement. Another limitation is that we did not evaluate tumor recurrence. Treatment of tumors in our study was not uniform and included surgical resection, Gamma Knife or Novalis® SRT, or chemotherapy alone. Thus, we could not evaluate tumor recurrence after treatment or necrotic changes after radiation therapy. The effect of treatment should be evaluated by

visualization of the tumor using different methods of contrast MR imaging in a larger cohort of patients and with a longer follow-up period.

## Conclusion

Delayed studies following a single injection of a double dose of contrast medium showed better delineation than delayed studies following separate injections. Therefore, the single injection method may improve delineation of lesions for the study of brain metastasis.

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