

Additional MR contrast dosage for radiologists' diagnostic performance in detecting brain metastases: a systematic observer study at 3 T

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Abstract

Purpose To evaluate the diagnostic performance of a double-dose administration of gadolinium for brain metastases at 3 T in a systematic observer test.

Materials and Methods Postcontrast MR images of 39 patients (total 104 metastases) were obtained by 3D T1-weighted sequences with both standard and cumulative double dose contrast administration. An observer test involving 9 radiologists (5 board-certified radiologists and 4 residents) was performed, and their diagnostic performance with the two doses was compared by means of sensitivity, false-positives, reading time, and a figure-of-merit.

Results Compared to the standard dose, the double dose showed higher sensitivity ($P < 0.0001$), higher false-positive/case ($P < 0.05$), longer reading time ($P < 0.05$), and higher figure-of-merit ($P < 0.0001$). Particularly in small lesions (<5 mm), sensitivity with the double dose (61.5 %, $P < 0.0001$) was approximately twice as high as that with the standard dose (29.5 %). Artifacts and blood vessels were the most common imaging findings resulting in false-positives.

Conclusions The double dose improved detection for metastases smaller than 5 mm at 3 T and thus resulted in better diagnostic performance of radiologists. However, a higher dose might result in prolonged reading time and increased false-positives, presumably due to increased vessel signals and frequency of flow-related artifacts.

Keywords Magnetic resonance imaging · Brain metastasis · Contrast agent · Gadolinium · Double dose

Introduction

Metastasis to the brain is the most feared complication of systemic cancer and the most common intracranial tumors in adults, affecting 20 % of patients with cancer [1, 2]. It represents one of the most frequent neurologic complications of systemic cancer as a major cause of morbidity and mortality. Not only the presence or absence but also the number of brain metastases critically affects therapeutic strategies [3, 4]. For example, the detection of additional lesions is important when considering surgical treatment. In the management of patients with multiple brain metastases, stereotactic radiosurgery along with whole-brain radiation therapy has been recommended when the number of lesions is smaller than four [4, 5]. Based on this clinical background, strong radiologic efforts should be made to increase the detection performance for brain metastasis.

An intravenous administration of 0.1 mmol/kg gadolinium (Gd)-based MR contrast agent has been widely accepted as a standard dose for a variety of routine clinical examinations. However, an improvement of lesion contrast with higher doses of gadolinium for brain metastases has been repeatedly demonstrated since the early 1990s [6–9]. It was reported that the contrast between enhancing metastases and normal brain tissue improved in a dose-dependent manner up to triple dose at 1.5 T [10]. Another way to increase the detection of small, low-contrast lesions is the use of a high magnetic field [11]. Increased signal-to-noise ratios at 3 T compared with 1.5 T can translate into a higher contrast-to-noise ratio between enhancing and non-enhancing tissues. The effectiveness of the T1-shortening

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effect of a gadolinium-based contrast depends on the baseline T1 relaxation time of local tissue. With the longer baseline T1 relaxation times brought about by a higher magnetic field strength, the T1-shortening effect of gadolinium-based contrast agents will be greater, as the relaxivity of such contrast agents changes only marginally between 1.5 and 3 T. It was reported that only a half-dose contrast at 3 T could be superior to a full-dose contrast at 1.5 T [12]. In addition, the time after an administration of contrast agent can modify the visualization of metastasis on contrast enhanced MR imaging. Previous studies reported that delaying imaging up to 30 min improved the detection of brain metastases [8, 13].

Although many researchers have shown the efficacy of the use of high-dose Gd administration and higher magnetic field strength for imaging brain metastases, to the best of our knowledge no studies have fully investigated whether the higher-dose gadolinium at 3 T improves the radiologist's performance in detecting brain metastasis. In addition, the false positive rate or reading time for diagnosing brain metastases with higher dosage has not been evaluated in detail. Our purpose in the present study was to investigate the efficacy of a double dose gadolinium administration for diagnostic performance at 3 T in detecting brain metastases, by carrying out a systematic observer test study.

Materials and methods

Patients

This retrospective study was institutional review board approved, and informed consent was waived. From October 2007 to November 2010, a total of 131 patients were examined with MR imaging for possible brain metastasis and were scanned with the protocol using cumulative double dose gadolinium administration. From this database, patients with a history of pathologically proved cancer and with at least one follow-up MR imaging examination were retrospectively selected. Two board-certified radiologists reviewed all images of these patients in a consensus reading and selected intraparenchymal enhancing lesions that were visualized in both standard-dose and cumulative double-dose MR imaging. We excluded lesions visualized with only one of the two doses, to stay conservative in determining the criterion standard. Our best effort was made to exclude artifacts and enhancing vessels, by carefully comparing the two images. Among the selected lesions, those satisfying any of the following conditions were determined to be metastases: (1) the size of the lesion increased in the follow-up period, (2) the lesion newly appeared during the follow-up period, and

(3) the lesion size changed after a treatment (either systemic chemotherapy or brain radiation therapy) according to the definition in another study [14]. Patients with more than 15 metastases were excluded. A total of 104 metastases were found in 27 patients. The number of lesions for each criteria is as follows: (1) the size increased in the follow-up period: 24 lesions, (2) newly appeared during the follow-up period: 39 lesions, and (3) the size changed after a treatment (increased in size: 21 lesions, decrease in size: 20 lesions). In addition, 12 patients without any enhancing intracranial lesions were also included in the study. These patients were selected based on the consensus of the two neuroradiologists, and the non-existence of lesions was confirmed in the follow-up examinations in all patients. Two board-certified radiologists reviewed all images of these patients in a consensus reading and selected intraparenchymal enhancing lesions that were visualized in both standard-dose and cumulative double-dose MR imaging. The details are described below.

MR imaging protocol

A 3 T MR imaging scanner (Achieva 3.0 T, Philips Electronics, Best, the Netherlands) and an 8-channel array head coil were used for the imaging. Three-dimensional (3D) gradient-echo T1-weighted sequences (3D fast field echo sequence) were obtained with the following parameters: repetition time (TR) = 25 ms, echo time (TE) = 2.2 ms, flip angle = 30°, field of view = 230 mm × 219 mm × 140 mm, voxel size = 0.9 mm × 0.9 mm × 1 mm, average = 1, scan time = 4 min 26 s. The time course of the administration of gadolinium contrast agent and MR imaging is shown in Fig. 1. The 3D T1-weighted gradient-echo images were obtained after the administration of a 0.1 mmol/kg (standard dose) and an additional 0.1 mmol/kg (cumulative double dose) of gadoteridol (Pro-Hance; Eisai, Tokyo). The first scan was obtained 5 min after the administration of the first dose of 0.1 mmol/kg. The additional dose of 0.1 mmol/kg (cumulative double dose) was injected immediately after the first scan. The second scan was obtained 13 min after the first Gd administration.

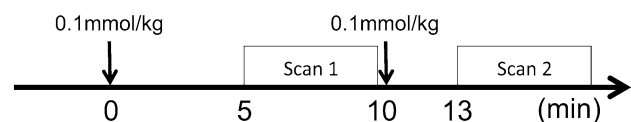


Fig. 1 Diagram of the protocol. The first scan is obtained 5 min after the administration of the first dose of 0.1 mmol/kg. The additional dose of 0.1 mmol/kg (cumulative double dose) is injected immediately after the first scan. The second scan is obtained 13 min after the first Gd administration

Contrast-to-enhancement ratio

The lesion-to-normal contrast-to-enhancement ratio (CER) was compared between the standard and double doses. For the CER evaluation, we selected lesions with a diameter larger than 5 mm and homogeneous solid enhancement. As a result, 37 metastatic lesions were selected in the database. The CER was calculated as follows:

$$\text{CER} = \text{SI}_{\text{lesion}} / \text{SI}_{\text{background}},$$

where $\text{SI}_{\text{lesion}}$ and $\text{SI}_{\text{background}}$ represent the mean signal intensities of the lesion and background, respectively. The signal intensity of the background was measured in the contralateral normal-appearing white matter in the same imaging slice. These parameters were obtained by defining circular regions of interest (ROIs) of 5 mm in each location.

Observer study

A total of 104 metastases including 56 small lesions (<5 mm), 27 medium-sized lesions (≥ 5 mm and <10 mm), and 21 large lesions (≥ 10 mm) were observed in 27 patients (18 men, 9 women; 60.3 ± 10.9 years old; 19 patients with lung cancer, 3 with breast cancers, 1 with renal cancer, 1 with esophageal cancer, 1 with rectal cancer, 1 with oral floor carcinoma, and 1 with parotid gland cancer). In addition, 12 cases without any enhancing lesions (7 men, 5 women; 59.6 ± 13.4 years old; 10 patients with lung cancer, 2 patients with breast cancer) were selected. These 39 cases were used for the observer tests. The diameter of the lesion was measured in the image obtained with the cumulative double dose.

Nine radiologists who were blinded to the patients' clinical information and were not informed of the purpose of the study, including four first-year radiology residents who each had 2 years of experience in radiology practice and five board-certified radiologists who had 15, 12, 11, 10, and 7 years of experience, respectively, participated in the observer test. None of the nine radiologists participated in the case selection. Each radiologist took part in two reading sessions, which were each at least 1 month apart. Each session was comprised of half single-dose images and half cumulative double-dose images in a random manner so that the observers were blinded to the dose in these images. The observers were blinded to the number of lesions, but were informed that the reading time was measured. All images were displayed by one of the authors, who did not participate in the test, on a 20.8-in. liquid crystal display monitor of a picture archiving and communication system (PACS, Toshiba Medical Systems, Japan). Other images than the selected images for the test were not displayed.

The radiologists were allowed to freely increment the sections by using a mouse with a wheel. In each reading session, the 39 cases were presented in a randomized order. For a training session before the test, three training cases, each of which had 10–12 metastases, were provided to the radiologists to familiarize them with the operation of the PACS and the rating system. The radiologists were asked to place an arrow electronically in each location where they found a metastasis, to record the results of the readings. The radiologists were asked to report their level of confidence in the presence of metastasis at each location by using a rating bar scale, on which the right and left ends corresponded to the highest (100) and lowest (0) confidence levels, respectively. The reading time for each case was recorded.

Statistical analyses

The CER was compared between the single dose and cumulative double dose by paired *t*-test. To evaluate the radiologists' performances in the observer test, we used a jackknife free-response receiver operating characteristic (JAFROC) analysis [15, 16]. This analysis has been proposed to statistically estimate the differences in diagnostic performance between different modalities when location issues are relevant. We applied the JAFROC analysis with method 1 of Chakraborty and Berbaum [15] to estimate a figure-of-merit (FOM) value as an index of each radiologist's performance in each session. A free software package (JAFROC1, <http://www.devchakraborty.com>) was used. We also obtained the sensitivity and the number of false-positive results per case (FPs/case). Imaging findings related to the false-positive (FP) results judged by the consensus of two of the board-certified radiologists were reported. Additionally, sensitivities were compared between the two doses according to lesion size: small (<5 mm in shorter diameter), medium (≥ 5 and <10 mm) and large (≥ 10 mm). The sensitivity, FP/case, and reading time between the two doses were compared by paired *t*-test. For all analyses, $P < 0.05$ was considered significant.

Results

Contrast-to-enhancement ratio

The lesion-to-normal CER in the cumulative double dose examinations was significantly higher (1.3-fold; 1.88 ± 0.52 , $P < 0.00001$) than that in the standard dose examinations (1.42 ± 0.37) (Fig. 2).

Fig. 2 A 60-year-old man with a brain metastasis in the right parietal lobe. Transverse T1-weighted gradient echo MR images show a brain metastasis (arrows) imaged with the standard dose (a) and the cumulative double dose (b). Note that the contrast-enhancement ratio (CER) is markedly increased with the cumulative double dose

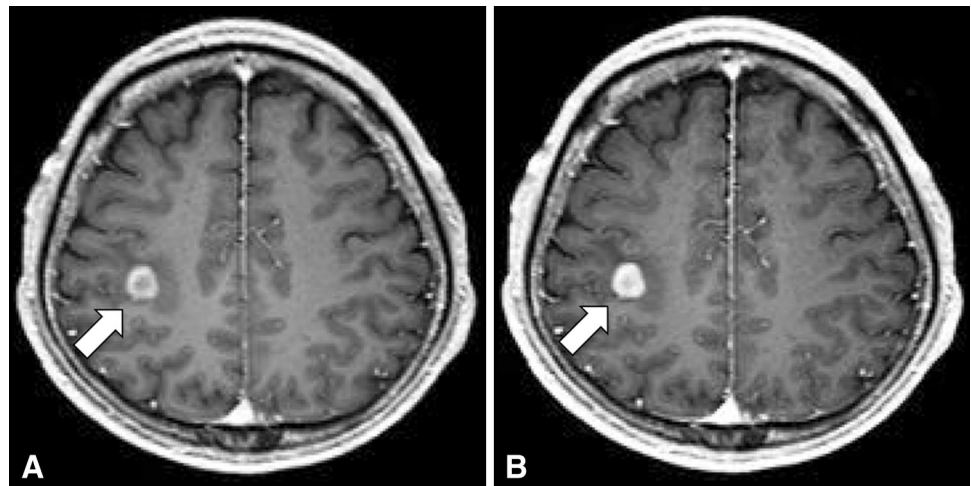


Table 1 Sensitivity for two reading sessions according to the observer groups

Observer	All lesions			Small lesions (<5 mm)		
	Standard dose	Double dose	<i>P</i> value*	Standard dose	Double dose	<i>P</i> value*
Residents						
A	58.7	76.9		26.8	60.7	
B	65.4	85.6		37.5	73.2	
C	50.0	63.5		12.5	35.7	
D	62.5	76.0		32.1	55.4	
Average	59.1	75.5	0.0024	27.2	56.2	0.0005
Board-certified radiologists						
E	61.1	79.6		27.3	61.8	
F	63.1	75.7		30.1	54.5	
G	69.9	89.3		43.6	80	
H	63.1	86.4		30.9	74.5	
I	57.7	76.9		25	57.1	
Average	63.0	81.6	0.0007	31.4	65.6	0.0033
Overall average	61.3	78.9	<0.0001	29.5	61.5	<0.0001
Observer	Medium-sized lesions (≥5 and <10 mm)			Large lesions (≥10 mm)		
	Standard dose	Double dose	<i>P</i> value*	Standard dose	Double dose	<i>P</i> value*
Residents						
A	92.6	96.3		100	100	
B	96.3	100		100	100	
C	88.9	92.6		100	100	
D	96.3	100		100	100	
Average	93.5	97.2	<0.0001	100	100	NS
Board-certified radiologists						
E	100	100		100	100	
F	100	100		100	100	
G	100	100		100	100	
H	100	100		100	100	
I	92.6	100		100	100	
Average	98.5	100	NS	100	100	NS
Overall average	96.3	98.8	0.02	100	100	NS

* *P* values are for comparisons between standard and double dose using paired *t*-test

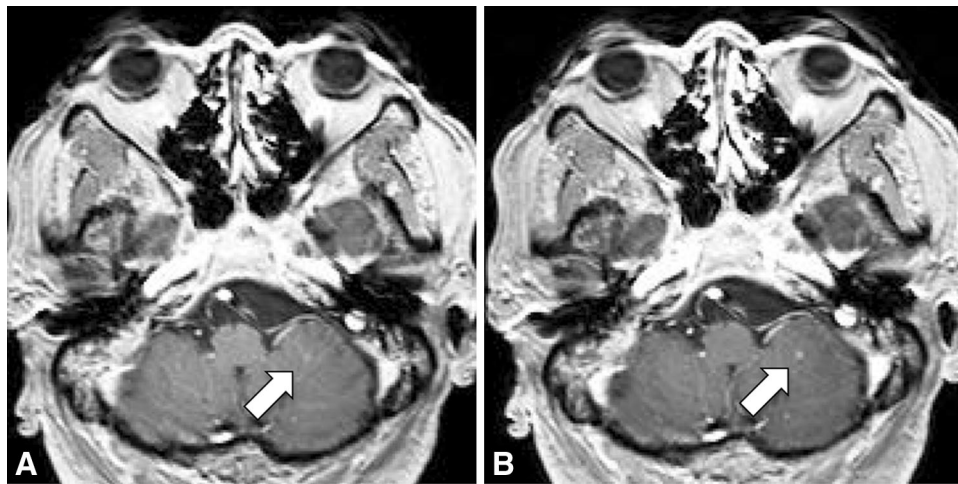


Fig. 3 A 66-year-old man with a brain metastasis in the left cerebellar hemisphere. Transverse T1-weighted gradient echo MR images show a small metastasis (2 mm diameter, *arrows*) imaged with the standard dose (**a**) and the cumulative double dose (**b**). The lesion is clearly identified with the cumulative double dose, whereas it

is barely visible with the standard dose. In the observer study, this lesion was overlooked by all nine radiologists with the standard dose, but was correctly detected by all observers with the cumulative double dose

Table 2 False-positive results per case for two reading sessions according to the observer groups

Observer	FPs/case		P value*
	Standard dose	Double dose	
Residents			
A	0.26	0.19	
B	0.28	0.31	
C	0.08	0.15	
D	0.05	0.03	
Average	0.17	0.17	NS
Board-certified radiologists			
E	0.08	0.18	
F	0.15	0.38	
G	0.13	0.18	
H	0.13	0.15	
I	0.03	0.23	
Average	0.10	0.23	0.028
Overall average	0.13	0.20	NS (0.06)

* P values are for comparisons between standard and double dose using paired t-test

FPs/case false-positives per case

Observer study

Table 1 summarizes the results for the sensitivity of the observer study. Sensitivity with the cumulative double dose was significantly higher than that with the standard dose for all radiologists in all lesions ($P < 0.0001$). In the small lesions (< 5 mm), sensitivity with the cumulative double dose was approximately twice as high as that with the

standard dose for all nine radiologists ($P < 0.0001$). In the medium-sized lesions (≥ 5 and < 10 mm), the cumulative double dose showed higher sensitivity than the standard dose for the four first-year residents ($P < 0.0001$), but not for the five board-certified radiologists, whose sensitivities were approximately 100 % in both doses (98.5 % for single dose, 100 % for cumulative double dose). In the large lesions (≥ 10 mm), both doses showed 100 % sensitivity for all nine radiologists. Figure 3 shows a patient with a solitary small brain metastasis in which the cumulative double-dose image better delineates the lesion with higher lesion-to-normal contrast than the standard dose. This lesion was detected by none of the radiologists in the standard-dose image but by all nine radiologists in the cumulative double-dose image.

The FP/case values (Table 2) for all radiologists was slightly higher for the cumulative double dose than for the standard dose, although this difference was not significant ($P = 0.06$). The FP/case values by the board-certified radiologists were higher for the cumulative double dose

Table 3 Summary of imaging findings related to false-positive results for 2 reading sessions

Findings	Standard dose	Double dose
Artifacts	28	38
Blood vessels	17	28
Choroid plexus	2	3
Pineal body	0	1
Total	47	70

Numbers are frequencies of findings observed in each reading session

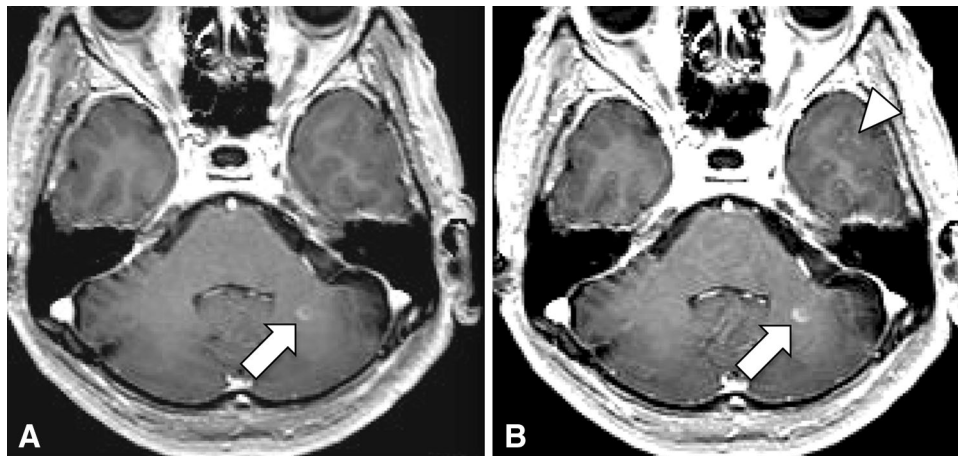


Fig. 4 A 72-year-old woman with false positives. Post contrast transverse T1-weighted gradient echo MR images show a high intensity area (arrows) in the left cerebellar hemisphere both in the standard dose (a) and the cumulative double dose (b). This is considered a flow-related artifact from the sigmoid sinus, and is more

clearly observed with the cumulative double dose than with the standard dose. Small, high intensity spots (arrowhead), which are considered to be blood vessels, are seen in the left temporal lobe more clearly in the cumulative double dose than in the standard dose

Table 4 Figure of merit (FOM) for two reading sessions according to the observer groups

Observer	Standard dose	Double dose	<i>P</i> value*
Residents			
A	0.732	0.869	
B	0.785	0.887	
C	0.730	0.792	
D	0.801	0.876	
Average	0.762	0.856	0.01
Board-certified radiologists			
E	0.771	0.877	
F	0.784	0.835	
G	0.822	0.929	
H	0.778	0.907	
I	0.783	0.856	
Average	0.788	0.880	0.0025
Overall average	0.776	0.870	<0.0001

* *P* values are for comparisons between standard and double dose using paired *t*-test

than for the standard dose ($P < 0.05$), whereas no significant difference was found among the residents. For each reading session, artifacts and blood vessels were the most common imaging findings resulting in FPs (Table 3; Fig. 4).

The FOM (Table 4) with the cumulative double dose was significantly higher than that with the standard dose for all radiologists ($P < 0.0001$).

The average reading time with the cumulative double dose (129.5 ± 50.8 s) was significantly longer than that

with the standard dose (119.9 ± 48.3 s) for all radiologists ($P < 0.05$).

Discussion

Our study demonstrated that the cumulative double dose of administration of gadolinium substantially increased the CER of brain metastases at 3 T, and it improved radiologists' diagnostic performance especially for small lesions (< 5 mm). The sensitivity for these small lesions in the cumulative double dose was improved and approximately twice as high as that in the standard dose. To our knowledge, there have been no studies that evaluated, in a systematic observer test, the efficacy of the double-dose Gd administration at 3 T for improving radiologists' diagnostic performance in detecting brain metastases.

Small brain metastases, frequently located close to the corticomedullary junction, may lack vasogenic edema or mass effect, which makes the detection of such lesions challenging. In general, an improvement of spatial resolution may help detect small lesions, and thus high-resolution 3D T1-weighted images with a resolution of approximately 1 mm voxel is replacing conventional 2D images with thick slices (~ 5 mm), and it is becoming a current standard for the imaging of brain metastases [17]. A more important factor for detecting such small lesions is an increase in lesion contrast, which can be achieved by the use of a higher dose, higher magnetic field strength or longer interval between the administration of contrast agent and imaging acquisition. For an intraparenchymal lesion to be detected with MR imaging, a signal intensity difference of at least 21 % must exist between the lesion and its

background [18]. Our present results showed that using the standard dose resulted in a 42 % difference (CER 1.42 ± 0.37) between the lesion with an enhancing area (> 5 mm) and the normal white matter, whereas an 88 % difference (CER 1.88 ± 0.52) was found with the use of the cumulative double dose. Since it was reported that the lesion contrast is a function of lesion size [10], the small lesions (< 5 mm) might have lower contrast and drop below a threshold for detection in the standard dose. The advantage of a higher contrast dose for brain metastases has been described mostly at ≤ 1.5 T [6–9]. Studies by Yuh et al. [6, 7] and Runge et al. [9] showed that both the visualization and the detection of brain metastases were improved with triple-dose contrast material (0.3 mmol/kg). In one study [6], Yuh et al. [7] demonstrated improved visualization in 80 of 81 metastatic lesions for 19 of 27 patients examined, and an additional 46 new lesions were identified. In a multicenter trial, unblinded observers found improved diagnostic confidence and detected 105 additional lesions (309 vs 204) with a triple dose compared with the standard dose. Yuh et al. also revealed in an observer study at 0.5 or 1.5 T that the sensitivity for small metastases (< 5 mm) was markedly improved with a cumulative triple dose compared to the standard dose [8]. The interval between the two doses of contrast agent injection in this study might have had an effect of delayed enhancement on the increased CER for the cumulative double dose and not just the higher dose. There have been reports that delayed imaging (20–30 min) improves the detection rate, especially for small metastases [8, 13]. The delay effect, however, tended to be less pronounced than the dose effect [8]. In this study, the delayed effect of Gd administration might not be sufficient for the first scan. However, the second scan could benefit from the combination of the delayed effect and additional dose of contrast agent.

Our present findings revealed that this increase in detectability for small metastases was also obtained at 3 T. A triple dose is not permitted for clinical usage in some countries. However, we found it effective to apply even a double dose of contrast agent to increase the sensitivity for detecting metastases at 3 T. Regarding medium and larger metastases (≥ 5 mm), the sensitivities were excellent with both doses; however, there was still room for improvement for the medium-sized lesions (≥ 5 and < 10 mm) among the residents. Consequently, the sensitivity for larger lesions was nearly 100 % with the cumulative double dose in all radiologists.

In this study, we excluded the cases with more than 15 metastases since the presence of many lesions (more than 15 lesions) does not affect therapeutic strategy. However, in patients with 10–15 metastases, it is possible that a single dose examination detects only a few metastases out

of many lesions, which could alter the therapeutic strategy. In fact, two residents and one board-certified radiologist in the observer study detected only 4 or 5 out of 13 metastases in a patient.

In the present study, the mean FOM value for the cumulative double dose was significantly higher than that for the single dose, which indicates improved radiologists' diagnostic performance due to the increased sensitivity. Nevertheless, the cumulative double dose results showed higher FPs/case compared to the standard dose, and the difference was significant in the group of five board-certified radiologists. Analyses of FP results have revealed that enhancing vessels and artifacts are the most common mimickers of metastases. The higher FPs/case at the higher dose of Gd administration in our study might be the result of increased signal intensities of blood vessels and flow-related artifacts that could have been misdiagnosed as metastases. The elimination half-life of gadoteridol in blood was reported to be 1.57 ± 0.08 h [19]. The interval between first and second scans was only 8 min and thus it was likely that the concentration in blood vessels was not much reduced during the interval. Since the second scan was obtained after the double dose Gd injection, the concentration in blood vessels should be higher in the second scan than in the first scan. The reading time for the cumulative double dose was significantly longer than that for the single dose. A possible explanation for this is that the increased FPs caused by those blood vessels or artifacts could delay the radiologists' decision in making the diagnosis of metastases. Another explanation would be that the observer might take time to mark the lesions when the number of lesions was increased.

The limitations of this study include a lack of histopathologic confirmation of the diagnosis of metastasis. This was often a problem, especially for the small brain metastases. Instead, the diagnoses of metastasis were made based on the consensus of two experienced neuroradiologists, using the clinical criteria described in a previous study, which might be too generous. Distinctions between artifacts or vessels and small metastases were difficult in some patients in the case selection. Contamination of other pathologies with enhancement, such as subacute infarction, cannot be completely eliminated from imaging findings alone. In addition, because we included only lesions that were visualized in both standard- and cumulative-double-dose images, true metastatic lesions that were seen only in the cumulative double dose might have been excluded. Nevertheless, we believe that our performance comparisons of the two doses are convincing since this study involved a large number of lesions and observers.

In conclusion, the double dose of MR contrast agent showed higher lesion-to-normal CER for brain metastases at 3 T compared with the standard dose. The double dose

improved the detection of metastases smaller than 5 mm at 3 T, and thus resulted in better overall diagnostic performance by the radiologists. However, we need to keep in mind that a higher dose might result in prolonged reading time and increased false positive cases, presumably due to increased vessel signals and frequency of flow-related artifacts.

Conflict of interest The authors declare that they have no conflict of interest.

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