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Comparison of Single- and Triple-Dose Contrast Material in the MR Screening of Brain Metastases

Gordon Sze, Carl Johnson, Yasutaka Kawamura, S. Nahum Goldberg, Robert Lange, Richard J. Friedland, and Robert J. Wolf

PURPOSE: Although studies obtained with triple-dose contrast administration can show more brain metastases than those obtained with single-dose contrast material in patients with multiple metastases, such studies are costly and of limited clinical benefit. Since most patients who undergo screening have negative findings or a single metastasis, this study was performed to compare the clinical utility of single-dose versus triple-dose contrast administration in this large group of patients who could benefit from the possible increased sensitivity in lesion detection.

METHODS: Ninety-two consecutive patients with negative or equivocal findings or a solitary metastasis on single-dose contrast-enhanced MR images underwent triple-dose studies. Findings were compared with a standard of reference composed of panel review and long-term follow-up. Further analysis was performed by comparing results with those obtained by two blinded readers.

RESULTS: In all 70 negative single-dose studies, the triple-dose studies depicted no additional metastases in terms of the standard of reference. No statistically significant difference was seen between the results of the single- and triple-dose studies. For 10 equivocal single-dose studies, the triple-dose study helped clarify the presence or absence of metastases in 50% of the cases. In 12 patients with a solitary metastasis seen on the single-dose study, the triple-dose study depicted additional metastases in 25% of the cases. In the results of one of the two blinded readers, use of triple-dose contrast led to a statistical difference by decreasing the number of equivocal readings but at the expense of increasing the number of false-positive readings.

CONCLUSION: Routine triple-dose contrast administration in all cases of suspected brain metastasis is not helpful. On the basis of our investigation, we conclude that the use of triple-dose contrast material is beneficial in selected cases with equivocal findings or solitary metastasis, although with the disadvantage of increasing the number of false-positive results.

The use of higher doses of gadolinium-based contrast material for MR imaging has been reported to improve the detectability of intraparenchymal metastatic lesions to the brain (1-6); however, in the majority of published cases in which improved lesion detection was found with this technique, one or more metastases were seen on single-dose studies. These results, therefore, seem to be of limited clinical sig-

nificance, since the identification of more punctate lesions in patients with known multiple metastases will not change clinical management (7, 8).

Many patients referred for evaluation of suspected brain metastases have negative findings on MR studies obtained with single-dose contrast material. A few have indeterminate MR results, in which the presence of a single metastatic lesion is in question, and some have studies positive for a single potentially resectable metastasis. Increased sensitivity of lesion detection in all these circumstances would be desirable, as clinical management of these patients would be potentially altered.

In this study, we prospectively evaluated the utility of triple-dose contrast material in the MR screening for brain metastases in patients with negative or equivocal findings or with a solitary metastasis on single-dose MR images. Our goal was to determine if

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a higher contrast dose aids in lesion detection in situations in which clinical management might be altered.

Methods

Patients

Of 136 consecutive patients referred for evaluation of possible brain metastases, 93 had standard, single-dose contrast MR studies that were interpreted as negative, equivocal, or positive for solitary intracerebral metastasis. These patients formed the basis for this study. All patients had a clinical history of systemic tumors, such as lung cancer, melanoma, and breast carcinoma, with a high likelihood of brain metastasis and a clinical indication for scanning, such as mental status changes, seizures, or preoperative screening.

Forty-three of the 136 consecutive patients were excluded from the analysis. Thirty-three had more than one definite metastasis on single-dose scans and 10 refused further scanning with triple-dose contrast material. Written informed consent was obtained for each patient, and this study had appropriate human investigation committee approval.

MR Imaging

MR imaging was performed with a 1.5-T magnet. Proton density-weighted (2000–2500/30 [TR/TE]), T2-weighted (2000–2500/80–110), and T1-weighted (550–667/26) images were obtained with contiguous 5-mm-thick sections in the axial plane. To shorten the scan time of the long-TR sequences, 96 patients were studied with fast spin-echo sequences (2500/26,82–104; echo train length, 8; echo spacing, 14). Thirty-four scans were performed using conventional spin-echo sequences, and six patients underwent both fast and conventional spin-echo imaging.

In all T1-weighted sequences, identical imaging parameters and options were selected in a given patient, including TR, TE, matrix size (256 × 192), number of excitations (two), and first-order flow compensation. To facilitate accurate direct comparison, images were obtained at the same location and at the same angle in all sequences for a given patient.

Contrast Injection

Single-dose contrast scans were obtained first using 0.1 mmol/kg intravenous gadopentetate dimeglumine. In 77 cases, T1-weighted images with triple-dose contrast material were obtained immediately after the standard-dose scans to avoid delayed enhancement effects (9). The decision to proceed with triple-dose contrast imaging was made when the initial findings were determined to be negative, equivocal, or to show only one metastasis. The time interval between the initial 0.1 mmol/kg contrast injection and an additional 0.2 mmol/kg injection was less than 5 minutes. In 16 cases, including five patients with a solitary metastasis on the single-dose study, a single injection of 0.3 mmol/kg of contrast material was administered after non-contrast T1-weighted imaging at an interval of 24 hours to 1 week after the single-contrast MR study. These 16 patients did not receive the usual additional 0.2 mmol/kg dose after the single-dose study owing to either unavoidable technical or logistic factors at the time or to a revised interpretation of the study on subsequent evaluation.

Imaging Analysis

Image analysis was performed both by consensus reading and by blinded review. Images were first reviewed by a panel of three radiologists who viewed all single- and triple-dose scans simultaneously. A reading of positive, equivocal, or negative for metastases was made for the single- and triple-dose images

separately. A final consensus reading was then undertaken for the total study.

In a second imaging analysis, two neuroradiologists, who had no previous knowledge of the cases and who were blinded to clinical history, individually interpreted the axial T1-weighted sequences with single-dose contrast separately from the triple-dose sequences. These reviewers marked the locations of lesions on schematic diagrams of brain images.

MR results were interpreted as negative when no abnormal enhancement was noted or if the enhancement pattern was incompatible with metastasis (10). Equivocal scans were defined as those in which the radiologists were unsure as to the presence of a metastatic lesion and therefore would have preferred further clarification. Positive cases were considered to be those in which a single enhancing focus, consistent with a metastasis, was detected.

With the use of methodology similar to that used in previous published studies to verify the presence or absence of metastatic disease, diagnostic confirmation was based on clinical neurologic examination after 6 months or longer or on follow-up examination with MR and/or CT after 3 to 6 months (10, 11). In cases interpreted as negative in the consensus reading, subsequent negative neurologic examination after 6 months or longer was considered verification of the lack of brain involvement. In addition, follow-up imaging examination was performed in 78 of the 93 patients, including most of the patients with negative studies and all the patients whose studies were interpreted as equivocal or positive in the consensus reading. These follow-up imaging studies were considered positive if lesions decreased in size with radiation therapy or if lesions increased in size without treatment (10). The standard of reference consisted of the consensus reading combined with follow-up imaging studies and/or clinical neurologic follow-up examinations serving as the ultimate verification.

The statistical analysis was based on a comparison of the distribution of positive, equivocal, and negative readings for the true-positive and true-negative cases as a function of the number of contrast doses administered. The statistical test used was a contingency table analysis, performed with the Stat View SE and Graphics program (Abacus Concepts, Inc, Aurora, Ill). Both the consensus readings and the blinded reviews were analyzed.

Results

Using the criteria of the reference standard, 78 of the 93 patients had negative findings and 14 had positive findings. One case did not fulfill the criteria of the reference standard, as the consensus reading was equivocal and the patient was lost to follow-up. This patient was excluded from further analysis, leaving a total of 92 patients in the study group.

Consensus Review

The data are summarized in Table 1. Seventy (76%) of the 92 patients were considered to have no metastasis on the standard, single-dose contrast studies. In these cases, triple-dose contrast revealed no additional metastases. In one of these cases, the use of triple-dose contrast led to an indeterminate result, as an abnormal punctuate enhancement was seen only on the triple-dose study (Fig 1). This focus did not change on follow-up MR examination and was not thought to represent a metastasis.

Ten studies (11%) were read as equivocal for metastasis on the single-dose study. In five (50%) of these cases the use of triple-dose contrast proved

TABLE 1: Consensus results relative to standard of reference in 92 cases

	Reference Standard			
	Negative	No.	Positive	No.
	Read as negative on single-dose studies. Of these, 69 were read as negative on triple-dose studies and one was false positive.	70	Read as positive on single- and triple-dose studies.	12
	Read as equivocal on single-dose studies. Three were negative on triple-dose studies, five remained equivocal but were negative at follow-up.	8	Read as equivocal on single-dose studies. Both were positive on triple-dose studies.	2
Total		78		14

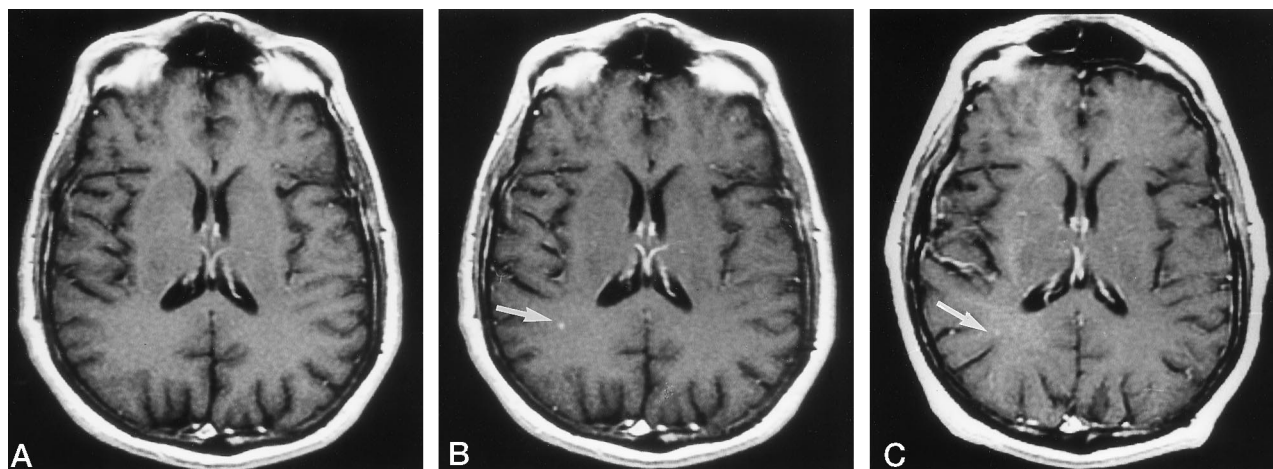


FIG 1. T1-weighted (600/26) images with single-dose (A) and triple-dose (B) contrast in a 55-year-old man with melanoma. A punctate focus of enhancement is only seen on the triple-dose image (arrow). The 6-month follow-up MR study with triple-dose contrast (C) shows this focus less obviously (arrow), suggesting that it is not a small metastasis but more likely a vascular structure.

helpful. In two cases, the triple-dose study confirmed the presence of a solitary metastasis (Fig 2). In the other three cases, the lesion in question proved to be an artifact, and no real abnormalities were identified on the triple-dose study. The other five cases remained equivocal. Although lesions became more prominent, follow-up MR studies showed them not to be metastases. Abnormal enhancement proved to be caused by vascular enhancement (Fig 3), flow artifact, or an enhancing lesion of nontumoral origin (Fig 4).

In 12 cases (13%), a solitary metastasis was identified on the single-dose images. In eight cases, the triple-dose study confirmed the presence of the single metastasis. In the remaining four cases (33%), the triple-dose study provided further information. Additional metastases were identified in three cases (25%). In a fourth case, in which two additional possible metastases were thought to be equivocal on the single-dose study, the triple-dose MR study revealed only a solitary metastasis. In this case, a solitary metastasis was confirmed at surgery.

Statistical Analysis.—The data are summarized in Table 2. Of the 14 cases that were positive according to the standard of reference, 12 were positive and two were equivocal on the single-dose study as read in the consensus review. All 14 cases were positive on the triple-dose study, but this difference was not statistically significant ($P = .46$).

Of the 78 cases that were negative by the standard of reference, 70 were negative and eight were equivocal on the single-dose study as read in the consensus review. Among the triple-dose studies, 72 were negative, five were equivocal, and one was positive. The distribution of cases among the three categories for the single- and triple-dose studies was not statistically different ($P = .42$).

The negative predictive value with the use of triple-dose contrast material was 100%. The positive predictive value in going from single to triple dose actually decreased from 100% to 91%.

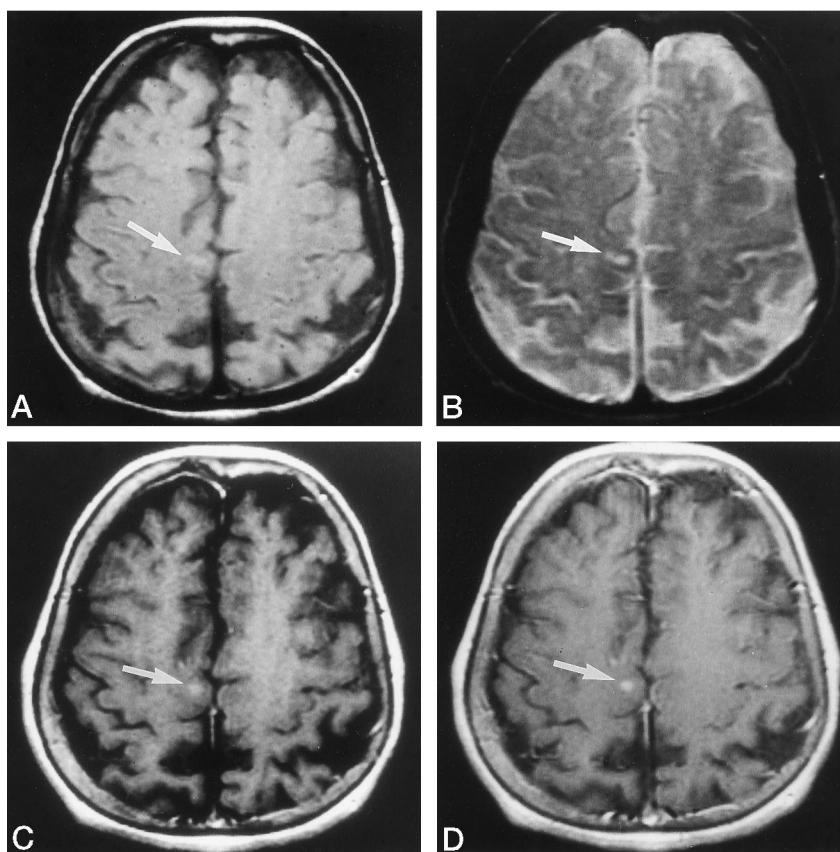
Blinded Review

The data from the two blinded reviewers were interpreted separately (Table 3).

Negative Studies.—On the single-dose contrast studies, reader A identified 69 studies as negative. Of these, all 69 proved to be truly negative when compared with the reference standard. On the triple-dose contrast studies, reader A identified 67 studies as negative for metastases. These 67 were truly negative when compared with the reference standard. Thus, the use of triple-dose contrast material reduced the percentage of negative cases read correctly from 88% (69/78) to 86% (67/78) for reader A.

On the single-dose contrast studies, reader B iden-

FIG 2. An 81-year-old woman with adenocarcinoma of unknown origin, proved later to be lung carcinoma. Proton density- (A) and T2-weighted spin-echo (2000/30,80) (B) images barely show a small high-intensity lesion (arrow) in the right paracentral lobule. T1-weighted image (617/26) with single-dose contrast (C) shows mild enhancement (arrow). This study was interpreted as equivocal. The triple-dose study (D) shows intense enhancement and confirms the presence of a solitary metastasis (arrow).



tified 70 studies as negative for metastases. All 70 of these cases were negative by the reference standard. On the triple-dose studies, reader B interpreted 66 cases as negative. These 66 cases were all negative on the reference standard. Thus, the use of triple-dose contrast material reduced the percentage of negative cases interpreted correctly from 90% (70/78) to 85% (66/78) for reader B.

There were no false-negative readings for readers A and B on either the single- or triple-dose studies.

Equivocal Studies.—Reader A identified nine studies as equivocal on the single-dose contrast series. Of these nine, six proved to be negative according to the reference standard and three proved to be positive. On the triple-dose studies, reader A identified eight cases as equivocal. Of these, six were negative according to the reference standard and two were positive. Thus, the use of triple-dose contrast material reduced the percentage of equivocal cases from 10% (9/92) to 9% (8/92).

Reader B identified 10 studies as equivocal on the single-dose contrast series. Of these 10 studies, seven proved to be negative and three proved to be positive by the reference standard. On the triple-dose studies, reader B identified six cases as equivocal. Of these, four proved to be negative and two proved to be positive. Thus, the use of triple-dose contrast material reduced the percentage of equivocal cases from 11% (10/92) to 6.5% (6/92).

Positive Studies—On the single-dose contrast studies, reader A identified 14 cases as definitely positive

for solitary intracranial metastases. Of these, 11 were true-positive and three were false-positive readings. On the triple-dose studies, reader A identified 17 cases as positive. Of these, 12 were true-positive and five were false-positive readings. Thus, the use of triple-dose contrast material increased the percentage of positive cases read correctly from 79% (11/14) to 86% (12/14). However, it also led to an increase in the percentage of false-positive cases from 21% (3/14) to 36% (5/14) for reader A.

On the single-dose studies, reader B identified 12 as definitely positive for intracranial metastases. Of these, 11 were true-positive readings and one was a false-positive reading as compared with the standard of reference. On the triple-dose studies, reader B identified 20 cases as positive. Of these, 12 were true-positive and eight were false-positive readings. Thus, the use of triple-dose contrast material increased the percentage of positive cases read correctly from 79% (11/14) to 86% (12/14). However, it also led to an increase in the percentage of false-positive readings from 7% (1/14) to 57% (8/14) for reader B.

Statistical Analysis.—For reader A, there was no statistical difference between the distribution of results for the single-dose and triple-dose readings (see Table 4). However, for reader B, when the 78 negative cases were considered, there was a statistically significant difference between the distribution of results for the single-dose and triple-dose readings ($P =$

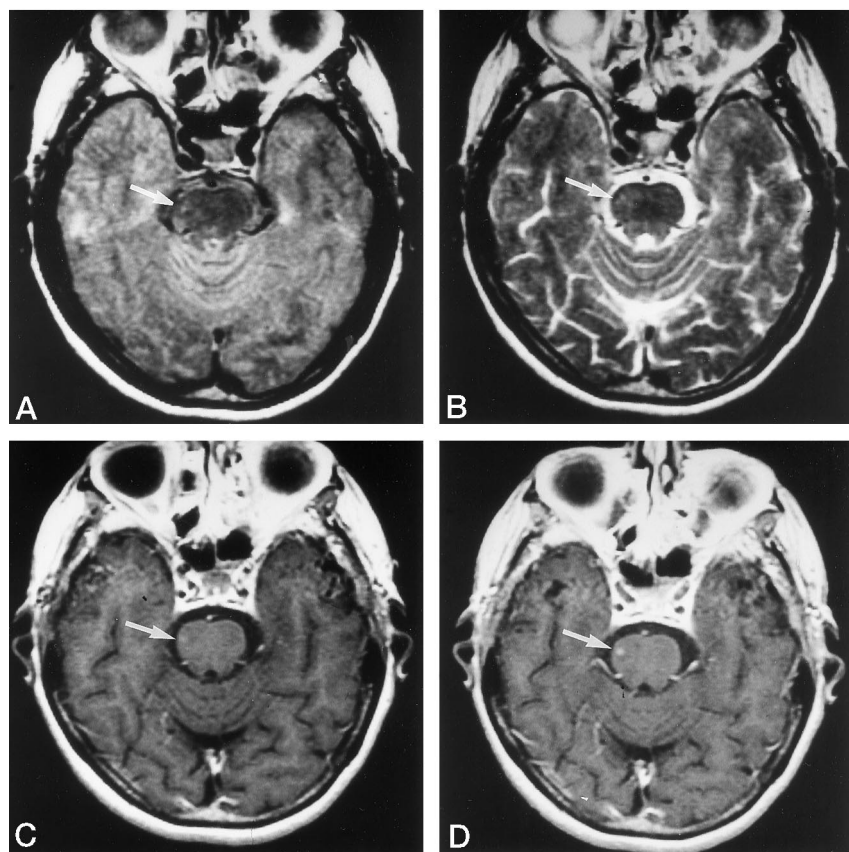


FIG 3. Proton density– (A) and T2-weighted fast spin-echo (2500/26,104) (B) images in an 80-year-old woman with lung cancer show a pinpoint signal abnormality in the right pons (arrow). T1-weighted image (600/26) with single-dose contrast (C) shows a slightly enhancing lesion (arrow). On the triple-dose scan (D), intense enhancement is noted (arrow). The 12-month clinical follow-up revealed no neurologic symptoms and the probable diagnosis was capillary telangiectasia. The 2-year MR imaging follow-up study was unchanged.

.024). This difference was primarily due to an increase in the number of false-positive readings.

The negative predictive value with the use of triple-dose contrast material was 100%. The positive predictive value in going from single to triple dose decreased for reader A from 78% to 70% and for reader B from 92% to 60%.

Discussion

Intracranial metastases are the most common brain neoplasms in adults and are a serious complication of systemic cancer. Posner and Chernik (12) found that intracranial metastases were present at autopsy in 24% of 2735 patients with metastatic cancer. Aronson et al (13) found that 16.5% of 2406 patients with extracranial neoplasms had intracranial metastasis at autopsy. And using contrast-enhanced CT as a screening test, Salvatierra et al (14) and Butler et al (15) reported that the incidence of brain metastasis from lung cancer is between 5% and 13%.

It is well recognized that contrast-enhanced MR imaging is more sensitive than contrast-enhanced CT in the detection of brain metastasis (11, 16–18). Given the improved treatment techniques and survival rates for primary cancers, the role of MR imaging in detecting brain metastases has become increasingly important.

Studies by Yuh et al (1, 2) and Runge et al (3) have shown both improved visualization of individual lesions and increased detection of lesions with triple-

dose contrast material (0.3 mmol/kg) in patients with identified intracerebral metastases on routine contrast-enhanced (0.1 mmol/kg) MR images. In one study, Yuh et al (1) noted improved visualization in 80 of 81 metastatic lesions for 19 of 27 patients studied. An additional 46 new metastases were identified. In a multicenter trial, unblinded reviewers found improved diagnostic confidence and detected 105 additional lesions (309 versus 204) with triple-dose compared with single-dose gadoteridol (2). Runge et al (3) reported finding four additional brain metastases in the 12 patients they studied (25%). A comparison of immediate and delayed single-dose contrast studies with immediate triple-dose contrast studies by Yuh et al (4) revealed improved detection of small (<10 mm) lesions on the triple-dose contrast scans compared with either the immediate or delayed single-dose scans. In seven of eight patients, two lesions were reported on the triple-dose studies versus one on either the immediate or delayed single-dose studies. In two patients, one lesion was found on the triple-dose study and none was seen on the single-dose examinations.

Although these studies support the use of higher doses of contrast material for increased metastatic lesion detection and improved lesion enhancement and delineation (1–3), they should be interpreted with caution. Because these studies were based primarily on patients shown to have brain metastases, their results seem to be of limited clinical importance, particularly since the additional metastases found

FIG 4. A 79-year-old woman with melanoma and colon carcinoma. A small high-intensity lesion (*arrow*) is seen on the proton density-weighted fast spin-echo (2500/26) image. The lesion (*arrow*) shows mild enhancement on the single-dose study (B) and marked enhancement on the triple-dose scan (C). This case was interpreted as equivocal because the possibility of a tiny metastasis could not be excluded. The 5-month follow-up MR study with triple-dose contrast (D) shows no interval changes (*arrow*) and confirms that this is not metastasis but more likely a vascular anomaly.

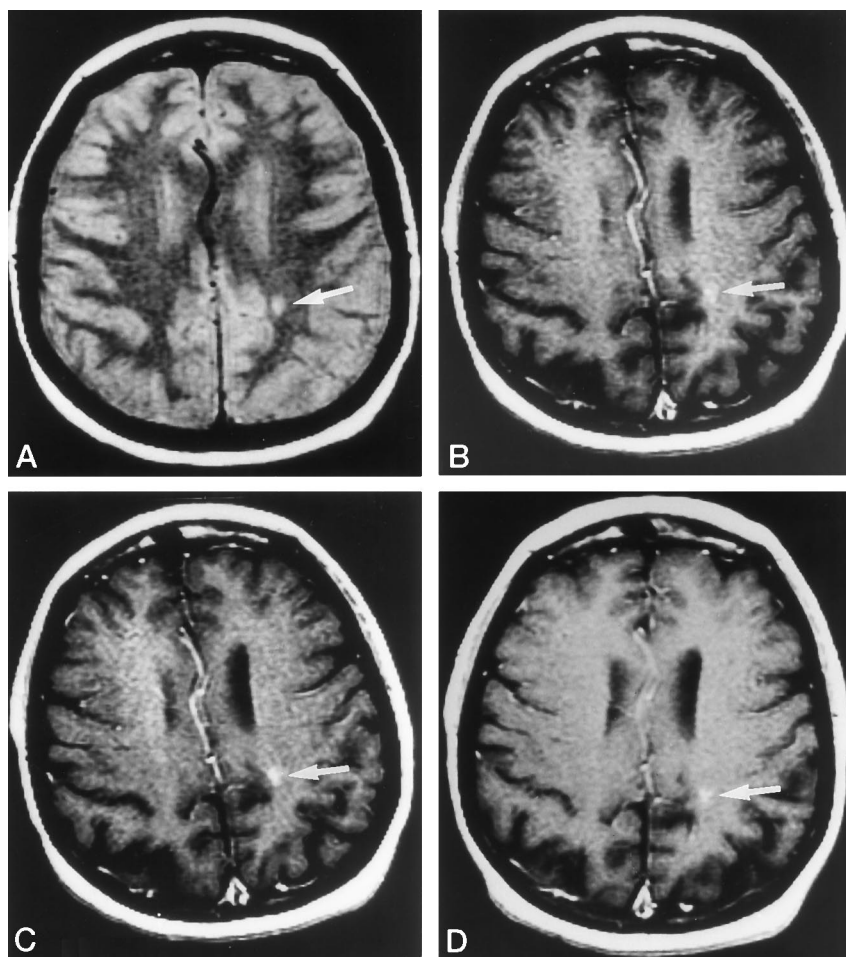


TABLE 2: Distribution of readings in the consensus review of single-dose and triple-dose studies

	True Positives (n = 14)		True Negatives (n = 78)		
	Positive	Equivocal	Negative	Equivocal	Positive
Single dose	12	2	70	8	0
Triple dose	14	0	72	5	1

$P = .46$ (not significant)

with triple-dose contrast were small and punctate. Once two or more lesions have been identified, the finding of more punctate lesions generally will not change the way the patient is managed. Therefore, the difference in identifying none, one, and more than one metastatic intracranial lesion is of utmost importance. Patients with a solitary metastasis located in a resectable region can be treated surgically (7), but patients with two or more metastatic lesions are usually treated with radiation therapy and/or systemic chemotherapy. It is rare for patients with multiple lesions to be treated surgically. While stereotactic radiosurgery is increasingly used in patients with up to three metastases, even in these cases, treatable metastases are nearly always seen on single-dose contrast studies. The additional punctate metastases that are found with triple-dose contrast material are generally below the appropriate size limit. The advantage to precisely delineating more punctate lesions with tri-

ple-dose contrast once two or more metastases have been found with single-dose contrast is minimal.

Our study was specifically designed to include consecutive patients with a reasonable indication for MR screening with triple-dose contrast; that is, those patients with negative or equivocal results or with a single metastasis on a routine single-dose contrast study. In the negative single-dose studies, the addition of triple-dose contrast material did not show a truly positive missed case for the nonblinded panel or the blinded reviewers.

On the other hand, the use of triple-dose contrast material was found to be helpful in confirming the appearance of an equivocal metastatic lesion. Triple-dose contrast was also useful in the detection of additional metastases in patients with a known lesion detected on the single-dose study. We, therefore, recommend the use of triple-dose contrast material in only two circumstances: when the findings on single-

TABLE 3: Results by blinded readers, A and B, of single- and triple-dose studies compared with standard of reference

	Single-Dose Study				Triple-Dose Study			
	Negative	Equivocal	Positive	Total	Negative	Equivocal	Positive	Total
Reference Standard								
Negative								
A	69	6	3	78	67	6	5	78
B	70	7	1		66	4	8	
Positive								
A	0	3	11	14	0	2	12	14
B	0	3	11		0	2	12	
Total								
A	69	9	14	92	67	8	17	92
B	70	10	12		66	6	20	

TABLE 4: Distribution of readings assigned to the true-positive and true-negative cases by reviewers A and B

	True Positives (n = 14)	
	Positive	Equivocal
Single dose		
A and B	11	3
Triple dose		
A and B	12	2

	True Negatives (n = 78)		
	Negative	Equivocal	Positive
Single dose			
A	69	6	3
B	70	7	1
Triple dose			
A	67	6	5
B	66	4	8

A and B: $P = 1.00$ (not significant)A: $P = .77$ (not significant)B: $P = .024$ (significant)

dose contrast images are equivocal or when one potentially surgically resectable lesion is identified. In these cases, useful information may be obtained. For routine screening, the use of the more expensive triple-dose regimen is not warranted.

Enhancement itself is nonspecific to metastases. In the present study, both nonblinded and blinded reviewers identified false-positive cases more frequently on triple-dose studies. This was attributed to an increase in detected artifacts, better vascular demonstration, and nontumoral enhancement, such as in vascular malformations. Given these findings, it is likely that routine use of triple-dose contrast material may not only increase detection of metastases in specific circumstances but may also increase the number of false-positive findings. In cases of preoperative screening, a false-positive result might prevent appropriate surgery or lead to biopsy, surgical resection, or boost radiation when perhaps it is not indicated, significantly increasing cost and morbidity (17). In a study retrospectively evaluating the data of a multicenter trial (2) with respect to the potential cost-effectiveness of the use of triple-dose contrast, Mayr et al (19) found that the use of high-dose contrast

material had an apparent positive impact on the cost-effectiveness of treating brain metastases. Since the multicenter study did not include follow-up, it is unknown if any of the additional metastases identified represented false-positive lesions.

Magnetization transfer (MT) imaging has been shown to increase lesion enhancement with the addition of contrast material (20–22). Finelli et al (21) reported that use of single-dose contrast material with a short-TR spin-echo MT technique produced the same relative contrast improvement as was seen on the triple-dose contrast studies. Mehta et al (22) reported a statistically significant increase in contrast-to-noise ratios in lesion enhancement with MT techniques. Although our present study was begun before MT imaging was available in our institution, these reports seem to further support our conclusion that the routine use of triple-dose contrast material may not be warranted. Currently in our institution, on the basis of the data in this study, we perform our contrast-enhanced short-TR studies without MT techniques. If there is an equivocal finding or if there is only a single metastasis in a patient in whom resection is considered, we suggest a limited repeat MR study with either MT techniques or with triple-dose contrast material.

Conclusion

We performed MR imaging with single- and triple-dose contrast material in patients in whom the finding of additional lesions could have altered the choice of therapy. In patients with negative single-dose studies, the use of triple-dose contrast did not reveal additional metastases. No statistical difference could be found between the single- and triple-dose studies. Therefore, we believe that the use of triple-dose contrast material for screening brain metastases in patients with negative single-dose contrast studies is not helpful. In cases in which equivocal results or single metastases were seen on the single-dose studies, the use of triple-dose contrast was of benefit, although it must be used with caution, since it also led to an increased number of false-positive findings.

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