Experience with High-Dose Gadolinium MR Imaging in the Evaluation of Brain Metastases

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Purpose: To assess the effectiveness and safety of higher doses of gadoteridol in the MR evaluation of patients with brain metastases. **Materials and Methods:** Thirty-one patients with a clinical suspicion of brain metastases were studied prospectively with gadoteridol, a new, nonionic, low-osmolality contrast agent. Each patient received an initial injection of 0.1 mmol/kg and an additional dose of 0.2 mmol/kg 30 minutes later. Images were obtained before, immediately after, and 10 and 20 minutes after the initial dose. Images also were acquired immediately after the additional dose of gadoteridol. **Results:** No adverse effects were attributed to the injection of gadoteridol. Four patients' examinations were excluded from analysis because of machine malfunction (two patients) and excessive motion artifact (two patients). Four patients had no detectable metastases. After the additional dose of gadoteridol, there was a marked qualitative improvement in lesion conspicuity and detection. The conspicuity of 80 of 81 lesions was increased in the high-dose studies, and 46 new lesions were detected in 19 of 27 patients. Quantitative image analysis demonstrated a significant increase in normalized mean lesion contrast between the initial-dose and high-dose studies (35 lesions identified in 13 patients, $P < .0001$). The additional information gained by high-dose examinations contributed to a potential modification of the treatment in 10 of 27 patients. High-dose examinations increased flow-related artifact in the posterior fossa in 12 of 27 patients. **Conclusion:** Based on our preliminary results, high-dose gadolinium-enhanced MR examinations may have advantages over 0.1 mmol/kg examinations in detecting early and/or small metastases. This may be significant in the management of patients with cerebral metastases.

Index terms: Brain neoplasms, magnetic resonance; Magnetic resonance, contrast enhancement; Contrast media, paramagnetic

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The application of gadolinium at the commonly used dose of 0.1 mmol/kg has proved to be valuable in the evaluation of primary tumors and metastases to the central nervous system (CNS) (1–13). However, the optimum dose of magnetic resonance (MR) contrast agent for imaging pathologic processes in the CNS has not been well established. Gadoteridol, a nonionic, low-osmolality contrast agent, has been developed recently and tested at higher doses. Preliminary studies suggest that gadoteridol can be administered safely at doses up to 0.3 mmol/kg and that increased lesion contrast, delineation, and detection can be attained (1–3). Higher doses (0.2 or 0.3 mmol/kg) may have clinical usefulness for imaging CNS neoplasms, especially for imaging small and/or early metastases that would otherwise be undetected using a dose of 0.1 mmol/kg (1, 2, 4). The purpose of this study was to investigate the safety and efficacy of higher doses of gadoteridol in the evaluation of brain metastases.

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Materials and Methods

We are one of the clinical sites selected for the phase II and phase III multicenter, open-label, dose-ranging, safety, and efficacy trials of the new contrast agent gadoteridol (Gd-HPDO3A, ProHance, Squibb Diagnostics, Princeton, NJ). All patients involved in this study gave informed

consent and were studied in compliance with a protocol previously approved by our institution's Human Subjects Research Committee.

MR examinations with gadoteridol were obtained in 31 consecutive patients with a clinical suspicion of brain metastases using an incremental dose technique. Patients were recruited into our study after showing evidence of metastatic lesions in the brain by angiography, computed tomography (CT), or MR studies or by having a known primary tumor and clinical evidence of brain metastases.

Patient monitoring included history, physical examination, vital signs, and extensive laboratory tests within 24 hours of the MR examinations. Blood analysis consisted of a complete blood count (hemoglobin level, hematocrit, mean corpuscular volume, and total leukocyte count including differential and platelet count), blood chemistry (glucose, creatinine, urea nitrogen, calcium, phosphorus, uric acid, total cholesterol, total protein, albumin, alkaline phosphatase, aspartate aminotransferase, lactic dehydrogenase, alanine aminotransferase, and gamma glutamyl transpeptidase), electrolytes (sodium, potassium, and chloride), a clotting function panel (prothrombin time and partial thromboplastin time), and an iron metabolism panel (serum iron and iron binding capacity). Urinalysis included evaluation of pH, specific gravity, protein, glucose, blood, and ketones and microscopic examination of the sediment. The patients' vital signs were checked immediately after the precontrast MR examinations, immediately after the completion of all scans, and 2 hours after the administration of gadoteridol. Twenty-four hours after the administration of gadoteridol, patient monitoring, including a physical examination, vital signs, and all laboratory tests, was repeated.

Imaging was performed with both medium-field (11 patients, 0.5 T, Picker International, Highland Heights, OH) and high-field (20 patients, 1.5 T, General Electric Signa, Milwaukee, WI) strength scanners. Axial T1-weighted, 350-583/15-20/2 (TR/TE/excitations), and T2-weighted, (2000-2500/90-100/1-2), images were obtained in precontrast examinations. Each patient received an initial bolus injection of 0.1 mmol/kg of gadoteridol followed immediately by a T1-weighted initial-dose examination. T1-weighted images were also acquired at 10 and 20 minutes after the initial injection. At 30 minutes, an additional bolus injection of 0.2 mmol/kg was administered (cumulative dose, 0.3 mmol/kg). T1-weighted images were acquired immediately after this additional dose of contrast agent. Each patient's MR examinations were performed on the same MR scanner using identical scanning protocols. For all imaging sequences, the field of view was 24 cm with a 192 × 256 matrix size. The slice thickness was constant for each patient's images (5 mm with 50% gap for the 1.5-T system and 10-mm contiguous slice thickness for the 0.5-T system).

The MR examinations of all 31 patients were reviewed prospectively and independently by a radiologist, neurosurgeon, and radiation oncologist. Each patient's precontrast studies were reviewed first, followed by the initial-dose, delayed, and high-dose studies. A lesion was defined as an abnormal parenchymal enhancement that did not appear as a thin linear structure in contiguous slices (blood vessel). For each MR examination, the number of lesions was totaled independently by each reviewer. Areas that were thought to be lesions by all three reviewers were classified as definite lesions. Each area for which there was no consensus was discussed in a conference and classified as a definite lesion, possible lesion, or normal tissue. Areas were classified as possible lesions if a consensus could not be reached by all reviewers after discussion. In addition, the initial-dose and high-dose examinations were compared with each other with regard to lesion conspicuity (lesion contrast, size, and border definition) and confidence of diagnostic reading.

A neurosurgeon and radiation oncologist determined if the additional information gained by a high-dose examination would have modified or altered a patient's treatment. Since all MR examinations were obtained within 45 minutes of each other, no definite treatment plan was based solely on the initial-dose studies. Therefore, modifications in treatment that resulted from the additional information gained in the high-dose studies are referred to as "potential" modifications.

Quantitative image analysis was performed on a total of 35 lesions identified in the first 13 patients studied. Lesion borders were detected in the high-dose studies using an automatic edge detection program. Regions of interest (ROIs) in the precontrast, initial-dose, and delayed studies were generated by duplicating ROI locations from the corresponding high-dose study. Image statistics were then computed for these ROIs for each of the studies.

An ROI delineating the entire brain parenchyma was also defined manually. For each lesion, a normalized lesion contrast estimate was calculated using the lesion mean intensity and the normal brain parenchyma ROI statistics. A normal distribution model was used; lesion contrast was expressed in terms of the number of standard deviations that the mean lesion contrast was from the mean brain parenchyma intensity. This approach to quantitative analysis allowed linear scale factors to be cancelled and compensated partially for scan-dependent variations beyond experimental control. A paired, one-tailed Student's *t*-test was performed between each of the studies. A $P < .05$ was considered significant.

Results

Clinical monitoring revealed no adverse reactions to gadoteridol for cumulative doses up to 0.3 mmol/kg in any of the 31 patients studied. None of the patients had injection site pain, burning, or erythema after the initial or additional injection of contrast agent. In addition, no patient experienced headache, dizziness, or taste perturbation, and there were no clinically significant changes in physical examination or vital signs. Minor changes in the laboratory specimens obtained 24 hours after the administration of gado-

teridol were noted in nine of 31 patients. Increases in white blood cell count (one patient), polymorphonucleocytes (five), band cells (four), monocytes (one), and glucose (two) and decreases in eosinophils (two), lymphocytes (one), and monocytes (one) were noted in six patients who received corticosteroid therapy after the MR examinations. The initiation of corticosteroid therapy was thought to have been responsible for these changes. One patient had a minor decrease in total protein and albumin levels, which was attributed to malnutrition and rehydration. Another patient had a small decrease in hemoglobin and hematocrit levels after rehydration. The serum iron levels remained constant in two patients, decreased in 14 patients, and increased in 12 patients. Two patients, however, had a notable decrease in serum iron levels. In one patient, serum iron levels decreased from 56–8 μg/dL 1 day after surgery and were accompanied by increases in hemoglobin (9.1–11.3 g/dL), hematocrit (31%–37%), and red blood cell indices (3.04 to 3.67 million/mL). These changes were thought to be caused by massive hematopoiesis. This could not be confirmed, however, since a reticulocyte count was not part of the routine laboratory tests. The second patient had a decrease in serum iron levels (126–63 μg/dL) and associated decreases in hemoglobin (14.7–13.7 g/dL) and hematocrit (46%–40%). These changes were thought to be due to extensive phlebotomy. A paired Student's *t*-test was performed on preexamination and 24-hour postexamination serum iron values (n = 28), and no significant change was detected ($P < .05$).

Four patients were excluded from the qualitative and quantitative analyses because of excessive motion artifact (two patients) and machine malfunction (two patients). The remaining 27 patients (14 men and 13 women) had an age range from 43 to 76 years. Table 1 is a summary of patient information and MR examinations.

Of the 27 patients suspected of having metastatic lesions in the brain, all but four had demonstrable lesions. Patient 6 had a known primary melanoma and clinical symptoms that suggested brain metastases. A CT examination performed 7 days earlier showed mild asymmetry of the parietal lobes but no detectable lesions. Patient 17 had a known primary squamous cell carcinoma of the larynx, widespread metastatic disease, and neurologic symptoms. An angiogram performed 2 days before the MR study was suggestive of tumor. Patient 25 had a known small cell lung carcinoma. A head CT showed a possible brain metastasis 2 weeks before the MR examination. Patient 26 had a known breast carcinoma and developed a generalized tonic clonic seizure. A head CT 2 days before the MR study showed a possible lesion. None of these four patients had detectable lesions on MR evaluation.

Overall, the high-dose studies demonstrated an increase in lesion conspicuity (lesion contrast, size, and border definition) when compared with the initial-dose studies (Figs. 1–6). The high-dose gadoteridol examinations yielded additional information in all 23 patients with metastatic disease to the brain. A total of 59 definite lesions and 22 possible lesions were identified in the initial-dose (0.1 mmol/kg) examinations. High-dose (cumulative dose, 0.3 mmol/kg) studies improved the diagnostic reading confidence in 21 of the 22 areas classified as possible lesions on the initial-dose scans. In the high-dose studies, 19 of these areas were identified as definite lesions (Figs. 5 and 6), and two areas were identified as normal tissue in the high-dose examinations (Fig. 7). The high-dose examinations allowed the detection of 21 definite lesions and 25 possible lesions (18 patients) that were not identified on the initial-dose examinations as either possible or definite lesions (Figs. 3, 4, and 6). Most of the lesions detected exclusively on the high-dose studies were less than 5 mm in diameter. The smallest detectable lesion on the high-dose examinations was approximately two pixels in diameter (1.9 mm) (Fig. 5).

In the delayed studies, a few metastases had slightly greater contrast, whereas others had slightly less contrast when compared with the immediate initial-dose studies (Fig. 8). One lesion that was seen in the immediate initial-dose study was not detected in delayed studies. This lesion was again detected in the high-dose study.

The results of the quantitative analysis are shown in Fig. 9. Mean normalized lesion contrast and 95% confidence intervals are plotted for each of the five MR study types (35 lesions, 13 patients). The mean normalized lesion contrast increased significantly between the precontrast and initial-dose studies and also between the initial-dose and high-dose studies ($P < .0001$). The mean normalized lesion contrast of the high-dose studies increased dramatically from 1.01 to 1.81 standard deviations above the mean brain parenchyma intensity when compared with the initial-dose studies. The 10- and 20-minute delayed studies demonstrated a slight increase in mean

TABLE 1: Summary of patient data and MR results

Patient Information				Precontrast T2		0.1 mmol/kg		0.3 mmol/kg		Comparison of 0.3 mmol/kg with 0.1 mmol/kg					
No.	Age (yr)	Sex	Primary Cancer Site	Definite Lesion	Possible Lesion	Definite Lesion	Possible Lesion	Definite Lesion	Possible Lesion	Improved Confidence	Improved Conspicuity	New Lesion	Change in SURG TX	Change in RAD TX	Increased Artifact
1	66	M	Lung	1	1	2	0	3	2	0	2	3	−	+	+
2	63	F	Lung	7	2	13	7	25	4	7	20	9	−	−	−
3	55	M	Unknown	1	1	2	2	5	0	2	4	1	−	−	−
4	65	M	Lung	3	1	2	2	7	4	2	4	7	−	−	+
5	76	F	Breast	1	5	2	1	3	0	1	3	0	−	−	+
6	53	F	Melanoma	0	0	0	0	0	0	0	0	0	−	−	+
7	75	F	Rectum	1	3	1	0	2	2	0	1	3	+	+	+
8	55	M	Lung	1	1	1	2	1	0[a]	2[a]	3	0	+	+	+
9	43	F	Kidney	3	0	1	0	1	2	0	1	2	+	+	−
10	61	M	Lung	1	0	2	0	2	0	0	2	0	−	−	−
11	64	M	Unknown	1	0	2	0	2	1	0	2	1	−	−	−
12	57	F	Lung	1	1	4	3	8	2	3	7	3	−	−	−
13	48	M	Lung	3	0	0	1	1	2	1	1	2	−	−	−
14	61	F	Unknown	1	0	1	0	2	0	0	1	1	+	+	−
15	64	F	Lung	5	0	9	2	13	0	2	11	2	−	−	−
16	57	F	Colon	2	0	1	0	1	2	0	1	2	+	+	−
17	49	M	Larynx	0	0	0	0	0	0	0	0	0	−	−	−
18	69	M	Kidney	0	1	1	0	3	0	0	1	2	+	+	−
19	67	M	Esophagus	1	0	1	0	1	0	0	1	0	−	−	+
20	60	F	Unknown	1	0	2	0	2	3	0	2	3	−	−	−
21	69	F	Lung	1	0	1	0	2	0	0	1	1	+	+	−
22	58	F	Lung	2	0	2	0	3	0	0	2	1	−	−	+
23	70	M	Lung	0	5	0	1	1	1[b]	0	0	1	+	+	+
24	56	M	Kidney	1	0	1	0	2	1	0	1	2	+	+	+
25	67	M	Lung	0	0	0	0	0	0	0	0	0	−	−	+
26	64	F	Breast	0	0	0	0	0	0	0	0	0	−	−	−
27	56	F	Lung	8	0	8	1	9	0	1	9	0	−	−	+
Totals				46	21	59	22	99	26	21	80	46	9	10	12

Note.—SURG TX = surgical treatment; RAD TX = radiation treatment.

[a] Exclusion of possible lesion.

[b] Lesion was also detected in 0.1 mmol/kg study.

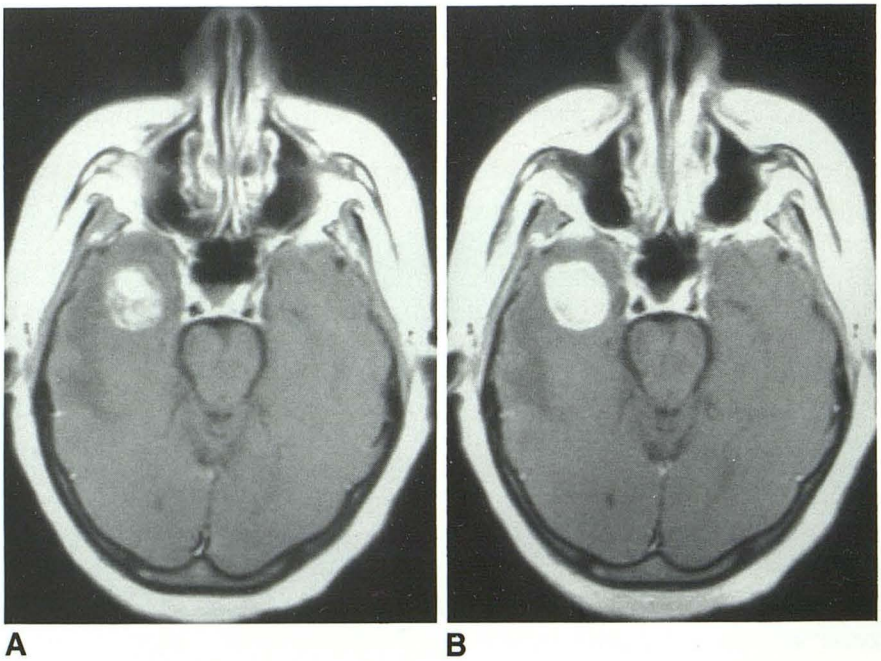


Fig. 1. Increased lesion conspicuity.

A, Axial T1-weighted (583/20) initial-dose study shows a lesion in the right temporal lobe.

B, The high-dose study shows a larger apparent lesion size and higher degree of lesion enhancement.

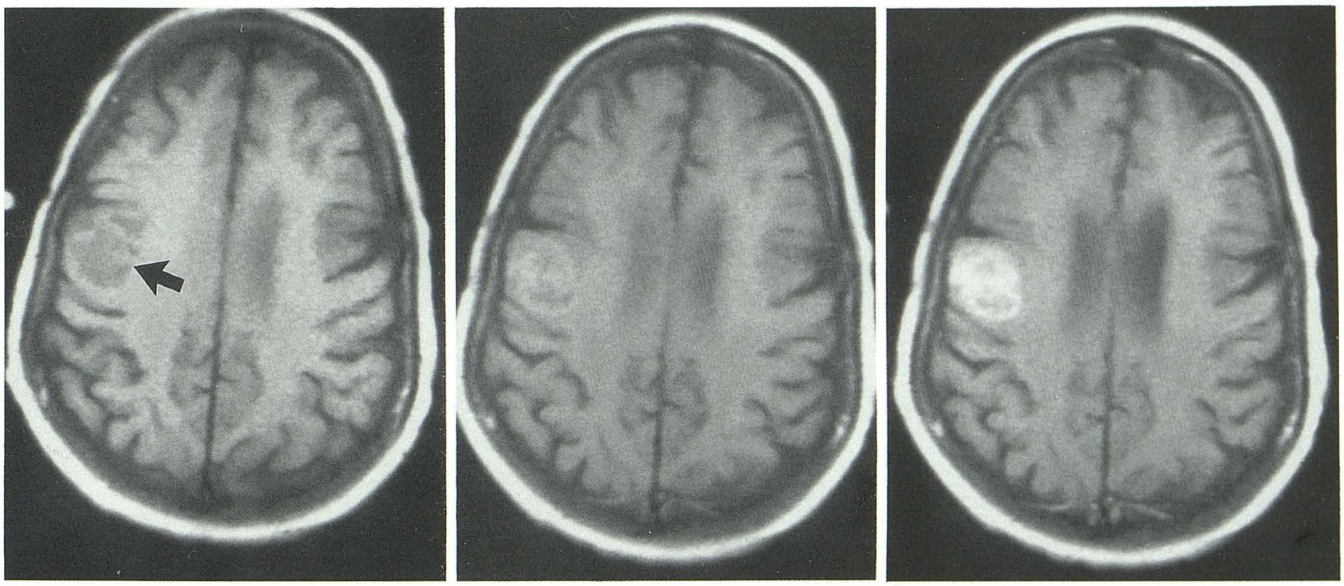


Fig. 2. Increased conspicuity of a relatively isointense lesion.
A, Axial precontrast T1-weighted (583/20) image shows a hypointense lesion (*arrow*) in the right parietal lobe.
B, Axial T1-weighted initial-dose study shows the lesion to be relatively isointense to the white matter.
C, The high-dose examination shows this lesion to be significantly enhanced.

normalized lesion contrast (1.16 and 1.18, respectively) when compared with the immediate initial-dose studies ($P < .005$) but were not themselves significantly different from one another.

Pulsatile flow-related artifacts in the posterior fossa were increased in the high-dose examinations in 12 of the 27 patients studied. Despite the increased artifact, the high-dose studies in these 12 patients provided better conspicuity and detection of metastases in the posterior fossa than did the initial-dose studies.

The high-dose examinations yielded additional information that contributed to a potential modification in the treatment of 10 of 27 patients, changing both the planning of surgery and radiation therapy in eight patients and radiation therapy in one patient. Details of potential therapeutic changes based on the additional information gained from the high-dose studies are summarized in Table 2. Eight of these patients had a solitary metastasis detected in the initial-dose study. The high-dose studies revealed multiple parenchymal metastases in seven of these eight patients, precluding possible surgical excision and a high-dose radiation boost in addition to whole brain irradiation. The eighth patient (patient 23) had two lesions in close proximity to one another detected in the high-dose study that could be treated with surgical excision and whole brain and boost radiation therapy.

Patient 1 had two lesions in close proximity to one another detected in the initial-dose examination that could be treated with whole brain and boost radiation therapy. After viewing the high-dose examination, however, an additional metastasis remote from the initial lesions was detected, and boost radiation therapy was no longer considered beneficial. Patient 8 had one definite and two possible lesions seen in the initial-dose study. The two possible lesions were thought to be normal tissue after viewing the high-dose study (Fig. 7). Therefore, this patient was thought to be a candidate for more aggressive therapy including whole brain and boost radiation therapy after surgical excision of the solitary metastasis. This potential change in therapy, however, was not attributed to the dose of contrast agent given.

Discussion

Previous studies have shown that 0.1 mmol/kg of gadopentetate dimeglumine is a well-tolerated, safe, and efficacious dose for imaging intracranial pathologic processes (1, 4–14). Although 0.1 mmol/kg of gadolinium is generally considered to be the standard dose for such contrast-enhanced MR examinations, the optimum dose

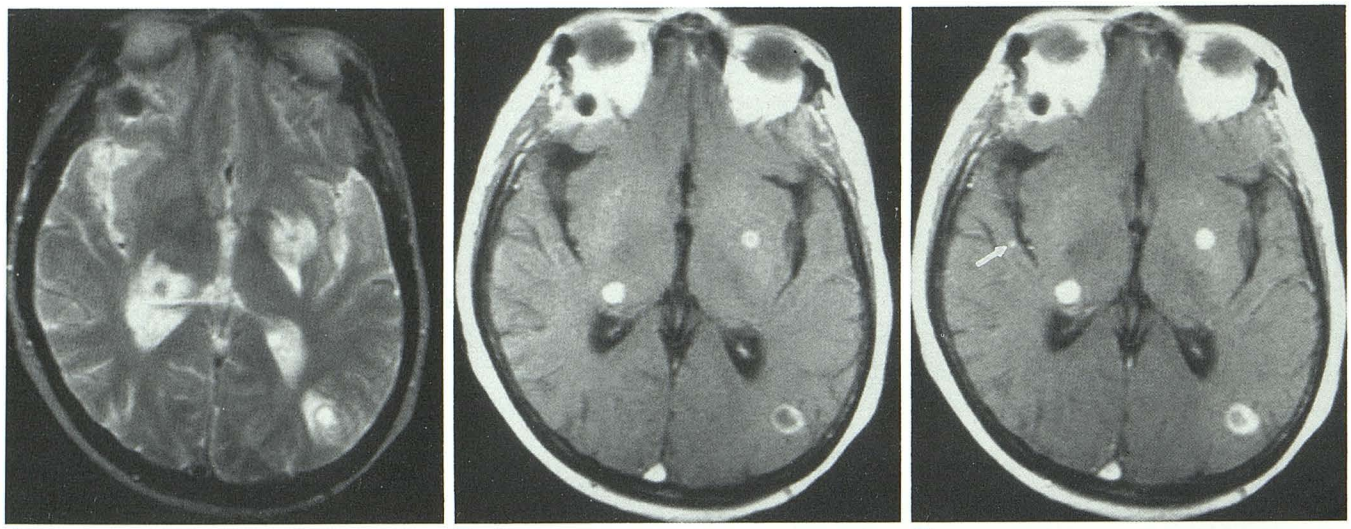


Fig. 3. Increased lesion conspicuity and detection.
A, Axial T2-weighted (2000/100) image shows multiple areas with abnormal signal.
B, Axial T1-weighted (583/20) initial-dose study shows three enhancing lesions.
C, The high-dose study shows greater enhancement and increased apparent size of these lesions. An additional lesion (*arrow*) in the right temporal lobe was also detected.

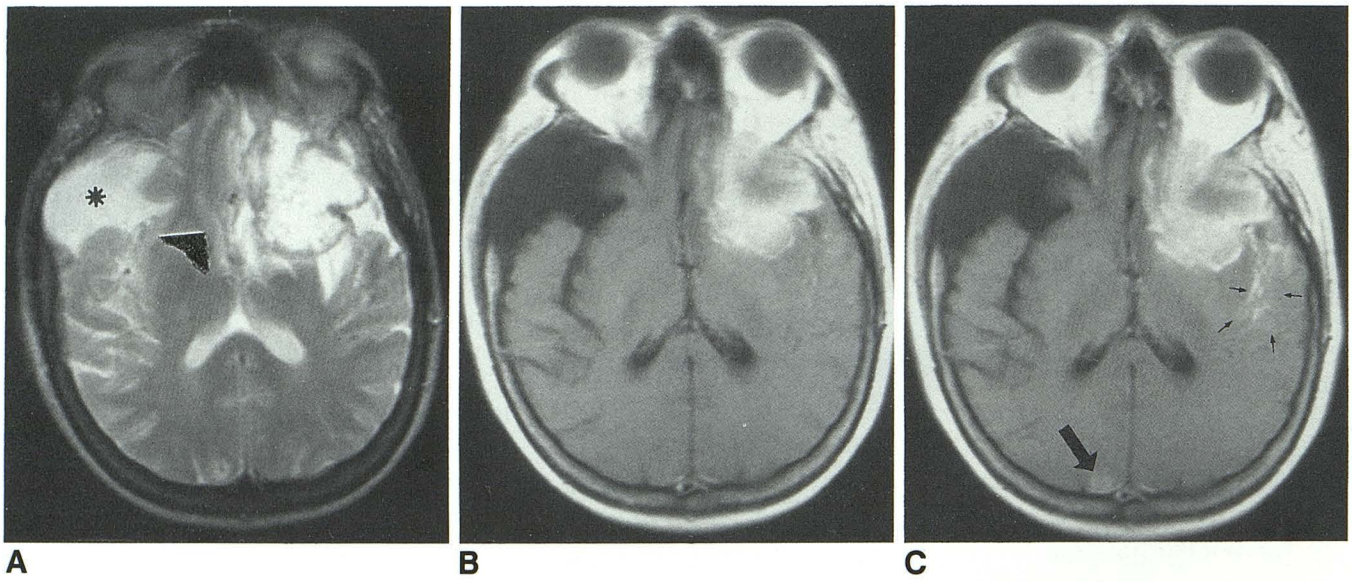


Fig. 4. Increased lesion conspicuity and detection.
A, Axial T2-weighted (2000/100) image shows an area with abnormal signal in the left frontal lobe and a subarachnoid cyst (*asterisk*) near the temporal lobe.
B, Axial T1-weighted (583/20) initial-dose study demonstrates an enhancing left frontal lobe mass and the nonenhancing subarachnoid cyst.
C, The high-dose examination shows slightly greater enhancement, improved border definition, and more extensive involvement of the left frontal lobe mass (*small arrows*) than either the initial-dose or T2-weighted study shows. An additional lesion (*large arrow*) was also detected in the right occipital lobe.

of gadolinium for these studies has not been well established (1, 2).

Several studies have shown gadoteridol and gadopentetate to have nearly identical enhancement effects when administered in equal doses (1, 15, 16). Both gadoteridol and gadopentetate have been studied at different doses in the same patients. These studies have shown that higher doses of gadolinium (0.2 and 0.3 mmol/kg) provide increased lesion enhancement, contrast, bor-

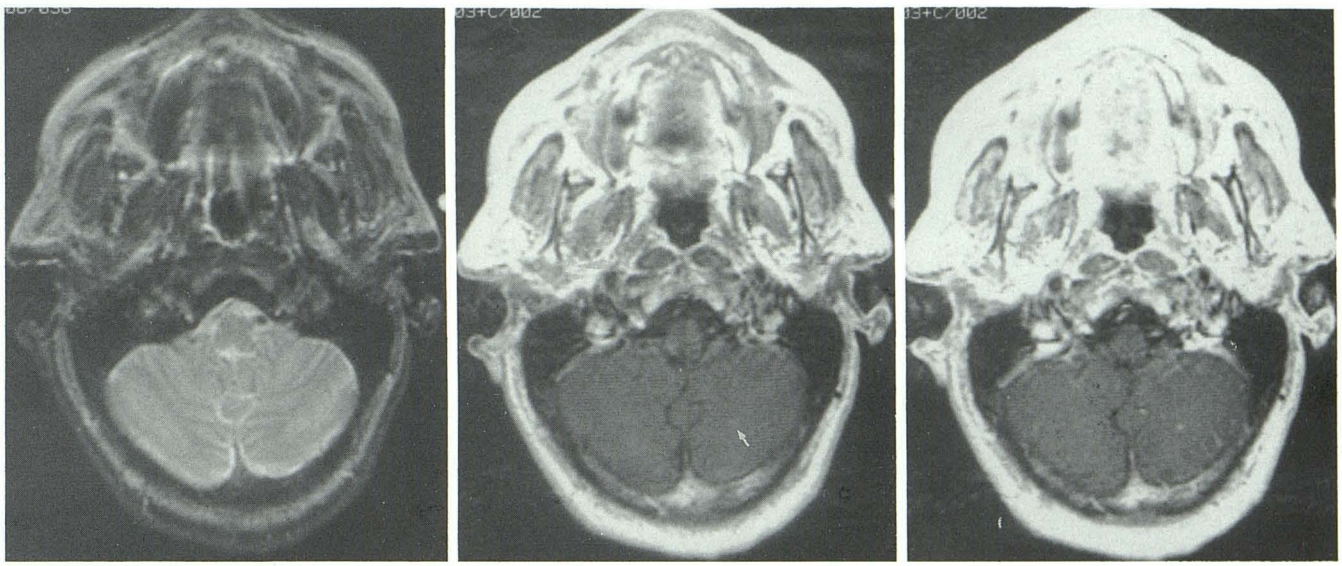


Fig. 5. Improved confidence of lesion detection.

A, Axial T2-weighted (2350/90) image shows no significant abnormality.

B, Axial T1-weighted (350/15) initial-dose study demonstrates mild pulsation artifact and a small focal area (*arrow*) with faint enhancement thought to be a possible lesion.

C, The high-dose study shows further enhancement and border delineation of the small definite lesion (approximately 1.9 mm).

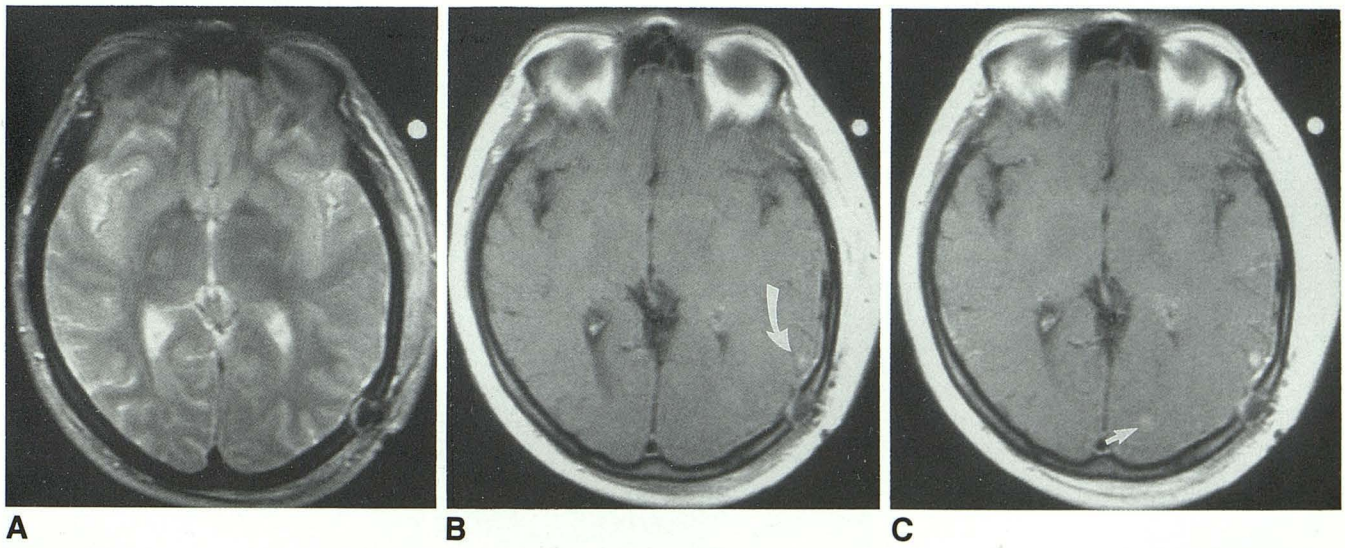


Fig. 6. Improved confidence and increased lesion conspicuity and detection in a postoperative patient.

A, Axial T2-weighted (2000/100) image shows postoperative changes in the left parietal region.

B, Axial T1-weighted (583/20) initial-dose study shows abnormal enhancement in the region of the surgical site (*arrow*). This focal area of faint enhancement was suspicious for tumor, but postoperative changes could not be excluded completely.

C, The high dose examination demonstrates increased enhancement and border delineation of this left parietal lesion. An additional lesion (*arrow*) in the left occipital lobe is also demonstrated.

der definition, and detection when compared with examinations using 0.1 mmol/kg (1, 4).

Previous phantom studies demonstrated lesion detectability to be dependent on lesion size and contrast (1). Because of the increased partial-volume effect in smaller lesions, they require a higher degree of contrast to be detected than do larger lesions. By the same mechanism, examinations with a lower dose of contrast agent may result in an apparent reduction in lesion size. Since metastases grow at an exponential rate and may remain relatively small for years (17), a

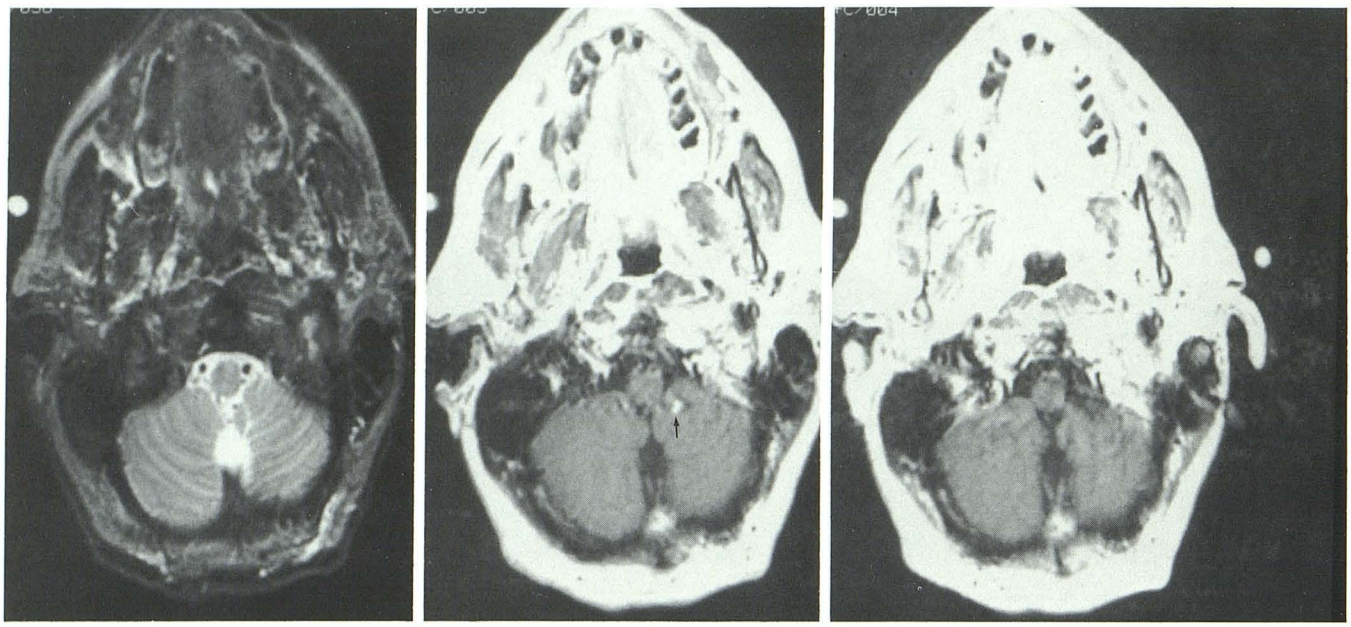
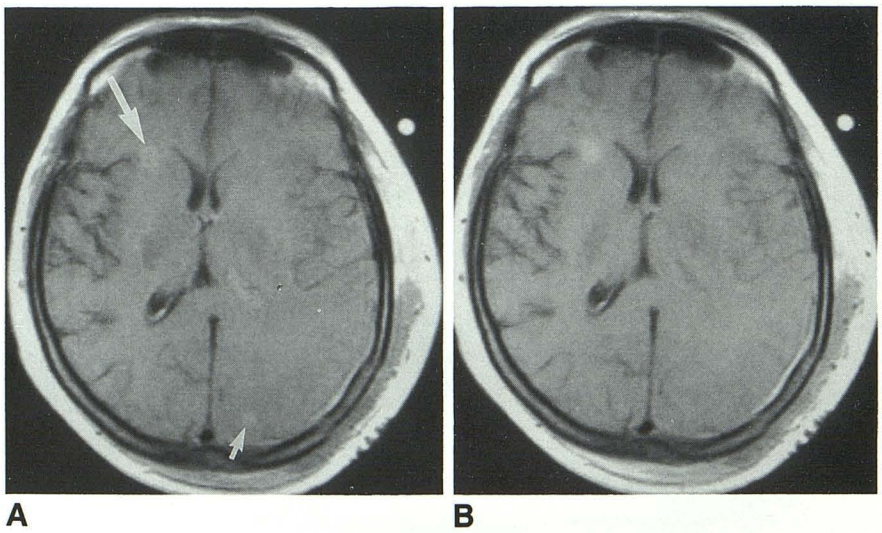


Fig. 7. Exclusion of a possible lesion.
A, Axial T2-weighted (2350/90) image shows no abnormalities.
B, Axial T1-weighted (350/15) initial-dose study shows significant pulsation artifact and a possible lesion (*arrow*).
C, The high-dose examination demonstrates no such lesion. This area was thought to be an artifact probably resulting from cyclic variations caused by the cardiac cycle rather than the dose of gadolinium administered.

Fig. 8. Time-related changes in lesion enhancement.
A, Axial T1-weighted (583/20) immediate initial-dose image demonstrates a right frontal lobe lesion (*large arrow*) and a left occipital lobe lesion (*small arrow*).
B, Axial T1-weighted delayed (20 min) initial-dose image shows a progressive increase in enhancement of the right frontal lobe lesion and a decrease in enhancement of the left occipital lobe lesion.



higher dose of gadolinium (greater than 0.1 mmol/kg) may be required before these small metastases can be visualized.

In our clinical trials with gadoteridol, there were no significant adverse clinical effects noted that were attributed to the injection of this contrast agent for doses up to 0.3 mmol/kg. Other studies have shown no adverse effects with this agent (1, 2).

An incremental dose technique similar to that used by Niendorf et al (4) was applied in our study. This method of studying patients yields improved data comparability and reliability. Metastatic disease is progressive, and metastases may change size and/or enhancing patterns over time. When the incremental dose technique is used, all images are obtained under identical circumstances within 45 minutes of one another.

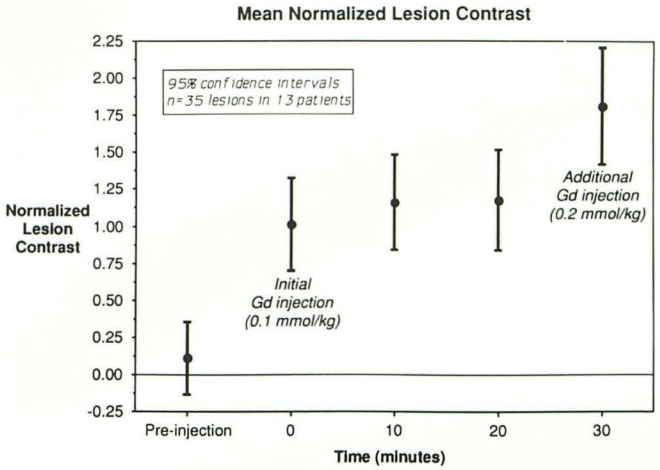


Fig. 9. Quantitative analysis. Mean normalized lesion contrast and 95% confidence intervals are plotted for a total of 35 lesions identified in 13 patients. The normalized lesion contrast increased significantly ($P < .0001$) between precontrast studies and initial-dose studies and also between initial-dose studies and high-dose studies. Both the 10- and 20-minute delayed examinations demonstrated a slight but significant increase in mean normalized lesion contrast when compared with the immediate initial-dose studies ($P < .005$).

Therefore, differences between the initial-dose and high-dose examinations can be attributed solely to the concentration of gadolinium injected and not to disease progression, interventional therapy, or the image acquisition process.

Qualitative analysis of our results revealed that lesion conspicuity and detection increased with increasing doses of gadolinium up to a cumulative dose of 0.3 mmol/kg. Additional metastases were seen in the high-dose examinations of 18 of 27 patients (Figs. 3, 4, and 6), and the conspicuity of lesions improved in 23 of 27 patients (Figs. 1–6). No metastases were detected in two patients; however, the high-dose examination improved the reviewers' confidence that brain metastases in these patients were unlikely.

Quantitative analysis performed on the first 13 patients studied demonstrated that mean normalized lesion contrast increased by nearly an entire standard deviation between initial-dose and high-dose studies, relative to the image statistics of the overall brain parenchyma (Fig. 9). The image analysis also revealed that lesions in the 10- and 20-minute delayed studies had slightly increased contrast over those in the immediate initial-dose studies; only a few lesions studied demonstrated contrast increases large enough to be detected visually. Other investigators have demonstrated that the small increases in lesion contrast produced by delayed postcontrast imaging are not, in general, visually detectable (2, 12, 18).

Qualitative and quantitative analyses of our data revealed that lesion enhancement and contrast increased with a higher dose of gadolinium. Earlier studies suggested that higher doses of gadolinium may cause a decrease in lesion enhancement due to T2 shortening effects (12, 19, 20). Our data support the recent gadoteridol studies that demonstrated an increase in lesion enhancement with increasing dose up to 0.3 mmol/kg without visibly noticeable T2 shortening effects (1, 2).

Although the time-signal intensity curves of individual tumors may differ, it has been shown that most tumor tissue markedly enhances immediately after the intravenous injection of gadolinium (2, 12, 18). Some metastases did show a slight increase or decrease in enhancement (Fig. 8). Interestingly, however, one metastatic lesion was undetectable in delayed studies that was seen in both the immediate initial-dose and high-dose studies.

Previous work has shown that biopsy specimens may contain brain tumor involvement beyond the areas defined by T2-weighted MR images (21). In our study, one high-dose examination revealed lesion involvement beyond that which was identified in the initial-dose and precontrast T2-weighted images (Fig. 4), which suggests that high-dose studies may be useful to better define tumor extent and aid in surgical excision.

Based on our experience, there appear to be several circumstances in which the use of high-dose gadoteridol is advantageous. High-dose examinations may allow recurrent metastatic disease to be differentiated from postoperative changes and further enhance lesions that are isointense at a dose of 0.1 mmol/kg (Figs. 2 and 7). Although pulsatile artifacts increased in the posterior fossa of several patients when a higher dose of gadolinium was used, the high-dose studies still provided superior lesion conspicuity and detection in the posterior fossa when compared with the initial-dose studies.

The options for treatment of metastases to the brain include corticosteroid therapy, surgery, radiation therapy, and chemotherapy, either alone or in various combinations. The primary role of surgery is directed toward patients with a single brain metastasis who do not have widespread or rapidly progressive cancer (22). This represents about 20% of patients with parenchymal brain

TABLE 2: Potential therapeutic changes

No.	Treatment on Viewing 0.1 mmol/kg Scan		Potential Change on Viewing 0.3 mmol/kg Scan	
	Radiation Therapy	Surgical Intervention	Radiation Therapy	Surgical Intervention
1	WBI + boost	Diag. Bx	No boost	None
7	WBI + boost	Excis. Bx	No boost	Diag. Bx
8	WBI	Diag. Bx	Add boost	Excis. Bx
9	WBI + boost	Excis. Bx	No boost	Diag. Bx
14	WBI + boost	Excis. Bx	No boost	Diag. Bx
16	WBI + boost	Excis. Bx	No boost	Diag. Bx
18	WBI + boost	Excis. Bx	No boost	Diag. Bx
21	WBI + boost	Excis. Bx	↑ Boost area	Diag. Bx
23	No treatment	Excis. Bx	WBI + boost	Excis. Bx (both lesions)
24	WBI + boost	Excis. Bx	No boost	Diag. Bx

Note.—WBI = whole brain irradiation; boost = boost radiation treatment; Diag. Bx = diagnostic biopsy; Excis. Bx = excisional biopsy.

metastases (23). In these patients, surgical resection of the metastasis plus radiotherapy has been shown to increase the length of survival by 6 months, compared with patients receiving radiotherapy alone and by longer periods compared with patients receiving no treatment. Patients who undergo surgical resection plus radiotherapy also have fewer recurrences of brain metastases and a better quality of life (24). The major role of surgery in patients with multiple brain metastases is to obtain a tissue diagnosis.

Solitary brain metastases (or a few metastases in very close proximity) are often treated with a higher localized radiation dosage (boost) to the lesion itself, in addition to whole brain irradiation. However, for multiple brain metastases, such a radiation boost offers no advantage, and whole brain irradiation alone is used.

In 10 of 27 patients in our study, the therapeutic approach potentially was influenced by the additional information afforded by the high-dose examinations (Table 2). There may be several advantages to the use of gadolinium at higher doses (greater than 0.1 mmol/kg) to evaluate CNS metastases. 1) Inappropriate local therapy for primary neoplasms with unsuspected brain metastases may be reduced. 2) Isolated brain metastases may be identified and removed surgically and/or given boost radiotherapy. 3) Patients with a solitary metastasis detected with 0.1 mmol/kg of gadolinium and additional metastases detected with higher doses may avoid unnecessary surgical excision and boost radiotherapy. 4) In patients with multiple metastases, the lesions most amenable to uncomplicated diagnostic biopsy may be identified. 5) Increased lesion delineation may identify an area for diagnostic biopsy that has less surgical morbidity. 6) The appropriate surgery, radiation therapy, and/or chemotherapy may be instituted earlier.

In conclusion, no significant adverse effects were noted in the 31 patients receiving a cumulative dose of 0.3 mmol/kg of gadoteridol. Lesion conspicuity and detection increased with an increasing dose up to 0.3 mmol/kg. There appear to be advantages to the use of higher doses of gadolinium in patients with suspected brain metastases. The additional information gained from these high-dose studies may lead to improved management of these patients.

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