MR Enhancement of Brain Lesions: Increased Contrast Dose Compared with Magnetization Transfer

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PURPOSE: To compare image contrast and lesion conspicuity of enhancing intracranial lesions obtained with T1-weighted and magnetization transfer T1-weighted spin-echo sequences after administration of standard (0.1 mmol/kg body weight) and triple doses of gadobutrol. **METHODS:** Twenty-four patients with a total of 34 enhancing intracranial lesions were studied with T1-weighted and magnetization transfer T1-weighted spin-echo MR imaging. An incremental dose technique was used with intravenous injections of 0.1 and 0.2 mmol/kg body weight gadobutrol. Lesion–to–white matter contrast and white matter–to–edema contrast were calculated. **RESULTS:** The lesion–to–white matter contrast of the magnetization transfer T1-weighted studies was significantly higher than that of the T1-weighted studies when identical doses of gadobutrol were compared. The lesion–to–white matter contrast was not significantly different on the triple-dose T1-weighted study and the standard-dose magnetization transfer T1-weighted study. Two lesions were visible only on the standard-dose magnetization transfer T1-weighted and the triple-dose studies. **CONCLUSION:** Standard-dose magnetization transfer T1-weighted and triple-dose T1-weighted spin-echo MR studies are equally well suited to increase the lesion–to–white matter contrast in patients with enhancing intracranial lesions. Triple-dose magnetization transfer T1-weighted studies further increase lesion–to–white matter contrast but do not show additional lesions.

Index terms: Magnetic resonance, comparative studies; Magnetic resonance, contrast enhancement; Magnetic resonance, magnetization transfer

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The effectiveness of intravenous (IV) administration of paramagnetic contrast agents in detecting and differentiating intracranial lesions by magnetic resonance (MR) imaging is well known. Image contrast and thus visibility and detectability of lesions may be improved by increasing the agent's dose from the standard 0.1 mmol/kg body weight; a considerably better lesion contrast has been shown for doses up to 0.3 mmol/kg (1–4). Increasing the dose of contrast medium unfortunately also increases imaging costs. Another strategy to make intracranial lesions more visible is to suppress the signal of the (nonenhancing) background tissue by preapplying an off-resonance radio frequency pulse (5–12), thus generating the so-called magnetization transfer effect. The first strategy for improving lesion contrast was used in several MR studies (1–4), the second in several others (5–12). We wanted to compare image contrast and lesion conspicuity obtained with conventional spin-echo T1-weighted sequences after standard and triple doses of gadobutrol with image contrast and lesion conspicuity obtained with magnetization transfer T1-weighted spin-echo sequences after identical doses of gadobutrol.

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Materials and Methods

This study was part of a phase III, open-label, nonrandomized, dose-comparative, intraperson controlled clinical trial, the results of which are pending. An incremental dosing technique was used, with two injections of gadobutrol (Gadovist; Schering AG, Berlin, Germany) (0.1 and 0.2 mmol/kg) that added up to a total dose of 0.3 mmol/kg. Gadobutrol belongs to the class of nonionic macrocyclic gadolinium chelates. We used a solution of 1 mol/L, which has an osmolality of 1.39 osmol/L; the T1 relaxivity of gadobutrol in water is similar to that of gadopentetate dimeglumine. Whereas the phase III trial only required us to compare the lesion-to-white matter contrast of the T1-weighted images after IV administration of 0.1 and 0.3 mmol/kg gadobutrol, we additionally obtained magnetization transfer T1-weighted images after each injection of gadobutrol.

A total of 30 patients were enrolled in this study. The clinical trial was approved by the local ethical committee and informed consent was obtained from each patient. To be included in the trial a patient had to have clinical or imaging findings suggestive of a lesion of the brain. Exclusion criteria were age under 18 years, pregnancy, lactation, renal disease, and a history of severe allergylike reaction to drugs or contrast material. One patient withdrew her consent on the day of the scheduled MR study. One MR examination had to be terminated after the first dose of gadobutrol because the patient became affected with nausea. Four patients had nonenhancing tumors and thus were excluded from the study. The remaining 24 patients had at least one enhancing intracranial lesion and they are the subjects of this article. The mean age of the patients was 57 ± 17 years (range, 24 to 80 years), the mean body weight was 75 ± 17 kg (range, 44 to 120 kg). Fifteen patients were men, nine were women. The reason for imaging was suspected high-grade astrocytoma in 12 patients, suspected meningeoma in one patient, and suspected cerebral metastases in 11 patients. All 24 patients had had previous imaging studies: 18 had had computed tomography (CT) only, four had had MR imaging only, and two had had both CT and MR.

MR examinations were performed on a 1.0-T imager. Noncontrast studies included axial spin-echo proton density–weighted, T2-weighted, and T1-weighted images. Proton density–weighted images were acquired at 2460/20/1 (repetition time/echo time/excitations). T2-weighted images were acquired at 2460/100/1. Both standard T1-weighted and magnetization transfer T1-weighted images were acquired at 640/20/1. Section thickness was 8 mm, field of view was 200 to 250 mm, and matrix size was 192 × 256 in all studies. T1-weighted and magnetization transfer T1-weighted images were obtained 5 minutes after injection of 0.1 mmol/kg gadobutrol. An additional dose of 0.2 mmol/kg of gadobutrol was administered 10 minutes after this first injection. Five minutes after the second injection another set of standard T1-weighted and magnetization transfer T1-weighted images was obtained; an interval of 5 minutes between the injection and imaging was chosen because enhancement peaks at about this time and remains high for about 20 minutes (3). To avoid a bias toward one of the sequences the magnetization transfer T1-weighted images were acquired first in every other patient.

For the magnetization transfer saturation pulse we used a 1 kHz off-resonance sinc pulse of 10 milliseconds duration, whose amplitude was chosen to maximize saturation of macromolecularly bound protons without inappropriately increasing the specific absorption rate, thus preserving multisection acquisition. The effective flip angle of the magnetization transfer pulse in the sequence that we finally used for the examination of patients was about 450°.

The signal intensities of lesion(s), normal white matter, and, if present, edema were measured in identical regions of interest (ROIs) in each of the five studies (T1-weighted noncontrast and T1-weighted and magnetization transfer T1-weighted after administration of 0.1 and 0.3 mmol/kg gadobutrol, respectively); the minimum ROI size was 10 pixels. Lesion–to–white matter contrast and white matter–to–edema contrast were calculated. Paired, two-tailed Student's *t* tests were performed for each pair of studies; a *P* value of less than .05 was considered significant. Except in one patient, the diagnoses were verified histologically.

Results

Thirty-four intracranial lesions were detected: 19 metastases, 12 high-grade astrocytomas (grade III or IV astrocytoma and glioblastoma multiforme), and three meningiomas. These numbers were derived from the triple-dose images and the standard-dose magnetization transfer T1-weighted images; two cerebral metastases were invisible on standard-dose T1-weighted images.

The average lesion–to–white matter contrast before gadobutrol injection was 0.9. After the first injection of gadobutrol the average lesion–to–white matter contrast was 1.38 on the standard T1-weighted images and 1.81 on the magnetization transfer T1-weighted images. After the second injection of gadobutrol lesion–to–white matter contrast was 1.79 on the T1-weighted images and 2.15 on the magnetization transfer T1-weighted images. The mean lesion–to–white matter contrast values for the different studies are listed in Table 1. On the triple-dose magnetization transfer T1-weighted study the lesion–to–white matter contrast was significantly higher than on any of the other studies ($P < .001$). On standard-dose magnetization transfer T1-weighted images and on triple-dose T1-weighted images the lesion–to–white matter values were significantly higher than the values on standard-dose T1-weighted images ($P < .001$). The difference between the lesion–to–white matter values on triple-dose T1-weighted images and those on standard-dose magnetization transfer T1-weighted images was not sig-

TABLE 1: Image contrasts for the different studies

Study	Lesion–to–White Matter Contrast	White Matter–to–Edema Contrast	Gray Value		
			Lesion	White Matter	Edema
Noncontrast T1-weighted	0.90	1.25	459	510	408
T1-weighted with 0.1 mmol/kg*	1.38	1.27	720	522	411
Magnetization transfer T1-weighted with 0.1 mmol/kg*	1.81	1.07	653	361	337
T1-weighted with 0.3 mmol/kg*	1.79	1.25	918	513	410
Magnetization transfer T1-weighted with 0.3 mmol/kg*	2.15	1.08	753	350	324

* Dose of gadobutrol.

TABLE 2: Paired *t* tests comparing the lesion–to–white matter contrast of the studies

Dose of Gadobutrol	Dose of Gadobutrol			
	T1-Weighted with 0.1 mmol/kg	Magnetization Transfer T1-Weighted with 0.1 mmol/kg	T1-Weighted with 0.3 mmol/kg	Magnetization Transfer T1-Weighted with 0.3 mmol/kg
T1-weighted with 0.1 mmol/kg	· · ·	Less	Less	Less
Magnetization transfer T1-weighted with 0.1 mmol/kg	$P < .001$	· · ·	Equal	Less
T1-weighted with 0.3 mmol/kg	$P < .001$	$P = .72$	· · ·	Less
Magnetization transfer T1-weighted with 0.3 mmol/kg	$P < .001$	$P < .001$	$P < .001$	· · ·

Note.—The upper right part of the table shows which of the studies has the higher lesion-to-white matter contrast. The Lower left part gives the level of significance (*P* value; paired *t* test).

nificant ($P = .72$); Table 2 lists the results of the paired *t* tests.

The increase of lesion–to–white matter contrast on the triple-dose images and on the standard-dose magnetization transfer T1-weighted images revealed two metastases (in two patients) that were not visible on the standard-dose T1-weighted images. One of the patients had been referred for MR imaging with only one previously known metastasis: detection of the second metastasis changed the therapeutic strategy. Figure 1 shows one of the metastases that was visible only on the magnetization transfer T1-weighted and the triple-dose T1-weighted images. No lesion was detected on the triple-dose studies that had not been found on the standard-dose magnetization transfer T1-weighted studies.

In patients with astrocytomas, the increased lesion–to–white matter contrast had two effects: the enhancing part of the lesion was better demarcated and often there was enhancement not visible on the standard-dose T1-weighted study. In six of the 12 patients with astrocytoma, the extension of enhancing tumor increased on the triple-dose studies as well as on the standard-dose magnetization transfer T1-weighted study (Fig 2). In two cases, the triple-dose magnetization transfer T1-weighted study showed enhancing tumor that escaped detection on both the standard-dose magnetization transfer T1-weighted study and the triple-dose T1-weighted study.

The contrast between edema and white matter was significantly higher on the T1-weighted studies than on the magnetization transfer T1-weighted studies. No difference in the white matter–to–edema contrast was found between the various T1-weighted studies. The white matter–to–edema contrast on the two magnetization transfer T1-weighted studies was not significantly different either. Edema extension was thus more clearly visible on the T1-weighted images (Fig 3). Table 1 lists the white matter–to–edema contrast values for the various studies.

Discussion

Previous MR studies have shown that conspicuity and detectability of intracranial lesions

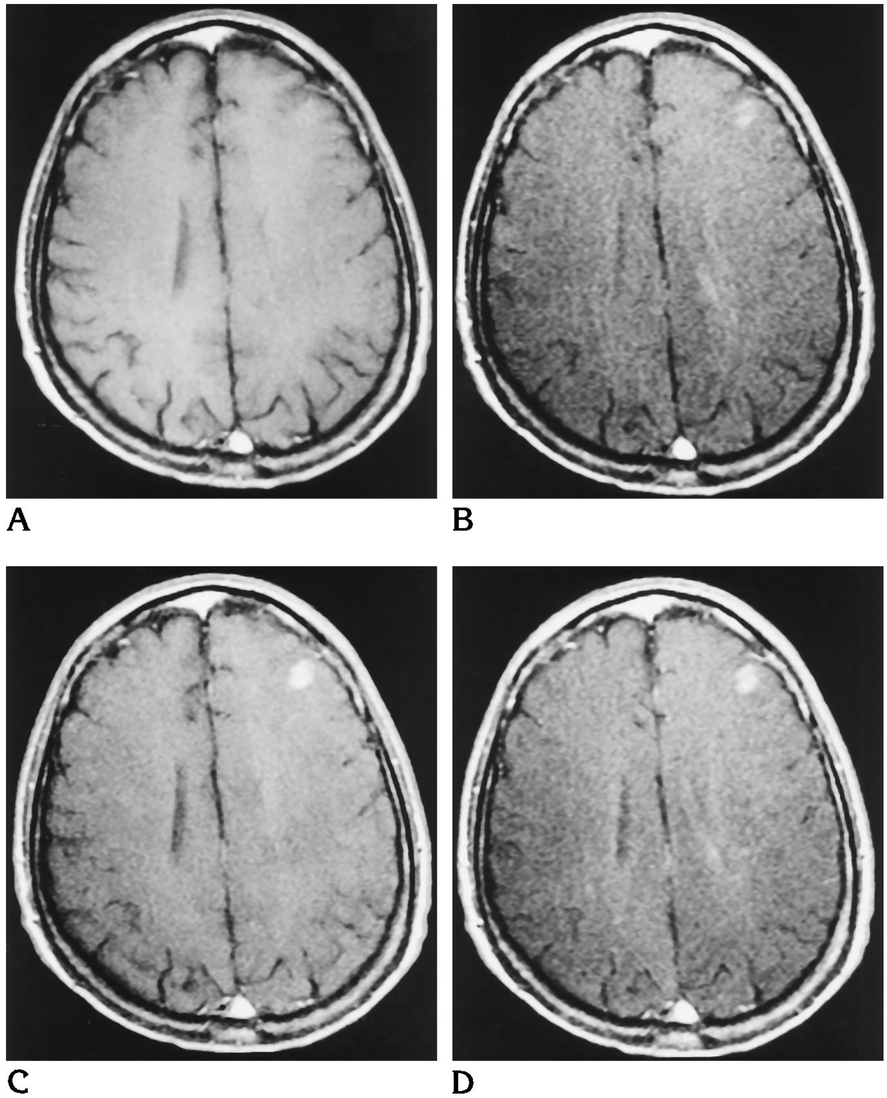

Fig 1. The left frontal metastasis of a bronchial carcinoma is not visible on the single-dose T1-weighted (640/20/1) study (*A*). All other studies (*B*: single-dose magnetization transfer T1-weighted [640/20/1]; *C*: triple-dose T1-weighted; *D*: triple-dose magnetization transfer T1-weighted) show the lesion.

can be considerably improved by increasing the contrast dose or by preapplying an off-resonance radio frequency pulse (1–12). The most significant result of our study was that lesion–to–white matter contrast seen on standard-dose magnetization transfer T1-weighted images was as good as the contrast seen on triple-dose T1-weighted images. In other words, the same number of lesions could be detected on standard-dose magnetization transfer T1-weighted images as on triple-dose T1-weighted images. Both the triple-dose studies and the standard-dose magnetization transfer T1-weighted studies showed two metastases that were not visible on the standard-dose T1-weighted images. No additional lesion was found on triple-dose magnetization transfer T1-weighted images; that is, on images that showed the highest lesion–to–white matter contrast. We attribute this to the composition of our patient group. Because an increased lesion–to–white matter contrast led to the detection of two additional lesions, it is likely that a further increase in contrast will result in the detection of additional lesions in a larger patient population.

Greater extension of enhancing tumor in patients with high-grade astrocytoma has also been noted on high-dose T1-weighted studies (13) and in a study in which magnetization transfer contrast was used (9). These findings, which we were able to confirm, may influence therapy: it has been shown that the absence of enhancing residual tumor on early postoperative MR images has the greatest predictive value for survival time (14, 15). However, these authors used standard-dose T1-weighted MR im-

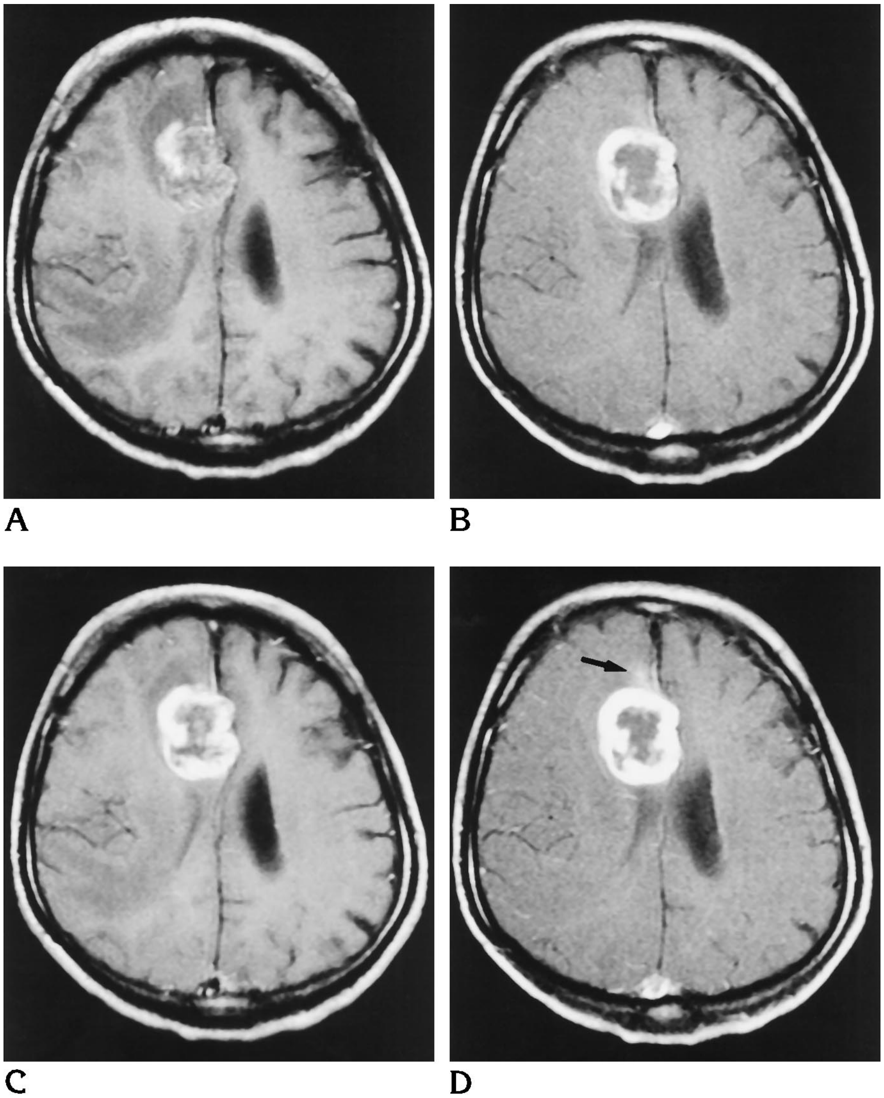

Fig 2. Glioblastoma multiforme. The demarcation and extension of the enhancing tumor on the single-dose T1-weighted (640/20/1) study (*A*) are smaller than on the other studies. Note the additional enhancement visible only on the triple-dose magnetization transfer T1-weighted (640/20/1) study (*D*, *arrow*) (*B*: single-dose magnetization transfer T1-weighted; *C*: triple-dose T1-weighted).

aging to define enhancing tumor, and it is unclear whether the surgical removal of enhancing tumor visible only on standard-dose magnetization transfer T1-weighted or triple-dose images would have further increased survival time.

The standard T1-weighted images were superior in depicting cerebral edema. As information regarding edema is much more readily available on T2-weighted images, we do not consider this a major disadvantage of the magnetization transfer T1-weighted images. The principles of magnetization transfer easily explain why the magnetization transfer technique results in a decrease in white matter–to–edema contrast compared with conventional T1-weighted sequences. Edema, defined by increased tissue water, is characterized by a low exchange rate between the proton pools. The signal reduction by magnetization transfer pulses is less in edema than in white matter, leading to an increase of white matter–to–edema contrast on magnetization transfer T2-weighted sequences (14). With magnetization transfer T1-weighted sequences, however, the contrast between edema and white matter is reduced.

Recently, several authors reported that a good lesion–to–white matter contrast can be achieved if spin locking and saturation effects contribute strongly to the signal (16, 17). Ulmer et al (18) showed that spin locking and the direct saturation effects, and thus the lesion–to–white matter contrast, can be improved if a smaller frequency offset and a higher pulse power are used.

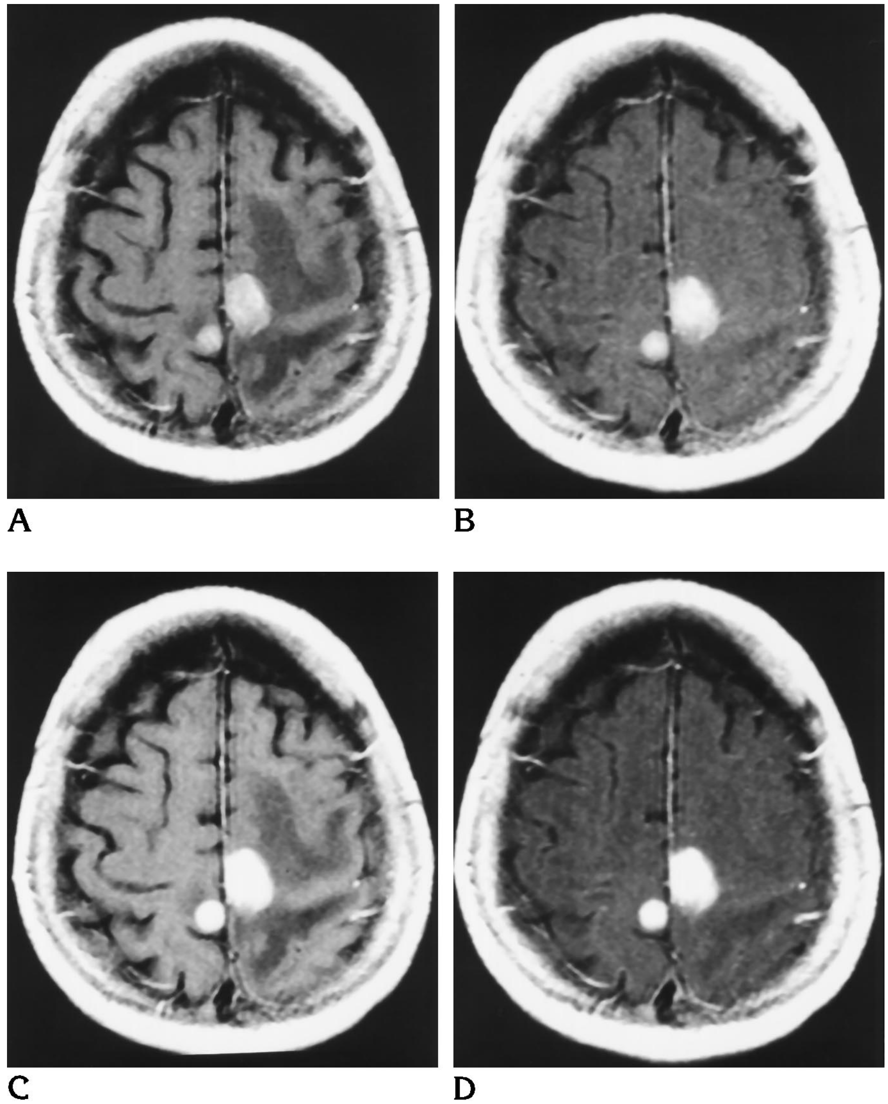

Fig 3. Two metastases of a mammary carcinoma. The extension of the peritumoral edema is much better depicted on the T1-weighted study (640/20/1) (*A*: single-dose T1-weighted; *B*: single-dose magnetization transfer T1-weighted (640/20/1); *C*: triple-dose T1-weighted; *D*: triple-dose magnetization transfer T1-weighted).

How much image contrast is enough? Should we routinely use triple doses of contrast medium (including triple-dose costs) plus magnetization transfer pulses to increase lesion–to–white matter contrast further? While our results do not allow a definitive answer to these questions, there seems to be a decreasing benefit of an increase in lesion–to–white matter contrast. No additional lesions were detected with the triple-dose magnetization transfer T1-weighted sequence. Also, triple-dose T1-weighted and standard-dose magnetization transfer T1-weighted images showed a greater extent of enhancing tumor in patients with astrocytoma as compared with standard-dose T1-weighted images in six of 12 patients, whereas triple-dose magnetization transfer T1-weighted images showed additional enhancing tumor in only two of these six patients.

Another aspect of better lesion–to–white matter contrast and lesion detectability is the therapeutic implications. Greater diagnostic accuracy should be followed by better treatment. We do not know, however, whether the detection by MR imaging of two metastases rather than one would change the therapeutic strategy; that patients with a solitary metastasis benefit from surgery has been assumed on the basis of CT data (19); we were unable to find any MR studies that corroborated this finding. Likewise, we do not know whether patients with astrocytoma would benefit from the resection of enhancing tumor visible only on triple-dose or standard-dose magnetization transfer T1-weighted images.

The next step should thus be the design of larger studies to evaluate the therapeutic consequences of improved diagnostic accuracy based on triple-dose contrast enhancement or the less expensive but equally effective use of magnetization transfer pulse sequences combined with the standard-dose contrast agents.

We did not try to determine the overall cost effectiveness of the triple-dose studies or the standard-dose magnetization transfer T1-weighted study. As Black (20) has pointed out, even if cost-neutral per se, increased detection of intracranial lesions may lead to an increase in treatment costs, the effectiveness of which can only be assessed by well-designed prospective cost analysis and outcome studies.

In summary, our study suggests that with standard-dose magnetization transfer T1-weighted imaging, the same increase in lesion detectability and conspicuity can be achieved as with triple-dose T1-weighted imaging. The therapeutic implications of such an increase in diagnostic yield and accuracy should be the subject of further investigations.

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