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Single-Dose Gadolinium with Magnetization Transfer versus Triple-Dose Gadolinium in the MR Detection of Multiple Sclerosis Lesions

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PURPOSE: To compare the efficacy of single-dose gadolinium with magnetization transfer contrast (MTC) with that of triple-dose gadolinium in detecting enhancing multiple sclerosis lesions. **METHODS:** Twenty-one patients with multiple sclerosis were examined with MR imaging first with 0.1 mmol/kg gadolinium (single dose) and then, after 24 to 72 hours, with 0.3 mmol/kg gadolinium (triple dose). T2-weighted fast spin-echo and T1-weighted spin-echo MR images with and without MTC were obtained before contrast administration followed by either T1-weighted spin-echo images with MTC (single dose) or conventional T1-weighted spin-echo images (triple dose), starting 5, 17, and 29 minutes after contrast administration. All images were evaluated in a blinded fashion and scored in random order by two readers. Outcome parameters included number of enhancing lesions, number of active MR examinations (those containing at least one enhancing lesion), contrast ratio (signal intensity of enhancing lesion divided by signal intensity of normal-appearing white matter), and size of enhancing lesions. **RESULTS:** Eighty-one percent more enhancing lesions and 49% more active MR examinations were detected when a triple dose of gadolinium was used as compared with a single dose. The level of agreement between readers as to the number of enhancing lesions was significantly higher for triple-dose than for single-dose gadolinium. With triple-dose gadolinium, contrast ratios and areas of enhancement increased by 10% and 33%, respectively. Delayed imaging increased the size of the lesion by 11% on single-dose MTC images and by 18% on triple-dose images. **CONCLUSION:** Triple-dose gadolinium is more effective (higher sensitivity and interobserver agreement) than single-dose gadolinium in combination with MTC in detecting enhancing multiple sclerosis lesions.

Index terms: Magnetic resonance, comparative studies; Magnetic resonance, magnetization transfer; Sclerosis, multiple

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Inflammation, accompanied by blood-brain barrier breakdown, represents the acute stage of multiple sclerosis (MS) lesions (1–3), and is characterized by contrast enhancement on enhanced T1-weighted spin-echo magnetic resonance (MR) images (4–8). When a conventional (single dose) of gadolinium (0.1 mmol/kg) is used, MR imaging depicts five to 10 times more disease activity in patients with MS than can be assumed on the basis of clinical examination (9–17), and two times more new lesions than seen with conventional T2-weighted spin-echo imaging (18). Because of its high sensitivity in detecting disease activity, contrast-enhanced MR imaging is presently used to increase the specificity and positive predictive value in the diagnosis of MS (19, 20) and to monitor treatment effects (21, 22).

An increase in sensitivity in detecting disease activity may be achieved by increasing contrast between gadolinium-enhanced lesions and sur-

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rounding tissue (23). Delayed imaging (24, 25), more frequent imaging (26, 27), and a combination of enhanced MR imaging of the brain and of the spinal cord (28) do not increase the yield of enhancing lesions significantly. Only triple-dose gadolinium (24, 29, 30) and enhanced T1-weighted spin-echo imaging combined with magnetization transfer contrast (MTC) (31, 32) increase the sensitivity of MR imaging in detecting disease activity. Triple-dose gadolinium appears to be more effective than single-dose gadolinium in combination with MTC: a 66% (29) versus 18% (32) increase in number of enhancing MS lesions compared with conventional single-dose gadolinium in patients with relapsing-remitting and secondary-progressive disease.

The purpose of our study was to compare the efficacy of single-dose MTC with that of triple-dose gadolinium in detecting enhancing MS lesions. This was done by comparing the sensitivity and interobserver reproducibility of these sequences in a multicenter setting.

Materials and Methods

Subjects

Patients with definite MS were studied at four different sites. The protocol was approved by the Institutional Review Board of the Academic Hospital Vrije Universiteit in Amsterdam. Informed consent was obtained from all patients. Our study population consisted of 21 patients with MS (14 women, seven men; 19 to 57 years old), 16 with relapsing-remitting disease and five with secondary-progressive disease. Expanded disability status scale scores of these patients ranged from 0.0 to 7.0 (median, 4.0). Four patients had a clinical relapse in the month preceding the examination.

MR Examination

MR imaging was performed with four different MR units with standard circularly polarized head coils. MR images were acquired on two separate occasions with an interval of 24 to 72 hours. For the first examination, 0.1 mmol/kg (single-dose) gadolinium was administered. For the second examination, 0.3 mmol/kg (triple-dose) gadolinium was used. During both examinations, precontrast MR imaging included T2-weighted fast spin-echo (2000–2400/16–30,80–98/1 [repetition time/echo time/excitations]) and T1-weighted spin-echo (500–620/15–20/2) pulse sequences with and without MT presaturation. On three units, MTC was obtained by using the standard MT option (gaussian-shaped pulse, −1.5 kHz off-resonance, 7.6-milliseconds duration, 250-Hz bandwidth, 500° flip angle, delivered once per repetition time). In one unit, a gaussian-shaped pulse was used, −1.0 kHz off-resonance, 12-milliseconds duration, 250-Hz bandwidth, and 490° flip angle. For all sites, the MT pulse resulted in a mean signal intensity reduction of normal-appearing white matter of 22% (±2%) on the MT-prepared T1-weighted images. Contrast-enhanced MR imaging included T1-weighted spin-echo (500–620/15–20/2) sequences with MTC added only to the single-dose studies or conventional T1-weighted spin-echo (500–620/15–20/2) imaging (triple dose). Both sequences were applied 5, 17, and 29 minutes after contrast administration. At each site, the repetition time for the sequences with and without MT was identical. In all MR sequences, a section thickness of 5 mm and a pixel size of approximately 1 × 1 mm were used. An interleaved image mode with an intersection gap of 5 mm was used to obtain 2 × 12 contiguous sections.

Image Analysis

Outcome parameters included number of enhancing lesions per MR examination, number of active examinations, and contrast ratios and size of enhancing lesions. An enhancing lesion was defined as a well-demarcated area of unequivocally increased signal intensity as compared with normal-appearing white matter not related to enhancing vessels or flow artifacts. Precontrast T1-weighted spin-echo MR images were used to ascertain that the area of increased signal intensity was visible only on postcontrast images. In case of doubt, T2-weighted fast spin-echo images were used to confirm the presence of lesions. An active MR examination was one that contained at least one enhancing lesion.

Analysis of the images was performed in four stages. Stage 1 included assessment by two independent readers. All images were blinded for patient's name and time of imaging, and were scored in random order. Because the difference in contrast between gadolinium-enhanced imaging with and without MTC is obvious, single-dose MTC and triple-dose gadolinium images were scored separately with an interval of 1 week. Enhancing MS lesions were marked, and each MR exam was scored for the presence of high signal intensity lesions on precontrast T1-weighted images and for presence of artifacts. In stage 2, all lesions upon which readers disagreed were reassessed until a consensus was reached. The reasons for discrepancy between readers were analyzed and classified. In stage 3, all lesions seen exclusively on only one sequence were reviewed to determine whether lesions could be identified retrospectively on other sequences. In stage 4, contrast ratios of those lesions depicted with both strategies were calculated by the following expression: signal intensity of enhancing lesion divided by signal intensity of surrounding normal-appearing white matter. Signal intensity of lesions was measured for the area of enhancement of a lesion. Signal intensity of normal-appearing white matter was measured as the mean signal intensity of three rectangular regions of interest surrounding the enhancing lesion, each with an area of at least 10 mm^2. The size of the enhancing lesions was measured with a local thresholding method, connecting all pixels with enhanced signal intensity

TABLE 1: Number of enhancing lesions and active MR examinations seen with single-dose gadolinium with MTC and with triple-dose contrast-enhanced T1-weighted imaging 5, 17, and 29 minutes after contrast administration

Time, min	No. of Enhancing MS Lesions						No. of Active MR Examinations					
	Single-Dose MTC			Triple-Dose Gadolinium			Single-Dose MTC			Triple-Dose Gadolinium		
	Observer 1	Observer 2	Consensus	Observer 1	Observer 2	Consensus	Observer 1	Observer 2	Consensus	Observer 1	Observer 2	Consensus
5	32	23	29	55	49	56	9	9	9	14	15	15
17	34	29	35	59	55	59	10	11	11	15	17	16
29	36	26	34	60	57	62	11	11	10	15	15	15

Note.—MTC indicates magnetization transfer contrast. Significantly more lesions and active MR exams were detected with the use of triple-dose gadolinium than with single-dose MTC ($P < .02$ and $P < .01$, respectively, Wilcoxon's). Agreement as to number of enhancing lesions or active exams does not necessarily mean that the same lesions or active exams were depicted.

TABLE 2: Mean contrast ratio and mean size of enhancement of enhancing lesions

Time, min	Mean Contrast Ratio (SE)		Mean Area of Enhancement, mm^2	
	Single-Dose MTC	Triple-Dose Gadolinium	Single-Dose MTC	Triple-Dose Gadolinium
5	1.26 (0.02)	1.36 (0.04)	21.72	27.91
17	1.28 (0.03)	1.40 (0.04)	23.96	31.58
29	1.24 (0.02)	1.39 (0.05)	24.01	33.18

Note.—SE indicates standard error of the mean; MTC, magnetization transfer contrast. Note the significant increase in contrast ratio and area of enhancement on the triple-dose images compared with the single-dose MTC images ($P < .01$; Wilcoxon's). No significant increase in contrast ratio was found for delayed imaging; however, the area of enhancement did increase significantly with the use of delayed imaging. For both single-dose MTC and triple-dose gadolinium (5 to 29 min: $P < .01$; Wilcoxon's).

caused by enhancement. Calculations were done by one observer who was blinded to patients' names and time of imaging.

Statistical Analysis

To compare the various imaging strategies, only consensus readings were used. Comparisons of the number of enhancing lesions were made using Wilcoxon's signed rank test. A one-tailed Fisher's Exact Test was used to compare the number of active MR exams. Level of agreement between the two readers as to the number of enhancing lesions and active MR exams at all time points was expressed by κ coefficients; κ coefficients, averaged over all time points, were compared for gadolinium dose (33). Wilcoxon's signed rank test was used to compare contrast ratios and total area of enhancement (size) between single- and triple-dose gadolinium images.

Results

No adverse effects resulted from administration of either single- or triple-dose gadolinium, and no residual contrast enhancement was visible on the precontrast images preceding the triple-dose images.

The number of enhancing lesions and active MR examinations per time point, per reader, and after reaching consensus are given in Table 1. The number of enhancing lesions increased significantly when triple-dose gadolinium was used as compared with single-dose MTC ($P < .02$ at 5 minutes; $P < .01$ at 17 minutes; and $P < .01$ at 29 minutes; Wilcoxon's) (Figs 1 and 2). The number of active MR exams was also significantly higher with triple-dose gadolinium compared with single-dose MTC at all time points after contrast administration ($P < .03$ at 5 minutes; $P < .02$ at 17 minutes; and $P < .01$ at 29 minutes; Fisher's) (Fig 3). Compared with early imaging (5 minutes), the number of enhancing lesions increased by 17% for single-dose MTC and by 11% for triple-dose gadolinium at delayed imaging (29 minutes). However, this was not statistically significant. Contrast ratios of enhancing lesions were significantly higher at each time point on triple-dose gadolinium images as compared with single-dose MTC images ($P < .01$, Wilcoxon's) (Table 2, Fig 2). The size of enhancing lesions, detected with both strategies at all time points, was also significantly higher when triple-dose gadolinium was used as compared with single-dose MTC at each time point after contrast administration (Wilcoxon's, $P < 0.01$), and also increased significantly for both doses of gado-

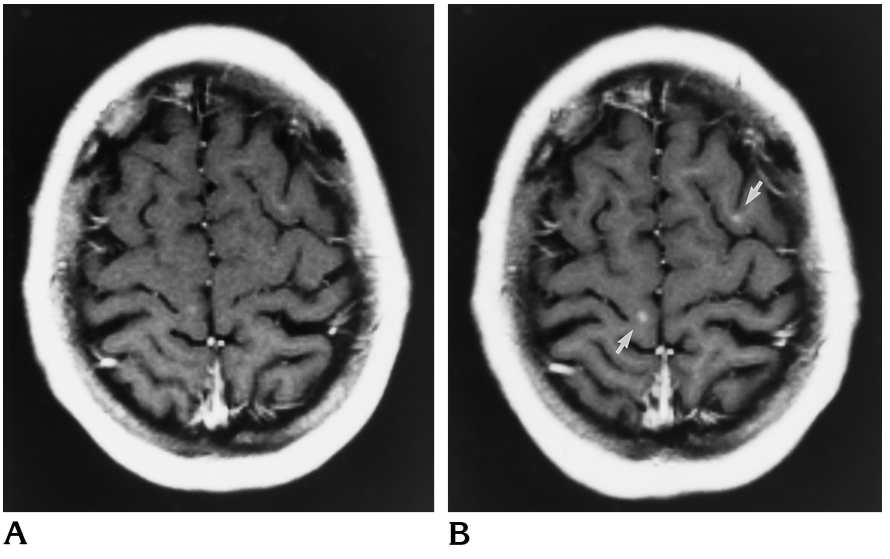

Fig 1. Single-dose MTC contrast-enhanced T1-weighted (500/15/2) image (*A*) versus triple-dose contrast-enhanced T1-weighted (500/15/2) image (*B*), both obtained 29 minutes after gadolinium administration. Only one enhancing lesion was seen by one observer on the single-dose MTC image, compared with two enhancing lesions seen by both readers on the triple-dose gadolinium image (*arrows*). Retrospectively, both lesions can be identified, although the signal intensity of these lesions is low.

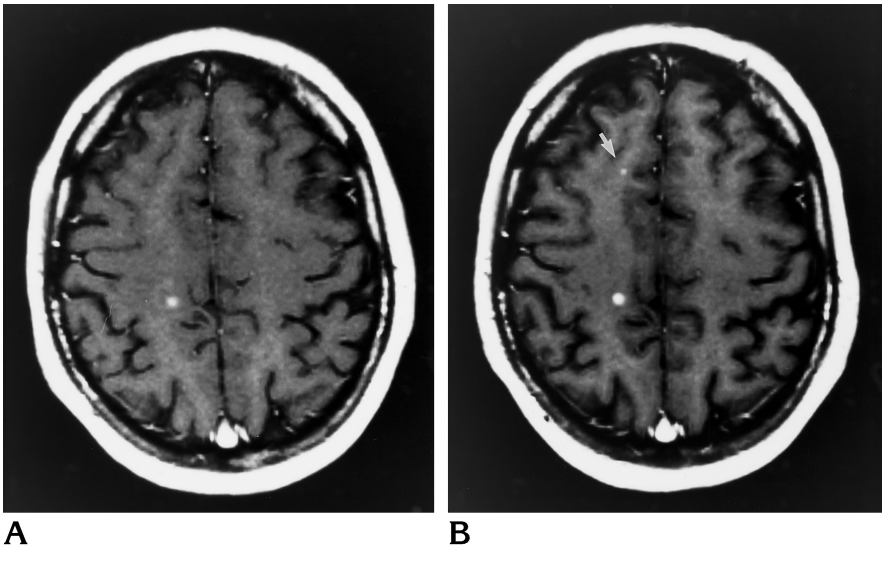

Fig 2. Single-dose MTC contrast-enhanced T1-weighted (500/15/2) image (*A*) versus triple-dose contrast-enhanced T1-weighted (500/15/2) image (*B*), both obtained 5 minutes after gadolinium administration. On the triple-dose gadolinium image an additional enhancing lesion is visible in the right frontal lobe (*arrow*) compared with the single-dose MTC image. The contrast ratio of the enhancing lesion visible on both images increased from 1.30 to 1.50 by using triple-dose gadolinium instead of single-dose MTC. The size of the enhancing lesion increased from 8 to 11 mm^2.

linium by increasing the time to 29 minutes after administration of gadolinium ($P < .01$, Wilcoxon's) (Table 2). Hyperintense lesions were seen on 70% of all precontrast MT-prepared T1-weighted images as compared with only 3% of conventional precontrast T1-weighted images (Fig 3). More flow-related artifacts and enhancing vessels were seen on triple-dose gadolinium images than on single-dose MTC images.

Readers initially disagreed on 42 (35%) of the 121 lesions as scored on single-dose MTC images, and on 29 (16%) of the 182 lesions as scored on triple-dose gadolinium images. As to active MR exams, readers disagreed on five (8%) of the 63 single-dose MTC exams and on three (5%) of the 63 triple-dose gadolinium exams. The κ coefficients for agreement on number of enhancing lesions between readers ranged from 0.54 to 0.68 for single-dose MTC, and from 0.85 to 0.87 for triple-dose gadolinium images. For the number of active MR exams, κ coefficients ranged from 0.72 to 1.00 and from 0.74 to 0.88 for single-dose MTC and triple-dose gadolinium, respectively. The level of agreement for number of enhancing lesions was significantly higher on triple-dose gadolinium images than on single-dose MTC images ($z = 2.49$, $P = .012$). No statistically significant difference was found regarding agreement on active exams between the two strategies.

Once a consensus was reached, 29 lesions were classified as false negative and 13 as false positive on single-dose MTC images. On triple-

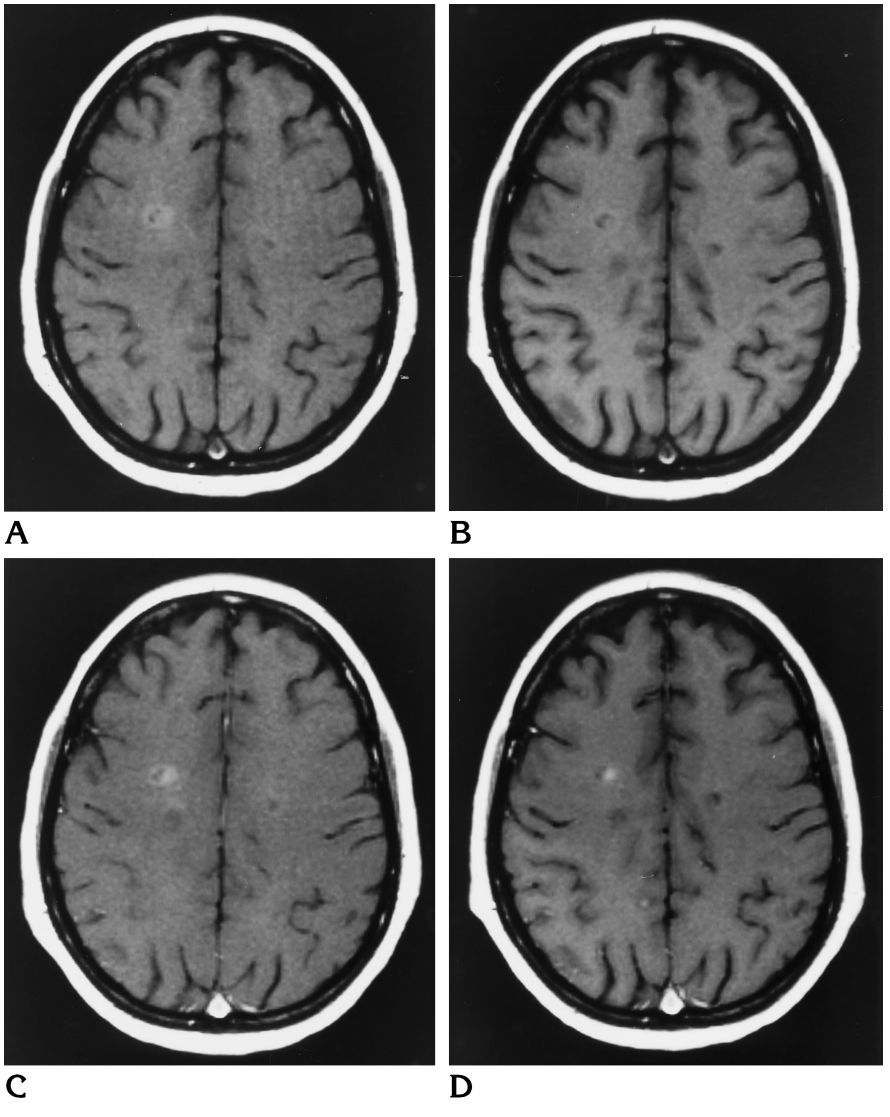

Fig 3. Unenhanced T1-weighted image with MTC (*A*) versus unenhanced T1-weighted image without MTC (*B*), and single-dose MTC contrast-enhanced T1-weighted image (*C*) versus triple-dose contrast-enhanced T1-weighted image (*D*) obtained 17 minutes after gadolinium administration. Note the hyperintense signal surrounding the hypointense lesion on the unenhanced T1-weighted image with MTC, which interfered with the detection of enhancement; both readers interpreted this exam as inactive, and both detected an enhancing lesion on the triple-dose gadolinium image, which changed this exam from "inactive" to "active."

dose gadolinium images, 24 lesions were regarded as false negative and five as false positive. The main reasons for misclassification of lesions included low signal intensity of enhancing lesions (15 [two false positive] versus eight [no false positives] for single-dose MTC and triple-dose gadolinium, respectively); high signal intensity on the precontrast images (11 [three false positive] versus five [two false positive]); and misjudgment caused by flow artifacts or enhancing vessels (15 [eight false positive] versus 13 [three false positive]). One lesion on a single-dose MTC sequence and three lesions on a triple-dose gadolinium sequence were overlooked.

At 17 minutes after contrast administration, 24 lesions were seen only on triple-dose gadolinium images. Nineteen of these lesions could not be identified retrospectively. Five lesions could be identified on the single-dose MTC images retrospectively, although signal intensity of these lesions was low. Adding the retrospectively detectable enhancing lesions, triple-dose gadolinium images showed significantly more lesions at 17 minutes after contrast administration than did single-dose MTC images ($P < .01$, Wilcoxon's). None of the enhancing lesions detected on single-dose MTC images were missed on triple-dose gadolinium images.

Discussion

We found a significant increase (81%) in the number of enhancing MS lesions on triple-dose gadolinium images as compared with single-dose MTC sequences. Our direct comparison of

the two strategies in an identical patient population substantiates trends suggested by other studies in which triple-dose gadolinium was more effective (66%) than single-dose MTC (18%) in detecting enhancing lesions (29, 32). Compared with figures found for single-dose MTC, we also found a significant increase in the number of active exams (49%) and an improvement in the contrast of enhancing lesions (10%) and in the size of lesions (33%) on triple-dose gadolinium images.

Besides an improvement in the identification of enhancing MS lesions, interobserver agreement in the detection of these lesions was significantly higher with the use of triple-dose gadolinium than with single-dose MTC. In agreement with other reports, we saw that for single-dose MTC, hyperintense signal intensity of MS lesions, already present on unenhanced MT-prepared T1-weighted images (32, 34), interfered with proper identification of enhancing MS lesions, leading to greater discrepancy between the two interpretations (Fig 3).

A potential disadvantage of the use of triple-dose gadolinium may be the large number of flow artifacts and enhancing vessels, which may interfere with interpretation of enhancing MS lesions. Although more artifacts were noted on the triple-dose gadolinium images by the two readers, this did not influence the interobserver agreement dramatically, and is in accordance with an earlier report (35). Actually, even more lesions were classified as false positive because of flow artifacts or enhancing vessels with the use of single-dose MTC (especially on a percentage basis).

Delayed imaging did not significantly influence the number of enhancing MS lesions, active exams, and contrast ratios. However, the size of enhancing lesions did increase significantly with delayed imaging, which also is in accordance with other reports (6, 25).

Although triple-dose gadolinium was superior to single-dose MTC in detecting enhancing MS lesions, the relevance of this finding needs further evaluation. By using triple-dose gadolinium, a higher transmembrane gradient of contrast agent is reached, leading to detection of those lesions that have lesser blood-brain barrier permeability (6, 36). When enhanced MR imaging is used in a cross-sectional study—for example, to support the diagnosis (19, 20) or as a snapshot analysis of the effects of treatment (21)—the use of triple-dose gadolinium may increase the value of enhanced MR imaging, revealing an increase of active exams (dissociation in time) and a greater number of enhancing MS lesions. On the other hand, in serial monthly treatment trials, in which enhanced MR imaging is used as an outcome parameter, triple-dose gadolinium may not be superior to single-dose gadolinium. Given the higher costs and the fact that some of the enhancing lesions seen on the triple-dose gadolinium images were persisting lesions seen on images obtained 1 month earlier, monthly triple-dose contrast-enhanced MR studies may not be superior to monthly single-dose contrast-enhanced MR studies. However, if it is possible to reduce the frequency of imaging in treatment trials monitored by serial enhanced MR studies while keeping the same statistical power (15, 22, 37, 38), triple-dose gadolinium may prove cost effective.

In conclusion, triple-dose gadolinium was more effective and reproducible in the detection of enhancing MS lesions than single-dose MTC and is the best option for increasing sensitivity in MR studies.

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