

Magnetic Resonance Imaging of Brain Metastases: Magnetisation Transfer or Triple Dose Gadolinium?

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Abstract

Magnetic resonance (MR) imaging of brain metastases relies on the neovascularity of metastases and the associated breach of blood-brain barrier manifesting as enhancement on T1-weighted images. There are 2 main strategies to improve the detection of brain metastases. One may increase the dose of gadolinium and increase the signal of the lesion. Alternatively, one may also lower the signal of the background (by magnetisation transfer suppression), in which case the enhancing lesion is rendered more conspicuous without increasing the dose of gadolinium.

We aim to compare the efficacy of single-dose conventional spin-echo T1 scans with magnetisation transfer (MT) suppression with triple-dose conventional spin-echo T1 scans in the detection of brain metastases in 18 patients undergoing imaging for brain metastases. An incremental dose technique was employed. After administration of a single dose of gadolinium, MT suppressed T1-weighted scans were obtained, followed by a conventional T1 scan. Two doses of gadolinium were subsequently given, achieving a cumulative triple-dose, and a conventional T1-weighted scan was then performed.

We found single-dose MT suppressed and triple-dose scans performed equally well and detected 26 metastatic lesions. They detected 5 (5/26, 19%) more lesions than the conventional single-dose T1 scans. Five (5/21, 24%) questionable lesions on single-dose conventional scans were confidently diagnosed on the single-dose MT suppressed and the triple-dose conventional scan. We conclude that single-dose MT suppressed scans are a cost-effective technique of detecting brain metastases.

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Introduction

Accurate detection of brain metastases is an important part of tumour staging. Magnetic resonance (MR) imaging is well accepted as a sensitive tool in the detection of brain metastases.^{1,2} Metastatic lesions exhibit neovascularity. Vascular endothelial proliferation may be found in and around metastatic deposits. The blood-brain barrier at the metastases is also defective.³ These pathological features manifest as enhancement following administration of gadolinium. MR detection of metastases relies on this feature of enhancement with contrast. Improvement of lesion detection will result from increase in contrast between the enhancing metastatic lesions and the brain parenchyma. There are 2 main strategies to achieve this.⁴ One may increase the dose of gadolinium. The signal from the enhancing metastatic lesions will increase over the background and lead to better contrast and increased detection. Gadolin-

ium, whether in its ionic or non-ionic formulation, may be safely given up to a dose three times its usual. Yuh et al⁵ have shown that triple-dose gadoteridol is safe and provided improved lesion detectability and additional diagnostic information.

Alternatively, the other strategy is to decrease the signal of the background to allow the signal from the lesion to stand out and thus increasing contrast. Magnetisation transfer (MT) suppression may be used to achieve this effect.⁶

Finelli et al⁴ compared contrast-to-noise ratios of patients with metastases and other enhancing brain lesions and found a 108% improvement in contrast-to-noise ratio for MT suppressed T1 images compared with conventional T1. They suggest that these values are at least equivalent to those reported for triple-dose gadolinium enhanced T1 images.

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Knauth et al⁷ compared T1 triple-dose conventional spin-echo with single-dose MT suppressed T1 scans in patients with metastases and primary brain tumours and found equal detection between standard dose MT spin-echo and triple-dose conventional spin-echo. They found that triple-dose MT spin-echo did not reveal additional lesions.

Yuh et al,⁵ Finelli et al⁴ and Knauth et al⁷ studied patients with a variety of brain lesions. However, the technique of magnetisation transfer may vary between centres.

We aim to compare the efficacy of a commercially available MT suppression technique applied on conventional spin-echo T1 images performed after a single-dose of gadolinium with triple-dose gadolinium conventional spin-echo T1 technique on 18 patients being imaged for possible brain metastases.

Materials and Methods

Eighteen patients with histologically proven extracranial primary tumours were enrolled into the study from 1 August 1997 to 31 October 1997. There were 10 female and 8 male patients with an age range of 37 to 84 years (mean 63.2 years).

Nine patients had lung carcinoma, 3 patients had breast carcinoma, 2 patients had colorectal carcinoma, 1 patient had hepatocellular carcinoma, 1 patient had cervical carcinoma, 1 patient had thyroid carcinoma, and 1 patient had undifferentiated carcinoma from unknown primary. All patients had neurological signs and symptoms and were referred for computed tomography (CT) or MR imaging to rule out brain metastases.

Imaging was performed with a 1.5T imager in 16 cases (Siemens, Vision) and with a 1.0T imager (Siemens, Expert) in 2 cases. Conventional spin-echo T1 images were acquired with TR500 to 680 ms, TE 12 to 15 ms. Two excitations were obtained. The conventional spin-echo T1 scans with MT suppression pulse was obtained after application of the commercially provided MT pulse with TR 640 to 760 ms and TE 12 to 15 ms. Two excitations were obtained.

The MT pulse provided commercially consisted of an untruncated sinc pulse 7.7 ms in duration with a 2000 Hz frequency offset. There is a 4 ms interval following the RF excitation before the conventional spin-echo sequence. The magnetisation transfer ratio (MTR) as defined by Dousset et al⁸ was calculated for the centrum semiovale.

$$\text{MTR} = [(SI_0 - SI_{\text{MT}}) / SI_0] \times 100, \text{ where}$$

SI_0 = baseline signal intensity, and

SI_{MT} = signal intensity with MT indirect saturation

The mean MTR for the study was 15.7%. Supplementary T2 weighted images were also obtained prior to contrast administration employing a Turbo spin-echo

technique with TR 5000 to 5400 ms, TE 99 to 120 ms. Two excitations were obtained.

Conventional T1 sequences were performed with matrix size ranging from 144 x 256 to 224 x 256. Slice thickness of 5 mm with interslice gap of 2 mm was employed. The specific absorption rate (SAR) was set at 1.5 W/kg for the whole body and 3.2 W/kg for the head. An incremental dose technique was employed. Pre-contrast conventional T1 scans were obtained with and without MT suppression.

Gadolinium was administered in the form of gadodiamide, a non-ionic agent. A single dose (0.1 mmol/kg) of gadodiamide was given via an intravenous line.

Post-contrast MT suppressed conventional spin-echo T1 scans were obtained followed by conventional spin-echo T1 scans without MT suppression in that order. A further dose of 0.2 mmol/kg (cumulative dose of 0.3 mmol/kg) was subsequently given resulting in a cumulative triple dose. A conventional spin-echo T1 scan was then performed immediately after the additional dose.

An enhancing lesion that cannot be explained by a normal vessel was presumed to be metastatic. No pathological confirmation was obtained. The scans were evaluated for number of lesion detected. The level of diagnostic confidence for each lesion detected was graded as definite or probable.

Results

A total of 26 enhancing brain lesions were detected by the triple dose and single-dose MT suppressed images. One patient had only meningeal metastases. Three patients had only vault metastases. These 4 patients were excluded in the analysis of brain metastases and only parenchymal lesions were considered. Incidental abnormalities detected included 1 case of acoustic neuroma and 1 case of meningioma. Three patients had no metastases.

Of the 9 patients with intra-axial metastases, 5 patients had single metastases, 3 patients have 2 metastatic foci and 1 patient had miliary metastases.

Lesion Detection

A total of 26 enhancing brain lesions were detected by the triple-dose and single-dose MT suppressed sequences. Single-dose MT and triple-dose conventional spin-echo detected equal numbers of lesions. Five (19%) additional lesions were detected by MT/ triple-dose sequences (Figs. 1a, 1b, 1c, 1d & 1e) compared with non-MT single dose. However, all 5 additional lesions occurred in a single patient with miliary metastases.

Diagnostic Confidence

Additional diagnostic confidence was obtained in 5 (19%) lesions from a single-dose conventional SE se-

quence when MT/ triple-dose sequences were applied. These lesions were graded as "probable" on the single-dose conventional T1 images but graded as "definite" on the MT suppressed/ triple-dose images.

Discussion

The importance of detecting brain metastases lies not only in staging but also in management of malignant diseases.

Salvatierra et al⁹ evaluated potentially resectable non-

small cell carcinoma of the lung and found that 13% have brain metastases. Of these, 21% were asymptomatic. Salbeck et al¹⁰ studied lung tumours of all stages and found that 10.8% of asymptomatic patients and 33.3% of symptomatic patients have brain metastases. Neurological symptoms are not a useful tool for differentiating patients with or without brain metastases. Schaefer et al¹¹ advocated screening of asymptomatic patients with Stage III non-small cell lung cancer for brain metastases.

Another issue relevant to the management of brain



Fig. 1a. Conventional spin-echo T1-weighted, unenhanced

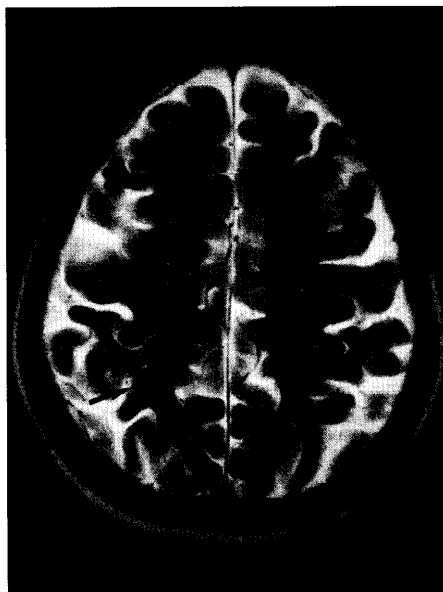


Fig. 1b. Turbo spin-echo T2-weighted, unenhanced.

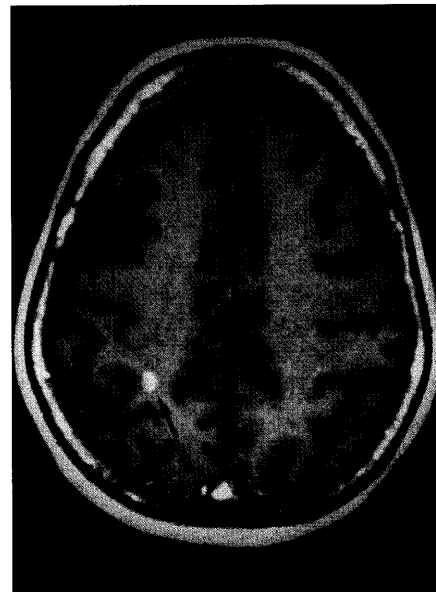


Fig. 1c. Conventional spin-echo T1-weighted, after single-dose of gadodiamide.

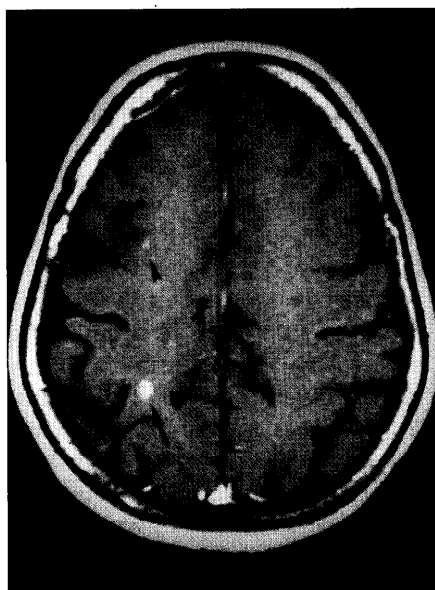


Fig. 1d. MT suppressed conventional spin-echo T1-weighted, after single-dose of gadodiamide.

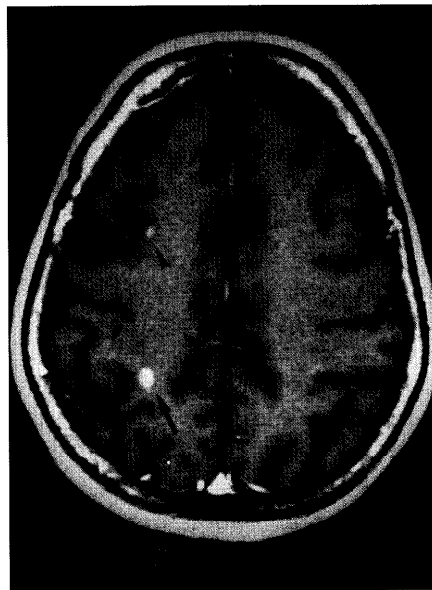


Fig. 1e. Conventional spin-echo T1-weighted, after triple-dose of gadodiamide.

The above figures are different sequences obtained over the same slice position of the same patient. There are 2 metastases in this slice. One is located in the right parietal lobe (arrow, Figs. 1a, 1b, 1c, 1d & 1e), and the other in the right frontal lobe (arrowhead, Figs. 1d & 1e). Note that the second metastasis was not seen on the T1- and T2-weighted images (Fig. 1a, Fig. 1b). It was not seen even after administration of a single-dose of gadodiamide (Fig. 1c). It is only seen on the MT suppressed single-dose T1-weighted image (Fig. 1d) and the triple-dose T1-weighted image (Fig. 1e).

metastases is whether the metastasis is single or multiple. Single metastases may be treated by more focussed radiotherapy or even surgery in selected cases¹¹ while whole brain external beam therapy is generally employed for multiple metastases.

Gadolinium-enhanced MR imaging is generally accepted as a better technique at demonstrating metastases compared with non-enhanced MR and enhanced CT. Lesions missed on CT and non-enhanced MR imaging are usually small and less than 10 mm in size.¹² CT has difficulty identifying lesions in the posterior fossa and may miss isodense haemorrhagic metastases. Non-enhanced MR has weaknesses with peripheral grey matter lesions and small nodules obscured by oedema.^{13,14}

In an attempt to improve detection of brain metastases, work has focussed on three areas: increasing the dose of gadolinium, employing delayed scans, and magnetisation transfer suppression.

Increased doses of gadolinium have been given in a direct attempt to increase the signal from the lesion.^{5,15} Delayed scans, up to 20 or 30 minutes after administration of contrast, may allow more time for gadolinium to move from the blood pool to the extracellular spaces of the brain. Yuh et al¹⁶ compared increased gadolinium doses with delayed imaging and found that although delayed imaging showed improvement in lesion detection for small lesions, high dose imaging showed the most lesions. However, the above strategies have disadvantages. Triple-dose gadolinium scans incur prohibitive costs and are not feasible for routine clinical practice. Delayed scans result in extra sequences performed and longer imaging time and pose inconvenience to technicians and patients.

Magnetisation transfer has been advocated with success as a method of improving the contrast of enhancing lesions.^{4,6,7} Instead of increasing the signal of the enhancing lesions by additional contrast, the background is suppressed to improve contrast and detection of these lesions.

Magnetisation transfer imaging is a technique whereby a off-resonant radio-frequency pulse is used to saturate bound proton. The saturated bound proton in turn transfers some of the saturation to the free proton as a result of interaction by cross-relaxation and chemical exchange. The transferred saturation results in loss of signal and thus background suppression.⁶

Finelli et al⁴ evaluated magnetisation transfer T1-weighted conventional spin-echo sequences in a mixed pool of patients. They found 108% improvement in contrast-to-noise ratio for magnetisation transfer T1-weighted images compared with conventional T1-weighted gadolinium enhanced images.

Quantitative evaluation of the magnetisation transfer ratio in patients with metastatic lesions of the brain

shows abnormally low values in areas surrounding the metastatic lesions even when these do not show abnormal enhancement on conventional images." The low magnetisation transfer ratio results in the lesion having a higher signal on a MT suppressed image. This may be another contributory factor leading to better detection of metastatic lesion on MT suppressed T1 spin-echo images.

There is variation of the type and magnitude of the MT pulse. A stronger MT pulse results in a higher specific absorption rate (SAR) for the patient. The SAR safety limits were not exceeded for this study. Finelli et al⁴ were able to achieve a MTR of 37% by modifying the flip angle of his sequences. Without modification of the commercially provided MT pulse and sequences, we were able only to achieve a MTR of 15.7%. However, this degree of MT suppression was able to give comparable results to triple-dose conventional scans in our study. We feel that a more optimised MT pulse would be able to provide better results but the commercially provided MT pulse was shown to be adequate in our study.

One limitation of our study is the lack of histological confirmation of the diagnosis of metastases. Histological confirmation is often difficult to justify clinically, as is the experience of other investigators. Typical enhancement, morphological appearance and characteristic position at gray-white interface were used as a marker for metastases in Yuh's study." We employed similar criteria for our study.

Another limitation of the study is its small size and small number of additional lesions detected. Although the study demonstrated increased detection with MT suppression, this occurred only in a single patient with miliary metastases. Clinical management was not changed in this patient. Knauth et al⁷ share our problem. They detected 2 additional metastases in 2 out of 19 patients with brain metastases. Clinical management was changed only in 1 of the 2 patients. Treatment decisions are most affected in patients with additional metastases detected in the setting of a solitary brain metastasis detected by single-dose studies. Sze et al¹⁸ studied triple-dose administration in a selected oncologic population and found 3 (25%) additional metastases in 12 patients with single metastasis seen on single-dose examinations. Future work studying the clinical impact of additional metastases detected by MT suppression and triple-dose studies would be needed to shed more light.

The high cost of triple-dose imaging makes MT suppression an attractive method of improving detection of intracranial metastatic lesions in scanners capable of this technique.¹⁹ Although Mayr et al²⁰ had demonstrated some cost-effectiveness with triple-dose MR, it is generally felt that screening asymptomatic patients for intrac-

ranial metastases with high-dose studies is not clinically justifiable due to cost constraints.^{19,21,22} High-dose studies are not performed in routine clinical practice due to high cost.¹⁹

Our findings concur with Knauth et al⁷ and Finelli et al.⁴

Conclusion

We feel that MT suppression is potentially a cost-effective method of detecting metastases in scanners capable of offering this technique. It avoids the prohibitive costs of increased doses of gadolinium but achieves similar results of increased detection. Further optimisation of the commercially available technique may give better results.

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REFERENCES

1. Shaefer P W, Budzik R F, Gonzalez R G. Imaging of cerebral metastases. *Neurosurg Clin North Am* 1996; 7:393-423.
2. Davis P C, Hudgins P A, Peterman S B, Hoffman J C. Diagnosis of cerebral metastases: Double-dose delayed CT vs contrast-enhanced MR imaging. *AJNR Am J Neuroradiol* 1991;12:293-300.
3. Russell D S, Rubenstein L J. Pathology of Tumours of the Nervous System. 5th ed. Baltimore: Williams & Wilkins, 1989:825-842, 857-8.
4. Finelli D A, Hurst G C, Gullapali R I, Errol M B. Improved contrast of enhancing brain lesions of postgadolinium, T1-weighted spin-echo images with use of magnetization transfer. *Radiology* 1994; 190:553-9.
5. Yuh W T C, Fisher D J, Runge V M, Atlas S W, Harms S E, Maravilla K R, et al. Phase III multicenter trial of high-dose gadoteridol in MR evaluation of brain metastases. *AJNR Am J Neuroradiol* 1994;15:1037-51.
6. Wolff S D, Balaban R S. Magnetization transfer imaging: Practical aspects of clinical applications. *Radiology* 1994; 192:593-9.
7. Knauth M, Forsting M, Hartmann M, Heiland S, Balzer T, Sartor K. MR enhancement of brain lesions: Increased contrast dose compared with magnetization transfer. *AJNR Am J Neuroradiol* 1996;17:1853-9.
8. Dousset V, Grossman R I, Ramer K N, Schnall M D, Young L H, Gonzalez-Scarano F, et al. Experimental allergic encephalomyelitis and multiple sclerosis: lesion characterization with magnetization transfer imaging. *Radiology* 1992; 182:483-91.
9. Salvatierra A, Baamonde C, Llamas J M, Cruz F, Lopez-Pujol J. Extrathoracic staging of bronchogenic carcinoma. *Chest* 1990; 97:1052-8.
10. Salbeck R, Grau H C, Artmann H. Cerebral tumor staging in patients with bronchial carcinoma by computed tomography. *Cancer* 1990; 66:2007-11.
11. Young R F. Radiosurgery for the treatment of brain metastases. *Semin Surg Oncol* 1998; 14:70-8.
12. Healy M E, Hesselink J R, Press G A, Middleton M S. Increased detection of intracranial metastases with intravenous Gd-DTPA. *Radiology* 1987; 165:619-24.
13. Sze G, Milano E, Johnson C, Heier L. Detection of brain metastases: Comparison of contrast-enhanced MR with unenhanced MR and enhanced CT. *AJNR Am J Neuroradiol* 1990;11:785-91.
14. Russell E J, Geremia G K, Johnson C E, Huckman M S, Ramsey R G, Washburn-Bleck J, et al. Multiple cerebral metastases: Detectability with Gd-DTPA-enhanced MR imaging. *Radiology* 1987; 165:609-17.
15. Akeson I, Larsson E M, Kristofferson D T, Jonsson E, Holtas S. Brain metastases-comparison of gadodiamide injection-enhanced MR imaging at standard and high dose. Contrast-enhanced CT and non-contrast-enhanced MR imaging. *Acta Radio* 1995; 36:300-6.
16. Yuh W T C, Tali E T, Nguyen H D, Simonson T M, Mayr N A, Fisher D J. The effect of contrast dose, imaging time, and lesion size in the MR detection of intracerebral metastases. *AJNR Am J Neuroradiol* 1995;16:373-80.
17. Boortsein J M, Wong K T, Grossman R I, Bolinger L, McGowan J C. Metastatic lesions of the brain: imaging with magnetization transfer. *Radiology* 1994; 191:799-803.
18. Sze G, Johnson C, Kawamura Y, Goldberg S N, Lange R, Friedland R J, et al. Comparison of single- and triple-dose contrast material in the MR screening of brain metastases. *AJNR Am J Neuroradiol* 1998; 19:821-8.
19. Ginsberg L E, Lang F F. Neuroradiologic screening for brain metastases-Can quadruple gadolinium be far behind [commentary]? *AJNR Am J Neuroradiol* 1998; 19:820-30.
20. Mayr N A, Yuh W T, Muhonnenn M G, Fisher D J, Nguyen H D, Ehrhardt J C, et al. Cost-effectiveness of high-dose MR contrast studies in evaluation of brain metastases. *AJNR Am J Neuroradiol* 1994; 15:1053-61.
21. Black W C. High-dose MR in the evaluation of brain metastases: will increased detection decrease costs [commentary]? *AJNR Am J Neuroradiol* 1994; 15:1062-4.
22. Mayr A, Hussey D H, Yuh W T. Cost-effectiveness of high-contrast-dose MR screening of asymptomatic brain metastasis. [letter; comment] *AJNR Am J Neuroradiol* 1995; 16:215-7.