

Contrast-enhanced synthetic MRI for the detection of brain metastases

Akifumi Hagiwara^{1,2}, Masaaki Hori¹, Michimasa Suzuki¹, Christina Andica¹, Misaki Nakazawa^{1,3}, Kouhei Tsuruta^{1,3}, Nao Takano¹, Shuji Sato¹, Nozomi Hamasaki¹, Mariko Yoshida¹, Kanako Kunishima Kumamaru¹, Kuni Ohtomo² and Shigeki Aoki¹

Acta Radiologica Open
5(2) 1–6
© The Foundation Acta Radiologica
2016
Reprints and permissions:
sagepub.co.uk/journalsPermissions.nav
DOI: 10.1177/2058460115626757
arr.sagepub.com



Abstract

Background: Synthetic magnetic resonance imaging (MRI), a technique that enables creation of various contrast-weighted images from a single MRI quantification scan, is a useful clinical tool. However, there are currently no reports examining the use of contrast-enhanced synthetic MRI for detecting brain metastases.

Purpose: To assess whether contrast-enhanced synthetic MRI is suitable for detecting brain metastases.

Material and Methods: Ten patients with a combined total of 167 brain metastases who underwent quantitative MRI and conventional T1-weighted inversion recovery fast spin-echo (conventional T1IR) MRI before and after administration of a contrast agent were included in the study. Synthetic T1IR and T1-weighted (synthetic T1W) images were produced after parameter quantification. Lesion-to-white matter contrast and contrast-to-noise ratio were calculated for each image. The number of visible lesions in each image was determined by two neuroradiologists.

Results: The mean lesion-to-white matter contrast and mean contrast-to-noise ratio of the synthetic T1IR images were significantly higher than those of the synthetic T1W ($P < 0.001$ and $P < 0.001$, respectively) and conventional T1IR ($P = 0.04$ and $P = 0.002$, respectively) images. Totals of 130 and 124 metastases were detected in the synthetic T1IR images by the first and second radiologists, respectively. The corresponding numbers were 91 and 85 in the synthetic T1W images and 119 and 119 in the conventional T1IR images. Statistical significance was not found among detected numbers of lesions.

Conclusion: Synthetic T1IR imaging created better contrast compared with synthetic T1W or conventional T1IR imaging. The ability to detect brain metastases was comparable among these imaging.

Keywords

Magnetic resonance imaging (MRI), synthetic MRI, contrast-enhanced MRI, T1-weighted inversion recovery, metastases, brain

Date received: 9 December 2015; accepted: 20 December 2015

Introduction

Brain metastases are the most common tumor of the central nervous system (1). It is estimated that more than 21,000 patients per year develop brain metastases in the United States (2). In cancer patients, the incidence of brain metastases is 9–17%, although the exact incidence is likely to be higher (3). The incidence of brain metastases is increasing (1), partly because of increase in the incidence of primary cancers and partly because improvements in treatment options have

¹Department of Radiology, Juntendo University School of Medicine, Tokyo, Japan

²Department of Radiology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

³Department of Radiological Sciences, Graduate School of Human Health Sciences, Tokyo Metropolitan University, Tokyo, Japan

Corresponding author:

Akifumi Hagiwara, Department of Radiology, 1-2-1, Hongo, Bunkyo-ku, Tokyo, 113-8421, Japan.

Email: a-hagiwara@juntendo.ac.jp



prolonged survival of patients with cancer, which increases the chance of primary tumors metastasizing.

Contrast-enhanced magnetic resonance imaging (MRI) is useful for detecting brain metastases. Early detection of brain metastases is crucial because the management strategies available after early diagnosis result in a better patient quality of life (4). T1-weighted (T1W) imaging is the most commonly used MRI sequence for evaluating brain metastases. T1-weighted inversion recovery (T1IR) is a newer pulse sequence that offers better contrast between gray and white matter of the brain than does a typical T1W sequence (5). However, there are contradictory reports regarding the sensitivity of contrast-enhanced T1IR and T1W images for detecting brain lesions (6–8).

Synthetic MRI is a technique that can produce images with almost any contrast weighting by virtually changing repetition time (TR), echo time (TE), and inversion time (TI) after quantification of longitudinal T1 and transverse T2 relaxation times and proton density (PD) (9,10). A recently developed MRI quantification pulse sequence, QRAPMASTER, is now in clinical use and has dramatically shortened the time needed for parameter quantification (11). The QRAPMASTER method assumes the process of T1 and T2 relaxation times to be monoexponential, whereas it may be multiexponential for many tissues. However, a phantom study has revealed good accuracy and reproducibility for T1, T2, and PD measurements by the QRAPMASTER method (12). Synthetic MRI is particularly useful when many different contrast settings are required. Synthetic MRI of the brain without the use of a contrast agent has been reported to produce images that have inferior image quality but diagnostic power comparable to that of images obtained via conventional MRI sequences (13). Therefore, if the diagnostic power of images obtained via synthetic MRI after administration of a contrast agent is also proved to be comparable to that of conventional MRI, synthetic MRI would be a useful means of screening for brain metastases. However, there are currently no reports in the literature of studies examining the use of contrast-enhanced synthetic MRI for detecting brain metastases.

In the present study, we assessed the use of synthetic MRI to detect brain metastases by comparing lesion-to-white matter contrast, contrast-to-noise ratio, and number of brain metastases detected in images obtained with synthetic and conventional MRI sequences.

Material and Methods

The present study was approved by the institutional review board of Juntendo University Hospital, Japan. Written informed consent was not required for this

study because of its retrospective nature. All the patient information was anonymized and de-identified prior to analysis.

Data from 19 consecutive cancer patients (11 men, 8 women; mean age, 63.1 years; age range, 44–75 years) suspected of having brain metastases who underwent quantitative MRI and conventional T1-weighted inversion recovery fast spin-echo MRI (conventional T1IR) before and after administration of a gadolinium-based contrast agent from April 2015 through July 2015 were retrospectively reviewed. Ten patients (6 men, 4 women; mean age, 62.3 years; age range, 44–75 years) had at least one brain metastasis and were included in the study. The primary lesions of these metastases were lung cancer (n=6), breast cancer (n=2), and esophageal cancer (n=2). Diagnoses were made on the basis of clinical history, presentation, or follow-up imaging studies.

MRI

In all patients, MRI was performed on a 3.0-T MRI system (Discovery MR750w, GE Healthcare, Milwaukee, WI, USA) with a 12-channel head coil. All patients underwent conventional T1IR imaging and quantitative imaging before and after intravenous administration of a gadolinium-based contrast agent. The dose of contrast medium was 0.1 mmol/kg and the contrast agent used was one of the followings: Omniscan (Daiichi-Sankyo, Tokyo, Japan), ProHance (Bracco-Eisai, Tokyo, Japan), Magnevist (Bayer Vital, Leverkusen, Germany). Contrast-enhanced conventional T1IR imaging and quantitative MRI were performed before administration of a contrast agent and approximately 1 and 7 min after administration of a contrast agent, respectively. Axial, sagittal, and coronal images were obtained, in that order, for conventional T1IR imaging, and only axial images were obtained for quantitative MRI.

Quantitative MRI was performed by using the two-dimensional QRAPMASTER pulse sequence (11). The QRAPMASTER pulse sequence is a multi-slice, multi-echo, and multi-saturation delay saturation recovery turbo spin-echo acquisition method with which images are collected for different combinations of TE and saturation delay time (TD). In our institution, two sets of TE values and four sets of TD values are used to make eight real images and eight imaginary images for quantification of longitudinal T1 and transverse T2 relaxation times and PD. The TE values used were 16.9 and 84.5 ms, and TD was set as defined by the manufacturer (SyntheticMR AB, Linköping, Sweden). The parameters used for quantitative MRI were: field of view (FOV), 240 mm × 240 mm; matrix, 320 × 320; ETL, 10; bandwidth, 31.25 kHz; slice thickness/gap,

4.0 mm/1.0 mm; slices, 30. The acquired data were used to calculate T1, T2, and PD maps at each slice position, which were then used to calculate the synthetic MR images. Quantification map acquisition and raw data processing were performed with SyMRI software (v. 7.2 RC2, SyntheticMR AB) on a commercial personal computer in less than 1 min and synthetic images were created in real-time.

Two experienced neuroradiologists (AH and MH) reviewed the synthetic images of 19 original patients and determined the most appropriate parameters for detecting brain metastases visually while maintaining the T1-weighting contrast. Synthetic T1-weighted inversion recovery (synthetic T1IR) images were produced by using the following parameters: TR, 500 ms; TE, 5 ms; TI, 440 ms. Synthetic T1-weighted (synthetic T1W) images were produced for comparison by using the following parameters: TR, 390 ms; TE, 15 ms. Conventional T1IR images before and after administration of a gadolinium-based contrast agent were obtained by using the following parameters: TR, 3294 ms; TE, 18 ms; TI, 908 ms; FOV, 240 × 216 mm; matrix, 352 × 256; ETL, 8; slice thickness/gap, 4 mm/1 mm; slices, 30. Acquisition time was 1 min 50 s for conventional T1IR and 7 min 12 s for quantitative MRI before and after administration of a contrast agent. Images were saved as DICOM files (Digital Imaging and Communications in Medicine) and analyzed by using OsiriX MD software (v. 6.5.2, Pixmeo, Geneva, Switzerland).

Image analysis

Two neuroradiologists (MH and AH) reviewed all the MRI sequences and agreed that a total of 167 nodules were included in the study. The image quality of the contrast-enhanced synthetic T1IR images was compared with that of the contrast-enhanced synthetic T1W and contrast-enhanced conventional T1IR images by using two quantitative and one qualitative criteria. Only axial images were used for the quantitative and qualitative analyses. Sagittal and coronal conventional T1IR images were used only for counting the total number of brain metastases with axial images (as “Gold Standards”) by MH and AH.

Quantitative analysis

The quantitative criteria were lesion-to-white matter contrast and contrast-to-noise ratio. Region-of-interest (ROI) analyses were performed on the contrast-enhanced synthetic T1IR, contrast-enhanced synthetic T1W, and contrast-enhanced conventional T1IR images by a single investigator (MN). For the quantitative analysis, the signal intensity of the tumors and

corresponding white matter were measured by means of ROI analyses and mean values were recorded. Tumors that were found on both the contrast-enhanced synthetic images and the contrast-enhanced conventional T1IR images were included in the analysis. In most cases, an ROI of approximately 3 mm² that covered the lesion and corresponding white matter was used, but its size was adjusted for lesions smaller than 3 mm². The corresponding white matter for supratentorial lesions was defined as the white matter adjacent to lesions that showed no edema. The corresponding white matter for infratentorial lesions was defined as the white matter in the brainstem in the same slice that showed no edema.

In synthetic MRI, the signal intensity of the surrounding air is set at zero. Hence, the median standard deviation of the signal intensities of the following 12 ROIs, all of which were approximately 3 mm² in size, was defined as the noise for each patient: ROIs in the cerebrospinal fluid (bilaterally in the anterior horns of the lateral ventricles), in the gray matter (bilaterally in the thalamus, occipital cortex, and frontal cortex), and in the white matter (bilaterally in the centrum semiovale and in the corpus callosum—one in the genu and one in the splenium). This method was modified from the technique used by Blystad et al. (13).

Lesion-to-white matter contrast was defined as the difference between the mean signal intensities of a lesion and the corresponding white matter divided by the signal intensity of the corresponding white matter. Contrast-to-noise ratio was defined as the difference between the signal intensities of a lesion and the corresponding white matter divided by the noise of each sequence.

Qualitative analysis

For the qualitative analysis, two experienced neuroradiologists (MS and MY) counted the number of lesions in the axial contrast-enhanced synthetic T1IR, contrast-enhanced synthetic T1W, and contrast-enhanced conventional T1IR images from the 10 patients with brain metastases, which were shown in a random order. Radiologists were blinded to different types of images. Each contrast-enhanced image was shown with the corresponding non-contrast-enhanced image for reference. Counted lesions that were not included in the 167 lesions determined by MH and AH were categorized as false positive.

Statistical analysis

Statistical computing was performed with the free software R Ver. 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria. URL

Table 1. Lesion-to-white matter contrast and contrast-to-noise ratio of contrast-enhanced synthetic T1-weighted inversion-recovery (T1IR), contrast-enhanced synthetic T1-weighted (T1W), and contrast-enhanced conventional T1IR images.

	Lesion-to-white matter contrast	Contrast-to-noise ratio
Synthetic T1IR	0.51 ± 0.47	20.98 ± 18.65
Synthetic T1W	0.34 ± 0.38	14.20 ± 14.98
Conventional T1IR	0.47 ± 0.47	18.65 ± 18.00
<i>P</i> value	<i>P</i> < 0.05*	<i>P</i> < 0.05 [†]

The lesion-to-white matter contrast and contrast-to-noise ratio of the contrast-enhanced synthetic T1IR images were significantly higher than those of the contrast-enhanced synthetic T1W and contrast-enhanced conventional T1IR images.

Each set of values represents the mean ± standard deviation.

*Synthetic T1IR vs. synthetic T1W (*P* < 0.001) and conventional T1IR (*P* = 0.04), by post-hoc pairwise comparison.

[†]Synthetic T1IR vs. synthetic T1W (*P* < 0.001) and conventional T1IR (*P* = 0.002), by post-hoc pairwise comparison.

<http://www.R-project.org/>). Because all of the datasets were not normally distributed, we used the Friedman test, which is a non-parametric test, to compare the lesion-to-white matter contrast, contrast-to-noise ratio, and number of lesions detected in the synthetic T1IR, synthetic T1W, and conventional T1IR images. Post-hoc pairwise tests with Holm correction were performed to determine statistical significance. A two-sided *P* value of less than 0.05 was considered significant.

Results

The lesion-to-white matter contrast and contrast-to-noise ratio of the contrast-enhanced synthetic T1IR images were significantly higher than those of the contrast-enhanced synthetic T1W and contrast-enhanced conventional T1IR images (Table 1). The number of lesions detected by two neuroradiologists in the synthetic T1IR images was higher than those in the synthetic T1W and conventional T1IR images without statistical significance (Table 2, Fig. 1).

In the present study, contrast-enhanced synthetic T1IR produced the best quality contrast for detecting brain metastases. Although the numbers of lesions detected did not differ statistically, contrast-enhanced synthetic T1IR images enabled detection of more metastases than contrast-enhanced conventional T1IR and synthetic T1W images.

In the qualitative analysis, several metastases were detected in the synthetic T1IR and synthetic T1W images but not in the conventional T1IR images. These included metastases that were hidden by flow-related artifacts from the sigmoid sinus

Table 2. Numbers of lesions detected by two neuroradiologists in contrast-enhanced synthetic T1-weighted inversion recovery (T1IR), contrast-enhanced synthetic T1-weighted (T1W), and contrast-enhanced conventional T1IR images.

	Neuroradiologist 1	Neuroradiologist 2
Synthetic T1IR	130 (5)	124 (1)
Synthetic T1W	91 (2)	85 (1)
Conventional T1IR	119 (3)	119 (2)
<i>P</i> value	<i>P</i> > 0.05*	<i>P</i> > 0.05 [†]

The number of lesions detected by two neuroradiologists in the synthetic T1IR images was higher than those in the synthetic T1W and conventional T1IR images without statistical significance.

Each value represents the total number of detected lesions with the number of false-positive lesions in parentheses.

*Synthetic T1IR vs. synthetic T1W (*P* = 0.11) and conventional T1IR (*P* = 0.30), by post-hoc pairwise comparison.

[†]Synthetic T1IR vs. synthetic T1W (*P* = 0.065) and conventional T1IR (*P* = 0.525), by post-hoc pairwise comparison.

(Fig. 2). In the present study, the transverse and sigmoid sinuses tended to cause signal voids on contrast-enhanced synthetic images and flow-related artifacts were less pronounced in the contrast-enhanced synthetic images than in the contrast-enhanced conventional T1IR images. Indeed, some small cortical metastases were identifiable only in the contrast-enhanced synthetic T1IR and synthetic T1W images because they resembled blood vessels in the contrast-enhanced conventional T1IR images, especially when they were adjacent to superficial vessels (Fig. 3). These results demonstrate the potential advantages of synthetic MRI compared with conventional MRI, although further investigation is needed.

Discussion

A potential advantage of synthetic MRI over conventional MRI is the creation of any contrast weighting after image acquisition. Although in the present study we used identical parameters for all 10 patients, it would also have been possible to synthesize images with parameters tailored to each individual to maximize the potential to detect brain metastases. Further optimization of contrast weighting is needed to maximize the ability to detect brain metastases by using synthetic MRI. Although the scan time for quantitative MRI (7 min 12 s) was longer than that of conventional T1IR sequence (1 min 50 s) after administration of a contrast agent, the ability to synthesize images optimized for each individual and the potential to avoid multiple scans needed for conventional T1W, T1IR, or FLAIR imaging are clear advantages of synthetic MRI. In addition, contrast-enhanced synthetic double

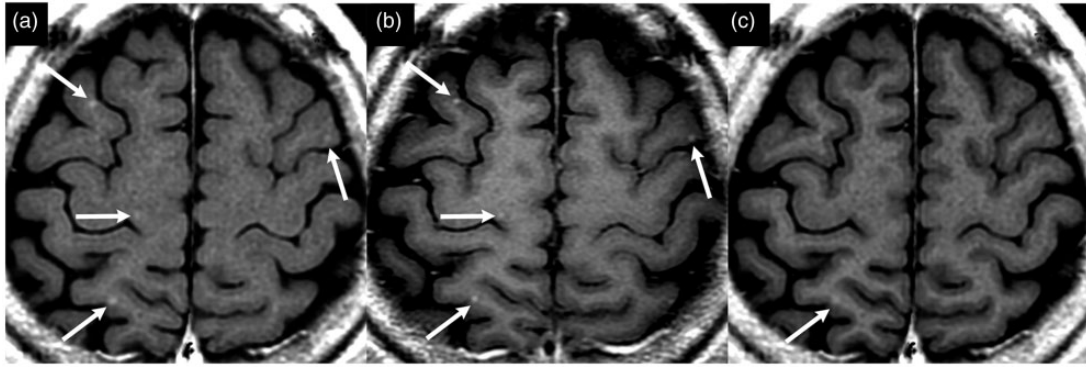


Fig. 1. Example MR images showing metastases that could not be identified with contrast-enhanced synthetic TI-weighted (TIW) imaging. (a) Contrast-enhanced synthetic TI-weighted inversion recovery (TIIR) image. (b) Contrast-enhanced conventional TIIR image. (c) Contrast-enhanced synthetic TIW image. Four small metastases can be identified in both (a) and (b) (arrows) but only one can be identified in (c) (arrow). These metastases were missed on synthetic TIW image by the two neuroradiologists in the qualitative analysis.

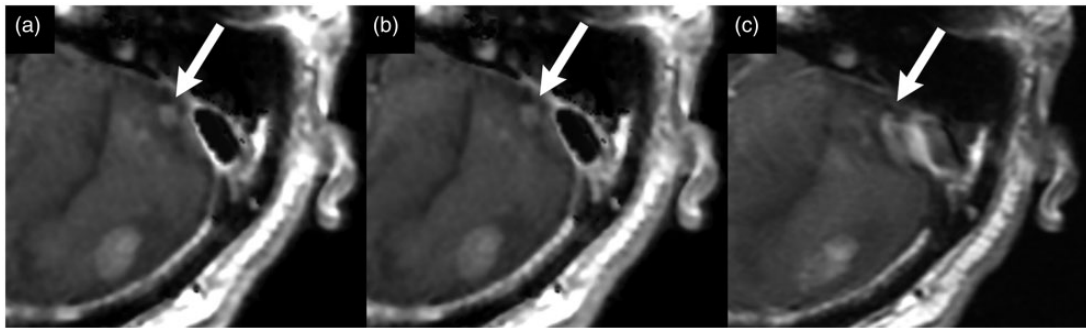


Fig. 2. Less flow-related artifacts from the sigmoid sinus were observed with contrast-enhanced synthetic TI-weighted inversion recovery (TIIR) and contrast-enhanced synthetic TI-weighted (TIW) imaging compared with contrast-enhanced conventional TIIR imaging. (a) Contrast-enhanced synthetic TIIR image. (b) Contrast-enhanced synthetic TIW image. (c) Contrast-enhanced conventional TIIR image. A metastasis (arrows) located next to the left sigmoid sinus is obvious in (a) and (b) but is obscured by flow-related artifacts from the sigmoid sinus in (c).

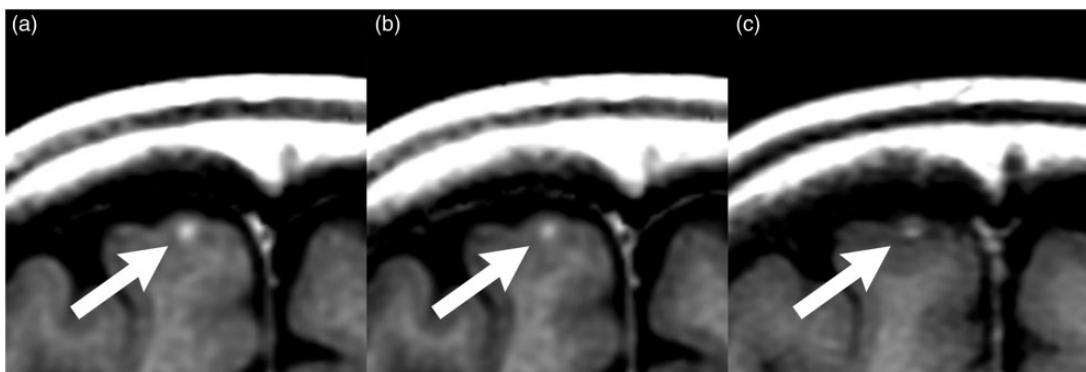


Fig. 3. Cortical metastases resembled blood vessels in contrast-enhanced conventional TI-weighted inversion recovery (TIIR) images. (a) Contrast-enhanced synthetic TIIR image. (b) Contrast-enhanced synthetic TI-weighted image. (c) Contrast-enhanced conventional TIIR image. A small cortical metastasis (arrow) is obvious in (a) and (b) but resembles a blood vessel in (c) because of its small size and clear demarcation.

inversion recovery imaging, which suppresses signals from the cerebrospinal fluid and bone marrow fat, may also be useful for evaluating dural enhancement (14).

There are some limitations in the present study. First, the number of patients was small. Second, since quantitative MRI was performed after conventional T1IR imaging after administration of a contrast agent, differences in the timing of image acquisition may have affected the degree of lesion enhancement. Acquiring spin-echo T1W images with delays of up to 30 min after administration of a contrast agent increased the rate of detection of cerebral metastases compared with acquiring the images immediately after administration of contrast agent (15,16). However, a delay of only 1 min after administration of a contrast agent offered better contrast between brain metastases and white matter than did a delay of 10 min (17).

In conclusion, contrast-enhanced synthetic T1IR imaging produced images with better lesion-to-white matter contrast and contrast-to-noise ratio than did contrast-enhanced synthetic T1W and contrast-enhanced conventional T1IR imaging. More brain metastases were detected with contrast-enhanced synthetic T1IR than with the other sequences, but this result was not statistically significant.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by grants from MEXT-Supported Program for the Strategic Research Foundation at Private Universities (2011–2015) and funded by ImPACT Program of Council for Science, Technology and Innovation (Cabinet Office, Government of Japan).

References

1. Tabouret E, Chinot O, Metellus P, et al. Recent trends in epidemiology of brain metastases: an overview. *Anticancer Res* 2012;32:4655–4662.
2. Stelzer KJ. Epidemiology and prognosis of brain metastases. *Surg Neurol Int* 2013;4:S192–202.
3. Nayak L, Lee EQ, Wen PY. Epidemiology of brain metastases. *Curr Oncol Rep* 2012;14:48–54.
4. Mayr NA, Yuh WT, Muhonen MG, et al. Cost-effectiveness of high-dose MR contrast studies in the evaluation of brain metastases. *Am J Neuroradiol* 1994;15:1053–1061.
5. Rydberg JN, Hammond CA, Huston J 3rd, et al. T1-weighted MR imaging of the brain using a fast inversion recovery pulse sequence. *J Magn Reson Imaging* 1996;6:356–362.
6. Hori M, Okubo T, Uozumi K, et al. T1-weighted fluid-attenuated inversion recovery at low field strength: a viable alternative for T1-weighted intracranial imaging. *Am J Neuroradiol* 2003;24:648–651.
7. Jeong B, Choi DS, Shin HS, et al. T1-weighted FLAIR MR imaging for the evaluation of enhancing brain tumors: comparison with spin echo imaging. *J Korean Soc Magn Reson Med* 2014;18:151.
8. Qian YF, Yu CL, Zhang C, et al. MR T1-weighted inversion recovery imaging in detecting brain metastases: could it replace T1-weighted spin-echo imaging? *Am J Neuroradiol* 2008;29:701–704.
9. Bobman SA, Riederer SJ, Lee JN, et al. Cerebral magnetic resonance image synthesis. *Am J Neuroradiol* 1985;6:265–269.
10. Riederer SJ, Suddarth SA, Bobman SA, et al. Automated MR image synthesis: feasibility studies. *Radiology* 1984;153:203–206.
11. Warntjes JB, Leinhard OD, West J, et al. Rapid magnetic resonance quantification on the brain: Optimization for clinical usage. *Magn Reson Med* 2008;60:320–329.
12. Krauss W, Gunnarsson M, Andersson T, et al. Accuracy and reproducibility of a quantitative magnetic resonance imaging method for concurrent measurements of tissue relaxation times and proton density. *Magn Reson Imaging* 2015;33:584–591.
13. Blystad I, Warntjes JB, Smedby O, et al. Synthetic MRI of the brain in a clinical setting. *Acta Radiol* 2012;53:1158–1163.
14. Hagiwara A, Nakazawa M, Andica C, et al. Dural Enhancement in a patient with Sturge-Weber syndrome revealed by double inversion recovery contrast using synthetic MRI. *Magn Reson Med Sci* 2015 November 6. (Epub ahead of print).
15. Healy ME, Hesselink JR, Press GA, et al. Increased detection of intracranial metastases with intravenous Gd-DTPA. *Radiology* 1987;165:619–624.
16. Yuh WT, Tali ET, Nguyen HD, et al. The effect of contrast dose, imaging time, and lesion size in the MR detection of intracerebral metastasis. *Am J Neuroradiol* 1995;16:373–380.
17. Jeon JY, Choi JW, Roh HG, et al. Effect of imaging time in the magnetic resonance detection of intracerebral metastases using single dose gadobutrol. *Korean J Radiol* 2014;15:145–150.