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MAJOR PAPER

Estimation of Gadolinium-based Contrast Agent Concentration Using Quantitative Synthetic MRI and Its Application to Brain Metastases: A Feasibility Study

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Purpose: Gadolinium-based contrast agents (GBCA) provide valuable information for assessing and differentiating lesions in the body. However, contrast enhancement evaluation on conventional MRI is qualitative because the signal intensity uses an arbitrary scale. An approach that allows more quantitative assessment of tissue enhancement that can be integrated into clinical use is desirable. This study aimed to provide a method that can estimate GBCA concentration in a clinically applicable scan-time.

Methods: Gadolinium-based contrast agent concentrations were quantified in phantoms containing water and nine different concentrations of Gadoteridol (Gd-HP-DO3A), ranging from 0.02 to 1.00 mmol/L, using quantitative synthetic MRI. Simple linear regression analysis between the estimated GBCA concentration and the reference values were performed to assess the accuracy. We performed region of interest analysis on each phantom, and recorded the mean and standard deviation. We evaluated the precision of the GBCA map by calculating the coefficient of variation (CV) for each concentration. The GBCA concentration quantification method was applied for 10 patients with metastatic brain tumors to demonstrate the feasibility of this method.

Results: For the phantom study, estimated GBCA concentrations were in a strong linear relationship (R^2 = 0.998) with reference values, with a slope and intercept on simple linear regression analysis of 0.98 and 0.02, respectively. On precision assessment, the CV was <5%, with the exception of concentrations under 0.07 mmol/L. In the range of 0.07–0.99 mmol/L, the mean CV was 1.5 ± 1.2%. For application to brain metastases, the maximum estimated GBCA concentration in the metastases was 0.73 mmol/L, which was under the upper limit evaluated in the phantom study (i.e. –0.99 mmol/L).

Conclusion: The concentration of Gd-HP-DO3A in the range of 0.07–0.99 mmol/L can be measured in a clinically applicable scan time using quantitative synthetic MRI, even though this study's results are only preliminary due to several limitations.

Keywords: *brain metastasis, gadolinium-based contrast agent, quantitative imaging, relaxivity, synthetic magnetic resonance imaging*

Introduction

Gadolinium-based contrast agents (GBCA) are widely used in daily clinical practice to improve visibility of physiological internal body structures and lesions. Although administration of GBCA improves the efficacy of image assessment and differential diagnosis, signal intensity on T_1-weighted images is not in a linear relationship with the absolute GBCA concentration, since the conventional MRI techniques express signal intensity on an arbitrary scale.[1] Thus, in clinical practice, evaluation of contrast enhancement effects is based on a visual inspection of each interpreter. Quantification of GBCA

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concentration could allow objective characterization of the lesion among different scans, patients, and platforms.

The change in longitudinal relaxation rate (inverse of longitudinal relaxation time T_1) is directly proportional to the concentration of GBCA in a lesion.[2,3] Thus, calculating the absolute T_1 values in the lesion before and after administration of contrast agents would provide absolute concentration of the GBCA within the lesion.

Although some previous studies have created and evaluated the effectiveness of a gadolinium concentration map,[2,4] these studies required a long scan time and were impractical for use in clinical settings. Recently, it has become feasible to perform quantitative measurement of the absolute value of the T_1, transverse relaxation time (T_2) and proton density using quantitative synthetic MRI.[1,5] A routine brain study can now be obtained in about 6 min with synthetic MRI, with the creation of contrast-weighted images after image acquisition.[1,6] Quantitative synthetic MRI has been shown to yield performance comparable to that of conventional MRI for routine neuroimaging of brain lesions,[7–9] and has already been approved by the Food and Drug Administration and Conformité Européenne. It can be integrated into a picture archiving and communication system and used on GE Healthcare (Milwaukee, WI, USA), Philips (Best, the Netherlands), and Siemens (Munich, Germany) platforms.

The objective of this study was to demonstrate and evaluate the feasibility of estimating GBCA concentration in a clinically applicable MRI scan-time. We first evaluated the accuracy and precision of the estimated GBCA concentration by comparison with reference values, using a phantom study. Next, we applied the apparent GBCA concentration map to brain metastases and confirmed the validity of this method.

Materials and Methods

Phantoms

We prepared test phantoms with water and different concentrations of Gadoteridol (Gd-HP-DO3A; ProHance, Eisai, Tokyo, Japan). The original Gd-HP-DO3A (500 mmol/L) was mixed with distilled water to 500-, 600-, 700-, 1000-, 2000-, 4000-, 8000-, 16000-, and 24000-fold dilutions (i.e. 0.02–1.00 mmol/L). Each solution was used to fill a plastic syringe. These syringes were placed parallel to each other in a custom-built container holding water at 37°C.

Imaging protocols

The phantoms were scanned by two-dimensional (2D) quantification of relaxation times and proton density by multiecho acquisition of a saturation-recovery using turbo spin-echo readout (QRAPMASTER) pulse sequence[1] using a 3.0T MRI system (Discovery MR750w, GE Healthcare). Imaging parameters were set as follows: TR, 4000 ms; TE, 16.9 and 84.5 ms; delay times, 146, 546, 1879, and 3879 ms; echo train length (ETL), 10; acceleration factor, 2; FOV 240 × 240 mm^2; matrix, 512 × 512; bandwidth (BW), 31.25 Hz; slice thickness/gap, 4 mm/1 mm; slices, 20. T_1 quantitative maps were retrieved on a commercially available standalone version of SyMRI 8.0.0 software (SyntheticMR, Linkoping, Sweden).

Reconstruction of gadolinium concentration map

A GBCA concentration map was created by calculating the GBCA concentration for each voxel using the following formula:

$$cr = \frac{1}{T_{1post}} - \frac{1}{T_{1pre}}$$

where T_{1post} is the longitudinal relaxation times of a solution containing contrast media, T_{1pre} is the longitudinal relaxation times of a solvent without contrast media (i.e., water), r is the relaxivity of Gd-HP-DO3A, and c is the concentration of GBCA. We set relaxivity r to 2.8 [L $mmol^{-1}s^{-1}$] for Gd-HP-DO3A based on previous research.[10] These calculations were performed using an in-house program developed with MATLAB (The MathWorks, Inc., Natick, MA, USA) (Fig. 1).

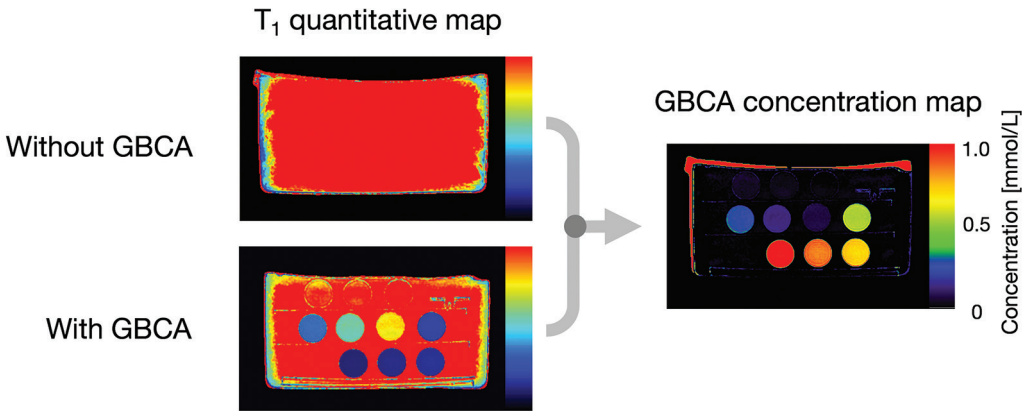

Fig. 1 GBCA concentration map of phantoms containing contrast agent solutions. The change in longitudinal relaxation rate (inverse of longitudinal relaxation time T_1) is proportional to the concentration of GBCA. According to this relationship, the GBCA concentration was calculated using the absolute T_1 values of the pixel with and without GBCA. Calculations were performed for each pixel to obtain the GBCA concentration map. GBCA, gadolinium based contrast agents.

Comparison of measured and reference GBCA concentrations

Quantitative GBCA concentration measurements were performed using manually defined ROIs. Circular ROIs (20 mm^2) were placed at the center of each syringe to record the mean signal intensities of the solution within the syringes. This was repeated for 10 consecutive slices, and the mean values and standard deviations (SDs) were obtained for each syringe. For statistical analysis, we performed a simple linear regression analysis between the estimated GBCA concentration and the reference values. We evaluated the precision of the GBCA map by calculating the coefficient of variation (CV) for each ROI, defined as the SD normalized to the mean values.

Application to brain metastases

The study was approved by the relevant Institutional Review Board. Informed consent was waived for this study because of its retrospective nature. Data from 10 patients with metastatic brain tumors (eight men and two women; mean age, 64.8 years; age range, 44–75 years, 152 lesions) who were imaged with conventional T_1-weighted sequence and synthetic quantitative MRI each before administration of GBCA (0.1 mmol/kg body weight) and approximately 1 and 7 min after administration, respectively, were analyzed. Axial, sagittal, and coronal images were obtained for conventional T_1-inversion recovery (T_1IR) imaging, and only axial images were obtained for quantitative MRI. Conventional T_1IR images were obtained 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. Quantitative MRI scans were obtained using the following parameters: FOV, 240 × 240 mm^2; matrix, 320 × 320; ETL, 10; BW, 31.25 Hz; slice thickness/gap, 4 mm/1 mm; slices, 30. The acquisition time was 1 min 50 s for conventional T_1IR images and 7 min 12 s for quantitative synthetic MRI scans. The patients in this study partially overlapped with those enrolled in a previously published study.[11]

For each patient, we created an apparent GBCA concentration map as described in the phantom study, with additional 2D rigid-body registration between two images in each patient, using Statistical Parametric Mapping (Statistical Parametric Mapping (SPM; Wellcome Trust Centre, London, United Kingdom, http://www.fil.ion.ucl.ac.uk/spm/software/spm12). The term "apparent" was used here because of the uncertainty of relaxivity r in each lesion, which is affected by background physiological environments. For the tentative relaxivity r of the Gd-HP-DO3A, we used the value for bovine plasma, 3.7 [L $mmol^{-1}s^{-1}$], based on previous research.[10] An experienced neuroradiologist identified brain metastases on contrast-enhanced conventional T_1-weighted images and marked the lesions. Referring to these marks, manual ROI analysis was performed on the apparent GBCA concentration map, and maximum values were recorded for each lesion.

Results

Phantom study

For the phantom study, measured GBCA concentrations were in a strong linear relationship (R^2 = 0.998) with reference values, with the slope and intercept on simple linear regression analysis being 0.98 and 0.02, respectively (Fig. 2). Figure 3 shows the CV of each concentration. The CVs were <5%, with the exception of that of concentrations lower than 0.07 mmol/L. In the range of 0.07–0.99 mmol/L, the mean CV was 1.5 ± 1.2%.

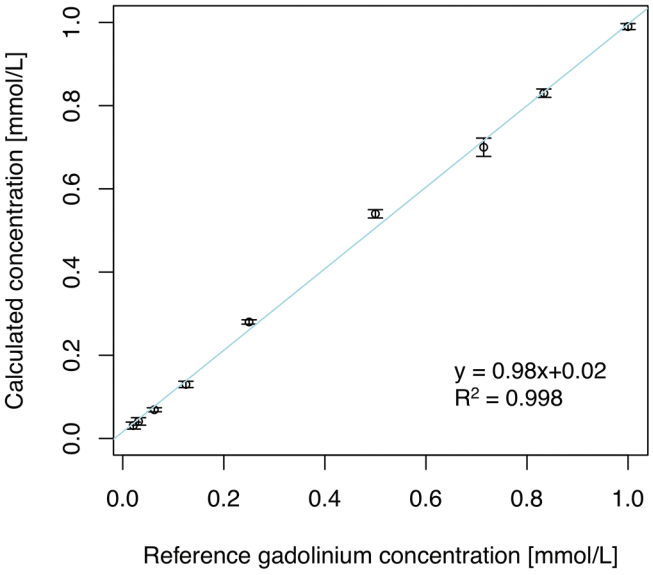

Fig. 2 Correlation plot comparing the estimated gadolinium-based contrast agent concentration to reference values. Error bars represent ±2 SDs. The regression line is superimposed in light blue. SD, standard deviation.

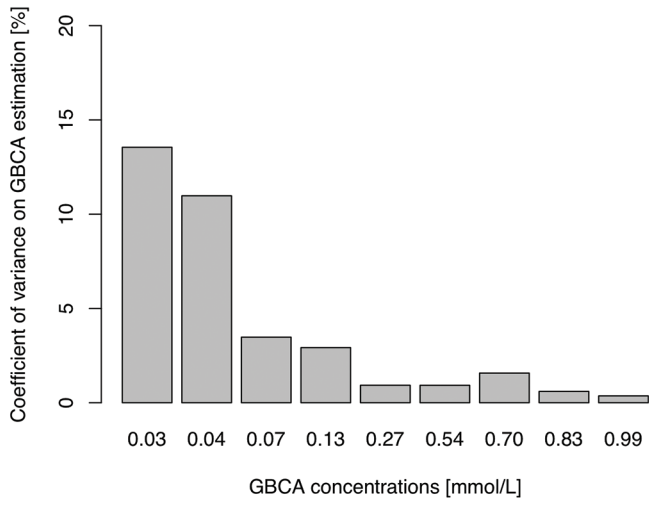

Fig. 3 Coefficients of variation on gadolinium-based contrast agent concentration estimation. The coefficient of variation is the standard deviation normalized by the mean values. GBCA, gadolinium based contrast agents.

Application to brain metastases

The maximum apparent GBCA concentration of brain metastases ranged from 0.04 to 0.73 mmol/L (mean, 0.19 ± 0.13 mmol/L), which was under the upper limit obtained in the phantom study (i.e. −0.99 mmol/L). A representative apparent GBCA concentration map of a metastatic lesion is shown in Fig. 4.

Discussion

In this study, we demonstrated that GBCA concentrations in the range of 0.07–0.99 mmol/L could be measured with high accuracy (R^2 = 0.998) and precision (CV < 5%) *in vitro*, in a clinically applicable scan time. Application of this approach to brain metastases showed that the maximal apparent GBCA concentration in brain metastases were under the upper limit evaluated in the phantom study, indicating the usefulness of apparent GBCA concentration maps in a clinical setting.

While the conventional evaluation of contrast enhancement depends on the interpreter, this method makes it possible to obtain an objective index of contrast enhancement characteristics of the lesion. These absolute values could be used to standardize contrast agent accumulation by calculating the ratio of the GBCA in the lesion to the total amount of GBCA administrated. This provides a comparison between scans obtained from different times, clarifying the time-dependent changes in lesions showing contrast enhancement. The estimated local GBCA concentration would not only help assessing individual lesion, but also enable to collect lesion characteristics across different scans and platforms. This could help accumulate information from multiple centers to conduct clinical research and trials, and drug discovery. Hence, apparent GBCA concentration map has the potential to serve as a quantitative imaging biomarker of diseases.

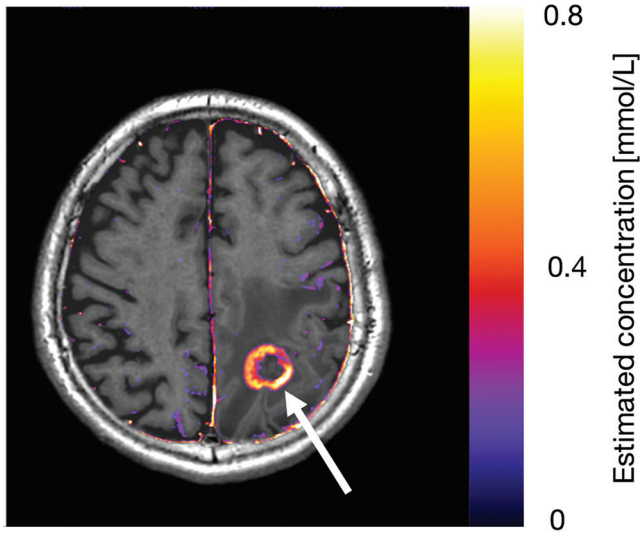

Fig. 4 A representative apparent gadolinium-based contrast agent (GBCA) concentration map, additively overlaid on a non-enhanced T_1-weighted image. The estimated GBCA concentration is expressed using a color scale. The maximum apparent GBCA concentration value of the metastasis in the left hemisphere (arrow) was 0.73 mmol/L.

The CVs of measured GBCA concentrations in the phantoms were <5%, with the exception of those of concentrations lower than 0.07 mmol/L. Low GBCA concentrations had higher CVs than those of high GBCA concentrations, because the CV is sensitive to small changes when the mean value used as the denominator approaches zero. Our aim was to quantify GBCA concentration, and not to detect lesions that have subtle enhancement. Thus, a CV of <5% for concentrations in the range of 0.07–0.99 mmol/L would be sufficient for our purpose.

Because the dynamic ranges of T_1 values in the SyMRI software 8.0.0 is 300–4300 ms,[12] lesions that have T_1 values <300 ms cannot be measured accurately. No brain tissue has such a low T_1 value,[13,14] and indeed, all T_1 values for maximum GBCA concentration in the ROIs measured in the brain metastases in this study were above the lowest limit of T_1 that can be measured by SyMRI software.

A potential limitation of the study could be the uncertainty of relaxivity r in the lesion, since relaxivity is affected by background physiological environments.[10] As opposed to the phantom study where the solvent in which the contrast agent is dissolved is already-known, only the apparent concentration could be measured for accumulation of GBCA in actual lesions. Further studies are needed to identify the experimental conditions that represent the *in vivo* environment most appropriately. Another limitation is that this study used only one scanner. It is possible that scanner variations among different vendors may affect the estimation of GBCA concentration. However, we think the effect of scanner variation is small because quantitative values derived from the QRAPMASTER pulse sequence have been shown to be overall robust for brain relaxometry performed on scanners from different vendors, namely, GE, Siemens, and Philips.[15] Furthermore, this study was based on a widely used, typical GBCA, namely, Gd-HP-DO3A, but not on other GBCAs. Our findings may be applicable to other GBCAs, but this requires further validation.

Subtle patient movement during and between scans could cause misregistration of images before and after administration of contrast agents. Without using the properly registered T_{1pre} and T_{1post} maps, the calculated apparent GBCA concentration could be over/under estimated. Registration based on 2D data set cannot correct for tilting movement, and hence registration accuracy in 2D data set is generally inferior to that of three-dimensional (3D) data sets. A recent study reported simultaneous 3D acquisition of T_1 and T_2 in a clinically applicable time.[16] In future work, application of 3D quantitative synthetic MRI to the brain could refine registration between pre- and post-enhanced images, facilitating the development of a more robust system for estimating GBCA concentrations.

Conclusion

The concentration of Gd-HP-DO3A in the range of 0.07–0.99 mmol/L *in vitro* can be quantified in a clinically applicable time, with high accuracy and precision, using quantitative synthetic MRI. Apparent GBCA concentration map could be obtained *in vivo* using this method, even though this study's results are only preliminary due to several limitations.

Acknowledgments

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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