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Improved display of abdominal contrast-enhanced MRA using gadobutrol: comparison with Gd-DTPA

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AIM: To qualitatively and quantitatively compare gadobutrol with gadopentetate dimeglumine (Gd-DTPA) in abdominal contrast-enhanced magnetic resonance angiography (CE-MRA) and contrast-enhanced magnetic resonance imaging (CE-MRI) during one-stop imaging.

MATERIALS AND METHODS: This prospective, blinded, multicentre, intra-individual comparison study was approved by the institutional review board. All patients underwent gadobutrol- and Gd-DTPA-enhanced MRA and MRI. Qualitative analysis for vessels was performed using a three-point scale while quantity analysis was performed by signal-to-noise ratio (SNR). Visceral organs enhancements were also analysed. A Wilcoxon matched-pair signed-rank test was used to evaluate the quality and quantity results.

RESULTS: One hundred and twelve patients were enrolled. Quality analyses results for large vessels and small vessels of gadobutrol and Gd-DTPA were 18.38±1.51 and 6.76±1.58 and 17.87±1.84 and 6.09±1.55, respectively. Wilcoxon signed-rank tests revealed gadobutrol was significantly superior to Gd-DTPA (p=0.036) for small vessels. For large vessel quantity analysis, gadobutrol demonstrated significantly higher signal-to-noise ratios (SNR; p=0.041) than Gd-DTPA, with mean values of 948.156±349.731 and 838.925±248.197. There was no statistically significant in enhancement of liver, spleen, and renal tissue during gadobutrol- and Gd-DTPA-enhanced imaging (p>0.05). One patient reported an adverse event. Dizziness and vomiting occurred after injection of Gd-DTPA.

CONCLUSIONS: The present study demonstrates gadobutrol-enhanced MRA was superior to that of Gd-DTPA without statistical significance in visceral organ enhancement. It indicates gadobutrol may be more suitable for abdominal one-stop imaging for CE-MRA and CE-MRI by improving depiction of vessels in MRA images.

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Introduction

Contrast-enhanced (CE) magnetic resonance angiography (MRA) and CE magnetic resonance imaging (MRI) have been recognised as non-invasive powerful and accurate imaging tools, which are crucial for diagnostic medicine. Compared to computed tomography, CE-MRA and CE-MRI provide high soft-tissue resolution without the risk of exposure to ionising radiation. They can also provide improved reproducibility and a lower propensity for inter-reader variability than ultrasonography.

Gadolinium-based contrast agents (GBCAs) enhance tissue contrast and are essential for CE-MRA and CE-MRI.[1] Gadobutrol (Gadovist, Bayer Healthcare Pharmaceuticals, Berlin, Germany) is a non-ionic macrocyclic GBCA displaying with high relaxivity and low osmolarity and viscosity.[2–4] The physical properties of this extracellular neutral gadolinium chelate allow for a concentration of 1 mmol Gd/ml, which is double the concentration of gadopentetate dimeglumine (Gd-DTPA, Magnevist, Bayer Healthcare Pharmaceuticals, Berlin, Germany). It has been assumed that the reduced injection volume of gadobutrol facilitates a sharper bolus peak and increased intravascular first-pass gadolinium concentration.[5] Previous studies report gadobutrol improving delineation of small vessels with comparatively increased signal-noise ratios (SNRs) and contrast-to-noise ratio (CNRs) in the vascular territory.[6–8] Whereas contradictory results showed no advantage of gadobutrol for CE-MRA.[9,10] For CE-MRI of the abdominal visceral organs, the value of gadobutrol still needs to be defined.[11–13]

In recent years, improvements in MRI hardware and techniques have greatly increased image spatial resolution and reduced acquisition time.[14] A comprehensive MRI protocol is used to assess the arteries and organ parenchyma, called one-stop imaging. It allows simultaneous acquisition of both MRA and post-enhancement images in the same examination. This approach can reduce the injection of contrast agents and make reasonable use of medical resources.[15,16]

This study aims to qualitatively and quantitatively compare gadobutrol with Gd-DTPA at equimolar doses of gadolinium in abdominal CE-MRA and CE-MRI as part of a one-stop imaging protocol.

Materials and methods

This prospective designed, blinded, multicentre, intra-individual comparison study was approved by the institutional review board.

Patients

Patients met the following inclusion criteria: 18–75 years old; voluntarily signed the informed consent form. The exclusion criteria were as follows: pregnancy or lactation; contraindications to MRI examination such as claustrophobia; contraindications to the use of GBCAs (including suspected or confirmed patients); use of any contrast agent within 72 hours prior to the examination; risk of clinical deterioration that could have an adverse impact on participation. From December 2014 to December 2015, 120 patients in six medical centres were consecutively enrolled. Seven patients voluntarily withdrew from the study. One patient withdrew the research because of an adverse event. Finally these 112 patients finished the study.

MRI

All examinations were performed using a 1.5 or 3 T MRI system with a body coil containing at least six parallel channels (Siemens Avanto, Enlargen, Germany; GE Signa HDX/Discovery, GE Medical Systems, Milwaukee, WI, USA). A standard and comprehensive MRI protocol was performed, including pre- and post-T1-weighted and MRA sequences. Three-dimensional T1-weighted imaging at equilibrium phase (180 seconds after injection). Detailed parameters are shown in Table 1. Test boluses were 1 ml of Gd-DTPA and 0.5 ml of gadobutrol, with an injection rate of 3 or 1.5 ml/s respectively, followed by a 30 ml saline flush with the same injection rate. For enhancement, contrast materials were injected using a power injector with 0.1 mmol/kg Gd-DTPA at a rate of 3 ml/s or 0.1 mmol/kg gadobutrol at a rate of 1.5 ml/s, followed a 30 ml saline flush with the same injection rate. All contrast materials were injected using a powerful injector (Medrad, Indianola, PA, USA).

All patients underwent both gadobutrol- and Gd-DTPA-enhanced MRA and MRI on the same equipment using the same parameters with an interval of 3–5 days. Patients received gadobutrol in the first scan and Gd-DTPA in the second scan (Group A) or vice versa (Group B), which were determined randomly by the SAS program (Version 9.2, SAS Institute, Cary, NC, USA). The investigators followed up participants and documented any signs and symptoms within 72 hours of contrast agent administration.

Image analyses

Three radiologists read the images on Syngo Imaging Workplaces (version VB35A, Siemens AG, Erlangen, Germany) independently, blinded to the contrast agents.

Abdominal vessels were divided into large and small vessels. Large vessels included the coeliac trunk, hepatic artery, the left gastric artery, splenic artery, proper hepatic artery, gastro-duodenal artery, left hepatic artery, right hepatic artery, renal artery, the superior mesenteric artery, and the inferior mesenteric artery. Small vessels included the primary branches of the left and right hepatic arteries, primary branches of the left gastric arteries, primary branches of the renal arteries, and primary branches of the superior mesenteric arteries.

MRA analyses included qualitative analyses and quantitative analyses. Qualitative analyses for large and small vessels were performed with a three-point scale as follows: 0, not displayed; 1, displayed but not insufficient for diagnosis; 2, displayed well for diagnosis.[7] The final scores of large and small vessels were the score sum of relevant vessels, respectively. Quantitative analyses were performed for large vessels by measuring the signal intensity (SI). The

Table 1
Sequence parameters.

	Siemens Avanto1.5 T		GE Signa HDxt 1.5 T		GE discovery MR750 3 T	
	Pre and gadolinium-enhanced T1W imaging	Pre and gadolinium-enhanced MRA Asset	Pre and gadolinium-enhanced T1W imaging	Pre and gadolinium-enhanced MRA Asset	Pre and gadolinium-enhanced T1W imaging	Pre and gadolinium-enhanced MRA Asset
Repetition time (ms)	4.74–5.41	2.94–3.02	6.036	3.476	4.2	3.2
Echo time (ms)	2.38	0.97–1.04	4.168	1.22	1.9	1.1
Flip angle (degree)	10	22–25	12	25	15	25
Bandwidth (Hz/pixel)	260	449	488.281	244.141	200	125
Acquisition matrix (pixel)	288×179,320×110	384×202,384×264	320×160	320×180	320×224	320×200
Field of view (mm^2)	528×576,160×320	384×252,384×264	512×512	512×512	360×360	380×380
Section thickness (mm)	2–2.8	1.2–1.4	4.8	3.6	4.8	3.2
No. of sections	80–88	80–88	88	88	84	84

In Siemens Avanto 1.5T volumetric interpolated breath-hold examination is used for pre and gadolinium enhance T1W imaging, with liver acceleration volume acquisition in GE 1.5 and 3 T; Fl3d1 is used for pre and enhanced MRA in Siemens, with Corce Asset in GE.
MRA, magnetic resonance angiography.

standard deviation of the background noise (SD_{noi}) was measured in the background region on the frequency-encoding direction. The corresponding sizes of the regions of interest (ROIs) for vessels were half of the diameter. The pixel size for SD_{noi} was 50. The final values of SI and SD_{noi} were the average of two measurements. The SNR was calculated as follows[17]: $SNR = SI / SD_{noi}$.

For visceral organ enhancement analysis, pre T1-weighted image (SI_{pre}) and equilibrium phase images (SI_{enh}) were analysed. The ROIs (pixel size = 50) avoided vessels and lesions and were standardised for each organ (Fig 1): liver: on two different areas of the liver (left and right lobe) at the level of the hepatic hilum and right portal vein; spleen: in the parenchyma centre at the level of the spleen hilum and spleen vein; kidney: containing the cortex and medulla at the level of the renal hilum and renal vein. For each organ, a corresponding circular ROI was placed in the background region (pixel size = 50) on the frequency-encoding direction and defined as SD_{noi}. The final value of SI and SD_{noi} were the average of two measurements. The contrast-to-noise ratios (CNRs) were calculated using the following equation[18]: $CNR=(SI_{enh}-SI_{pre})/SD_{noi}$.

Statistical analysis

Paired sample *t*-test was used to compare the difference of basic data of patients between Group A and Group B, including age, gender, and height. A two-sided Wilcoxon signed-rank test was used to compare the qualitative results of vessels in gadobutrol- and Gd-DTPA-enhanced MRA images. For assessment of quantitative parameters of large vessels and visceral organ enhancement in the intra-individual MRI examinations with gadobutrol and Gd-DTPA, the pairwise Wilcoxon signed-rank test was applied. A p-value <0.05 was established to indicate a statistically significant difference between contrast agents. The interobserver agreement for qualitative analysis was assessed by Cohen's kappa statistics.[19] Kappa values >0.75 were taken to represent excellent agreement, values between 0.4–0.75 represented good agreement and values <0.4, poor agreement. All statistical analyses were performed using SPSS software (version 19, Chicago, IL, USA).

Results

Patient characteristics

The demographic data of 112 patients are demonstrated in Table 2. Ninety-six (86.6%) patients had physical examinations. Fifty-six patients received gadobutrol in the first scan and Gd-DTPA in the second scan whereas the other 56 patients received GBCAs in opposite sequence. Paired sample *t*-tests showed there was no statistical difference

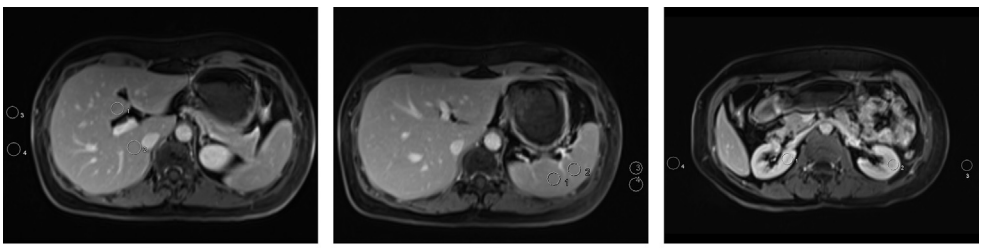

Figure 1 The ROIs were drawn in the left and right lobe of liver at the level of the hepatic hilum and right portal vein (a); spleen, in the parenchyma centre at the level of the spleen hilum (b); kidney, containing cortex and medulla at the level of the renal hilum (c). The ROIs representing background noise was placed in the background region on the frequency-encoding direction. The circles indicate ROIs.

Table 2
Demographics and baseline characteristics of the study population.

Demographic data	Number
Total patients	112
Gender	
Female	64
Male	48
Age (years, mean±standard deviation)	49.13±11.80
Height (cm, mean+standard deviation)	163.02±7.17
Diagnosis	
Normal	96 (85.7%)
Relative disease	16 (14.3%)
Cirrhosis	5 (4.5%)
Nasopharyngeal carcinoma	4 (3.6%)
Cervical carcinoma	2 (1.8%)
Hepatitis B virus carrier	2 (1.8%)
jaundice	1 (0.9%)
Fever	1 (0.9%)
Ependymoma	1 (0.9%)

among basic data of patients in Group A and Group B ($p>0.05$). Of 120 patients enrolled, one patient reported an adverse event. This patient had a diagnosis of lung cancer with multiple metastases to the skull. Dizziness and vomiting occurred after injection of Gd-DTPA. With symptomatic treatment, the symptoms disappeared and patient was withdrawn from the study.

Comparing of the image quality of MRA

The qualitative analysis results for large vessels and small vessels of gadobutrol- and Gd-DTPA-enhanced MRA examinations of 112 patients were 18.38±1.51 and 6.76±1.58 and 17.87±1.84 and 6.09±1.55, respectively (Table 3). Wilcoxon signed-rank test revealed gadobutrol to be significantly superior to Gd-DTPA ($p=0.036$) for small vessels, with no statistical difference for large vessels ($p=0.082$; Fig 2). For large vessel quantitative analysis, gadobutrol demonstrated significantly higher mean SNRs than that of Gd-DTPA, with mean value of 948.156±349.731 and 838.925±248.197 respectively ($p=0.041$).

Comparing of visceral organ enhancement of CE-MRI

The CNR of liver, spleen, and kidney in gadobutrol- and Gd-DTPA-enhanced equilibrium phase imaging were 105.64±96.51 and 103.26±95.98, 176.32±123.41 and 168.33±119.78, and 205.8±137.45 and 192.6±136.78, respectively (Fig 3). The CNRs of three visceral organs on gadobutrol-enhanced MRI were slightly higher than these on Gd-DTPA-enhanced images without statistical difference ($p>0.05$).

Table 3
Qualitative and quantitative analyses results for contrast-enhanced MRA.

	Qualitative analyses		Quantitative analyses for large vessels
	Large vessels	Small vessels	SNR
Gadobutrol			
Reader 1	18.48±1.821	7.04±1.414	980.128±331.105
Reader 2	18±2.08	6.74±1.5	1081.739±330.582
Reader 3	18.48±1.821	7.06±1.42	883.384±311.496
Average	18.378±1.512	6.756±1.583	948.156±349.731
Gd-DTPA			
Reader 1	17.92±1.7	6.10±1.787	853.527±298.385
Reader 2	17.08±3.05	6.32±1.932	904.526±308.132
Reader 3	17.84±1.754	6.06±1.822	728.935±283.216
Average	17.867±1.841	6.089±1.55	838.925±248.197

MRA, magnetic resonance angiography; SNR, Signal-to-noise ratio.

Agreement analysis

The kappa values of the three readers for qualitative analysis were 0.931, 0.767, and 0.788, which indicate excellent agreement.

Discussion

CE-MRA and CE-MRI have been recognised as powerful and accurate non-invasive imaging tools in abdominal disease. A “one-stop” MRI approach is used to acquire MRA and organ parenchyma enhancement images in a single step. Previous studies determined the suitability and feasibility of one-stop abdominal imaging.[15,16,20]

The present study compared gadobutrol with Gd-DTPA qualitatively and quantitatively at equimolar doses of gadolinium during abdominal one-stop CE-MRA and CE-MRI. Qualitative analysis results show gadobutrol-enhanced MRA is superior to that of Gd-DTPA for small vessels. Quantitative analysis of CE-MRA for large vessels found gadobutrol demonstrated higher mean SNR than that of Gd-DTPA. No significant differences in the CNR on equilibrium phase of liver, spleen, and kidney were found between these two contrast agents.

Gadobutrol is an extracellular non-ionic macrocyclic paramagnetic contrast agent that is uniquely formulated at 1 mmol/ml, i.e., twice the gadolinium concentration of other currently licensed GBCAs, such as Gd-DTPA. Gadobutrol has high relaxivity and provides the highest T1-shortening effect per millilitre,[21] which contributes to an increase in signal intensity.[22,23] The high gadolinium concentration of gadobutrol halves the injection volume and provides a small bolus, yielding a higher intravascular concentration during the MRA acquisition.[24,25] The current study demonstrates that gadobutrol (1 mol/l) improves MRA image quality as small vessels demonstrating better and enhanced significantly higher mean SNR values in large vessels than that of Gd-DTPA in abdomen. Previous studies are in accordance with the present results.[26,27] Goyen *et al.*[7] reported gadobutrol-enhanced MRA improved the pelvic arterial morphology compared with Gd-DTPA; however, Fink *et al.* compared the signal characteristics and bolus dynamics of 1 M gadobutrol and 0.5 M Gd-DTPA for CE-MRA of the upper torso and reported that gadobutrol offered no relevant advantages.[9] One explanation may be the injection rate. They injected gadobutrol and Gd-DTPA with rates of 2.5 and 5 ml/s, which were higher than usual. The fast injection rate is likely to affect the distinction between two materials. Their study has another limitation with a small sample size of 10 volunteers, which may lead to deviation.

A recent research including 168 patients for gadobutrol-enhanced MRI reported that gadobutrol was well tolerated

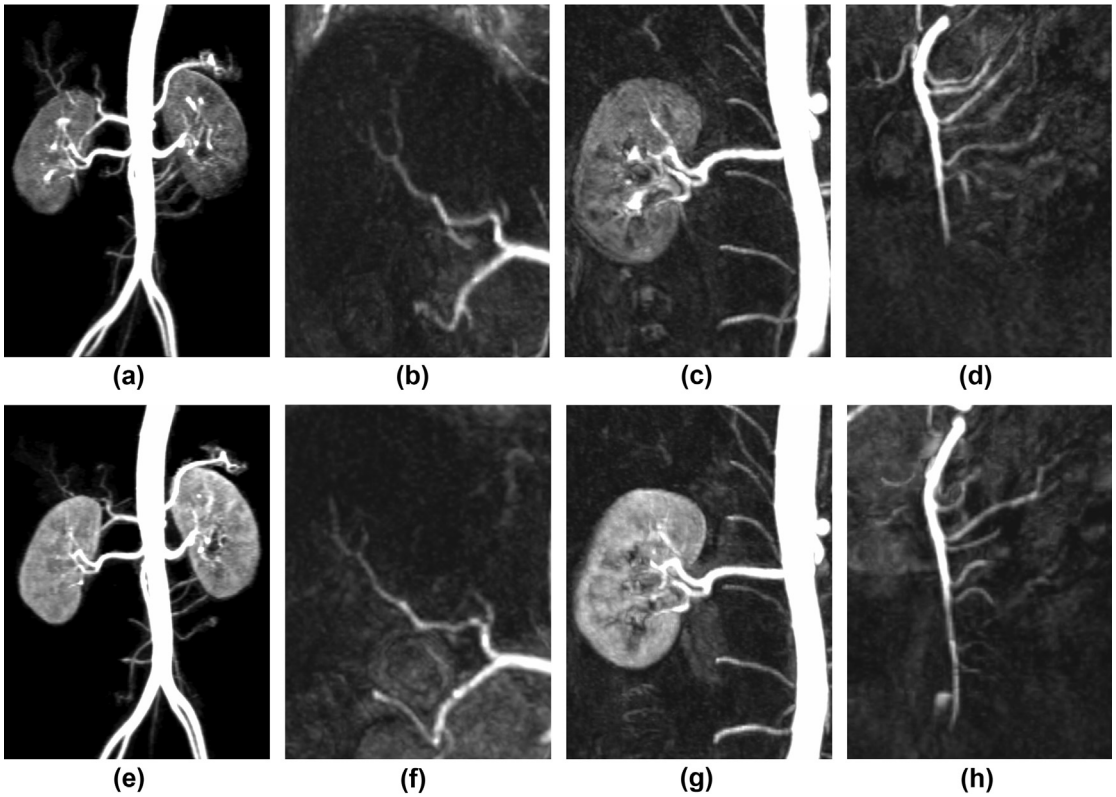

Figure 2 Contrast-enhanced MRA images of a 42-year-old man. Gadobutrol-enhanced MRA images: (a) maximum intensity projection (MIP) image; (b) multiplanar reformation (MPR) image of hepatic artery, (c) right kidney artery and (d) the superior mesenteric artery. Gd-DTPA-enhanced MRA images: (e) MIP image; MPR image of (f) hepatic artery, (g) right kidney artery and (h) the superior mesenteric artery.

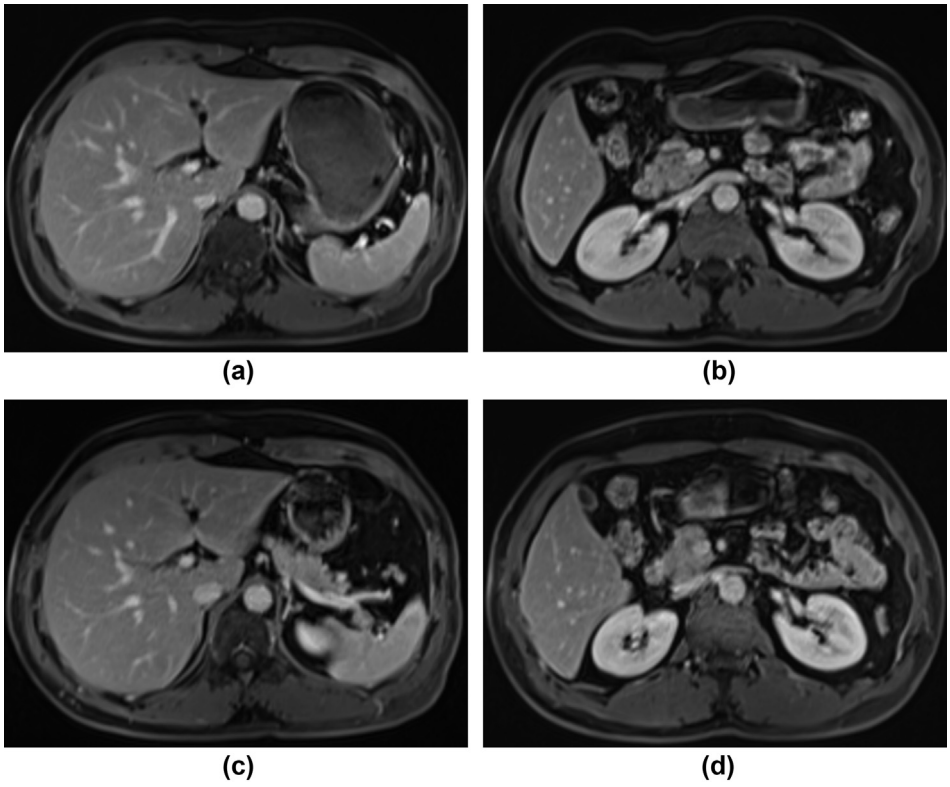

Figure 3 Abdominal visceral organ enhanced images of a 53-year-old man. Gadobutrol-enhanced images on equilibrium phase: (a) liver (CNR, 42.80) and spleen (CNR, 83.11), (b) kidney (CNR, 143.57). Gd-DTPA-enhanced images equilibrium phase: (c) liver (CNR, 20.18) and spleen (CNR, 71.32), (d) kidney (CNR, 89.53).

and effective in Asian patients referred for CE-MRI of the body.[28] Significantly high enhancement of the liver on gadobutrol-enhanced MRI was reported by Kim *et al.*, compared with gadoxetic acid.[13] The results of the present study demonstrate that there is no statistical difference between gadobutrol- and Gd-DTPA-enhanced MRI for abdominal visceral organ enhancement in equilibrium phase of a one-stop imaging protocol.

GBCAs have excellent safety with low rates of acute adverse reactions (0.07–2.4%). Most reactions are mild, including nausea, vomiting, and dizziness.[29] In the present study, one patient reported dizziness and vomiting after injection of Gd-DTPA. This patient had a diagnosis of lung cancer with multiple metastases to the skull. It is speculated that this may have been caused by the skull metastases. Another explanation might be intracranial hypertension after injection of Gd-DTPA.

The present study was prospectively designed as an intra-individual comparison of two different contrast agents; however, there are some limitations. Firstly, considering the small diameter bringing about measurement error, quantitative analysis of CE-MRA was not applied to small vessels in this study, and the CE-MRA results were not compared with arterial digital subtraction angiography. The excellent agreement between the three readers in analyses perhaps makes up for this problem. Secondly, some non-contrast agent-related effects are inevitable and may affect the results. For example, differences in the location between the respective ROI and the imaging coil due to physical positioning variations, movement, coil artefacts, variations in section orientation, etc., might exist.[30] Thirdly, there may be patient selection bias.

The present study demonstrates gadobutrol-enhanced MRA was superior to that of Gd-DTPA without in enhancement of visceral organs in abdominal CE-MRI. Generally speaking, gadobutrol might be more suitable for abdominal one-stop imaging examinations for CE-MRA and CE-MRI by improving depiction of vessels in MRA images.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

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