Diagnostic efficacy of gadoxetic acid-enhanced MRI in the detection of hepatocellular carcinomas: comparison with gadopentetate dimeglumine

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ABSTRACT. This study compared the efficacy of gadoxetic acid-enhanced MRI and gadopentetate dimeglumine-enhanced MRI in the detection of small hepatocellular carcinoma (HCC). Both MRI techniques were performed on 43 patients with a total of 59 HCCs (size range, 0.5–2.0 cm), with a mean interval between the two MRI studies of 3 days (range, 2–7 days). Two observers reviewed both data sets in consensus. Diagnostic accuracy and sensitivity were evaluated using the alternative-free response receiver operator characteristic (ROC) method. The gadoxetic acid set showed a trend toward increased area under the ROC curve (Az value=0.958) compared with the gadopentetate dimeglumine set (Az value=0.927), but the difference was not significant ($p=0.362$). The sensitivity of the gadoxetic acid set ($n=51$, 86.4%) was significantly higher than that of the gadopentetate dimeglumine set ($n=38$, 64.4%) ($p=0.0001$). Gadoxetic acid-enhanced MRI is a more sensitive diagnostic tool for detection of HCC than gadopentetate dimeglumine-enhanced MRI.

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Gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (gadoxetic acid disodium or Gd-EOB-DTPA) is a recently introduced liver-specific MR contrast agent that has the combined properties of an extracellular space contrast (ECS) agent and a liver-specific agent [1–8]. This combination of gadolinium chelates and superparamagnetic iron oxide particles is considered the most reliable, non-invasive diagnostic MR tool for evaluating hepatocellular carcinoma (HCC), so the dual properties of gadoxetic acid make it a good candidate for the early detection and accurate characterisation of HCC [9–12]. Gadoxetic acid-enhanced MRI has demonstrated satisfactory results in both the characterisation of lesions during early dynamic phases and the detection of malignancies during the hepatobiliary phase when compared with conventional gadolinium chelate or CT [3–6]. Although gadoxetic acid MRI has a promisingly high sensitivity for detecting small malignant liver tumours by hepatocyte-phase imaging, it has a theoretical shortcoming in delineating hypervascular HCC during the early vascular phase of arterial perfusion. The dosage of commercially available gadoxetic acid is, at present, one-fourth that of conventional gadolinium chelates ($0.025 \text{ mmol kg}^{-1}$ vs 0.1 mmol kg^{-1}). Thus, even though the T_1 relaxivity of gadoxetic acid measured in human blood is, at 1.5 T, double that of conventional gadolinium chelates [13], the degree of enhancement of

hypervascular lesions and vessels in the vascular phases of gadoxetic acid-enhanced MRI is expected to be about half that provided by conventional gadolinium chelates.

To the best of our knowledge, no study has compared MRI using gadoxetic acid with MRI using conventional gadolinium chelates for diagnostic accuracy and sensitivity in detecting small HCC ($\leq 2.0 \text{ cm}$). Non-specific extracellular gadolinium chelates are still the most widely used MR contrast agents for HCC work-up, and hence the relative detecting capabilities of gadoxetic acid-enhanced MRI and gadopentetate dimeglumine-enhanced MRI must be determined. Accordingly, we compared the diagnostic accuracy and sensitivity of the two agents for detecting HCC, using alternative-free response receiver operating characteristic (ROC) analysis.

Methods and materials

Patients

We retrospectively reviewed our database for liver MRIs conducted at our institution, a tertiary referral hospital, between January and December 2008 for patients suspected of having a HCC. We identified a total of 47 patients who underwent double-contrast MRI with gadopentetate dimeglumine-enhanced and gadoxetic acid-enhanced MRI. Our institution policy is to perform dual-contrast MRI when HCC is found or suspected by ultrasonography and/or CT, because pre-treatment diagnosis of most small HCCs tends to be made through the combined reading of multiple imaging modalities. In addition, early vascular-phase

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gadoxetic acid-enhanced MRI and MRI using conventional gadolinium chelates have not been compared in terms of their abilities to detect small hypervascular HCC. Hence, dual-contrast MRI was especially indicated for those suspected of having small HCCs (of 2.0 cm or less in diameter) or those who received conventional single or two-phase CT examination at local clinics. The institutional review board of our hospital approved the study.

Of the 47 patients, we excluded 4 who each had more than 10 lesions. Consequently, the study population was 43 patients (28 men and 15 women; age range, 44–70 years) with a total of 59 HCCs (size range, 0.5 cm–2.0 cm; mean, 1.5 cm). 42 patients had liver cirrhosis or chronic hepatitis associated with viral hepatitis B, and 1 had viral hepatitis C-induced liver cirrhosis. The final diagnosis of HCC was confirmed for 19 patients (25 HCCs) by pathological analysis of surgical specimens. Of these 25 HCCs, 19 lesions corresponded to Grade I ($n=3$) or Grade II ($n=16$) according to Edmondson's classification of HCC [14]; the remaining 6 lesions were Grade III. For the 28 patients (34 HCCs) who underwent transarterial chemoembolisation ($n=33$) or radiofrequency ablation ($n=1$), reference standards were based on a consensual interpretation of the findings of 2 experienced radiologists on all diagnostic procedures. The diagnostic procedures included image-guided biopsy ($n=1$), characteristic image findings on dynamic CT and/or MRI [1, 3, 15, 16], persistent dense compact nodular Lipiodol uptake of lesions detected only by CT and/or MRI after transarterial chemoembolisation [17] and aggravation (local recurrence) seen on a follow-up multidetector CT (MDCT) or MRI at 6 months or later ($n=5$). Follow-up contrast-enhanced CT or MRI was performed after a minimum of 6 months (range, 6–15 months) on all patients.

MRI examination

All MRIs were performed using a 1.5 T superconducting imager (Magnetom Symphony; Siemens, Erlangen, Germany) with a combination of a phased array body coil and a spine array coil for signal reception. The interval between the gadopentetate dimeglumine-enhanced MRI and the gadoxetic acid-enhanced MRI ranged from 2 to 7 days (mean interval, 3.3 days).

The liver was imaged in the axial plane in all sequences. The baseline MR images included a half-Fourier acquisition single-shot turbo spin-echo (HASTE) sequence (time of repetition (TR)/time to echo (TE) infinite/85, 180° refocusing flip angle, 192 echoes, 146 × 256 matrix, 35 cm field of view, 6 mm slice thickness) and a breath-hold T_1 weighted fast low-angle shot (FLASH) sequence (TR/TE 159/2.7, 70° flip angle, 144 × 256 matrix, 6 mm slice thickness, signal average one and two acquisitions).

A volumetric three-dimensional fat-suppressed spoiled gradient echo acquisition (volumetric interpolated breath-hold examination, VIBE; Siemens) with mSENSE was performed before and after the administration of contrast agents using the following parameters: TR/TE 4.3/2.0, 12° flip angle, 450 Hz/Px bandwidth, 256 (read) × 135 (phase) × 40–46 (partition) matrix, 2.5–3.0 mm effective slice thickness and field of view 32–35 cm. After the unenhanced images were acquired, gadopentetate dimeglumine

was administered intravenously at 3 ml sec⁻¹ for a dose of 0.1 mmol kg⁻¹ body weight or gadoxetic acid was administered at 2 ml sec⁻¹ for a dose of 0.025 mmol kg⁻¹ body weight, followed by a 20 ml saline flush. The time for the dynamic arterial-phase imaging was achieved using the MR fluoroscopic bolus detection technique (CARE Bolus; Siemens). The mean delay times (interval between bolus administration and the start of image acquisition) for the arterial, portal and equilibrium phases were approximately 25–30 s, 60 s and 3 min, respectively. For gadoxetic acid-enhanced MRI, a hepatocyte-specific phase image was acquired at 10 min and 20 min after administration of the agent.

Imaging analysis

Images were analysed by two faculty-level gastrointestinal radiologists with daily clinical experience of interpreting liver MRIs. All acquired images were reviewed on a 2000 × 2000 picture archiving and communication systems (PACS; Marotech, Seoul, Korea) monitor. The two radiologists were unaware of other findings and of the final diagnosis. Two separate sets, using either gadopentetate dimeglumine (HASTE and T_1 FLASH plus contrast-enhanced dynamic images) or gadoxetic acid (HASTE and T_1 FLASH plus early dynamic and hepatocyte-phase images), were analysed in random order. To minimize any learning bias, there was a 3-week interval between the blinded interpretations. The purpose of the evaluation was not to measure the absolute sensitivity of MRI, but to investigate the relative efficacy of gadoxetic acid and gadopentetate dimeglumine in detecting HCC. Therefore, the two radiologists first evaluated the images independently at an initial reading session and then jointly until a consensus was reached on the results. Disagreements were minimal and easily resolved.

The observers recorded the presence and location of the lesions, assigning each lesion a confidence level based on a four-point scale, scored as follows: 0 for not visible; 1 for lesions that showed only arterial hypervascularisation with no delayed capsular enhancement [18], wash out or T_2 hyperintensity; 2 for lesions that showed arterial hypervascularisation with suspicion of delayed capsular enhancement; 3 for lesions that showed arterial hypervascularisation with a definitive capsular rim on the portal and/or equilibrium phase or suspicion of delayed washout; 4 for lesions that showed arterial hypervascularisation with definitive delayed washout (including hypointensity on gadoxetic acid-enhanced hepatocyte-phase images) and/or hyperintensity on T_2 weighted images. In addition, lesions that were hypointense during early dynamic MRI, or at the 10 and 20 min hepatocyte-phase MRI, were regarded as category 1 or 2, according to subjective judgment, if there was no accompanying T_2 hyperintensity.

Statistical analysis

On the basis of the evaluator reviews, alternative-free response receiver operator characteristic (ROC) curve analysis was performed on each lesion [19]. For each

imaging set, an alternative-free response ROC curve was fitted to the confidence rating data using a maximum likelihood estimation program (ROCKIT 0.9B; courtesy of C. E. Metz, University of Chicago, Chicago, IL, 1998) [20]. The diagnostic accuracy of each imaging set and observer was assessed by calculating the area under the alternative-free response ROC curve (Az). Differences between the imaging sets were statistically analysed as mean area under the ROC curves using the two-tailed Student's *t*-test for paired data. Sensitivities were calculated for each image set. The sensitivity of each set was evaluated as the number of the 59 lesions assigned confidence levels of 3 or 4. The sensitivities of both image sets were compared using the McNemar test. A two-tailed *p*-value of less than 0.05 was considered significant. In order to provide a range of plausible sensitivity differences, we also calculated the 95% confidence intervals (CIs) [21]. All statistical analyses were calculated with SPSS 8.0 software (SPSS, Chicago, IL).

Results

Of the 43 patients, 32 had solitary lesions, 7 had 2 lesions, 3 had 3 lesions and 1 patient had 4 lesions. Of the 59 lesions, 47 were 15 mm or less in diameter and the remaining 12 ranged from 16 to 20 mm in diameter. Table 1 shows the distributions of the 59 HCCs according to confidence levels for HCC detection. The Az value for consensus between the two observers was slightly better for the gadoxetic acid set (0.958 ± 0.027) than for the gadopentetate dimeglumine set (0.927 ± 0.040), but this difference was not statistically significant ($p=0.362$). The gadoxetic acid set allowed the visualisation of 51 of the 59 lesions (sensitivity, 86.4%; 95% CI, 75.0–93.9%), whereas the gadopentetate dimeglumine set allowed the visualisation of 38 (sensitivity, 64.4%; 95% CI, 50.9–76.4%). Accordingly, the sensitivity of the gadoxetic acid set was significantly higher than that of the gadopentetate dimeglumine set ($p=0.0001$) (Figure 1).

Seven HCCs (size range, 0.5–1.3 cm) were not verified upon review of both image sets. During the retrospective lesion review, five of these were regarded as hypovascular HCCs as neither image showed arterial hypervascularisation. Two were shown as hypointense nodules on the gadoxetic acid-enhanced 3 min delayed-phase and hepatocyte-phase images and on the gadopentetate dimeglumine-enhanced delayed-phase images. Three

lesions were depicted as hypointense only by gadoxetic acid-enhanced hepatocyte-phase imaging, but not by other MR sequences or gadopentetate dimeglumine-enhanced MRI, and two proved to be well-differentiated HCCs (Figure 2). The remaining two lesions were seen as enhancing hyperintense nodules on the arterial-phase imaging of both MRIs but were occult on other images, including portal- and equilibrium-phase imaging and hepatocyte-phase MRI.

14 lesions that were clearly revealed by the gadoxetic acid set with a confidence rating of 3 or 4 were not discerned by the gadopentetate dimeglumine set. Two of these lesions were occult on the gadopentetate dimeglumine set, and were rated at confidence level 0. 11 showed only arterial hypervascularisation with no definitive delayed peripheral rim or wash-out on the gadopentetate dimeglumine set (confidence level 1 or 2), but showed delayed capsular rim or washout on the 3 min late-phase images and/or hypointensity in the hepatocyte phase of the gadoxetic acid set (Figure 3). The remaining lesion showed subtle delayed hypointensity with no definitive arterial hypervascularisation on the gadopentetate dimeglumine set, but was depicted on the gadoxetic acid set.

By contrast, one lesion was detected only on the gadopentetate dimeglumine set, and was not verifiable on the gadoxetic acid set. It appeared as hypervascular nodules on gadoxetic acid-enhanced arterial-phase imaging, but was occult on other sequences including hepatocyte-phase imaging (confidence rating of 2), and proved to be grade II HCC according to Edmondson's HCC classification.

Neither image set gave false-positives at the confidence level of 3 or 4. However, three nodules (0.5 cm–0.9 cm) were hypointense only on gadoxetic acid-enhanced hepatocyte-phase imaging (confidence rating of 1), and these proved to be cirrhosis-related benign nodules (regenerative or dysplastic nodules) (Figure 4): no evidence of HCC was revealed by other imaging modalities, either at follow-up or in the biopsy specimen.

Discussion

When comparing gadoxetic acid-enhanced MRI and gadopentetate dimeglumine-enhanced MRI for the detection of HCC, two issues need to be addressed. The first is the need to determine whether delineation of arterial hypervascularisation of small HCC by gadoxetic acid is comparable to that achieved by conventional gadolinium chelates. The other is the need to determine whether gadoxetic acid-enhanced hepatocyte-phase imaging provides any additional efficacy in detecting HCC over portal- or equilibrium-phase conventional gadolinium chelates. We hypothesised that gadoxetic acid-enhanced MRI would show higher sensitivity and diagnostic accuracy than gadopentetate dimeglumine-enhanced MRI because of the increased delineation of HCC on hepatocyte-phase imaging. Clinical trials have shown that gadoxetic acid provides haemodynamic information for lesion characterisation during early vascular-interstitial phases that is comparable to that provided by conventional gadolinium chelates [3–6], but a major concern in using gadoxetic acid for HCC imaging

Table 1. Confidence levels for dictation of 59 hepatocellular carcinomas according to gadoxetic acid-enhanced and gadopentetate dimeglumine-enhanced MRI grading (see text for information on scoring)

Gadoxetic acid	Gadopentetate dimeglumine				
	0	1	2	3	4
0	0	0	0	0	0
1	2	2	1	0	0
2	1	0	1	1	0
3	1	0	6	6	0
4	1	2	4	7	24

Figure 1. A 1.2 cm hepatocellular carcinoma in a 55-year-old man. (a) An axial arterial-phase three-dimensional MRI after the administration of gadopentetate dimeglumine (4.3/2.0) shows a nodular enhancement at the right hepatic lobe (arrow). (b) An axial 3 min equilibrium MRI after the administration of gadopentetate dimeglumine (4.3/2.0) shows no definitive washout. (c) An axial arterial-phase three-dimensional MRI after the administration of gadoxetic acid (4.3/2.0) shows a nodular enhancement at the same location as that in (a) (arrow). (d) An axial gadoxetic acid-enhanced 20 min hepatocyte-phase image (4.3/2.0) clearly shows a hypointense mass (arrow).

Figure 2. A well-differentiated hypovascular HCC in a 62-year-old woman. (a) An axial arterial-phase three-dimensional MRI after the administration of gadoxetic acid (4.3/2.0) shows no visible mass. (b) An axial gadoxetic acid-enhanced 20 min hepatocyte-phase image (4.3/2.0) clearly shows a hypointense mass (arrow). This nodule was not found in the gadopentetate dimeglumine set (not shown).

Figure 3. Tiny nodular hepatocellular carcinoma in a 61-year-old man. (a) An axial arterial-phase three-dimensional MRI after the administration of gadopentetate dimeglumine (4.3/2.0) shows a tiny nodular enhancement at right hepatic lobe capsular area (arrow). (b) An axial 3 min equilibrium-phase MRI after the administration of gadopentetate dimeglumine (4.3/2.0) shows no definitive washout. (c) An arterial-phase three-dimensional MRI after the administration of gadoxetic acid (4.3/2.0) shows a nodular enhancement at the same location as that in (a) (arrow). (d) An axial gadoxetic acid-enhanced 20 min hepatocyte-phase image (4.3/2.0) clearly shows a hypointense mass (arrow).

Figure 4. A 58-year-old man with multinodular hepatocellular carcinoma. (a) An axial arterial-phase three-dimensional MRI after the administration of gadoxetic acid (4.3/2.0) shows no enhancing liver mass. (b) An axial gadoxetic acid-enhanced 20 min hepatocyte-phase image (4.3/2.0) shows a small hypointense nodule (arrow), which was assigned a confidence level of 1 and proved to be a cirrhosis-related benign nodule. This nodule was not seen in the gadopentetate dimeglumine set (not shown).

is the lack of evidence to prove whether the ability of gadoxetic acid to show arterial hypervascularisation of HCC is comparable with that of conventional ECS agents.

In this study, no significant difference was found in the diagnostic accuracies of the two image sets, but the sensitivity of the gadoxetic acid set was significantly better than that of the gadopentetate dimeglumine set. 11 lesions showed only arterial hypervascularisation with no definitive delayed capsular rim or washout in the gadopentetate dimeglumine set, but showed arterial hypervascularisation and delayed capsular rim or washout on a 3 min late-phase MRI and/or hypointensity at the hepatocyte phase in the gadoxetic acid set. By contrast, only one lesion was clearly discerned by the gadopentetate dimeglumine set and not verifiable in the gadoxetic acid set. This lesion was seen as isointense because of the uptake of contrast media on gadoxetic acid-enhanced 3 min late and hepatocyte-phase imaging, which may occur more frequently in cases of a well-differentiated HCC. No HCC showed arterial enhancement only on the gadopentetate dimeglumine set and not on the gadoxetic acid set, and thus we confirmed that the delineation of arterial hypervascularisation of HCC by gadoxetic acid is comparable to that of conventional gadolinium chelates, even though a lesser degree of enhancement was expected with gadoxetic acid than with gadopentetate dimeglumine. Considering that 11 lesions were hypointense on hepatocyte-phase imaging but occult on gadopentetate dimeglumine-enhanced delayed-phase images, the major factor in the higher sensitivity of the gadoxetic acid set could be an improved ability to delineate HCC washout.

With improved MRI quality and a screening programme for those at high risk of developing HCC, small atypical HCCs that are seen only as arterially enhanced nodules are frequently encountered clinically when using ECS agents [22–24]. When ECS agents are used alone, they are often difficult to differentiate from non-neoplastic hypervascular pseudolesions caused by small arteriportal shunts [22–24]. Therefore, gadoxetic acid-enhanced MRI could be a promising tool for evaluating small HCCs that manifest only as arterially enhancing nodules upon conventional CT or MRI.

In this study, seven HCCs could not be verified by both imaging modalities. Five were categorised as hypovascular HCCs because neither image showed arterial hypervascularisation. Two lesions appeared as hypointense nodules on the gadoxetic acid-enhanced 3 min delayed-phase and hepatocyte-phase images and on the gadopentetate dimeglumine-enhanced delayed-phase imaging. The remaining three were hypointense only on hepatocyte-phase imaging. We therefore faced a dilemma in interpreting the hypointense nodules that were depicted only on hepatocyte-phase imaging because five cirrhosis-related benign nodules also appeared as hypointense areas only on hepatocyte-phase imaging. No features were found to differentiate early HCC from cirrhosis-related benign nodules appearing as hepatocyte phase-only hypointense nodules. Nonetheless, as they have malignant potential, early recognition of these risky hepatic nodules could lead to early detection of HCC or a better treatment outcome if patients with these nodules are encouraged to undergo more careful follow-up or further diagnostic steps and

therapeutic planning. Future studies are warranted to characterise these hypointense nodules as either cirrhosis-related benign nodules or early HCC.

Our results indicated that gadoxetic acid could replace the conventional gadolinium chelate in HCC work-ups. It offers both comparable haemodynamic information for hypervascular HCC during early vascular phases and additional delineation of HCC during hepatocyte-phase imaging. However, in addition to problems in interpreting the hypointense nodules depicted only on hepatocyte-phase imaging, it is not easy to interpret hepatic nodules that show arterial hypervascularisation but are isointense on hepatocyte-phase imaging because of contrast uptake. This is because, as for the iso- or hyperintense nodules on hepatocyte-phase imaging that result from their contrast uptake, there have been no exact guidelines for differentiating between HCC and cirrhosis-related benign nodules, except when they show T_2 hyperintensity. It could be said, therefore, that the main limitation of gadoxetic acid-enhanced MRI is not detecting HCC but characterising some early types of HCC. Nevertheless, no HCC detected by gadoxetic acid-enhanced MRI was assigned a confidence rating of 0, so gadoxetic acid-enhanced MRI could be a promising tool for early HCC detection.

Several limitations of this study should be noted. First, not all of the lesions were surgically confirmed, which could reduce the number of false-negatives, resulting in an overestimation of the sensitivity of each image. This study included only patients who had undergone surgery or who had lesions that showed matched findings after investigations by multiple imaging modalities (including CT, MRI and Lipiodol CT), and who had at least a 6-month follow-up MDCT or MRI. These criteria are used at many institutions and are considered sufficient for clinical diagnosis of HCC [25]. Furthermore, even if we had pathological specimens for all study cases, histological determination of a high-grade dysplastic nodule or well-differentiated HCC is still controversial. Second, only patients who underwent both MRIs were retrospectively analysed, causing a selection bias. Third, the signal intensities of HCCs and cirrhosis-related benign nodules on gadoxetic acid-enhanced hepatocyte-phase imaging have not yet been determined. Therefore, the Az values and sensitivity of both MRIs were based on consensus between two observers to avoid introducing individual bias into the statistical results. Further, we were not interested in determining the reproducibility of diagnosis by the imaging modalities. Instead, we wished to determine the differential imaging features of HCC, as well as the relative diagnostic capabilities of two MRI agents.

In conclusion, for the detection of HCCs, gadoxetic acid-enhanced liver MRI was better than gadopentetate dimeglumine-enhanced MRI because the delineation of hypointensity of HCC was best on hepatocyte-phase images.

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